CLINICAL RESEARCH STUDY

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# Mistaken Identity: Many Diagnoses are Frequently Misattributed to Lyme Disease

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## ABSTRACT

**BACKGROUND:** Prior studies have demonstrated that Lyme disease is frequently over-diagnosed. However, few studies describe which conditions are misdiagnosed as Lyme disease.

**METHODS:** This retrospective observational cohort study evaluated patients who lacked evidence for *Borrelia burgdorferi* infection referred for Lyme disease to a Mid-Atlantic academic center from 2000-2013. The primary outcome is clinically described diagnoses contributing to symptoms. Secondary outcomes included symptom duration and determination whether diagnoses were new or attributed to existing medical conditions.

**RESULTS:** Of 1261 referred patients, 1061 (84%) had no findings of active Lyme disease, with 690 (65%) receiving other diagnoses; resulting in 405 (59%) having newly diagnosed medical conditions, 134 (19%) attributed to pre-existing medical issues, and 151 (22%) with both new and pre-existing conditions. Among the 690 patients, the median symptom duration was 796 days, and a total of 139 discrete diagnoses were made. Infectious disease diagnoses comprised only 3.2%. Leading diagnoses were anxiety/depression 222 (21%), fibromyalgia 120 (11%), chronic fatigue syndrome 77 (7%), migraine disorder 74 (7%), osteoarthritis 62 (6%), and sleep disorder/apnea 48 (5%). Examples of less frequent but non-syndromic diseases newly diagnosed included multiple sclerosis (n = 11), malignancy (n = 8), Parkinson's disease (n = 8), sarcoidosis (n = 4), or amyotrophic lateral sclerosis (n = 4).

**CONCLUSIONS:** Most patients with long-term symptoms have either new or pre-existing disorders accounting for their symptoms other than Lyme disease, suggesting overdiagnosis in this population. Patients referred for consideration of Lyme disease for chronic symptoms deserve careful assessment for diagnoses other than *Borrelia burgdorferi* infection.

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**KEYWORDS:** Chronic Lyme disease; Fatigue; Long-term symptoms; Lyme disease; Misdiagnosis; Pain; Post-treatment Lyme syndrome; Tick-borne infections

## BACKGROUND

Lyme disease is the most common vector-borne infection in North America and Europe, commonly caused by 1 of 3 pathogenic genospecies of the spirochete *Borrelia*.[1,2] *Borrelia burgdorferi sensu stricto* is transmitted solely in North America, mostly by the tick *Ixodes scapularis.* The infection typically causes dermatologic, musculoskeletal, neurologic, and cardiac illnesses. Both under- and over-diagnosis of Lyme disease have been well described.[3-5] While antibiotic therapy resolves symptoms for most infected patients, some are left with persistent subjective problems such as pain, fatigue, or brain fog that may fall within the proposed

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**Conflicts of Interest:** PGA reports consulting for DiaSorin, Adaptive Biotherapeutics, and Pfizer; doing research sponsored by MicroB-Plex; being an expert witness in malpractice cases involving Lyme disease; and is an unpaid board member of the American Lyme Disease Foundation.

**Authorship:** All authors had access to the data and a role in writing this manuscript.

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entity post-treatment Lyme disease syndrome.[6] Some alternative practitioners have adopted the term "chronic Lyme disease" to describe these symptoms regardless of whether objective evidence for *B. burgdorferi* infection exists.[7]

Published case reports and series have highlighted concerns that diagnoses as diverse as cancer and vasculitis may be missed in such patients.[8,9] In addition, 2 US studies published in the 1990s evaluated patients sent to a rheumatology clinic who were thought to have Lyme disease but instead were found to have chronic fatigue syndrome and fibromyalgia as the 2 most common explanations.[10,11] However, these studies were performed when first-generation Lyme disease serologic assays yielded higher false-positive rates than the current standard 2-tier testing introduced in 1995. There has not been a recent sizeable US study examining diagnoses in patients arising from infectious diseases consultation that potentially reflects some Lyme disease community practices.

Inappropriate attribution of Lyme disease often leads to unneeded antibiotic therapies.[12,13] Multiple complications and adverse outcomes due to unnecessary antibiotics, antibiotics prescribed longer than recommended, or unconventional treatments for Lyme disease have been reported, such as *Clostridioides difficile* infections, clots from venous catheters, catheter-associated bloodstream infection, cholecystitis, and death.[14-16] Given the potentially serious consequences of unnecessary antimicrobial treatments, it is essential to understand frequent and uncommon diagnoses that explain symptoms in this population. This study aims to identify specific diagnoses that explain symptoms previously attributed to Lyme disease.

**CLINICAL SIGNIFICANCE**

- The majority of patients with long-term symptoms referred for evaluation of Lyme disease had alternative diagnoses to explain their symptoms.
- Among 1061 patients, the 139 diagnoses described suggest that Lyme disease may be a frequent inappropriate diagnosis in this population.
- Both new and pre-existing conditions should be considered in the differential diagnosis.
- Patients referred for Lyme disease, especially with chronic symptoms, deserve careful assessment for diagnoses other than Lyme disease.

## METHODS

This retrospective observational study was performed in a single-center, outpatient suburban infectious diseases clinic of the Johns Hopkins University School of Medicine located in Lutherville, Md. Between January 1, 2000 and December 31, 2013, all infectious disease referrals were screened for a presumptive Lyme disease diagnosis or referral to rule out Lyme disease. Individuals younger than 12 years old were excluded, as the clinic did not treat children below this age. Clinical data extraction used a standardized accounting of symptoms, physical examination findings, and laboratory data. Patients who had active/recent Lyme disease as a cause of their symptoms were determined based on established criteria.[6,17] Additional details about this cohort are further discussed in an earlier published paper.[18] Any subsequent testing performed was directed at the discretion of the evaluating physician and follow-through of the patient.

The prior study comprised 1261 patients referred for a presumed diagnosis or concern for Lyme disease, of which 1061 (84.1%) did not have evidence of active or recent Lyme disease, including post-treatment Lyme disease syndrome,[18] and were included in this present study (Figure 1). The primary outcome of interest was the clinically documented diagnoses contributing to their symptoms upon review of all available records. These diagnoses were evaluated by 2 infectious diseases specialists (PGA and MTM) based upon documentation available within medical records at our institution, including those from primary care and subspecialty clinicians. All clinically suspected and documented diagnoses were included if symptoms were attributed to more than one process by treating providers. Each individual could have more than one diagnosis (eg, depression and migraine). Diagnoses used reflected only those described in the medical records. Diagnoses were not included if only a differential diagnosis was offered or lack of follow-up dictated no conclusions. Diagnoses made were further categorized using the following categories: cardiac, dermatologic, endocrine, gastrointestinal/hepatic, hematologic, infectious, inflammatory (eg, rheumatic arthritis), musculoskeletal (eg, osteoarthritis), neoplastic, neurologic (eg, migraine headache), psychiatric/functional, syndromic (eg, fibromyalgia, chronic fatigue syndrome), and other diseases. Patients without definitive diagnoses were placed in the "no diagnosis" category.

Secondary outcomes included symptom duration, the total number of visits to infectious disease and specialty clinics for work-up of complaints, duration of follow-up within available records, the determination of whether the diagnoses were new or based upon attribution to pre-existing medical conditions, and complications or side effects due to antibiotics prescribed by referring providers for presumptive Lyme disease. We also described 5 illustrative examples where other diagnoses were made after work-up in our health care system through infectious disease consultations.

A single visit was defined as a one-time evaluation at our Infectious Diseases clinic for concern of Lyme disease. Any follow-up in our health care system, including any outpatient and inpatient evaluation for symptoms attributed to Lyme disease, was included for the number of visits and follow-up time. If patients followed up with their primary care physicians for the symptoms attributed to Lyme disease, these visits were included to identify the duration of

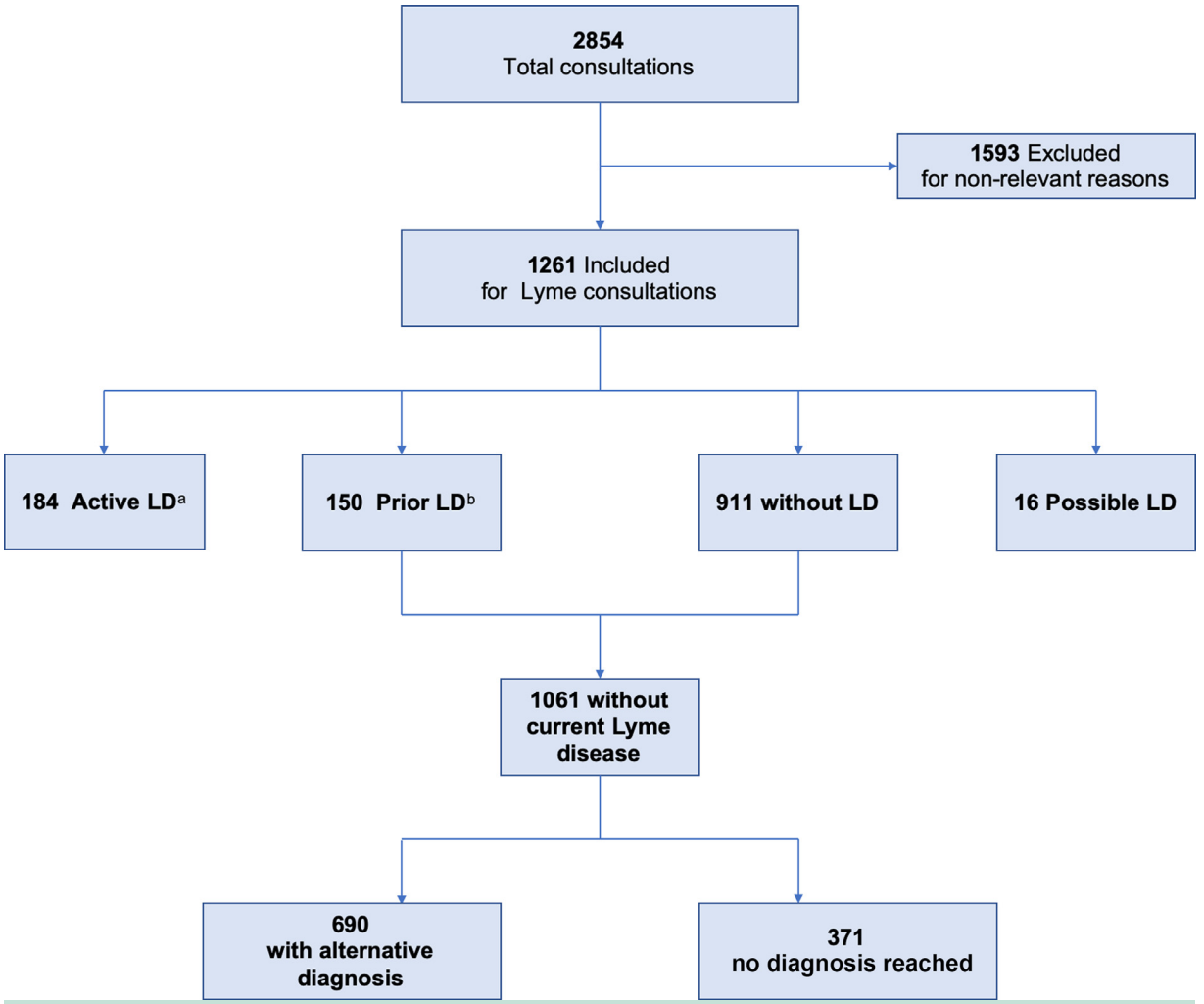


**Figure 1** Study flow chart.
LD = Lyme disease.
[a]Includes patients with post-treatment Lyme syndrome.
[b]Patients with remote Lyme disease had symptoms that had started at least 2 years after complete recovery from an earlier episode of Lyme disease.

follow-up. It was considered a new diagnosis if the diagnosis had not been included as part of past medical history at the initial Infectious Diseases clinic. Complications and side effects due to antibiotics were recorded. The Johns Hopkins University School of Medicine Institutional Review Board approved this study.

## RESULTS

Of 1061 referred patients determined not to have Lyme disease, 690 (65%) had at least one different diagnosis, and 371 (35%) had no diagnoses reached (Figure 1). Of those diagnosed, 402 (58%) had one diagnosis, 204 (30%) had 2 diagnoses, and 84 (12%) had more than 2 diagnoses. Overall, 139 discrete diagnoses were found. Median symptom duration was 796 days (range 10-18,518 days) in those with diagnoses and 567 days (range 0-11,308 days) in those without securing a diagnosis (Table 1). Within the study period, 363/690 (52.6%) patients with diagnoses and 205/371 (55.3%) patients without diagnoses had only a single visit. Regarding additional visits, the median follow-up duration was 35 days for those with diagnoses and 28 days for those without diagnoses.

Of 690 patients with diagnoses, 405 (59%) patients were diagnosed with a new medical issue, 134 (19%) patients had symptoms attributed to pre-existing medical problems, and 151 (22%) had both new diagnoses and pre-existing medical problems as explanations.

The most frequent diagnoses were anxiety/depression in 222 patients (21%), fibromyalgia (120, 11%), chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME; 77, 7%), migraine disorder (74, 7%), osteoarthritis (62, 6%), and sleep disorder/apnea (48, 4%) (Table 2). Among newly made diagnoses, the most frequent diagnoses were anxiety/

**Table 1** Symptom Duration, Follow-Up Duration, and New or Pre-Existing Issues as Diagnoses in 1061 Patients Without Lyme Disease

| Without Current Lyme Disease, n = 1061 | With Diagnosis n = 690 (65%) | No Diagnosis n = 371 (35%) |
|---|---|---|
| Symptom duration prior to referral (days) | | |
| Mean | 1554.9 | 1182.0 |
| Median | 796.0 | 567.0 |
| Range | 10-18,518 | 0-11,308 |
| Follow-up duration (days) | | |
| Mean, all | 70.6 | 38.7 |
| Median, all* | 0 | 0 |
| Mean of those with follow-up | 149.0 | 86.6 |
| Median of those with follow-up | 35.0 | 28.0 |
| Range | 0-2371 | 0-2177 |
| Number of clinic visits for complaints attributed to Lyme disease | | |
| Mean, all | 1.8 | 1.6 |
| Median, all | 1.0 | 1.0 |
| Mean of those with follow-up | 2.6 | 2.3 |
| Median of those with follow-up | 2.0 | 2.0 |
| Range | 1-11 | 1-7 |
| Types of diagnoses | | |
| New diagnosis | 405 (59%) | N/A |
| Pre-existing diagnoses | 134 (19%) | |
| Both new and pre-existing diagnoses | 151 (22%) | |
| Number of diagnoses to which symptoms were attributed | | |
| 1 diagnosis | 402 (58%) | N/A |
| 2 diagnoses | 204 (30%) | |
| 3 or more diagnoses | 84 (12%) | |

Dx = diagnosis, FU = follow-up, N/A = not applicable.
*Median follow-up was 0 days for both groups because 363 patients in the diagnosis group and 205 patients in the No Diagnosis group did not have any follow-up for symptoms previously attributed to Lyme disease, respectively.

depression (91, 9%), fibromyalgia (85, 8%), CFS/ME (70, 7%), migraine disorder (51, 5%), osteoarthritis (42, 4%), and other arthritis (34, 3%) patients.

Examples of less frequent but non-syndromic diseases newly diagnosed included multiple sclerosis (11 patients), malignancy (n = 8), Parkinson disease (n = 8), sarcoidosis (n = 4), or amyotrophic lateral sclerosis (n = 4). Table 2 and Supplementary Table 1 (available online) outline 35 diagnoses frequently made (n ≥5) and 104 diagnoses (n <4), respectively. Eight patients with malignancies were newly diagnosed only after their referral for Lyme disease: chondrosarcoma, metastatic prostate cancer, metastatic lung cancer, lymphocytic leukemia, multiple myeloma with systemic amyloidosis, metastatic squamous cell tumor, glioblastoma multiforme, and myelodysplastic syndrome.

The most common disease category of the final diagnoses was syndromic (35.7%), followed by psychiatric/functional (35.4%), neurological (26.8%), musculoskeletal (17.8%), inflammatory (11.9%), and gastrointestinal/hepatic (7.1%) (Figure 2, Supplementary Table 2, available online).

Infectious disease diagnoses comprised 3.4% (22/690). Seventeen different infectious disease diagnoses were made: Epstein-Barr virus infection (4 patients), methicillin-resistant *Staphylococcus aureus* skin infection (n = 2), chronic hepatitis B (n = 2), chronic hepatitis C (n = 1), osteomyelitis (n = 1), cellulitis (n = 1), syphilis (n = 1), shingles (n = 1), babesiosis (n = 1), Rocky Mountain spotted fever (n = 1), leprosy (n = 1), viral meningitis (n = 1), parvovirus (n = 1), otitis media (n = 1), enterovirus (n = 1), cytomegalovirus (n = 1), viral infection, unspecified (n = 1). Five brief patient case presentations and clinical courses that reflect a few of the interesting diagnoses are further described in Table 3.[9]

In terms of complications due to antibiotics prescribed earlier by referring providers, there were 4 (0.4%) with *C. difficile* infection, 2 (0.2%) with adverse reactions to antibiotics, and 1 (0.1%) with venous thrombosis due to IV antibiotic administration.

## DISCUSSION

This 14-year retrospective observational study revealed that 65% of patients referred for Lyme disease but without objective evidence of the infection had other diagnoses that could explain their frequently long-term symptoms. The breadth reflecting 139 distinct diagnoses other than Lyme disease points to the broad spectrum of potential problems that may be initially blamed on tick-borne disease. Of those with attributable diagnoses, pre-existing conditions explained complaints in 19%. Approximately one-third of patients had no diagnoses, reflecting both a lack of follow-up and non-specific complaints. Misdiagnosis of Lyme disease potentially offers false hope to patients with long-term symptoms

**Table 2** Diagnoses, Symptom Duration, and Numbers of New or Pre-Existing Medical Issues in 1061 Patients Without Lyme Disease (Diagnosed ≥5 Times)

| Diagnosis | Number with Diagnosis | Symptom Duration | | | | | Pre-Existing Diagnosis | New Diagnosis |
|---|---|---|---|---|---|---|---|---|
| | | 0-182 Days | 183-730 Days | ≥731 Days | Mean | Median | | |
| No diagnosis | 371 | 84 | 127 | 160 | 1182.0 | 567.0 | n/a | n/a |
| Anxiety/depression | 222 | 15 | 63 | 144 | 1749.1 | 1096.0 | 131 | 91 |
| Fibromyalgia | 120 | 7 | 40 | 73 | 1914.0 | 952.5 | 35 | 85 |
| Chronic fatigue | 77 | 2 | 23 | 52 | 2156.9 | 1248.0 | 7 | 70 |
| Migraine headache | 74 | 4 | 29 | 41 | 1666.6 | 802.5 | 23 | 51 |
| Osteoarthritis | 62 | 9 | 24 | 29 | 1206.3 | 676.5 | 20 | 42 |
| Sleep disorder or apnea | 48 | 0 | 18 | 30 | 2111.3 | 1019.5 | 25 | 23 |
| Other arthritis, NOS | 38 | 5 | 16 | 17 | 1411.6 | 486.5 | 4 | 34 |
| Chronic regional pain | 32 | 3 | 5 | 24 | 2106.5 | 1402.0 | 0 | 32 |
| Irritable bowel syndrome | 26 | 1 | 9 | 16 | 1426.6 | 1348.0 | 12 | 14 |
| Post-infectious fatigue syndrome, not Lyme disease | 26 | 9 | 13 | 4 | 388.9 | 276.5 | 0 | 26 |
| Peripheral neuropathy | 20 | 1 | 9 | 10 | 2197.1 | 800.5 | 6 | 14 |
| Obesity, morbid | 16 | 1 | 5 | 10 | 2317.5 | 1552.5 | 3 | 13 |
| Multiple sclerosis | 15 | 2 | 2 | 11 | 2249.8 | 1725.0 | 4 | 11 |
| Postural orthostatic tachycardia syndrome (POTS) | 14 | 0 | 1 | 13 | 2179.1 | 1663.5 | 2 | 12 |
| Parkinson disease | 12 | 0 | 5 | 7 | 1636.9 | 1153.0 | 4 | 8 |
| Thyroid disease | 11 | 1 | 6 | 4 | 789.9 | 581.0 | 9 | 2 |
| Alcohol abuse | 10 | 0 | 4 | 6 | 1841.6 | 1509.0 | 1 | 9 |
| Dementia | 10 | 0 | 3 | 7 | 968.5 | 952.5 | 2 | 8 |
| Hypogonadism | 9 | 0 | 4 | 5 | 1949.0 | 1223.0 | 2 | 7 |
| Iron deficiency | 9 | 0 | 4 | 5 | 2386.3 | 735.0 | 0 | 9 |
| Cancer† | 8 | 0 | 4 | 4 | 1288.9 | 846.0 | 0 | 8 |
| Inflammatory bowel disease | 8 | 1 | 2 | 5 | 2511.5 | 1254.0 | 6 | 2 |
| Amyotrophic lateral sclerosis (ALS) | 7 | 0 | 2 | 5 | 951.6 | 828.0 | 3 | 4 |
| Heart disease | 7 | 2 | 2 | 3 | 2384.6 | 384.0 | 3 | 4 |
| Gastroparesis | 6 | 0 | 4 | 2 | 1058.7 | 543.5 | 0 | 6 |
| Postviral arthralgia syndrome | 6 | 2 | 2 | 2 | 533.3 | 276.0 | 0 | 6 |
| Restless leg syndrome | 6 | 0 | 1 | 5 | 3301.0 | 2792.0 | 1 | 5 |
| Rheumatoid arthritis | 6 | 1 | 1 | 4 | 1648.0 | 872.0 | 2 | 4 |
| Dermatitis, non-infectious | 5 | 1 | 2 | 2 | 749.4 | 718.0 | 2 | 3 |
| Gout or pseudogout | 5 | 1 | 2 | 2 | 763.4 | 378.0 | 3 | 2 |
| Idiopathic hearing loss | 5 | 2 | 1 | 2 | 601.8 | 581.0 | 0 | 5 |
| Meniscal tear | 5 | 1 | 1 | 3 | 1048.6 | 1143.0 | 0 | 5 |
| Sarcoidosis | 5 | 1 | 0 | 4 | 1710.8 | 1208.0 | 1 | 4 |
| Spondyloarthritis | 5 | 0 | 2 | 3 | 2787.4 | 1241.0 | 0 | 5 |
| Uveitis | 5 | 1 | 1 | 3 | 1710.8 | 1415.0 | 1 | 4 |

n/a = not applicable; NOS = not otherwise specified.

*Only diagnoses made in ≥5 patients are included in this table. For diagnoses made in four or fewer patients, see Supplementary Table 1.

†Cancer diagnosis: chondrosarcoma, metastatic prostate cancer, metastatic lung cancer, lymphocytic leukemia, multiple myeloma with systemic amyloidosis, metastatic squamous cell tumor, glioblastoma multiforme, and myelodysplastic syndrome.

and leads to an inadequate workup with potential delay in securing an accurate diagnosis.

The present study demonstrated that approximately two-thirds of patients had other diagnoses that could explain their symptoms. Studies similar to this study, conducted since 1990, show differing frequencies of diagnoses in patients without Lyme disease, ranging from 44% to 81% (Table 4[10,11,16,18-22]). One explanation for this relative heterogeneity is likely due to differences in study design and diagnosis definitions.

A retrospective study of 788 patients published by Steere et al[11] revealed that 23% had Lyme disease, and the remaining 77% had an alternative diagnosis. Reid et al[16] demonstrated that, among 209 patients, 21% had Lyme disease and 79% had an alternative diagnosis. These 2 studies, published in the 1990s, appeared to have an answer for all patients, in part considering subjective syndromes (eg, "subjective neurological symptoms") as a diagnosis. In contrast, the current study would have labeled those patients as "no diagnosis." Two recent studies from France published in 2018 and 2019[19,20] and our study showed very similar rates of alternative diagnoses. These 3 studies revealed that ~55% of all referral patients had diagnoses other than Lyme disease.

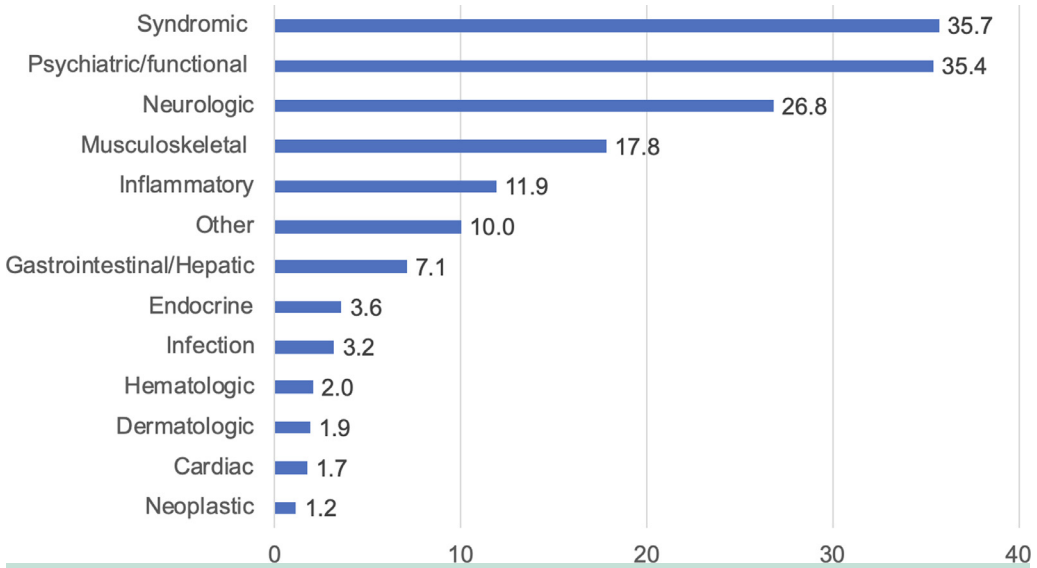


**Figure 2** Categories of diagnoses in patients without Lyme disease (% of n = 690*).
*Individual patients can have more than one diagnosis.

Interestingly, one study conducted by Haddad et al[21] in 2019 had patients without Lyme disease follow up at least once to further discuss diagnosis options, leading to a higher rate (81%) of making non-Lyme disease diagnoses. More than half (55%, 205/371) of patients without a diagnosis did not have follow-up visits in our study. They likely contributed to a relatively lower number of patients with diagnoses reached in our study.

**Table 3** Description of Five Patients with Final Diagnoses

| Patient | Clinical Course |
|---|---|
| #1 | A 77-year-old woman with a 7-year history of advancing progressive supranuclear palsy (PSP) experienced some dizziness. Her primary care provider ordered *Borrelia burgdorferi* immunoglobulin M (IgM) and immunoglobulin G (IgG) immunoblots without the first-tier enzyme-linked immunoassay (EIA), revealing only a single 23-kd IgM band. The patient was referred to consider neuroborreliosis and lumbar puncture to determine whether Lyme disease, and not PSP, caused her neurologic disease. The serological findings were discussed with the patient as non-significant. |
| #2 | Over 6 months, a 62-year-old man developed decreased right-sided hearing, musculoskeletal pain, numbness, arthralgia, low-grade fever, and sweats. Three weeks of doxycycline did not yield improvement. He was referred for antibiotic unresponsive Lyme disease despite negative Lyme serology and was diagnosed with granulomatosis with polyangiitis.[9] |
| #3 | A 67-year-old man was referred for consideration of Lyme disease despite negative *B. burgdorferi* serologic testing with a more than a 4-month history of fatigue along with bilateral shoulder and hip pain. Testing ordered following consultation yielded elevated inflammatory markers, erythrocyte sedimentation rate, and C-reactive protein. Polymyalgia rheumatica was diagnosed, and treatment yielded subsequent improvement. |
| #4 | A 45-year-old man experienced a 2-year history of unexplained 70-pound weight loss, headaches, fatigue, and low-grade fevers. He was referred after a positive Lyme EIA with positive IgM immunoblot (3 bands) but negative IgG immunoblot (single band). He had received a 30-day course of ceftriaxone for neuroborreliosis without response, prompting referral. Following infectious disease consultation, the Lyme serology was determined as not significant based on the duration of symptoms and lack of sufficient IgG immunoblot response. The further evaluation discovered hilar lymphadenopathy on chest computed tomography. He underwent mediastinoscopy with lymph node biopsy revealing non-necrotizing granuloma with cultures yielding neither tuberculosis nor histoplasmosis. Sarcoidosis was diagnosed, and additional testing confirmed that the disease caused panhypopituitarism attributable to neurosarcoidosis. |
| #5 | A 47-year-old woman was seen presenting with a 2-year history of fatigue, sleep disturbance, migratory myalgia, and arthralgia. She had positive *B. burgdorferi* EIA with negative IgG immunoblot; a referring provider had treated her with 21 days of doxycycline. She did not have any improvement and developed facial tingling. She was referred for additional treatment for possible neuroborreliosis. Repeat *B. burgdorferi* EIA was negative, and rheumatologic work-up was negative, including inflammatory markers. She was diagnosed with fibromyalgia by rheumatology. Her symptoms significantly improved with reassurance, serial follow-up at our facility, sleep counseling, and an exercise program. |

**Table 4** Frequency of Patients with Final Diagnoses in Patients Referred for Possible Lyme Disease in Studies During 1993-2021

| | Sigal[10]USA 1990 n = 100 | Steere[11]USA 1993 n = 788 | Reid[16]USA 1998 n = 209 | Cottle[22]UK 2012 n = 115 | Jacqet[19]France 2018 n = 468 | Haddad[21]France 2018 n = 301 | Bouiller[20]France 2019 n = 355 | Present Study[18]USA 2021 n = 1261 |
|---|---|---|---|---|---|---|---|---|
| Duration of symptoms | 1 wk to 9 y | Mean 3 y<br>Range 1 mo to 22 y* | Medan 19 mo<br>Range 3-175 mo† | NA | NA | Median 16 mo<br>Range 1-68 mo | NA | Median 558 d<br>Mean 1248 d<br>Range 1-18,518 d |
| Active or recent Lyme disease | 37 (37%) | 180 (23%) | 44 (21%) | 26 (23%) | 69 (15%) | 38 (13%) | 48 (14%) | 184 (15%) |
| With a diagnosis | 47 (47%) | 608 (77%) | 165 (79%) | 51 (44%) | 277 (59%) | 243 (81%) | 196 (55%) | 690 (55%) |
| No diagnosis | 16 (16%) | 0 | 0 | 38 (33%) | 122 (26%) | 20 (6%) | 111 (31%) | 371 (30%) |

*Symptom duration for patients with a diagnosis.
†Symptom duration for patients without Lyme disease.
NA: data not available.

One novel finding of this present study was that one-fifth of referred patients had symptoms explained by known pre-existing medical issues prior to referral. This finding might suggest that either the patient or the health care provider hoped for a different explanation for a symptom complex, perhaps treatable with antibiotics. In addition, 40% of patients with diagnoses had more than one diagnosis contributing to their symptoms. This finding suggests that patients with long-term symptoms with suspicion of Lyme disease may be best served by a clinician committing to a comprehensive evaluation and appropriate specialist referral prior to employing antibiotics. Our study also revealed that 8 patients were newly diagnosed with cancer only after their referral for Lyme disease. Not all patients with non-specific symptoms need aggressive evaluation for malignancy; however, awareness of the broad range of illnesses outlined in the supplementary Table 2 can help avoid delayed diagnosis.

Notably, the 2 most common diagnostic categories were syndromic and psychiatric/functional disease, with fibromyalgia and anxiety/depression as the common final diagnoses, with 21% and 11%, respectively. Similarly, Hassett et al[23] also demonstrated that 21% (21/96) of the patients referred for Lyme disease lacked evidence for the infection but had depression. These rates are close to the frequency of depression observed in the general population.[24,25] On the other hand, Steere et al[11] showed that among 788 patients referred for possible Lyme disease, more than half of patients appeared never to have had Lyme disease, and about 50% (298/608) qualified for a diagnosis of chronic fatigue syndrome or fibromyalgia. In some instances, psychological factors play a significant role in the manifestation and mediation of medical illness, particularly true of a chronic pain syndrome like fibromyalgia. In our study, among patients diagnosed with depression to explain ongoing symptoms, ~60% (131/222) had depression as a pre-existing medical condition upon referral to our clinic. Because frustrations are common for both clinicians and patients with chronic symptoms, it may be an attractive relief to offer a seemingly curative diagnosis such as Lyme disease as a diagnosis. On the flip side, merely stating that Lyme disease often does not explain long-term symptoms through a quick dismissal, without offering an evaluative pathway or alternative diagnosis, leaves patients frustrated and disillusioned with mainstream medical practices. Instead, patients may seek therapeutic approaches outside of mainstream medicine, including long-term antibiotics, unproven medications or supplements, and fringe treatments.[7,26] Patients who believe that chronic Lyme disease explains their current symptoms require an objective and complete evaluation, with an honest discussion acknowledging their concerns that may lead to better outcomes.[27]

The reason why Lyme disease is an attractive diagnosis to patients with chronic complaints such as pain, fatigue, or subjective neurocognitive dysfunction likely rests in the subset of bona fide Lyme disease patients who have

persistent symptoms despite appropriate antibiotic therapy. Commonly cited estimates place 10%-20% with lingering, usually subjective complaints persisting for months or years without active infection evidence.[28] For those with symptoms for >6 months deemed as post-treatment Lyme disease syndrome, cross-sectional studies suggest that patients eventually appear to return to health similar to the general population.[28,29] However, some practitioners and patients have adopted a liberal, non-evidence-based diagnosis of Lyme disease or other tick-borne infections to account for symptoms that prompt prolonged or combination antimicrobial therapy.[14] Despite the lack of benefit from protracted antibiotic treatment for chronic symptoms,[30] inappropriate antibiotic use remains common, and antibiotics are often used longer than recommended.[18]

Both community-level and provider-level education are required to reduce unnecessary antibiotic use. In our study, adverse events due to antibiotics were confirmed in 0.7% of referred patients (7/1061). This relatively low number might be due to appropriately prescribed antibiotics in our outpatient clinic or incomplete acknowledgment of complications by patients or referral records. Due to the study design, the actual rate of adverse events is unknown. Further studies need to be done, especially in communities following treatment not supported by randomized controlled trials.

There are several significant limitations in our study. First, diagnoses were not systematically or prospectively assessed but reflected real-world clinical diagnoses documented by treating clinicians. Second, the study is subject to biases associated with a retrospective, observational series (eg, selection bias). Third, as a single-center study at an academic hospital with potentially medically complicated patients sent for referral, this population may differ from the broader community or other hospital settings. Fourth, self-reported histories were not evaluated for validity if medical record data were missing. Fifth, 568/1061 patients (54%) had a single visit for their complaints attributed to Lyme disease, and loss of follow-up may have biased the findings.

In conclusion, the over-diagnosis of Lyme disease remains a significant public concern, especially for the subset of patients with long-term symptoms. Most in this study referred for Lyme disease did not have evidence of Lyme but have other diagnoses arising from a dedicated infectious diseases consultation and further medical follow-up that didn't stop at merely saying Lyme disease wasn't the explanation, but sought to chart a pathway for the patient based on appropriate alternative diagnoses. Patients with pre-existing medical issues should not be overlooked as an explanation, especially if signs, symptoms, and laboratory testing are not consistent with active Lyme disease. Although many in this study had syndromic diagnoses such as CFS/ME and fibromyalgia, others had serious non-infectious processes that delay diagnosis, leading to poor outcomes or decreased quality of life. The sheer breadth of different diagnoses indicates that Lyme disease has often become a common scapegoat for poorly understood problems. Dedication to thorough evaluation and consideration of alternative diagnoses should be routine for these challenging patients.

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## SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.amjmed.2021.10.040.

**Supplemental Table 1** Diagnoses of 1061 Patients Without Lyme Disease (Diagnoses with Less than 4 in Number [a])

| Diagnosis | Number with Diagnosis | Symptom Duration | | | | | Pre-existing Diagnosis | New Diagnosis |
|---|---|---|---|---|---|---|---|---|
| | | 0-182 days | 183-730 days | >= 731 days | Mean | Median | | |
| Bell's palsy, not related to LD | 4 | 2 | 1 | 1 | 1749.5 | 247.0 | 2 | 2 |
| Infectious mononucleosis | 4 | 2 | 2 | 0 | 219.8 | 185.5 | 2 | 2 |
| Liver disease | 4 | 0 | 1 | 3 | 4226.8 | 2776.5 | 0 | 4 |
| Low back pain or sciatica | 4 | 1 | 2 | 1 | 2067.3 | 303.5 | 0 | 4 |
| Menopause | 4 | 0 | 2 | 2 | 1622.8 | 1563.0 | 0 | 4 |
| Post-traumatic stress disorder (PTSD) | 4 | 0 | 1 | 3 | 1721.5 | 1591.0 | 1 | 3 |
| Substance abuse | 4 | 0 | 1 | 3 | 2028.5 | 1537.0 | 1 | 3 |
| Tick or insect bite hypersensitivity | 4 | 2 | 1 | 1 | 263.5 | 141.5 | 0 | 4 |
| Vasculitis [b] | 4 | 1 | 1 | 2 | 1362.8 | 1117.5 | 1 | 3 |
| Movement disorder | 3 | 0 | 1 | 2 | 1006.3 | 1096.0 | 0 | 3 |
| Myopathy or myositis | 3 | 0 | 1 | 2 | 1167.7 | 734.0 | 0 | 3 |
| Transverse myelitis | 3 | 1 | 1 | 1 | 694.7 | 548.0 | 2 | 1 |
| Amyloidosis | 2 | 0 | 0 | 2 | 3158.0 | 3158.0 | 1 | 1 |
| Benign fasciculations | 2 | 0 | 0 | 2 | 2846.5 | 2846.5 | 0 | 2 |
| Cervical dystonia | 2 | 0 | 1 | 1 | 1692.5 | 1692.5 | 0 | 2 |
| Chronic Hepatitis B | 2 | 0 | 0 | 2 | 4437.5 | 4437.5 | 2 | 0 |
| Ehlers Danlos syndrome | 2 | 0 | 1 | 1 | 593.0 | 593.0 | 0 | 2 |
| Interstitial cystitis | 2 | 0 | 0 | 2 | 2055.0 | 2055.0 | 0 | 2 |
| Methicillin-resistant staphylococcus aureus (MRSA) | 2 | 1 | 1 | 0 | 248.0 | 248.0 | 0 | 2 |
| Pulmonary hypertension | 2 | 0 | 0 | 2 | 3260.5 | 3260.5 | 1 | 1 |
| Retinal vasculitis | 2 | 1 | 1 | 0 | 219.0 | 219.0 | 1 | 1 |
| Rotator cuff injury | 2 | 1 | 0 | 1 | 654.5 | 654.5 | 0 | 2 |
| Seizure disorder | 2 | 0 | 0 | 2 | 4496.5 | 4496.5 | 0 | 2 |
| Sjogren's syndrome | 2 | 0 | 2 | 0 | 430.5 | 430.5 | 1 | 1 |
| Somatization disorder | 2 | 0 | 0 | 2 | 6126.5 | 6126.5 | 0 | 2 |
| Systemic lupus erythematosus | 2 | 0 | 0 | 2 | 2043.0 | 2043.0 | 0 | 2 |
| Tinea corporis | 2 | 1 | 1 | 0 | 269.0 | 269.0 | 0 | 2 |
| Anemia | 1 | 0 | 1 | 0 | 333.0 | 333.0 | 0 | 1 |
| Aortic stenosis | 1 | 0 | 1 | 0 | 587.0 | 587.0 | 0 | 1 |
| Appendicitis | 1 | 1 | 0 | 0 | 10.0 | 10.0 | 0 | 1 |
| Argyria, self-induced | 1 | 0 | 0 | 1 | 1535.0 | 1535.0 | 0 | 1 |
| Arsenicosis | 1 | 0 | 0 | 1 | 890.0 | 890.0 | 0 | 1 |
| Aseptic meningitis | 1 | 1 | 0 | 0 | 63.0 | 63.0 | 0 | 1 |
| Attention deficit disorder (ADD) | 1 | 0 | 0 | 1 | 3935.0 | 3935.0 | 0 | 1 |
| Babesia infection | 1 | 1 | 0 | 0 | 152.0 | 152.0 | 1 | 0 |
| Benign joint hypermobility syndrome | 1 | 0 | 0 | 1 | 1816.0 | 1816.0 | 0 | 1 |
| Brachial plexopathy | 1 | 0 | 0 | 1 | 912.0 | 912.0 | 0 | 1 |
| Carpal tunnel | 1 | 0 | 0 | 1 | 1738.0 | 1738.0 | 0 | 1 |
| Cellulitis | 1 | 1 | 0 | 0 | 44.0 | 44.0 | 1 | 0 |
| Chronic Hepatitis C | 1 | 0 | 0 | 1 | 3136.0 | 3136.0 | 0 | 1 |
| Chronic idiopathic diarrhea | 1 | 0 | 1 | 0 | 643.0 | 643.0 | 1 | 0 |
| Chronic myelopathic syndrome | 1 | 0 | 1 | 0 | 568.0 | 568.0 | 0 | 1 |
| CNS demyelinating disease | 1 | 0 | 0 | 1 | 1537.0 | 1537.0 | 0 | 1 |
| Coccygitis | 1 | 0 | 0 | 1 | 1499.0 | 1499.0 | 0 | 1 |
| Conversion disorder | 1 | 1 | 0 | 0 | 42.0 | 42.0 | 0 | 1 |
| Cryptogenic portal hypertension | 1 | 0 | 1 | 0 | 282.0 | 282.0 | 0 | 1 |
| CSF leak | 1 | 0 | 1 | 0 | 584.0 | 584.0 | 0 | 1 |
| Cyclic vomiting syndrome | 1 | 0 | 0 | 1 | 932.0 | 932.0 | 0 | 1 |
| Cytomegalovirus (CMV) infection | 1 | 1 | 0 | 0 | 14.0 | 14.0 | 0 | 1 |
| Deltoid strain | 1 | 0 | 1 | 0 | 552.0 | 552.0 | 0 | 1 |
| | 1 | 0 | 0 | 1 | 738.0 | 738.0 | 0 | 1 |

**Supplemental Table 1** (*Continued*)

| Diagnosis | Number with Diagnosis | Symptom Duration | | | | | Pre-existing Diagnosis | New Diagnosis |
|---|---|---|---|---|---|---|---|---|
| | | 0-182 days | 183-730 days | >= 731 days | Mean | Median | | |
| Diffuse idiopathic skeletal hyperostosis | | | | | | | | |
| Enterovirus | 1 | 1 | 0 | 0 | 24.0 | 24.0 | 0 | 1 |
| Epicondylitis | 1 | 0 | 0 | 1 | 1107.0 | 1107.0 | 0 | 1 |
| Extensor tendon rupture | 1 | 0 | 0 | 1 | 871.0 | 871.0 | 0 | 1 |
| Facial pain, chronic | 1 | 0 | 1 | 0 | 236.0 | 236.0 | 0 | 1 |
| Fever of unknown origin | 1 | 0 | 0 | 1 | 1222.0 | 1222.0 | 0 | 1 |
| Guillain-Barre or vestibulocerel-lar syndrome | 1 | 0 | 0 | 1 | 776.0 | 776.0 | 1 | 0 |
| Hemochromatosis | 1 | 0 | 0 | 1 | 788.0 | 788.0 | 1 | 0 |
| Hemophagocytic lymphohistiocytosis | 1 | 0 | 0 | 1 | 2006.0 | 2006.0 | 0 | 1 |
| Hypermobility with bilateral con-genital femoral anteversion | 1 | 0 | 0 | 1 | 1210.0 | 1210.0 | 0 | 1 |
| Hypopituitarism | 1 | 0 | 0 | 1 | 912.0 | 912.0 | 0 | 1 |
| Idiopathic brachial neuritis | 1 | 1 | 0 | 0 | 51.0 | 51.0 | 0 | 1 |
| Kennedy disease (spinobulbar muscular atrophy) | 1 | 0 | 0 | 1 | 1403.0 | 1403.0 | 1 | 0 |
| Leprosy | 1 | 0 | 1 | 0 | 196.0 | 196.0 | 0 | 1 |
| Lewy body dementia | 1 | 0 | 0 | 1 | 973.0 | 973.0 | 0 | 1 |
| Lumbar stenosis | 1 | 0 | 1 | 0 | 553.0 | 553.0 | 0 | 1 |
| Meniere's disease | 1 | 0 | 1 | 0 | 581.0 | 581.0 | 0 | 1 |
| Methotrexate toxicity | 1 | 1 | 0 | 0 | 132.0 | 132.0 | 0 | 1 |
| Morphea | 1 | 0 | 1 | 0 | 393.0 | 393.0 | 0 | 1 |
| Multiple system atrophy | 1 | 0 | 0 | 1 | 3799.0 | 3799.0 | 1 | 0 |
| Myasthenia gravis | 1 | 0 | 1 | 0 | 365.0 | 365.0 | 0 | 1 |
| Neurocognitive dysfunction | 1 | 0 | 0 | 1 | 11280.0 | 11280.0 | 0 | 1 |
| Non-specific palpitations | 1 | 1 | 0 | 0 | 99.0 | 99.0 | 0 | 1 |
| Normal pressure hydrocephalus | 1 | 0 | 0 | 1 | 2606.0 | 2606.0 | 1 | 0 |
| Optic neuritis | 1 | 0 | 1 | 0 | 249.0 | 249.0 | 0 | 1 |
| Osteomyelitis, pubic | 1 | 1 | 0 | 0 | 98.0 | 98.0 | 0 | 1 |
| Otitis media | 1 | 0 | 1 | 0 | 730.0 | 730.0 | 0 | 1 |
| Paget’s disease of bone | 1 | 0 | 0 | 1 | 2139.0 | 2139.0 | 0 | 1 |
| Paroxysmal hypertension | 1 | 0 | 0 | 1 | 1096.0 | 1096.0 | 0 | 1 |
| Parvovirus | 1 | 1 | 0 | 0 | 133.0 | 133.0 | 0 | 1 |
| Pelvic floor dysfunction | 1 | 0 | 0 | 1 | 937.0 | 937.0 | 1 | 0 |
| Pigmented villonodular synovitis | 1 | 1 | 0 | 0 | 135.0 | 135.0 | 0 | 1 |
| Polycythemia vera | 1 | 0 | 0 | 1 | 1630.0 | 1630.0 | 0 | 1 |
| Polymyalgia rheumatica | 1 | 0 | 1 | 0 | 605.0 | 605.0 | 0 | 1 |
| Post-herpetic neuralgia | 1 | 0 | 1 | 0 | 730.0 | 730.0 | 1 | 0 |
| Progressive supranuclear palsy | 1 | 0 | 0 | 1 | 2900.0 | 2900.0 | 0 | 1 |
| Pseudotumor cerebri | 1 | 0 | 0 | 1 | 1056.0 | 1056.0 | 1 | 0 |
| Psoriasis | 1 | 0 | 0 | 1 | 855.0 | 855.0 | 1 | 0 |
| Retinitis, unclear etiology | 1 | 1 | 0 | 0 | 112.0 | 112.0 | 1 | 0 |
| Right sacrolilitis | 1 | 0 | 1 | 0 | 285.0 | 285.0 | 0 | 1 |
| Rocky mountain spotted fever (RMSF) | 1 | 1 | 0 | 0 | 125.0 | 125.0 | 1 | 0 |
| S2 nerve compression | 1 | 0 | 0 | 1 | 887.0 | 887.0 | 0 | 1 |
| Sensorineural hearing loss | 1 | 0 | 0 | 1 | 982.0 | 982.0 | 0 | 1 |
| Shingles | 1 | 1 | 0 | 0 | 101.0 | 101.0 | 0 | 1 |
| Stroke | 1 | 0 | 1 | 0 | 604.0 | 604.0 | 0 | 1 |
| Syphilis | 1 | 0 | 1 | 0 | 378.0 | 378.0 | 0 | 1 |
| Temporal arteritis (GCA) | 1 | 1 | 0 | 0 | 124.0 | 124.0 | 0 | 1 |
| Tendonitis | 1 | 0 | 1 | 0 | 684.0 | 684.0 | 0 | 1 |
| Tinnitus | 1 | 0 | 1 | 0 | 233.0 | 233.0 | 0 | 1 |

**Supplemental Table 1** (*Continued*)

| Diagnosis | Number with Diagnosis | Symptom Duration | | | | | Pre-existing Diagnosis | New Diagnosis |
|---|---|---|---|---|---|---|---|---|
| | | 0-182 days | 183-730 days | >= 731 days | Mean | Median | | |
| Undifferentiated connective tissue disease | 1 | 0 | 0 | 1 | 1595.0 | 1595.0 | 0 | 1 |
| Vestibular neuritis | 1 | 0 | 1 | 0 | 422.0 | 422.0 | 1 | 0 |
| Viral infection, unspecified | 1 | 0 | 1 | 0 | 254.0 | 254.0 | 0 | 1 |
| viral meningitis | 1 | 1 | 0 | 0 | 57.0 | 57.0 | 0 | 1 |
| Vitamin B12 deficiency | 1 | 0 | 1 | 0 | 551.0 | 551.0 | 0 | 1 |

n/a: not applicable

[a]Diagnoses $\geq 5$ in number are shown in Table 2.

[b]Vasculitis: two granulomatosis with polyangiitis, medication-induced vasculitis

**Supplemental Table 2** All Diagnoses by Category (139 Diagnoses)

All Diagnoses by Category

| Category | Diagnosis | Number |
|---|---|---|
| Cardiac | Heart disease | 7 |
| | Pulmonary hypertension | 2 |
| | Aortic stenosis | 1 |
| | Non-specific palpitations | 1 |
| | Paroxysmal hypertension | 1 |
| Dermatologic | Dermatitis, non-infectious | 5 |
| | Tick or insect bite hypersensitivity | 4 |
| | Tinea corporis | 2 |
| | Morphea | 1 |
| | Psoriasis | 1 |
| Endocrine | Thyroid disease | 11 |
| | Hypogonadism | 9 |
| | Menopause | 4 |
| | Hypopituitarism | 1 |
| Gastrointestinal/Hepatic | Irritable bowel syndrome | 26 |
| | Inflammatory bowel disease | 8 |
| | Gastroparesis | 6 |
| | Liver disease | 4 |
| | Appendicitis | 1 |
| | Chronic idiopathic diarrhea | 1 |
| | Cryptogenic portal hypertension | 1 |
| | Cyclic vomiting syndrome | 1 |
| | Hemochromatosis | 1 |
| Hematologic | Iron deficiency | 9 |
| | Amyloidosis | 2 |
| | Anemia | 1 |
| | Polycythemia vera | 1 |
| | Vitamin B12 deficiency | 1 |
| Infection | Infectious mononucleosis | 4 |
| | Chronic Hepatitis B | 2 |
| | Methicillin-resistant staphylococcus aureus (MRSA) | 2 |
| | Babesia infection | 1 |
| | Cellulitis | 1 |
| | Chronic Hepatitis C | 1 |

**Supplemental Table 2** (*Continued*)

All Diagnoses by Category

| Category | Diagnosis | Number |
|---|---|---|
| | Cytomegalovirus (CMV) infection | 1 |
| | Enterovirus | 1 |
| | Leprosy | 1 |
| | Osteomyelitis, pubic | 1 |
| | Otitis media | 1 |
| | Parvovirus | 1 |
| | Rocky Mountain spotted fever (RMSF) | 1 |
| | Shingles | 1 |
| | Syphilis | 1 |
| | Viral infection, unspecified | 1 |
| | Viral meningitis | 1 |
| Inflammatory | Other arthritis, NOS | 38 |
| | Rheumatoid arthritis | 6 |
| | Gout or pseudogout | 5 |
| | Sarcoidosis | 5 |
| | Spondyloarthritis | 5 |
| | Uveitis | 5 |
| | Vasculitis | 4 |
| | Myopathy or myositis | 3 |
| | Systemic lupus erythematosus | 2 |
| | Retinal vasculitis | 2 |
| | Sjogren's syndrome | 2 |
| | Hemophagocytic lymphohistiocytosis | 1 |
| | Polymyalgia rheumatica | 1 |
| | Retinitis, unclear etiology | 1 |
| | Temporal arteritis (GCA) | 1 |
| | Undifferentiated connective tissue disease | 1 |
| Musculoskeletal | Osteoarthritis | 62 |
| | Chronic regional pain | 32 |
| | Meniscal tear | 5 |
| | Low back pain or sciatica | 4 |
| | Ehlers Danlos syndrome | 2 |
| | Rotator cuff injury | 2 |
| | Benign joint hypermobility syndrome | 1 |
| | Carpal tunnel | 1 |
| | Coccygitis | 1 |
| | Deltoid strain | 1 |
| | Diffuse idiopathic skeletal hyperostosis | 1 |
| | Epicondylitis | 1 |
| | Extensor tendon rupture | 1 |
| | Facial pain | 1 |
| | Hypermobility with bilateral congenital femoral anteversion | 1 |
| | Kennedy disease (spinobulbar muscular atrophy) | 1 |
| | Lumbar stenosis | 1 |
| | Paget’s disease of bone | 1 |
| | Pigmented villonodular synovitis | 1 |
| | Right sacroiliitis | 1 |
| | S2 nerve compression | 1 |
| | Tendonitis | 1 |
| Neoplastic | Chondrosarcoma | 1 |
| | Metastatic prostate cancer | 1 |
| | Metastatic lung cancer | 1 |
| | Lymphocytic leukemia | 1 |
| | Multiple myeloma with systemic amyloidosis | 1 |
| | Metastatic squamous cell tumor | 1 |
| | Glioblastoma multiforme | 1 |
| | Myelodysplastic syndrome | 1 |

**Supplemental Table 2** (*Continued*)

All Diagnoses by Category

| Category | Diagnosis | Number |
|---|---|---|
| Neurologic | Migraine headache | 74 |
| | Peripheral neuropathy | 20 |
| | Multiple sclerosis | 15 |
| | Parkinson's disease | 12 |
| | Dementia | 10 |
| | Amyotrophic lateral sclerosis (ALS) | 7 |
| | Restless leg syndrome | 6 |
| | Idiopathic hearing loss | 5 |
| | Bell's palsy, not related to LD | 4 |
| | Movement disorder | 3 |
| | Transverse myelitis | 3 |
| | Benign fasciculations | 2 |
| | Cervical dystonia | 2 |
| | Seizure disorder | 2 |
| | Aseptic meningitis | 1 |
| | Brachial plexopathy | 1 |
| | CNS demyelinating disease | 1 |
| | CSF leak | 1 |
| | Guillian Barre or vestibulocerellar syndrome | 1 |
| | Idiopathic brachial neuritis | 1 |
| | Lewy Body dementia | 1 |
| | Meniere's disease | 1 |
| | Multiple system atrophy | 1 |
| | Myasthenia gravis | 1 |
| | Neurocognitive dysfunction | 1 |
| | Normal pressure hydrocephalus | 1 |
| | Optic neuritis | 1 |
| | Post-herpetic neuralgia | 1 |
| | Progressive supranuclear palsy | 1 |
| | Pseudotumor cerebri | 1 |
| | Sensorineural hearing loss | 1 |
| | Stroke | 1 |
| | Tinnitus | 1 |
| | Vestibular neuritis | 1 |
| Other | Sleep disorder or apnea | 48 |
| | Obesity, morbid | 16 |
| | Interstitial cystitis | 2 |
| | Argyria, self-induced | 1 |
| | Arsenicosis | 1 |
| | Methotrexate toxicity | 1 |
| Psychiatric/functional | Anxiety/depression | 222 |
| | Alcohol abuse | 10 |
| | Post-traumatic stress disorder (PTSD) | 4 |
| | Substance abuse | 4 |
| | Somatization disorder | 2 |
| | Attention deficit disorder (ADD) | 1 |
| | Conversion disorder | 1 |
| Syndromic | Fibromyalgia | 120 |
| | Chronic fatigue | 77 |
| | Post-infectious fatigue syndrome, not Lyme disease | 26 |
| | Postural orthostatic tachycardia syndrome (POTS) | 14 |
| | Post viral arthralgia syndrome | 6 |
| | Chronic myelopathic syndrome | 1 |
| | Fever of unknown origin | 1 |
| | Pelvic floor dysfunction | 1 |