Supplemental Table S1. Repository inclusion and exclusion criteria for Lyme disease patients

Category	Inclusion Criteria	Exclusion Criteria	Additional Information Obtained
Early localized with EM	≥ 18 years of age, appropriate epidemiological risk, a skin lesion consistent with an EM ≥5 cm in diameter and, whenever possible, corroboration of *B. burgdorferi* infection by culture and/or PCR.[a]	A known significant immunocompromising condition[b] and being unable/unwilling to follow the described protocol for sample collection.	Number, size and duration of EMs present, age, gender, state of residence, tick exposure, history of physician diagnosed Lyme disease and year diagnosed, history of other tick transmitted infections and year diagnosed, comorbidities, immunocompromising conditions, history of rheumatoid arthritis, syphilis, fibromyalgia, syphilis, severe periodontitis, influenza, mononucleosis, EKG results, results from physical examination at time of enrollment and at time of follow-up visit, serologic testing if available, treatment prescribed and outcome.
Early disseminated Lyme carditis	≥18 years of age, appropriate epidemiological risk and an objective clinical manifestation consistent with Lyme carditis (usually manifesting in varying degrees of heart block) and, whenever possible, corroboration of *B. burgdorferi* infection by culture and/or PCR.[c]	A known significant immunocompromising condition[b] and unable/unwilling to follow the described protocol for sample collection.	Number, size and duration of EMs present, age, gender, state of residence, tick exposure, history of physician diagnosed Lyme disease and year diagnosed, history of other tick transmitted infections and year diagnosed, comorbidities, immunocompromising conditions, history of rheumatoid arthritis, syphilis, fibromyalgia, syphilis, severe periodontitis, influenza, mononucleosis, EKG results, results from physical examination at time of enrollment and at time of follow-up visit, serologic testing if available, treatment prescribed and outcome.
Lyme neuroborreliosis	≥ 18 years of age, appropriate epidemiological risk and an objective clinical manifestation consistent with neuroborreliosis (such as cranial nerve palsy, lymphocytic meningitis, or radiculopathy) and, whenever possible, corroboration of *B. burgdorferi* infection by culture and/or PCR.[c]	A known significant immunocompromising condition[b] and unable/unwilling to follow the described protocol for sample collection.	Number, size and duration of EMs present, age, gender, state of residence, tick exposure, history of physician diagnosed Lyme disease and year diagnosed, history of other tick transmitted infections and year diagnosed, comorbidities, immunocompromising conditions, history of rheumatoid arthritis, syphilis, fibromyalgia, syphilis, severe periodontitis, influenza, mononucleosis, EKG results, results from physical examination at time of enrollment and at time of follow-up visit, serologic testing if available, treatment prescribed and outcome.
Late Lyme (arthritis)	Meets the CDC criteria for Lyme arthritis as defined by a patient with intermittent or chronic oligoarticular arthritis, primarily in the joints. Additionally, the diagnosis is accompanied by a positive two-tier test that is interpreted according to CDC guidelines (3) and whenever possible, corroboration of *B. burgdorferi* infection by PCR of joint fluid.[d]	A previous history of rheumatoid arthritis, multiple sclerosis, fibromyalgia or syphilis.	Tick exposure, state of residence, previous diagnosis of Lyme disease, previous treatment of Lyme disease with antibiotics, date of Lyme arthritis diagnosis, joint affected, duration of initial joint symptoms to sample date, duration of antibiotic treatment prior to sample collection, degree of joint swelling, and date of resolution of joint swelling.

[a] Of 40 patients, 26 (65%) were positive for B. burgdorferi by culture and/or PCR.

[b] Patients categorized as having a significant immunocompromising condition included those with HIV, or any patient on immunosuppressive drugs.

[c] Of 17 early Lyme carditis and neuroborreliosis patients, 5 (29%) were positive for *B. burgdorferi* by culture and/or PCR.

[d] Of 29 Lyme arthritis patients, 7 (29%) were positive for *B. burgdorferi* by PCR.

Supplemental Table S2. Repository inclusion and exclusion criteria for negative control healthy donors

Category	Inclusion Criteria	Exclusion Criteria	Additional Information
Healthy endemic	Must have lived in the lower Hudson Valley of NY for at least the last 5 years.	History of Lyme disease, tested or treated for Lyme disease or any tick-borne infection, history of rheumatoid arthritis, multiple sclerosis, fibromyalgia, syphilis, or severe periodontitis.	History of influenza and mononucleosis was obtained and if a history existed, the year when the subject was ill was collected.
Healthy non-endemic	Must have lived in a Lyme disease non-endemic state for at least the last 5 years.	History of Lyme disease, ill at time of blood draw, lived in one of the following states in the past 5 years (Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, or Wisconsin). Traveled to above state(s) within the previous 5 years and noticed a tick bite while there.	History of influenza, mononucleosis, rheumatoid arthritis, multiple sclerosis, fibromyalgia, syphilis, and severe periodontitis.

Supplemental Table S3. Repository inclusion and exclusion criteria for negative control disease patients

Category	Inclusion Criteria[a]	Exclusion Criteria	Additional Information Collected
Fibromyalgia	Patients ≥ 18 years of age with fibromyalgia defined by the criteria of Wolfe et al. in 1990 (1) and 2010 (2).	History of Lyme disease, a systemic autoimmune disease including systemic lupus erythematous and rheumatoid arthritis that may be related to fibromyalgia symptoms, active malignancy or received an experimental agent for malignancy in the last 30 days and pregnancy or breastfeeding.	State of residence and history of mononucleosis, influenza, syphilis and mononucleosis.
Infectious mononucleosis	Patients ≥ 18 years of age with acute mononucleosis by clinical and laboratory (complete blood count and Monospot) diagnosis.	History of Lyme disease, pregnancy, or weighed < 110 pounds.	States of residence during the past 5 years, age, gender and immunocompromising conditions.
Rheumatoid arthritis	Patients ≥ 18 years of age who satisfy the 1987 American College of Rheumatology revised criteria for rheumatoid arthritis (3) and either a positive test for rheumatoid factor (RF) or anti-CCP antibodies.	History of Lyme disease, a concomitant known chronic infectious disease (e.g. HIV), anemia with Hct <30, pregnancy, weighed < 110 pounds.	Age, gender, race, immunocompromising conditions, comorbidities and current medications.
Multiple sclerosis	Patients with relapsing remitting multiple sclerosis (4), regardless of prior serologic testing results for Lyme disease.	Patients with intrathecal production of anti-*B. burgdorferi* antibodies, previous treatment for neuroborreliosis.	Age, gender, state of residence at birth and current state of residence, current or past optic neuritis or myelitis, potential for having Lyme disease and history of serologic testing for antinuclear antibody, rheumatoid factor, Lyme ELISA and neuromyelitis.
Severe periodontitis	Patients ≥ 18 years of age meeting the American Academy for Periodontology definition of severe periodontitis (5) that is at least a 5mm of clinical attachment loss around 1 or more teeth.	History of Lyme disease, severe chronic periodontitis and any blood disorder that would preclude the participant from providing a peripheral blood sample.	Age, gender and race.

Syphilis	Patients ≥ 18 years of age with active syphilis as defined by 1) reactive nontreponemal (RPR, VDRL) and treponemal (*Treponema pallidum* particle agglutination assay (TPPA), fluorescent treponemal antibody absorption test (FTA-ABS), T. *pallidum*-specific EIA or ELISA) serological tests. If the subject has a history of syphilis, the current nontreponemal test titer must be at least 4-fold higher than the last recorded post-treatment titer, consistent with relapse or reinfection, 2) reactive nontreponemal tests and clinical evidence of syphilis (characteristic rash or dark field-positive chancre), or 3) reactive nontreponemal tests and a known contact to a proven case of untreated early syphilis (primary, secondary or early latent disease) in the last 90 days. Subjects were eligible if they had already initiated treatment for active syphilis, as long as the treatment was no more than 30 days before study entry.	History of Lyme disease, pregnancy.	Age, gender, race, state of residence, history of tick exposure, influenza, multiple sclerosis, fibromyalgia, severe periodontitis and mononucleosis.

[a] See Supplemental References section for references used.

Supplemental References.

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