Diagnostic testing for Lyme disease: Beware of false positives

Lyme disease is caused by the spirochete *Borrelia burgdorferi* and transmitted mainly via the tick vector *Ixodes pacificus* in British Columbia.[1] Polymerase chain reaction testing finds *Borrelia burgdorferi* in only 1 in 200 ticks, whether they are collected from the wild or submitted by patients. This frequency is fiftyfold lower than in high-incidence areas of North America.

Early Lyme disease is a clinical diagnosis based on exposure to a tick bite followed by the characteristic erythema migrans rash within 4 weeks of exposure. Later in the course of infection serological testing is used.[2] As with all other tests it is necessary to consider the validity of the test, including sensitivity and specificity.

The Centers for Disease Control and Prevention recommend a two-step process for serologic testing:[3,4] when a positive or equivocal positive using a highly sensitive enzyme immunoassay is found, it is followed by a Western blot test, which is highly specific. This method is used by major labs across North America, including the BC Public Health Microbiology and Reference Laboratory. Enzyme immunoassay alone is not very specific because antibodies to *Borrelia burgdorferi* proteins can cross react with common bacterial antigens,[5] leading to false positives. The BC Public Health Microbiology and Reference Laboratory uses a commercial whole-cell enzyme assay that can detect Lyme IgG and IgM simultaneously. More robust screening tests are being evaluated using the *Borrelia* VlsE1/pepC10 IgG/IgM ELISA to detect IgG and IgM antibodies to VlsE1 and pepC10 antigens of both European and North American strains of *Borrelia burgdorferi*.

Alternative laboratories have devised their own nonvalidated tests, which do not follow the two-step process. While these labs strive for high sensitivity they do not outperform reference labs in finding Lyme disease.[6]

Prevalence has marked ramifications for the positive predictive value and negative predictive value.

Moreover, specificity as low as 43% is reported, indicating that 57% of results coming from such labs are false positives.

In BC less than 1% of people tested for Lyme disease have the infection (personal communication with M. Morshed, 2015). Prevalence has marked ramifications for the positive predictive value and negative predictive value. Performance of the two-step method (sensitivity = 87%, specificity = 99%[5]) compared to that of an alternative laboratory (sensitivity = 70%, specificity = 43%[6]) in a population of 10 000 people with a Lyme disease prevalence of 1% is presented in the **Table**. Even with the reference method, positive predictive value (47%) is rather low with a low prevalence of Lyme disease. With this test the proportion of errors due to false negatives is 12%, with an overall error rate of 1%. However, when specificity is also low, as for the alternative lab,[6] positive predictive value is markedly lower (approximately 1%). The alternative lab may have a lower proportion of errors due to false negatives (0.5%), but the overall error rate is high at 57%. Improving positive predictive value in such a lab would require both a high pretest chance of Lyme disease through much more careful patient selection as well as vastly improved specificity of the test.

Advocates of alternative tests express concern about false negative results, so it must be noted that 99.5% of errors (5643 out of 5673) in alternative lab testing come from false positives and that they do not lower the false negative rate. Meanwhile, reference laboratories have vastly

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Table. Performance of (a) reference two-step testing compared with (b) alternative laboratory testing for Lyme disease in a population of 10 000 people with a Lyme disease prevalence of 1%.

(a) Reference two-step testing

	Disease is positive	Disease is negative	Total
Test is positive	87	99 (false positives)	186
Test is negative	13 (false negatives)	9801	9814
Number of people tested	100	9900	10 000

(b) Alternative laboratory testing

	Disease is positive	Disease is negative	Total
Test is positive	70	5643 (false positives)	5713
Test is negative	30 (false negatives)	4257	4287
Number of people tested	100	9900	10 000

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Women living with HIV face higher rates of cancer diagnosis: Study

Due to the introduction of modern highly active antiretroviral therapy (HAART) people living with HIV are now less likely to develop AIDS-related cancers. However, a recent study published in *HIV Medicine* shows women living with HIV still have a higher likelihood of being diagnosed with certain cancers when compared with the general population. This trend primarily involves cancers with underlying infectious causes such as human papillomavirus (HPV) and hepatitis.

The study shows a need for improved women-centred access and support:

- Women living with HIV with a cancer diagnosis were more likely than those without cancer to have an AIDS-defining illness at the time of diagnosis, a higher viral load, and a lower CD4 count.
- A significant portion of women were less than 95% adherent to combination antiretroviral therapy (cART) in the year prior to cancer diagnosis.
- Nearly 69% of the women did not achieve virological suppression in the year prior to cancer diagnosis.

HIV-positive women with cancer had a significantly higher likelihood of mortality compared with HIV-positive women without cancer (46.2% compared to 17.5%).

The study was conducted as a collaboration between the BC Centre for Excellence in HIV/AIDS and BC Women's Hospital's Oak Tree Clinic. The resulting article, "Cancer incidence among HIV-positive women in British Columbia, Canada: Heightened risk of virus-related malignancies" is available at www.ncbi.nlm.nih.gov/pubmed/26268461.

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lower error rates and are working on ways to further improve test sensitivity.

With a high rate of false positive results and an exceedingly low positive predictive value obtained from alternative labs testing in low prevalence settings like BC, it is imperative that caution be taken when interpreting a positive result from such a source. It is suggested that Lyme disease tests be ordered from accredited labs such as the BC Public Health Microbiology and Reference Laboratory and interpreted based on the clinical likelihood of Lyme disease in the patient.

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References

Available at bcmj.org.