



Saint Luke's Regional Laboratories Clinical Laboratory Letter



August 2007

JAK2 Mutation Screening to be Performed by Saint Luke's Regional Laboratories

JAK2 (Janus kinase 2) is a tyrosine kinase which plays an important role in normal hematopoietic growth factor signaling. An acquired point mutation in JAK2 has been described in the blood and bone marrow of patients with BCR/ABL-negative chronic myeloproliferative disorders. This mutation was previously discussed in some detail in the October 2006 issue of Clinical Laboratory Letter.

Using sensitive assays, the JAK2 mutation can be detected in approximately 90-95% of cases of polycythemia vera, 50-70% of patients with essential thrombocythemia, and 40-50% of cases of idiopathic myelofibrosis. The mutation has also been described in rare cases of myelodysplastic syndromes, acute myeloid leukemia, systemic mastocytosis and hypereosinophilic syndrome. It is specific for diagnosis of a clonal myeloid lineage proliferative disorder. The mutation has not been described in BCR/ABL-positive chronic myeloid leukemia, any acute or chronic lymphoid disorders, any healthy persons, or any patient with secondary polycythemia or a reactive blood count elevation.

Indications for the assay (performed on either peripheral blood or bone marrow) include the following:

- Evaluation of polycythemia - the test should be ordered in addition to serum erythropoietin level. An algorithm for this approach was included in the October 2006 edition of Laboratory Letter, which may be accessed at www.saintlukeshealthsystem.org.
- Evaluation of an elevated platelet count, clinically not consistent with reactive thrombocytosis.
- Unusual thrombotic events including abdominal or cerebral thrombosis or arterial events at a young age, which may be a presenting sign of an underlying chronic myeloproliferative disorder.

It is important to keep in mind that a positive JAK2 mutation is not specific for a particular sub-type of

myeloproliferative disorder, and must be correlated with other clinical and laboratory findings for definitive diagnosis. Furthermore, a negative result does not exclude the presence of a chronic myeloproliferative disorder or other neoplastic disorder.

JAK2 mutation analysis has previously been sent to a reference laboratory, however starting in early September 2007, the assay will be performed in-house by Saint Luke's Regional Laboratories. The sample requirement is one lavender-top tube containing at least 3mL of peripheral blood or bone marrow. The assay will be performed twice a week.

PSA Performance

The FDA approved the use of PSA for early detection of prostate cancer in 1994. Since that time, the percentage of men who have metastatic prostate cancer at the time of diagnosis has decreased by 70 percent and the death rate has decreased by 32.5 percent.

A recent study published in *BJU International* (2007;99:1427-31) examined the performance of the five most commonly used methods to measure PSA concentration. One of the methods examined was the Beckman Coulter assay, which has been utilized throughout the Saint Luke's Health System since January 2007. This article provided valuable information about the performance of this assay in detecting prostate cancer.

The study was comprised of 596 untreated Caucasian males referred to a urology clinic. Of this total, 314 men had histologically confirmed prostate cancer while 282 did not have detectable cancer in 8 to 12 biopsy cores. The median age of men with cancer was 66 years and the median age of the men without cancer was 63 years. The median PSA concentration in men with cancer was 6.2 ng/mL (range 5.8-6.6) compared to a median value of 3.8 ng/mL (range 3.1-4.5) in men without cancer.

The most commonly used reference range in the United States for PSA is 0–4.0 ng/mL. Persistently elevated levels >4.0 ng/mL have been used as the threshold for recommending prostate biopsy. However, a more recent trend has been to lower the threshold to 2.5 ng/mL. The following table compares the performance of the Beckman PSA assay at both of these thresholds.

	4.0 ng/mL	2.5 ng/mL
True Positive n = 314	246 (78%)	288 (92%)
True Negative n = 282	143 (51%)	95 (34%)

Another way to look at this data is to realize that 68 out of 314 men with prostate cancer (22%) had PSA values less than 4.0 ng/mL and would not have been referred for biopsy using this threshold. In contrast, only 26 men with prostate cancer (8%) were missed, when the PSA threshold was lowered to 2.5 ng/mL. Clearly, lowering the PSA threshold detects significantly more cancer cases.

However, the trade off for increased sensitivity is decreased specificity. When a PSA threshold of 4.0 ng/mL was used, 139 of 282 men without cancer (49%) had elevated PSA values, but the number of false positives increased to 187 (66%) when the threshold was lowered to 2.5 ng/mL. Thus, lowering the PSA threshold to 2.5 ng/mL, meant that almost two thirds of men referred for biopsy did not have detectable cancer.

The National Comprehensive Cancer Network guidelines recommend biopsy for men with a PSA higher than 2.5 ng/mL. The method used at Saint Luke’s detected 92% of men with prostate cancer at this threshold.

Another interesting finding of this study was the significant variation in PSA values obtained with the 5 different methods when testing the same serum samples. A sample with a median PSA value of 3.8 ng/mL varied from 2.8 to 5.0 ng/mL. Clearly, recommendations to standardize PSA assays have not been successful. Because of variation, physicians should not compare PSA values obtained from different laboratories using different

methods. This precaution is particularly important when trending PSA results over time or calculating PSA velocity.

Detection of Prostate Cancer After Radical Prostatectomy

All of the Saint Luke’s Regional Laboratories converted to a more sensitive PSA method by January 2007. With this conversion, the lower limit of detection decreased tenfold from 0.1 ng/mL to 0.01 ng/mL. After radical prostatectomy, the reference interval is less than 0.05 ng/mL if there is no residual disease. The new method is sufficiently sensitive to detect cancer recurrence. Therefore, orders for ultrasensitive PSA will now be performed in-house instead of being sent to a reference laboratory.

ACTH Stimulation Test

When a physician orders an ACTH (Cortrosyn) Stimulation Test, the laboratory often receives specimens for ACTH levels instead of cortisol levels. The specimen requirements for ACTH cortisol measurements are different, so the laboratory is unable to run cortisol levels. Since these are timed blood draws, the specimens cannot be redrawn. To help alleviate the confusion surrounding this test, a query has been added to Horizon Order Management that appears whenever an ACTH is ordered and asks if an ACTH Stimulation Test has been ordered. If the answer is yes, it instructs the user to order cortisol instead of ACTH. Hopefully, this intervention will eliminate the problems encountered with this test.

Reference Range Changes

The following tests have been assigned new reference ranges.

Analyte	Old Range	New Range
Protime	12.0–13.8 sec	11.9–14.3 sec
Total Bilirubin	0.3–1.2 mg/dL	0.3–1.4 mg/dL
Total Protein	6.5–8.1 g/dL	6.0–8.0 g/dL