



Lunch & Learn: Science, Statistics, and Getting it Right
ASIP 2018 Annual Meeting at Experimental Biology

Vignette 3

While investigating enzymes responsible for branched chain fatty acid metabolism in liver cells, you identify a novel protein that appears to interact with alpha-methylacyl-CoA racemase (AMACR), an enzyme involved in fatty acid metabolism. Reading about AMACR, you discover that it is used diagnostically in prostate cancer pathology, as it is overexpressed in the majority of prostate cancers but not in benign prostate tissue. Realizing that your novel protein may also be overexpressed in prostate cancer, you hypothesize that expression of your novel protein may also have diagnostic utility in prostate cancer.

Working with the genitourinary pathology pathologist at your institution, you obtain 20 transurethral resection of the prostate (TURP) specimens that were obtained after surgical intervention to relieve obstructive symptoms. The specimens all contain benign prostate tissue. Likewise, you obtain 20 treatment-refractory prostate cancer metastasis samples obtained at biopsy or resection. After validating the performance of an antibody against your novel protein using positive and negative control cell lines, you perform immunohistochemistry for expression of your novel protein on the 40 tissue samples. You find moderate to strong staining in the majority of cancer cells in 18 of 20 prostate cancer metastasis samples, and weak staining in benign prostate epithelial cells in only one of 20 TURP specimens. Based on these results, you conclude that expression of your novel protein may have utility in the diagnosis of prostate cancer.

One of the major areas to consider when evaluating the potential utility of a diagnostic biomarker is the area of intended clinical use. This often requires a deep understanding of the clinical issues regarding the diagnosis of the disease you are interested in, and will likely require consultation or collaboration with clinical experts. One of the most critical aspects to consider when planning the evaluation of a novel diagnostic biomarker is the current diagnostic process for the disease. For example, the majority of men in the US diagnosed with prostate cancer were identified from the population by an elevated level of serum PSA, which prompted a transrectal ultrasound-guided biopsy of the prostate, where multiple small cores of prostatic tissue are obtained with histopathologic evaluation by a pathologist. Most series find that about 30 to 40% of men undergoing prostate biopsy in the US are found to have prostate cancer on biopsy. In diagnostically challenging cases, the pathologist most commonly will utilize immunohistochemistry for basal cell markers (which are lost in prostate cancer), and AMACR (which is overexpressed in most prostate cancers).

Prior to submitting your findings for publication and releasing a statement claiming that you have discovered a novel diagnostic biomarker for prostate cancer that you expect will be used in practice soon, what are the major issues to consider?

- 1) What are the sensitivity and specificity of your novel biomarker for the diagnosis of prostate cancer in the set of 40 tissue specimens?
- 2) How can you improve the cohort used to assess the diagnostic utility of your novel protein?
- 3) How can you evaluate whether assessment of your diagnostic biomarker is reproducible?
- 4) What experiments should you plan to best determine whether your biomarker will be adopted in clinical management?
- 5) If instead of developing a biomarker for prostate cancer, you instead found that your biomarker was a strong predictor of future development of a rare genetic disease, how would that impact your assessment of the potential diagnostic utility?