CORRESPONDENCE

Thyroid Nodules with Indeterminate Cytology

TO THE EDITOR: Alexander et al. (Aug. 23 issue)[1] report findings from a prospective, multicenter gene-expression classifier validation study that raises several questions. For the 265 indeterminate fine-needle aspirates they tested, the gene-expression classifier had a sensitivity of 92%, a specificity of 52%, a positive predictive value of 47%, and a negative predictive value of 93%. Why the observed reduction in the performance of the gene-expression classifier, which was reported in their earlier study to have a sensitivity of 100% and a specificity of 73.3%?[2] With a high negative predictive value and a low positive predictive value, the gene-expression classifier is useful as an adjunct to fine-needle aspiration biopsy for diagnosing indeterminate nodules as benign and potentially avoiding diagnostic thyroid surgery.[3] However, the appropriate management of nodules diagnosed as "suspicious" (positive predictive value, 47%) according to the results of gene-expression classification is less obvious. Unfortunately, the gene-expression classifier does not have a positive predictive value that will allow us, as surgeons, to confidently plan an operation tailored to treat thyroid cancer (i.e., total thyroidectomy and central neck dissection). When considering the clinical and economic effect of a gene-expression classifier on the management of indeterminate nodules, avoiding thyroid surgery is not appropriate as the sole end point, and future studies must carefully evaluate the treatments and outcomes of all patients who undergo such testing.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: With the advent of gene-expression classification tests to minimize unnecessary surgery for thyroid nodules in cases of indeterminate results on fine-needle aspiration biopsy, as reported by Alexander et al. and in the accompanying editorial by Jameson,[1] other helpful ancillary tests seem to have been set aside. Although gene-expression classifier testing is a great step forward in the selection of patients who require surgery, excellent results may also be achieved with the use of immunocytochemical testing with HBME-1 and cytokeratin 19,[2] which are considered to be universal markers of thyroid cancer.[3,4] In the recent study by Cochand-Priollet et al.,[2] the sensitivity and negative predictive value of these two markers combined were 85.2% and 100%, respectively. In comparison, the sensitivity of the gene-expression classifier was 52% and the negative predictive value was 85 to 95%. One of the main advantages of immunocytochemical testing over gene-expression classifier

testing is that it can be performed retrospectively on previously stained slides on which the atypical cells have been identified. Moreover, there are no sampling issues, since an additional fine-needle aspiration biopsy is not required for the ancillary test. Finally, in this era of focusing on high-quality outcomes at lower cost, immunocytochemical testing may still be a valuable alternative to the more expensive gene-expression classifier test.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Alexander et al. described a gene-expression classifier with a high negative predictive value for thyroid cancer when applied to cytologically indeterminate nodules. Though their results should be very useful, it must be stated that the negative predictive value varies with the prevalence of the disease and is applicable only to the population in which the study was done.[1] Therefore, it is advisable to use the negative likelihood ratio instead, which indicates by how much a negative result on a diagnostic test will lower the pretest probability of the target disorder. This ratio is not affected by prevalence, making the calculation applicable to any population.[1] In its extreme values, a negative likelihood ratio that is less than 0.1 or equal to 1 generates, respectively, a large change or no change from pretest to posttest probability.[1] One easy way to estimate the post-test probability of a disease is to use the Fagan nomogram.[2]

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Wiseman and Walker express uncertainty regarding the treatment of patients with cytologically indeterminate thyroid nodules and suspicious results when tested with the gene-expression classifier. The gene-expression classifier was designed to maximize sensitivity and thereby achieve a high negative predictive value. Those with benign results on gene-expression classification may be considered for nonsurgical monitoring given the negative predictive value of 94 to 95% in atypia (or follicular lesions) of undetermined significance and follicular neoplasms. Approximately 50% of patients with indeterminate cytologic findings on fine-needle aspiration biopsy may benefit from a benign result on gene-expression classification.[1] However, we stress the importance of considering all variables (clinical, sonographic, cytologic, and molecular) for any given patient. This is especially true for those with cytologically indeterminate nodules that are deemed suspicious on gene-expression classification, since such nodules still carry a higher, but nonetheless indeterminate, risk of cancer.

As noted by Pusztaszeri, many molecular markers have been applied to the problem of indeterminate results on fine-needle aspiration biopsy. HBME-1 and cytokeratin 19 may prove useful, though data regarding their performance are variable. In another single-center study, immunostaining for HBME-1, cytokeratin 19, galectin-3, and the RET/PTC oncoprotein showed individual marker sensitivities of 85 to 93% and specificities of 43 to 71%.[2] Testing for HBME-1 and cytokeratin 19 in combination had a sensitivity of only 82% and a specificity of only 73%. We report gene-expression values for cytokeratin 19 in Figure 2 of our article. Low values are observed in many samples of malignant thyroid nodules correctly labeled suspicious by the Afirma gene-expression classifier, indicating imperfect sensitivity for cytokeratin 19 at the RNA level. HBME-1 is less accurate in several important

neoplasms[3,4] that were excluded from the analysis performed by Cochand-Priollet et al. Most important, blinded, prospective, large-scale, multicenter clinical trials to investigate these markers are lacking. High-quality investigations are critical for any molecular analysis before findings can be translated into clinical practice. Lastly, we note an error in the letter from Pusztaszeri: the sensitivity of the gene-expression classifier was 92%, not 52%.

We agree with Dominguez that both negative and positive predictive values are influenced by the prevalence of cancer in a population. It is reasonable to characterize the performance of a diagnostic test with negative likelihood ratios, which is independent of the disease prevalence. However, computation of the negative likelihood ratio is accurate only when all other characteristics of the cohort are the same — a condition that is rare in the clinical setting.[5] Our validation study included many sites and ethnic groups across the United States, including academic and community practices, patients ranging in age from 22 to 85 years, various nodule sizes, and many methods of fine-needle aspiration biopsy. We therefore believe our results are applicable for broad routine use.

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Since publication of their article, the authors report no further potential conflict of interest.

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Tofacitinib in Active Ulcerative Colitis

TO THE EDITOR: Sandborn et al. (Aug. 16 issue)[1] report that tofacitinib has efficacy in the treatment of ulcerative colitis. The authors note that Janus kinase (JAK) inhibitors JAK1 and JAK3 are surprisingly ineffective in the treatment of Crohn's disease.[2] In Crohn's disease, the major cytokines arise from the differentiation of two subtypes of CD4+ T cells — Th1 and Th17 — whereas in ulcerative colitis a Th2-like differentiation process seems to be involved. Several recent reports on different experimental models seem to indicate that JAK inhibitors such as tofacitinib suppress Th2 but potentiate Th1 and Th17 responses. For example, a low dose of tofacitinib accelerates the onset of experimental autoimmune encephalomyelitis by potentiating Th17 differentiation.[3] JAK inhibitors such as tofacitinib and pyridone 6, a pan-JAK inhibitor, also strongly reduce Th2 response and potentiate Th1 and Th17 responses in different diseases.[4]

Moreover, tofacitinib has been also described as inhibiting interleukin-4–dependent Th2 cell differentiation in both murine and human T cells.[5]

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