Correspondence

Rapid review of cervical cytology

I read with interest the recent report by Faraker and Boxer.[1] The salient result of their endeavour is the claim to have reduced the false negative rate in their laboratory from 5.0% to 0.4%. They are to be lauded for such enviable statistics. However, the reality of a broader view of the cytology scene is not compatible with those figures. Their article commences by citing Dr Koss's paper which calls attention to the tragedy of the high incidence of false negative smear reports issued by cytology laboratories. Dr Koss states that "it is clear that the error rate of cytologic screening for precancerous lesions and invasive cancer of the uterine cervix is quite substantial."[2] Reports of false negative rates vary, reflecting numerous factors including the negative motivation in addressing this most humbling of revelations. What must be appreciated and accepted is the intrinsic search limitation of manually screening millions of cells each working day. The authors state that "errors must be due to a major lapse in concentration" and that "There is not usually anything difficult about false negative smears". It is time we jettisoned the myth that cytology is a 'simple test'. The fact that interpretation of abnormalities may frequently be less problematic than the monotonous search does in no way obviate the cumulative difficulty of this applied science. With that said, it is hard to posit a mechanism to account for the empirical claim of improving on the meticulous conventional microscopic search for a 'needle in the haystack' by a second rapid partial rescreen. One should anticipate further pickup by such a process does indeed represent cases missed due to major lapses.

It is also interesting that in spite of the authors' excellent results with the combination of conventional screening and rapid rescreening, they admit PAPNET's superiority. They conclude that where they should find 21 of a theoretical 25 false negatives, PAPNET will find 24 of 25. Further, they derive their false negative maximum of 25 as 5% of the total—the suggested benchmark.[3] This benchmark is based on the intrinsic limitations of manual cytology. It is this limit which is extended another 25–30% by PAPNET. The added spectrum of sensitivity afforded by PAPNET pertains to cases characterised by a scant number of small abnormal cells. Therefore, PAPNET should reveal more than 30 false negatives in the authors' archives—an improvement of 50%. The value of this improvement is then formulated in solely financial terms. The source of their economic evaluation is not given and is erroneous. A more appropriate source of economic impact is to be obtained from professional studies addressing this aspect. Scientific analysis of cost effectiveness of PAPNET testing has appeared in the literature. In a comparison of various methods of health intervention using the model developed under contract from the US Congress Office of Technological Assessment, PAPNET testing is cost effective.

The Pap test is not, as popularly believed, a "cheap and easy" test. It is a serious scientific challenge requiring many resources. PAPNET testing is, even as inadvertently demonstrated by Faraker and Boxer, an improvement in the quality of cytology. The reason being it assists cytologists in overcoming a major intrinsic limitation of cervical cytology: the search for suspect cells. Its ultimate value is to be judged by women—and their loved ones.

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1 Faraker CA, Boxer ME. Rapid review (partial rescreening) of cervical cytology. Four years experience and quality assurance implications. *J Clin Pathol* 1996;**49**:587–91.
2 Koss LG. The papanicolaou test for cervical cancer detection. A triumph and a tragedy. *JAMA* 1989;**261**:737–43.
3 Achievable standards, benchmarks for reporting, criteria for evaluating cervical cytology. Report of a working party set up by the Royal College of Pathologists, the British Society for Clinical Cytology and the NHS Cervical Screening Programme. *Cytopathology* 1995; **6(Suppl 2)**:1–32.

Drs Faraker and Boxer comment:

We are pleased that NSI take rapid review as a method of internal quality assurance for cervical cytology sufficiently seriously to write to this journal. There are errors and distortions in their letter that we would like to correct.

By quoting us out of context, the impression is given that we believe all screening errors are due to major lapses in concentration and, therefore, the detection of these false negatives by rapid review should be anticipated. Our paper[1] clearly states that we have identified three categories of screening error: those due to misinterpretation; those due to the scarcity of abnormal cells on the slide; and those due to a major concentration lapse. The latter cause accounted for only 10 of the 62 false negatives in the study group. As these conclusions were drawn from reviewing false negative smears that had been detected by rapid review, it is evident that rapid review is able to detect more than just errors due to major concentration lapse. Dr Frist states that it is hard to posit a mechanism for rapid review detecting abnormalities missed by full screening. We must remind the author that in science, counterintuitive observations are frequently true and that evidence precedes and must be explained by theory. The fact that the efficacy of rapid review is unexpected does not make it untrue.

We did not, as stated, derive our false negative rate from the 5% suggested benchmark. It would be ridiculous to suggest that merely because a benchmark is suggested, we would assume that to be our false negative rate. Again, our paper clearly states how we calculated our false negative rate. It is derived from the number of false negatives detected by targeted full rescreening and by rapid review, and by using a correction factor to adjust for the sensitivity of rapid review.

We fully agree that professional studies addressing the economic impact of such methods are more appropriate than our simple calculations and were therefore interested to see the editorial by Professor Hutchinson in *Acta Cytologica*.[2] In her cost effectiveness analysis for evaluating alternative rescreening strategies, it was determined that for a cytologist with a 75% sensitivity, the increases in the sensitivity of screening provided by rapid review and PAPNET are almost identical (9.4% and 9.9%, respectively). What is not similar is the cost for each additional abnormal case discovered, which is calculated as $348 for rapid review and $4486 for PAPNET rescreening.

Dr Frist states that we admit PAPNET's superiority over rapid review and that we inadvertently demonstrated this. We did neither. We compared our detection rate by rapid review to that quoted for PAPNET which was determined by an entirely different study design. What we were suggesting was that if the two studies could be directly compared, PAPNET would produce only a tiny additional yield for a huge extra cost. However, the only valid way to compare rapid review with PAPNET is to apply both techniques to the same population of slides in a laboratory which can practise both rapid review and PAPNET screening to a high standard. It is possible that PAPNET is superior to rapid review, but in the present state of evidence it is equally possible that it is no better, or worse. The answer to this question could be determined by PAPNET screening of our archived slides which have already undergone rapid review. If NSI are willing to fund such a study, we would be delighted to participate.

1 Faraker CA, Boxer ME. Rapid review (partial rescreening) of cervical cytology: Four years experience and quality assurance implications. *J Clin Pathol* 1996;**49**:587–91.
2 Hutchinson ML. Assessing the costs and benefits of alternative rescreening strategies. *Acta Cytol* 1996;**40**:4–8.

Bcl-2 protein does not help to distinguish benign from malignant lymphoid nodules in bone marrow biopsy specimens

We read the recent article by Chetty *et al* with interest.[1] The authors concluded that strong bcl-2 immunoexpression in lymphoid cells and their aggregates in bone marrow specimens is indicative of the malignant lymphomatous nature of these lymphoid cells and can be used to detect minimal residual lymphomatous infiltration. They also mentioned in the Abstract, but not in the Results section, that "reactive lymphoid nodules did not show the same degree of bcl-2 positivity, and negative cells could be discerned within the reactive nodules".[1]

The possible role of anti-bcl-2 protein immunostaining in distinguishing benign from malignant lymphoid infiltrates in bone marrow specimens was first proposed by Ben-Ezra *et al*[2] and recently has been mentioned briefly in abstract form.[3] In contrast to Chetty *et al*,[1] we have observed a strong bcl-2 protein immunoreactivity in various proportions of lymphoid cells in both reactive and malignant lymphoid aggregates in all bone marrow specimens in our recent study.[4] All samples had been fixed in formalin, processed routinely and embedded in paraffin wax. Prior to incubation with the bcl-2 protein antibody (clone 124; Dako, Glostrup, Denmark), the sections were microwaved for 4 × 5 minutes at 700 W. In our study, all lymphoid aggregates in the bone marrow samples from the patients with a previously diagnosed lymphoma were consistently strongly positive for bcl-2 protein. In addition, all lymphoid aggregates with benign