The merits of new alternatives to the Papanicolaou test

The claim by Eduardo Franco and colleagues that “nearly half of specimens [cervical smears] yield false-negative results” is misleading, as are several of their claims regarding the value of liquid-based and automated cytology. Most studies quote a false-negative rate of approximately 1–5%. Any laboratory with a 50% false-negative rate would be shut down.

Liquid-based preparations are not free of drawbacks, including the loss of necroinflammatory background that can be a clue to malignancy. Although it is true that “virtually all cellular material is made available to the laboratory,” only a small proportion of this material is placed on the slide for screening. Conventional preparations contain many more cells. The newer methodologies are also very expensive and tightly controlled by a few companies, drawbacks that are not just “perceived.” Their claims of improved false-negative rates are questioned by a recent meta-analysis, which concluded that most of the studies of liquid-based preparations and automation were “severely limited by design, inadequate reference standards, and incomplete verification of cytological diagnoses.” Finally, none of these technologies will reduce the number of false-negative cases that are due to suboptimal sampling or interval disease progression.

If the jury is still out on the statistical value of these methodologies, the societal value is even less certain. Traditional cervical smears have been successful because they are inexpensive, easy to perform and generally accurate. Because of slow progression to malignancy, yearly smears will detect almost all serious disease even if it is missed on one specimen. The greatest gain in cervical cancer control is in first-time screening, and the increase in cost associated with new techniques will reduce access by underserved populations. Increased costs will also follow the inevitable rise in false-positive tests.

There is a social cost in quoting questionable statistics about false-negative cervical smears, eroding both patients’ and clinicians’ confidence in a test that is fundamentally sound. Calculated from 8 representative studies, the predictive value of a negative smear for significant disease is 99.96%. It’s hard to improve on that.

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References

[The authors respond:] Erin Ellison has challenged our contention that the false-negative rate for conventional Papanicolaou (Pap) smears is much higher than it is generally perceived to be. A recent meta-analysis conducted in primary screening settings indicated an average sensitivity of 51% (95% confidence interval 0.37–0.66). This figure will be shocking to anyone, like Ellison, whose knowledge base includes studies that were plagued by verification bias (also known as diagnostic workup bias) or involved the triage of equivocal or minor abnormalities, which are situations with a high prevalence of lesions. Screening sensitivity in studies affected by verification bias is invariably overestimated and should not be included in pooled overviews, a precaution that was taken in the aforementioned meta-analysis. In fact, it has been recommended that cost-effectiveness models of cervical cancer screening should be revised to use more conservative estimates of Pap test sensitivity.

Ellison’s arguments about the draw-
backs of liquid-based cytology notwithstanding, this technique does represent an improvement over conventional smear techniques. The few studies that satisfy today’s stringent criteria for quality of evidence have found liquid-based cytology to be significantly more sensitive than the conventional Pap test.2,5

The evidence for the effectiveness of the Pap test as a cancer control measure was obtained in an era before the randomized controlled trial paradigm became widespread. Newer techniques are being judged by criteria that are far more stringent than the ones used to place the Pap test on its current pedestal. Well-designed studies with suitable endpoints are expensive and take many years. Privileged observers of the cervical screening scene, such as Ellisson, should take this into account before prematurely repudiating new methods.

We agree that it is unfortunate that reliance on new technologies may limit the practice of cervical cancer screening to a few commercial interests. However, as these technologies gain ground, competition is likely to ensue and the present monopolies will disappear.

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Support groups for people carrying a BRCA mutation

The study by Lisa Di Prospero and colleagues on the psychosocial impact of genetic testing for BRCA1 and BRCA2 mutations is important and one of the first to explore the perceptions of tested women in Canada.2 We believe, however, that it may be premature to state that the “organization of support groups for people found to have the gene mutation should be a priority” for clinical programs providing testing.

We are currently conducting a prospective study describing a range of outcomes of BRCA1 and BRCA2 testing among Quebecers during pretest genetic counselling and 1 month, 1 year and 3 years after result disclosure. Nearly half the projected consecutive series of 900 participants have been recruited to date. Participation exceeds 85%. Our data indicate relatively low interest in support groups in this population. Of the 91 subjects questioned to date at 1 year after they learned their test result, 27% of the people with a BRCA mutation (10/37), 20% of people with inconclusive results (2/10) and 14% of people without a BRCA mutation (6/44) expressed moderate or great interest in having access to support groups. Recent research among breast cancer patients suggests that peer discussion groups may be harmful to women who already have high levels of support.7 This is an important point, as 75% of the participants in the study by Di Prospero and colleagues felt that support from family and friends was meeting their needs.

We believe that psychosocial interventions for people undergoing genetic testing for breast cancer susceptibility are justified, given the current consensus that all people should have access to psychosocial care. However, given that our present state of knowledge is based on data from small numbers of tested people, more research may be needed before a clear-cut recommendation can be made concerning support groups.

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References

[The authors respond]

We thank Michel Dorval and colleagues for their interest in our study1 and agree with their statement that the majority of people carrying a BRCA1 or BRCA2 mutation do not need support groups. By no means were we trying to suggest that all people carrying one of these mutations should be encouraged to join support groups. Genetic testing populations are heterogeneous and one would not expect a single intervention to address the psychosocial needs of all people carrying a BRCA mutation.

What we did say was that “a significant minority of [people carrying a BRCA1 mutation] desire such a service.” This “significant minority” was 9 of the 24 patients who participated in our study (38%); this is not statistically sig-