with sensitivity of 100%, with specificity and prevalence varying as shown.

Screening tests play an important part in public health, and new diagnostic tests will undoubtedly improve patients' management in the years ahead. Clear thinking about diagnostic statistics can help ensure the rational application of new and existing tests to appropriate populations.

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1 Petricoin III EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet* 2002; **359:** 572–77.
2 Kopans DB, Moore RH, McCarthy KA, et al. Positive predictive value of breast biopsy performed as a result of mammography: there is no abrupt change at age 50 years. *Radiology* 1996; **200:** 357–60.
3 Detmer WM, Nicoll D. Diagnostic testing and medical decision making. In: Tierney LM, McPhee SJ, Papadakis MA, eds. Current medical diagnosis and treatment. Norwalk: Appleton and Lange, 1995: 19–29.

Sir—Emanuel Petricoin and colleagues' discussion[1] is hampered by a misapplication of positive predictive value; they say that a positive-predictive value of 94% might be acceptable for high-risk-population screening.

In high-risk screening, the positive predictive value given by their test will be nothing like 94%, since that calculation applies only to their study design in which 50 of the 116 patients assessed had ovarian cancer. Even if their test results of 100% sensitivity and 95% specificity were confirmed in larger relevant groups, these values would translate to a low positive predictive value.

For example, in 1601 self-referred women with family history, 11 had ovarian or peritoneal cancer diagnosed over up to 44 months.[2] Application of the proteomic pattern results would give 11 true-positive results and 5% of 1590, that is 80 false-positive results, which gives a positive predictive value of 12%. In a population-based study of 8455 women screened three times, 16 had ovarian or pevitoneal cancers;[3] the positive predictive value there would be lower than 4%. A specificity of 95% is not very high for a putative screening test, and further development should aim to increase this to 99% or more.

Mark Elwood

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1 Petricoin III EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet* 2002; **359:** 572–77.
2 Bourne TH, Campbell S, Reynolds KM, et al. Screening for early familial ovarian cancer with transvaginal ultrasonography and colour blood flow imaging. *BMJ* 1993; **306:** 1025–29.
3 Jacobs IJ, Skates SJ, MacDonald N, et al. Screening for ovarian cancer: a pilot randomised controlled trial. *Lancet* 1999; **353:** 1207–10.

Sir—A limitation of Emanuel Petricoin and colleagues' report[1] is that the major discriminatory proteins or peptides of the algorithm have not been positively identified.

Similar approaches in the past have revealed that such proteins and peptides are abundant in serum and are generally found in the μg/mL to mg/mL concentration range.[2] The best cancer markers known to date, all documented to be tumour-derived products (eg, prostate-specific antigen, α-fetoprotein, carcinoembryonic antigen), are present in serum at much lower concentrations (1–10 ng/mL in the normal state). Early cancer generally sheds small amounts of such biomarkers in the circulation. These proteins are then diluted and eliminated with a certain clearance rate and vast accumulation does not occur, except in late-stage disease.

Therefore, the discriminating proteins and peptides identified by Petricoin and colleagues might not be tumour-derived products, but rather epiphenomena of metabolic changes due to the presence of the tumour. It is unlikely that such epiphenomena will be specific for one type of cancer.

Currently, it is generally agreed that one cancer biomarker will not be sufficient for diagnosis of early ovarian or other cancers. The multiparametric analyses of Petricoin and colleagues, and others, is a logical approach. Efforts should focus on identifying a group of the most informative substances that are released by tumours for use as a diagnostic panel (eg, 5–50 proteins) along with a bioinformatic approach. Such substances are expected to be present in serum in the ng/mL range, similar to most other well-known cancer markers. Appropriate quantitative techniques for such analysis would include protein microarrays and mass spectrometry, provided that the sensitivity of these techniques is suitable for this range.

I fully endorse multiparametric analysis and bioinformatics, but think that the proteomic patterns should be based on proteins of known identity, preferably tumour-derived antigens and not epiphenomena of a generalised metabolic change.

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1 Petricoin III EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet* 2002; **359:** 572–77.
2 Mok SC, Chao J, Skates S, et al. Prostasin, a potential serum marker for ovarian cancer: identification through microarray technology. *J Natl Cancer Inst* 2001; **93:** 1458–64.

Authors' reply

Sir—By use of an artificial intelligence method we discovered a discriminatory proteomic pattern and tested it against a masked test set of 116 serum samples. When the results were unblinded, all 50 ovarian cancers were correctly classified, including all 18 stage I cancers, whereas 63 of 66 unaffected or benign cases were classified as non-cancer, which gives a 100% sensitivity and 95% specificity.

Although these findings show great promise, as correctly pointed out by Beverly Rockhill, Douglas Pearl, and Mark Elwood, a test with 100% sensitivity and 95% specificity is still not suitable to screen the general population for ovarian cancer.

Ovarian cancer has a reported prevalence of one per 2500. Consequently, if we screened 2500 women the test would correctly identify the one true-positive result, but would generate 125 (5% of 2500) false-positive results in the process. As an optimal standard, of course, we should strive for a 100% specific and 100% sensitive screening test for ovarian cancer, given its low prevalence. Proteomic pattern analysis may be able to reach this seemingly elusive goal.

Artificial intelligence systems can learn and improve their performance as new data is added. Furthermore, we can postulate that multiple sets of discriminatory patterns exist. Combinations of patterns may boost the specificity. We have repeated our study with a different SELDI chip surface (WCX-2), and have discovered a new pattern set that achieves 100% specificity and 97% sensitivity. All the new spectra are posted on our web site.[1] The combination of patterns yields 100% sensitivity and specificity in this pilot series. As a further means to increase specificity, proteomic pattern analysis can be combined with emerging promising biomarkers