



The tip of the iceberg

A Countercurrents Series^a
with S.A. Narod MD

In February 2012, Ambry Genetics, a testing company based in Aliso Viejo, California, began to offer the BreastNext genetic test to women with early-onset or familial breast cancer. The test is marketed to women who have already undergone genetic testing for *BRCA1* and *BRCA2* and who have been found to be negative. Given that only about 10%–15% of women who are tested at Myriad Genetics (Salt Lake City, UT, U.S.A.) for *BRCA1* and *BRCA2* mutations receive a positive result, and given that all the Myriad Genetics negatives now qualify for a BreastNext test, the market is potentially quite big. The 14 genes in the BreastNext panel—*ATM*, *BARD1*, *BRIP1*, *CDH1*, *CHEK2*, *MRE11A*, *MUTYH*, *NBN*, *PALB2*, *PTEN*, *RAD50*, *RAD51C*, *STK11*, and *TP53*—have all been identified as being causative for a syndrome that includes breast cancer.

I have argued in the past in favour of testing for *CHEK2* mutations¹, and I am comfortable with that choice, but I don't yet see a justification for adding the other 13 genes. Perhaps if the test were inexpensive? But the current cost is US\$3850.

Mutations in *TP53* are extremely rare, even in the case of early-onset breast cancer, and when they are seen, they are usually in a family with Li–Fraumeni syndrome². *NBN* is a *bona fide* breast cancer gene, but susceptibility seems to be limited to a few founder mutations present in Eastern Europe that have an idiosyncratic effect on gene expression³. *NBN* is not a classical tumour suppressor gene, in that not all truncating mutations are pathogenic. Mutations in *CDH1* are vanishingly rare, even in families with predominantly lobular breast cancer⁴. In 2008, our group concluded that *MUTYH* mutations had little or nothing to do with breast cancer⁵. *RAD51C* (like *RAD51D*) predisposes to ovarian cancer, but does not appear to increase the risk of breast cancer⁶.

Mutations in *BRIP1*, *ATM*, and *PALB2* also appear to be very rare. I estimate that fewer than 3% of the women who qualify for testing according to Ambry Genetics guidelines will carry a mutation in 1 of the 14 BreastNext genes, and that more than one half the mutations found will be the 1100delC mutation in *CHEK2*.

At the product Web page, <http://www.ambrygen.com/tests/breastnext>, Ambry Genetics shows a pie chart, which predicts that up to 50% of tested samples will be positive for 1 of the 14 genes. That is, of 100 woman with familial breast cancer, 46 will have a *BRCA* mutation, 27 will have a BreastNext mutation, and 26 will have no mutation. I am not sure who sliced the pie, but those numbers are not derived from their own data nor from any published data. We cannot both be right. To resolve the discrepancy, it will be important to sequence a large number of families and premenopausal breast cancer patients that meet the Ambry Genetics criteria and to estimate the prevalence of mutations by gene—single and in combination.

In his new book *The Wandering Gene and the Indian Princess*, Jeff Wheelwright says that he is of the mind that the discovery of the *BRCA1* and *BRCA2* genes is the greatest triumph of the DNA age and that, in terms of clinical medicine, it outranks other successes of the Human Genome Project⁷. Will Foulkes, in an opinion piece in the *New York Review of Books*, uses the example of hereditary breast and ovarian cancer in rebuttal to Richard Lewontin, who states that the promises of the Human Genome Project remain unfulfilled⁸. The ability to prevent cancer and cancer mortality through gene identification, combined with enhanced surveillance, preventive surgery, and chemoprevention, is what makes the *BRCA* gene discoveries important. In 1995, when *BRCA2* was discovered, university-based pundits proclaimed that this revelation was merely the tip of the iceberg, and with linkage studies, genome-wide association studies, multinational consortia, and so forth, it was only

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a matter of time before the entire family of breast cancer genes would be assembled. And based on the commercial success of Myriad Genetics, funding agencies such as Genome Canada were keen to ensure that genetic findings were commercialized.

Fast forward to 2012. None of the genome-wide association studies that have been conducted (at a cost of many millions) has resulted in a clinically useful test in the cancer domain. The Ambry Genetics panel is a fairly anemic collection. At US\$3850 per test, the company proposes to double the cost of genetic testing and might increase the sensitivity by 6%. I hope there is more to personalized medicine than this.

A different example comes from prostate cancer. In an excellent study, Cooney and her group provided the first convincing evidence for a prostate cancer susceptibility gene, *HOXB13*⁹. The susceptibility allele conferred a risk of prostate cancer that was increased by a factor of 20 (clearly of clinical significance to a man with the mutation), but the allele is present in fewer than 1 in 1000 men in the United States and accounts for less than 1% of prostate cancer cases. A commercial test is undoubtedly on the way, but most physicians will probably never encounter a positive result.

It is also challenging to come to a conclusion about how to interpret a positive test. It will be difficult to interpret a genetic variant in *NBN* if it is not the known founder mutation. I have pointed out how complex genetic counselling for *CHEK2* mutations is, despite the fact that dozens of clinical papers have been written¹. It is not merely a matter of estimating prevalence and penetrance (which is hard enough); it is also imperative to have a good idea of the typical ages of onset and the clinical characteristics of the mutation-associated breast cancers. For example, if the typical cancer is estrogen receptor–negative and aggressive (as is the case with *BRCA1*), then preventive mastectomy might be favored. By contrast, if most cancers are estrogen receptor–positive and low grade, then tamoxifen might be a reasonable choice. In the absence of histologic characteristics, the choices are limited to preventive surgery (which few will accept if the penetrance is unknown) and screening by magnetic resonance imaging. Surveillance by magnetic resonance imaging is probably a good idea for *BRCA1* carriers, in whom cancers are typically high-grade and estrogen receptor–negative, but may lead to a problematic number of overdiagnosed cancers in which the typical presentation is low grade and estrogen receptor–negative.

Based on the genes identified since 1995, it seems to me that the commercial investment into the identification of new genes for breast cancer

and other cancers is marginal. Funding agencies such as the Canadian Institutes of Health Research, Genome Canada, and the U.S. National Institutes of Health might be better off investing in a proper evaluation of the benefits of current tests for cancer susceptibility before those tests enter into the health care domain.

CONFLICT OF INTEREST DISCLOSURES

The author has no financial conflicts of interest to declare.

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