



# Personalized medicine: a personal view

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## KEY WORDS

Genetics, preventive medicine, personalized medicine

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After the discovery of the breast cancer–associated genes *BRCA1* in 1994 and *BRCA2* in 1995, genetic testing was introduced into clinical practice in North America and Europe. One of the goals of genetic testing is to identify women at high risk of cancer, who may then reduce their risk by adopting one or more preventive measures<sup>1</sup>. This theme of individualized risk assessment was widely heralded and is part of what is now called “personalized medicine.” The idea here is that humans can divide themselves into two (or more) groups, each with a different inherent risk of cancer. Group membership is determined simply by having a genetic test. Based on the result of a genetic test (for example, for *BRCA* mutations), a woman may or may not be offered a particular intervention. In this case, eligibility for the intervention is based on a high inherent risk of cancer. The implicit assumption is that the intervention isn’t recommended for everyone—for example, preventive breast surgery is not recommended for women not at high risk of breast cancer.

Personalized medicine has also been adopted into cancer treatment. Several scenarios are relevant:

- Genetic testing of blood DNA may predict response to treatment—for example, *BRCA1* status predicts response to cis-platinum<sup>2</sup>, and *CYP2D6* genotype predicts benefit with tamoxifen<sup>3</sup>.
- Genetic testing for tumour DNA or measurements of protein expression within tumour cells may predict response to therapies such as tamoxifen and trastuzumab.

Several studies are now attempting to identify other targets within breast cancers so that the individualized approach can be further extended.

The idea of personalized prevention attracts a lot of enthusiasm. Several companies are marketing gene

testing over the Internet, and collaborative groups of researchers are pursuing genetic variants that may, singly or in combination, define cohorts of women at higher-than-average risk of breast cancer and other diseases. Much is promised, but to date, little has been demonstrated. For evaluative purposes, it may be illustrative to consider the case of tamoxifen chemoprevention for carriers of *BRCA1* mutations.

Tamoxifen has not been particularly well-received among women at moderate risk; perhaps its benefit will be more readily demonstrated among women at high risk, who derive greater potential benefit than do low-risk women, but who experience side effects in similar numbers. Some uncertainty remains regarding the utility of tamoxifen in primary prevention in high-risk women, but a large study of contralateral breast cancer in *BRCA* carriers demonstrated a strong benefit. The multivariate odds ratio for contralateral breast cancer associated with tamoxifen use was 0.50 for carriers of *BRCA1* mutations [95% confidence interval (CI): 0.30 to 0.85] and 0.42 for carriers of *BRCA2* mutations (95% CI: 0.17 to 1.02)<sup>4</sup>. In contrast, a small prospective study of tamoxifen and primary prevention in *BRCA* carriers demonstrated no benefit for *BRCA1* carriers and a nonsignificant benefit for *BRCA2* carriers<sup>5</sup>.

Testing for *BRCA1* has been available for 15 years in Ontario, and the fates of a large number of mutation carriers are being tracked. Using that database, the number of breast cancers prevented annually by prescription of tamoxifen to *BRCA1* carriers in Ontario can be estimated. First, an assumption is made that 4% of breast cancers in Ontario are attributable to *BRCA1* and *BRCA2* mutations and that, of those cases, one half (2%) are attributable to *BRCA1*. Probably 1 woman in 10 with a *BRCA1* mutation in Ontario knows that she is a mutation carrier. Of women who know that they are carriers and who are unaffected with breast cancer, 8% are estimated to take tamoxifen<sup>6</sup> and therefore presumably to cut their breast cancer risk in half<sup>4</sup>. In sum, then, it can be estimated that 1 case of breast cancer in 12,500 ( $0.02 \times 0.10 \times 0.08 \times 0.50$ ) is prevented annually in Ontario by the administration of tamoxifen to *BRCA1* carriers. But only 8000 breast cancers are

diagnosed in Ontario every year! We must conclude that the administration of prophylactic tamoxifen to healthy *BRCA1* carriers is not a stellar example of the benefit to be gained by personalizing medicine. To do better, improvements must be considered. The frequency of mutations in the population cannot be changed, but perhaps other relevant factors can be modified. Among women with a mutation, strategies are needed to increase the proportion that know their mutation status. Such strategies might include loosening government testing criteria or promoting genetic testing directly to the consumer.

Our group recently showed that only about 1 woman in 5 with ovarian cancer in Ontario undergoes genetic testing, even though all are eligible, and 80% are willing to be tested<sup>7</sup>. We also showed that it is reasonable to offer genetic testing to all women in the Ashkenazi Jewish population<sup>8</sup> and that, using a notice in a magazine, genetic testing can be marketed directly to women without incurring obvious harm<sup>9</sup>. In Quebec, founder mutations in *BRCA1* and *BRCA2* are common in French Canadian women with breast cancer (about 6% of cases diagnosed before the age of 50 years), and testing is relatively inexpensive<sup>10</sup>. Nevertheless, no provincial strategy is in place to translate those findings into better clinical care.

Approximately one half of breast cancers in *BRCA1* carriers occur before the age of 40 (Narod SA, Finch A, Metcalfe K, *et al.* The impact of genetic testing and genetic counselling on the penetrance of breast and ovarian cancer in *BRCA1* and *BRCA2* carriers. Submitted), but most women tested receive their test result after that age. Strategies are needed to bring testing into the early 20s so that the potential benefits of prevention can be realized. The reasons why women forgo chemoprevention need to be evaluated, and strategies to overcome the barriers need to be developed.

New strategies for cancer prevention also need to be developed. The principal weakness in the prevention paradigm is probably the proportion of the population at large that will eventually be tested. The *BRCA1* test is covered in Ontario, but it is unlikely that provincial government health insurance schemes in Canada or third-party payers in the United States will pay for predictive genetic testing using large panels of multiple single nucleotide polymorphisms. It is therefore likely that few Canadians (probably fewer than 1%) will be tested. If preventive options are offered only to the fraction of that 1% that fall into the high-risk category, it becomes clear that the scope

for reducing the burden of cancer is small. Perhaps a better approach is to provide genetic testing at the time of cancer diagnosis, with the hope of offering individualized treatment. The target population is relatively small, and its members are highly motivated. If a cancer treatment could be developed that would reduce the risk of recurrence in women with a *BRCA* gene mutation specifically, it would be rational to offer genetic testing across the board at the time of cancer diagnosis.

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