

The 21-gene assay and its impact on breast cancer treatment

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Every year, many Canadians are receiving adjuvant chemotherapy for breast cancer that may not be required. Like many therapies given to large unselected populations, it is evident that some individuals benefit a great deal, some less, and some not at all. There is increasing evidence that the recently developed 21-gene assay test^{1,2,3} can identify breast cancer patients considered for adjuvant chemotherapy who will not benefit from this treatment.

In the US, the 21-gene assay test was approved by the US Food and Drug Administration (FDA) in 2005. Since 2007, this test has become routine for node-negative breast cancer patients whose tumours test positive for hormone receptors and who are candidates for adjuvant chemotherapy.^{4,5} The cost-benefit analyses in the US project substantial quality of life and cost benefits due to avoided chemotherapy.

While most US-based insurance companies fund this test if ordered by an oncologist, only a handful of Canadian oncologists recommend the assay and, at the time of writing (April 2010), aside from very recent changes in Ontario, no institution has funded this test consistently within Canada, outside the clinical trial setting.

From 2007-2009, a total of 822 breast cancer patients had the 21-gene assay test as part of the TailorX trial (fully funded). In the same time period, 140 women had their tests ordered outside of the TailorX trial, and thus were obligated to pay for the test themselves. This compares to the estimates of close to 10,000 patients in Canada each year who, according to the American Society for Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines,^{4,5} would be eligible for the 21-gene assay.

Due to pressure from the media and the Canadian Advocacy Coalition of Canada (CACC), coverage for the assay has become available in Ontario through the Ontario Health Insurance Plan (OHIP) since January 2010. From January to April of this year, 29 patients in Ontario have had access to the 21-gene assay, outside the TailorX trial, on a funded basis.

As seen from the published data, if used appropriately, the 21-gene assay may potentially save thousands of patients from chemotherapy they do not benefit from. This review addresses the role of the 21-gene assay and why it is not as yet being used to its full extent in Canada.

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THE 21-GENE ASSAY: PROGNOSTIC SIGNIFICANCE

Between 2001–2003, Paik et al developed an assay to identify 21 genes from tumour samples that collectively predicted recurrences, breast cancer deaths and response to chemotherapy.¹

The 21-gene assay is based on advances in recent genetic techniques that provide “tumour signatures” — a collection of information reflecting tumour biology and risk of relapse.^{6,7} An algorithm was developed defining a Recurrence Score (RS) based on the various constellations of the 21 genes isolated from the tumour samples. RS was expressed as low (RS<18), medium (RS=18-30), or high (RS>31).

It was shown that among node-negative breast cancer patients with positive estrogen receptors (ER), 51% had a low RS, 22% a medium RS, and 27% a high RS. Recent data for node-positive patients demonstrate close to 40% had low RS.³

According to the 2004 analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) chemotherapy-tamoxifen trials, if the RS was low, patients had recurrences significantly less often than patients with medium or high RS. The rates of distant recurrence at 10 years were respectively 6.8 %, 14.3 % and 30.5 %. Importantly, a similar correlation of recurrence rate and level of RS was established very recently among cases with node-positive disease.³

In 2005, Genomic Health Inc. (Redwood City, California) obtained a worldwide patent for a centralized 21-gene assay (Oncotype DX®). That year, the Trial Assigning Individualized Options for Treatment (TailorX) was initiated (and is still ongoing), which is testing the effect of chemotherapy vs no chemotherapy in the medium-RS breast cancer group.

In 2007, the expert panels of both ASCO and NCCN recommended the 21-gene assay as evidence-based practice for routine use in early breast cancer.^{4,5}

THE 21-GENE ASSAY: PREDICTIVE BIOMARKER FOR CHEMOTHERAPY EFFECT

In 2006, Paik et al² showed that the 21-gene assay not only predicted recurrences, but also demonstrated chemotherapy effectiveness. Specifically, chemotherapy benefit (i.e. as seen in the proportion of patients free of distant recurrences at 10 years) was restricted to patients with high RS (relative risk [RR] = 0.26, 95% CI = 0.13–0.53), while cases with low RS had no chemotherapy benefit (RR = 1.31, 95% CI = 0.46–3.78). The chemotherapy impact in the intermediate group was not fully determined (RR = 0.61, 95% CI = 0.24–1.59).

21-gene assay guideline proposals for Canada

For NODE-NEGATIVE BREAST cancer cases:

- Include the 21-gene assay in early breast cancer guidelines and provide funding for this test in all newly diagnosed node-negative breast cancer cases that meet the current ASCO and NCCN guidelines.

For NODE-POSITIVE breast cancer cases:

- Determine criteria for the use of 21-gene assay test (i.e. all newly diagnosed ER-positive, Her2/Neu-negative, good-grade cancer cases where chemotherapy may not be required).
- Develop oncology guidelines to identify a policy of no adjuvant chemotherapy for low-RS cases.

IMPACT ON PRACTICE

Erb et al at the University of Pennsylvania compared more than 1200 breast cancer patients diagnosed in 2003, before the practice of the 21-gene assay had begun, with a similarly matched node-negative ER-positive patient population from 2005–2006, after the assay had been introduced. Between the two time periods, the indication for adjuvant chemotherapy dropped by 30%, from 55% to 25%.¹⁰ Subsequently, Lo et al evaluated a similar population of patients and recorded that 22.5% of oncologists had switched the recommendation from chemotherapy + hormone therapy to hormone therapy alone, due to a low RS.¹¹ The most recent evaluation of a cohort of node-positive ER-positive patients assessed before and after the RS score availability showed that of the 89 cases planned for chemotherapy + hormone therapy, 48 patients (35%) had been changed to hormone therapy alone as a result of testing with the 21-gene assay.¹²

Thus, overall, with an increasing utilization trend since the assay had been introduced, the change from chemotherapy + hormone therapy to hormone therapy alone has been recorded in somewhere between 22.5% and 35% of cases.

With over 220,000 breast cancer cases diagnosed annually in US, these estimates may currently represent over 10% of all breast cancer cases each year. The figures will probably increase based on the additional information on node-positive ER-positive cases³ that became available in late December 2009. In those patients, close to 40% had a low RS (indication of no chemotherapy benefit), yet at the present time most are receiving adjuvant chemotherapy.

In December 2009, *Lancet Oncology* published a confirmatory study by Albain et al in breast cancer patients who had positive-involved axillary nodes. As seen in the node-negative cases, there was also no chemotherapy benefit documented in the node-positive patients if the RS was low (disease-free survival, cyclophosphamide, doxorubicin and fluorouracil [CAF] + tamoxifen vs tamoxifen alone, RR = 1.02, 95% CI = 0.54–1.93), even though they were in a much higher-risk group and were undergoing a more standardized intensive chemotherapy regimen that included anthracyclines.³ Similarly, the chemotherapy benefit for the intermediate-RS group was not statistically significant (RR = 0.72, 95% CI = 0.39–1.31). The only group where there was substantial chemotherapy benefit approaching statistical significance was the high-RS group (RR = 0.33, 95% CI = 0.35–1.01).

NEW CANCER MANAGEMENT PARADIGM

The introduction of genetic analyses to refine the indications for chemotherapy is recognized by many scientists as a turning point for cancer management. Attention is shifting from therapy indications based on the “anatomic and geographic” extent of tumour spread — the long-accepted Tumour, Nodes, Metastasis (TNM) criteria — to one based on molecular and functional tumour biology, as represented by the 21-gene assay biomarker test. Molecular expression is emerging as the prime method for determining both risk assessment and treatment options.

THE 21-GENE ASSAY: LOGISTICS AND COST

Currently, each tumour sample to be tested must be shipped to a centralized laboratory of the patent-holding company (Genomic Health, Inc.), located in California. An oncologist is required to request the assay and the regional pathology hospital staff must be versed with specimen procurement and shipment procedures, in order to ensure strict quality control and a standardized shipment process. For this entire procedure, which includes a charge of US\$ 3,700.00 per patient, Genomic Health successfully obtained a worldwide patent in 2005.

Recent US-based pharmacoeconomic analyses have shown that the RS-guided therapy, despite the upfront cost, provides a net cost savings. The savings are due to a substantially lower number of patients (i.e. 20–35%) receiving chemotherapy, and a higher overall survival rate due to the addition of curative chemotherapy to the 5% of high-RS patients, otherwise considered in the pre-RS testing practice for treatment with hormones alone.

The most comprehensive pharmacoeconomic analysis of the 21-gene assay is the report by Lyman et al showing several thousand dollars in savings per patient.^{8,9}

COST-BENEFIT ESTIMATES IN CANADA

According to the Annual Report Card of the Cancer Advocacy Coalition of Canada,¹³ the individual assay cost (after all Canadian system expenses are included) is estimated to be \$4,000 per patient. Assuming 1000 patients are eligible, the estimated cost will be \$4 million. However, there will be large savings expected from avoiding chemotherapy treatment in 25% to 35% of patients.

Assuming the cost of chemotherapy and support therapy is over \$15,000 per patient (not including indirect costs such as pharmacy and nursing staff, transportation, work absence, etc.), the direct savings of avoiding chemotherapy in 25% of breast cancer cases (i.e. 250 out of the 1000) is \$3.75 million/1000 patients, bringing the overall cost compared to the no RS approach to \$0.25 million.

If estimates are based on 35% chemotherapy avoidance due to low RS — a more realistic projection — then adjuvant therapy based on RS compared to empiric therapy, will save \$5.25 million/1000 eligible cases, due to avoided chemotherapy. This would make the introduction of 21-gene assay a profitable guideline recommendation, with Canadian taxpayers expected to save \$1.25 million/1000 patients tested.

WHY IS THE 21-GENE ASSAY NOT WIDELY AVAILABLE IN CANADA?

The concern over potential false results is important. One cannot justify denying curative therapy because of unreliable test results. Current concerns might be attributed to the fact that the test is relatively new, with only five years of experience to draw on. Undoubtedly, more research and experience are required.

The existing level of evidence provides reassurance for patients with low RS that their cancers can be cured. However, the emphasis is on the fact that the main benefit will be derived from hormonal therapy and not from chemotherapy.


An editorial in the December 2009 *Lancet Oncology* expressed it succinctly:

“... the consistency across [the 21-gene assay] studies suggests that there is little risk of falsely concluding that there is no chemotherapy benefit in patients with low recurrence score.”

Unlike the ER and Her2/Neu assays which are performed in multiple laboratories, the 21-gene assay is centralized in one laboratory. This means that patients' tumour samples are procured under protocol guidelines that not only involve complex gene testing, but also the shipment of human samples to the laboratory. While this may contribute to a fiscal monopoly, it also ensures quality control, including expertise and reproducibility — both essential attributes of laboratory conditions for cancer biomarkers.

SUMMARY

These data indicate that the 21-gene assay is emerging as an affordable and cost-beneficial intervention for all eligible patients (i.e. those who are ER positive and who are candidates for adjuvant therapy). For the many Canadians presently

undergoing adjuvant chemotherapy, this test may enable a hormone-alone option thus avoiding chemotherapy and its associated side effects. While the upfront cost of the 21-gene assay is presently perceived as high, the savings from avoided chemotherapy may entirely offset the upfront costs. Importantly as well is the beneficial impact on quality of life for thousands of Canadian patients (with low RS) who may avoid the toxicity of chemotherapy for the same outcome with hormone-alone treatment. Thus, the policy of not funding the 21-gene assay in Canada for eligible cases requires urgent reassessment. 

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Disclosure

The author reports no potential conflicts of interest pertaining to this article.

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