

THE 21-GENE ASSAY: Impact on breast cancer in Canada

ETHICALLY AND ECONOMICALLY WHEN DO WE ACT?

by JOSEPH RAGAZ

The 21-Gene Recurrence Score Assay

Between 2001–2003 Paik and others, from a US-based multi-institutional clinical trials group (the NSABP) that includes many Canadian centres, developed an assay to identify 21 genes from tumour samples that collectively significantly predicted patients' outcomes (recurrences, breast cancer deaths, and response to chemotherapy).¹

The 21-gene assay was based on advances in genetic techniques, refining the molecular significance of related genes to produce a “portrait” of tumour or “tumour signature” reflecting tumour biology and risk of relapse.^{2, 3} An algorithm was developed defining a Recurrence Score (RS) based on the various constellations of the 21 genes isolated from the tumour sample. RS was expressed as low (RS<18), medium (RS=18-30), or high (RS>31).

Overall, it was shown that among node negative breast cancer patients with positive estrogen receptors, 51 per cent had a low RS, 22 per cent a medium, and 27 per cent a high RS. More recently, data became available for node positive patients, and among those, close to 40 per cent had low RS (Albain et al.7).

According to the 2004 pivotal analysis, if the RS was low, patients relapsed significantly less often than patients with intermediate or high RS. The rates of distant recurrence at 10 years were respectively 6.8 percent, 14.3 percent, and 30.5 per cent.

The 21-Gene Assay as a Prognostic Biomarker

In 2005, Genomic Health Inc. obtained a world-wide patent for a centralized 21-gene assay (Oncotype Dx). That year, the TailorX clinical trial was initiated, which tested the effect of chemotherapy versus no chemotherapy in the intermediate-RS group. Patients of Canadian oncologists participated in this trial.

Also in 2005, the 21-gene assay was approved by the US Food and Drug Administration (FDA) and has been used increasingly throughout the US. In 2007, the expert panels of both ASCO and NCCN recommended the 21-gene assay as evidence-based. Since then, in most parts of USA, the Oncotype Dx testing became routine care for all node negative breast cancer patients whose tumours tested positive for hormone receptors.^{4,5}

In parallel with the 21-gene assay developments, European researchers identified 70 genes which were considered the most relevant for breast cancer, and labelled as the “Amsterdam 70-gene breast cancer gene signature”.³

Validation of the 70-gene assay also showed a strong correlation with breast cancer relapse. Low-risk patients had 87 per cent 10-year metastatic-free survival, while only 44 per

cent of high risk patients were free of metastases at 10 years. This microarray assay has been designated the MammaPrint test and was approved by the US FDA in 2007 as an alternative molecular gene assay for use in lymph node negative breast cancer patients under 61 years of age with tumours equal to or less than 5 cm.

The 21-Gene Assay as a Predictive Biomarker for Chemotherapy Effect

A further series of evaluations⁶ showed that the 21-gene assay would not only be prognostic for recurrences, but also predicted the impact of chemotherapy and chemotherapy ineffectiveness. Specifically, chemotherapy benefit was restricted to patients with high-RS, while cases with low-RS, despite having other clinical features of higher risk, had virtually no benefit from chemotherapy. (Table 1).

In December 2009, *Lancet Oncology* published a confirmatory study⁷ of breast cancer patients who had positive involved axillary nodes.

As in the node negative cases, there was also no chemotherapy benefit documented in this node positive cohort if RS was low, despite the much higher risk group, and a more standardized intensive chemotherapy regimen which included anthracyclines.

New Paradigm Established

The introduction of genetic analyses is heralded by many scientists as a turning point for cancer management with a new paradigm established. Attention is shifting from risk-assessment based on the “anatomical-geographical” extent of tumour spread—the long-accepted Tumour, Nodes, Metastases (TNM) criteria—to one based on molecular functional tumour biology, as represented by 21-gene assay biomarker test. Thus, the molecular expression is emerging as the prime method for determining both risk assessment and treatment options.

Logistics and Cost

Currently, each tumour sample to be tested must be shipped to a centralized laboratory of the patent-holding company in Redwood, California. They receive specimens from around the world, and no other laboratory is in position to perform the test. The test costs \$3,700 per sample.

The referring oncologist must request the assay, and the regional pathology hospital staff is required to be versed in specimen procurement and shipment procedures, in order to send the representative portion of patients' tumours with strict quality control, through a standardized shipment process to the designated laboratory.

Recent US-based pharmacoeconomic analyses have shown that the RS-guided therapy, despite the upfront cost, provides a net cost savings compared with the therapeutic strategy without the assistance of the 21-gene assay.

The savings are due to:

- a substantially lower number (20-35 per cent) of patients receiving chemotherapy;
- a higher overall survival rate due to the addition of curative chemotherapy to the five per cent 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.^{8,9} The cost-effectiveness ratio of adjuvant therapies of early breast cancer favours the RS-guided therapy strategy. The cost for one year of life saved (life-year saved, LYS) using the RS-guided approach, was shown to be substantially less, at \$16,162 compared to empirical planning of chemotherapy and tamoxifen at \$18,418 treatments.

RS-guided therapy strategy was found to be more expensive for low-cost chemotherapy regimens not requiring additional supportive care, whereas it was most cost-effective for standard adjuvant chemotherapy regimens which included anthracyclines, taxanes, and dose-dense approaches requiring supportive therapy, because of the larger savings.

The authors indicated that the cost saving figures provided for RS-guided therapy were probably underestimates, because they did not take into account other indirect savings related to not treating the 20-35 per cent low-RS patients, such as drug administration costs, professional fees, laboratory testing, and the costs of complications. In addition, their model did not consider additional indirect costs associated with transportation, loss of work productivity and out-of-pocket expenses. Therefore, it is highly likely that additional savings from a societal perspective would be associated with the RS-guided therapy strategy.

How Has the 21-Gene Assay Affected Oncology Practice In the US?

In one of the first reports on practice changes related to utilization of 21-gene assay, Erb et al. at the University of Pennsylvania compared more than 1,200 patients diagnosed in 2003, before the practice of the 21-gene assay had begun, with similarly matched node negative ER positive patients from 2005–2006, after the RS had been introduced. Between the two time periods, the indication for adjuvant chemotherapy had dropped by 30 per cent, from 55 per cent to 25 per cent.⁹

More recently, Lo et al. evaluated a similar population of patients and recorded that 22.5 per cent of oncologists had switched the recommendation from chemotherapy plus hormones to hormones alone, due to low RS.¹⁰

The most recent evaluation of node positive ER positive patients assessed before and after the era of the RS score availability, found that, of the 89 cases planned for chemotherapy plus hormonal therapy, 48 patients (35 per cent) had been changed to hormones alone, as a result of testing with the 21-gene assay.¹¹

Overall, with an increasing utilization trend since the assay was introduced, the change from chemotherapy plus hormones to hormones alone has been recorded among 20–35 per cent of cases.

With more than 220,000 breast cancer cases diagnosed annually in USA, these estimates may currently represent over 20,000 American breast cancer cases each year. The figures will probably increase, based on the additional information on node positive ER positive cases,⁷ information that first became available in late December 2009. In those, close to 40 per cent of patients had a low-RS (indicating there would be no benefit from chemotherapy), yet at the present time all are candidates for adjuvant chemotherapy.

As seen from the post-RS decision-based analyses,⁹⁻¹¹ most US-based oncologists are willing to forgo chemotherapy for node negative cases if low RS is seen, and increasingly, also for low risk node positive cases. Currently, the majority of US

TABLE 1

SURVIVAL FREE OF DISTANT RECURRENCE according to the 21-gene assay recurrence score (RS) among node negative ER+ breast cancer patients treated with Tamoxifen alone (Tam alone) vs Tamoxifen plus CMF-based Chemotherapy (CT + Tam). (According to Paik et al¹)

#RS	Tam alone	CT + Tam	Abs difference %	RR*	"P"
All Pts (651, 100%)	87.8%	92.2%	+ 4.5%	0.67	0.003
Low RS (352 pts, 54%)	96.8%	95.6%	- 1.2%	1.31	n.s.
Medium RS (134 pts, 20.6%)	90.9%	89.1%	+ 1.8%	0.61	n.s.
High RS (164 pts, 25.2%)	60.5%	88.1%	+ 27.6%	0.26	<0.001

#RS = Recurrence Score of the 21-gene assay

Abs%: Difference in Absolute per cent. The "+" sign= increased survival and the "-" sign= reduced survival

*RR = Relative Risk. If RR>1.0 chemotherapy has no impact; if RR is <1.0 chemotherapy has benefit for the patient; if RR>1, the patient outcome is worse from chemotherapy.

"P" = statistical measure of significance of the RR; if P is < 0.05 then the observation is significant; if P>0.05 then the observation is not significant (n.s.)

These very conservative estimates mean that it would cost the health system \$0.25 million to test 1,000 breast cancer patients and protect 250 of them from the toxicity, risks and wasted time of chemotherapy that will not help them.

At the moment, it is costing these same breast cancer patients \$3,700 of their own money to discover if they can avoid chemo and save their government \$15,000.

insurance companies cover the cost of the assay. Thus, the 21-gene assay is available to virtually all US breast cancer patients who are node negative and, recently, also to the low risk node positive cases, if estrogen receptor positive.

Has the 21-Gene Assay Affected Oncology Practice in Canada?

Apart from the TailorX trial (studying the impact on therapy of testing patients with intermediate RS), the practice of most Canadian oncologists has not been influenced by the 21-gene assay information, with chemotherapy indications for node negative patients not changing appreciably.

No institution in any of the Canadian provinces consistently covers the cost of the assay, although, most recently, as a result of mounting pressures, some patients with a strong oncologist advocate have had the 21-gene assay cost covered by their provincial health care plan, but this is an exceptional event. In the last few weeks, patients in Ontario can be covered by the “Out-of Country Health Services” branch of the health ministry, if requested by an oncologist and approved in advance.

In the years 2007–9, a total of 121, 309, and 392 Canadian breast cancer patients had the 21-gene assay as part of the TailorX trial (fully funded). However, in the same years, only 29, 39, and 72 respectively, had their tests ordered outside of the TailorX trial.¹²

This compares to an estimated 10,000 patients in Canada, annually, who, according to the present ASCO/NCCN guidelines, would have been eligible for the 21-gene assay each year. If the group of node positive hormone positive cases is added, the numbers would increase by several thousand more each year.

Cost Benefit of the 21-Gene Assay in Canada

The assay cost, after all health system expenses are added, is estimated at \$4,000 per patient (Table 2). Assuming a low range of 6,000 node negative cases per year are eligible for the 21-gene assay test, the estimated cost to test them is \$24 million annually.

However, there will be large savings from at least 25 per cent of patients (1,500 cases) avoiding chemotherapy. Assuming the cost of chemotherapy and support therapy per patient to be more than \$15,000 (not counting indirect cost such as pharmacy and nursing staff, transportation, work absence, etc.), the offset saving is \$22.5 million.

This relatively low overall cost renders the 21-gene assay a highly affordable and cost-beneficial intervention for all eligible patients (Table 2). If we assume that the low risk node positive cases are included, and that Canadian oncologists will become comfortable not treating the low RS cases with chemotherapy, there will be a further cost savings in Canada annually. This is, after all, what most American pharmacoeconomic analyses indicate.

Until recently most oncologists in Canada considered that the adoption of the 21-gene assay results may be premature, and not cost-beneficial within in the Canadian system. However, as a result of the recent publications as outlined in this report, an increasing number of Canadian oncologists indicate that they would utilize the 21-gene assay if it were funded.

Recent approval instances by the Ontario Health Insurance Plan (OHIP) are encouraging, with approvals on a patient-by-patient basis, but only if all the paperwork is submitted by the oncologist before the test is ordered. While this process is not optimal, in the short run, it provides an avenue for Oncotype Dx assay to be reimbursed for eligible patients.

Why Is This test Not Widely Available in Canada?

A genuine concern over false results must be rated as important. Nothing can be justified if curative therapy is denied because of unreliable results.

Present doubts might be attributed to the fact that the test is relatively new, with only five years of experience to draw from, and more research in this arena is required.

But reluctance to accept evidence, or an expectation of guarantees that do not exist in human judgement, does not help cancer patients.

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.”

Most therapeutic decisions in other areas of medicine are based on laboratory or histological assessments with identifiable margins of error. While quality control (QC) and standardized testing procedures have been increasingly more rigorously applied by healthcare professionals, errors of judgement may still occur.

Laboratory analysis of estrogen receptors and Her2/Neu assays have contributed to better outcome of breast cancer and have been approved, incorporated into guidelines, and practiced by thousands of laboratories worldwide. Nevertheless, the quality control for these tests is not ideal. Despite decades of experience, errors have been recorded in five to 10 per cent of all ER or Her2/Neu cases, largely due to the non-standardization of testing and subjectivity of reporting.

Unlike the ER and Her2/Neu assays performed in multiple laboratories, the 21-gene assay is centralized in one laboratory. This means that patients’ tumour samples are procured under strict protocol guidelines which not only involve the complex gene testing, but also the shipment of human sam-

TABLE 2

ESTIMATED COST-BENEFIT OF THE 21-GENE RECURRENCE SCORE

One year; 1,000 newly diagnosed Estrogen Receptor (ER) positive cases who are candidates for adjuvant chemotherapy (CT), with or without using the test. Showing a conservative avoidance rate of 25% and a more realistic avoidance rate of 35%.

Cost per 1000 cases	No RS	With RS	
		CT avoidance rate:	
		25%	35%
CT	\$15M	\$11.25M	\$9.75M
21 gene assay	–	\$4M	\$4M
Total	\$15M	\$15.25M	\$13.75M
Difference compared to No RS		+\$0.25M	-\$1.25M

- At an avoidance rate of 25%, it would cost the health system \$0.25 million per 1,000 breast cancer patients to protect 250 women from unnecessary chemotherapy.
- At an avoidance rate of 35%, the health system will gain \$1.25 million per 1,000 breast cancer patients to protect 350 women from unnecessary chemotherapy.

ples to the laboratory. While this may perpetuate a fiscal monopoly, it also maximizes a centralized approach, with expertise and reproducibility—both essential attributes of laboratory conditions for cancer biomarkers.

Conclusions

Annually, more than 1,500 Canadians, and likely many more, receive chemotherapy for breast cancer that may not be needed. With the 21-gene assay these patients could avoid chemotherapy, and its associated side effects of hair loss, nausea, vomiting, immunosuppression, and occasionally leukemia or even drug-induced death.

Arguably, one must accept some side effects of chemotherapy, and likely all of them, when benefits are evidence-based. In such instances, lives are saved and side effects are acceptable on medical, psychological, and fiscal grounds. However, should there be a lack of benefits, then the side effects are neither medically nor ethically acceptable.

In summary, progress in cancer management is being achieved, even in quantum leaps, yet for many patients and their families, access to discovery is slow. We are extremely fortunate to have witnessed these advances, expressed in a steep breast cancer mortality decline in the last decade, no doubt as a result of these innovations. However, the full impact these innovations will materialize only when they are effectively and flexibly transferred to practice.

Recommendations

Patient participation in randomized trials for the testing of biomarkers remains an essential aspect of an ongoing service, however the evolving 21-gene assay guidelines deserve special recommendations.

For node negative breast cancer cases:

- Incorporate into guidelines and fund the 21-gene assay for all newly diagnosed node negative breast cancer cases that meet the current ASCO and NCCN guidelines.

For node positive breast cancer cases:

- Oncology Guidelines should be prepared for Canadian

oncologists to determine the criteria for using the 21-gene assay—e.g., all newly diagnosed cancer cases where there is a reasonable chance that chemotherapy may not be required i.e., all ER positive, less than four axillary nodes involved, Her2/Neu negative, good grade, etc.

- As for node negative cases, the 21-gene assay should be funded for all node positive cases found eligible for a “no chemotherapy option” i.e., those with ER positive, Her2/Neu negative, good grade tumors.

For all applicable cases:

- Guidelines must articulate a policy regarding the best practice, and optimum standard of care when the 21-gene assay indicates a patient will not benefit from chemotherapy. Oncologists require clarity and consensus on this question in order to adapt to the 21-gene assay and act in the best interests of their patients.

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