

PART 2

# The 21-Gene Assay

## CANADA'S UNEVEN RESPONSE

By JOSEPH RAGAZ, MD, FRCPC

In 2010, the first part of this series<sup>1</sup> reported that the 21-gene assay recurrence score (RS), when used at the point of diagnosis of breast cancer, can predict the effectiveness of adjuvant chemotherapy in reducing cancer recurrence more accurately than any known biomarker.

Adjuvant chemotherapy is one of the key factors responsible for decreasing breast cancer mortality in the western world. The Oxford-based Early Breast Cancer Trialists' Collaborative Group conducted a review of all randomized trials over the last 20 years, documenting the benefit of adjuvant chemotherapy in reducing recurrences and mortality by 25-30 per cent<sup>2</sup> according to subsets.

However, the benefits of adjuvant therapy are not guaranteed. The molecular classification of the tumour specimen based on the 21-gene assay RS is a vital tool to distinguish those who will have considerable benefits from those who may derive less, or no benefit, from standard chemotherapy.

On a scale of one to 100, a score less than 19 predicts little or no benefit, while a score of 30 or more indicates a very high impact of adjuvant chemotherapy, reducing recurrences by 50-70 per cent. Scores between 19-30 are less clearly predictive, but answers are expected shortly from the recently completed TAILORx trial, which compared the impact of chemotherapy or no chemotherapy in this intermediate group.

The RS score creates an opportunity for physicians to spare cancer patients from any unnecessary toxicity and side effects of chemotherapy. Anyone, especially cancer patients, would wonder why that step is not automatically in place, pursued with enthusiasm. Perhaps the learning curve in Canada is not what it should be.

Since 2007, the American Society of Clinical Oncology (ASCO) and the U.S. National Comprehensive Cancer Network (NCCN) guidelines have recommended that the 21-gene assay (Oncotype Dx) be part of the routine management for early stage breast cancer patients with hormone receptor positive tumours.

However, until 2009, this test was virtually unavailable in Canada outside clinical trials. If the test were more widely used in Canada it could facilitate the avoidance of thousands of rounds of unnecessary, toxic chemotherapy in the sizable patient subset with low RS.

Since our report last year, two Canadian studies have shown the rising value of molecular classification with the 21-gene assay,<sup>3,4</sup> with one of them concluding, "The 21-gene assay appears cost-effective from a Canadian health care perspective."<sup>4</sup>

With data mounting on the benefit of using the 21-gene assay, Canadian provinces have responded as follows:

- British Columbia began a registration study for the 21-gene assay in 2010. However, it is restricted to node negative cases and until recently was active only in the Vancouver clinic.
- Ontario started funding the 21-gene assay more consistently, using an OHIP provision for out-of-country health services, which requires an application by the oncologist and prior approval from the health ministry.
- In the last few months, Quebec's RAMQ has started funding an increasing number of 21-gene assay tests.

Table 1 shows the trend of increased use of the 21-gene assay in Canada since 2007.

A significant increase occurred in the number of tests ordered between 2009 and 2010, from 464 to 962. Also, more recently, the medical advisory secretariat to Ontario's Ministry of Health and Long-Term Care drafted an in-depth analysis and recommendations regarding the 21-gene assay test, basically approving the use of the test for newly diagnosed node negative breast cancer patients with estrogen receptor (ER) positive tumours.<sup>5</sup>

While these are positive trends, there is still massive under-utilization of this predictive tool in Canada. Research data show that of all ER positive tumours more than half will have low RS, whether node negative or node positive. Thus, the test could be used for all node negative and the low risk node positive cases if they are ER positive (70 per cent of all diagnosed) and candidates for chemotherapy (65 per cent of those). Thus, out of the 22,000+ newly diagnosed with new breast cancer each year in Canada, at least 10,000 women

TABLE 1  
**NUMBER OF 21-GENE ASSAYS PER YEAR IN CANADA 2007-2010**

Year	Breast cancer patients tested
2007	150
2008	348
2009	464
2010	962

Source: Feb 2011 updates, Genomic Health Database

TABLE 2  
**RECURRENCE SCORES OF CANADIAN PATIENTS  
2007–2010**

Score	Node Negative Cases		Node Positive Cases		Total Cases	
	Number of Patients	Per Cent	Number of Patients	Per Cent	Number of Patients	Per Cent
Low (< 19)	1,029	55.03%	29	55.77%	1,058	55.05%
Intermediate (19–30)	654	34.97%	18	34.62%	672	34.96%
High (>30)	187	10.00%	5	9.62%	192	9.99%
<b>Totals</b>	<b>1,870</b>	<b>100%</b>	<b>52</b>	<b>100%</b>	<b>1,922</b>	<b>100%</b>

Source: Feb 2011 updates, Genomic Health Database

TABLE 3  
**ESTIMATED COST-BENEFIT OF THE 21-GENE  
RECURRENCE SCORE**

Based on one year, 10,000 newly diagnosed ER positive cases (i.e., those who are candidates for the 21 gene assay) and variable rates of avoiding chemotherapy.

\$ in millions

Cost Factors	Rate of Chemotherapy Avoidance			
	0 (no test)	25%	35%	50%
Cost of chemotherapy	\$150	\$112.5	\$97.5	\$75.0
Cost of 21-gene assay	\$0	\$40	\$40	\$40
Health system cost	\$150	\$152.5	\$137.5	\$115.0
Costs Added (+) or Saved (-) /10,000 cases	\$0	+ \$2.5	- \$12.50	- \$35.0

These estimates are based on \$4,000 for the test and a conservative estimate of \$15,000 per course of adjuvant chemotherapy, potentially avoided in 2,500, 3,500 or 5,000 patients.

would be eligible for the 21 gene assay test. Instead, in 2010, only 962 were done, representing approximately 10 per cent of eligible women.

The significance of not doing the molecular test at diagnosis on those who are eligible is considerable. Of the 10,000 cases eligible for the test each year, more than half (5,000/year) would be in the low RS category (Table 2).

Based on the available statistics from the most recent research,<sup>3,4</sup> chemotherapy in these patients will have only minimal or no effect on the recurrence rates. However, without the test, all 5,000 would be considered candidates for chemotherapy under present guidelines. If given the choice, this course of action should likely be avoided as the well known toxicity of chemotherapy can only be justified when the treatment benefits are documented more clearly.

Added to this are the cost benefits of adjuvant policy based on molecule classification, rather than the present empirical approach, using the 21 gene test to identify 5,000 women, of whom most, if not all, could avoid chemotherapy. The estimates of dollars spent versus dollars saved are based on the present practice, which still represents less than optimum use of the 21-gene assay. At one end of the spectrum, perhaps the ideal way, is the possibility that none of the low RS cases should have chemotherapy as very few, or none will benefit.

As the low RS occurred in more than 50 per cent of Canadians already tested, this represents a 50 per cent avoidance of chemotherapy costs (see Table 3). However, many, if not most oncologists confronted with a low RS would still prescribe the chemotherapy for what is considered in the conventional staging a high risk situation, such as large tumour, vessel invasion, nodes involved, etc. This would diminish the rate of avoidance to less than 50 per cent of all tested, e.g., 35 per cent or even 25 per cent.

If 50 per cent avoidance were achieved, representing a full compliance in withholding chemotherapy to all low RS cases, a substantial societal saving becomes possible, estimated to be \$35 million saved for every 10,000 tested. A smaller rate of avoidance of chemotherapy will lead to smaller savings, or even an extra cost.

These estimates are based on \$4,000. for the test and a conservative estimate of \$15,000. per course of adjuvant chemotherapy, potentially avoided in 2,500, 3,500 or 5,000 patients.

**DISCUSSION**

The data indicate that for node negative cases and likely also for the low risk node positive cases, the 21-gene assay could be used for all breast cancer patients with well differentiated, ER positive tumours, whenever adjuvant chemotherapy is potentially indicated, regardless of tumour size or vessel invasion. Once a low RS is doc-

## There is still massive under-utilization of this predictive tool in Canada.

umented, chemotherapy should not be given as incurring toxicity for minimum benefits is clearly unacceptable. If the RS is high, chemotherapy ought to be considered even if not originally planned; for intermediate RS cases, individualized decisions need to be made. This approach should become a guideline policy for treatment across Canada.

**Node positive cases.** Preparations are underway in the U.S. for a randomized trial of chemotherapy vs. no chemotherapy in node positive breast cancer cases where RS is low. Canadian participation is expected. This study will be required due to the present international policy of using chemotherapy in all node positive cases. This is still the case despite the study of Albain et.al.<sup>6</sup> showing little benefit from chemotherapy in low RS cases among node positive breast cancer patients, regardless of the number of nodes involved, exactly as was the case for node negative cases.<sup>7</sup> The chance of chemotherapy having a meaningful effect among low RS cases in the new study of node positive cases is understandably extremely low, posing a dilemma for prescribing chemotherapy to this cohort of patients, at least to some of the lower risk subsets (e.g., less than four nodes, those with focal nodal involvement only, etc.).

In addition, a related challenge to the present guidelines emerges for patients not participating in the above study: in all situations with low RS, chemotherapy may have to become the “experimental” option.

In summary, several key questions need consideration.

- Is it feasible to obtain, within a reasonable time, much higher levels of evidence in order to bring molecular classification with the 21-gene assay into guidelines? Reviewing the data, this approach seems unlikely, at least not for node negative and low risk node positive cases.
- Which is worse, over-treating large numbers of breast cancer patients with chemotherapy that we already know will be pointless yet toxic and immunosuppressive, or not treating a few who could receive a slight benefit?
- Can the medical establishment be more pragmatic about accepting the present data into practice guidelines more swiftly and yet continue research into unanswered questions?
- Should patients be informed about these issues and have their own input into pursuing the 21-gene assay and acting on the RS score, i.e., declining or accepting chemotherapy?

### Conclusion

At this point the 21-gene assay is the only validated test based on molecular classification to guide decisions for or against chemotherapy. Without it, the status quo of empirical approaches towards chemotherapy selection leads to considerable over-treatment with chemotherapy in a large number of low RS cases routinely planned for adjuvant chemotherapy, or in some cases under-treatment in cases with high RS not planned for adjuvant chemotherapy.

Unquestionably, more research is required to refine the molecular classifications for patients with cancer, especially the cost and comparability with surrogate markers. However, the data reviewed in this report document very low expectations of a meaningful benefit from adjuvant chemotherapy for breast cancer patients with low RS scores. If the 21-gene assay became a requirement in Canada, as part of routine policy for all eligible patients, we would see less cost, less toxicity and far less suffering on the part of most patients—and no less effective treatment. We have a choice to make.

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