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Cost-Effectiveness of the 21-Gene Assay for Guiding Adjuvant Chemotherapy Decisions in Early Breast Cancer

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ABSTRACT

Objectives: Adjuvant chemotherapy decisions in early breast cancer are complex. The 21-gene assay can potentially aid such decisions, but costs US $4175 per patient. Adjuvant! Online is a freely available decision aid. We evaluate the cost-effectiveness of using the 21-gene assay in conjunction with Adjuvant! Online, and of providing adjuvant chemotherapy conditional upon risk classification. **Methods:** A probabilistic Markov decision model simulated risk classification, treatment, and the natural history of breast cancer in a hypothetical cohort of 50-year-old women with lymph node–negative, estrogen receptor– and/or progesterone receptor–positive, human epidermal growth factor receptor 2/neu–negative early breast cancer. Cost-effectiveness was considered from an Ontario public-payer perspective by deriving the lifetime incremental cost (2012 Canadian dollars) per quality-adjusted life-year (QALY) for each strategy, and the probability each strategy is cost-effective, assuming a willingness-to-pay of $50,000 per QALY. **Results:** The 21-gene assay has an incremental cost per QALY in patients at low, intermediate, or high Adjuvant Online! risk of $22,440 (probability cost-effective 78.46%), $2,526 (99.40%), or $1,111 (99.82%), respectively. In patients at low (high) 21-gene assay risk, adjuvant chemotherapy increases (reduces) costs and worsens (improves) health outcomes. For patients at intermediate 21-gene assay risk and low, intermediate, or high Adjuvant! Online risk, chemotherapy has an incremental cost per QALY of $44,088 (50.59%), $1,776 (77.65%), or $1,778 (82.31%), respectively. **Conclusions:** The 21-gene assay appears cost-effective, regardless of Adjuvant! Online risk. Adjuvant chemotherapy appears cost-effective for patients at intermediate or high 21-gene assay risk, although this finding is uncertain in patients at intermediate 21-gene assay and low Adjuvant! Online risk.

Keywords: breast cancer, chemotherapy, cost-effectiveness analysis, decision making, pharmacogenetics.

Introduction

Adjuvant chemotherapy decisions for women with early stage breast cancer are complex. At present, decisions are informed by clinical judgment, often supplemented through the use of Adjuvant! Online [1]. Adjuvant! Online is a free online diagnostic tool that estimates a woman's risk of breast cancer–specific mortality (BCSM) or relapse on the basis of information entered by the physician, including the woman's age, comorbidities, tumor size, estrogen receptor status, number of involved lymph nodes, and proposed course of treatment [2]. Results can be categorized as "low" (BCSM $< 9\%$), "intermediate" ($9\% \leq$ BCSM $< 17\%$), or "high" (BCSM $\geq 17\%$) risk [3]. A validation study of Adjuvant! Online has found a high degree of correlation between predicted and observed survival [4].

An alternative predictive tool has recently become available. The 21-gene assay (Oncotype DX, Genomic Health, Redwood City, CA) quantifies the expression of 21 genes in breast cancer tissue by performing reverse transcription polymerase chain reaction on formalin-fixed paraffin-embedded tumor blocks that are obtained during initial surgery. Results are summarized by a "Recurrence Score" (RS) between 0 and 100, with scores categorized as "low" (RS < 18), "intermediate" ($18 \leq$ RS < 30), or "high" (RS ≥ 30) risk [5]. It has been validated both in women with estrogen receptor–positive early stage breast cancer that is lymph node–negative, and in women with estrogen receptor–positive breast cancer that is lymph node–positive, as a means to predict the risk of distant recurrence and magnitude of chemotherapy benefit when added to endocrine therapy [6–9].

As of April 2012, the 21-gene assay cost US $4175 per patient [10]. Its cost-effectiveness is therefore a matter of considerable policy interest. There is also uncertainty as to the clinical- and cost-effectiveness of providing adjuvant chemotherapy, particularly to patients at intermediate risk [11,12]. We present a cost-effectiveness analysis that comprehensively addresses both these issues. An earlier version of our analysis formed part of a

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recent review of gene expression profiling tests carried out by the Ontario Ministry of Health and Long-Term Care [13].

Methods

Overview

We conducted a cost-effectiveness analysis from the perspective of the Ontario Ministry of Health and Long-Term Care. The analysis had two objectives:

1. To evaluate the outcomes, costs, effectiveness, and cost-effectiveness of the 21-gene assay, when used in conjunction with Adjuvant! Online.
2. To evaluate the outcomes, costs, effectiveness, and cost-effectiveness of providing adjuvant chemotherapy, conditional upon a patient's predicted risk of distant recurrence.

The patient population was a hypothetical cohort of 50-year-old women diagnosed with lymph node–negative, estrogen receptor– and/or progesterone receptor– positive, human epidermal growth factor receptor 2 (HER2/neu)–negative early breast cancer, who are candidates for adjuvant chemotherapy. The cohort was followed over a lifetime. Costs were measured in 2012 Canadian dollars, and a discount rate of 5% was applied to costs and outcomes [14]. The analysis was conducted in April 2012.

We conducted our analysis in consultation with an expert panel convened by the Ontario Ministry of Health and Long-Term Care [15]. The expert panel provided input on the appropriate model structure and parameters.

Model

The model is described in Figure 1. The structure was informed by an existing model by Tsoi et al. [16]. Patients were first stratified by Adjuvant! Online risk group. Each Adjuvant! Online risk group might then be provided with the 21-gene assay; if provided, the respective Adjuvant! Online risk group was further stratified by 21-gene assay risk group. This resulted in patients being assigned to 1 of 12 risk categories (see Fig. 1 legend). All patients were then assumed to undertake adjuvant tamoxifen treatment for 5 years, with some patients also receiving adjuvant chemotherapy. Higher risk patients were assumed to receive more complex chemotherapy regimens, as detailed below. All chemotherapy patients risked toxicity requiring hospital treatment. Patients were initially assumed to be distant recurrence free, but risked developing a distant recurrence over their lifetime. All patients eventually died, either because of breast cancer or for other reasons. The model was developed by using TreeAge Pro 2009 (TreeAge Software, Inc., Williamstown, MA), Microsoft Excel 2010 (Microsoft, Seattle, WA), and WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

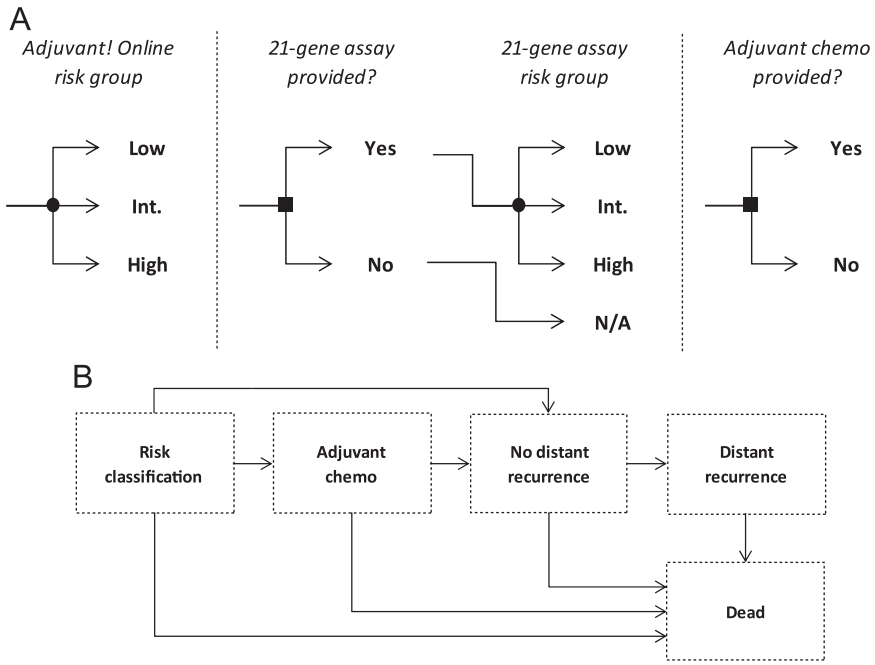

Fig. 1 – Model schematic. (A) Decision tree representing the risk classification process and adjuvant chemotherapy decision. Decision nodes are represented by squares, while chance nodes are represented by circles. The decision about whether to provide the 21-gene assay is made independently for each Adjuvant! Online risk group. The 21-gene assay stratifies patients into three possible risk groups when provided ("low," "int.," and "high") or one possible risk group when not provided ("N/A"). Because patients in the N/A risk group face a different risk of distant recurrence to patients in any of the low-, int.-, and high-risk groups, the model considers four unique risk groups resulting from the decision to provide or not provide the 21-gene assay. Because patients in any one of the three Adjuvant! Online risk groups may be assigned to any one of the four 21-gene assay risk groups, the model assigns each patient to 1 of 12 (3 × 4) unique risk "categories." Each risk category represents a unique combination of the Adjuvant! Online and 21-gene assay risk groups. The adjuvant chemotherapy decision is considered independently for each of the 12 risk categories resulting from risk classification. (B) Markov model representing patients' progression through risk classification and the possible provision of adjuvant chemotherapy, possible distant recurrence, and death. Int., intermediate; N/A, not available.