

Technology evaluation criteria – how coverage decisions are made

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Priority Health
September 18, 2006



The process of determining coverage

- Technology assessment
- Demand
- Alternatives
- Medical benefit



What is Technology Assessment?

- Review and evaluation of new procedures, devices, treatments, prevention strategies
- New application of existing technology
- Outcome: coverage decision
- Experimental exclusion
- NCQA requirement

TA Process

- Formal and Informal
- Reactive and Proactive
- Research and Resources



TA Resources

- Medical Literature
- Other payors
- Technology Assessment Vendor: Hayes, Inc.
- Professional Organizations
- Regulatory Guidelines

Technology Assessment Committee (TAC)

- Quarterly meetings
- Advisory role
- Composition

TAC review



- Background – general topic overview
- Literature review
- Indications / contraindications
- Alternatives / Stnd of Care
- Risks / Benefits
- Professional org. statements
- Outside review agencies
- Regulatory guidelines
- Other payers
- Clinical trials
- Cost analysis / legal issues

TA Topic examples

- Carotid Artery Stenting
- Lap Band for Obesity
- Artificial Intervertebral Discs
- Fecal DNA analysis
- Endoscopic treatments for GERD

Gene Expression Profiling

Predicting breast cancer recurrence
September 9, 2005



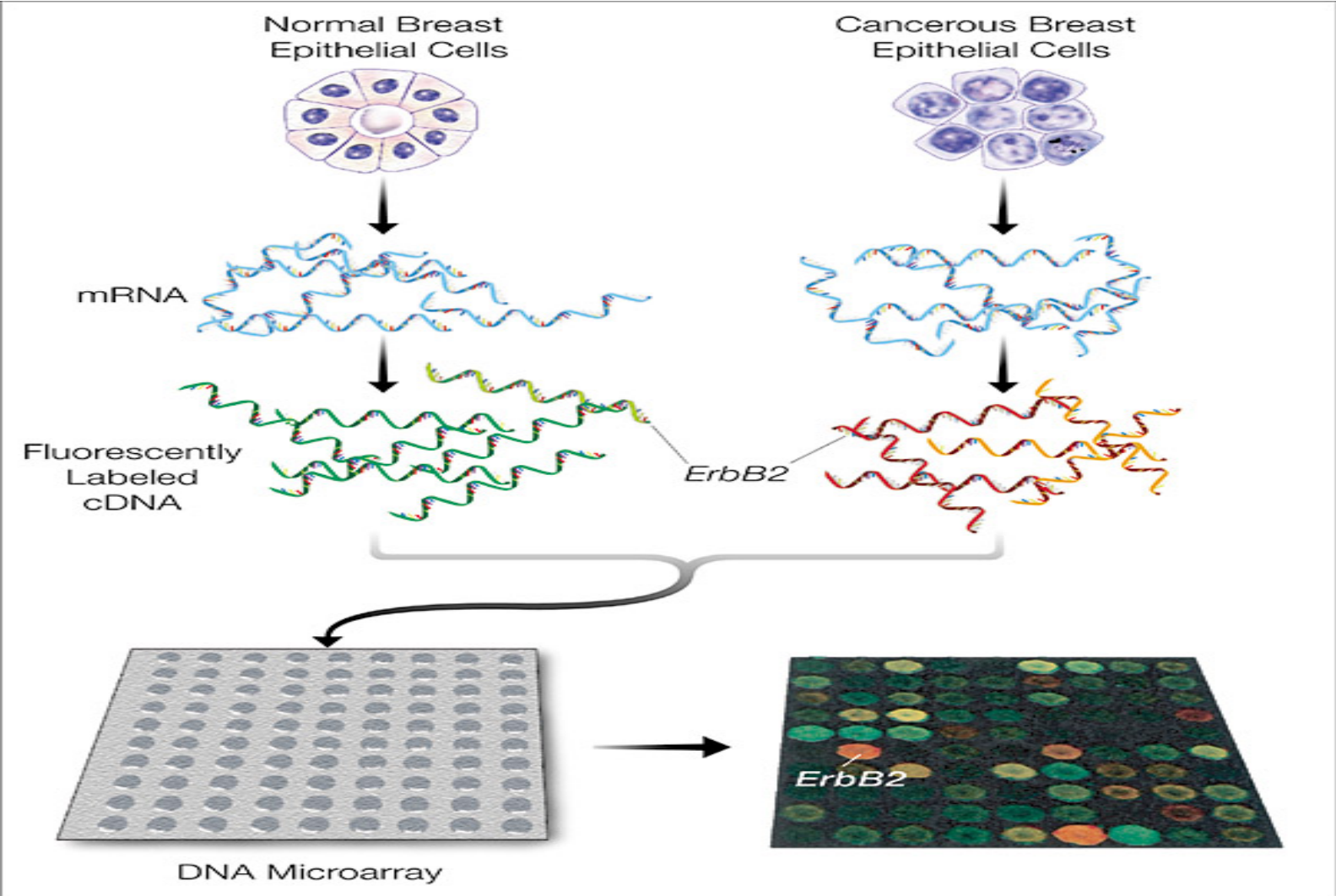
Gene Expression

- **Gene expression** (also **protein expression** or often simply **expression**) is the process by which a gene's information is converted into the structures and functions of a cell.
- The amount of protein that a cell expresses depends on the tissue, the developmental stage of the organism and the metabolic or physiologic state of the cell.

Expression Information

- Expression is one of the first things you might want to look at in things like a diseased tissue or tumor; what proteins are now being made that a healthy cell/tissue doesn't make or what proteins aren't being made that were being made before

Use of DNA Microarray to Detect Differences in Gene Expression in Normal vs Malignant Breast Epithelial Cells



What do we want to know?

- Is a gene specific to a cell or tissue?
- Is a gene expressed more in one place than another?
- What set of genes might be expressed at the same time?
- Does expression change when I try a specific treatment (drug, heat, etc?)

Gene Expression Profiling for Managing Breast Cancer Treatment



- Recently, several groups have identified panels of gene expression markers that appear to predict the likelihood of breast cancer recurrence in various populations of women with node-negative disease.
- These panels may be useful for identifying women who are unlikely to experience recurrence and, thus, unlikely to benefit from adjuvant chemotherapy.
- If validated for clinical utility, such panels could be used to identify women who can safely avoid adjuvant chemotherapy, without negatively affecting disease-free and overall survival outcomes.

Approval from the appropriate governmental regulatory bodies.



- There are no assay kits approved by the U.S. Food and Drug Administration (FDA) for gene expression analysis of breast tumor tissue, nor are any kits being actively manufactured and marketed for distribution.
- Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).
- The laboratory offering the service must be licensed by CLIA for high-complexity testing.
- While the FDA has technical authority to regulate home-brew tests, there is currently no active oversight nor any known plans to begin such oversight.

The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.



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Key Question 1:

- **In women with early stage, node-negative breast cancer, can gene expression profiling predict which patients will benefit from adjuvant chemotherapy?**
- **Will the results of gene expression analyses change management decisions and safely avoid unnecessary chemotherapy and toxicity without adversely affecting disease free or overall survival outcomes?**

4 different gene expression profiling assays that are intended to help identify those patients at low risk of breast cancer recurrence for whom post-surgery adjuvant chemotherapy can be safely avoided. These assays are:

- Oncotype DX™ (21-gene panel; Genomic Health);
- MammaPrint® (70-gene panel; also referred to as the “Amsterdam signature;” Agendia);
- a 76-gene panel (also called the “Rotterdam signature”; Veridex);
- a 41-gene panel reported in Germany.

Using current, traditional clinical and histopathological criteria, most patients are selected for adjuvant chemotherapy. However, as exemplified in the tamoxifen-only treated arm of the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-20, for which the 10-year distant recurrence rate was 83%, only a small proportion of patients can benefit from adjuvant chemotherapy. Thus, it is likely that a significant number of women could safely avoid chemotherapy and its adverse effects if more accurate selection methods were available.

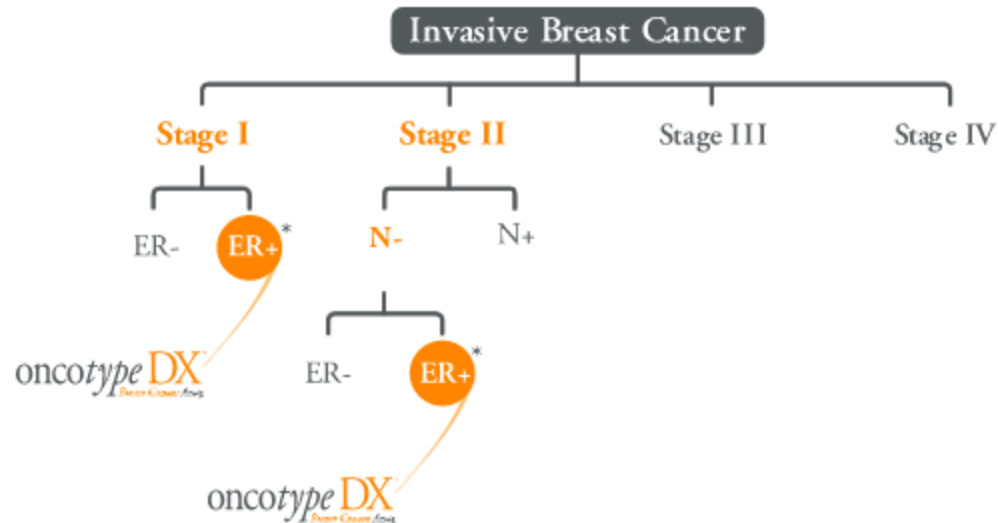
Development of panels

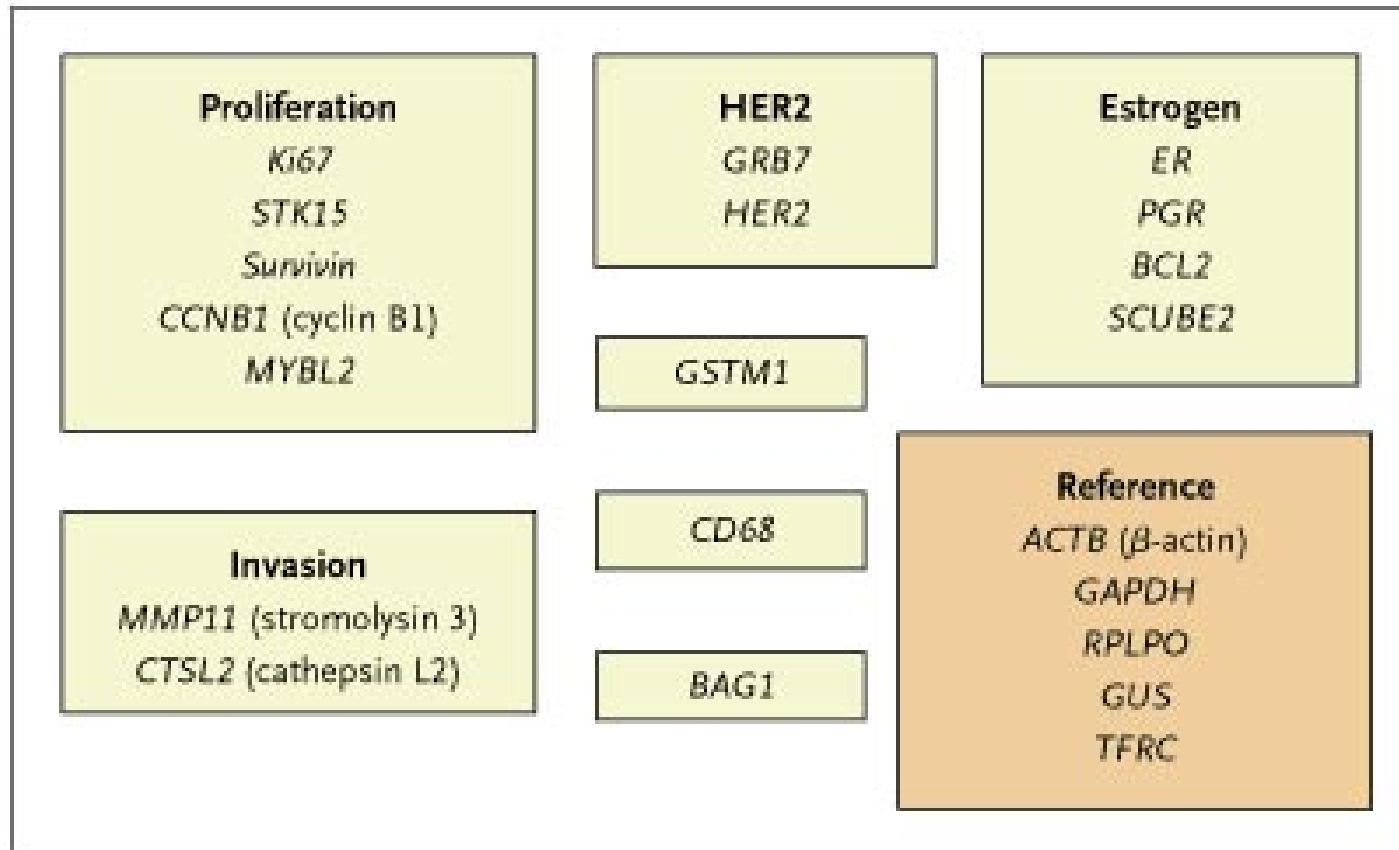
- The 4 panels were developed and tested on banked tumor tissue from different sub-populations of women with early stage breast cancer, varying according to nodal involvement, estrogen receptor positivity, patient age, and use of tamoxifen;
- Results from one panel are not generalizable to the patient populations of the other panels, nor to the totality of early stage breast cancer patients.

Onco^{type} DX™

- The assay — performed using formalin-fixed, paraffin-embedded tumor tissue — analyzes the expression of a panel of 21 genes and the results are provided as a Recurrence Score™ (0-100). The gene panel was selected and the Recurrence Score calculation was derived through extensive laboratory testing and multiple independent clinical development studies.

- *Oncotype DX* is validated for use in breast cancer patients whose disease is:
 - Newly diagnosed
 - Stage I or II
 - Node-negative
 - Estrogen receptor-positive
- and who will be treated with tamoxifen.





Paik, S. et al

Oncotype Dx con't

- Based on the levels of gene expression detected by the Oncotype assay, patients are assigned a Recurrence Score from 0 to 100, in which a higher score indicates a greater risk of recurrence.
- Several clinical applications are proposed for this Recurrence Score, but the current research is focused on its use in determining the best course of adjuvant treatment for women with estrogen receptor–positive, lymph node–negative breast cancer that is amenable to complete surgical resection.
- Clinical trials are underway to determine if the Recurrence Score correlates with the magnitude of benefit conferred by adjuvant chemotherapy, such that those patients receiving hormonal therapy to reduce their risk for breast cancer recurrence who are unlikely to achieve improved outcomes with added chemotherapy may be spared the subsequent treatment.

Study Design and End Points

- determine whether the proportion of patients who were free of a distant recurrence for more than 10 years after surgery was significantly greater in the low-risk group than in the high-risk group
- determine whether there was a statistically significant relation between the recurrence score and the risk of distant recurrence (beyond the standard measures of the patient's age and the size of the tumor).

Paik S, Tang G, Shak S, et al.

Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol.

2006 May 23

- Of the 651 women for whom adequate archived tissue samples were available for testing with the Oncotype DX, 353 scored at low risk, 134 scored at intermediate risk, and 164 scored at high risk.
- Overall, 10-year rates of distant recurrence did not significantly differ between patients treated with tamoxifen plus chemotherapy and those given tamoxifen alone.
- Among high-risk patients however, the added chemotherapy significantly reduced risk for distant recurrence by an absolute 27.6% compared with tamoxifen alone.
- Conversely, patients in the low-risk category randomized to received the additional chemotherapy did no better than those treated with tamoxifen alone.
- It was unclear if patients in the intermediate-risk category benefited from the added chemotherapy

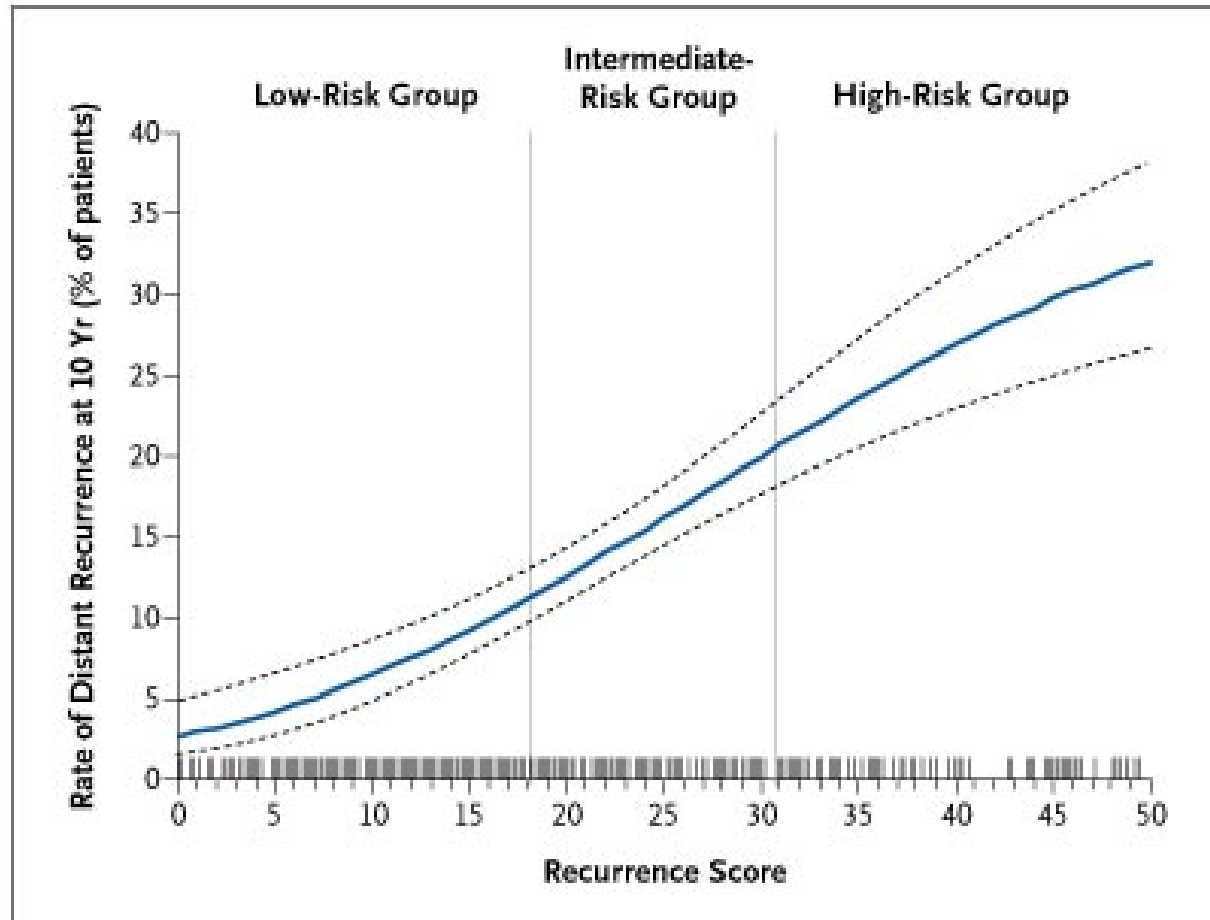
Table 1. Kaplan–Meier Estimates of the Rate of Distant Recurrence at 10 Years, According to Recurrence-Score Risk Categories.*

Risk Category	Percentage of Patients	Rate of Distant Recurrence at 10 Yr (95% CI) [†] <i>percent</i>
Low	51	6.8 (4.0–9.6)
Intermediate	22	14.3 (8.3–20.3)
High	27	30.5 (23.6–37.4) [‡]

* A low risk was defined as a recurrence score of less than 18, an intermediate risk as a score of 18 or higher but less than 31, and a high risk as a score of 31 or higher.

[†] CI denotes confidence interval.

[‡] $P < 0.001$ for the comparison with the low-risk category.



Paik, S

Clinical utility

- The evidence is insufficient to permit conclusions regarding the use of gene expression profiling to improve the selection of beneficial chemotherapy regimens and improve disease-free or overall survival outcomes.
- Additional studies in different populations are needed to confirm whether risk prediction is sufficiently accurate for physicians and patients to choose with confidence whether to withhold adjuvant chemotherapy.

Additional TAC criteria:

- **The technology must improve the net health outcome; and**
- **The technology must be as beneficial as any established alternatives;**
 - There is insufficient evidence to permit conclusions regarding the use of gene expression profiling for managing breast cancer treatment.
- **The improvement must be attainable outside the investigational settings.**
 - Whether or not the use of gene expression profiling for managing breast cancer treatment improves health outcomes has not been demonstrated in the investigational setting.

Current trials:



- On May 23, 2006, the National Cancer Institute (NCI) announced the launch of a large-scale trial to determine the best-course adjuvant treatment for women with HER2/neu-negative, estrogen receptor–positive, lymph node–negative, early-stage breast cancer.
- The Trial Assigning Individualized Options for Treatment (RX), or TAILORx, will use the Oncotype DX Recurrence Score Assay to stratify an estimated 10,000 participants by risk for distant recurrence of disease.
 - Women who score at low risk (less than 11) will be assigned to adjuvant treatment with hormonal therapy alone
 - women who are at intermediate risk (a score of 11 to 25) will be randomly assigned to receive either adjuvant hormonal therapy with or without chemotherapy
 - those at risk for recurrence (score higher than 25) will receive both hormonal therapy and chemotherapy.

American Journal of Managed Care Publishes Economic Analysis

On Friday, May 13, the American Journal of Managed Care published a comprehensive economic analysis that demonstrated Oncotype DX, when used appropriately, can reduce treatment costs and simultaneously improve net medical outcomes, including survival, when adjusted for the negative impact on quality of life associated with chemotherapy treatment.