Endopredict score per la stima del rischio residuo di ripresa di malattia nelle pazienti ER+ trattate con 5 anni di ormonoterapia adiuvante e confronto con il RS (OncotypeDX)

Valter Torri

Lab. di Metodologia per la RicercaClinica
Dipartimento di Oncologia
Istituto "Mario Negri" Milano - I.R.C.C.S.

A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

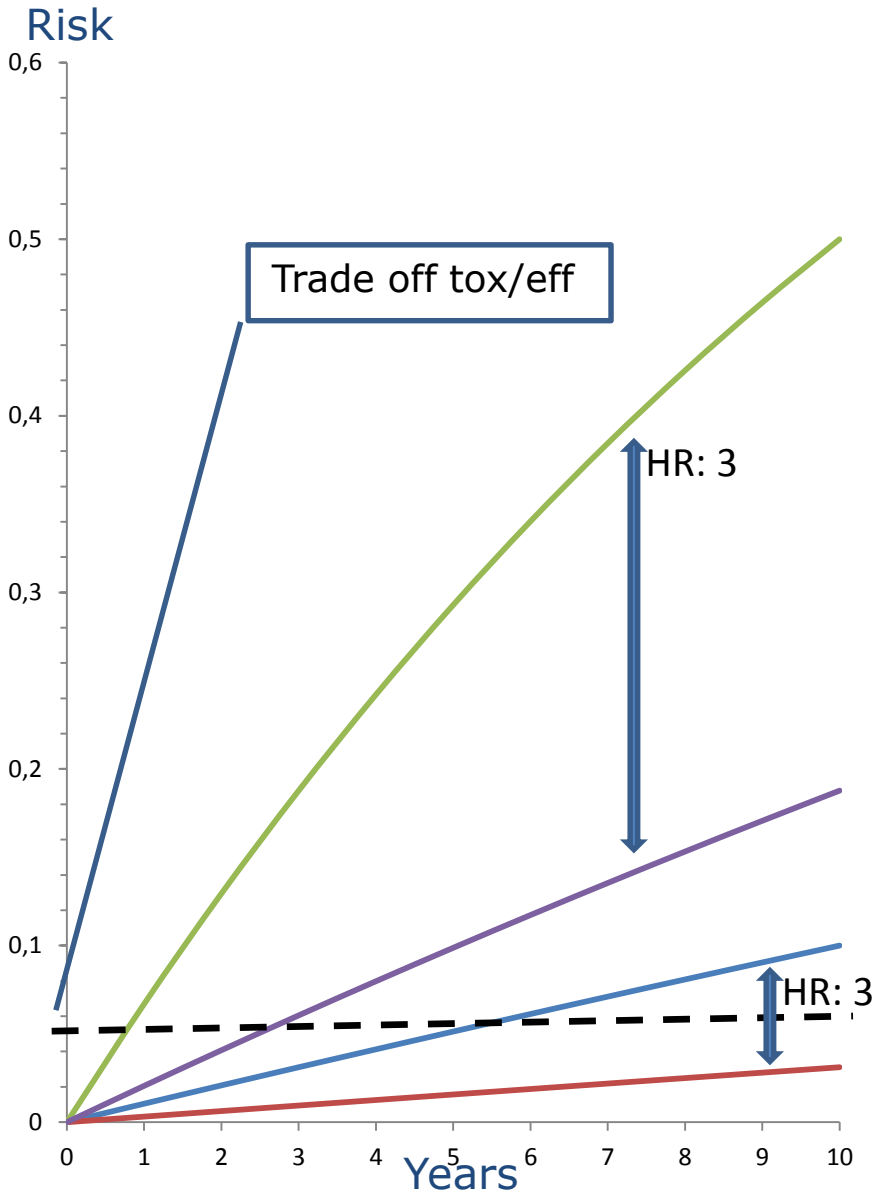
- Prognostic biomarkers
  - Measured before treatment to indicate long-term outcome for patients untreated or not receiving chemotherapy
  - Used to determine who who doesn't need more treatment
- Predictive biomarkers
  - Measured before treatment to identify who will benefit from a particular treatment
- Early detection biomarkers
- Disease progression biomarkers

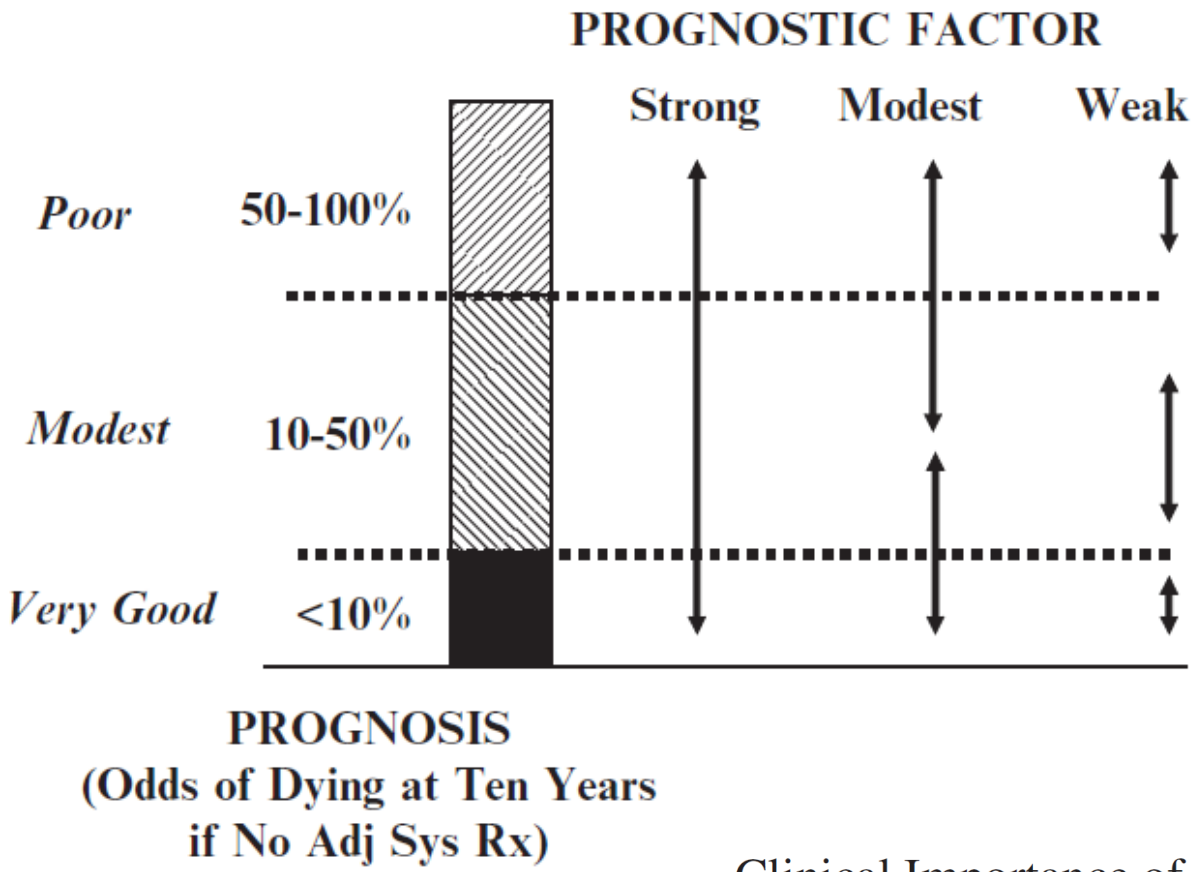
- Most gene expression signatures are developed as prognostic biomarkers.
- Like numerous previously developed prognostic markers, most will never be used because they have not been demonstrated to be therapeutically relevant
- Most prognostic marker studies are not conducted with an intended use clearly in mind
  - Most use a convenience sample of heterogeneous patients for whom tissue is available rather than patients selected for evaluating an intended use

- Importance of analytical validation
- Need of a separate validation study that addresses medical utility
  - Without a defined intended use, validation is meaningless and impossible
- Validation = Fitness for Intended Use

- Analytical validation
  - Accuracy in measurement of analyte
  - Robustness and reproducibility
- Clinical validation
  - Correlation of score/classifier with clinical state or outcome
- Medical utility
  - Use results in patient benefit by improving medical decision

- A prognostic signature for patients with breast cancer may correlate with outcome, but *does it identify a set of patients who have such good outcome without chemotherapy that they do not require treatment?*





Clinical Importance of Prognostic Factors

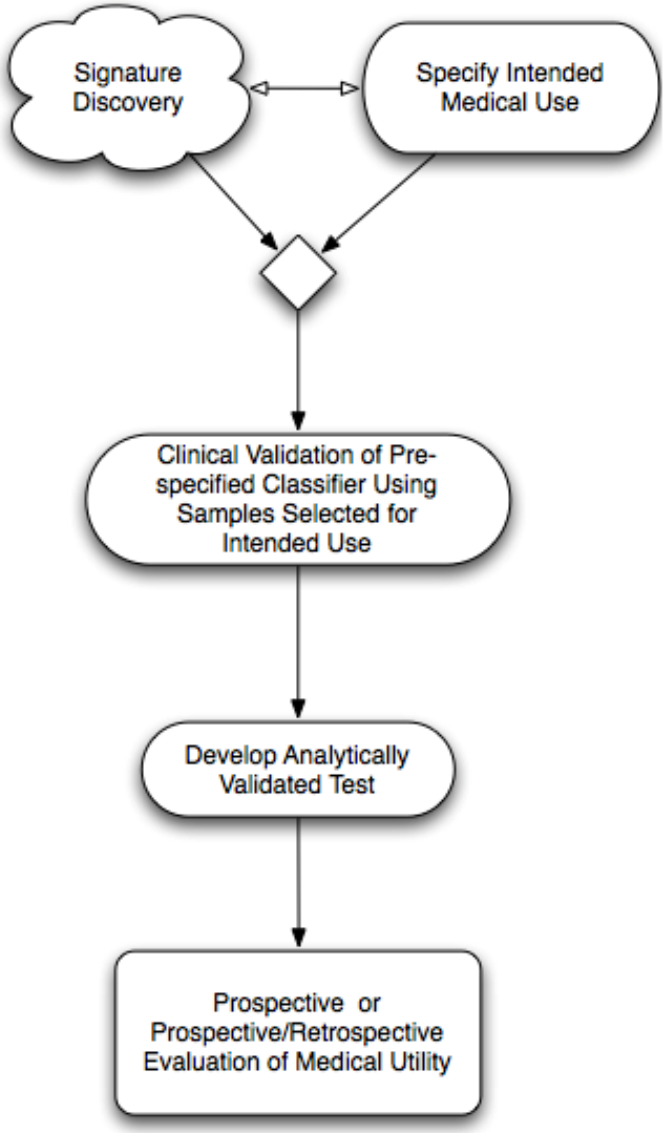
Moving from Scientifically Interesting
to Clinically Useful

N. Lynn Henry and Daniel F. Hayes

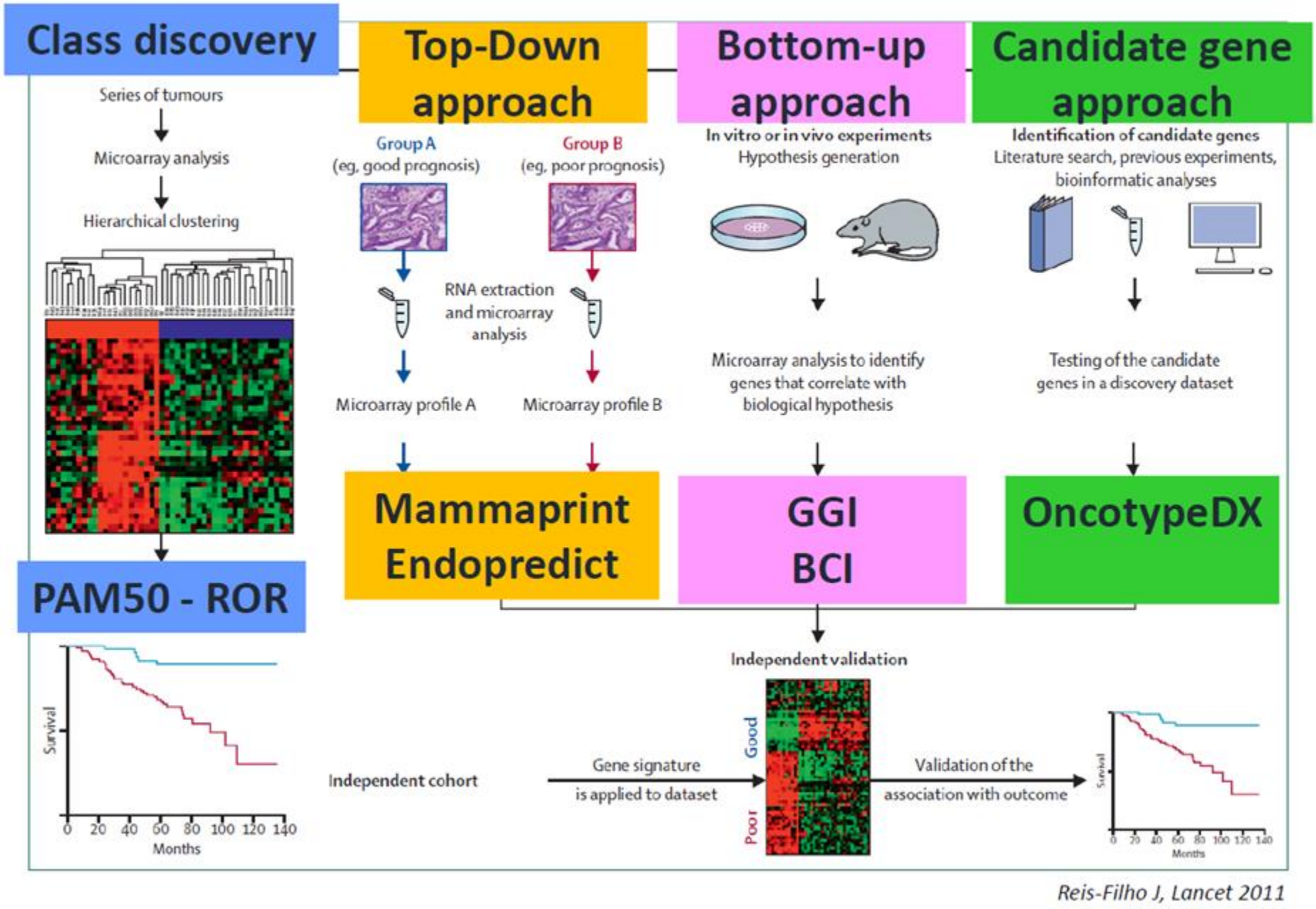
- Developmental studies
  - screen candidate markers to develop biomarker scores or classifiers
    - Train classifiers, set cut-off values for classification
  - often use validation on the same data set (cross-validation or split-sample) to provide a preliminary estimate of the accuracy of the marker/classifier for predicting a clinical outcome
  - generally address clinical validity (prediction accuracy), not medical utility

- Validation studies
  - use previously developed, completely specified classifiers/scores
  - should use analytically validated tests
  - focus on medical utility, not predictive accuracy
    - This often requires a prospective clinical trial
      - A trial with optimal structure for evaluating a new biomarker may have been previously performed and will have pre-treatment tumor specimens archived
      - A focused analysis based on specimens from the previously conducted clinical trial can provide highly reliable evidence for the medical utility of a prognostic or predictive biomaker
      - In some cases, it may be the only way of obtaining high level evidence

1. Identify specific intended use of the biomarker
2. Perform developmental study using samples appropriate for the intended use
3. Use independent data to clinically validate the predictive accuracy of the pre-specified marker, classifier or score
4. Develop an analytically validated test
5. Perform a prospective study that addresses the medical utility of the biomarker or biomarker score/classifier



Key steps in development and validation of biomarkers



Reis-Filho J, Lancet 2011

For women with early-stage invasive breast cancer and with known estrogen and progesterone receptor (ER/PgR) and human epidermal growth factor receptor 2 (HER2) status, which other biomarkers have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy?

PTS Subgroups	Oncotype DX	Mammaprint	PAM50	EndoPredict
HER2-; N-	POSITIVE STRONG	NEGATIVE MODERATE	POSITIVE STRONG	POSITIVE MODERATE
HER2-; N+	NEGATIVE MODERATE	NEGATIVE MODERATE	NEGATIVE STRONG	NEGATIVE MODERATE
HER2+	NEGATIVE STRONG	NEGATIVE MODERATE	NEGATIVE STRONG	NEGATIVE STRONG
TN	NEGATIVE STRONG	NEGATIVE STRONG	NEGATIVE STRONG	NEGATIVE STRONG

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Lyndsay N. Harris, Nofisat Ismaila, Lisa M. McShane, Fabrice Andre, Deborah E. Collyar, Ana M. Gonzalez-Angulo, Elizabeth H. Hammond, Nicole M. Kuderer, Minetta C. Liu, Robert G. Mennel, Catherine Van Poznak, Robert C. Bast, and Daniel F. Hayes

A B S T R A C T

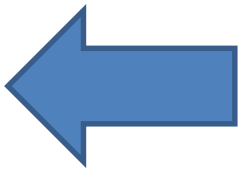
Purpose
To provide recommendations on appropriate use of breast tumor biomarker assay results to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer.

Methods
A literature search and prospectively defined study selection sought systematic reviews, meta-analyses, randomized controlled trials, prospective-retrospective studies, and prospective comparative observational studies published from 2006 through 2014. Outcomes of interest included overall survival and disease-free or recurrence-free survival. Expert panel members used informal consensus to develop evidence-based guideline recommendations.

Results
The literature search identified 50 relevant studies. One randomized clinical trial and 18 prospective-retrospective studies were found to have evaluated the clinical utility, as defined by the guideline, of specific biomarkers for guiding decisions on the need for adjuvant systemic therapy. No studies that met guideline criteria for clinical utility were found to guide choice of specific treatments or regimens.

Recommendations
In addition to estrogen and progesterone receptors and human epidermal growth factor receptor 2, the panel found sufficient evidence of clinical utility for the biomarker assays Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, and urokinase plasminogen activator and plasminogen activator inhibitor type 1 in specific subgroups of breast cancer. No biomarker except for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 was found to guide choices of specific treatment regimens. Treatment decisions should also consider disease stage, comorbidities, and patient preferences.

J Clin Oncol 34:1134-1150.



ASCO GL 2016