

Use of Genetic Profiling in the NCCN Breast Cancer Guideline

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Rationale for Profiling

- Provide prognostic information
- Provide predictive information
- Allow biological sub-setting of breast cancer
 - For treatment decision making
 - For clinical investigation

Established Anatomic and Biological Factors

	Prognostic	Predictive
Lymph nodes	Yes	
Tumor size	Yes	
Tumor type	Yes	
Tumor grade	Yes	
LVI	Yes	
Proliferation	Yes	
ER/PR status	Yes	Yes
HER2 status	Yes	Yes

Advantages of Established Anatomic and Biological Factors

- Decades of experience
- Enormous databases
- Multiple prospective trials (although often retrospectively analyzed)
- Methodologies widely available
- Technology is inexpensive
- Biology fairly well understood

Disadvantages of Established Anatomic and Biological Factors

- Current tests for ER, PR, and HER2 are often inaccurate *as performed*
- Individualizing treatment not fully possible

Advantages of Genetic Profiling

- Tests are probably highly accurate and reproducible
- Number of genes/pathways that can be included is enormous
- *Potential* of highly individualized therapy

Disadvantages of Genetic Profiling

- Limited experience
- Modest sized databases
- No prospective trials
- Methodologies not widely available
- Technology is expensive
- Biology usually not well understood
- Individualizing treatment not yet possible

MammaPrint: USA-FDA Language

H. Intended Use:

1. Intended use(s):

MammaPrint® is a qualitative in vitro diagnostic test service, performed in a single laboratory, using the gene expression profile of fresh breast cancer tissue samples to assess a patients' risk for distant metastasis.

The test is performed for breast cancer patients who are less than 61 years old, with Stage I or Stage II disease, with tumor size <5.0 cm and lymph node negative. The MammaPrint® result is indicated for use by physicians as a prognostic marker only, along with other clinicopathological factors.

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MammaPrint: USA-FDA Language

3. Special conditions for use statement(s):

For prescription use only

MammaPrint® is not intended for diagnosis, or to predict or detect response to therapy, or to help select the optimal therapy for patients.

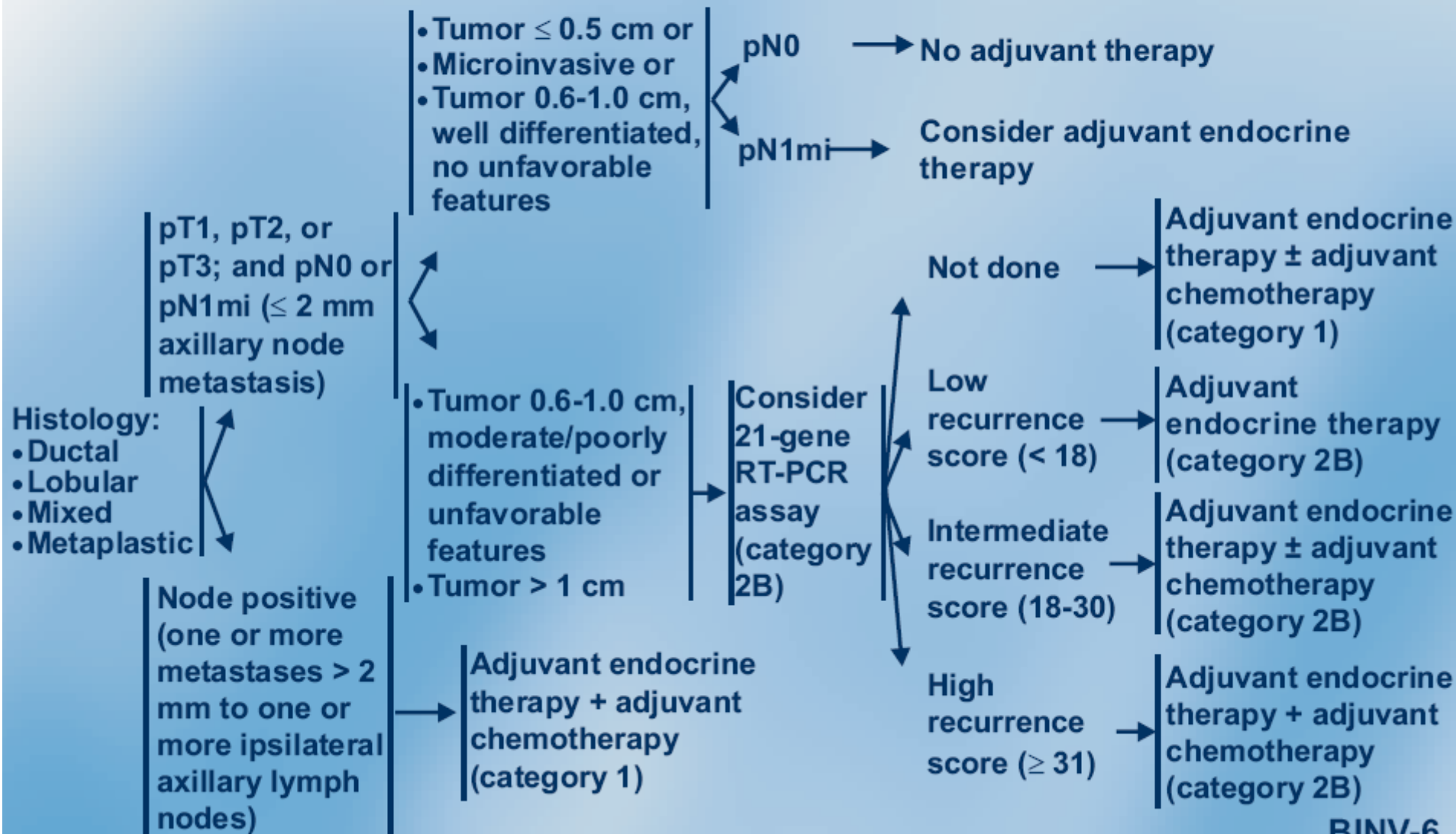
OncoTypeDX: USA-FDA Language

- None.
- Testing is Clinical Laboratory Improvement Amendment certified.

Invasive Breast Cancer

Clinical Practice Guidelines in Oncology – v.1.2009

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR POSITIVE - HER2 NEGATIVE DISEASE

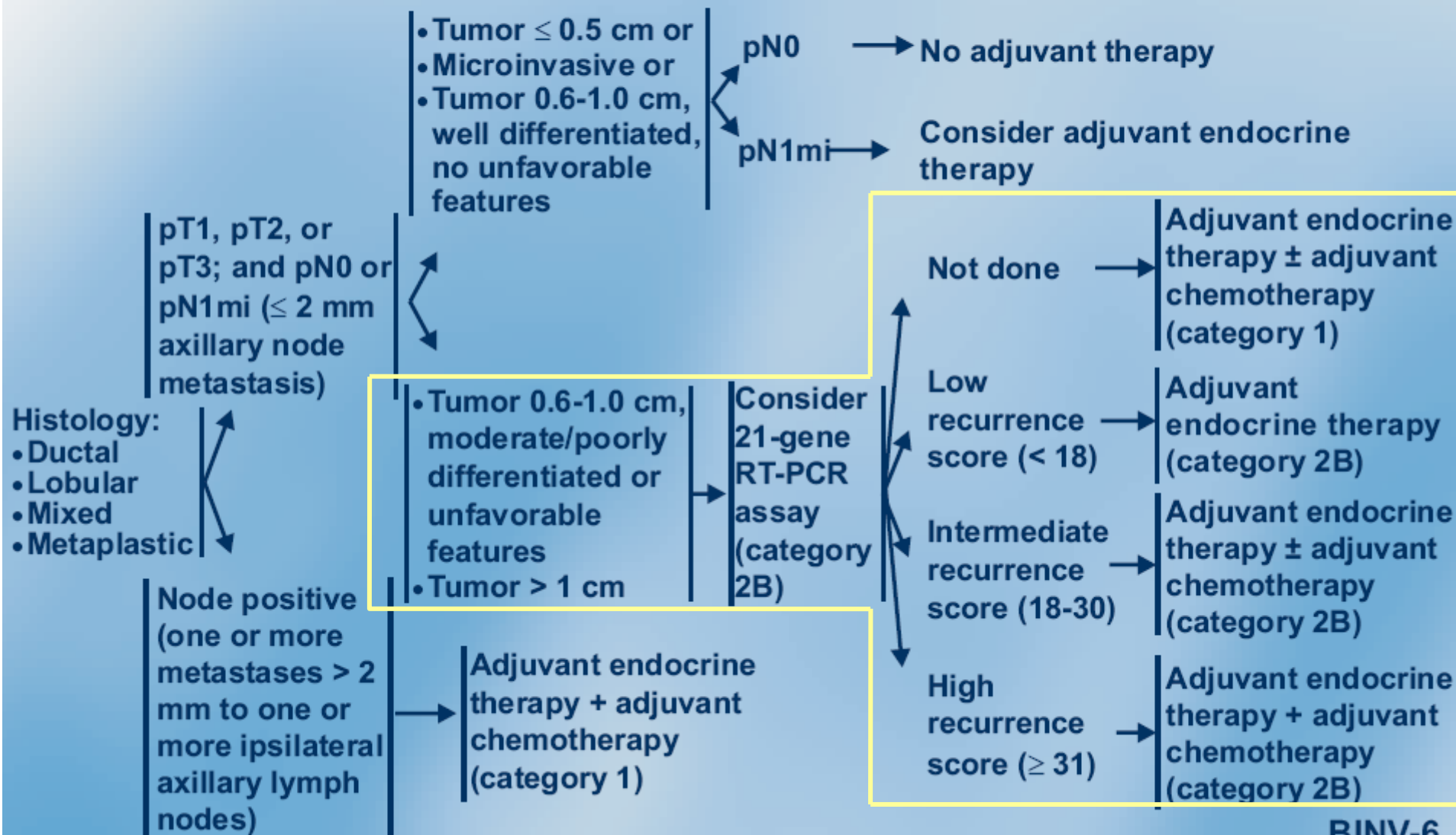


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Invasive Breast Cancer

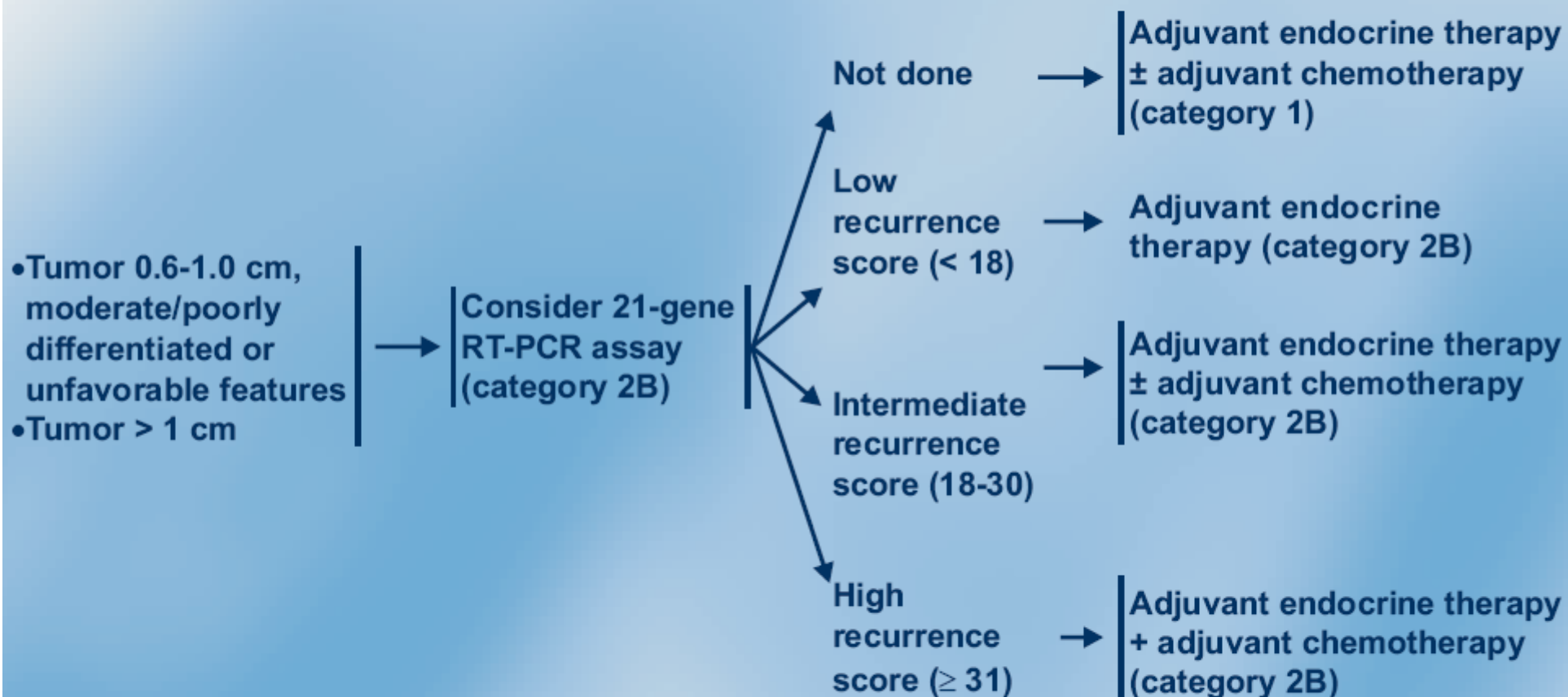
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St Gallen 2009

In an important change from the previous St Gallen conference and after a long debate, the Panel supported the use of a validated multigene-profiling assay, if readily available, as an adjunct to high-quality phenotyping of breast cancer in cases in which the indication for adjuvant chemotherapy remained uncertain.

Goldhirsch et al, *Annals of Oncology* 20:1319-29, 2009.

ASCO 2007

Multiparameter Gene Expression Analysis for Breast Cancer

- *Oncotype DX*[™] can be used to determine prognosis in newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer who will receive tamoxifen. Indications:
 - To predict risk of recurrence in patients considering treatment with tamoxifen
 - To identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy
 - Patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically CMF) than from tamoxifen

ASCO 2007

Multiparameter Gene Expression Analysis for Breast Cancer

- Conclusions may not be generalizable to hormonal therapies other than tamoxifen, or to other chemotherapy regimens.
- Several other multi-parameter assays have been reported and a few are commercially available, including Mammaprint and the Rotterdam Signature. However, the Committee felt that the precise clinical utility and appropriate application for these other assays were insufficiently defined to recommend their use.

ESMO Clinical Recommendations 2009 Primary Breast Cancer

The place of gene/molecular profiling shows promise
but requires prospective validation before routine use.

Kataja, et al, Annals of Oncology 2009 20(Suppl 4):iv10-iv14.

Conclusions

- Technology exists to assess multiple gene expression in breast cancer
- Early retrospective data suggests ability to provide prognostic and/or predictive information
- Relative value of various multi-gene expression assays not defined
- Uncertainty in how to best integrate into current clinical guidelines and recommendations