Update: genomic assays in N+ patients

Luke Hughes-Davies

Latest ASCO Biomarker Guideline published two weeks ago.

(CPD learning goal: review of the ASCO guideline)

Started in 2005

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JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Reporting Recommendations for Tumor Marker Prognostic Studies

Lisa M. McShane, *Biometric Research Branch, National Cancer Institute, Bethesda, MD*
Douglas G. Altman, *Medical Statistics Group, Cancer Research UK, Centre for Statistics in Medicine, Wolfson College, Oxford, UK*
Willi Sauerbrei, *Institut fuer Medizinische Biometrie und Medizinische Informatik, Universitaetsklinikum Freiburg, Freiburg, Germany*
Sheila E. Taube, *Cancer Diagonisis Program, National Cancer Institute, Bethesda, MD*
Massimo Gion, *Centro Regionale Indicatori Biochimici di Tumore, Ospedale Civile, Venezia, Italy*
Gary M. Clark, *OSI Pharmaceuticals Inc, Boulder, CO*
For the Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics

Moved from blood tests to genomic assays

Last guideline was in 2016

The Panel recommends against ordering two different tests for the same patients as these tests will provide similar information

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AMERICAN SOCIETY OF CLINICAL ONCOLOGY

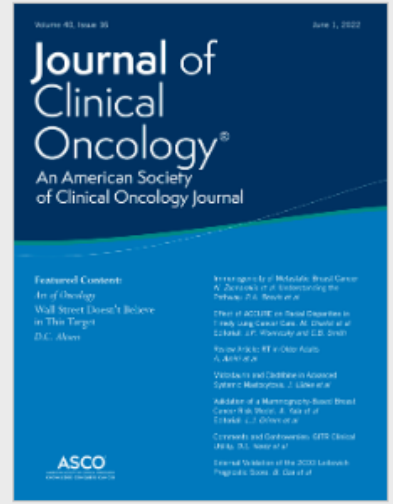
Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer

Adapted from:

Fabrice A, et al. *J Clin Oncol*. 2022 April 19.
doi: 10.1200/JCO.22.00069.

Key Points

Diagnosis



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Bidard et al.

Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update
Andre et al.

Guideline Panel Members

Name	Affiliation/Institution	Role/Area of Expertise
Fabrice Andre, MD (co-chair)	Institute Gustave Roussy, Paris, France	Medical Oncology
Vered Stearns, MD, FASCO (co-chair)	Johns Hopkins University, Baltimore, MD	Medical Oncology
N. Lynn Henry, MD, PhD	University of Michigan Comprehensive Cancer Center, Ann Arbor, MI	Medical Oncology
Antonio C. Wolff, MD	Johns Hopkins University, Baltimore, MD	Medical Oncology
Komal Jhaveri, MD, FACP	Memorial Sloan Kettering Cancer Center, New York, NY	Medical Oncology
Senthil Damodaran, MD, PhD	MD Anderson Cancer Center, Houston, TX	Medical Oncology
Kevin Kalinsky, MD, MS	Winship Cancer Institute of Emory University, Atlanta, GA	Medical Oncology
Erica L. Mayer, MD MPH	Dana-Farber Cancer Institute, Boston, MA	Medical Oncology
Nicole M. Kuderer, MD	Advanced Cancer Research Group, Kirkland, WA	Medical Oncology
Lajos Pusztai, MD	Yale Cancer Center, New Haven, CT	Medical Oncology
Kimberly Allison, PhD	Stanford University Medical Center, Stanford, CA	Breast Pathology
William E Barlow, PhD	Cancer Research and Biostatistics, Seattle, WA	Biostatistics
Rachel Raab, MD	Messino Cancer Centers-A Division of American Oncology Partners, Asheville, NC	PGIN representative
Anya Litvak, MD	Cancer Center at Saint Barnabas Medical Center, Livingston, NJ	PGIN representative
Deborah E. Collyar	Patient Advocates in Research, Danville, CA	Patient representative
Nofisat Ismaila, MD	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

JOHNS HOPKINS
MEDICINE

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

(They’ve stopped talking about CYP2D6 and tamoxifen)

- Oncotype (21 gene signature)
- Mammaprint (70 gene signature)
- Endopredict (12 gene signature)
- PAM50 (50 gene signature)
- Ki67
- IHC4
- BCI two gene ratio ([*HOXB13/IL17BR* ratio (H/I)])

There are no data on use of genomic tests in patients with 4 or more positive nodes.

No test should be used in premenopausal patient with positive nodes

Newly Diagnosed ER-Positive, HER2-Negative Breast Cancer

Oncotype DX (21-gene recurrence score, 21-gene RS).

Recommendation 1.1. If a patient has node-negative breast cancer, the clinician may use the Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

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Recommendation 1.6. If a patient is premenopausal and has node-positive breast cancer with 1-3 positive nodes, the Onco*type* DX test should not be offered to guide decisions for adjuvant systemic chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: moderate).

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Recommendation 1.7. If a patient has node-positive breast cancer with ≥ 4 positive nodes, the evidence on the clinical utility of routine Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).
Qualifying statement: The genomic assay is prognostic and may be used for shared patient-physician treatment decision making.

TailoRx patients younger than 50

RS	hormones	Hormone plus chemo
16-20	92%	94.7%
21-25	86.3%	92.1%

mammaprint

MammaPrint (70-gene signature).

Recommendation 1.8. If a patient is older than 50 and has high clinical risk breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician may use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

THE BOTTOM LINE (CONTINUED)

Recommendation 1.9. If a patient is 50 years of age or younger and has high clinical risk, node-negative or node-positive with 1-3 positive nodes breast cancer, the clinician should not use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.10. If a patient has low clinical risk, regardless of age, the evidence on clinical utility of routine MammaPrint test is insufficient to recommend its use (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.11. If a patient has node-positive breast cancer with ≥ 4 positive nodes, the evidence on the clinical utility of routine MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).
Qualifying statement: The genomic assay is prognostic and may be used for shared patient-physician treatment decision making.

Prosigna

Prosigna (PAM50).

Recommendation 1.15. If a patient is postmenopausal and has breast cancer that is node-negative, the clinician may use the Prosigna test to guide decisions for adjuvant systemic chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.16. If a patient is premenopausal and has node-negative or node-positive breast cancer, the clinician should not use the Prosigna test to guide decisions for adjuvant systemic chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 1.17. If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the evidence is inconclusive to recommend the use of the Prosigna test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.18. If a patient has node-positive breast cancer with ≥ 4 positive nodes, evidence on the clinical utility of routine use of the Prosigna test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Ki67

Ki67 combined with other parameters or immunohistochemistry 4 score may be used in postmenopausal patients without access to genomic tests to guide adjuvant therapy decisions.

Essentially, all studies show that among ER-positive cancers, the higher the Ki67, the worse the long-term survival. Also, the higher the Ki67, the higher the likelihood of pathologic complete response to NACT.

However, unlike ER or HER2, the expression distribution of Ki67 is not bimodal, and there is no natural threshold to define high or low Ki67 status.

Different studies have used different definitions of high Ki67, which makes interpretation of the literature challenging. Interobserver and interlaboratory variability in Ki67 assessment and a lack of standards further hinder setting a universal Ki67 threshold.

In an attempt to standardize a prognostic threshold, the St Gallen International Consensus on the Primary Therapy of Early Breast Cancer recommended > 20% as the threshold to define high risk.

In the past decade, the International Ki67 Breast Cancer Working Group has attempted to standardize Ki67 testing. The group recently reported that expression levels of Ki67 < 5% or > 30% can be reliably reported, but levels between those thresholds are unreliable.

Most studies of Ki67 expression have been conducted using samples from postmenopausal patients

Endocrine extension beyond five year decisions

Recommendation 1.23. If a patient has node-negative breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, there is insufficient evidence to use Onco*type* DX, EndoPredict, Prosigna, Ki67, or IHC4 scores to guide decisions about extended endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

CTS⑤ CALCULATOR

The CTS⑤ is an online model for clinicians to predict late distant metastasis for women with ER-positive breast cancer who are recurrence-free 5 years after endocrine therapy. Patients should always seek advice from their doctors when interpreting the results from this tool.

Read more

Tumour size (mm)

Tumour Grade Grade 1

Patient age (years)

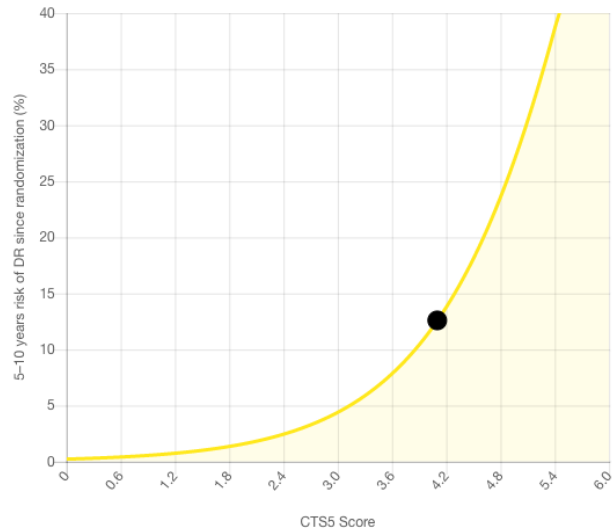
Number of nodes involved

CALCULATE RESULT ⇨

CTS⑤ CALCULATOR

Tumour size (mm)	30
Tumour Grade	Grade 2
Patient age (years)	63
Number of nodes involved	1

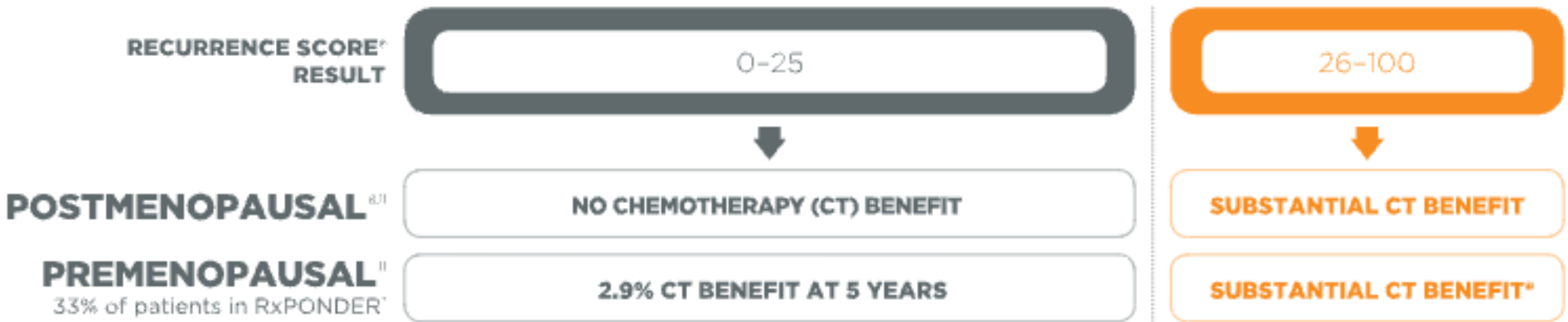
UPDATE RESULT ⇨



CTS5 SCORE	5–10 YEAR RISK	CTS5 RISK GROUP
4.1	12.6%	High

Are the companies compliant with ASCO?

Patient selection using the Oncotype DX test in node-positive patients[8]



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OUR TESTS

The molecular profile to define and defeat her unique cancer.

Overview | MammaPrint | BluePrint

Will my patient's breast cancer return after surgery?

The MammaPrint® test analyzes the 70 most important genes associated with breast cancer recurrence. Results are typically available in 6 days or less, MammaPrint enables quicker, more informed decisions on pre- and post-operative treatment and can easily be integrated into diagnostic workups.[1]

ORDER A TEST >

> **I see MammaPrint as a great tool which helps you to navigate through difficult decisions."**
>
> — Andrea, a breast cancer survivor

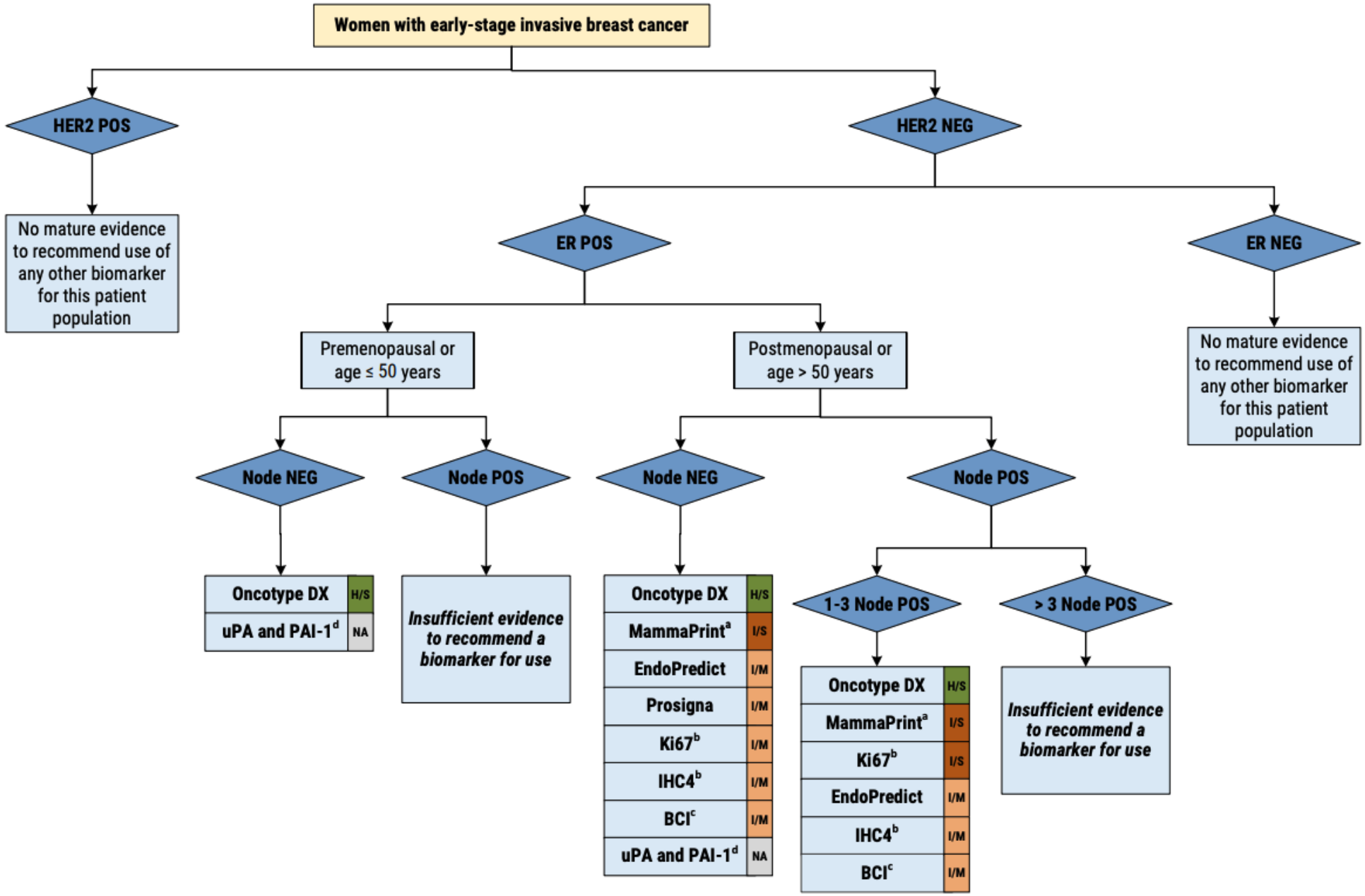
Women who benefit.

- Newly diagnosed with invasive breast cancer (stage I, or II or operable stage III)
- Lymph node-negative or those with 1-3 positive lymph nodes[2]
- Tumor size up to 5cm
- All Ages

No test should be used in premenopausal patient with positive nodes

ASCO® Guidelines

Algorithm on Biomarkers to Guide Decisions on Adjuvant Endocrine and Chemotherapy



There are no data on use of genomic tests in patients with 4 or more positive nodes.

Criticisms of the guideline

- We don’t have much information on higher risk N1 patients

(ie the patient with high grade disease or 3 positive nodes)

- Contribution of suboptimal hormonal therapy

- non-inferiority not proved, could be missing 3% difference

What does 3% mean?

OPTIMA addresses plenty of important unanswered questions, and ASCO strongly endorses research….

- Younger patients
- Higher risk N1 patients
- 4+ node patients
- True non-inferiority
- Properly controlled endocrine treatment