NCCN Clinical Practice Guidelines in Oncology
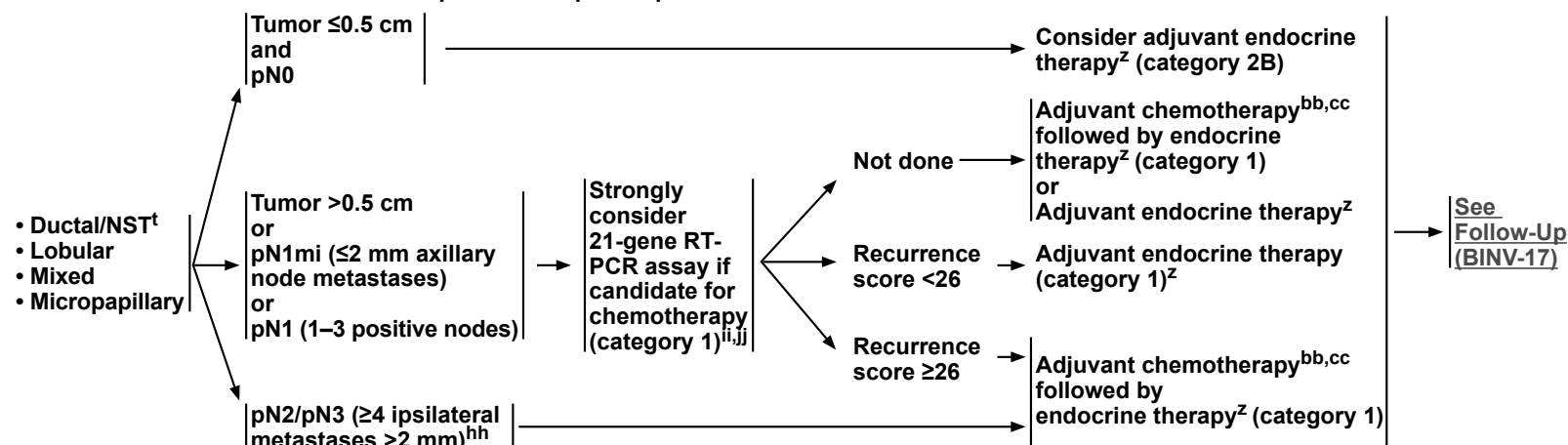(NCCN Guidelines®)

Breast Cancer

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SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-NEGATIVE DISEASE^d,q,y
POSTMENOPAUSAL^gg PATIENTS with pT1–3 AND pN0 or pN+ TUMORS

- Ductal/NST^t
- Lobular
- Mixed
- Micropapillary

Tumor ≤0.5 cm and pN0 → **Consider adjuvant endocrine therapy^z (category 2B)**

Tumor >0.5 cm or pN1mi (≤2 mm axillary node metastases) or pN1 (1–3 positive nodes) → **Strongly consider 21-gene RT-PCR assay if candidate for chemotherapy (category 1)^ii,jj**

- **Not done** → **Adjuvant chemotherapy^bb,cc followed by endocrine therapy^z (category 1) or Adjuvant endocrine therapy^z**
- **Recurrence score <26** → **Adjuvant endocrine therapy (category 1)^z**
- **Recurrence score ≥26** → **Adjuvant chemotherapy^bb,cc followed by endocrine therapy^z (category 1)**

pN2/pN3 (≥4 ipsilateral metastases >2 mm)^hh → **Adjuvant chemotherapy^bb,cc followed by endocrine therapy^z (category 1)**

See Follow-Up (BINV-17)

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d See Principles of Biomarker Testing (BINV-A).

q See Special Considerations for Breast Cancer in Men (Sex Assigned Male at Birth) (BINV-J).

t According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.

y Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).

z Consider adjuvant bisphosphonate therapy in patients with natural or induced menopause.

bb Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with RT is acceptable. See Adjuvant Endocrine Therapy (BINV-K) and Preoperative/Adjuvant Therapy Regimens (BINV-L).

cc There are limited data to make chemotherapy recommendations for those ≥70 y of age. See NCCN Guidelines for Older Adult Oncology.

gg See Definition of Menopause (BINV-O).

hh There are few data regarding the role of gene expression assays in those with ≥4 ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors.
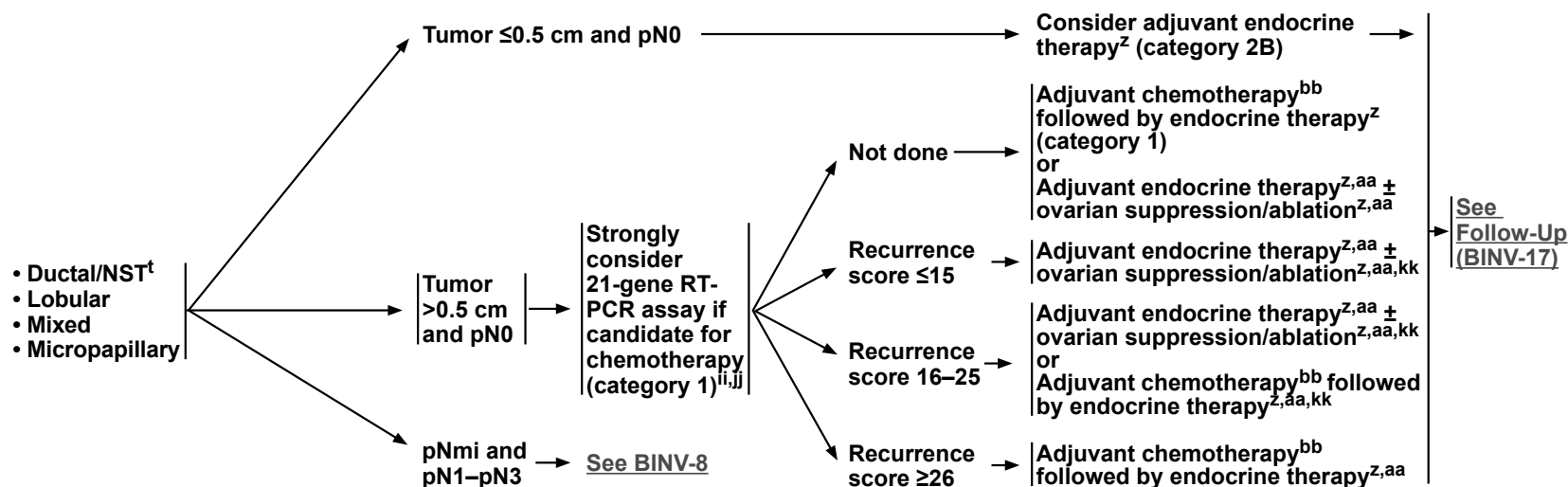
ii Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N).

jj Patients with T1b tumors with low-grade histology and no lymphovascular invasion should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.

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BINV-6

**SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-NEGATIVE DISEASE[d,q,y]
PREMENOPAUSAL[gg] PATIENTS with pT1–3 AND pN0 TUMORS**

Flow diagram:

- Ductal/NST[t]
- Lobular
- Mixed
- Micropapillary

→ **Tumor ≤0.5 cm and pN0** → Consider adjuvant endocrine therapy[z] (category 2B) → See Follow-Up (BINV-17)

→ **Tumor >0.5 cm and pN0** → **Strongly consider 21-gene RT-PCR assay if candidate for chemotherapy (category 1)[ii,jj]**

- **Not done** → Adjuvant chemotherapy[bb] followed by endocrine therapy[z] (category 1) or Adjuvant endocrine therapy[z,aa] ± ovarian suppression/ablation[z,aa] → See Follow-Up (BINV-17)
- **Recurrence score ≤15** → Adjuvant endocrine therapy[z,aa] ± ovarian suppression/ablation[z,aa,kk]
- **Recurrence score 16–25** → Adjuvant endocrine therapy[z,aa] ± ovarian suppression/ablation[z,aa,kk] or Adjuvant chemotherapy[bb] followed by endocrine therapy[z,aa,kk]
- **Recurrence score ≥26** → Adjuvant chemotherapy[bb] followed by endocrine therapy[z,aa]

→ **pNmi and pN1–pN3** → See BINV-8

[d] See Principles of Biomarker Testing (BINV-A).
[q] See Special Considerations for Breast Cancer in Men (Sex Assigned Male at Birth) (BINV-J).
[t] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).
[z] Consider adjuvant bisphosphonate therapy in patients with natural or induced menopause.
[aa] Evidence suggests that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal patients with HR-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-K).

[bb] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with RT is acceptable. See Adjuvant Endocrine Therapy (BINV-K) and Preoperative/Adjuvant Therapy Regimens (BINV-L).
[gg] See Definition of Menopause (BINV-O).
[ii] Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N).
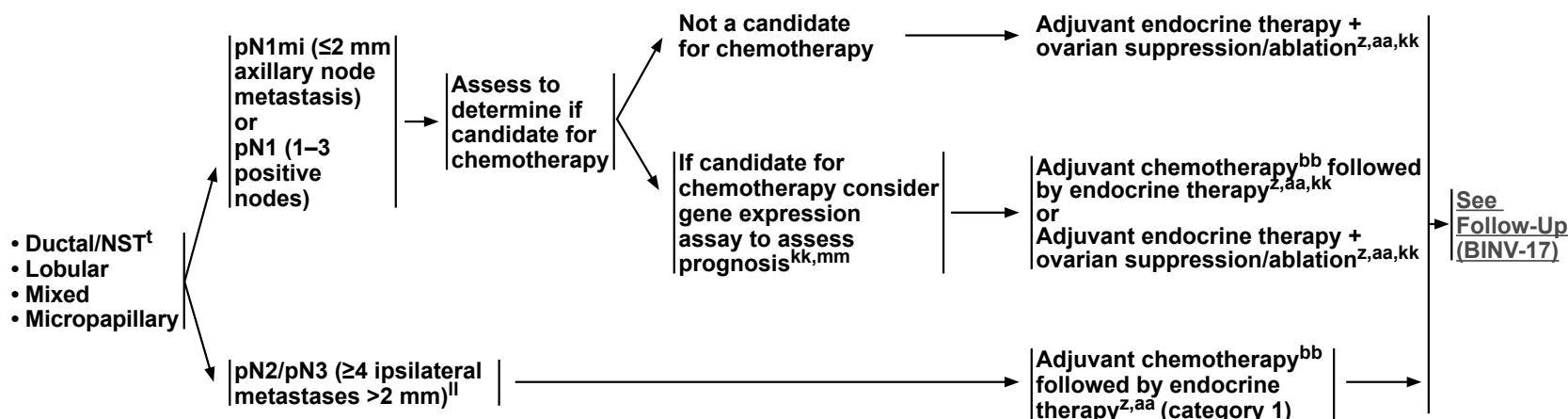[jj] Patients with T1b tumors with low-grade histology and no lymphovascular invasion should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.
[kk] In premenopausal patients with RS <26, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy, but it is unclear if the benefit was due to the ovarian suppression effects promoted by chemotherapy.

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SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-NEGATIVE DISEASE[d,q,y]
PREMENOPAUSAL[gg] **PATIENTS with pT1–3 AND pN+ TUMORS**

- Ductal/NST[t]
- Lobular
- Mixed
- Micropapillary

→ **pN1mi (≤2 mm axillary node metastasis) or pN1 (1–3 positive nodes)** → **Assess to determine if candidate for chemotherapy**

- → **Not a candidate for chemotherapy** → **Adjuvant endocrine therapy + ovarian suppression/ablation**[z,aa,kk]
- → **If candidate for chemotherapy consider gene expression assay to assess prognosis**[kk,mm] → **Adjuvant chemotherapy**[bb] **followed by endocrine therapy**[z,aa,kk] **or Adjuvant endocrine therapy + ovarian suppression/ablation**[z,aa,kk]

→ **pN2/pN3 (≥4 ipsilateral metastases >2 mm)**[ll] → **Adjuvant chemotherapy**[bb] **followed by endocrine therapy**[z,aa] **(category 1)**

→ **See Follow-Up (BINV-17)**

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[d] See Principles of Biomarker Testing (BINV-A).

[q] See Special Considerations for Breast Cancer in Men (Sex Assigned Male at Birth) (BINV-J).

[t] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.

[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).

[z] Consider adjuvant bisphosphonate therapy in patients with natural or induced menopause.

[aa] Evidence suggests that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal patients with HR-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-K).

[bb] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with RT is acceptable. See Adjuvant Endocrine Therapy (BINV-K) and Preoperative/Adjuvant Therapy Regimens (BINV-L).

[gg] See Definition of Menopause (BINV-O).

[kk] In premenopausal patients with RS <26, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy, but it is unclear if the benefit was due to the ovarian suppression effects promoted by chemotherapy.

[ll] There are few data regarding the role of gene expression assays in those with ≥4 ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors.

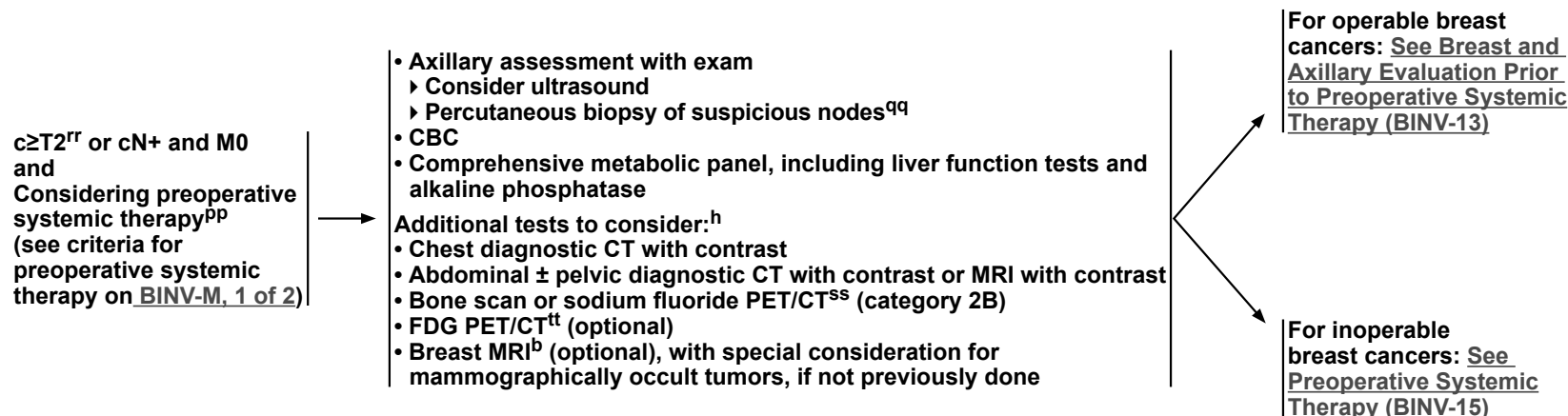[mm] See Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N).

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WORKUP PRIOR TO PREOPERATIVE SYSTEMIC THERAPY

CLINICAL STAGE

ADDITIONAL WORKUP[a]

c≥T2[rr] or cN+ and M0
and
**Considering preoperative
systemic therapy[pp]
(see criteria for
preoperative systemic
therapy on** BINV-M, 1 of 2**)**

• **Axillary assessment with exam**
  ‣ **Consider ultrasound**
  ‣ **Percutaneous biopsy of suspicious nodes[qq]**
• **CBC**
• **Comprehensive metabolic panel, including liver function tests and
  alkaline phosphatase**

Additional tests to consider:[h]
• **Chest diagnostic CT with contrast**
• **Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast**
• **Bone scan or sodium fluoride PET/CT[ss] (category 2B)**
• **FDG PET/CT[tt] (optional)**
• **Breast MRI[b] (optional), with special consideration for
  mammographically occult tumors, if not previously done**

**For operable breast
cancers:** See Breast and
Axillary Evaluation Prior
to Preoperative Systemic
Therapy (BINV-13)

**For inoperable
breast cancers:** See
Preoperative Systemic
Therapy (BINV-15)

[a] For tools to aid optimal assessment and management of older adults, see NCCN
  Guidelines for Older Adult Oncology.
[b] Breast MRI may be useful for characterizing axillary and/or internal mammary nodal
  disease. See Principles of Dedicated Breast MRI Testing (BINV-B).
[h] Routine systemic staging is not indicated for non-metastatic (M0) cancer in the absence of
  signs or symptoms. If metastatic disease is suspected, see Workup on BINV-18.
[pp] See Principles of Preoperative Systemic Therapy (BINV-M).
[qq] At the time of axillary node sampling, a clip or tattoo should be placed to permit verification
  that the biopsy-positive lymph node has been removed at the time of definitive surgery.
[rr] If considering preoperative therapy, consider use of a gene expression assay during
  workup for postmenopausal patients with cN0, operable ER-positive, HER2-negative
  disease. (Iwata H, et al. Breast Cancer Res Treat 2019;173,123-133; Pease AM, et al. Ann
  Surg Oncol 2019;26:366-371.)

[ss] Bone scan or sodium fluoride PET/CT may not be needed if FDG
  PET/CT is performed and clearly indicates bone metastasis, on both
  the PET and CT component.
[tt] FDG PET/CT may be performed at the same time as diagnostic
  CT, and may be helpful in situations where standard staging studies
  are equivocal or suspicious. FDG PET/CT may also be helpful
  in identifying unsuspected regional nodal disease and/or distant
  metastases when used in addition to standard staging studies.

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BINV-12

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus	Recurrence Risk and Treatment Implications
21-gene (Oncotype Dx) (for pN0)	Yes	Yes	Preferred	1	BINV-N (2 of 5)
21-gene (Oncotype Dx) for pN1 (1–3 positive nodes)[c]	Yes	Yes	Postmenopausal: Preferred	1	BINV-N (2 of 5)
			Premenopausal: Other	2A	
70-gene (MammaPrint) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	1	BINV-N (3 of 5)
50-gene (Prosigna) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3 of 5)
12-gene (EndoPredict) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3 of 5)
Breast Cancer Index (BCI)	Predictive of benefit of extended adjuvant endocrine therapy	Yes	Other	2A	BINV-N (4 of 5)

[a] Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.
[b] See Special Considerations for Breast Cancer in Men (Sex Assigned Male at Birth) (BINV-J).
[c] In the overall study population of the RxPONDER trial, 10.3% had high grade disease and 9.2% had 3 involved nodes.

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References

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

Assay	Recurrence Risk	Treatment Implications
21-gene (Oncotype Dx) for postmenopausal patients with pN0 and pN1 (1–3 positive nodes)[c]	<26	Patients with T1b/c–2, pN0, HR-positive, HER2-negative tumors, with risk scores (RS) between 0–10 have a risk of distant recurrence of <4% and those with RS 11–25, derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study.[1] Postmenopausal patients with pT1–3, pN1, HR-positive, HER2-negative, with RS <26 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective RxPONDER study.[2]
	≥26	In postmenopausal patients with pT1–3, HR-positive, HER2-negative, and pN0 and pN1 (1–3 positive nodes) tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[1,2]
21-gene (Oncotype Dx) (for premenopausal patients: pN0)	≤15	Premenopausal patients with T1b/c –2, pN0, HR-positive, HER2-negative tumors with RS <16 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study.[1]
	16–25	In premenopausal patients with RS between 16–25, a small benefit from the addition of chemotherapy could not be ruled out, but it is unclear if the benefit was due to the ovarian suppression effect promoted by chemotherapy in premenopausal patients.[1,2] For this group, consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI.
	≥26	In premenopausal patients with HR-positive, HER2-negative, and pN0 tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[1]
21-gene (Oncotype Dx) (for premenopausal patients with 1–3 positive nodes)[c]	<26	In premenopausal patients with pT1–3 and pN1 (1–3 positive nodes) tumors and an RS <26, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy[2] but it is unclear if the benefit was due to the ovarian suppression effects promoted by chemotherapy. For this group of patients, consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI.[2]
	≥26	In premenopausal patients with HR-positive, HER2-negative, pT1–3 and pN1 (1–3 positive nodes) tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[2]

[a] Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.
[b] See Special Considerations for Breast Cancer in Men (Sex Assigned Male at Birth) (BINV-J).
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GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

Assay	Recurrence Risk	Treatment Implications
70-gene (MammaPrint) (for pN0 and 1–3 positive nodes)	Low	With a median follow-up of 5 years, among patients at high clinical risk and low genomic risk, the rate of survival without distant metastasis in this group was 94.7% (95% CI, 92.5%–96.2%) among those who did not receive adjuvant chemotherapy. Among patients with 1–3 positive nodes, the rates of survival without distant metastases were 96.3% (95% CI, 93.1–98.1) in those who received adjuvant chemotherapy vs. 95.6 (95% CI, 92.7–97.4) in those who did not receive adjuvant chemotherapy.[3] Therefore, the additional benefit of adjuvant chemotherapy may be small in this group. In a subset analyses, the benefit of chemotherapy was mostly seen in patients under 50 years of age. The absolute difference in distant metastatic-free survival at 8 years in those receiving chemotherapy for patients ≤ 50 years was 5.4% ± 2.8% versus 0.2% ± 2.3% for those >50 years.[4] It is not known whether the benefit of chemotherapy observed in women ≤ 50 years is related to chemotherapy-induced ovarian function suppression.
	High	
50-gene (Prosigna) (for pN0 and 1–3 positive nodes)	Node negative: Low (0–40)	For patients with T1 and T2 HR-positive, HER2-negative, pN0 tumors, a risk of recurrence score in the low range, regardless of T size, places the tumor into the same prognostic category as T1a–T1b,N0,M0.[5]
	Node negative: Intermediate (41–60)	
	Node negative: High (61–100)	
	Node positive: Low (0–40)	In patients with HR-positive, HER2-negative, pN+ tumors (1–3 positive lymph nodes) with low risk of recurrence score, treated with endocrine therapy alone, the distant recurrence risk was less than 3.5% at 10 years and no distant recurrence was seen at 10 years in the TransATAC study in a similar group.[6]
	Node positive: High (41–100)	
12-gene (EndoPredict) (pN0 and 1–3 positive nodes)	Low (≤3.3)	For patients with T1 and T2 HR-positive, HER2-negative, and pN0 tumors, a 12-gene low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a–T1b,N0,M0.[7] In ABCSG 6/8, patients in the low-risk group had risk of distant recurrence of 4% at 10 years and in the TransATAC study, patients with 1–3 positive nodes in the low-risk group had a 5.6% risk of distant recurrence at 10 years.[6,7] The assay is prognostic in endocrine and chemo-endocrine treated patients.[8]
	High (>3.3)	

[a] Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.

[b] See Special Considerations for Breast Cancer in Men (Sex Assigned Male at Birth) (BINV-J).

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GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

Assay	Recurrence Risk/ Predictive Result	Treatment Implications
Breast Cancer Index (BCI)	BCI (H/I) Low	• For patients with T1 and T2 HR-positive, HER2-negative, and pN0 tumors, a BCI (H/I) in the low-risk range (0–5), regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0,M0. • Patients with BCI (H/I) low demonstrated a lower risk of distant recurrence (compared to BCI [H/I] high) and no significant improvement in DFS or OS compared to the control arm in terms of extending endocrine therapy duration.[9]
	BCI (H/I) High	• For patients with T1 HR-positive, HER2-negative, and pN0 tumors, a BCI (H/I) high (5.1–10) demonstrated significant rates of late distant recurrence. • In secondary analyses of the MA.17, Trans-aTTom, and IDEAL trials, patients with HR-positive, T1–T3, pN0 or pN+ who had a BCI (H/I) high demonstrated significant improvements in DFS when adjuvant endocrine therapy was extended, compared to the control arm.[9-12] • In contrast, BCI (H/I) low patients derived no benefit from extended adjuvant therapy.[9]

[a] Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.
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BINV-N
4 OF 5

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY
References

[1] Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 2018;379:111-121.

[2] Kalinsky K, Barlow WE, Meric-Bernstam F, et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) < 25: SWOG S1007 (RxPonder). SABCS 2021;81(4): Abstract GS3-00.

[3] Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 2016;375:717-729.

[4] Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol. 2021:S1470-2045(21)00007-3.

[5] Laenkholm AV, Jensen MB, Eriksen JO, et al. PAM50 risk of recurrence score predicts 10-year distant recurrence in a comprehensive Danish cohort of postmenopausal women allocated to 5 years of endocrine therapy for hormone receptor-positive early breast cancer. J Clin Oncol 2018;36:735-740.

[6] Sestak I, Buus R, Cuzick J, et al. Comparison of the performance of 6 prognostic signatures for estrogen receptor–positive breast cancer: A secondary analysis of a randomized clinical trial. JAMA Oncol 2018;4:545-553.

[7] Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin Cancer Res 2011;17:6012-6020.

[8] Sestak I, Martín M, Dubsky P, et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. Breast Cancer Res Treat 2019;176:377-386.

[9] Noordhoek I, Treuner K, Putter H, et al. Breast cancer index predicts extended endocrine benefit to individualize selection of patients with HR(+) early-stage breast cancer for 10 years of endocrine Therapy. Clin Cancer Res 2021;27:311-319.

[10] Sgroi DC, Carney E, Zarrella E, et al. Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker. J Natl Cancer Inst 2013;105:1036-1042.

[11] Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al. Optimal duration of extended adjuvant endocrine therapy for early breast cancer; Results of the IDEAL Trial (BOOG 2006-05). J Natl Cancer Inst 2017;110:40-48.

[12] Bartlett JMS, Sgroi DC, Treuner K, et al. Breast cancer index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial. Ann Oncol 2019;30:1776-1783.

[a] Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.

[b] See Special Considerations for Breast Cancer in Men (Sex Assigned Male at Birth) (BINV-J).

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Table 4. **Pathological Prognostic Stage (continued)**

TNM	Grade	HER2	ER	PR	Stage
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	
			Negative	Positive	IIIB
				Negative	
		Negative	Positive	Positive	IIIA
				Negative	
			Negative	Positive	IIIB
				Negative	
	G2	Positive	Positive	Positive	IIIA
				Negative	
			Negative	Positive	IIIB
				Negative	
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	
				Negative	IIIC
	G3	Positive	Positive	Positive	IIIB
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	IIIC
				Negative	
Any T Any N M1	Any	Any	Any	Any	IV

Notes:
1. For cases with lymph node involvement with no evidence of primary tumor (e.g. T0 N1, etc.) or with breast ductal carcinoma *in situ* (e.g. Tis N1, etc.), the grade, HER2, ER and PR information from the tumor in the lymph node should be used for assigning stage group.
2. For cases where HER2 is determined to be "equivocal" by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, HER2 "negative" category should be used for staging in the Pathological Prognostic Stage Group.
3. The prognostic value of these Prognostic Stage Groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).

Table 5. **Genomic Profile for Pathologic Prognostic Staging**

When Oncotype DX Score is Less than 11...

TNM	Grade	HER2	ER	PR	Stage
T1 N0 M0 T2 N0 M0	Any	Negative	Positive	Any	IA

Notes:
1. Obtaining genomic profiles is NOT required for assigning Pathological Prognostic Stage. However genomic profiles may be performed for use in determining appropriate treatment. If the OncotypeDx® test is performed in cases with a T1N0M0 or T2N0M0 cancer that is HER2-negative and ER-positive, and the recurrence score is less than 11, the case should be assigned Pathological Prognostic Stage Group IA.
2. If OncotypeDx® is not performed, or if it is performed and the OncotypeDx® score is not available, or is 11 or greater for patients with T1–2 N0 M0 HER2– negative, ER-positive cancer, then the Prognostic Stage Group is assigned based on the anatomic and biomarker categories shown above.
3. OncotypeDx® is the only multigene panel included to classify Pathologic Prognostic Stage because prospective Level I data supports this use for patients with a score less than 11. Future updates to the staging system may include results from other multigene panels to assign cohorts of patients to Prognostic Stage Groups based on the then available evidence. Inclusion or exclusion in this staging table of a genomic profile assay is not an endorsement of any specific assay and should not limit appropriate clinical use of any genomic profile assay based on evidence available at the time of treatment.

***N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively.

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