Individualize the Risk of Recurrence in **Early Breast Cancer**

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The Importance of Assessing Risk in HR+/HER2- eBC

Too many patients with HR+ eBC remain at risk of both early and late recurrence, even after ET[1-4]

Patients with stage II or III disease face a considerable risk of recurrence, regardless of nodal involvement. This risk persists despite adjuvant ET and remains a significant concern for decades.

- **~50%** of women who **experience a recurrence** do so **within 5 years** of diagnosis[5,6]

For patients with no to low nodal involvement, this risk is often underestimated[1-4]

Risk of recurrence despite ET for patients with stage II/III (N0–N1) HR+ eBC

	Risk of invasive disease, including risk of recurrence, within 3 YEARS of diagnosis	Risk of distant recurrence within 20 YEARS of diagnosis
N0 (no nodal involvement)	Up to **11%**	**29%**
N1 (1–3 positive nodes)	Up to **13%**	**31%**

20-year figures reflect patients with T1/T2 disease.

MOST RECURRENCES will be to metastatic disease, for which there is currently NO CURE

The 3-year and 20-year data are not from a longitudinal study.
3-year risk is based on the iDFS outcomes of patients with HR+/HER2- eBC who received ET alone in select CDK4/6 inhibitor clinical trials.[1,2]
20-year risk of distant recurrence is from a meta-analysis of 78 randomized trials in the EBCTCG database of 74,194 women with ER+ breast cancer who had 5 years of scheduled ET.[3]

CDK4/6, cyclin-dependent kinase 4/6; eBC, early breast cancer; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; ER+, estrogen receptor–positive; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2–negative; HR+, hormone receptor–positive; iDFS, invasive disease–free survival; N, lymph node; T, tumor size.

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Risk of recurrence can be underestimated for patients with no to low nodal involvement[1-4]

Risk within 3 years of diagnosis

Risk of invasive disease, including risk of recurrence for patients with stage II/III HR+/HER2- eBC[1,2]

	Patient Type	Risk (Up To)
NODAL STATUS	**N0** (no nodal involvement)	11%
	N1 (1–3 nodes)	13%
	N2–N3 (4+ nodes)	24%
STAGE	Stage II	12%
	Stage III*	21%

*The 3-year rate listed for stage III includes some stage IIB patients, due to differentiated data breakouts between trials.

3-year risk is based on the iDFS outcomes of patients with HR+/HER2- eBC who received ET alone in select CDK4/6 inhibitor clinical trials.[1,2]

The 3-year and 20-year data are not from a longitudinal study.

Risk within 20 years of diagnosis

Risk of distant recurrence for patients with stage II/III HR+ eBC[3,4]

	Patient Type	Risk
NODAL STATUS	**N0** (no nodal involvement)	29%
	N1 (1–3 nodes)	31%
	N2 (4–9 nodes)	52%
STAGE	Stage II	27%–37%
	Stage III	46%–57%

Analysis included patients with T1/T2 disease and <10 involved nodes.

20-year risk of distant recurrence is from a meta-analysis of 78 randomized trials in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) database of 74,194 women with ER+ breast cancer who had 5 years of scheduled ET.[3]

The 3-year and 20-year data are not from a longitudinal study.

Although assessment varies on an individual basis, risk of recurrence can remain for decades despite adjuvant ET treatment[3,4,7-9]

Estimates of recurrence risk can guide treatment decisions

Risk assessments are used to inform treatment decisions for adjuvant chemotherapy and adjuvant ET. Most risk assessments are based on[7-9]:

Clinical/pathological features

AND/OR

Genomic risk

LOW RISK
Adjuvant ET

HIGH RISK
Adjuvant chemotherapy

- ⊕ Alone, may be useful in patients at low to intermediate risk; in combination with other therapies, may have utility for higher-risk patients[7,9]
- ⊖ Women with node-positive HR+/HER2- eBC receiving ET alone may experience recurrence or death within 5 years of initiating treatment[10-13]

Some patients are neither clearly high risk nor low risk, further complicating treatment decisions

- ⊕ Often indicated for patients at high risk, independent of menopausal status[7,9]
- ⊖ Benefits of chemotherapy may not outweigh the risk of avoidable adverse events for all high-risk patients[14]

Despite established utility of current risk assessment methodologies, questions remain

- Where do newer treatment options fit? For whom are they suitable?
- What is the best method to assess recurrence risk?
- Can recurrence risk be further personalized?
- What level of risk of recurrence is my patient comfortable with?

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Clinical and Pathologic Features Provide Important Information for Risk Assessment[9,15]

Key prognostic features include:

- **Nodal status**
- Age
- Menopausal status
- **Tumor grade**
- **Tumor size**
- Tumor type
- ER/PR/HER2 status
- CTCs/ctDNA[7]
- Comorbidities[6,16,17]

Many of these factors have been incorporated into online risk calculators[18,19]

Several studies have observed **significant limitations when prognosis is based only on clinical/pathologic features**, including inter-observer variability and high heterogeneity in disease course[19]

Despite limited clinical utility, Ki-67 may be used in conjunction with clinical-pathologic features to estimate recurrence risk in eBC[7]

- However, because of **analytic and reproducibility concerns with Ki-67 testing**, ASCO recommends its use when GEP assays are unavailable[7]

ASCO, American Society of Clinical Oncology; CTCs, circulating tumor cells; ctDNA, circulating tumor DNA; GEP, gene expression profiling; PR, progesterone receptor.

GEP Assays Were Developed to Improve Prognostic Precision

GEP assays assess the normalized gene expression of proliferation and invasion genes (among others) to generate a quantitative risk assessment[12,19,20]

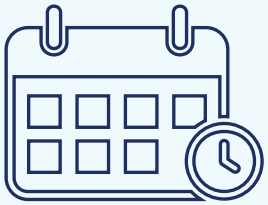
- The number and function of genes measured vary by assay[12,19,20]

Multiple commercial GEP assays exist and differ by[7,19]:

Number of genes assessed

Place in guideline recommendations

Established clinical utility[7,8,10]



- Assess the risk of recurrence within 0–10 years
- Identify patients who may benefit from:
  - Adjuvant chemotherapy
  - Extended ET after 5 years

Since 2007, HR+ eBC treatment decisions have been guided by GEP risk assessments[8,21]

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ASCO guideline recommendations on appropriate use of commercially available GEP assays[7,8,19,a]

Assay	Genes Assessed[b]	Predictive Utility	Prognostic Utility
Oncotype DX®	21	**Yes**, if patient is node-neg, or postmenopausal and node-pos with 1–3 pos nodes	✓
Prosigna®	50	**Yes**, if patient is postmenopausal and node-neg	✓
MammaPrint®	70	**Yes**, if patient is >50 years with high clinical risk (per MINDACT trial criteria), and node-neg or node-pos with 1–3 pos nodes	✓
EndoPredict®	12	**Yes**, if patient is postmenopausal and node-neg or node-pos with 1–3 pos nodes	✓
Breast Cancer Index®	7	**Yes**, if patient is node-neg or node-pos with 1–3 pos nodes, and has been treated with 5 years of primary ET	✓

Per ASCO guidelines, all GEP assays may guide decisions for adjuvant therapy in select patients[7]

Breast Cancer Index is a registered trademark of Hologic, Inc.; **EndoPredict** is a registered trademark of Myriad Genetics, Inc.; **MammaPrint** is a registered trademark of Agendia; **Oncotype DX** is a registered trademark of Exact Sciences Corporation; **Prosigna** is a registered trademark of Veracyte, Inc.

[a]Includes strong and moderate recommendations only for patients with ER+ and HER2- early-stage invasive breast cancer.
[b]Includes both reference genes and cancer-associated genes.

MINDACT, Microarray In Node negative Disease may Avoid ChemoTherapy; neg, negative; pos, positive.

Despite established clinical utility, many patients do not receive GEP testing, including:

- Black women[22-26]
- Patients with lymph node–positive disease[22]
- Patients with lower SES[22,23]
- Patients with larger tumors[24-26]
- Patients in rural areas[27]
- Patients of older age[22-26]

Many of these patients **may not receive guideline-concordant care**[7]

ASCO recommends all premenopausal women with HR+, HER2-, node-negative breast cancer receive GEP testing[7]

ASCO recommends all postmenopausal women with HR+, HER2- breast cancer with <4 positive lymph nodes receive GEP testing[7]

Limitations of GEP testing

- Different GEP assays may provide different risk assessments for the same patient[28]
- Key trials and retrospective analyses examining the utility of GEP assays suggest these tests underestimate risk of recurrence in:

Black and Hispanic patients[24,29-31]

Despite similar risk scores, Black and Hispanic patients have worse outcomes than others

Male patients[32]

Men have higher mortality rates than women with the same GEP risk score

- The suboptimal performance of GEP assays in select patient populations deserves further investigation and calls for more diversity in clinical trials[29,32]

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SES, socioeconomic status.

GEP Assays Are Key to Risk Estimates. Integrating Clinical Features May Refine Them

Many GEP assays do not directly evaluate key prognostic factors like[19,33]:

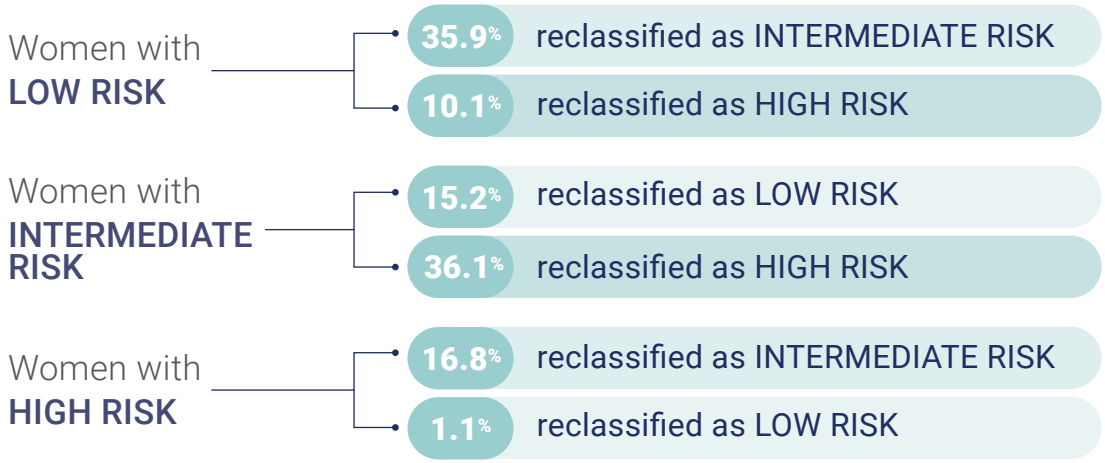
- Nodal status
- Age
- Menopausal status
- Tumor size
- Tumor grade

Some commercial GEP reports may include the impact of nodal status, age, and menopause on risk estimates and expected therapy benefit using subgroup analyses from key trials[34,35]

ASCO recommendations for GEP test result interpretation incorporate age, menopausal status, and nodal status[7]

Studies suggest that combining clinical/pathologic features with GEP assays may improve risk estimates[15,36-39]

- An RWE study demonstrated that **integrating a clinical-pathologic prognosis with a GEP assay changed the prognosis for[38]:**



Original low-, intermediate-, and high-risk estimates were based on the original Oncotype DX® risk score definitions, where low risk is defined as having an RS<18, intermediate risk is defined as having an RS where 18≤RS≤30, and high risk is defined as having an RS≥31. Updated risk estimates were defined as the following: low (<12% risk), intermediate (12%-20% risk), and high (>20% risk).

- Appropriate risk assessment for N0 patients requires consideration beyond nodal status, encompassing factors that also play a role in risk of recurrence, like age, tumor size, and grade[40]
- Trials on new risk tools that incorporate clinical pathologic features with GEP assays show improved risk assessments with narrower confidence intervals[39]

RS, recurrence score; RWE, real-world evidence.

NOTES

Combining complementary prognostic information may provide **the full picture of your patient's individualized risk of recurrence**[18,38,39,41]

Clinical-pathologic features + Genomic risk = Personalized prognosis

Establishing this full picture facilitates a more personalized discussion with your patient on their individual risk, their comfort with that risk, and potential treatment options to manage it[7]

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Appropriate risk assessment identifies the risk of recurrence for a patient and treatment recommendations[7]

Prognosis based on **clinical-pathologic features alone lacks the precision** of newer risk assessment methodologies[12,19]

GEP assays are essential to personalized assessments **but may not provide the full picture of a patient's risk when used alone**[7,9,24,29-31]

Integrating a prognosis from clinical-pathologic features with GEP assay results may create a **more personalized recurrence risk estimate**[32,38,39]

Understanding and discussing your patients' personalized risk of recurrence enables **informed shared decision-making**[9]

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