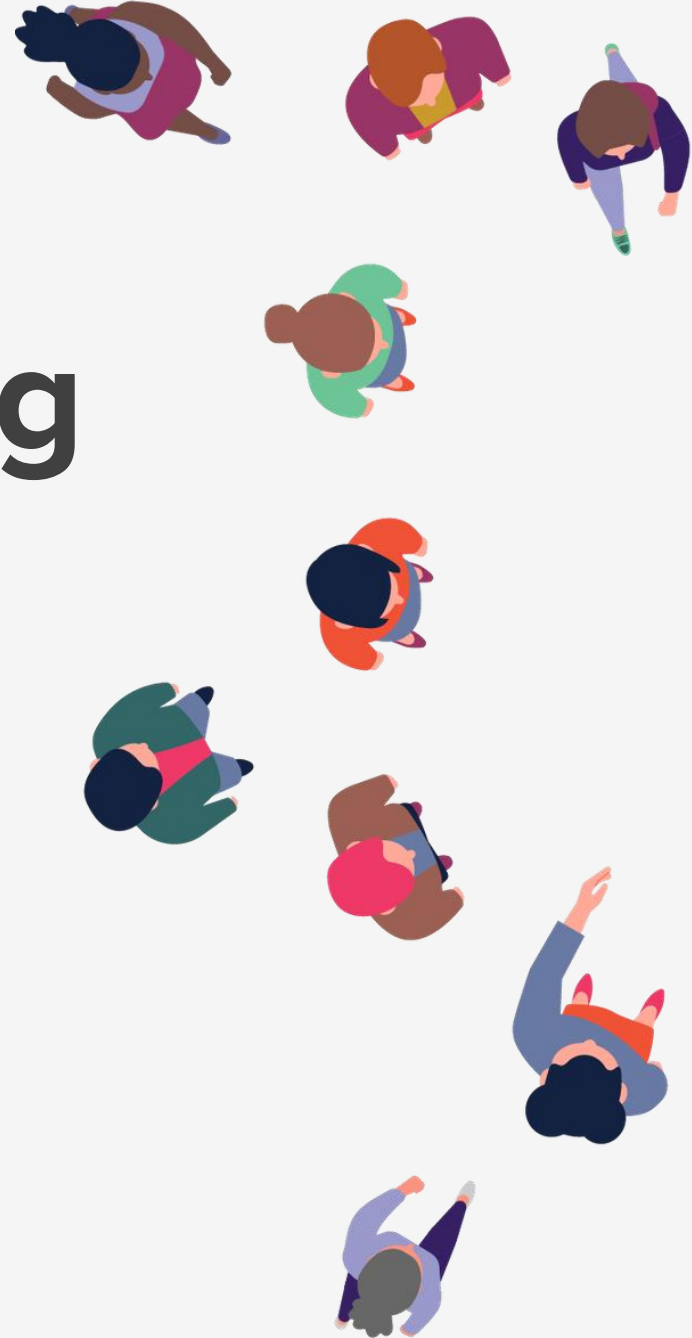


Understanding testing

Early-stage breast cancer

Speaker: Eleonora Teplinsky, MD, FASCO



Biomarkers in Early-Stage Breast Cancer

Eleonora Teplinsky, MD, FASCO

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October 3, 2026

@drteplinsky



Disclosures

- Honoraria: Sermo, MJH Life Sciences, Total Health Conferencing
- Consulting/Advisory Role: Novartis, Daiichi Sankyo, Astra Zeneca, Pfizer, Abbvie
- Travel: MJH Life Sciences, Total Health Conferencing, Novartis

What is a biomarker?



A measurable molecular feature (such as a gene or protein) that signals how a cancer is likely to behave or respond to treatment.



A biomarker can be prognostic (for example: risk of the cancer coming back) and/or predictive (whether a specific treatment will work)



We will discuss what we test, what we don't and what's coming

The biomarkers we check in
everyone with early-stage
breast cancer

For every invasive breast cancer:

- Estrogen receptor/progesterone receptor: hormone receptors that predict endocrine therapy benefit
- HER2: predicts benefit from HER2 targeted therapy
- Ki67: marker of proliferation/aggressiveness
- In early-stage (stage 1-3) breast cancer, we can use genomic assays for HR+/HER2- disease to help make decisions about chemotherapy

Genomic tests that help us
omit chemotherapy

Genomic Assays

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)
21-gene (Oncotype Dx) for pN1 (1–3 positive nodes)^c	Yes	Yes	Postmenopausal: Preferred	1	BINV-N (2)
			Premenopausal: Other	2A	
70-gene (MammaPrint) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	1	BINV-N (3)
50-gene (Prosigna) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3)
12-gene (EndoPredict) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3)
Breast Cancer Index (BCI)	Predictive of benefit of extended adjuvant endocrine therapy	Yes	Other	2A	BINV-N (4)

Oncotype Dx

Oncotype DX Breast Recurrence Score® Report Node Positive (N1mic and N1) Premenopausal

EXACT
SCIENCES

PATIENT, SAMPLE

Date of Birth: 01-Jan-1950 Gender: Female Report Number: OR000123456-3008 Report Date: 12-Dec-2023
Specimen Source/ID: Breast/SP-16_0123456 Date of Collection: 27-Nov-2023
Ordering Physician: Dr. First-Name I. Ordering-Physician-Last-Name

Recurrence Score® (RS) Result

16

Clinical factors may be considered with the RS when making individual treatment decisions.

Distant Recurrence Risk at 5 Years

ET Alone

6%

95% CI (5%, 8%)

RxPONDER¹

ET = Endocrine Therapy
CI = Confidence Intervals

Group Average Absolute Chemotherapy (CT) Benefit*

RS 14-25

2.7%

95% CI (-0.5%, 5.9%)

RxPONDER²

*It is not known whether the benefit observed with chemotherapy is due to chemotherapy alone, ovarian function suppression or a combination of the two.

Oncotype DX Breast Recurrence Score® Report Node Positive (N1mic and N1) Premenopausal

EXACT
SCIENCES

PATIENT, SAMPLE

Date of Birth: 01-Jan-1950 Gender: Female Report Number: OR000123456-3008 Report Date: 12-Dec-2023
Specimen Source/ID: Breast/SP-16_0123456 Date of Collection: 27-Nov-2023
Ordering Physician: Dr. First-Name I. Ordering-Physician-Last-Name

Medical Record/Patient #: 1234567-01

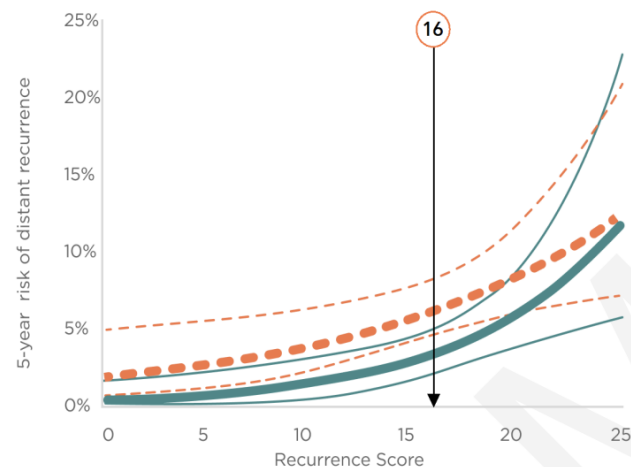
Client: Community Medical Center

Specimen Received: 29-Nov-2023

Additional Recipient: Dr. First-Name I. Recipient-Physician-Last-Name

Pathologist: Dr. First-Name I. Pathologist-Last-Name

RxPONDER²



ET+CHEMO

95% CI

ET ALONE

95% CI

Methods and Limitations

The Oncotype DX Breast Recurrence Score test uses RT-PCR to provide information on prognosis and the magnitude of chemotherapy benefit to guide chemotherapy treatment decisions in patients with early-stage, HR+, HER2-negative and lymph node-negative or lymph node-positive (N1) breast cancer. Decisions on treatment should also be based on independent medical judgment of the treating physician taking into consideration all available information concerning the patient's medical condition, in accordance with your community's standard of care.

The **Recurrence Score (RS) Result** which ranges from 0-100 is calculated from the quantitative RT-PCR analysis of 21 specific genes.

Quantitative Single-Gene Scores for quality control. The Oncotype DX test uses quantitative RT-PCR to determine the RNA expression of ER, PR and HER2, using the published validated cut-offs.^{3,4} The standard deviations of single-gene results are less than 0.5 units. The RT-PCR single-gene results may differ from ER, PR, or HER2 results reported using other methods or reported by other laboratories.

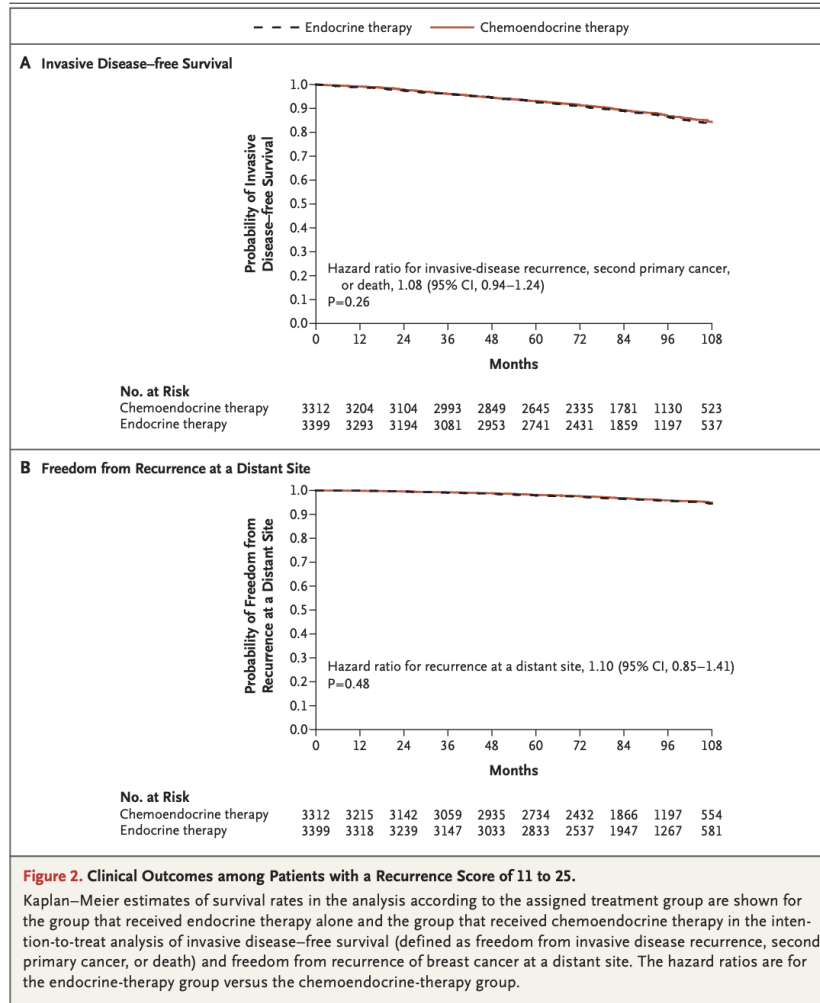
The definitions of **menopausal status** based upon the RxPONDER² trial are as follows:

- **Premenopausal:** Less than 6 months since last menstrual period and no prior bilateral oophorectomy and not on estrogen replacement.
- **Postmenopausal:** Prior bilateral oophorectomy or more than 12 months since last menstrual period with no prior hysterectomy.
- If these definitions did not apply, patients were categorized as premenopausal if <50 years and postmenopausal if ≥50 years.

Distant Recurrence-Free Interval (DRFI): Time from randomization to distant recurrence or death from breast cancer.

Invasive Disease-Free Survival (IDFS): Time from randomization to invasive breast cancer recurrence (local, regional, or distant), second invasive primary cancer (breast cancer or not) or death from any cause.

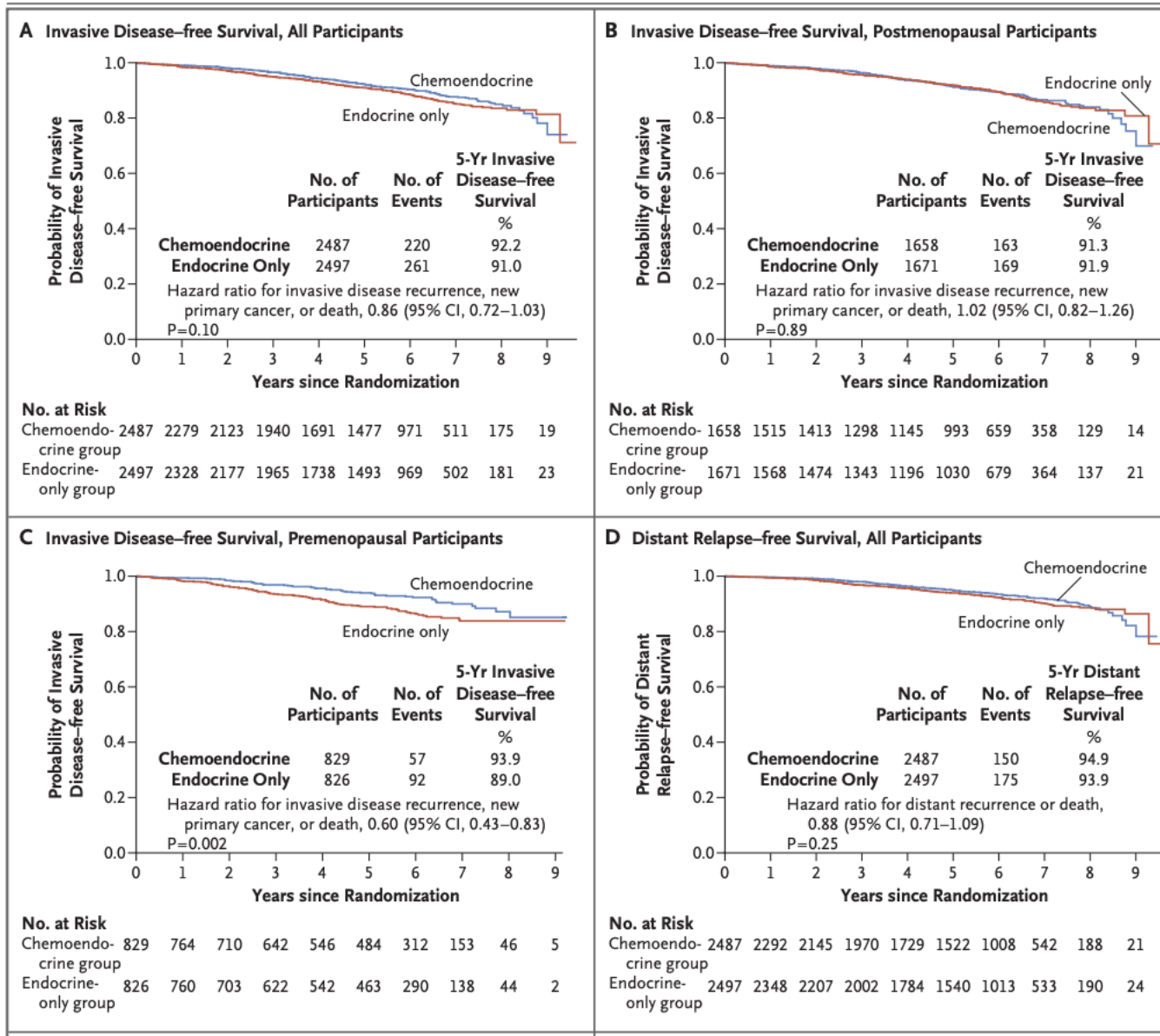
TAILORx Trial: Chemo + Endocrine Therapy vs Endocrine Therapy alone for Oncotype 11-25



- Endocrine therapy was noninferior to chemoendocrine therapy for invasive disease-free survival and freedom from recurrence at a distant site.
- At 9 years the two treatment groups had similar rates of invasive disease-free survival: 83.3% ET vs 84.3% chemo+ET
- Freedom from disease recurrence at a distant site: 94.5% and 95%
- Overall survival: 93.9% vs 93.8%
- Some benefit of chemotherapy found in women 50 years of age or younger with a recurrence score of 16 to 25 (but also could be due to the impact of chemotherapy on ovarian function).

RxPONDER Trial: ChemoET vs ET alone for Oncotype 25 or lower and 1-3 positive LNs

*Is it chemo or is it ovarian
suppression?*



NCCN Guidelines for Oncotype Use:

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY^{a,b}

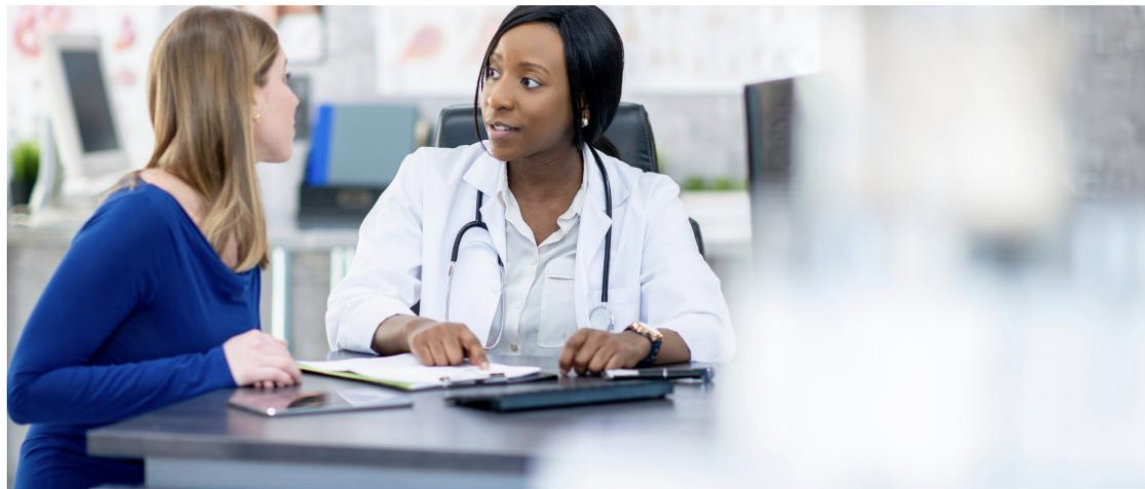
Assay	Recurrence Risk	Treatment Implications
21-gene (Oncotype Dx) (for postmenopausal patients with pN0 and pN1 [1–3 positive nodes])^c	<26	Patients with pT1b/c–2, pN0, HR-positive, HER2-negative tumors, with recurrence scores between 0–10 have a risk of distant recurrence of <4% and those with recurrence scores 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 recurrence scores <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 a recurrence score ≥26, the addition of chemotherapy to endocrine therapy is recommended. ^{1,2}
21-gene (Oncotype Dx) (for premenopausal patients: pN0)	≤15	Premenopausal patients with pT1b/c –2, pN0, HR-positive, HER2-negative tumors with recurrence scores <16 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study. ¹
	16–25	In premenopausal patients with recurrence scores 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, OFS combined with either tamoxifen or an aromatase inhibitor.
	≥26	In premenopausal patients with HR-positive, HER2-negative, and pN0 tumors and a recurrence score ≥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 a recurrence score <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, OFS combined with either tamoxifen or an aromatase inhibitor. ²
	≥26	In premenopausal patients with HR-positive, HER2-negative, pT1–3 and pN1 (1–3 positive nodes) tumors and a recurrence score ≥26, the addition of chemotherapy to endocrine therapy is recommended. ²

Ongoing OFSET Trial

The OFSET Study: Testing the addition of chemotherapy to the usual treatment of ovarian function suppression plus hormonal therapy in premenopausal ER-positive/HER2-negative breast cancer patients who are at high risk of cancer returning.

NRG
ONCOLOGY

Advancing Research. Improving Lives.™



Visit the patient
webpage for this
study:



ABOUT THE TRIAL

NRG-BR009: The OFSET Study

A Phase III Adjuvant Trial Evaluating the Addition of Adjuvant Chemotherapy to Ovarian Function Suppression plus Endocrine Therapy in Premenopausal Patients with pN0-1, ER-Positive/HER2-Negative Breast Cancer and an Oncotype Recurrence Score ≤ 25 (OFSET)

MammaPrint

- Clinical-pathologic features (tumor size, grade, nodes) tell you a patient looks high-risk, but that can end up overtreating patients with chemotherapy
- MammaPrint evaluates 70 genes tied to metastatic potential
- Genomic low risk vs high risk
- MINDACT prospectively enrolled ~6,700 women (0-3 positive nodes), scored each by clinical risk (modified Adjuvant! Online) and genomic risk (MammaPrint), and randomized the discordant patients.
- A total of 1550 patients (23.2%) were deemed to be at high clinical risk and low genomic risk.
- The key group: high clinical risk but low genomic risk, randomized to chemo or no chemo

MammaPrint – MINDACT Trial

- At 5 years, the rate of survival without distant metastasis in this group was 94.7% among those not receiving chemotherapy. The absolute difference in this survival rate between these patients and those who received chemotherapy was 1.5 percentage points, with the rate being lower without chemotherapy.
- 8-year estimates for distant metastasis free survival was 92% for chemotherapy vs 89.4% for no chemotherapy (absolute benefit of 2.6%)
- ~46% of clinically high-risk patients were reclassified as genomically low-risk and could safely forgo chemotherapy.
- The chemo benefit in the high-clinical/low-genomic group was age-dependent: a clinically meaningful ~5 percentage point 8-year DMFS gain in women ≤ 50 , versus essentially none (0.2 points) in women > 50 .
- Benefit of chemotherapy was not enhanced by nodal positivity
- This is likely chemotherapy-induced ovarian suppression rather than a true cytotoxic effect.

MammaPrint

Explore BluePrint Molecular Subtypes

Luminal-Type

- ✓ Driven primarily by estrogen and progesterone hormone pathways
- ✓ Stratified by MammaPrint into Luminal A-Type and Luminal B-Type
- ✓ Luminal A-Type is associated with Low Risk
- ✓ Luminal B-Type is associated with High Risk
- ✓ Distinct outcomes support more informed treatment planning

HER2-Type

- ✓ Driven primarily by the HER2 pathway
- ✓ May not always align with IHC- or FISH-derived HER2 results
- ✓ Often responds well to HER2-targeted therapies in the neoadjuvant setting
- ✓ HER2-targeted agents are associated with good long-term outcomes

Basal-Type

- ✓ Not driven by ER, PR, or HER2 pathways
- ✓ Acts more like triple-negative breast cancer clinically
- ✓ More aggressive subtype that may benefit from standard or novel TNBC regimens
- ✓ Select patients may benefit from neoadjuvant treatment

Prosigna Breast Cancer Prognostic Gene Signature Assay (PAM50)

- 50-gene signature → 4 intrinsic subtypes: luminal A, luminal B, HER2-enriched, basal-like
- Combines gene expression + tumor size → Risk of Recurrence (ROR) score, 0–100
- Risk group: low, intermediate and high
- Prosigna is driven largely by proliferation genes, in contrast to Oncotype DX (more estrogen-related genes)
 - You can get discordance between Prosigna and Oncotype scores

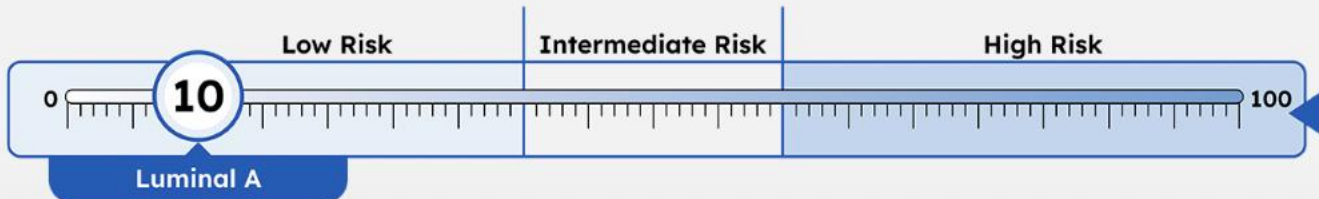
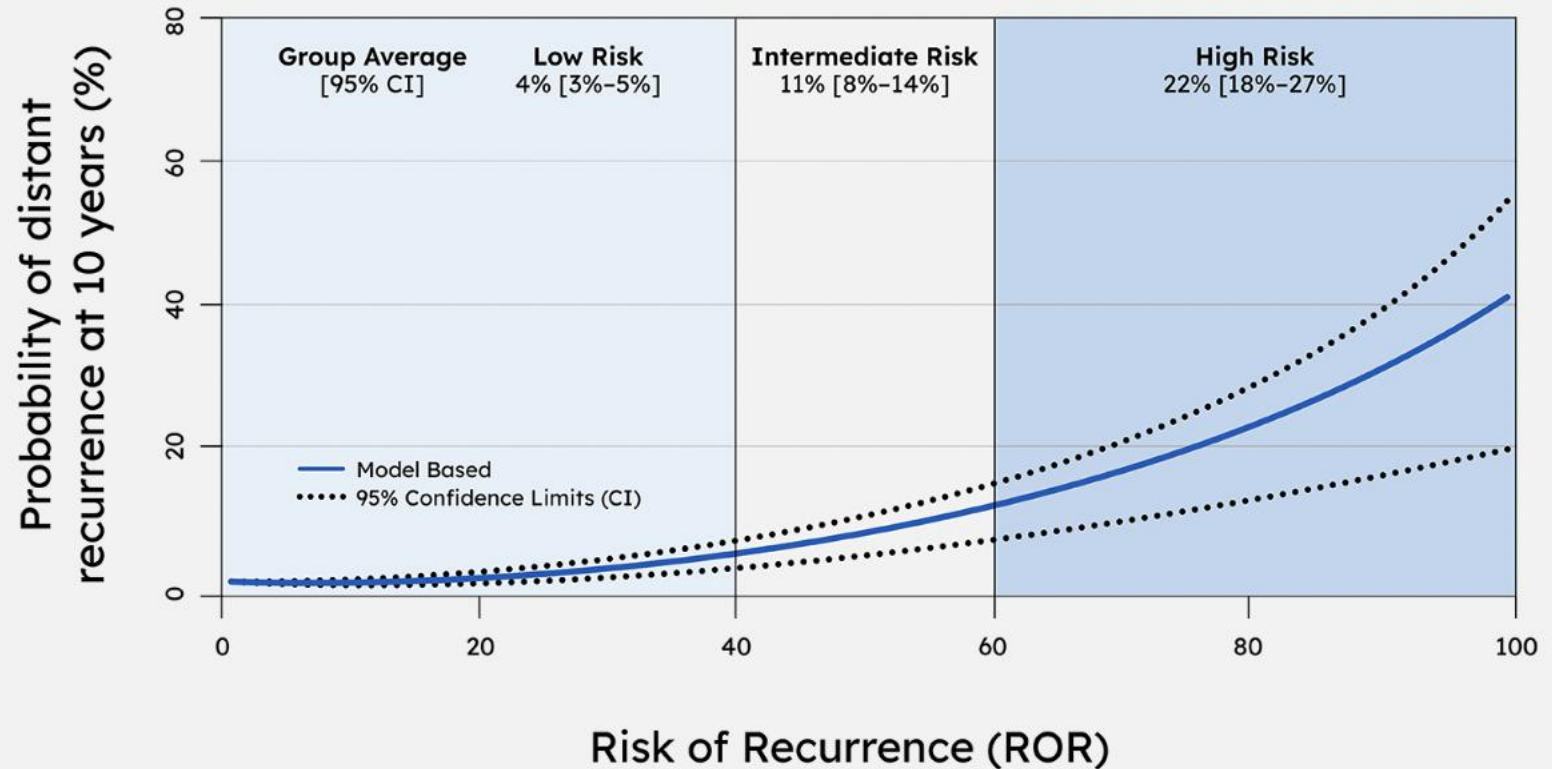
Prosigna

Reports:

- Risk Group (Low, Intermediate, High)
- Risk of Recurrence (ROR) Score
- Intrinsic Subtype (Luminal A, Luminal B, HER2-enriched, Basal-like)

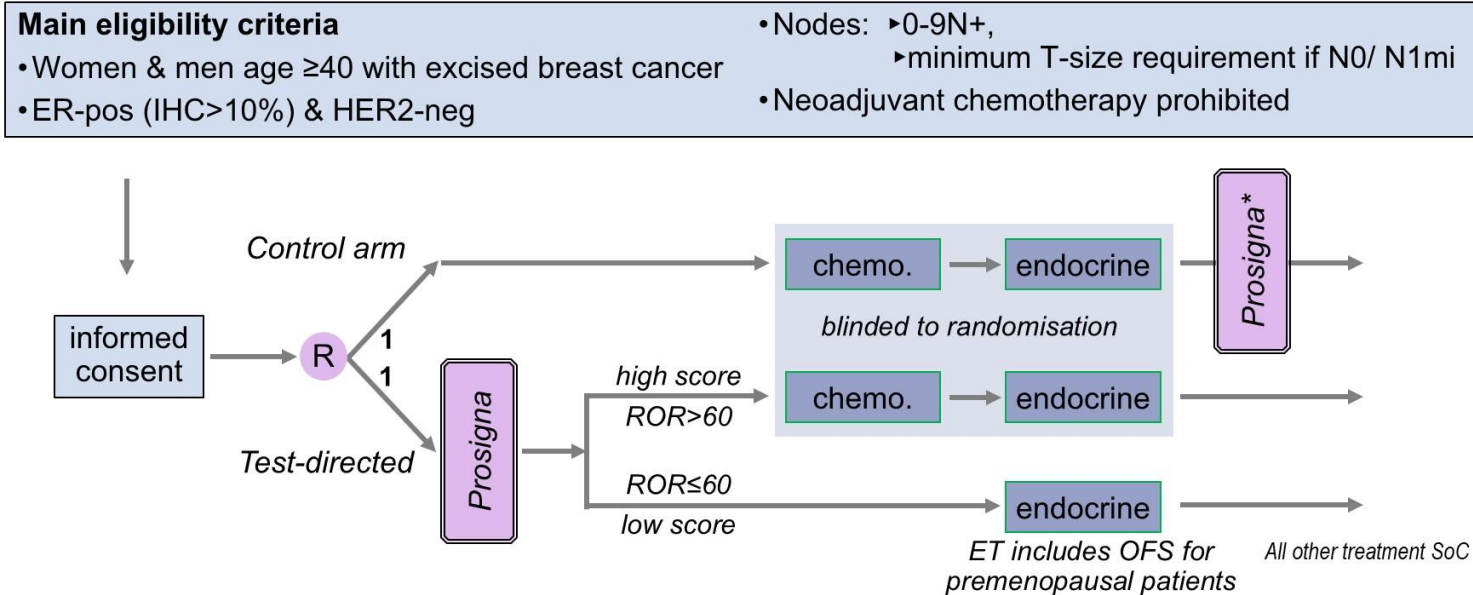
Clinical Trial Results: Probability of Distant Recurrence

(based on combined analysis of 2,400 women from the ABCSG-8 and TransATAC cohorts)



OPTIMA Trial

OPTIMA design



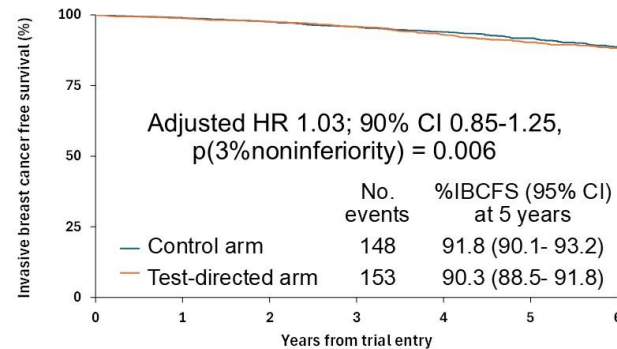
*Control arm Prosigna testing used for analysis only. U.K. control arm testing performed following recruitment completion

- 4153 patients total;
2059=control arm; 2094= test directed arm
- Median age 56 (40-84) yrs
- 37% premenopausal; 62% postmenopausal, 1% men
- 69% had grade 1-2 tumors; 54% with tumor size $<3\text{cm}$
- Nodal status: 8% lymph node negative/ micrometastases; 73% had 1-3 positive lymph nodes and 19% had 4-9 positive lymph nodes

OPTIMA Trial Results

Invasive Breast Cancer Free Survival

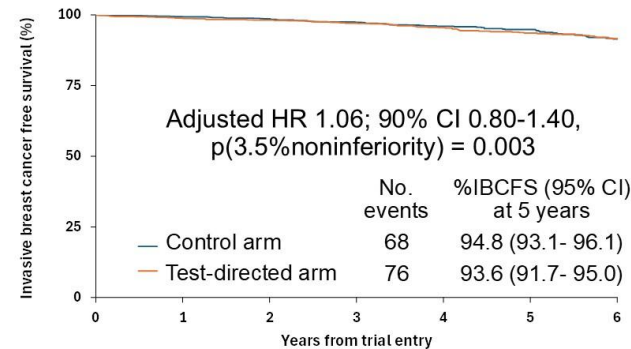
Complete Per Protocol population



Number at risk:							
Control	2059	1818	1563	1283	999	741	485
Test-directed	2094	1857	1591	1303	989	724	481

Demonstrated non-inferiority limit = 2%
 No certainty of chemotherapy benefit
 1.5% observed 5-year difference –favors chemotherapy

ROR ≤60 subpopulation



Number at risk:							
Control	1358	1207	1043	862	672	504	337
Test-directed	1421	1257	1086	905	694	503	342

Demonstrated non-inferiority limit = 2%
 No certainty of chemotherapy benefit
 1.2% observed 5-year difference –favors chemotherapy

- No difference in distant recurrence free interval
- In low ROR score population, IBCFS by menopausal status: 1.3% observed 5-year difference favoring chemotherapy in both pre- and postmenopausal women
- In low ROR score population, IBCFS by nodal status: 1.6% observed 5-year difference, favoring chemotherapy in both 1-3 involved nodes and 4-9 involved nodes groups

OPTIMA Trial

- Limitations: excluded premenopausal women <40; time driven analysis and 63% of patients have under 5 years f/u; predominantly white population
- Need longer term follow-up
- Caution re extrapolating data from OPTIMA using Prosigna ROR to utilizing Oncotype or MammaPrint to make similar treatment choices as there is discordance between the tests
- Premenopausal women were mandated to receive ovarian function suppression- not everyone can tolerate OFS
- Do CDK 4/6 inhibitors attenuate benefit of chemotherapy? How will SERDs change this landscape as well?
- OFSET and OPTIMA YOUNG trials will help us further in premenopausal population

Extended Endocrine Therapy & BCI

- Gene expression assay (sent on your pathology specimen) that provides prognostic information about distant (metastatic) recurrence risk and predicts benefit from extended endocrine therapy (beyond 5 years) in patients with HR+ stage I-III breast cancer.
- Looks at two biomarker panels: the Molecular Grade Index (MGI), which assesses tumor proliferation (by measuring 5 cell cycle related genes), and the two-gene ratio: *HOXB13/IL17BR (H/I)*, which measures endocrine sensitivity and estrogen signaling. The two components are integrated into the BCI score which provides risk estimates for distant recurrence.
- **Predictive Result: Am I likely to benefit from extended endocrine therapy?**
- **Prognostic Result: What is my risk of late distant recurrence (5-10 years)?**

Sample BCI Report

Suzie Smith		BREAST CANCER INDEX™	
Patient and Order Information			
Order ID:.....ORD-####	Specimen ID:.....A1-001234	Date Received:.....11/01/2019	
DOB (Gender): 02/02/1960 (Female)	Date of Collection: 10/01/2014	Date Reported:.....11/10/2019	

1

Results are based on the following information (provided with order):

Nodal Status: Lymph Node-Negative (N0)

2

Breast Cancer Index Test Results

Extended Endocrine Therapy Benefit & Risk of Late Distant Recurrence

PREDICTIVE RESULT

Am I likely to benefit from extended endocrine therapy?

YES

3a

PROGNOSTIC RESULT

What is my risk of late distant recurrence (5-10 years)?

With 5 total years of adjuvant endocrine therapy:

8.0%

3b

With 10 total years of adjuvant endocrine therapy:

2.6 - 3.4%

Across trials, those identified by BCI as YES (H/I-High) experienced a 58-67% relative risk reduction with extended endocrine therapy*

*Individual benefit may vary based on treatment history, risk factors and treatment adherence. Data to support interpretation of the Predictive and Prognostic Results above, including assay description, applicability of results and clinical validation data, are provided on page 2.

Additional Comments

Ordering Provider	Submitting Pathologist
First I. Last, M.D. ABC Facility 1234 ABC Street Anywhere, USA 12345 Phone: 111.222.3333 Fax: 100.200.3000	First I. Last, M.D. XYZ Pathology 456 XYZ Street Anywhere, USA 12345 Phone: 444.555.6666 Fax: 400.500.6000

Biotheranostics, Inc.

A Hologic Company

Laboratory Director: _____
Electronically Signed By: _____

6333 Sequence Dr.
San Diego, CA 92121
Tel: 877.886.6739

Page 1 of 2
BCI-479

BCI Data

	Stockholm ³	MA.17 ⁴	Trans-aTTom ⁵	IDEAL ⁶	B-42 ⁷
Study Design	600 Patients TAM vs No therapy 2 or 5 Years Adjuvant	249 Patients TAM vs AI / Placebo 5 Years Adjuvant / 5 Years Extended	789 Patients TAM vs TAM / Stop 5 Years Adjuvant / 5 Years Extended	908 Patients TAM vs AI 5 Years Adjuvant / 2.5 or 5 Years Extended	2,179 Patients AI vs TAM / Placebo 5 Years Adjuvant / 5 Years Extended
YES (High Predictive) 38-51% patients	65% Relative risk reduction (p=0.005)	65% Relative risk reduction (p=0.007)	67% Relative risk reduction (P=0.02)	58% Relative risk reduction (p=0.011)	71%* Relative risk reduction (p=0.003)
NO (Low Predictive) 49-62% patients	No significant benefit (p=0.204)	No significant benefit (p=0.35)	No significant benefit (p=0.58)	No significant benefit (p=0.8354)	No significant benefit** (p=0.28)
Nodal Status	100% N-	58% N+ / 42% N-	100% N+	73% N+ / 27% N-	40% N+ / 60% N-
Conclusions	PROOF OF CONCEPT Breast Cancer Index predictive evidence of endocrine responsiveness (primary adjuvant therapy)		LEVEL 1B EVIDENCE⁹ Breast Cancer Index test established as consistent, reproducible predictor of benefit from extended endocrine therapy[†]		

ASCO Guidelines for BCI

Breast Cancer Index.

Recommendation 1.24.

If a patient has node-negative or node-positive breast cancer with 1-3 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.25.

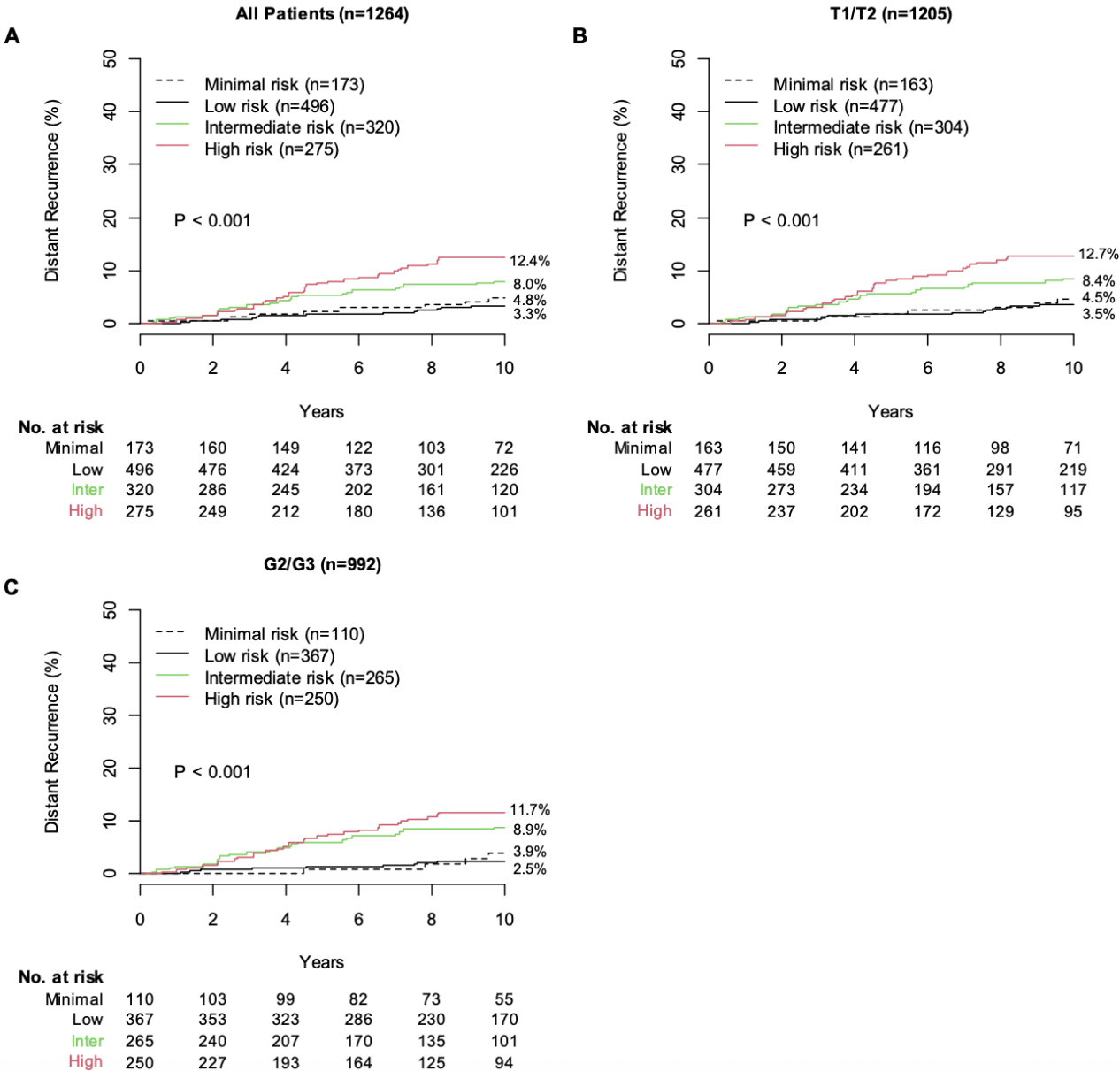
If a patient has node-positive breast cancer with ≥ 4 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

- ASCO: “Majority of patients in the above trials are postmenopausal. Hence, similar recommendations for premenopausal and perimenopausal women also cannot be definitively made.”
- ASCO does not recommend BCI for HR+/HER2+ because there is limited data. The limited data does appear to show benefit of BCI in HR+/HER2+ (and it is done occasionally in clinical practice).
- Unclear value of BCI in pts who received ovarian function suppression, CDK4/6 inhibitors, or olaparib

New Expanded Use of BCI

- Premenopausal: Can help to personalize treatment and it may be able to guide whether OFS is recommended and duration of endocrine therapy
- Postmenopausal: Helps optimize endocrine therapy duration and answers whether someone can do even less than 5 years

Minimal Risk by BCI (Postmenopausal)



Jilderda MF et al. npj Breast
Cancer| (2026) 12:21.

Fig. 1 | Performance of the adjusted BCI model in the NCR cohort. A NCR cohort overall. **B, C** Clinical subsets of the NCR cohort. BCI, Breast Cancer Index; G2/G3, grade 2/3; NCR, Netherlands Cancer Registry; T1/T2, T stage 1/2; TAM, tamoxifen; TEAM, Tamoxifen and Exemestane Adjuvant Multinational trial.

Page 1: Results to Inform Adjuvant Therapy (Prognostic Risk of Recurrence in Years 0-10)

Postmenopausal, node-negative patients classified as **Minimal Risk** experienced **<5% average risk of 10-year distant recurrence even without adjuvant endocrine therapy** and may be considered candidates for de-escalation if clinically indicated.^{1,2}

[illegible]

Results to Inform Adjuvant Therapy

PROGNOSTIC RESULT

Risk of Overall Distant Recurrence (0-10 Years)

Without adjuvant endocrine therapy:

<5%

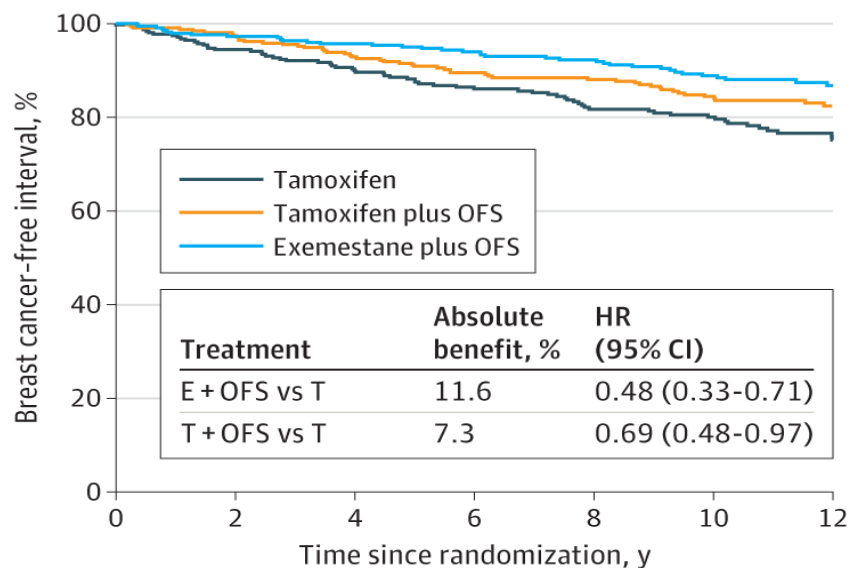
Represents the average risk of patients in the Minimal Risk group based on the NCR study.

Patients in the Minimal Risk group experienced <5% risk of distant recurrence in the absence of both adjuvant endocrine therapy and chemotherapy and may be considered candidates for omission or shorter duration of endocrine therapy if clinically indicated.

From: **Breast Cancer Index in Premenopausal Women With Early-Stage Hormone Receptor–Positive Breast Cancer**

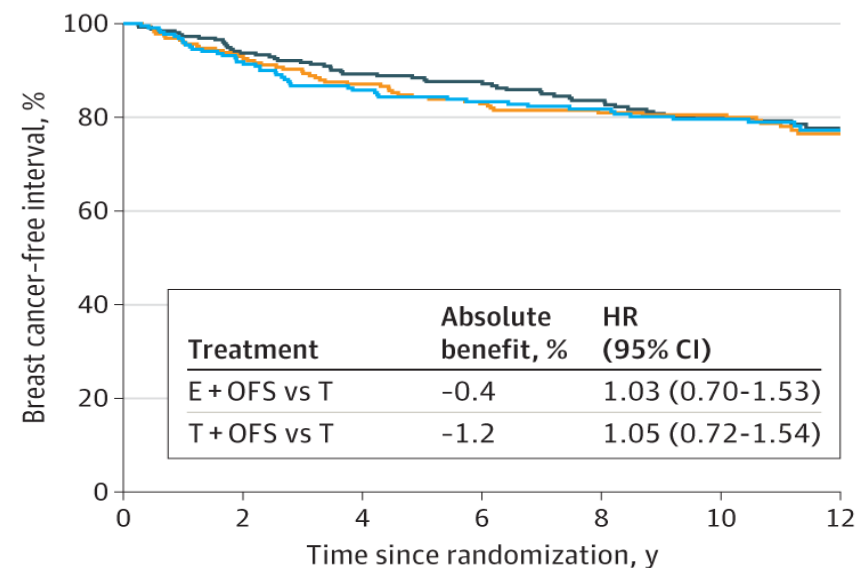
JAMA Oncol. 2024;10(10):1379-1389. doi:10.1001/jamaoncol.2024.3044

A BCI(H/I)-low tumors



No. at risk							
Tamoxifen	314	280	258	231	206	182	101
Tamoxifen plus OFS	321	302	278	261	244	214	135
Exemestane plus OFS	337	310	295	274	255	218	125

B BCI(H/I)-high tumors



No. at risk							
Tamoxifen	259	236	217	205	181	147	88
Tamoxifen plus OFS	230	209	189	176	166	149	79
Exemestane plus OFS	226	199	181	166	154	132	77

The Established Test for Extended Endocrine Therapy with **NEW Results** to Personalize Therapy for Premenopausal Women

Full 0-10 Year Report Helps Personalize Endocrine Therapy for Premenopausal Patients:
Omission of OFS? 5 vs. 10 Years of Endocrine Therapy?

Page 1: Results to Inform Adjuvant Therapy (Prognostic Risk of Recurrence in Years 0-10)

Premenopausal, node-negative patients classified as **Minimal Risk** experienced **<5% risk of 10-year distant recurrence even without the addition of ovarian function suppression (OFS)** to primary adjuvant endocrine therapy and may be considered candidates for omission if clinically indicated.¹

Page 1

Specimen ID: XXXXXXXXXX
Date of Collection: XXXXXXXX
Data Received: XXXXXXXX
Data Reported: XXXXXXXX

Breast Cancer Index® Test Results

Results are based on the following information (provided with entry):
Hologic Status: Lymph Node Negative (N0) Premenopausal Patient, Premenopausal

Results to Inform Adjuvant Therapy

Prognostic Risk of Overall Distant Recurrence (0-10 years)

With 5 total years of adjuvant endocrine therapy and no ovarian function suppression (OFS):

<5%

Represents the average risk of patients in the Minimal Risk group based on the SOFT study.

Additional Comments:
Patients in the Minimal Risk group experienced <5% risk of distant recurrence without the addition of OFS to adjuvant endocrine therapy and may be considered candidates for omission of OFS if clinically indicated.

Ordering Provider:
Dr. J. Doe
Phone: (913) 222-2222
Fax: (913) 222-2222

Submitting Pathologist:
Dr. J. Doe
Phone: (913) 222-2222
Fax: (913) 222-2222

Breast Cancer Index®

Page 1 of 2

Results to Inform Adjuvant Therapy

PROGNOSTIC RESULT
Risk of Overall Distant Recurrence (0-10 Years)

With 5 total years of adjuvant endocrine therapy and no ovarian function suppression (OFS):

<5%

Represents the average risk of patients in the Minimal Risk group based on the SOFT study.

Patients in the Minimal Risk group experienced <5% risk of distant recurrence without the addition of OFS to adjuvant endocrine therapy and may be considered candidates for omission of OFS if clinically indicated.

Available but
limitations persist in
using broadly

Not yet endorsed by
guidelines

Data is not yet
robust

Unclear impact in
patients who
received CDK 4/6
inhibitors

Note that while omission of OFS may be considered, results are based on at least 5 years of standard endocrine therapy.

Are SERDs coming?

Lots of excitement about SERDs (selective estrogen receptor degraders) in early-stage BC

FDA set to decide on giredestrant by end of November 2026

SERDs currently approved in MBC for patients with HR+/HER2- metastatic breast cancer and ESR1 mutations

Available:
elacestrant,
imlunestrant,
camizestrant

Why we do not check ESR1 in early disease

- ESR1 mutations: <1% of primary tumors, <5% of treatment-naïve disease
- ACQUIRED under aromatase-inhibitor pressure → ~20–40% of AI-treated metastatic disease
- Currently only in the metastatic setting (elacestrant, camizestrant, imlunestrant)
- ESR1 mutations are a treatment-driven, late phenomenon — they are essentially absent in the primary tumor and emerge only under prolonged estrogen-deprivation pressure, overwhelmingly in the metastatic setting.

HER2DX

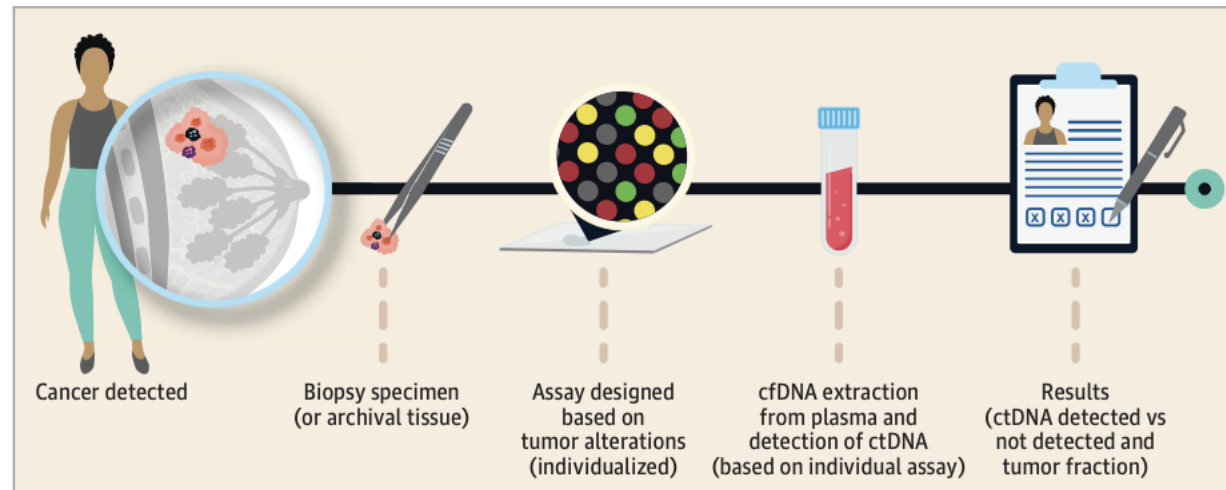
- HER2DX is a 27-gene expression assay (combined with limited clinical features) for stage I–III HER2-positive breast cancer that measures four biological signatures and translates them into three clinical scores
- Assay that generates three outputs: prognostic relapse risk score, pathologic complete response (pCR) score and ERBB2 messenger RNA expression score
- HER2DX risk score is associated with survival outcomes
- Not currently in guidelines but while prospective validation is ongoing, HER2DX may be considered a complementary biological decision-support tool alongside established clinical and pathologic factors in select situations

Circulating Tumor DNA: The Basics

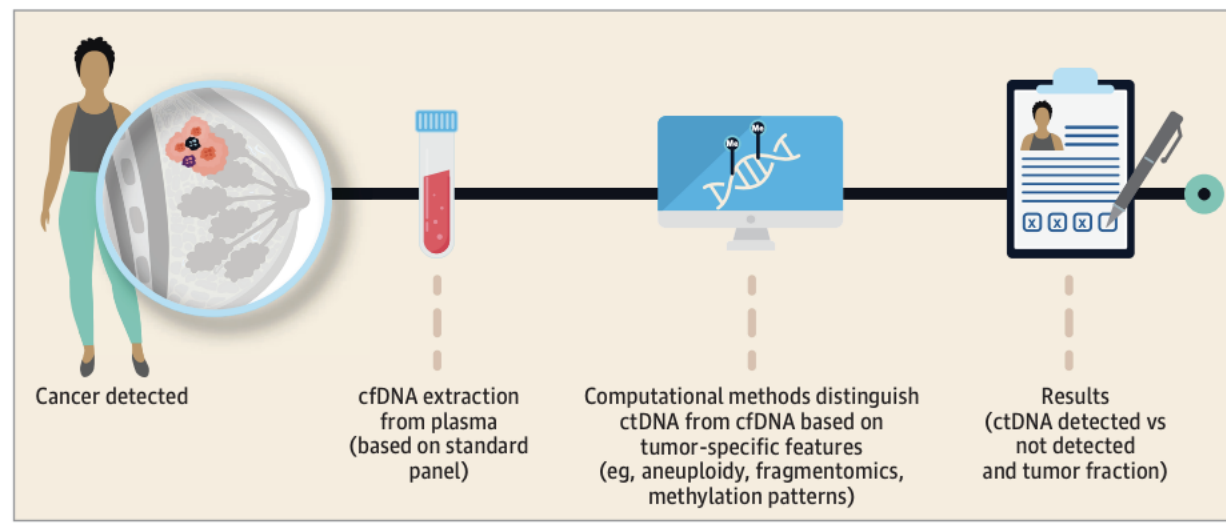
- Circulating tumor DNA (ctDNA) are tiny fragments of tumor DNA shed into the bloodstream — a “liquid biopsy” detected with a simple blood draw
- Tests like Signatera are “tumor-informed”: your original tumor is sequenced first to build a personalized test that looks for that same DNA signature in your blood over time. There are also tumor-agnostic tests that don’t need your original tumor.
- A positive result after treatment usually reflects minimal residual disease (MRD) — cancer cells that persist below what any scan can see (but there are rarely false positives)
- ctDNA can flag a possible recurrence months before it would show up on imaging or in symptoms — the big question is what do we do about the results?

Figure 1. Illustration of Tissue-Informed vs Tissue-Agnostic Circulating Tumor DNA (ctDNA) Assays for Minimal Residual Disease (MRD) Detection

A Tissue-informed MRD assays



B Tissue-agnostic MRD assays



Circulating Tumor DNA

- ctDNA / MRD: Strongly Prognostic
- Sisca 2026 meta-analysis (18 prospective cohorts, 1,670 patients):
ctDNA+ → ~7-fold higher recurrence risk (
- Molecular relapse precedes clinical/radiologic relapse by a median of 6–15 months
- ctDNA is generally less sensitive in HR+/HER2– disease
 - HR+/HER2– tumors are intrinsically "low-shedding": their lower proliferation and cell-turnover rates mean less tumor DNA is released into the circulation, so baseline detection rates and ctDNA concentrations are consistently lower than in TNBC (and often HER2+)

Outcomes Based on ctDNA

Table 3 | Analysis of 24-month disease-free survival rate (DFS) and post-operative ctDNA clearance by TNM stage

			Stage I-II	Stage III
24-month DFS (%)	All patients	No ctDNA information	96.1% (123/128)	82.9% (29/35)
	Clinically high-risk patients	No ctDNA information	94.0% (79/84)	81.3% (26/32)
24-month DFS (%)	All patients	Pre-operative ctDNA(+)	90.7% (39/43)	77.8% (21/27)
		Pre-operative ctDNA(–)	100.0% (82/82)	100.0% (8/8)
	Clinically high-risk patients	Pre-operative ctDNA(+)	89.5% (34/38)	76.9% (20/26)
		Pre-operative ctDNA(–)	100.0% (43/43)	100.0% (6/6)
	All patients	Post-operative ctDNA(+)	25.0% (1/4)	28.6% (2/7)
		Post-operative ctDNA(–)	100.0% (101/101)	100.0% (25/25)
	Clinically high-risk patients	Post-operative ctDNA(+)	25.5% (1/4)	28.6% (2/7)
		Post-operative ctDNA(–)	100.0% (61/61)	100.0% (23/25)
Percentage of patients having post-operative ctDNA clearance by adjuvant therapy	Clearance (Pos → Neg)		100.0% (4/4)	63.6% (7/11)
	No clearance (Pos → Pos or relapse)		0.0% (0/0)	36.4% (4/11)

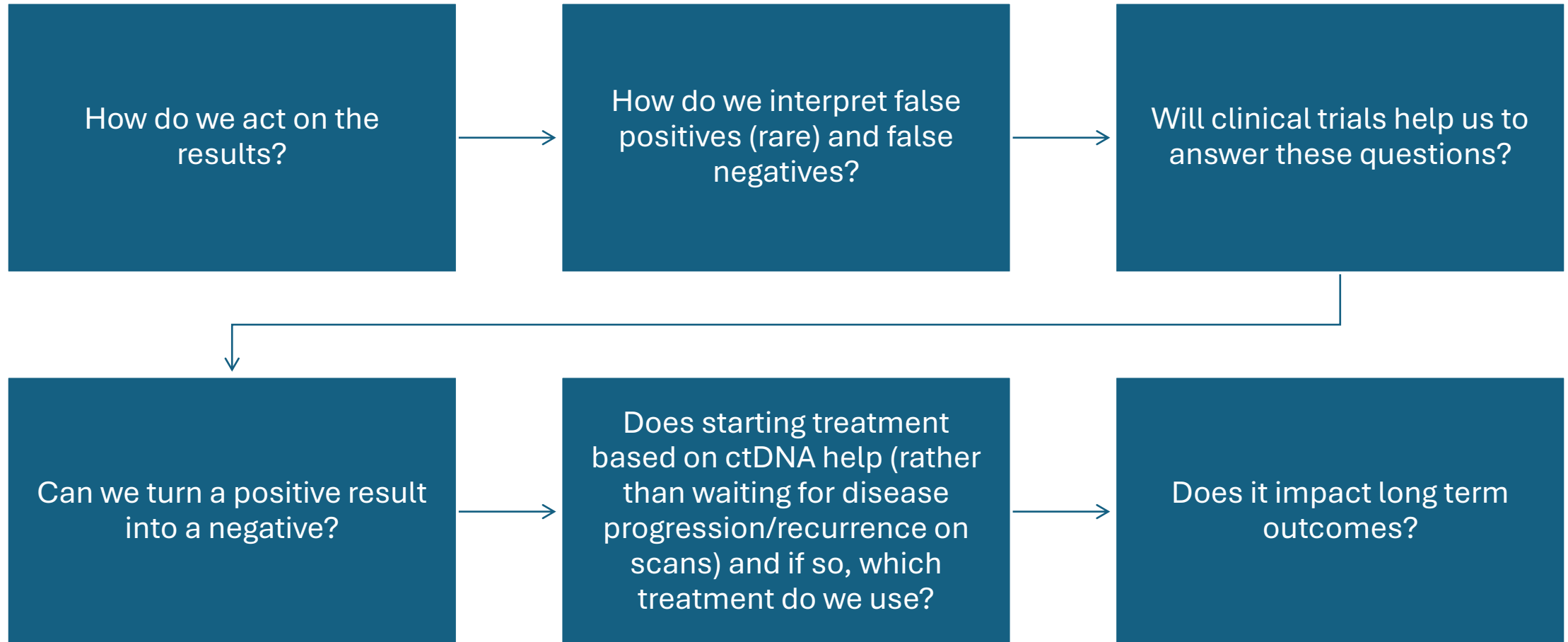
Examples of Ongoing Trials with ctDNA

					of ctDNA emergence	
SIGNAL-ER 202 study (NCT07214532)	Phase 2, single arm (n = 725)	Adjuvant setting, ctDNA testing every 3 mo for up to 4 y	High-risk HR-positive and <i>ERBB2</i> -negative	Signatera Genome	Patients initiate ET and CDK4/6i if MRD-positive and ET alone if MRD-negative, with continued surveillance and delayed CDK4/6i initiation in case of molecular relapse	iDFS (compared with historical controls from NATALEE ⁵⁶)
DARE (NCT04567420)	Phase 2, randomized (n = 100 for the intervention part)	Surveillance (ctDNA testing every 6 mo)	High-risk HR-positive/ <i>ERBB2</i> -negative, 6 mo to 7 y receiving adjuvant ET	Signatera Exome	Randomization to fulvestrant-palbociclib or continuation of standard ET for 2 y	RFS
LEADER (part 2) (NCT03285412)	Phase 2, single-arm (n = 30 for the intervention part)	Surveillance (ctDNA testing at baseline, 6 mo, and 12 mo during surveillance at 3 mo, 6 mo, and 12 mo during intervention)	High-risk; HR-positive/ <i>ERBB2</i> -negative, ≥1 y of adjuvant ET remaining	Signatera Exome	Addition of ribociclib to ongoing ET for 1 y	12-mo ctDNA clearance
MIRaDoR (NCT05708235)	Phase 2, multiarm, noncomparative (n = 1260 surveillance, n = 40 for each arm)	Surveillance (ctDNA testing every 3 mo for 1 y, then every 6 mo during surveillance; every 3 mo during intervention)	High-risk HR-positive/ <i>ERBB2</i> -negative, receiving adjuvant ET for 2-4 y	Signatera Exome	Continuation of ET; giredestrant; giredestrant + abemaciclib; giredestrant + inavolisib	3-mo ctDNA decrease or clearance in each arm
TRAK-ER (NCT04985266)	Phase 2, randomized (n = 1100 surveillance, n = 132 randomized)	Surveillance (ctDNA testing every 3 mo during surveillance)	High-risk HR-positive/ <i>ERBB2</i> -negative, up to 7 y receiving adjuvant ET	Invitae personalized cancer monitoring	Standard ET or palbociclib-fulvestrant for 24 mo	RFS
TREAT-ctDNA (NCT05512364)	Phase 3, randomized (n = 1960 surveillance; n = 220 intervention)	Surveillance (ctDNA testing every 6 mo during surveillance; at wk 4, wk 16, and every 4 mo during treatment)	High-risk, HR-positive/ <i>ERBB2</i> -negative, 4.5 to 7 y receiving ET	Signatera Exome	Standard ET or elacestrant for 24 mo	Distant metastases-free survival

Why ctDNA Is NOT Yet Routine

- It is not recommended to currently use ctDNA to guide adjuvant decisions
- Acting early on MRD has not yet been proven to improve survival
- Biologic/analytic limits: low shedding (esp. HR+, lobular), no positivity-threshold consensus
- If available, recommend a clinical trial if ctDNA positive

ctDNA Questions

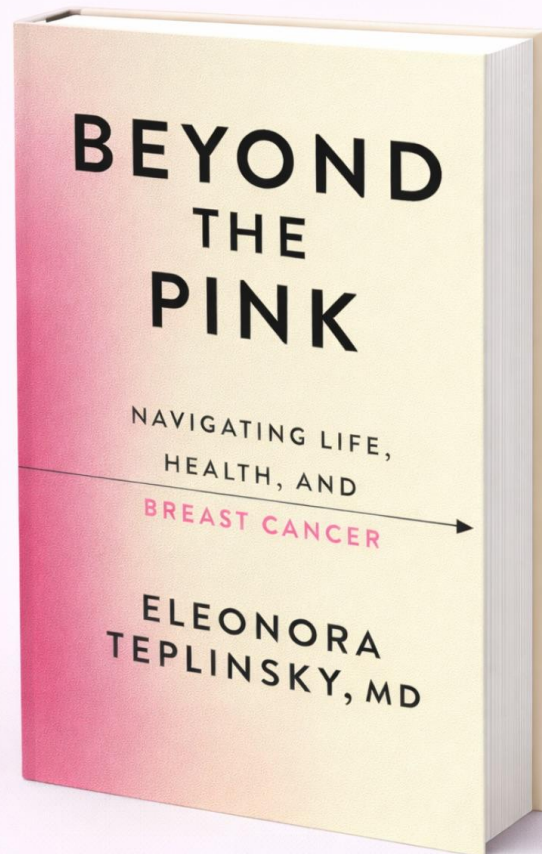


Take Home Messages

- Biomarkers are helping us personalize breast cancer treatment more than ever.
- Genomic assays can help us determine who needs chemotherapy and, increasingly, who may safely do less.
- Menopausal status and ovarian function matter. In premenopausal patients, the benefit attributed to chemotherapy may sometimes be related to ovarian suppression.
- Biomarkers can also help to personalize endocrine therapy — including who may benefit from ovarian suppression and how long endocrine therapy may be needed.
- ctDNA is incredibly promising and eagerly awaiting ongoing trials
- Biomarkers are one piece of the picture alongside tumor characteristics, age/menopausal status, overall health, treatment risks, and what matters most to you.

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