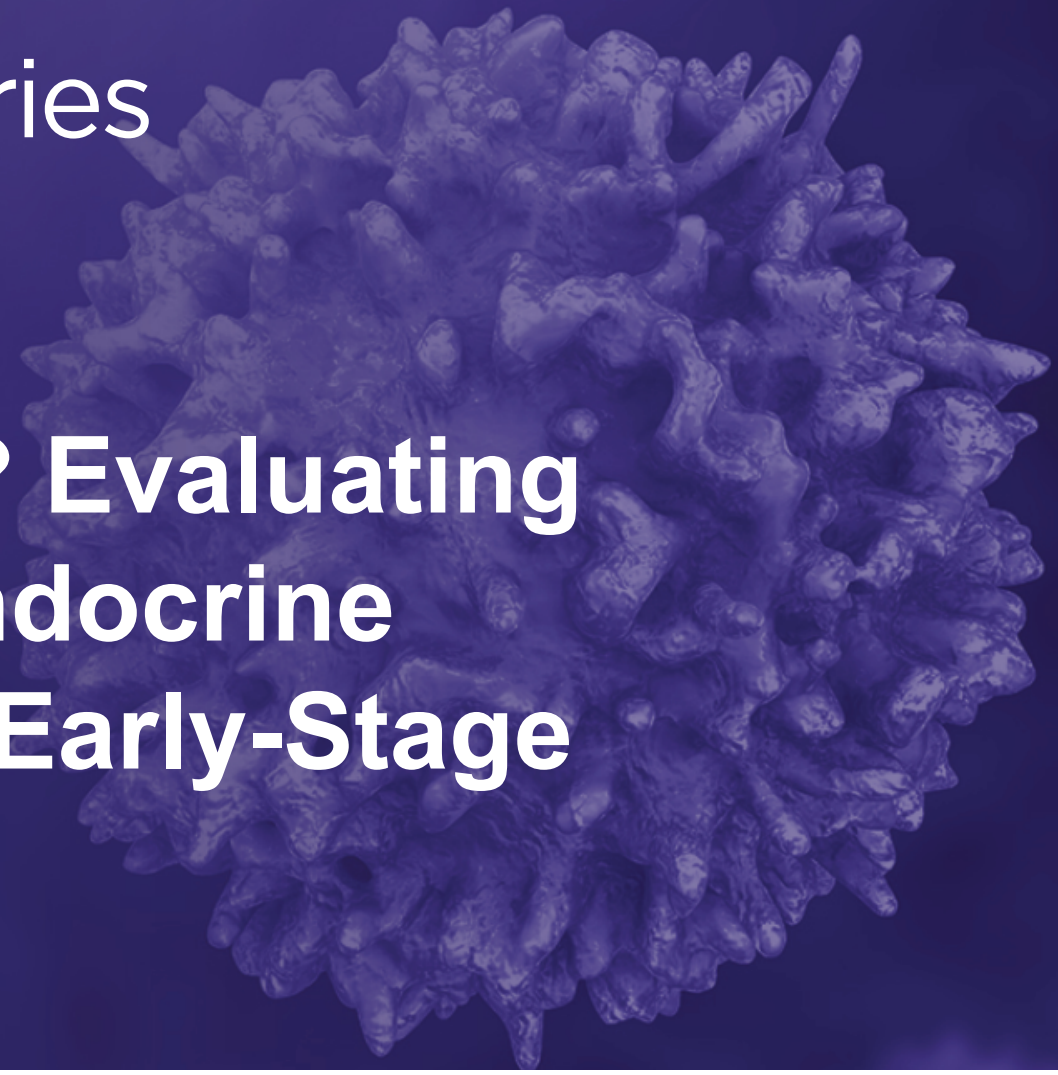
JADPRO Clinical Case Series

To Extend or Not Extend? Evaluating the Need for Extended Endocrine Therapy in Patients With Early-Stage HR+ Breast Cancer



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BREAST CANCER INDEX™
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PRESENTER

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Introduction

Extended Endocrine Therapy: Pros and Cons

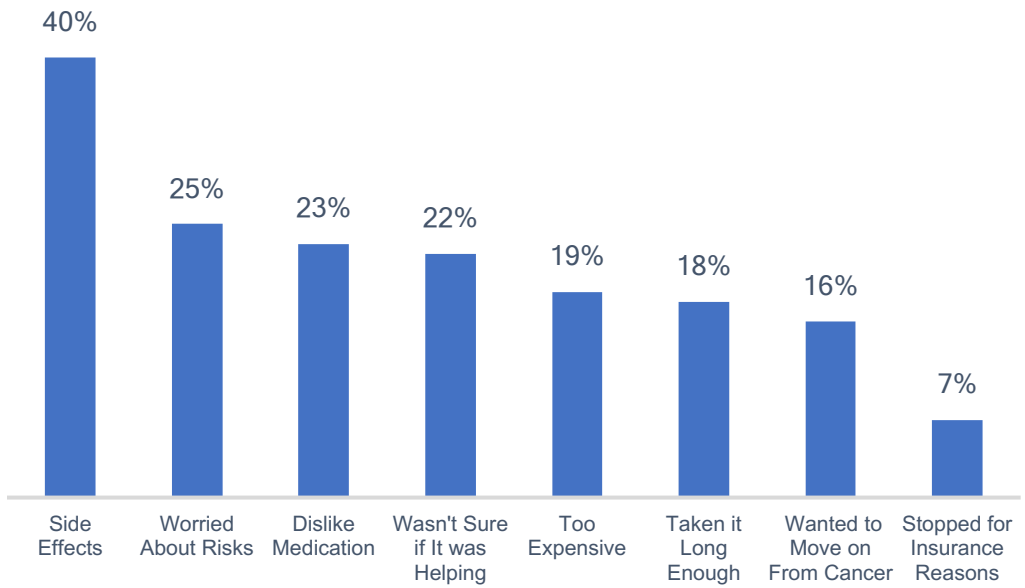
Benefit	Adverse events	Challenges

• ~5% decrease in local, regional, and metastatic recurrence
• Extended endocrine trials showed only marginal increases in disease-free survival
	• 10% of patients
	  • Bone toxicity
	  • Endometrial cancer
	  • Embolisms
	  • Heart disease
		• 50% of patients
		  • Hot flashes
		  • Sexual dysfunction
		  • Arthralgias
		  • Myalgias
		  • Mild to moderate cognitive impairment

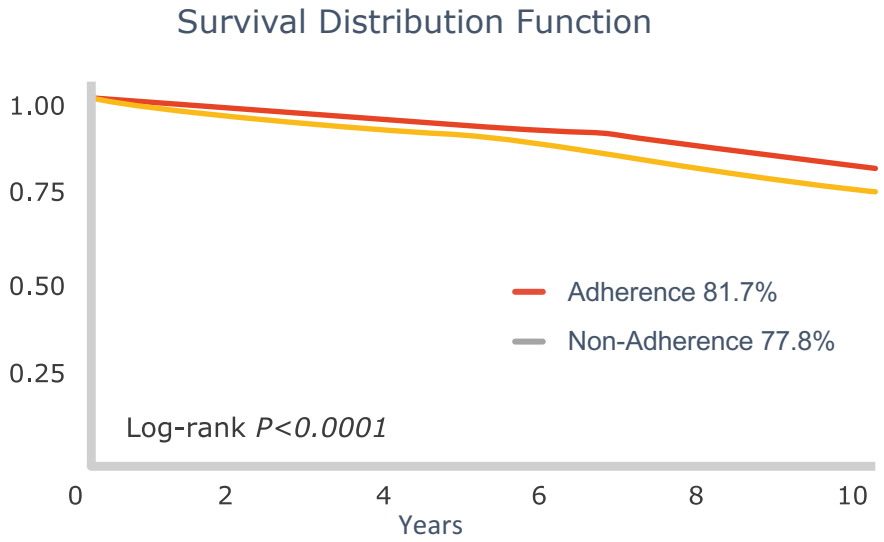
Davies C, et al. *Lancet.* 2013;381:805-816; Goss PE, et al. *N Engl J Med.* 2016;375:209-219; Mamounas EP, et al. S1-05; SABCS December 2016.

Extended Endocrine Therapy Compliance

Reasons for Discontinuation[a1]



Poor Compliance Negatively Affects Outcomes[1]



a. Data from adjuvant setting.

1. Hershman DL, et al. *Breast Cancer Res Treat.* 2011;126:529-537.

Audience Response Question

How many patients do you talk to each week about extending endocrine therapy?

A. 0-2

B. 3-5

C. 6-10

D. More than 10

Using Clinicopathologic Factors to Predict Treatment Benefit

- Common clinical and pathologic prognostic factors:
  - Tumor size
  - Tumor grade
  - Quantitative ER/PR
  - Menopausal status
  - Ki67
  - Age
  - Other genomic assays
- Studies show they do not reliably predict benefit from extended endocrine therapy[1-4]

ER = estrogen receptor; PR = progesterone receptor

1. Davies C, et al. *Lancet.* 2013;381:805-816. 2. Goss PE, et al. *J Natl Cancer Inst.* 2005;97:1262-1271. 3. Goss PE, et al. *N Engl J Med.* 2016;375:209-219. 4. Mamounas EP, et al. *Lancet Oncol.* 2020.

BCI: Single Test With Two Components

- Predictive: Predicts likelihood of benefit from extended endocrine therapy
  - Uses separate algorithm based on H/I biomarker, HOXB13/IL17BR
- Prognostic: Assess individual risk of late distant recurrence
  - Uses algorithmic combination of 11 genes + HOXB13/IL17BR biomarker
  - Factors in tumor size and grade for node-positive patients

BCI = Breast Cancer Index

Predictive vs Prognostic Tests

Predictive

- Provides information about the effect of a therapeutic intervention
- Few tests are predictive, and they are extremely valuable

Prognostic

- Provides information about the patient's overall cancer outcome, regardless of therapy
- Many tests are prognostic

Oldenhuis C et al. *Eur J Cancer*. 2008;44:946-953.

	Stockholm[1]	MA.17[2]	Trans-aTTom[3]	IDEAL[4]	B-42[5]
Study design	600 patients; TAM vs no therapy, 2 or 5 years adjuvant	249 patients; 5 years adjuvant TAM randomized to 5 years extended AI or placebo	789 patients; 5 years adjuvant TAM randomized to 5 years extended TAM or stop therapy	908 patients; 5 years adjuvant TAM, AI, or TAM/AI randomized to AI 2.5 or 5 years extended therapy	2,179 patients; 5 years adjuvant AI or TAM/AI randomized to 5 years extended AI or placebo
YES (high predictive) 38-51% patients	65% RR reduction (p=0.0005)	65% RR reduction (p=0.007)	67% RR reduction (p=0.02)	58% RR reduction (p=0.0111)	71%[a] RR 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=0.35)	No significant benefit (p=0.8354)	No significant benefit[a] (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 test predictive evidence of endocrine responsiveness (primary adjuvant therapy)	Level 1B evidence[6]: Breast Cancer Index test established as consistent, reproducible predictor of benefit from extended endocrine therapy[b]			

AI = aromatase inhibitor; TAM = tamoxifen; RR = relative risk

a Time-dependent DR analysis >4y post-randomization; primary RFI endpoint not met due to significant powering challenges; Only HER2- subset demonstrated significant treatment to biomarker interaction; b For patients disease-free at year 5.

1. Zhang Y, et al. *Clin Cancer Res.* 2013;19:4196-4205. 2. Sgroi DC, et al. *J Natl Cancer Inst.* 2013;105:1036-1042. 3. Bartlett JMS, et al. Clin Cancer Res DOI: 10.1158/1078-0432.CCR-21-3385. 2022 4. Noordhoek I, et al. *Clin Cancer Res.* 2021;27:311-319. 5. Mamounas EP, et al. 501; ASCO June 2021. 6. Simon RM, et al. *J Natl Cancer Inst.* 2009;101:1446-1452.

Ability to Predict Benefit from Endocrine Therapy > 5 Years

	Breast Cancer Index[1-7]	OncotypeDX[1,2,8]	Mammaprint[2,9,10]	EndoPredict[2,11]	Clinpath[1-8,12,13]
Predictive of chemotherapy benefit	No	Yes; included in guidelines for selecting patients for chemotherapy[1,2]	Yes; for clinically high, genomically low risk patients per MINDACT[2]	No	No
Recognized by NCCN Guidelines to predict EET benefit	Yes	No	No	No	No
Recognized by ASCO Guidelines to predict EET benefit	Yes	No; insufficient evidence to guide EET[2]	No	No; insufficient evidence to guide EET[2]	No; IHC-4 and Ki76 = insufficient evidence to guide EET[2]; CTS5 = prognostic only[14]
Predictive performance for EET benefit demonstrated in validation studies	Yes; 58%-71% RR reduction for those likely to benefit from EET	N/A; no prediction by qER (n=587; p=0.72), RS not tested[8]	No; not significant for prediction of DR benefit; biomarker to treatment interaction not significant[9,10]	N/A	No; clinicopathologic factors not associated with EET benefit prediction[3,6,15-17]
No. of studies evaluating EET predictive capability	5	N/A	2	N/A	10
No. of patients evaluated	>4,700	N/A	~2,300	N/A	>10,000

ASCO – American Society of Clinical Oncology; EET = extended endocrine therapy; NCCN = National Comprehensive Cancer Network.

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.8.2021. 2. Andre F, et al. *J Clin Oncol.* 2022;40:1816-1837. 3. Zhang Y, et al. *Clin Cancer Res.* 2013;19:4196-4205. 4. Sgroi DC, et al. *J Natl Cancer Inst.* 2013;105:1036-1042. 5. Bartlett JMS, et al. *Clin Cancer Res.* 2022;28:1871-1880. 6. Noordhoek I, et al. *Clin Cancer Res.* 2021;27:311-319. 7. Mamounas EP, et al. 501; ASCO June 2021. 8. Mamounas EP, et al. SABCS 2021. PD15-05. 9. Rastogi et al. Abstract 502; ASCO 2021 10. Liefers et al. 2022 SABCS Abstract GS5-10 11. https://myriad-oncology.com/endopredict/ Accessed December 2021 12. Davies C, et al. *Lancet.* 2013;381:805-816. 13. Goss PE, et al. *J Natl Cancer Inst.* 2005;97:1262-1271. 14. Dowsett M, et al. *J Clin Oncol.* 2018;36:1941-1948. 15. Zhang Y, et al. *Clin Cancer Res.* 2017;23:7217-7224 16. Data on file. 17. Schroeder B, et al. *NPJ Breast Cancer.* 2017;3:28.

Inclusion in Guidelines for Extended Endocrine Therapy Decision-Making

- January 2021: National Comprehensive Cancer Network (NCCN)[1]
- April 2022: American Society of Clinical Oncology (ASCO)[2]

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.3.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed April 25, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 2. Andre F, et al. *J Clin Oncol.* 2022;40:1816-1837.

NCCN Guideline Inclusion

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF EXTENDED 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 disease-free survival (DFS) or OS compared to the control arm in terms of extending endocrine therapy duration.[8]
	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.[8-11] • In contrast, BCI (H/I) low patients derived no benefit from extended adjuvant therapy.[8]

Audience Response Question

Were you aware that the BCI test is included in both the NCCN and ASCO guidelines?

A. Yes

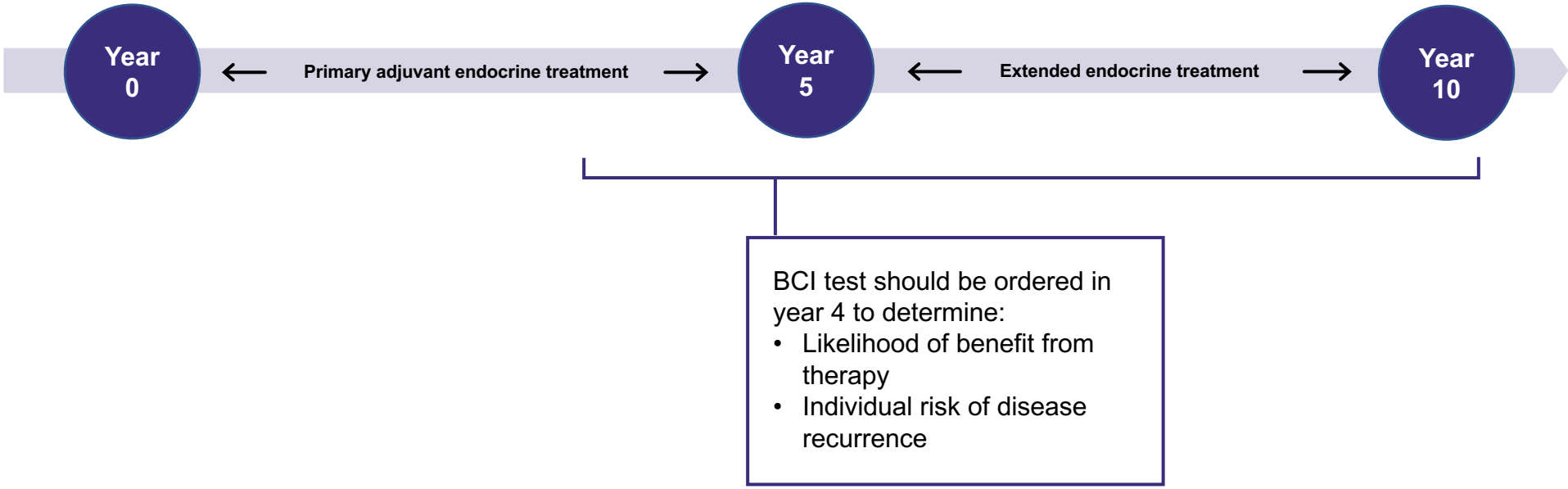
B. No

ASCO Guideline Inclusion

- BCI test may be offered to patients with 0-3 positive nodes who received 5 years of endocrine therapy without evidence of recurrence to guide decisions about extended endocrine therapy
  - 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
  - OncotypeDX, EndoPredict, Prosigna, Ki67, and IHC4 are identified as having insufficient evidence to predict benefit from extended endocrine therapy

Andre F, et al. *J Clin Oncol*. 2022;40:1816-1837.

BCI Testing in the Breast Cancer Treatment Continuum



- Clinically indicated patient population:
  - Hormone receptor positive
  - Early stage (node negative or positive with no more than 3 lymph nodes)
  - Disease-free

Impact on Clinical Practice

Physician Treatment Recommendations and Patient Compliance

Impact on Physician Decision

- Women with history of stage I-III, HR+ breast cancer treated at Yale Cancer Center or University of Pittsburgh Medical Center
- BCI test results changed physician treatment recommendations regarding extended endocrine therapy in 30% of patients

30%

HR = hormone receptor.
Sanft T, et al. *Breast Cancer Manag*. 2019;8.

Impact on Joint Decision-Making and Patient Compliance

- Physician/patient conflict significantly decreased following BCI testing (44.8-36.3; $p<0.0001$)
- 82% of patients recommended for extended endocrine therapy stated they would be more likely to be compliant based on the BCI test results

Sanft T, et al. *Breast Cancer Manag*. 2019;8.

Transforming Clinical Assumptions

In patients assumed to have clinically HIGH-RISK disease (N1):

- BCI test identified 22% as having *limited risk* (2.1%) of late distant recurrence[1]
- 69% of those were not likely to benefit from extended endocrine therapy[2]

In patients assumed to have clinically LOW-RISK disease (T1N0):

- BCI test identified 25% as likely to benefit from extended endocrine therapy and at *higher risk* of late distant recurrence[3]

1. Zhang Y et al. *Clin Cancer Res.* 2017;23:7217-7224. 2. Data on file. 3. Schroeder B, et al. *NPJ Breast Cancer.* 2017;3:28.

BCI Test Patient Eligibility Criteria

Criteria	Accepted	Not Accepted
Sex	Female	Male
Hormone receptor status	• ER+/PR+ • ER+/PR- • ER-/PR+	• ER- and PR-
Breast cancer type	• Breast primary invasive tumor • Multifocal tumor (same specimen) • Bilateral breast cancer (BBC) • Contralateral new primary • Local recurrence has occurred (submit original tumor or biopsy) • Invasive ductal carcinoma including most unusual subtypes such as mucinous, tubular, medullary, micropapillary, papillary, cribriform	• Metastatic breast cancer • No evidence of invasive (ductal, lobular, or mixed ductal lobular) carcinoma • Metaplastic breast cancer • Carcinosarcoma • Sarcoma • Neuroendocrine carcinoma • Phyllodes tumor • Adenoid cystic carcinoma
Biopsy site	Breast	• Chest wall • Axilla • Lymph node • Skin

BCI Test Patient Eligibility Criteria (cont)

Criteria	Accepted	Not Accepted
Nodal status	• Node negative (pN0) • Isolated tumor cell clusters (pN0(i+)) • Micrometastases in 1-3 lymph nodes (pN1mi) • Node positive with 1-3 lymph nodes (pN1) • No lymph node dissection (pNX) • Unknown nodal status	≥4 positive nodes
Tumor size	T1, T2, T3	• Tis (DCIS) • Tis (LCIS) • T4 • Microinvasive carcinoma T1mi
Tumor grade	1, 2, 3	
HER2 status	• HER- • HER2+	
Menopausal status	• Premenopausal • Postmenopausal • Perimenopausal	
Adjuvant treatment	• Tamoxifen • Aromatase inhibitor (Submit specimen obtained prior to initiation or treatment)	

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ

Case Studies

Case 1: Young Patient

- 55-year-old female stage II T2N1M0 left breast multifocal invasive ductal carcinoma, grade 2, ER 99%, PR 71%, HER2/*neu* 0 by IHC and Ki67 18%

- Residual disease consistent with treatment effect (8 x 8 cm; 1% of area sampled)
- Clear margins obtained
- Residual isolated tumor cells in 1 of 18 LNs

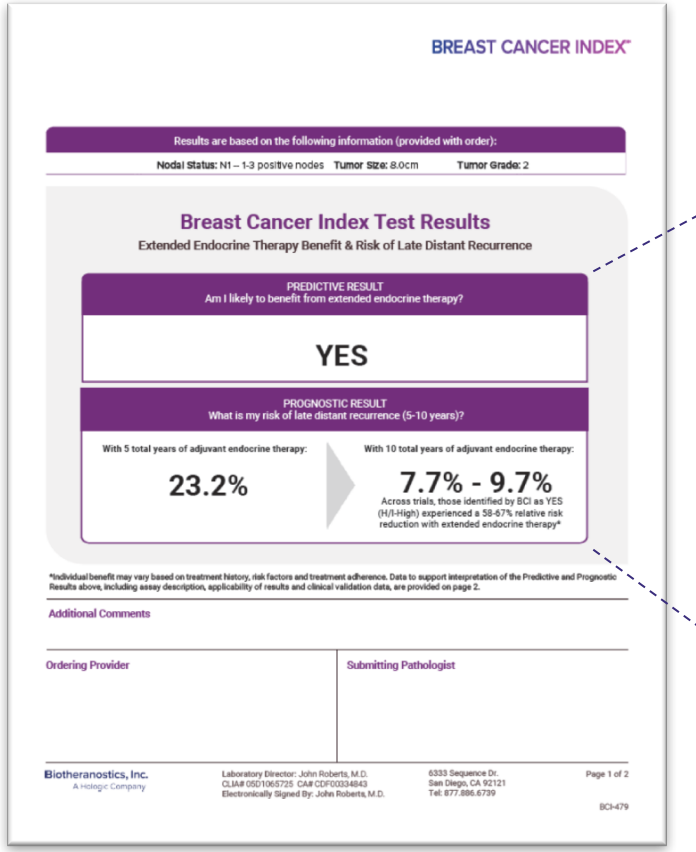
- After 4.5 years on tamoxifen:
  - Experiencing mild arthralgias and hot flashes
  - Taking denosumab for osteoporosis

AC = doxorubicin HCl (Adriamycin)/cyclophosphamide; IHC = immunohistochemistry; LN = lymph node.

Case 1: Therapy Options

- Recommend continuing tamoxifen for 6 more months, for total of 5 years of endocrine therapy
- Consider ordering a BCI test to determine if she is likely to benefit from extended endocrine therapy
- Recommend continuing tamoxifen for a total of 10 years of endocrine therapy
- Discuss drawing estradiol levels and switching to an AI if she is postmenopausal, with the possibility of taking an AI for an additional 5 years

Case 1: BCI Test Report



BREAST CANCER INDEX™

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

Nodal Status: N1 – 1-3 positive nodes **Tumor Size:** 8.0cm **Tumor Grade:** 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

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

With 5 total years of adjuvant endocrine therapy: 23.2%

With 10 total years of adjuvant endocrine therapy: 7.7% - 9.7%
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

Biotheranostics, Inc. A Hologic Company
Laboratory Director: John Roberts, M.D.
CLIA# 05D1065725 CAP CDF0334843
Electronically Signed By: John Roberts, M.D.
6333 Sequence Dr.
San Diego, CA 92121
Tel: 877.886.6739
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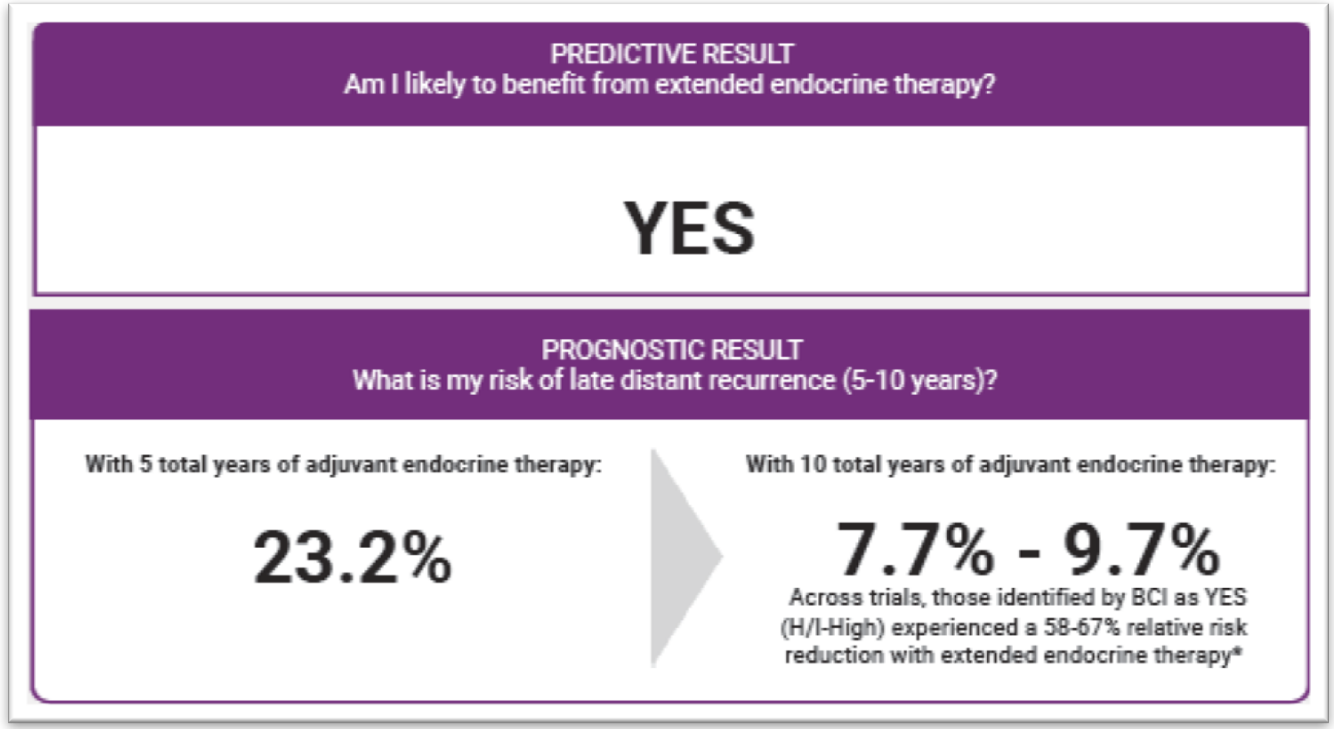

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Across trials, those identified by BCI as YES (H/I-High) experienced a 58-67% relative risk reduction with extended endocrine therapy*

- Continued on tamoxifen due to osteoporosis

Case 1: Poll Results

How do you determine which patients will benefit from extending endocrine therapy from 5 to 10 years?

A. I use clinical risk features **22%**

B. I make the decision based on tolerability/side effects **6%**

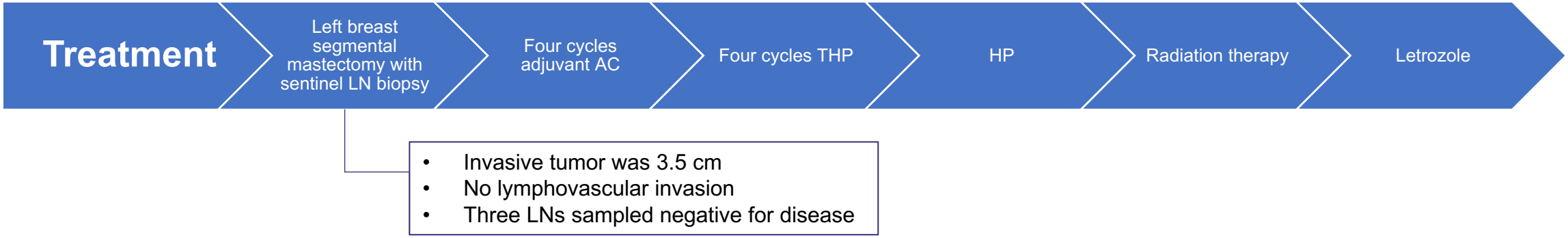
C. I order a BCI test **68%**

D. I extend for all patients **4%**

E. I do not extend for any patients **0%**

Case 2: Endocrine Therapy Side Effects

- 70-year-old female with stage I T2N0M0 left breast invasive ductal carcinoma, grade 2, ER 99%, PR 5%, HER2/*neu* 2+ by IHC, amplified by FISH, Ki67 17%



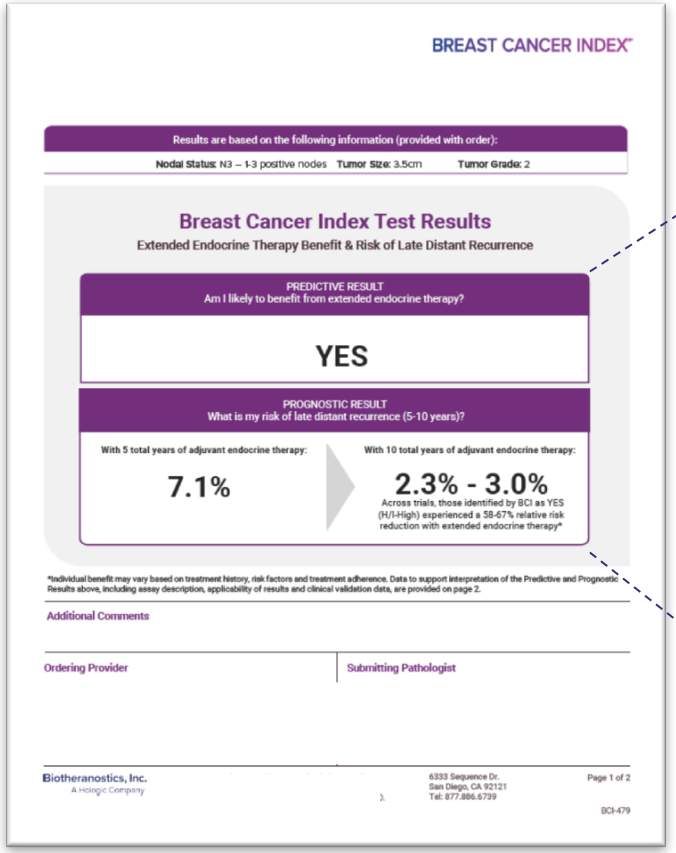
- After 4 years on letrozole:
  - Experiencing moderate arthralgias, mild osteopenia, and vaginal dryness

FISH = fluorescence in situ hybridization; HP = trastuzumab (Herceptin)/pertuzumab; THP = docetaxel (Taxotere)/trastuzumab (Herceptin)/pertuzumab.

Case 2: Therapy Options

- Recommend continuing letrozole for 1 more year, for a total of 5 years of endocrine therapy
- Consider ordering a BCI test to determine if she is likely to benefit from extended endocrine therapy
- Recommend continuing letrozole for a total of 10 years of endocrine therapy
- Discuss continuing endocrine therapy for 10 years, but plan to switch her to tamoxifen at year 5

Case 2: BCI Test Report



BREAST CANCER INDEX™

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

Nodal Status: N3 – 1-3 positive nodes **Tumor Size:** 3.5cm **Tumor Grade:** 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

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

With 5 total years of adjuvant endocrine therapy: 7.1%

With 10 total years of adjuvant endocrine therapy: 2.3% - 3.0%
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.

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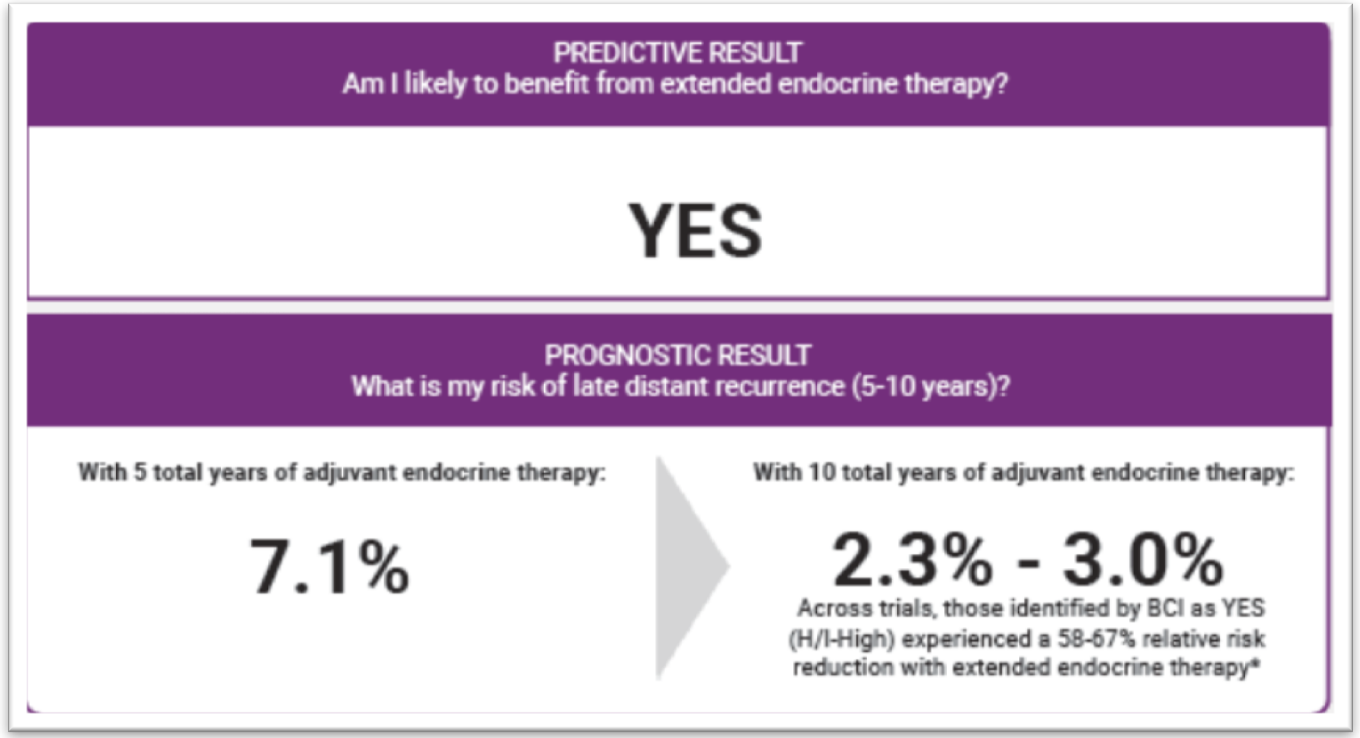

PREDICTIVE RESULT
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PROGNOSTIC RESULT
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With 10 total years of adjuvant endocrine therapy: 2.3% - 3.0%
Across trials, those identified by BCI as YES (H/I-High) experienced a 58-67% relative risk reduction with extended endocrine therapy*

- Elected to stay on letrozole
- initiated on denosumab due to osteopenia; moisturizers recommended for vaginal dryness

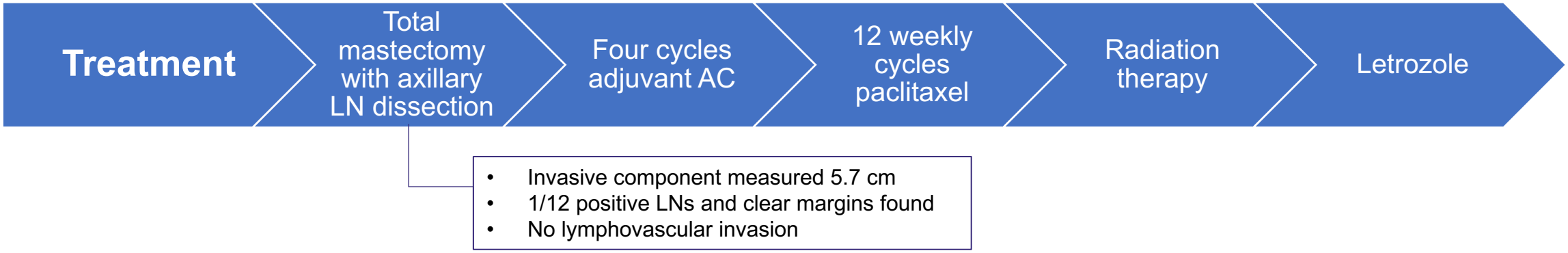
Case 2: Poll Results

What is the primary concern for your patients on endocrine therapy?

A. Side effects from medication **64%**
B. Fear of recurrence **30%**
C. Adherence to treatment recommendations **6%**
D. Cost of the medication **0%**

Case 3: Clinicopathologic Features

- 78-year-old female with stage II T2N1M0 right breast invasive lobular carcinoma, ER 99%, PR 40%, HER2/*neu* 0 by IHC, and Ki67 7%

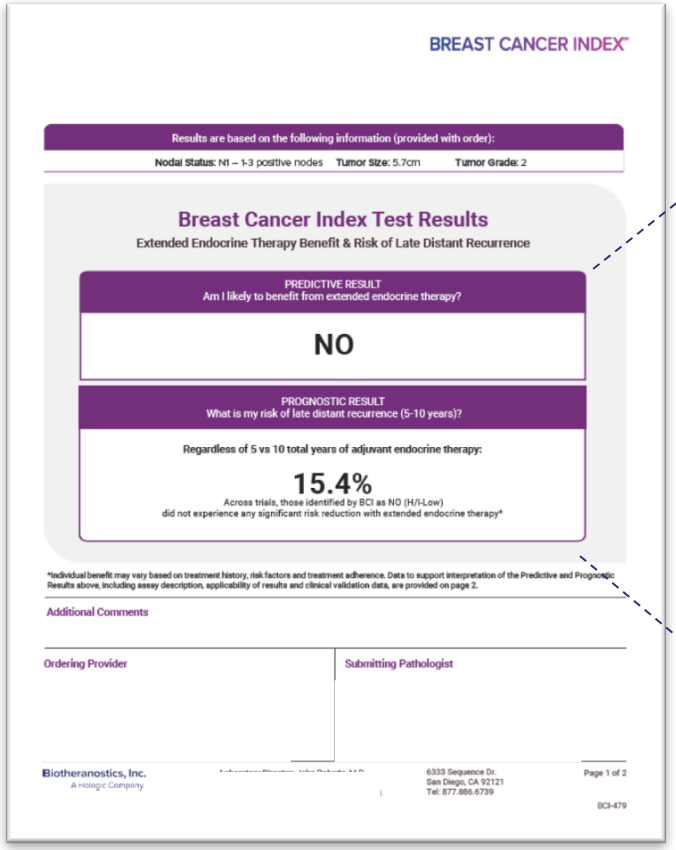


- After 5 years on letrozole
  - Experiencing mild to moderate arthralgias and osteopenia.

Case 3: Therapy Options

- Stop letrozole, with a total of 5 years of endocrine therapy
- Consider ordering a BCI test to determine if she is likely to benefit from extended endocrine therapy
- Recommend continuing letrozole for a total of 10 years of endocrine therapy, and refer her to bone health
- Recommend stopping letrozole and switching to tamoxifen for 5 years, to complete a total of 10 years of endocrine therapy

Case 3: BCI Test Report



BREAST CANCER INDEX™

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

Nodal Status: N1 – 1-3 positive nodes **Tumor Size:** 5.7cm **Tumor Grade:** 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?

NO

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

Regardless of 5 vs 10 total years of adjuvant endocrine therapy:

15.4%

Across trials, those identified by BCI as NO (H/I-Low)
did not experience any significant 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.

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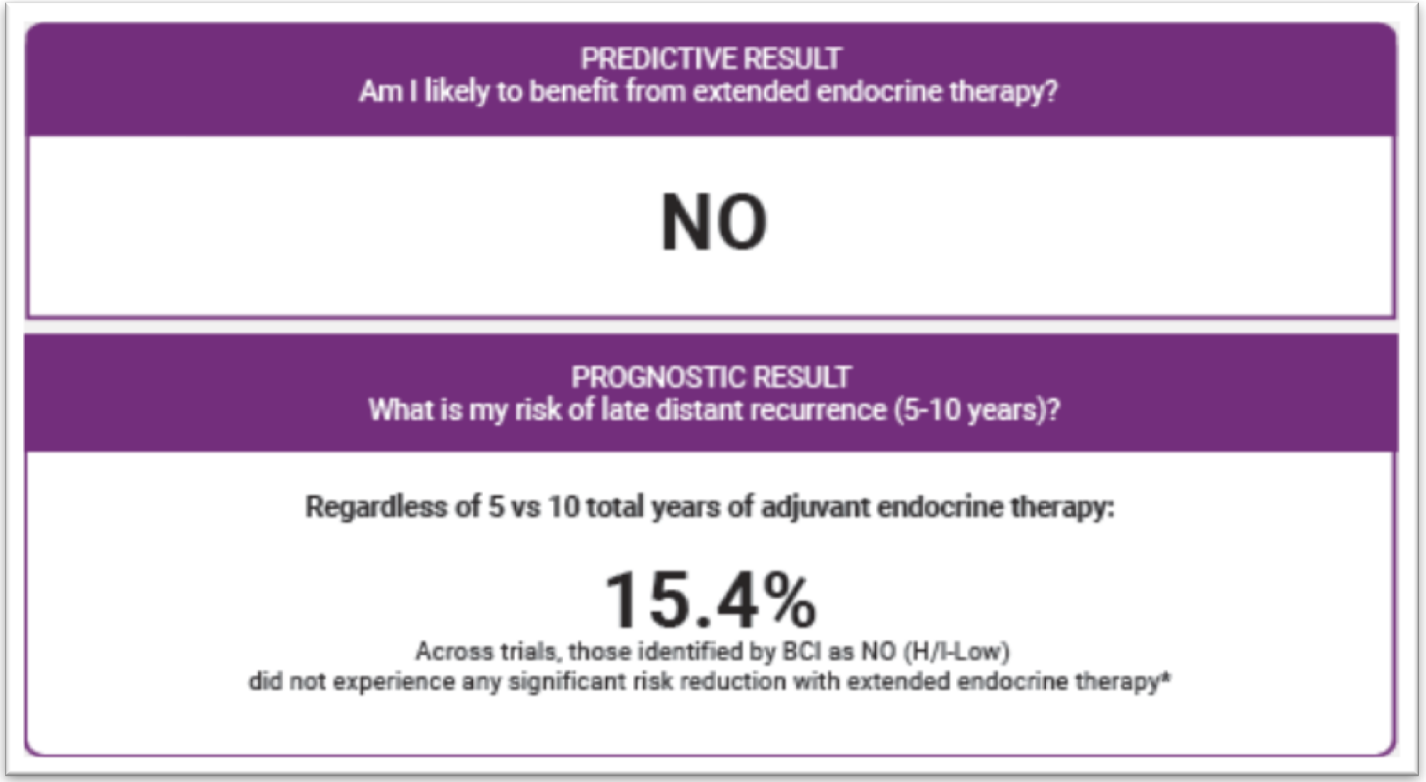

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15.4%

Across trials, those identified by BCI as NO (H/I-Low)
did not experience any significant risk reduction with extended endocrine therapy*

- Discontinued letrozole

Case 3: Poll Results

For which patients would you consider ordering a BCI test?

A. All eligible patients **72%**
B. Those who ask for a BCI test **6%**
C. Those with significant side effects **15%**
D. Those who are clinically low risk (ie, node-negative) **4%**
E. I do not order BCI testing **2%**

Audience Response Question

When do you most commonly talk to your patients about the BCI test?

A. At the time of diagnosis, to let them know that we have a tool to help inform future decisions

B. During year 4 of adjuvant therapy, when we begin to discuss whether to continue or end anti-estrogen therapy beyond year 5

C. Beyond year 5 if they have not had testing done and we're trying to decide whether to continue or restart anti-estrogen therapy

D. All of the above

Audience Response Question

Is there a standard place within your EHR where BCI test results can be found?

A. Yes

B. No

C. I don’t know

Audience Response Question

Who most commonly discusses BCI testing with patients in your practice?

A. The clinic nurse
B. The medical oncologist
C. The AP
D. All of the above

Clinical Pearls

- Intended to inform the decision of extended endocrine therapy beyond 5 years for early-stage, HR+ breast cancer patients
- A validated test that predicts the benefit of endocrine therapy beyond 5 years
- Recognized by ASCO and NCCN guidelines to predict which patients are likely to benefit from extended endocrine therapy

Q & A

Please type your questions for Michelle Butaud
into the **question box**.

Thank You