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FONDAZIONE onlus
EDO ed ELVO TEMPIA
per la lotta contro i tumori
dal 1981

Quali test genomici per indirizzare la scelta della terapia adiuvante?

LOM
Laboratorio
Oncologia Molecolare

3°Edizione

I tumori femminili

Dal gene profiling alla terapia personalizzata

22-23 Novembre 2023

Casale Monferrato, AL
Hotel Candiani

Test Genomici: Breast Unit Regione Piemonte

REGIONE PIEMONTE BU45S1 11/11/2021

Codice A1413C
D.D. 28 ottobre 2021, n. 1645
Individuazione delle Breast Unit deputate all'esecuzione ed alla validazione dei test genomici per il carcinoma mammario ormonoresponsivo in stadio precoce, di cui al Decreto del Ministro della Salute, 18 maggio 2021, ai sensi della D.G.R. n. 9-3819 del 24.09.2021.

REGIONE PIEMONTE

ATTO DD 1645/A1400A/2021 DEL 28/10/2021

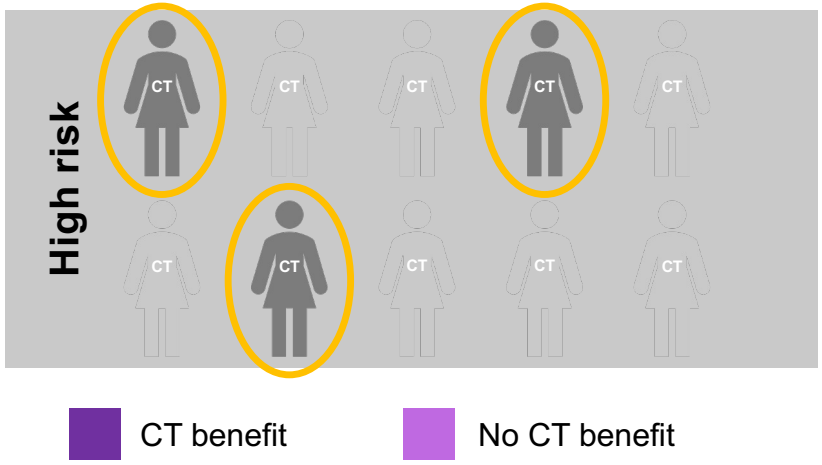
DETERMINAZIONE DIRIGENZIALE
A1400A - SANITA' E WELFARE

SEDE	TEST	Stato	QUANTITA' (casi/anno)	TEMPI DI REFERTAZIONE (giorni)
IRCC Candiolo	Prosigna®	attivo	100 incrementabile	10-14
AOU Città della Salute e della Scienza - Torino	Endopredict ®	attivabile	100 incrementabile	10-14
AOU Maggiore della Carità	Endopredict ®	attivo	100 incrementabile	10-14
Fondazione Edo Tempia	Endopredict® Prosigna®	attivo attivabile	100incrementabile 100 incrementabile	10-14

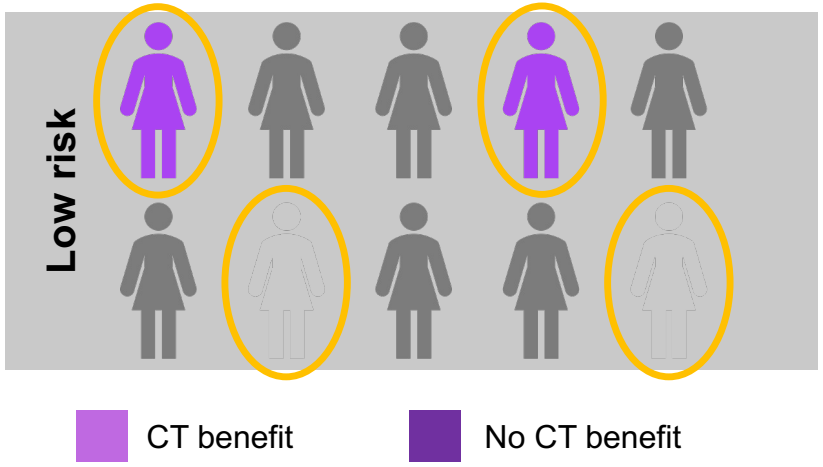
There is a medical need to help identify which patients are likely to benefit from chemotherapy[1]

Chemotherapy benefit has largely been independent of clinical pathological prognostic factors such as age, tumor size and grade, lymph node status, and ER and HER2 status[2]

Owing to a lack of predictive factors, patients with high-clinical-risk breast cancer may be **overtreated** and exposed to unnecessary adverse events[1,3]



Patients with low-clinical-risk breast cancer are not routinely given chemotherapy, and so some patients may be at risk of **undertreatment**[3,4]



Kindly provide by Exact Sciences

CT, chemotherapy; ER, estrogen receptor; HER2, human epidermal growth receptor 2.

1. Markopoulos C, et al. Eur J Surg Oncol. 2017;43:909–920; 2. EBCTCG. Lancet. 2012;379:432–444; 3. Sparano J, et al. N Engl J Med. 2018;379:111–121; 4. Goldhirsch A, et al. J Clin Oncol. 2003;21:3357–3365.

Test genomici (multigenici, espressione genica)

- **Oncotype DX** (21 geni, RT-qPCR) test esternalizzato USA
- **Endopredict** (12 geni, RT-qPCR) ***test disponibile in-house***
- **Mammaprint** (70 geni signature, microarray technology) test esternalizzato USA
- **Prosigna** (PAM50, nanostring technology) ***test disponibile in-house***
- **Breast cancer Index** (BCI,11 geni, RT-qPCR, per estendere ET oltre i 5ys)

Rischio di recidive/ Beneficio chemio adiuvante

LOM Laboratorio Oncologia Molecolare

Determining prognosis in early-stage breast cancer has evolved

Clinical
prognostic factors

- Age
- Tumor size
- Nodal status
- Grade
- Ki67
- HR status
- HER2 status

1st Generation
gene expression tests
(2002/2004)

- MammaPrint®
- Oncotype DX®

- TAILORx
- RxPonder
MINDACT

2nd Generation
gene expression tests
(2011/2013)

- EndoPredict®
- Prosigna®

Ongoing prospective trials

- RESCUE (EndoPredict)
- OPTIMA (Prosigna)

Algoritmo combina dati di espressione genica con variabili clinico-patologiche (T, N)

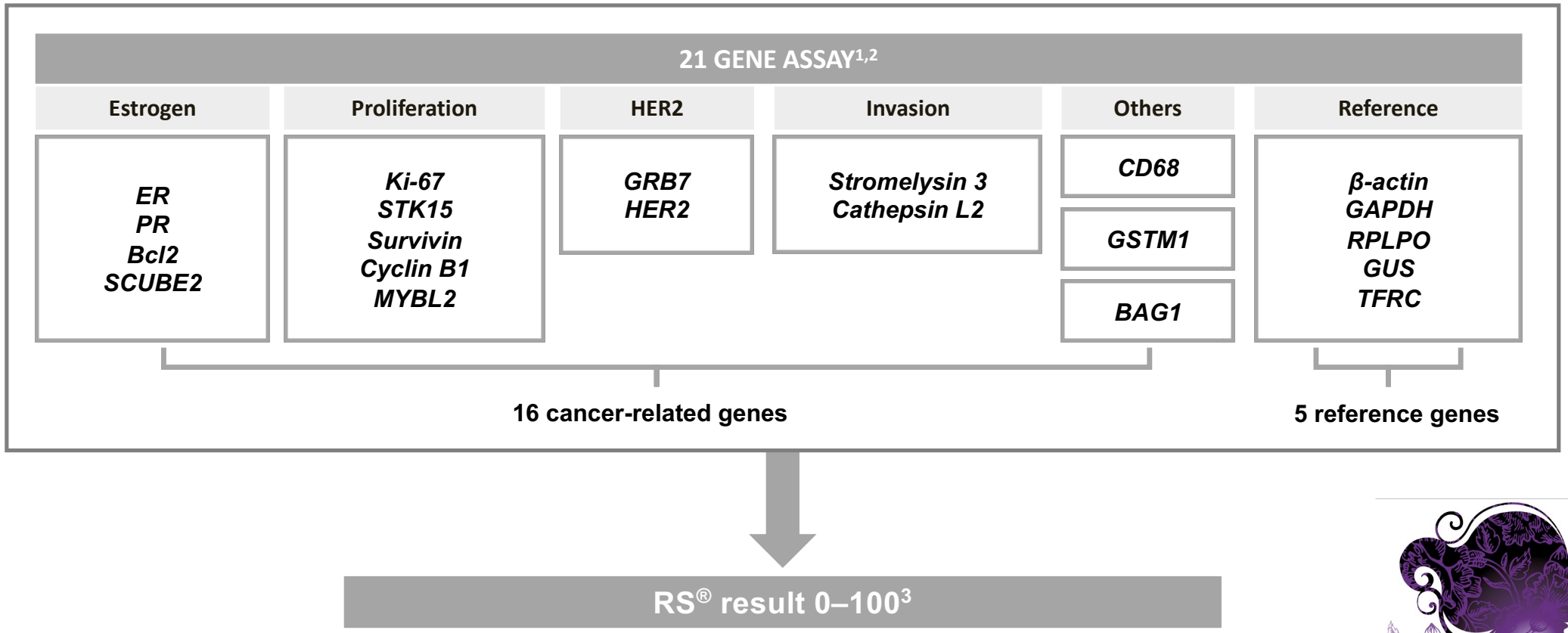
TAILORx N0
RxPonder N1/N+
MINDACT TNBC, HER2+, N1/N+

Kindly provided by Myriad Genetics

Oncotype DX

(21 gene panel, score RS)

The Oncotype DX® test uses 21 key genes linked to critical molecular pathways[1, 2]



RS®, Recurrence Score® result

1. Paik S, et al. N Engl J Med 2004; 351:2817-2826; 2. Cobleigh MA, et al. Clin Cancer Res. 2005;11:8623–8631; 3. Sparano J & Paik S. J Clin Oncol. 2008;26:721–728.

Kindly provide by Exact Sciences

Oncotype DX® test development: Demonstrating the prognostic and predictive value in HR+, HER2- early breast cancer[1–6]

	N0	N1/N+
Clinical validation for **prognosis** (retrospective analysis)	**NSABP B-14**[1] N=668	**TransATAC**[2] N=306
Clinical validation for chemotherapy benefit **prediction** (retrospective analysis)	**NSABP B-20**[3] N=651	**SWOG8814**[4] N=367
Clinical utility (prospective, randomized studies)	**TAILORx**[5] N=10 273 NCT00310180	**RxPONDER**[6] N=5018 NCT01272037

Kindly provide by Exact Sciences

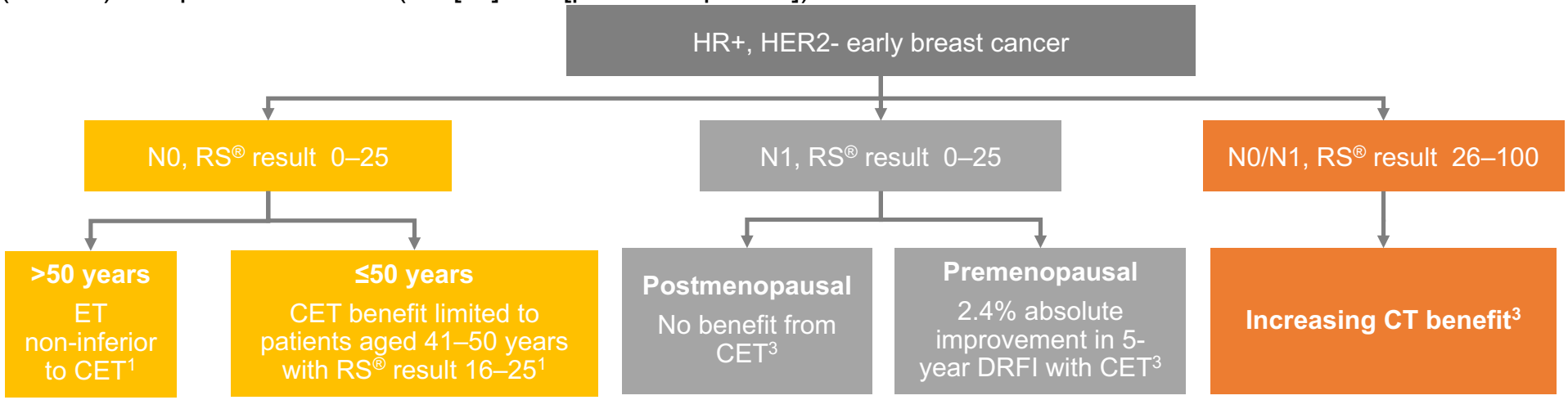
HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NSABP, National Surgical Adjuvant Breast and Bowel Project.

1. Paik S, et al. N Engl J Med 2004; 351:2817-2826; 2. Dowsett M, et al. J Clin Oncol. 2010;28:1829-34; 3. Paik, S. et al. J. Clin. Oncol. 2006;24:3726–3734; 4. Albain K, et al. Lancet Oncol. 2010;11:55–65; 5. Sparano J, et al. N Engl J Med. 2018;379:111-121; 6. Kalinsky K, et al. N Engl J Med 2021;385:2336-2347.

Tailoring treatment for HR+, HER2- early breast cancer in the era of precision medicine

The Oncotype DX® test can help identify which patients with HR+, HER2- breast cancer with up to three positive lymph nodes can forgo chemotherapy

- The large randomized, prospective TAILORx and RxPONDER trials have shown that the majority of newly diagnosed women with HR+, HER2- early breast cancer can be spared from chemotherapy[1–3]
- Key international guidelines recommend the use of the Oncotype DX® test, including prognostic (N0–N1) and predictive value (N0 [all]–N1 [postmenopausal])[4–7]



CET, chemoendocrine therapy; CT, chemotherapy; DRFI, distant recurrence-free interval; ET, endocrine therapy; HER, human epidermal growth factor receptor 2; HR, hormone receptor; RS®, Recurrence Score®.

1. Sparano J, et al. N Engl J Med. 2018;379:111–121; 2. Kalinsky K, et al. N Engl J Med. 2021;385:2336–2347; 3. Kalinsky K, et al. Clin Cancer Res. 2021;82:GS3–00; 4. Andre F, et al. J Clin Oncol. 2022;40:1816–1837; 5. NCCN. 2022. NCCN Guidelines: Breast Cancer, version 4. Available at: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf Accessed: December 2022; 6. Burstein HJ, et al. Ann Oncol. 2021;32:1216–1235; 7. Cardoso F, et al. Ann Oncol. 2019;30:1194–1220.

Kindly provide by Exact Sciences

Key guidelines recommend use of the Oncotype DX® test

ASCO
- Only test strongly recommended for **all N0 and postmenopausal N1** patients with ER+, HER2- early breast cancer
- Recommendation is irrespective of clinical risk, with high evidence quality

NCCN
- Only assay recognized to predict adjuvant chemotherapy benefit, and the only assay classified as the **"preferred" test in postmenopausal patients with N0/N1**, HR+, HER2- breast cancer

st gallen oncology conferences
- Test strongly endorsed **for most patients with N0/N1, HR+, HER2- early breast cancer, irrespective of grade or menopausal status***
- TAILORx and RxPONDER cut-offs to help guide treatment decisions

ESMO
- May be used to gain additional prognostic and/or predictive information with 1A evidence to **complement pathology assessment** and to **predict the benefit of adjuvant chemotherapy**

*As voted by a clear majority of the St. Gallen International Expert Consensus panel.

ER+, estrogen receptor positive; HR, hormone receptor; HER, human epidermal growth factor receptor; N0, node negative; N+, node positive.

1. Andre F, et al. J Clin Oncol. 2022;40:1816–1837; 2. NCCN. 2022. NCCN Guidelines: Breast Cancer, version 4. Available at: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf Accessed December 2022; 3. Burstein HJ, et al. Ann Oncol. 2021;32:1216–1235; 4. Cardoso F, et al. Ann Oncol. 2019;30:1194–1220.

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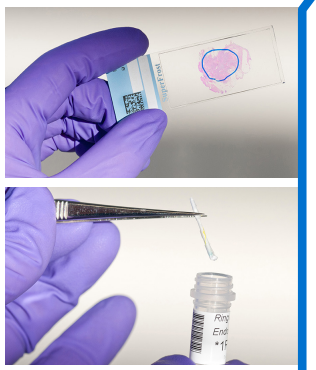
Endopredict

(12 genes panel, Epclin score, Alto/Basso)

RT-PCR-based EndoPredict

Tumor sample



FFPE tissue sample:

- ER +, HER2 -
- 10 µm section
- >30% tumor content
- Adjacent HE slide

RNA isolation

RNA-Isolation:

- Manually
- Automatically

▶ 3h for 12 samples

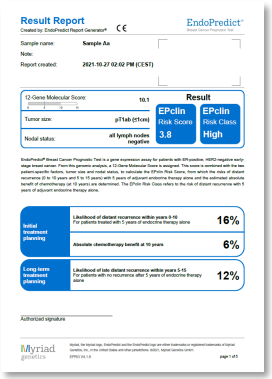
EndoPredict test

RT-qPCR:

- Pipetting of 96 well plates
- RT-PCR run

▶ 2h per plate

Test result



Analysis and report:

- Upload in software
- Quality control
- Report print-out

▶ 15 min

Laboratory turn-around-time < 8 h

Kindly provided by Myriad Genetics

How is risk of recurrence calculated?

Tumor Biology

12-Gene Molecular Score

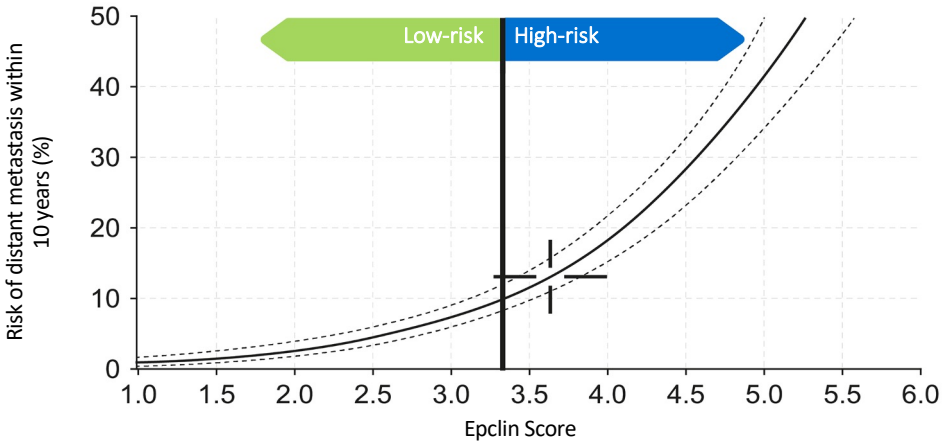
Gene expression measured in FFPE tumor tissue

+

Tumor Mass

Clinical Parameters

Tumor size (pT) + nodal status (pN)



Epclin Score	Epclin 10y risk	Epclin class
3.6	13%	High-risk

EPclin Risk Score

➔ Cut-off not changed since development

Kindly provided by Myriad Genetics

Gene selection (12 gene panel)

	Gene	Assigned biological processes
Proliferation associated genes	***UBE2C***	Protein degradation, cell division
	BIRC5	Anti-apoptosis, cell division, cytokinesis, chromosome localization
	DHCR7	Cholesterol biosynthesis
Hormone receptor associated genes	***STC2***	Cell-to-cell communication
	AZGP1	Cell adhesion
	IL6ST	Various signal transduction pathways, cell proliferation, T cell proliferation
	RBBP8	DNA repair
	MGP	Transcriptional regulation

Dubsky et al., Br J Cancer 2013

EndoPredict genes for early and late recurrence

3 proliferation-related genes

5 hormone receptor-related genes

Early recurrence (0-5 years)

- *UBE2C*
- *BIRC5*
- *DHCR7*

- *STC2*
- *AZGP1*
- *IL6ST*
- *RBBP8*
- *MGP*

Late recurrence (>5 years)

4 control genes

3 normalization genes: *CALM2, OAZ1*, and *RPL37A*
1 control gene for DNA contamination: *HBB*

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Validation in 6 independent cohorts

	UNIRAD (France, UK, Belgium)	RESCUE (Germany, Switzerland)
Study Type	Randomized, double-blind, multicenter, phase III trial ER+/HER2- early-stage BC High-risk N1, Any T	Prospective, multicenter, observational study ER+/HER2- early-stage BC Low-risk N0-N1, T1-T3
Rationale	Assess prognostic and predictive power of EPclin risk score	Assess prognostic power of EPclin risk score: safety of EPclin low-risk patients
Timing	Recruitment stopped 2020 First data presented 2021	First data expected 2026

Ongoing prospective studies for EndoPredict

Kindly provided by Myriad Genetics

E, Endocrine; CTx, Chemotherapy
Filipits et al., Clin Cancer Res 2011; Martin et al., Breast Cancer Res 2014; Buus et al., J Natl Cancer Inst 2016; Constantinidou et al., Clin Cancer Res 2022; Penault-Llorca et al., SABCS 2021

Recommendation of EndoPredict by clinical guidelines

ESMO (2019)
European Society of Medical Oncology

For **N0** and **N+** (1-3 positive lymph nodes)….
EndoPredict may be used to gain additional prognostic and/or predictive information to complement pathology assessment and to predict the benefit of adjuvant chemotherapy.

ASCO (2022)
American Society of Clinical Oncology

….may be used to guide decisions for adjuvant endocrine and chemotherapy in ER+, HER2-, N0 or N+ (1-3 positive nodes) **postmenopausal** breast cancer patients.

St. Gallen (2021)
International Expert Consensus

…. panelists favored consideration of genomic signature testing in the vast majority of instances when chemotherapy is being considered for ER+, HER2- cancers, **irrespective of grade or patient menopausal status** (and in male breast cancer),
and in both N0 or N1 clinical stage cases.

AJCC (2017)
American Joint Committee on Cancer

….low risk score, in HR+, HER2-, N0 patients, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0 with a level of **evidence II**.

NCCN (2022)
National Comprehensive Cancer Network

For the consideration of adjuvant chemotherapy:

EndoPredict: pN0 and pN1 (1-3 positive nodes)

The assay is **prognostic** in endocrine and chemo-endocrine treated patients.

NICE (2018)
National Institute for Health and Care Excellence

….may guide adjuvant chemotherapy decisions for ER+, HER2-, node negative (including micrometastatic), early breast cancer defined as intermediate risk of distant recurrence.

Kindly provided by Myriad Genetics

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

ASCO Giugno 2022

Fabrice Andre, MD[1]; Nofisat Ismaila, MD, MSc[2]; Kimberly H. Allison, PhD[3]; William E. Barlow, PhD[4]; Deborah E. Collyar, BSc[5]; Senthil Damodaran, MD, PhD[6]; N. Lynn Henry, MD, PhD[7]; Komal Jhaveri, MD[8,9]; Kevin Kalinsky, MD, MS[10]; Nicole M. Kuderer, MD[11]; Anya Litvak, MD[12]; Erica L. Mayer, MD, MPH[13]; Lajos Pusztai, MD[14]; Rachel Raab, MD[15]; Antonio C. Wolff, MD[16]; and Vered Stearns, MD[16]

TABLE 1. Biomarkers to Guide Decisions on Endocrine and Chemotherapy for Patients With Early-Stage Invasive Breast Cancer

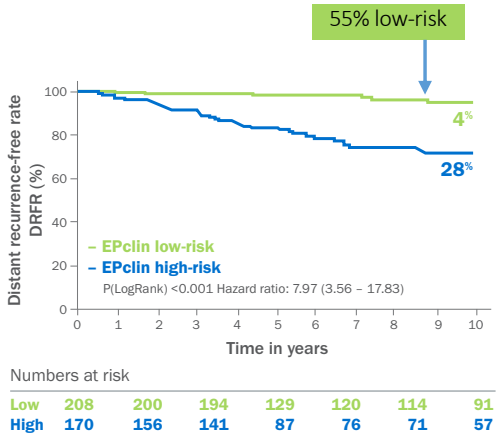
ER+ and HER2–	Premenopausal or Age ≤ 50 Years (evidence quality/strength of recommendation)	Postmenopausal or Age > 50 Years (evidence quality/strength of recommendation)
Node-negative	Oncotype DX (*high/strong*)	Oncotype DX (*high/strong*) MammaPrint[a] (*intermediate/strong*) EndoPredict (*intermediate/moderate*) Prosigna (*intermediate/moderate*) Ki67[b] (*intermediate/moderate*) IHC4[b] (*intermediate/moderate*) BCI[c] (*intermediate/moderate*)
1-3 positive nodes	Insufficient evidence to recommend a biomarker for use	Oncotype DX (*high/strong*) MammaPrint[a] (*intermediate/strong*) EndoPredict (*intermediate/moderate*) Ki67[b] (*intermediate/strong*) IHC4[b] (*intermediate/moderate*) BCI[c] (*intermediate/moderate*)
≥ 4 positive nodes	Insufficient evidence to recommend a biomarker for use	
HER2+ (ER+ or ER–)	No mature evidence to recommend use of any other biomarker for this patient population	
ER–/HER2–	No mature evidence to recommend use of any other biomarker for this patient population	

Abbreviations: BCI, Breast Cancer Index; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC4, immunohistochemistry 4.
[a]Only in women with high clinical risk.
[b]Only if locally validated and together with other parameters in patients who do not have access to genomic tests.
[c]May also be offered to women who received 5 years of endocrine therapy without evidence of recurrence.

Kindly provided by Myriad Genetics

Pre-menopausal:
Consistent results with previous post-menopausal studies

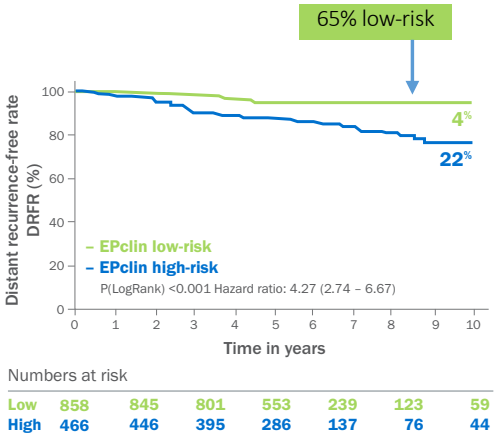
ASCSG-6 (N=378)
Post-menopausal



Numbers at risk

Low	208	200	194	129	120	114	91
High	170	156	141	87	76	71	57

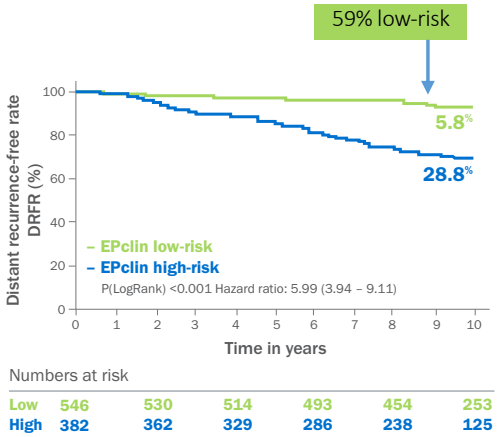
ABCSG-8 (N=1324)
Post-menopausal



Numbers at risk

Low	858	845	801	553	239	123	59
High	466	446	395	286	137	76	44

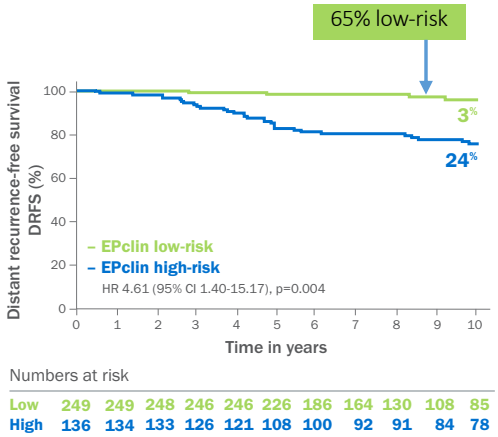
TransATAC (N=928)
Post-menopausal



Numbers at risk

Low	546	530	514	493	454	253	
High	382	362	329	286	238	125	

Pre-menopausal (N=385)
Pre-menopausal



Numbers at risk

Low	249	249	248	246	246	226	186	164	130	108	85
High	136	134	133	126	121	108	100	92	91	84	78

Consistent results, regardless of menopausal status

Filipits et al., Clin Cancer Res 2011; Buus et al., J Natl Cancer Inst 2016; Constantinidou et al., Clin Cancer Res 2022

Clin Cancer Res. Ottobre 2022

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Clinical Validation of EndoPredict in Pre-Menopausal Women with ER-Positive, HER2-Negative Primary Breast Cancer

Anastasia Constantinidou[1,2,3], Yiola Marcou[2], Michael S. Toss[4], Timothy Simmons[5], Ryan Bernhisel[5], Elisha Hughes[5], Braden Probst[5], Stephanie Meek[5], Eleni Kakouri[2], Georgios Georgiou[6], Ioanna Zouvani[6], Gabriella Savvidou[1], Vanessa Kuhl[7], Jennifer Doedt[7], Susanne Wagner[5], Alexander Gutin[5], Thomas P. Slavin[5], Jerry S. Lanchbury[5], Ralf Kronenwett[7], Ian O. Ellis[4], and Emad A. Rakha[4]

12 Dicembre 2022, SABCS

- Due studi prospettici in “real world” presentati al San Antonio Breasr Cancer Simposio (SABCS) mostrano che EndoPredict guida con precisione le decisioni relative alla chemioterapia nel tumore al seno ER+, HER2-
  - Technical University Munich (TUM) Germany - prospective outcome study
  - Charité Germany - prospective EndoPredict registry

EndoPredict summary

- **Trained and validated in** the most clinically relevant ER+, HER2-, N0/N+ population
- Combines tumor gene expression analysis and key clinico-pathological **prognostic factors**
- Consistent results **from five clinical studies with Level of Evidence 1B** confirmed by a prospective study with LoE1A

- Accurate risk assessment for early and late distant recurrence – **assisting patient selection for chemotherapy and extended endocrine therapy**
- **Good performance in** node negative and node positive **patients**
- **Validated in** pre- and postmenopausal **patients**

- **Ability to** predict chemotherapy benefit **in women with a high EPclin Risk Score**
- **Reliable** binary classification of low- / high-risk
- **Performed in** local **molecular pathology laboratory or at a** reference **laboratory**

Kindly provided by Myriad Genetics

Take home message

- I test genomici prognostici hanno dimostrato di avere un'importante ruolo clinico nell'identificare quelle pazienti mammella (HR+, HER2-) ad elevato rischio di recidiva, che potranno beneficiare della chemioterapia adiuvante.
- Tre recenti studi prospettivi randomizzati: *Oncotype DX TAILORx e RxPonder* ed il trial *Mammaprint MINDACT* hanno dimostrato un differente potere predittivo delle signature molecolari sulla base delle **stato menopausale** della paziente.
- Lo studio di *Costantinidou* et a. 2022 ha dimostrato un'associazione fra l'Epclin score e le recidive a 10 anni in una corte di donne in *pre-menopausa*.
- Sono in corso trial prospettici *OPTIMA (Prosigna), UNIRAD e RESCUE (Endopredict)*
- Ciascun test genomico ha un differente «design» che spiega il non completo overlapping dei risultati.
- Inoltre, esiste un **bias di campionamento** delle pazienti da inviare al test, da parte del clinico, che può spiegare le differenti % di alti/bassi rischi nelle diverse casistiche analizzate.

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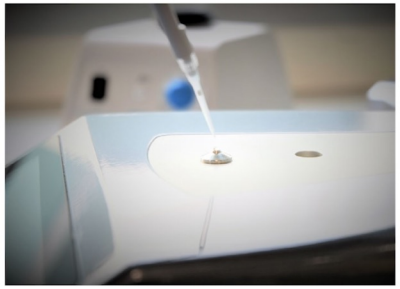
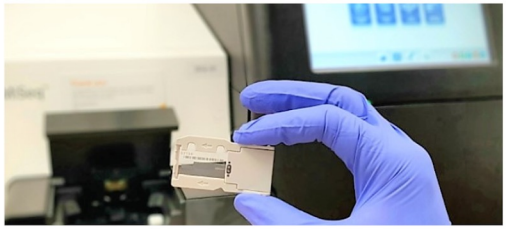
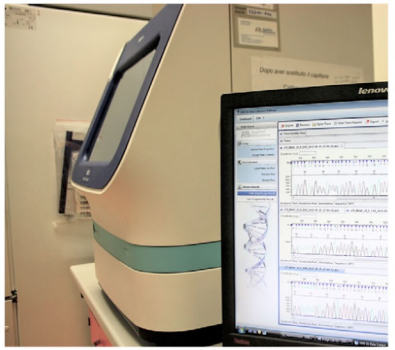


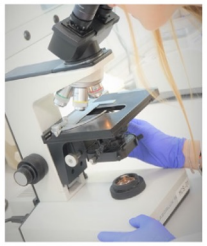







Grazie
per
l'Attenzione!



FONDAZIONE onlus
EDO ed ELVO TEMPIA
per la lotta contro i tumori
dal 1981