© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

FORSCHEN
LEHREN
HEILEN

Prognostic and Predictive Factors

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

www.ago-online.de
FORSCHEN
LEHREN
HEILEN

Prognostic and Predictive Factors

- **Versions 2002–2023:**
  Costa / Fasching / Fersis / Friedrichs / Gerber / Gluz / Göhring / Harbeck / Jackisch / Janni / Kolberg-Liedtke / Kreipe / Loibl / Lück / Mundhenke / Nitz / Rody / Schaller / Schmidt / Schmutzler / Schneeweiss / Simon / Solomayer / Thill / Thomssen / Untch / Witzel / Wöckel

- **Version 2024:**
  Thill / Friedrich / Kreipe

Data bases screened
Pubmed 2008 - 2023, ASCO 2017-2023, SABCS 2003 – 2023, ESMO 2023, Cochrane data base (n.d.)

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

www.ago-online.de
FORSCHEN
LEHREN
HEILEN

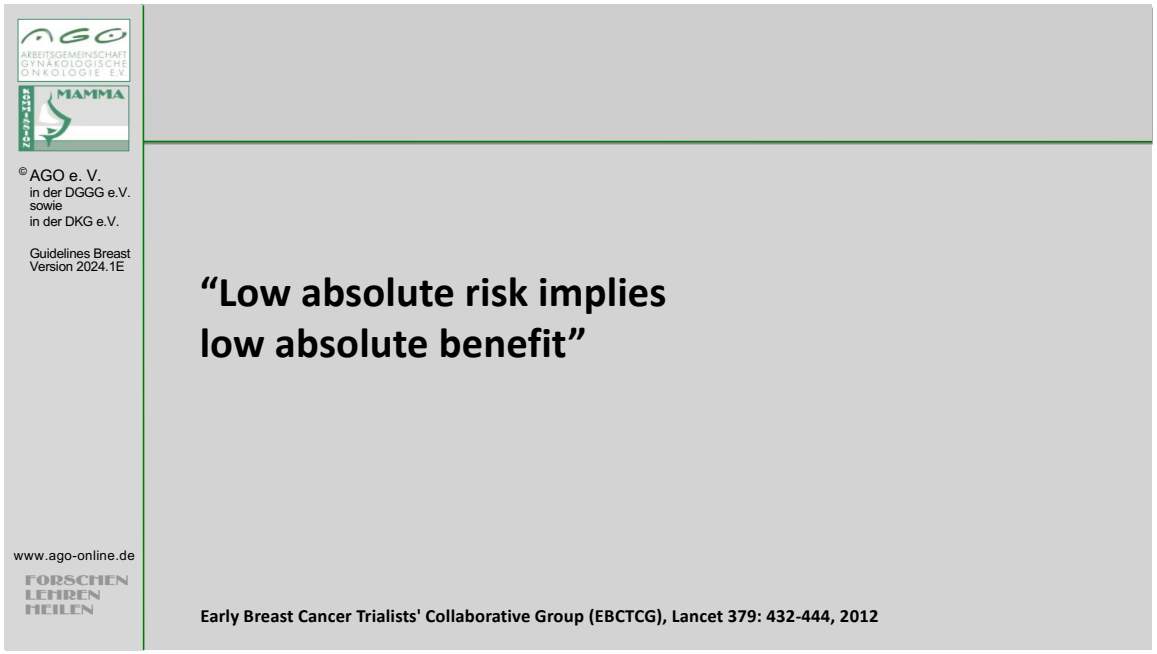
Definition

A **Prognostic Factors** is associated with the probability of the course of the disease (e.g. disease-free or progression-free survival, overall survival). The probability can be influenced by therapy.

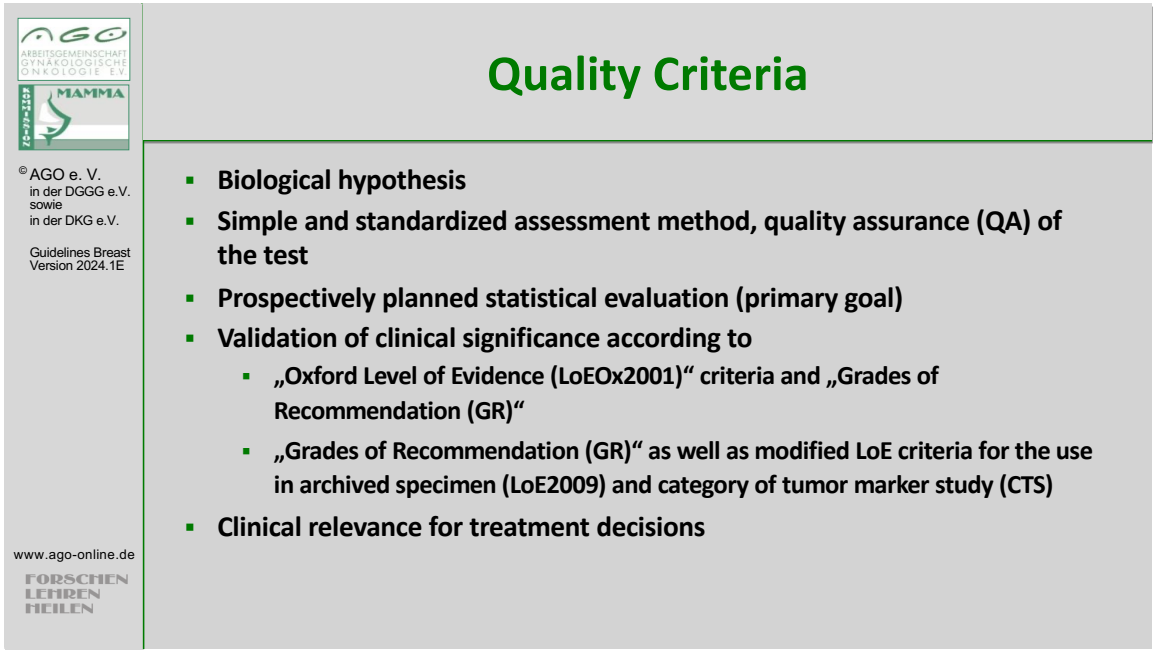
A **Predictive Factor** is associated with the probability of the effect of a given therapy.

Definition of Prognosis and Prediction

1. Hayes DF, Bast RC, Desch CE et al.:Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst. 1996 Oct 16;88(20):1456-66.
2. McGuire WL, Clark GM. Prognostic factors and treatment decisions in axillary-node-negative breast cancer. N Engl J Med. 1992 Jun 25;326(26):1756-61.



1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 379: 432-444, 2012
2. Peto, R., Davies, C., Godwin, J., et al. 2012. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 379, 432–444.
3. Nielsen TO, Jensen MB, Burugu S, et al. High-Risk Premenopausal Luminal A Breast Cancer Patients Derive no Benefit from Adjuvant Cyclophosphamide-based Chemotherapy: Results from the DBCG77B Clinical Trial. Clin Cancer Res. 2017 Feb 15;23(4):946-953.



1. Febbo PG, Ladanyi M, Aldape KD, et al. (2011) NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw 9 Suppl 5: S1-32; quiz S33.
2. Hayes DF, Bast RC, Desch CE et al. (1996) Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J. Natl. Cancer Inst. 88 (20): 1456–1466.
3. Jeremy Howick, Iain Chalmers, Paul Glasziou, et al. Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document). Oxford Centre for Evidence-Based Medicine.
4. McShane LM, Altman DG, Sauerbrei W et al. (2005) Reporting recommendations for tumor marker prognostic studies. J. Clin. Oncol. 23 (36): 9067–9072.
5. McShane LM, Hayes DF (2012) Publication of tumor marker research results: the necessity for complete and transparent reporting. J. Clin. Oncol. 30 (34): 4223–4232.
6. Simon RM, Paik S, Hayes DF (2009) Use of archived specimens in evaluation of prognostic and predictive biomarkers. J. Natl. Cancer Inst. 101 (21): 1446–1452.

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

www.ago-online.de
FORSCHEN
LEHREN
HEILEN

Prognostic Factors for an Ipsilateral Recurrence after DCIS I

	LoE
Resection margins	**1a**
Age	**1a**
Size	**1a**
Grade	**1a**
Comedo necrosis	**1a**
Method of diagnosis	**1a**
Focality	**1a**
HER2-overexpression	**1a**
ER / PR (positive vs. negative)	**1a**

#see chapter „DCIS“

1. Visser LL, Elshof LE, Schaapveld M et al. Clinicopathological Risk Factors for an Invasive Breast Cancer recurrence after Ductal Carcinoma In Situ-A Nested Case-Control Study. Clin Cancer Res. 2018 Aug 1;24(15):3593-3601.
2. Rakovitch E, Gray R, Baehner FL et al. Refined estimates of local recurrence risks by DCIS score adjusting for clinicopathological features: a combined analysis of ECOG-ACRIN E5194 and Ontario DCIS cohort studies. Breast Cancer Res Treat. 2018 Jun;169(2):359-369
3. Cutuli B: Ductal carcinoma in situ in 2019: Diagnosis, treatment, prognosis. Presse Med. 2019 Oct;48(10):1112-1122
4. Badve SS, Gökmen-Polar: Ductal carcinoma in situ of breast: update 2019. Pathology. 2019 Oct;51(6):563-569.
5. Van Bockstal MR, Agahozo MC, Koppert LB: A retrospective alternative for active surveillance trials for ductal carcinoma in situ of the breast. Int J Cancer. 2020 Mar 1;146(5):1189-1197
6. Solin LJ: Management of Ductal Carcinoma In Situ (DCIS) of the Breast: Present Approaches and Future Directions. Curr Oncol Rep. 2019 Mar 5;21(4):33
7. Giannakeas V, Sopik V, Narod SA. Association of a Diagnosis of Ductal Carcinoma In Situ With Death From Breast Cancer. JAMA Netw Open. 2020 Sep; 3(9): e2017124. Published online 2020 Sep 16. doi: 10.1001/jamanetworkopen.2020.17124
8. Groen EJ, Hudecek J, Mulder L, et al. Prognostic value of histopathological DCIS features in a large-scale international interrater reliability study. Breast Cancer Res Treat. 2020; 183(3): 759–770. Published online 2020 Jul 30. doi: 10.1007/s10549-020-05816-x

Diagnostische Methode

1. Park HS, Park S, Cho J, et al. Risk predictors of underestimation and the need for sentinel node biopsy in patients diagnosed with ductal carcinoma in situ by preoperative needle biopsy. J Surg Oncol. 2013 Mar;107(4):388-92. doi: 10.1002/jso.23273. Epub 2012 Sep 24.
2. Schulz S, Sinn P, Golatta M, et al. Prediction of underestimated invasiveness in patients with ductal carcinoma in situ of the breast on percutaneous biopsy as rationale for recommending concurrent sentinel lymph node biopsy. Breast. 2013 Aug;22(4):537-42.
3. Elshof LE, Schmidt MK, Rutgers EJ, et al. Cause-specific Mortality in a Population-based Cohort of 9799 Women Treated for Ductal Carcinoma In Situ. Ann Surg. 2017 Apr 3. doi: 10.1097/SLA.0000000000002239. [Epub ahead of print]
4. Punglia RS, Jiang W, Lipsitz SR, et al. Clinical risk score to predict likelihood of recurrence after ductal carcinoma in situ treated with breast-conserving surgery. Breast Cancer Res Treat. 2017 Oct 28. doi: 10.1007/s10549-017-4553-5. [Epub ahead of print]

Fokalität

1. Meijnen P, Bartelink H. Multifocal ductal carcinoma in situ of the breast: A contraindication for breast-conserving treatment? J Clin Oncol 2007;25:5548–5549
2. Rakovitch E, Pignol JP, Hanna W, et al. Significance of multifocality in ductal carcinoma in situ: outcomes of women treated with breast-conserving therapy. J Clin Oncol 2007;25:5591–5596

(mod.) Van Nuys Prognose Index und MSKCC Nomogramm

1. Lagios MD, Page DL, Silverstein MJ. Prospective study of wide excision alone for ductal carcinoma in situ of the breast. J Clin Oncol 2006;24:3809-11
2. Rudloff U, Jacks LM, Goldberg JL, et al. Nomogram for predicting the risk of local recuurence after breast conserving surgery for ductal carcinoma in situ. J Clin Oncol 2010; 28(23): 3762-9
3. Van Zee KJ, Patil S. Validation of a nomogram for predicting risk of local recurrence for ductal carcinoma in situ. J Clin Oncol 2012; 30(25): 3143-4.
4. Sweldens C, Peeters S, van Limbergen E, et al. Öocal relapse after breast-conserving therapy for ductal carcinoma in situ: a European single-center experience and external validation of the Memorial Sloan-Kettering Cancer Center DCIS nomogram. Cancer J 2014; 20(1): 1-7.
5. Lei RY, Carter DL, Antell AG, et al. A Comparison of Predicted Ipsilateral Tumor Recurrence Risks in Patients With Ductal Carcinoma in

Situ of the Breast After Breast-Conserving Surgery by Breast Radiation Oncologists, the Van Nuys Prognostic Index, the Memorial Sloan Kettering Cancer Center DCIS Nomogram, and the 12-Gene DCIS Score Assay. Adv Radiat Oncol 2020;6(2):100607.

6. Grimm LJ , Rahbar H , Abdelmalak M, et al: Ductal Carcinoma in Situ: State-of-the-Art Review. Radiology. 2021 Dec 21;211839. doi: 10.1148/radiol.211839. Online ahead of print.
7. Wärnberg F, Karlsson P, Holmberg E, et al: Prognostic Risk Assessment and Prediction of Radiotherapy Benefit for Women with Ductal Carcinoma In Situ (DCIS) of the Breast, in a Randomized Clinical Trial (SweDCIS). Cancers 2021, 13,6103

Palpables DCIS
Palpabel + COX-2+p16+Ki-67+
Palpabel + ER-, HER2, +Ki-67+
HER2-Überexpression
ER/PgR (positiv vs. negativ)
DCIS-Score

1. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst. 2013 May 15;105(10):701-10.
2. Sarah Patricia Cate, Alyssa Gillego, Manjeet Chadha, et al. Does the Oncotype DCIS score impact treatment decisions? J Clin Oncol 31, 2013 (suppl 26; abstr 91)
3. Rakovitch E, Nofech-Mozes S, Hanna W et al. A large prospectively-designed study of the DCIS score. Predicting recurrence risk after local excision for ductal carcinoma in situ patients with and without irradiation. SABCS 2015. S5-04
4. Wood WC, Alvarado M, Buchholz DJ, et al. The current clinical value of the DCIS Score. Oncology (Williston Park). 2014 May;28 Suppl 2:C2, 1-8, C3.
5. O'Keefe TJ, Blair SL, Hosseini A et al. HER2-Overexpressing Ductal Carcinoma In Situ Associated with Increased Risk of Ipsilateral Invasive Recurrence, Receptor Discordance with Recurrence. Cancer Prev Res (Phila). 2020 Sep;13(9):761-772. doi: 10.1158/1940-6207.CAPR-20-0024.
6. Lazzeroni M, DeCensi A, Guerrieri-Gonzaga A et al. Prognostic and predictive value of cell cycle progression (CCP) score in ductal carcinoma in situ of the breast. Mod Pathol. 2020 Jun;33(6):1065-1077. doi: 10.1038/s41379-020-0452-0.
7. Hwang KT , Suh YJ, PARK CH, et al: Hormone Receptor Subtype in Ductal Carcinoma in Situ: Prognostic and Predictive Roles of the Progesterone Receptor. The Oncologist 2021;26:e1939–e1950

DCIS mit Mikroinvasion – Behandlung analog zum invasiven Karzinom

1. Eng-Wong J, JP Costantino et al. The Impact of Systemic Therapy Following Ductal Carcinoma In Situ. J Natl Cancer Inst Monogr 2010; 41: 200 – 203
2. Ryan R, Tawfik O, Jensen RA, Anant S. Current Approaches to Diagnosis and Treatment of Ductal Carcinoma In Situ and Future Directions. Prog Mol Biol Transl Sci. 2017;151:33-80.

Intrinsische Subgruppen (Luminal A,B, HER+, triple negativ)

1. Noh JM, Lee J, Choi DH, et al. HER-2 overexpression is not associated with increased ipsilateral breast tumor recurrence in DCIS treated with breast-conserving surgery followed by radiotherapy. Breast. 2013 Oct;22(5):894-7.
2. Solin LJ.: Management of Ductal Carcinoma In Situ (DCIS) of the Breast: Present Approaches and Future Directions. Curr Oncol Rep. 2019 Mar 5;21(4):33. doi: 10.1007/s11912-019-0777-3.
3. Visser LL, Groen EJ, van Leeuwen FE, et al.: Predictors of an Invasive Breast Cancer Recurrence after DCIS: A Systematic Review and Meta-analyses. Cancer Epidemiol Biomarkers Prev. 2019 May;28(5):835-845. doi: 10.1158/1055-9965.EPI-18-0976. Epub 2019 Apr 25.
4. Van Bockstal MR, Agahozo MC, Koppert LB, et al. A retrospective alternative for active surveillance trials for ductal carcinoma in situ of the breast. Int J Cancer. 2019 Apr 24. doi: 10.1002/ijc.32362. [Epub ahead of print]
5. Liu Y, Shou K, Li J, et al. Ductal Carcinoma In Situ of the Breast: Perspectives on Tumor Subtype and Treatment. Biomed Res Int. 2020; 2020: 7251431. Published online 2020 May 27. doi: 10.1155/2020/7251431

Familiäre Karzinombelastung, Menopausenstatus, BMI und Brustdichte

1. Alaeikhanehshir S, Engelhardt EG, van Duijnhoven FH, et al. The impact of patient characteristics and lifestyle factors on the risk of an ipsilateral event after a primary DCIS: A systematic review. Breast. 2020 Apr; 50: 95–103. Published online 2020 Feb 19. doi: 10.1016/j.breast.2020.02.006

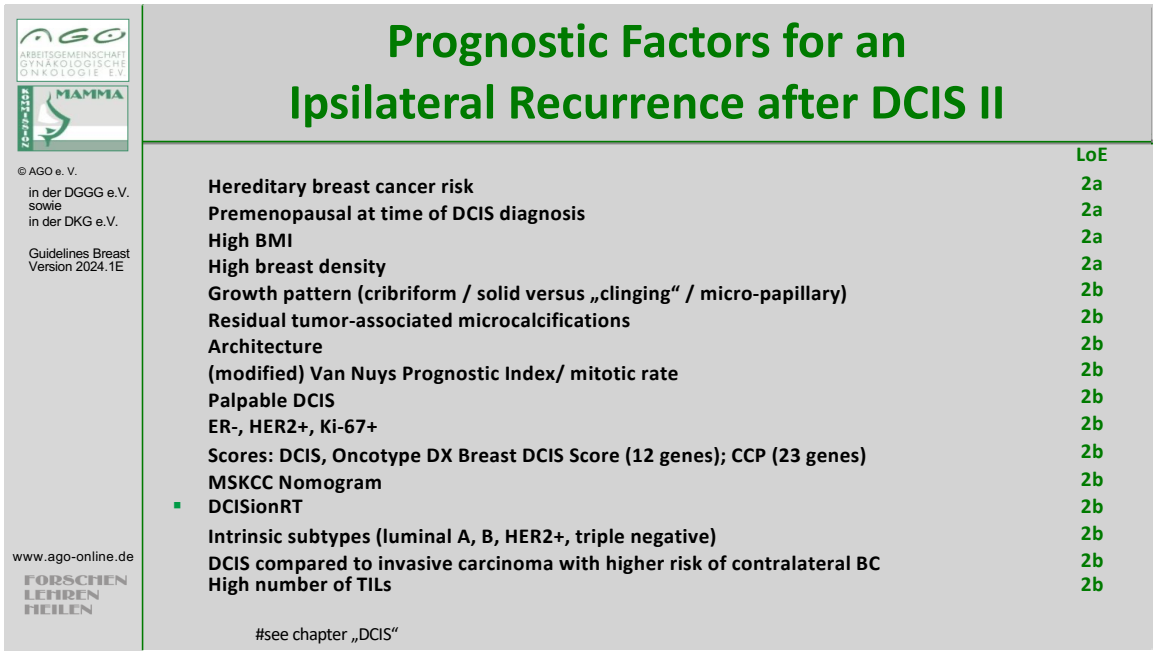
Kontralaterales Mammakarzinom

1. Giardiello D, Kramer I, Hooning MJ, et al. Contralateral breast cancer risk in patients with ductal carcinoma in situ and invasive breast

cancer. NPJ Breast Cancer. 2020; 6: 60. Published online 2020 Nov 3. doi: 10.1038/s41523-020-00202-8

Molecular Subtyping

1. Nofech-Mozes S, Hanna W, Rakovitch E. Molecular Evaluation of Breast Ductal Carcinoma in Situ with Oncotype DX DCIS. Am J Pathol. 2018 Dec 31. pii: S0002-9440(18)30581-9
2. Lei RY, Carter DL, Antell AG, et al. A Comparison of Predicted Ipsilateral Tumor Recurrence Risks in Patients With Ductal Carcinoma in Situ of the Breast After Breast-Conserving Surgery by Breast Radiation Oncologists, the Van Nuys Prognostic Index, the Memorial Sloan Kettering Cancer Center DCIS Nomogram, and the 12-Gene DCIS Score Assay. Adv Radiat Oncol 2020;6(2):100607.
3. Wärnberg F, Karlsson P, Holmberg E, et al: Prognostic Risk Assessment and Prediction of Radiotherapy Benefit for Women with Ductal Carcinoma In Situ (DCIS) of the Breast, in a Randomized Clinical Trial (SweDCIS). Cancers (Basel). 2021 Dec 3;13(23):6103. doi: 10.3390/cancers13236103.



1. Visser LL, Elshof LE, Schaapveld M et al. Clinicopathological Risk Factors for an Invasive Breast Cancer recurrence after Ductal Carcinoma In Situ-A Nested Case-Control Study. Clin Cancer Res. 2018 Aug 1;24(15):3593-3601.
2. Rakovitch E, Gray R, Baehner FL et al. Refined estimateos of local recurrence risks by DCIS score adjusting for clinicopathological features: a combined analysis of ECOG-ACRIN E5194 and Ontario DCIS cohort studies. Breast Cancer Res Treat. 2018 Jun;169(2):359-369
3. Cutuli B: Ductal carcinoma in situ in 2019: Diagnosis, treatment, prognosis. Presse Med. 2019 Oct;48(10):1112-1122
4. Badve SS, Gökmen-Polar: Ductal carcinoma in situ of breast: update 2019. Pathology. 2019 Oct;51(6):563-569.
5. Van Bockstal MR, Agahozo MC, Koppert LB: A retrospective alternative for active surveillance trials for ductal carcinoma in situ of the breast. Int J Cancer. 2020 Mar 1;146(5):1189-1197
6. Solin LJ: Management of Ductal Carcinoma In Situ (DCIS) of the Breast: Present Approaches and Future Directions. Curr Oncol Rep. 2019 Mar 5;21(4):33
7. Giannakeas V, Sopik V, Narod SA. Association of a Diagnosis of Ductal Carcinoma In Situ With Death From Breast Cancer. JAMA Netw Open. 2020 Sep; 3(9): e2017124. Published online 2020 Sep 16. doi: 10.1001/jamanetworkopen.2020.17124
8. Groen EJ, Hudecek J, Mulder L, et al. Prognostic value of histopathological DCIS features in a large-scale international interrater reliability study. Breast Cancer Res Treat. 2020; 183(3): 759–770. Published online 2020 Jul 30. doi: 10.1007/s10549-020-05816-x

Diagnostische Methode

1. Park HS, Park S, Cho J, et al. Risk predictors of underestimation and the need for sentinel node biopsy in patients diagnosed with ductal carcinoma in situ by preoperative needle biopsy. J Surg Oncol. 2013 Mar;107(4):388-92. doi: 10.1002/jso.23273. Epub 2012 Sep 24.
2. Schulz S, Sinn P, Golatta M, et al. Prediction of underestimated invasiveness in patients with ductal carcinoma in situ of the breast on percutaneous biopsy as rationale for recommending concurrent sentinel lymph node biopsy. Breast. 2013 Aug;22(4):537-42.
3. Elshof LE, Schmidt MK, Rutgers EJ, et al. Cause-specific Mortality in a Population-based Cohort of 9799 Women Treated for Ductal Carcinoma In Situ. Ann Surg. 2017 Apr 3. doi: 10.1097/SLA.0000000000002239. [Epub ahead of print]
4. Punglia RS, Jiang W, Lipsitz SR, et al. Clinical risk score to predict likelihood of recurrence after ductal carcinoma in situ treated with breast-conserving surgery. Breast Cancer Res Treat. 2017 Oct 28. doi: 10.1007/s10549-017-4553-5. [Epub ahead of print]

Fokalität

1. Meijnen P, Bartelink H. Multifocal ductal carcinoma in situ of the breast: A contraindication for breast-conserving treatment? J Clin Oncol 2007;25:5548–5549
2. Rakovitch E, Pignol JP, Hanna W, et al. Significance of multifocality in ductal carcinoma in situ: outcomes of women treated with breast-conserving therapy. J Clin Oncol 2007;25:5591–5596

(mod.) Van Nuys Prognose Index, MSKCC Nomogramm und DCISonRT

1. Lagios MD, Page DL, Silverstein MJ. Prospective study of wide excision alone for ductal carcinoma in situ of the breast. J Clin Oncol 2006;24:3809-11
2. Rudloff U, Jacks LM, Goldberg JL, et al. Nomogram for predicting the risk of local recuurence after breast conserving surgery for ductal carcinoma in situ. J Clin Oncol 2010; 28(23): 3762-9
3. Van Zee KJ, Patil S. Validation of a nomogram for predicting risk of local recurrence for ductal carcinoma in situ. J Clin Oncol 2012; 30(25): 3143-4.
4. Sweldens C, Peeters S, van Limbergen E, et al. Öocal relapse after breast-conserving therapy for ductal carcinoma in situ: a European single-center experience and external validation of the Memorial Sloan-Kettering Cancer Center DCIS nomogram. Cancer J 2014; 20(1): 1-7.
5. Lei RY, Carter DL, Antell AG, et al. A Comparison of Predicted Ipsilateral Tumor Recurrence Risks in Patients With Ductal Carcinoma in

Situ of the Breast After Breast-Conserving Surgery by Breast Radiation Oncologists, the Van Nuys Prognostic Index, the Memorial Sloan Kettering Cancer Center DCIS Nomogram, and the 12-Gene DCIS Score Assay. Adv Radiat Oncol 2020;6(2):100607.

6. Grimm LJ , Rahbar H , Abdelmalak M, et al: Ductal Carcinoma in Situ: State-of-the-Art Review. Radiology. 2021 Dec 21;211839. doi: 10.1148/radiol.211839. Online ahead of print.
7. Wärnberg F, Karlsson P, Holmberg E, et al: Prognostic Risk Assessment and Prediction of Radiotherapy Benefit for Women with Ductal Carcinoma In Situ (DCIS) of the Breast, in a Randomized Clinical Trial (SweDCIS). Cancers 2021, 13,6103

Palpables DCIS
Palpabel + COX-2+p16+Ki-67+
Palpabel + ER-, HER2, +Ki-67+
HER2-Überexpression
ER/PgR (positiv vs. negativ)
DCIS-Score

1. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst. 2013 May 15;105(10):701-10.
2. Sarah Patricia Cate, Alyssa Gillego, Manjeet Chadha, et al. Does the Oncotype DCIS score impact treatment decisions? J Clin Oncol 31, 2013 (suppl 26; abstr 91)
3. Rakovitch E, Nofech-Mozes S, Hanna W et al. A large prospectively-designed study of the DCIS score. Predicting recurrence risk after local excision for ductal carcinoma in situ patients with and without irradiation. SABCS 2015. S5-04
4. Wood WC, Alvarado M, Buchholz DJ, et al. The current clinical value of the DCIS Score. Oncology (Williston Park). 2014 May;28 Suppl 2:C2, 1-8, C3.
5. O'Keefe TJ, Blair SL, Hosseini A et al. HER2-Overexpressing Ductal Carcinoma In Situ Associated with Increased Risk of Ipsilateral Invasive Recurrence, Receptor Discordance with Recurrence. Cancer Prev Res (Phila). 2020 Sep;13(9):761-772. doi: 10.1158/1940-6207.CAPR-20-0024.
6. Lazzeroni M, DeCensi A, Guerrieri-Gonzaga A et al. Prognostic and predictive value of cell cycle progression (CCP) score in ductal carcinoma in situ of the breast. Mod Pathol. 2020 Jun;33(6):1065-1077. doi: 10.1038/s41379-020-0452-0.
7. Hwang KT , Suh YJ, PARK CH, et al: Hormone Receptor Subtype in Ductal Carcinoma in Situ: Prognostic and Predictive Roles of the Progesterone Receptor. The Oncologist 2021;26:e1939–e1950

DCISionRT:

1. Weinmann S, Leo MC, Francisco M, et al. Validation of a Ductal Carcinoma *In Situ* Biomarker Profile for Risk of Recurrence after Breast-Conserving Surgery with and without Radiotherapy. Clin Cancer Res. 2020 Aug 1;26(15):4054-4063.
2. Shah C, Bremer T, Cox C, The Clinical Utility of DCISionRT® on Radiation Therapy Decision Making in Patients with Ductal Carcinoma In Situ Following Breast-Conserving Surgery. Ann Surg Oncol. 2021 Oct;28(11):5974-5984.

DCIS mit Mikroinvasion – Behandlung analog zum invasiven Karzinom

1. Eng-Wong J, JP Costantino et al. The Impact of Systemic Therapy Following Ductal Carcinoma In Situ. J Natl Cancer Inst Monogr 2010; 41: 200 – 203
2. Ryan R, Tawfik O, Jensen RA, Anant S. Current Approaches to Diagnosis and Treatment of Ductal Carcinoma In Situ and Future Directions. Prog Mol Biol Transl Sci. 2017;151:33-80.

Intrinsische Subgruppen (Luminal A,B, HER+, triple negativ)

1. Noh JM, Lee J, Choi DH, et al. HER-2 overexpression is not associated with increased ipsilateral breast tumor recurrence in DCIS treated with breast-conserving surgery followed by radiotherapy. Breast. 2013 Oct;22(5):894-7.
2. Solin LJ.: Management of Ductal Carcinoma In Situ (DCIS) of the Breast: Present Approaches and Future Directions. Curr Oncol Rep. 2019 Mar 5;21(4):33. doi: 10.1007/s11912-019-0777-3.
3. Visser LL, Groen EJ, van Leeuwen FE, et al.: Predictors of an Invasive Breast Cancer Recurrence after DCIS: A Systematic Review and Meta-analyses. Cancer Epidemiol Biomarkers Prev. 2019 May;28(5):835-845. doi: 10.1158/1055-9965.EPI-18-0976. Epub 2019 Apr 25.
4. Van Bockstal MR, Agahozo MC, Koppert LB, van Deurzen CHM. A retrospective alternative for active surveillance trials for ductal carcinoma in situ of the breast. Int J Cancer. 2019 Apr 24. doi: 10.1002/ijc.32362. [Epub ahead of print]
5. Liu Y, Shou K, Li J, et al. Ductal Carcinoma In Situ of the Breast: Perspectives on Tumor Subtype and Treatment. Biomed Res Int. 2020; 2020: 7251431. Published online 2020 May 27. doi: 10.1155/2020/7251431

Familiäre Karzinombelastung, Menopausenstatus, BMI und Brustdichte

1. Alaeikhanehshir S, Engelhardt EG, van Duijnhoven FH, et al. The impact of patient characteristics and lifestyle factors on the risk of an

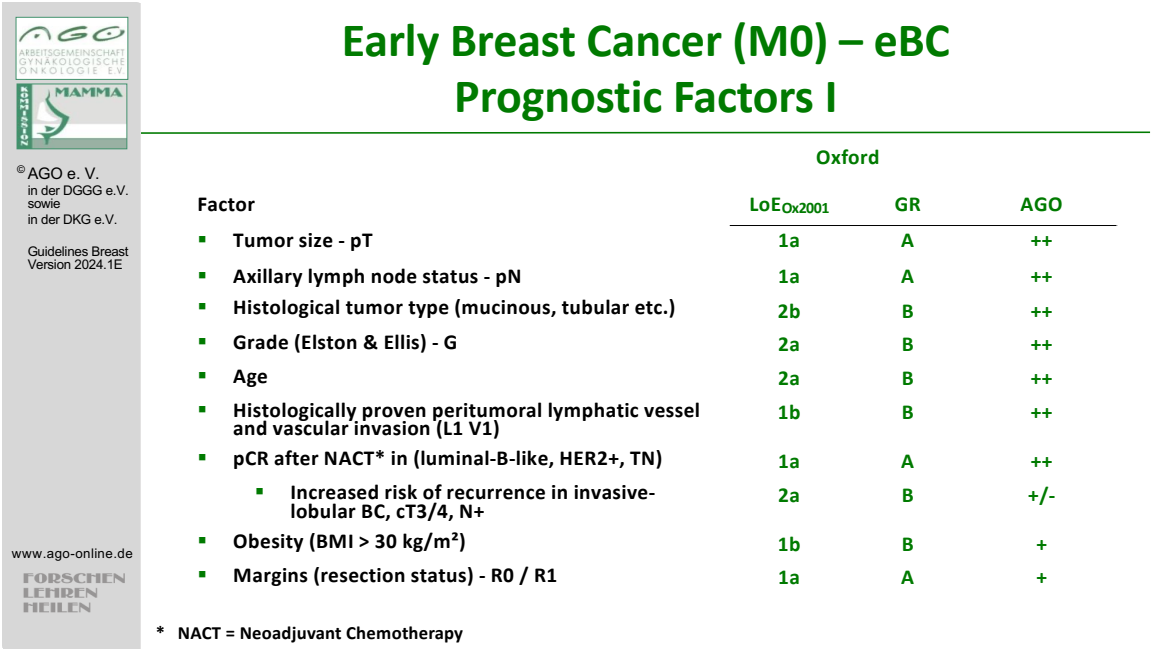
ipsilateral event after a primary DCIS: A systematic review. Breast. 2020 Apr; 50: 95–103. Published online 2020 Feb 19. doi: 10.1016/j.breast.2020.02.006

Kontralaterales Mammakarzinom

1. Giardiello D, Kramer I, Hooning MJ, et al. Contralateral breast cancer risk in patients with ductal carcinoma in situ and invasive breast cancer. NPJ Breast Cancer. 2020; 6: 60. Published online 2020 Nov 3. doi: 10.1038/s41523-020-00202-8

Molecular Profile

1. Nofech-Mozes S, Hanna W, Rakovitch E. Molecular Evaluation of Breast Ductal Carcinoma in Situ with Oncotype DX DCIS. Am J Pathol. 2018 Dec 31. pii: S0002-9440(18)30581-9
2. Rakovitch E, Gray R, Baehner FL, et al: Refined estimates of local recurrence risks by DCIS score adjusting for clinico-pathological features: a combined analysis of ECOG-ACRIN E5194 and Ontario DCIS cohort studies. Breast Cancer Res Treat. 2018; 169(2):359-369
3. Tumour-infiltrating lymphocytes add prognostic information for patients with low-risk DCIS: findings from the SweDCIS randomised radiotherapy trial. Schiza A, Thurfjell V, Stenmark Tullberg A; Eur J Cancer. 2022 Jun; 168:128-137
4. Wu SL, Yu X, Mao X, Jin F. Prognostic value of tumor-infiltrating lymphocytes in DCIS: a meta-analysis. BMC Cancer. 2022 Jul 18;22(1):782. doi: 10.1186/s12885-022-09883-9.



General references

1. Harris LN, Ismaila N, McShane LM et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016 Apr 1;34(10):1134-50.
2. Balic M, Thomssen C, Würstlein R et al. St. Gallen/Vienna 2019: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. Breast Care (Basel). 2019 Apr;14(2):103-110.
3. Balic M, Thomssen C, Würstlein R et al. St. Gallen/Vienna 2023: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. Breast Care (Basel). 2023 Apr;18(3):213-222.

Tumor size

1. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015 Aug;26(8):1533-46.
2. Balic M, Thomssen C, Würstlein R et al. St. Gallen/Vienna 2019: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. Breast Care (Basel). 2019 Apr;14(2):103-110.

Lymph node status

1. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015 Aug;26(8):1533-46.
2. Balic M, Thomssen C, Würstlein R et al. St. Gallen/Vienna 2019: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. Breast Care (Basel). 2019 Apr;14(2):103-110.
3. Balic M, Thomssen C, Würstlein R et al. St. Gallen/Vienna 2023: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. Breast Care (Basel). 2023 Apr;18(3):213-222.

Histological type (mucinous, tubular etc.)

1. Weigelt B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: how special are they? Mol Oncol. 2010 Jun;4(3):192-208
2. Horlings HM, Weigelt B, Anderson EM et al. Genomic profiling of histological special types of breast cancer. Breast Cancer Res Treat. 2013 Nov;142(2):257-69
3. Dieci MV, Orvieto E, Dominici M. Rare breast cancer subtypes: histological, molecular, and clinical peculiarities. Oncologist. 2014 Aug;19(8):805-13
4. Mouabbi JA, Hassan A, Lim B, Hortobagyi GN et al. Invasive lobular carcinoma: an understudied emergent subtype of breast cancer. Breast Cancer Res Treat. 2022 Jun;193(2):253-264

Tumor grade (Elston & Ellis)

1. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015 Aug;26(8):1533-46.
2. Rakha EA, Aleskandarani M, Toss MS et al. Breast cancer histologic grading using digital microscopy: concordance and outcome association. J Clin Pathol. 2018 Aug;71(8):680-686.
3. Balic M, Thomssen C, Würstlein R et al. St. Gallen/Vienna 2019: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. Breast Care (Basel). 2019 Apr;14(2):103-110.
4. Balic M, Thomssen C, Würstlein R et al. St. Gallen/Vienna 2023: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. Breast Care (Basel). 2023 Apr;18(3):213-222.

Age

1. Brandt J, Garne JP, Tengrup I et al. Age at diagnosis in relation to survival following breast cancer: a cohort study. World J Surg Oncol. 2015 Feb 7;13:33.

2. Liu YR, Jiang YZ, Yu KD et al. Different patterns in the prognostic value of age for breast cancer-specific mortality depending on hormone receptor status: a SEER population-based analysis. Ann Surg Oncol. 2015 Apr;22(4):1102-10.
3. Johnson HM, Irish W, Muzaffar M et al. Quantifying the relationship between age at diagnosis and breast cancer-specific mortality. Breast Cancer Res Treat. 2019 Oct;177(3):713-722.

Histologically proven lymph and/or blood vessel invasion

1. Ryu YJ, Kang SJ, Cho JS et al. Lymphovascular invasion can be better than pathologic complete response to predict prognosis in breast cancer treated with neoadjuvant chemotherapy. Medicine (Baltimore). 2018 Jul;97(30):e11647
2. Lin Y, Zhang Y, Fang H et al. Survival and clinicopathological significance of blood vessel invasion in operable breast cancer: a systematic review and meta-analysis. Jpn J Clin Oncol. 2023 Jan 6;53(1):35-45.
3. Zhong YM, Tong F, Shen J. Lympho-vascular invasion impacts the prognosis in breast-conserving surgery: a systematic review and meta-analysis. BMC Cancer. 2022 Jan 25;22(1):102.

pCR after NACT* in Luminal B-like, HER2 and TN Breast Cancer

1. Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Jul 12;384(9938):164-72.
2. Cortazar P, Geyer CE Jr. Pathological complete response in neoadjuvant treatment of breast cancer. Ann Surg Oncol. 2015 May;22(5):1441-6.
3. Nekljudova V, Loibl S, von Minckwitz G et al. Trial-level prediction of long-term outcome based on pathologic complete response (pCR) after neoadjuvant chemotherapy for early-stage breast cancer (EBC). Contemp Clin Trials. 2018 Aug;71:194-198.

Increased risk of recurrence in invasive-lobular BC, cT3/4, N+

1. Thomas M, Kelly ED, Abraham J et al. Invasive lobular breast cancer: A review of pathogenesis, diagnosis, management, and future directions of early stage disease. Semin Oncol. 2019 Apr;46(2):121-132.
2. Van Baelen K, Geukens T, Maetens M et al. Current and future diagnostic and treatment strategies for patients with invasive lobular breast cancer. Ann Oncol. 2022 Aug;33(8):769-785. Erratum in: Ann Oncol. 2022 Dec 16; PMID: 35605746.

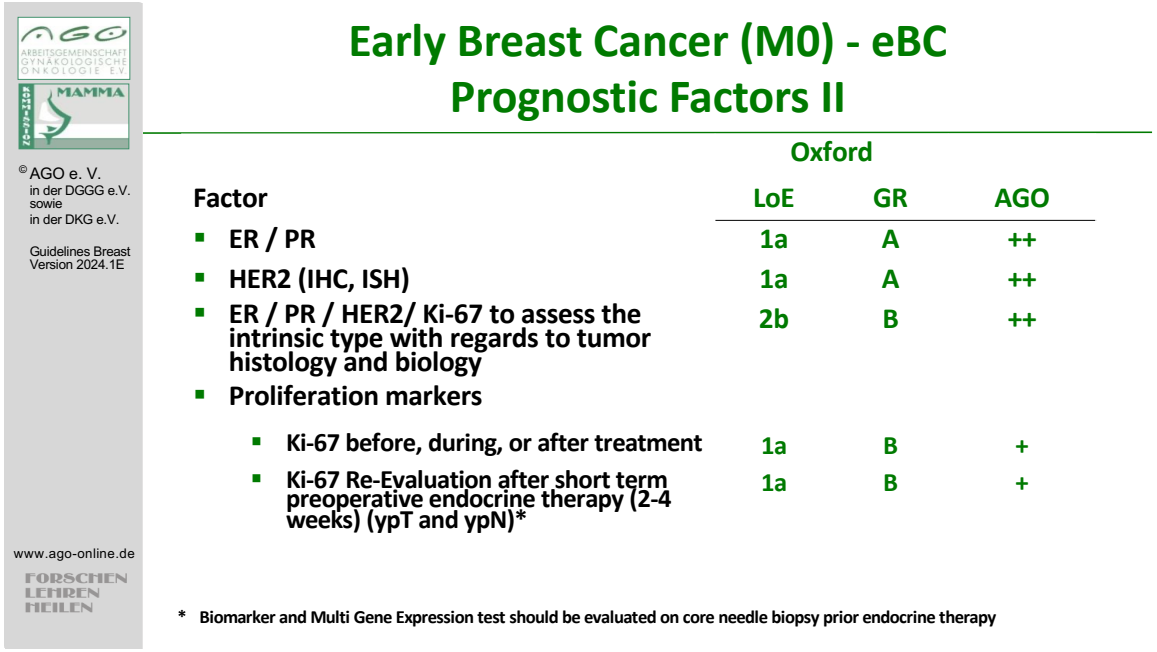
Obesity (BMI > 30 kg/m²)

1. Chan DSM et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82

follow-up studies Ann Oncol. Oct 2014; 25(10): 1901–1914.
2. Nguyen HL, Geukens T, Maetens M, et al. Obesity-associated changes in molecular biology of primary breast cancer. Nat Commun. 2023 Jul 21;14(1):4418.
3. Van Baelen K, Nguyen HL, Hamy-Petit AS, et al. Association of body mass index with clinicopathological features and survival in patients with primary invasive lobular breast cancer. Eur J Cancer. 2023 Sep;191:112988
4. Chen H, Yuan M, Quan X, et al. The relationship between central obesity and risk of breast cancer: a dose-response meta-analysis of 7,989,315 women. Front Nutr. 2023 Nov 9;10:1236393.

Resection status (R0 / R1)

1. Houssami, N., et al. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol, 2014. 21(3): 717-30.
2. Harris LN, Ismaila N, McShane LM et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016 Apr 1;34(10):1134-50.



Early Breast Cancer (M0) - eBC
Prognostic Factors II

Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ ER / PR	1a	A	++
▪ HER2 (IHC, ISH)	1a	A	++
▪ ER / PR / HER2/ Ki-67 to assess the intrinsic type with regards to tumor histology and biology	2b	B	++
▪ Proliferation markers			
▪ Ki-67 before, during, or after treatment	1a	B	+
▪ Ki-67 Re-Evaluation after short term preoperative endocrine therapy (2-4 weeks) (ypT and ypN)*	1a	B	+

* Biomarker and Multi Gene Expression test should be evaluated on core needle biopsy prior endocrine therapy

ER/PR

1. Allison KH, Hammond MEH, Dowsett M et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. J Clin Oncol. 2020 Apr 20;38(12):1346-1366
2. Allison KH, Hammond MEH, Dowsett M et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. Arch Pathol Lab Med. 2020 May;144(5):545-563
3. Jorns JM. Breast Cancer Biomarkers: Challenges in Routine Estrogen Receptor, Progesterone Receptor, and HER2/neu Evaluation. Arch Pathol Lab Med. 2019 Dec;143(12):1444-1449

HER2

1. Ross JS, Slodkowska EA, Symmans WF et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 2009; 14, 320–368
2. Slamon DJ, Clark GM, Wong SG et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987; 235: 177–182
3. Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO-College of American Pathologists Guideline Update. J Clin Oncol. 2023 Aug 1;41(22):3867-3872
4. Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. Arch Pathol Lab

Med. 2023 Sep 1;147(9):993-1000

HER2 low vs. HER2 0:

1. Zhang H, Katerji H, Turner BM, Audet al. HER2-low breast cancers: incidence, HER2 staining patterns, clinicopathologic features, MammaPrint and BluePrint genomic profiles. Mod Pathol. 2022 Aug;35(8):1075-1082
2. Roy AM, Jiang C, Perimbeti S, et al. Oncotype Dx Score, HER2 Low Expression, and Clinical Outcomes in Early-Stage Breast Cancer: A National Cancer Database Analysis. Cancers (Basel). 2023 Aug 25;15(17):4264

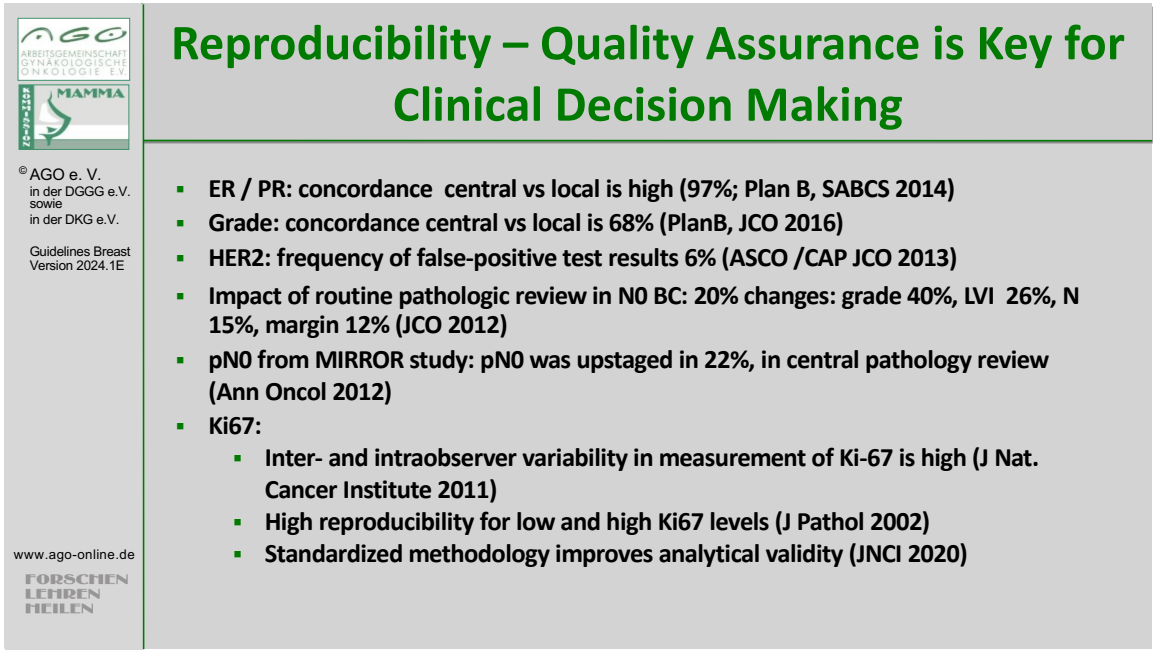
Ki-67

1. de Azambuja E, Cardoso F, de Castro G Jr, et al. Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients. Br J Cancer. 2007 May 21;96(10):1504-13
2. Petrelli, F., et al., Prognostic value of different cut-off levels of Ki-67 in breast cancer: a systematic review and meta-analysis of 64,196 patients. Breast Cancer Res Treat, 2015. 153(3): 477-91
3. Nitz U, Gluz O, Huober J et al. Final analysis of the prospective WSG-AGO EC-Doc versus FEC phase III trial in intermediate-risk (pN1) early breast cancer: efficacy and predictive value of Ki67 expression. Ann Oncol. 2017 Nov 1;28(11):2899
4. Denkert C, Budczies J, Regan MM, et al. Clinical and analytical validation of Ki-67 in 9069 patients from IBCSG VIII + IX, BIG1-98 and GeparTrio trial: systematic modulation of interobserver variance in a comprehensive in silico ring trial. Breast Cancer Res Treat. 2019 Aug;176(3):557-568.
5. Dowsett M, Ellis MJ, Dixon JM, et al. Evidence-based guidelines for managing patients with primary ER+ HER2- breast cancer deferred from surgery due to the COVID-19 pandemic. Breast Cancer. 2020 Jun 8;6:21
6. Smith I, Robertson J, Kilburn L, et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. Lancet Oncol. 2020 Nov;21(11):1443-1454
7. Nielsen TO, Leung SCY, Rimm DL, et al. Assessment of Ki67 in Breast Cancer: Updated recommendations from the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst. 2021 Jul 1;113(7):808-819
8. Gluz O, Nitz UA, Christgen M, et al. Impact of age, recurrence score (RS) and ovarian function suppression (OFS) on endocrine response to short preoperative endocrine therapy (ET): Analysis of ADAPT and ADAPTcycle trials. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089
9. Martins-Branco D, Nader-Marta G, Molinelli C et al. Ki-67 index after neoadjuvant endocrine therapy as a prognostic biomarker in

patients with ER-positive/HER2-negative early breast cancer: a systematic review and meta-analysis. Eur J Cancer. 2023 Nov;194:113358

Post-treatment Ki-67

1. Dowsett M, Smith IE, Ebbs SR, et al. Prognostic Value of Ki67 Expression After Short-Term Presurgical Endocrine Therapy for Primary Breast Cancer. Journal of the National Cancer Institute 2007: 99:167-170
2. DeCensi A, Guerrieri-Gonzaga A, Gandini S, et al. Prognostic significance of Ki-67 labeling index after short-term presurgical tamoxifen in women with ER-positive breast cancer. Annals Oncol 2011 Mar;22(3):582-7
3. Gluz O, Nitz UA, Christgen M, et al. Impact of age, recurrence score (RS) and ovarian function suppression (OFS) on endocrine response to short preoperative endocrine therapy (ET): Analysis of ADAPT and ADAPTcycle trials. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089
4. Martins-Branco D, Nader-Marta G, Molinelli C, et al. Ki-67 index after neoadjuvant endocrine therapy as a prognostic biomarker in patients with ER-positive/HER2-negative early breast cancer: a systematic review and meta-analysis. Eur J Cancer. 2023 Nov;194:113358



1. Dowsett M, Nielsen TO, A'Hern R, et al: Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst 2011, 103(22):1656-1664.
2. Gluz O, Nitz UA, Christgen M, et al. West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment. J Clin Oncol. 2016 Jul 10;34(20):2341-9.
3. Hammond, M.E.H., Hayes, D.F., Dowsett, M., et al. 2010. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J. Clin. Oncol. 28, 2784–2795.
4. Sloane, J.P., Amendoeira, I., Apostolikas, N., et al. 1999. Consistency achieved by 23 European pathologists from 12 countries in diagnosing breast disease and reporting prognostic features of carcinomas. European Commission Working Group on Breast Screening Pathology. Virchows Arch. 434, 3–10.
5. Vestjens, J.H.M.J., Pepels, M.J., Boer, M. de, et al. 2012. Relevant impact of central pathology review on nodal classification in individual breast cancer patients. Ann. Oncol. 23, 2561–2566.
6. Kennecke, H.F., Speers, C.H., Ennis, C.A., et al. 2012. Impact of routine pathology review on treatment for node-negative breast cancer. J. Clin. Oncol. 30, 2227–2231.
7. Wolff AC, Hammond ME, Hicks DG, et al.: Recommendations for human epidermal growth factor receptor 2 testing in breast cancer:

American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 2013, 31(31):3997-4013.

8. Mengel M, von Wasielewski R, Wiese B, et al. Inter-aloboratory and inter-observer reporducibility of immunohistochemical assessment of the Ki67 labelling index in a large multi-centre trial. J Pathol. 2002 Nov;198(3):292-9.
9. Nielsen TO, Leung SCY, Rimm DL, et al. Assessment of Ki67 in Breast Cancer: Updated recommendations from the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst. 2020 Dec 28:djaa201.

Predictive pathology of endocrine responsiveness

	Oxford		
	LoE	GR	AGO
▪ **Immunhistochemical detection of estrogen- and progesterone-receptors in paraffin-embedded tissue; scored as percentage of positive tumor cell nuclei (ER positive if ≥ 1%, low positivity ≥ 1% to 10%; PR positive if ≥10%)**	1a	A	++
▪ **Detection of endocrine responsiveness by Ki-67 decrease to ≤ 10% after 3-4 weeks of preoperative endocrine therapy in primary breast cancer**	1b	A	+
▪ **Detection of secondary, i.e. acquired endocrine resistance by analysis of activating ESR-1 mutations in liquid biopsy or metastatic tissue**	1b	A	+

see chapter „Pathology“

ASCO/CAP Guideline for ER- and PR-testing

1. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. *J Clin Oncol*. 2020;38(12):JCO1902309–1366. doi:10.1200/JCO.19.02309
2. Duffy MJ, Harbeck N, Nap M, et al. Clinical use of biomarkers in breast cancer: Updated guidelines from the European Group on Tumor Markers (EGTM). *Eur J Cancer*. 2017;75:284-298. doi:10.1016/j.ejca.2017.01.017.

IHC-testing for ER-positivity

1. Duffy MJ, Harbeck N, Nap M, et al. Clinical use of biomarkers in breast cancer: Updated guidelines from the European Group on Tumor Markers (EGTM). *Eur J Cancer*. 2017;75:284-298. doi:10.1016/j.ejca.2017.01.017.
2. Schrijver WAME, Suijkerbuijk KPM, van Gils CH, van der Wall E, Moelans CB, van Diest PJ. Receptor Conversion in Distant Breast Cancer Metastases: A Systematic Review and Meta-analysis. *J Natl Cancer Inst*. 2018;110(6):568-580. doi:10.1093/jnci/djx273.
3. Traub L, Thill M, Nitschmann S. 20-Jahres-Ergebnisse einer 5-jährigen Hormontherapie bei Mammakarzinom : Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Internist (Berl)*. 2018;59(4):410-412. doi:10.1007/s00108-018-0398-1.

4. Allred, D. C. (2010). Issues and updates: evaluating estrogen receptor-alpha, progesterone receptor, and HER2 in breast cancer. Modern Pathology, 23 Suppl 2, S52–9. doi:10.1038/modpathol.2010.55

5. Allred, D. C., Carlson, R. W., Berry, D. A., et al. (2009). NCCN Task Force Report: Estrogen Receptor and Progesterone Receptor Testing in Breast Cancer by Immunohistochemistry. Journal of the National Comprehensive Cancer Network, 7 Suppl 6, S1–S21– quiz S22–3. Retrieved from http://www.nccn.org/JNCCN/PDF/2009_estrogen_receptor_and_progesterone_receptor_immunohistochemistry.pdf

6. Gown, A. M. (2008). Current issues in ER and HER2 testing by IHC in breast cancer. Modern Pathology, 21, S8–S15

7. Hammond, M. E., Hayes, D. F., & Wolff, A. C. (2011). Clinical Notice for American Society of Clinical Oncology-College of American Pathologists Guideline Recommendations on ER/PgR and HER2 Testing in Breast Cancer. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 29(15), e458–e458.

8. Cheang MC, Treaba DO, Speers CH, et al. Immunohistochemical detection using the new rabbit monoclonal antibody SP1 of estrogen receptor in breast cancer is superior to mouse monoclonal antibody 1D5 in predicting survival. J Clin Oncol. 2006 Dec 20;24(36):5637-44. Epub 2006 Nov 20.

9. Hammond et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med (2010) vol. 134 (6) pp. 907-22

10. Rocha R, Nunes C, Rocha G et al. Rabbit monoclonal antibodies show higher sensitivity than mouse monoclonals for estrogen and progesterone receptor evaluation in breast cancer by immunohistochemistry. Pathol Res Pract. 2008;204(9):655-62. Epub 2008 Jun 18.

<u>IHC Scores</u>

1. Allred, D. C., Harvey, J. M., Berardo, M., et al. (1998). Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Modern Pathology, 11(2), 155–168.

2. Remmele, W., & Stegner, H. (1987). Vorschlag zur einheitlichen Definition eines Immunreaktiven Score (IRS) fur den immunhistochemischen Ostrogenrezeptor-Nachweis (ER-ICA) im Mammakarzinomgewebe. Der Pathologe, 8(3), 138–140.

Monoclonal Antibodies for ER-Testing

1. Cheang MC, Treaba DO, Speers CH, et al. Immunohistochemical detection using the new rabbit monoclonal antibody SP1 of estrogen receptor in breast cancer is superior to mouse monoclonal antibody 1D5 in predicting survival.J Clin Oncol. 2006 Dec 20;24(36):5637-44.

ER low (ER 1%-10%)

1. Deyarmin, B. et al. Effect of ASCO/CAP guidelines for determining ER status on molecular subtype. Annals of Surgical Oncology 20, 87–93 (2013).

2. Prabhu, J. S. et al. A Majority of Low (1-10%) ER Positive Breast Cancers Behave Like Hormone Receptor Negative Tumors. Journal of Cancer 5, 156–165 (2014).

3.Sanford, R. A. et al. High incidence of germline BRCA mutation in patients with ER low-positive/PR low-positive/HER-2 neu negative tumors. Cancer 121, 3422–3427 (2015).

4. Yi M, Huo L, Koenig KB, Mittendorf EA, Meric-Bernstam F, Kuerer HM, Bedrosian I, Buzdar AU, Symmans WF, Crow JR, Bender M, Shah RR, Hortobagyi GN, Hunt KK. Which threshold for ER positivity? a retrospective study based on 9639 patients. Ann Oncol. 2014 May;25(5):1004-11. doi: 10.1093/annonc/mdu053

Primary endocrine resistence

1. Tryfonidis K, Zardavas D, Katzenellenbogen BS, Piccart M. Endocrine treatment in breast cancer: Cure, resistance and beyond.Cancer Treat Rev. 2016 Nov;50:68-81. doi: 10.1016/j.ctrv.2016.08.008

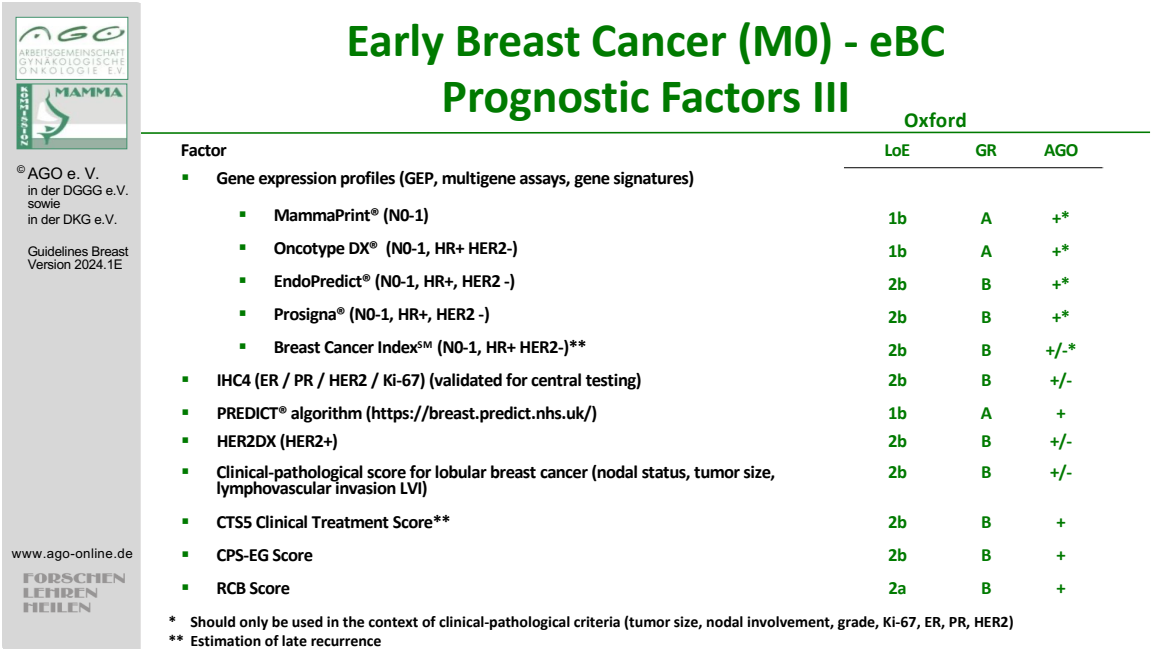
2. Nitz UA, Gluz O, Kümmel S, Christgen M, Braun M, Aktas B, Lüdtke-Heckenkamp K, Forstbauer H, Grischke EM, Schumacher C, Darsow M, Krauss K, Nuding B, Thill M, Potenberg J, Uleer C, Warm M, Fischer HH, Malter W, Hauptmann M, Kates RE, Gräser M, Würstlein R, Shak S, Baehner F, Kreipe HH, Harbeck N. Endocrine Therapy Response and 21-Gene Expression Assay for Therapy

Guidance in HR+/HER2- Early Breast Cancer. J Clin Oncol. 2022 Aug 10;40(23):2557-2567. doi: 10.1200/JCO.21.02759

3. Bliss JM, Tovey H, Evans A, Holcombe C, Horgan K, Mallon E, Vidya R, Skene A, Dodson A, Hills M, Detre S, Zabaglo L, Banerji J, Kilburn L, Morden JP, Robertson JFR, Smith I, Dowsett M; POETIC Trialists. Clinico-pathologic relationships with Ki67 and its change with short-term aromatase inhibitor treatment in primary ER + breast cancer: further results from the POETIC trial (CRUK/07/015). Breast Cancer Res. 2023 Apr 12;25(1):39. doi: 10.1186/s13058-023-01626-3.

Secondary endocrine resistence (*ESR1* mutation)

1. Bidard FC, Kaklamani VG, Neven P, Streich G, Montero AJ, Forget F, Mouret-Reynier MA, Sohn JH, Taylor D, Harnden KK, Khong H, Kocsis J, Dalenc F, Dillon PM, Babu S, Waters S, Deleu I, García Sáenz JA, Bria E, Cazzaniga M, Lu J, Aftimos P, Cortés J, Liu S, Tonini G, Laurent D, Habboubi N, Conlan MG, Bardia A. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial.J Clin Oncol. 2022 Oct 1;40(28):3246-3256. doi: 10.1200/JCO.22.00338.
2. Wong NZH, Yap DWT, Ong RJM, Zhao JJ, Chan YH, Tey JCS, Sundar R, Lim JSJ, Dawood SS. Efficacy of Oral SERDs in the treatment of ER+, HER2 - metastatic breast cancer, a stratified analysis of the ESR1 wild type and mutant subgroups. Ann Oncol. 2023 Oct 21:S0923-7534(23)04328-4. doi: 10.1016/j.annonc.2023.10.122.
3. Grote I, Poppe A, Lehmann U, Christgen M, Kreipe H, Bartels S. Frequency of genetic alterations differs in advanced breast cancer between metastatic sites.Genes Chromosomes Cancer. 2024 Jan;63(1):e23199. doi: 10.1002/gcc.23199.



Early Breast Cancer (M0) - eBC
Prognostic Factors III

Factor	LoE	GR	AGO Oxford
▪ Gene expression profiles (GEP, multigene assays, gene signatures)			
▪ MammaPrint® (N0-1)	1b	A	+*
▪ Oncotype DX® (N0-1, HR+ HER2-)	1b	A	+*
▪ EndoPredict® (N0-1, HR+, HER2 -)	2b	B	+*
▪ Prosigna® (N0-1, HR+, HER2 -)	2b	B	+*
▪ Breast Cancer Index℠ (N0-1, HR+ HER2-)**	2b	B	+/-*
▪ IHC4 (ER / PR / HER2 / Ki-67) (validated for central testing)	2b	B	+/-
▪ PREDICT® algorithm (https://breast.predict.nhs.uk/)	1b	A	+
▪ HER2DX (HER2+)	2b	B	+/-
▪ Clinical-pathological score for lobular breast cancer (nodal status, tumor size, lymphovascular invasion LVI)	2b	B	+/-
▪ CTS5 Clinical Treatment Score**	2b	B	+
▪ CPS-EG Score	2b	B	+
▪ RCB Score	2a	B	+

* Should only be used in the context of clinical-pathological criteria (tumor size, nodal involvement, grade, Ki-67, ER, PR, HER2)
** Estimation of late recurrence

Gene expression profiles (GEP; Multigene Assays, Gene expression signatures)
(*Should only be used in the context of clinico-pathological criteria (e.g. tumor size, number involved lymph nodes, grade, Ki67) for therapeutic decision making)

1. Andre F, Ismaila N, Allison KH, et al. Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update. J Clin Oncol. 2022 Jun 1;40(16):1816-1837. doi: 10.1200/JCO.22.00069. Epub 2022 Apr 19. Erratum in: J Clin Oncol. 2022 Aug 1;40(22):2514. Lemij AA, Baltussen JC, de Glas NA, et al. Gene expression signatures in older patients with breast cancer: A systematic review. Crit Rev Oncol Hematol. 2023 Jan;181:103884.

MammaPrint®

1. Cardoso F, van't Veer LJ et al.; MINDACT Investigators. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med. 2016 Aug 25;375(8):717-29.
2. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med. 2016 Aug 25;375(8):717-29.
3. Mittempergher L, Delahaye LJMJ, Witteveen AT et al. MammaPrint and BluePrint Molecular Diagnostics Using Targeted RNA Next-

Generation Sequencing Technology. J Mol Diagn. 2019 Sep;21(5):808-823

4. Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol. 2021 Apr;22(4):476-488. doi: 10.1016/S1470-2045(21)00007-3. Epub 2021 Mar 12. PMID: 33721561.
5. Slembrouck L, Darrigues L, Laurent C et al. Decentralization of Next-Generation RNA Sequencing-Based MammaPrint® and BluePrint® Kit at University Hospitals Leuven and Curie Institute Paris. Transl Oncol. 2019 Dec;12(12):1557-1565.
6. Viale G, de Snoo FA et al.; MINDACT investigators. Immunohistochemical versus molecular (BluePrint and MammaPrint) subtyping of breast carcinoma. Outcome results from the EORTC 10041/BIG 3-04 MINDACT trial. Breast Cancer Res Treat. 2018 Jan;167(1):123-131

Oncotype DX®

1. Gluz O, Nitz UA, Christgen M, et al. West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment. J Clin Oncol. 2016 Jul 10;34(20):2341-9.
2. Kalinsky K, Barlow WE, Gralow JR et al. 21-Gene Assay to inform chemotherapy benefit in node-positive breast cancer. N Engl J Med. 2021 Dec 16;385(25):2336-2347. doi: 10.1056/NEJMoa2108873. Epub 2021 Dec 1.
3. Nitz U, Gluz O, Christgen M et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. Breast Cancer Res Treat. 2017 Oct;165(3):573-583.
4. Nitz UA, Gluz O, Kümmel S, et al. Endocrine Therapy Response and 21-Gene Expression Assay for Therapy Guidance in HR+/HER2- Early Breast Cancer. J Clin Oncol. 2022 Aug 10;40(23):2557-2567. doi: 10.1200/JCO.21.02759. Epub 2022 Apr 11. PMID: 35404683.
5. Sparano JA, Gray RJ, Makower DF et al. Clinical Outcomes in Early Breast Cancer With a High 21-Gene Recurrence Score of 26 to 100 Assigned to Adjuvant Chemotherapy Plus Endocrine Therapy: A Secondary Analysis of the TAILORx Randomized Clinical Trial. JAMA Oncol. 2019 Sep 30.
6. Sparano JA, Gray RJ, Makower DF et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018 Jul 12;379(2):111-121.
7. Zhang S, Fitzsimmons KC, Hurvitz SA Oncotype DX Recurrence Score in premenopausal women. Ther Adv Med Oncol. 2022 Mar

10;14:17588359221081077. doi: 10.1177/17588359221081077. eCollection 2022.PMID: 35295864
8. Shaw VR, Amos CI, Cheng C. Predicting Chemotherapy Benefit across Different Races in Early-Stage BreastCancer Patients Using the Oncotype DX Score. Cancers (Basel). 2023 Jun 16;15(12):3217.
9. Davey MG, Cleere EF, O'Donnell JP, et al. Value of the 21-gene expression assay in predicting locoregional recurrence rates in estrogen receptor-positive breast cancer: a systematic review and network meta-analysis. Breast Cancer Res Treat. 2022 Jun;193(3):535-544.

EndoPredict®

1. Buus R, Sestak I, Kronenwett R et al. Comparison of EndoPredict and EPclin With Oncotype DX Recurrence Score for Prediction of Risk of Distant Recurrence After Endocrine Therapy. J Natl Cancer Inst. 2016 Jul 10;108(11).
2. Buus, R., I. Sestak, R. Kronenwett, et al (2016). "Comparison of EndoPredict and EPclin With Oncotype DX Recurrence Score for Prediction of Risk of Distant Recurrence After Endocrine Therapy." J Natl Cancer Inst 108(11)
3. Filipits M, Dubsky P, Rudas M et al. Prediction of Distant Recurrence Using EndoPredict Among Women with ER+, HER2- Node-Positive and Node-Negative Breast Cancer Treated with Endocrine Therapy Only. Clin Cancer Res. 2019 Jul 1;25(13):3865-3872.
4. Martin M, Brase JC, Ruiz A et al. Prognostic ability of EndoPredict compared to research-based versions of the PAM50 risk of recurrence (ROR) scores in node-positive, estrogen receptor-positive, and HER2-negative breast cancer. A GEICAM/9906 sub-study. Breast Cancer Res Treat. 2016 Feb;156(1):81-9.
5. Sestak I, Buus R, Cuzick J et al. Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. 2018 Apr 1;4(4):545-553.
6. Sestak I, Martín M, Dubsky P et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. Breast Cancer Res Treat. 2019 Jul;176(2):377-386.
7. Constantinidou A, Marcou Y, Toss MS, et al. .Clinical Validation of EndoPredict in Pre-Menopausal Women with ER-Positive, HER2-Negative Primary Breast Cancer. Clin Cancer Res. 2022 Oct 14;28(20):4435-4443.

Prosigna®

1. Berchtold E, Vetter M, Gündert M et al. Comparison of six breast cancer classifiers using qPCR. Bioinformatics. 2019 Sep 15;35(18):3412-3420.

2. Buus R, Szijgyarto Z, Schuster EF, et al. Development and validation for research assessment of Oncotype DX® Breast Recurrence Score, EndoPredict® and Prosigna®. NPJ Breast Cancer. 2021 Feb 12;7(1):15. doi: 10.1038/s41523-021-00216-w.
3. Erber R, Angeloni M, Stöhr R, et al. Molecular Subtyping of Invasive Breast Cancer Using a PAM50-Based Multigene Expression Test-Comparison with Molecular-Like Subtyping by Tumor Grade/Immunohistochemistry and Influence on Oncologist's Decision on Systemic Therapy in a Real-World Setting. Int J Mol Sci. 2022 Aug 5;23(15):8716. doi: 10.3390/ijms23158716.
4. Fernandez-Martinez A, Pascual T, Perrone G et al. Limitations in predicting PAM50 intrinsic subtype and risk of relapse score with Ki67 in estrogen receptor-positive HER2-negative breast cancer. Oncotarget. 2017 Mar 28;8(13):21930-21937.
5. Jensen MB, Lænkholm AV, Nielsen TO et al. The Prosigna gene expression assay and responsiveness to adjuvant cyclophosphamide-based chemotherapy in premenopausal high-risk patients with breast cancer. Breast Cancer Res. 2018 Jul 27;20(1):79.
6. Lænkholm AV, Jensen MB, Eriksen JO etal. PAM50 Risk of Recurrence Score Predicts 10-Year Distant Recurrence in a Comprehensive Danish Cohort of Postmenopausal Women Allocated to 5 Years of Endocrine Therapy for Hormone Receptor-Positive Early Breast Cancer. J Clin Oncol. 2018 Mar 10;36(8):735-740.
7. Laenkholm AV, Jensen MB, Eriksen JO et al. The ability of PAM50 risk of recurrence score to predict 10-year distant recurrence in hormone receptor-positive postmenopausal women with special histological subtypes. Acta Oncol. 2018 Jan;57(1):44-50.
8. Ohnstad HO, Borgen E, Falk RS et al. Prognostic value of PAM50 and risk of recurrence score in patients with early-stage breast cancer with long-term follow-up. Breast Cancer Res. 2017 Nov 14;19(1):120.
9. Ohara AM, Naoi Y, Shimazu K et al. PAM50 for prediction of response to neoadjuvant chemotherapy for ER-positive breast cancer. Breast Cancer Res Treat. 2019 Feb;173(3):533-543
10. Prat A, Lluch A, Turnbull AK et al. A PAM50-Based Chemoendocrine Score for Hormone Receptor-Positive Breast Cancer with an Intermediate Risk of Relapse. Clin Cancer Res. 2017 Jun 15;23(12):3035-3044.
11. Kjällquist U, Acs B, Margolin S, et al. Real World Evaluation of the Prosigna/PAM50 Test in a Node-Negative Postmenopausal Swedish Population: A Multicenter Study. Cancers (Basel). 2022 May 25;14(11):2615.

Breast Cancer Index®

1. Bartlett JMS, Sgroi DC, Treuner K et al. Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial. Ann Oncol. 2019 Nov 1;30(11):1776-1783.
2. Noordhoek I, Treuner K, Putter H, et al. Breast Cancer Index Predicts Extended Endocrine Benefit to Individualize Selection of Patients with HR^+ Early-stage Breast Cancer for 10 Years of Endocrine Therapy. Clin Cancer Res. 2021 Jan 1;27(1):311-319. doi: 10.1158/1078-

0432.CCR-20-2737. Epub 2020 Oct 27. PMID: 33109739.
3. Sgroi DC, Treuner K, Zhang Y, et al. Correlative studies of the Breast Cancer Index (HOXB13/IL17BR) and ER, PR, AR, AR/ER ratio and Ki67 for prediction of extended endocrine therapy benefit: a Trans-aTTom study. Breast Cancer Res. 2022 Dec 16;24(1):90.
4. Woolpert KM, Ahern TP, Lash TL,Biomarkers predictive of a response to extended endocrine therapy in breastcancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2023 Oct 25. doi: 10.1007/s10549-023-07149-x. Online ahead of print.PMID: 37878151

IHC-4 Score

1. Cuzick J, Dowsett M, Pineda S et al. Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor-2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. J Clin Oncol 2011;29(32):4273-4278.
2. Sheri A, Smith IE, Hills M et al. Relationship between IHC4 Score and response to neo-adjuvant chemotherapy in estrogen receptor positive breast cancer. Breast Cancer Res Treat 2017;164(2):395-400

PREDICT (https://breast.predict.nhs.uk/)

1. Candido Dos Reis FJ, Wishart GC, Dicks EM, et al. An updated PREDICT breast cancer prognostication and treatment benefit prediction model with independent validation. Breast Cancer Res. ; 2017;19(1):58.
2. Gunda A, Eshwaraiah MS, Gangappa K, et al. A comparative analysis of recurrence risk predictions in ER+/HER2- early breast cancer using NHS Nottingham Prognostic Index, PREDICT, and CanAssist Breast. Breast Cancer Res Treat. 2022 Nov;196(2):299-310.
3. Gray E, Marti J, Brewster DH, Wyatt JC, Hall PS; SATURNE Advisory Group. Independent validation of the PREDICT breast cancer prognosis prediction tool in 45,789 patients using Scottish Cancer Registry data. Br J Cancer 2018 Oct;119(7):808-814.

HER2DX

1. Guarneri V, Bras-Maristany F, Dieci MV, et al. HER2DX genomic test in HER2-positive/hormone receptor-positive breast cancertreated with neoadjuvant trastuzumab and pertuzumab: A correlative analysis from the PerELISA trial. EBioMedicine. 2022 Nov;85:104320.
2. Prat A, Guarneri V, Paré L, et al. A multivariable prognostic score to guide systemic therapy in early-stage HER2-positive breast cancer: a retrospective study with an external evaluation. Lancet Oncol. 2020 Nov;21(11):1455-1464.
3. Villacampa G, Tung NM, Pernas S, et al. Association of HER2DX with pathological complete response and survival outcomes in

HER2-positive breast cancer. Ann Oncol. 2023 Sep;34(9):783-795.

Lobular Score:

1. De Nonneville A, Jauffret C, Goncalves A. et al. Adjuvant chemotherapy in lobular carcinoma of the breast: a clinicopathological score identifies high-risk patient with survival benefit Breast Cancer Res Treat. 2019 Jun;175(2):379-387. : Points-based risk score: pN1 = 6 points, tumnor size > 2cm = 3 points, LVI = 2 points; low risk = < 5 points; high risk 5-11 points.
2. Fu R, Yang J, Wang H et al.: A nomogram for determining the disease-specific survival in invasive lobular carcinoma of the breast: A population study. Medicine (Baltimore). 2020 Oct 23;99(43):e22807.

CTS Clinical Treatment Score

1. Lakhanpal R, Sestak I, Shadbolt B, et al. IHC4 score plus clinical treatment score predicts locoregional recurrence in early breast cancer. *Breast*. 2016;29:147–152.
2. Richman J, Ring A, Dowsett M, Sestak I. Clinical validity of clinical treatment score 5 (CTS5) for estimating risk of late recurrence in unselected, non-trial patients with early oestrogen receptor-positive breast cancer. Breast Cancer Res Treat. 2020 Nov 21.
3. Wang C, Xu Y, Lin Y, et al. Comparison of CTS5 risk model and 21-gene recurrence score assay in large-scale breast cancer population and combination of CTS5 and recurrence score to develop a novel nomogram for prognosis prediction. Breast. 2022 Jun;63:61-70.
4. Dejthevaporn T, Patanayindee P Clinical Treatment Score Post-5 Years as a Tool for Risk Estimation of Late Recurrence in Thai Patients With Estrogen-Receptor-Positive, Early BreastCancer: A Validation Study. Breast Cancer (Auckl). 2023 Jul 31;17:11782234231186869.
5. Ning L, Liu Y, He X, et al. Validation of CTS5 Model in Large-scale Breast Cancer Population and Combination of CTS5 and Ki-67 Status to Develop a Novel Nomogram for Prognosis Prediction. Am J Clin Oncol. 2023 Dec 22. doi: 10.1097/COC.0000000000001080. Online ahead of print.PMID: 38131531

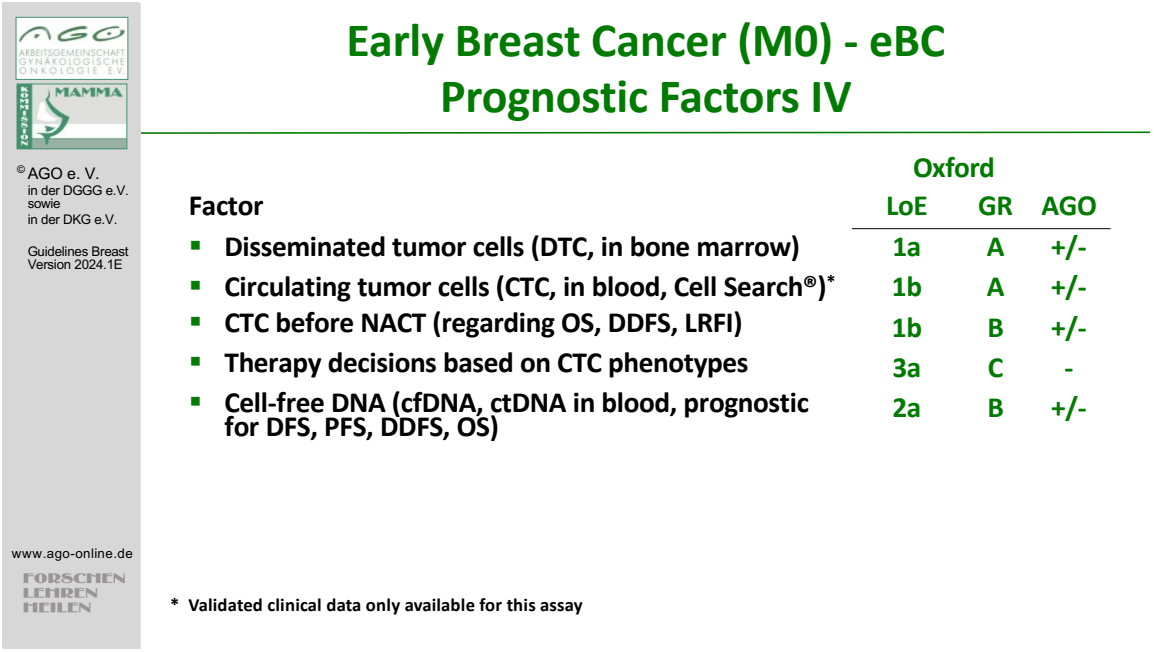
CPS-EG Score

1. Loibl S, Weber K, Huober J et al.: Risk Assessment after Neoadjuvant Chemotherapy in Luminal Breast Cancer Using a Clinicomolecular Predictor. Cancer Res. 2018 Jul 15;24(14):3358-3365.
2. Marmé F, Solbach C, Michel L, et al. Utility of the CPS + EG scoring system in triple-negative breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer. 2021 Aug;153:203-212. doi: 10.1016/j.ejca.2021.05.027. Epub 2021 Jun 26. PMID: 34186505.

3. Mittendorf EA, Jeruss JS, Tucker SL et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. J Clin Oncol. 2011 May 20;29(15):1956-62.

RCB

1. Yau C, Osdoit M, van der Noordaa M, et al. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. Lancet Oncol. 2022 Jan;23(1):149-160.



Early Breast Cancer (M0) - eBC
Prognostic Factors IV

Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Disseminated tumor cells (DTC, in bone marrow)	1a	A	+/-
▪ Circulating tumor cells (CTC, in blood, Cell Search®)*	1b	A	+/-
▪ CTC before NACT (regarding OS, DDFS, LRFI)	1b	B	+/-
▪ Therapy decisions based on CTC phenotypes	3a	C	-
▪ Cell-free DNA (cfDNA, ctDNA in blood, prognostic for DFS, PFS, DDFS, OS)	2a	B	+/-

* Validated clinical data only available for this assay

DTC

1. Hartkopf AD, Brucker SY, Taran FA, et al. Disseminated tumour cells from the bone marrow of early breast cancer patients: Results from an international pooled analysis. Eur J Cancer. 2021 Sep;154:128-137.
2. Janni, W., Vogl, F.D., Wiedswang, G. et al. Persistence of disseminated tumor cells in the bone marrow of breast cancer patients predicts increased risk for relapse--a European pooled analysis. Clin. Cancer Res. 2011; 17, 2967–2976.

DTC and radiation

1. Mignot F, Loirat D, Dureau S, et al. Disseminated Tumor Cells Predict Efficacy of Regional Nodal Irradiation in Early Stage Breast Cancer. Int J Radiat Oncol Biol Phys. 2019 Feb 1;103(2):389-396.
2. Goodman CR, Seagle BL, Friedl TWP, et al. Association of Circulating Tumor Cell Status With Benefit of Radiotherapy and Survival in Early-Stage Breast Cancer. JAMA Oncol. 2018 Aug 1;4(8):e180163.

CTC

1. Bidard FC, Michiels S, Riethdorf S, et al. Circulating Tumor Cells in Breast Cancer Patients Treated by Neoadjuvant Chemotherapy: A Meta-analysis. J Natl Cancer Inst. 2018 Jun 1;110(6):560-567.
2. Cristofanilli, M., Budd, G.T., Ellis, M.J., et al. 2004. Circulating tumor cells, disease progression, and survival in metastatic breast

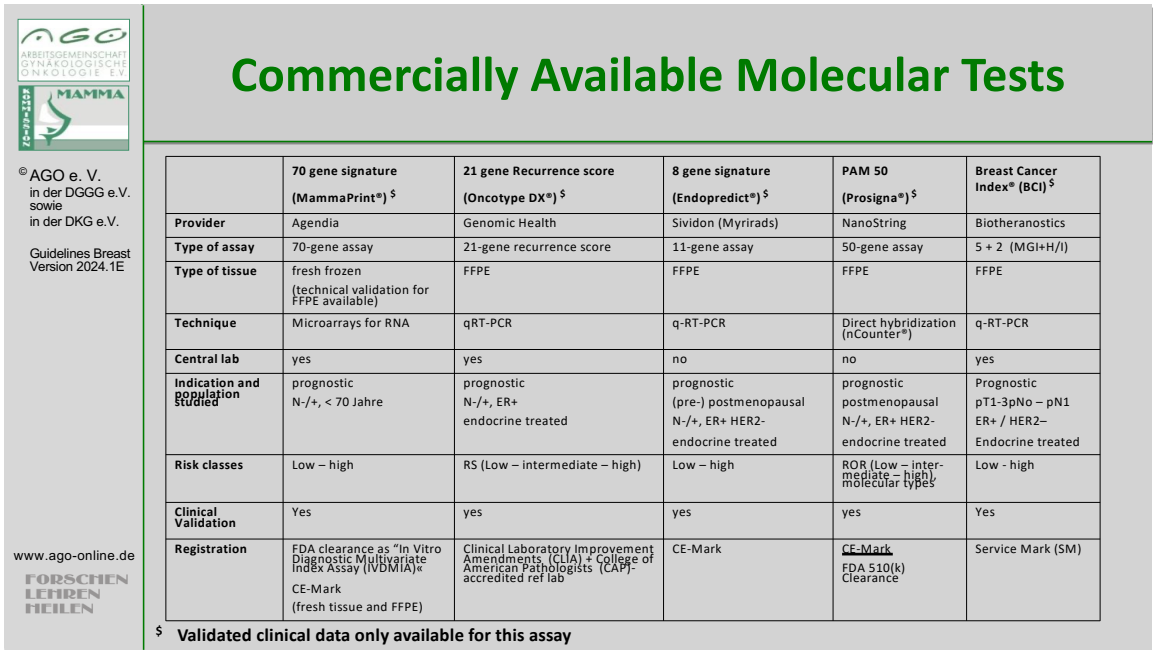
cancer. N. Engl. J. Med. 351, 781–791. doi:10.1056/NEJMoa040766.
3. Garcia-Murillas I, Chopra N Comino-Méndez I et al. Assessment of molecular relapse detection in early stage breast cancer. JAMA Oncol 2019;5(10):1473-1478)
4. Trapp E, Janni W, Schindlbeck C, et al; SUCCESS Study Group. Presence of Circulating Tumor Cells in High-Risk Early Breast Cancer During Follow-Up and Prognosis. J Natl Cancer Inst. 2018 Oct 11.
5. Radovich M, Jiang G, Hancock BA, et al. Association of Circulating Tumor DNA and Circulating Tumor Cells After Neoadjuvant Chemotherapy With Disease Recurrence in Patients With Triple-Negative Breast Cancer: Preplanned Secondary Analysis of the BRE12-158 Randomized Clinical Trial. JAMA Oncol. 2020 Sep 1;6(9):1410-1415.
6. Munoz-Arcos LS, Nicolò E, Serafini MS, et al.Latest advances in clinical studies of circulating tumor cells in early and metastatic breast cancer. Int Rev Cell Mol Biol. 2023;381:1-21.
7. Stergiopoulou D, Markou A, Strati A, et al. Comprehensive liquid biopsy analysis as a tool for the early detection of minimal residual disease in breast cancer. Sci Rep. 2023 Jan 23;13(1):1258.

Therapy decision based on CTCs

1. Turner NC, Kingston B, Kilburn LS et al. Circulating tumor DNA analysis to direct therapy in advanced breast cancer(plasmaMATCH):a multicentre, multicohort, phase 2a, plattform trial. Lancet Oncol 2020;21(10):1296-1308.

Cell-free DNA/ctDNA:

1. Cullinane C, Fleming C, O'Leary DP, et al. Association of Circulating Tumor DNA With Disease-Free Survival in Breast Cancer: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020 Nov 2;3(11):e2026921.
2. Janni W et al., Analysis of ctDNA for the detection of minimal residual disease (MRD) using a tissue-free, multiomic assay in patients with early-stage breast cancer, SABCS 2023, #PS06-06
3. Agostinetto E, Nader-Marta G, Ignatiadis M Circulating tumor DNA in breast cancer: a biomarker for patient selection. Curr Opin Oncol. 2023 Sep 1;35(5):426-435.
4. Mazzitelli C, Santini D, Corradini AG, et al. Liquid Biopsy in the Management of Breast Cancer Patients: Where Are We Now and Where Are We Going. Diagnostics (Basel). 2023 Mar 25;13(7):1241.
5. Vlataki K, Antonouli S, Kalyvioti C, et al. Circulating Tumor DNA in the Management of Early-Stage Breast Cancer. Cells. 2023 Jun 7;12(12):1573.



Head to head comparisons

1. Varga Z, Sinn P, Seidman AD. Summary of head-to-head comparisons of patient risk classifications by the 21-gene Recurrence Score® (RS) assay and other genomic assays for early breast cancer. Int J Cancer. 2019 Aug 15;145(4):882-893.
2. Berchtold E, Vetter M, Gündert M et al. Comparison of six breast cancer classifiers using qPCR. Bioinformatics. 2019 Sep 15;35(18):3412-3420.
3. Sestak I, Buus R, Cuzick J, et al. Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. 2018 Apr 1;4(4):545-553.

Endopredict

1. Blank PR, Filipits M, Dubsky P, et al.: Cost-effectiveness analysis of prognostic gene expression signature-based stratification of early breast cancer patients. Pharmacoeconomics. 2015 Feb;33(2):179-90.
2. Buus R, Sestak I, Kronenwett R, et al.: Comparison of EndoPredict and EPclin with Oncotype DX Recurrence Score for Prediction of Risk of Distant Recurrence after endocrine therapy J Natl Cancer Inst. 2016 Jul 10;108(11).
3. Denkert, C., Kronenwett, R., Schlake, W. et al. 2012. Decentral gene expression analysis for ER+/Her2- breast cancer: results of a proficiency testing program for the EndoPredict assay. Virchows Arch. 460, 251–259. doi:10.1007/s00428-012-1204-4.
4. Dubsky, P., Filipits, M., Jakesz, R. et al. 2012. EndoPredict improves the prognostic classification derived from common clinical

guidelines in ER-positive, HER2-negative early breast cancer. Ann Oncol. 2013 Mar;24(3):640-7.
5. Dubsky P, Brase JC, Jakesz R et al.: Austrian Breast and Colorectal Cancer Study Group (ABCSG). T al.: The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. Br J Cancer. 2013 Dec 10;109(12):2959-64
6. Filipits, M., Rudas, M., Jakesz, R. et al. 2011. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin. Cancer Res. 17, 6012–6020.
7. Kronenwett, R., Bohmann, K., Prinzler, J. et al. 2012. Decentral gene expression analysis: analytical validation of the Endopredict genomic multianalyte breast cancer prognosis test. BMC Cancer 12, 456.
8. Martin M, Brase JC, Calvo L, et al. Clinical validation of the EndoPredict test in node-positive, chemotherapy-treated ER+/HER2- breast cancer patients: results from the GEICAM 9906 trial. Breast Cancer Res 2014; 16(2): R38.
9. Constantinidou A, Marcou Y, Toss MS, et al. .Clinical Validation of EndoPredict in Pre-Menopausal Women with ER-Positive, HER2-Negative Primary Breast Cancer. Clin Cancer Res. 2022 Oct 14;28(20):4435-4443.

MammaPrint

1. Buyse, M., Loi, S., van't Veer, L., et al. 2006. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J. Natl. Cancer Inst. 98, 1183–1192.
2. Drukker CA, Elias SG, Nijenhuis MV, et al. Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. Breast Cancer Res Treat. 2014 Dec;148(3):599-613.
3. Exner R, Bago-Horvath Z, Bartsch R et al. The multigene signature MammaPrint impacts on multidisciplinary team decisions in ER+, HER2- early breast cancer. Br J Cancer. 2014 Aug 26;111(5):837-42.
4. Jonsdottir K, Assmus J, Slewa A, et al. Prognostic value of gene signatures and proliferation in lymph-node-negative breast cancer. PLoS One. 2014 Mar 5;9(3):e90642.
5. Mook, S., Schmidt, M.K., Weigelt, B., et al. 2010. The 70-gene prognosis signature predicts early metastasis in breast cancer patients between 55 and 70 years of age. Ann. Oncol. 21, 717–722.
6. Mook, S., Schmidt, M.K., Rutgers, E.J., et al. 2009a. Calibration and discriminatory accuracy of prognosis calculation for breast cancer with the online Adjuvant! program: a hospital-based retrospective cohort study. Lancet Oncol. 10, 1070–1076.
7. Mook, S., Schmidt, M.K., Viale, G. et al. 2009b. The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1-3 positive lymph nodes in an independent validation study. Breast Cancer Res. Treat. 116, 295–302.
8. van de Vijver, M.J., He, Y.D., van't Veer, L.J., et al. 2002. A gene-expression signature as a predictor of survival in breast cancer. N. Engl. J. Med. 347, 1999–2009. doi:10.1056/NEJMoa021967.

9. van Veer, L.J. 't, Dai, H., van de Vijver, M.J., et al. 2002. Gene expression profiling predicts clinical outcome of breast cancer. Nature 415, 530–536. doi:10.1038/415530a.
10. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med. 2016 Aug 25;375(8):717-29.
11. Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol. 2021 Apr;22(4):476-488. doi: 10.1016/S1470-2045(21)00007-3. Epub 2021 Mar 12. PMID: 33721561.
12. Vliek SB, Hilbers FS, Jager A, et al.Ten-year follow-up of the observational RASTER study, prospective evaluation of the 70-gene signature in ER-positive, HER2-negative, node-negative, early breastcancer. Eur J Cancer. 2022 Nov;175:169-179.

Oncotype DX

1. Albain, K.S., Barlow, W.E., Shak, S. et al. 2010. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol. 11, 55–65. Cronin, M., Sangli, C., Liu, M.-L., et al. 2007. Analytical validation of the Oncotype DX genomic diagnostic test for recurrence prognosis and therapeutic response prediction in node-negative, estrogen receptor-positive breast cancer. Clin. Chem. 53, 1084–1091.
2. Dowsett, M., Cuzick, J., Wale, C. et al. 2010. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. J. Clin. Oncol. 28, 1829–1834.
3. Geyer CE Jr, Tang G, Mamounas EP, et al. 21-Gene assay as predictor of chemotherapy benefit in HER2-negative breast cancer. NPJ Breast Cancer. 2018 Nov 14;4:37.
4. Gluz O, Nitz UA, Christgen M, et al.: West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment. J Clin Oncol. 2016 Jul 10;34(20):2341-9.
5. Kalinsky K, Barlow WE, Gralow JR et al. 21-Gene Assay to inform chemotherapy benefit from node positive breast cancer. Engl J Med DOI: 10.1056/NEJMoa2108873
6. Khan SS, Karn T, Symmans WF, et al. Genomic predictor of residual risk of recurrence after adjuvant chemotherapy and endocrine therapy in high risk estrogen receptor-positive breast cancers. Breast Cancer Res Treat. 2015 Feb 5.

7. Mamounas, E.P., Tang, G., Fisher, B., et al. 2010. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. J. Clin. Oncol. 28, 1677–1683.
8. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial.Breast Cancer Res Treat. 2017 Oct;165(3):573-583.
9. Nitz UA, Gluz O, Kümmel S et al. Endocrine Therapy Response and 21-Gene Expression Assay for Therapy Guidance in HR+/HER2- Early Breast Cancer. J Clin Oncol. 2022 Aug 10;40(23):2557-2567. doi: 10.1200/JCO.21.02759. Epub 2022 Apr 11.
10. Paik, S., Shak, S., Tang, G. et al. 2004. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N. Engl. J. Med. 351, 2817–2826. doi:10.1056/NEJMoa041588.
11. Paik, S., Tang, G., Shak, S., et al. 2006. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J. Clin. Oncol. 24, 3726–3734.
12. Penault-Llorca F, Filleron T, Asselain B, et al. The 21-gene Recurrence Score® assay predicts distant recurrence in lymph node-positive, hormone receptor-positive, breast cancer patients treated with adjuvant sequential epirubicin- and docetaxel-based or epirubicin-based chemotherapy (PACS-01 trial). BMC Cancer. 2018 May 4;18(1):526.
13. Sparano JA, Gray RJ, Makower DF, et al: Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med 2015, 373(21):2005-2014.
14. Sparano JA, Gray R, Oktay MH, et al. A metastasis biomarker (MetaSite Breast™ Score) is associated with distant recurrence in hormone receptor-positive, HER2-negative early-stage breast cancer. NPJ Breast Cancer. 2017 Nov 8;3:42.
15. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018 Jul 12;379(2):111-121.
16. Tang, G., Cuzick, J., Costantino, J.P., et al. 2011. Risk of recurrence and chemotherapy benefit for patients with node-negative, estrogen receptor-positive breast cancer: recurrence score alone and integrated with pathologic and clinical factors. J. Clin. Oncol. 29, 4365–4372.
17. Zhao X, Rødland EA, Sørlie T, et al. Systematic assessment of prognostic gene signatures for breast cancer shows distinct influence of time and ER status. BMC Cancer. 2014 Mar 19;14:211.
18. *Sparano J, Gray RJ, Makower D, Albain KS, Hayes DF, Geyer C, Dees E, Goetz MP, Olson Jr JA, Lively TG, Badve S, Saphner T, Wagner LI, Whelan T, Kaklamani V, Sledge Jr GW. Trial Assigning Individualized Options for Treatment (TAILORx): An update including 12-year event rates. SABCS 2022, GS 1-05*

19. Zhang S, Fitzsimmons KC, Hurvitz SA Oncotype DX Recurrence Score in premenopausal women. Ther Adv Med Oncol. 2022 Mar 10;14:17588359221081077. doi: 10.1177/17588359221081077. eCollection 2022.PMID: 35295864
20. Shaw VR, Amos CI, Cheng C. Predicting Chemotherapy Benefit across Different Races in Early-Stage BreastCancer Patients Using the Oncotype DX Score. Cancers (Basel). 2023 Jun 16;15(12):3217.
21. Davey MG, Cleere EF, O'Donnell JP, et al. Value of the 21-gene expression assay in predicting locoregional recurrence rates in estrogen receptor-positive breast cancer: a systematic review and network meta-analysis. Breast Cancer Res Treat. 2022 Jun;193(3):535-544.

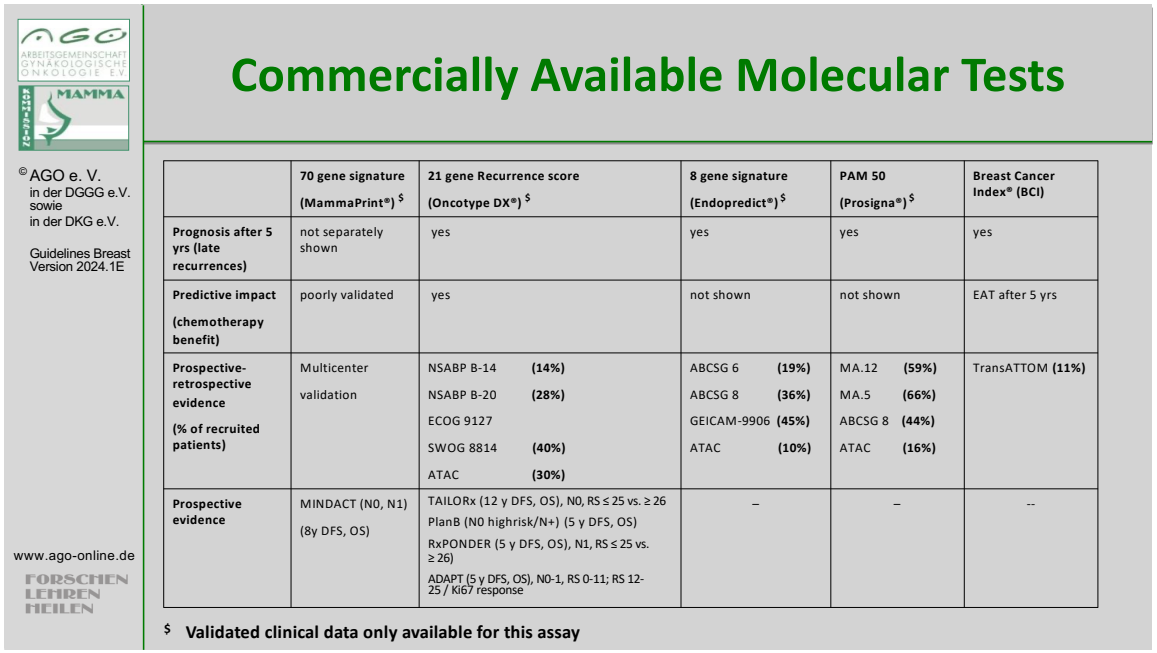
Prosigna (ROR / PAM50)

1. Chia, S.K., Bramwell, V.H., Tu, Det al. 2012. A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. Clin. Cancer Res. 18, 4465–4472.
2. Gnant M, Filipits M, Greil R, et al. Austrian Breast and Colorectal Cancer Study Group. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. Ann Oncol. 2014 Feb;25(2):339-45
3. Jensen MB, Lænkholm AV, Nielsen TO, et al. The Prosigna gene expression assay and responsiveness to adjuvant cyclophosphamide-based chemotherapy in premenopausal high-risk patients with breast cancer.Breast Cancer Res. 2018 Jul 27;20(1):79.
4. Lænkholm AV, Jensen MB, Eriksen JO, et al. PAM50 Risk of Recurrence Score Predicts 10-Year Distant Recurrence in a Comprehensive Danish Cohort of Postmenopausal Women Allocated to 5 Years of Endocrine Therapy for Hormone Receptor-Positive Early Breast Cancer.J Clin Oncol. 2018 Mar 10;36(8):735-740.
5. Liu S, Chapman JA, Burnell MJ, et al. Prognostic and predictive investigation of PAM50 intrinsic subtypes in the NCIC CTG MA.21 phase III chemotherapy trial. Breast Cancer Res Treat. 2015 Jan;149(2):439-48Nielsen, T.O., Parker, J.S., Leung, S., et al. 2010. A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer. Clin. Cancer Res. 16, 5222–5232.
6. Ohnstad HO, Borgen E, Falk RS, et al. Prognostic value of PAM50 and risk of recurrence score in patients with early-stage breast cancer with long-term follow-up.Breast Cancer Res. 2017 Nov 14;19(1):120.
7. Parker, J.S., Mullins, M., Cheang, M.C.U., et al. 2009. Supervised risk predictor of breast cancer based on intrinsic subtypes. J. Clin. Oncol. 27, 1160–1167.
8. Prat, A., Cheang, M.C.U., Martín, M., et al. 2012b. Prognostic Significance of Progesterone Receptor-Positive Tumor Cells Within

Immunohistochemically Defined Luminal A Breast Cancer. J. Clin. Oncol.
9. Prat, A., Parker, J.S., Fan, C., et al. 2012a. Concordance among gene expression-based predictors for ER-positive breast cancer treated with adjuvant tamoxifen. Ann. Oncol. 23, 2866–2873.
10. Perou, C.M., Sørlie, T., Eisen, M.B. et al. 2000. Molecular portraits of human breast tumours. Nature 406, 747–752.
11. Pogue-Geile KL, Song N, Jeong JH, et al. Intrinsic Subtypes, PIK3CA Mutation, and the Degree of Benefit From Adjuvant Trastuzumab in the NSABP B-31 Trial. J Clin Oncol. 2015 Jan 5.
12. Sestak I, Cuzick J, Dowsett M. et al.. Prediction of Late Distant Recurrence After 5 Years of Endocrine Treatment: A Combined Analysis of Patients From the Austrian Breast and Colorectal Cancer Study Group 8 and Arimidex, Tamoxifen Alone or in Combination Randomized Trials Using the PAM50 Risk of Recurrence Score. J Clin Oncol. 2014 Oct 20. pii: JCO.2014.55.6894
13. Kjällquist U, Acs B, Margolin S, et al. Real World Evaluation of the **Prosigna**/PAM50 Test in a Node-Negative Postmenopausal Swedish Population: A Multicenter Study. Cancers (Basel). 2022 May 25;14(11):2615.

<u>Breast Cancer Index</u>

1. Bartlett JMS, Sgroi DC, Treuner K et al. Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial. Ann Oncol. 2019 Nov 1;30(11):1776-1783.
2. Jerevall PL, Brommesson S, Strand C, et al. Exploring the two-gene ratio in breast cancer--independent roles for HOXB13 and IL17BR in prediction of clinical outcome. *Breast Cancer Res Treat*. 2008;107(2):225–234.
3. Jansen MP, Sieuwerts AM, Look MP, et al. HOXB13-to-IL17BR expression ratio is related with tumor aggressiveness and response to tamoxifen of recurrent breast cancer: a retrospective study. *J Clin Oncol*. 2007;25(6):662–668.
4. Ma XJ, Hilsenbeck SG, Wang W, et al. The HOXB13:IL17BR expression index is a prognostic factor in early-stage breast cancer. *J Clin Oncol*. 2006;24(28):4611–4619.
5. Woolpert KM, Ahern TP, Lash TL,Biomarkers predictive of a response to extended endocrine therapy in breastcancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2023 Oct 25. doi: 10.1007/s10549-023-07149-x. Online ahead of print.PMID: 37878151



Head to head comparisons

1. Varga Z, Sinn P, Seidman AD. Summary of head-to-head comparisons of patient risk classifications by the 21-gene Recurrence Score® (RS) assay and other genomic assays for early breast cancer. Int J Cancer. 2019 Aug 15;145(4):882-893.
2. Berchtold E, Vetter M, Gündert M et al. Comparison of six breast cancer classifiers using qPCR. Bioinformatics. 2019 Sep 15;35(18):3412-3420.
3. Sestak I, Buus R, Cuzick J, et al. Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. 2018 Apr 1;4(4):545-553.

Endopredict

1. Blank PR, Filipits M, Dubsky P, et al.: Cost-effectiveness analysis of prognostic gene expression signature-based stratification of early breast cancer patients. Pharmacoeconomics. 2015 Feb;33(2):179-90.
2. Buus R, Sestak I, Kronenwett R, et al.: Comparison of EndoPredict and EPclin with Oncotype DX Recurrence Score for Prediction of Risk of Distant Recurrence after endocrine therapy J Natl Cancer Inst. 2016 Jul 10;108(11).
3. Denkert, C., Kronenwett, R., Schlake, W. et al. 2012. Decentral gene expression analysis for ER+/Her2- breast cancer: results of a proficiency testing program for the EndoPredict assay. Virchows Arch. 460, 251–259. doi:10.1007/s00428-012-1204-4.
4. Dubsky, P., Filipits, M., Jakesz, R. et al. 2012. EndoPredict improves the prognostic classification derived from common clinical

guidelines in ER-positive, HER2-negative early breast cancer. Ann Oncol. 2013 Mar;24(3):640-7.
5. Dubsky P, Brase JC, Jakesz R et al.: Austrian Breast and Colorectal Cancer Study Group (ABCSG). T al.: The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. Br J Cancer. 2013 Dec 10;109(12):2959-64
6. Filipits, M., Rudas, M., Jakesz, R. et al. 2011. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin. Cancer Res. 17, 6012–6020.
7. Kronenwett, R., Bohmann, K., Prinzler, J. et al. 2012. Decentral gene expression analysis: analytical validation of the Endopredict genomic multianalyte breast cancer prognosis test. BMC Cancer 12, 456.
8. Martin M, Brase JC, Calvo L, et al. Clinical validation of the EndoPredict test in node-positive, chemotherapy-treated ER+/HER2- breast cancer patients: results from the GEICAM 9906 trial. Breast Cancer Res 2014; 16(2): R38.
9. Constantinidou A, Marcou Y, Toss MS, et al. .Clinical Validation of EndoPredict in Pre-Menopausal Women with ER-Positive, HER2-Negative Primary Breast Cancer. Clin Cancer Res. 2022 Oct 14;28(20):4435-4443.

MammaPrint

1. Buyse, M., Loi, S., van't Veer, L., et al. 2006. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J. Natl. Cancer Inst. 98, 1183–1192.
2. Drukker CA, Elias SG, Nijenhuis MV, et al. Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. Breast Cancer Res Treat. 2014 Dec;148(3):599-613.
3. Exner R, Bago-Horvath Z, Bartsch R et al. The multigene signature MammaPrint impacts on multidisciplinary team decisions in ER+, HER2- early breast cancer. Br J Cancer. 2014 Aug 26;111(5):837-42.
4. Jonsdottir K, Assmus J, Slewa A, et al. Prognostic value of gene signatures and proliferation in lymph-node-negative breast cancer. PLoS One. 2014 Mar 5;9(3):e90642.
5. Mook, S., Schmidt, M.K., Weigelt, B., et al. 2010. The 70-gene prognosis signature predicts early metastasis in breast cancer patients between 55 and 70 years of age. Ann. Oncol. 21, 717–722.
6. Mook, S., Schmidt, M.K., Rutgers, E.J., et al. 2009a. Calibration and discriminatory accuracy of prognosis calculation for breast cancer with the online Adjuvant! program: a hospital-based retrospective cohort study. Lancet Oncol. 10, 1070–1076.
7. Mook, S., Schmidt, M.K., Viale, G. et al. 2009b. The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1-3 positive lymph nodes in an independent validation study. Breast Cancer Res. Treat. 116, 295–302.
8. van de Vijver, M.J., He, Y.D., van't Veer, L.J., et al. 2002. A gene-expression signature as a predictor of survival in breast cancer. N. Engl. J. Med. 347, 1999–2009. doi:10.1056/NEJMoa021967.

9. van Veer, L.J. 't, Dai, H., van de Vijver, M.J., et al. 2002. Gene expression profiling predicts clinical outcome of breast cancer. Nature 415, 530–536. doi:10.1038/415530a.
10. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med. 2016 Aug 25;375(8):717-29.
11. Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol. 2021 Apr;22(4):476-488. doi: 10.1016/S1470-2045(21)00007-3. Epub 2021 Mar 12. PMID: 33721561.
12. Vliek SB, Hilbers FS, Jager A, et al.Ten-year follow-up of the observational RASTER study, prospective evaluation of the 70-gene signature in ER-positive, HER2-negative, node-negative, early breastcancer. Eur J Cancer. 2022 Nov;175:169-179.

Oncotype DX

1. Albain, K.S., Barlow, W.E., Shak, S. et al. 2010. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol. 11, 55–65. Cronin, M., Sangli, C., Liu, M.-L., et al. 2007. Analytical validation of the Oncotype DX genomic diagnostic test for recurrence prognosis and therapeutic response prediction in node-negative, estrogen receptor-positive breast cancer. Clin. Chem. 53, 1084–1091.
2. Dowsett, M., Cuzick, J., Wale, C. et al. 2010. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. J. Clin. Oncol. 28, 1829–1834.
3. Geyer CE Jr, Tang G, Mamounas EP, et al. 21-Gene assay as predictor of chemotherapy benefit in HER2-negative breast cancer. NPJ Breast Cancer. 2018 Nov 14;4:37.
4. Gluz O, Nitz UA, Christgen M, et al.: West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment. J Clin Oncol. 2016 Jul 10;34(20):2341-9.
5. Kalinsky K, Barlow WE, Gralow JR et al. 21-Gene Assay to inform chemotherapy benefit from node positive breast cancer. Engl J Med DOI: 10.1056/NEJMoa2108873
6. Khan SS, Karn T, Symmans WF, et al. Genomic predictor of residual risk of recurrence after adjuvant chemotherapy and endocrine therapy in high risk estrogen receptor-positive breast cancers. Breast Cancer Res Treat. 2015 Feb 5.

7. Mamounas, E.P., Tang, G., Fisher, B., et al. 2010. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. J. Clin. Oncol. 28, 1677–1683.
8. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial.Breast Cancer Res Treat. 2017 Oct;165(3):573-583.
9. Nitz UA, Gluz O, Kümmel S et al. Endocrine Therapy Response and 21-Gene Expression Assay for Therapy Guidance in HR+/HER2- Early Breast Cancer. J Clin Oncol. 2022 Aug 10;40(23):2557-2567. doi: 10.1200/JCO.21.02759. Epub 2022 Apr 11.
10. Paik, S., Shak, S., Tang, G. et al. 2004. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N. Engl. J. Med. 351, 2817–2826. doi:10.1056/NEJMoa041588.
11. Paik, S., Tang, G., Shak, S., et al. 2006. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J. Clin. Oncol. 24, 3726–3734.
12. Penault-Llorca F, Filleron T, Asselain B, et al. The 21-gene Recurrence Score® assay predicts distant recurrence in lymph node-positive, hormone receptor-positive, breast cancer patients treated with adjuvant sequential epirubicin- and docetaxel-based or epirubicin-based chemotherapy (PACS-01 trial). BMC Cancer. 2018 May 4;18(1):526.
13. Sparano JA, Gray RJ, Makower DF, et al: Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med 2015, 373(21):2005-2014.
14. Sparano JA, Gray R, Oktay MH, et al. A metastasis biomarker (MetaSite Breast™ Score) is associated with distant recurrence in hormone receptor-positive, HER2-negative early-stage breast cancer. NPJ Breast Cancer. 2017 Nov 8;3:42.
15. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018 Jul 12;379(2):111-121.
16. Tang, G., Cuzick, J., Costantino, J.P., et al. 2011. Risk of recurrence and chemotherapy benefit for patients with node-negative, estrogen receptor-positive breast cancer: recurrence score alone and integrated with pathologic and clinical factors. J. Clin. Oncol. 29, 4365–4372.
17. Zhao X, Rødland EA, Sørlie T, et al. Systematic assessment of prognostic gene signatures for breast cancer shows distinct influence of time and ER status. BMC Cancer. 2014 Mar 19;14:211.
18. *Sparano J, Gray RJ, Makower D, Albain KS, Hayes DF, Geyer C, Dees E, Goetz MP, Olson Jr JA, Lively TG, Badve S, Saphner T, Wagner LI, Whelan T, Kaklamani V, Sledge Jr GW. Trial Assigning Individualized Options for Treatment (TAILORx): An update including 12-year event rates. SABCS 2022, GS 1-05*

19. Zhang S, Fitzsimmons KC, Hurvitz SA Oncotype DX Recurrence Score in premenopausal women. Ther Adv Med Oncol. 2022 Mar 10;14:17588359221081077. doi: 10.1177/17588359221081077. eCollection 2022.PMID: 35295864
20. Shaw VR, Amos CI, Cheng C. Predicting Chemotherapy Benefit across Different Races in Early-Stage BreastCancer Patients Using the Oncotype DX Score. Cancers (Basel). 2023 Jun 16;15(12):3217.
21. Davey MG, Cleere EF, O'Donnell JP, et al. Value of the 21-gene expression assay in predicting locoregional recurrence rates in estrogen receptor-positive breast cancer: a systematic review and network meta-analysis. Breast Cancer Res Treat. 2022 Jun;193(3):535-544.

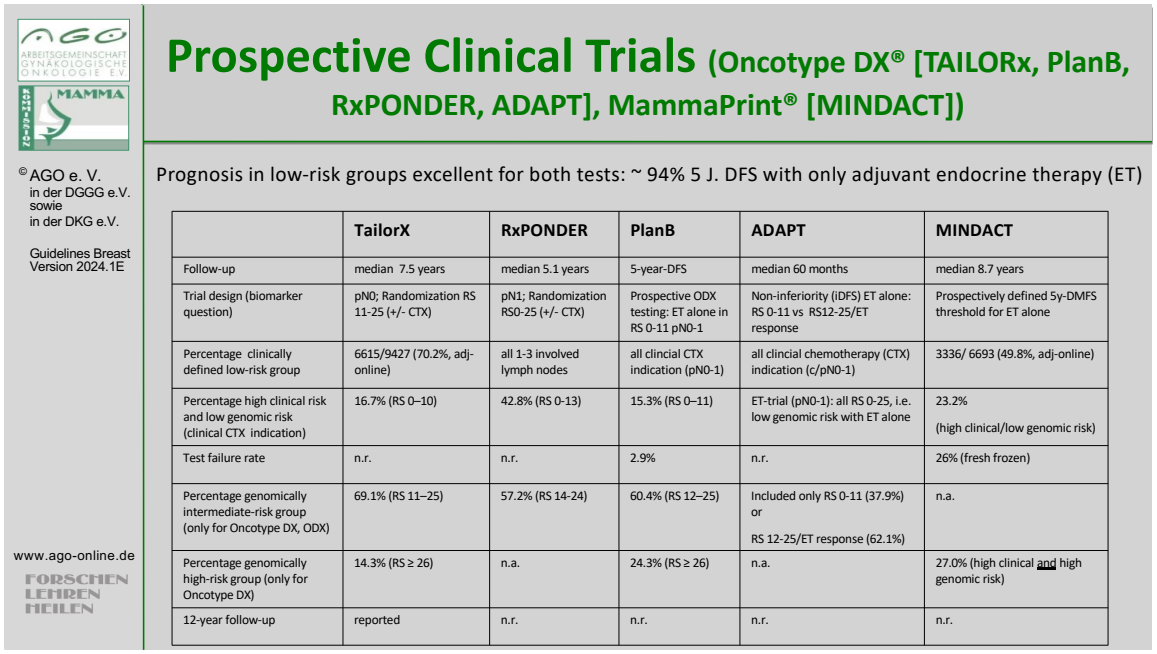
Prosigna (ROR / PAM50)

1. Chia, S.K., Bramwell, V.H., Tu, Det al. 2012. A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. Clin. Cancer Res. 18, 4465–4472.
2. Gnant M, Filipits M, Greil R, et al. Austrian Breast and Colorectal Cancer Study Group. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. Ann Oncol. 2014 Feb;25(2):339-45
3. Jensen MB, Lænkholm AV, Nielsen TO, et al. The Prosigna gene expression assay and responsiveness to adjuvant cyclophosphamide-based chemotherapy in premenopausal high-risk patients with breast cancer.Breast Cancer Res. 2018 Jul 27;20(1):79.
4. Lænkholm AV, Jensen MB, Eriksen JO, et al. PAM50 Risk of Recurrence Score Predicts 10-Year Distant Recurrence in a Comprehensive Danish Cohort of Postmenopausal Women Allocated to 5 Years of Endocrine Therapy for Hormone Receptor-Positive Early Breast Cancer.J Clin Oncol. 2018 Mar 10;36(8):735-740.
5. Liu S, Chapman JA, Burnell MJ, et al. Prognostic and predictive investigation of PAM50 intrinsic subtypes in the NCIC CTG MA.21 phase III chemotherapy trial. Breast Cancer Res Treat. 2015 Jan;149(2):439-48Nielsen, T.O., Parker, J.S., Leung, S., et al. 2010. A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer. Clin. Cancer Res. 16, 5222–5232.
6. Ohnstad HO, Borgen E, Falk RS, et al. Prognostic value of PAM50 and risk of recurrence score in patients with early-stage breast cancer with long-term follow-up.Breast Cancer Res. 2017 Nov 14;19(1):120.
7. Parker, J.S., Mullins, M., Cheang, M.C.U., et al. 2009. Supervised risk predictor of breast cancer based on intrinsic subtypes. J. Clin. Oncol. 27, 1160–1167.
8. Prat, A., Cheang, M.C.U., Martín, M., et al. 2012b. Prognostic Significance of Progesterone Receptor-Positive Tumor Cells Within

Immunohistochemically Defined Luminal A Breast Cancer. J. Clin. Oncol.
9. Prat, A., Parker, J.S., Fan, C., et al. 2012a. Concordance among gene expression-based predictors for ER-positive breast cancer treated with adjuvant tamoxifen. Ann. Oncol. 23, 2866–2873.
10. Perou, C.M., Sørlie, T., Eisen, M.B. et al. 2000. Molecular portraits of human breast tumours. Nature 406, 747–752.
11. Pogue-Geile KL, Song N, Jeong JH, et al. Intrinsic Subtypes, PIK3CA Mutation, and the Degree of Benefit From Adjuvant Trastuzumab in the NSABP B-31 Trial. J Clin Oncol. 2015 Jan 5.
12. Sestak I, Cuzick J, Dowsett M. et al.. Prediction of Late Distant Recurrence After 5 Years of Endocrine Treatment: A Combined Analysis of Patients From the Austrian Breast and Colorectal Cancer Study Group 8 and Arimidex, Tamoxifen Alone or in Combination Randomized Trials Using the PAM50 Risk of Recurrence Score. J Clin Oncol. 2014 Oct 20. pii: JCO.2014.55.6894
13. Kjällquist U, Acs B, Margolin S, et al. Real World Evaluation of the **Prosigna**/PAM50 Test in a Node-Negative Postmenopausal Swedish Population: A Multicenter Study. Cancers (Basel). 2022 May 25;14(11):2615.

<u>Breast Cancer Index</u>

1. Bartlett JMS, Sgroi DC, Treuner K et al. Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial. Ann Oncol. 2019 Nov 1;30(11):1776-1783.
2. Jerevall PL, Brommesson S, Strand C, et al. Exploring the two-gene ratio in breast cancer--independent roles for HOXB13 and IL17BR in prediction of clinical outcome. *Breast Cancer Res Treat*. 2008;107(2):225–234.
3. Jansen MP, Sieuwerts AM, Look MP, et al. HOXB13-to-IL17BR expression ratio is related with tumor aggressiveness and response to tamoxifen of recurrent breast cancer: a retrospective study. *J Clin Oncol*. 2007;25(6):662–668.
4. Ma XJ, Hilsenbeck SG, Wang W, et al. The HOXB13:IL17BR expression index is a prognostic factor in early-stage breast cancer. *J Clin Oncol*. 2006;24(28):4611–4619.
5. Woolpert KM, Ahern TP, Lash TL,Biomarkers predictive of a response to extended endocrine therapy in breastcancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2023 Oct 25. doi: 10.1007/s10549-023-07149-x. Online ahead of print.PMID: 37878151



	TailorX	RxPONDER	PlanB	ADAPT	MINDACT
Follow-up	median 7.5 years	median 5.1 years	5-year-DFS	median 60 months	median 8.7 years
Trial design (biomarker question)	pN0; Randomization RS 11-25 (+/- CTX)	pN1; Randomization RS0-25 (+/- CTX)	Prospective ODX testing: ET alone in RS 0-11 pN0-1	Non-inferiority (iDFS) ET alone: RS 0-11 vs RS12-25/ET response	Prospectively defined 5y-DMFS threshold for ET alone
Percentage clinically defined low-risk group	6615/9427 (70.2%, adj-online)	all 1-3 involved lymph nodes	all clincial CTX indication (pN0-1)	all clincial chemotherapy (CTX) indication (c/pN0-1)	3336/ 6693 (49.8%, adj-online)
Percentage high clinical risk and low genomic risk (clinical CTX indication)	16.7% (RS 0–10)	42.8% (RS 0-13)	15.3% (RS 0–11)	ET-trial (pN0-1): all RS 0-25, i.e. low genomic risk with ET alone	23.2% (high clinical/low genomic risk)
Test failure rate	n.r.	n.r.	2.9%	n.r.	26% (fresh frozen)
Percentage genomically intermediate-risk group (only for Oncotype DX, ODX)	69.1% (RS 11–25)	57.2% (RS 14-24)	60.4% (RS 12–25)	Included only RS 0-11 (37.9%) or RS 12-25/ET response (62.1%)	n.a.
Percentage genomically high-risk group (only for Oncotype DX)	14.3% (RS ≥ 26)	n.a.	24.3% (RS ≥ 26)	n.a.	27.0% (high clinical and high genomic risk)
12-year follow-up	reported	n.r.	n.r.	n.r.	n.r.

TailorX

1. Sparano JA, Gray RJ, Makower DF, et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2015 Nov 19;373(21):2005
2. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018 Jul 12;379(2):111-121.
3. Sparano JA, Gray RJ, Makower DF, et al. 12-Year Recurrence and Survival Outcomes for Patients With Early-Stage Breast Cancer. SABCS 2022. GS1-05

RxPONDER

1. Kalinsky K, Barlow WE, Gralow JR et al. 21-Gene Assay to inform chemotherapy benefit in node-positive breast cancer. N Engl J Med DOI: 10.1056/NEJMoa2108873

Plan B

1. Gluz O, Nitz UA, Christgen M, et al. West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment. J Clin Oncol. 2016 Jul 10;34(20):2341-9.

2. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. Breast Cancer Res Treat. 2017 Oct;165(3):573-583.

ADAPT

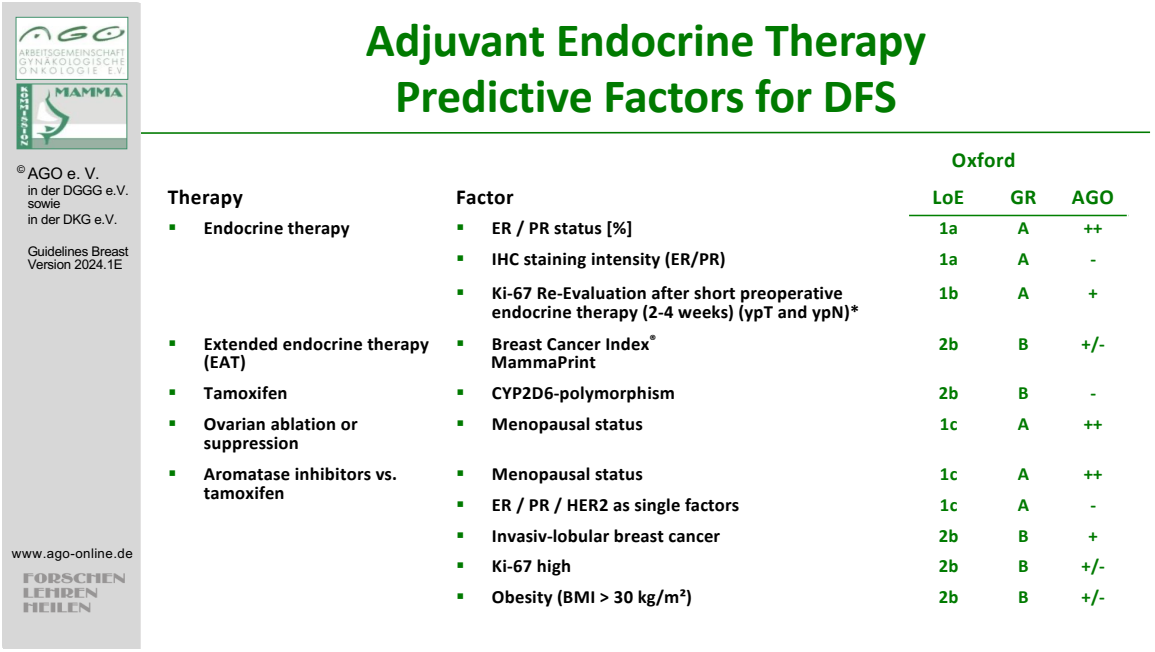
1. *Gluz O, Nitz UA, Christgen M, et al. Impact of age, recurrence score (RS) and ovarian function suppression (OFS) on endocrine response to short preoperative endocrine therapy (ET): Analysis of ADAPT and ADAPTcycle trials. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089*
2. Nitz UA, Gluz O, Kümmel S et al. Endocrine Therapy Response and 21-Gene Expression Assay for Therapy Guidance in HR+/HER2- Early Breast Cancer. J Clin Oncol. 2022 Aug 10;40(23):2557-2567. doi: 10.1200/JCO.21.02759. Epub 2022 Apr 11.

MINDACT

1. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med. 2016 Aug 25;375(8):717-29.
2. Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol. 2021 Apr;22(4):476-488. doi: 10.1016/S1470-2045(21)00007-3. Epub 2021 Mar 12. PMID: 33721561.

Several tests

1. Bartlett JM, Bayani J, Marshall A, et al; OPTIMA TMG. Comparing Breast Cancer Multiparameter Tests in the OPTIMA Prelim Trial: No Test Is More Equal Than the Others. J Natl Cancer Inst. 2016 Apr 29;108(9).
2. Varga Z, Sinn P, Seidman AD. Summary of head-to-head comparisons of patient risk classifications by the 21-gene Recurrence Score® (RS) assay and other genomic assays for early breast cancer. Int J Cancer. 2019 Aug 15;145(4):882-893.
3. Berchtold E, Vetter M, Gündert M et al. Comparison of six breast cancer classifiers using qPCR. Bioinformatics. 2019 Sep 15;35(18):3412-3420.
4. Sestak I, Buus R, Cuzick J, et al. Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. 2018 Apr 1;4(4):545-553.



Adjuvant Endocrine Therapy
Predictive Factors for DFS

Therapy	Factor	Oxford LoE	GR	AGO
▪ Endocrine therapy	▪ ER / PR status [%]	1a	A	++
	▪ IHC staining intensity (ER/PR)	1a	A	-
	▪ Ki-67 Re-Evaluation after short preoperative endocrine therapy (2-4 weeks) (ypT and ypN)*	1b	A	+
▪ Extended endocrine therapy (EAT)	▪ Breast Cancer Index® MammaPrint	2b	B	+/-
▪ Tamoxifen	▪ CYP2D6-polymorphism	2b	B	-
▪ Ovarian ablation or suppression	▪ Menopausal status	1c	A	++
▪ Aromatase inhibitors vs. tamoxifen	▪ Menopausal status	1c	A	++
	▪ ER / PR / HER2 as single factors	1c	A	-
	▪ Invasiv-lobular breast cancer	2b	B	+
	▪ Ki-67 high	2b	B	+/-
	▪ Obesity (BMI > 30 kg/m²)	2b	B	+/-

General publications

1. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J. Natl. Cancer Inst. 2009; 101(21): 1446 – 1452
2. Curigliano G, Burstein HJ, Gnant M, et al. Understanding breast cancer complexity to improve patient outcomes: The St Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023. Ann Oncol. 2023 Nov;34(11):970-986.

Endocrine therapy

1. Colleoni M et al. Tamoxifen after adjuvant chemotherapy for premenopausal women with lymph node-positive breast cancer: International Breast Cancer Study Group Trial 13-93. J Clin Oncol 2006; 24 (9): 1332-4.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365 (9472): 1687-717.
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011 Aug 27;378(9793):771-84
4. Harvey JM, Clark GM, Osborne CK, et al. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay

for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol 1999; 17 (5): 1474-8.
5. Thürliman B et al. Is chemotherapy necessary for premenopausal women with lower-risk node-positive, endocrine responsive breast cancer? 10-year update of International Breast Cancer Study Group Trial 11-93. Breast Cancer Res Treat. 2009; 113:137-44.
6. Ellis MJ, Suman VJ, Hoog J, et al. Ki67 Proliferation Index as a Tool for Chemotherapy Decisions During and After Neoadjuvant Aromatase Inhibitor Treatment of Breast Cancer: Results From the American College of Surgeons Oncology Group Z1031 Trial (Alliance). J Clin Oncol. 2017 Apr 1;35(10):1061-1069.
7. Dowsett M, Ellis MJ, Dixon JM, et al. Evidence-based guidelines for managing patients with primary ER+ HER2- breast cancer deferred from surgery due to the COVID-19 pandemic. Breast Cancer. 2020 Jun 8;6:21.
8. Smith I, Robertson J, Kilburn L, et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. Lancet Oncol. 2020 Nov;21(11):1443-1454.

EAT

1. Bartlett JMS, Sgroi DC, Treuner K et al. Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial. Ann Oncol. 2019 Nov 1;30(11):1776-1783.
2. Rastogi P, et al. Utility of the 70-gene MammaPrint assay for prediction of benefit from extended letrozole therapy (ELT) in the NRG Oncology/NSABP B-42 trial. Journal of Clinical Oncology 2021; 39(15_suppl): 502-502.
3. Liefers GJ, Meershoek-Klein Kranenbarg E, Duijm-de Carpentier M et al. Utility of the 70-gene MammaPrint test for prediction of extended endocrine therapy benefit in patients with early-stage breast cancer in the IDEAL Trial, SABCS 2022 GS5-10

Amenorrhoea

1. Anders C, Marcom PK, Peterson B, et al. A pilot study of predictive markers of chemotherapy-related amenorrhea among premenopausal women with early stage breast cancer. Cancer Invest. 2008 Apr-May;26(3):286-95.
2. Anderson RA, Cameron DA. Pretreatment serum anti-müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. J Clin Endocrinol Metab. 2011 May;96(5):1336-43.

Body Mass Index

1. Chan DSM et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82

follow-up studies Ann Oncol. Oct 2014; 25(10): 1901–1914.

2. Xia X, Chen W, Li J, et al. Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies. Sci Rep. 2014 Dec 15;4:7480.
3. Lammers SWM, Geurts SME, van Hellemond IEG, et al. The prognostic and predictive effect of body mass index in hormone receptor-positive breast cancer. JNCI Cancer Spectr. 2023 Oct 31;7(6):pkad092.

CYP2D6

1. Bezerra LS, Santos-Veloso MAO, Bezerra Junior NDS, et al. Impacts of Cytochrome P450 2D6 (CYP2D6) Genetic Polymorphism in Tamoxifen Therapy for Breast Cancer. Rev Bras Ginecol Obstet. 2018 Dec;40(12):794-799.
2. Brooks JD, Comen EA, Reiner AS, et al; WECARE Study collaborative group, Malone KE, Bernstein JL. CYP2D6 phenotype, tamoxifen, and risk of contralateral breast cancer in the WECARE Study. Breast Cancer Res. 2018 Dec 10;20(1):149.
3. Bai Y, Wu HW, Zhang YH. Effects of CYP2D6*10 polymorphism on tamoxifen pharmacokinetics in patients with breast cancer in Asia: a meta-analysis. Cancer Chemother Pharmacol. 2019 Jan;83(1):71-79.
4. Schroth W, Winter S, Mürdter T, et al. Improved Prediction of Endoxifen Metabolism by CYP2D6 Genotype in Breast Cancer Patients Treated with Tamoxifen. Front Pharmacol. 2017 Aug 24;8:582.
5. Hertz DL, Kidwell KM, Hilsenbeck SG, et al. CYP2D6 genotype is not associated with survival in breast cancer patients treated with tamoxifen: results from a population-based study. Breast Cancer Res Treat. 2017 Nov;166(1):277-287.
6. Hwang GS, Bhat R, Crutchley RD, et al. Impact of CYP2D6 polymorphisms on endoxifen concentrations and breast cancer outcomes. Pharmacogenomics J. 2018 Apr;18(2):201-208.
7. Wang T, Zhou Y, Cao G. Pharmacogenetics of tamoxifen therapy in Asian populations: from genetic polymorphism to clinical outcomes. Eur J Clin Pharmacol. 2021 Aug;77(8):1095-1111.

Ki-67 Bestimmung nach kurzer präoperativer endokriner Therapie

1. Dowsett M, Torsten O, A´Hern R et al. Assessemnt of Ki-67 in Breast Cancer: Recommendations from the International Ki67 Breast Cancer Working Group. J Natl Cancer Inst 2011;103:1656-1664
2. Kim HJ, Noh WC, Lee ES et al. Efficacy of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy in pre-menopausal patients with estrogen receptor positive and HER2-negative lymph-node positive breast cancer. Breast Cancer Res 202;22(1):54-59.

3. Ellis MJ, Suman VJ, Hoog J et al. Ki-67 Proliferation Index as a tool for chemotherapy decision during and after neoadjuvant aromatase inhibitor treatment of breast cancer: Results from the American College of Surgeons Oncology Group Z1031 Trial (Alliance). J Clin Oncol 2017;35(10):1061-1069.
4. Smith I, et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. The Lancet Oncology 2020; 21(11): 1443-1454.
5. Nitz UA, et al. Endocrine Therapy Response and 21-Gene Expression Assay for Therapy Guidance in HR+/HER2- Early Breast Cancer. J Clin Oncol 2022; 40(23): 2557-2567.
6. Martins-Branco D, Nader-Marta G, Molinelli C et al. Ki-67 index after neoadjuvant endocrine therapy as a prognostic biomarker in patients with ER-positive/HER2-negative early breast cancer: a systematic review and meta-analysis. Eur J Cancer. 2023 Nov;194:113358.

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

www.ago-online.de
FORSCHEN
LEHREN
HEILEN

Adjuvant Chemotherapy and Targeted Therapy
Predictive Factors for DFS

Therapy	Factor	Oxford LoE	Oxford GR	AGO
▪ Adjuvant Chemotherapy	70-Gene-signature (Mammaprint®)	1b	A	+
	21-Gene-signature (Oncotype DX RS®)	1b	A	+
	EPclin (Endopredict®)	2b	B	+
	PAM-50 (Prosigna®)	2b	B	+
	Histological type (lobular vs. NST)	2b	B	-
	TIL´s in TNBC	2b	B	+/-
▪ Anti-HER2-Therapy	HER2 (IHC, ISH)	1a	A	++
▪ PARP-Inhibitors	gBRCA1/Mutation (HER2 neg.)	1a	A	+

*Consider decision according to age/menopausal status, prospective evidence available for Mammaprint and OncotypeDX only (see next slide)

70-Gene-Signature (Mammaprint®)

1. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. *N Engl J Med*. 2016;375(8):717–729.
2. Cardoso F, van 't Veer L, Poncet C, et al. MINDACT: Long-term results of the large prospective trial testing the 70-gene signature MammaPrint as guidance for adjuvant chemotherapy in breast cancer patients. ASCO 2020, #506
3. Vliek SB, Hilbers FS, Jager A, et al.Ten-year follow-up of the observational RASTER study, prospective evaluation of the 70-gene signature in ER-positive, HER2-negative, node-negative, early breastcancer. Eur J Cancer. 2022 Nov;175:169-179.

OncotypeDX

1. Paik, S., Tang, G., Shak, S., et al. 2006. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J. Clin. Oncol. 24, 3726–3734.
2. Sparano JA, Gray RJ, Makower DF, et al. Clinical Outcomes in Early Breast Cancer With a High 21-Gene Recurrence Score of 26 to 100 Assigned to Adjuvant Chemotherapy Plus Endocrine Therapy: A Secondary Analysis of the TAILORx Randomized Clinical Trial [published online ahead of print, 2019 Sep 30]. *JAMA Oncol*. 2019;e194794.
3. Kalinsky K, Barlow WE, Meric-Bernstam F, et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine

therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) < 25: SWOG S1007 (RxPonder). SABCS 2020, GS3-00
4. Harbeck N, Gluz O, Kuemmel S, et al. Endocrine therapy alone in patients with intermediate or high-risk luminal early breast cancer (0-3 lymph nodes), Recurrence Score <26 and Ki67 response after preoperative endocrine therapy: Primary outcome results from the WSG-ADAPT HR+/HER2- trial. SABCS 2020, GS4-04.
5. Davey MG, Cleere EF, O'Donnell JP, et al. Value of the 21-gene expression assay in predicting locoregional recurrence rates in estrogen receptor-positive breast cancer: a systematic review and network meta-analysis. Breast Cancer Res Treat. 2022 Jun;193(3):535-544.

EPclin (EndoPredict®)

1. Sestak I, Martín M, Dubsky P et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. Breast Cancer Res Treat. 2019 Jul;176(2):377-386.

PAM-50 (Prosigna®)

1. Prat A, Galván P, Jimenez B et al. Prediction of Response to Neoadjuvant Chemotherapy Using Core Needle Biopsy Samples with the Prosigna Assay. Clin Cancer Res. 2016 Feb 1;22(3):560-6.
2. Gnant M, Filipits M, Greil R, et al.; Austrian Breast and Colorectal Cancer Study Group.Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. Ann Oncol. 2014 Feb;25(2):339-45.
3. Gnant M, Sestak I, Filipits M, et al. Identifying clinically relevant prognostic subgroups of postmenopausal women with node-positive hormone receptor-positive early-stage breast cancer treated with endocrine therapy: a combined analysis of ABCSG-8 and ATAC using the PAM50risk of recurrence score and intrinsic subtype. Ann Oncol. 2015 Aug;26(8):1685-91.
4. Ohnstad HO, Borgen E, Falk RS, et al. Prognostic value of PAM50 and risk of recurrence score in patients with early-stage breast cancer with long-term follow-up. Breast Cancer Res. 2017 Nov 14;19(1):120.
5. Jensen MB, Lænkholm AV, Nielsen TO et al. The Prosigna gene expression assay and responsiveness to adjuvant cyclophosphamide-based chemotherapy in premenopausal high-risk patients with breast cancer. Breast Cancer Res. 2018 Jul 27;20(1):79.
6. Asleh K, Lluch A, Goytain A et al. Triple-Negative PAM50 Non-Basal Breast Cancer Subtype Predicts Benefit from Extended Adjuvant Capecitabine. Clin Cancer Res. 2023 Jan 17;29(2):389-400.

Histological type:

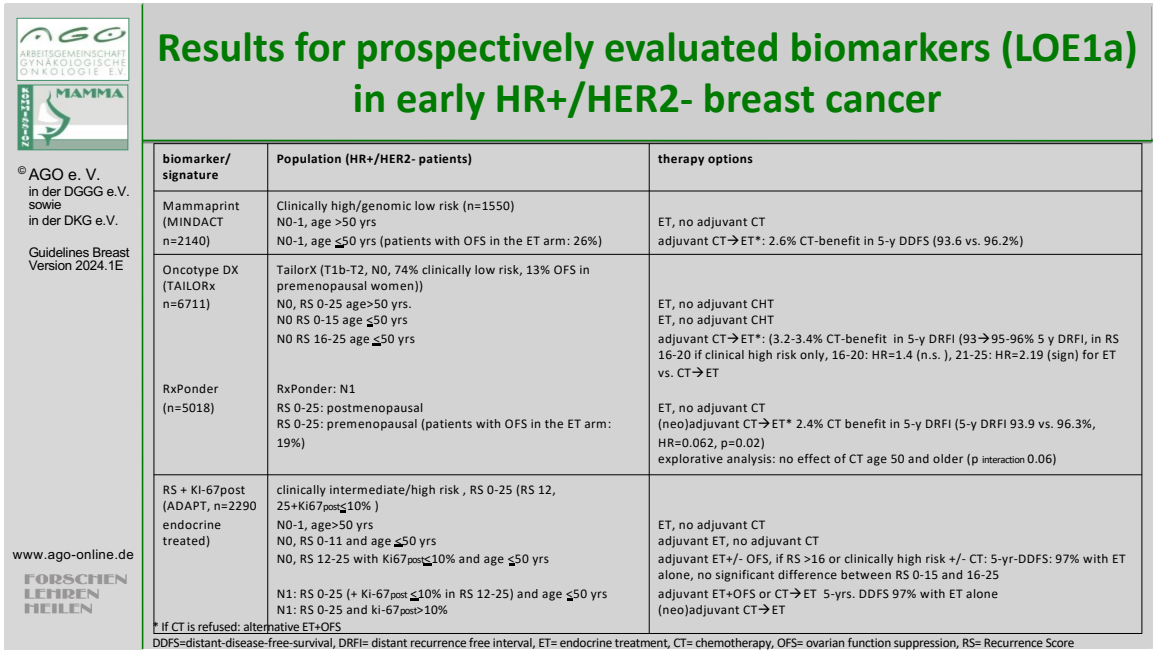
1. De Nonneville A, Jauffret C, Goncalves A. Adjuvant chemotherapy in lobular carcinoma of the breast: a clinicopathological score identifies high-risk patient with survival benefit Breast Cancer Res Treat. 2019 Jun;175(2):379-387.
2. Fu R, Yang J, Wang H et al.: A nomogram for determining the disease-specific survival in invasive lobular carcinoma of the breast: A population study. Medicine (Baltimore). 2020 Oct 23;99(43):e22807.

Anti-HER2 therapy

see evidence in chapter "Chemotherapy and targeted therapy"

PARPi

1. Tutt ANJ, Garber JE, Kaufmann B et al. Adjuvant Olaparib for patients with BRCA1- or BRCA2 mutated Breast Cancer. N Engl J Med 2021:384(25):2394.
2. Garber HR, Litton JR. Integrating poly(ADP-ribose) polymerase inhibitors in the treatment of early breast cancer. Curr Opin Oncol 2019;31(3):247-255.



1. Sparano JA, Gray RJ, Ravdin PM et al. Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer. New England Journal of Medicine 2019; 380: 2395-2405.
2. Sparano JA, Gray RJ, Makower DF et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. New England Journal of Medicine 2018
3. Kalinsky K, Barlow WE, Gralow JR, et al. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. N Engl J Med. 2021 Dec 16;385(25):2336-2347.
4. Kalinsky KM, Barlow WE, Gralow JR et al. Abstract GS2-07: Updated results from a phase 3 randomized clinical trial in participants (pts) with 1-3 positive lymph nodes (LN), hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) ≤ 25 randomized to endocrine therapy (ET) +/- chemotherapy (CT): SWOG S1007 (RxPONDER). Cancer Research 2022; 82: GS2-07-GS02-07.
5. Piccart M, van 't Veer LJ, Poncet C et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. The Lancet Oncology 2021; 22: 476-488.
6. Gluz O, Nitz U, Christgen M et al. Prognostic impact of recurrence score, endocrine response and clinical-pathological factors in high-risk luminal breast cancer: Results from the WSG-ADAPT HR+/HER2- chemotherapy trial. Journal of Clinical Oncology 2021; 39: 504-504.
7. Gluz O, Kuemmel S, Nitz U, et al. Nab-paclitaxel weekly versus dose-dense solvent-based paclitaxel followed by dose-dense

epirubicin plus cyclophosphamide in high-risk HR+/HER2- early breast cancer: results from the neoadjuvant part of the WSG-ADAPT-HR+/HER2- trial. Ann Oncol. 2023 Jun;34(6):531-542.

8. Nitz UA, Gluz O, Kummel S et al. Endocrine Therapy Response and 21-Gene Expression Assay for Therapy Guidance in HR+/HER2- Early Breast Cancer. J Clin Oncol 2022; 40: 2557-2567.

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

www.ago-online.de
FORSCHEN
LEHREN
HEILEN

Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR I

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Young age	↑	1a	A	+
▪ Obesity	↓	2a	B	+
▪ cT1 / cT2 tumors o. N0 o. G3	↑↑	1a	A	++
▪ Negative hormone receptor status	↑↑	1a	A	++
▪ Triple negative breast cancer	↑↑	1a	A	++
▪ Positive HER2-status	↑↑	1a	A	++
▪ Early clinical response	↑	1b	A	+
▪ Lobular tumor type	↓	1a	A	+
▪ Metaplastic tumor type	↓↓	4	C	+

* High (↑) or very high (↑↑) probability to reach pCR, low (↓) or very low (↓↓) probability to reach pCR
See aso chapter „Prognostic and predictive factors"

General evidence

1. von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 2012;366: 299-309.
2. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012;30: 1796-804.
3. Gerber B, Loibl S, Eidtmann H, et al. Neoadjuvant bevacizumab and anthracycline-taxane-based chemotherapy in 678 triple-negative primary breast cancers; results from the geparquinto study (GBG 44). Ann Oncol 2013;24: 2978-84.
4. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384: 164-72.
5. van Mackelenbergh MT, Denkert C, Nekljudova V, et al. Outcome after neoadjuvant chemotherapy in estrogen receptor-positive and progesterone receptor-negative breast cancer patients: a pooled analysis of individual patient data from ten prospectively randomized controlled neoadjuvant trials. Breast Cancer Res Treat. 2018 Jan;167(1):59-71.
6. van Mackelenbergh MT, Loibl S, Untch M, et al. Pathologic Complete Response and Individual Patient Prognosis After Neoadjuvant Chemotherapy Plus Anti-Human Epidermal Growth Factor Receptor 2 Therapy of Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer. J Clin Oncol. 2023 Jun 1;41(16):2998-3008.

Body mass index

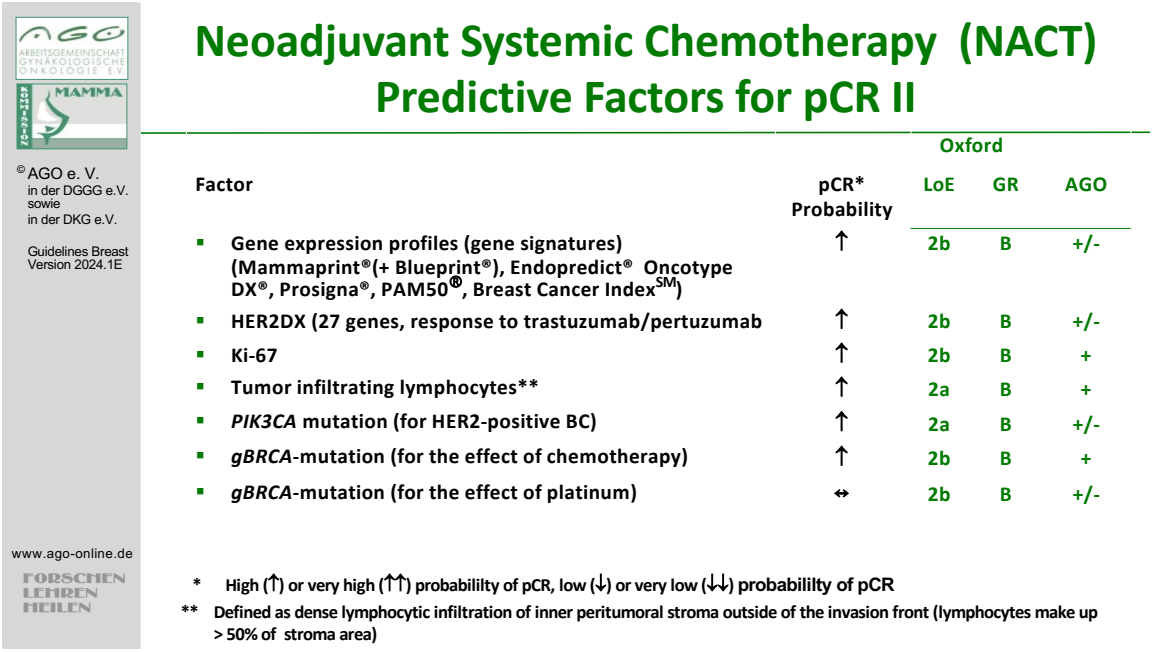
1. Wang H, Zhang S, Yee D, et al. Impact of body mass index on pathological complete response following neoadjuvant chemotherapy in operable breast cancer: a meta analysis. Breast Cancer 2021;28(3):616-629

Lobular cancer

1. Loibl S, Volz C, Mau C, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014;144: 153-62.

Metaplastic breast cancer

1. McMullen ER, Zoumberos NA, Kleer CG. Metaplastic Breast Carcinoma: Update on Histopathology and Molecular Alterations. Arch Pathol Lab Med. 2019 Dec;143(12):1492-1496.
2. Tzanninis IG, Kotteas EA, Ntanasis-Stathopoulos I et al. Management and Outcomes in Metaplastic Breast Cancer. Clin Breast Cancer. 2016 Dec;16(6):437-443.
3. Al-Hilli Z, Choong G, Keeney MG, et al. Metaplastic breast cancer has a poor response to neoadjuvant systemic therapy. *Breast Cancer Res Treat*. 2019;176(3):709–716.
4. Balasubramanian A, Iyer P, Ranganathan R, Murhekar K, et al. Metaplastic carcinoma of the breast: real-world outcome from a tertiary cancer centre in India. Ecancermedicalscience. 2022 Jul 14;16:1429.
5. Haque W, Verma V, Schwartz MR, et al. Neoadjuvant Chemotherapy for Metaplastic Breast Cancer: Response Rates, Management, and Outcomes. Clin Breast Cancer. 2022 Jul;22(5):e691-e699.
6. Yam C, Abuhadra N, Sun R, et al. Molecular Characterization and Prospective Evaluation of Pathologic Response and Outcomes with Neoadjuvant Therapy in Metaplastic Triple-Negative Breast Cancer. Clin Cancer Res. 2022 Jul 1;28(13):2878-2889.



Neoadjuvant Systemic Chemotherapy (NACT) Predictive Factors for pCR II

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Gene expression profiles (gene signatures) (Mammaprint®(+ Blueprint®), Endopredict® Oncotype DX®, Prosigna®, PAM50®, Breast Cancer Index^{SM})	↑	2b	B	+/-
▪ HER2DX (27 genes, response to trastuzumab/pertuzumab	↑	2b	B	+/-
▪ Ki-67	↑	2b	B	+
▪ Tumor infiltrating lymphocytes**	↑	2a	B	+
▪ *PIK3CA* mutation (for HER2-positive BC)	↑	2a	B	+/-
▪ *gBRCA*-mutation (for the effect of chemotherapy)	↑	2b	B	+
▪ *gBRCA*-mutation (for the effect of platinum)	↔	2b	B	+/-

* High (↑) or very high (↑↑) probabililty of pCR, low (↓) or very low (↓↓) probabililty of pCR

** Defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up > 50% of stroma area)

TIL

1. Denkert, C., Loibl, S., Noske, A., et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. 2010. J. Clin. Oncol. 28, 105–113. doi:10.1200/JCO.2009.23.7370.
2. Denkert C, von Minckwitz G, Brase JC, et al. Tumor-Infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy With or Without Carboplatin in Human Epidermal Growth Factor Receptor 2-Positive and Triple-Negative Primary Breast Cancers. J Clin Oncol. 2014 Dec 22. pii: JCO.2014.58.1967.
3. Ibrahim EM, Al-Foheidi ME, Al-Mansour MM, et al. The prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancer: a meta-analysis. Breast Cancer Res Treat. 2014 Dec;148(3):467-76
4. Loi S, Michiels S, Salgado R, et al. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. Ann Oncol. 2014 Aug;25(8):1544-50. Doi
5. Mao Y, Qu Q, Zhang Y, et al. The Value of Tumor Infiltrating Lymphocytes (TILs) for Predicting Response to Neoadjuvant Chemotherapy in Breast Cancer: A Systematic Review and Meta-Analysis. PLoS One. 2014 Dec 12;9(12)
6. Tung NM, Winer EP. Tumor-Infiltrating Lymphocytes and Response to Platinum in Triple-Negative Breast Cancer. J Clin Oncol. 2015 Jan 5. pii: JCO.2014.59.6031.

7. Denkert C, von Minckwitz G, Darb—Esfahani S et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvanttherapy. Lancet Oncol 2018;19(1):40-50.

PIK3CA

1. Loibl S, von Minckwitz G, Schneeweiss A, et al. PIK3CA mutations are associated with lower rates of pathologic complete response to anti-human epidermal growth factor receptor 2 (her2) therapy in primary HER2-overexpressing breast cancer. J Clin Oncol. 2014 Oct
2. Nuciforo PG, Aura C, Holmes E, et al: Benefit to neoadjuvant anti–Human Epidermal Growth Factor Receptor 2 (HER2)-targeted therapies in HER2-positive primary breast cancer is independent of Phosphatase and tensin homolog deleted from chromosome 10 (PTEN) status. Ann Oncol. 2015 Jul;26(7):1494-500.
3. Pogue-Geile KL, Song N, Jeong JH, et al: Intrinsic Subtypes, PIK3CA Mutation, and the Degree of Benefit From Adjuvant Trastuzumab in the NSABP B-31 Trial. Clin Oncol. 2015 Jan 5. pii: JCO.2014.56.2439
4. Sueta A, Yamamoto Y, Yamamoto-Ibusuki M, et al. An Integrative Analysis of PIK3CA Mutation, PTEN, and INPP4B Expression in Terms of Trastuzumab Efficacy in HER2-Positive Breast Cancer. PLoS One. 2014 Dec 26;9(12):e116054.
5. Loibl S, Majewski I, Guarneri V, et al. PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol. 2016 Aug;27(8):1519-25.
6. Loibl S, Majewski I, Guarneri V, et al. PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol. 2019; 30(7):1180.
7. Fan H, Li C, Xiang Q, et al. PIK3CA mutations and their response to neoadjuvant treatment in early breast cancer: A systematic review and meta-analysis. Thorac Cancer. 2018 May;9(5):571-579.
8. Zardavas D, Te Marvelde L, Milne RL, et al. Tumor PIK3CA Genotype and Prognosis in Early-Stage Breast Cancer: A Pooled Analysis of Individual Patient Data. J Clin Oncol. 2018 Apr 1;36(10):981-990.

gBRCA bei TNBC

1. Loibl S, Weber KE, Timms KM et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol. 2018 Dec 1;29(12):2341-2347.

PAM50 neoadjuvant:

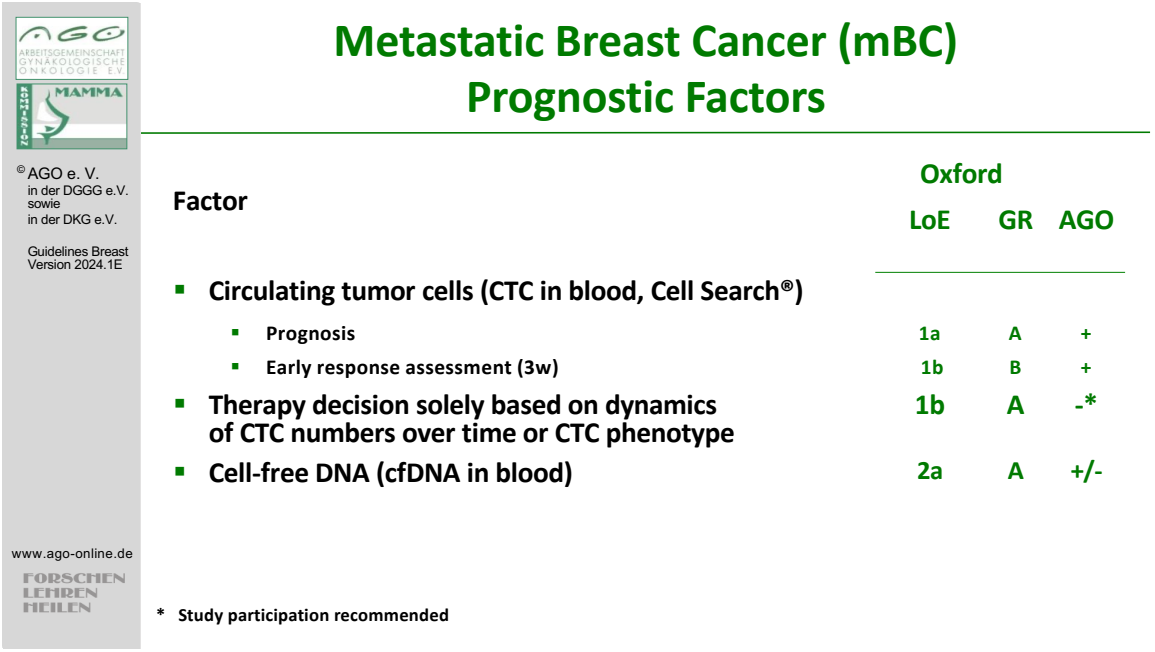
1. Ohara AM, Naoi Y, Shimazu K, et al. PAM50 for prediction of response to neoadjuvant chemotherapy for ER-positive breast cancer. Breast Cancer Res Treat. 2019 Feb;173(3):533-543.
2. Pascual T, Fernandez-Martinez A, Tanioka M, et al. Independent Validation of the PAM50-Based Chemo-Endocrine Score (CES) in Hormone Receptor-Positive HER2-Positive Breast Cancer Treated with Neoadjuvant Anti-HER2-Based Therapy. Clin Cancer Res. 2021 Jun 1;27(11):3116-3125.
3. Díaz-Redondo T, Lavado-Valenzuela R, Jimenez B, et al. Different Pathological Complete Response Rates According to PAM50 Subtype in HER2+ Breast Cancer Patients Treated With NeoadjuvantPertuzumab/Trastuzumab vs. Trastuzumab Plus Standard Chemotherapy: An Analysis of Real-World Data. Front Oncol. 2019 Nov 5;9:1178.
4. Gluz O, Kolberg-Liedtke C, Prat A, et al. Efficacy of deescalated chemotherapy according to PAM50 subtypes, immune and proliferation genes in triple-negative early breast cancer: Primary translational analysis of the WSG-ADAPT-TN trial. Int J Cancer. 2020 Jan 1;146(1):262-271.

Blueprint:

1. Beitsch P, Whitworth P, Baron P, et al. Pertuzumab/Trastuzumab/CT Versus Trastuzumab/CT Therapy for HER2+ Breast Cancer: Results from the Prospective Neoadjuvant Breast Registry Symphony Trial (NBRST). Ann Surg Oncol. 2017 Sep;24(9):2539-2546.
2. Whitworth P, Stork-Sloots L, de Snoo FA, et al. Chemosensitivity predicted by BluePrint 80-gene functional subtype and MammaPrint in the Prospective Neoadjuvant Breast Registry Symphony Trial (NBRST). Ann Surg Oncol. 2014 Oct;21(10):3261-7.
3. Whitworth P, Beitsch PD, Pellicane JV et al. ; NBRST Investigators Group.Age-Independent Preoperative Chemosensitivity and 5-Year Outcome Determined by Combined 70- and 80-Gene Signature in a Prospective Trial in Early-Stage Breast Cancer. Ann Surg Oncol. 2022 Apr 4;29(7):4141-52.
4. Pellicane JV, Beitsch PD, Rock DT, et al. ; NBRST Investigators Group.Combined 70- and 80-gene signatures identify tumors with genomically luminal biology responsive to neoadjuvant endocrine therapy and are prognostic of 5-year outcome in early-

stage breast cancer. Surg Oncol. 2022 Dec;45:101885.
5. Liefaard MC, van der Voort A, van Ramshorst MS, et al. BluePrint molecular subtypes predict response to neoadjuvant pertuzumab in HER2-positive breast cancer. Breast Cancer Res. 2023 Jun 19;25(1):71.
6. Göker E, Hendriks MP, van Tilburg M et al.; of the NBREaST II Investigators Group. Treatment response and 5-year distant metastasis-free survival outcome in breastcancer patients after the use of MammaPrint and BluePrint to guide preoperative systemic treatment decisions. Eur J Cancer. 2022 May;167:92-102.

HER2DX:
1. Guarneri V, Bras-Maristany F, Dieci MV, et al. HER2DX genomic test in HER2-positive/hormone receptor-positive breast cancertreated with neoadjuvant trastuzumab and pertuzumab: A correlative analysis from the PerELISA trial. EBioMedicine. 2022 Nov;85:104320.
2. Prat A, Guarneri V, Paré L, et al. A multivariable prognostic score to guide systemic therapy in early-stage HER2-positive breast cancer: a retrospective study with an external evaluation. Lancet Oncol. 2020 Nov;21(11):1455-1464.
3. Villacampa G, Tung NM, Pernas S, et al. Association of HER2DX with pathological complete response and survival outcomes in HER2-positive breast cancer. Ann Oncol. 2023 Sep;34(9):783-795.



Metastatic Breast Cancer (mBC)
Prognostic Factors

Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Circulating tumor cells (CTC in blood, Cell Search®)			
▪ Prognosis	1a	A	+
▪ Early response assessment (3w)	1b	B	+
▪ Therapy decision solely based on dynamics of CTC numbers over time or CTC phenotype	1b	A	-*
▪ Cell-free DNA (cfDNA in blood)	2a	A	+/-

* Study participation recommended

CTC

1. Bidard FC, Peeters DJ, Fehm T, et al. 2014. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. Lancet Oncol. 2014 Apr;15(4):406-14.
2. Cristofanilli, M., Budd, G.T., Ellis, M.J., et al. 2004. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N. Engl. J. Med. 351, 781–791. doi:10.1056/NEJMoa040766.
3. Cristofanilli, M., Hayes, D.F., Budd, G.T.et al 2005. Circulating tumor cells: a novel prognostic factor for newly diagnosed metastatic breast cancer. J. Clin. Oncol. 23, 1420–1430. doi:10.1200/JCO.2005.08.140.
4. Giuliano, M., Giordano, A., Jackson, S., et al. 2011. Circulating tumor cells as prognostic and predictive markers in metastatic breast cancer patients receiving first-line systemic treatment. Breast Cancer Res. 13, R67. doi:10.1186/bcr2907.
5. Smerage JB, Barlow WE, Hortobagyi GN, et al. 2014. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. J Clin Oncol. 2014 Nov, 1;32(31):3483-9
6. Sparano J, O'Neill A, Alpaugh K, et al. Association of Circulating Tumor Cells With Late Recurrence of Estrogen Receptor-Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. 2018 Dec 1;4(12):1700-1706.
7. Jauch SF, Riethdorf S, Sprick MR, et al. Sustained prognostic impact of circulating tumor cell status and kinetics upon further progression of metastatic breast cancer. Breast Cancer Res Treat. 2018 Oct 1.
8. Munoz-Arcos LS, Nicolò E, Serafini MS, et al.Latest advances in clinical studies of circulating tumor cells in early and

metastatic breast cancer. Int Rev Cell Mol Biol. 2023;381:1-21.

Cell-free DNA/ctDNA:

1. Cheng J, Holland-Letz T, Wallwiener M, et al. Circulating free DNA integrity and concentration as independent prognostic markers in metastatic breast cancer. Breast Cancer Res Treat. 2018 May;169(1):69-82.
2. Yang J, Cheng L, Zhang J, et al. Predictive value of circulating cell-free DNA in the survival of breast cancer patients: A systemic review and meta-analysis. Medicine (Baltimore). 2018 Jul 97(28):e11417.
3. Zill OA, Banks KC, Fairclough SR, et al. The Landscape of Actionable Genomic Alterations in Cell-Free Circulating Tumor DNA from 21,807 Advanced Cancer Patients. Clin Cancer Res. 2018 Aug 1;24(15):3528-3538.
4. Prat A, Brasó-Maristany F, Martínez-Sáez O, et al. Circulating tumor DNA reveals complex biological features with clinical relevance in metastatic breast cancer. Nat Commun. 2023 Mar 1;14(1):1157.
5. Agostinetto E, Nader-Marta G, Ignatiadis M Circulating tumor DNA in breast cancer: a biomarker for patient selection. Curr Opin Oncol. 2023 Sep 1;35(5):426-435.
6. Chiu J, Su F, Joshi M, Masuda N, et al. Potential value of ctDNA monitoring in metastatic HR + /HER2 - breast cancer: longitudinal ctDNA analysis in the phase Ib MONALEESASIA trial. BMC Med. 2023 Aug 15;21(1):306.

Treatment of Metastatic Breast Cancer
Markers for Indication

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

www.ago-online.de
FORSCHEN
LEHREN
HEILEN

Therapy	Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Endocrine therapy	ER / PR (prim. tumor, better: metastasis)	1a	A	++
	Response to prior therapy	2b	B	++
▪ Elacestrant	Autocrine receptor mutation (*ESR1*) (metastases, plasma)	1b	B	++
▪ Alpelisib	*PIK3CA* mutation (prim. tumor, metastases, plasma)	1b	A	++
▪ Capivasertib	*PIK3CA, AKT1, PTEN* alterations (primary tumor, metastases, plasma)	1b	A	+
▪ Trastuzumab Deruxtecan	HER2-low or HER2-positive	1b	A	++
▪ Chemotherapy	Response to prior therapy	1b	A	++
▪ Anti-HER2-therapy	HER2 (prim. tumor, better: metastasis)	1a	A	++
▪ Checkpoint-Inhibitors	PD-L1 positivity# (IC, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
	MSI/TMB	3	C	+
▪ PARP-Inhibitors	*gBRCA1/2*-mutation	1a	A	++
	sBRCA1/2/gPALB2	2b	B	+

Endocrine therapy

1. Campbell FC, Blamey RW, Elston CW, et al. Quantitative oestradiol receptor values in primary breast cancer and response of metastases to endocrine therapy. *Lancet*. 1981;2(8259):1317–1319.

Endocrine therapy - ESR1:

1. Dustin D, Gu G, Fuqua SAW (2019) ESR1 mutations in breast cancer. Cancer 125:3714-3728 doi: 10.1002/cncr.32345.
2. Fribbens C, Garcia Murillas I, Beaney M et al. (2018) Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA analysis in metastatic breast cancer. Ann Oncol.29:145-153. doi: 10.1093/annonc/mdx483
3. Fribbens C, O'Leary B, Kilburn L et al. (2016) Plasma ESR1 Mutations and the Treatment of Estrogen Receptor-Positive Advanced Breast Cancer. J Clin Oncol. 34:2961-8. doi: 10.1200/JCO.2016.67.3061
4. FC, Hardy-Bessard AC, Dalenc F, et al.; PADA-1 investigators.Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial.Lancet Oncol. 2022 Nov;23(11):1367-1377.
5. Berger F, Marce M, Delaloge S, et al.; PADA-1 investigators Randomised, open-label, multicentric phase III trial to evaluate the safety and efficacy of palbociclib in combination with endocrine therapy, guided by ESR1 mutation monitoring in oestrogen receptor-positive, HER2-negative metastatic breast cancer patients: study design of PADA-1. BMJ Open. 2022 Mar 3;12(3):e055821.

Alpelisib

1. André F, Ciruelos E, Rubovszky G et al. (2019) Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 380:1929-1940. doi: 10.1056/NEJMoa1813904

Capivasertib

1. Turner NC, Oliveira M, Howell Set al. (2022) Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: results from the Phase III CAPItello-291 trial. N Engl J Med 388(22):2058–2070. doi:10.1056/NEJMoa221413123
2. Hopcroft L, Wigmore EM, Williamson SC (2023) Combining the AKT inhibitor capivasertib and SERD fulvestrant is effective in palbociclib-resistant ER+ breast cancer preclinical models. NPJ Breast Cancer 9(1):64. doi:10.1038/s41523-023-00571-w

Chemotherapy

1. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. *Ann Oncol*. 2018;29(8):1634–1657.

Anti-HER2-Therapy

1. Seidman AD, Fornier MN, Esteva FJ, et al. Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol*. 2001;19(10):2587–2595.

Checkpoint-Inhibitors

1. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018 Nov 29;379(22):2108-2121.
2. Cortes J, Cescon DW, Rugo HS et al.: KEYNOTE-355 Investigators. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020 Dec 5;396(10265):1817-1828.
3. Hattori M, Masuda N, Takano T, et al. Pembrolizumab plus chemotherapy in Japanese patients with triple-negative breast cancer: Results from KEYNOTE-355. Cancer Med. 2023 May;12(9):10280-10293.

PARP-Inhibitors

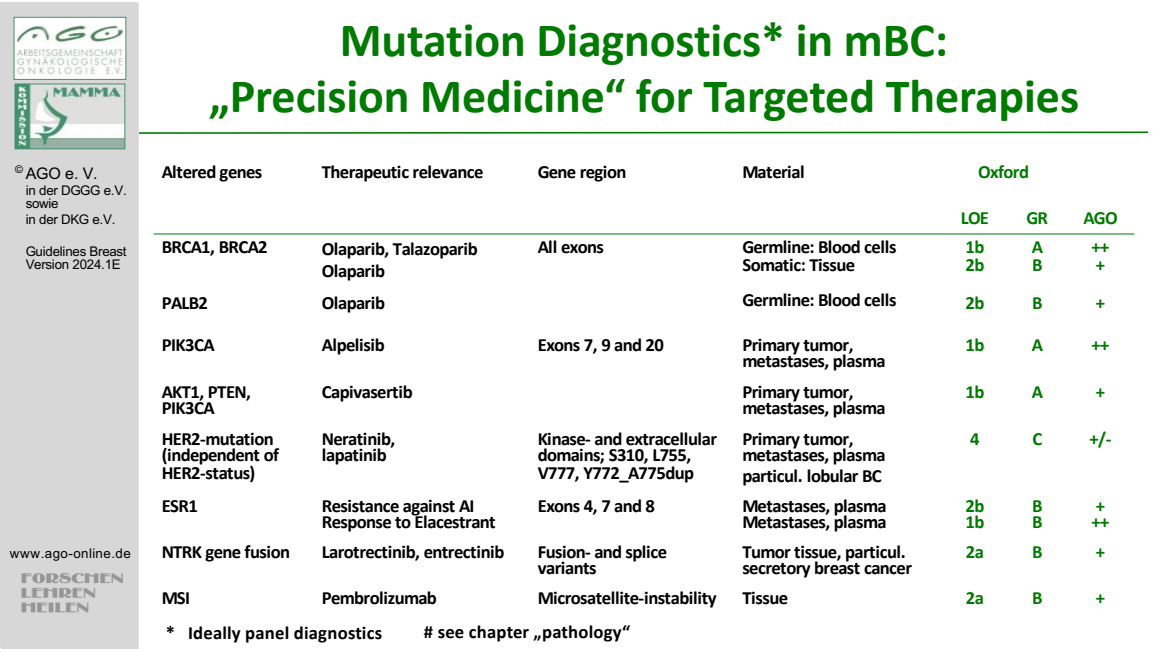
1. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017;377(6):523-533.
2. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018;379(8):753-763.
3. Tung NM, Robson ME, Ventz S, TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. J Clin Oncol. 2020 Dec 20;38(36):4274-4282.

Bone modifying drugs

1. Aktas B, Kasimir-Bauer S, Lehmann N, et al.: Validity of bone marker measurements for monitoring response to bisphosphonate therapy with zoledronic acid in metastatic breast cancer. *Oncol Rep*. 2013;30(1):441–447.
2. Loftus LS, Edwards-Bennett S, Sokol GH. Systemic therapy for bone metastases. *Cancer Control*. 2012;19(2):145–153.
3. Coleman R, Gnant M, Morgan G, Clezardin P. Effects of bone-targeted agents on cancer progression and mortality. *J Natl Cancer Inst*. 2012;104(14):1059–1067.

CTC monitoring (any therapy)

1. Bidard FC, Peeters DJ, Fehm T, et al. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. Lancet Oncol. 2014;15:406-14.
2. Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. J Clin Oncol. 2014;32(31):3483-9.



Mutation Diagnostics* in mBC: „Precision Medicine“ for Targeted Therapies

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

www.ago-online.de
FORSCHEN
LEHREN
HEILEN

Altered genes	Therapeutic relevance	Gene region	Material	Oxford		
				LOE	GR	AGO
BRCA1, BRCA2	Olaparib, Talazoparib Olaparib	All exons	Germline: Blood cells Somatic: Tissue	1b 2b	A B	++ +
PALB2	Olaparib		Germline: Blood cells	2b	B	+
PIK3CA	Alpelisib	Exons 7, 9 and 20	Primary tumor, metastases, plasma	1b	A	++
AKT1, PTEN, PIK3CA	Capivasertib		Primary tumor, metastases, plasma	1b	A	+
HER2-mutation (independent of HER2-status)	Neratinib, lapatinib	Kinase- and extracellular domains; S310, L755, V777, Y772_A775dup	Primary tumor, metastases, plasma particul. lobular BC	4	C	+/-
ESR1	Resistance against AI Response to Elacestrant	Exons 4, 7 and 8	Metastases, plasma Metastases, plasma	2b 1b	B B	+ ++
NTRK gene fusion	Larotrectinib, entrectinib	Fusion- and splice variants	Tumor tissue, particul. secretory breast cancer	2a	B	+
MSI	Pembrolizumab	Microsatellite-instability	Tissue	2a	B	+

* Ideally panel diagnostics # see chapter „pathology“

BRCA 1/2:

1. Robson M, Im SA, Senkus E et al. (2017) Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 377:523-533. doi: 10.1056/NEJMoa1706450
2. Kaufman B, Shapira-Frommer R, Schmutzler RK et al. (2015) Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015 Jan 20;33(3):244-50. doi: 10.1200/JCO.2014.56.2728.
3. Tung NM, Robson ME, Ventz S, et al. TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. J Clin Oncol. 2020 Dec 20;38(36):4274-4282.
4. Davies H, Glodzik D, Morganella S, et al. HRDetect is a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures. *Nat Med*. 2017;83:1301. doi:10.1038/nm.4292.
5. Gross E, van Tinteren H, Li Z, et al. Identification of BRCA1-like triple-negative breast cancers by quantitative multiplex-ligation-dependent probe amplification (MLPA) analysis of BRCA1-associated chromosomal regions: a validation study. *BMC Cancer*. 2016;16(1):811. doi:10.1186/s12885-016-2848-2.
6. Telli ML, Timms KM, Reid J, et al. Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer. *Clin Cancer Res*. 2016;22(15):3764-3773. doi:10.1158/1078-0432.CCR-15-2477.

7. Petrillo M, Nero C, Amadio G, Gallo D, Fagotti A, Scambia G. Targeting the hallmarks of ovarian cancer: The big picture. *Gynecologic Oncology*. 2016;142(1):176-183. doi:10.1016/j.ygyno.2016.03.037.
8. Azzollini J, Scuvera G, Bruno E, et al. Mutation detection rates associated with specific selection criteria for BRCA1/2 testing in 1854 high-risk families: A monocentric Italian study. *Eur J Intern Med*. 2016;32:65-71. doi:10.1016/j.ejim.2016.03.010.
9. De Picciotto N, Cacheux W, Roth A, Chappuis PO, Labidi-Galy SI. Ovarian cancer: Status of homologous recombination pathway as a predictor of drug response. *Critical Reviews in Oncology/Hematology*. 2016;101:50-59. doi:10.1016/j.critrevonc.2016.02.014.
10. Lord CJ, Ashworth A. BRCAness revisited. *Nat Rev Cancer*. 2016;16(2):110-120. doi:10.1038/nrc.2015.21.

PIK3CA:

1. Andre F, Ciruelos E, Rubovszky G, Campone M et al. (2019) Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 380:1929-1940. doi: 10.1056/NEJMoa1813904
2. Luen SJ, Asher R, Lee CK, et al. Association of Somatic Driver Alterations With Prognosis in Postmenopausal, Hormone Receptor-Positive, HER2-Negative Early Breast Cancer: A Secondary Analysis of the BIG 1-98 Randomized Clinical Trial. *JAMA Oncol*. 2018;4(10):1335-1343. doi:10.1001/jamaoncol.2018.1778.
3. Stearns V, Park BH. PIK3CA Mutations in Hormone Receptor-Positive Breast Cancers: PIKing Biomarkers to Inform Adjuvant Endocrine Therapy Decisions. *JAMA Oncol*. 2018;4(10):1330-1332. doi:10.1001/jamaoncol.2018.1766.
4. Lasota J, Felisiak-Golabek A, Wasąg B, et al. Frequency and clinicopathologic profile of PIK3CA mutant GISTs: molecular genetic study of 529 cases. *Mod Pathol*. 2016;29(3):275-282. doi:10.1038/modpathol.2015.160.
5. Wilson TR, Yu J, Lu X, et al. The molecular landscape of high-risk early breast cancer: comprehensive biomarker analysis of a phase III adjuvant population. *npj Breast Cancer*. 2016;2(1):16022. doi:10.1038/npjbcancer.2016.22.
6. Bosch A, Li Z, Bergamaschi A, et al. PI3K inhibition results in enhanced estrogen receptor function and dependence in hormone receptor-positive breast cancer. *Sci Transl Med*. 2015;7(283):283ra51-283ra51. doi:10.1126/scitranslmed.aaa4442.
7. Papaxoinis G, Kotoula V, Alexopoulou Z, et al. Significance of PIK3CA Mutations in Patients with Early Breast Cancer Treated with Adjuvant Chemotherapy: A Hellenic Cooperative Oncology Group (HeCOG) Study. *PLoS ONE*. 2015;10(10):e0140293. doi:10.1371/journal.pone.0140293.

8. Baselga J, Cortés J, Im S-A, et al. Biomarker analyses in CLEOPATRA: a phase III, placebo-controlled study of pertuzumab in human epidermal growth factor receptor 2-positive, first-line metastatic breast cancer. *J Clin Oncol*. 2014;32(33):3753-3761. doi:10.1200/JCO.2013.54.5384.
9. Henry NL, Schott AF, Hayes DF. Assessment of PIK3CA mutations in human epidermal growth factor receptor 2-positive breast cancer: clinical validity but not utility. *J Clin Oncol*. 2014;32(29):3207-3209. doi:10.1200/JCO.2014.57.6132.
10. André F, Bachelot T, Commo F, et al. Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER). *Lancet Oncol*. 2014;15(3):267-274. doi:10.1016/S1470-2045(13)70611-9.
11. Tandon M, Chen Z, Pratap J. Runx2 activates PI3K/Akt signaling via mTORC2 regulation in invasive breast cancer cells. *Breast Cancer Res*. 2014;16(1):R16. doi:10.1186/bcr3611.
12. Lehmann BD, Bauer JA, Schafer JM, et al. PIK3CA mutations in androgen receptor-positive triple negative breast cancer confer sensitivity to the combination of PI3K and androgen receptor inhibitors. *Breast Cancer Res*. 2014;16(4):406. doi:10.1186/s13058-014-0406-x.
13. Cizkova M, Dujaric M-E, Lehmann-Che J, et al. Outcome impact of PIK3CA mutations in HER2-positive breast cancer patients treated with trastuzumab. *Br J Cancer*. 2013;108(9):1807-1809. doi:10.1038/bjc.2013.164.
14. Vinayak S, Carlson RW. mTOR inhibitors in the treatment of breast cancer. *Oncology (Williston Park, NY)*. 2013;27(1):1-13
15. Campone M, Im SA, Iwata H, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant for postmenopausal, hormone receptor-positive, human epidermal growth factor receptor 2-negative, advanced breast cancer: Overall survival results from BELLE-2. Eur J Cancer. 2018 Nov;103:147-154.
16. Dickler MN, Saura C, Richards DA, et al. Phase II Study of Taselisib (GDC-0032) in Combination with Fulvestrant in Patients with HER2-Negative, Hormone Receptor-Positive Advanced Breast Cancer. Clin Cancer Res. 2018 Sep 15;24(18):4380-4387.

AKT1/PTEN:

1. Turner NC, Oliveira M, Howell Set al. (2022) Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: results from the Phase III CAPItello-291 trial. N Engl J Med 388(22):2058–2070. doi:10.1056/NEJMoa221413123

2. Hopcroft L, Wigmore EM, Williamson SC (2023) Combining the AKT inhibitor capivasertib and SERD fulvestrant is effective in palbociclib-resistant ER+ breast cancer preclinical models. NPJ Breast Cancer 9(1):64. doi:10.1038/s41523-023-00571-w

HER2-Mutation:

1. Hyman DM, Piha-Paul SA, Won H, et al. (2018) HER kinase inhibition in patients with HER2- and HER3-mutant cancers. Nature 554:189-194. doi: 10.1038/nature25475.
2. Ma CX, Bose R, Gao F, et al. (2017) Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations in HER2 Nonamplified Metastatic Breast Cancer. Clin Cancer Res. 23:5687-5695. doi: 10.1158/1078-0432.CCR-17-0900.
3. Hanker AB, Brewer MR, Sheehan JH, et al. An Acquired HER2(T798I) Gatekeeper Mutation Induces Resistance to Neratinib in a Patient with HER2 Mutant-Driven Breast Cancer. Cancer Discov 2017;7: 575-85.
4. Xu X, De Angelis C, Burke KA, et al. HER2 Reactivation through Acquisition of the HER2 L755S Mutation as a Mechanism of Acquired Resistance to HER2-targeted Therapy in HER2(+) Breast Cancer. Clin Cancer Res 2017;23: 5123-34.
5. Petrelli F, Tomasello G, Barni S, et al.: Clinical and pathological characterization of HER2 mutations in human breast cancer: a systematic review of the literature. *Breast Cancer Res Treat*. 2017;166(2):339-349. doi:10.1007/s10549-017-4419-x.
6. Ross JS, Gay LM, Wang K, et al. Nonamplification ERBB2 genomic alterations in 5605 cases of recurrent and metastatic breast cancer: An emerging opportunity for anti-HER2 targeted therapies. *Cancer*. 2016;122(17):2654-2662. doi:10.1002/cncr.30102.
7. Bose R, Kavuri SM, Searleman AC, et al. Activating HER2 mutations in HER2 gene amplification negative breast cancer. *Cancer Discov*. 2013;3(2):224-237. doi:10.1158/2159-8290.CD-12-0349.
8. Weigelt B, Reis-Filho JS. Activating mutations in HER2: neu opportunities and neu challenges. *Cancer Discov*. 2013;3(2):145-147. doi:10.1158/2159-8290.CD-12-0585.
9. Herter-Sprie GS, Greulich H, Wong K-K. Activating Mutations in ERBB2 and Their Impact on Diagnostics and Treatment. *Front Oncol*. 2013;3:86. doi:10.3389/fonc.2013.00086.
10. Greulich H, Kaplan B, Mertins P, et al. Functional analysis of receptor tyrosine kinase mutations in lung cancer identifies oncogenic extracellular domain mutations of ERBB2. *Proc Natl Acad Sci U S A*. 2012;109(36):14476-14481. doi:10.1073/pnas.1203201109.
11. Zito CI, Riches D, Kolmakova J, Simons J, Egholm M, Stern DF. Direct resequencing of the complete ERBB2 coding sequence reveals an absence of activating mutations in ERBB2 amplified breast cancer. *Genes Chromosomes Cancer*. 2008;47(7):633-638.

doi:10.1002/gcc.20566.

12. Lee JW, Soung YH, Seo SH, et al. Somatic mutations of ERBB2 kinase domain in gastric, colorectal, and breast carcinomas. *Clin Cancer Res*. 2006;12(1):57-61. doi:10.1158/1078-0432.CCR-05-0976.

ESR1:

1. Bidard FC, Kaklamani VG, Neven P, et al. (2022) Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. J Clin Oncol. 2022 Oct 1;40(28):3246-3256. doi: 10.1200/JCO.22.00338. Epub 2022 May 18. PMID: 35584336; PMCID: PMC9553388.
2. Dustin D, Gu G, Fuqua SAW (2019) ESR1 mutations in breast cancer. Cancer 125:3714-3728 doi: 10.1002/cncr.32345.
3. Fribbens C, Garcia Murillas I, Beaney M et al. (2018) Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA analysis in metastatic breast cancer. Ann Oncol.29:145-153. doi: 10.1093/annonc/mdx483
4. Fribbens C, O'Leary B, Kilburn L et al. (2016) Plasma ESR1 Mutations and the Treatment of Estrogen Receptor-Positive Advanced Breast Cancer. J Clin Oncol. 34:2961-8. doi: 10.1200/JCO.2016.67.3061
5. Bidard FC, Hardy-Bessard AC, Dalenc F, et al.; PADA-1 investigators.Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial.Lancet Oncol. 2022 Nov;23(11):1367-1377.
6. Berger F, Marce M, Delaloge S, et al.; PADA-1 investigators Randomised, open-label, multicentric phase III trial to evaluate the safety and efficacy of palbociclib in combination with endocrine therapy, guided by ESR1 mutation monitoring in oestrogen receptor-positive, HER2-negative metastatic breast cancer patients: study design of PADA-1. BMJ Open. 2022 Mar 3;12(3):e055821.
7. Wong NZH, Yap DWT, Ong RJM, Zhao JJ, Chan YH, Tey JCS, Sundar R, Lim JSJ, Dawood SS. Efficacy of Oral SERDs in the treatment of ER+, HER2 - metastatic breast cancer, a stratified analysis of the ESR1 wild type and mutant subgroups. Ann Oncol. 2023 Oct 21:S0923-7534(23)04328-4. doi: 10.1016/j.annonc.2023.10.122.
8. Grote I, Poppe A, Lehmann U, Christgen M, Kreipe H, Bartels S. Frequency of genetic alterations differs in advanced breast cancer between metastatic sites. Genes Chromosomes Cancer. 2024 Jan;63(1):e23199. doi: 10.1002/gcc.23199.
9. D, Gu G, Fuqua SAW. ESR1 mutations in breast cancer. *Cancer*. 2019;125(21):3714-3728. doi:10.1002/cncr.32345.

10. Jeselsohn R, Bergholz JS, Pun M, et al. Allele-Specific Chromatin Recruitment and Therapeutic Vulnerabilities of ESR1 Activating Mutations. *Cancer Cell*. 2018;33(2):173-186.e175. doi:10.1016/j.ccell.2018.01.004.
11. Bartels S, Christgen M, Luft A, et al. Estrogen receptor (ESR1) mutation in bone metastases from breast cancer. *Mod Pathol*. 2018;31(1):56-61. doi:10.1038/modpathol.2017.95.
12. Toy W, Weir H, Razavi P, et al. Activating ESR1 Mutations Differentially Affect the Efficacy of ER Antagonists. *Cancer Discov*. 2017;7(3):277-287. doi:10.1158/2159-8290.CD-15-1523.
13. Chandarlapaty S, Chen D, He W, et al. Prevalence of ESR1 Mutations in Cell-Free DNA and Outcomes in Metastatic Breast Cancer: A Secondary Analysis of the BOLERO-2 Clinical Trial. *JAMA Oncol*. 2016;2(10):1310-1315. doi:10.1001/jamaoncol.2016.1279.
14. Jeselsohn R, Yelensky R, Buchwalter G, et al. Emergence of constitutively active estrogen receptor-α mutations in pretreated advanced estrogen receptor-positive breast cancer. *Clin Cancer Res*. 2014;20(7):1757-1767. doi:10.1158/1078-0432.CCR-13-2332.
15. Segal CV, Dowsett M. Estrogen receptor mutations in breast cancer--new focus on an old target. *Clin Cancer Res*. 2014;20(7):1724-1726. doi:10.1158/1078-0432.CCR-14-0067.
16. Giguère V. Estrogen receptor mutations in breast cancer-an anticipated "rediscovery?". *Mol Endocrinol*. 2014;28(4):427-428. doi:10.1210/me.2014-1071.
17. Fuqua SAW, Gu G, Rechoum Y. Estrogen receptor (ER) α mutations in breast cancer: hidden in plain sight. *Breast Cancer Res Treat*. 2014;144(1):11-19. doi:10.1007/s10549-014-2847-4.

NTRK:

1. Maund SL, Sokol ES, Ang Houle A, et al. NTRK gene fusions are detected in both secretory and non-secretory breastcancers. Pathol Int. 2022 Mar;72(3):187-192.
2. Stenzinger A, van Tilburg CM, Tabatabai G, et al. [Diagnosis and therapy of tumors with NTRK gene fusion].Pathologe. 2021 Feb;42(1):103-115.
3. Remoue A, Conan-Charlet V, Bourhis A, et al. Non-secretory breast carcinomas lack NTRK rearrangements and TRK protein expression. *Pathol Int*. 2019;69(2):94-96. doi:10.1111/pin.12766.

4. Ricciuti B, Genova C, Crinò L, Libra M, Leonardi GC. Antitumor activity of larotrectinib in tumors harboring NTRK gene fusions: a short review on the current evidence. *Onco Targets Ther*. 2019;12:3171-3179. doi:10.2147/OTT.S177051.
5. Condorelli R, Mosele F, Verret B, et al. Genomic alterations in breast cancer: level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol*. 2019;30(3):365-373. doi:10.1093/annonc/mdz036.
6. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol*. 2018;15(12):731-747. doi:10.1038/s41571-018-0113-0.
7. Pfarr N, Kirchner M, Lehmann U, et al. Testing NTRK testing: Wet-lab and in silico comparison of RNA-based targeted sequencing assays. *Genes Chromosomes Cancer*. 2020;59(3):178-188. doi:10.1002/gcc.22819.

MSI:

1. FDA approval across tumor entities (23.5.17): see full prescribing information for pembrolizumab

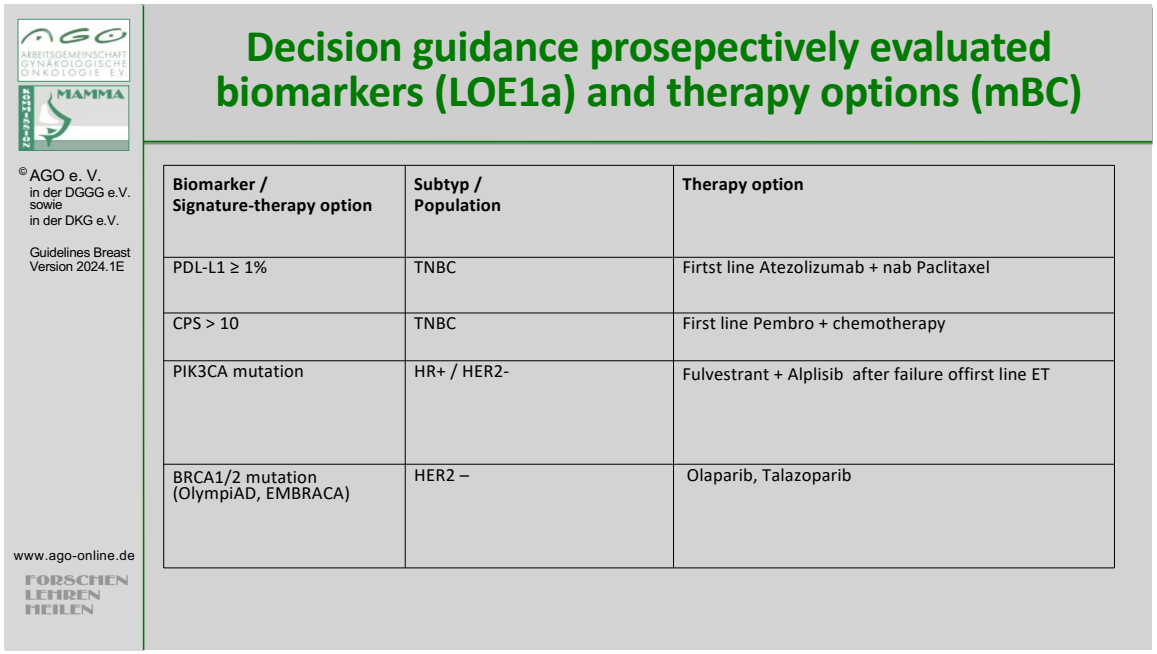
PALB2:

1. Antoniou AC, Casadei S, Heikkinen T et al. Breast Cancer Risk in families with mutations in PALB2. N Engl J Med 2014;371(6):497-506.
2. Breast Cancer Association Consortium, Dolling L, Carvahlo S, Allen J et al. Breast Cancer Risk Genes - Association Analysis in more than 113,000 women. N Engl J Med 2021;384(5):428-439.
3. Couch FJ, Shimelis H, Hu C et al. Associations between cancer predisposition testing panel genes and breast cancer. JAMA Oncol 2017;3(9):1190-1196.
4. Tung NM, Robson ME, Ventz S, TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. J Clin Oncol. 2020 Dec 20;38(36):4274-4282.

1. Cortes-Ciriano I, Lee S, Park W-Y, Kim TM, Park PJ. A molecular portrait of microsatellite instability across multiple cancers. *Nature Communications*. 2017;8:15180. doi:10.1038/ncomms15180.
2. Win AK, Lindor NM, Jenkins MA. Risk of breast cancer in Lynch syndrome: a systematic review. *Breast Cancer Res*. 2013;15(2):R27.

doi:10.1186/bcr3405.

3. Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. *J Clin Oncol*. 2012;30(35):4409-4415. doi:10.1200/JCO.2012.43.2278.



Decision guidance prosepectively evaluated biomarkers (LOE1a) and therapy options (mBC)

Biomarker / Signature-therapy option	Subtyp / Population	Therapy option
PDL-L1 ≥ 1%	TNBC	Firtst line Atezolizumab + nab Paclitaxel
CPS > 10	TNBC	First line Pembro + chemotherapy
PIK3CA mutation	HR+ / HER2-	Fulvestrant + Alplisib after failure offirst line ET
BRCA1/2 mutation (OlympiAD, EMBRACA)	HER2 –	Olaparib, Talazoparib

Head to head comparisons

1. Varga Z, Sinn P, Seidman AD. Summary of head-to-head comparisons of patient risk classifications by the 21-gene Recurrence Score® (RS) assay and other genomic assays for early breast cancer. Int J Cancer. 2019 Aug 15;145(4):882-893.
2. Berchtold E, Vetter M, Gündert M et al. Comparison of six breast cancer classifiers using qPCR. Bioinformatics. 2019 Sep 15;35(18):3412-3420.
3. Sestak I, Buus R, Cuzick J, et al. Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. 2018 Apr 1;4(4):545-553.

Endopredict

1. Blank PR, Filipits M, Dubsky P, et al.: Cost-effectiveness analysis of prognostic gene expression signature-based stratification of early breast cancer patients. Pharmacoeconomics. 2015 Feb;33(2):179-90.
2. Buus R, Sestak I, Kronenwett R, et al.: Comparison of EndoPredict and EPclin with Oncotype DX Recurrence Score for Prediction of Risk of Distant Recurrence after endocrine therapy J Natl Cancer Inst. 2016 Jul 10;108(11).
3. Denkert, C., Kronenwett, R., Schlake, W. et al. 2012. Decentral gene expression analysis for ER+/Her2- breast cancer: results of a proficiency testing program for the EndoPredict assay. Virchows Arch. 460, 251–259. doi:10.1007/s00428-012-1204-4.
4. Dubsky, P., Filipits, M., Jakesz, R. et al. 2012. EndoPredict improves the prognostic classification derived from common clinical

guidelines in ER-positive, HER2-negative early breast cancer. Ann Oncol. 2013 Mar;24(3):640-7.
5. Dubsky P, Brase JC, Jakesz R et al. Austrian Breast and Colorectal Cancer Study Group (ABCSG). T al.: The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. Br J Cancer. 2013 Dec 10;109(12):2959-64
6. Filipits, M., Rudas, M., Jakesz, R. et al. 2011. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin. Cancer Res. 17, 6012–6020.
7. Kronenwett, R., Bohmann, K., Prinzler, J. et al. 2012. Decentral gene expression analysis: analytical validation of the Endopredict genomic multianalyte breast cancer prognosis test. BMC Cancer 12, 456.
8. Martin M, Brase JC, Calvo L, et al. Clinical validation of the EndoPredict test in node-positive, chemotherapy-treated ER+/HER2- breast cancer patients: results from the GEICAM 9906 trial. Breast Cancer Res 2014; 16(2): R38.
9. Sinn P, Aulmann S, Wirtz R, et al. Multigene Assays for Classification, Prognosis, and Prediction in Breast Cancer: a Critical Review on the Background and Clinical Utility. A. Geburtshilfe Frauenheilkd. 2013 Sep;73(9):932-940

MammaPrint

1. Buyse, M., Loi, S., van't Veer, L., et al. 2006. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J. Natl. Cancer Inst. 98, 1183–1192.
2. Drukker CA, Elias SG, Nijenhuis MV, et al. Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. Breast Cancer Res Treat. 2014 Dec;148(3):599-613.
3. Exner R, Bago-Horvath Z, Bartsch R et al. The multigene signature MammaPrint impacts on multidisciplinary team decisions in ER+, HER2- early breast cancer. Br J Cancer. 2014 Aug 26;111(5):837-42.
4. Jonsdottir K, Assmus J, Slewa A, et al. Prognostic value of gene signatures and proliferation in lymph-node-negative breast cancer. PLoS One. 2014 Mar 5;9(3):e90642.
5. Mook, S., Schmidt, M.K., Weigelt, B., et al. 2010. The 70-gene prognosis signature predicts early metastasis in breast cancer patients between 55 and 70 years of age. Ann. Oncol. 21, 717–722.
6. Mook, S., Schmidt, M.K., Rutgers, E.J., et al. 2009a. Calibration and discriminatory accuracy of prognosis calculation for breast cancer with the online Adjuvant! program: a hospital-based retrospective cohort study. Lancet Oncol. 10, 1070–1076.
7. Mook, S., Schmidt, M.K., Viale, G. et al. 2009b. The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1-3 positive lymph nodes in an independent validation study. Breast Cancer Res. Treat. 116, 295–302.
8. van de Vijver, M.J., He, Y.D., van't Veer, L.J., et al. 2002. A gene-expression signature as a predictor of survival in breast cancer. N. Engl. J. Med. 347, 1999–2009. doi:10.1056/NEJMoa021967.

9. van Veer, L.J. 't, Dai, H., van de Vijver, M.J., et al. 2002. Gene expression profiling predicts clinical outcome of breast cancer. Nature 415, 530–536. doi:10.1038/415530a.
10. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med. 2016 Aug 25;375(8):717-29.
11. Cardoso F, van 't Veer L, Poncet C, et al. MINDACT: Long-term results of the large prospective trial testing the 70-gene signature MammaPrint as guidance for adjuvant chemotherapy in breast cancer patients. ASCO 2020, #506

Oncotype DX

1. Albain, K.S., Barlow, W.E., Shak, S. et al. 2010. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol. 11, 55–65. Cronin, M., Sangli, C., Liu, M.-L., et al. 2007. Analytical validation of the Oncotype DX genomic diagnostic test for recurrence prognosis and therapeutic response prediction in node-negative, estrogen receptor-positive breast cancer. Clin. Chem. 53, 1084–1091.
2. Dowsett, M., Cuzick, J., Wale, C. et al. 2010. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. J. Clin. Oncol. 28, 1829–1834.
3. Gluz O, Nitz UA, Christgen M, et al.: West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment. J Clin Oncol. 2016 Jul 10;34(20):2341-9.
4. Khan SS, Karn T, Symmans WF, et al. Genomic predictor of residual risk of recurrence after adjuvant chemotherapy and endocrine therapy in high risk estrogen receptor-positive breast cancers. Breast Cancer Res Treat. 2015 Feb 5.
5. Mamounas, E.P., Tang, G., Fisher, B., et al. 2010. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. J. Clin. Oncol. 28, 1677–1683.
6. Paik, S., Shak, S., Tang, G. et al. 2004. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N. Engl. J. Med. 351, 2817–2826. doi:10.1056/NEJMoa041588.
7. Paik, S., Tang, G., Shak, S., et al. 2006. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J. Clin. Oncol. 24, 3726–3734.

8. Sparano JA, Gray RJ, Makower DF, et al: Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med 2015, 373(21):2005-2014.
9. Tang, G., Cuzick, J., Costantino, J.P., et al. 2011. Risk of recurrence and chemotherapy benefit for patients with node-negative, estrogen receptor-positive breast cancer: recurrence score alone and integrated with pathologic and clinical factors. J. Clin. Oncol. 29, 4365–4372.
10. Zhao X, Rødland EA, Sørlie T, et al. Systematic assessment of prognostic gene signatures for breast cancer shows distinct influence of time and ER status. BMC Cancer. 2014 Mar 19;14:211.
11. Geyer CE Jr, Tang G, Mamounas EP, et al. 21-Gene assay as predictor of chemotherapy benefit in HER2-negative breast cancer. NPJ Breast Cancer. 2018 Nov 14;4:37.
12. Penault-Llorca F, Filleron T, Asselain B, et al. The 21-gene Recurrence Score® assay predicts distant recurrence in lymph node-positive, hormone receptor-positive, breast cancer patients treated with adjuvant sequential epirubicin- and docetaxel-based or epirubicin-based chemotherapy (PACS-01 trial). BMC Cancer. 2018 May 4;18(1):526.
13. Sparano JA, Gray R, Oktay MH, et al. A metastasis biomarker (MetaSite Breast™ Score) is associated with distant recurrence in hormone receptor-positive, HER2-negative early-stage breast cancer. NPJ Breast Cancer. 2017 Nov 8;3:42.
14. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018 Jul 12;379(2):111-121.
15. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. Breast Cancer Res Treat. 2017 Oct;165(3):573-583.
16. Harbeck N, Gluz O, Kuemmel S, et al. Endocrine therapy alone in patients with intermediate or high-risk luminal early breast cancer (0-3 lymph nodes), Recurrence Score <26 and Ki67 response after preoperative endocrine therapy: Primary outcome results from the WSG-ADAPT HR+/HER2- trial. SABCS 2020, GS4-04.
17. Kalinsky K, Barlow WE, Meric-Bernstam F, et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) < 25: SWOG S1007 (RxPonder). SABCS 2020, GS3-00.

Prosigna (ROR / PAM50)

1. Chia, S.K., Bramwell, V.H., Tu, Det al. 2012. A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. Clin. Cancer Res. 18, 4465–4472.

2. Gnant M, Filipits M, Greil R, et al. Austrian Breast and Colorectal Cancer Study Group. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. Ann Oncol. 2014 Feb;25(2):339-45
3. Liu S, Chapman JA, Burnell MJ, et al. Prognostic and predictive investigation of PAM50 intrinsic subtypes in the NCIC CTG MA.21 phase III chemotherapy trial. Breast Cancer Res Treat. 2015 Jan;149(2):439-48.
4. Nielsen, T.O., Parker, J.S., Leung, S., et al. 2010. A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer. Clin. Cancer Res. 16, 5222–5232.
5. Parker, J.S., Mullins, M., Cheang, M.C.U., et al. 2009. Supervised risk predictor of breast cancer based on intrinsic subtypes. J. Clin. Oncol. 27, 1160–1167.
6. Prat, A., Cheang, M.C.U., Martín, M., et al. 2012b. Prognostic Significance of Progesterone Receptor-Positive Tumor Cells Within Immunohistochemically Defined Luminal A Breast Cancer. J. Clin. Oncol.
7. Prat, A., Parker, J.S., Fan, C., et al. 2012a. Concordance among gene expression-based predictors for ER-positive breast cancer treated with adjuvant tamoxifen. Ann. Oncol. 23, 2866–2873.
8. Perou, C.M., Sørlie, T., Eisen, M.B. et al. 2000. Molecular portraits of human breast tumours. Nature 406, 747–752.
9. Pogue-Geile KL, Song N, Jeong JH, et al. Intrinsic Subtypes, PIK3CA Mutation, and the Degree of Benefit From Adjuvant Trastuzumab in the NSABP B-31 Trial. J Clin Oncol. 2015 Jan 5.
10. Sestak I, Cuzick J, Dowsett M. et al.. Prediction of Late Distant Recurrence After 5 Years of Endocrine Treatment: A Combined Analysis of Patients From the Austrian Breast and Colorectal Cancer Study Group 8 and Arimidex, Tamoxifen Alone or in Combination Randomized Trials Using the PAM50 Risk of Recurrence Score. J Clin Oncol. 2014 Oct 20. pii: JCO.2014.55.6894
11. Jensen MB, Lænkholm AV, Nielsen TO, et al. The Prosigna gene expression assay and responsiveness to adjuvant cyclophosphamide-based chemotherapy in premenopausal high-risk patients with breast cancer.Breast Cancer Res. 2018 Jul 27;20(1):79.
12. Lænkholm AV, Jensen MB, Eriksen JO, et al. PAM50 Risk of Recurrence Score Predicts 10-Year Distant Recurrence in a Comprehensive Danish Cohort of Postmenopausal Women Allocated to 5 Years of Endocrine Therapy for Hormone Receptor-Positive Early Breast Cancer.J Clin Oncol. 2018 Mar 10;36(8):735-740.
13. Ohnstad HO, Borgen E, Falk RS, et al. Prognostic value of PAM50 and risk of recurrence score in patients with early-stage breast cancer with long-term follow-up.Breast Cancer Res. 2017 Nov 14;19(1):120.

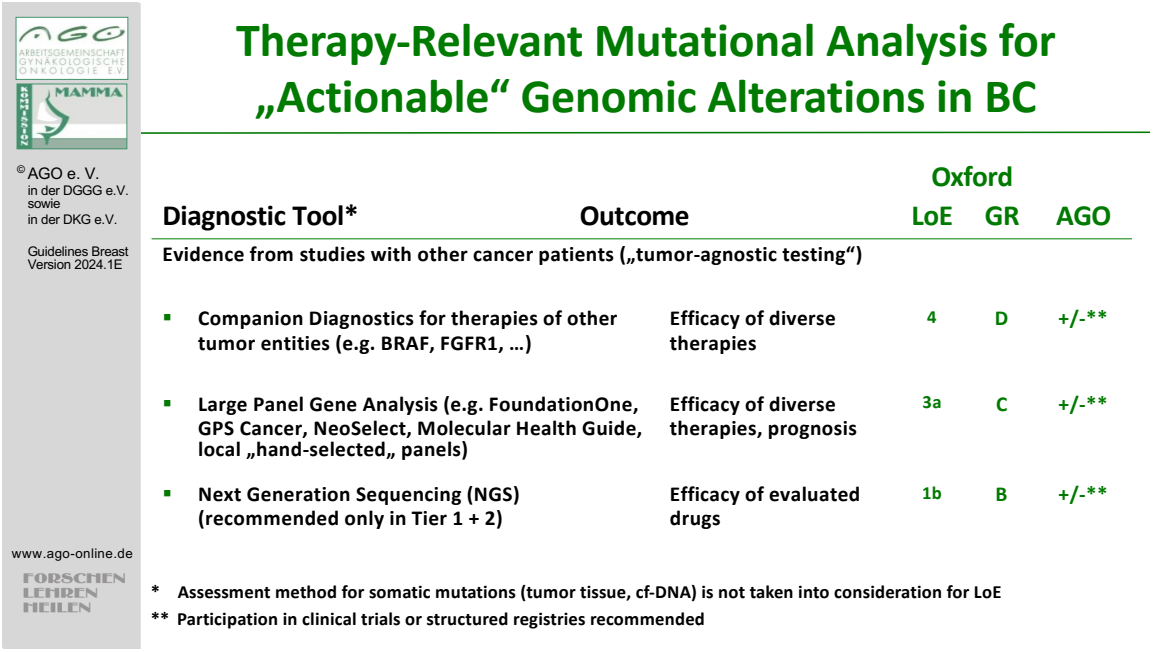
<u>Breast Cancer Index</u>

1. Bartlett JMS, Sgroi DC, Treuner K et al. Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast

cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial. Ann Oncol. 2019 Nov 1;30(11):1776-1783.
2. Jerevall PL, Brommesson S, Strand C, et al. Exploring the two-gene ratio in breast cancer--independent roles for HOXB13 and IL17BR in prediction of clinical outcome. *Breast Cancer Res Treat*. 2008;107(2):225–234.
3. Jansen MP, Sieuwerts AM, Look MP, et al. HOXB13-to-IL17BR expression ratio is related with tumor aggressiveness and response to tamoxifen of recurrent breast cancer: a retrospective study. *J Clin Oncol*. 2007;25(6):662–668.
4. Ma XJ, Hilsenbeck SG, Wang W, et al. The HOXB13:IL17BR expression index is a prognostic factor in early-stage breast cancer. *J Clin Oncol*. 2006;24(28):4611–4619.

PARPi

1. Robson M, Im SA, Senkus E et al. Olaparib for metastatic breast cancer in patients with germline BRCA Mutation. N Engl J Med 2017;377(6);523-533.
2. Litton JK, Rugo HS, Ettl J et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation N Engl J Med 2018;379(8):753-763.



Therapy-Relevant Mutational Analysis for „Actionable“ Genomic Alterations in BC

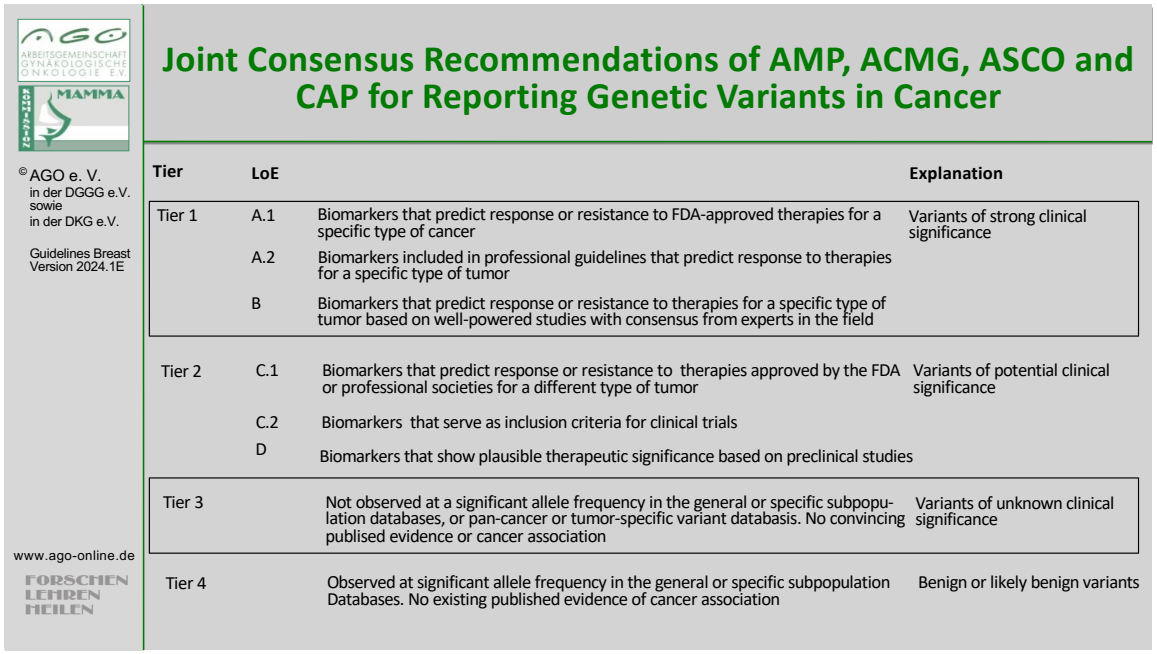
Diagnostic Tool*	Outcome	Oxford LoE	Oxford GR	AGO
Evidence from studies with other cancer patients („tumor-agnostic testing“)				
▪ Companion Diagnostics for therapies of other tumor entities (e.g. BRAF, FGFR1, …)	Efficacy of diverse therapies	4	D	+/-**
▪ Large Panel Gene Analysis (e.g. FoundationOne, GPS Cancer, NeoSelect, Molecular Health Guide, local „hand-selected„ panels)	Efficacy of diverse therapies, prognosis	3a	C	+/-**
▪ Next Generation Sequencing (NGS) (recommended only in Tier 1 + 2)	Efficacy of evaluated drugs	1b	B	+/-**

* Assessment method for somatic mutations (tumor tissue, cf-DNA) is not taken into consideration for LoE

** Participation in clinical trials or structured registries recommended

NGS in breast cancer:

1. Mosele F, Remon J, Mateo J, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2020 Nov;31(11):1491-1505.
2. André F, Bachelot T, Commo F, et al. Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER). Lancet Oncol. 2014 Mar;15(3):267-74.
3. van Geelen CT, Savas P, Teo ZL, et al. Clinical implications of prospective genomic profiling of metastatic breast cancer patients. Breast Cancer Res. 2020 Aug 18;22(1):91.
4. Hempel D, Ebner F, Garg A, et al. Real world data analysis of next generation sequencing and protein expression in metastatic breast cancer patients. Sci Rep. 2020 Jun 26;10(1):10459.
5. Sultova E, Westphalen CB, Jung A, et al. NGS-guided precision oncology in metastatic breast and gynecological cancer: first experiences at the CCC Munich LMU. Gynecol Obstet. 2020 Dec 4. doi: 10.1007/s00404-020-05881-z.



Treatment Recommendations for genetic variants

1. Li MM, Datto M, Duncavage EJ, et al. Standardsand guidelines for the interpretation and reporting of sequence variants in cancer: a joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology,and College of American Pathologists. J MolDiagn2017;19:4–23.
2. Leichsenring J, Horak P, Kreuzfeldt S et al. Variant classification in precision oncology. Int J. Cancer 2019;145:,2996–3010
3. Condorelli R, Mosele F, Verret B et al. Genomic alterations in breast cancer: level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ECAT). Ann Oncol 2019;30(3):365-373.