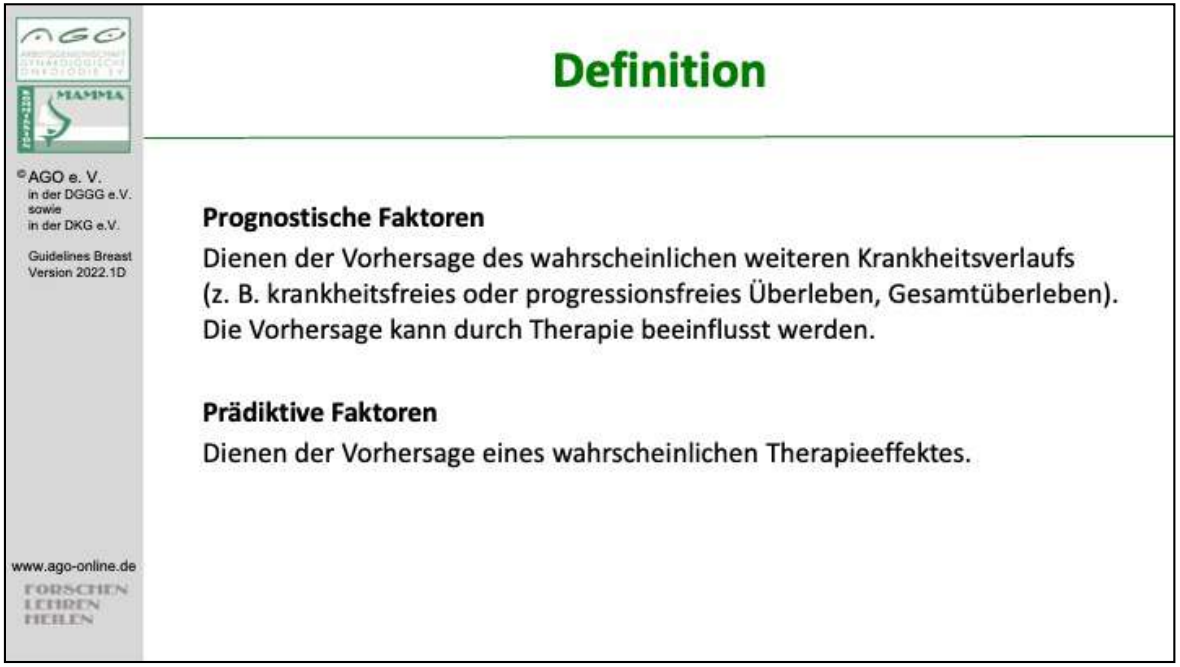
Guidelines Breast
Version 2022.1D

Prognostische und prädiktive Faktoren

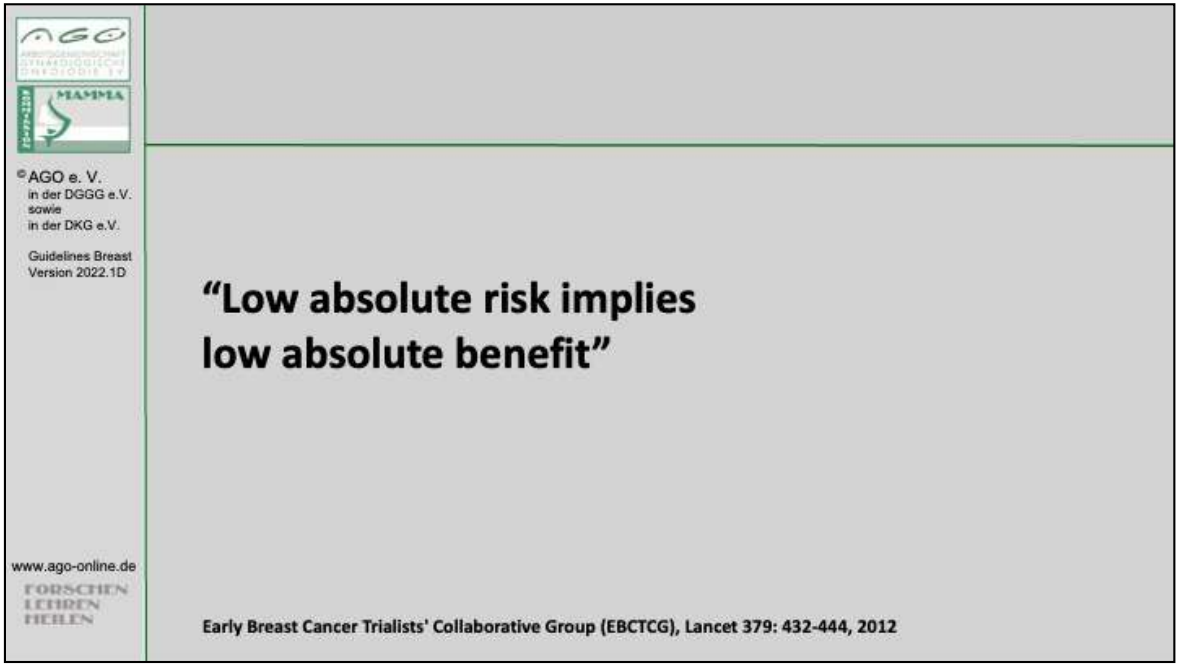
Data bases screened

Pubmed 2008 - 2021, ASCO 2017-2021, SABCS 2003 – 2021, ESMO 2021, Cochrane data base (n.d.)

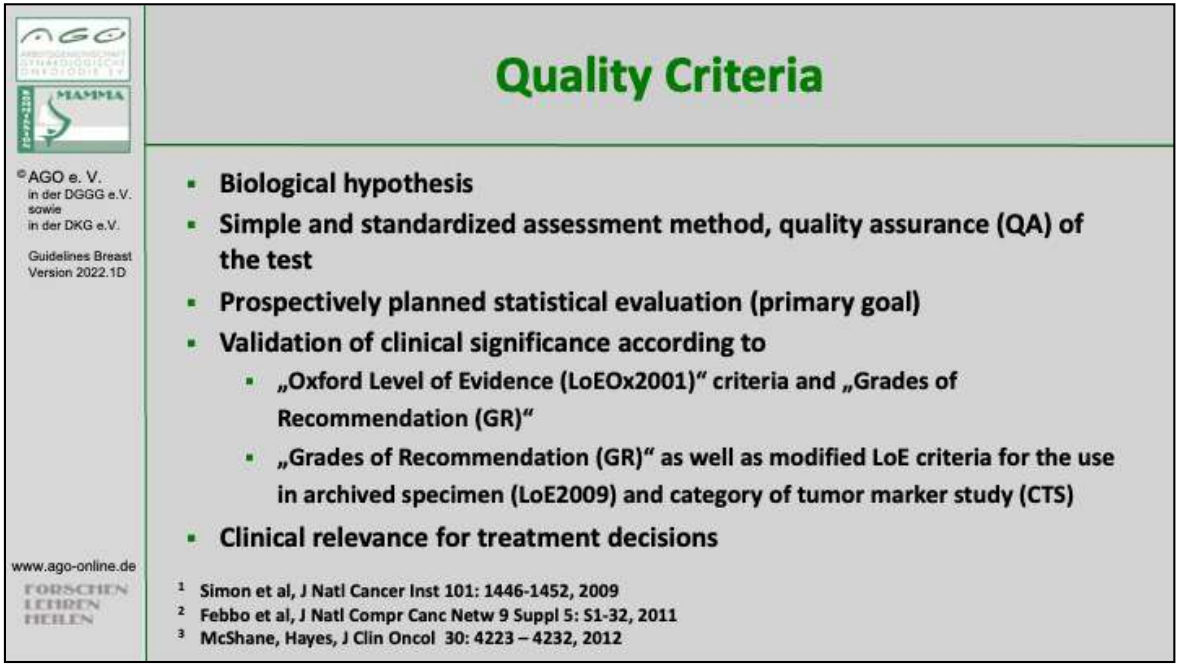


<u>Definition of Prognosis and Prediction</u>

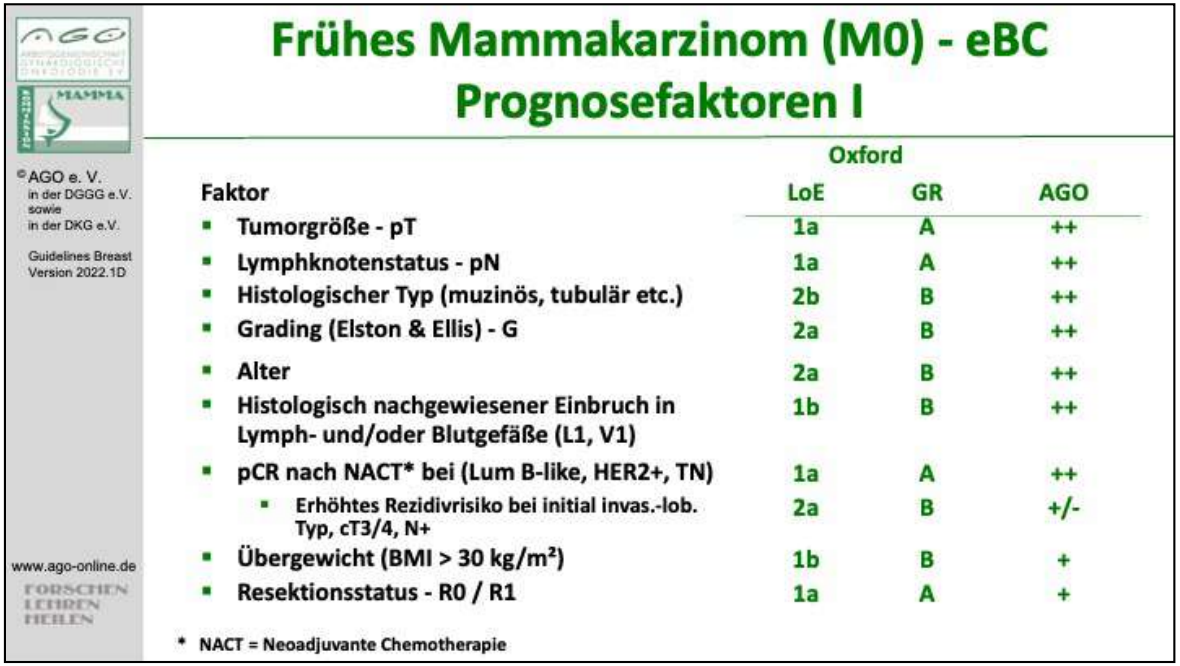
1. Hayes DF, Bast RC, Desch CE et al.:Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst. 1996 Oct 16;88(20):1456-66.
2. McGuire WL, Clark GM. Prognostic factors and treatment decisions in axillary-node-negative breast cancer. N Engl J Med. 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. 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.
4. 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.
5. McShane LM, Altman DG, Sauerbrei W et al. (2005) Reporting recommendations for tumor marker prognostic studies. J. Clin. Oncol. 23 (36): 9067–9072. Available:
6. 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.
7. 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.



Frühes Mammakarzinom (M0) - eBC
Prognosefaktoren I

Faktor	Oxford LoE	Oxford GR	AGO
Tumorgröße - pT	1a	A	++
Lymphknotenstatus - pN	1a	A	++
Histologischer Typ (muzinös, tubulär etc.)	2b	B	++
Grading (Elston & Ellis) - G	2a	B	++
Alter	2a	B	++
Histologisch nachgewiesener Einbruch in Lymph- und/oder Blutgefäße (L1, V1)	1b	B	++
pCR nach NACT* bei (Lum B-like, HER2+, TN)	1a	A	++
Erhöhtes Rezidivrisiko bei initial invas.-lob. Typ, cT3/4, N+	2a	B	+/-
Übergewicht (BMI > 30 kg/m²)	1b	B	+
Resektionsstatus - R0 / R1	1a	A	+

* NACT = Neoadjuvante Chemotherapie

General references

1. 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.
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.
3. 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.
4. 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.

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.

Histological type (mucinous, tubular etc.)

1. Dieci MV, Orvieto E, Dominici M. Rare breast cancer subtypes: histological, molecular, and clinical peculiarities. Oncologist. 2014 Aug;19(8):805-13.
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. Weigelt B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: how special are they? Mol Oncol. 2010 Jun;4(3):192-208.

Tumor grade (Elston & Ellis)

1. Thomas JS, Kerr GR, Jack WJ et al. Histological grading of invasive breast carcinoma--a simplification of existing methods in a large conservation series with long-term follow-up. Histopathology. 2009 Dec;55(6):724-31.
2. 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.
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. 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.
5. O'Shea AM, Rakha EA, Hodi Z et al. Histological grade of invasive carcinoma of the breast assessed on core needle biopsy – modifications to mitotic count assessment to improve agreement with surgical specimens. Histopathology. 2011 Sep;59(3):543-8.

Age

1. 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

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. 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.

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

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

1. 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.
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. 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.

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

1. Huober J, Schneeweiss A, Blohmer J-U, et al. Factors predicting relapse in early breast cancer patients with a pathological complete response after neoadjuvant therapy – Results of a pooled analysis based on the GBG meta-database, SABCS 2018; P2-08-01
2. 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.

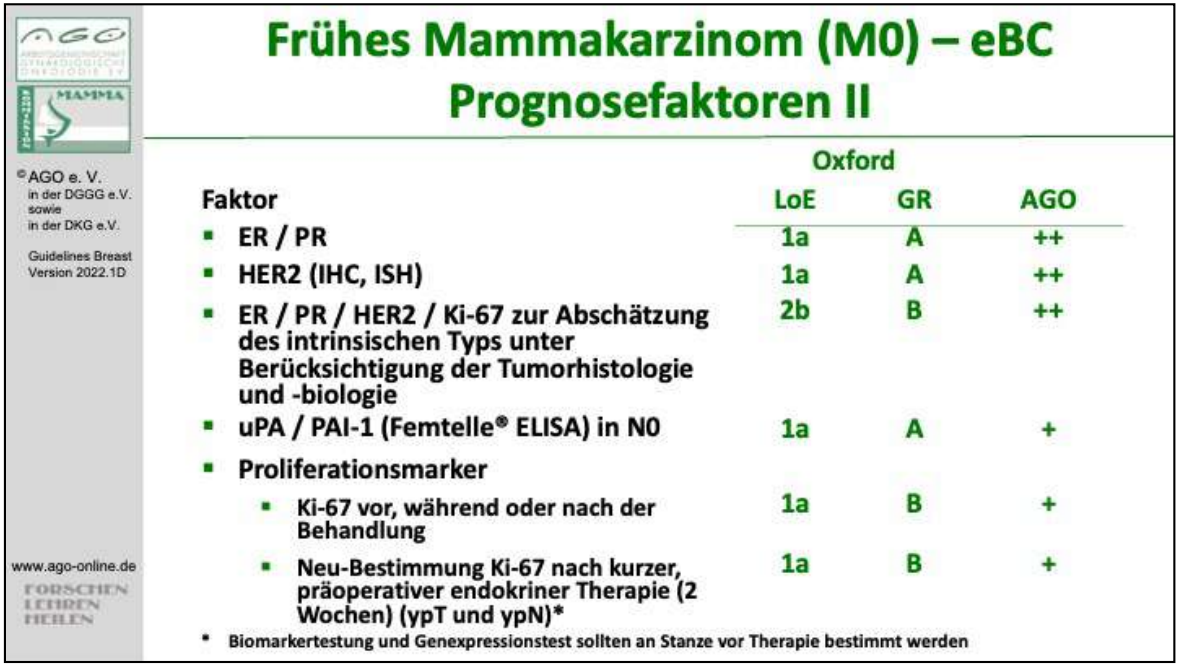
Obesity (BMI > 30 kg/m²)

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. 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. 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): p. 717-30.

Resection status (R0 / R1)

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. 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.



Frühes Mammakarzinom (M0) – eBC
Prognosefaktoren II

Faktor	Oxford LoE	Oxford GR	Oxford AGO
▪ ER / PR	1a	A	++
▪ HER2 (IHC, ISH)	1a	A	++
▪ ER / PR / HER2 / Ki-67 zur Abschätzung des intrinsischen Typs unter Berücksichtigung der Tumorhistologie und -biologie	2b	B	++
▪ uPA / PAI-1 (Femtelle® ELISA) in N0	1a	A	+
▪ Proliferationsmarker			
▪ Ki-67 vor, während oder nach der Behandlung	1a	B	+
▪ Neu-Bestimmung Ki-67 nach kurzer, präoperativer endokriner Therapie (2 Wochen) (ypT und ypN)*	1a	B	+

* Biomarkertestung und Genexpressionstest sollten an Stanze vor Therapie bestimmt werden

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 Jan 13:JCO1902309 (und: Arch Pathol Lab Med. 2020 Jan 13).
2. 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, J.S., Slodkowska, E.A., Symmans, W.F., et al. 2009. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 14, 320–368.
2. Slamon, D.J., Clark, G.M., Wong, S.G. et al. 1987. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235, 177–182.
3. 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.

uPA/PAI-1

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. Jänicke, F., Prechtl, A., Thomssen, C., et al. 2001. Randomized adjuvant chemotherapy trial in high-risk, lymph node-negative breast cancer patients identified by urokinase-type plasminogen activator and plasminogen activator inhibitor type 1. J. Natl. Cancer Inst. 93, 913–920.
3. Look, M.P., van Putten, W.L.J., Duffy, M.J., et al. 2002. Pooled analysis of prognostic impact of urokinase-type plasminogen activator and its inhibitor PAI-1 in 8377 breast cancer patients. J. Natl. Cancer Inst. 94, 116–128.
4. Thomssen, C., Harbeck, N., Dittmer, J et al.: 2009. Feasibility of measuring the prognostic factors uPA and PAI-1 in core needle biopsy breast cancer specimens. J. Natl. Cancer Inst. 101, 1028–1029.
5. Harbeck N, Schmitt M, Meisner C, et al. Ten-year analysis of the prospective multicentre Chemo-N0 trial validates American Society of Clinical Oncology (ASCO)-recommended biomarkers uPA and PAI-1 for therapy decision making in node-negative breast cancer patients. Eur J Cancer. 2013 May;49(8):1825-35.
6. Ettl J, Klein E, Hapfelmeier A, et al. Decision impact and feasibility of different ASCO-recommended biomarkers in early breast cancer: Prospective comparison of molecular marker EndoPredict and protein marker uPA/PAI-1. PLoS One. 2017 Sep 6;12(9):e0183917.

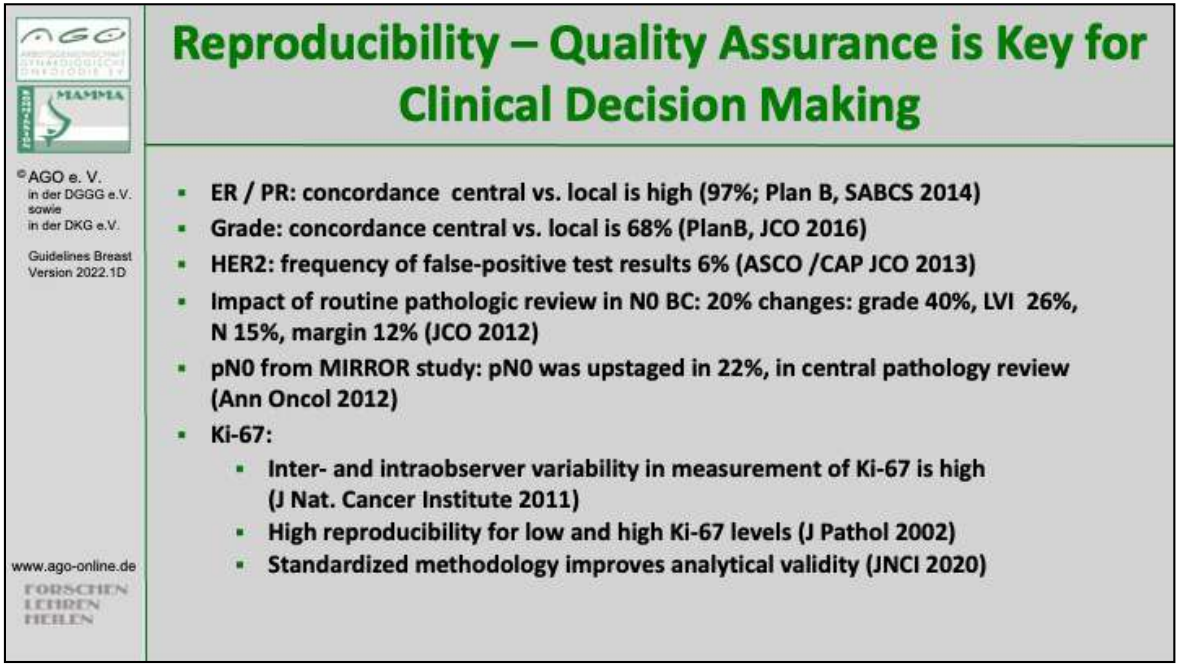
<u>Ki-67</u>

1. Cheang, M.C.U., Chia, S.K., Voduc, D. et al.: 2009. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J. Natl. Cancer Inst. 101, 736–750. doi:10.1093/jnci/djp082.
2. Fasching, P.A., Heusinger, K., Haeberle, L., et al. 2011. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer 11, 486.
3. 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.
4. Luporsi, E., André, F., Spyratos, F., et al. 2012. Ki-67: level of evidence and methodological considerations for its role in the clinical management of breast cancer: analytical and critical review. Breast Cancer Res. Treat. 132, 895–915.
5. Urruticoechea, A., Smith, I.E. & Dowsett, M. 2005. Proliferation marker Ki-67 in early breast cancer. J. Clin. Oncol. 23, 7212–7220..
6. Varga, Z., Diebold, J., Dommann-Scherrer, C. et al. 2012. How reliable is Ki-67 immunohistochemistry in grade 2 breast carcinomas? A QA study of the Swiss Working Group of Breast- and Gynecopathologists. PLoS ONE 7, e37379.

7. Viale, G., Giobbie-Hurder, A., Regan, M.M., et al. 2008a. Prognostic and predictive value of centrally reviewed Ki-67 labeling index in postmenopausal women with endocrine-responsive breast cancer: results from Breast International Group Trial 1-98 comparing adjuvant tamoxifen with letrozole. J. Clin. Oncol. 26, 5569–5575.
8. Viale, G., Regan, M.M., Mastropasqua, M.G. et al. 2008b. Predictive value of tumor Ki-67 expression in two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer. J. Natl. Cancer Inst. 100, 207–212.
9. 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): p. 477-91.
10. 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.
11. 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.
12. 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
13. 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.

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 99:167-170, 2007
2. Ellis MJ, Tao Y, Luo J, et al: Outcome Prediction for Estrogen Receptor-Positive Breast Cancer Based on Postneoadjuvant Endocrine Therapy Tumor Characteristics. J. Natl. Cancer Inst. 100:1380-1388, 2008
3. Ellis M, Luo J, Tao Y, et al: Tumor Ki67 Proliferation Index within 4 Weeks of Initiating Neoadjuvant Endocrine Therapy for Early Identification of Non-Responders. Cancer Res 69, 2010
4. 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.



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. 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.
3. 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.
4. 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.
5. 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.
6. 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.

7. 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.
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.

<u>Gene expression profiles (GEP; Multigene Assays, Gene expression signatures)</u>

(*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)

<u>MammaPrint®</u>

1. 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.
2. 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
3. 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
4. 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 Apr;75:284-298.
5. 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.

6. 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. doi:10.1093/jnci/djj329.
7. Drukker CA, Elias SG, Nijenhuis M. 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.
8. 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.
9. 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.
10. 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. doi:10.1093/annonc/mdp388.
11. 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. doi:10.1016/S1470-2045(09)70254-2.
12. 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. doi:10.1007/s10549-008-0130-2.
13. 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.
14. 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.
15. 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.
16. 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. 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.
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, Paik S. Development of the 21-gene assay and its application in clinical practice and clinical trials. J Clin Oncol. 2008 Feb 10;26(5):721-8.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
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.
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. 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.

13. Tang, G., Cuzick, J., Costantino, J.P., e 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.
14. 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.
15. 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

EndoPredict®

1. 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.
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. 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.
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.
5. 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.
6. Dubsky P, Brase JC et al.; Austrian Breast and Colorectal Cancer Study Group (ABCSG). 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.
7. Dubsky P, Filipits M, et al.; Austrian Breast and Colorectal Cancer Study Group (ABCSG). 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.
8. 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.

9. 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)
10. 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.
11. 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. doi:10.1093/annonc/mds334.
12. Dubsky P, Brase JC, Jakesz R, et 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
13. Dubsky, San Antonio 2017
14. 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. doi:10.1158/1078-0432.CCR-11-0926.
15. 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. doi:10.1186/1471-2407-12-456.
16. 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.
17. 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. Geburtshilfe Frauenheilkd. 2013 Sep;73(9):932-940.

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. 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.
3. 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.
4. 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.

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. 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 Apr;75:284-298.
7. Harris LN, Ismaila N et al.; American Society of Clinical Oncology. 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.
8. Liu MC, Pitcher BN, Mardis ER et al. PAM50 gene signatures and breast cancer prognosis with adjuvant anthracycline- and taxane-based chemotherapy: correlative analysis of C9741 (Alliance). NPJ Breast Cancer. 2016;2. pii: 15023.
9. Liu S, Chapman JA, Burnell M 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.
10. Gnant M, Filipits M 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.
11. Dowsett M, Sestak I, Lopez-Knowles E, et al. Comparison of PAM50 risk of recurrence score with oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. *J Clin Oncol*. 2013;31(22):2783–2790.
12. 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.
13. Chia, S.K., Bramwell, V.H., Tu, D., et al. A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. Clin. Cancer Res. 2012; 18, 4465–4472.
14. Nielsen, T.O., Parker, J.S., Leung, S., et al. A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer. Clin. Cancer Res. 2010; 16, 5222–5232.
15. 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.
16. 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.
17. Wuerstlein R, Sotlar K, Gluz O et al. The West German Study Group Breast Cancer Intrinsic Subtype study: a prospective multicenter decision impact study utilizing the Prosigna assay for adjuvant treatment decision-making in estrogen-receptor-positive, HER2-negative early-stage breast cancer. Curr Med Res Opin. 2016 Jul;32(7):1217-24.

18. 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*. 2015;33(8):916–922.
19. Wallden B, Storhoff J, Nielsen T et al. Development and verification of the PAM50-based Prosigna breast cancer gene signature assay. BMC Med Genomics. 2015 Aug 22;8:54.
20. Prat A, Cheang MC, Martín M, et al. Prognostic significance of progesterone receptor-positive tumor cells within immunohistochemically defined luminal A breast cancer. *J Clin Oncol*. 2013;31(2):203–209.
21. Prat, A., Parker, J.S., Fan, C., et al. Concordance among gene expression-based predictors for ER-positive breast cancer treated with adjuvant tamoxifen. Ann. Oncol. 2012; 23, 2866–2873.
22. Parker, J.S., Mullins, M., Cheang, M.C.U., et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. J. Clin. Oncol. 2009; 27, 1160–1167.
23. Perou, C.M., Sørlie, T., Eisen, M.B., et al. 2000. Molecular portraits of human breast tumours. Nature 2000; 406, 747–752.

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. 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.

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

1. Wishart GC, Azzato EM, Greenberg DC, et al. PREDICT: a new UK prognostic model that predicts survival following surgery for invasive breast cancer. Breast Cancer Res. 2010; 12(1): R1.
2. 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.

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

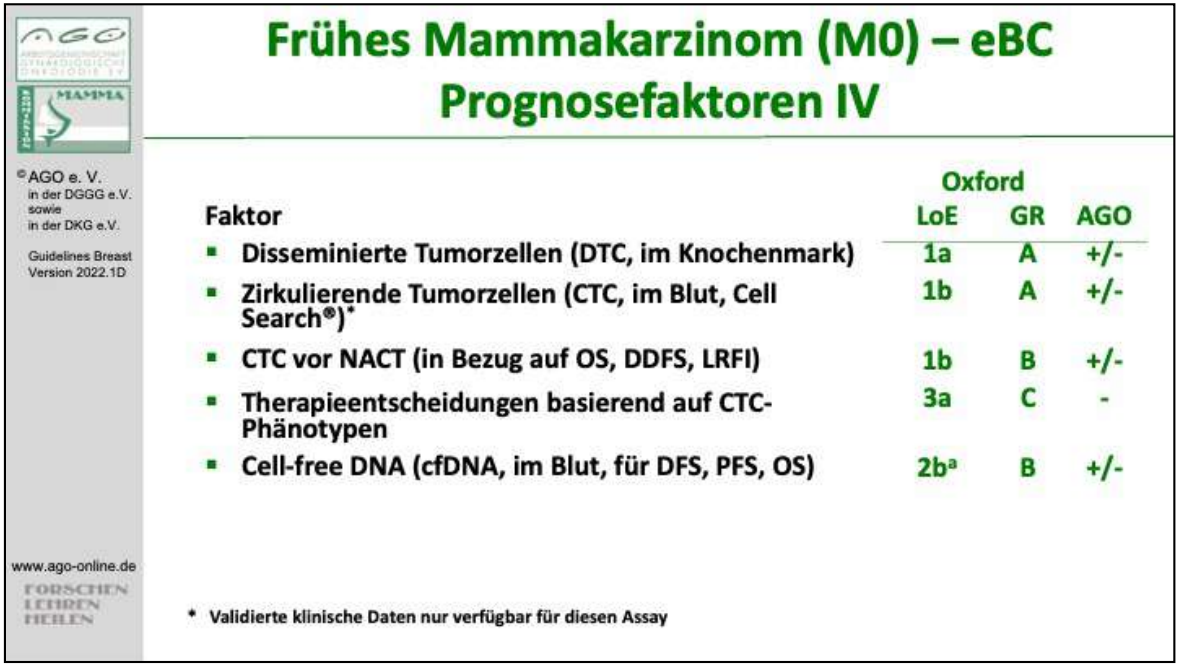
1. Lakhanpal R, Sestak I, Shadbolt B, et al. IHC4 score plus clinical treatment score predicts locoregional recurrence in early breast cancer. *Breast*. 2016;29:147–152.
2. Richman J, Ring A, Dowsett M, Sestak I. Clinical validity of clinical treatment score 5 (CTS5) for estimating risk of late recurrence in unselected, non-trial patients with early oestrogen receptor-positive breast cancer. Breast Cancer Res Treat. 2020 Nov 21.

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. 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.

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 20217;164(2):395-400



Frühes Mammakarzinom (M0) – eBC
Prognosefaktoren IV

Faktor	Oxford LoE	Oxford GR	AGO
▪ Disseminierte Tumorzellen (DTC, im Knochenmark)	1a	A	+/-
▪ Zirkulierende Tumorzellen (CTC, im Blut, Cell Search®)*	1b	A	+/-
▪ CTC vor NACT (in Bezug auf OS, DDFS, LRFI)	1b	B	+/-
▪ Therapieentscheidungen basierend auf CTC-Phänotypen	3a	C	-
▪ Cell-free DNA (cfDNA, im Blut, für DFS, PFS, OS)	2b[a]	B	+/-

* Validierte klinische Daten nur verfügbar für diesen Assay

DTC

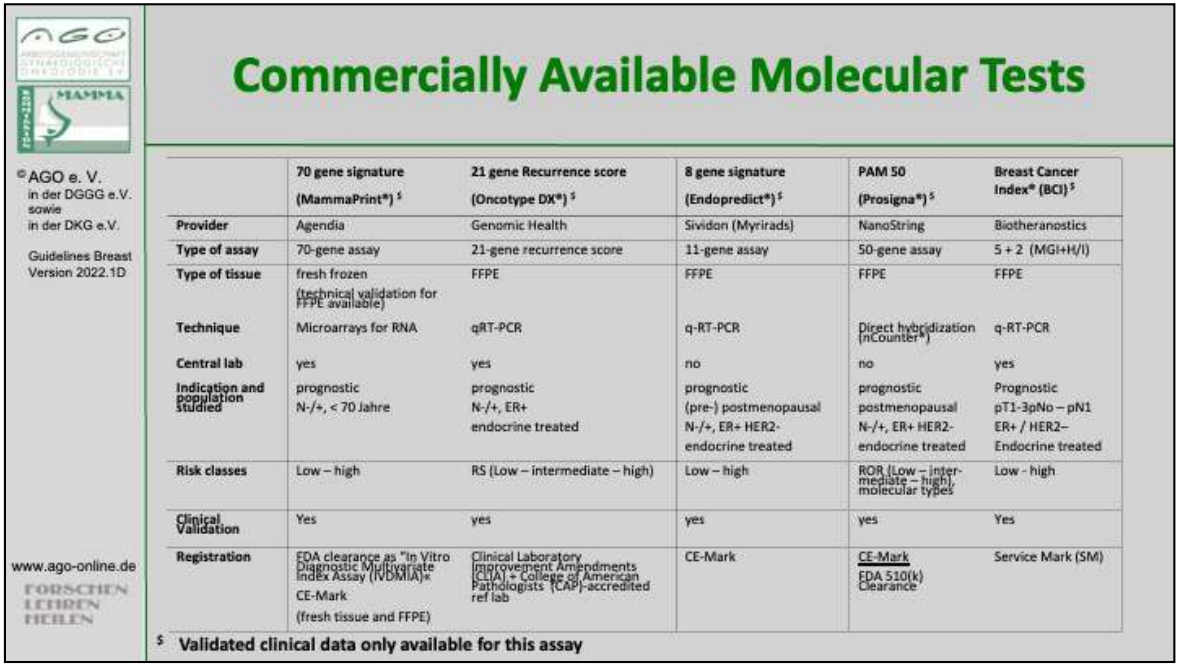
1. Diel, I.J., Kaufmann, M., Costa, S.D., et al. Micrometastatic breast cancer cells in bone marrow at primary surgery: prognostic value in comparison with nodal status. J. Natl. Cancer Inst.1996; 88, 1652–1658.
2. Janni, W., Vogl, F.D., Wiedswang, G. et al. Persistence of disseminated tumor cells in the bone marrow of breast cancer patients predicts increased risk for relapse--a European pooled analysis. Clin. Cancer Res. 2011; 17, 2967–2976.
3. Mathiesen, R.R., Borgen, E., Renolen, A., et al. 2012. Persistence of disseminated tumor cells after neoadjuvant treatment for locally advanced breast cancer predicts poor survival. Breast Cancer Res. 2012; 14, R117.
4. Molloy, T.J., Bosma, A.J., Baumbusch, L.O., et al. The prognostic significance of tumour cell detection in the peripheral blood versus the bone marrow in 733 early-stage breast cancer patients. Breast Cancer Res. 2011;13, R61.

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. 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.
2. 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.
3. 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.
4. Lucci, A., Hall, C.S., Lodhi, A.K., et al. 2012. Circulating tumour cells in non-metastatic breast cancer: a prospective study. Lancet Oncol. 13, 688–695. doi:10.1016/S1470-2045(12)70209-7.
5. Rack B, Schindlbeck C, Jückstock J, et al. Circulating tumor cells predict survival in early average-to-high risk breast cancer patients.; SUCCESS Study Group. J Natl Cancer Inst. 2014 May 15;106(5).
6. Riethdorf, S., Müller, V., Zhang, L., et al. 2010. Detection and HER2 expression of circulating tumor cells: prospective monitoring in breast cancer patients treated in the neoadjuvant GeparQuattro trial. Clin. Cancer Res. 16, 2634–2645. doi:10.1158/1078-0432.CCR-09-2042.
7. Zhang, L., Riethdorf, S., Wu, G., et al. 2012. Meta-analysis of the prognostic value of circulating tumor cells in breast cancer. Clin. Cancer Res. 18, 5701–5710. doi:10.1158/1078-0432.CCR-12-1587.
8. Bidard F-C, Michiels S, Mueller V, et al. IMENEO: International MEta-analysis of circulating tumor cell detection in early breast cancer patients treated by NEOadjuvant chemotherapy. SABCS 2016, S3-01
9. Hartkopf AD, Brucker SY, Taran F-A, et al. International pooled analysis of the prognostic impact of disseminated tumor cells from the bone marrow in early breast cancer: Results from the PADDY study. SABCS 2018, GS5-07
10. 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. doi: 10.1093/jnci/djy152. [Epub ahead of print] PMID: 30312434
11. 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.
12. 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)
13. 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.



Commercially Available Molecular Tests

	70 gene signature (MammaPrint®) $	21 gene Recurrence score (Oncotype DX®) $	8 gene signature (Endopredict®) $	PAM 50 (Prosigna®) $	Breast Cancer Index® (BCI) $
Provider	Agendia	Genomic Health	Sividon (Myrirads)	NanoString	Biotheranostics
Type of assay	70-gene assay	21-gene recurrence score	11-gene assay	50-gene assay	5 + 2 (MGI+H/I)
Type of tissue	fresh frozen (technical validation for FFPE available)	FFPE	FFPE	FFPE	FFPE
Technique	Microarrays for RNA	qRT-PCR	q-RT-PCR	Direct hybridization (nCounter®)	q-RT-PCR
Central lab	yes	yes	no	no	yes
Indication and population studied	prognostic N-/+, < 70 Jahre	prognostic N-/+, ER+ endocrine treated	prognostic (pre-) postmenopausal N-/+, ER+ HER2- endocrine treated	prognostic postmenopausal N-/+, ER+ HER2- endocrine treated	Prognostic pT1-3pNo – pN1 ER+ / HER2– Endocrine treated
Risk classes	Low – high	RS (Low – intermediate – high)	Low – high	ROR (Low – intermediate – high), molecular types	Low - high
Clinical Validation	Yes	yes	yes	yes	Yes
Registration	FDA clearance as "in Vitro Diagnostic Multivariate Index Assay (IVDMIA)" CE-Mark (fresh tissue and FFPE)	Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab	CE-Mark	CE-Mark FDA 510(k) Clearance	Service Mark (SM)

$ **Validated clinical data only available for this assay**

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, Gralow JR et al. 21-Gene Assay to inform chemotherapy benefit from node positive breast cancer. Engl J Med DOI: 10.1056/NEJMoa2108873

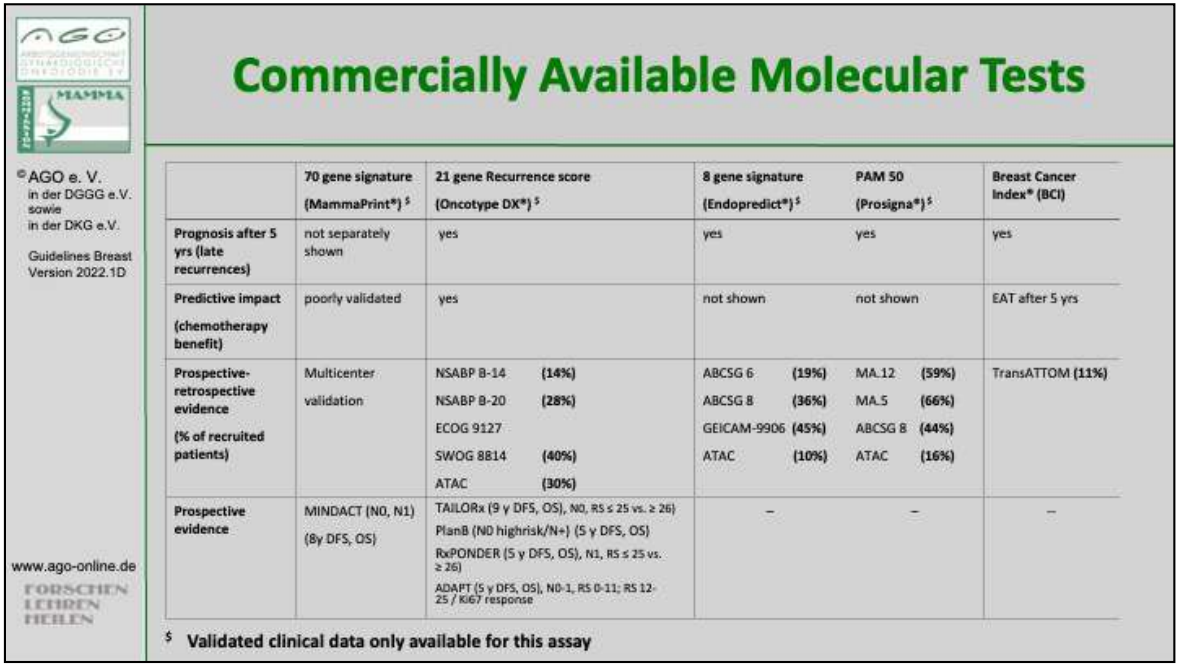
Prosigna (ROR / PAM50)
1. Chia, S.K., Bramwell, V.H., Tu, Det al. 2012. A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. Clin. Cancer Res. 18, 4465–4472.

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.



Commercially Available Molecular Tests

	70 gene signature (MammaPrint®) $	21 gene Recurrence score (Oncotype DX®) $	8 gene signature (Endopredict®) $	PAM 50 (Prosigna®) $	Breast Cancer Index® (BCI)
Prognosis after 5 yrs (late recurrences)	not separately shown	yes	yes	yes	yes
Predictive impact (chemotherapy benefit)	poorly validated	yes	not shown	not shown	EAT after 5 yrs
Prospective-retrospective evidence (% of recruited patients)	Multicenter validation	NSABP B-14 (14%) NSABP B-20 (28%) ECOG 9127 SWOG 8814 (40%) ATAC (30%)	ABCSG 6 (19%) ABCSG 8 (36%) GEICAM-9906 (45%) ATAC (10%)	MA.12 (59%) MA.5 (66%) ABCSG 8 (44%) ATAC (16%)	TransATTOM (11%)
Prospective evidence	MINDACT (N0, N1) (8y DFS, OS)	TAILORx (9 y DFS, OS), N0, RS ≤ 25 vs. ≥ 26) PlanB (N0 highrisk/N+) (5 y DFS, OS) RxPONDER (5 y DFS, OS), N1, RS ≤ 25 vs. ≥ 26) ADAPT (5 y DFS, OS), N0-1, RS 0-11; RS 12-25 / Ki67 response	–	–	–

$ **Validated clinical data only available for this assay**

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

Prosigna (ROR / PAM50)

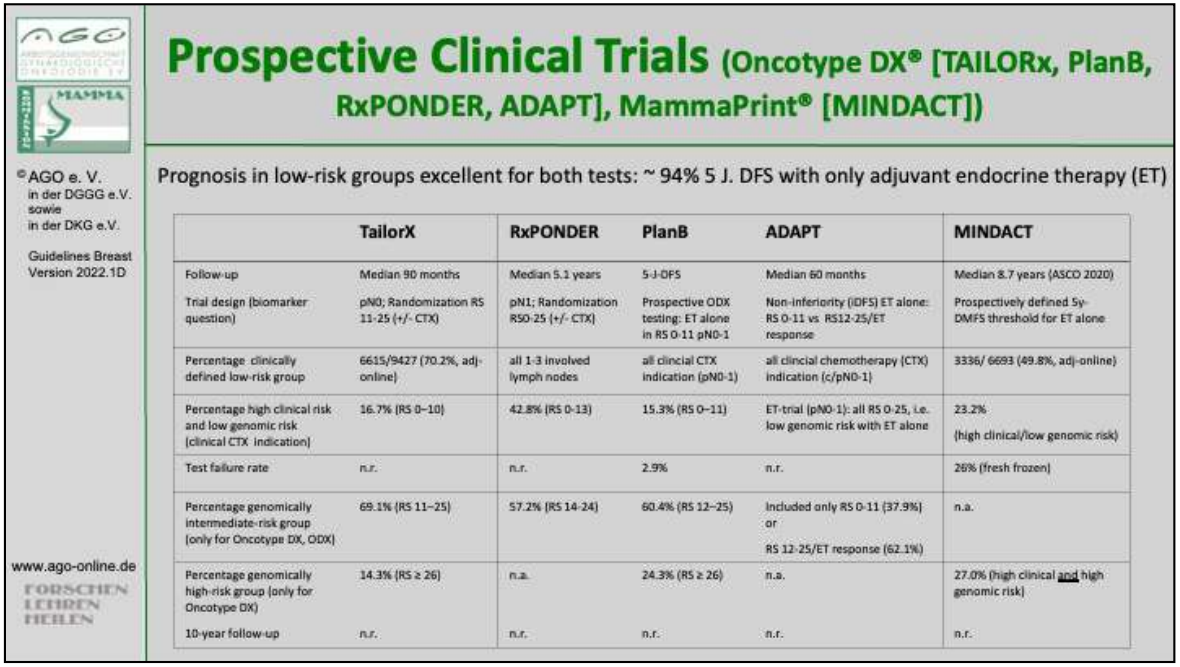
1. Chia, S.K., Bramwell, V.H., Tu, Det al. 2012. A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. Clin. Cancer Res. 18, 4465–4472.
2. Gnant M, Filipits M, Greil R, et al. Austrian Breast and Colorectal Cancer Study Group. Predicting distant recurrence 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.



Prospective Clinical Trials (Oncotype DX® [TAILORx, PlanB, RxPONDER, ADAPT], MammaPrint® [MINDACT])

Guidelines Breast
Version 2022.1D

Prognosis in low-risk groups excellent for both tests: ~ 94% 5 J. DFS with only adjuvant endocrine therapy (ET)

	TailorX	RxPONDER	PlanB	ADAPT	MINDACT
Follow-up	Median 90 months	Median 5.1 years	5-J-DFS	Median 60 months	Median 8.7 years (ASCO 2020)
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)
10-year follow-up	n.r.	n.r.	n.r.	n.r.	n.r.

www.ago-online.de
FORSCHEN LEHREN HEILEN

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 Aug 25;375(8):717-29.
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

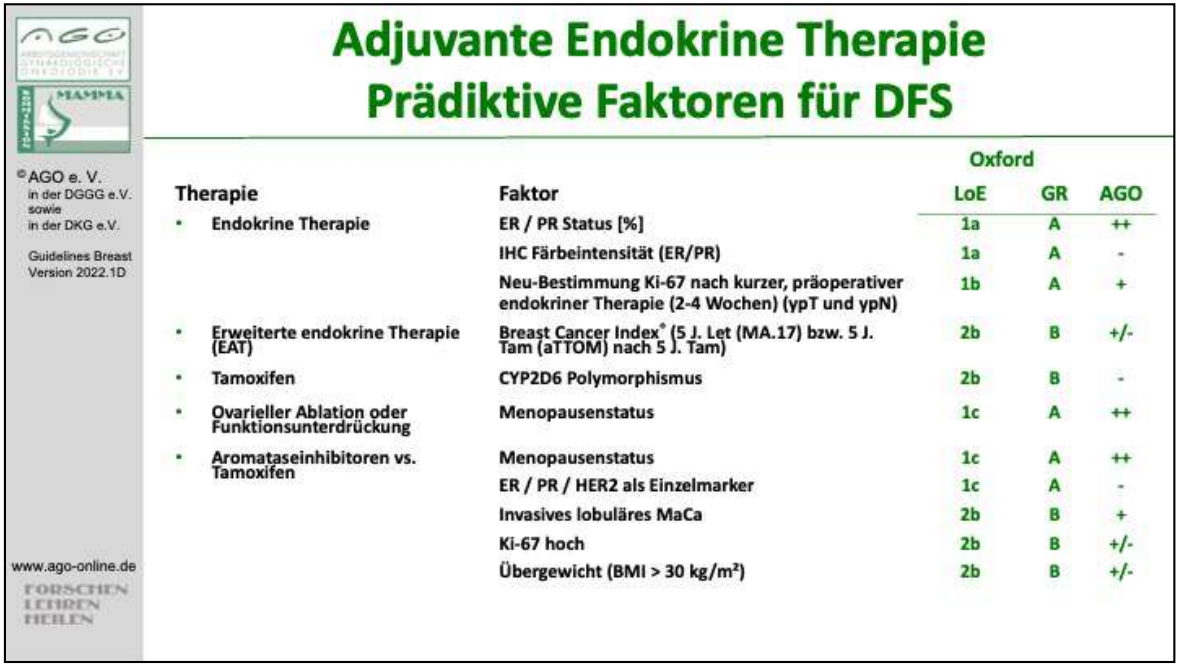
Oncotype DX

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. 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.
3. 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

4. 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.
5. 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.
6. 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

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.



Adjuvante Endokrine Therapie
Prädiktive Faktoren für DFS

Therapie	Faktor	Oxford LoE	Oxford GR	AGO
• Endokrine Therapie	ER / PR Status [%]	1a	A	++
	IHC Färbeintensität (ER/PR)	1a	A	-
	Neu-Bestimmung Ki-67 nach kurzer, präoperativer endokriner Therapie (2-4 Wochen) (ypT und ypN)	1b	A	+
• Erweiterte endokrine Therapie (EAT)	Breast Cancer Index® (5 J. Let (MA.17) bzw. 5 J. Tam (aTTOM) nach 5 J. Tam)	2b	B	+/-
• Tamoxifen	CYP2D6 Polymorphismus	2b	B	-
• Ovarieller Ablation oder Funktionsunterdrückung	Menopausenstatus	1c	A	++
• Aromataseinhibitoren vs. Tamoxifen	Menopausenstatus	1c	A	++
	ER / PR / HER2 als Einzelmarker	1c	A	-
	Invasives lobuläres MaCa	2b	B	+
	Ki-67 hoch	2b	B	+/-
	Übergewicht (BMI > 30 kg/m²)	2b	B	+/-

General publications

1. Clark GM et al. Prognostic and predictive factors. In: Diseases of the breast, 2nd edition: Seiten 489-514. Harris JR, Lippmann ME, Morrow M, Osborne CK (Hrsg). Lippincott-Raven Publishers, Philadelphia 2000.
2. 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
3. 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.

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 24 (9): 1332-41, 2006.
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 365 (9472): 1687-717, 2005
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 17 (5): 1474-81, 1999.
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.

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

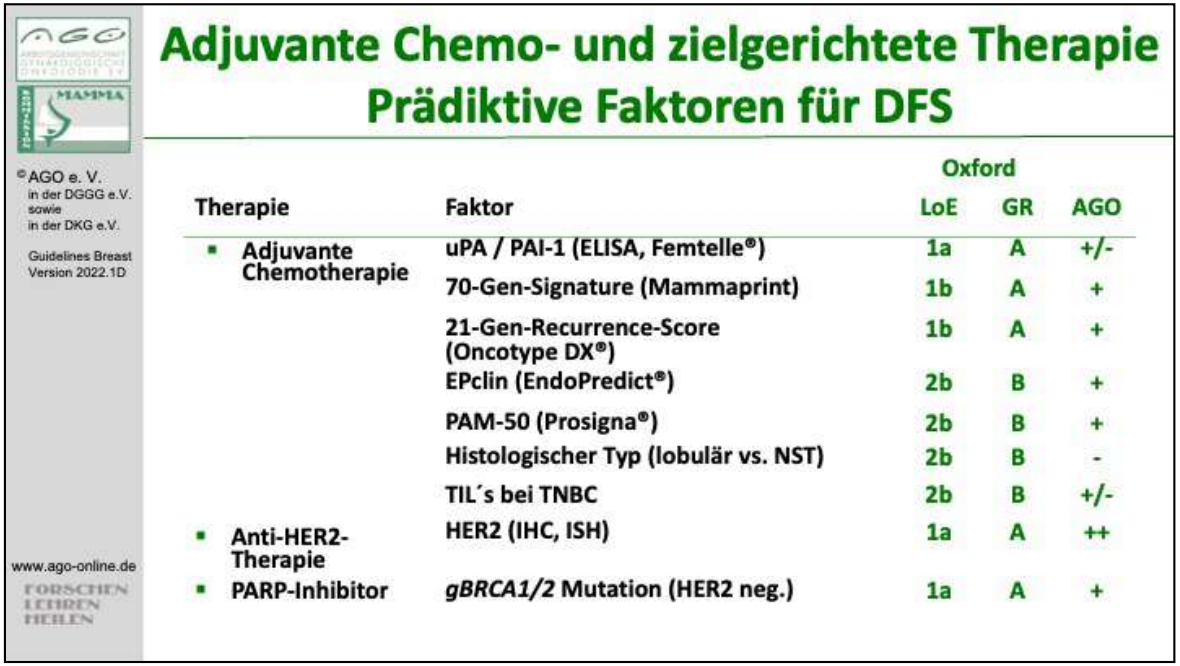
1. Chan DSM et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82 follow-up studies Ann Oncol. Oct 2014; 25(10): 1901–1914.
2. Xia X, Chen W, Li J, et al. Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies. Sci Rep. 2014 Dec 15;4:7480. doi: 10.1038/srep07480.

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. 2018 Oct 24. doi: 10.1007/s00280-018-3703-8. [Epub ahead of print] PMID: 30357449
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. doi: 10.3389/fphar.2017.00582. eCollection 2017. PMID: 28955222
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.

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. Etreatment of breast cancer: Results from the American College of Surgeons Oncology Group Z1031 Trial (Alliance). J Clin Oncol 2017;35(10):1061-1069.
4. llis 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.



uPA/PAI-1

1. Harbeck N, Kates RE, Look MP, et al. Enhanced benefit from adjuvant systemic chemotherapy in breast cancer patients classified high-risk according to uPA and PAI-1 (n=3,424). Cancer Res 62 (16): 4617-22, 2002.
2. Harbeck N, Schmitt M, Meisner C, et al. Ten-year analysis of the prospective multicentre Chemo-N0 trial validates American Society of Clinical Oncology (ASCO)-recommended biomarkers uPA and PAI-1 for therapy decision making in node-negative breast cancer patients. Eur J Cancer. 2013 May;49(8):1825-35.
3. Ettl J, Klein E, Hapfelmeier A, et al. Decision impact and feasibility of different ASCO-recommended biomarkers in early breast cancer: Prospective comparison of molecular marker EndoPredict and protein marker uPA/PAI-1. PLoS One. 2017 Sep 6;12(9):e0183917.

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

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.

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. 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.

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.

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

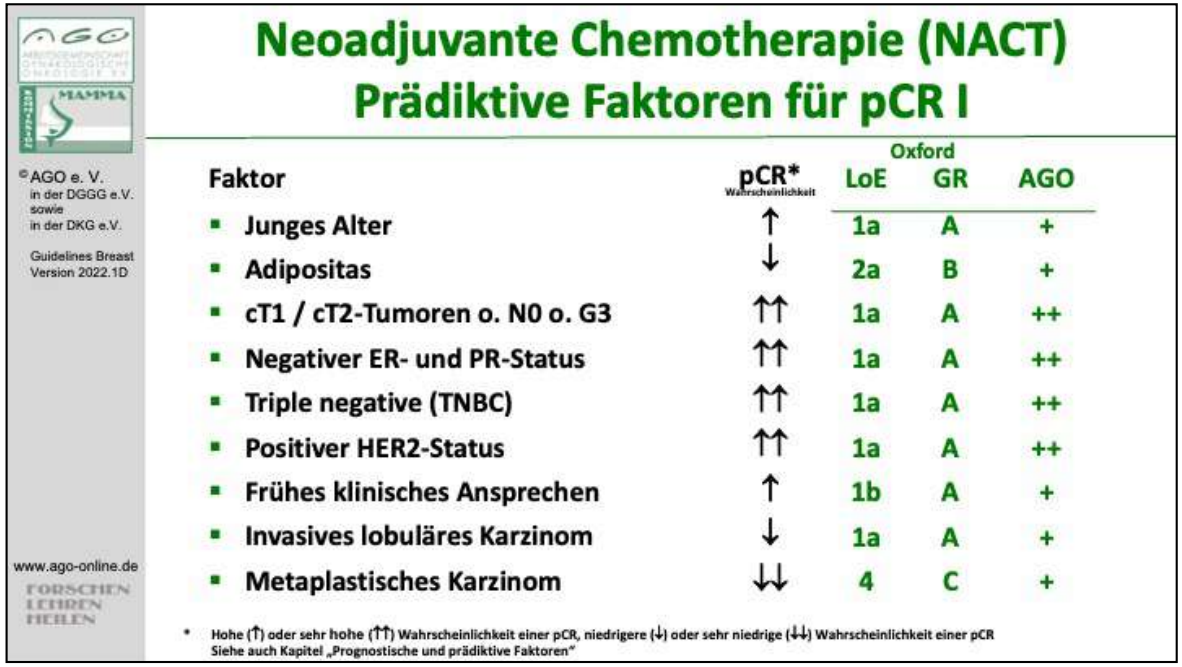
Oncotype DX

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

PARPi

1. 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.



General evidence

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;384: 164-72.
2. 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.
3. 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 2017.
4. 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.
5. 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.

Body mass index

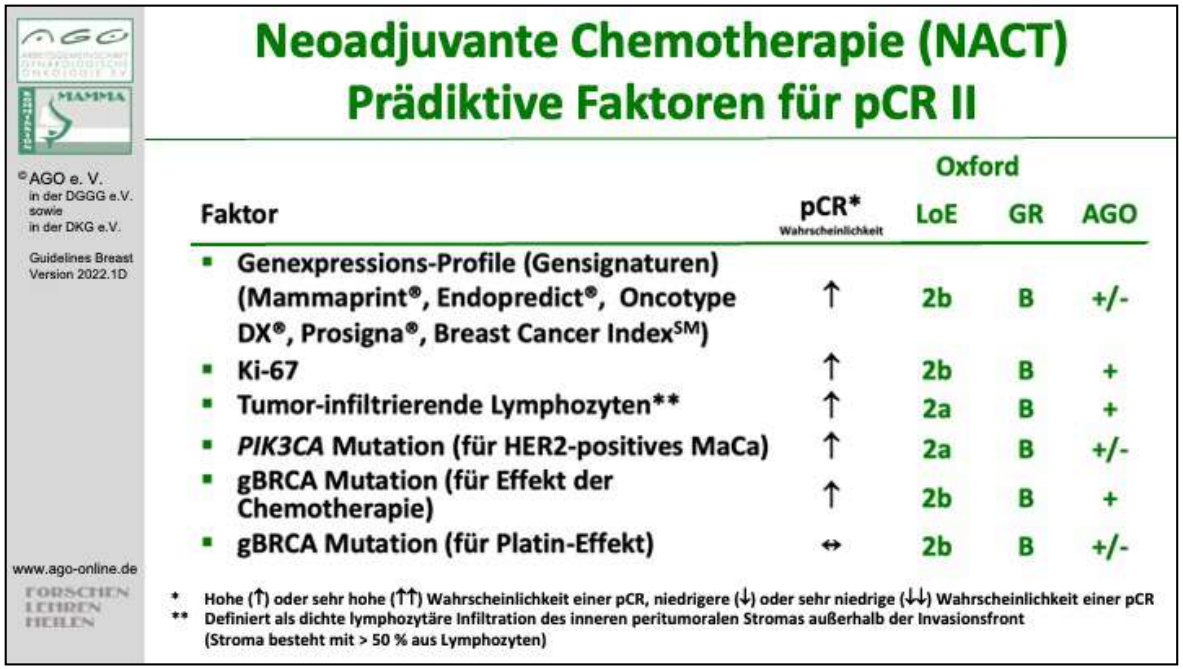
1. Wang H, Zhang S, Yee D, et al. Impact of body mass index on pathological complete response following neoadjuvant chemotherapy in operable breast cancer: a meta analysis. Breast Cancer 2021;28(3):616-629

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.



TIL

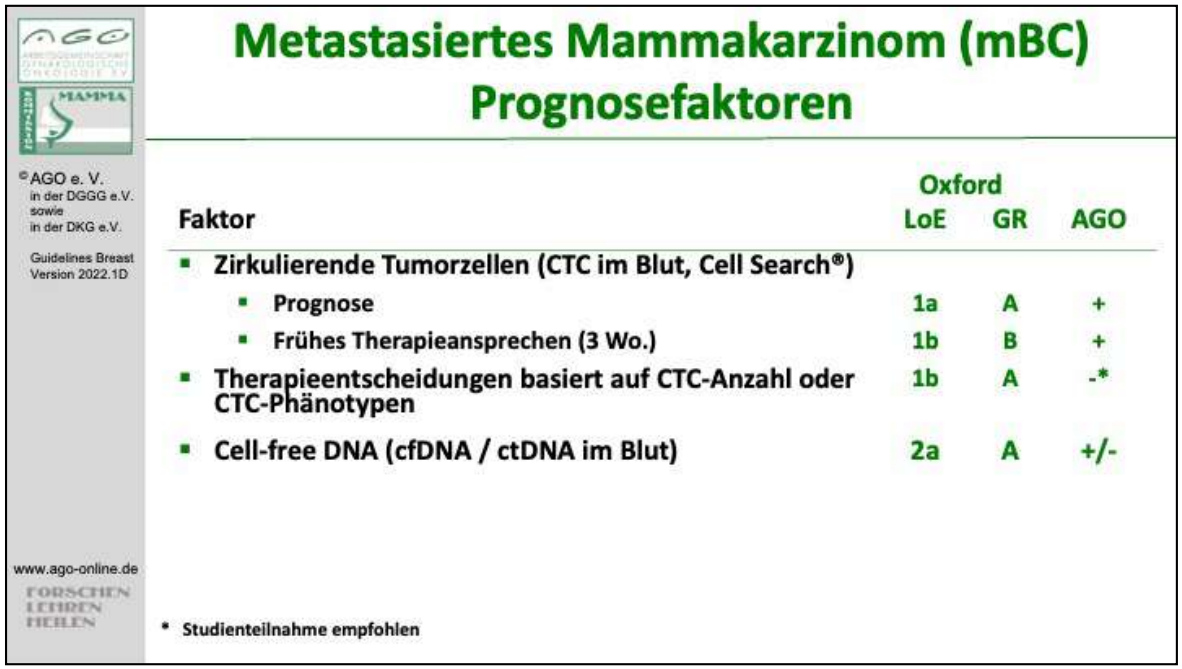
1. Denkert, C., Loibl, S., Noske, A., et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. 2010. J. Clin. Oncol. 28, 105–113. doi:10.1200/JCO.2009.23.7370.
2. Denkert C, von Minckwitz G, Brase JC, et al. Tumor-Infiltrating Lymphocytes 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.

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. doi: 10.1093/annonc/mdv175. Epub 2015 Apr 7.

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 Jan 9. doi: 10.1093/annonc/mdy536. [Epub ahead of print]
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.

<u>gBRCA bei TNBC</u>

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.



1. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). Breast. 2017 Feb;31:244-259.

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

from 21,807 Advanced Cancer Patients. Clin Cancer Res. 2018 Aug 1;24(15):3528-3538.

Metastasiertes Mammakarzinoms (mBC)
Prädiktive Faktoren für Ansprechen

Therapie	Faktor	Oxford LoE	Oxford GR	AGO
▪ Endokrine Therapie	ER / PR (Primärtumor, besser Metastase)	1a	A	++
	Ansprechen auf vorherige Therapie	2b	B	++
	autokrine Rezeptormutation (ESR1)	2b	B	+
▪ Alpelisib	PIK3CA Mutation (Primärtumor, Metastase, Plasma)	1b	A	++
▪ Chemotherapie	Ansprechen auf vorherige Therapie	1b	A	++
▪ Anti-HER2- Therapie	HER2 (Primärtumor, besser Metastase)	1a	A	++
▪ Checkpoint-Inhibitors	PD-L1 positivity# (PD-L1ic, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
▪ PARP-Inhibitoren	gBRCA1/2-Mutation	1a	A	++
▪ Bone modifying drugs	Knochenmetastasen	1a	A	++
▪ Diverse Therapien	CTC monitoring	1b	A	+*

* In klinischen Studien; # Siehe auch Kapitel „Pathologie“

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

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

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.

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.

Bone modifying drugs

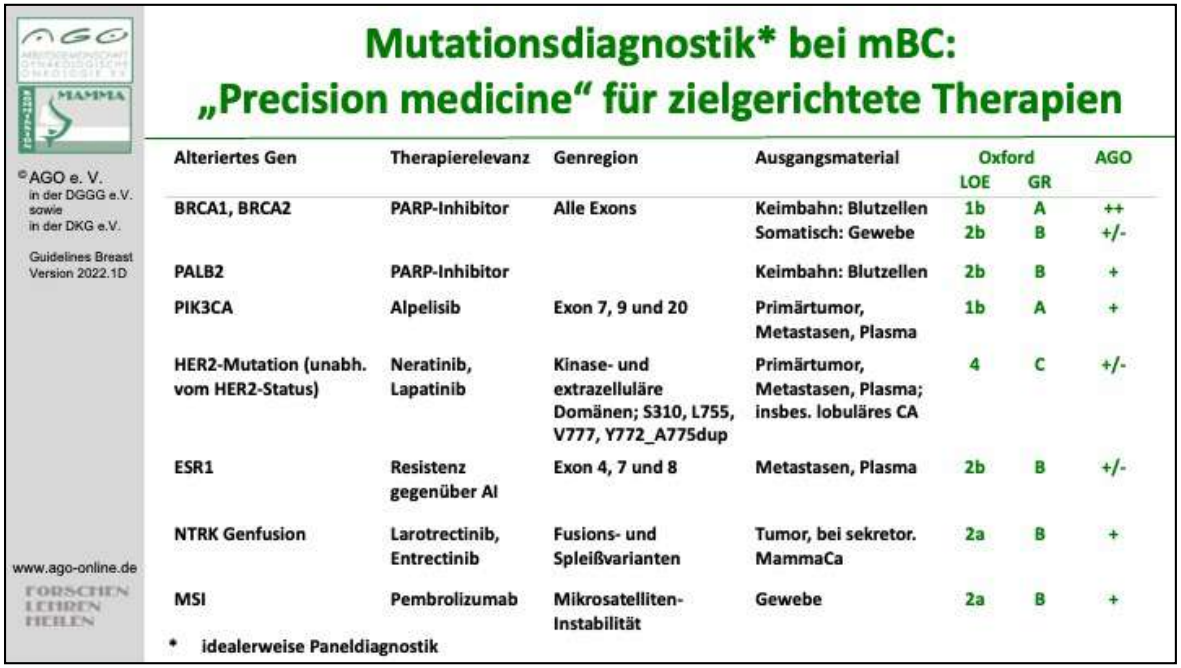
1. Aktas B, Kasimir-Bauer S, Lehmann N, et al.: Validity of bone marker measurements for monitoring response to bisphosphonate therapy with zoledronic acid in metastatic breast cancer. *Oncol Rep*. 2013;30(1):441–447.
2. Loftus LS, Edwards-Bennett S, Sokol GH. Systemic therapy for bone metastases. *Cancer 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.



Mutationsdiagnostik* bei mBC: „Precision medicine“ für zielgerichtete Therapien

Alteriertes Gen	Therapierelevanz	Genregion	Ausgangsmaterial	Oxford LOE	Oxford GR	AGO
BRCA1, BRCA2	PARP-Inhibitor	Alle Exons	Keimbahn: Blutzellen	1b	A	++
			Somatisch: Gewebe	2b	B	+/-
PALB2	PARP-Inhibitor		Keimbahn: Blutzellen	2b	B	+
PIK3CA	Alpelisib	Exon 7, 9 und 20	Primärtumor, Metastasen, Plasma	1b	A	+
HER2-Mutation (unabh. vom HER2-Status)	Neratinib, Lapatinib	Kinase- und extrazelluläre Domänen; S310, L755, V777, Y772_A775dup	Primärtumor, Metastasen, Plasma; insbes. lobuläres CA	4	C	+/-
ESR1	Resistenz gegenüber AI	Exon 4, 7 und 8	Metastasen, Plasma	2b	B	+/-
NTRK Genfusion	Larotrectinib, Entrectinib	Fusions- und Spleißvarianten	Tumor, bei sekretor. MammaCa	2a	B	+
MSI	Pembrolizumab	Mikrosatelliten-Instabilität	Gewebe	2a	B	+

* idealerweise Paneldiagnostik

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.

PIK3CA:

1. André 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/NEJMoa1813904B
2. Baselga J, Im SA, Iwata H, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017 Jul;18(7):904-916.
3. 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.
4. 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

Acquired Resistance to HER2-targeted Therapy in HER2(+) Breast Cancer. Clin Cancer Res 2017;23: 5123-34.

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

NTRK:

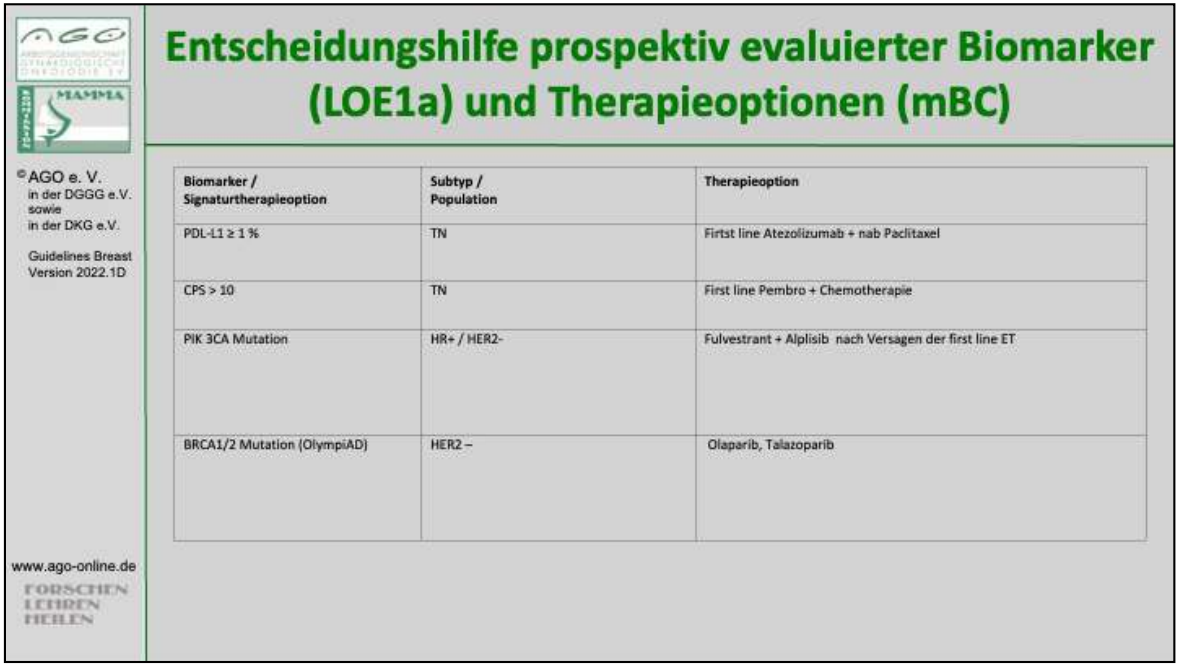
1. Cocco E, Scaltriti M, Drilon A (2018) NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol. 15(:731-747. doi: 10.1038/s41571-018-0113-0.

MSI:

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.



Biomarker / Signaturtherapieoption	Subtyp / Population	Therapieoption
PDL-L1 ≥ 1 %	TN	Firtst line Atezolizumab + nab Paclitaxel
CPS > 10	TN	First line Pembro + Chemotherapie
PIK 3CA Mutation	HR+ / HER2-	Fulvestrant + Alplisib nach Versagen der first line ET
BRCA1/2 Mutation (OlympiAD)	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.

<u>Prosigna (ROR / PAM50)</u>

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.

Therapierelevante Mutationsdiagnostik beim Mammakarzinom („actionable“)

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

Guidelines Breast
Version 2022.1D

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

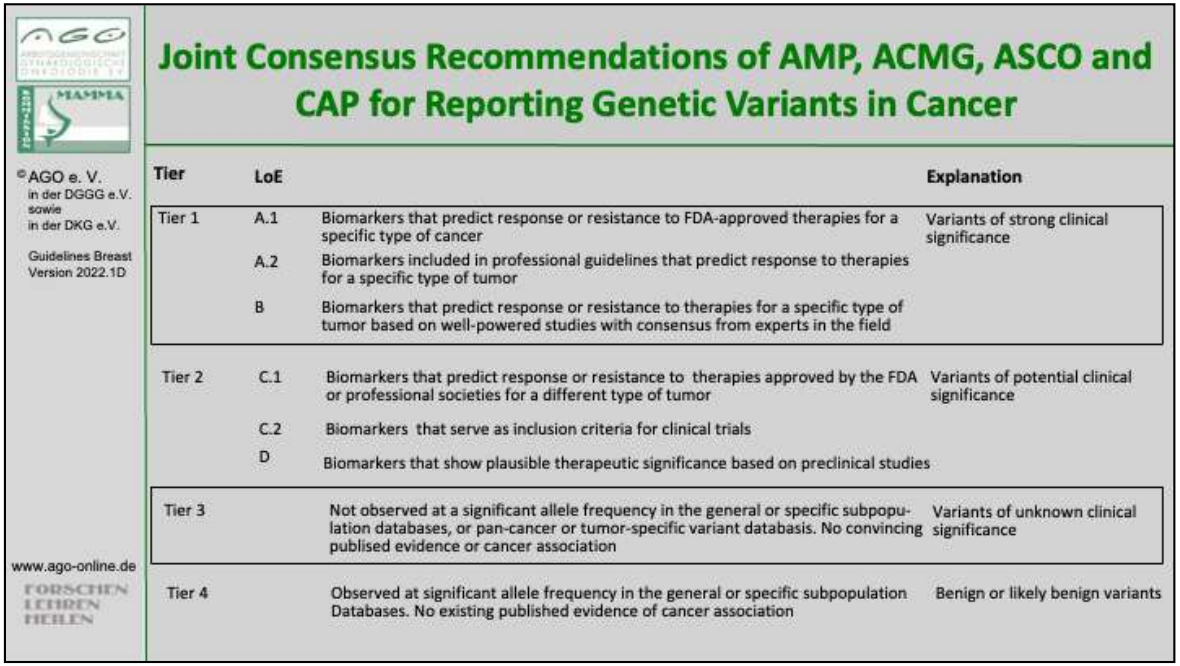
Diagnostik*	Faktor	Oxford LoE	Oxford GR	Oxford AGO
Aus Studien bei anderen Karzinomen („tumoragnostische Testung“)				
▪ Companion Diagnostics Mutations bei Therapien für andere Karzinome (z. B. BRAF, FGFR1, …)	Effektivität verschiedener Medikamente	4	D	+/-**
▪ Large Panel Gene Analysis (e.g. FoundationOne, GPS Cancer, NeoSelect, Molecular Health Guide, lokale „hand selected„ Panels)	Effektivität verschiedener Medikamente, Prognose	3a	C	+/-**
▪ Next Generation Sequencing (NGS) (möglichst nur bei Tier 1 + 2)	Effektivität verschiedener Medikamente	1b	B	+/-**

* Bestimmungsmethode somatischer Veränderungen nicht bewertet. Prinzipiell möglich aus Tumorfrischmaterial, Paraffin-Gewebe, zirkulierenden Nukleinsäuren

** Teilnahme an Studien oder strukturierten Programmen empfohlen

<u>NGS in breast cancer:</u>

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.