

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

Prognostische und prädiktive Faktoren

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■ Versionen 2002–2017:

Costa / Fersis / Friedrichs / Gerber / Göhring / Harbeck /
Janni / Liedtke / Loibl / Mundhenke / Nitz / Rody / Schaller /
Schmidt / Schmutzler / Schneeweiss / Simon / Solomayer /
Thomssen / Witzel

■ Version 2018:

Fasching / Wöckel

Data bases screened

Pubmed 2008 - 2016, ASCO 2003 – 2016, SABCS 2003 – 2016, Cochrane data base (n.d.)

Guidelines screened

St. Gallen 2015: 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.

ABC3: 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.

NCCN 2016: www.nccn.org

ASCO 2016: 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.

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. Harbeck N, Gnant M. Breast cancer. Lancet. 2016 Nov 16. pii: S0140-6736(16)31891-8.

Definition

Ein **prognostischer Faktor*** ist ein Parameter, der zu einem interessierenden Zeitpunkt z.B. bei Erstdiagnose vorliegt und, sofern keine weitere Therapie erfolgt, mit dem krankheitsfreien oder dem Gesamtüberleben d.h. mit dem natürlichen Krankheitsverlauf korreliert.

Ein **prädiktiver Faktor** ist ein Parameter, der das Ansprechen auf eine bestimmte Therapie definiert.

* Im Sinne dieser Leitlinie gemeint sind Faktoren, die mit einem Krankheitsrezidiv assoziiert sind.

“Low absolute risk implies low absolute benefit”

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 379: 432-444, 2012

1. 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. doi:10.1016/S0140-6736(11)61625-5.
2. Nielsen T, Jensen B, et al High risk premenopausal luminal A breast cancer patients derive no benefit from adjuvant chemotherapy: results from DBCG77B, SABCS 2015S1-08

Qualitätskriterien

- **Biologisches Modell**
- **Einfache und standardisierte Bestimmung, Qualitätssicherung des Tests**
- **Prospektive Planung der statistischen Auswertung (primäres Zielkriterium)**
- **Validierung der klinischen Bedeutung nach**
 - „Oxford Level of Evidence (LoE_{Ox2001})“-Kriterien und „Grades of Recommendation (GR)“
 - Modifizierte LOE Kriterien am archivierten Gewebe (LoE₂₀₀₉) und CTS-Kategorie¹⁻³ für Biomarker, deren Validierung ausschließlich an archiviertem Material erfolgt ist
- **Klinische Relevanz für Therapieentscheidung**

¹ Simon et al, J Natl Cancer Inst 101: 1446-1452, 2009

² Febbo et al, J Natl Compr Canc Netw 9 Suppl 5: S1-32, 2011

³ McShane, Hayes, J Clin Oncol 30: 4223 – 4232, 2012

1. Febbo PG, Ladanyi M, Aldape KD, et al. (2011) NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw 9 Suppl 5: S1-32; quiz S33.
2. Hayes DF, Bast RC, Desch CE et al. (1996) Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J. Natl. Cancer Inst. 88 (20): 1456–1466.
3. Jeremy Howick, Iain Chalmers, Paul Glasziou, et al. Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document). Oxford Centre for Evidence-Based Medicine.
4. McShane LM, Altman DG, Sauerbrei W et al. (2005) Reporting recommendations for tumor marker prognostic studies. J. Clin. Oncol. 23 (36): 9067–9072. Available: doi:10.1200/JCO.2004.01.0454.
5. McShane LM, Hayes DF (2012) Publication of tumor marker research results: the necessity for complete and transparent reporting. J. Clin. Oncol. 30 (34): 4223–4232. Available: doi:10.1200/JCO.2012.42.6858.
6. Simon RM, Paik S, Hayes DF (2009) Use of archived specimens in evaluation of prognostic and predictive biomarkers. J. Natl. Cancer Inst. 101 (21): 1446–1452. Available: doi:10.1093/jnci/djp335.

Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination

Category Element	A Prospective	B Prospective using archived samples	C Prospective/ observational	D Retrospective/ observational
Clinical trial	Prospective controlled trial (PCT) designed to address tumor marker	Prospective trial not designed to address tumor marker, but design accommodates tumor marker utility Accommodation of predictive marker requires Prospective randomized controlled trial (PRCT)	Prospective observational registry, treatment and follow-up not dictated	No prospective aspect to study
Patients and patient data	Prospectively enrolled, treated, and followed in PCT	Prospectively enrolled, treated, and followed in clinical trial and, especially if a predictive utility is considered, a PRCT addressing the treatment of interest	Prospectively enrolled in registry, but treatment and follow-up standard of care	No prospective stipulation of treatment or follow-up; patient data collected by retrospective chart review
Specimen collection, processing, and archival	Specimens collected, processed, and assayed for specific marker in real time	Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion	Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion	Specimens collected, processed and archived with no prospective SOPs
Statistical design and analysis	Study powered to address tumor marker question	Study powered to address therapeutic question and underpowered to address tumor marker question Focused analysis plan for marker question developed before doing assays	Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study Focused analysis plan for marker question developed before doing assays	Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study No focused analysis plan for marker question developed before doing assays
Validation	Result unlikely to be play of chance Although preferred, validation not required	Result more likely to be play of chance than A but less likely than C Requires one or more validation studies	Result very likely to be play of chance Requires subsequent validation studies	Result very likely to be play of chance Requires subsequent validation studies

Simon, Paik, Hayes, J Natl Cancer Inst 101: 1446-1452, 2009

1. McShane LM, Hayes DF. Publication of tumor marker research results: the necessity for complete and transparent reporting. J. Clin. Oncol. 2012; 30(34): 4223 – 4232
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

Revised Determination of Levels of Evidence Using Elements of Tumor Marker Studies

Level of Evidence	Category	Validation studies available
I	A	None required
I	B	One or more with consistent results
II	B	None or inconsistent results
II	C	2 or more with consistent results
III	C	None or 1 with consistent results or inconsistent results
IV–V	D	Not applicable because LOE IV and V studies will never be satisfactory for determination of medical utility

Simon, Paik, Hayes, J Natl Cancer Inst 101: 1446-1452, 2009

1. McShane LM, Hayes DF. Publication of tumor marker research results: the necessity for complete and transparent reporting. J. Clin. Oncol. 2012; 30(34): 4223 – 4232
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

Requirements for a Marker-Based Test to Reach Level IB Evidence

- **1. Adequate amounts of archived specimen must be available from enough patients from a prospective trial ... for analyses to have adequate statistical power and for the patients included in the evaluation to be clearly representative of the patients in the trial.**
- **2. The marker-based test should be analytically and preanalytically validated for use with archived specimens.**
- **3. The plan for marker evaluation should be completely specified in writing before the performance of marker assays on archived specimens and should be focused on evaluation of a single completely defined marker-based test.**
- **4. The results from archived specimens should be validated using specimens from one or more similar, but separate, studies.**

McShane & Hayes, J Clin Oncol 30: 4223-4232, 2012

1. McShane LM, Hayes DF. Publication of tumor marker research results: the necessity for complete and transparent reporting. J. Clin. Oncol. 2012; 30(34): 4223 – 4232
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

Prognosefaktoren I – Primäres Mammakarzinom

Faktor	Oxford		
	LoE _{Ox2001}	GR	AGO
▪ Tumorgroße	1a	A	++
▪ Lymphknotenstatus	1a	A	++
▪ Vorliegen von Fernmetastasen	1a	B	++
▪ Histologischer Typ (mucinös, tubulär etc.)	2b	B	++
▪ Grading (Elston & Ellis)	2a	B	++
▪ Alter	2a	B	++
▪ Einbruch in Lymph- und/oder Blutgefäße	2b	B	+
▪ pCR nach NACT* bei (HR+/G3, HER2+, TN)	1a	A	++
▪ Übergewicht (BMI > 30 kg/m ²)	1b	B	+
▪ Resektionsstatus	1a	A	+

* NACT = Neoadjuvante Chemotherapie

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.
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.

Statement: Obesity

1. D. S. M. Chan 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. Published online Apr 27, 2014. doi: 10.1093/annonc/mdu042 PMID: PMC4176449.
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.
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.

Reproducibility

- **ER/PR: concordance central vs local is high (97%; Plan B, SABCS 2014)**
- **Grading: concordance central vs local is 68% (PlanB, JCO 2016)**
- **HER2: frequency of false-positive test results 6% (ASCO /CAP JCO 2013)**
- **Impact of routine pathologic review in N0 BC: 20% changes : grading 40%, LVI 26%, N 15%, margin 12% (JCO 2012)**
- **pN0 from MIRROR study: pN0 was upstaged in 22%, in central pathology review (Ann Oncol 2012)**
- **Inter- and intraobserver variability in measurement of ki-67 is high (J Nat. Cancer Institute 2011)**

1. Dowsett M, Nielsen TO, A'Hern R, et al: Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. *J Natl Cancer Inst* 2011, 103(22):1656-1664.
2. 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. doi:10.1200/JCO.2009.25.6529.
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. doi:10.1093/annonc/mds072.
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. doi:10.1200/JCO.2011.38.9247.
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.

Prognosefaktoren II – Primäres Mammakarzinom

Es muss betont werden, dass die *Levels of Evidence* mittels Oxford- und CTS-Kriterien nicht direkt verglichen werden können.

Die prospektiv-geplante retrospektive Validierung von Biomarkern (CTS-Level 1) kann durch eine unzureichende Anzahl von Proben aus einer klinischen Studie verzerrt werden.

Diese Gewebesammlung könnte möglicherweise nicht das Ergebnis der Gesamtstudie repräsentieren. Ein optimaler Prozentsatz von Proben einer klinischen Studie für eine optimale Biomarker-Evaluierung ist bislang nicht etabliert.*

* Simon, Paik, Hayes, J Natl Cancer Inst 101: 1446–1452, 2009

ER/PR

1. 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. doi:10.1200/JCO.2009.25.6529.

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. doi:10.1634/theoncologist.2008-0230.
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.

Ki-67

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. Dowsett, M., Nielsen, T.O., A'Hern, R., et al. 2011. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. *J. Natl. Cancer Inst.* 103, 1656–1664. doi:10.1093/jnci/djr393.
3. 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. doi:10.1186/1471-2407-11-486.
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.
5. Luporsi, E., André, F., Spyrtos, 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. doi:10.1007/s10549-011-1837-z.
6. Urruticoechea, A., Smith, I.E. & Dowsett, M. 2005. Proliferation marker Ki-67 in early breast cancer. *J. Clin. Oncol.* 23, 7212–7220. doi:10.1200/JCO.2005.07.501.
7. 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. doi:10.1371/journal.pone.0037379.
8. 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. doi:10.1200/JCO.2008.17.0829.
9. 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. doi:10.1093/jnci/djm289.

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 of Oncology*, 2010

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., Prechtel, 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. doi:10.1093/jnci/djp145.
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.

Prognosefaktoren II – Primäres Mammakarzinom

Faktor	Oxford		
	LoE _{Ox2001}	GR	AGO
▪ ER / PgR	2a	B	+
▪ HER2 (IHC, FISH)	2b	B	+
▪ ER / PgR / HER2/Ki-67 als Surrogatmarker für molekulare Subtypen	2b	B	+
▪ uPA / PAI (Femtele® ELISA)§ in N0	1a	A	+
▪ Proliferationsmarker			
▪ Ki-67 vor, während oder nach der Behandlung	1a	B	+

§ Validierte klinische Daten sind nur verfügbar für diesen Assay

ER/PR

1. 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. doi:10.1200/JCO.2009.25.6529.

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. doi:10.1634/theoncologist.2008-0230.
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.

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doi:10.1093/jnci/djp082.

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3. 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. doi:10.1186/1471-2407-11-486.
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.
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6. Urruticoechea, A., Smith, I.E. & Dowsett, M. 2005. Proliferation marker Ki-67 in early breast cancer. *J. Clin. Oncol.* 23, 7212–7220. doi:10.1200/JCO.2005.07.501.
7. Varga, Z., Diebold, J., Dommann-Scherrer, C., Frick, H., Kaup, D., Noske, A., Obermann, E., Ohlschlegel, C., Padberg, B., 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. doi:10.1371/journal.pone.0037379.
8. 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. doi:10.1200/JCO.2008.17.0829.
9. 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. doi:10.1093/jnci/djm289.
10. 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.

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 of Oncology*, 2010

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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., Prechtel, 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. doi:10.1093/jnci/djp145.
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.

Commercially Available Molecular Tests

	70 gene signature (MammaPrint®) §	21 gene Recurrence score (Oncotype DX®) §	8 gene signature (Endopredict®) §	PAM 50 (Prosigna®) §
Provider	Agendia	Genomic Health	Sividon	NanoString
Type of assay	70-gene assay	21-gene recurrence score	11-gene assay	50-gene assay
Type of tissue	fresh frozen (technical validation for FFPE available)	FFPE	FFPE	FFPE
Technique	Microarrays for RNA	qRT-PCR	q-RT-PCR	Direct hybridization
Central lab	yes	yes	no	no
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
Clinical Validation	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

§ Validated clinical data only available for this assay

Endopredict

- 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. Doi
- 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 JNCI 2016 Jan (accepted)
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Mammaprint

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Oncotype

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. doi:10.1016/S1470-2045(09)70314-6.
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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. doi:10.1158/1078-0432.CCR-12-0286.
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Multiple assays

1. Sestak I, Buus R, Cuzick J, et al. Comprehensive comparison of prognostic

signatures for breast cancer in TransATAC. SABCS 2016: S6-05

Commercially Available Molecular Tests

	70 gene signature (MammaPrint®) §	21 gene Recurrence score (Oncotype DX®) §	8 gene signature (Endopredict®) §	PAM 50 (Prosigna®) §
Prognosis after 5 yrs (late recurrences)	not separately shown	no	yes	yes
Predictive impact (chemotherapy benefit)	poorly validated	yes *	not shown	not shown
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%)
Prospective evidence (5-year DFS, OS)	MINDACT (N0, N1)	TAILOR _x (N0, low-risk, RS<11) PlanB (N0, highrisk/N+)	—	—

§ Validated clinical data only available for this assay

* Trial performed before HER2 testing, HER2 positive patients may have been included

Endopredict

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Oncotype

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Multiple assays

1. Sestak I, Buus R, Cuzick J, et al. Comprehensive comparison of prognostic signatures for breast cancer in TransATAC. *SABCS 2016: S6-05*

Prospektiv randomisierte Studien

(Oncotype DX [TailorX, PlanB], MammaPrint [MINDACT])

Die Prognose in der Niedrigrisiko-Gruppe ist für beide Tests hervorragend
(ca. 94% 5-Jahres DFS mit adjuvanter endokriner Therapie)

	TailorX	PlanB	MINDACT
Nachbeobachtungszeit	Median 69 Mo	5-J-DFS	Median 60 Mo
Anteil Niedrigrisikogruppe (prinzipiell für Chemotherapie geeignete Studienpopulation)	16%	15,3%	23,2% (high clinical and low genomic risk)
Test failure rate	n.r.	2,9%	26% (fresh frozen tissue)
Anteil intermediäre Risikogruppe (gilt nur für OncotypeDX)	67,3%	60,4%	n.a.
Anteil intermediäre Risikogruppe (gilt nur für OncotypeDX)	67,3%	60,4%	n.a.

Mammaprint

- 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.

Onkotyper DX

- 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.
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Several tests

- 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).

Prognosefaktoren III – Primäres Mammakarzinom

Faktor	LoE ₂₀₀₉	CTS	AGO
▪ Disseminierte Tumorzellen (DTC, im Knochenmark)	I	B	+/-
▪ Zirkulierende Tumorzellen (CTC, im Blut, Cell Search®) §	I	A	+/-
▪ CTC vor NACT (in Bezug auf OS, DDFS, LRFI)	I ^a	B	+/-
▪ Therapieentscheidungen basierend auf CTC-Phänotypen	III	C	-
▪ Multigene assays			
▪ EndoPredict® (N0-1, HR+, Her2 -)	I	B	+*
▪ Prosigna® (N0-1, HR+, Her2 -)	I	B	+*
▪ MammaPrint® (70 gene signature) (N0-1)	I	A	+*
▪ Oncotype DX® (N0-1, HR+ HER2-, 5 Jahre)	I	A	+*

* Sollte nur bei ausgewählten Patientinnen angewandt werden, wenn alle anderen Kriterien keine Therapieentscheidung zulassen

§ Validierte klinische Daten nur verfügbar für diesen Assay

DTC

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CTC

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Oncotype

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Neoadjuvante Chemotherapie

Therapieprädiktion I

Faktor	CTS	LoE _{Ox2001}	GR	AGO
▪ Junges Alter	B	1a	A	+
▪ cT1 / cT2-Tumore o. N0 o. G3	B	1a	A	++
▪ Negativer ER- und PgR-Status	B	1a	A	++
▪ Triple negative breast cancer (TNBC)	B	1a	A	++
▪ Positiver HER2-Status	B	1a	A	++
▪ Nicht-lobulärer Subtyp	B	1a	A	+
▪ Frühes klinisches Ansprechen	B	1b	A	+

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.
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Neoadjuvante Chemotherapie

Therapieprädiktion II

Faktor	LoE ₂₀₀₉	CTS	AGO
▪ Multigensignatur (Mammaprint, Endopredict, Oncotype Dx, Prosigna [§])	II	C	+/-
▪ Ki-67	I	B	+
▪ Tumor infiltrating lymphocytes*	I	B	+
▪ PIK3CA mutation	I	B	+/-
▪ gBRCA bei TNBC	II	B	+

§ Validierte klinische Daten nur verfügbar für diesen Assay

* Definiert als dichte lymphozytäre Infiltration des inneren peritumoralen Stromas außerhalb der Invasionsfront (Stroma besteht mit > 50% aus Lymphozyten)

TIL

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PIK3CA

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Prädiktive Faktoren – Endokrine Therapie

Faktor	Oxford		
	LoE _{Ox2001}	GR	AGO
■ Endokrine Therapie			
■ ER/PgR Status	1a	A	++
■ IHC Färbeintensität (ER/PgR)	1a	A	+
■ Tamoxifen			
■ CYP2D6 Polymorphismus	2b	D	-
■ Ovarielle Ablation			
■ Menopausenstatus	1c	A	++
■ Aromataseinhibitoren vs. Tamoxifen			
■ Menopausenstatus	1c	A	++
■ ER / PgR / HER2 als Einzelmarker	1c	A	-
■ Lobulärer Subtyp	2b	B	+
■ Ki-67 hoch	2b	B	+/-
■ Übergewicht (BMI > 30 kg/m²)	2b	B	+/-

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Prädiktive Faktoren

HER2 gezielte Therapie / Adjuvante Chemotherapie

Faktor	LoE _{Ox2001} ([§] LoEO _{x2009})	GR ([§] CTS)	AGO
■ Anti-HER2-Therapie			
■ HER2	1a	A	++
■ Adjuvante Chemotherapie			
■ uPA / PAI1 (Femtelle®) ELISA [§]	1a	A	+
■ 21-Gen-Recurrence-Score (Oncotype DX®) [§]	I [§]	B [§]	+/-

[§] Validierte klinische Daten nur verfügbar für diesen Assay.

Onkotype

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. doi:10.1200/JCO.2005.04.7985.

uPA/PAI-1

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Prognosefaktoren – Metastasiertes Mammakarzinom

Faktor	LoE ₂₀₀₉	CTS	AGO
<ul style="list-style-type: none"> Zirkulierende Tumorzellen (CTC im Blut, Cell Search®) <ul style="list-style-type: none"> Prognose Frühes Therapieansprechen (3 Wo.) Therapieentscheidungen basiert auf CTC-Anzahl oder CTC-Phänotypen 	 I I I	 A B A	 + + -*

* Studienteilnahme empfohlen

- 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

- 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.
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Exome/Whole Gene Testing of Panel Genes or the Whole Genome (Genomic Profile Tests)

	Local Pathology based*, **, ***	Foundation one*	Molecular Health Guide*	NeoSelect*	GPS Cancer*
Provider	Local Pathologist	Roche	Molecular Health	Siemens Healthineers	NantHealth
Number of Genes	Ca. 25- ca. 150	>300	>600	39	whole genome
Central lab	no	yes	yes	yes/no	yes
Indication and population studied	not yet defined	not yet defined	not yet defined	not yet defined	not yet defined
Registration / QM	Local QC Standards, Analyse „CE konform“	FDA approved	ISO13485	„CE-konform“	CLIA certified CAP accredited
Implementation Status	part of clinical routine care	External Service Providers			

- * Interpretation of genomic alterations with regard to resistance or efficacy of therapies, eligibility for clinical trials etc. by bioinformatic, automated, quality controlled algorithms (e.g. OncoKb.org)
- ** Implemented in molecular tumor boards as part of clinical routine
- *** some of which are professionalized like MSK-IMPACT (FDA authorized)

Commercially Available Comprehensive Molecular Profiling Tests

1. <http://www.newoncology.com/neoonsite.html>
2. <http://www.molecularhealth.com/global/>
3. <https://www.foundationmedicine.com/genomic-testing/foundation-one>
4. <http://www.gpscancer.com/>

Therapierelevante genomische Faktoren beim Mammakarzinom („actionable“)

Faktor*	Outcome	LoE ₂₀₀₉	CTS	AGO
Aus Studien beim Mammakarzinom				
▪ sPI3K Mutation	Anti-HER-Therapie-Effektivität	I	B	..**
▪ sESR1 Mutation	Antihormon-Effektivität	II	B	+/-**
▪ sHER2 Mutation	Anti-HER2-Therapie-Effektivität	II	B	+/-**
▪ sBRCA1/2 oder gBRCA1/2	Platin-Effektivität	II	B	+/-**
▪ sBRCA1/2 oder gBRCA1/2	Chemotherapie-Effektivität	II	B	+/-**
▪ sBRCA1/2 oder gBRCA1/2	PARP-Inhibitor-Effektivität	I	A	+**
Aus Studien bei anderen Karzinomen				
▪ Companion Diagnostics Mutations bei Therapien für andere Karzinome (z.B. BRAF, FGFR1,)	Effektivität verschiedener Medikamente	IV	D	+/-**
▪ Large Panel Gene Analysis (e.g. FoundationOne, GPS Cancer, NeoSelect, Molecular Health Guide, Lokale „hand selected,, Panels)	Effektivität verschiedener Medikamente, Prognose	III	C	+/-**

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

** Teilnahme an Studien oder strukturierten Programmen empfohlen / s=somatisch / g = Keimbahn

1. Byrski T, Gronwald J, Huzarski T, et al. Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. J Clin Oncol 2010;28: 375-9.
2. 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.
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4. 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.
5. Huzarski T, Byrski T, Gronwald J, et al. Ten-year survival in patients with BRCA1-negative and BRCA1-positive breast cancer. J Clin Oncol 2013;31: 3191-6.
6. Robinson DR, Wu YM, Vats P, et al. Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet 2013;45: 1446-51.
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