Breast Cancer

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906-225-7804
### WHO classification of tumours of the breast

#### EPITHELIAL TUMOURS

**Invasive breast carcinoma**

- Invasive carcinoma of no special type (NST) 8500/3
- Pleomorphic carcinoma 8022/3
- Carcinoma with osteoclast-like stromal giant cells 8035/3
- Carcinoma with chorionicarionomatous features 8520/3
- Carcinoma with melanotic features 8520/3
- Classic lobular carcinoma 8520/3
- Solid lobular carcinoma 8520/3
- Alveolar lobular carcinoma 8520/3
- Pleomorphic lobular carcinoma 8520/3
- Tubulolobular carcinoma 8520/3
- Mixed lobular carcinoma 8520/3
- Tubular carcinoma 8520/3
- Cribriform carcinoma 8520/3
- Mucinous carcinoma 8540/3
- Carcinoma with medullary features 8540/3
- Medullary carcinoma 8540/3
- Atypical medullary carcinoma 8540/3
- Invasive carcinoma NST with medullary features 8540/3
- Carcinoma with apocrine differentiation 8575/3
- Carcinoma with signet-ring-cell differentiation 8575/3
- Invasive micropapillary carcinoma 8575/3
- Metaplastic carcinoma of no special type (NST) 8575/3
- Low-grade adenosquamous carcinoma 8575/3
- Fibromatosis-like metaplastic carcinoma 8575/3
- Squamous cell carcinoma 8575/3
- Spindle cell carcinoma 8575/3
- Metaplastic carcinoma with mesenchymal differentiation 8575/3
- Chondroid differentiation 8575/3
- Ossous differentiation 8575/3
- Other types of mesenchymal differentiation 8575/3
- Mixed metaplastic carcinoma 8575/3
- Myoepithelial carcinoma 8575/3

**Rare types**

- Carcinoma with neuroendocrine features 8574/3
- Neuroendocrine tumour, well-differentiated 8574/3
- Neuroendocrine carcinoma, poorly differentiated (small cell carcinoma) 8574/3
- Carcinoma with neuroendocrine differentiation 8574/3

#### Preceptor lesions

- Ductal carcinoma in situ 8500/2
- Lobular carcinoma in situ 8500/3
- Classic lobular carcinoma in situ 8520/3
- Atypical lobular hyperplasia 8519/2

#### Intraductal proliferative lesions

- Usual ductal hyperplasia 8500/3
- Columnar cell lesions including flat epithelial atypia 8500/3
- Atypical ductal hyperplasia 8500/3

#### Papillary lesions

- Intraductal papilloma 8503/0
- Intraductal papilloma with atypical hyperplasia 8503/0
- Intraductal papilloma with ductal carcinoma in situ 8503/2
- Intraductal papilloma with lobular carcinoma in situ 8502/2
- Intraductal papilloma with ductal carcinoma in situ 8503/3
- Intraductal papilloma with lobular carcinoma in situ 8502/2
- Intraductal papilloma with ductal carcinoma in situ 8503/3
- Encapsulated papillary carcinoma 8502/2
- Encapsulated papillary carcinoma with invasion 8504/2
- Solid papillary carcinoma 8509/2
- Invasive 8509/3

#### Benign epithelial proliferations

- Sclerosing adenosis 8509/3
- Apocrine adenosis 8509/3
GOALS

- IN SITU AND INVASIVE CARCINOMA

- SIGNIFICANCE OF ER/PR AND HER2

- MOLECULAR TESTING IN THE MANAGEMENT OF PATIENTS WITH BREAST CANCER
Ductal Carcinoma in Situ (DCIS)

• Definition – ‘proliferation of malignant epithelial cells that has not breached the myoepithelial layer of the ductolobular system’
  – Highly heterogeneous
  • Presentation
  • Morphology
  • Biomarker expression
  • Underlying cytogenetic alterations
  • Natural progression
Classification of DCIS

• Grade
  – G1, G2, G3
  – Necrosis
  – Morphologic variants

• DCIS with microinvasion
Differential dx

• Atypical ductal hyperplasia (ADH) and low grade DCIS
• Solid low grade DCIS and lobular carcinoma in situ (LCIS)
• High grade DCIS and pleomorphic lobular carcinoma in situ (PLCIS)
• DCIS with microinvasion
<table>
<thead>
<tr>
<th>Pathologic Lesion</th>
<th>Relative Risk (Absolute Lifetime Risk)</th>
</tr>
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<tbody>
<tr>
<td><strong>NONPROLIFERATIVE BREAST CHANGES</strong></td>
<td>1.0 (3%)</td>
</tr>
<tr>
<td>(Fibrocystic changes)</td>
<td></td>
</tr>
<tr>
<td>Duct ectasia</td>
<td></td>
</tr>
<tr>
<td>Cysts</td>
<td></td>
</tr>
<tr>
<td>Apocrine change</td>
<td></td>
</tr>
<tr>
<td>Mild hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Adenosis</td>
<td></td>
</tr>
<tr>
<td>Fibroadenoma w/o complex features</td>
<td></td>
</tr>
<tr>
<td><strong>PROLIFERATIVE DISEASE WITHOUT ATYPIA</strong></td>
<td>1.5 to 2.0 (5% to 7%)</td>
</tr>
<tr>
<td>Moderate or florid hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Sclerosing adenosis</td>
<td></td>
</tr>
<tr>
<td>Papilloma</td>
<td></td>
</tr>
<tr>
<td>Complex sclerosing lesion (radial scar)</td>
<td></td>
</tr>
<tr>
<td>Fibroadenoma with complex features</td>
<td></td>
</tr>
<tr>
<td><strong>PROLIFERATIVE DISEASE WITH ATYPIA</strong></td>
<td>4.0 to 5.0 (13% to 17%)</td>
</tr>
<tr>
<td>Atypical ductal hyperplasia (ADH)</td>
<td></td>
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<tr>
<td>Atypical lobular hyperplasia (ALH)</td>
<td></td>
</tr>
<tr>
<td><strong>CARCINOMA IN SITU</strong></td>
<td>8.0 to 10.0 (25% to 30%)</td>
</tr>
<tr>
<td>Lobular carcinoma in situ (LCIS)</td>
<td></td>
</tr>
<tr>
<td>Ductal carcinoma in situ (DCIS)</td>
<td></td>
</tr>
<tr>
<td>Total Cancers</td>
<td>Percentage</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>CARCINOMA IN SITU</td>
<td>15–30</td>
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<tr>
<td>Ductal carcinoma in situ</td>
<td>80</td>
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<tr>
<td>Lobular carcinoma in situ</td>
<td>20</td>
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<tr>
<td>INVASIVE CARCINOMA</td>
<td>70–85</td>
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<tr>
<td>No-special-type carcinoma (“ductal”)</td>
<td>79</td>
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<tr>
<td>Lobular carcinoma</td>
<td>10</td>
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<tr>
<td>Tubular/cribriform carcinoma</td>
<td>6</td>
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<td>Mucinous (colloid) carcinoma</td>
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<td>Medullary carcinoma</td>
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<tr>
<td>Papillary carcinoma</td>
<td>1</td>
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<tr>
<td>Metaplastic carcinoma</td>
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Molecular testing of breast cancers
Beyond hormone receptor and Her2 status

• Intrinsic (molecular) subtypes
• Multigene prognostic test
Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

Therese Sørlie\textsuperscript{a,b,c}, Charles M. Perou\textsuperscript{a,d}, Robert Tibshirani\textsuperscript{e}, Turid Aas\textsuperscript{f}, Stephanie Geisler\textsuperscript{g}, Hilde Johnsen\textsuperscript{b}, Trevor Hastie\textsuperscript{e}, Michael B. Eisen\textsuperscript{b}, Matt van de Rijn\textsuperscript{i}, Stefanie S. Jeffrey\textsuperscript{j}, Thor Thorsen\textsuperscript{k}, Hanne Quist\textsuperscript{l}, John C. Matrese\textsuperscript{c}, Patrick O. Brown\textsuperscript{m}, David Botstein\textsuperscript{c}, Per Eystein Lønning\textsuperscript{g}, and Anne-Lise Børresen-Dale\textsuperscript{b,n}

Departments of \textsuperscript{b}Genetics and \textsuperscript{l}Surgery, The Norwegian Radium Hospital, Montebello, N-0310 Oslo, Norway; \textsuperscript{d}Department of Genetics and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC 27599; Departments of \textsuperscript{c}Health Research and Policy and Statistics, \textsuperscript{c}Genetics, \textsuperscript{i}Pathology, \textsuperscript{j}Surgery, and \textsuperscript{m}Biochemistry and Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, CA 94305; Departments of \textsuperscript{g}Medicine (Section of Oncology), \textsuperscript{l}Surgery, and \textsuperscript{b}Biochemical Endocrinology, Haukeland University Hospital, N-5021 Bergen, Norway; and \textsuperscript{n}Life Sciences Division, Lawrence Orlando Berkeley National Laboratories, and Department of Molecular and Cellular Biology, University of California, Berkeley, CA 94720

Contributed by David Botstein, July 17, 2001
Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network

Predicted somatic non-silent mutations

<table>
<thead>
<tr>
<th>Subtype</th>
<th>PK3CA</th>
<th>MAP2K1</th>
<th>MAP3K4</th>
<th>GA1A3</th>
<th>MLL3</th>
<th>CDH1</th>
<th>PTEN</th>
<th>PIK3R1</th>
<th>AKT1</th>
<th>RB1</th>
<th>A5F2</th>
<th>PTEN22</th>
<th>CPD9D2</th>
<th>ER</th>
<th>PR</th>
<th>HER2</th>
<th>T</th>
<th>N</th>
<th>PK3CA</th>
<th>ERBB2</th>
<th>MAP2K4</th>
<th>MLL3</th>
<th>CDKNA2</th>
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<tbody>
<tr>
<td>Luminal A</td>
<td>36%</td>
<td>34%</td>
<td>8%</td>
<td>4%</td>
<td>11%</td>
<td>7%</td>
<td>7%</td>
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<td>2%</td>
<td>4%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>36%</td>
<td>15%</td>
<td>5%</td>
<td>2%</td>
<td>6%</td>
<td>5%</td>
<td>4%</td>
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<td>4%</td>
<td>4%</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>36%</td>
<td>15%</td>
<td>5%</td>
<td>2%</td>
<td>6%</td>
<td>5%</td>
<td>4%</td>
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<td>1%</td>
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<tr>
<td>Basal-like</td>
<td>36%</td>
<td>15%</td>
<td>5%</td>
<td>2%</td>
<td>6%</td>
<td>5%</td>
<td>4%</td>
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<tr>
<td>All</td>
<td>45%</td>
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<td>5%</td>
<td>2%</td>
<td>6%</td>
<td>5%</td>
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<td>1%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Percentages of cases with mutation by expression subtype

4 October 2012 Vol 490 Nature 63
The Emerging Role of the Molecular Diagnostics Laboratory in Breast Cancer Personalized Medicine

Francine B. De Abreu, Wendy A. Wells, and Gregory J. Tsongalis

From the Department of Pathology, Geisel School of Medicine at Dartmouth, Hanover; and the Dartmouth Hitchcock Medical Center and the Norris Cotton Cancer Center, Lebanon, New Hampshire

The American Journal of Pathology, Vol. 183, No. 4, October 2013

Table 1  Summary of Characteristics of Molecular Subtypes

<table>
<thead>
<tr>
<th>Molecular subtype</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>HER2 positive</th>
<th>Basal-like (or TNBC)</th>
<th>Claudin-low (or TNBC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%)</td>
<td>50-60</td>
<td>10-20</td>
<td>15-20</td>
<td>10-20</td>
<td>12-14</td>
</tr>
<tr>
<td>Genetic expression profile</td>
<td>ER-related genes, ↓proliferation genes</td>
<td>↑Proliferation genes</td>
<td>HER2-related genes, ↑proliferation genes</td>
<td>CkS, P-cadherin, CAV1/2, CD44, KIT</td>
<td>↓Cell-cell junction genes, ↑immune response genes</td>
</tr>
<tr>
<td>Histological grade</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>IHC markers</td>
<td>ER⁺, PR⁺, HER2⁻, Ki-67, CK8/18⁺, GATA3⁺</td>
<td>ER⁺, PR⁺⁻, HER2⁺⁻, EGFR⁺, ↑Ki-67</td>
<td>ER⁻, PR⁻, HER2⁻</td>
<td>ER⁻, PR⁻, HER2⁻</td>
<td>ER⁻, PR⁻, HER2⁻</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Good</td>
<td>Intermediate/poor</td>
<td>Poor</td>
<td>Poor</td>
<td>Poor</td>
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<tr>
<td>Response to chemotherapy</td>
<td>Low (7% CR)</td>
<td>Intermediate (17% CR)</td>
<td>High (43% CR)</td>
<td>High (36% CR)</td>
<td>Low</td>
</tr>
<tr>
<td>Treatment</td>
<td>AI and SERMs: tamoxifen PI3K/AKT/mTOR pathway</td>
<td>Tamoxifen and AI PI3K/AKT/mTOR pathway</td>
<td>HER2 target therapy PI3K/AKT/mTOR pathway</td>
<td>PARP-1 inhibitors PI3K/AKT/mTOR and RAS-RAF-MEK pathway</td>
<td>PARP-1 inhibitors</td>
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<tr>
<td>New treatment targets</td>
<td></td>
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</tr>
</tbody>
</table>

CAV, caveolin; CK, cytokine; CR, complete response; GATA, GATA binding protein; KIT, v-KIT Hardy-Zuckerman 4 feline sarcoma viral oncogene human homolog; SERM, selective estrogen receptor modulator.
Breast Cancer

- Estrogen Receptor Negative
- Estrogen Receptor Positive

- Basal-like
- HER2 Enriched
- Luminal B
- Luminal A

Other: Molecular apocrine, Claudin low
Do the intrinsic subtypes have value in current clinical practice?
• “The 12th St Gallen international Breast Cancer Conference (2011) expert panel adopted a new approach to the classification of patients for therapeutic purposes based on the recognition of intrinsic biological subtypes with the breast cancer spectrum”

St Gallen 2015

• “… in the clinical practice the key question is not the separation of the molecularly-defined intrinsic subtypes, but the discrimination between patients who will or will not benefit from particular therapies”

Coates 2015
Molecular diagnostics

- Oncotype DX
- PAM 50
- MammaPrint
A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer

Soonmyung Palk, M.D., Steven Shak, M.D., Gong Tang, Ph.D., Chungyeul Kim, M.D., Joffre Baker, Ph.D., Maureen Cronin, Ph.D., Frederick L. Baehner, M.D., Michael G. Walker, Ph.D., Drew Watson, Ph.D., Taesung Park, Ph.D., William Hiller, H.T., Edwin R. Fisher, M.D., D. Lawrence Wickerham, M.D., John Bryant, Ph.D., and Norman Wolmark, M.D.

NEJM 2004;351:2817

OncotypeDx (Genomic Health, Inc.)

RS = +0.47 x HER2 group score
-0.34 x ER group score
+1.04 x proliferation group score
+0.10 x invasion group score
+0.05 x CD68
-0.08 x GSMT1
-0.07 x BAG1

<18 Low
18-31 Intermediate
>31 High
Oncotype DX

• Predicts the probability of distant recurrence in node negative patients treated with tamoxifen, and in those with ER+ breast cancer
  – High
  – Intermediate
  – Low risk
Onco
type DX® Clinical Validation: RS as Continuous Predictor

My RS is 30. What is the chance of recurrence within 10 years?
The impact of the Oncotype Dx breast cancer assay in clinical practice: a systematic review and meta-analysis

Josh J. Carlson • Joshua A. Roth

Table 5 Pooled mean proportion of physicians changing adjuvant chemotherapy recommendation after ODX testing (vs. clinical-pathological factors only)

<table>
<thead>
<tr>
<th>Study</th>
<th>% Changing ACT recommendation after ODX test</th>
<th>Study weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ademuyiwa et al. [23]</td>
<td>38.0</td>
<td>0.19</td>
</tr>
<tr>
<td>de Boer et al. [42]</td>
<td>22.8</td>
<td>0.07</td>
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<td>Holt [43]</td>
<td>26.8</td>
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<td>Joh et al. [28]</td>
<td>24.9</td>
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<td>Klang et al. [30]</td>
<td>40.0</td>
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<tr>
<td>Lo et al. [31]</td>
<td>31.5</td>
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<td>Rezai et al. [44]</td>
<td>30.3</td>
<td>0.17</td>
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<td>Tatarian et al. [35]</td>
<td>42.9</td>
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<tr>
<td><strong>Pooled mean</strong></td>
<td><strong>33.4</strong></td>
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</table>
# Immunophenotyping to Approximate Molecular Subtype Using Three Markers

Brenton, 2005

<table>
<thead>
<tr>
<th></th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>HER2</th>
<th>Basal-like</th>
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<tbody>
<tr>
<td><strong>ER</strong></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>HER2</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Ki67 Index, HER2 Status, and Prognosis of Patients With Luminal B Breast Cancer

Maggie C. U. Cheang, Stephen K. Chia, David Voduc, Dongxia Gao, Samuel Leung, Jacqueline Snider, Mark Watson, Sherri Davies, Philip S. Bernard, Joel S. Parker, Charles M. Perou, Matthew J. Ellis, Torsten O. Nielsen


(A) Cumulative relapse-free survival

- Luminal A: 28/87, 5-year (95% CI) 80 (72-89), 10-year (95% CI) 69 (59-79)
- Luminal B: 43/84, 5-year (95% CI) 63 (53-74), 10-year (95% CI) 51 (42-63)
- Luminal/HER2+: 14/25, 5-year (95% CI) 55 (38-79), 10-year (95% CI) 42 (26-67)

Luminal B vs Luminal A log-rank \( P = .007 \)
Luminal/HER2+ vs Luminal A log-rank \( P = .006 \)

(B) Cumulative breast cancer-specific survival

- Luminal A: 26/87, 5-year (95% CI) 87 (80-95), 10-year (95% CI) 78 (69-87)
- Luminal B: 38/84, 5-year (95% CI) 81 (73-90), 10-year (95% CI) 58 (48-70)
- Luminal/HER2+: 14/25, 5-year (95% CI) 58 (42-82), 10-year (95% CI) 44 (28-70)

Luminal B vs Luminal A log-rank \( P = .014 \)
Luminal/HER2+ vs Luminal A log-rank \( P = .001 \)
• Strongly endocrine responsive, low proliferation, good prognosis “luminal A-like” can be distinguished from less endocrine responsive, higher proliferation, poorer prognosis “luminal B like” tumors using IHC assays for ER, PR and Ki67

• But, use of Ki67 requires knowledge of local laboratory values
Conclusions

• ER, PR and Her2 testing using ASCO/CAP guidelines remain the most important ancillary tests in the management of patients with breast cancer

• While molecular subtypes are of conceptual interest, clinically useful subgroups are defined by ER, PR and Her2 assay results

• Among patient’s with ER+/Her2- (“luminal”) disease, KI67 proliferation rate or multigene prognostic tests are of value in further defining risk of recurrence and potential benefit from chemotherapy in addition to endocrine therapy

• The major clinical role of genomic analysis at this time is to identify patients with advanced disease who may be candidates for targeted therapies based on specific genomic alterations