

Triple-Negative Breast Cancer (TNBC): A Demographic and Molecular Perspective

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“Triple-Negative” Carcinomas

- **Purported aggressive clinical course**
 - **Despite response to conventional chemotherapeutic regimens (neoadjuvant and adjuvant)**
- **Lack of targeted therapies**
- **Immunohistochemical surrogate of “basal-like” (BL) breast cancer**
 - **Triple-negative (TN) is an immunohistochemical definition**
 - **Basal-like stems from gene expression profiling (GEP)**

Triple-Negative: Definition

- Immunohistochemically negative for estrogen receptor (ER) and progesterone receptor (PgR)
- Lack of overexpression/amplification of the HER2 gene

Quite Easy, Isn't It?

- **What is negative for ER & PgR?**
 - **No immunoreactive cells?**
 - **Less than 1% immunoreactive cells?**
 - **Less than 10% immunoreactive cells?**
 - **Less than 20% immunoreactive cells?**

American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer

M. Elizabeth H. Hammond, Daniel F. Hayes, Mitch Dowsett, D. Craig Allred, Karen L. Hagerty, Sunil Badve, Patrick L. Fitzgibbons, Glenn Francis, Neil S. Goldstein, Malcolm Hayes, David G. Hicks, Susan Lester, Richard Love, Pamela B. Mangu, Lisa McShane, Keith Miller, C. Kent Osborne, Soonmyung Paik, Jane Perlmutter, Anthony Rhodes, Hironobu Sasano, Jared N. Schwartz, Fred C.G. Sweep, Sheila Taube, Emina Emilia Torlakovic, Paul Valenstein, Giuseppe Viale, Daniel Visscher, Thomas Wheeler, R. Bruce Williams, James L. Wittliff, and Antonio C. Wolff

- **Standardization of preanalytic variables**
 - **Type and duration of fixation**
- **Standardization of analytic variables**
 - **Antibody selection**
 - **Control samples**
- **Standardization of postanalytic variables**
 - **Interpretation of the results**
 - **Reporting**
 - **Internal quality control and validation**

“American Society of Clinical Oncology/College of American Pathologists Guidelines Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer”

	Recommendation
Optional algorithm for ER/PgR testing	<p>Positive for ER or PgR if finding of $\geq 1\%$ of tumor cell nuclei are immunoreactive</p> <p>Negative for ER or PgR if finding of $< 1\%$ of tumor cell nuclei are immunoreactive in the presence of evidence that the sample can express ER or PgR (positive intrinsic controls are seen).</p> <p>Uninterpretable for ER or PgR if finding that no tumor nuclei are immunoreactive and that internal epithelial elements present in the sample or separately submitted from the same sample lack any nuclear staining.</p>

Quite Easy, Isn't It?

- **What is negative for ER & PgR?**
 - No immunoreactive cells?
 - Less than 1% immunoreactive cells?
 - Less than 10% immunoreactive cell?
 - Less than 20% immunoreactive cells?
- **Are we reliable and reproducible?**
 - Up to 20% false-negative results for ER & PgR
 - More than 12% false-positive results for PgR
 - Up to 15% false-positive results for HER2

Triple-Negative Breast Carcinomas: Prototypical Features

- **Clinical features**
 - Younger patients (47-55 years)
 - African American women
 - Interval cancers
 - BRCA-1 mutations
- **Pathologic features**
 - High-grade, high mitotic count
 - Pushing borders
 - Geographic necrosis/central fibrosis
 - Stromal lymphocytic infiltrate
 - Metaplasia
 - Prevalence of brain and lung metastases

TN Tumors Are Heterogeneous

- IDC NOS, high grade
- ILC high grade, pleomorphic
- Metaplastic, high grade
- Myoepithelial carcinoma
- High-grade (oat-cell) neuroendocrine
- Apocrine
- Medullary
- Adenoid-cystic
- Metaplastic, low grade
 - Low-grade adenosquamous
 - Fibromatosis-like

Poor prognosis

Good prognosis

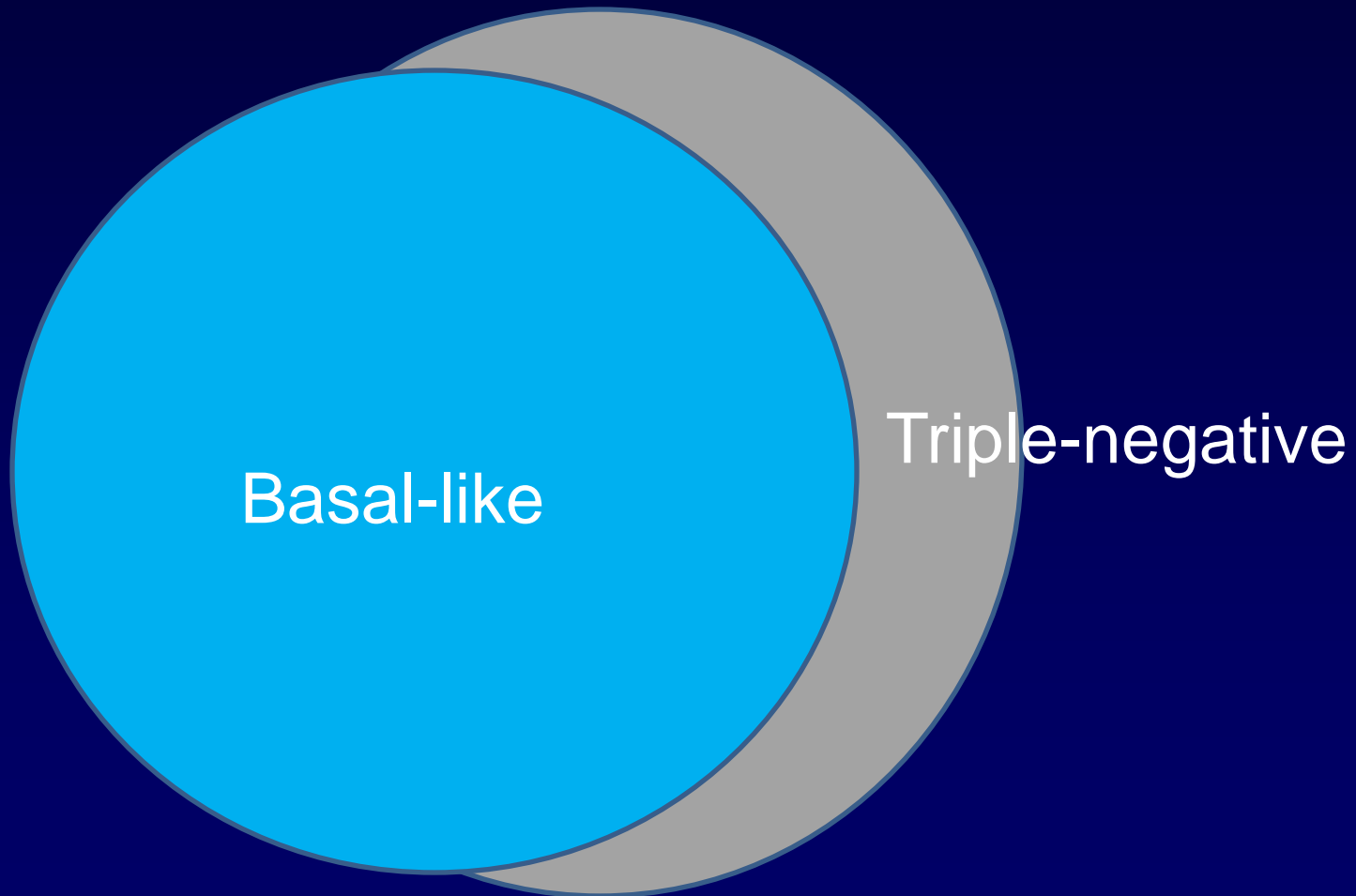
Basal-Like Breast Carcinomas

- Hierarchical clustering of the variations in the expression of 496 genes (“intrinsic” gene subset)
- Four to six molecular subtypes
- Basal-like carcinomas account for 14% to 26% of the investigated samples
- Express CK 5 and 17, EGFR, KIT, laminin, collagen type XVII, calponin 1, caveolin 2
- Do not express ER and HER2
- Aggressive course and poor clinical outcome

Are TN and BL the Same Entity?

- Only 71% to 91% of TN have a BL gene expression profile
 - Importance of the cut-off?
- Only 77% of BL carcinomas have a TN immunophenotype
 - They may express ER and/or HER2
- Almost 20% of non-TN have a BL gene expression profile

A Triple-Negative Negative Immunophenotype Does Not Overlap the Basal-Like Gene Expression Profile



A Clinically Meaningful Approach to Triple-Negative Breast Cancer

- **Identify special types with better prognosis**
 - Adenoid cystic, Medullary, Metaplastic low grade, Apocrine low grade
- **Identify truly non endocrine-responsive tumors**
 - <1% ER & PgR immunoreactive cells
- **Do not miss candidate patients to anti-HER2 interventions**
 - Equivocal IHC/FISH (CISH,SISH)
- **Add prognostically relevant markers (?)**
 - CK 5, 14, 17
 - EGFR

Take Home

- **We should eventually agree on the definition of “triple-negative” breast cancer**
- **TN does not equal basal-like breast cancer**
- **A hierarchical approach to the diagnosis of TN breast cancer should include:**
 - **Thorough evaluation of morphologic features**
 - **Accurate assessment of ER, PgR and HER2 status**
 - **Use of surrogate IHC markers or gene expression profiling assays for identifying basal-like carcinomas (whenever deemed necessary)**