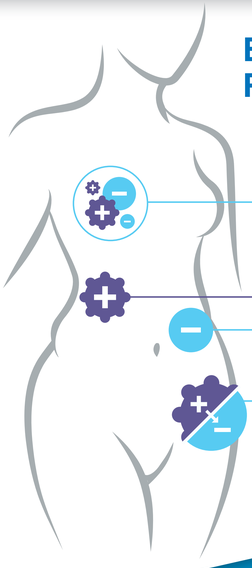
Receptor Discordance Affects Outcomes in Oncology:

Breast Cancer as an Illustrative Example

Breast Cancer: Receptor Discordance

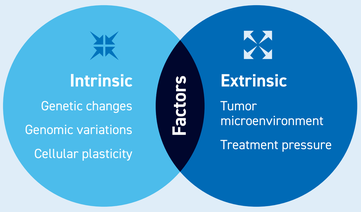


Intra-tumor discordance[1,2]
A single lesion may have receptor-positive and receptor-negative disease

Inter-tumor discordance[1]
Two lesions may have different receptor status

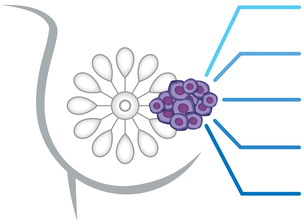
Temporal discordance[1-5]
Receptor status can change over time, especially following treatment

Receptor Discordance: Causative Factors[1,2,6]



Assessment of receptor status is critical for classifying breast cancer subtypes, prognosticating, and predicting treatment responses[2,6-10]

Breast Cancer Subtypes: Correlation with Receptor Status[7]



Subtype	ER/PR	HER2	Ki-67	Proliferation	Grade	Prognosis	Treatment
Luminal A	+	-	low ki-67 index	low	low	better	Endocrine therapy
Luminal B HER2-							
Luminal B HER2+		+	high ki-67 index				Anti-HER2 therapy
HER2-enriched	-						Chemotherapy
Basal-like/Triple Negative		-		high	high	worse	

ER, PR, and HER2 Status Support Prognosticating in Breast Cancer

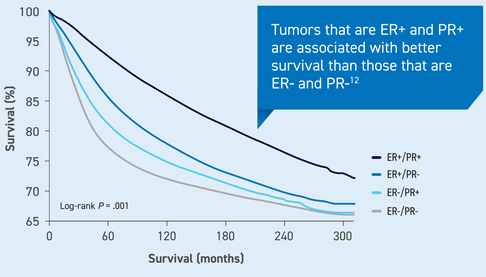
Less aggressive with better prognosis[7,8,11,12]

ER expression occurs in ~70-80% of tumors

PR expression occurs in ~60-70% of tumors

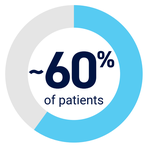
More aggressive with poorer prognosis[7,9-11]

HER2 overexpression or amplification occurs in ~15-20% of tumors



ER, PR, and HER2 Status may Aid with Predicting Treatment Response in Breast Cancer

Hormone Receptor (ER/PR)[7,11]



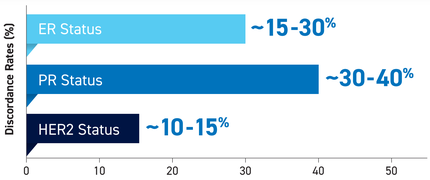
~60% of patients with ER+/PR+ breast cancer have a response to endocrine therapy

Human Epidermal Growth Factor Receptor (HER2)[11]

~50-60% of patients with HER2+ breast cancer have a response to HER2-targeted therapy

Unpredictable initial response and acquired resistance to targeted therapies may be due to: Lack/loss of receptor expression and/or receptor status discordance[1,3,5]

Receptor Status Discordance[2,3,7,11]



Key Take-Aways

1. Breast cancer is a heterogenous disease characterized by notable intra-tumor, inter-tumor, and temporal heterogeneity
2. Receptor biomarkers such as ER/PR and HER2 status are used to classify breast cancer subtypes, aid in prognosis, and inform clinical decisions
3. Normally, patients with ER+/PR+ breast cancer have a more favorable prognosis and better treatment response compared with other molecular subtypes
4. The functional status of tumor receptor expression commonly changes throughout disease progression, possibly influenced by treatments, and this instability could affect patient outcomes
5. Re-characterization of receptor status at recurrence or metastasis is crucial to guide choice of subsequent lines of treatment

References: **1.** 1. Kurland BF, Peterson LM, Lee JH, Linden HM, Schubert EK, Dunnwald LK, et al. Between-patient and within-patient (site-to-site) variability in estrogen receptor binding, measured in vivo by 18F-fluoroestradiol PET. *J Nucl Med.* 2011;52(10):1541-1549. **2.** Fumagalli C, Barberis M. Breast cancer heterogeneity. *Diagnostics (Basel).* 2021;11(9):1555. **3.** Yang Z, Sun Y, Zhang Y, Xue J, Wang M, Shi W, et al. Can fluorine-18 fluoroestradiol positron emission tomography-computed tomography demonstrate the heterogeneity of breast cancer in vivo? *Clin Breast Cancer.* 2013;13(5):359-363. **4.** Currin E, Peterson LM, Schubert EK, Link JM, Krohn KA, Livingston RB, et al. Temporal heterogeneity of estrogen receptor expression in bone-dominant breast cancer: 18F-fluoroestradiol PET imaging shows return of ER expression. *J Natl Compr Canc Netw.* 2016;14(2):144-147. **5.** Aitken SJ, Thomas JS, Langdon SP, Harrison DJ, Faratian D. Quantitative analysis of changes in ER, PR and HER2 expression in primary breast cancer and paired nodal metastases. *Ann Oncol.* 2010;21(6):1254-1261. **6.** Lüönd F, Tiede S, Christofori G. Breast cancer as an example of tumour heterogeneity and tumour cell plasticity during malignant progression. *Br J Cancer.* 2021;125(2):164-175. **7.** Balma M, Liberini V, Racca M, Laudicella R, Bauckneht M, Buschiazzo A, et al. Non-conventional and investigation PET radiotracers for breast cancer: a systematic review. *Front Med (Lausanne).* 2022;9:881051. **8.** Kurland BF, Wiggins JR, Coche A, Fontan C, Bouvet Y, Webner P, et al. Whole-body characterization of estrogen receptor status in metastatic breast cancer with 16 α-18F-fluoro-17 β-estradiol positron emission tomography: meta-analysis and recommendations for integration into clinical applications. *Oncologist.* 2020;25(10):835-844. **9.** Seol H, Lee HJ, Choi Y, Lee HE, Kim YJ, Kim JH, et al. Intratumoral heterogeneity of HER2 gene amplification in breast cancer: its clinicopathological significance. *Mod Pathol.* 2012;25(7):938-948. **10.** Lee HJ, Seo AN, Kim EJ, Jang MH, Suh KJ, Ryu HS, et al. HER2 heterogeneity affects trastuzumab responses and survival in patients with HER2-positive metastatic breast cancer. *Am J Clin Pathol.* 2014;142(6):755-766. **11.** Turashvili G, Brogi E. Tumor heterogeneity in breast cancer. *Front Med (Lausanne).* 2017;4:227. **12.** Li Y, Yang D, Yin X, Zhang X, Huang J, Wu Y, et al. Clinicopathological characteristics and breast cancer-specific survival of patients with single hormone receptor-positive breast cancer. *JAMA Netw Open.* 2020;3(1):e1918160.

Abbreviations: ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, PR = progesterone receptor.