UNC Network Lecture Series 2018

Using Biomarkers to Plan Adjuvant Therapy in Breast Cancer

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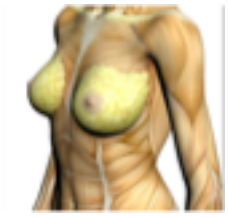
NC CANCER HOSPITAL

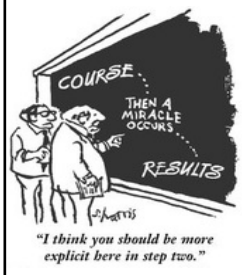
Early Breast Cancer Prognostication and Therapeutic Decision-Making



Anatomic features

Biologic features

Testing Biomarkers

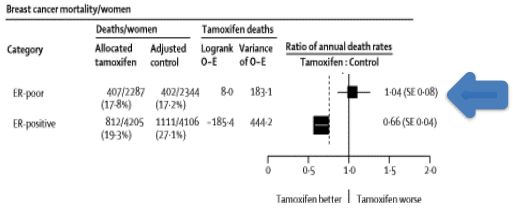


Key elements of assay development:

1. Analytical validity (reproducible and accurate?)
2. Clinical validity (differentiate cancers?)
3. Clinically useful (assay = better decisions)

Adapted from Simon R, JNCI 2009

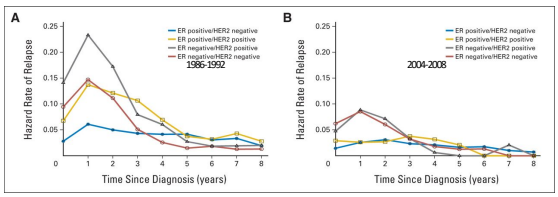
Clinical Utility



Why we don't give endocrine therapy to HR-negative tumors
ER assay reproducibility, accuracy, and validity previously established

Breast Cancer Outcomes Have Improved

- Better chemotherapy drugs and approaches
- Better endocrine therapy
- Development of anti-HER2 therapy



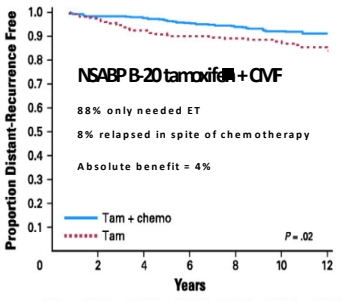
Cossetti RJ et al. JCO 2015

Not That Long Ago…

"Offer cytotoxic chemotherapy to most women with primary breast breast cancers larger than 1 cm."

The bar was set pretty low

The Problem of Overtreatment



Early 2000s:

Most ER+ node-negative breast cancer patients received chemo

Most did not benefit

Paik et al. J Clin Oncol 2006

Lots of RNA-Based Options for ER+ Disease

oncotype DX®

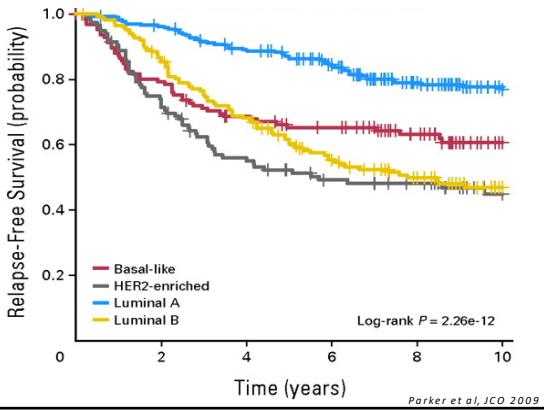
Breast Cancer INDEX™

prosigna® Breast cancer prognostic gene signature assay

mammaprint
decoding breast cancer.

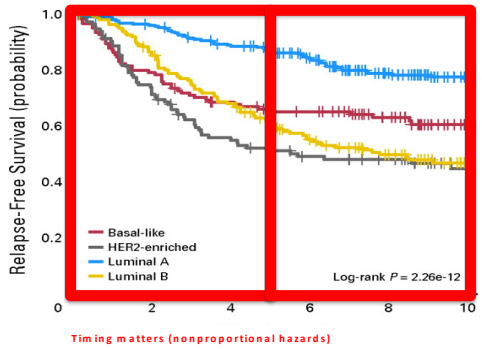
EndoPredict®

Breast Cancer Intrinsic Subtypes

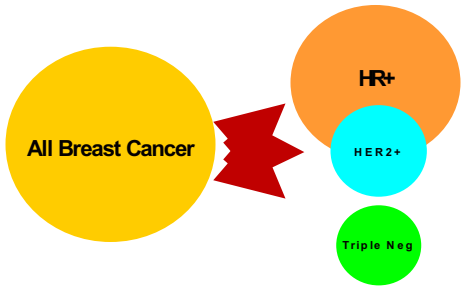


Parker et al, JCO 2009

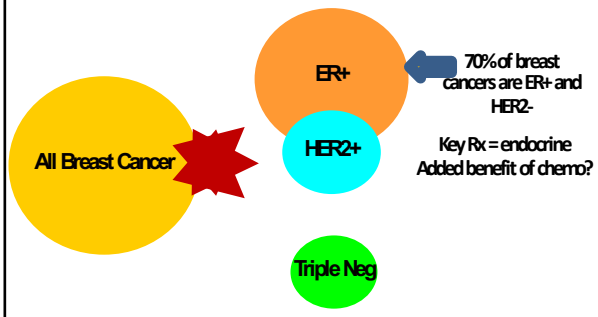
Intrinsic Subtypes and Prognosis



Questions by Clinical Phenotype



Breast Cancer Clinical Subsets



Clinical Questions in HR+ HER2-

We want to know:

- Who needs chemotherapy
- Who needs extended adjuvant endocrine therapy (> 5 years)
- Who needs nothing

What Are These Assays?

"top-down" = start with large unselected gene list, tailor to endpoint
"bottom-up" = start with known gene lists, tailor to endpoint

Assay	Provenance of RNA-based assays
Oncotype Dx® Recurrence Score	250 genes from literature tested for relapse in mixed population (dominated by NSABP B-20 HR+ N0 Rx tamoxifen) to derive 16 most relevant genes
Prosigna® ROR-PT	50 intrinsic subtype genes + proliferation genes + tumor size modeled for relapse (ROR-PT) in N0 untreated population
Mammaprint®	Top-down to 70 genes from case/control study of relapse within 5y (all N0, mostly HR+)
EndoPredict®	Top-down to 8 genes + T + N, predictive of distant mets from HR+ HER2- Rx tamoxifen.
BCI®	Top-down to 2-gene ratio (HOXB13:IL17BR), then bottom-up for Molecular Grade Index combined is predictive of distant mets

Paik S, NEJM 2004; Parker JS, JCO 2007; Van't Veer, Nature 2000; Filipits M, CCR 2011; Ma XJ, Cancer Cell 2004

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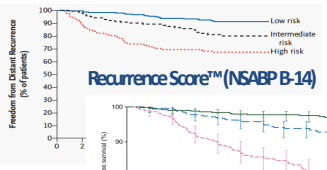
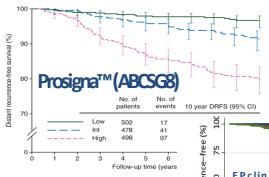
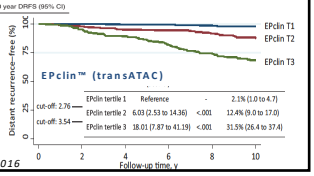
Risk of Distant Metastasis in ER+ Early Stage BrCa Treated only with Endocrine Rx



Recurrence Score™ (NSABP B-14)



Prosigna™ (ABCSG8)



Tested in "prospective/retrospective" studies

- Good tissue ascertainment
- High % included
- Homogeneous Rx

But..
relatively clinical low risk cohorts

Paik, NEJM 2006; Gnant, Ann Onc 2014; Buus, JNCI 2016

Mammaprint®

- Based on 70-gene signature
- Launched in Europe 2004
- 2007 FDA approval for test on frozen tissue
- 2015 FDA approval for test on FFPE
- $4200 per assay

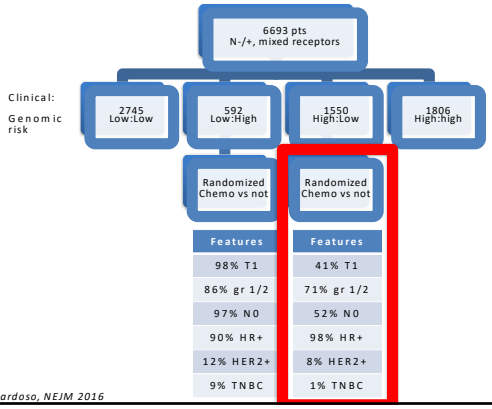
MINDACT Prospective Trial of Mammaprint®

70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer

Primary endpoint: Distant metastasis-free survival in clinical high risk but genomic low risk with no chemo. Threshold for success DMFS > 92%.

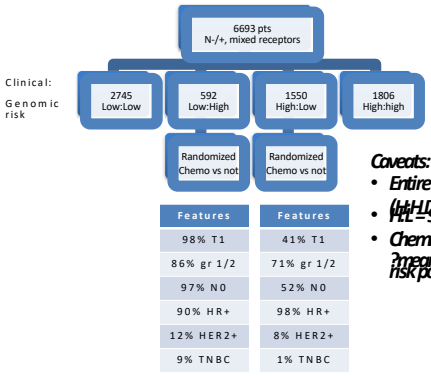
Result = DMFS 95% (largely ER+ HER2- population)

MINDACT



Cardoso, NEJM 2016

MINDACT



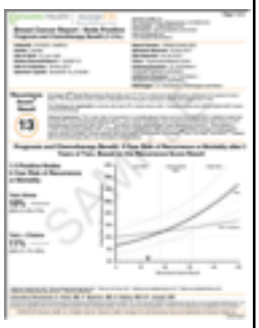
Caveats:

- *Entire population did well (4yr DDMFS=91%)*
- *HR+ = 98%HR+, mostly N0*
- *Chemotherapy Δ 22%, ?meaningful in a higher risk population?*

Cardoso, NEJM 2016

Oncotype Dx® Recurrence Score

- Available beginning 2006
- Wide adoption in U.S.
- Impact primarily in ↓ chemotherapy use
- Cost ~ $4500 per assay
- Recommended by ASCO, NCCN, Cancer Care Ontario (based on "prospective / retrospective" data)



Prospective trials: TailoRx, RxPonder (node +)

TailoRx

ORIGINAL ARTICLE

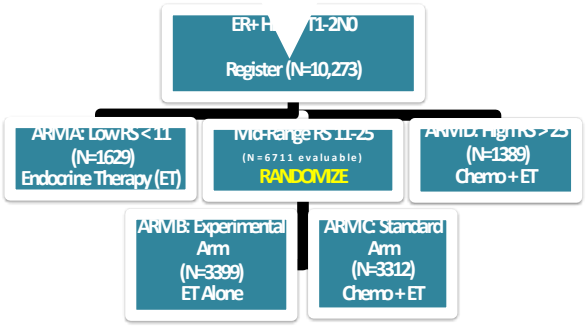
Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

Purpose:

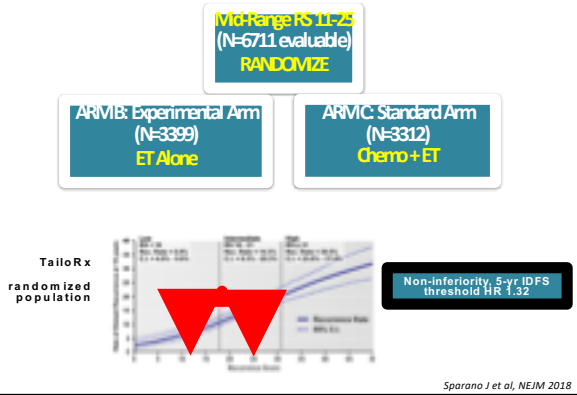
- to examine chemotherapy benefit in "intermediate" Recurrence Scores in node-negative ER+ HER2- breast cancer.
- To confirm excellent outcomes with endocrine therapy alone in low Recurrence Scores.

Sparano, NEJM 2018

TAILORx



TAILORx Randomized Trial



Sparano J et al, NEJM 2018

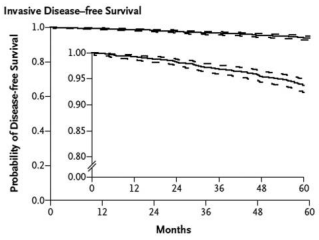
TailoRx Randomized Population

Prognostic Factor	TailoRx Population
Median age	55 (1/3 premenopausal, none > 75)
Median tumor size	1.5 cm (IQR 1.2 – 2.0 cm)
Grade	57% grade 2

~74% clinical low risk as defined in MINDACT

Sparano J et al, NEJM 2018

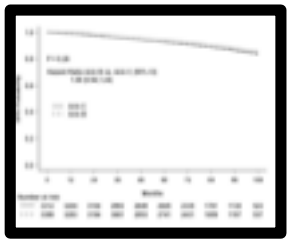
What We Knew Already:
RS < 11 has Great Prognosis with ET alone



At 9 year followup
97% distant metastasis-free

Sparano J et al, NEJM 2018

Primary Endpoint: iDFS in RS=11-25



836 (12%) events among ~ 6700 randomized patients at 7.5y
24% of events were distant mets

Noninferiority margin: HR 1.32;
[redacted]

= ET alone noninferior to ET + chemo

Sparano J et al, NEJM 2018

Practical Look at the Endpoint: Invasive Disease-Free Survival

Component	Impact of chemotherapy
Distant recurrence	+++
Locoregional recurrence	++
Second primary cancer	-
Death without recurrence	-

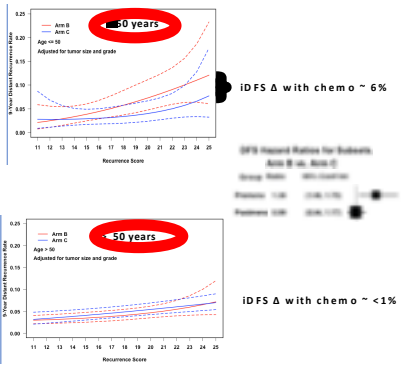
Other Endpoints

Arms B+C: Randomized participants are doing [redacted] well:
- RFI > 92% both arms
- DRFI > 94% both arms

Arm D (RS > 25, all received chemotherapy + ET): poorer prognosis
- Different population clinically and genomically - only 43% clinical low risk
- iDFS @ 9y = 76%
- Distant metastasis rate ~ 13%

Interesting Exploratory Analyses Randomized Arms

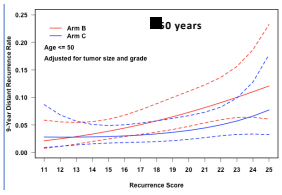
Interaction with [redacted]



iDFS Δ with chemo ~ 6%

iDFS Δ with chemo ~ <1%

Interesting Exploratory Analysis: Age

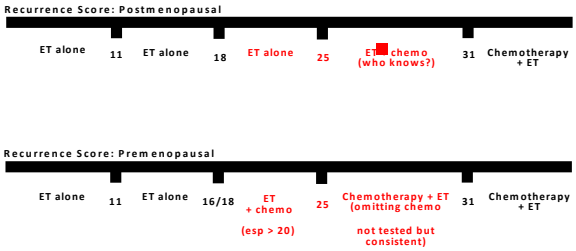


Exploratory + unplanned

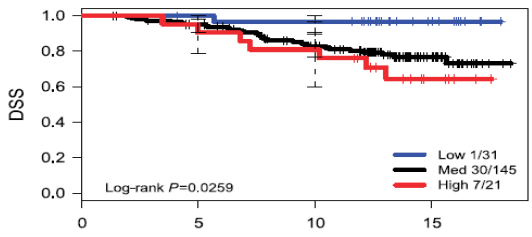
Ovarian suppression effect?

Other unmeasured features?

How Does This Affect Practice Tomorrow? (for node-negative patients appropriate for chemo)

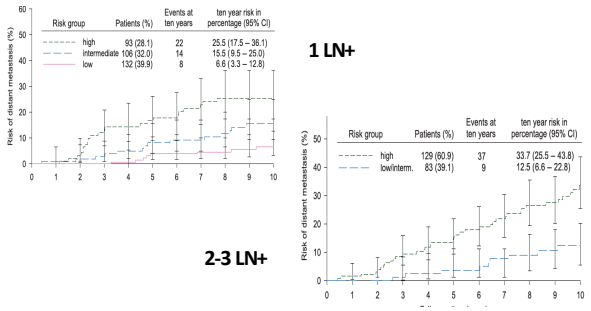


Prosigna® (ROR-PT)



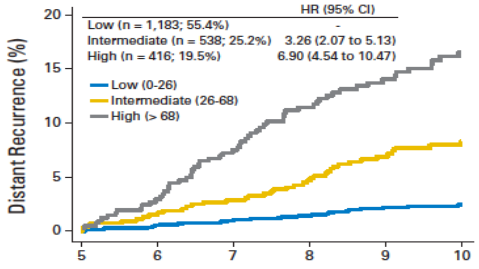
Nielsen, CCR 2010

Prosigna®: Distant Mets in N+ with ET alone (ABCSG8 + ATAC)



Gnant, Ann Oncol 2015

Prosigna®: Late Relapse (ABCSG8 + ATAC)



Prognostic for late distant mets with ET only

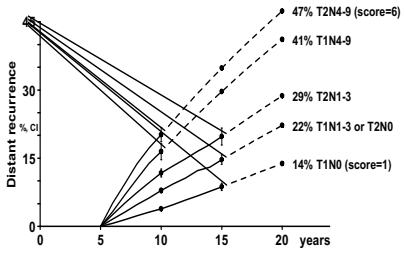
Sestak, JCO 2015

Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer: American Society of Clinical Oncology Endorsement of Cancer Care Ontario Guideline Recommendations

Updated 2017
Multiple genomic tests endorsed

[redacted]
to guide decisions in
node-negative ER+ HER2- disease.

The Problem of Late Recurrence



Pan et al, ASCO 2016

Oxford overview: > 46,000 women Rx 5 years on endocrine RCT
Relapse years 5-14 depended on stage, grade – no easily identifiable low risk group

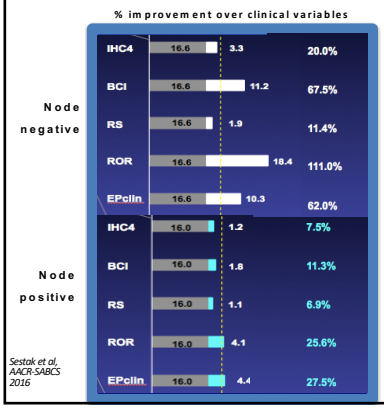
What Does This Mean?

"…(*assay name*) provided significant additional information on distant relapse after endocrine therapy"

1. **The assay is prognostic (or predictive of endocrine therapy benefit)**
2. **The clinical variables are prognostic**
3. **Both**

In all of these assay validation studies, clinical variables remained highly prognostic.

Assays and Late Distant Relapse (Years 5-10)



Sestak et al, AACR-SABCS 2016

TransATAC analysis

800 patients treated on trial with 5y ET

Early ≠ late relapse

- Clinical [redacted]y problem
- Clinical variables remain dominant
- This kind of analysis is usually impossible

Challenges of Biomarker Trials in Breast Cancer

- Level 1 evidence for biomarker utility is difficult, expensive, nearly impossible.
  - MINDACT cost > $50m
- Lower level evidence can determine clinical utility if:
  - Patient population homogeneous, interpretable
  - Assay is locked down and valid
  - Multivariable analyses
  - Similar findings from independent sources

Intratumoral Heterogeneity

- **In heterogeneous tumors, molecular assays may not illuminate "underlying biology"**

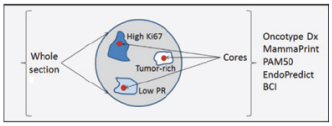


Table 1. Patients with discordant tumor samples identified by hierarchical clustering of GEP genes

	GEP	Number of endogenous genes	Patients with discordant tumor samples
1	BCI	7	52/71
2	Endo	8	30/71
3	Oncotype Dx	16	26/71
4	PAM50	50	25/71
5	MammaPrint	66	14/71
6	All genes	127	10/71

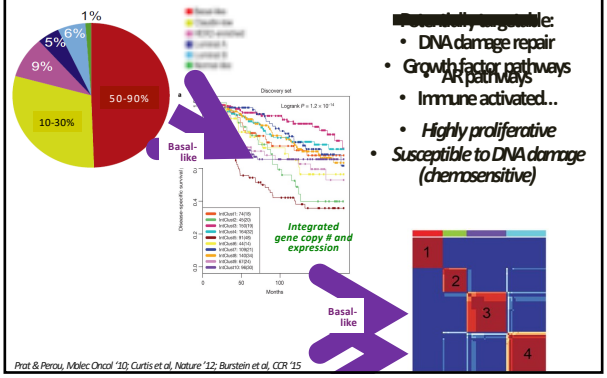
Gyanchandani R, CCR 2016

Other Clinical Questions (and where gene expression assays may help ...but it won't be easy)

We want to know how to tailor therapy for:

- **Triple negative**
- **HER2-positive**
- **Metastatic disease**

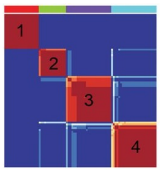
TNBC is Molecularly Heterogeneous



- [redacted]:
  - DNA damage repair
  - Growth factor pathways
  - AR pathways
  - Immune activated…
- *Highly proliferative*
- *Susceptible to DNA damage (chemosensitive)*

Prat & Perou, Molec Oncol '10; Curtis et al, Nature '12; Burstein et al, CCR '15

Subtypes within TNBC



Overlap with PAM50
Some overlap with "TNBCtype"

All characterized by basal, immune, and stromal signatures

No difference in response to conventional (neo)adjuvant chemotherapy
Work in progress regarding clinical utility

Burstein MD et al. Clin Cancer Res 2015

Regimens for Early HER2+

Regimens for HER2-positive disease[6,7,8]

Preferred regimens:
- AC followed by T + trastuzumab ± pertuzumab[9] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab

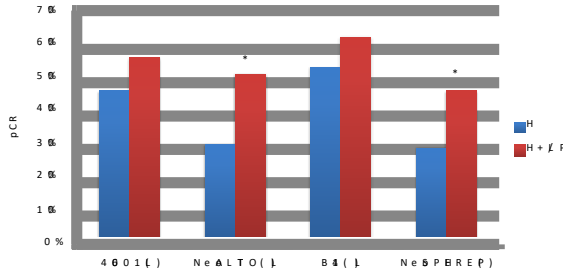
Other regimens:
- AC followed by docetaxel + trastuzumab ± pertuzumab[9]
- Docetaxel + cyclophosphamide + trastuzumab
- FEC followed by docetaxel + trastuzumab + pertuzumab[9]
- FEC followed by paclitaxel + trastuzumab + pertuzumab[9]
- Paclitaxel + trastuzumab[10]
- Pertuzumab + trastuzumab + docetaxel followed by FEC[9]
- Pertuzumab + trastuzumab + paclitaxel followed by FEC[9]

NCCN guidelines 3.2015

Polychemotherapy + 1-2 HER2-targeted drugs

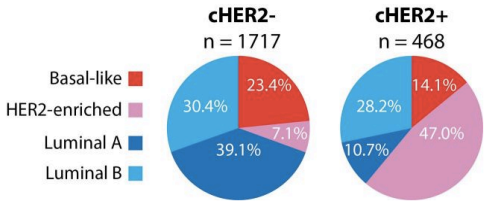
> $100,000

Large Neoadjuvant Randomized Trials Testing Dual HER2 Rx



1 pertuzumab, 3 lapatinib trials
All included chemotherapy (except HP in NeoSPHERE)
Widely variable magnitude of effect

Subtypes within HER2+ Disease

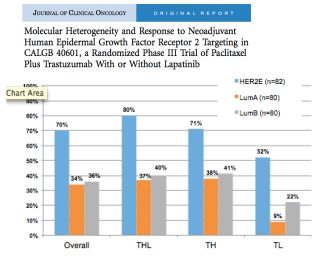


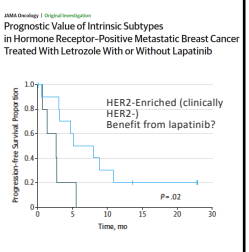
Subtype	Clinically HER2+
HER2-Enriched	66%
Luminal B	20%
Basal-like	14%
Luminal A	7%

Analysis TCGA + METABRIC:
Clinical HER2 and molecular HER2 are overlapping but different.

Prat et al, JNCI 2014

Intrinsic Subtype and Response to HER2-Targeting



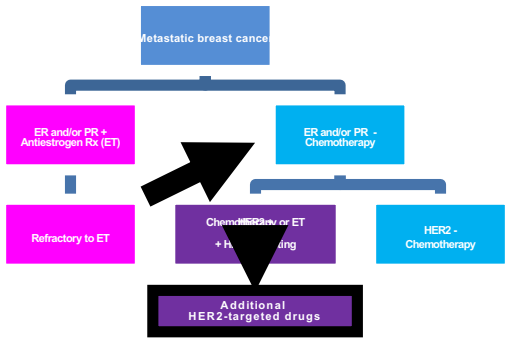


- HER2-Enriched: 2x ↑ sensitivity to any HER2-targeting
- *(Immune signatures/TILS also contribute to response/outcome)*

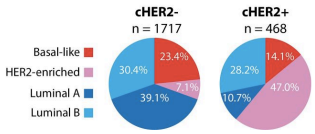
Challenge interpreting trials, also opportunity to limit/tailor drugs?

Carey, JCO 2016; Prat, JAMA Onc 2016

Treatment Based on Tumor Phenotype



Molecular Subtypes ≠ Clinical Subtypes

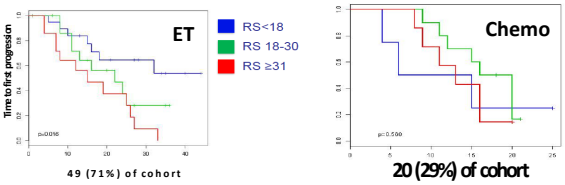


- Treatment based on ER, PR, HER2
- Molecular heterogeneity well-described in primary breast cancer
- Likely to be worse in relapsed disease

Prat et al, JNCI 2014

Treatment and Outcome in HR+ HER2- MBC

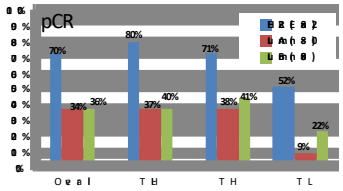
If the First Rx was….



TTP and 2-year OS worse in high RS treated first with ET
Small trial, not 1° endpoint or adequately powered, not preplanned

King T et al, JCO 2016

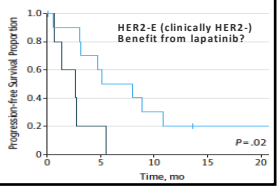
HER2-Targeting



EGF30008: Ph3 A + lapatinib

HER2-Enriched: 2x response

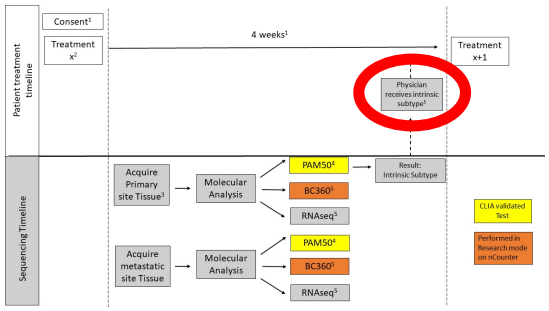
Does clinical HER2 matt



Carey, JCO 2016; Prat, JAMA Onc 2016

HARMONY Schema

Eligible patients: Metastatic breast cancer, no more than 1 prior treatment



Primary Objectives

To determine:

- **1a: if the clinical:molecular primary tumor subtype incongruence rate in patients with metastatic breast cancer is at least 15%**
- **1b: whether the results of intrinsic subtyping alters treatment options in at least 10% of metastatic breast cancer patients.**

RNA-based Biomarkers in Early Breast Cancer

- Do not replace clinical variables.
- ER+ HER2-, multiple assays guide chemotherapy decision-making.
  - Also may help with extended adjuvant endocrine therapy decisions.
- Unvalidated molecular assays should not override standardized, validated clinical assays
  - Would anyone recommend against adjuvant endocrine Rx if the tumor is ER-positive by IHC but ER-negative by mRNA?
- Triple negative and HER2+ disease heterogeneity = opportunities