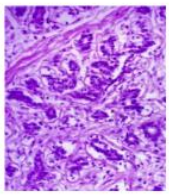
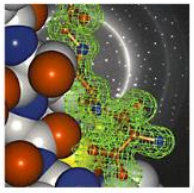
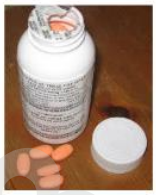
The Genomics of Metastatic Breast Cancer: What are we learning?

Nikhil Wagle
San Antonio Breast Cancer Symposium 2018



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Disclosure Information

SABCS - December 2018
Nikhil Wagle

- I have the following financial relationships to disclose (past 12 months):
  - Consultant/Advisor: Eli Lilly
  - Grant/Research Support: Puma Biotechnologies
  - Stockholder: Foundation Medicine

– and –

- I will not discuss off-label and/or investigational use of any agents in my presentation

Why study the genomics of metastatic breast cancer?

- Understand the biology of metastatic breast cancer / mechanisms of metastasis
- Identify predictors of metastatic disease
- Elucidate mechanisms of drug resistance
- Discover new therapies / therapeutic strategies



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Studies Discussed Today

Study	Patients	Samples	Subtypes	Sequencing Approach	Depth
Angus et al GS1-07	442	442 metastatic biopsies (purity >30%)	279 ER+/HER2- 77 HER2+ 58 TNBC 28 Unknown	Whole Genome Sequencing	107x
Andre et al GS1-08	629	629 metastatic biopsies (purity >30%)	387 ER+/HER2- 32 HER2+ 186 TNBC 24 Unknown	Whole Exome Sequencing (~20,000 genes)	120X
Desmedt et al GS1-06	66	72 metastatic biopsies 87 primaries *(30 matched pairs)*	All ER+ ILC	Targeted Panel (20 genes) Low pass WGS	150X

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Take-home Points

1. The genomic landscape of metastatic breast cancer is *different* than primary breast cancer
2. Metastatic breast cancer *evolves*
3. This may have significant *clinical* implications
4. DNA sequencing does not tell the whole story
5. These discoveries are enabled by collaboration and data sharing

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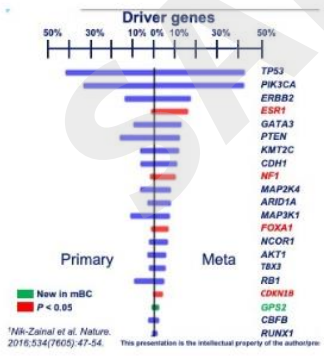
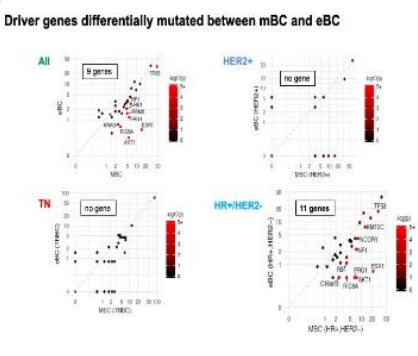
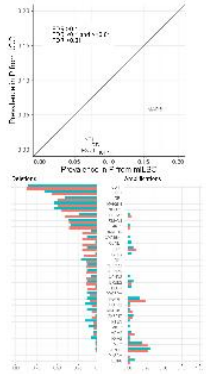
1a. The Genomic Landscape of Metastatic Breast Cancer is *Different* than Early Stage Breast Cancer: Mutations and Copy Number







Angus et al - GS1-07

Andre et al - GS1-08

Desmedt et al - GS1-06

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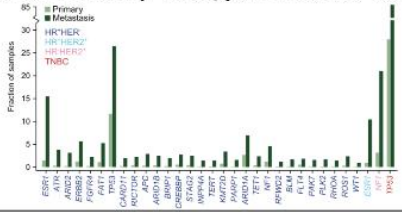
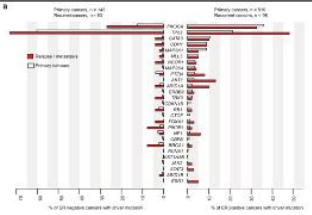
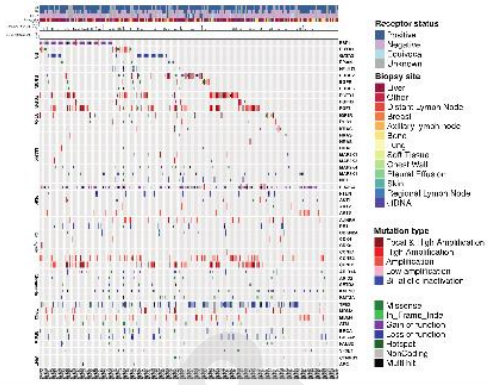


MSKCC-IMPACT - 450 genes panel - 1000 mets / 74 matched primaries
(Razavi, Chang et al, Cancer Cell 2018)



Sanger - 365 gene panel - 163 pts / 265 mets / 51 matched primaries
(Yates, Knappskog et al, Cancer Cell 2017)



DFCI-CCPM – WES/RNAseq (~20,000 genes) - 198 pts / 236 mets / 63 matched primaries
Ofir Cohen et al, SABCS 2016
*Ofir Cohen et al, SABCS 2018 – **PD9-02 – Friday 5-7pm***

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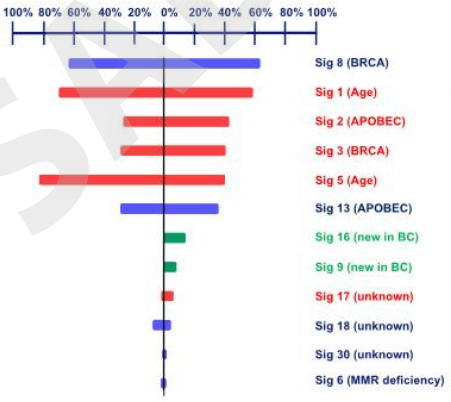
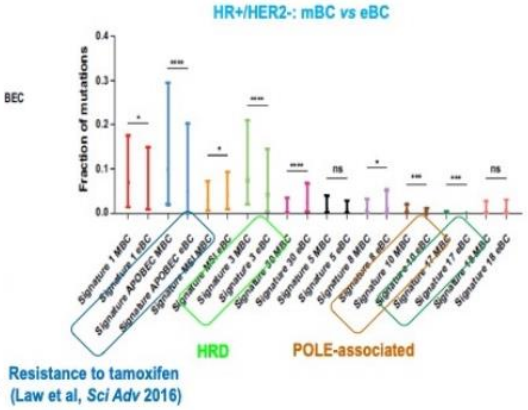
1b. The Genomic Landscape of Metastatic Breast Cancer is *Different* than Early Stage Breast Cancer: Mutational Signatures

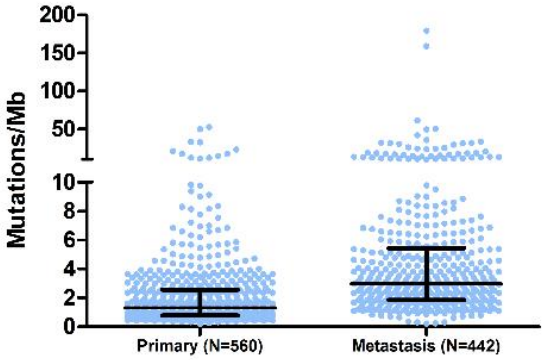


Angus et al - GS1-07

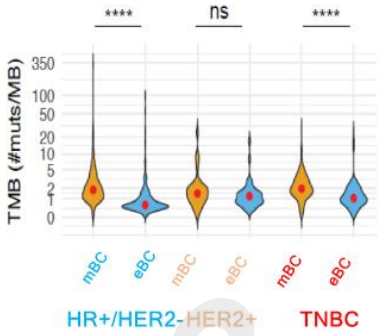


Andre et al - GS1-08

1c. The Genomic Landscape of Metastatic Breast Cancer is *Different* than Early Stage Breast Cancer: Tumor Mutational Burden



Angus et al - GS1-07



Andre et al - GS1-08

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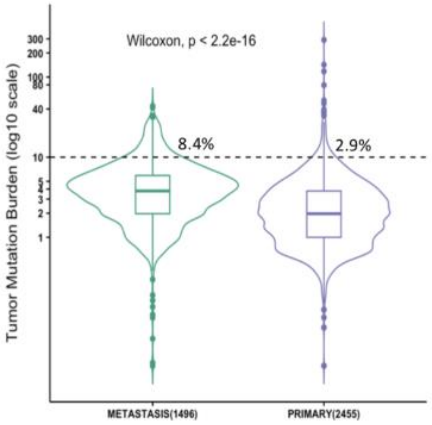
1c. The Genomic Landscape of Metastatic Breast Cancer is *Different* than Early Stage Breast Cancer: Tumor Mutational Burden

Dataset	Number of patients	Type of tissue	Site of tissue			Number of genes sequenced	Frequency of hypermutated tumors (%)
			Number of Primary Samples (N (%))	Number of Metastatic Samples (N (%))	Number of Unspecified or NA Samples (N (%))		
France 2016 Lefebvre et al. Plos Med 2016	213	FF	0 (0.0)	213 (100.0)	0 (0.0)	~20,000 (WES)	4.2
MBCProject Provisional, April 2018	126	FFPE	100 (79.4)	18 (14.3)	8 (6.3)	~20,000 (WES)	3.2
TCGA-BRCACell. 2015	977	FF	977 (100.0)	0 (0.0)	0 (0.0)	~20,000 (WES)	2.6
GENIE-DFCI-ONCOPANEL-3	301	FFPE	176 (58.5)	116 (38.5)	9 (3.0)	447	14.0
GENIE-MSK IMPACT410	1009	FFPE	388 (38.5)	621 (61.5)	0 (0.0)	410	7.3
GENIE-MSK IMPACT468	1071	FFPE	696 (65.0)	375 (35.0)	0 (0.0)	468	2.3
GENIE-VICC-01-T5A	92	FFPE	46 (50.0)	46 (50.0)	0 (0.0)	322	7.6
GENIE-VICC-01-T7	180	FFPE	72 (40.0)	107 (59.4)	1 (0.4)	429	6.7
Total	3969		2455 (61.9)	1496 (37.7)	18 (0.04)		5.0

R Barroso-Sousa, E Jain et al, ASCO 2018



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1d. The Genomic Landscape of Metastatic Breast Cancer is *Different* than Early Stage Breast Cancer: Summary

- Increased mutations and copy number alterations in many genes, including:
  - ESR1, FOXA1, NCOR1, AKT1, IGF1R, RB1, CDKN1B, KRAS, NF1, KMT2C, TP53
- Increase in APOBEC and HRD signatures
- Higher TMB on average, and greater proportion of hypermutated tumors
- New biology implicating new genes and mutational processes
- Most of the differences are found in ER+ breast cancers

Are these differences found in the initial primary breast cancer (as a marker of metastatic potential) or are they acquired/enriched over time?

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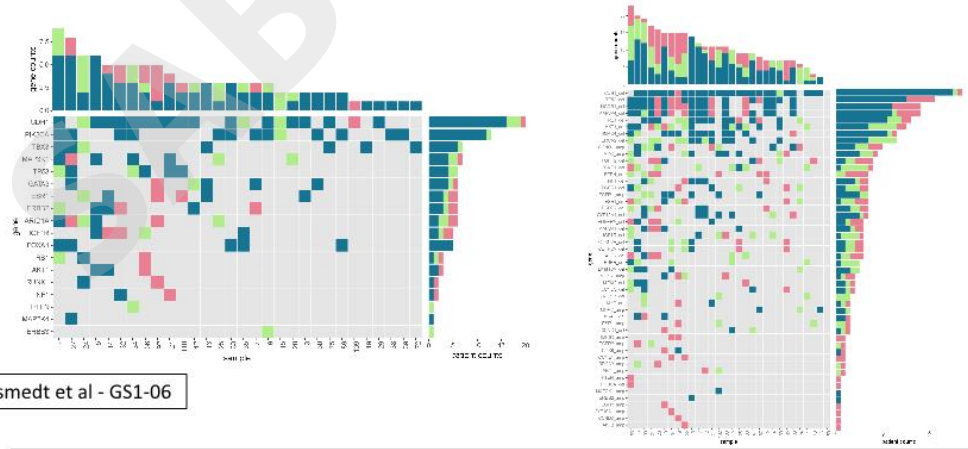
2. Metastatic Breast Cancer *Evolves*



Desmedt et al - GS1-06

Acquisition of mutations in ESR1, ERBB2, ESR1, AKT1, CDH1, NF1, MAP3K1, RUNX1 and copy number changes in TP53, PTEN, CCND1, ESR1, CCNE1, IGF1R, NF1

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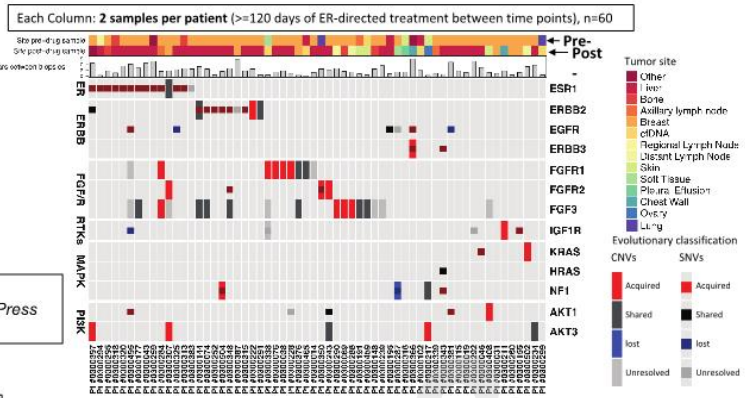
2. Metastatic Breast Cancer *Evolves*



~63% of patients (38 out of 60) have an acquired alteration in one of these genes

- *O Cohen, et al, SABCS 2018*
- *U Nayar, O Cohen, et al, Nature Genetics, In Press*
- *P Mao, et al., SABCS 2017*

Additional Studies of Evolution in MBC:
Razavi, Chang et al, Cancer Cell 2018
Siegel et al, JCI 2018
Vareślija D et al, JNCI 2018
Yates, Knappskog et al, Cancer Cell 2017

SPOTLIGHT - PD9 – Friday 5-7pm - Discussed by Katie Hoadley
Ofir Cohen, et al – Evolutionary Analysis of ER+ MBC
Ana Garrido-Castro et al – Genomics of acquired ER Loss in MBC
Esha Jain et al, -- De Novo MBC and synchronous primary/met pairs

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3. This may have significant *clinical* implications

- Prognostic:
  - RB1, NF1, and KMT2C mutations and PolE and Sig 17 signatures may be associated with decreased OS (Andre, GS1-08)
  - Mutations in ESR1, IGF1R, MAP3K1, NF1, RB1, TP53 in primary ILC may be associated with development of metastatic ILC (Desmedt, GS1-06)

- New therapeutic choices / overcoming resistance
  - ESR1
  - ERBB2
  - AKT1
  - MTOR pathway
  - MAPK pathway
  - Chromatin remodeling
  - HR: BRCA2, HRD signature (PARP inhibitors; platinums)
  - Hypermutation; MSI (immune checkpoint inhibitors)

These are frequently acquired in the metastatic tumor – need to profile in the metastatic setting

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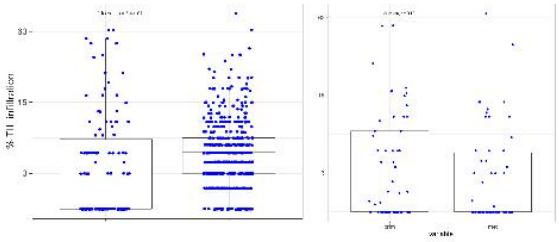
4. DNA sequencing does not tell the whole story

- RNA Expression
- Protein
- Epigenetics
- Microenvironment / Immune Cells

- Regulatory Regions
  - ESR1, FOXA1
- Fusions/structural changes
  - ESR1, RET, NTRK



Desmet et al - GS1-06

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5. These discoveries are enabled by collaboration and data sharing

AACR PROJECT GENIE
Genomics Evidence Neoplasia Information Exchange

NATIONAL CANCER INSTITUTE
GENOMIC DATA COMMONS

cBioPortal
FOR CANCER GENOMICS

Memorial Sloan Kettering Cancer Center
1884

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Translational Breast Cancer Research Consortium

The Breast Cancer Research Foundation
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Metastatic Breast Cancer - molecular aberrations

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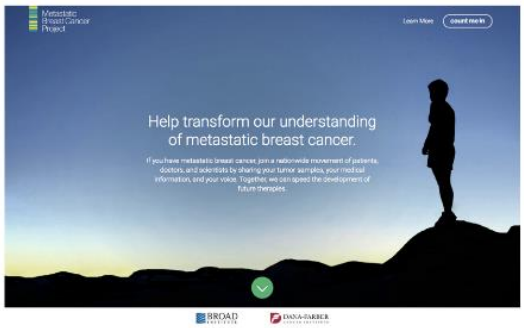

- *Over **5000 women and men** with metastatic breast cancer have joined at **MBCproject.org***
- *Over **3000 patients from >1000 institutions** have provided consent for genomic analysis (WES/RNAseq) of tumor and germline and public data sharing of deidentified clinically annotated genomic data*
- *WES from **180 patients (132 mets, 105 primaries; 42 matched pairs/series**) available on cbioportal.org*

Count Me In

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Summary and Conclusions

1. The genomic landscape of metastatic breast cancer is *different* than primary breast cancer
2. Metastatic breast cancer *evolves*
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