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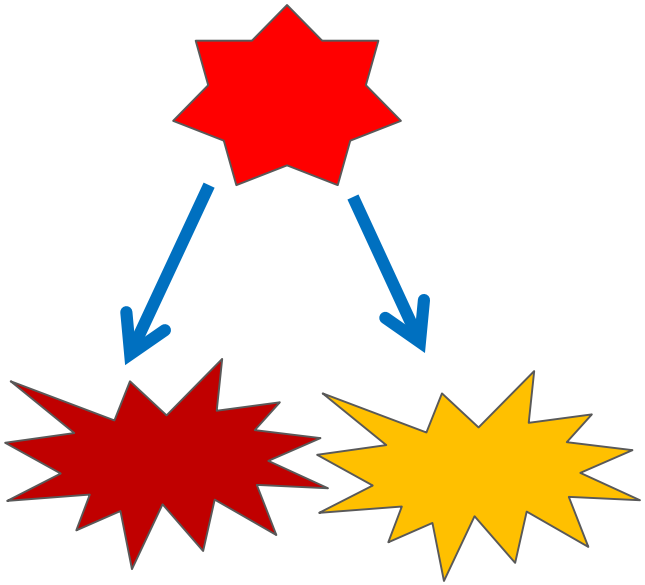
New Therapies for the Treatment of Metastatic Breast Cancers

~200,000 women in the USA are living with metastatic breast cancer

2015- original breast cancer



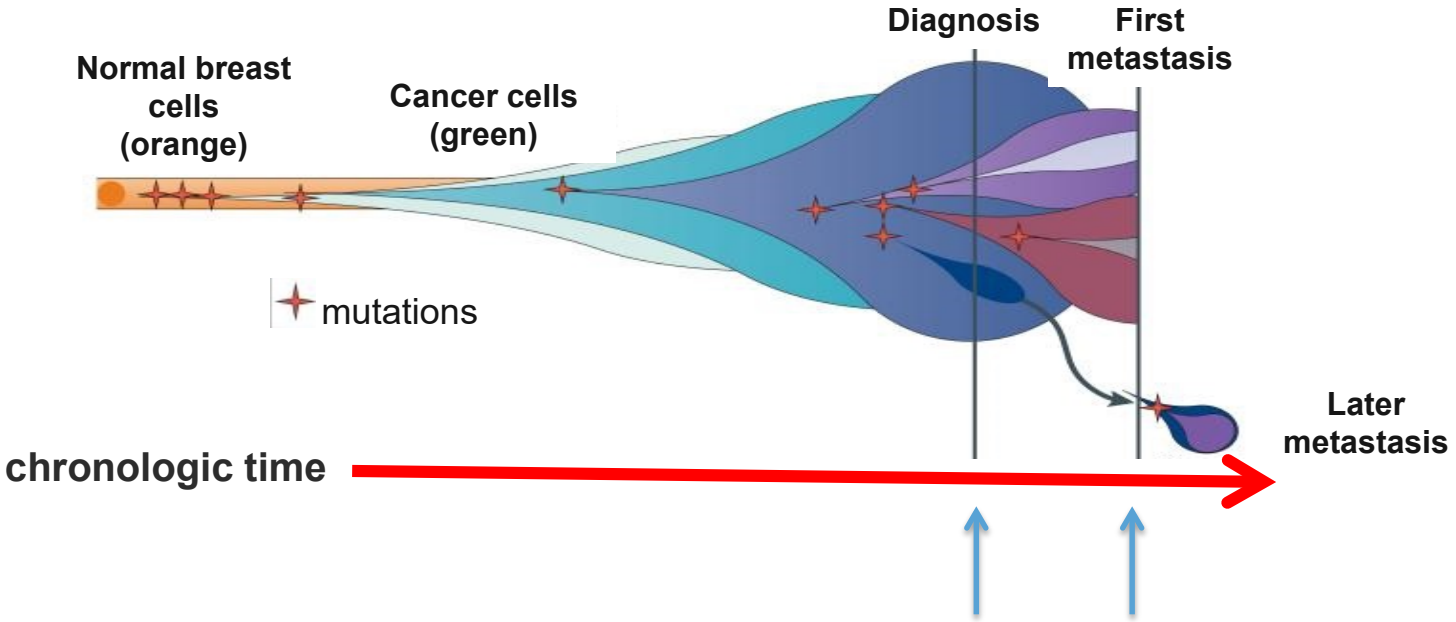
2019 - metastasis in liver, brain

We have the 2015 tumor for testing and "precision medicine"

However…
The 2015 tumor is not the problem, the 2019 tumors are.

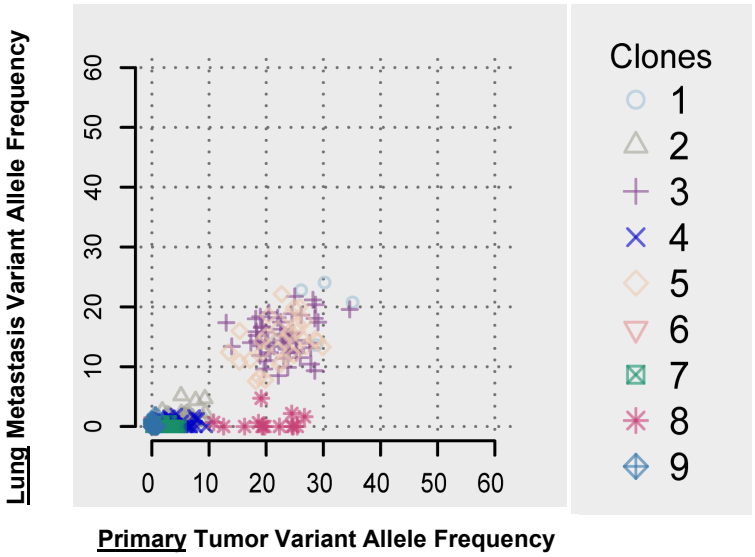
Slide courtesy of Lisa Carey

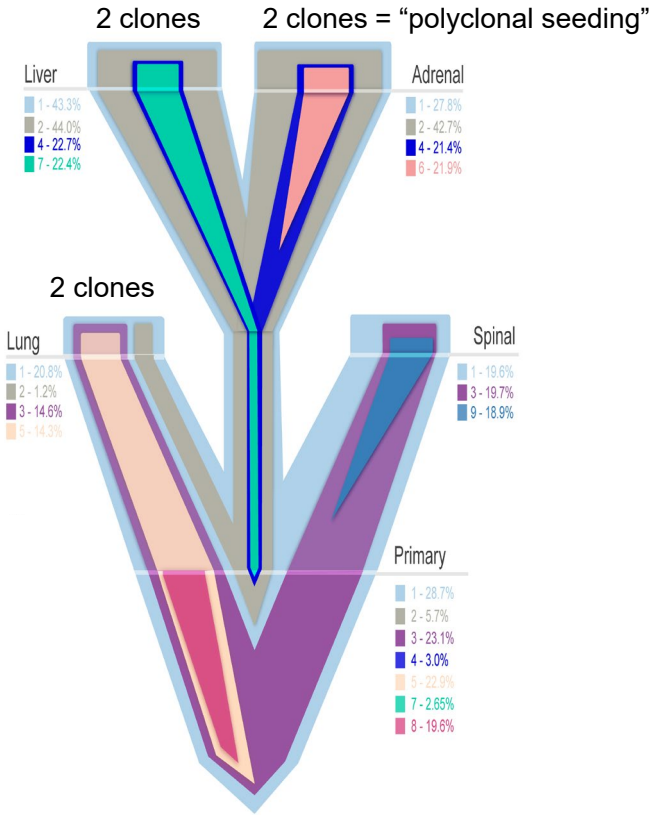
Cancers Evolve over time and space



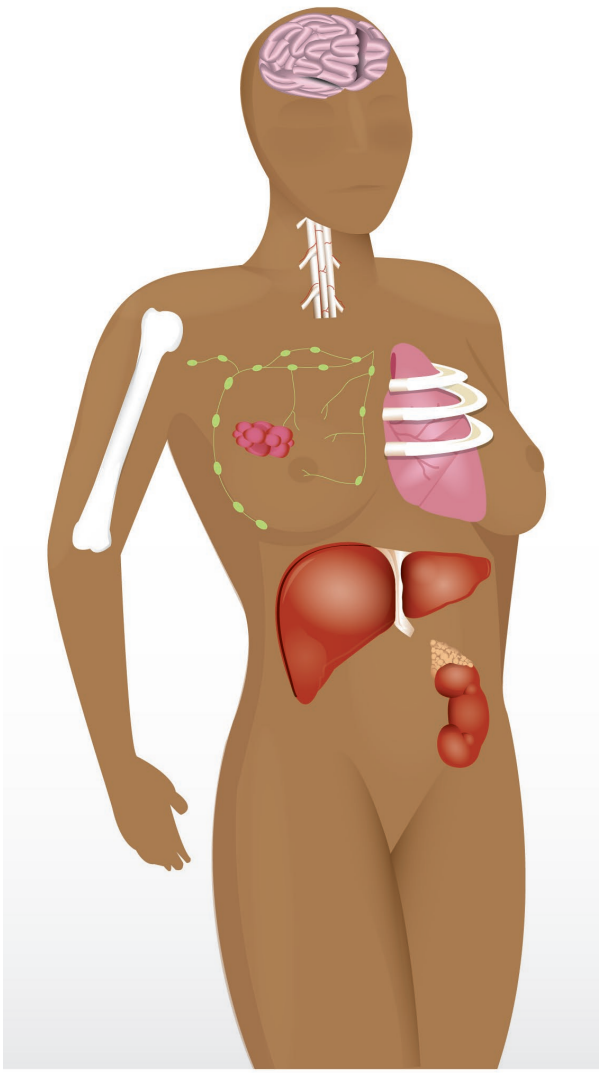
These are not the same,
They differ by a few genetic markers
(mutations, amp, delete)

Tumor Evolution in Two Patients with Basal-like Breast Cancer: a Retrospective Genomics Study of Multiple Metastases. Hoadley, Siegel, et al., PLoS Medicine, 2016 (PMID:27923045)





UNC Breast Tumor Donation Program (Lisa Carey – PI)



65 patients at UNC participated so far

Detailed genetics (DNA) and genomics (RNA expression) on the primary tumor and multiple metastases.

Key Findings:

- **Many cancers include multiple "subcancers / subclones".**
- **Polyclonal seeding by multiple subclones is common**
- **Each subclone has some different genetic alterations.**
- ***Which alterations are genetic drivers?***
- ***Which alterations to therapeutically target?***

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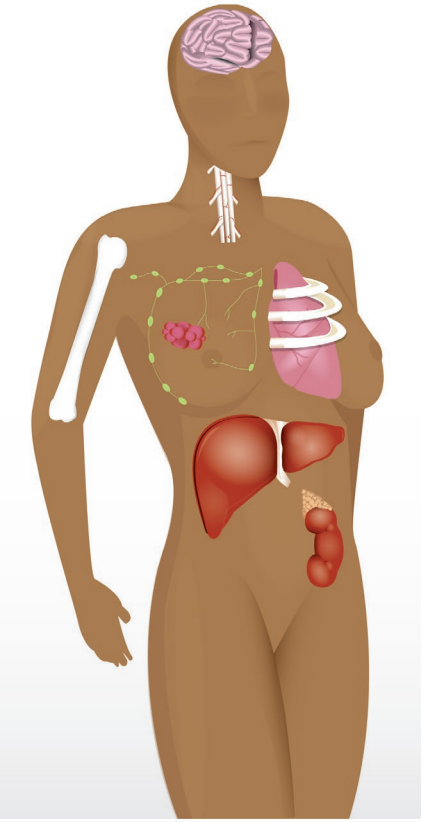
AURORA US Metastasis Project

- Primary goal
  - To identify the molecular features responsible for the development and progression of metastatic breast cancer, including the development of resistance to therapy

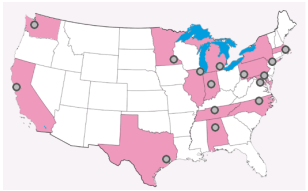
- Multi-platform genomic analysis of 250 metastatic breast cancer pairs (i.e. primary tumor and metastasis from the same patient) in a two tiered approach

  - Retrospective Study (n=50)
    - Already banked, clinically annotated biospecimens with appropriate consent and high quality materials
    - Patients with multiple metastases of particular focus

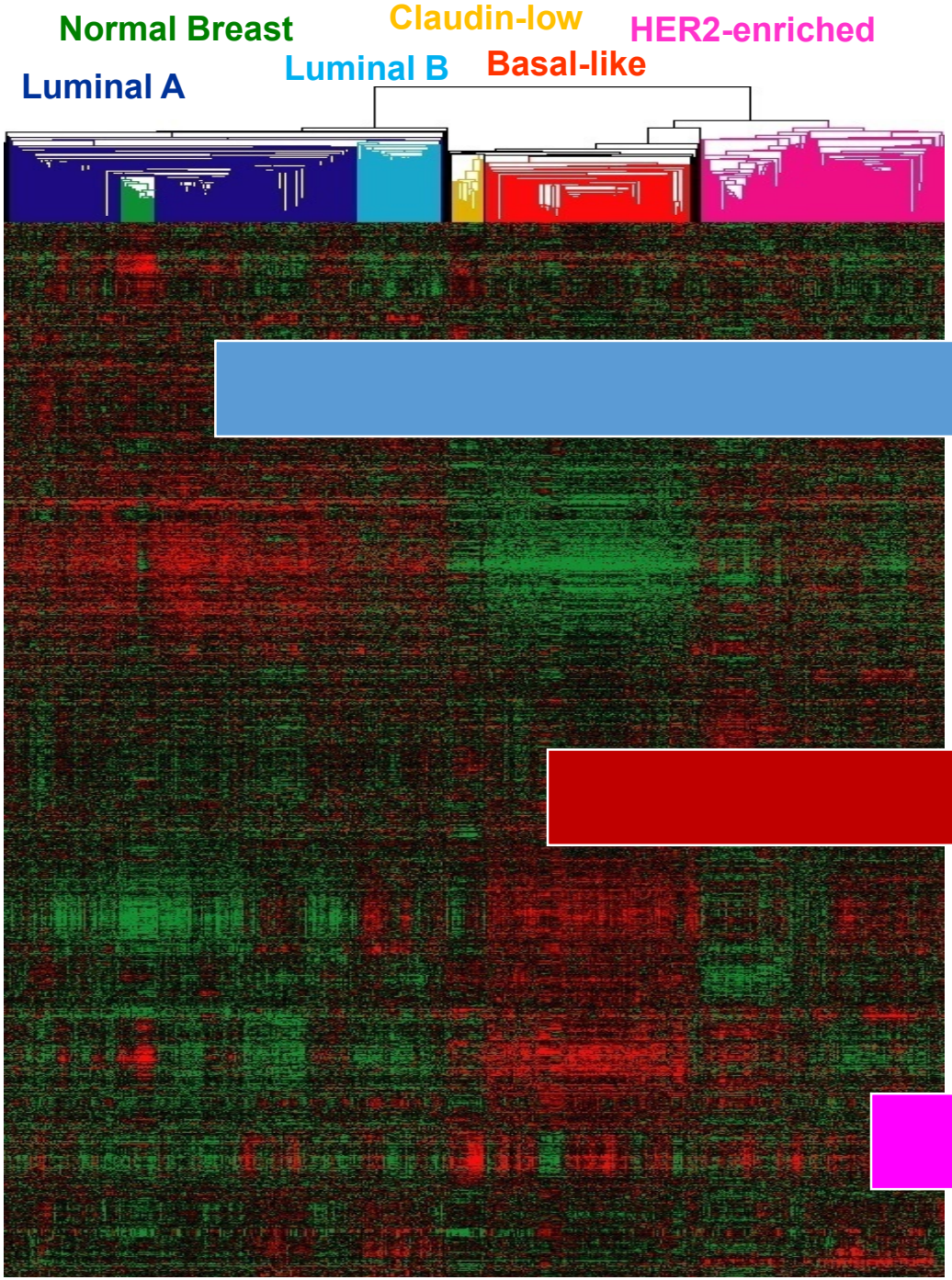
  - Prospective Study (n=200)
    - Prospectively enrolled patients with serially collected biospecimens with appropriate consent and follow up
    - return of genomic results



tbcrc
Translational Breast Cancer Research Consortium



The Breast Cancer Research Foundation



Clinical Treatment Groups for MBC Patients

Estrogen Receptor and/or Progesterone Receptor positive
Subtypes = LumA/B
Biomarkers = IHC
Drugs = tamoxifen and/or aromatase inhibitors

Triple-Negative (TNBC)
Subtypes = ~75% Basal-like
Biomarkers = IHC x3
Drugs = multi-agent chemotherapy

HER2 positive
Subtypes = ~66% HER2-E
Biomarkers = IHC or FISH
Drugs = trastuzumab, pertuzumab, tDM1

Therapies for ER+/HER2- Metastatic Breast Cancers

- **CDK4/6 Inhibitors =** (abemaciclib, palbociclib, or ribociclib)= **Approved**
  - First line in combination with an aromatase inhibitor or fulvestrant
  - MONALEESA-7 and MONARCH2 showed OS benefit

- **PIK3CA Inhibitor =** (alpelisib) = **Approved**
  - First line in combination with fulvestrant for PIK3CA-mutated tumors
  - Approved May 2019 based on results of the SOLAR-1 trial

- **mTOR inhibitor = (**everolimus**) = Approved**
  - Second line in combination with exemestane after progression on letrozole or anastrozole.

- **Selective Estrogen Receptor Degrader (SERDs)** = **Approved,** and more in development
  - Cause degradation of ER protein, and thus may target ESR1-mutants (~30-40% of AI treated MBCs)
  - Fulvestrant is approved, others in development (brilanestrant, elacestrant, more)

- **AKT Inhibitors** (capivasertib) = in testing, not yet approved
  - 10% of ER+ tumors have a somatic mutation in AKT1
  - ORR, PFS and OS benefit in phase II FAKTION trial

- **HDAC inhibitor** (entinostat) = = in testing, not yet approved
  - Showed PFS and OS benefit in Phase II trial ENCORE301
  - In Phase III testing (E2112)

- **Immune Checkpoint Inhibitors** = (pembrolizumab, durvalumab, atezolizumab) = none yet approved
  - PD-1 inhibitor (avelumab + palbociclib + fulvestrant, PACE Trial)
  - Very low response rates to date

Therapies for HER2+ Metastatic Breast Cancer

TARGETING HER2

- Lapatinib + capecitabine (approved 2007)
- Ado-trastuzumab emtansine (TDM1)(approved 2013)

- Neratinib + capecitabene approved for brain metastases and seeking FDA approval in the metastatic setting based on NALA trial results
- Neratinib is approved in extended adjuvant therapy after completion of 1 year of trastuzumab + pertuzumab
- Neratinib + TDM1 in clinical trials

- Tucatinib + trastuzumab + capecitabine (HER2Climb trial)= not yet approved

NON-HER2 TARGETING

- Immune checkpoint inhibitors = many in testing
  - atezolizumab/trastuzumab/pertuzumab/ in clinical trials
- CDK4/6 Inhibitors = in testing

Therapies for Metastatic Triple Negative Breast Cancer

- **Immune Checkpoint Inhibitors** (Atezolizumab) = approved March 2019
  - atezolizumab + nab-paclitaxel improves PFS and OS in PD-L1 positive metastatic TNBC (IMpassion130 trial)
  - MANY immune therapy trials underway!

- **PARP inhibitors** (targeting DNA repair in a unique way)
  - Olaparib for germline BRCA-mutated metastatic HER2-negative breast cancer (OlympiAD) = approved January 2018
  - Talazoparib for germline BRCA-mutated metastatic breast cancer (EMBRACA trial)= approved October 2018)
  - Somatic mutations in BRCA1/2 being tested as biomarkers for PARPi (TBCRC 048)

- **Sacituzumab Govitecan** (IMMU-132) = an antibody-drug conjugate (**ADC**) targeting the protein TROP-2 and delivering SN-38 (active metabolite of irinotecan), in Phase III testing

- **Combination Therapies**
  - pembrolizumab + niraparib (Immune therapy + PARPi)(TOPACIO trial)
  - durvalumab + olaparib (Immune therapy + PARPi) (MEDIOLA trial)
  - Pembrolizumab + cyclophosphamide (LCCC 1525)

Conclusions

There are many basic research studies being performed using model systems to identify the key genes/proteins that mediate metastasis. We need to continue to support basic research so that we can experimentally study the metastatic process, which is complex and mediated by cell-cell interactions

There are a number of translational initiatives, like AURORA US, being performed to identify the genetic and genomic ‘drivers’ of metastasis. These studies are critical to perform as they are based upon actual metastatic tumor specimens

There is a growing number of approved drugs for MBC patients (CDK4/6 inhibitors, TDM1, Atezolizumab, PARPi, PIK3CAi), and many more in Phase II and Phase III testing

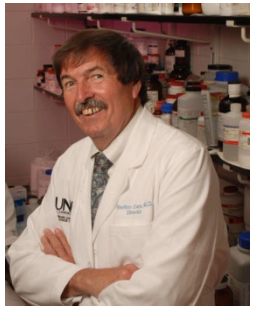












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