

Looking into the Future: Oligometastatic Disease



Himisha Beltran, MD

Dana Farber Cancer Institute
Harvard Medical School

himisha_beltran@dfci.harvard.edu



Oligometastatic Prostate Cancer: Summary of where we will be in two years

- Refined definitions for disease stratification
- Nominated molecular biomarkers to capture biologic disease states
- Defined goals of care and improved patient selection!

- Current Definitions

- “Oligometastatic” for metastasis directed therapy = based on number of metastases (1-5)
- “Low volume” disease for local radiation and/or systemic therapy choice= based on number and/or location of metastases (*not the same thing*)

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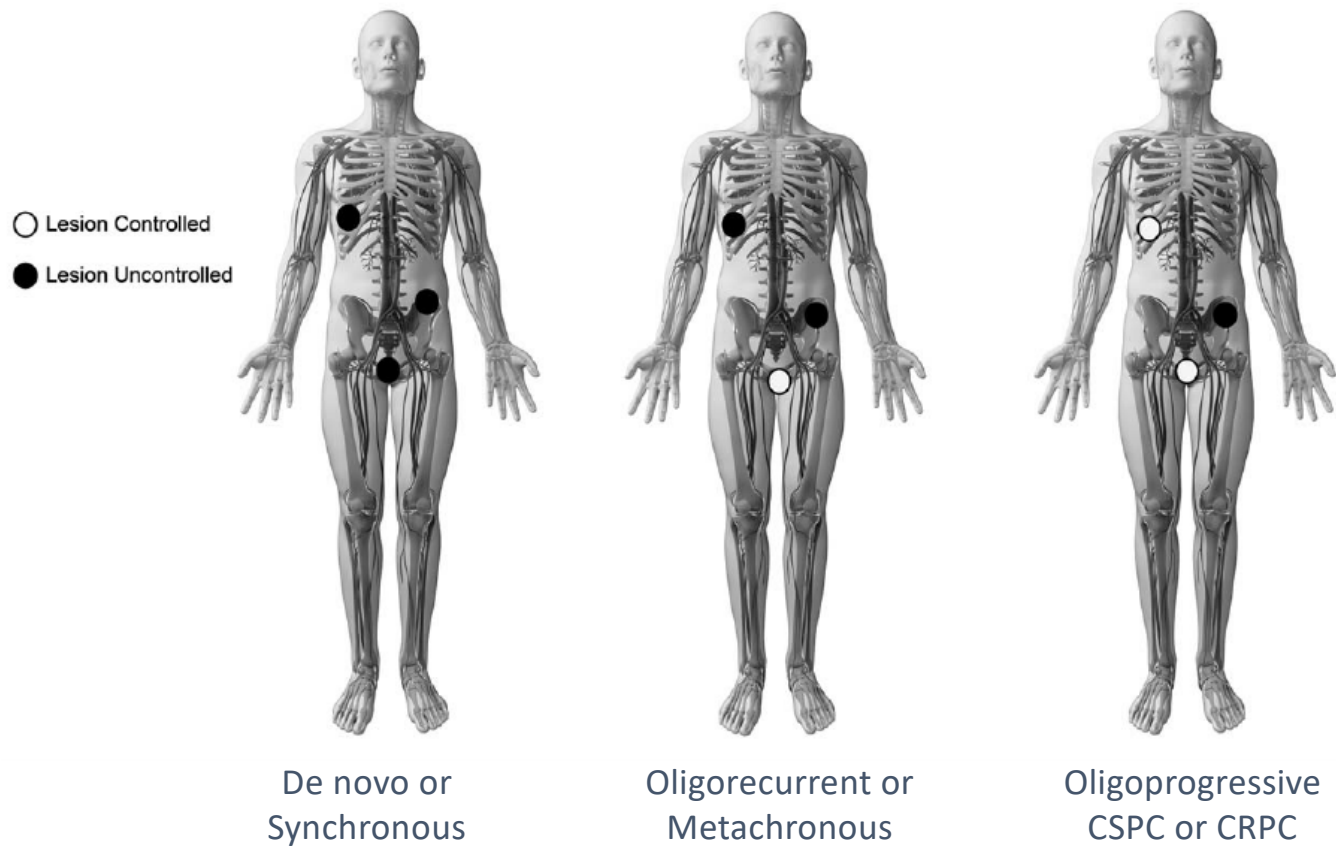
- And are further impacted by more sensitive imaging

- *For instance, a negative bone/CT scan but 3 lesions on PSMA PET-CT upstages patient to ‘metastatic’*
- *3 lesions on standard imaging but many on PSMA PET-CT upstages LV to HV*

Goals of care should be determined by biology

- 'Low metastatic potential'
- 'Intermediate' or 'heterogeneous' disease
- 'Systemic' disease

Relevant to different oligometastatic presentations

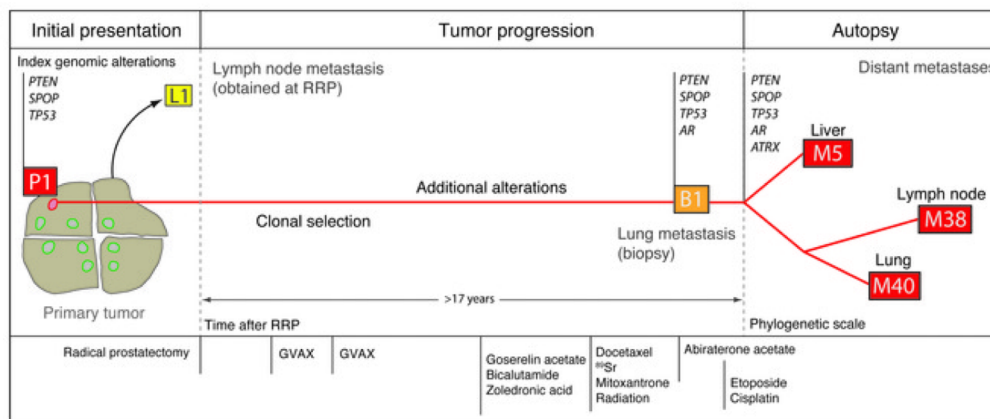


Goals of care should be determined by biology

- 'Low metastatic potential'
 - Goals: delay ADT, come off of systemic therapy, *cure*?
 - Do whatever it takes!
- 'Intermediate' or 'heterogeneous' disease
- 'Systemic' disease

Where do lethal metastases come from?

- For instance, primary tumors can metastasize to LN and not be the clone responsible for death



Haffner et al, JCI 2013

Non-index primary lesions can metastasize to LN (but may not be lethal)

Frequent clonal relations between metastases and non-index prostate cancer lesions

Jeroen Kneppers,^{1,2} Oscar Krijgsman,^{2,3} Monique Melis,⁴ Jeroen de Jong,^{2,5} Daniel S. Peeper,^{2,3} Elise Bekers,⁵ Henk G. van der Poel,⁶ Wilbert Zwart,^{1,2,7} and Andries M. Bergman^{1,8}

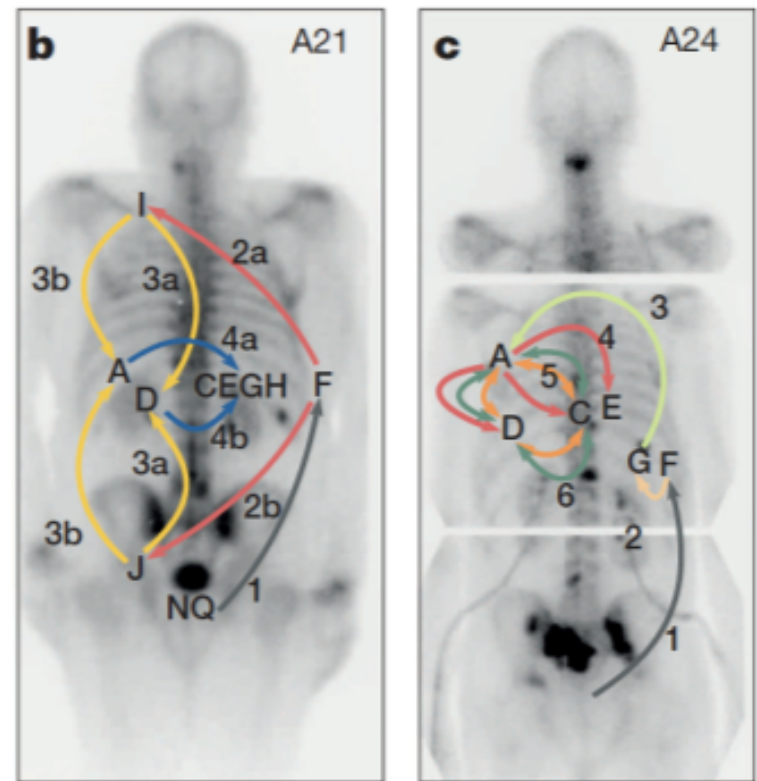
Kneppers et al, JCI Insight 2019

Could molecular alterations *in the primary* predict patterns of spread and the *relative indolence* of certain metastatic lesions?

Primary tumor can continue to seed metastases

- Rationale for treating the primary tumor in the setting of metastases
- STAMPEDE/HORRAD point to greater benefit for patients with low volume disease

... potentially due to greater contribution of primary (non-index) clones contributing



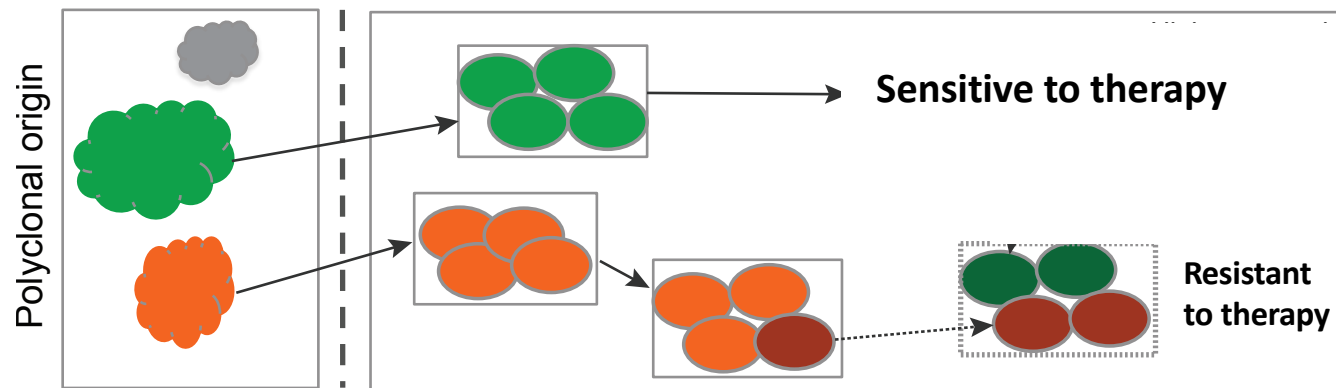
Gundem et al, 2016

Goals of care should be determined by biology

- 'Low metastatic potential'
- 'Intermediate' or 'heterogeneous' disease
 - For instance, one lesion progressing, others are stable
 - Combat heterogeneity with multimodal therapy
 - Goals= get to stay on same systemic therapy, slow progression?
- 'Systemic' disease

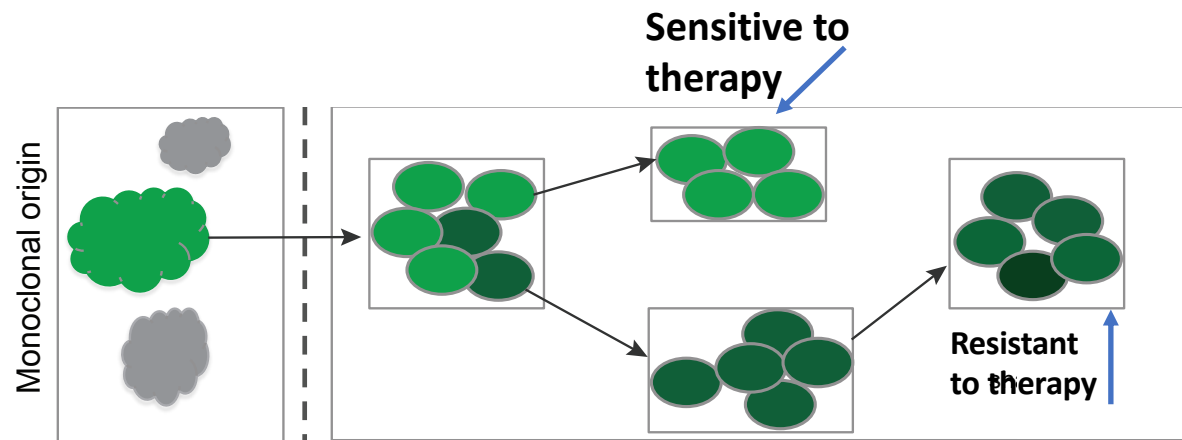
One lesion progressing, others are stable

- Different biology across metastases
- Did they come from different primary tumors?



One lesion progressing, others are stable

- Or did they come from *acquisition of resistance mutations*?



Implications for biomarker development (primary tumor and what to look for in metastatic lesion)

Goals of care should be determined by biology

- 'Low metastatic potential'
- 'Intermediate' or 'heterogeneous' disease
- 'Systemic' disease
 - Local/focal therapy may have no impact
 - Systemic therapy intensification

How to capture underlying 'systemic disease'?

- Molecular imaging
- ctDNA
- CTCs
- DTCs
- Exosomes
- other means?
- Seed vs. soil: Biology of tumor + metastatic niche ?
 - Little known about microenvironment in oligometastatic disease
- *But what exactly are we looking for? (eg., tumor burden, micromets, alterations in oncogenes/ tumor suppressors, metastasis markers)*

Capturing 'tumor burden' noninvasively

- PSMA PET: highly sensitive
- Tumor fraction by WGS of cfDNA associated with the presence and number of bone mets (TFx = 0.014 with no bone mets, 0.047 with 1-3 bone mets, 0.190 for 4+ bone mets; $P < 0.0001$) and with visceral metastases ($P < 0.0001$) in mCRPC (Choudhury et al, JCI Insight 2018)

But can we use these tools to *predict* metastatic patterns before “detecting” it?

Bone metastases

What we see may not be what is underneath (more aggressive biology)



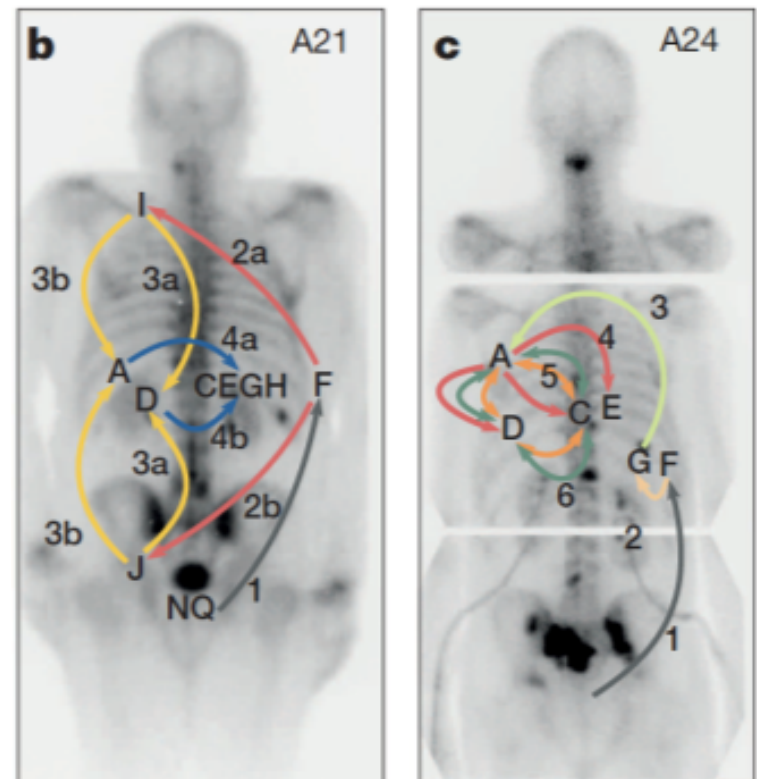
Pulmonary metastases

What we see may not be what is underneath (more indolent biology)



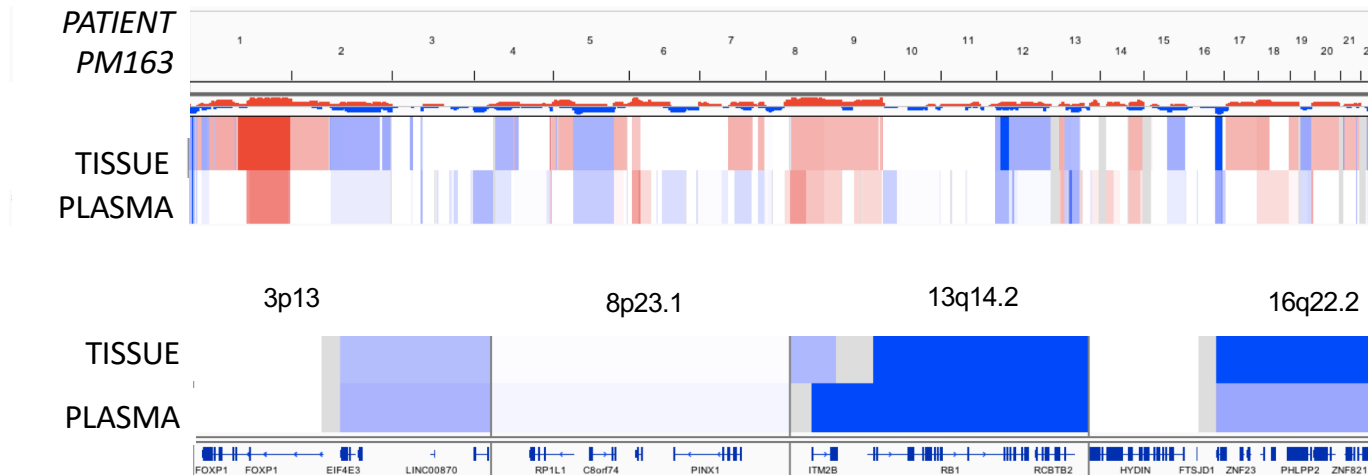
Metastases to metastases seeding

- Further leads to intra-patient heterogeneity
- Difficult to capture by single site biopsy
- Requires more refined analysis of:
 - ctDNA
 - CTCs
 - Molecular imaging
- Therapeutic implications
 - Multi-modality or combination therapy



Gundem et al, 2016

Use of liquid biopsies to detect intra-patient clonal heterogeneity

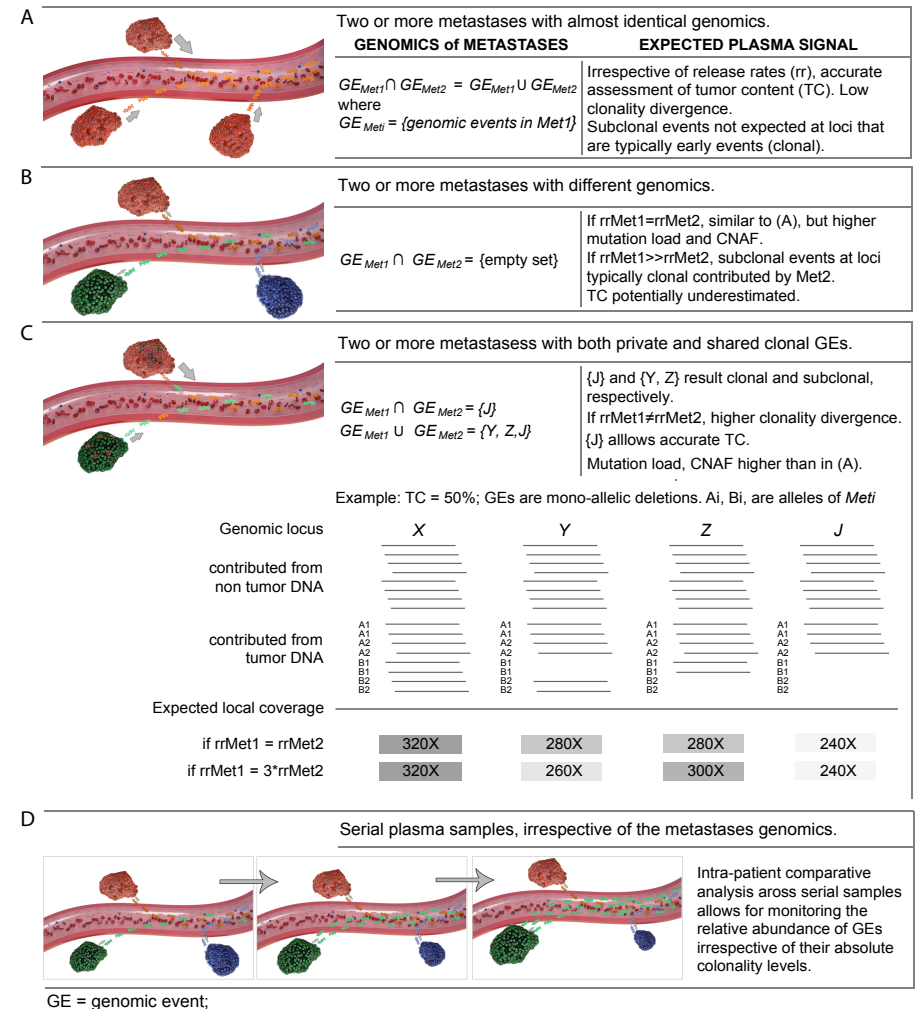


Whole exome sequencing of matched plasma ctDNA and metastatic tumor tissue

Cell free DNA to capture intra-patient heterogeneity

- A. 2 or more different metastases with identical genomics, equal or variable release rates into the circulation
- B. Different metastases with different genomics
- C. Different metastases with both private and shared genomic alterations
- A. Tracking abundance of genomic alterations, irrespective of absolute clonality

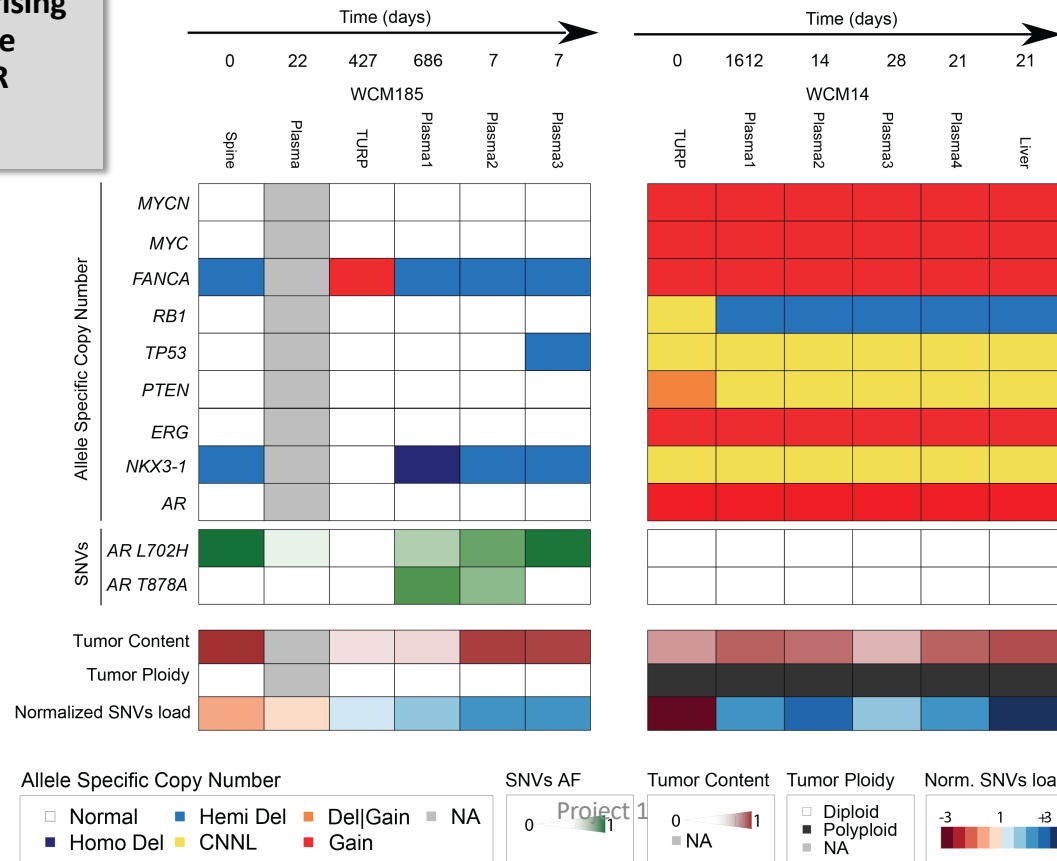
**note: ctDNA more challenging when low tumor burden*



Beltran/Demichelis, unpublished

Circulating tumor DNA to measure clonal fitness and clonal competition non-invasively and detect persistence or emergence of 'aggressive' lesions

PM185 (rising PSA, bone mets, "AR driven?"

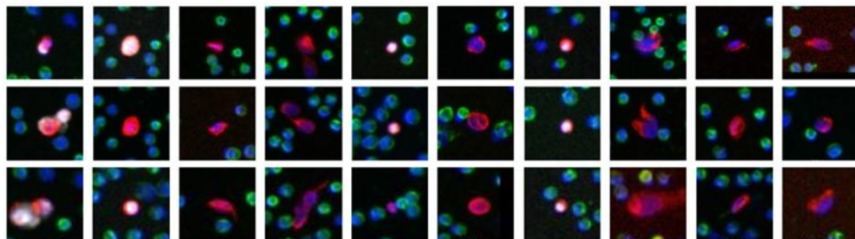


PM14 (low PSA, visceral mets, "AR independent?"

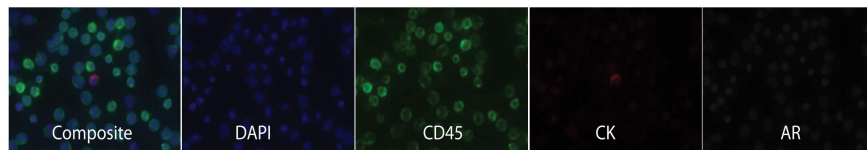
Beltran/Demichelis, unpublished

Circulating tumor cells

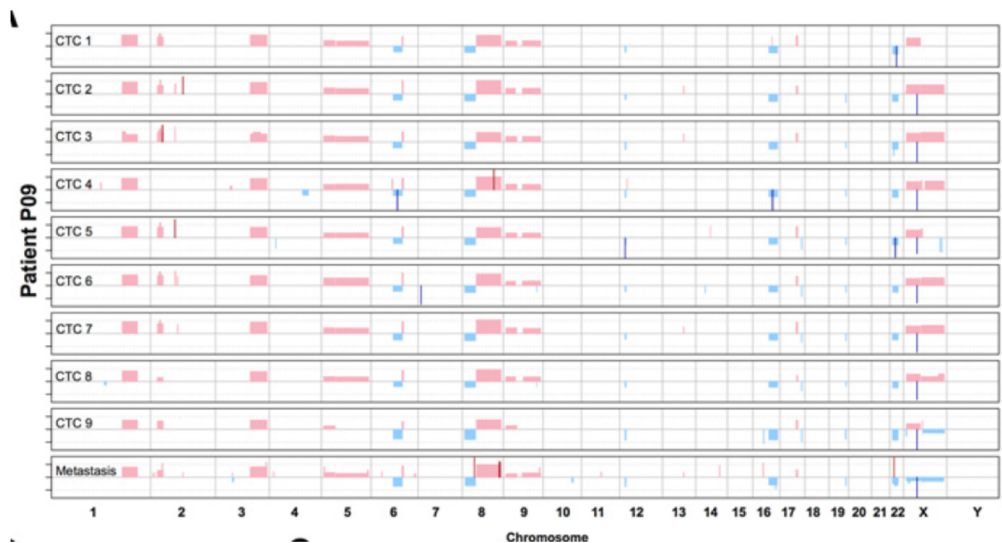
- Captures heterogeneity (shape, size, expression, genomics)
- Serial CTCs can also identify evolution/emergence of clones/subclones and evolution patterns



CTC phenotypic features- Scher et al Cancer Res 2018



Resistance mechanisms – Beltran et al, CCR 2016



Single CTC genomics, Lambros et al, CCR 2018

In two years, we will have more data regarding how we have altered the natural history of oligometastatic prostate cancer

- What happens to patients who progress after local therapy for oligometastatic prostate cancer?
 - More oligometastases
 - Same location or different? Do we give more local therapy?
 - May represent a more indolent biologic entity
 - Widespread systemic disease
 - Timing? Was this delayed by local Rx?

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Summary of where we will be in two years

- Refined clinical definitions for disease stratification
- Nominated molecular biomarkers to capture biologic disease states
- Defined goals of care and improved patient selection!
- **Molecular tools exist to help capture biologic subsets and tumor evolution patterns--- *we need to test them in our trials!***
This will ultimately lead to better biomarkers and improved patient selection