



Molecular Tumor Board



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Mary and Rob Gooze Chair in Metastatic Breast Cancer

University of Wisconsin- Madison



Disclosures

M.E.B. declares the following:

- Strata Oncology (**Medical Advisory Board**)
- Abbvie, Arcus, Apollomics, Elevation Oncology, Genentech, Puma, Loxo Oncology, Seagen (**Research funding**)
- Novartis, Strata Oncology (**Consultant**)



Many vendors

Genomics (somatic)

Tempus
Strata Oncology
Foundation Medicine
Caris
Guardant

Expression (somatic)

Exact
Sciences/Genomic
Health
Agendia
Prosigna
BioTheranostics

Germline

Myriad
Prevention Genetics
Color Genetics
Ambry Genetics



Many vendors

Genomics (somatic)

Tempus

Strata Oncology

Foundation Medicine

Caris

Guardant



Topics

1. How Next-Generation Sequencing (NGS) tests work
2. Differences in commercial NGS tests
3. What to do?
4. What's next?



Topics

- 1. How Next-Generation Sequencing (NGS) tests work**
2. Differences in commercial NGS tests
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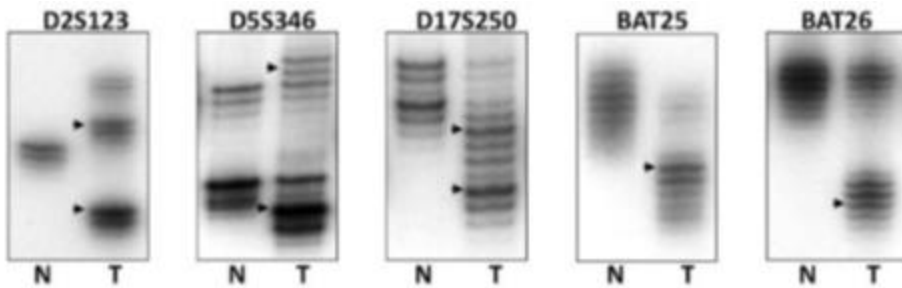
Types of alterations

<u>Type</u>	<u>Example</u>	<u>DNA/chromosome</u>	<u>Protein</u>	<u>Function</u>
Point mutation (missense)	ERBB2 S310F			Protein with aberrant function
Inframe deletion	EGFR L747_T451del			
Frameshift	CDH1 F317fs*39			Nonfunctional protein or No protein (<i>nonsense-mediated decay</i>)
Nonsense/Stop	CREBBP Q792*			
Amplification	ERBB2 amplification			Excess protein
Deletion	CDKN2A del or loss			Absent protein

MSI and tumor mutational burden

MSI

-changes in length in repetitive DNA (microsatellites)



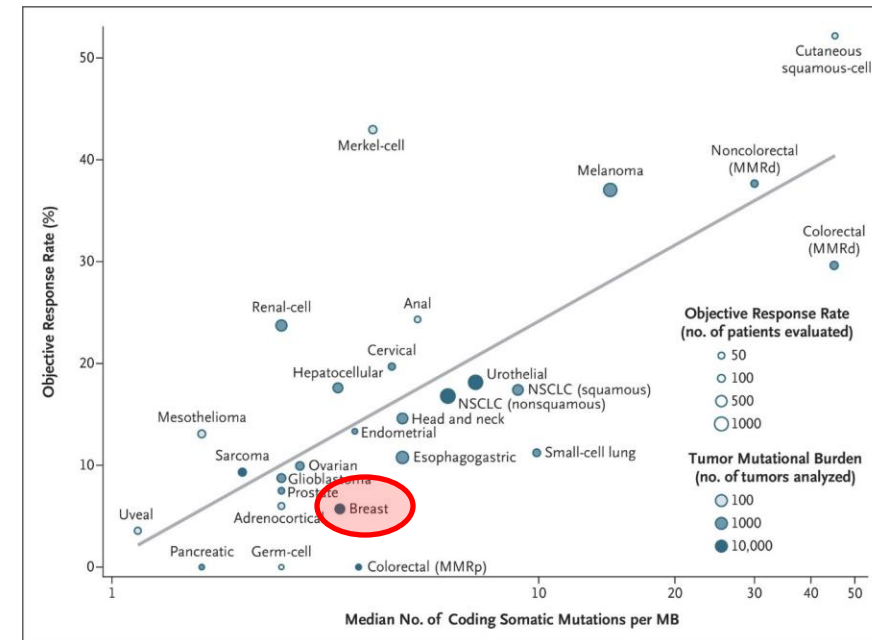
Boland and Goel, Gastroenterology 2010

-caused by mutations:

MLH1, MSH2, MSH6, PMS2

TMB

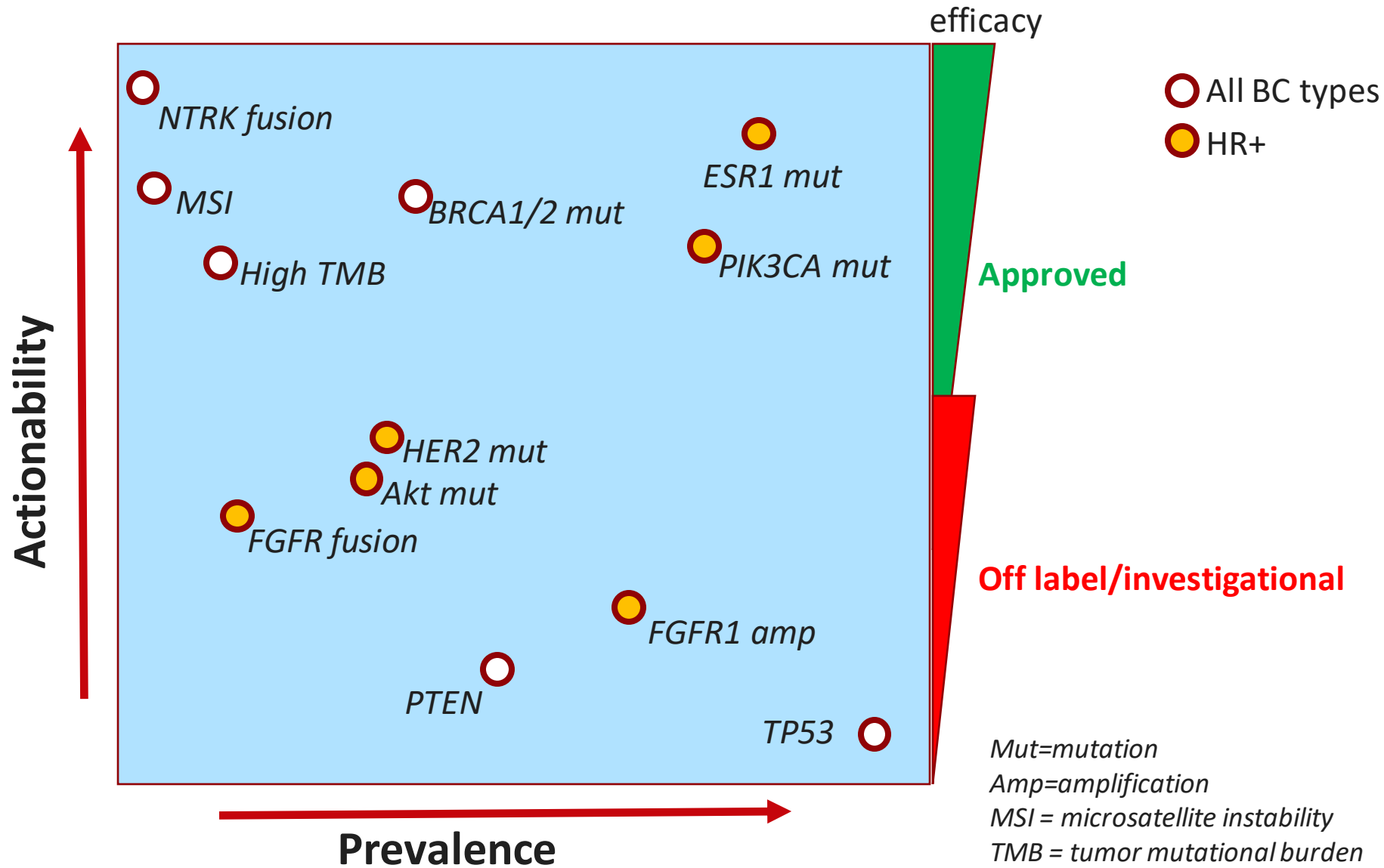
-number of non-synonymous mutations per Megabase

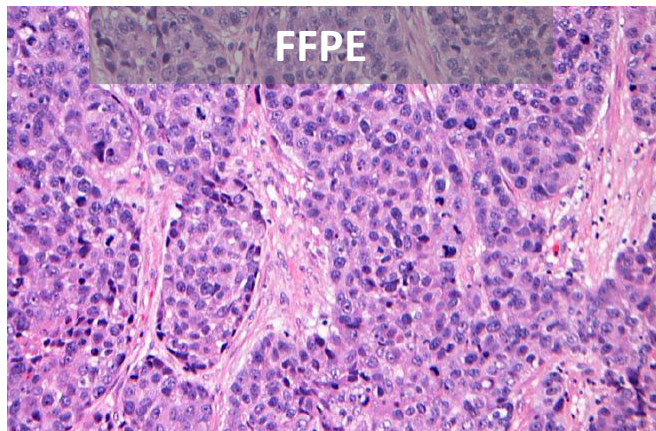


Yarchoan, Hopkins & Jaffee, NEJM 2017

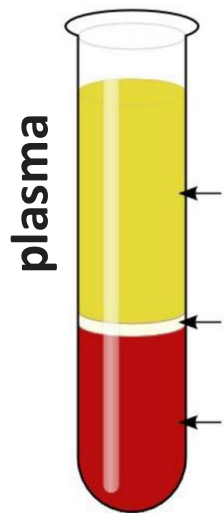


Druggable targets by NGS

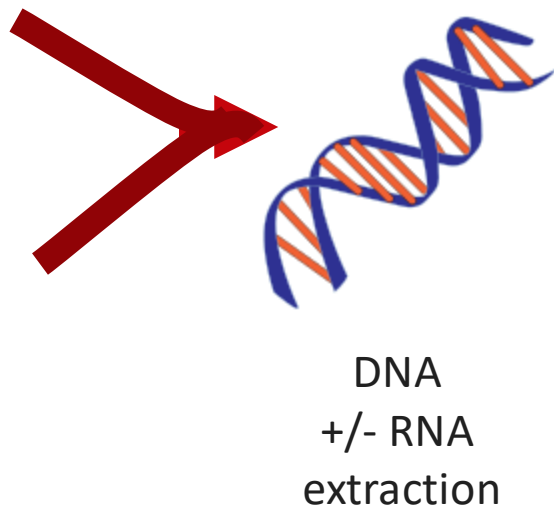




FFPE



plasma



200ng

Panel/
WES

capture

WGS



Sequencer

Reads

ATGGCATTGCAA
TGGCATTGCAATTTG
AGATGGTATTG
GATGGCATTGCAA
GCATTGCAATTTGAC
ATGGCATTGCAATTT
AGATGGTATTGCAATTTG



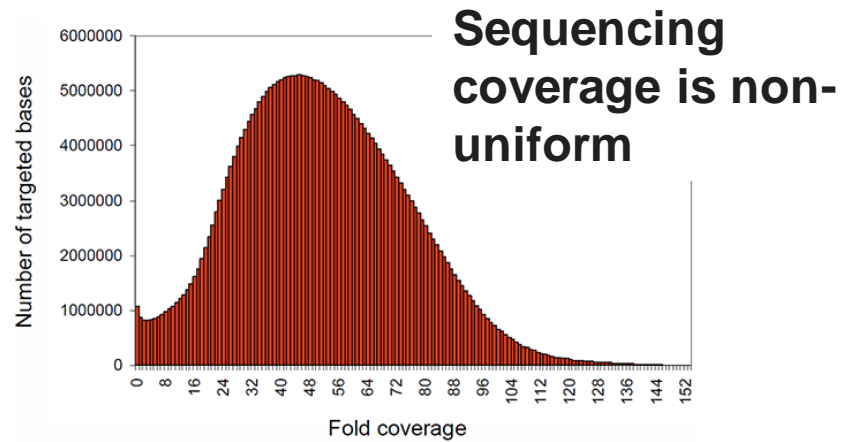
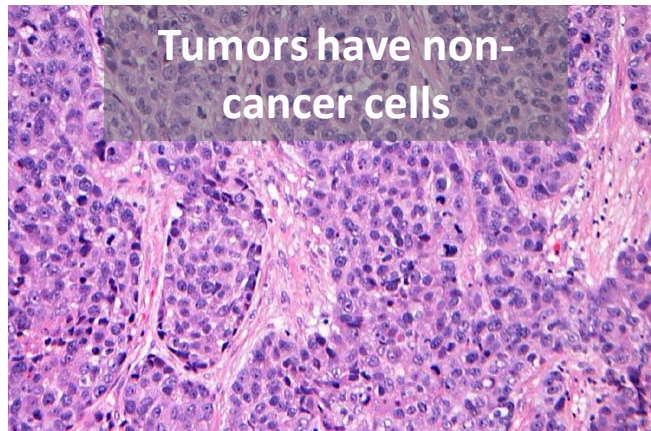
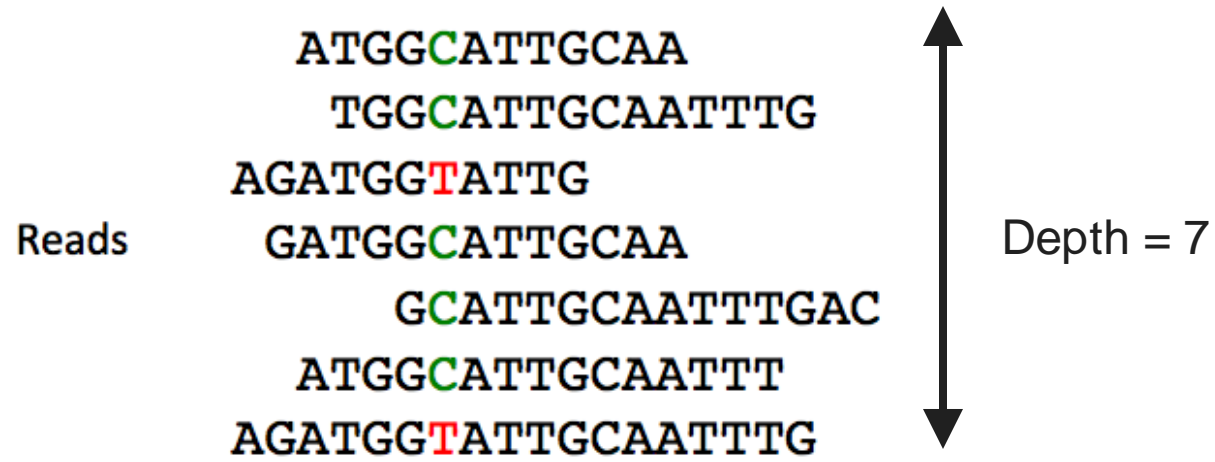
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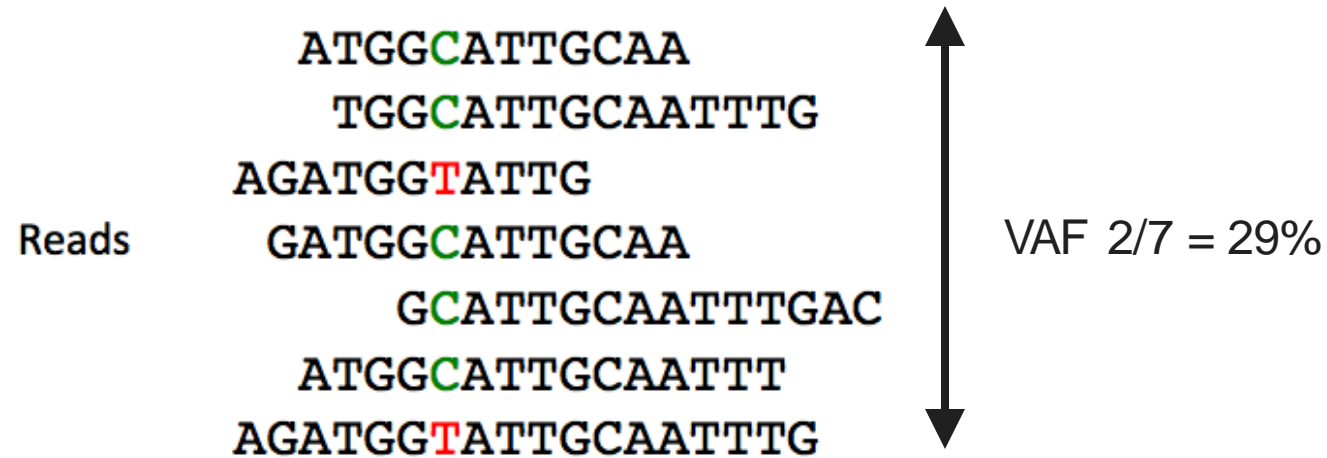
Difference 1: breadth and depth of sequencing

Depth: why it matters

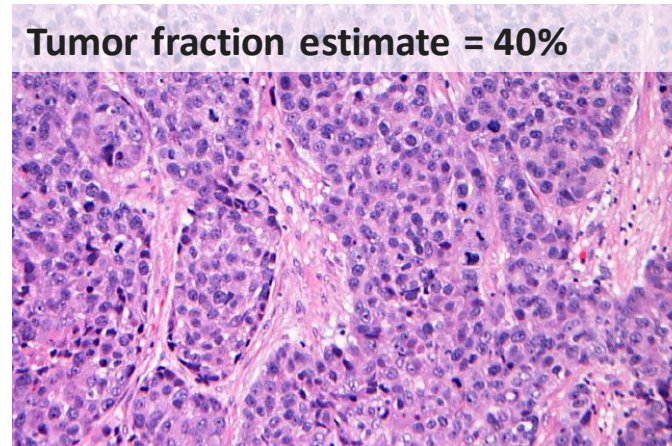




Variant allele frequency



Variant allele frequency (VAF)

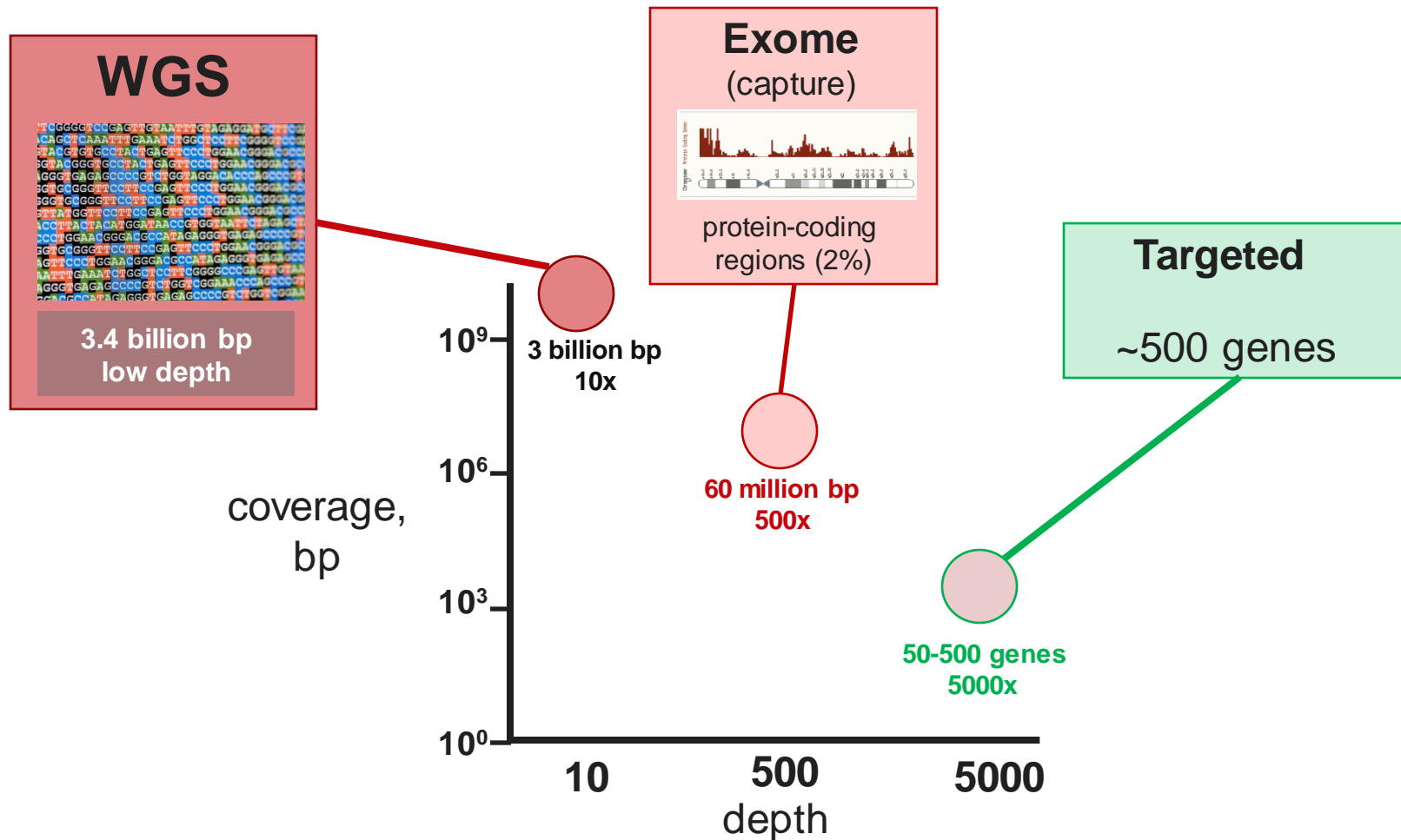


<u>VAF result</u>	<u>Interpretation*</u>	<u>Example</u>
0.2	tumor, heterozygous	<i>PIK3CA</i>
0.25	tumor, heterozygous + LOH	<i>TP53</i>
0.62	germline, heterozygous (LOH)	<i>BRCA1</i>

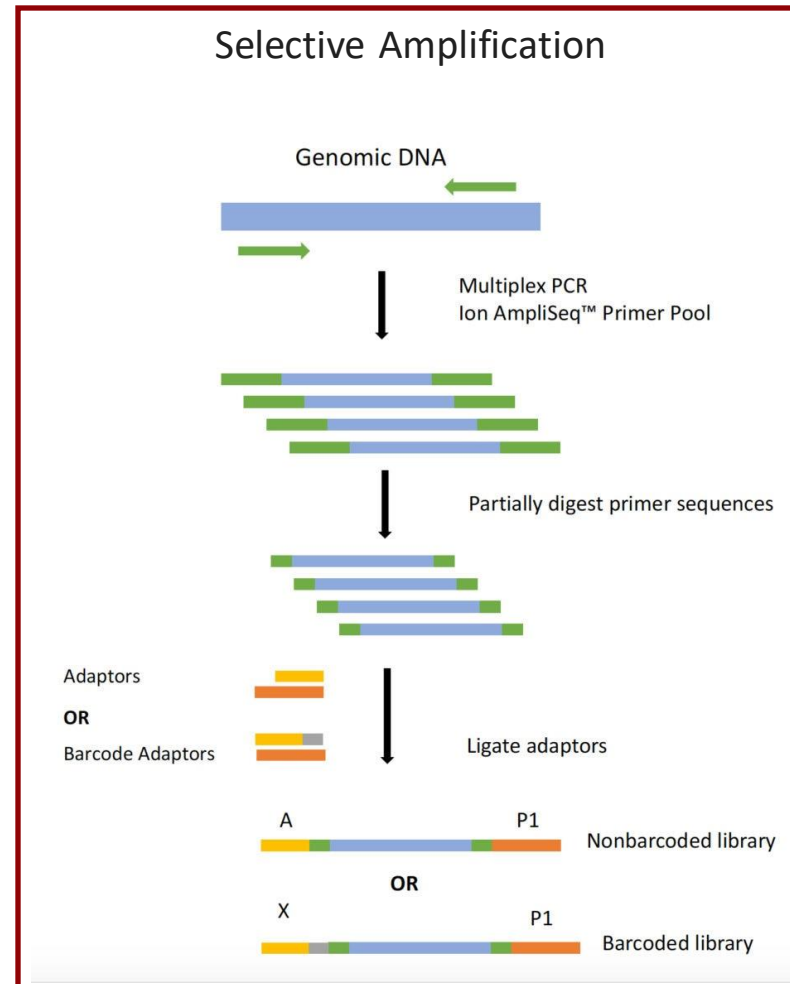
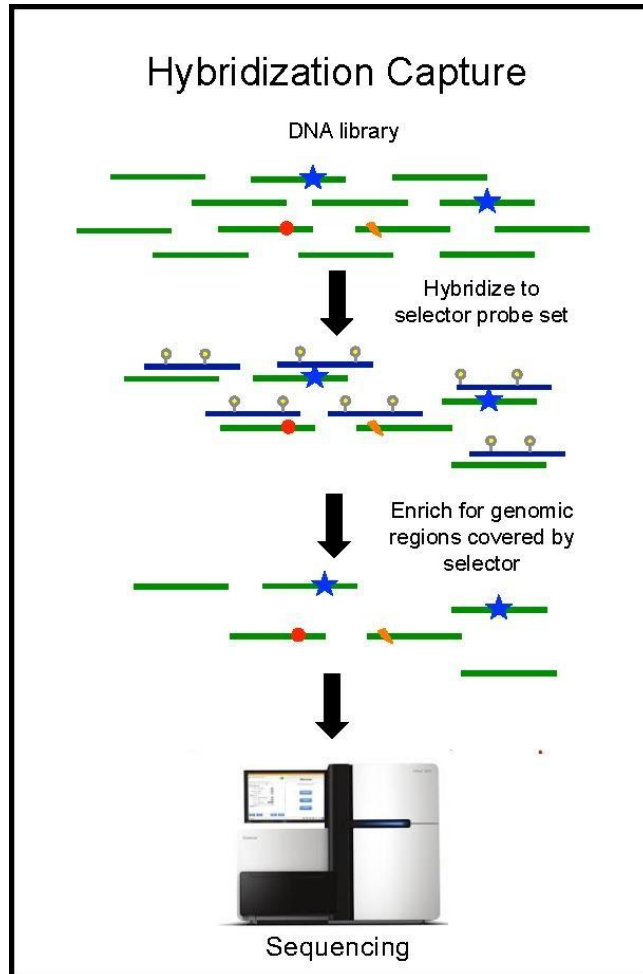
**take as 'hint' with a large grain of salt*



Genomic analyses



Selecting important parts of genome





Difference 2:

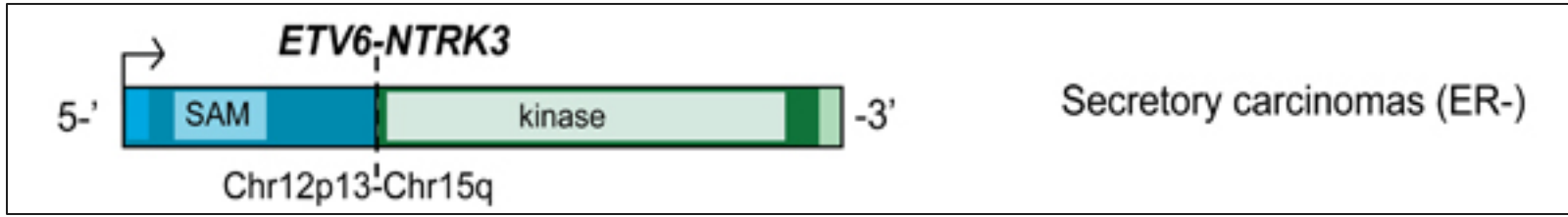
Detecting Fusions



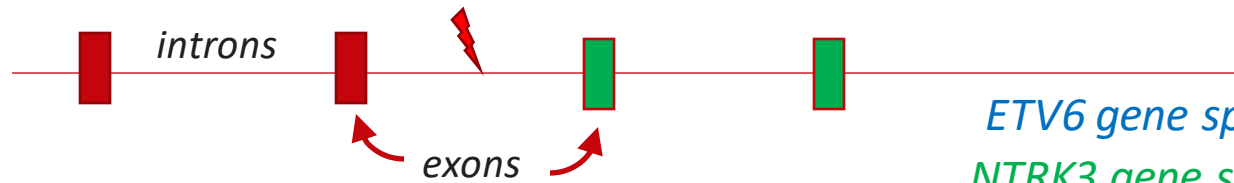
Potentially druggable fusions in breast cancer

Fusion gene structure	Breast Cancer subtype	Reference			
<p>ETV6-NTRK3 Chr12p13-Chr15q</p>	Secretory carcinomas (ER-)	Tognon et al (5)			
<p>MYB-NFIB Chr6q23-Chr9p23</p>	Adenoid-cystic carcinomas (ER-)	Persson et al (5)			
<p>various-MAST1/2 gene x-Chr19q13/Chr1p13</p>	ER+/ER-	Robinson et al (3)			
<p>various-NOTCH1/2 gene x-Chr9q34/Chr1p12</p>	ER-	Robinson et al (3)			
<p>ESR1-CCDC170 Chr6q25-Chr6q25</p>	ER+/Luminal B	Veeraraghavan et al (6)			
<p>KIAA1549-BRAF Chr7q34-Chr7q34</p>	Metastatic	Ross et al (7)			
<p>CAPZA2-MET Chr7q31-Chr7q31</p>	ER+	Yoshihara et al (8)			
			<p>FGFR3-TACC3 Chr7q34-Chr7q34</p>	Triple negative breast cancer	Shaver et al
			<p>ACTL6A-PIK3CA Chr3q26-Chr3q26</p>	ER+ advanced disease	Matiseek et al (1)
			<p>RPS6KC1-AKT3 Chr1q32-Chr7q31</p>	ER+ advanced disease	Matiseek et al (1)
			<p>CTNNB1-RAF1 Chr20q11-Chr7q31</p>	ER+ advanced disease	Matiseek et al (1)
			<p>ESR1-CoA5 Chr6q25-Chr2q11</p>	ER+ advanced disease	Matiseek et al (1)
			<p>Fgfr2-Dnm3 Chr7qF3-Chr1qH2</p>	<i>Tp53/Brca1</i> GEMM	Liu et al (2)
			<p>Dhx9-Raf1 Chr1qG3-Chr6qE3</p>	<i>Tp53/Brca1</i> GEMM	Liu et al (2)

Finding fusions



DNA



ETV6 gene spans 245,000 nucleotides
NTRK3 gene spans 397,000 nucleotides

mRNA



Exons are spliced

ETV6 mRNA 1,356 nucleotides
NTRK3 mRNA 2,517 nucleotides



Difference 3:

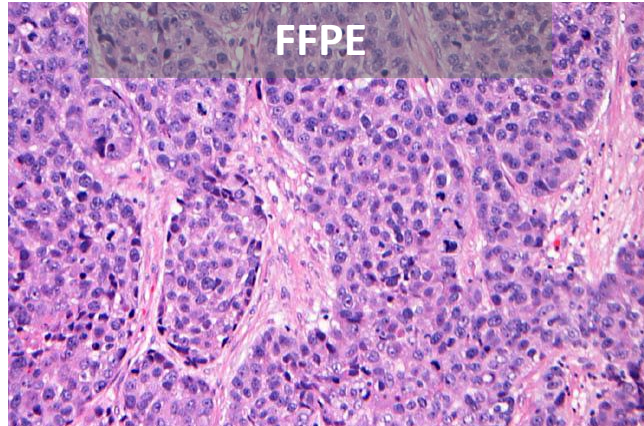
tissue vs. ctDNA

FFPE Advantages:

Sensitive

Less likely to be impacted by CHIP

Amplifications are more reliable



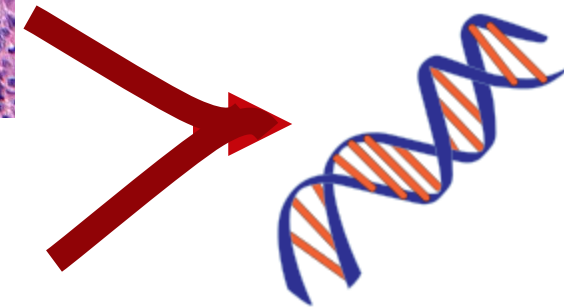
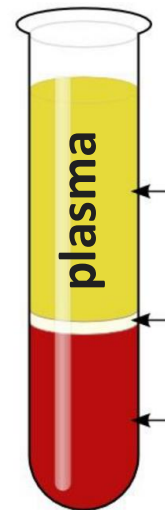
ctDNA Advantages:

Samples all sites of disease

Easy to obtain

Fast turnaround

Companion diagnostic



DNA
+/- RNA
extraction



Topics

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How to implement NGS into routine clinical practice

1. Decide what to do

2. What do you want to accomplish?

Help some patients?

Clinical trials?

Make discoveries?

- any multigene panel and/or ctDNA

- any multigene panel

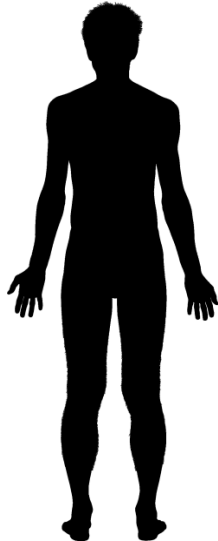
- whole genome panels or new technologies

3. Make it efficient!

UWCCC/WON Molecular Tumor Board



Committee of physicians, genomicists, bioinformatics, pharmacists, cancer biology researchers



Biomarker	Method	Result	Biomarker	Method	Result
ABL1	NGS	Mutation Not Detected	EDY1	NGS	Mutation Not Detected
AKT1	NGS	Mutation Not Detected	ERBB2	NGS	Mutation Not Detected
AKT2	NGS	Mutation Not Detected	ERBB3	NGS	Mutation Not Detected
AKT3	NGS	Mutation Not Detected	ERBB4	NGS	Mutation Not Detected
AR	NGS	Mutation Not Detected	ERBB5	NGS	Mutation Not Detected
ARHGAP35	HC	Not Amplified	ERBB6	NGS	Mutation Not Detected
ATM	NGS	Mutation Not Detected	ERBB7	NGS	Mutation Not Detected
ATM2	NGS	Mutation Not Detected	ERBB8	NGS	Mutation Not Detected
BRCA1	NGS	Mutation Not Detected	ERBB9	NGS	Mutation Not Detected
BRCA2	NGS	Mutation Not Detected	ERBB10	NGS	Mutation Not Detected
CDK2	NGS	Mutation Not Detected	ERBB11	NGS	Mutation Not Detected
CDK4	NGS	Mutation Not Detected	ERBB12	NGS	Mutation Not Detected
CDK6	NGS	Mutation Not Detected	ERBB13	NGS	Mutation Not Detected
EGFR	NGS	Mutation Not Detected	ERBB14	NGS	Mutation Not Detected
ERBB1	NGS	Mutation Not Detected	ERBB15	NGS	Mutation Not Detected
ERBB2	NGS	Mutation Not Detected	ERBB16	NGS	Mutation Not Detected
ERBB3	NGS	Mutation Not Detected	ERBB17	NGS	Mutation Not Detected
ERBB4	NGS	Mutation Not Detected	ERBB18	NGS	Mutation Not Detected
ERBB5	NGS	Mutation Not Detected	ERBB19	NGS	Mutation Not Detected
ERBB6	NGS	Mutation Not Detected	ERBB20	NGS	Mutation Not Detected
ERBB7	NGS	Mutation Not Detected	ERBB21	NGS	Mutation Not Detected
ERBB8	NGS	Mutation Not Detected	ERBB22	NGS	Mutation Not Detected
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ERBB20	NGS	Mutation Not Detected	ERBB34	NGS	Mutation Not Detected
ERBB21	NGS	Mutation Not Detected	ERBB35	NGS	Mutation Not Detected
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ERBB23	NGS	Mutation Not Detected	ERBB37	NGS	Mutation Not Detected
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ERBB54	NGS	Mutation Not Detected	ERBB68	NGS	Mutation Not Detected
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ERBB85	NGS	Mutation Not Detected	ERBB99	NGS	Mutation Not Detected
ERBB86	NGS	Mutation Not Detected	ERBB100	NGS	Mutation Not Detected

Submit pathology or genomics analysis



Recommendations

- Clinical trial
- Off-label treatment
- Standard treatment (not targeted)

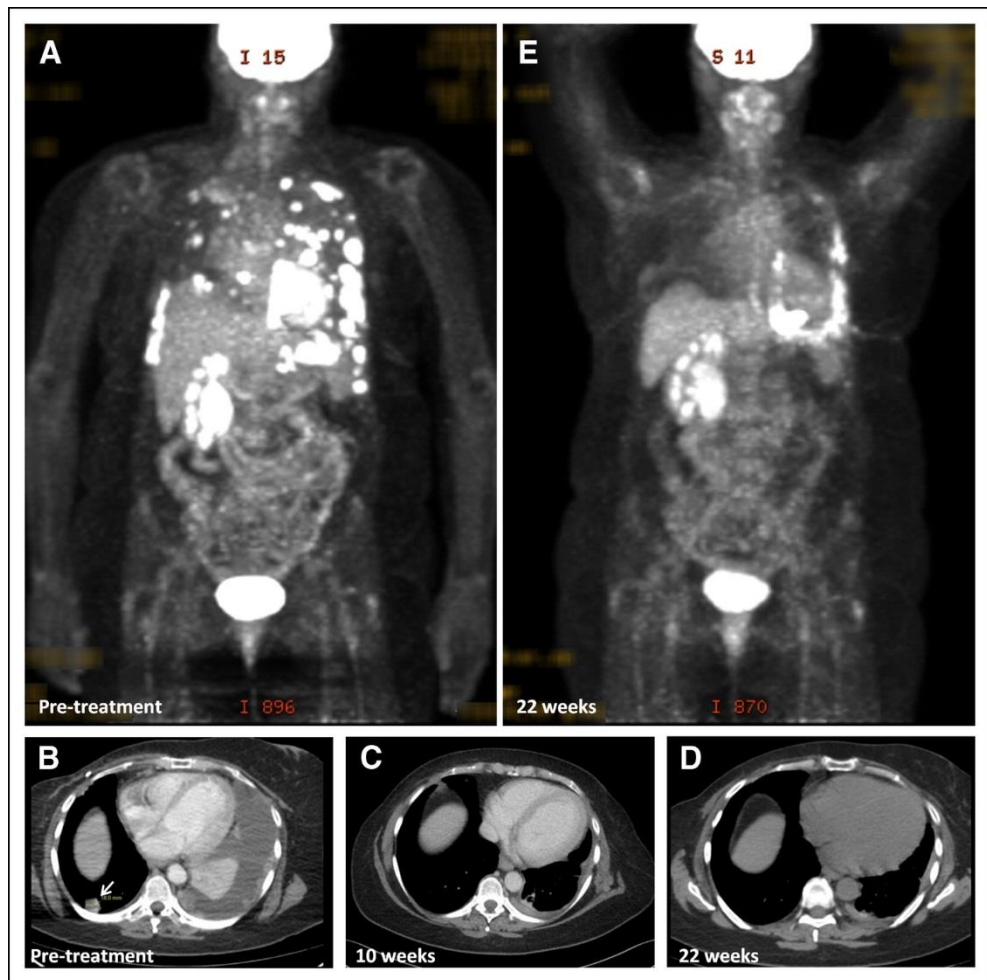
In return:

- Submit clinical outcome data
- Enrolled in registry protocol



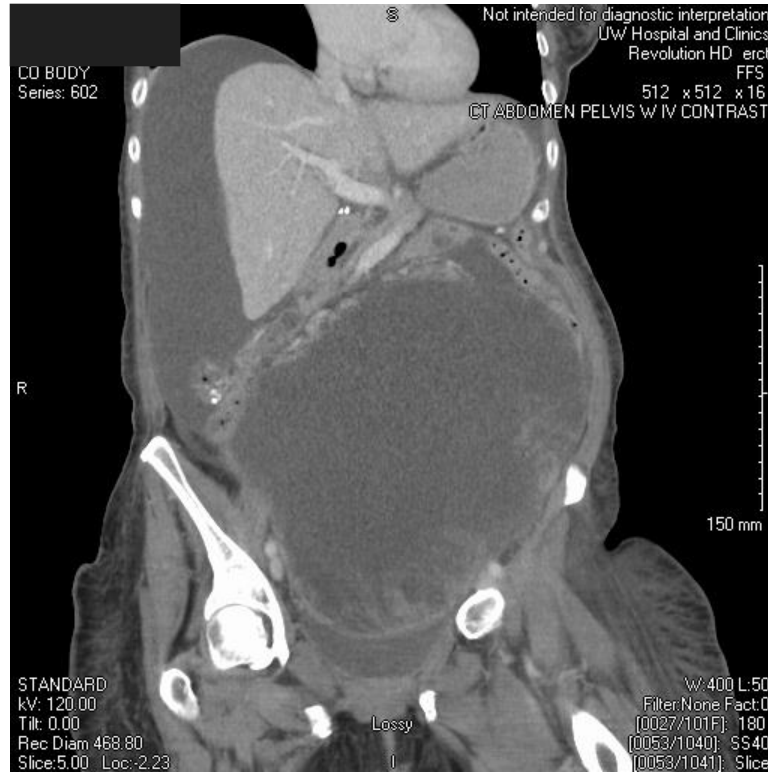
Oncogene amplification

Crizotinib for
MET
amplification





TRK fusion in GIST



6/15/17

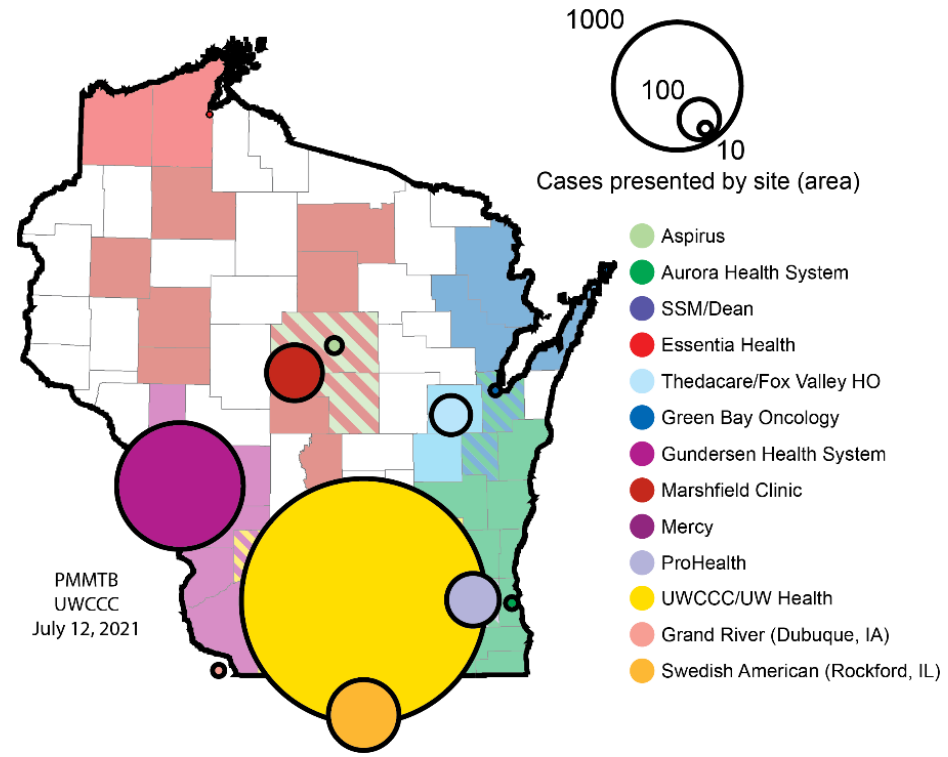
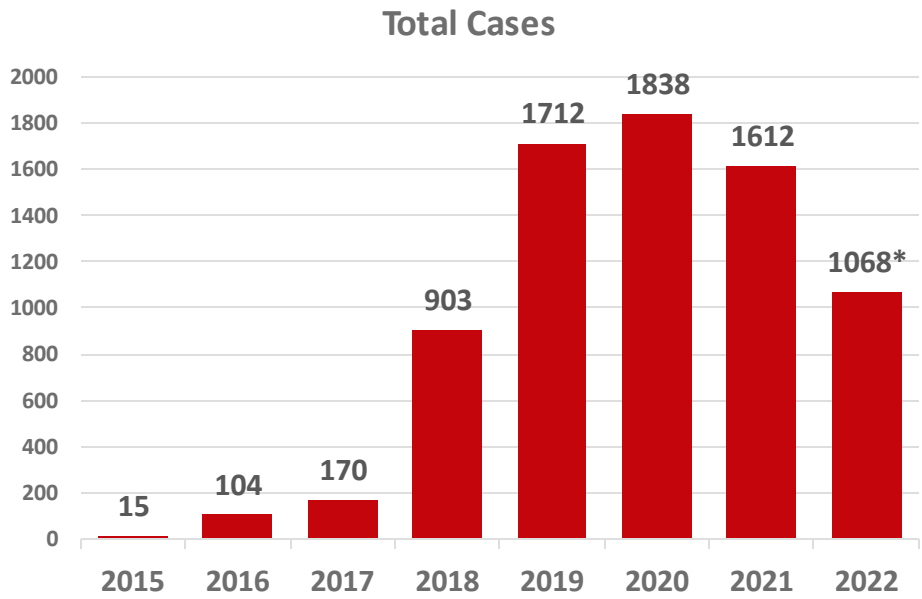


2/05/18



MTB activity to date

7,422 cases



Updated from Burkard et al. JCO Precision Oncology 2017

Clinical Trials Navigation Office



Sarah Kotila, RN, BSN
Clinical Trials Navigation Manager



Karen Arkin, RN, BSN
Clinical Trial
Nurse Navigator



Katie Browen, RN, BSN
Clinical Trial
Nurse Navigator

- **Provide general trial information**
- **Communicate with patients and physicians**
- **Conduct preliminary screenings for studies**
- **General education about clinical research**
- **Outreach to outside clinics and hospitals**
- **Work with external and internal referrals**
- **Connect the right people**



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Future opportunities in cancer genomics

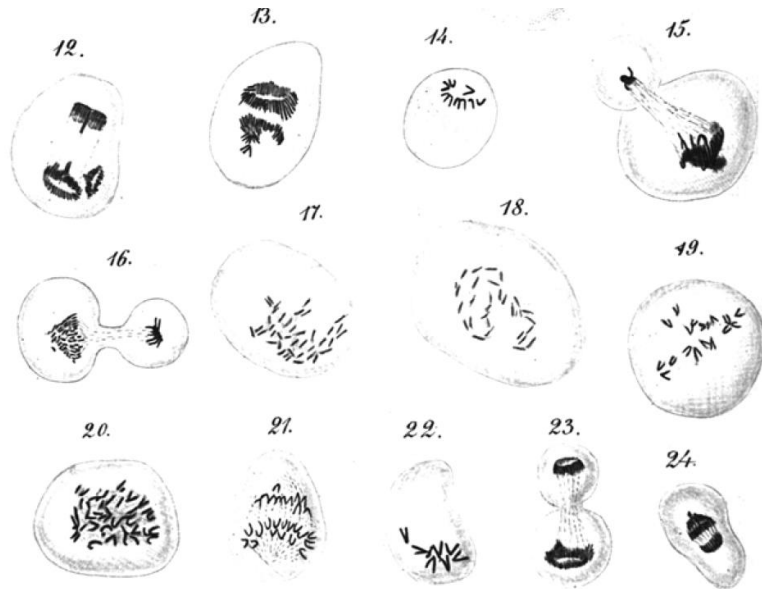
Things we find now:

- Point mutations
- Small indels
- Fusions
- Common drivers

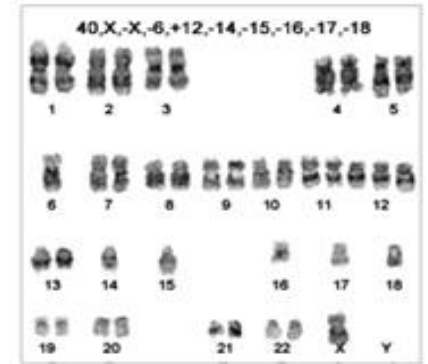
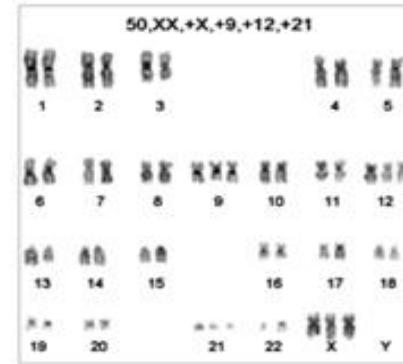
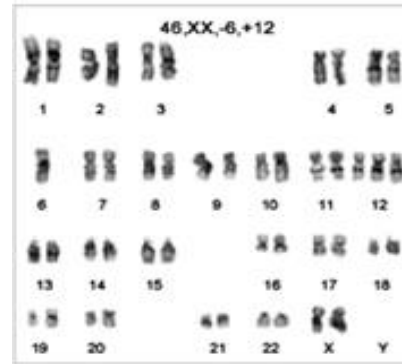
Things we are missing:

- Large-scale genomic alterations
- Centromere variation (T2T)
- Cell-cell variation
- Drivers restricted to rare populations

Chromosomal Instability



Von Hansemann D (1890) Arch
 Pathol Anat Physiol Klin Medicin
 119: 299-326.

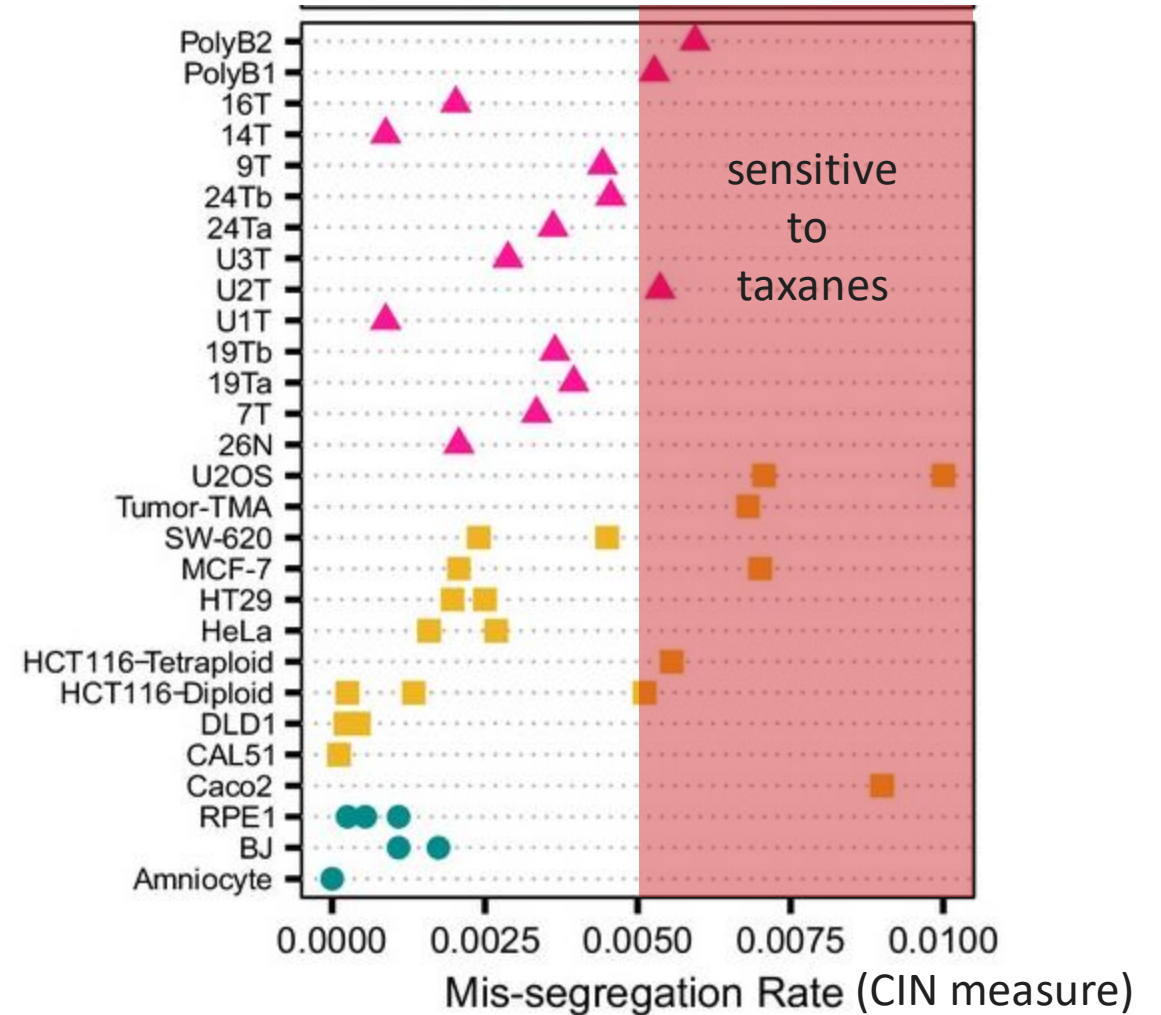
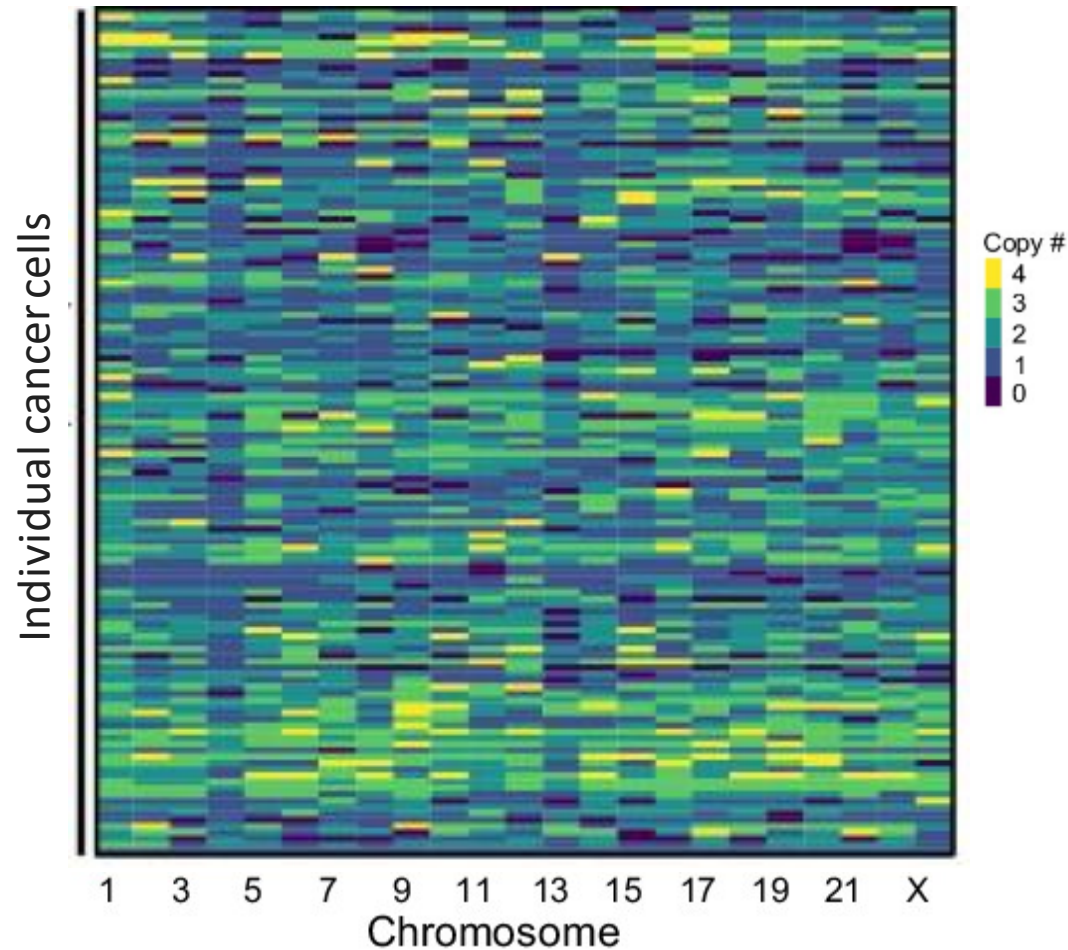


Hanks et al. (2004) Nature Genet 36: 1159-1161

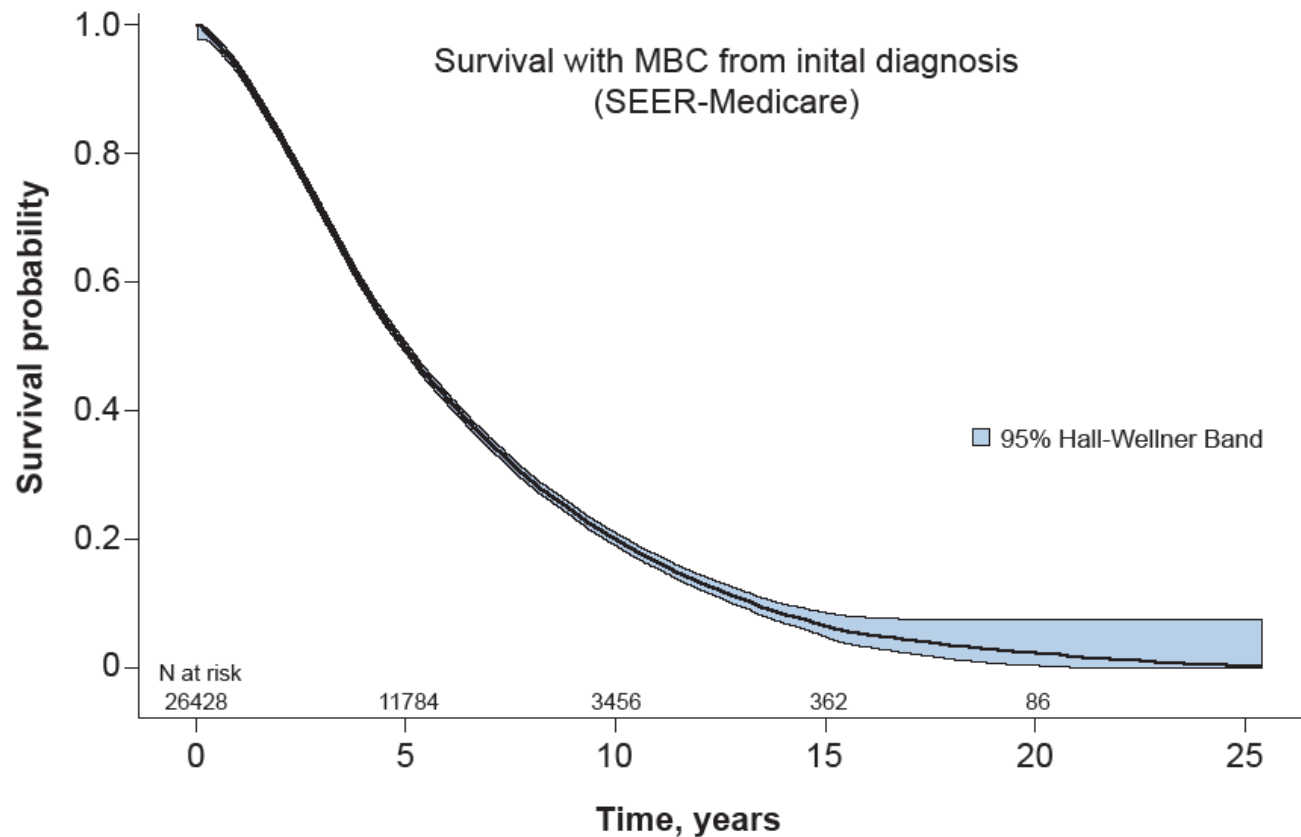


Chromosomal Instability

Single-cell DNA sequencing CNV by chromosome



Long term survival with MBC >20 years is uncommon



Gilbert and Rocque, unpublished

HOME / RESOURCES / PRECISION MEDICINE MOLECULAR TUMOR BOARD / OUTLIERS – EXTREME LONG-TERM SURVIVORS WITH METASTATIC CANCER

OUTLIERS – EXTREME LONG-TERM SURVIVORS WITH METASTATIC CANCER



Why do some people live for over a decade with incurable cancer?

Can others become extreme survivors?

We are looking for adults with metastatic breast cancer to help us find out!

QUICK LINKS

[ELIGIBILITY INFORMATION >](#)

[PRESS CENTER >](#)

ABOUT THE STUDY

We will identify long-term survivors with metastatic breast cancer and understand what has allowed them to be exceptional survivors.

The purpose of this research is to identify habits, medical care, and genes that help people live with cancer for a longer-than-expected time. We will first ask you questions about your medical history, your treatments, your habits, and your diet. After the survey is complete, we will re-contact some very long-term survivors who will have the option of having their genes tested. Genes are the material passed from parent to child that determines the make-up of our bodies. Tumors also contain genes that can be altered through mutations, or changes in genes. This research study hopes to identify genes in outliers and in their breast cancers that differ from other patients with a similar type of cancer.

PARTICIPATE NOW

Visit our [eligibility criteria](#) page to take our eligibility survey! This survey will determine if you are eligible to participate in the study.

outliers.cancer.wisc.edu



Conclusions

- Clinical NGS is ready for prime time with multiple approved therapies for: ESR1, PIK3CA, BRCA1/2, PALB2, MSI/high TMB, and NTRK fusions *(and many studies for other alterations)*
- All MBC should have NGS, preferably at diagnosis
- MTBs can help adjudicate and prioritize rare mutations and coordinate trial enrollment in a catchment area
- NGS is a tool and more discoveries are at hand



Acknowledgements

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Andrew Lynch

Rob Lera PhD

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Thank you.