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Atlanta

Jan 6, 2018

Genomics, Genetics and Biomarkers

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University of Wisconsin Carbone Cancer Center

Financial Disclosure

Disclosure Statement (Faculty)

I, Mark E. Burkard, declare that neither I nor any member of my family has a financial arrangement or affiliation with any corporate organization offering financial support or grant monies for this continuing medical education activity or with any corporate organization that might have an interest in the subject being presented.

Themes

1. Genomics—more than just point mutations and small indels
2. More on BRCA1/2 VUS
3. Predicting late recurrence
4. Predicting response and resistance

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1. Genomics—more than just point mutations and small indels
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Advances in genomics

- **Tumor evolution**
- **Druggable targets**
  - *ESR1*
  - *ERBB2*
  - *PIK3CA*
- **Genetic risk panels**
  - Myriad and others

‹ Back to search results for "color genetics"

Color - Hereditary Cancer Test - Genetic Test for Hereditary Cancer Risk, Including Breast, Ovarian, Colon, Prostate, and 4 Other Cancers - Analysis of 30 Genes, Including BRCA1 and BRCA2

Color Genomics

★★★★★ 60 customer reviews | 5 answered questions

All Color tests are physician-ordered. Either your own doctor or an independent physician will review your purchase and determine whether this genetic testing is appropriate. The cost will be refunded if the physician decides that testing is not appropriate.

About the product

- Simple 30 gene test, including BRCA1 and BRCA2, to learn your genetic risk for cancer
- Provide a saliva sample from the convenience of your home
- Speak with our board-certified genetic counselors, at no extra cost, to help you understand your results
- At this time state regulations don't allow us to ship the Color Test collection kit to NY State addresses through Amazon.
- All Color Tests are physician-ordered. Either your own doctor or an independent physician will review your purchase and determine whether this genetic testing is appropriate.

Price: $249.00 & **FREE Shipping**
Note: Not eligible for Amazon Prime.

In stock. Ships from and sold by Color Genomics.

Get it as soon as Jan. 9 - 12 when you choose **Standard Shipping** at checkout.

Ship to: Mark E. Burkard - 53528

Qty: 1 | Turn on 1-click ordering

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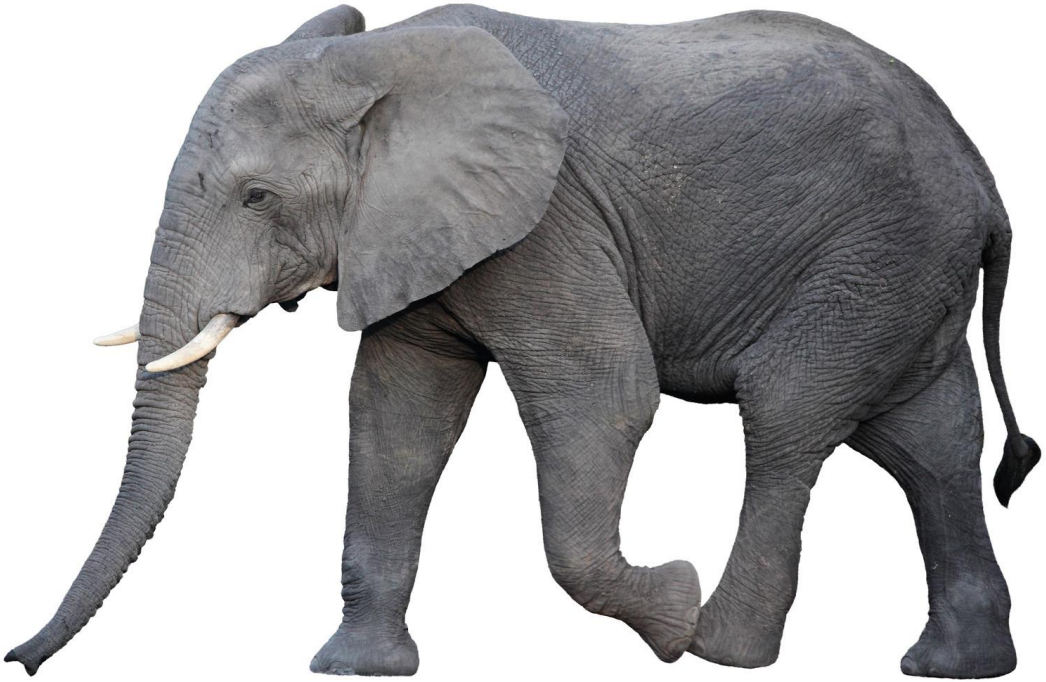
Advances in genomics

- **Tumor evolution**
- **Druggable targets**
  - *ESR1*
  - *ERBB2*
  - *PIK3CA*
- **Genetic risk panels**
  - Myriad and others

But Read length is only 36-125 base pairs

= 0.0000004% of genome



Putting the pieces together

Tandem Duplicator Phenotype
Edison Liu, Jackson Laboratory

Genome copy number in TNBC
Dan Stover, DFCI, now Ohio State

Tandem Duplicator Phenotypes defines 50% of Triple Negative Breast Cancers

Francesca Menghi, Floris Barthel, Vinod Yadav, Ming Tang, Bo Ji, Gregory Carter, Jos Jonkers, Roeland Verhaak, and Edison T. Liu

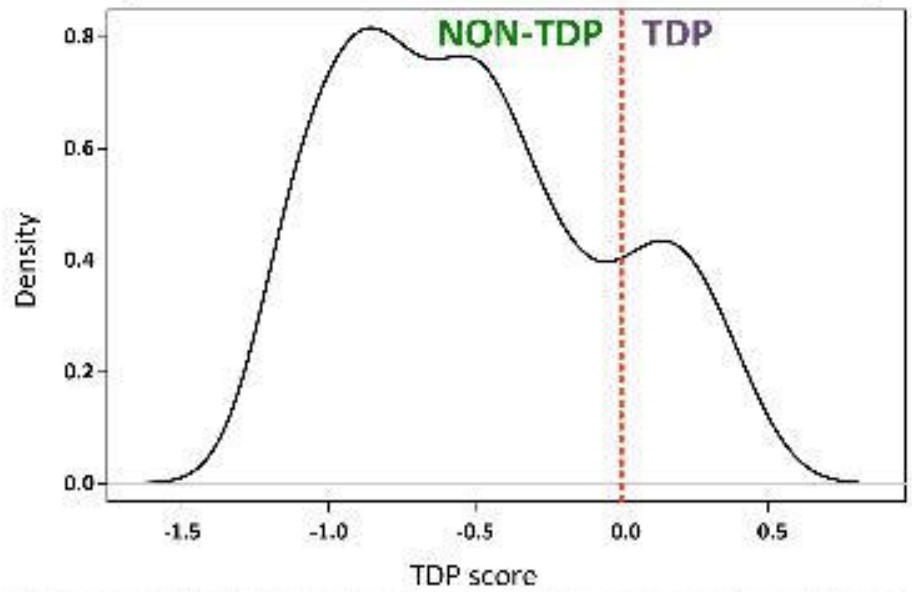
San Antonio
Breast Cancer Symposium
December 5 -9, 2017

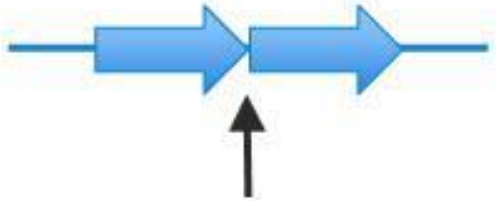
The Jackson Laboratory
Leading the search for tomorrow's cures

San Antonio Breast Cancer Symposium, December 5 -9, 2017

Tandem Duplicator Phenotype (TDP) score identifies a population of cancers with high numbers of TDs distributed across the genome

$$TDP\ Score = -\frac{\sum_i |Obs_i - Exp_i|}{TD} + k$$



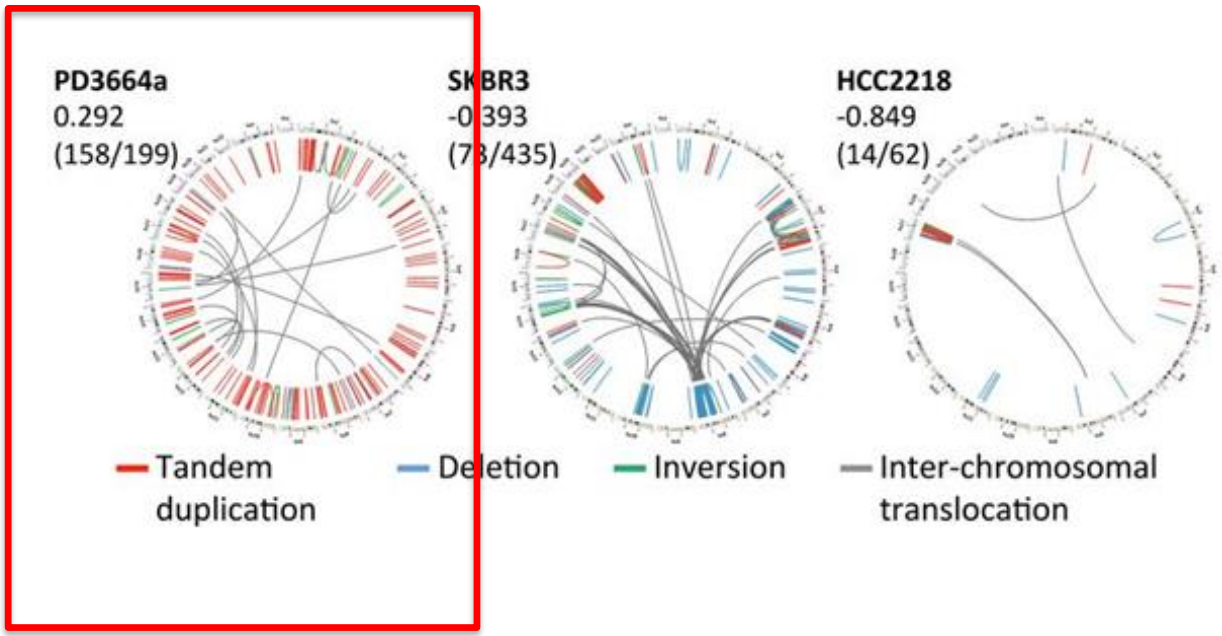


TDs identified by breakpoint junctions

Present in ~50% TNBC

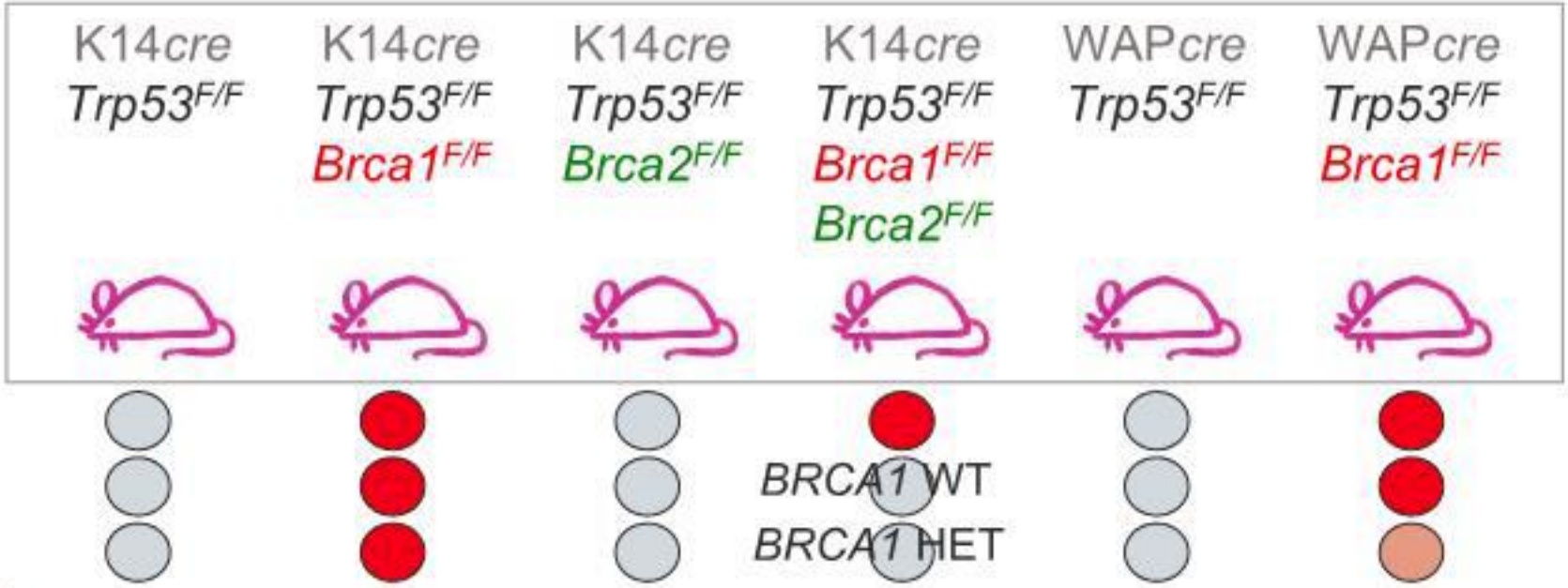
Menghi, et al. PNAS 113(17):E2373-82 (2016)

Tumor with tandem duplications



Menghi et al. PNAS 2016

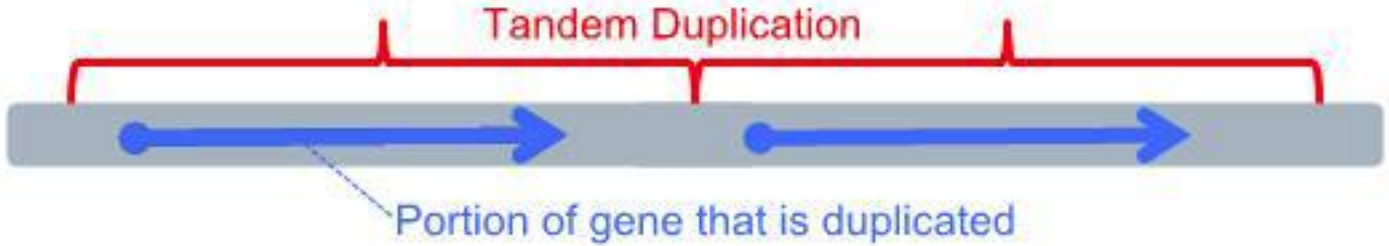
Mice with conditional BRCA1/TP53 disruption develop TDP group 1 (10Kb) mammary cancers



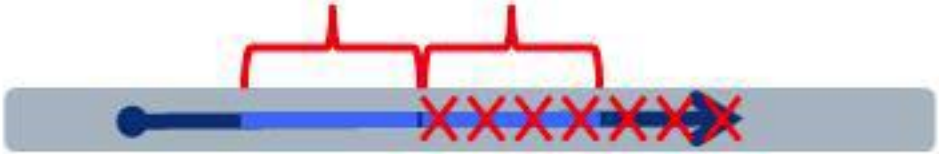
Menghi, Liu, Jonkers

Oncogenic consequences of Tandem Duplications in TDP

1) Gene Duplication **GENE GAIN**



2) Double Gene Transection **GENE LOSS**



Frequent Somatically Mutated Oncogenes and Tumor Suppressors in TNBC and Ovarian Cancers

Oncogene Duplication:

- ERBB2
- MYC (TNBC only)
- MALAT1 (TNBC only)
- MUC1 (OV only)
- MDM2(OV only)

Tumor Suppressor Disruption:

- PTEN
- RB1
- MLL3 (TNBC only)
- RUNX1 (TNBC only)
- NF1 (OV only)

Take home

- BRCA1 mutations can produce Tandem Duplications
- Tandem duplications are a mechanism of amplification

- Why doesn’t BRCA1 cause HER2-amplified cancer?

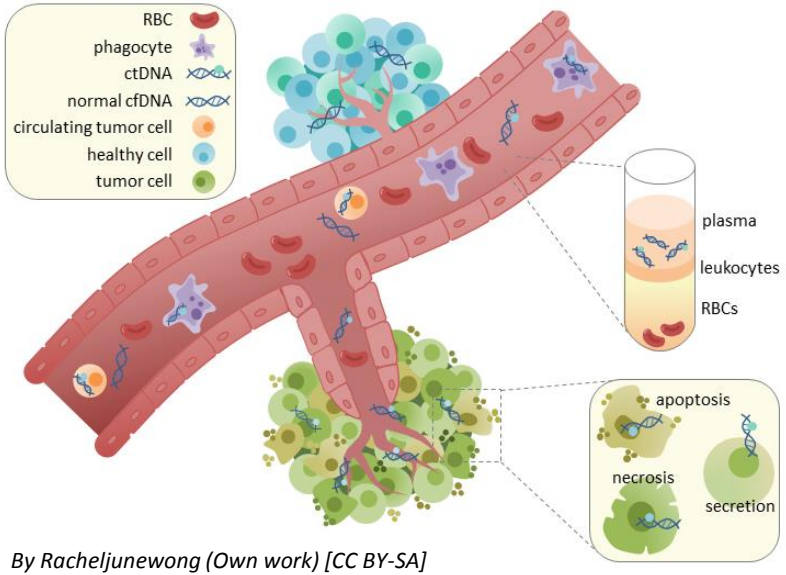
Putting the pieces together

Tandem Duplicator Phenotype
Edison Liu, Jackson Laboratory

Genome copy number in TNBC
Dan Stover, DFCI, now Ohio State

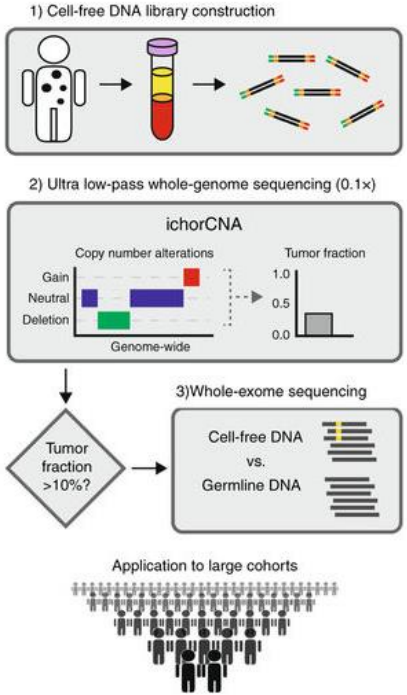
Circulating tumor DNA (ctDNA or cfDNA)

What is ctDNA?



By Racheljunewong (Own work) [CC BY-SA]

ichorCNA



Algorithm to see genome structures.

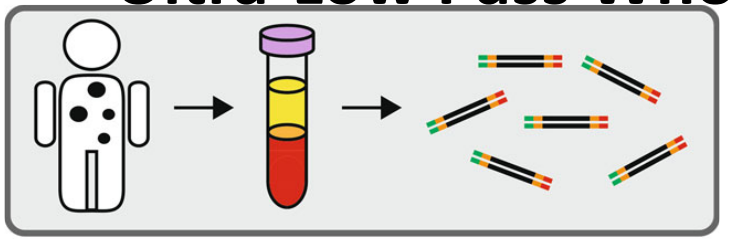
Adalsteinsson et al. (Meyerson) Nature Communications 8: 1324, 2017

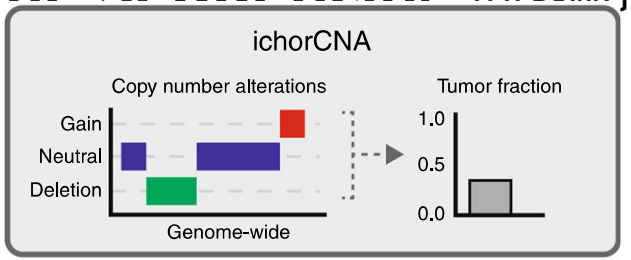
Genome-wide copy number analysis of chemotherapy-resistant metastatic triple-negative breast cancer from cell-free DNA

San Antonio Breast Cancer Symposium

Daniel G. Stover, Heather A. Parsons, Gavin Ha, Sam Freeman, William T. Barry, Hao Guo, Atish Choudhury, Gregory Gydush, Sarah Reed, Justin Rhoades, Denisse Rotem, Melissa E. Hughes, Deborah A. Dillon, Ann H. Partridge, Nikhil Wagle, Ian E. Krop, Gad Getz, Matthew Meyerson, Todd Golub, J. Christopher Love, Eric P. Winer, Sara M. Tolaney, Nancy U. Lin, Viktor A. Adalsteinsson

Ultra-Low Pass Whole Genome Sequencing (ULP-WGS)





Fresh or frozen plasma (4mL)

- EDTA, Streck, or CellSave tubes
- Sequence at very low coverage (0.1X)
  - 1 in 10 bases sequenced
  - Cannot resolve mutations/indels

Computational approach: ichorCNA

- Identify somatic copy number alterations
- Calculate '**tumor fraction**' (TFx) of cfDNA
  - TFx ≥10%: High confidence SCNA calls

Benefits

- Does not require prior tumor or germline sequence data
- Optimal for investigation of tumors with extensive SCNAs (e.g. TNBC)
- Cost-effective: Less than $200 per sample

Adalsteinsson V, *Nat Comm* 2017

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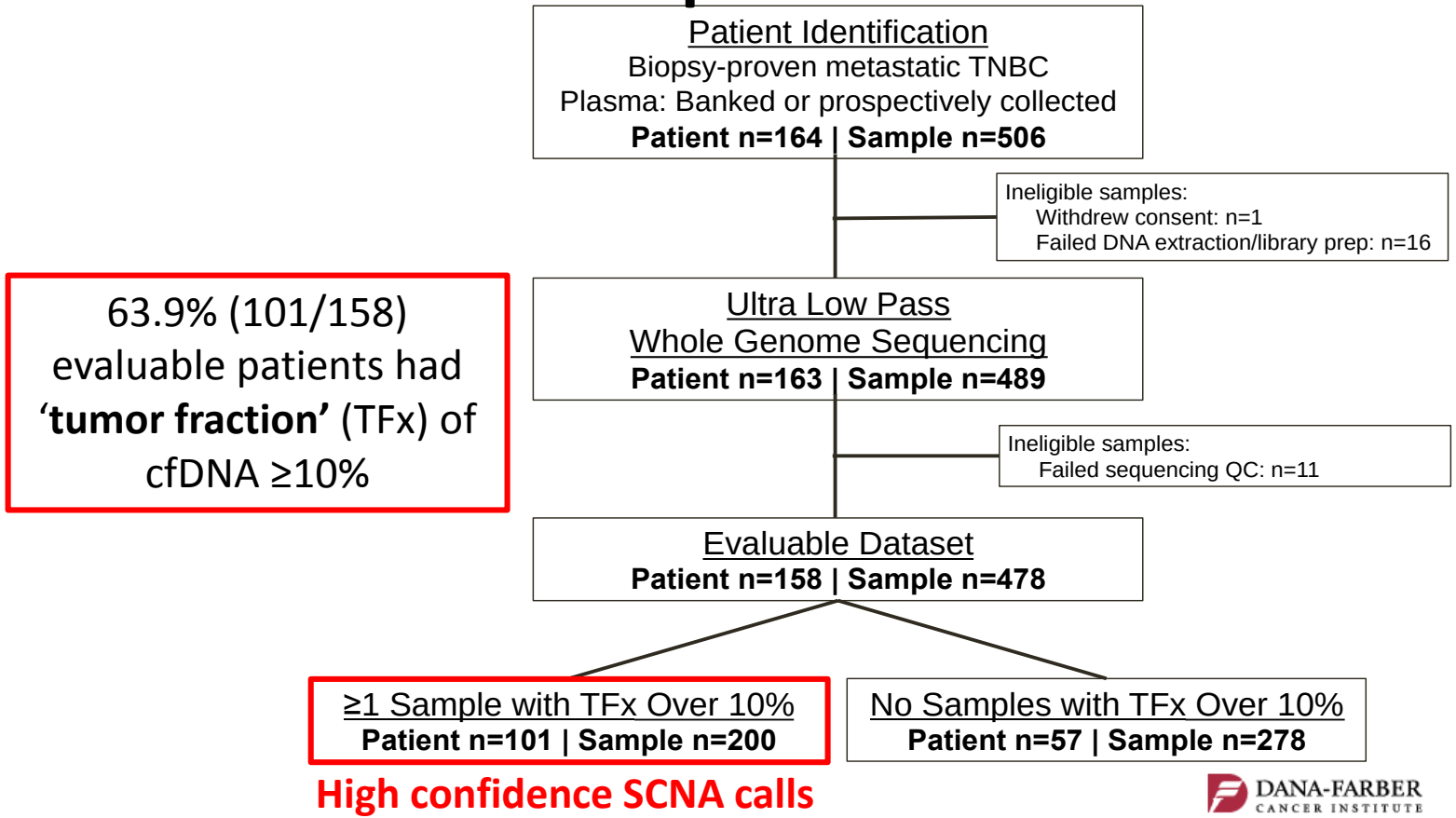
Patient & Sample Identification: REMARK



63.9% (101/158) evaluable patients had **'tumor fraction'** (TFx) of cfDNA ≥10%

High confidence SCNA calls

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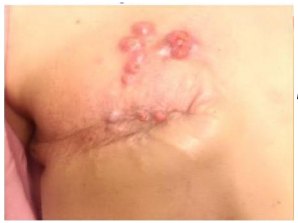
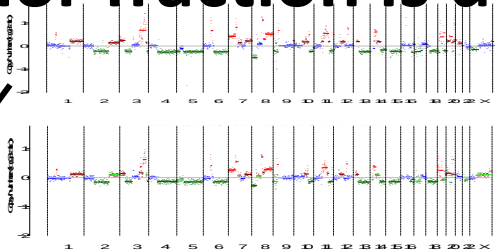
Tumor fraction is dynamic



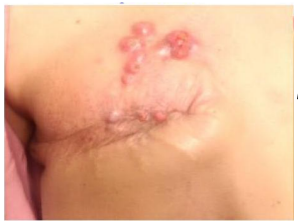


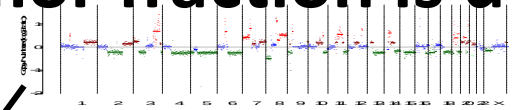
Cycle 1 (Day 0)
Tumor Fraction: 31.5%

Cycle 1 (Day +6)
Tumor Fraction: 19.3%

Stover DG, *J Clin Onc*, In press.
Tolaney SM, *Oncologist* 2017

Tumor fraction is dynamic





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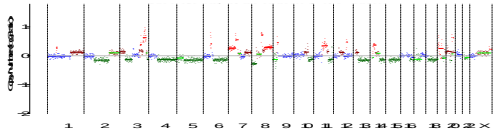
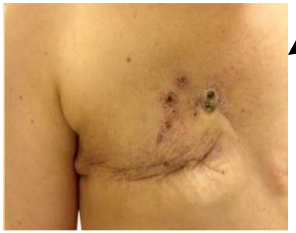
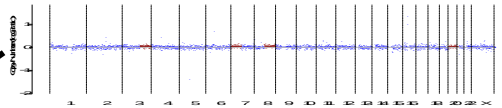
Tumor Fraction: 31.5%

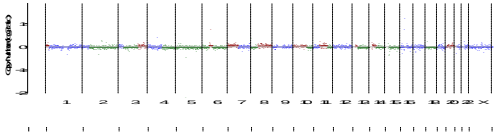


Cycle 1 (Day +6)
Tumor Fraction: 19.3%





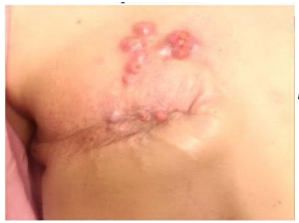
Cycle 2 (Day +20)
Tumor Fraction: 4.6%

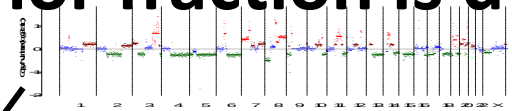


Cycle 4 (Day +62)
Tumor Fraction: 3.5%

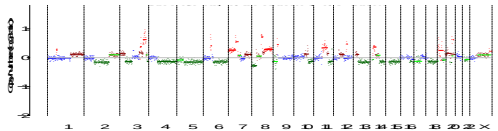
Stover DG, *J Clin Onc*, In press.
Tolaney SM, *Oncologist* 2017

Tumor fraction is dynamic

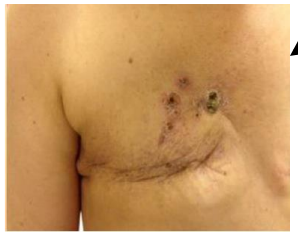


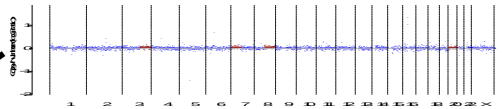


Cycle 1 (Day 0)
Tumor Fraction: 31.5%

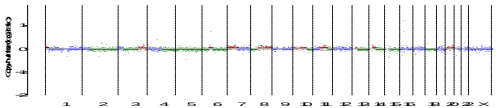


Cycle 1 (Day +6)
Tumor Fraction: 19.3%

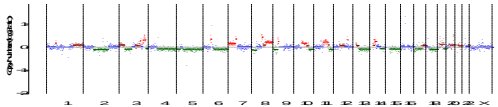




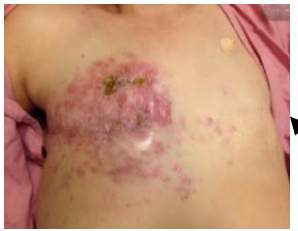
Cycle 2 (Day +20)
Tumor Fraction: 4.6%

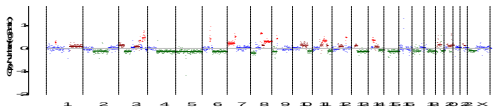


Cycle 4 (Day +62)
Tumor Fraction: 3.5%

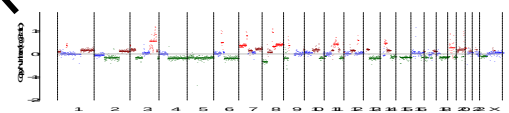


Cycle 6 (Day +104)
Tumor Fraction: 13.4%





Cycle 8 (Day +147)
Tumor Fraction: 17.9%



Off Study (Day +188)
Tumor Fraction: 48.2%

Primary Objective

To evaluate the association of cfDNA 'tumor fraction' and copy number alterations with metastatic survival in TNBC.

Hypotheses

- Specific SCNAs are more frequent in chemoresistant metastatic TNBCs relative to chemotherapy-naïve primary TNBCs.
- **Cell-free DNA 'tumor fraction' (TFx) ≥10% is associated with worse overall metastatic survival in TNBC.**

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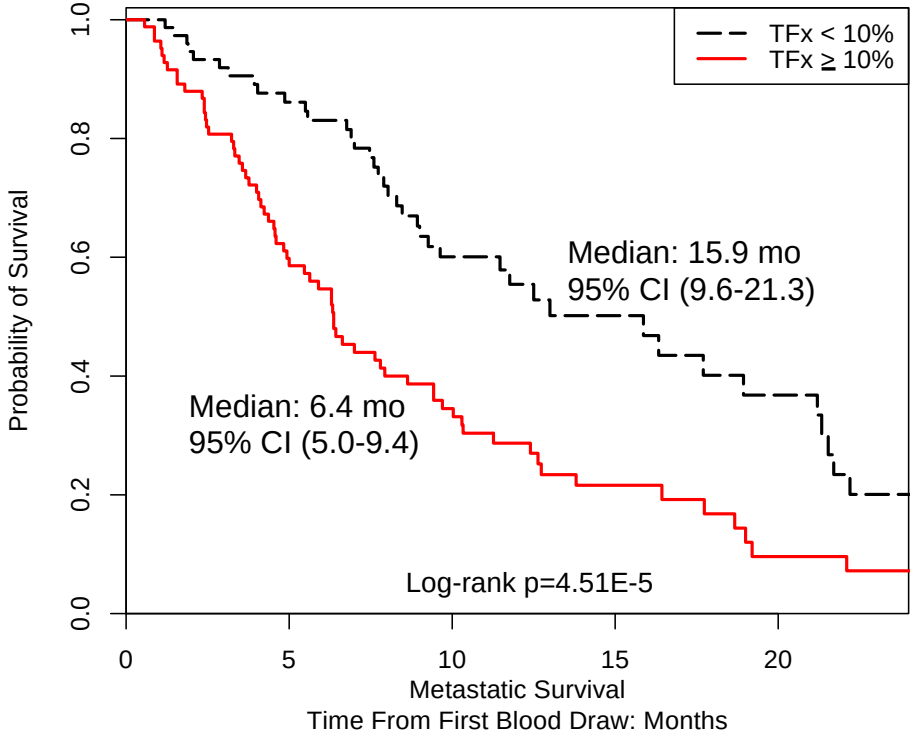
Tumor fraction is prognostic

- TFx of first available blood sample per patient
- Stratified by pre-specified TFx threshold
  - ≥10% versus <10%
- Overall metastatic survival:
  - Time from first blood sample
- Held up in multivariate analysis



# at risk					
TFx < 10%	75	57	34	16	11
TFx > 10%	83	48	25	11	4

Stover DG, *J Clin Onc*, In press.

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Take home

- 2/3 of TNBC have tumor-derived DNA ≥ 10% at some point
- Tfx ≥ 10% associates with poor survival
- Tfx follows clinical course (N=1)
- Could be a useful prognostic/predictive biomarker

- How repeatable/valid are the ichorCNA estimates of Tfx?
- Is this better than tumor markers?

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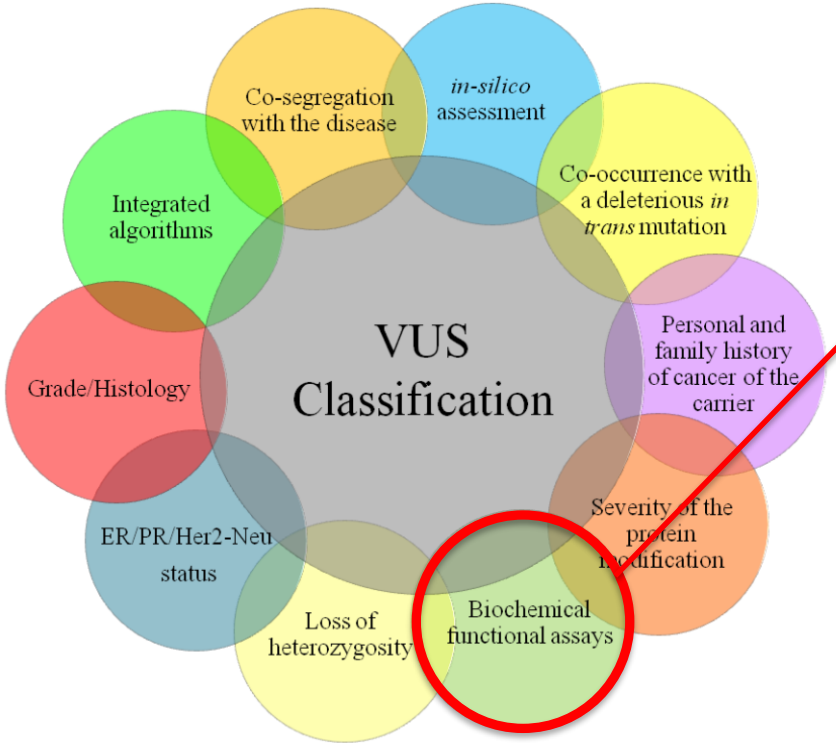
Variants of Uncertain Significance



A high-throughput functional complementation assay for *BRCA1* missense variants

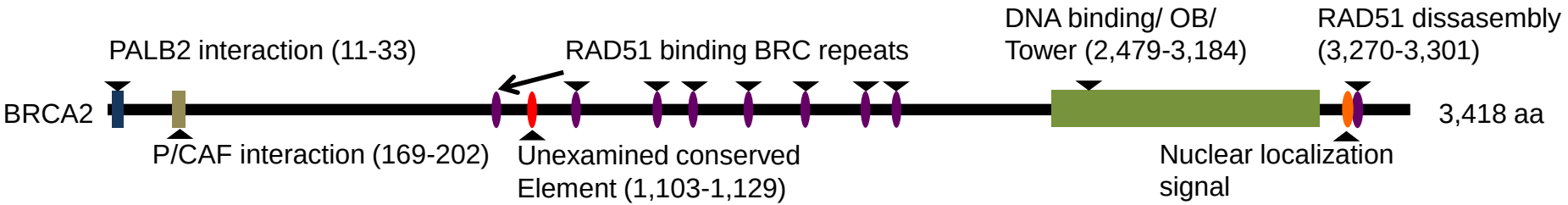
Bouwman et al. (Jonkers lab)
Cancer Discovery 2013

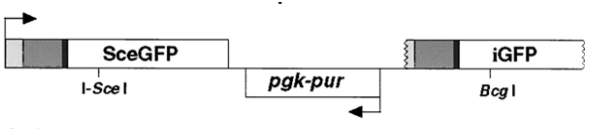
Cancer risks and response to targeted therapy associated with *BRCA2* variants of uncertain significance

Fergus J. Couch, Ph.D.

Mayo Clinic

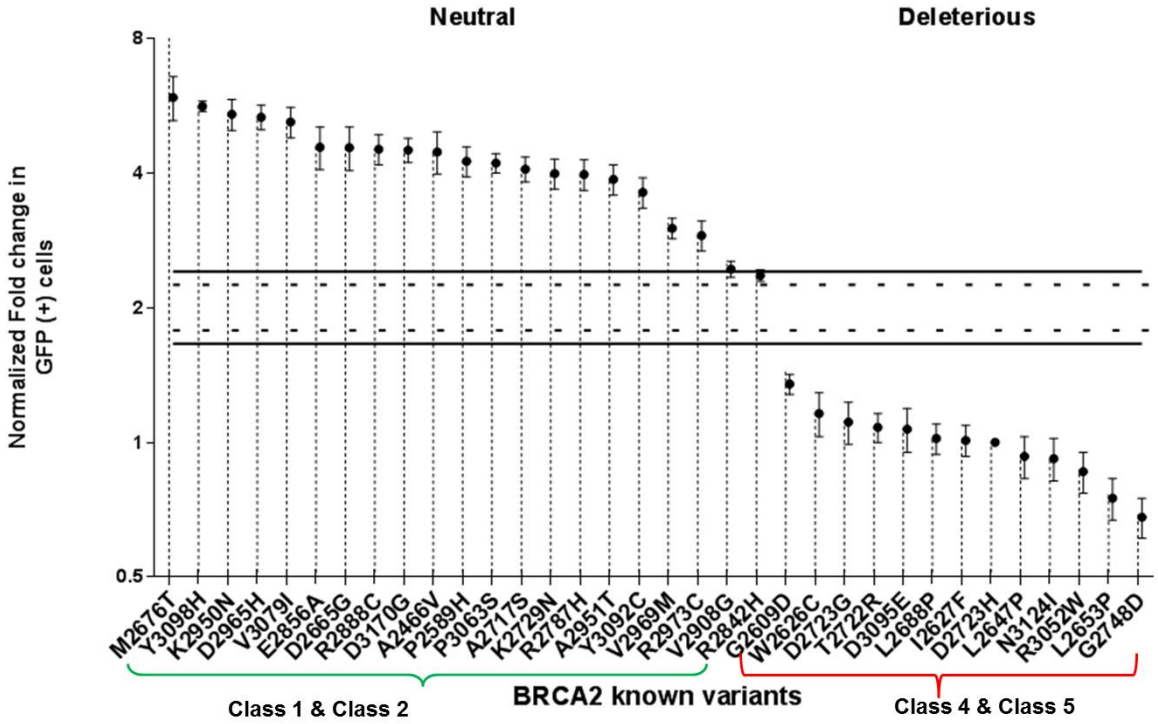
BRCA2 protein and Homology Directed Repair Assay



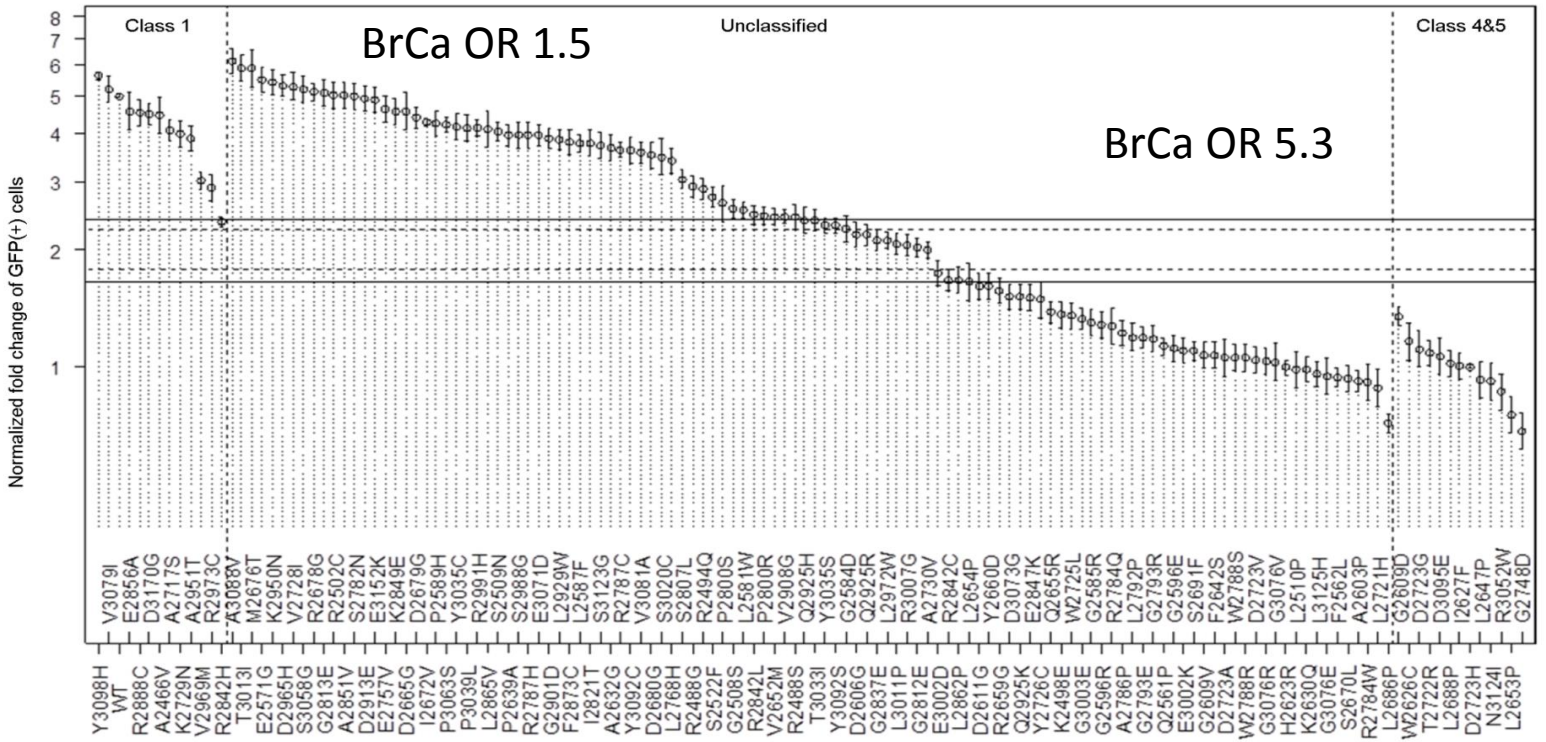


DR-GFP reporter construct

HDR assay sensitivity and specificity



Evaluated 139 BRCA2 DBD missense variants



Take home

- Robust functional assays can classify gene function
- VUS of BRCA1 and BRCA2 are becoming classified into *deleterious* versus *benign*
- Consider re-evaluation of your patients with BRCA2 VUS ClinVar and BRCA exchange

- Some risk of generalizability with single assay
- It will be necessary to re-evaluate on populations

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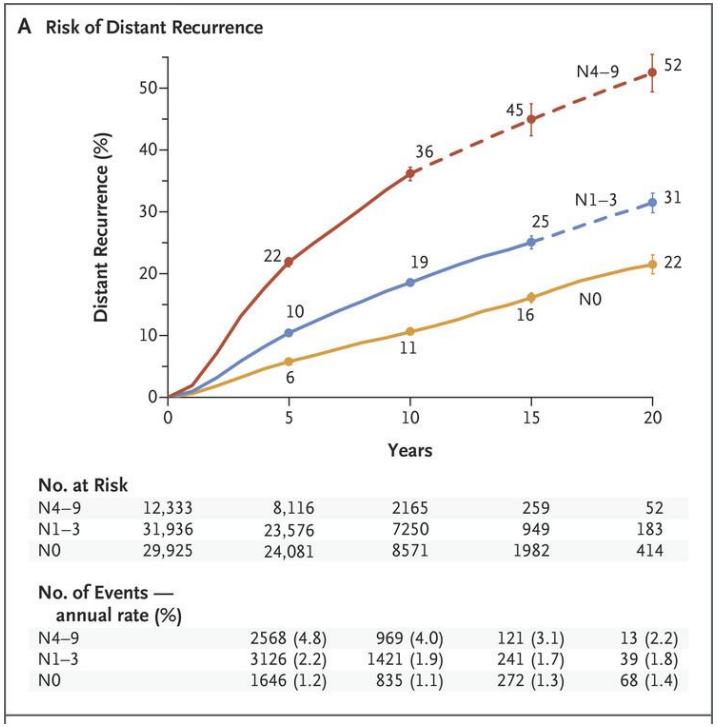
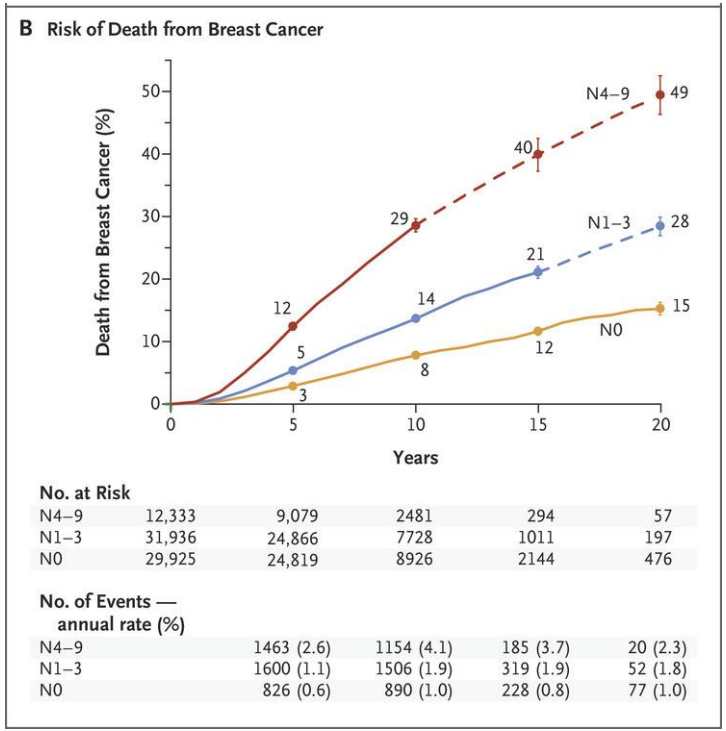
Association between Pathological Nodal Status and the Risk of Distant Recurrence or Death from Breast Cancer during the 20-Year Study Period.





Pan H et al. N Engl J Med 2017;377:1836-1846.

Predicting late recurrence

CTS5 clinical predictor

Ivana Sestak, Queen Mary University London

CTCs in ECOG E5103

Joseph Sparano, Einstein/Montefiore

Integration of clinical variables for the prediction of late distant recurrence in patients with estrogen receptor positive breast cancer treated with 5 years of endocrine therapy

Ivana Sestak[1]
Meredith M. Regan[2], Andrew Dodson[3], Giuseppe Viale[4],
Beat Thürlimann[5], Marco Colleoni[6], Jack Cuzick[1], Mitch Dowsett[3]

1. Centre for Cancer Prevention, Queen Mary University of London, London, United Kingdom
2. Dana Farber Cancer Institute, Boston, United States
3. Ralph Lauren Centre for Breast Cancer Research, Royal Marsden, London, United Kingdom
4. European Institute of Oncology & University of Milan, Milan, Italy
5. Kantonsspital St. Gallen, St. Gallen, Switzerland
6. European Institute of Oncology, Milan, Italy

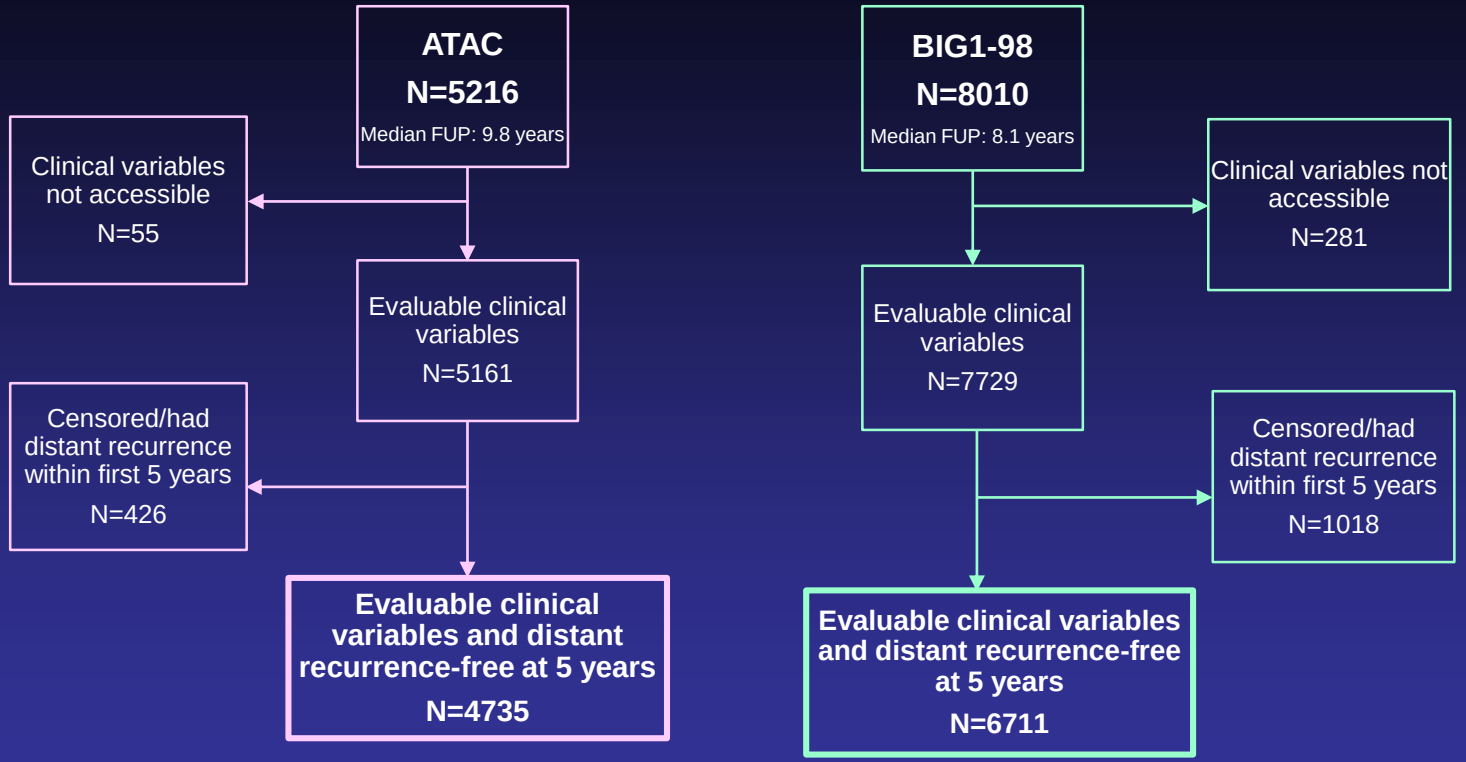
Aims

1. To develop a prognostic tool (CTS5) specifically for prediction of late distant recurrence using clinicopathological parameters

2. To compare prognostic performance of CTS5 to published Clinical Treatment Score (CTS0)

   ➔CTS0 developed in TransATAC (N=1125) in presence of IHC markers and in chemotherapy untreated women (Cuzick *et al*., 2011, JCO)

Training/validation cohorts



Distant recurrence >5 years: 7% 5.5%

CTS5 score development

- Univariate Cox regression to determine prognostic value of each variable:

Clinical variable	HR (95% CI)	P-value
Number of positive nodes	1.14 (1.12-1.15)	<0.0001
Tumor size (mm)	1.10 (1.08-1.12)	<0.0001
Grade (1 vs. 2, 1 vs. 3)	2.26 (1.58-3.22) / 3.37 (2.33-4.86)	<0.0001 / <0.0001
Age (years)	1.04 (1.02-1.05)	<0.0001
Endocrine therapy (T vs. A)	0.84 (0.67-1.04)	0.108

Final CTS5 model:

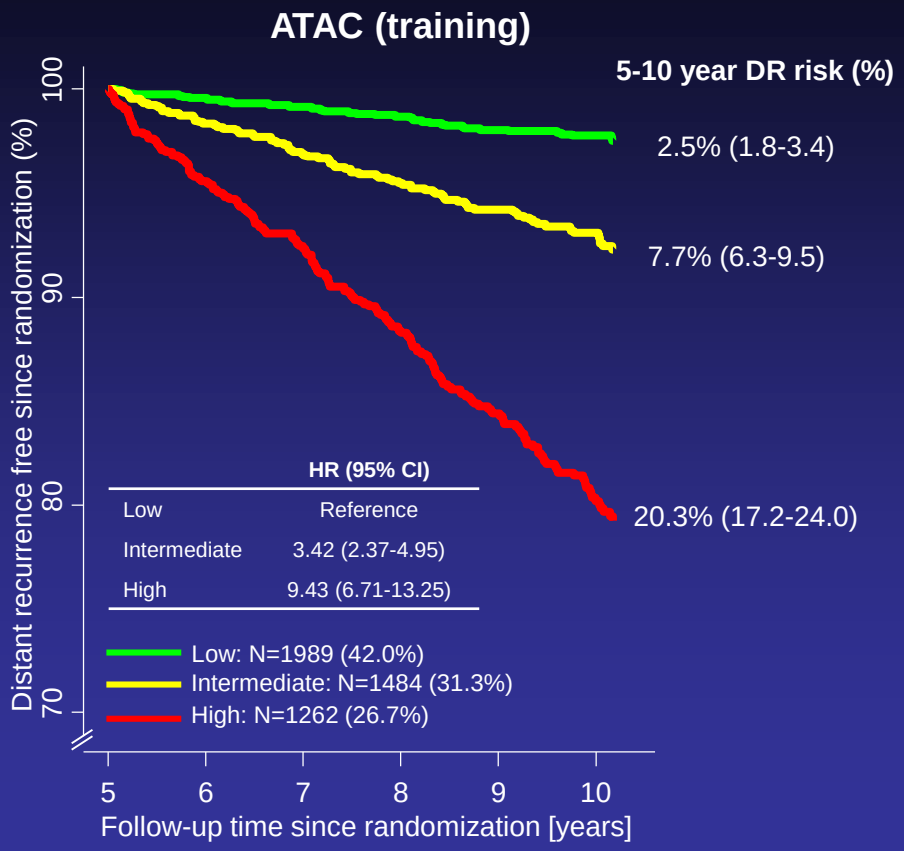
Node:
0 = Negative
1 = 1 positive
2 = 2-3 positive
3 = 4-9 positive
4 = >9 positive

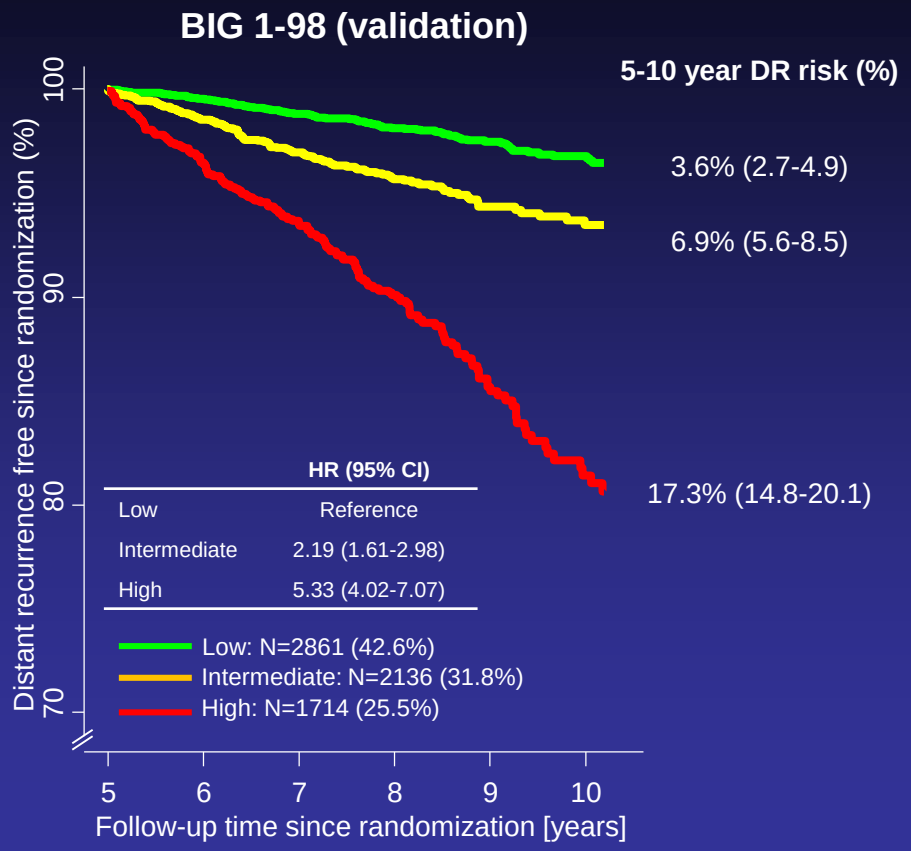
Size:
Continuous
(if >30 then = 30)

Grade:
0 = Grade 1
1 = Grade 2
2 = Grade 3

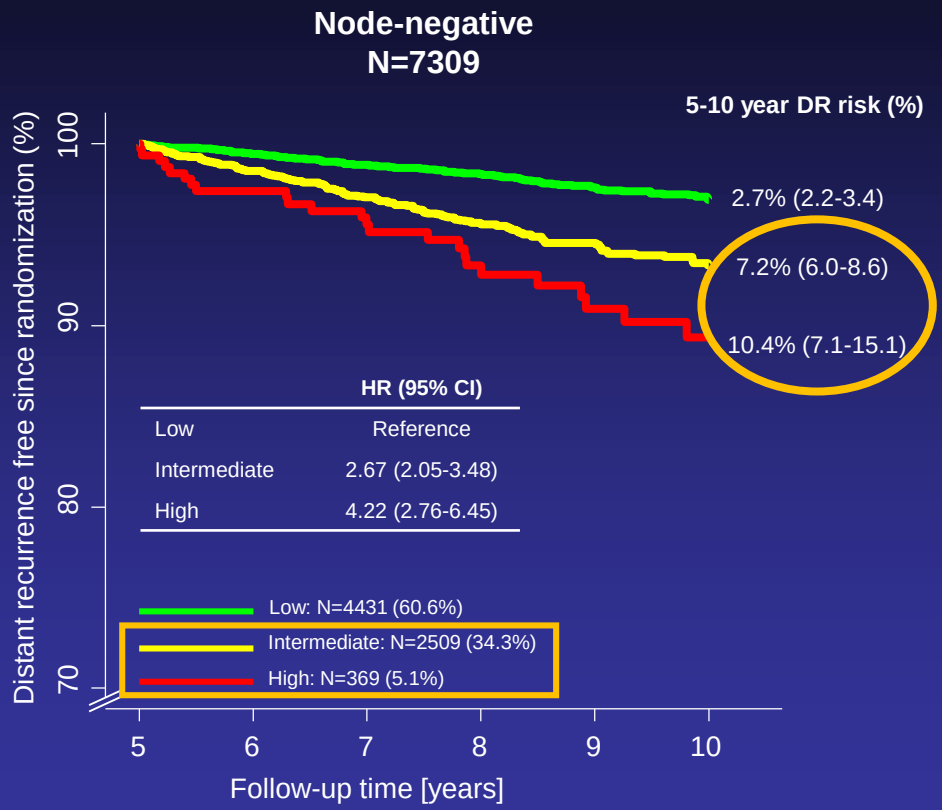
Age:
Continuous

DR free (%) in years 5-10

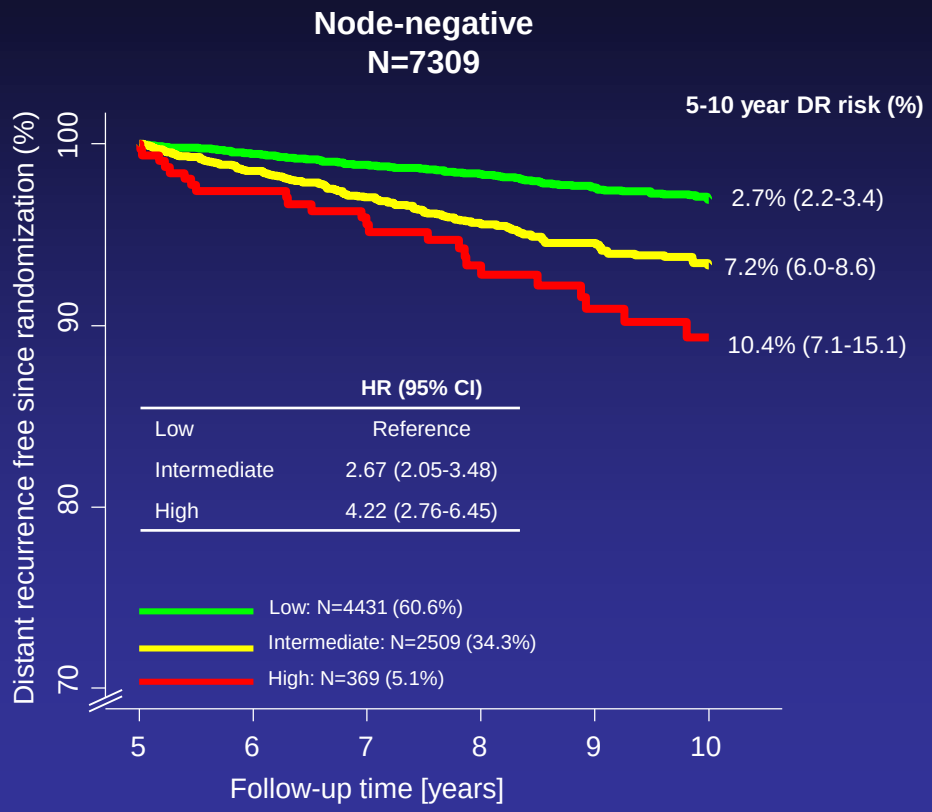


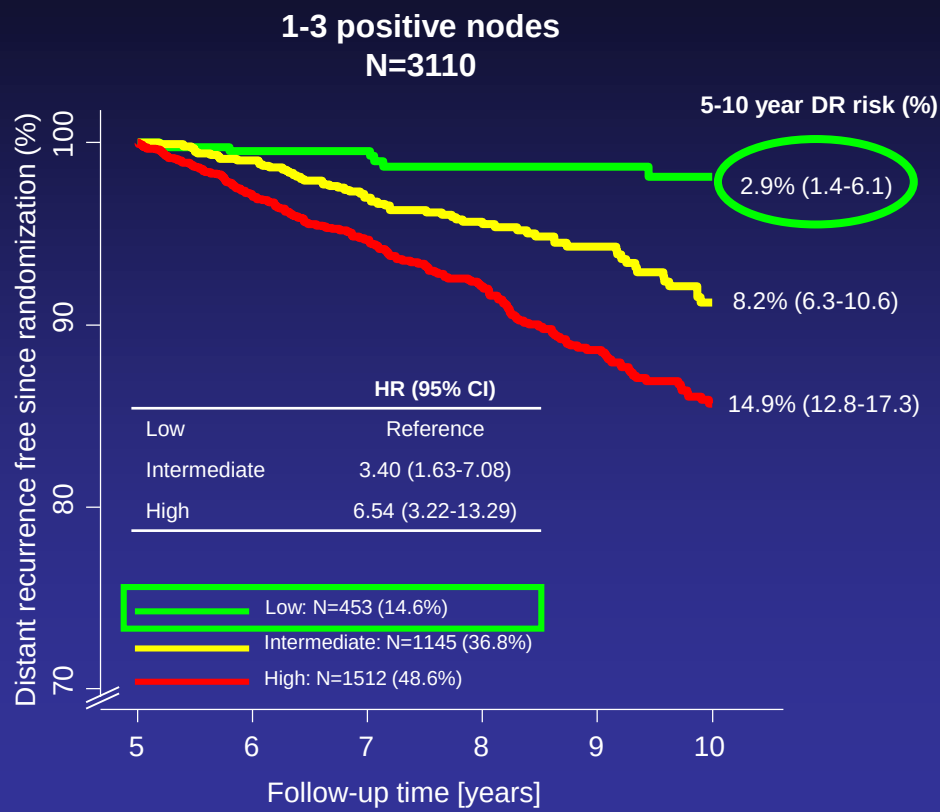


Combined dataset: DR free (%)



Combined dataset: DR free (%)





Conclusions

- CTS5 was highly prognostic for prediction of late DR
  ➔ Large proportion of women (42%) identified where value of extended endocrine therapy is limited

- CTS5 more accurate for late DR than CTS0
  (Cuzick *et al*., 2011, JCO)

- Strengths:
  - Large clinical trial data with long-term follow-up
  - Clinicopathological parameters measured in all patients

Conclusions II

- Limitations:
  - Only applicable to postmenopausal women
  - Both trials before routine HER2 testing and directed therapy

➔CTS5 simple tool to calculate risk of late distant recurrence

40th Annual San Antonio Breast Cancer Symposium, December 5-9, 2017

Circulating Tumor Cells and Late Recurrence of Breast Cancer

Joseph A. Sparano, MD[1], Anne O'Neill, MS[2], Katherine Alpaugh, PhD[3], Antonio C. Wolff, MD[4], Donald W. Northfelt, MD[5], Chau T. Dang, MD[6], George W. Sledge, MD[7], Kathy Miller, MD[8]

1. Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; 2. Dana Farber Cancer Institute, Boston, MA; 3. Fox Chase Cancer Center, Philadelphia, PA; 4. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; 5. Mayo Clinic, Scottsdale, AZ; 6.Memorial Sloan Kettering Cancer Center, New York, NY; 7. Stanford Cancer Center, Palo Alto, CA; 8. Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN

ECOG-ACRIN cancer research group

Reshaping the future of patient care

Methods: Hypothesis & Study Objectives

Hypothesis:

CTCs are prognostic for late recurrence

Study Objectives:

1. **Prevalence of CTCs ~ 5 years after diagnosis**
2. **Association between CTCs and recurrence**

Methods: Study Design

- **Population:** Stage II-III HER2-negative enrolled in E5103 (NCT00433511)
- **Treatment:** AC-weekly paclitaxel ± bevacizumab + endocrine therapy if ER+
- **Selection:** Recurrence-free 4.5-7.5 years after diagnosis & informed consent
- **CTC Assay**: Whole blood (7.5 ml) drawn into fixative-containing tube for CTC identification and enumeration using the CellSearch® system at entry
- **Assay results:** not reported to clinicians or patients due to uncertainty regarding prognostic information

San Antonio Breast Cancer Symposium December 5-9, 2017

Results: Patient Characteristics, Recurrences, & CTC Results

(Enrollment Period: February 2013 – July 2016)

Total	Total (N=547)
Age at diagnosis (n=547)	
< 50 years	44%
>= 50 years	56%
Tumor size (N=547)	
< 2 cm	41%
>/= 2 cm	59%
Nodal Status	
Negative	27%
Positive	73%
HR Expression (N=546)	
Negative	35%
Positive	65%
Histologic grade (N-534)	
Low-intermediate	45%
High	55%
Endocrine Therapy (N=330)	88%

- **Median followup - 1.8 years**
  - Range 0-3.9 years
- **Recurrences**
  - **HR-Positive (N=14/353): 4.0%**
    (95% CI 3.0 to 7.9%)
  - **HR-Negative (N=1/193): 0.5%**
    (95% CI 0, 2.9%)

- **CTC-Positive (1 cell/7.5 ml blood)**
  - **Overall (N=26): 4.8%**
    95% CI 3.1%-6.9%
  - **HR-Positive (N=18/353): 5.1%**
    95% CI 3.0%-7.9%
  - **HR-Negative (N=8/193): 4.1%**
    95% CI 1.8%-9.0%

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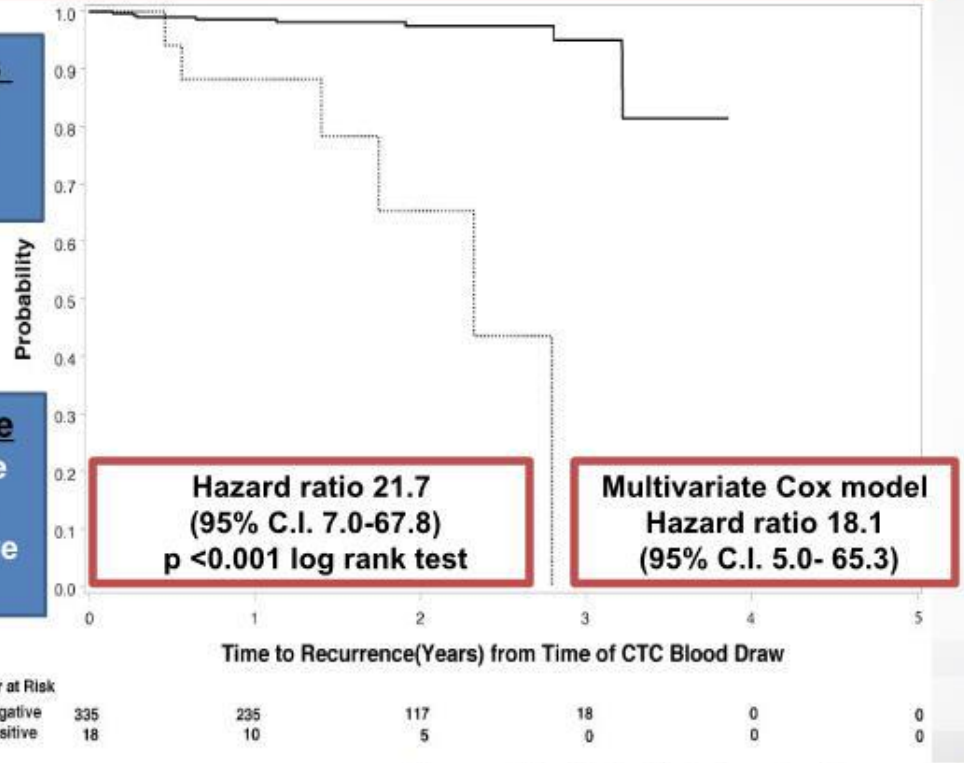
Results: Time to Recurrence in HR+ Disease (N=353)

Median time to recurrence in CTC+: 1.6 years (range 0.5-2.8 years)

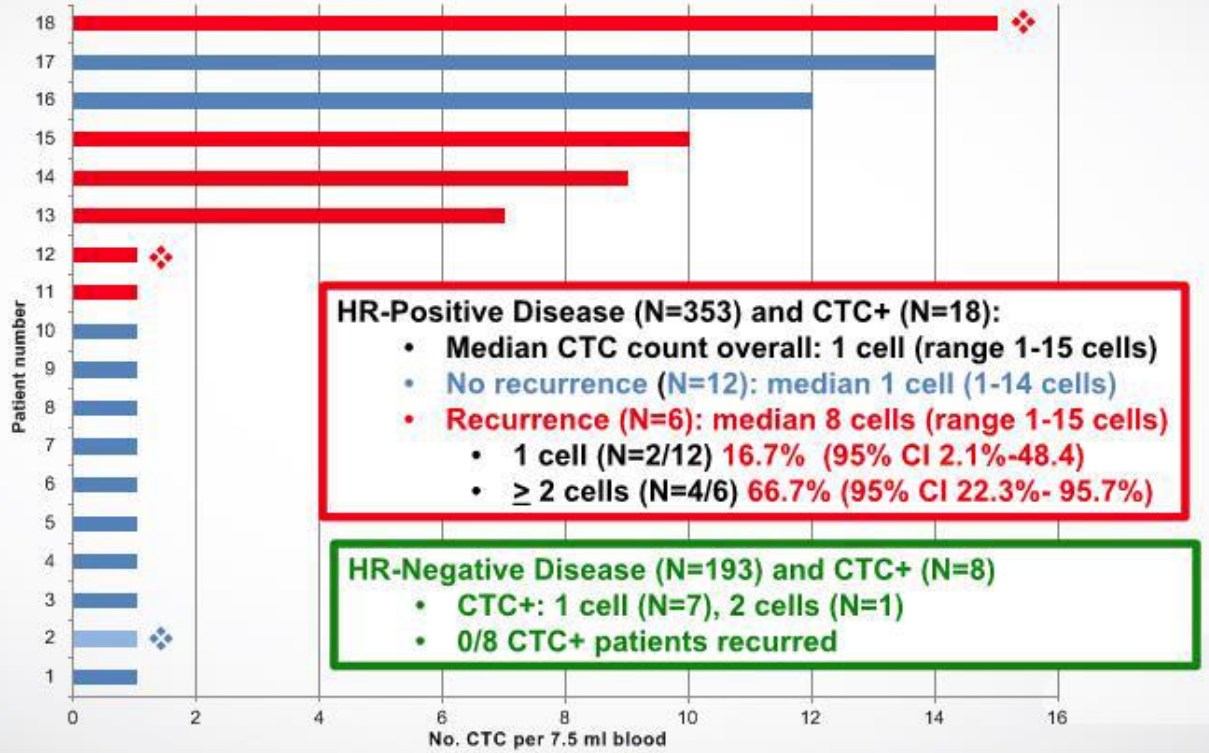
Recurrence rates per person-year
- CTC-Pos: 24.7%
- CTC-Neg: 1.5%

2-Year Recurrence
- Positive Predictive Value = 35%
- Negative Predictive Value = 98%



Results: CTC Burden & Recurrence in HR+ Disease (N=18)

(all taking endocrine therapy except 3 patients denoted by symbol ❖☽)



Conclusions

- **Study objective 1: prevalence of detectable CTCs**
  - Detectable in 5% with localized HR+, HER2- breast cancer 5 years or more after diagnosis
  - After adjuvant chemotherapy and concurrent endocrine therapy
  - Also detected in 4% of HR-, HER- ("triple-negative") disease
- **Study objective 2: CTCs and clinical recurrence**
  - Prospective study - level 1 evidence supporting clinical validity of a positive CTC assay with clinical recurrence in HR+ breast cancer
    - Robust risk stratification (hazard ratio ~20x↑)
    - High negative predictive value (98%)
  - No association with recurrence in ER- disease, although few events in this population

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Discussion: Strengths and Limitations

- **Strengths**
  - Prospective study - REMARK guidelines
  - Risk stratification in ER+ disease surpasses other assays by 10-fold
  - High negative predictive value (98%)
  - Clinicians blinded to CTC result
- **Limitations**
  - Positive CTC did not trigger imaging studies
  - Not designed to determine whether negative CTC assay could spare extended adjuvant endocrine therapy in ER+ disease
  - CTC performed only at a single time point - uncertain role of serial negative assays as a negative predictive test
  - Median followup of 1.8 years is relatively short for ER+ disease
  - CTC not evaluated in the context of other assays
  - Excluded HER2-positive disease
  - No association with recurrence in ER-negative disease

Take home

Sestak CTS5

- CTS5 is a simple predictor of outcome using clinical information you have
- Not validated on premenopausal women or HER2+
- Is grade sufficiently reliable outside of centralized review?

CTCs

- CTCs by Cellsearch is a validated and simple assay
- High negative predictive value
- Only 5% of patients have CTCs, far fewer than the number of recurrences
  - Only identifies the actively recurring tumors?
- Is this better than radiologic evaluations or tumor markers?
- Serial assessments will degrade NPV

Both

- Are they predictive?

Themes

1. Genomics—more than just point mutations and small indels
2. More on BRCA1/2 VUS
3. Predicting late recurrence
4. Predicting response and resistance

Predicting response and resistance

Endopredict and response to neoadjuvant therapy
Peter Dubsky, ABCSG

Resistance to CDK4/6i via FGFR
Luigi Formisano, Vanderbilt

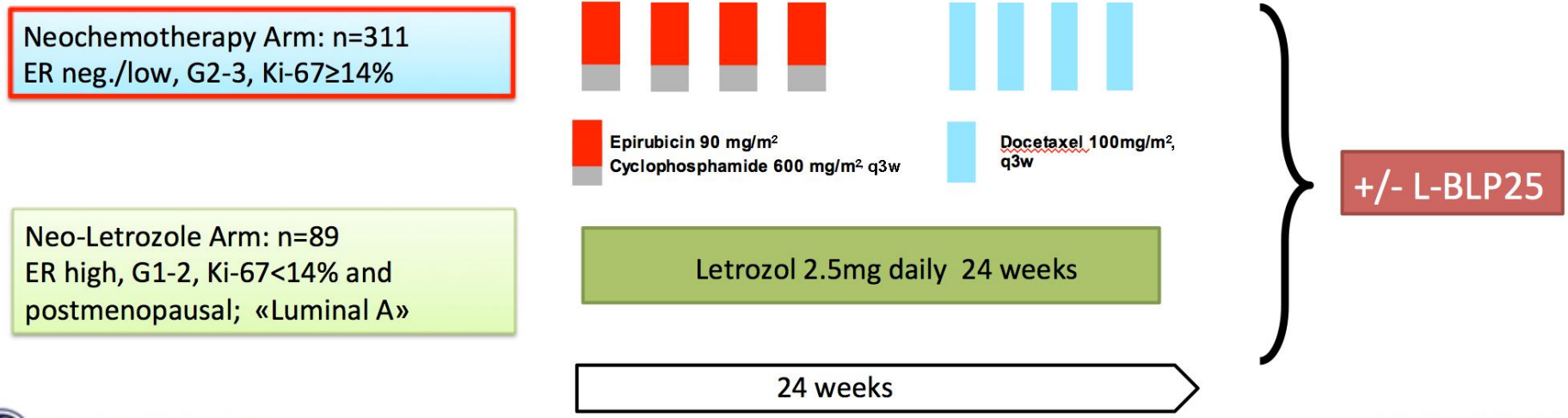
The Endopredict Score Predicts Residual Cancer Burden to Neoadjuvant Chemotherapy and to Neo-Endocrine Therapy in HR+/HER2- Breast Cancer Patients from ABCSG 34

Dubsky PC, Fesl C, Singer CF, Pfeiler G, Kronenwett R, Hubalek M, Bartsch R, Stoeger H, Pichler A, Petru E, Bjelic-Radisic V, Greil R, Rudas M, Tea M-KM, Wette V, Petzer AL, Sevelda P, Egle D, Fitzal F, Exner R, Jakesz R, Balic M, Tinchon C, Bago-Horvath Z, Lax S, Regitnig P, Gnant M, Filipits M

on behalf of the Austrian Breast and Colorectal Cancer Study Group

Background III:
ABCSG 34- Primary Endpoint Residual Cancer Burden

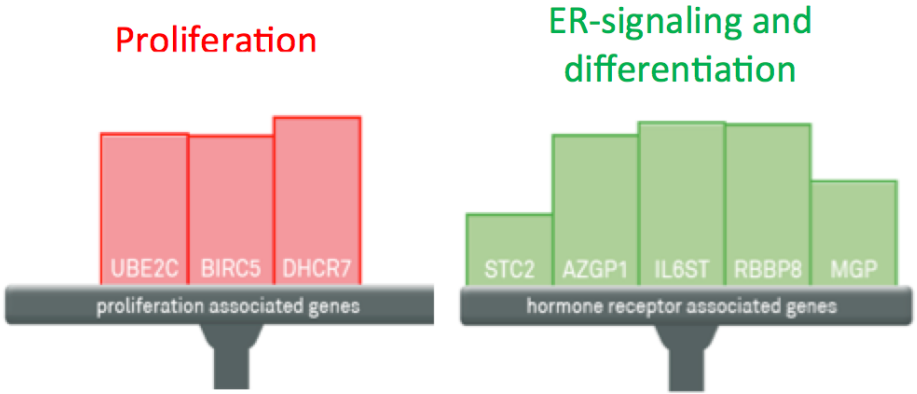
- 400 patient, randomized, phase II, academic trial
- In HER2 negative, early BC receiving **either** neoadjuvant chemotherapy **or** neo-endocrine therapy as their standard of care (SoC)
- The trial compared the neoadjuvant addition of Tecemotide (L-BLP25) to the neoadjuvant (SoC) alone:



Singer et al. SABCS 2016 (P6-10-01)

Endopredict: Validation in ER+/HER2 neg. and Genes

	Trial	n=	Breast cancer sub-type	Nodal status	Treatment	10y Dist. met. rate lowrisk group
Training	Multicenter	964	ER+/HER2-	N0, N+	ET	7%
Validation I	ABCSG-6	378	ER+/HER2-	N0, N+	ET	4%
Validation II	ABCSG-8	1,324	ER+/HER2-	N0, N+	ET	4%
Validation III	GEICAM/9906	555	ER+/HER2-	N+	ET+Chemo	0%
Validation IV	ATAC	928	ER+/HER2-	N0, N+	ET	5.8%



= EPscore

Retrospective validation in prospective data sets of ca. 3100 women- all ER+/HER2-

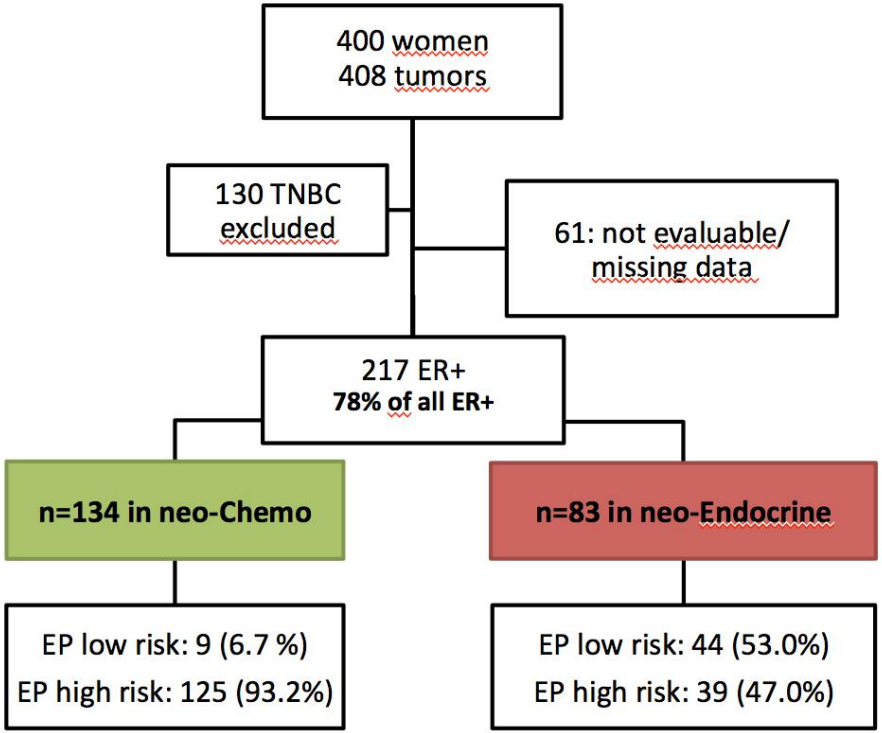
EP score + pT and pN= **EP**clin score

Filipits et al. CCR 2011; Dubsky et al. Annals of Oncol. 2012; Dubsky et al. BJC 2013, Martin et al. Breast Cancer Res. 2014; Martin et al. Breast Cancer Res. Treat. 2016; Buus et al. JNCI 201;, Sestak et al. SABCS 2016

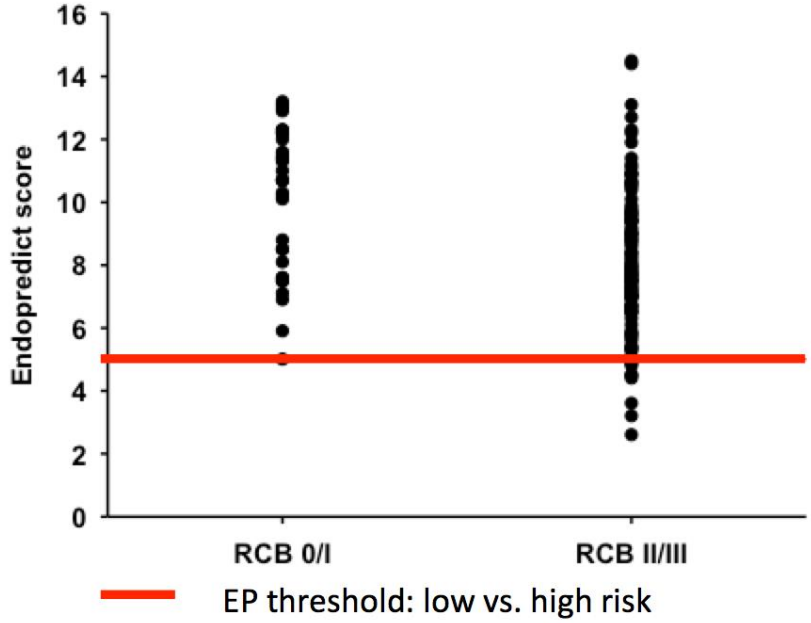
Primary Objective

- **To test for predictive value of EP concerning tumor response**
  - In a neoadjuvant chemotherapy treatment group
  - In a neo-endocrine treatment group

Patients,Samples

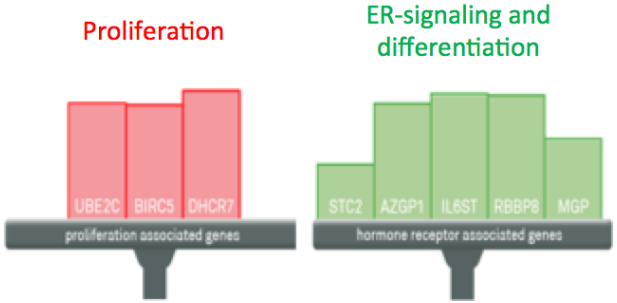


Results – EP risk groups: (Neo-Chemotherapy Group)



	RCB 0/I	RCB II/III	
EP **HIGH** risk	33	92	Pos. Pred. Val. 26.4% (18.9-35.0)
EP low risk	0	9	Neg. Pred. Val. 100.0% (66.4-100.0)
	True Pos. Rate 100.0% (89.4-100.0)	True Neg. Rate 8.9% (4.2-16.2)	Fisher's Exact test p=0.112

Multivariate logistic regression model
exploratory: incorporating Metagenes
(Neo Chemotherapy Group)



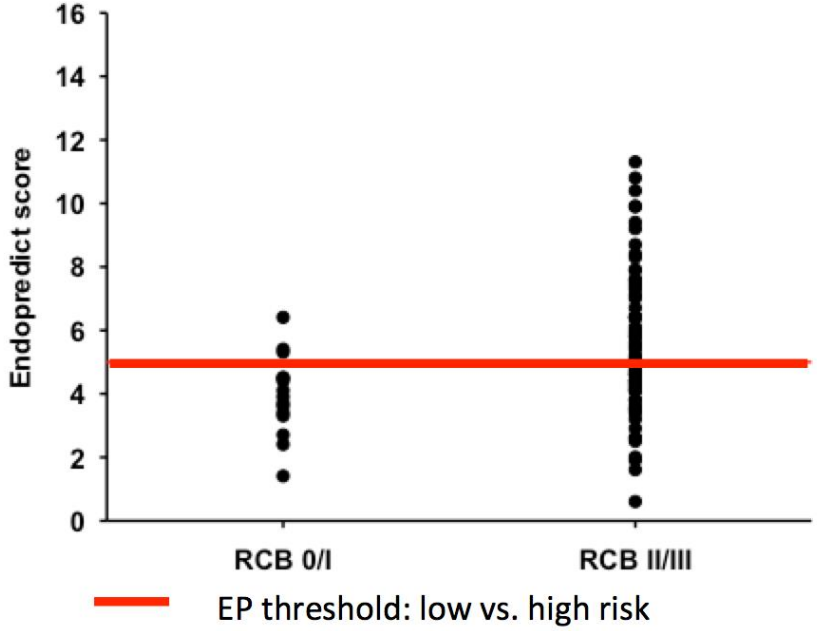
Parameter		n	Odds ratio (95% CI)	p-value
HR	high vs low	124	0.506 (0.19 - 1.32)	0.1655
*Log (Ki67)	continuous	124	1.498 (1.06 - 2.11)	0.0206
EP score	continuous	124	1.165 (0.92 - 1.48)	0.2134

Parameter		n	Odds ratio (95% CI)	p-value
HR	high vs low	124	0.440 (0.16 - 1.23)	0.1181
*Log (Ki67)	continuous	124	1.467 (1.04 - 2.07)	0.0292
Proliferation	continuous	124	1.468 (0.88 - 2.45)	0.1419
ER signaling	continuous	124	0.941 (0.54 - 1.63)	0.8288

EP score

*Grading was omitted from the MV Model due to high correlation with Ki-67

Results – EP risk groups: (Neo-Endocrine Group)

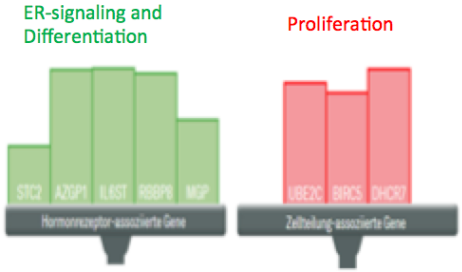


	RCB 0/I	RCB II/III	
EP low risk	12	32	Pos. Pred. Val. 27.3% (15.0-42.8)
EP high risk	3	36	Neg. Pred. Val. 92.3% (79.1-98.4)
	True Pos. Rate 80.0% (51.9-95.7)	True Neg. Rate 52.9% (40.5-65.2)	Fisher's Exact test p=0.024

Multivariate logistic regression model

Neo-Endocrine Treatment Group

exploratory: incorporating Metagenes



Parameter		N	Odds ratio (95% CI)	p-value
cT-stage	T2/T3/T4 vs T1	82	0.047 (0.01 - 0.40)	0.0049
EP score	continuous	82	0.673 (0.45 - 1.02)	0.0602

EP score

Parameter		N	Odds ratio (95% CI)	p-value
cT-stage	T2/T3/T4 vs T1	81	0.044 (<.01 - 0.40)	0.0057
Proliferation	continuous	81	0.237 (0.09 - 0.65)	0.0050
ER signaling	continuous	81	0.742 (0.29 - 1.88)	0.5292

Summary:

- **In women treated with 8 cycles of neoadjuvant EC-T Chemotherapy:**
  - **EP score and EP risk groups are associated with RCB**
  - **Notably EP low risk was highly associated to poor tumor shrinkage (NPV: 100%)**
  - Excellent tumor shrinkage was largely driven by covariates including cell proliferation:
    - Ki-67 LI ($p<0.05$); Proliferation Metagene and EP score

- **In women treated with 6 months of neoadjuvant Letrozole**
  - **EP score and EP risk groups are associated with RCB**
  - **Notably EP high risk was highly associated with poor tumor shrinkage (NPV: 92%)**
  - Tumor size was an independent predictor of RCB
  - Covariates including ER signaling/differentiation (ER signaling metagene, HR) did not drive response to Letrozole
  - The proliferation metagene but not Ki-67 showed statistically independent association to RCB
  - The narrow distribution of Ki-67 in the neo-endocrine cohort may have prevented the factor from influencing the model

Take home

- EP score can help predict response to endocrine therapy

- Unclear why EP score and Ki67 don't match
- Ki67 is the best predictor of chemo response

Summary

1. Tandem duplications are generated by BRCA1
2. cfDNA may provide information about genomic structure and recurrence risk
3. *BRCA2* VUS have functional annotation
4. Late recurrence can be predicted by clinical parameters (and CTCs)
5. Genomics may predict response/resistance.

Summary

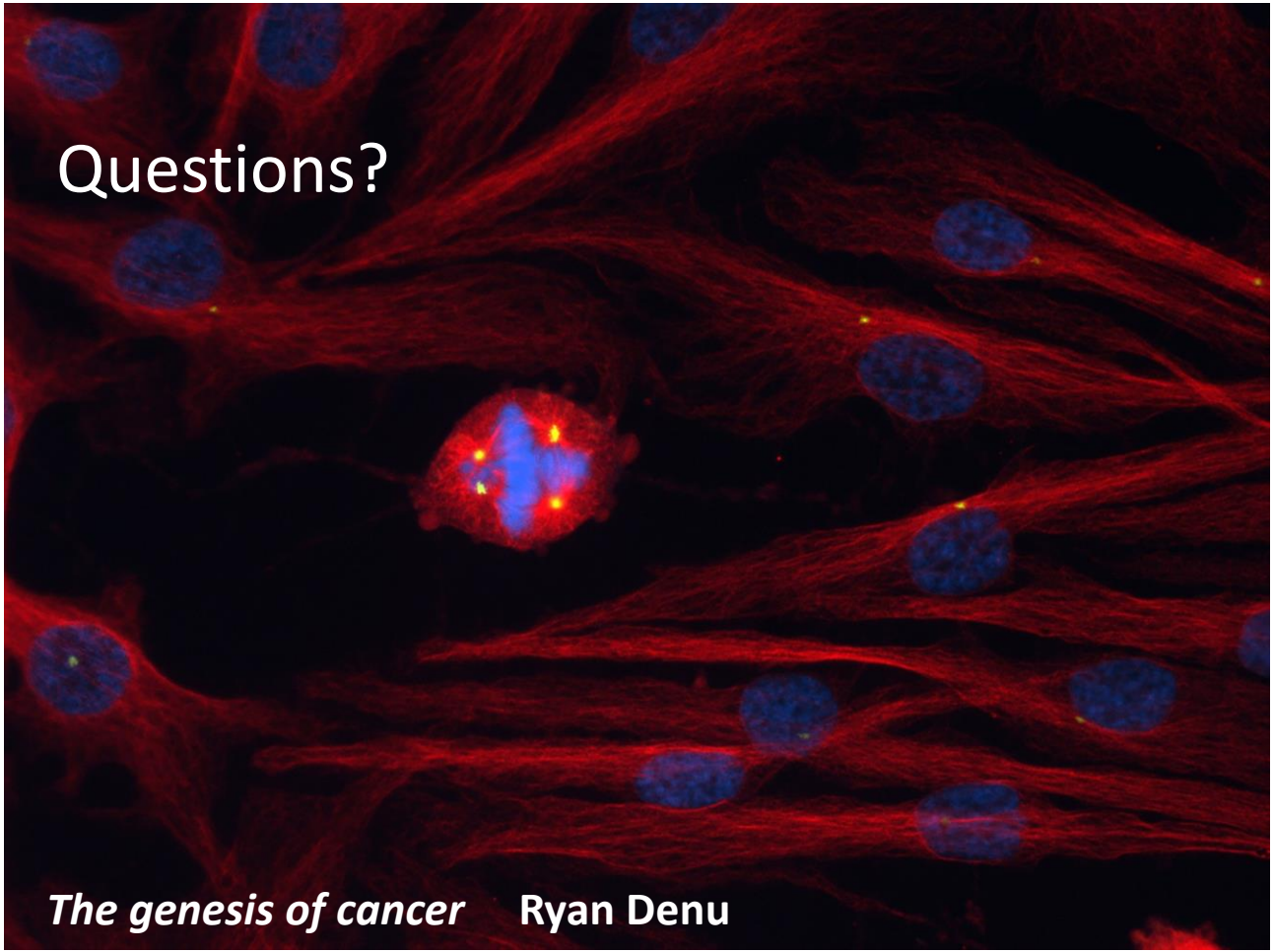
1. Tandem duplications are generated by BRCA1
2. cfDNA may provide information about genomic structure and recurrence risk
3. *BRCA2* VUS have functional annotation
4. Late recurrence can be predicted by clinical parameters (and CTCs)
5. Genomics may predict response/resistance.

Summary

BRCA2 VUS have functional annotation

ClinVar, BRCAexchange

Late recurrence can be predicted by clinical parameters



https://visualsonline.cancer.gov/