Under the auspices of

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12th International Symposium

ADVANCED OVARIAN CANCER

Optimal Therapy. Update

Precision Medicine in Epithelial Ovarian Cancer

Iain McNeish

Professor of Oncology, Imperial College London

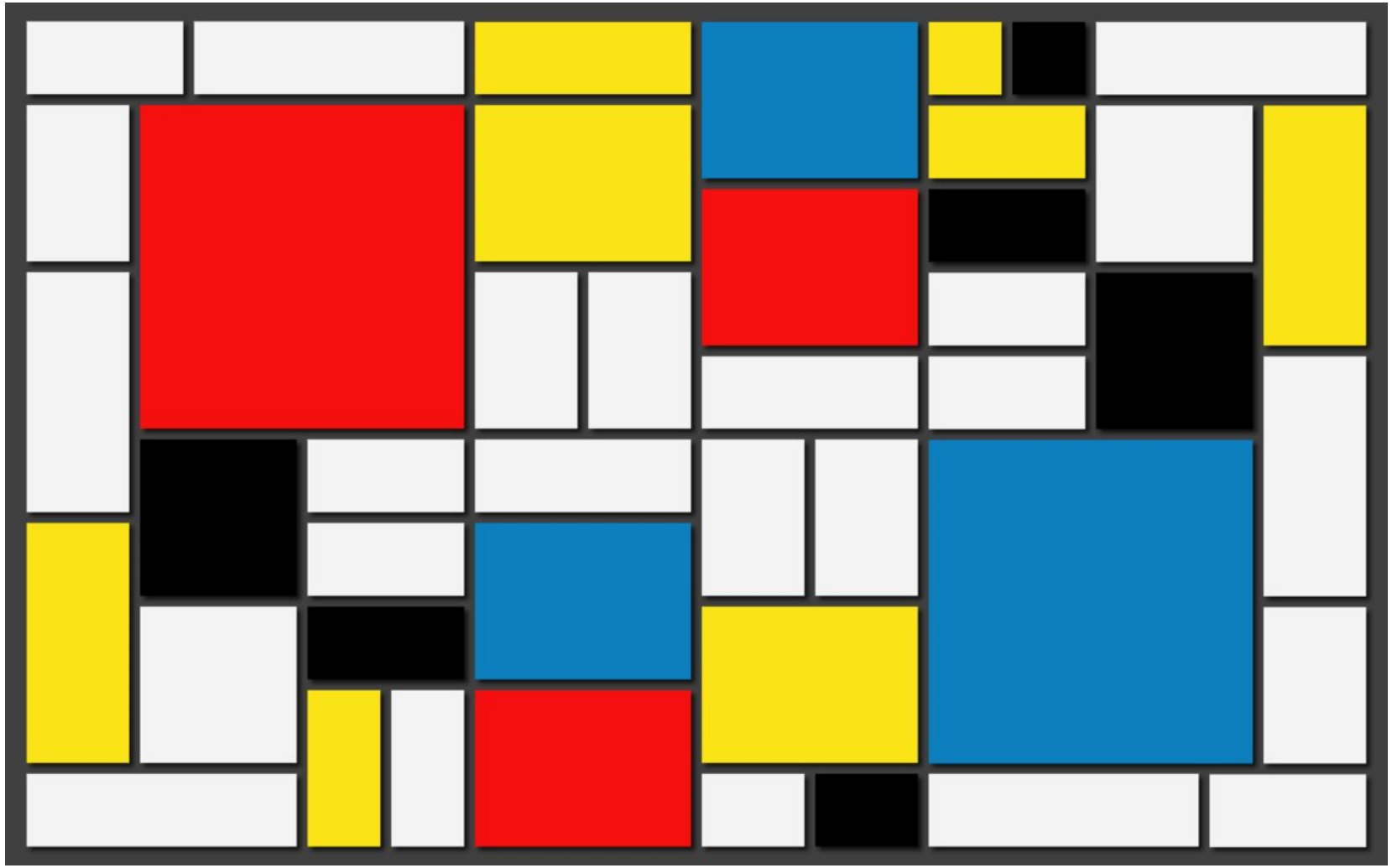
Disclosures

- I have sat on Advisory Boards for Clovis Oncology, Tesaro, AstraZeneca and Takeda.

- Co-chief investigator ARIEL2 (Clovis Oncology)
- Chief Investigator OCTAVE (PsiOxus Therapeutics)

- My institution receives grant support from AstraZeneca

Ovarian cancer is not like a Mondrian painting

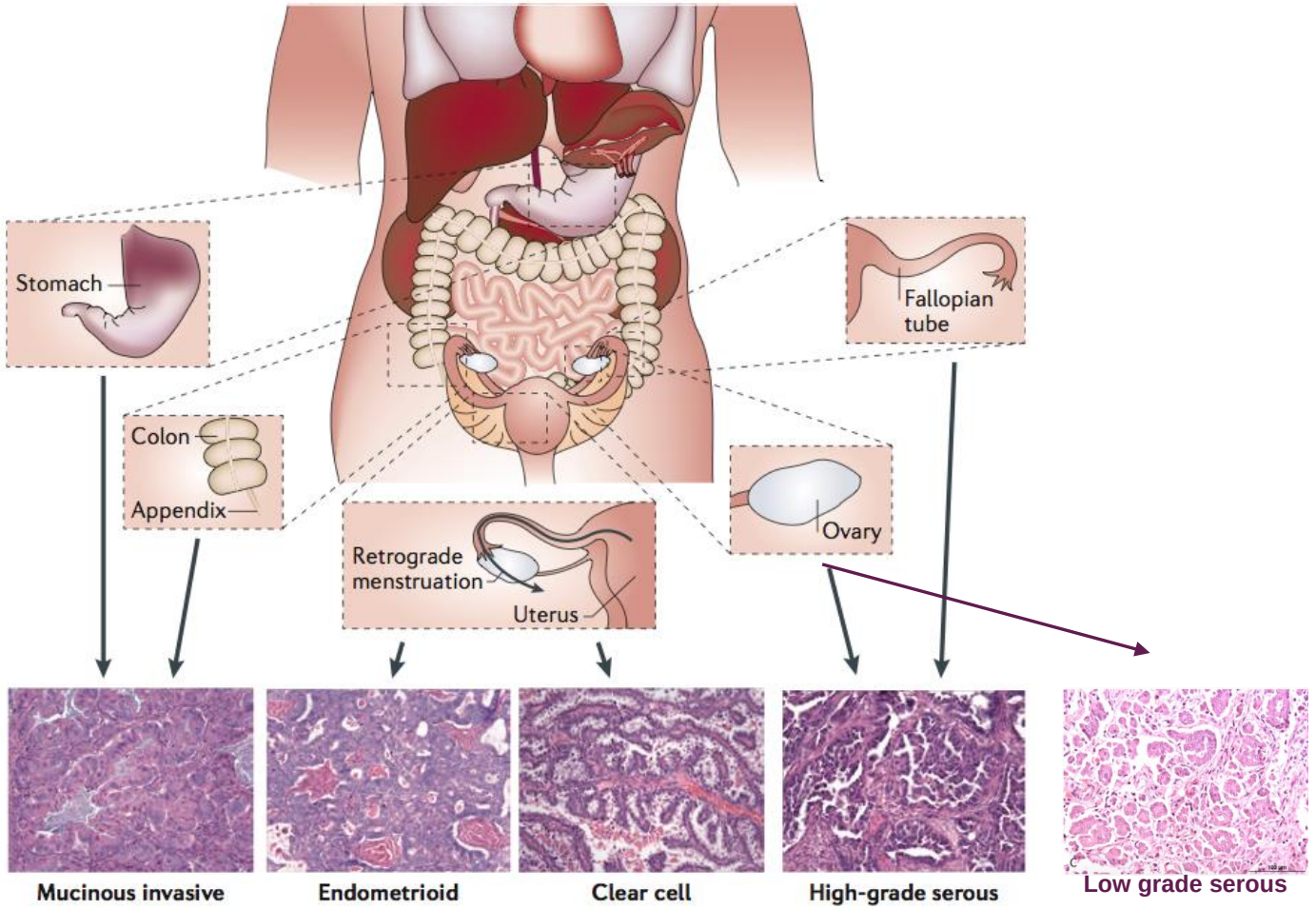


Line over form (1922) – Piet Mondrian

Ovarian cancer is more like this

Convergance (1952) – Jackson Pollock

Current view of ovarian cancer biology



Mucinous invasive	Endometrioid	Clear cell	High-grade serous	Low grade serous
KRas	PI3K ß-catenin PTEN	ARID1A PI3K IL-6/HIF1a	p53 HRD CNA	Kras Braf

Vaughan et al Nat Rev Cancer (2011) 11:719

Data on non-HGSC disease are very limited

CALYPSO

Histology	Number	%
Serous	700	71.9
Endometrioid	**73**	**7.5**
Clear cell	**27**	**2.8**
Mucinous	**17**	**1.7**
Other	104	10.7
Unspecified	52	5.3
TOTAL	973	

OCEANS

Histology	Number	%
Serous	391	80.8
Endometrioid	**29**	**6.0**
Clear cell	**15**	**3.1**
Mucinous	**4**	**0.8**
Other	45	9.3
TOTAL	484	

Aghajanian et al (2012) JCO 30:2039. Pujade-Lauraine et al (2010) JCO 28:3323

Clear cell carcinoma – response rates are dismal

Table 2. Response to second-line chemotherapy in the patients with treatment-free period 6 months or more (group A) and with treatment-free period less than 6 months (group B)

Regimen	PR	SD	PD	Response rate[a] (%)	Non-PD rate (%)
Group A					
CAP, CP	1	0	3	25	25
Platinum + etoposide	0	0	2	0	0
Paclitaxel + platinum	0	2	4	0	33
Docetaxel + platinum	0	0	1	0	0
CPT-11 + platinum	1	3	3	14	57
CPT-11 + mitomycin C	0	0	3	0	0
Docetaxel	0	0	1	0	0
Subtotal	2 (8%)	5 (21%)	17 (71%)	8	29
Group B					
CAP, CP	0	0	5	0	0
Platinum + etoposide	2	0	9	18	18
Paclitaxel + platinum	0	2	15	0	12
Docetaxel + platinum	0	0	3	0	0
Weekly paclitaxel	0	0	2	0	0
CPT-11 + platinum	1	2	5	13	38
CPT-11 + mitomycin C	0	1	2	0	33
CPT-11 + docetaxel	0	0	1	0	0
MEP	0	1	0	0	100
Subtotal	3 (6%)	6 (12%)	42 (82%)	6	18
Total	5 (7%)	11 (15%)	59 (79%)	6.7	21

Takano et al (2008)
IJGC 18:937

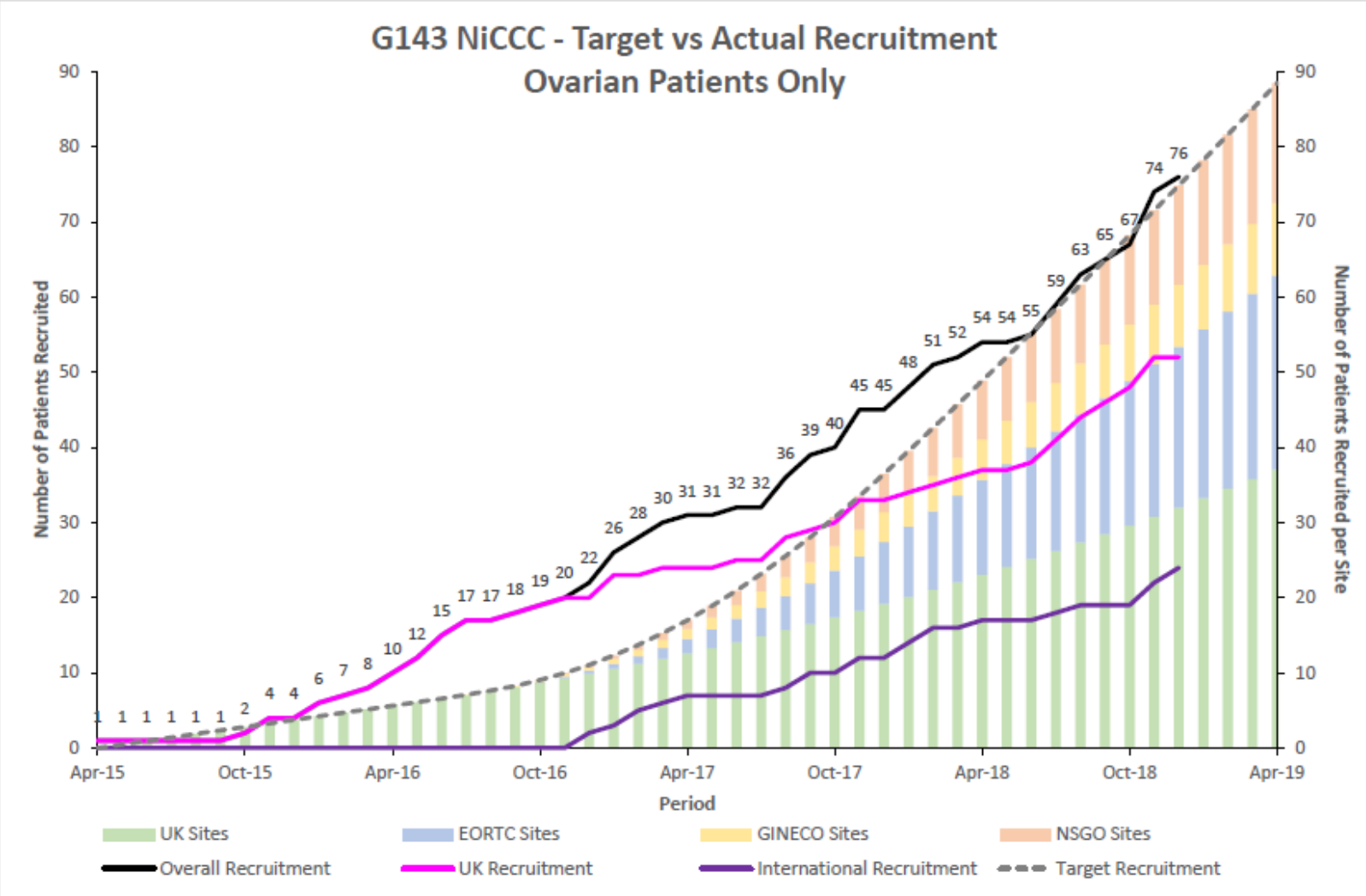
NiCCC

(ENGOT-ov36)
A Randomised Phase II study Of Nintedanib (BIBF1120) Compared To Chemotherapy in Patients With Recurrent Clear Cell Carcinoma Of The Ovary Or Endometrium

EudraCT Number:2013-002109-73

ISRCTN50772895

NiCCC Recruitment



Low grade serous carcinoma

Array BioPharma Announces Decision To Discontinue MILO Study In Ovarian Cancer

1st April 2016

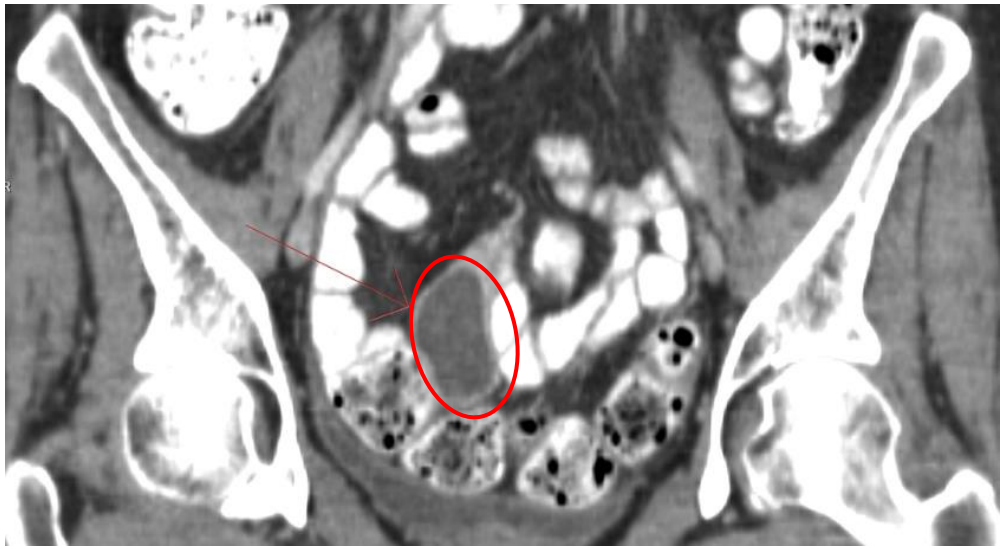
Case report

Binimetinib (MEK162) in recurrent low-grade serous ovarian cancer resistant to chemotherapy and hormonal treatment

Chanhee Han, Stefania Bellone, Luca Zammataro, Peter E. Schwartz, Alessandro D. Santin*

Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, CT 06520, USA

Han et al (2018) Gynecol Onc Rep 25:41



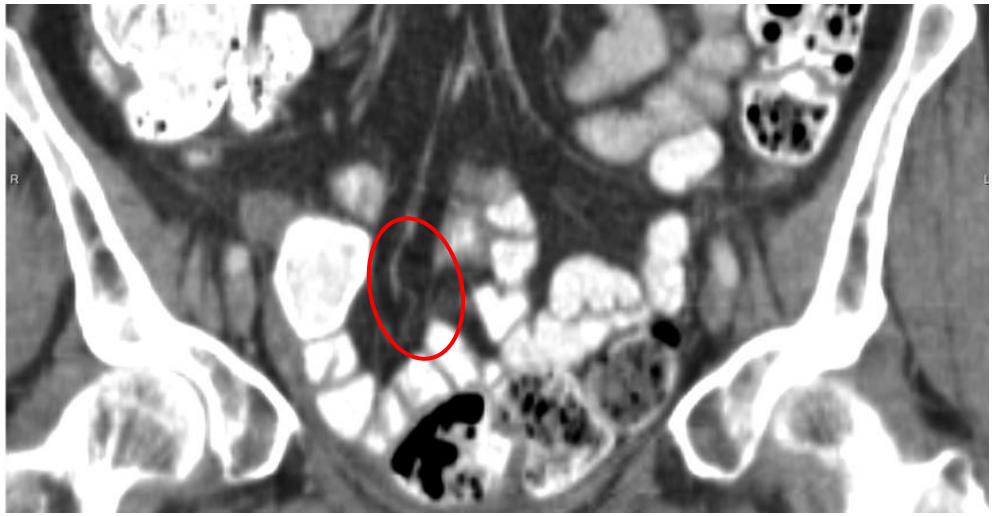
Case report

Dramatic clinical response following dabrafenib and trametinib therapy in a heavily pretreated low grade serous ovarian carcinoma patient with a BRAF V600E mutation

Alberto A. Mendivil[a], Paul K. Tung[b], Randy Bohart[c], Karen Bechtol[a], Bram H. Goldstein[a,*]

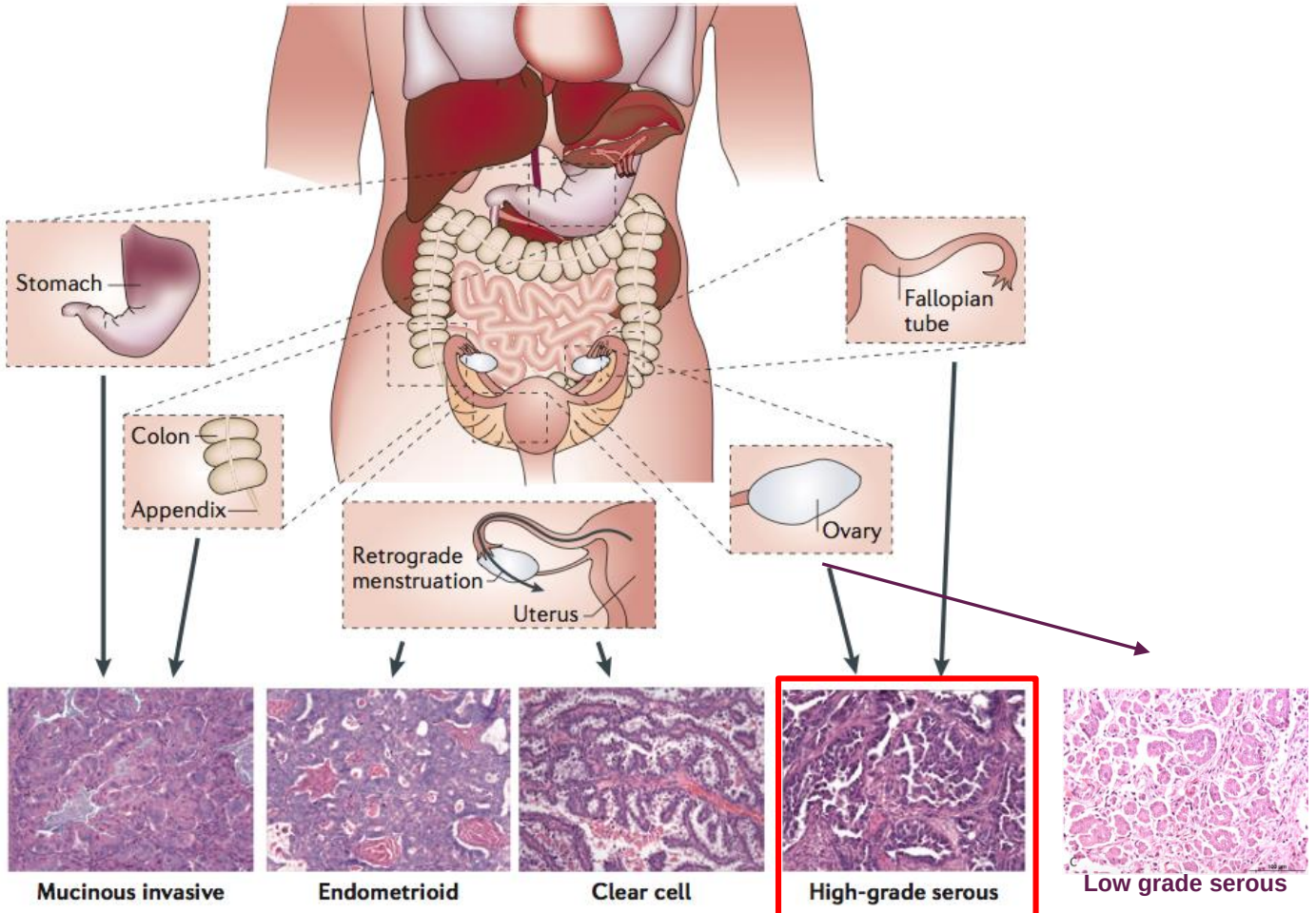
[a] *Gynecologic Oncology Associates, Newport Beach, CA 92663, United States*
[b] *University of California, Irvine, Department of Radiological Sciences, 1001 Health Sciences Road, Irvine, CA 92697-3950, United States*
[c] *Oso Home Care, 17175 Gillette Avenue, Irvine, CA 92614, United States*

Mendevil et al (2018) Gynecol Onc Rep 26:41



https://www.prnewswire.com/news-releases/array-biopharma-announces-decision-to-discontinue-milo-study-in-ovarian-cancer-300244593.html

Current view of ovarian cancer biology



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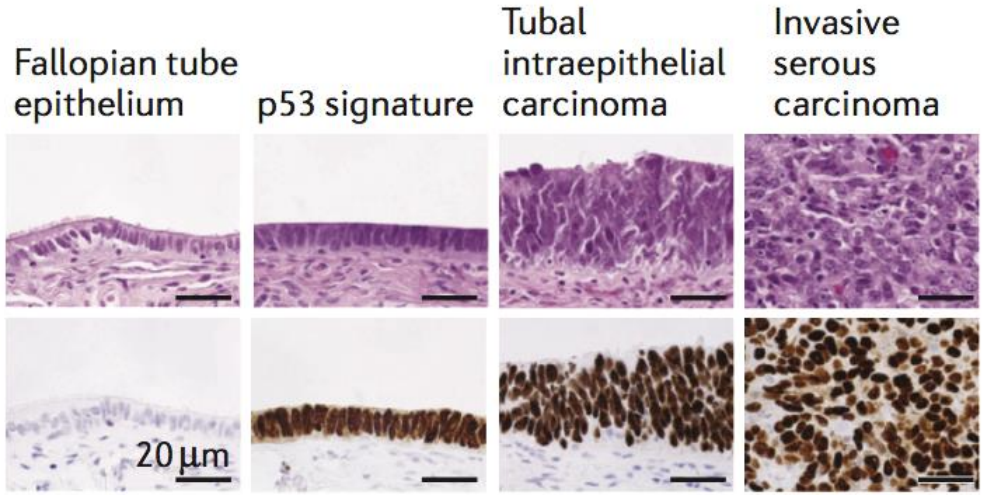
Vaughan et al Nat Rev Cancer (2011) 11:719

Ovarian high-grade serous carcinoma

- Mostly arises in distal fallopian tube



Journal of Pathology
J Pathol 2007; **211**: 26–35
Published online 20 November 2006 in Wiley InterScience
(www.interscience.wiley.com) **DOI:** 10.1002/path.2091

Original Paper

A candidate precursor to serous carcinoma that originates in the distal fallopian tube

Y Lee,[1†] A Miron,[2†] R Drapkin,[1,3] MR Nucci,[1] F Medeiros,[1] A Saleemuddin,[1] J Garber,[3] C Birch,[1] H Mou,[4] RW Gordon,[2] DW Cramer,[5] FD McKeon[4] and CP Crum[1*]

[1] *Division of Women's and Perinatal Pathology, Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA*
[2] *Department of Cancer Biology, Dana-Farber Cancer Institute, USA*
[3] *Department of Medical Oncology, Dana-Farber Cancer Institute, USA*
[4] *Department of Cell Biology, Harvard Medical School, USA*
[5] *Obstetrical and Gynecologic Epidemiology, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, MA, USA*

Lee et al, J Pathol (2007) 211:26

Bowtell et al Nat. Rev. Cancer (2015) **15**:668-79

Ovarian high-grade serous carcinoma

- Ovarian surface epithelium may still contribute…

Both Fallopian Tube and Ovarian Surface Epithelium Can Act as Cell-of-Origin for High Grade Serous Ovarian Carcinoma

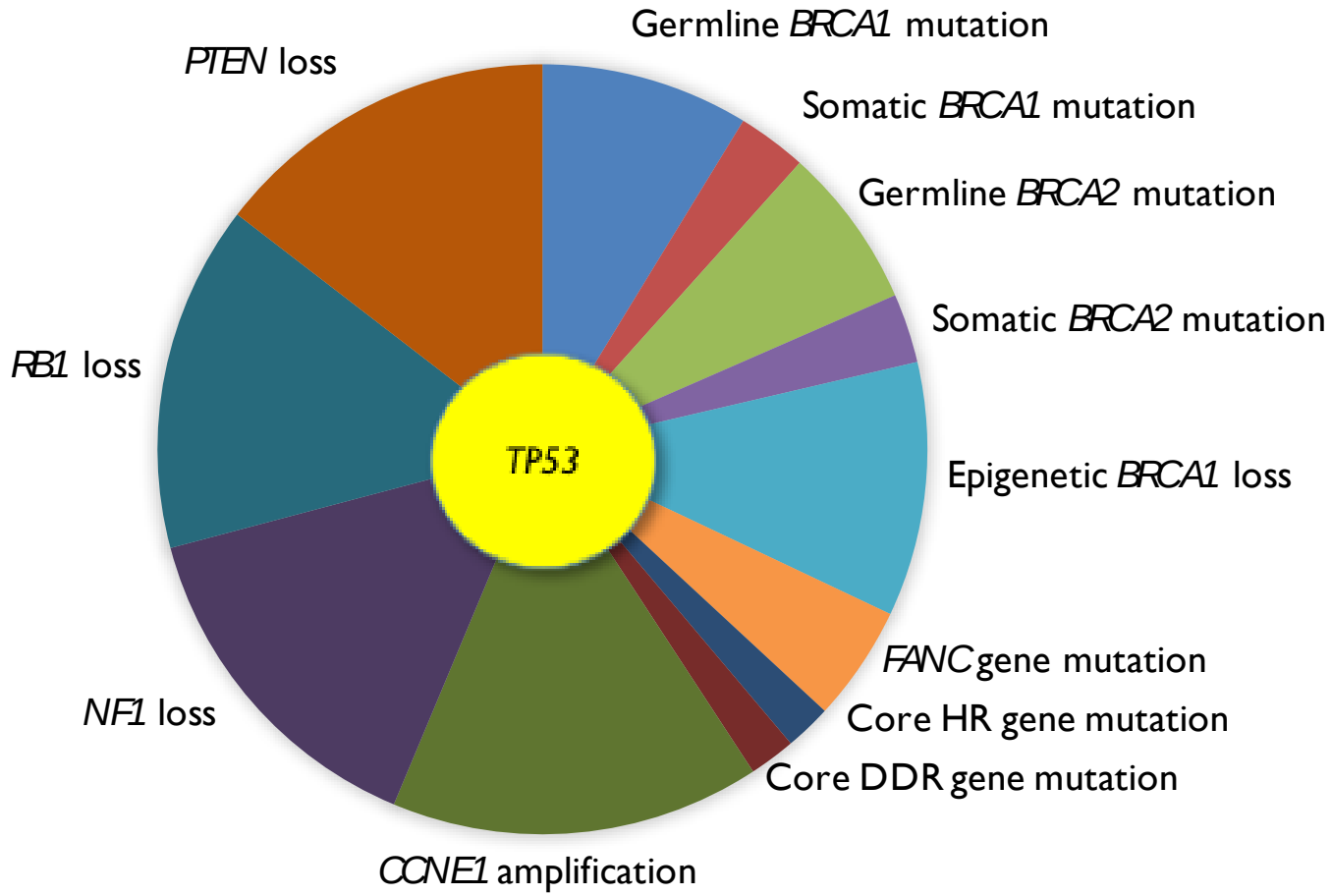
Shuang Zhang[#], Tao Zhang, Igor Dolgalev, Hao Ran, Douglas A. Levine, Benjamin G. Neel[#]

Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY, 10016, USA.

[#]Corresponding authors: Benjamin G. Neel, New York University School of Medicine, 522 First Avenue, Smilow Building 12th Floor, Suite 1201, New York, NY 10016. Phone: 212-263-3019; Fax: 212-263-9190; E-mail:Benjamin.Neel@nyumc.org; Shuang.Zhang@nyumc.org

Neel et al BioRxiv (2018) 481200

Genomic aberrations in HGSC

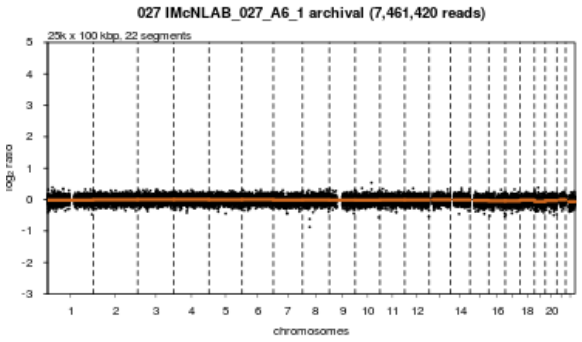


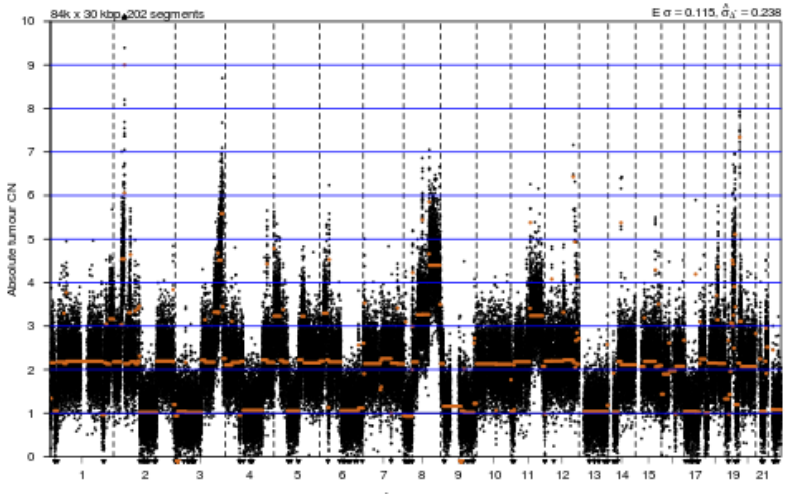
Original design – Doug Levine, NYU

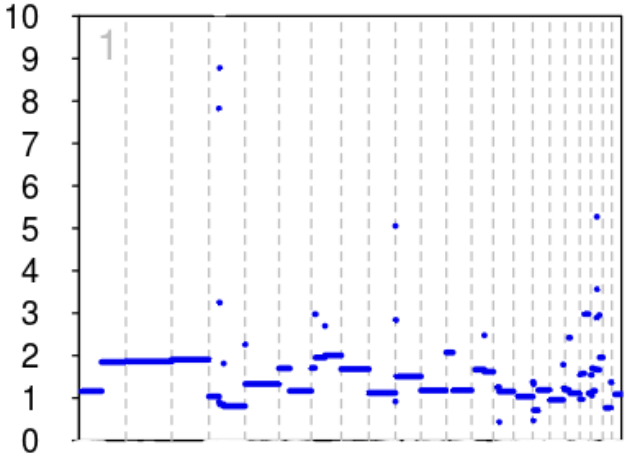
TCGA, Nature (2011) 474:609; Martins et al Genome Biol. (2014) 15:526; Patch et al Nature (2015) 521:489
Etemadmoghadam, D et al CCR (2009) 15:1417;

HGSC is driven by copy number (CN) change

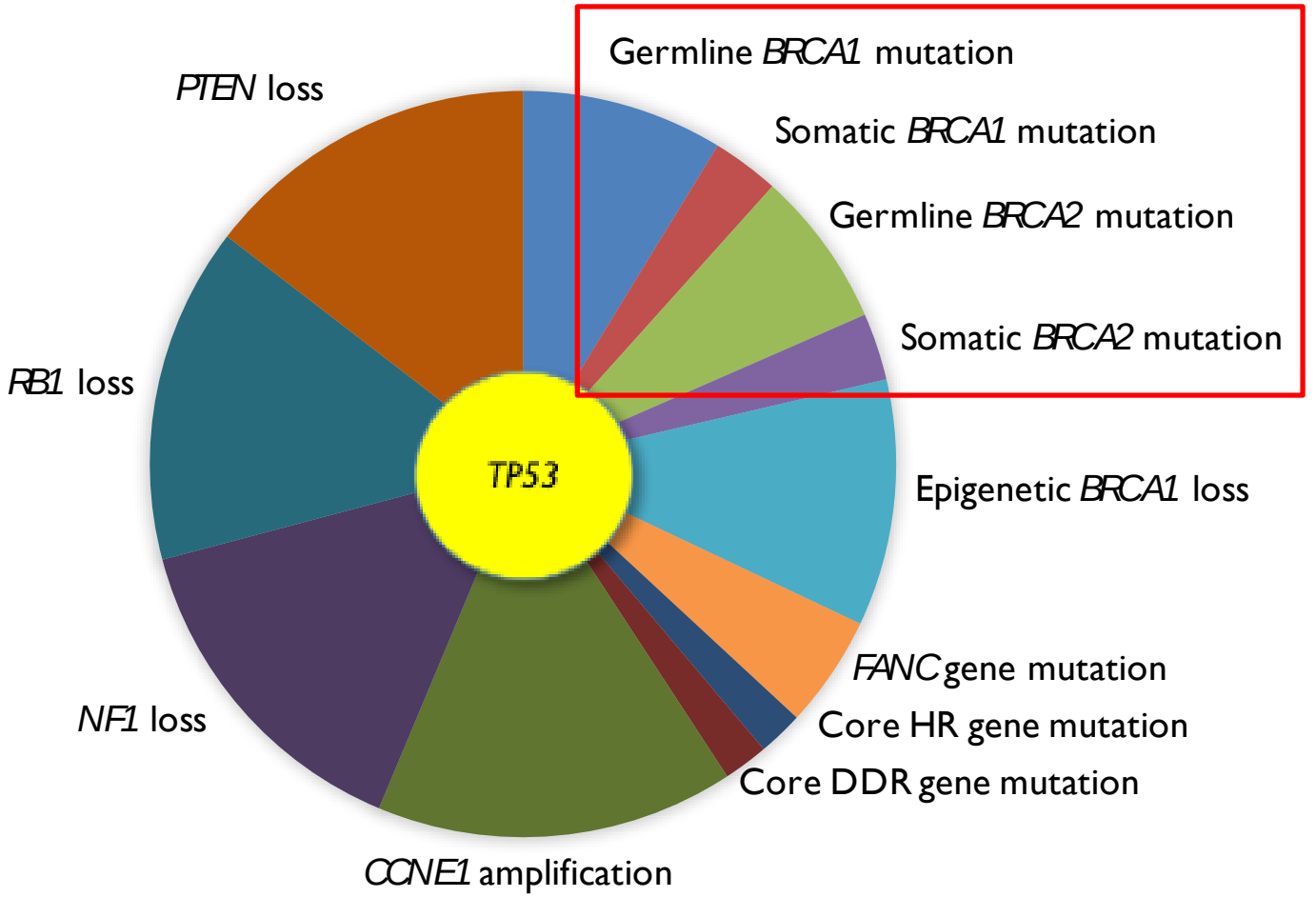
This is normal…!







Most progress has been in good-prognosis disease



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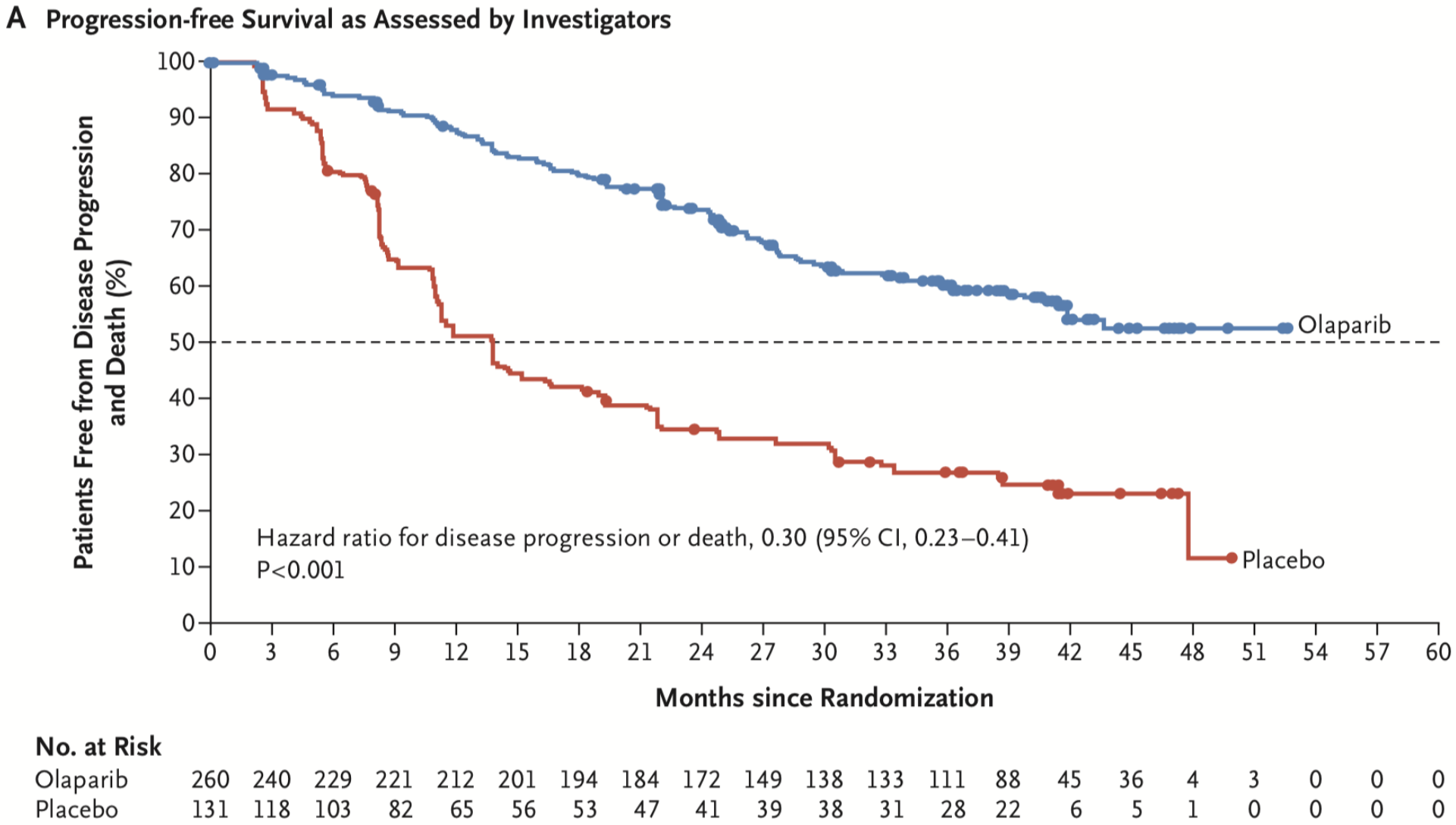
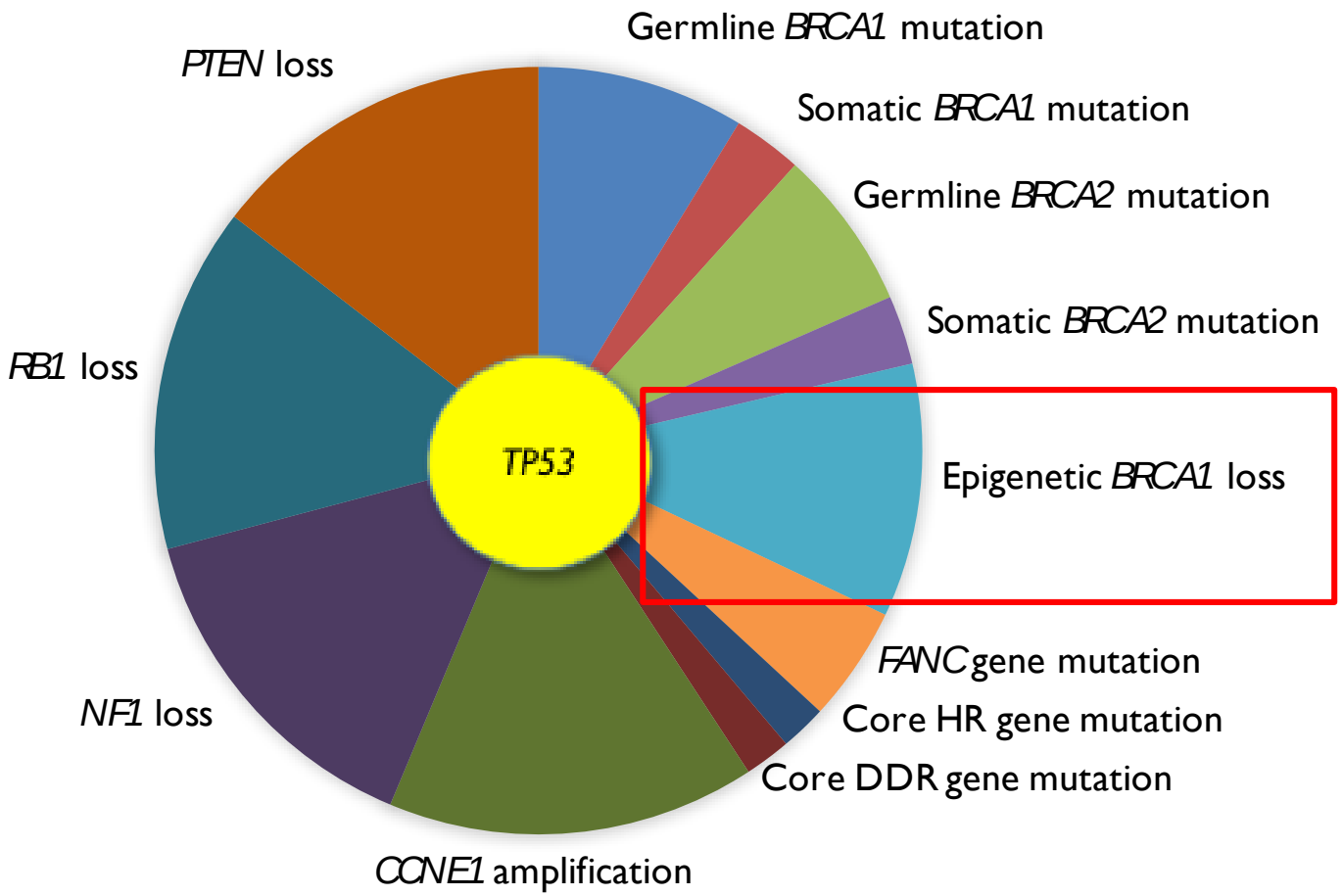
TCGA, Nature (2011) 474:609; Martins et al Genome Biol. (2014) 15:526; Patch et al Nature (2015) 521:489
Etemadmoghadam, D et al CCR (2009) 15:1417;

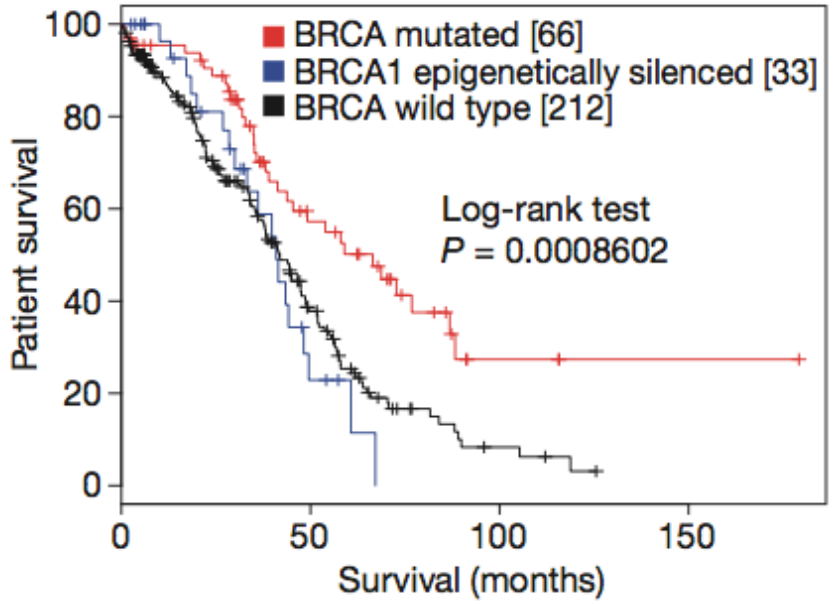
PARP inhibitors in *BRCA1/2*-mutated disease



Moore et al (2018) NEJM 379:2495

Genomic aberrations beyond *BRCA1/2*

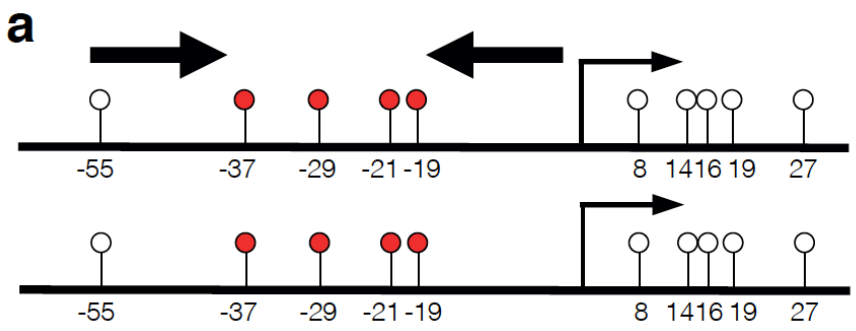




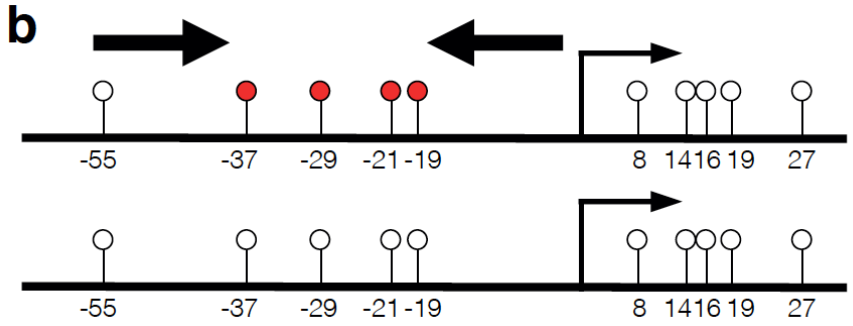
Original design – Doug Levine, NYU

TCGA, Nature (2011) 474:609; Martins et al Genome Biol. (2014) 15:526; Patch et al Nature (2015) 521:489
Etemadmoghadam, D et al CCR (2009) 15:1417;

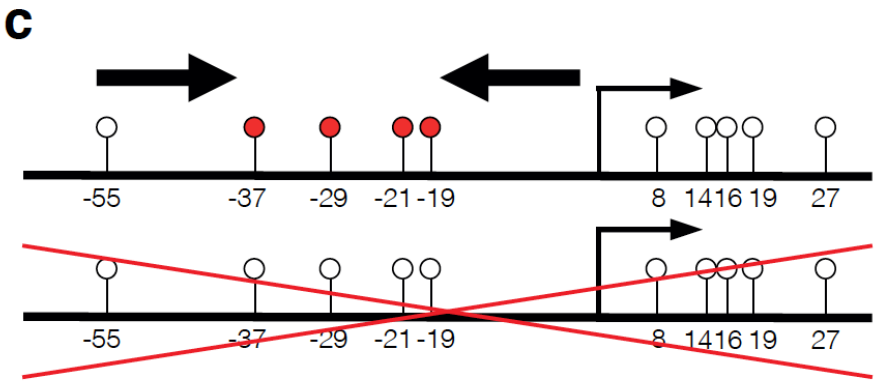
Methylation states



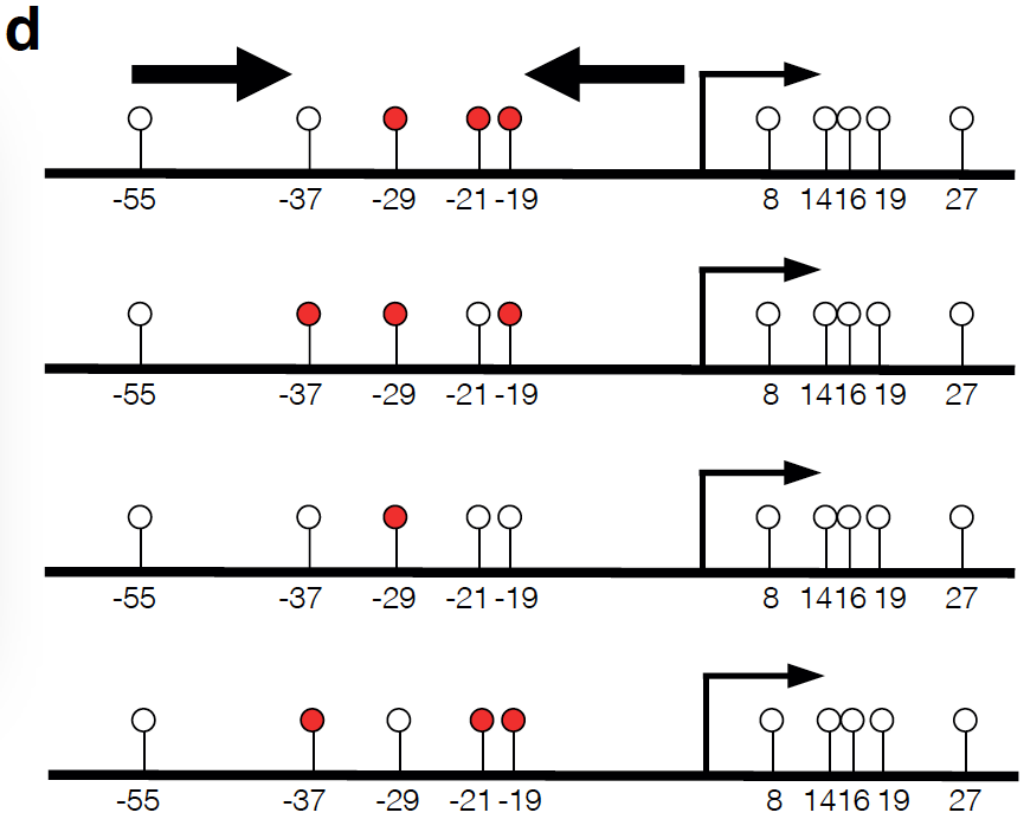
Homozygous



Heterozygous



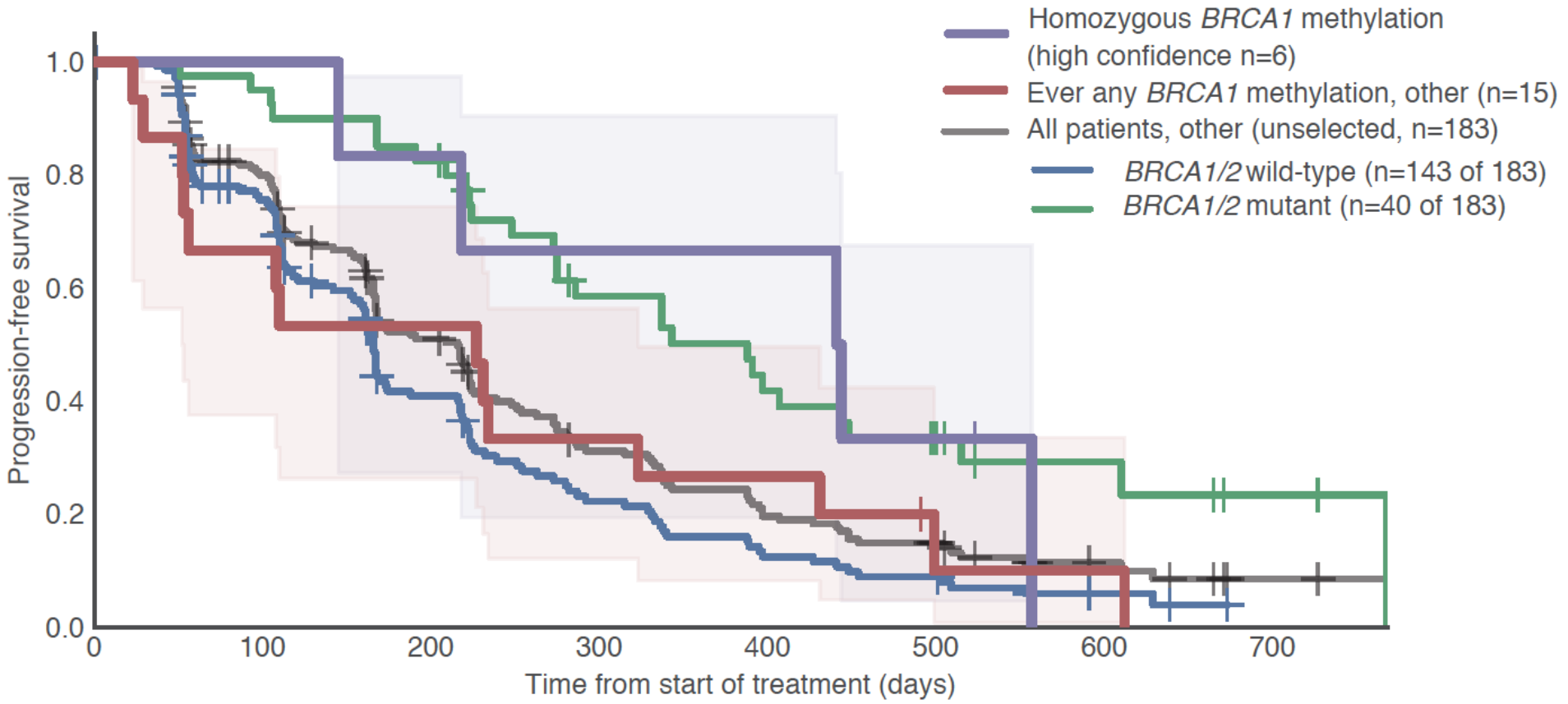
Hemizygous



Partial

Kondrashova et al (2018) Nat. Commun 9:3970

Methylation and rucaparib – ARIEL2



Kondrashova et al (2018) Nat. Commun 9:3970

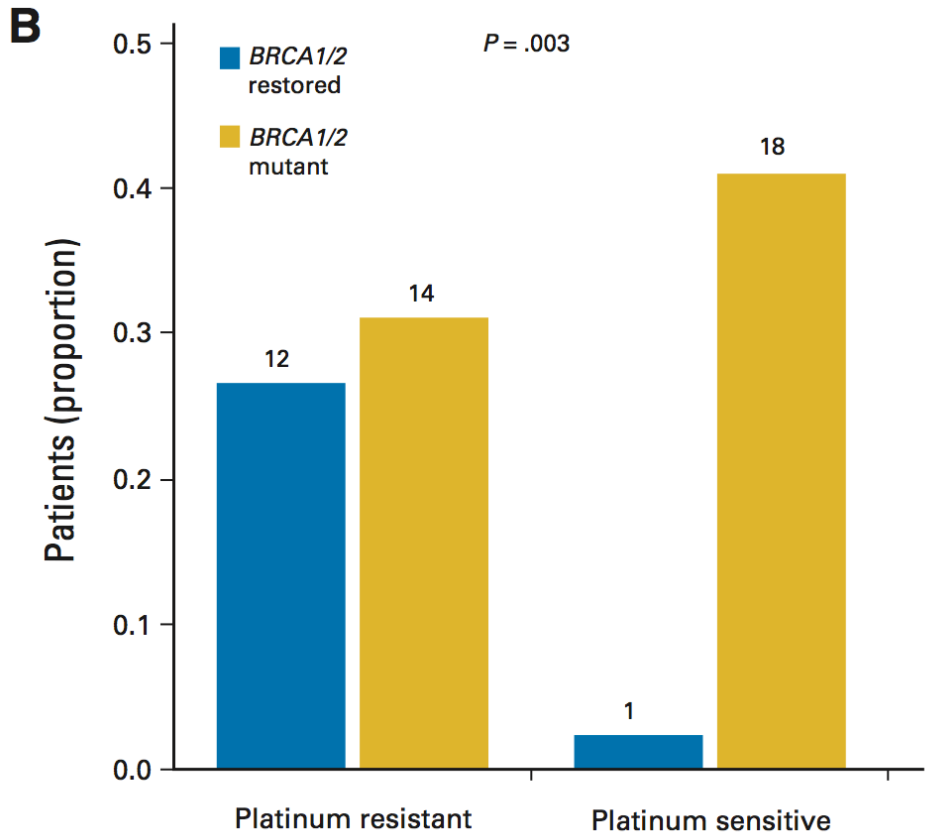
BRCA revertant mutations

Resistance to therapy caused by intragenic deletion in *BRCA2*

Stacey L. Edwards[1], Rachel Brough[1], Christopher J. Lord[1], Rachael Natrajan[1], Radost Vatcheva[1], Douglas A. Levine[2], Jeff Boyd[3], Jorge S. Reis-Filho[1] & Alan Ashworth[1]

Secondary mutations as a mechanism of cisplatin resistance in *BRCA2*-mutated cancers

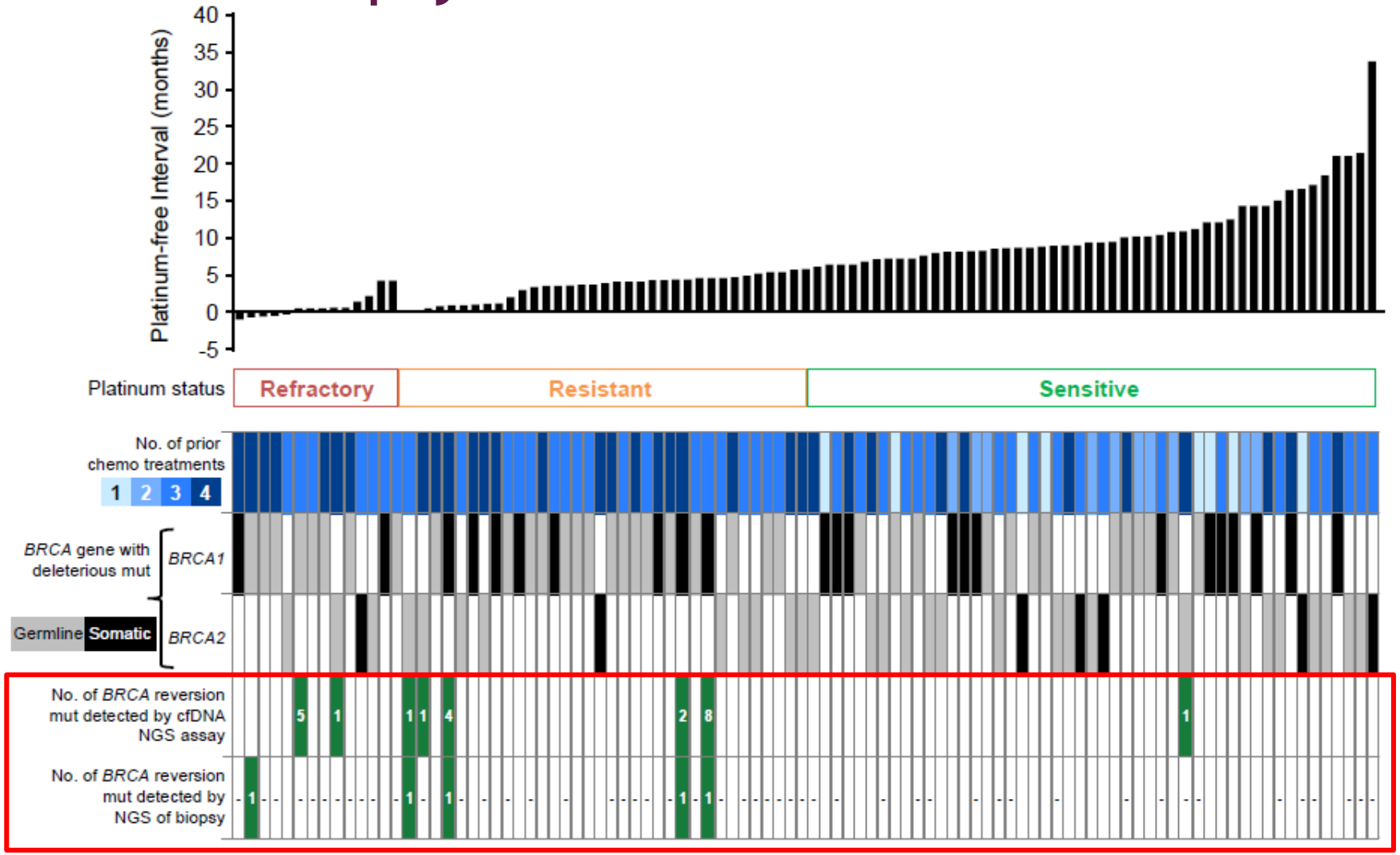
Wataru Sakai[1,2], Elizabeth M. Swisher[3,4], Beth Y. Karlan[5], Mukesh K. Agarwal[6], Jake Higgins[4,7], Cynthia Friedman[1], Emily Villegas[1,2], Céline Jacquemont[1,2], Daniel J. Farrugia[6], Fergus J. Couch[6], Nicole Urban[2] & Toshiyasu Taniguchi[1,2]



Edwards et al (2008) 451:1111
Sakai et al (2008) Nature 451:1116

Norquist et al (2011) JCO 29:3008

BRCA reversion mutations in pre-rucaparib treatment cfDNA and tumour biopsy



Lin et al (2019) Cancer Disc. 9:210

BRCA reversion mutations in pre-rucaparib treatment cfDNA and tumour biopsy

Platinum status	Cases with primary *BRCA* and *TP53* mut detected	Cases with *BRCA* reversion mut detected	*BRCA* reversion mut frequency
Sensitive	48	1*	2.1%
Resistant	35	5	14.3%
Refractory	14	2	14.3%

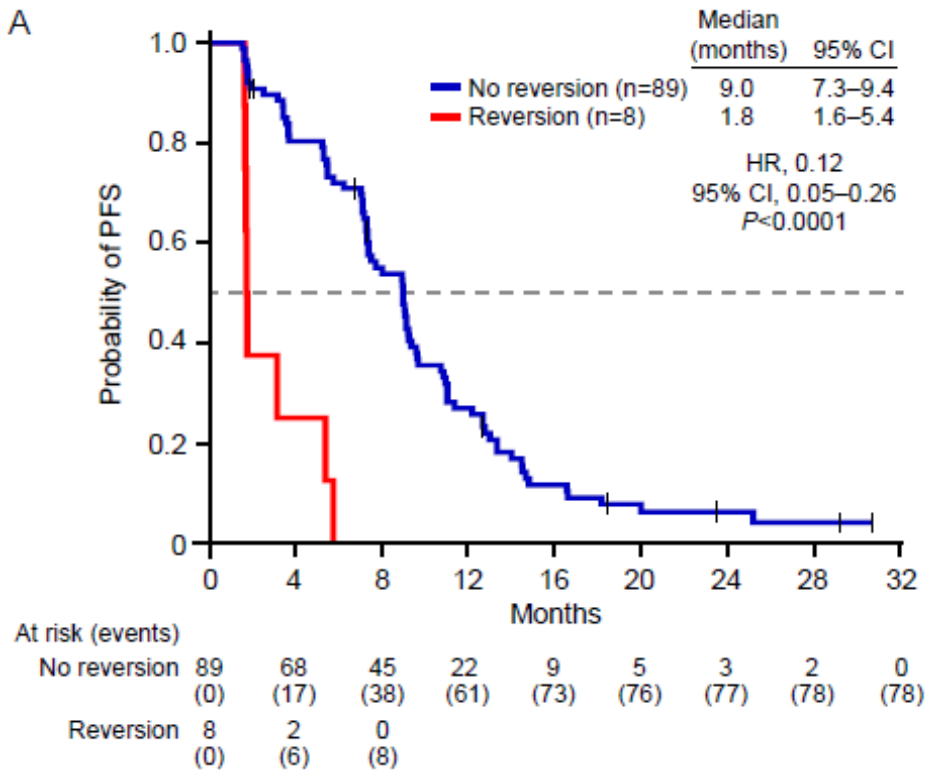
* Detected at MAF=0.42%

Overall reversion rate in cfDNA pre-rucaparib = 8/97 (8.2%)

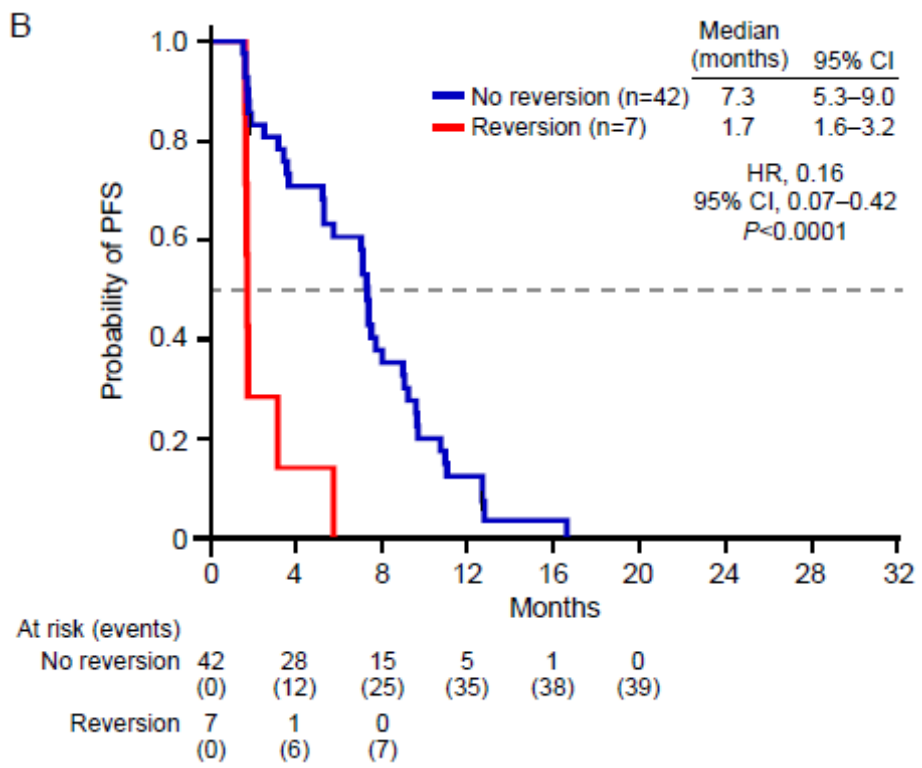
Lin et al (2019) Cancer Disc. 9:210

ARIEL2 - PFS according to reversion vs non-reversion

All cases



Platinum resistant/refractory cases



Lin et al (2019) Cancer Disc. 9:210

As of clinical data cut-off of 4JAN2018

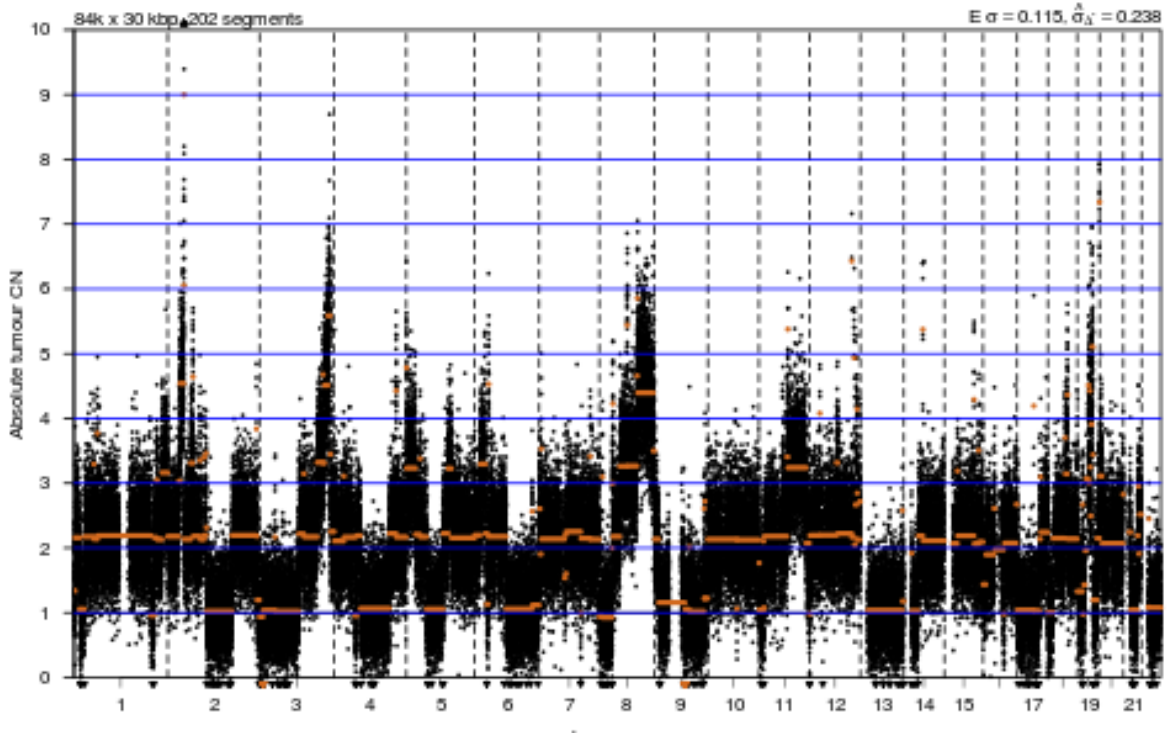
BRCA reversion mutations detected in post-progression cfDNA

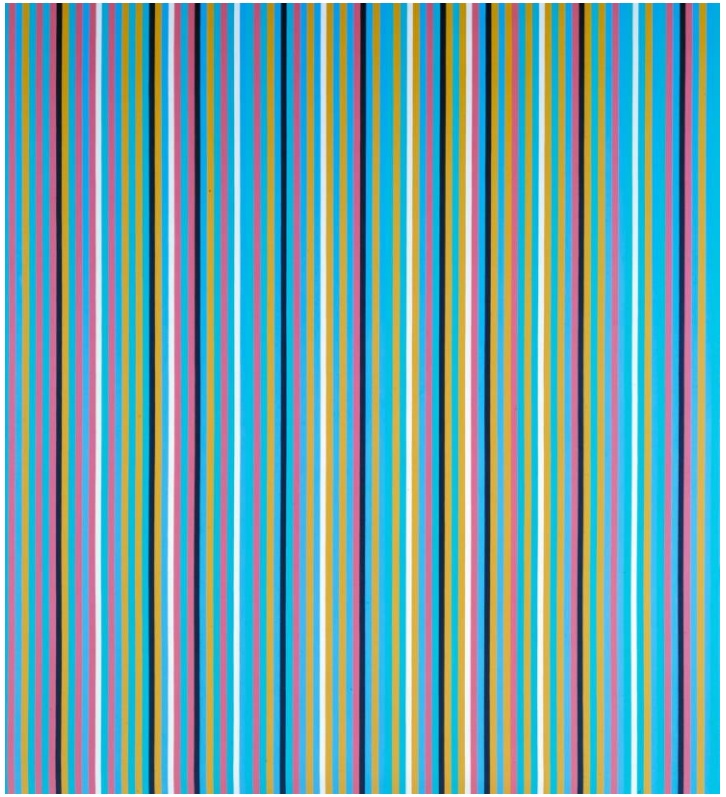
Platinum status	Cases with primary *BRCA* and *TP53* mut detected	Cases with *BRCA* reversion mut detected	*BRCA* reversion mut frequency
Sensitive	27	3 (1 also found in pre-tx)	11.1%
Resistant	27	8 (5 also found in pre-tx)	29.6%
Refractory	11	4 (1 also found in pre-tx)	36.4%

Overall reversion rate in cfDNA at progression = 15/65 (23.1%)

Lin et al (2019) Cancer Disc. 9:210

Can we identify meaningful patterns in apparent CN chaos?

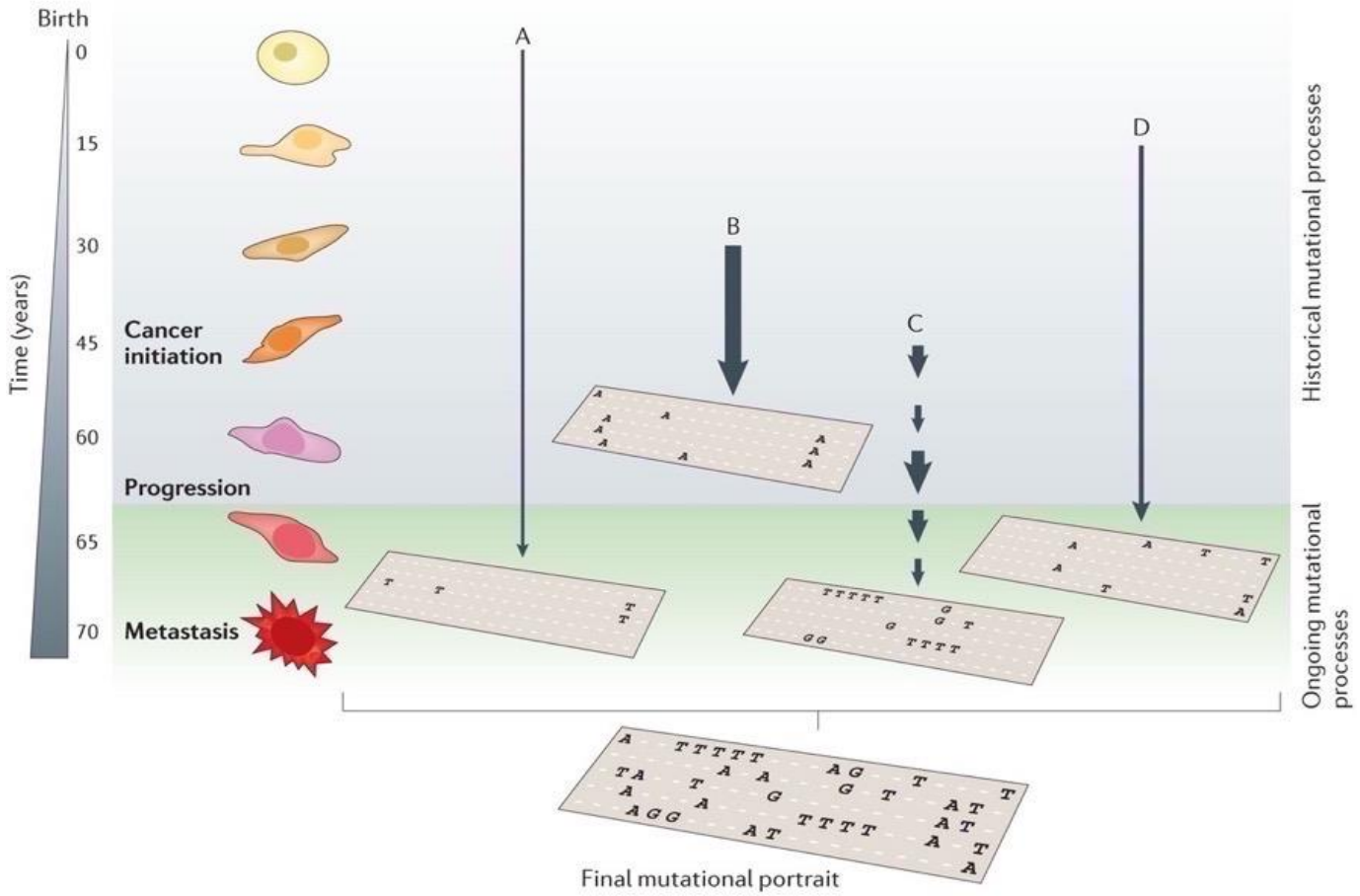




Convergance (1952) – Jackson Pollock

Archæan (1981) – Bridget Riley

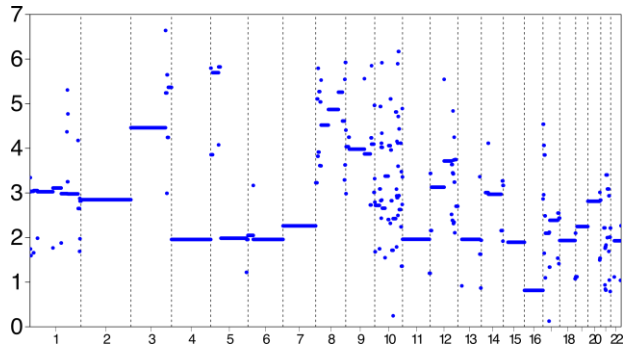
Mutational signatures



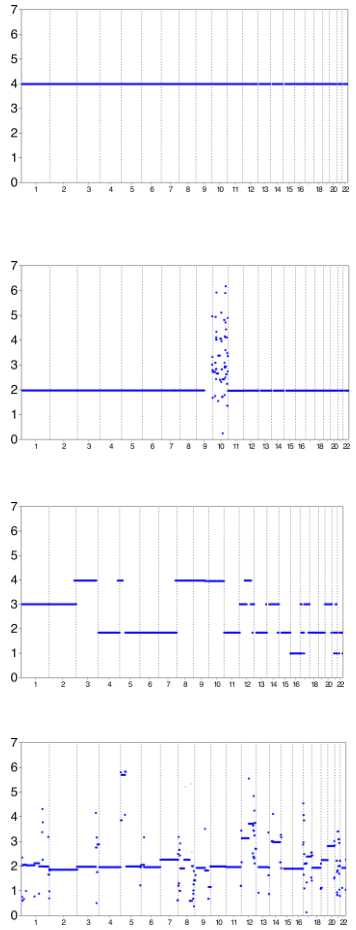
- Mutations are an *archaeological* record of exposure to mutational processes
- Signatures are the *patterns* of mutational processes
- Individual cancers have *multiple* mutational signatures

Helleday et al, Nat Rev Genet (2014) **15**: 585-98

Can we do the same with copy number?

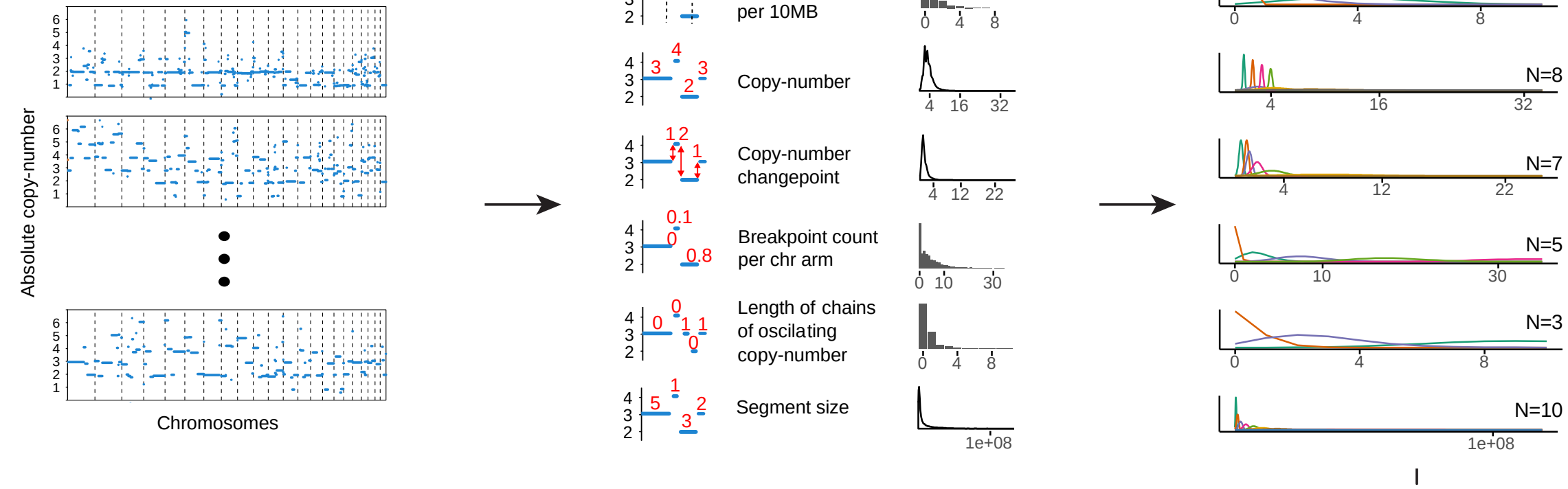


Copy-number profile



CN signature identification

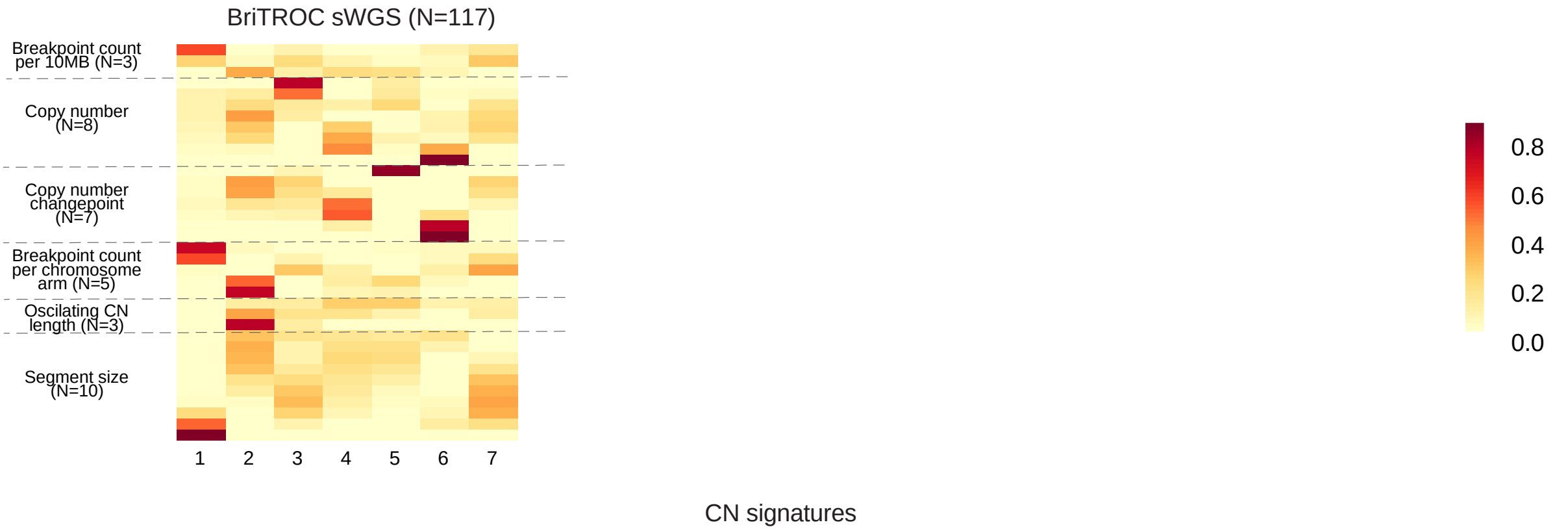
a



Macintyre, Goranova et al Nature Gen. (2018) **50**:1262-70

Are the CN signatures robust?

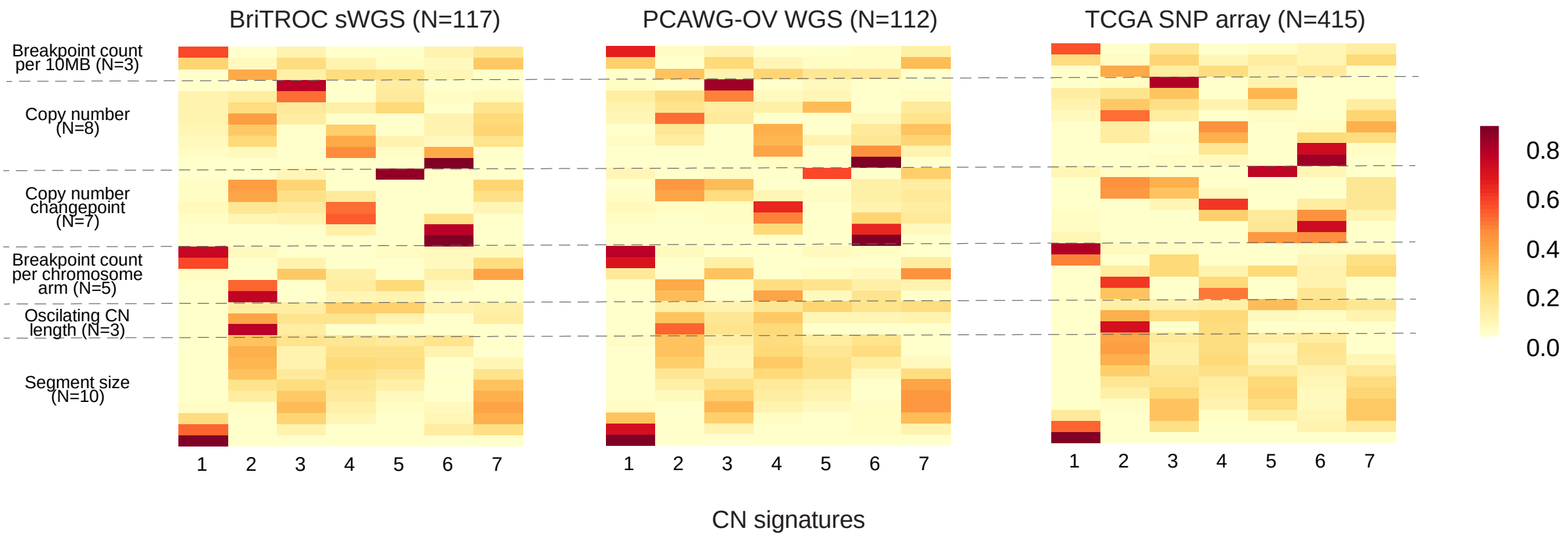
b



Macintyre, Goranova et al Nature Gen. (2018) **50**:1262-70

Are the CN signatures robust?

b

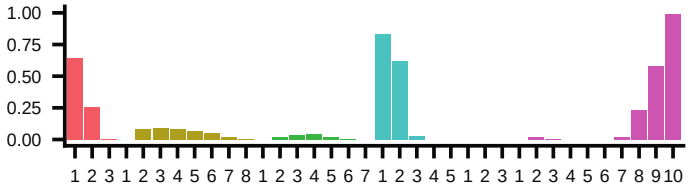


p<0.005

Macintyre, Goranova et al Nature Gen. (2018) **50**:1262-70

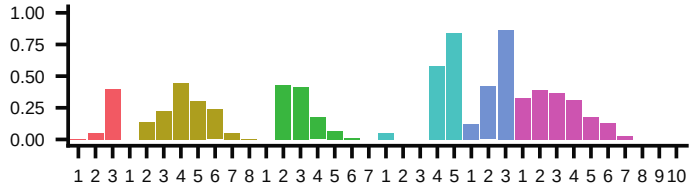
Do CN signatures reflect the underlying mutational processes?

1



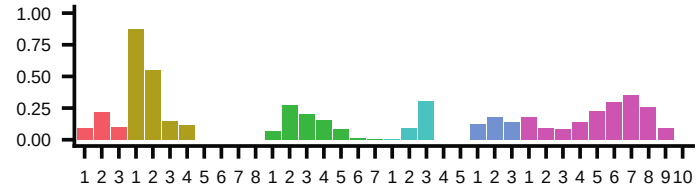
oncogenic MAPK signalling

2



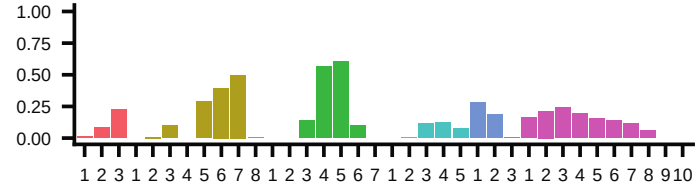
tandem duplications, CDK12 mutation

3



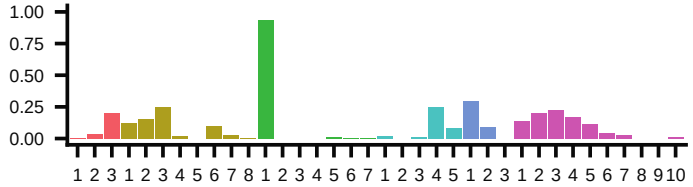
BRCA1/2HRD

4



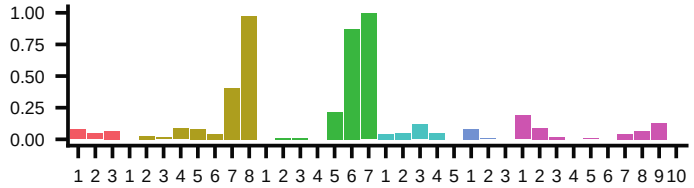
WGD
PI3K signalling

5



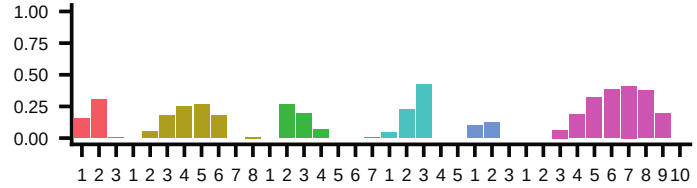
chromothripsis

6



Aberrant cell cycle (*CCNE1*)

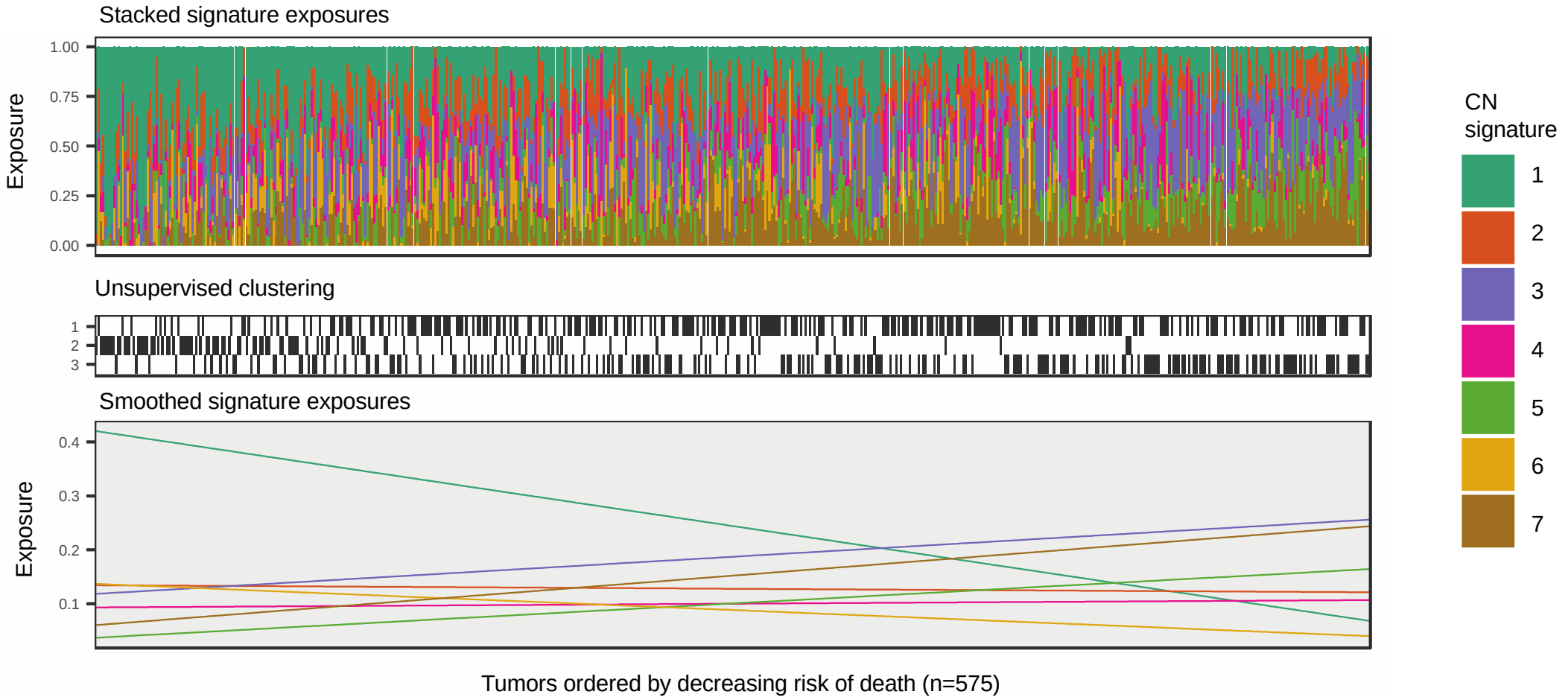
7



Non-BRCA1/2 HRD

Macintyre, Goranova et al Nature Gen. (2018) **50**:1262-70

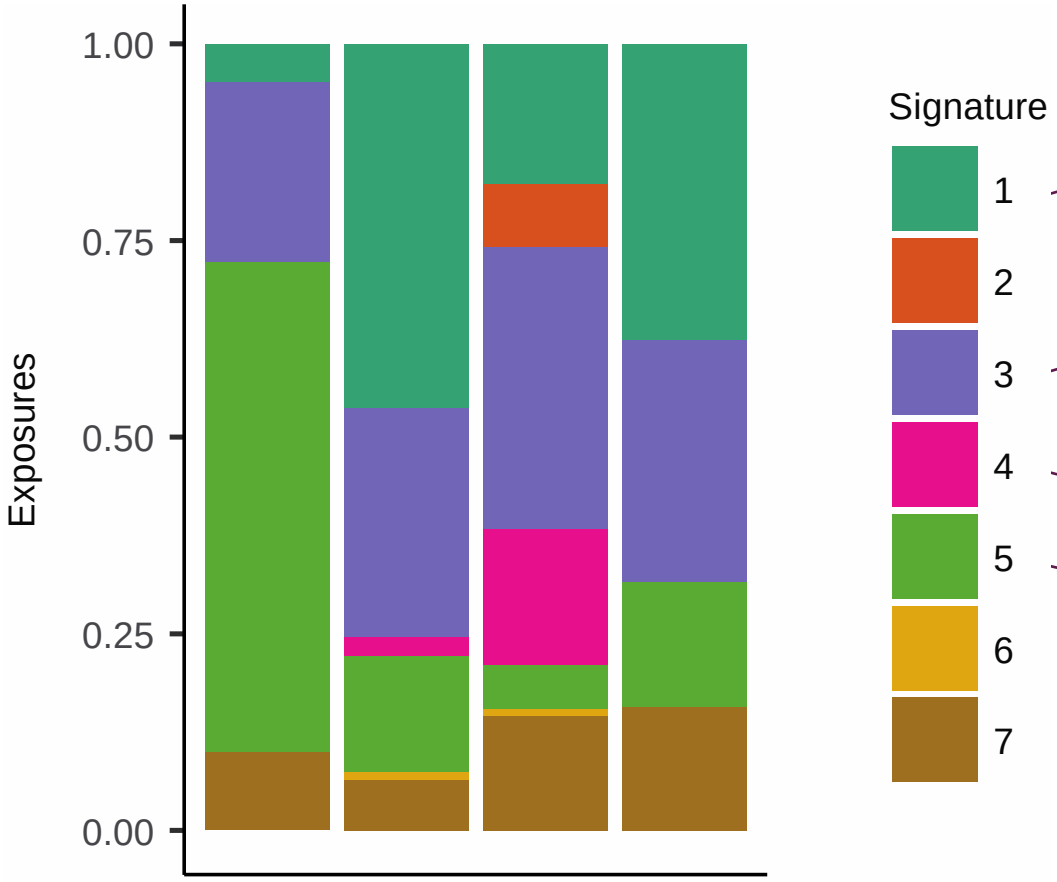
CN signatures predict survival



p=0.005 training set, p=0.03 test set

Macintyre, Goranova et al Nature Gen. (2018) **50**:1262-70

Patients have multiple signatures



BRCA2 germline mutation carriers + somatic LOH (n=4)

MAPK signalling

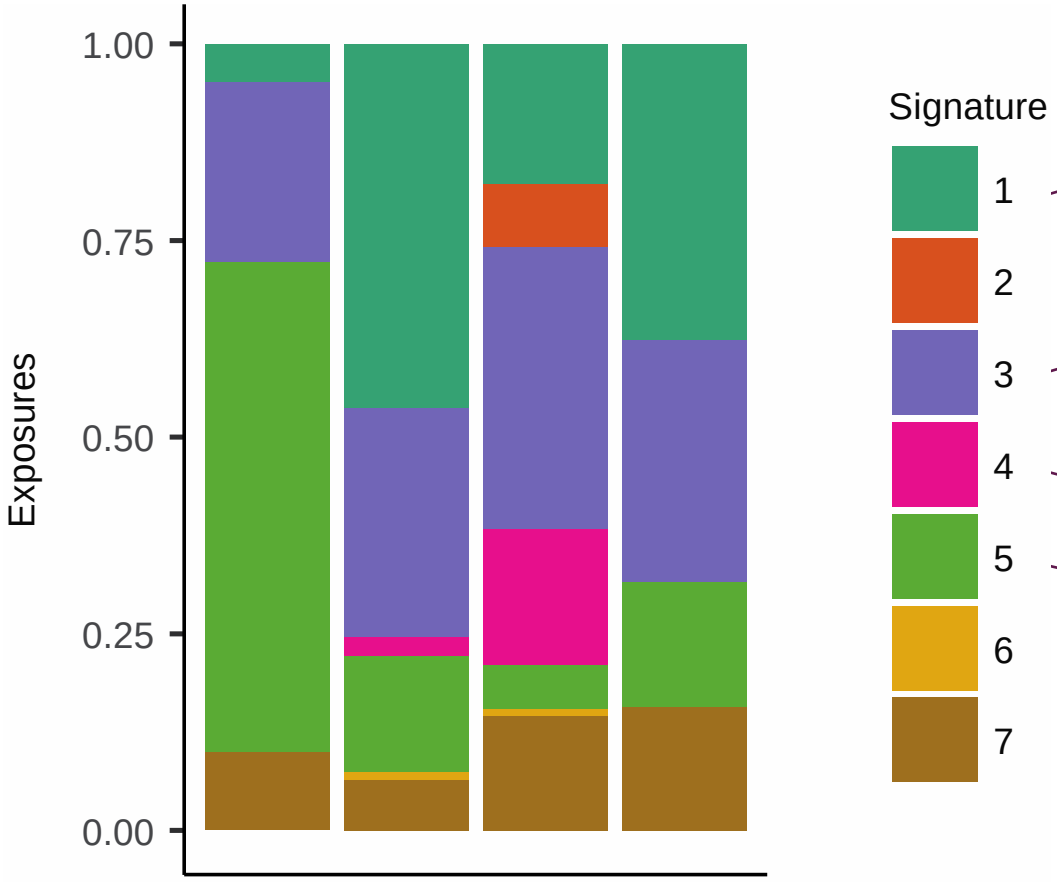
BRCA1/2 HRD N=130 (22%)

WGD PI3K

Chromothripsis

Macintyre, Goranova et al Nature Gen. (2018) **50**:1262-70

Could CN signatures predict treatment?



BRCA2 germline mutation carriers + somatic LOH (n=4)

MAPK signalling – MEK inhibitor

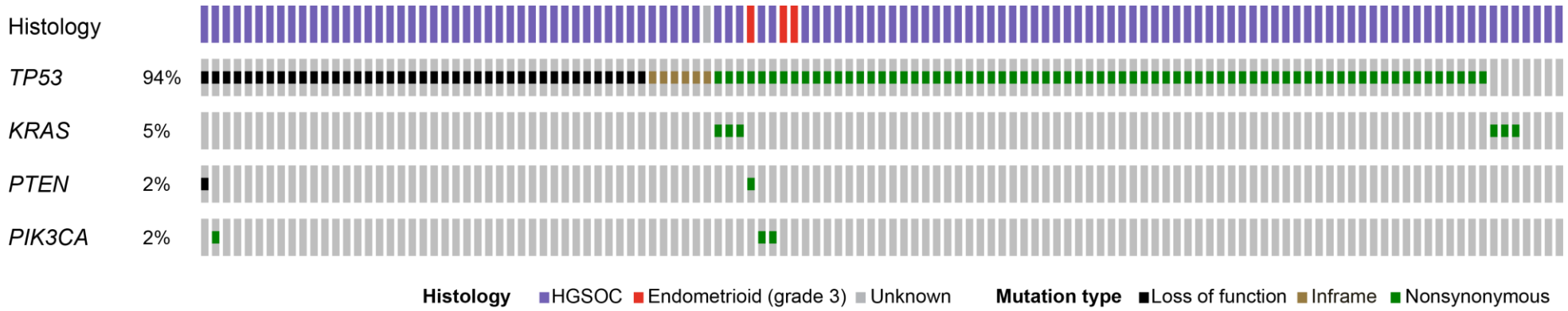
BRCA1/2 HRD – PARP inhibitor

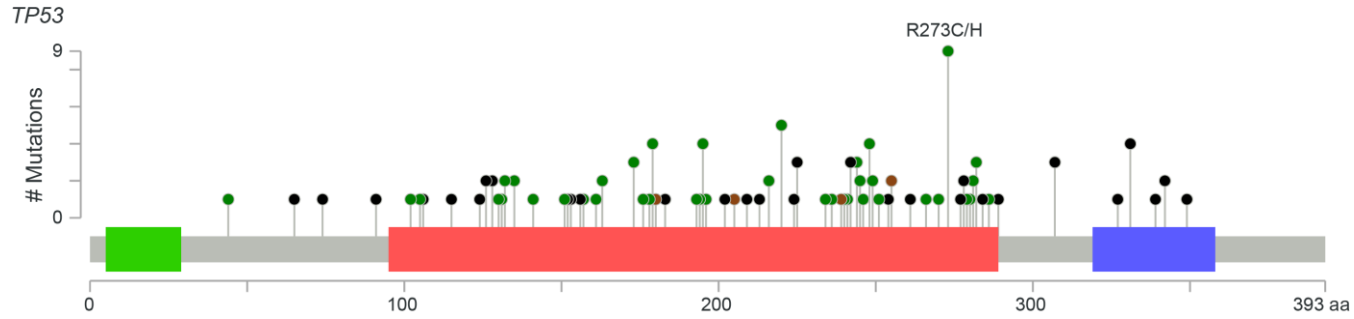
WGD PI3K – mTORC1/2 inhibitor

Chromothripsis

Macintyre, Goranova et al Nature Gen. (2018) **50**:1262-70

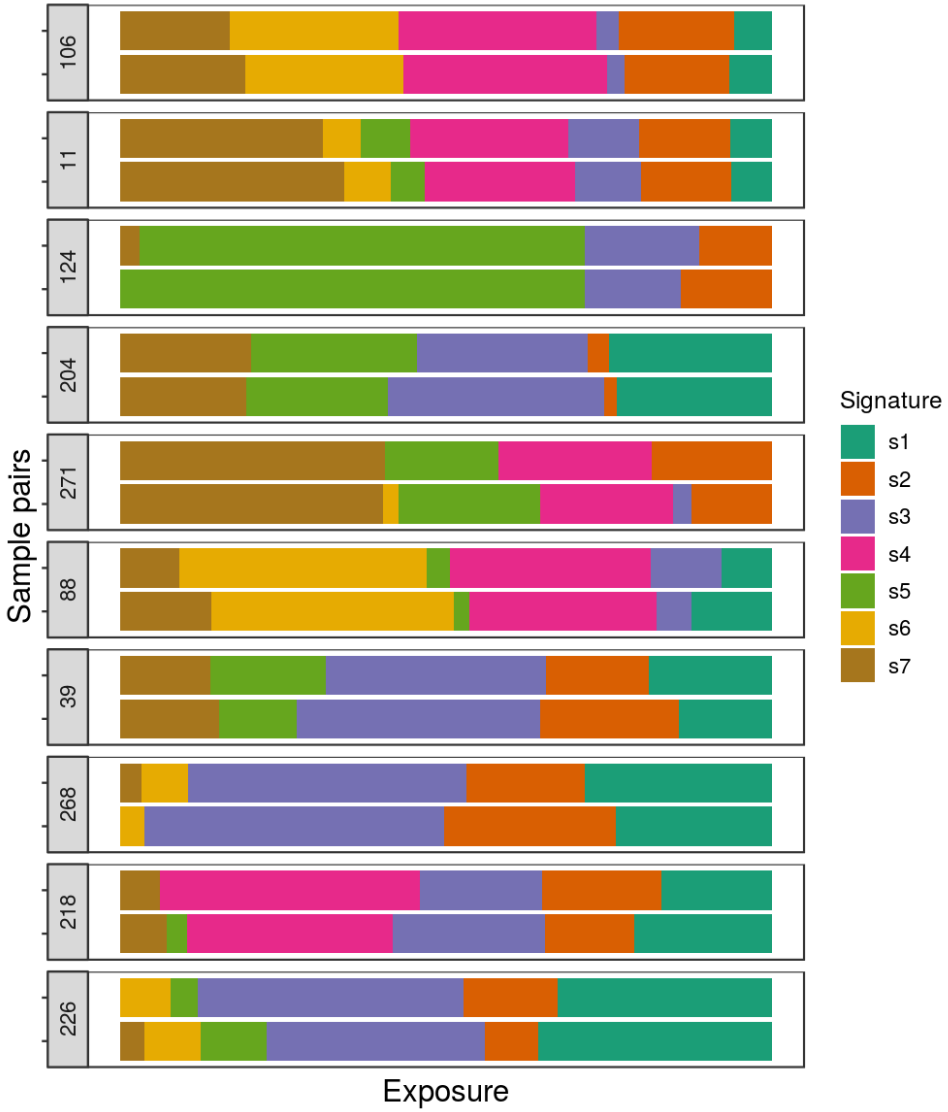
What about relapse?

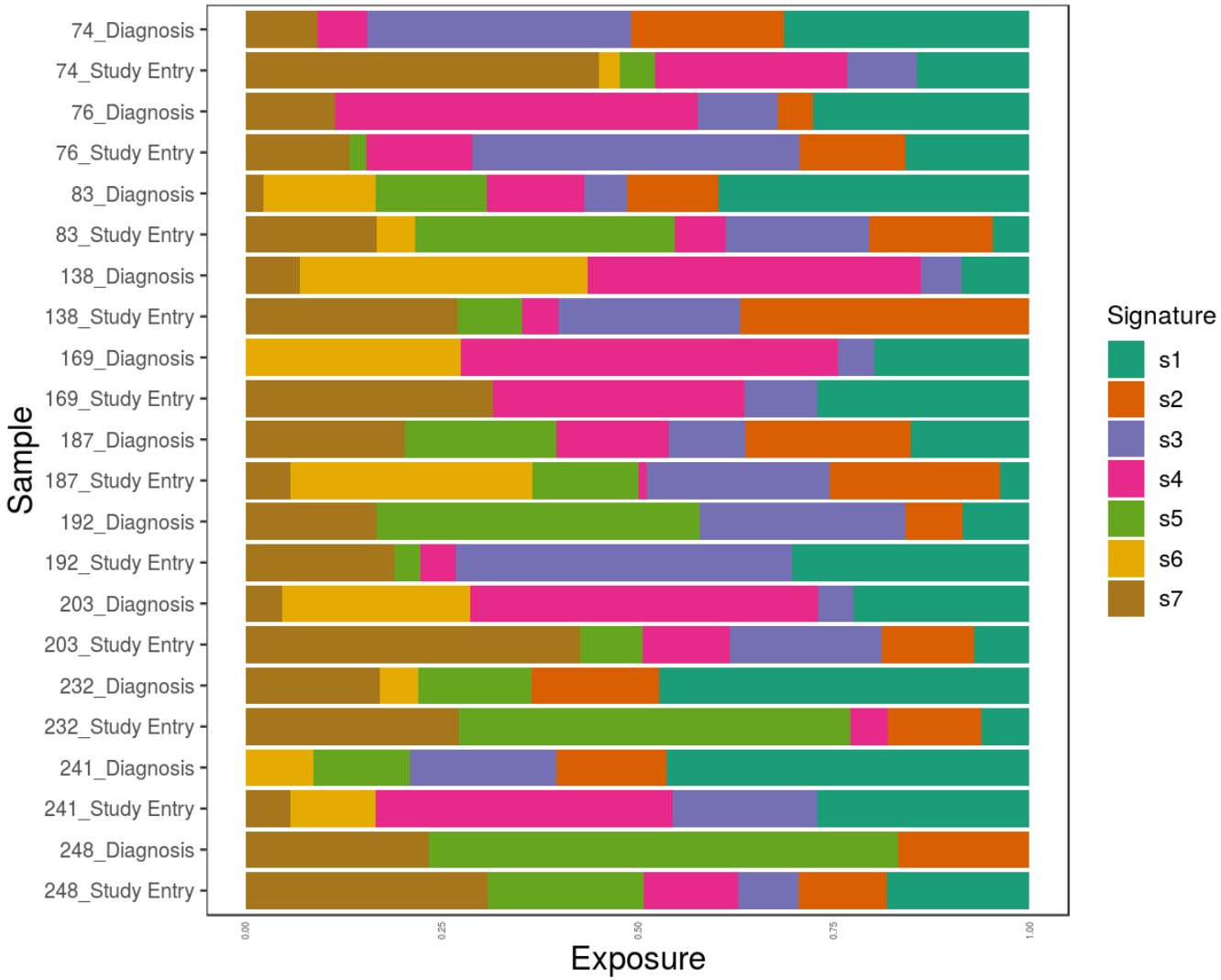




Anna Piskorz - unpublished

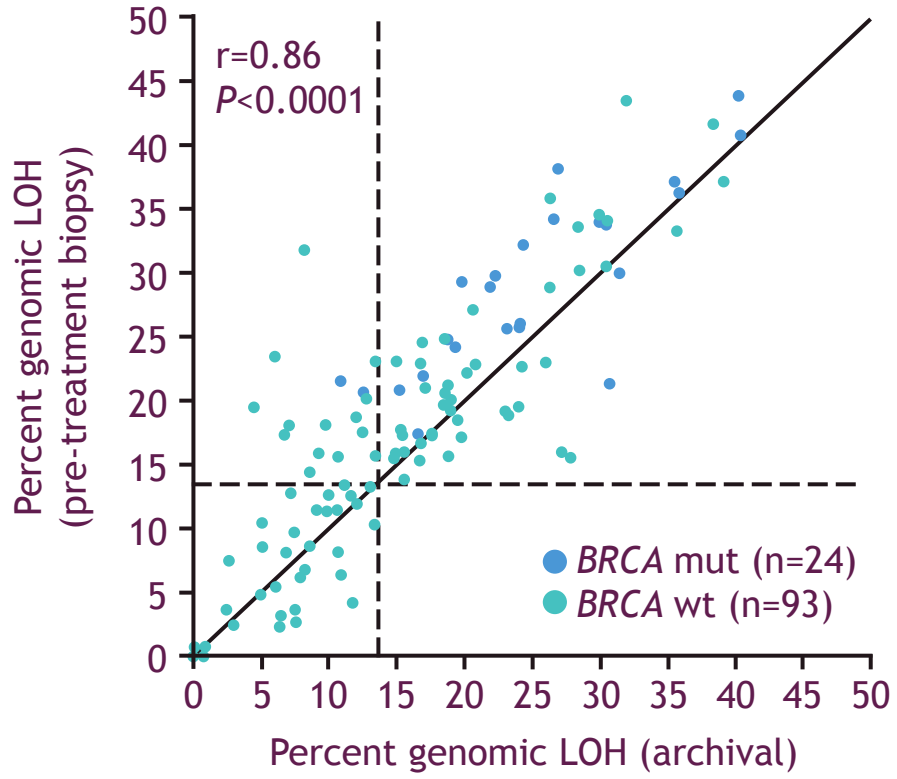
Comparison of diagnosis and relapse





Dilrini Da Silva - unpublished

Overall Similar Genomic LOH Levels Between Matched Archival Tumours and Screening Biopsies

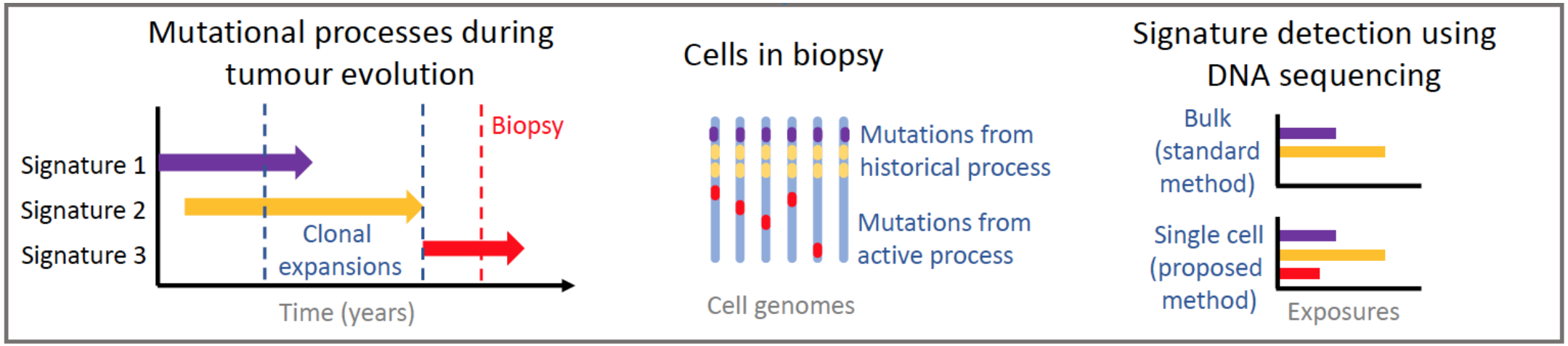


All patients (117 matched pairs)

	LOH-high archival	LOH-low archival
LOH-high screening	67	17
LOH-low screening	0	33

Swisher E et al (2017) *Lancet Oncol*. 18:75-87

Key challenges moving biology to the clinic



Conclusions

- Knowledge of tumour biology into our treatment strategies
- Trials in the rarer subtypes completely essential
- CN signatures suggest rational approaches for combination therapy
- Assessment of disease at relapse important – including methylation and cfDNA
- *Functional* assays required to assess what processes are active at any given time