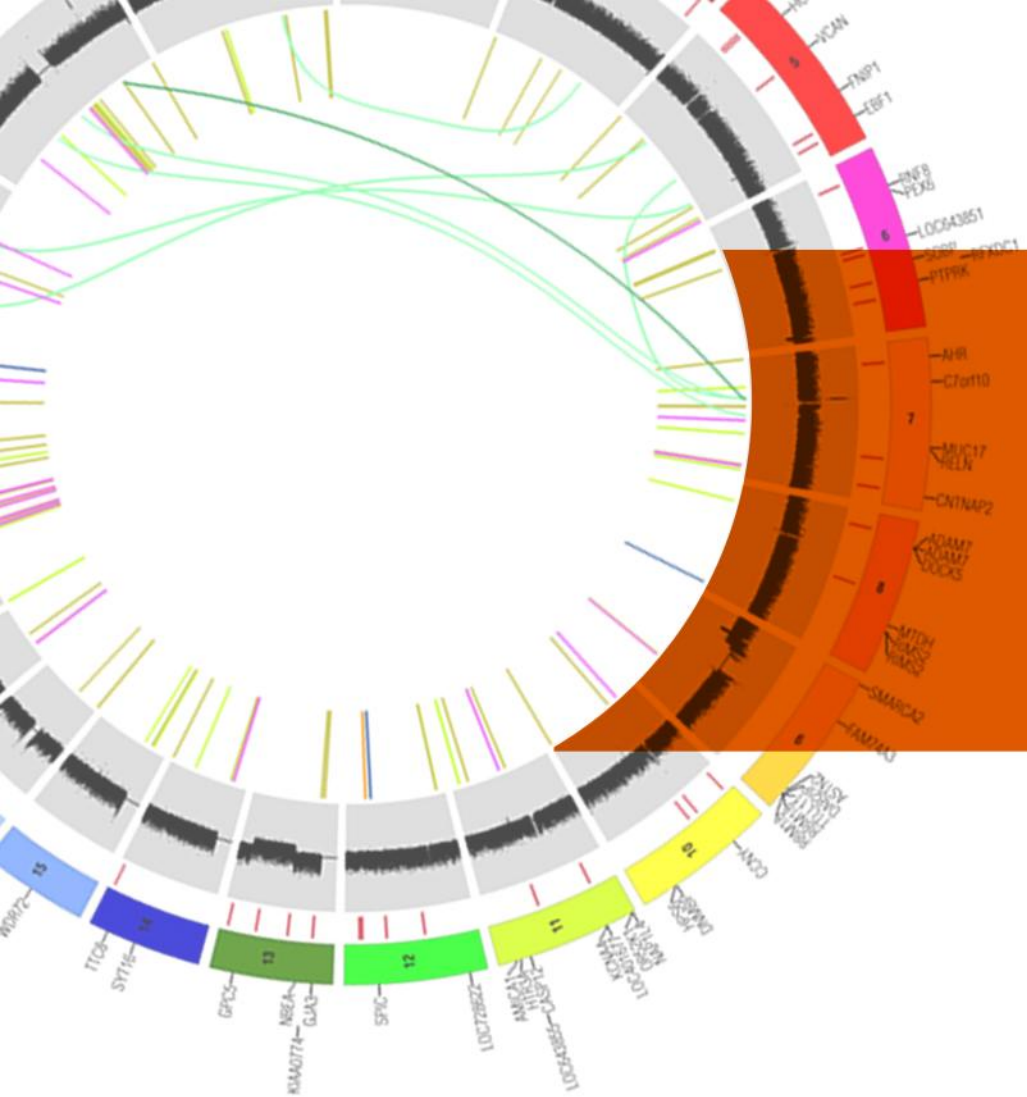


The Cancer Genome Atlas

Integrated Genomic Characterization of Endometrial Carcinoma

Endometrial Disease and Analysis Working Groups

and

The Cancer Genome Atlas Research Network

Washington

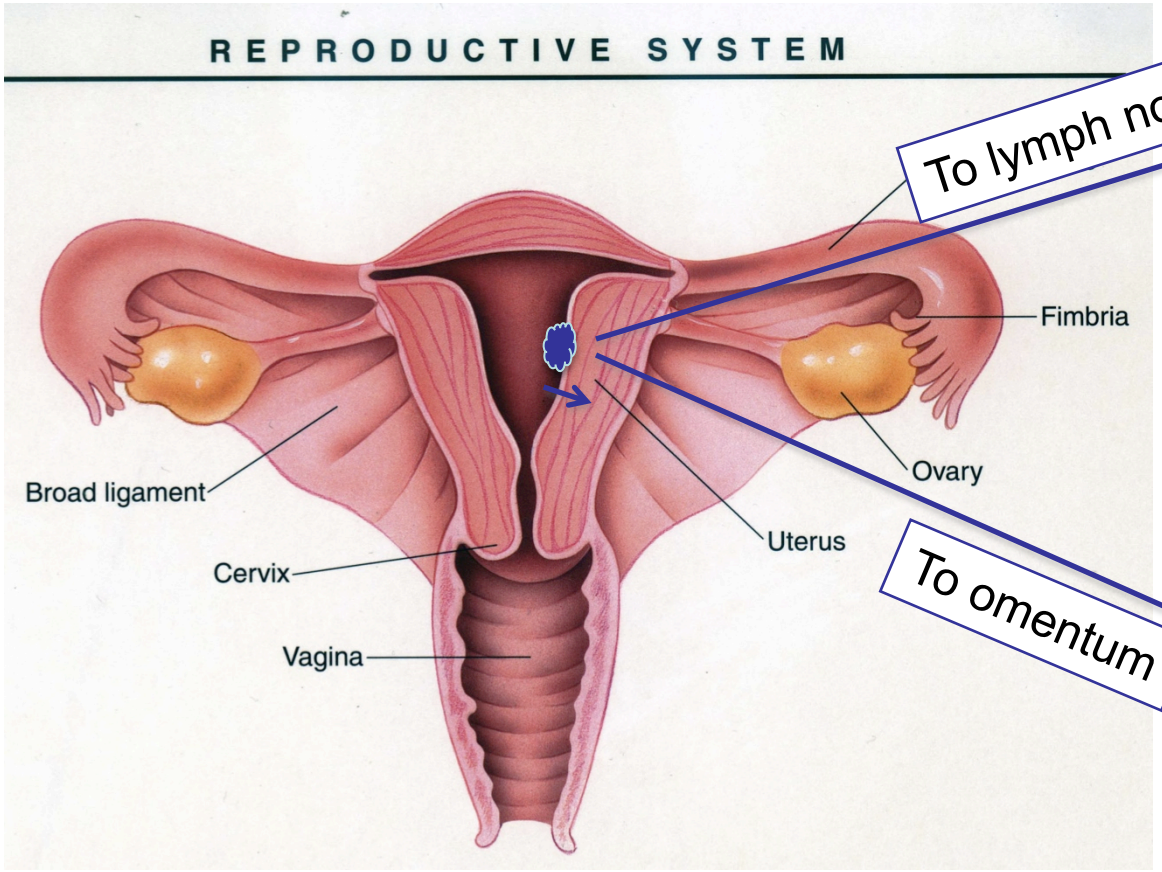

Government
Accountability
Office
Headquarters
US Army Corps
of Engineers

Washington

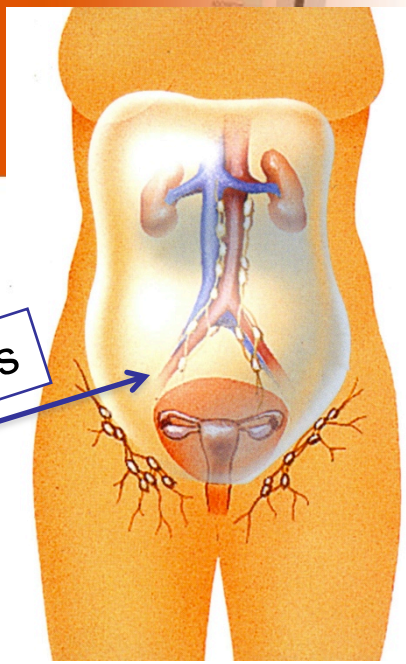

Government
Accountability
Office
Headquarters
US Army Corps
of Engineers


VRE Trains

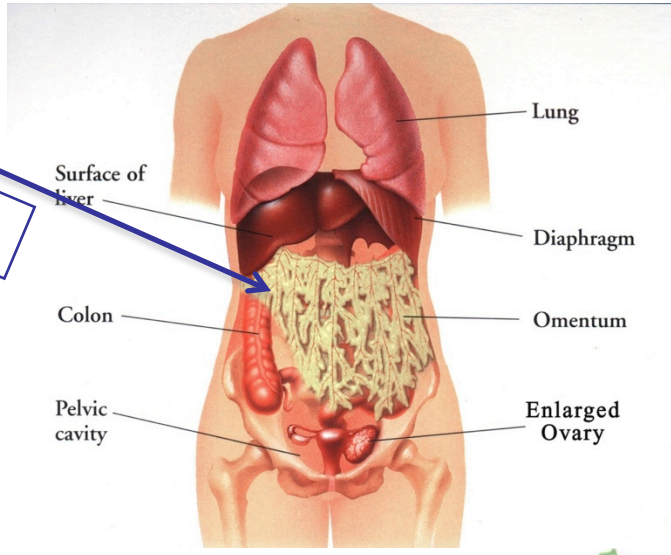
Endometrial Cancer Origins



To lymph nodes

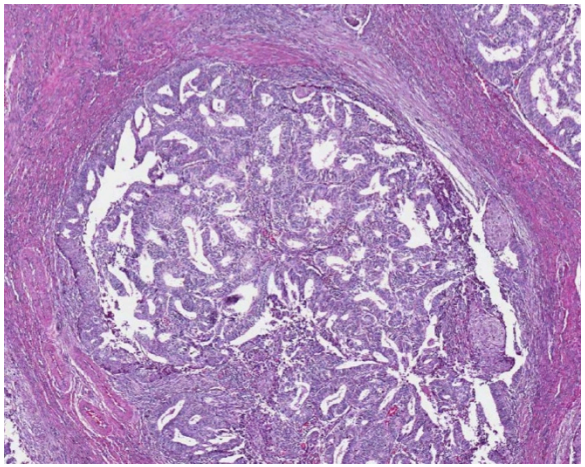


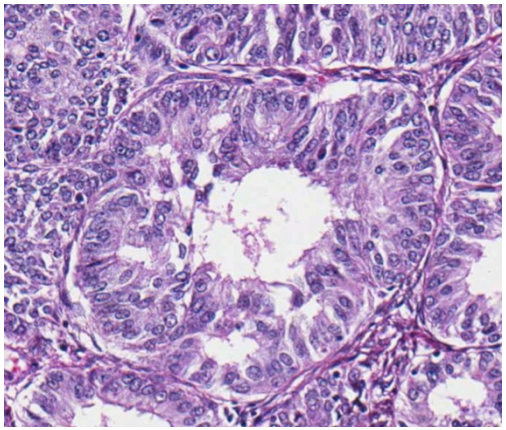
To omentum



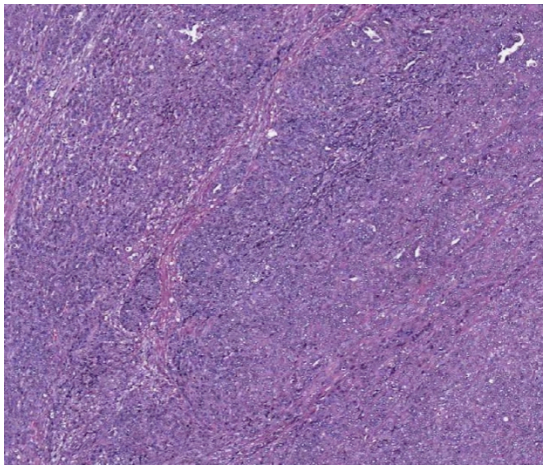
Types of Endometrial cancer

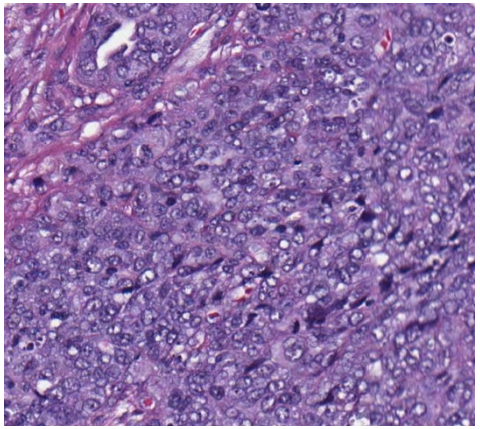
Endometrioid (low grade)





Serous (high grade)





Serous vs Endometrioid

- More solid
- Less glandular
- Higher grade nuclei
- Greater N:C ratio
- Loss of polarity

The Cancer Genome Atlas

Poor Inter-Observer Reproducibility in the Diagnosis of High-Grade Endometrial Carcinoma

C. Blake Gilks MD, Esther Oliva MD, Robert A. Soslow MD

- In press – Am J Surg Path
- In 20 of 56 (35.8%) cases [high-grade endometrial carcinoma] there was a major disagreement

TABLE 4. Intraobserver and Interobserver Reproducibility

Grading System/ Parameter	Intraobserver Reproducibility (kappa value)	Interobserver Reproducibility (kappa value)
New grade	0.8	0.76
FIGO grade (three-tiered, 1 vs 2 vs 3)	0.73	0.61
FIGO grade (two-tiered, 1 and 2 vs 3)	0.90	0.71
Binary grade	0.75	0.75
Architectural score	0.7	0.50
Nuclear grading (three-tiered)	0.66	0.33
Nuclear grading (two-tiered)	0.90	0.80
Mitotic activity (two categories)	0.75	0.50

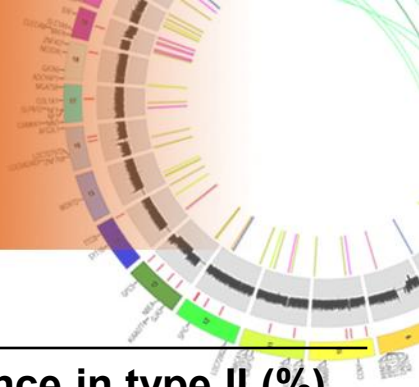
(*Am J Surg Pathol* 2005;29:295–304)

Endometrial Classification

- Type I (85%)
  - Endometrioid, prototype
  - Younger
  - Obese
  - Unopposed estrogen
  - Hyperplasia precursor
  - Usually confined to the uterus
  - Favorable outcome

- Type II (15%)
  - Serous, prototype
  - Older
  - Thin
  - Atrophic endometrium or endometrial polyp as precursor
  - More often metastatic at diagnosis
  - Worse prognosis

Mutation Spectrum



Alteration	Prevalence in type I (%)	Prevalence in type II (%)
PIK3CA mutation	~30	~20
Exon 9	7–15.5	0
Exon 20	10–34	21
PIK3CA amplification	2–14	46
KRAS2 mutation	11–26	2
AKT mutation	3	0
PTEN loss of function	83	5
Microsatellite instability	20–45	0–5
Nuclear accumulation of β-catenin	18–47	0
E-cadherin loss	5–50	62–87
TP53 mutation	~20	~90
Loss of function of p16	8	45
HER2 overexpression	3–10	32
HER2 amplification	1	17
FGFR2 mutations	12–16	1

Abbreviations: PI3K, phosphatidylinositol 3 kinase; PTEN, phosphatase and tensin homolog deleted on chromosome 10.

Dedes et al. Emerging therapeutic targets in endometrial cancer. *Nature Reviews Clinical Oncology* , 8:261-271, 2011.

Early stage vs late stage outcomes

Mixed epithelial carcinoma	24	3	49	3
Serous carcinoma	94	11	195	12
Tumor type				
Endometrioid adenocarcinoma	727	82	1,297	80
2009 FIGO surgical stage				
IA	1,128	69.6	604	68.6
IB	204	12.6	110	12.5
II	65	4.0	34	3.9
IIIA	42	2.6	22	2.5
IIIC1	77	4.8	40	4.5
IIIC2	66	4.1	43	4.9
IVB	39	2.4	28	3.2

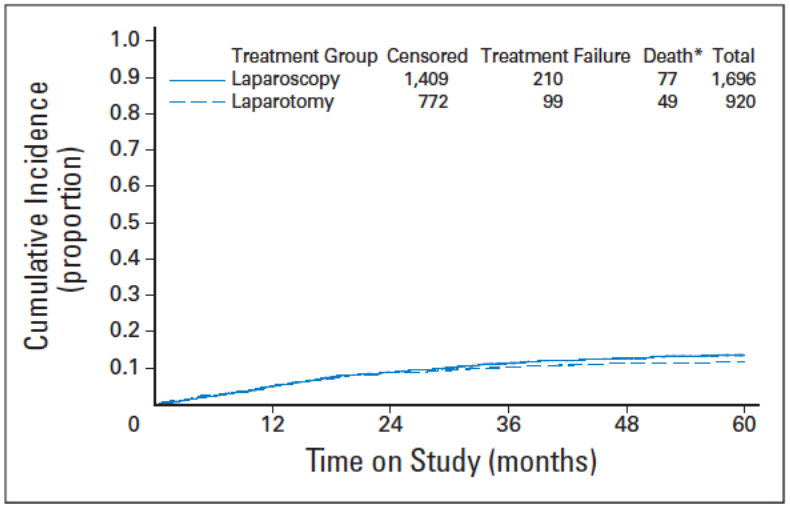
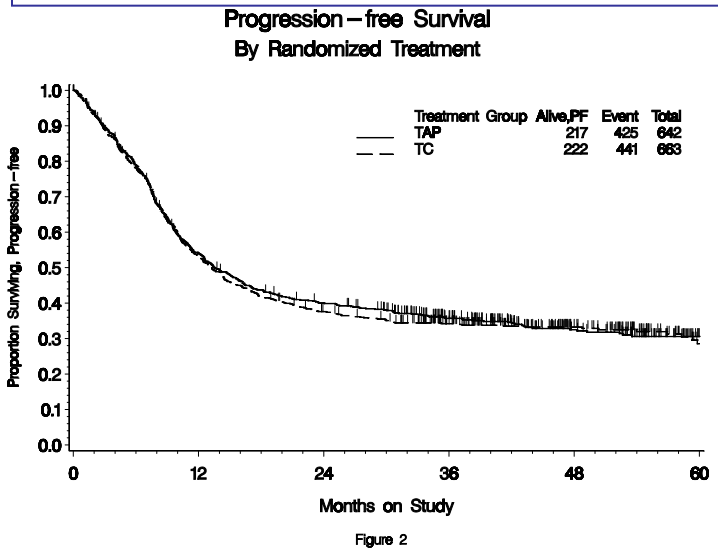


Fig 2. Cumulative incidence of recurrence by randomly assigned treatment group. (*) Deaths prior to recurrence.

J Clin Oncol 30:695-700. © 2012

Endometrioid, grade 1	182	89	13.9	93	14.0
Endometrioid, grade 2	345	161	25.1	184	27.8
Endometrioid, grade 3	272	127	19.8	145	21.9
Serous	258	136	21.2	122	18.4
Mixed Epithelial	117	55	8.6	62	9.4
III	551	273	42.5	278	41.9
IV	405	206	32.1	199	30.0
Recurrent/Progression	349	163	25.4	186	28.1



GOG-209, unpublished data, courtesy of D. Miller

Endometrial Tissue Requirements

- Primary, newly diagnosed, untreated, endometrial cancer
- Tissue specimen from the endometrium or uterus
- One of three general histologic subtypes as designated by DWG
  - Grade 1 or 2 endometrioid, grade 3 endometrioid, serous

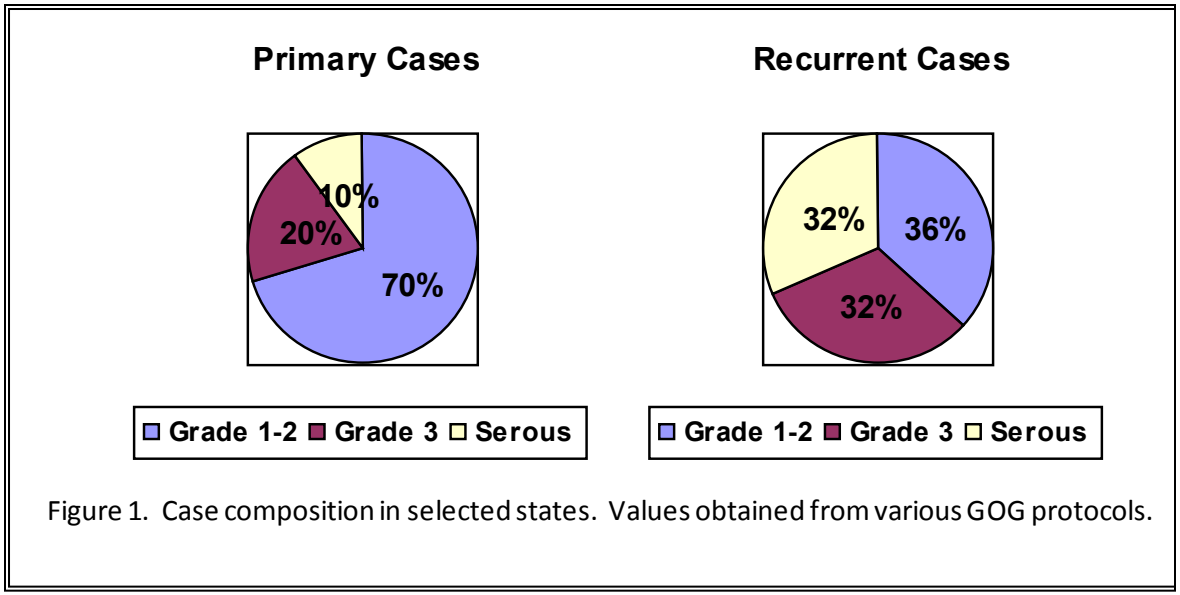


Figure 1. Case composition in selected states. Values obtained from various GOG protocols.

Sample Characteristics

Cohort	Total
Number of patients	373
Age	
Mean, years (STD)	63 (11)
Range	31-90
Recurrent Disease	
Yes	72 (19.3%)
No	279 (74.8%)
Unknown	22 (5.9%)
Vital Status	
Alive	332 (89%)
Dead	39 (10.5%)
Unknown	2 (0.5%)

Stage	EndoGr1	EndoGr2	EndoGr3	MixedGr3	SerousGr3	Total
Stage I	78 (89%)	83 (79%)	70 (63%)	6 (46%)	17 (32%)	254 (69%)
Stage II	3 (3%)	9 (9%)	6 (5%)	2 (15%)	5 (9%)	25 (7%)
Stage III	7 (8%)	12 (11%)	26 (23%)	4 (31%)	25 (47%)	74 (20%)
Stage IV	(0%)	1 (1%)	9 (8%)	1 (8%)	6 (11%)	17 (5%)
Total	88 (100%)	105 (100%)	111 (100%)	13 (100%)	53 (100%)	370 (100%)

Data summary

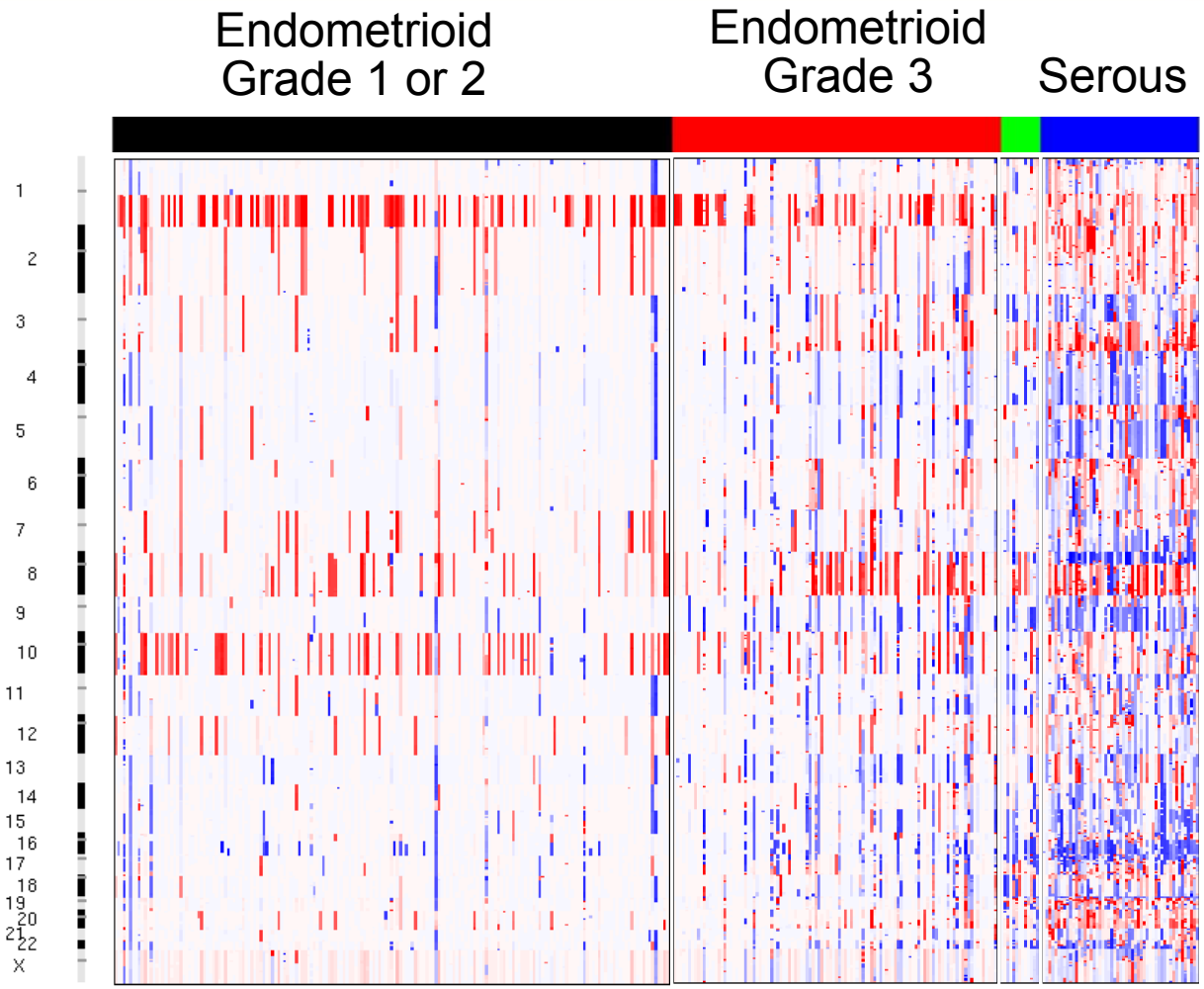
Assay	Number of endometrial patient specimens
Exome sequencing	248 pairs
Whole genome sequencing	107 pairs
RNA sequencing	333
miRNA sequencing	367
DNA methylation (Infinium HM450)	256
DNA methylation (Infinium HM27)	117
DNA copy number (Affymetrix SNP6.0)	363 pairs
Reverse phase protein arrays	293

DATA

CANCERGENOME.NIH.GOV

Somatic Copy Number Alterations

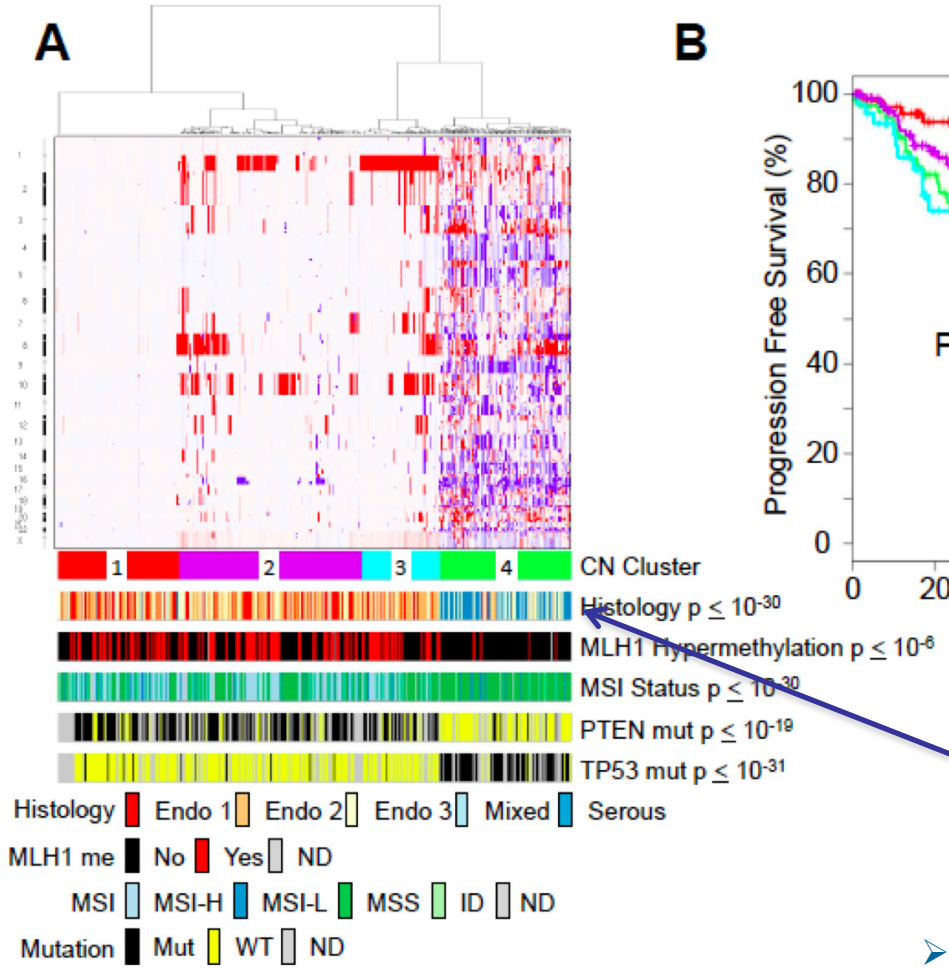
More genomic instability as tumors become less differentiated

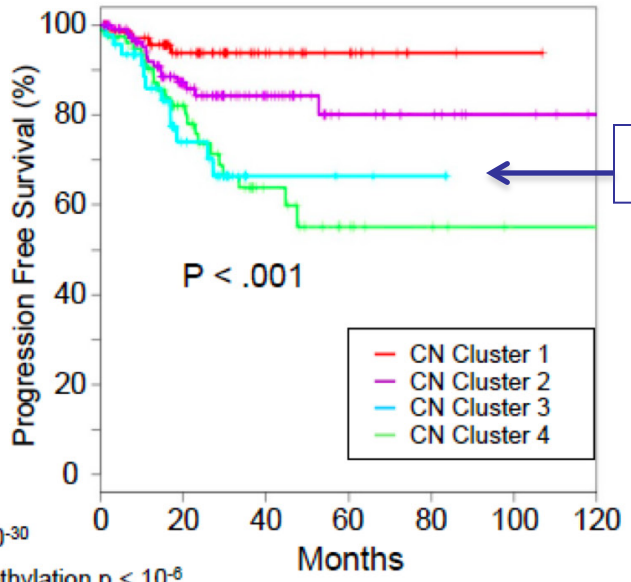


- **Andrew Cherniack, Broad**

Loss — Gain

Copy number alteration clusters





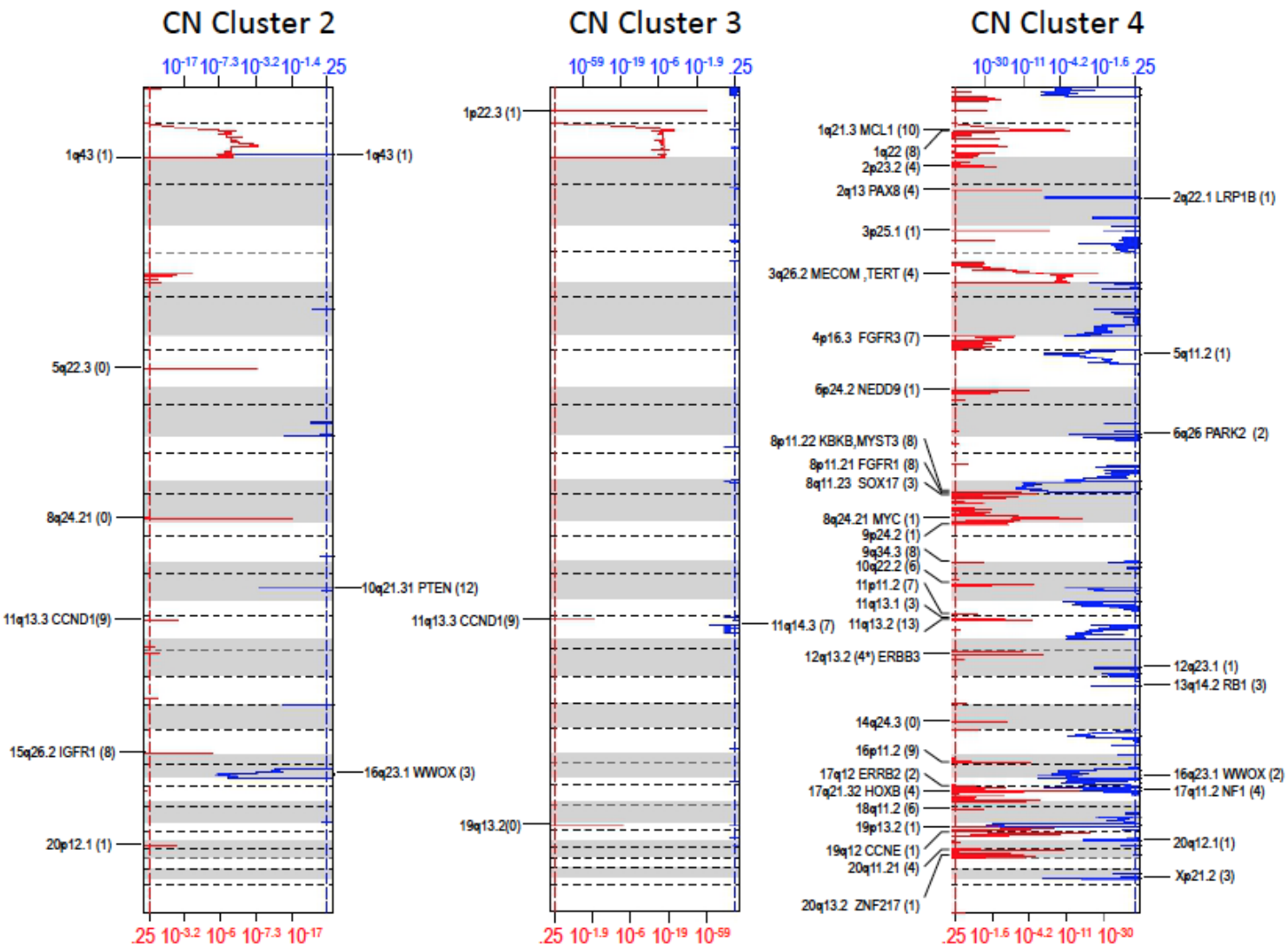
1q amplification

24% of high-grade endometrioid tumors cluster with serous tumors (**serous-like**)

- **Andrew Cherniack, Broad**

GISTIC focal peaks

CN Cluster 1



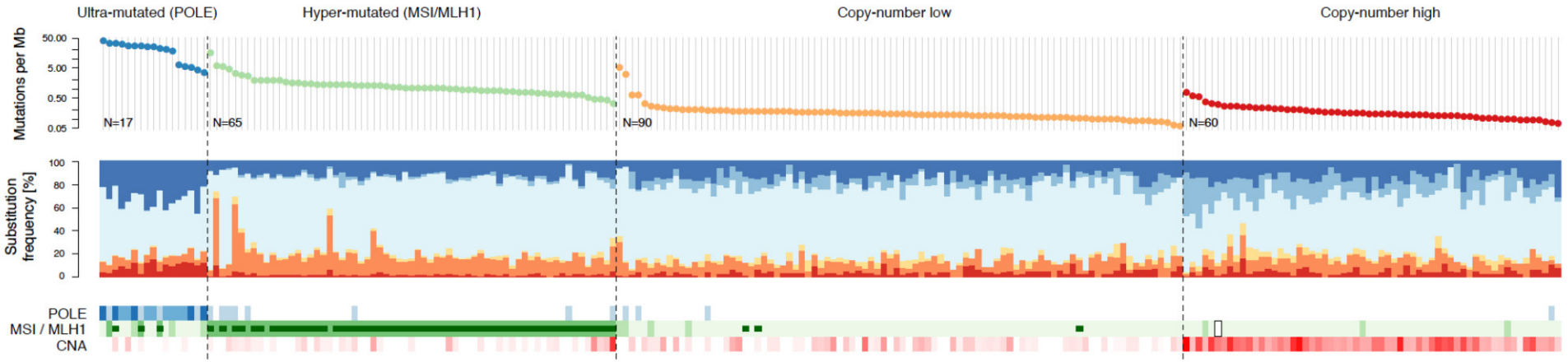
Mutations in select genes

- PTEN mutations are uncommon in Serous cases and very common in low grade Endometrioid cases
- TP53 mutations are uncommon in low grade Endometrioid cases and very common in serous cases
- PIK3CA mutations are distributed across histology and grade
- Higher frequencies than previous reports may be due to more comprehensive sequencing methods

HistologyGrade	PTEN	TP53	PIK3CA	Total
EndoGr1	62 (0.83)	3 (0.04)	43 (0.57)	75
EndoGr2	62 (0.82)	9 (0.12)	38 (0.5)	76
EndoGr3	35 (0.71)	17 (0.35)	30 (0.61)	49
SerousGr3	1 (0.02)	39 (0.89)	19 (0.43)	44
Total	**160 (0.66)**	**68 (0.28)**	**130 (0.53)**	**244**

- **Cyriac Kandoth and Li Ding, WashU**

Mutation spectrum



MSS, Few SCNA, very high mutation rate

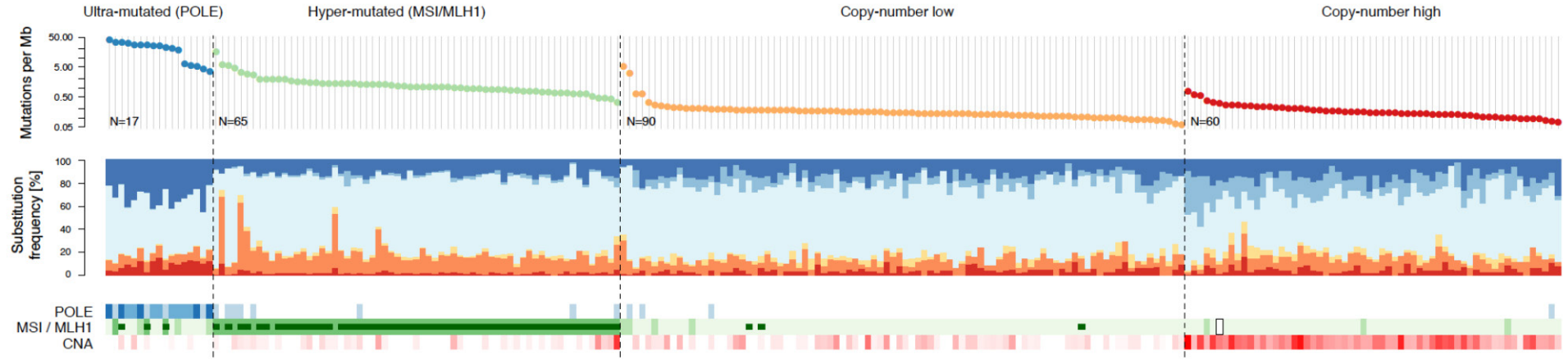
MSI, MLH1 meth, Few SCNA, high mutation rate

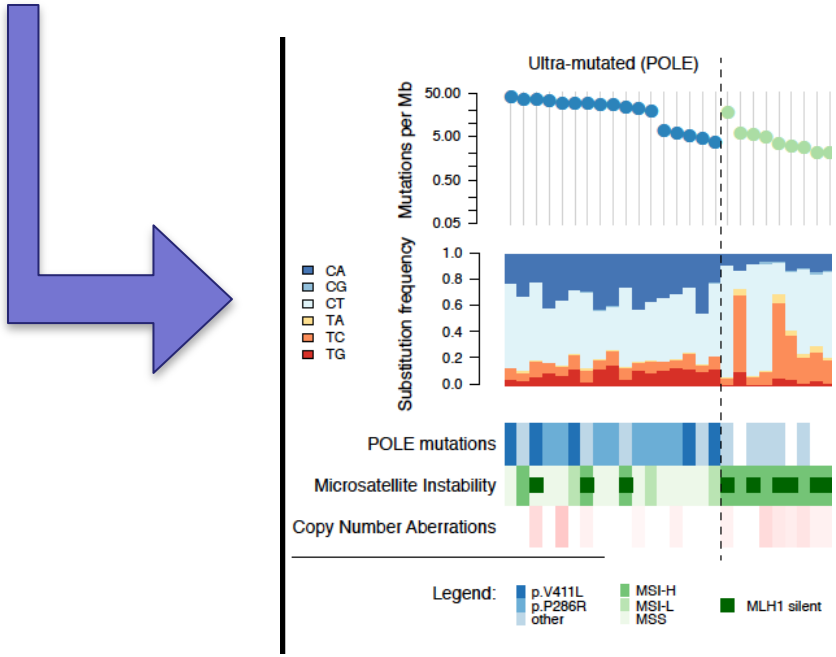
MSS, Few SCNA, Low mutation rate

MSS, Many SCNA, Low mutation rate

- **Cyriac Kandoth and Li Ding, WashU**
- **Niki Schultz, Nils Weinhold, MSKCC**

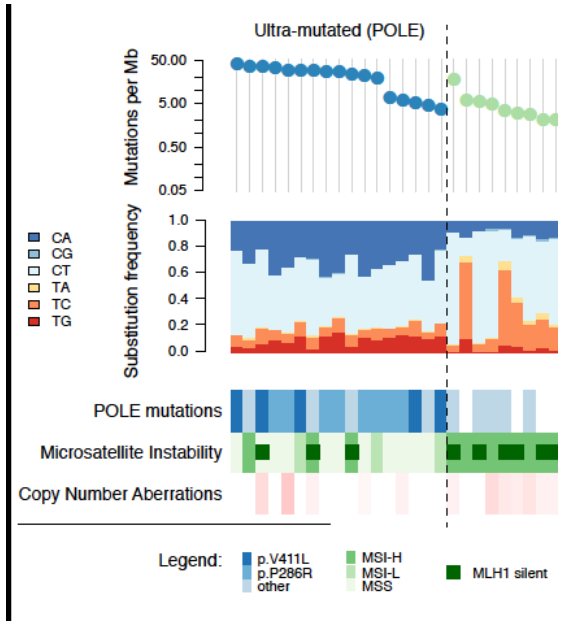
Ultramutator spectrum

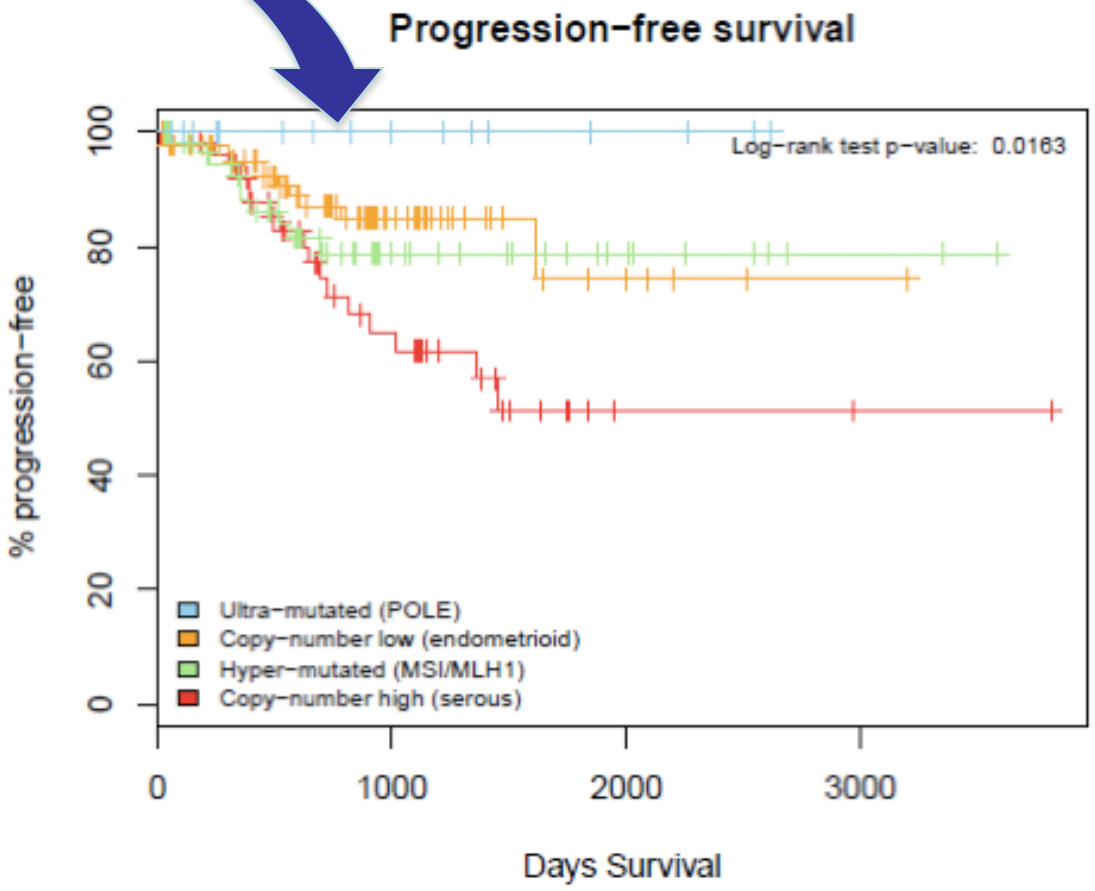




MSS, Few SCNA, very high mutation rate, different mutation spectrum (excess transversions), Universal POLE mutations, 13 of 17 (76%) with hotspot mutations, similar findings seen in CRC

Progression free survival



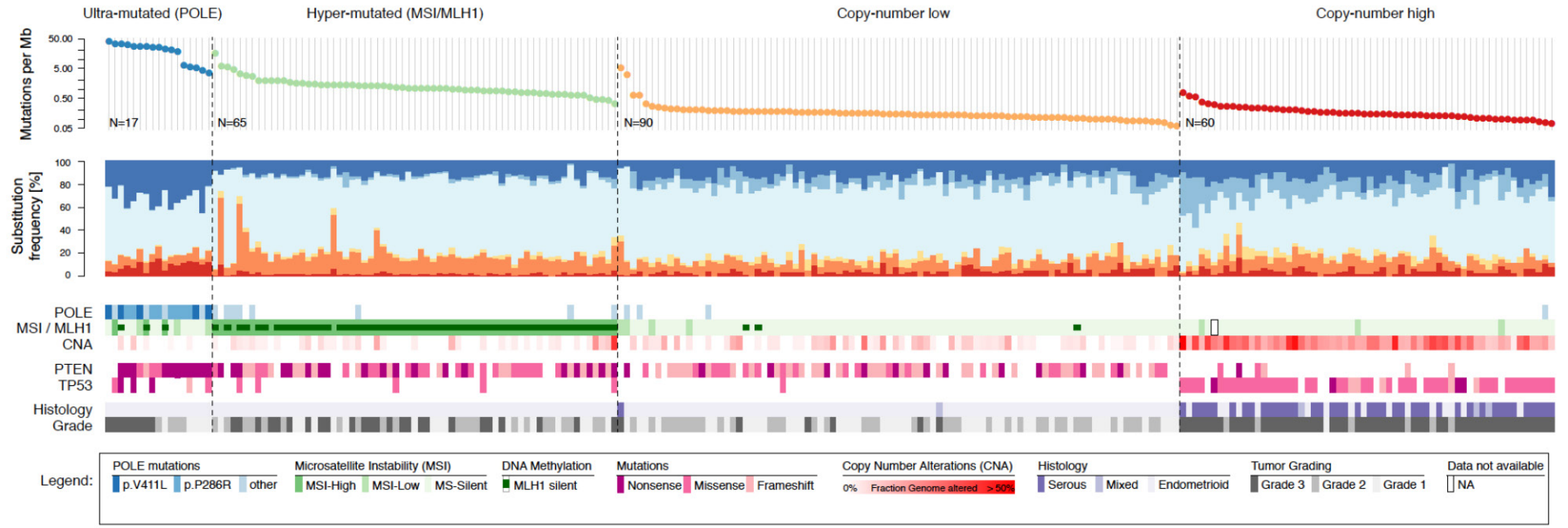


Serous – poorest PFS

No difference between MSI and MSS groups

No events in small POLE group

Mutation spectrum



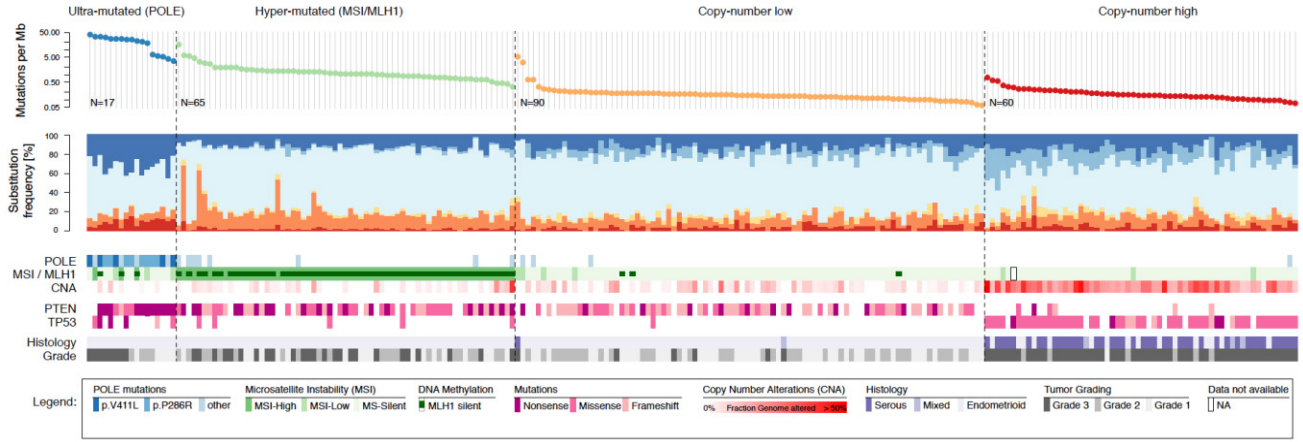
All endometrioid, PTEN mutations, few TP53 mutations

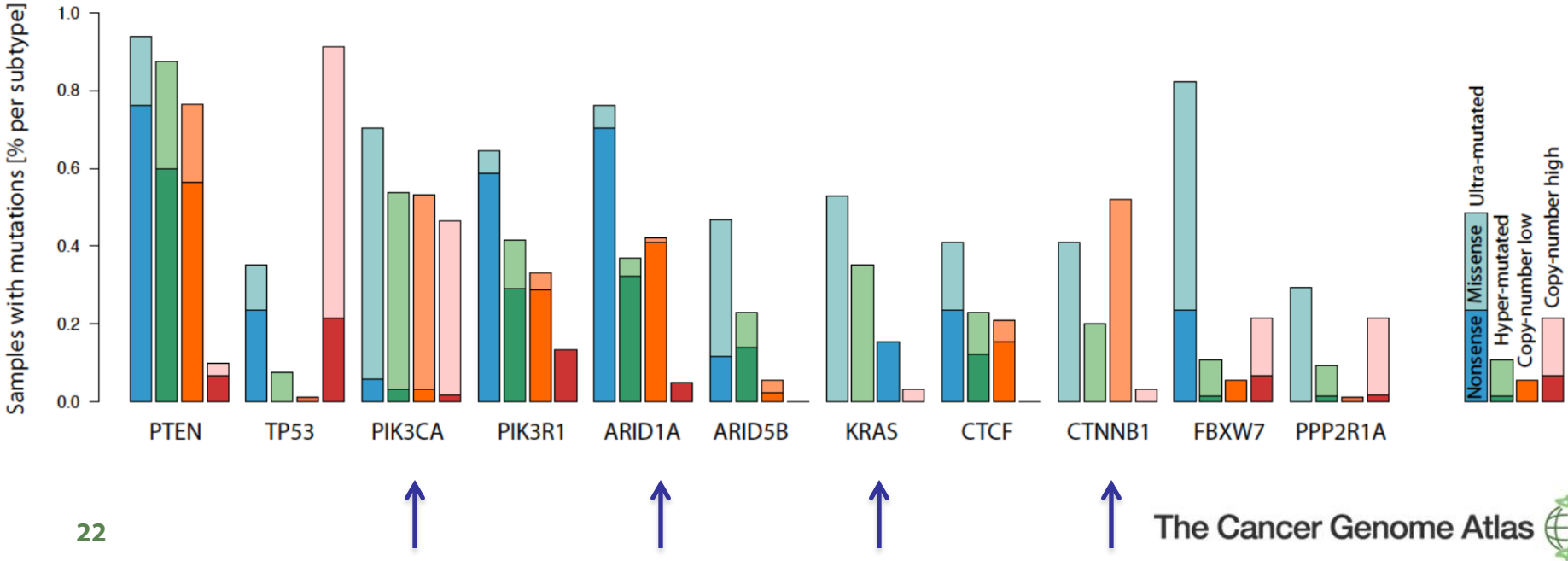
All endometrioid, PTEN mutations, no TP53 mutations

TP53 mutations, few PTEN mutations, high grade tumors, serous and some endometrioid

- **Cyriac Kandoth and Li Ding, WashU**
- **Niki Schultz, Nils Weinhold, MSKCC**

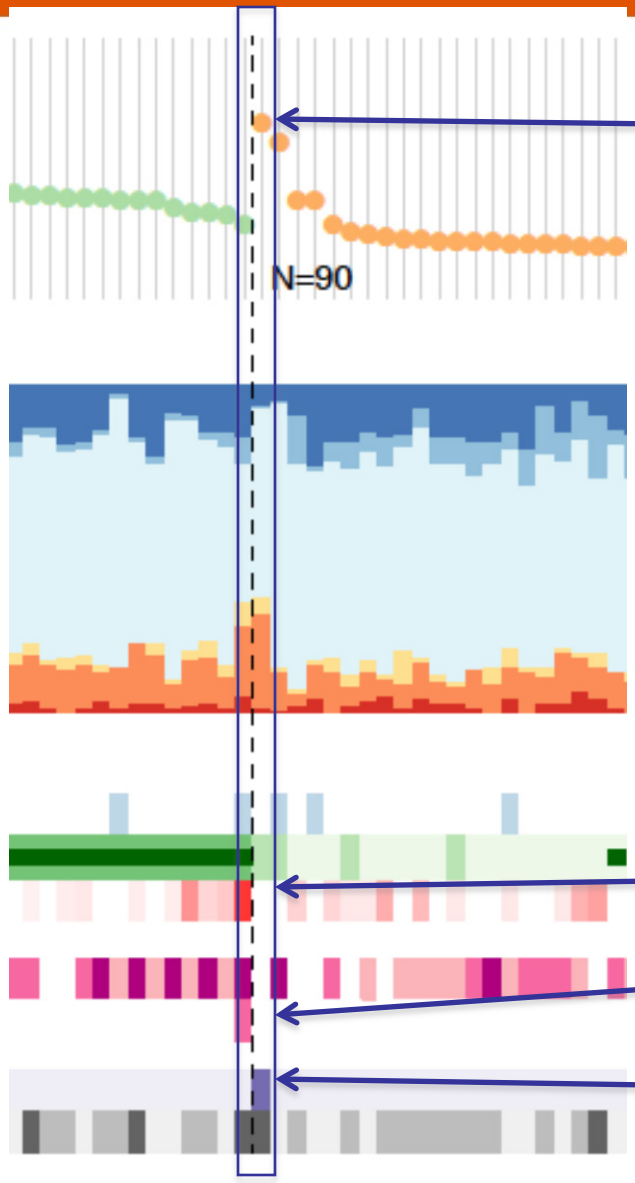
SMGs





The Cancer Genome Atlas

Unusual serous case



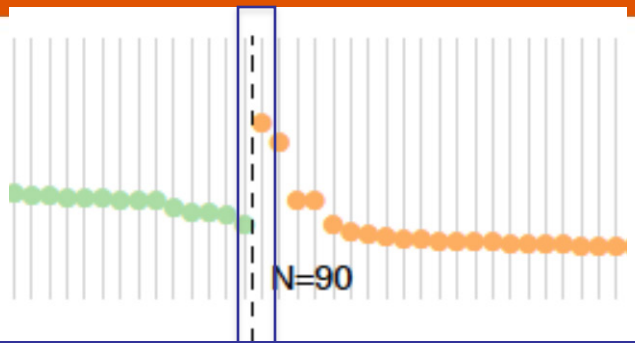
High mutation rate

No SCNA

No TP53 mutation

Serous histology

cBio patient portal



- Serous case, no TP53 mutation, no SCNA, high mutation rate
- Doesn't make sense

Uterine Corpus Endometrioid Carcinoma (TCGA, Provisional), Serous, Stage I, Grade 3

Living (29 months), DiseaseFree (29 months)

Summary | Mutations | Copy Number Alterations | Pathology Report

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y

CNA

MUT

0.1%

1308

Mutations of interest (54 of 1308) Search:

Gene	Protein Change	Type	Cohort	COSMIC	FIS	3D
KRAS	G13D	MS		2998	M	3D
FBXW7	R505C	MS		57	M	3D
PIK3CA	C420R	MS		26	M	3D
ARID1A	R2236P	MS		1	L	
EPHA10	R150H	MS		1	L	3D
TSC1	D47G	MS		1	M	

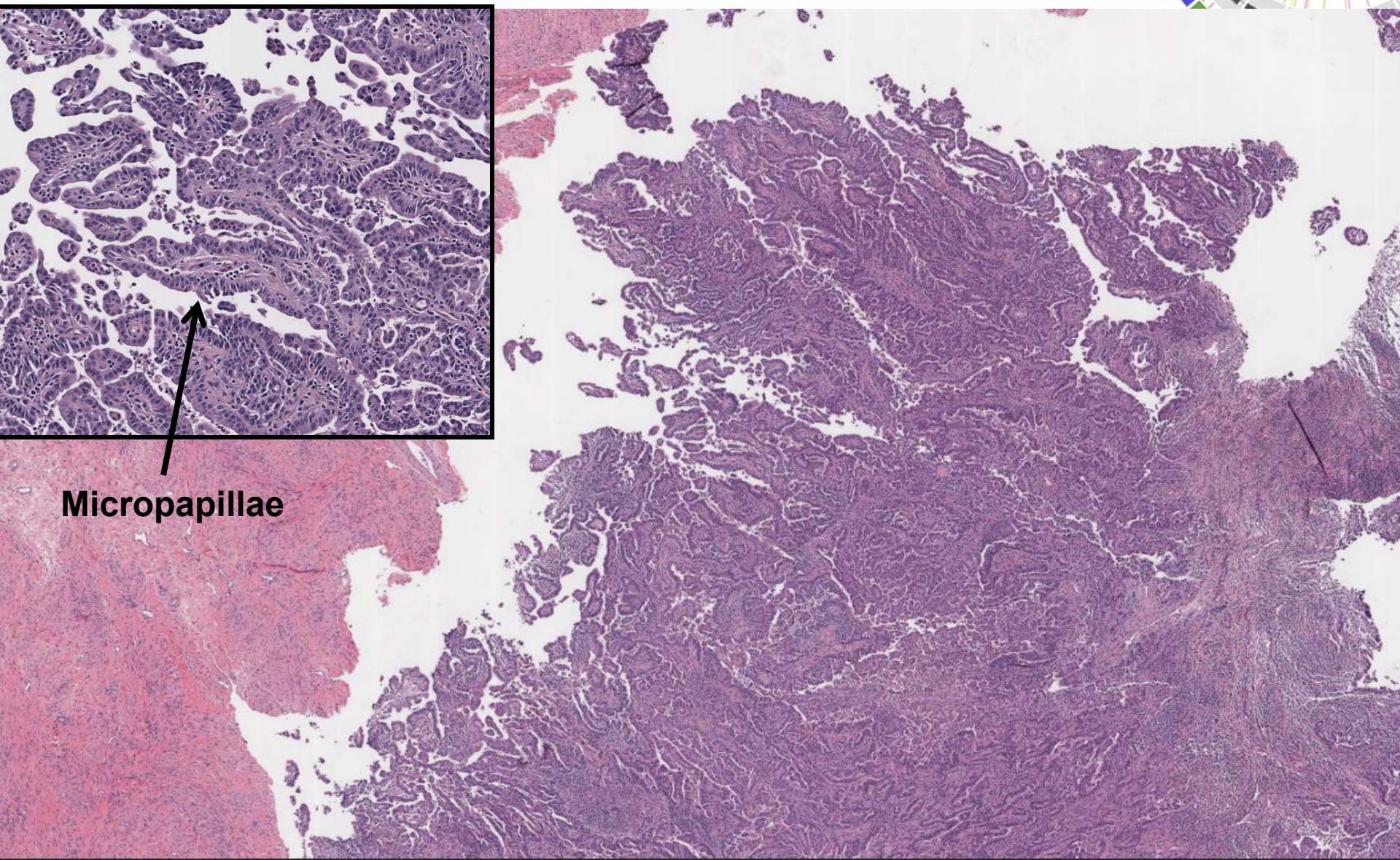
CNA of interest (0 of 5) Search:

Gene	CNA	% in Cohort
No CNA events of interest		

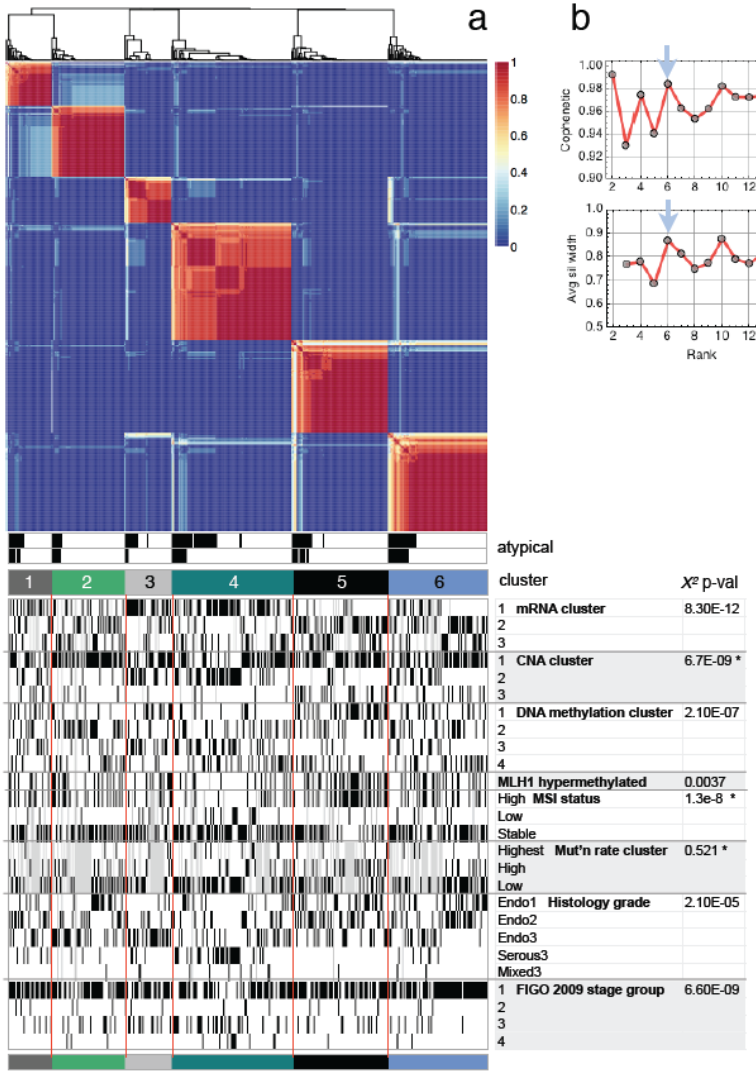
Show all 5 CNAs Show 25 per page

The Cancer Genome Atlas

Path c/w endometrioid histology, ?MSH6 mutatio



MicroRNA sequencing

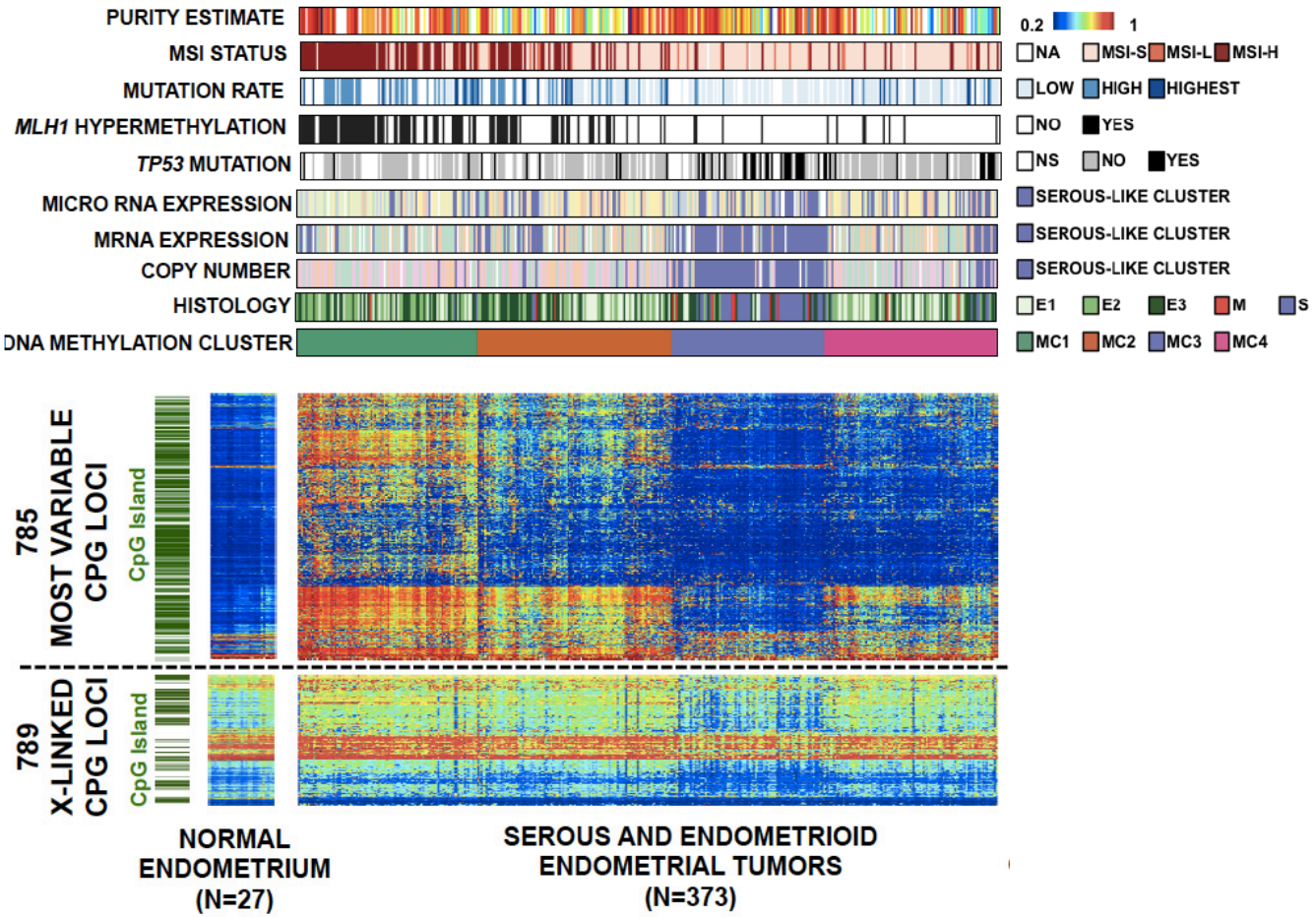


c	1	2	3	4	5	6	all
n	34	56	36	92	73	76	386
w	0.85	0.92	0.84	0.87	0.86	0.86	0.87

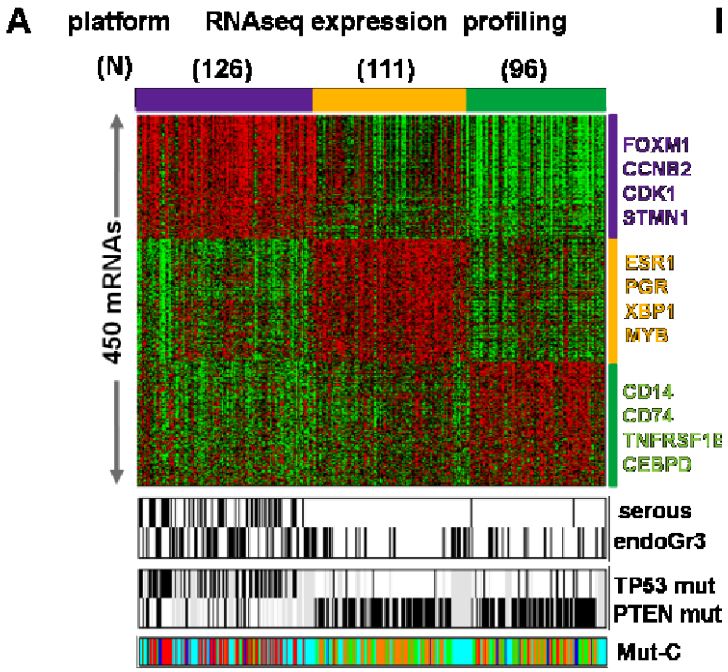
Supplemental Figure 1

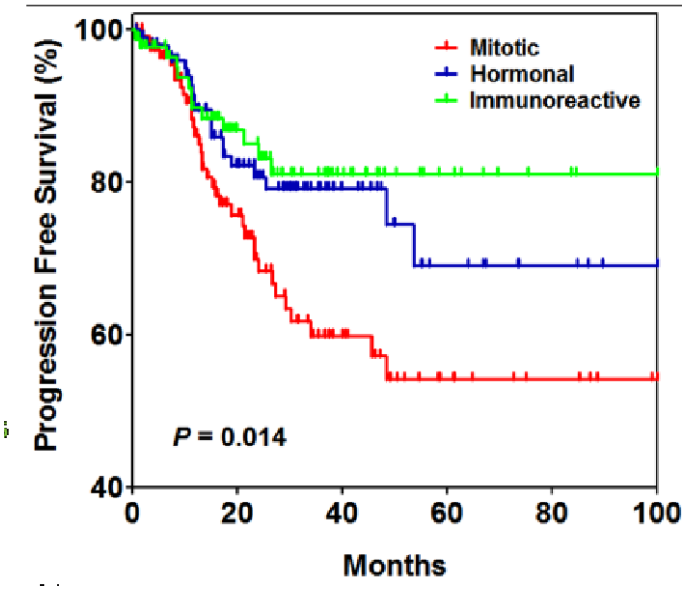
Genome Atlas

Methylation



Gene expression clusters

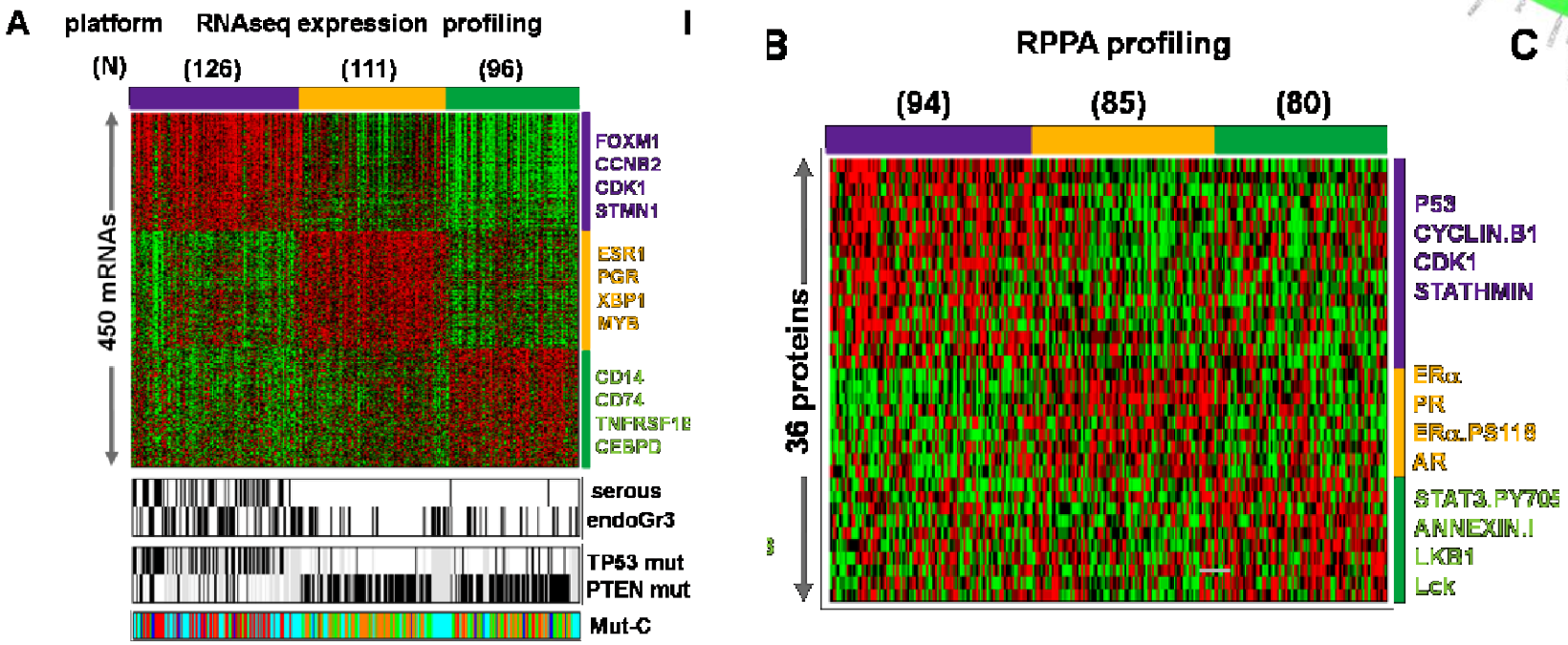




- Mitotic cluster contains serous and serous-like cases
- Hormonal cluster contains samples with greater ER/PR expression
- Immunoresponsive cluster contains immune activated genes

➢ **Wei Zhang and Yuexin Liu, MDACC**

Supervised RPPA



- DNA repair and proliferative genes in the RNASeq mitotic cluster
- High ER, PR, AR in the hormonal RNASeq subtype
- STAT3 activation and elevated LKB1, LCK and annexin in the immunoreactive RNASeq subtype.

Endometrial

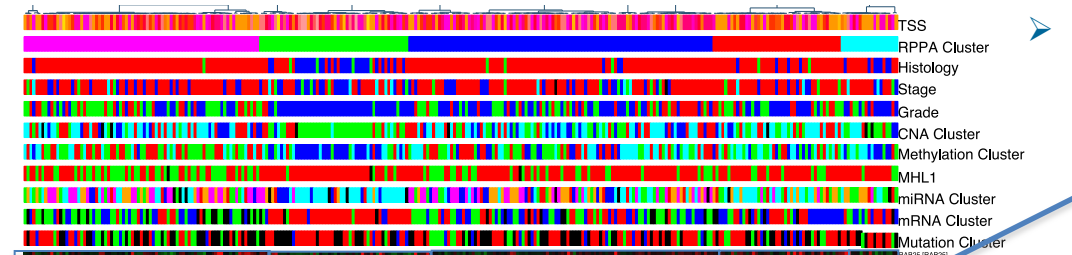
Proteomics Atlas

TCGA 210 samples

210 Antibodies

Median Centered Unsupervised Hierarchical Cluster

Gordon Mills, MDACC



Reactive

Rab25 SetD2 Met Snail Rad51 Casp9 BiD

Doris Siwak

Signaling

Pink
signaling on ER/PR/AR on

Green
serous proliferative erbB2, ErbB3

Blue dark
Signaling off ER/AR/PR off

Red
MAPK selective on reactive

Blue light \
Collagen, caveolin and VEGFR on metabolism off

Serous

Not Gata3 IGFBP2 BCL2

ER pER PR AR

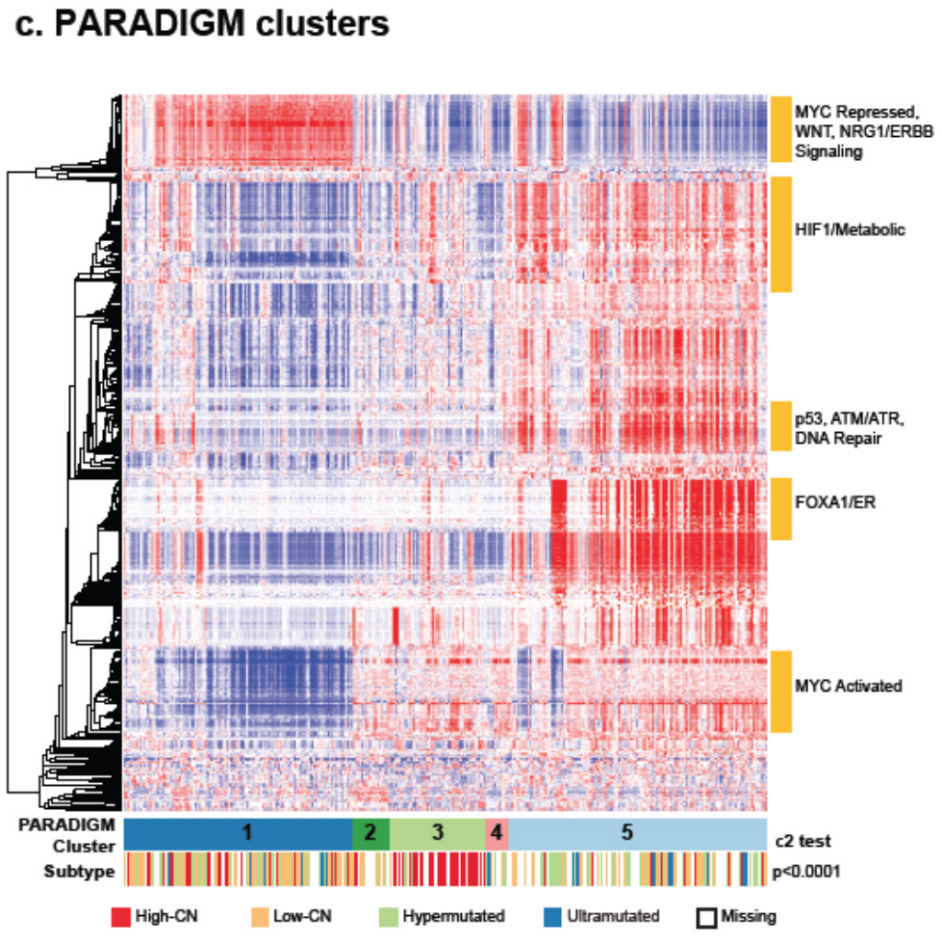
Cav1 Collagen VI

PKCa

MSH2/6

pHER2 HER2

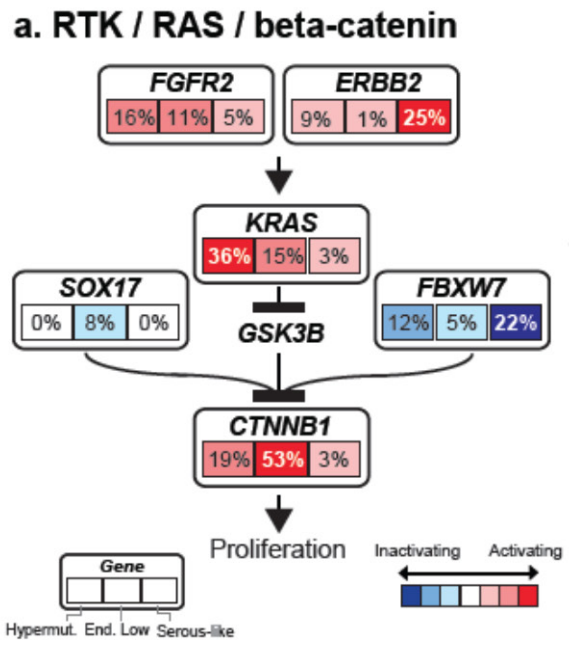
PARADIGM



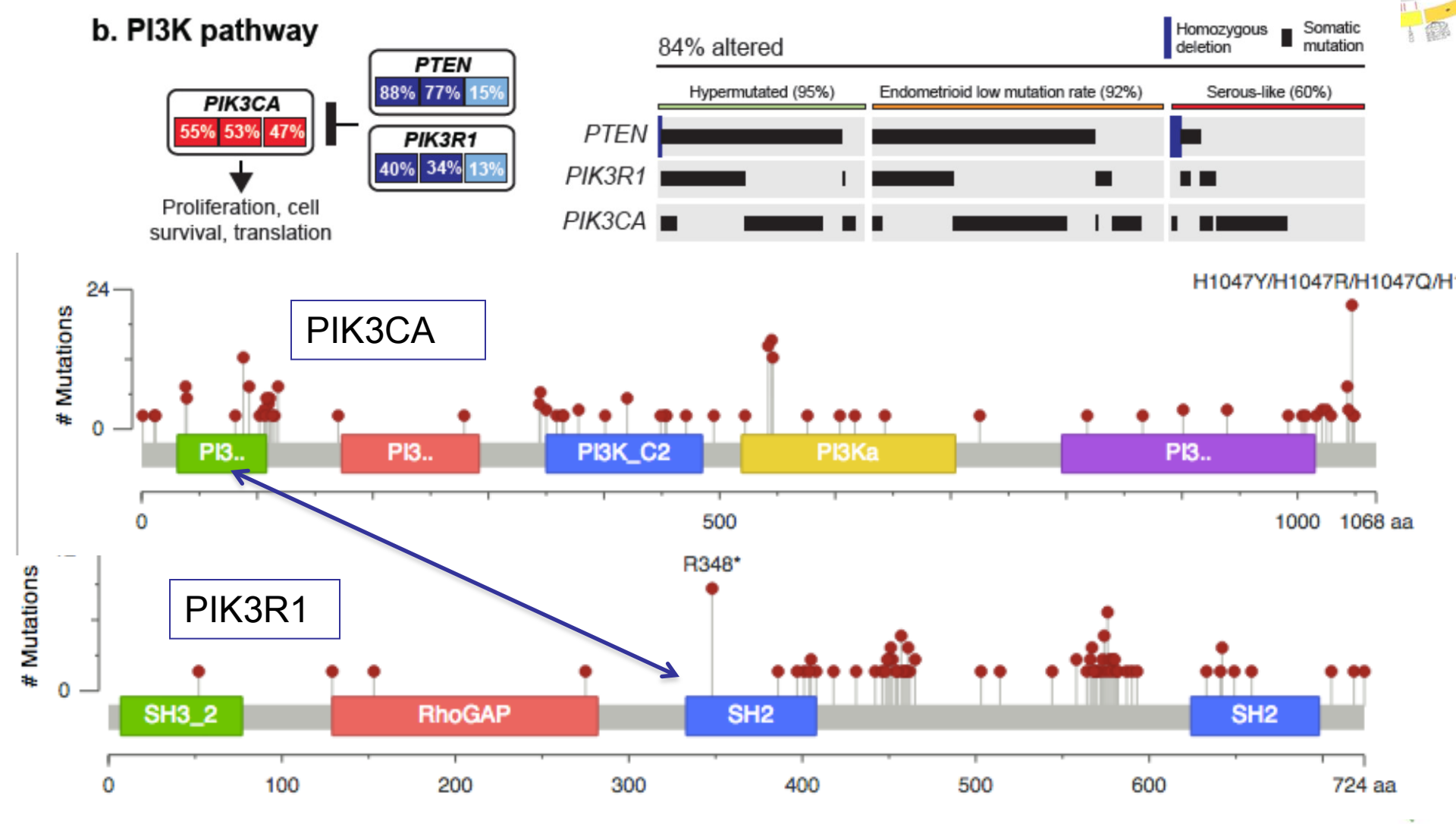
- Cluster 3: MYC activation, low TP53 pathway activation due to mutation
- Cluster 5: MYC and FOXA1/ER activity, TP53 intact
- Cluster 1: Low MYC, high WNT signalling c/w CTNNB1 mutation in the MSS/Low SCNA/Low mutations group

➢ **Christina Yau and Chris Benz, Buck Institute**

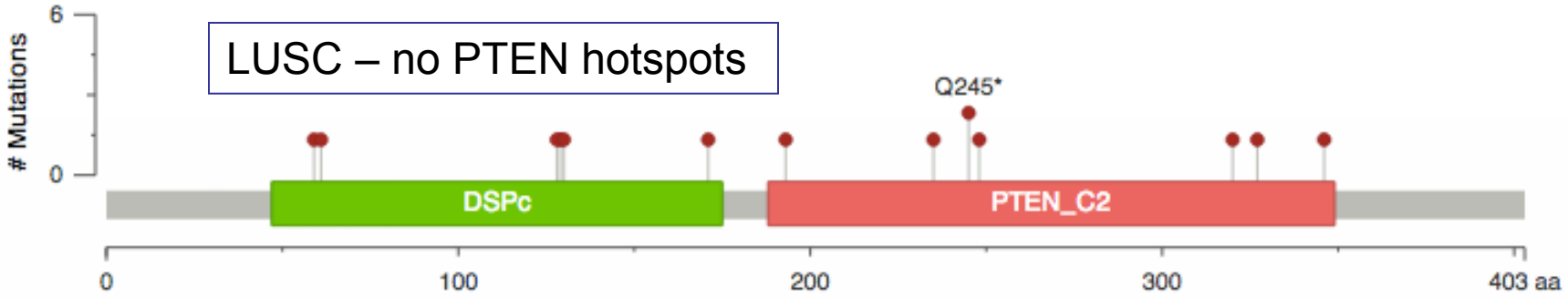
RAS/CTNNB1 pathway - MEMo

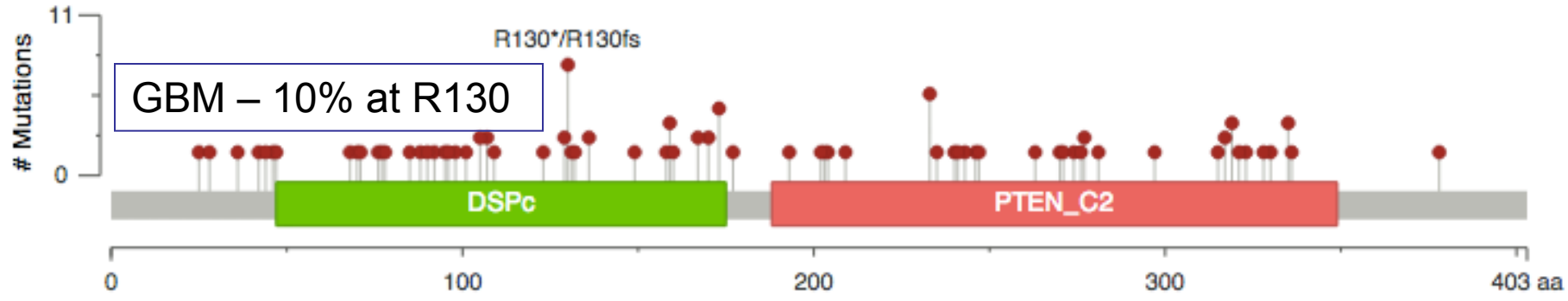


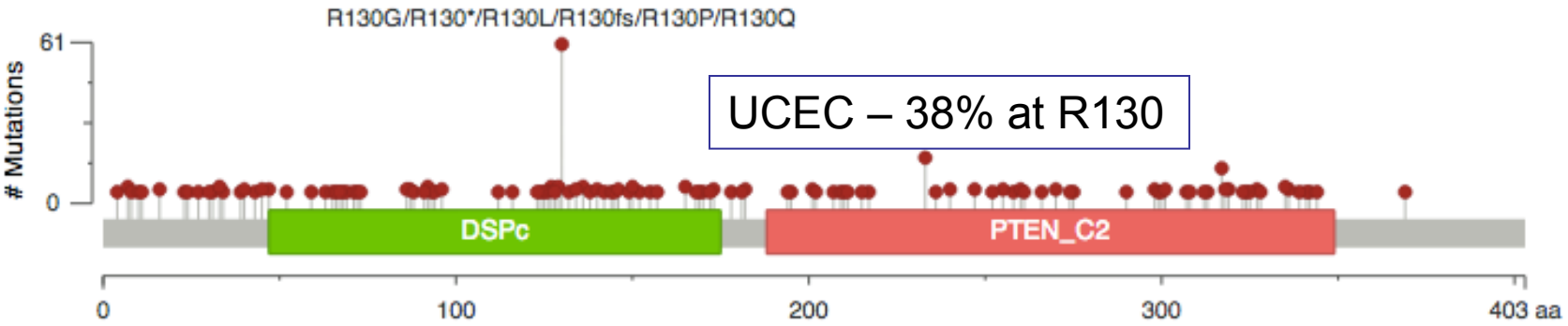
PI3K/AKT – most active in endometrial cancer



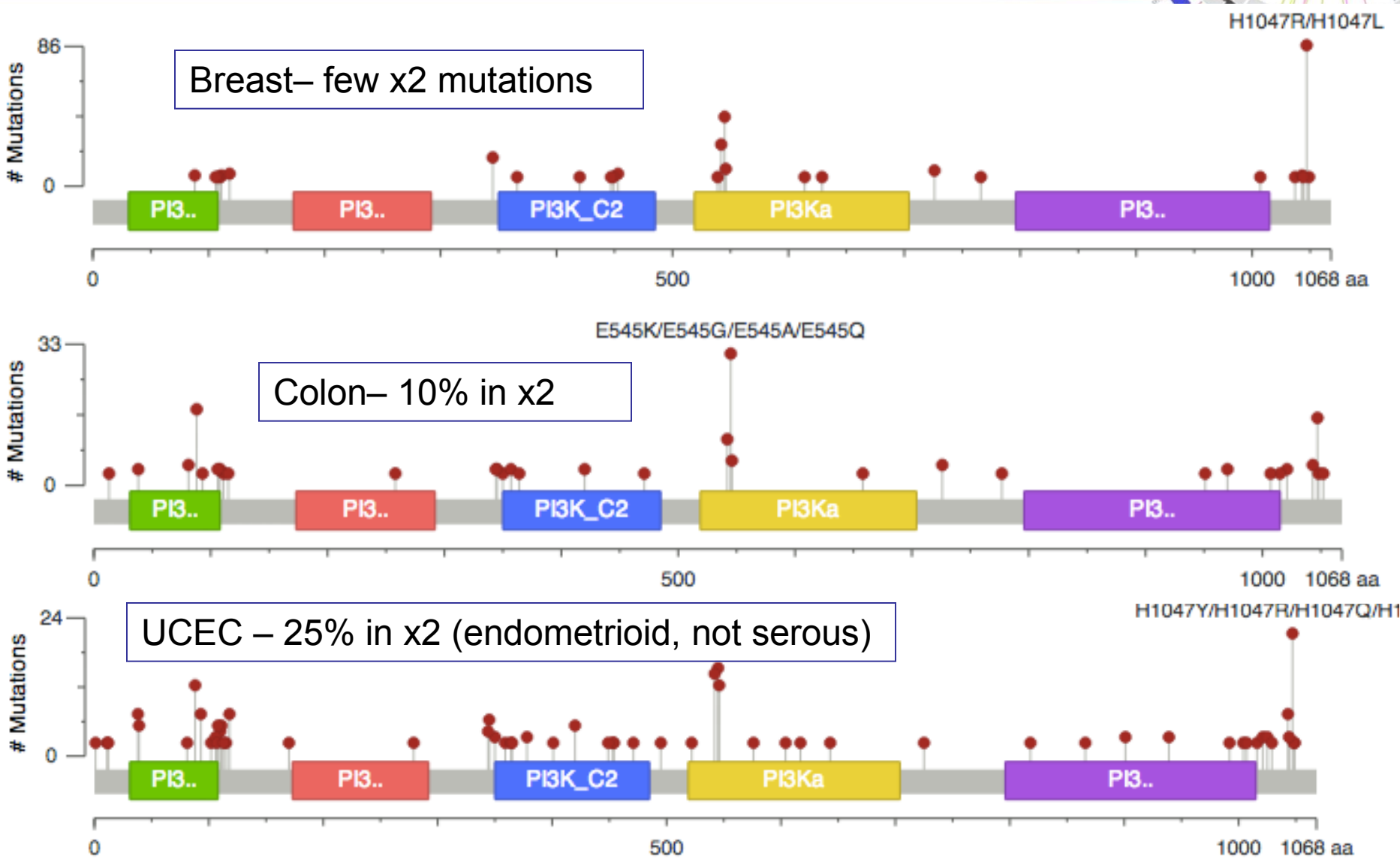
PTEN mutations



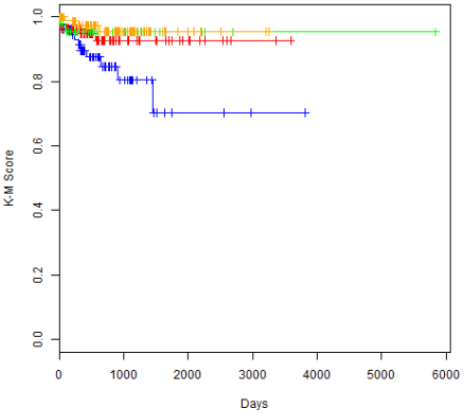


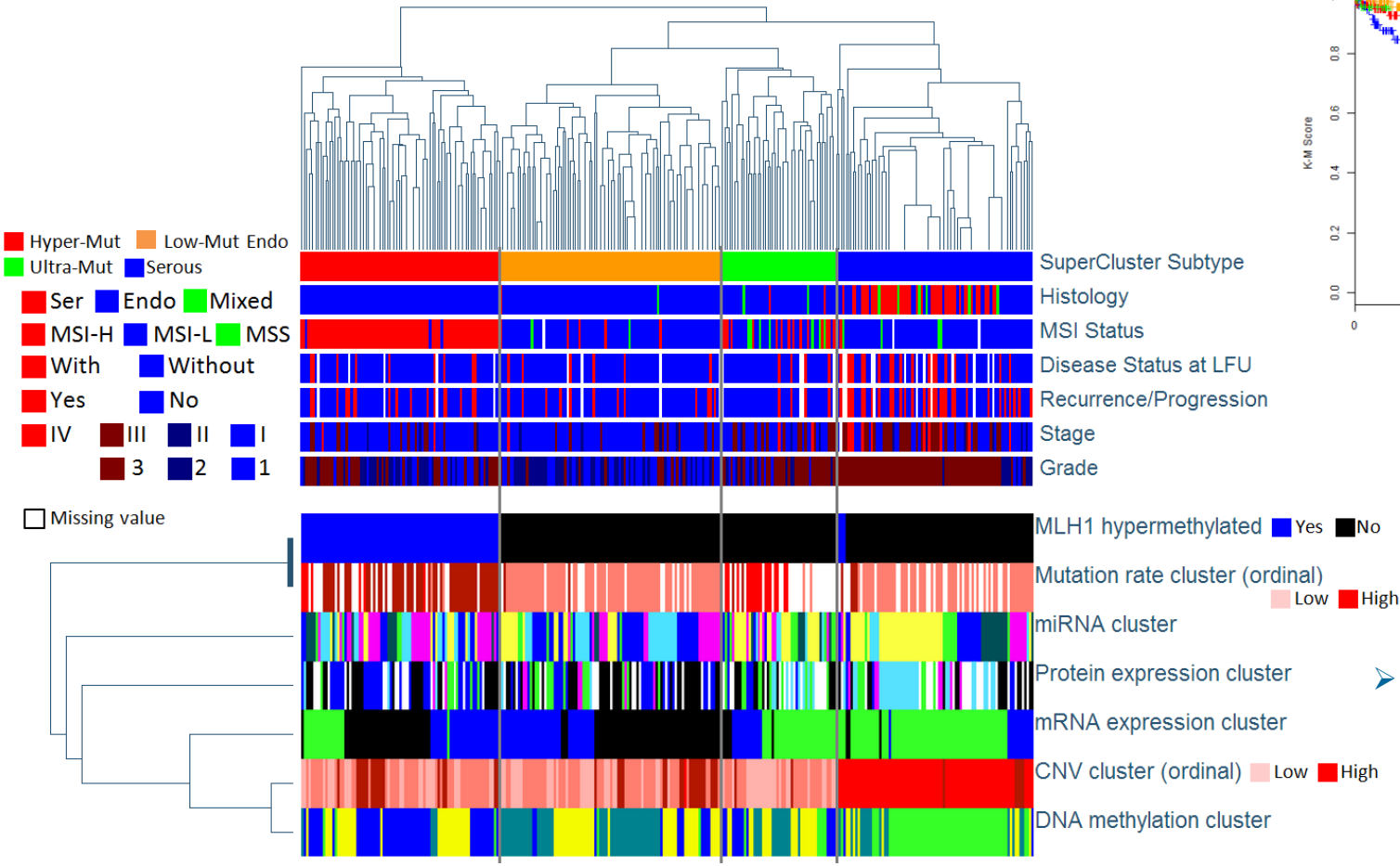


PIK3CA


H1047R/H1047L
86
Mutations
0
Breast– few x2 mutations
PI3..
PI3..
PI3K_C2
PI3Ka
PI3..
0
500
1000
1068 aa
E545K/E545G/E545A/E545Q
33
Mutations
0
Colon– 10% in x2
PI3..
PI3..
PI3K_C2
PI3Ka
PI3..
0
500
1000
1068 aa
H1047Y/H1047R/H1047Q/H1
24
Mutations
0
UCEC – 25% in x2 (endometrioid, not serous)
PI3..
PI3..
PI3K_C2
PI3Ka
PI3..
0
500
1000
1068 aa

SuperClusters



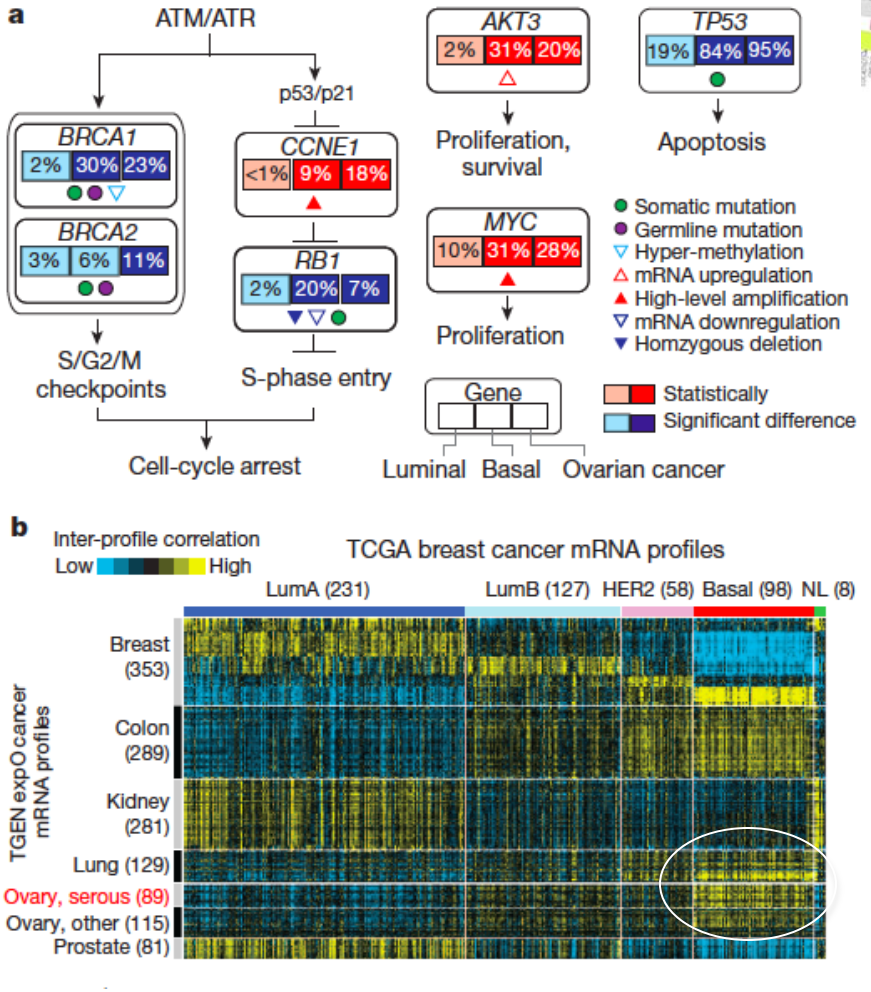


Rehan Akbani, MDACC

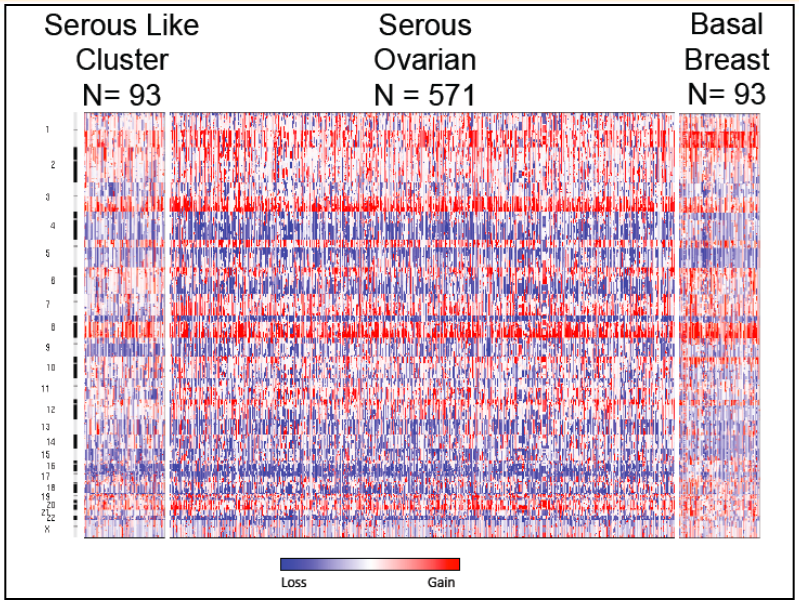
Genome Atlas

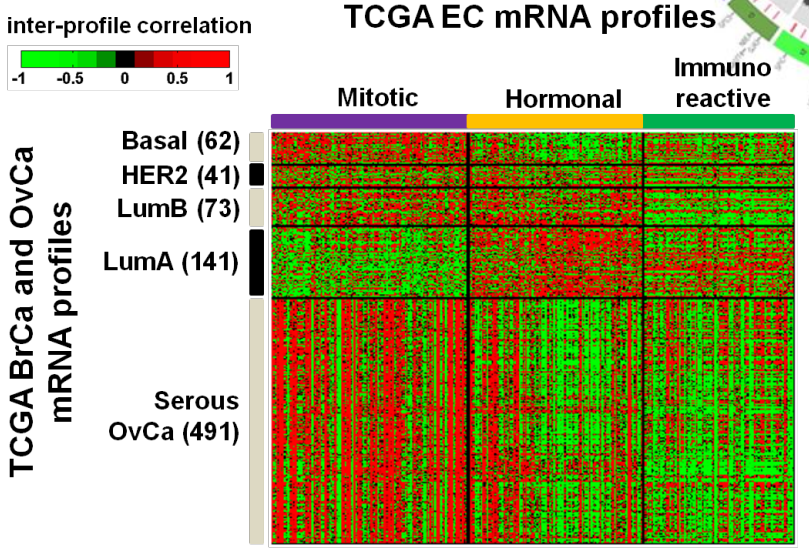
Case study – Cross-tumor comparisons: the power of TCGA

Do uterine serous, ovarian serous, and basal like breast carcinomas have a common molecular phenotype?

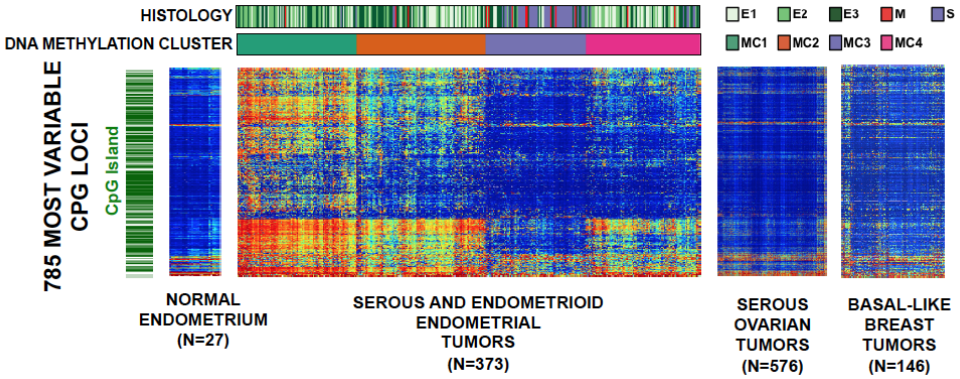


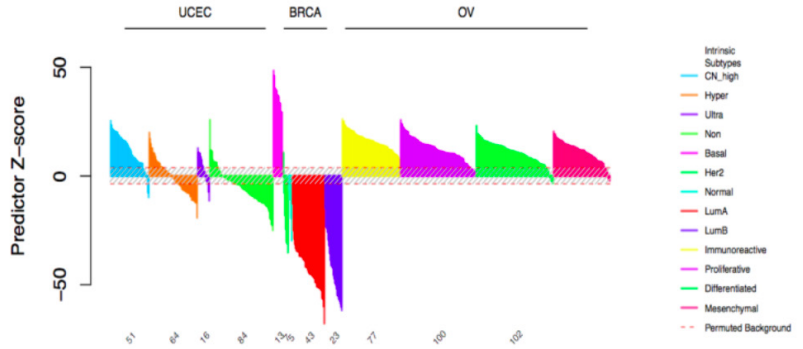
Multiplatform molecular similarities among ovarian serous, uterine serous, basal like breast





A

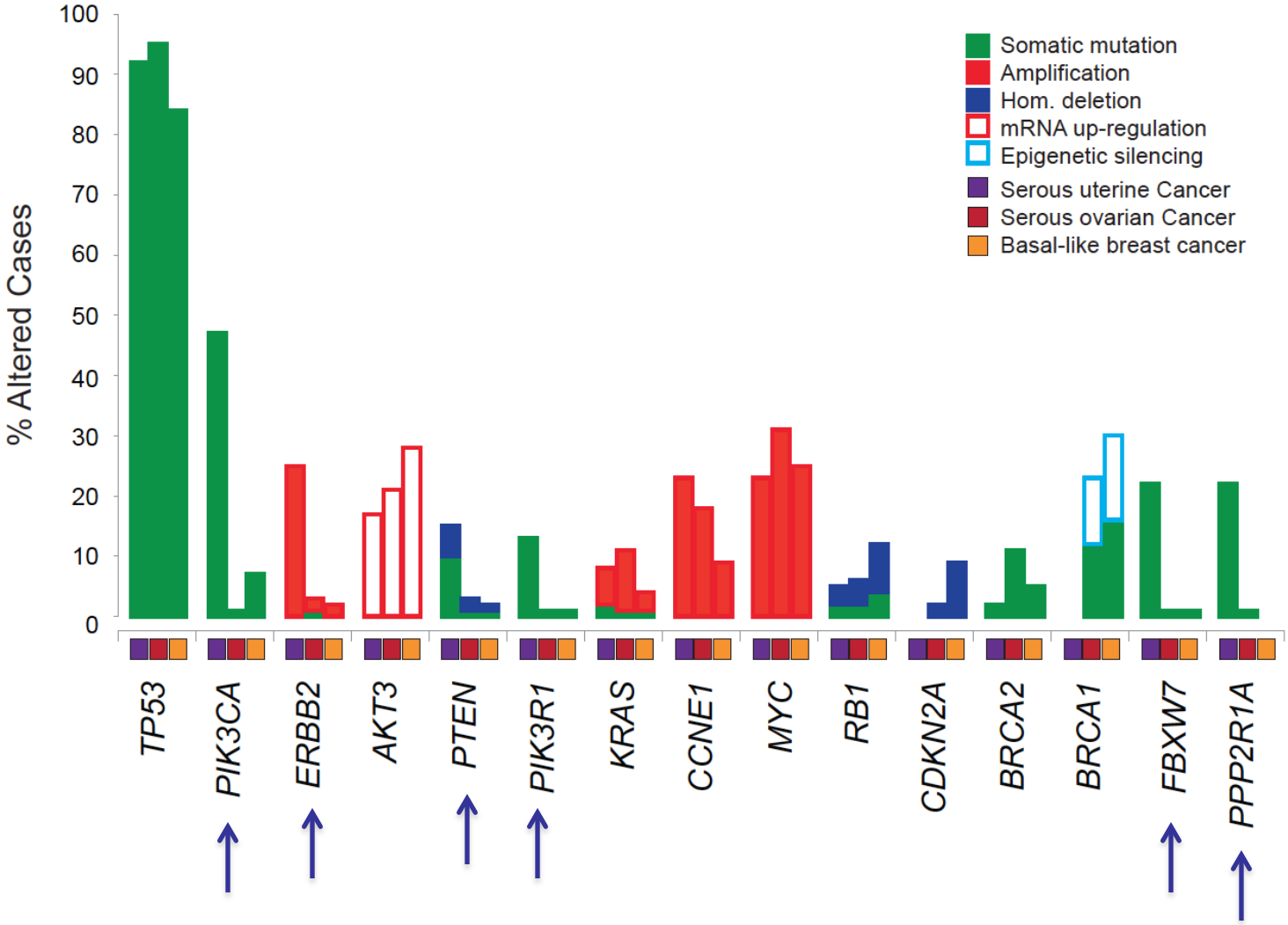




- **Andrew Cherniack, Hui Shen, Wei Zhang, Chris Benz, Peter Laird, Yuexin Liu, Christina Yau**

The Cancer Genome Atlas

Mutation frequencies vary across tumors



The Cancer Genome Atlas

Case study - Answer

Do uterine serous, ovarian serous, and basal like breast carcinomas have a common molecular phenotype? Mostly

Genomic similarities are likely due to shared TP53 mutations, but it is possible that ovarian serous and uterine serous do have a common site of origin and differentiate according to microenvironment.

Summary

- Recurrent POLE mutations identified and associated with altered mutation specturm and very high mutation rate
- PI3K/AKT pathway most activated in endometrial – ramifications for targeted inhibition, unique mutation spectra among genes
- Novel genomic stratification may complement or supplant histologic subtyping
  - Has immediate impact on current schizophrenic approaches to adjuvant treatment after hysterectomy
  - Warrants re-design of clinical trials with stratification or separation of subtypes
- In the era of 'precision medicine' these finding will help to bring targeted agents to the clinic in a rational manner

TCGA versus cigarettes

Announcement

- Endometrial Disease / Analysis Working Group meeting
- Today, Wednesday, 5pm – 7pm in Salon II
- Punch list

Acknowledgements

The Cancer Genome Atlas Research Network

Endometrial Tissue Source Sites

TCGA/NCI
Kenna Shaw
Brad Ozenberger
Andrew Cherniack
Katie Hoadley
Elaine Mardis
Li Ding
Cyriac Kandoth
Hui Shen
Peter Laird
Martin Ferguson
Gordon Mills
Rehan Akbani
Wei Zhang
Raju Kucherlapati
Yuexin Liu
Chris Benz
Christina Yau
Josh Stuart

TCGA/NCI
Itai Pastan
JJ Gao
Ari Kahn
Margi Sheth
Gordon Robertson
Andy Chu
Shauwo Meng
Nils Weinhold
Giovanni Ciriello

MSKCC
Marc Ladanyi
Chris Sander
Agnes Viale
Niki Schultz
Ethan Cerami
Ronglai Shen
Narciso Olvera
Fanny Dao
Faina Bogomolniy
Robert Soslow

Others
Paul Goodfellow
Russell Broaddus
Andrew Berchuck
Beth Karlan
Marc Goodman
David Mutch
Daphne Bell
Sean Dowdy
Boris Winterhoff
Jenny Lester

An AACR Special Conference on

ADVANCES IN OVARIAN CANCER RESEARCH: FROM CONCEPT TO CLINIC

September 18-21, 2013
J.W. Marriott Marquis, Miami, FL

AACR American Association for Cancer Research

www.aacr.org/meetingcalendar