Reframing tumor heterogeneity
gene mapping & precision treatments

Nicola J Camp, PhD

University of Utah

HEALTH
UNIVERSITY OF UTAH

HUNTSMAN
CANCER INSTITUTE
UNIVERSITY OF UTAH

Common diseases are heterogeneous

- Locus
- Allelic
- Tumor

- Impacts
  - Gene discovery
  - Risk stratification
    - Prevention
    - Clinical management
  - Drug response –precision treatments

Tumor heterogeneity
Universal approach = highest impact

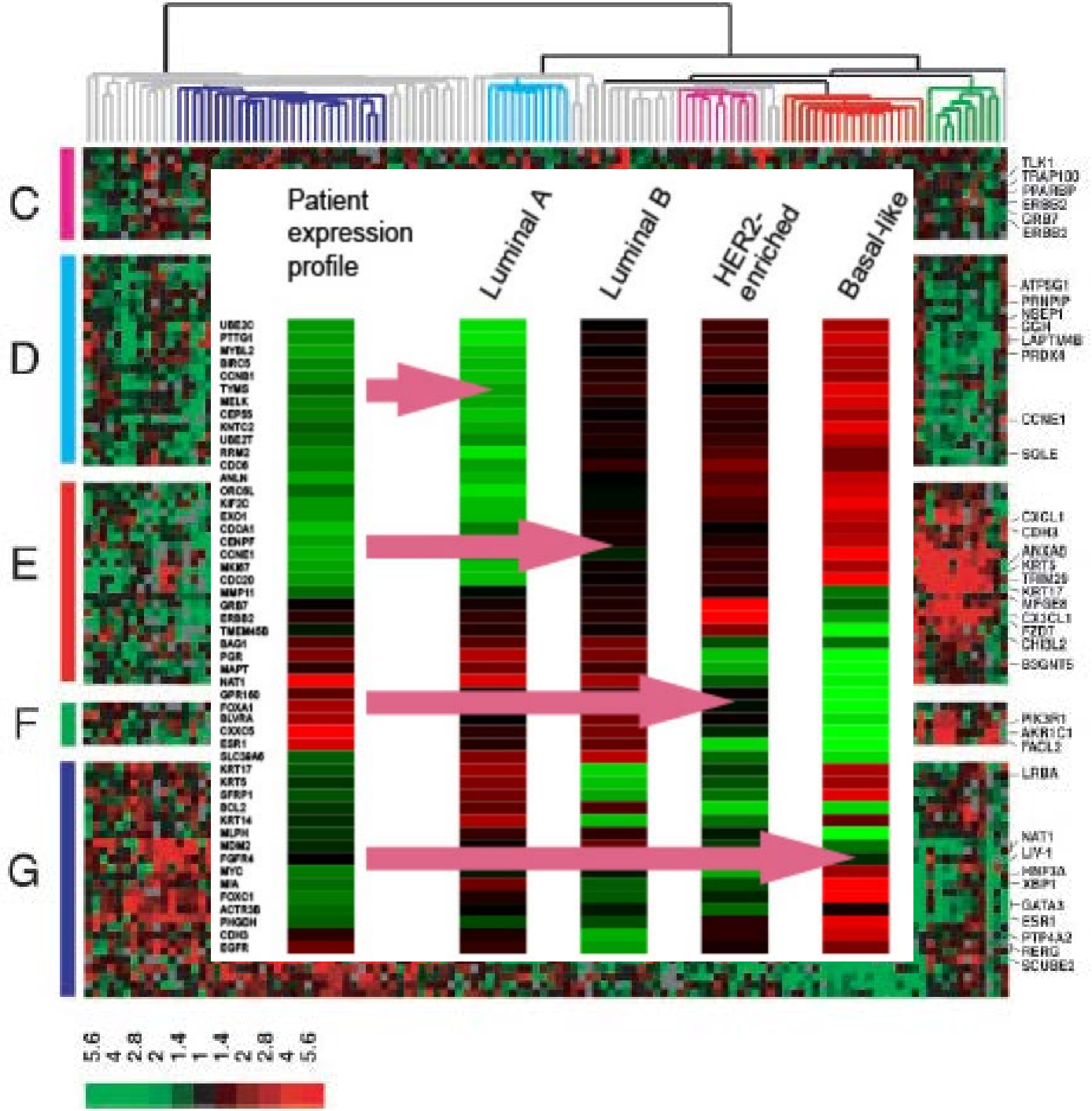
- Goal –approach relevant for research across the translational spectrum
  - Discover inherited susceptibility
  - Pre-clinical modeling
  - Clinical trials

- ‘Natural characteristics’ -- variability across patients
  - Gene expression

Breast tumors

- natural groupings
  - 2 epithelial cell lines
    - Luminal / ER (c)
    - Basal (myoepithelial) KRT 5, 17 (e)
  - Erb (d)
- Fine-t
  - Luminal-A (G)
  - Luminal-B (D)
  - HER2-enriched (C)
  - Basal-like (E)
  - Normal-like (F)

prosigna™

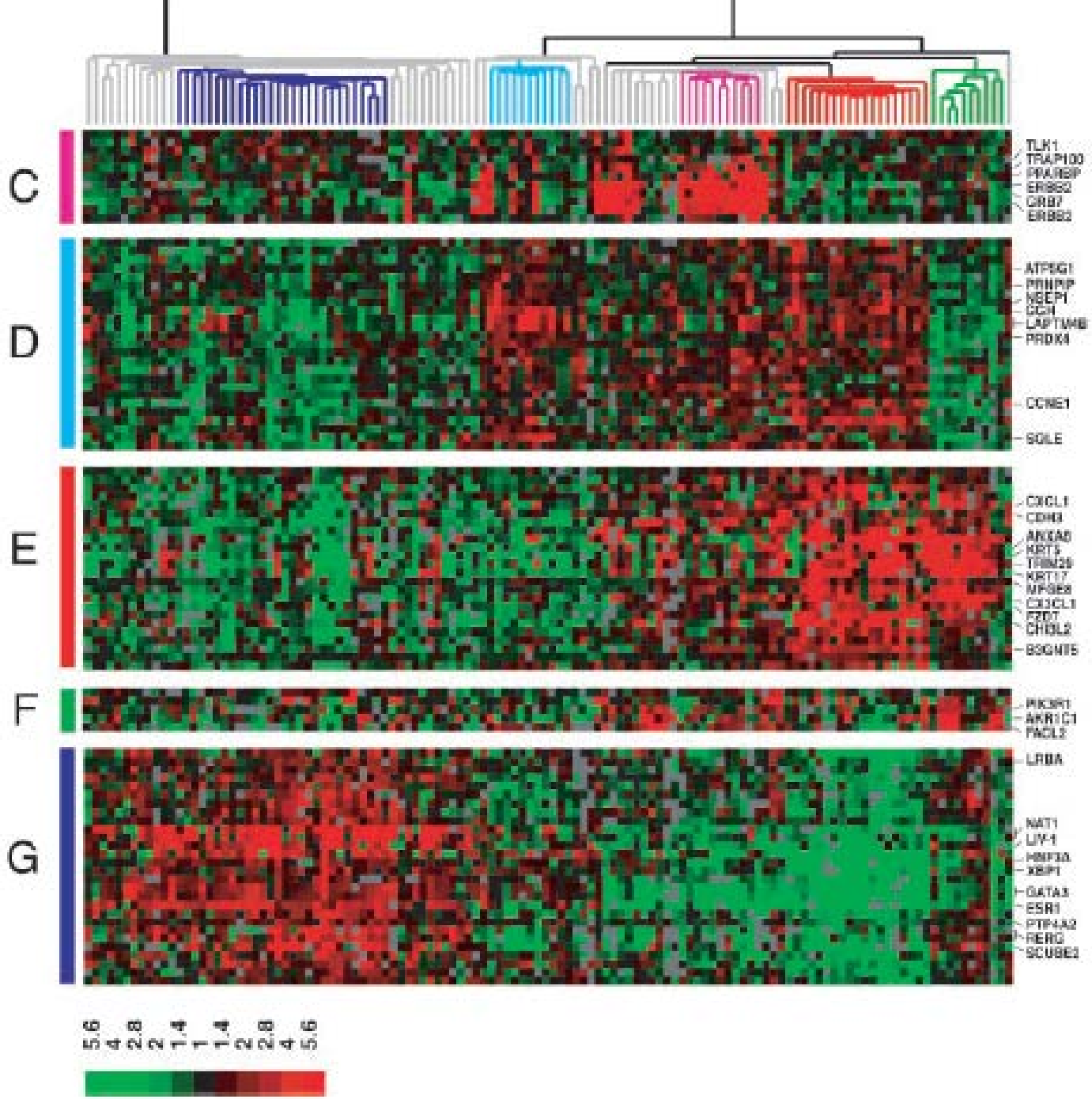


Intrinsic characteristics

Perou *et al* Nature 2000 Sørlie *et al* PNAS 2003

Could intrinsic subtype be the key to inherited susceptibility?

BRCA1 carriers associated with the basal tumor subtype

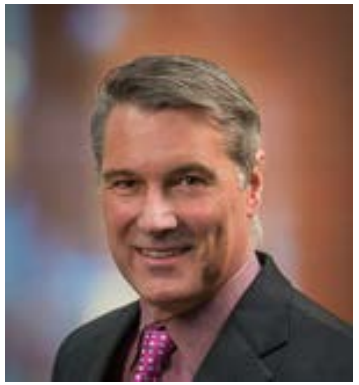


Intrinsic characteristics

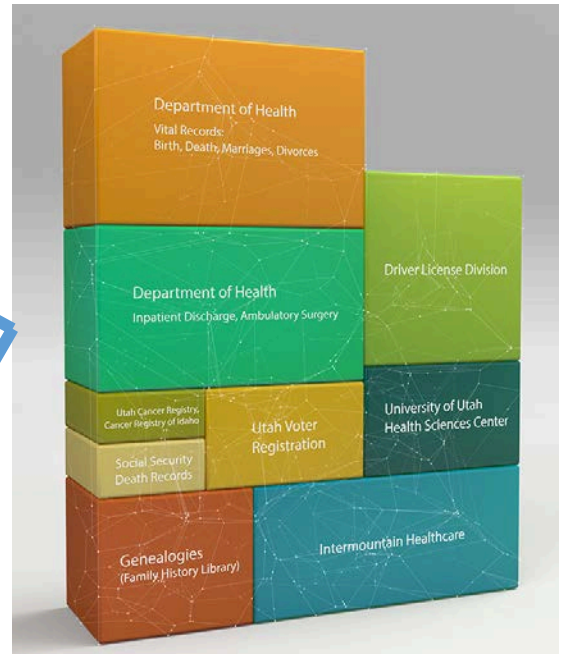
Sørlie *et al* PNAS 2003

Intrinsic subtypes in Utah high-risk pedigrees

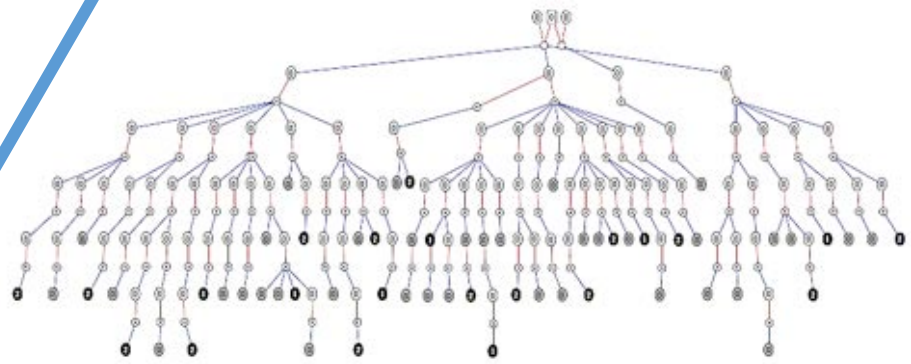
Pedigree	BC cases	Tumors
1817	138	35
1822	159	31
1819	114	26
1808	112	24
1800	66	20
1818	111	20
1820	68	20
1821	81	18
1801	57	17
1812	43	17
1809	50	15
TOTAL		243



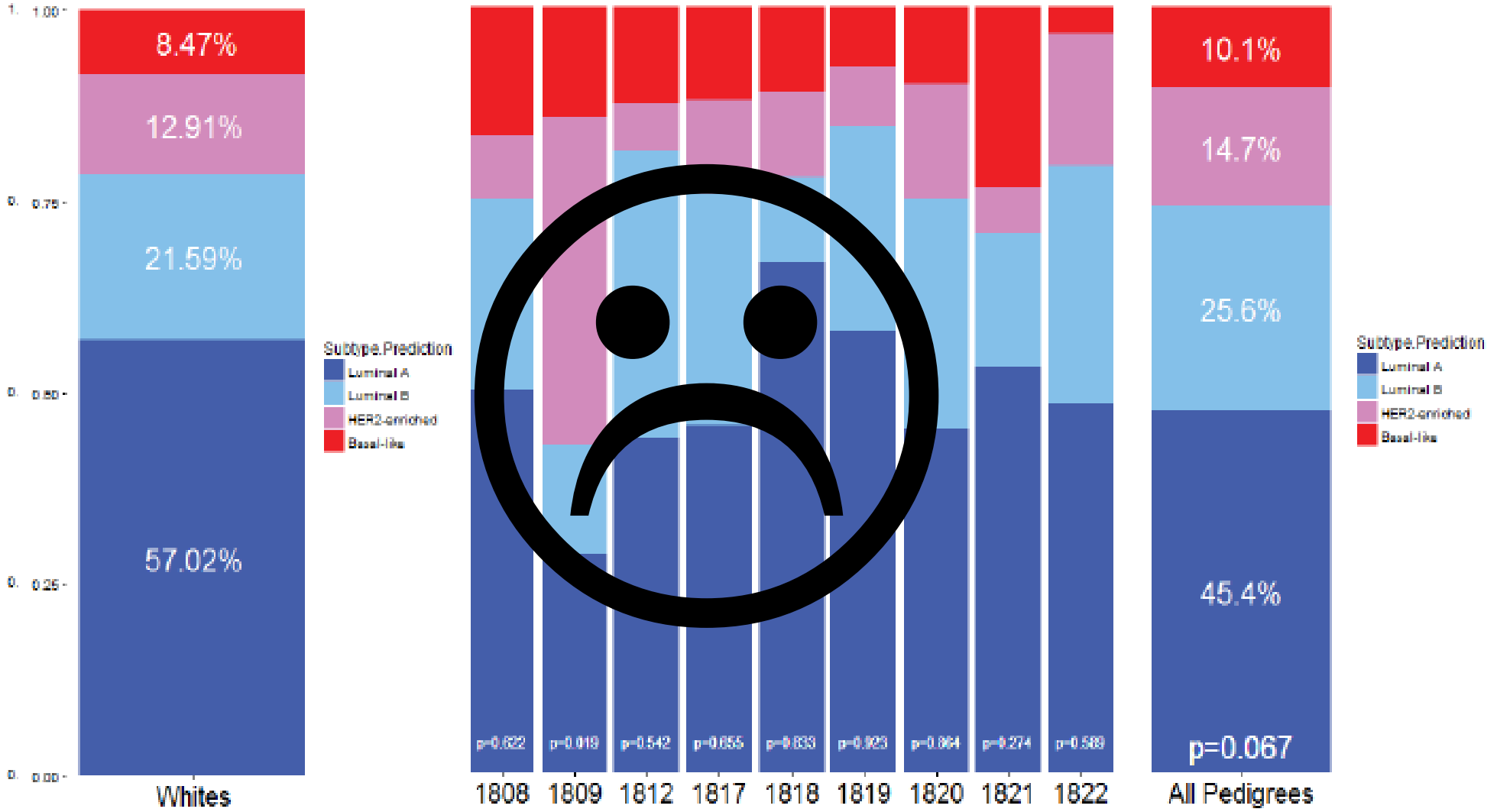
Phil Bernard, MD



Melissa Cessna, MD



Genesis Population vs Utah non-BRCA1/2 pedigrees

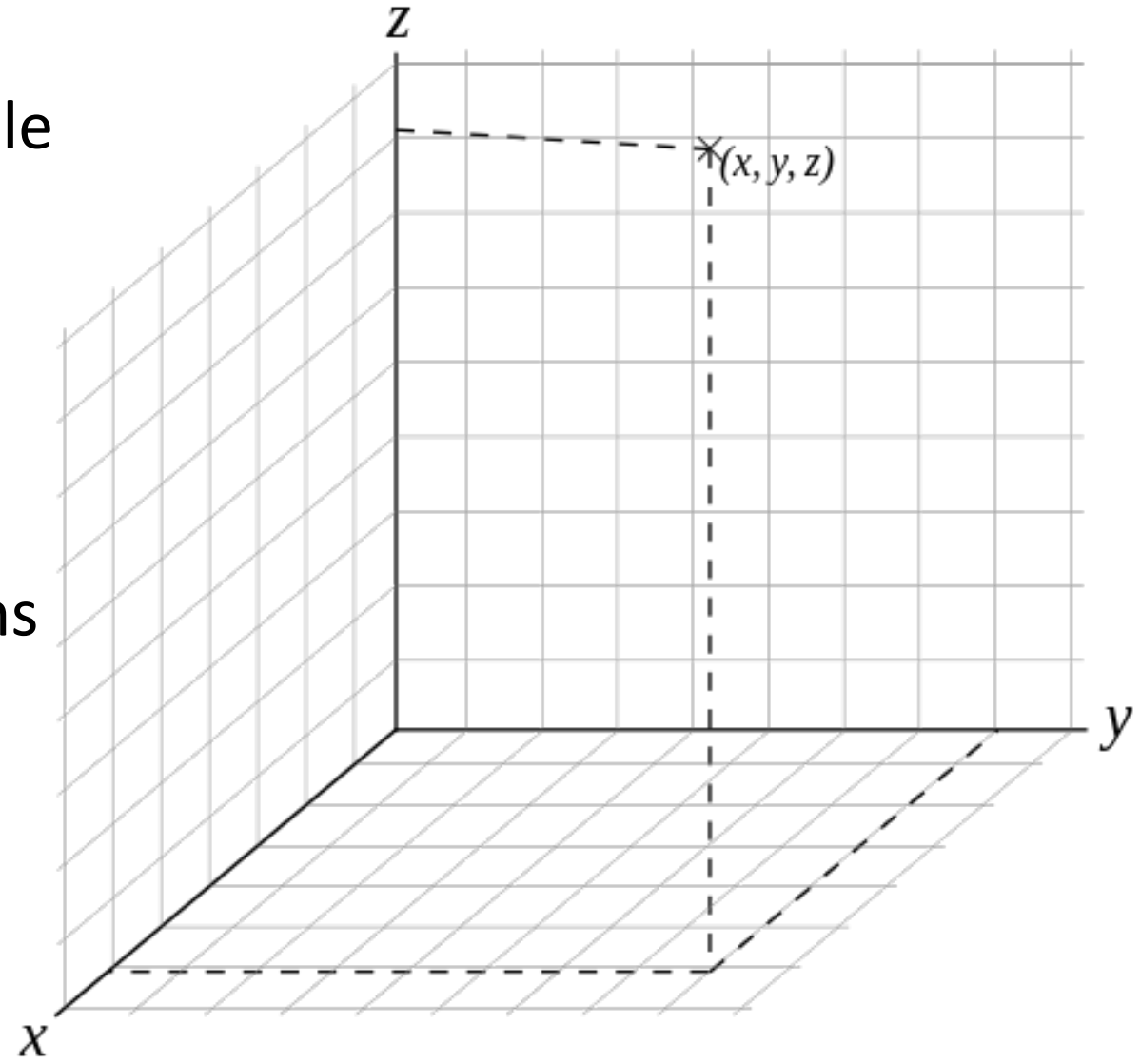


Sweeney *et al* CEBP 2014

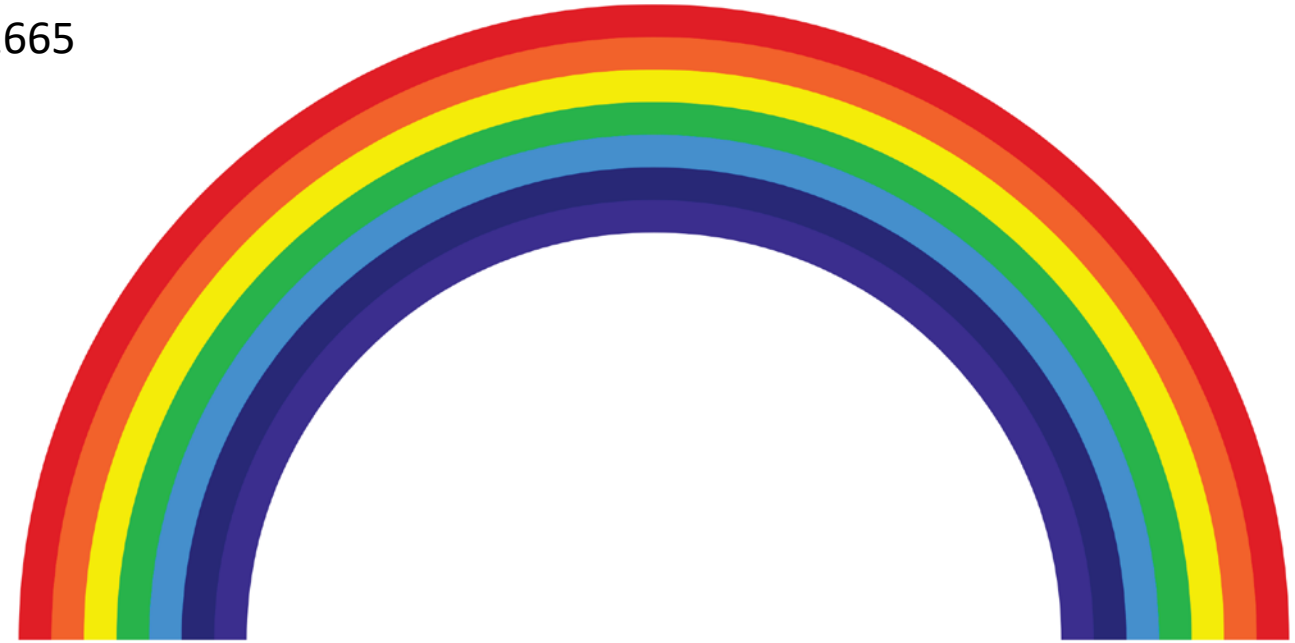
Single dimension: sufficient to describe a tumor?

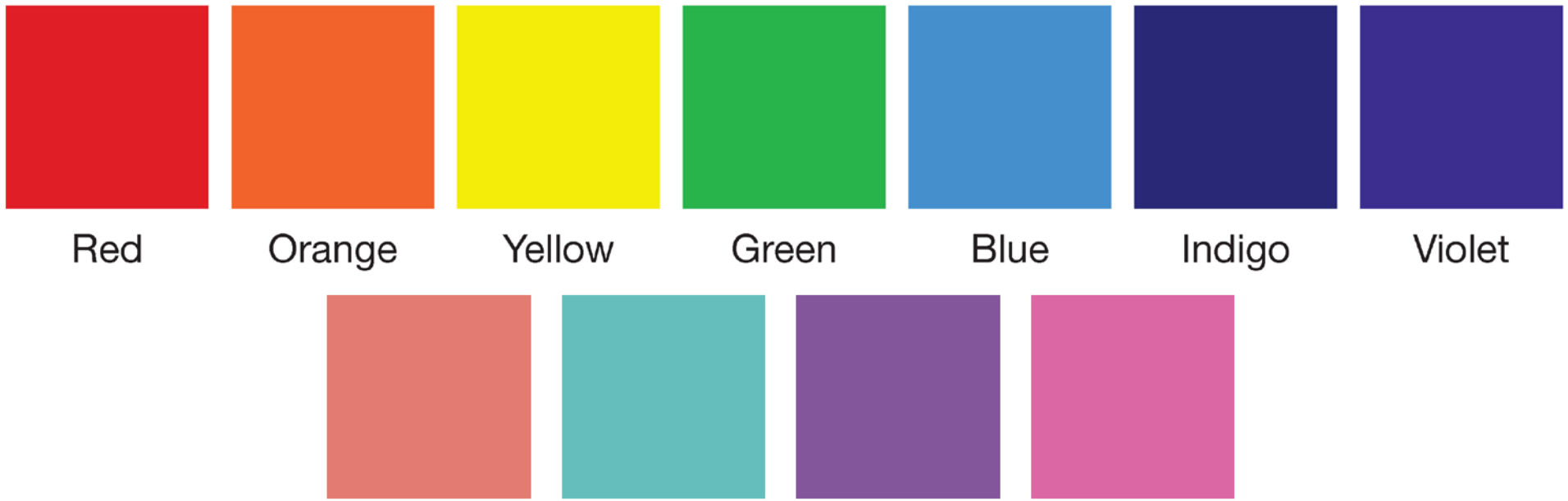
- Intrinsic subtype = 1 categorical variable
- ROR = 1 quantitative score

- More complex?
- Does the data require more dimensions to describe variability?

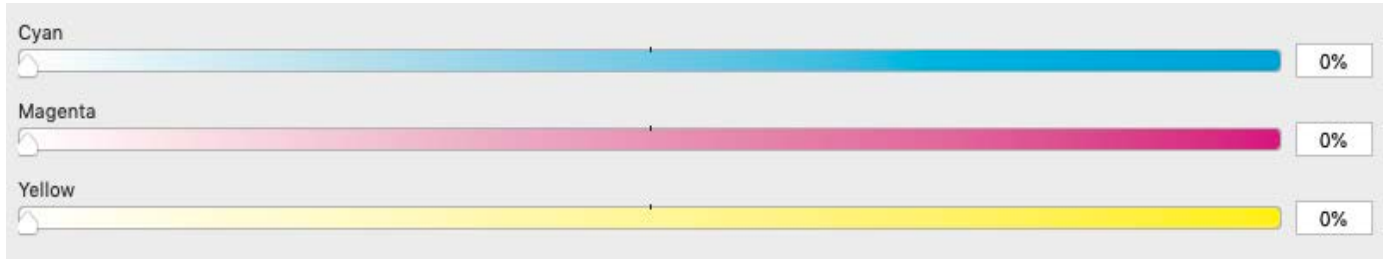


Newton’s Color Theory, ca. 1665





Society of Physics, 1892
William Kurtz, 1893

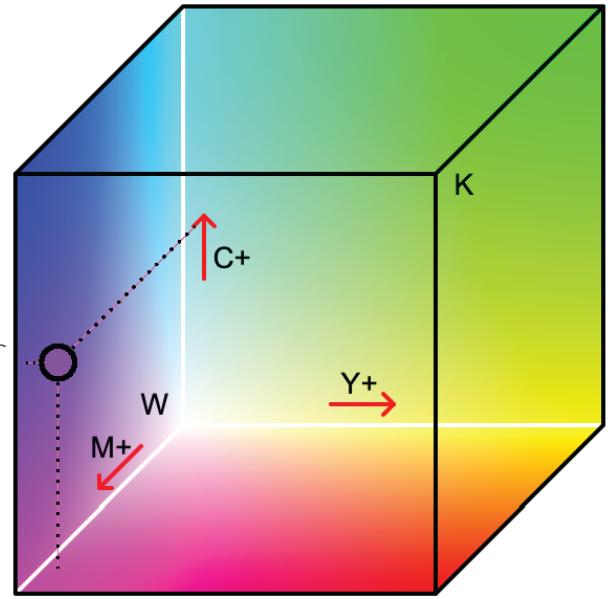


“Hot pink”
C: 0.10
M: 0.73
Y: 0.03

“Purple”
C: 0.57
M: 0.78
Y: 0.07

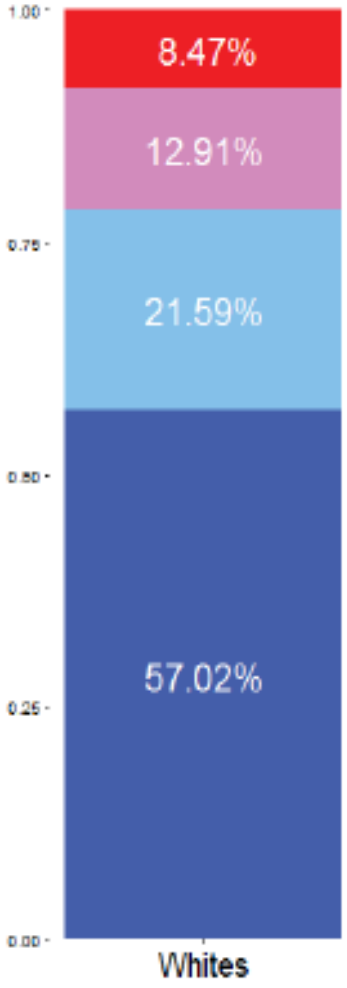
“Turquoise”
C: 0.58
M: 0.05
Y: 0.29

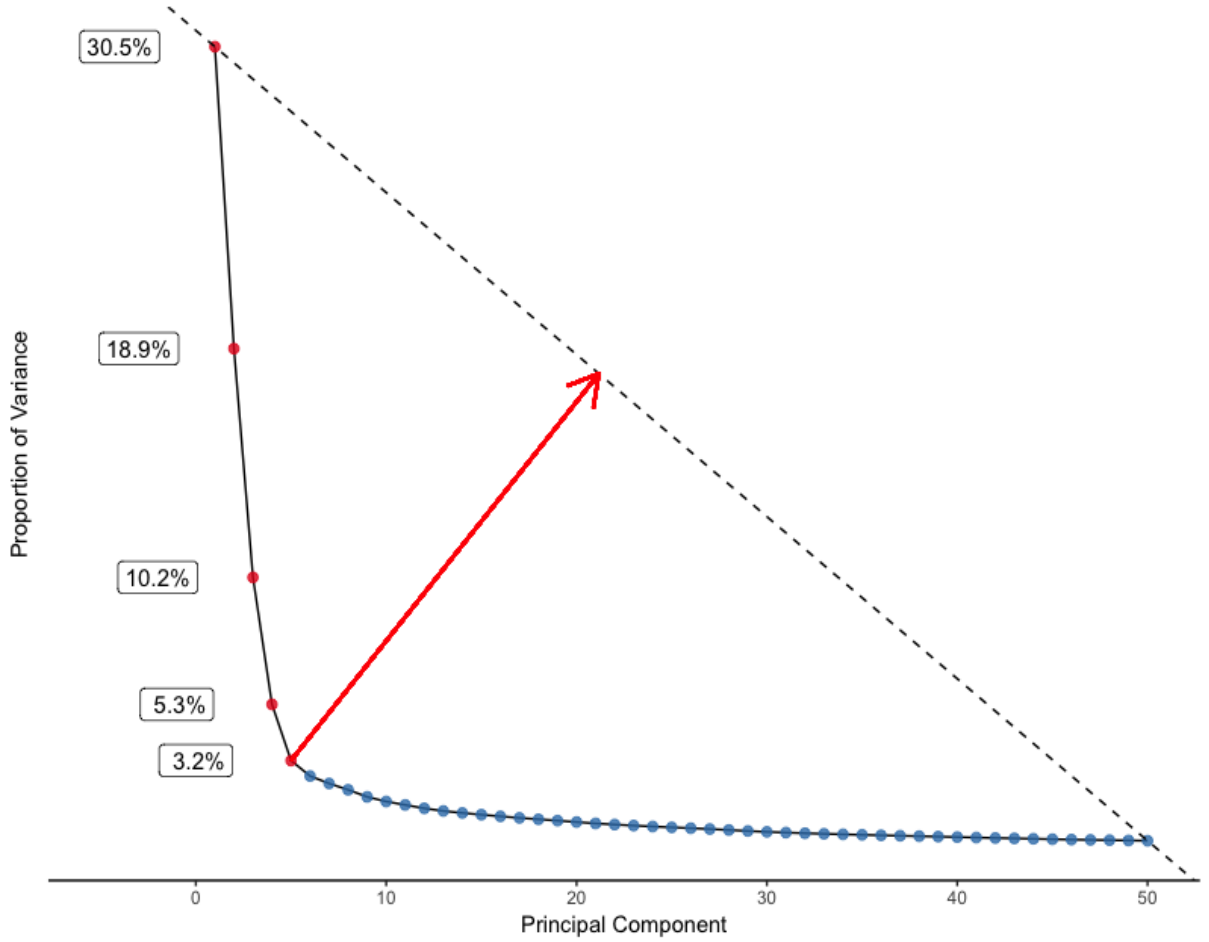
“Salmon”
C: 0.08
M: 0.63
Y: 0.49



Multiple quantitative dimensions

- Principal component analysis



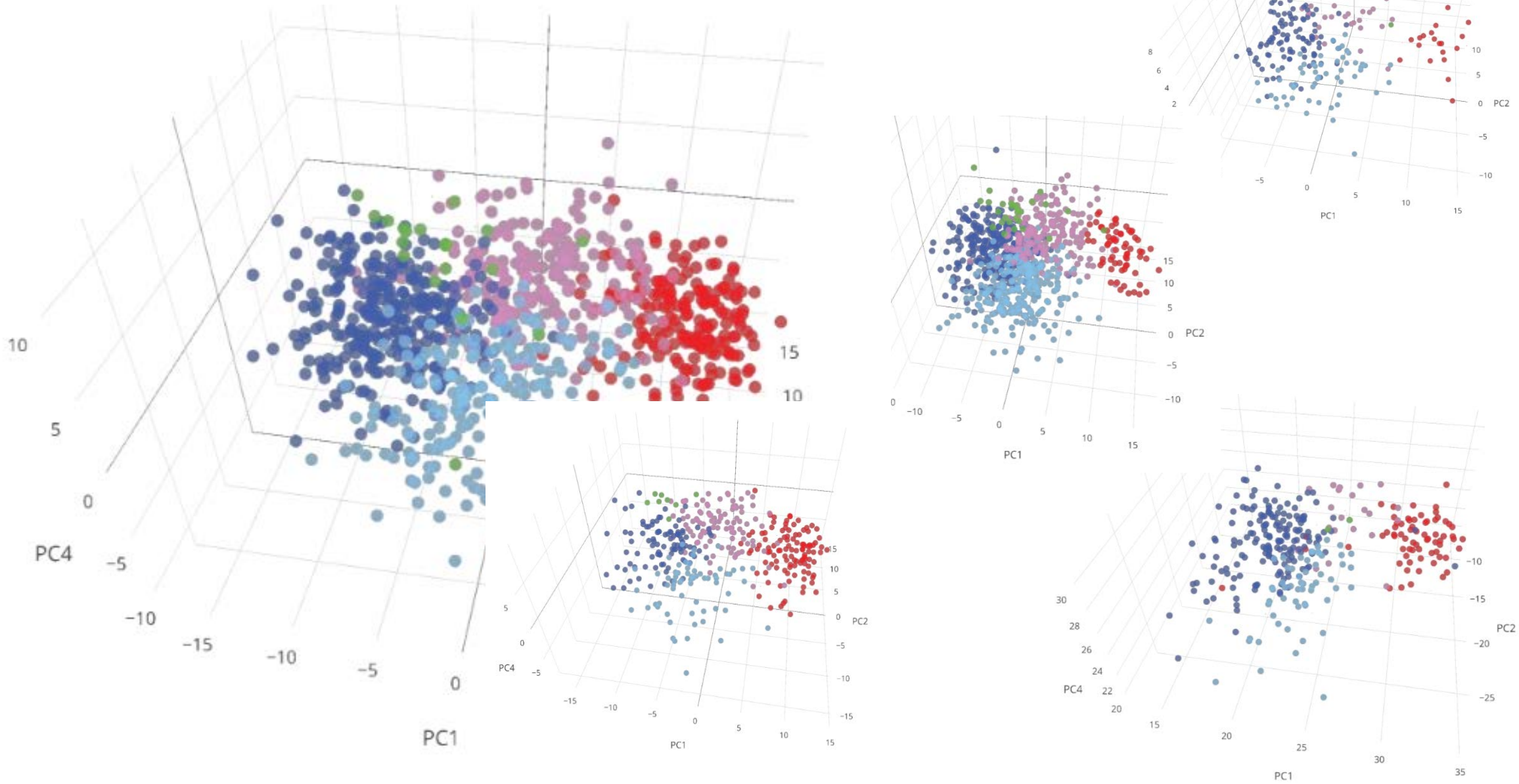


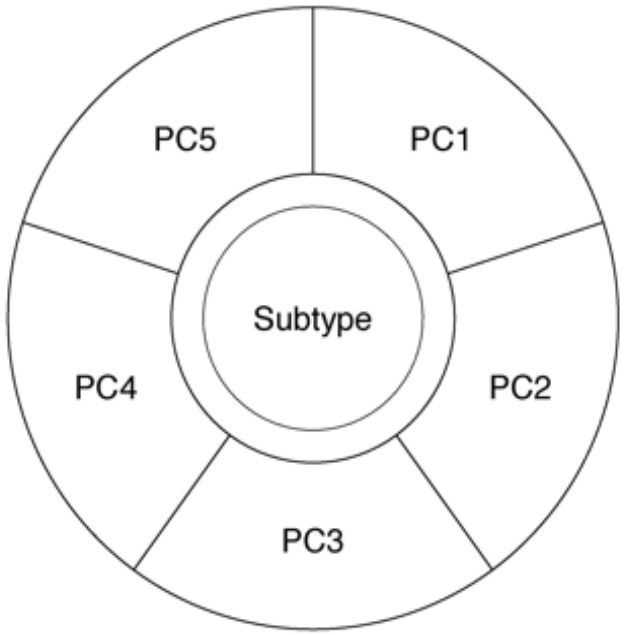
Myke Madsen, MSTAT

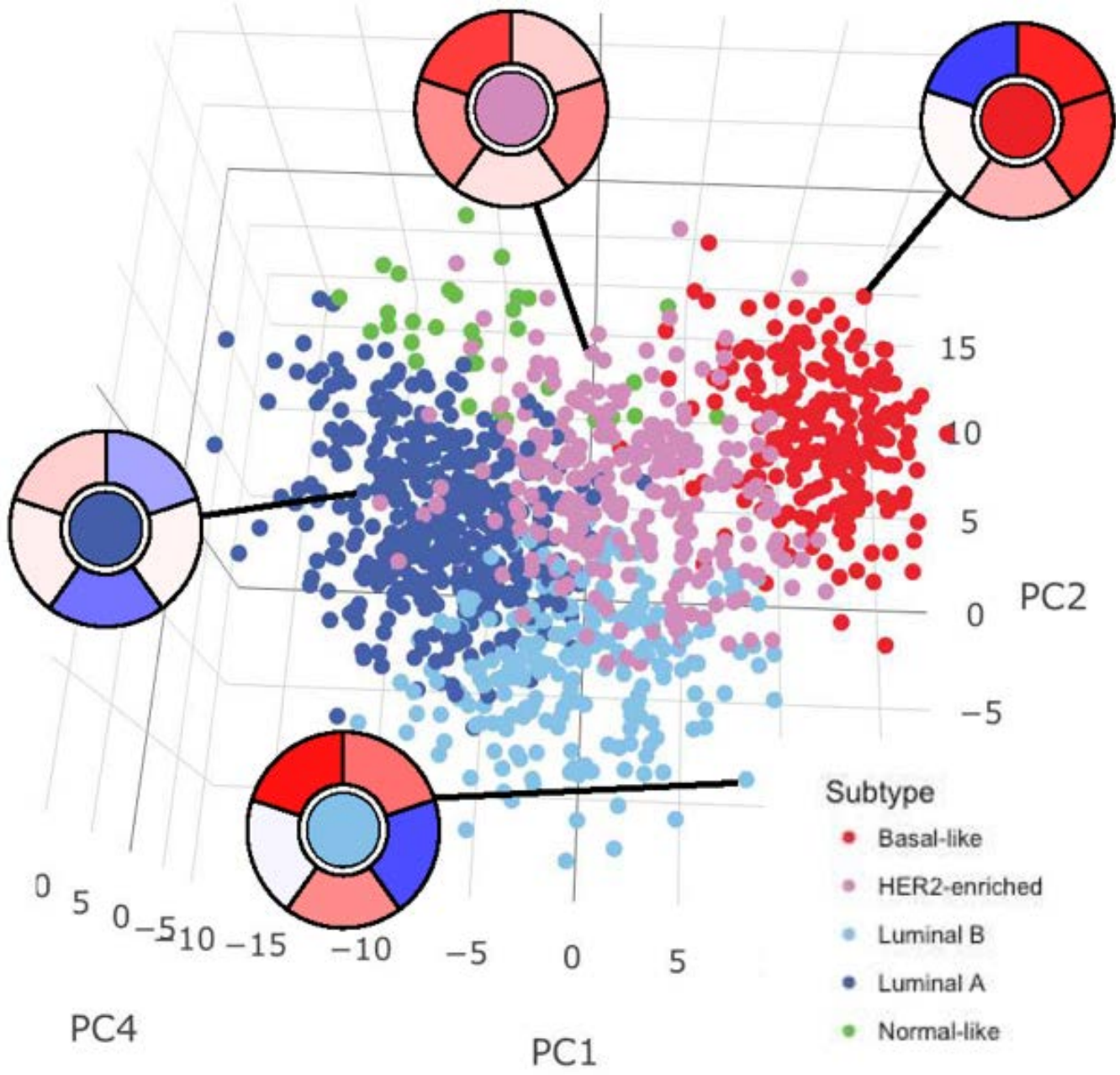
PC1	30.5%
PC2	18.9%
PC3	10.2%
PC4	5.3%
PC5	3.2%

Sweeney *et al* CEBP 2014

PC1, PC2, and PC5 quantitative framework for subtypes




PC5
PC1
Subtype
PC4
PC2
PC3


15
10
5
0
−5
PC2
0
5
0
−5
10
−15
−10
−5
0
5
PC4
PC1
Subtype
Basal-like
HER2-enriched
Luminal B
Luminal A
Normal-like

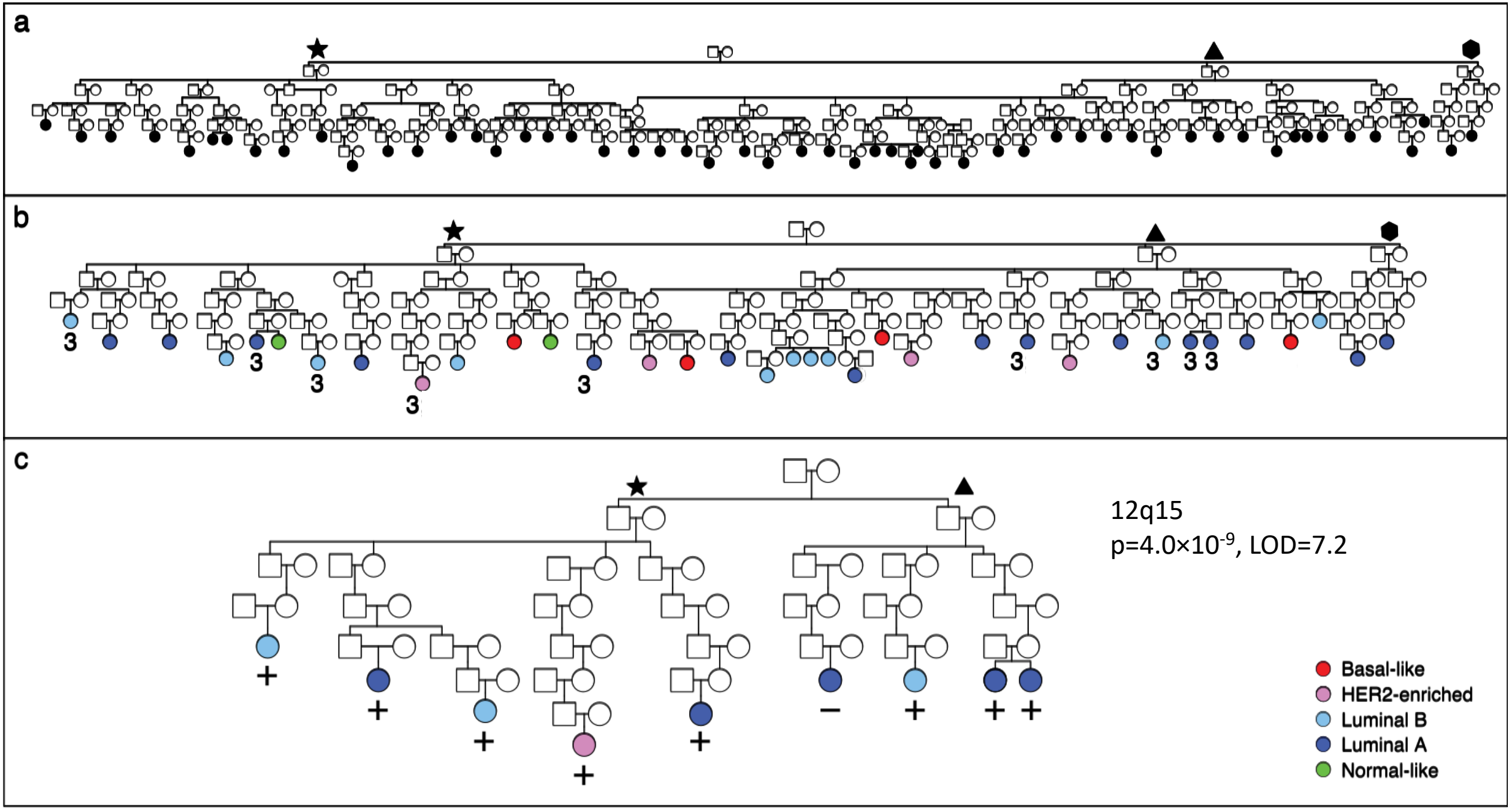
Any evidence for familial clustering?

$p<10^{-12}$ $p=7.6 \times 10^{-8}$

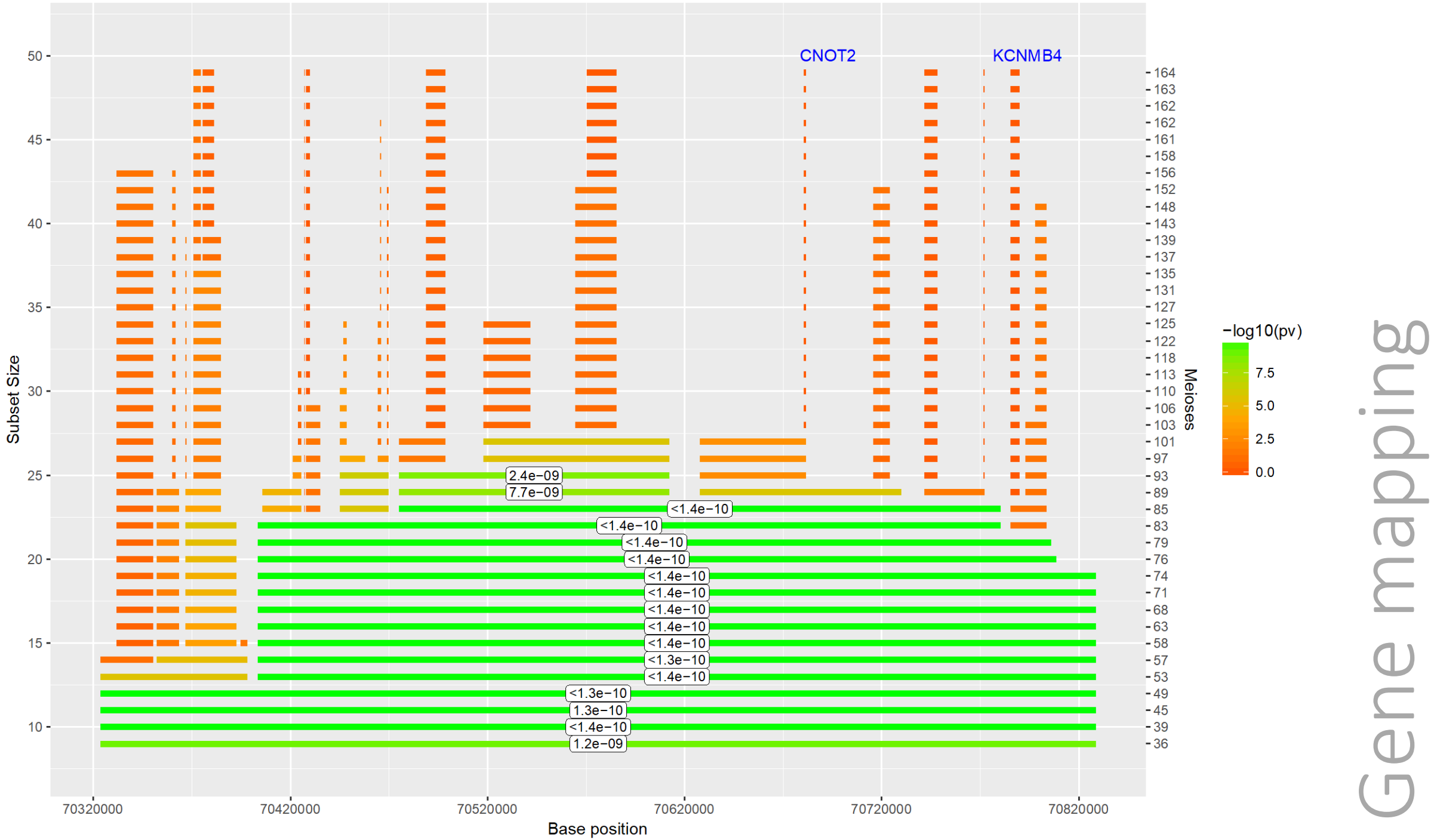
		PC3		PC5	
Pedigree	n	p	t	p	t
1800	20	ns	[illegible]	ns	-1.609
1801	17	ns	2.03	ns	-2.311
1808	24	0.0[illegible]	[illegible].76	0.0129	-3.674
1809	15	0.0778	3.13	ns	-2.468
1812	17	[illegible]s	2[illegible]2	ns	-0.305
1817	35	0.0[illegible]06	[illegible].55	0.0133	-3.508
1818	20	0.014[illegible]	3.72	ns	-0.230
1819	26	0.[illegible]001	[illegible]	ns	-1.437
1820	20	ns	1.60	0.0033	-4.352
1821	18	0.1014	2.92	ns	-1.735
1822	31	0.00004	5.54	ns	-0.184

Comparing to the population (LACE/Pathways). Bonferroni correction already performed

Potentially promising for gene mapping!



Madsen *et al* CEBP 2018

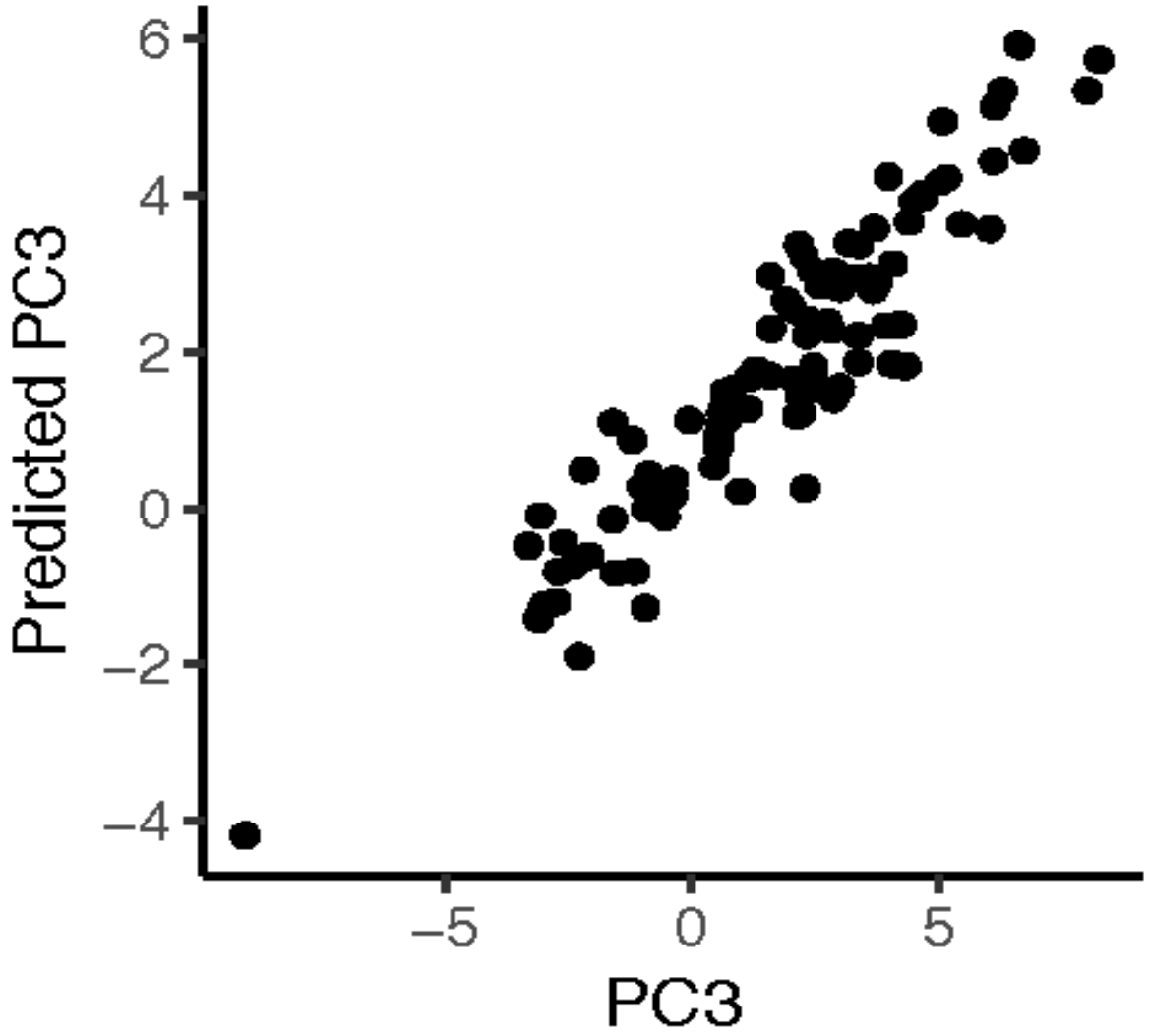


Gene mapping

Polygenic risk?

- 38 SNPs (from GWAS hits)
- Multivariate r^2=0.93

- Precision risk?
- Prevention trials?



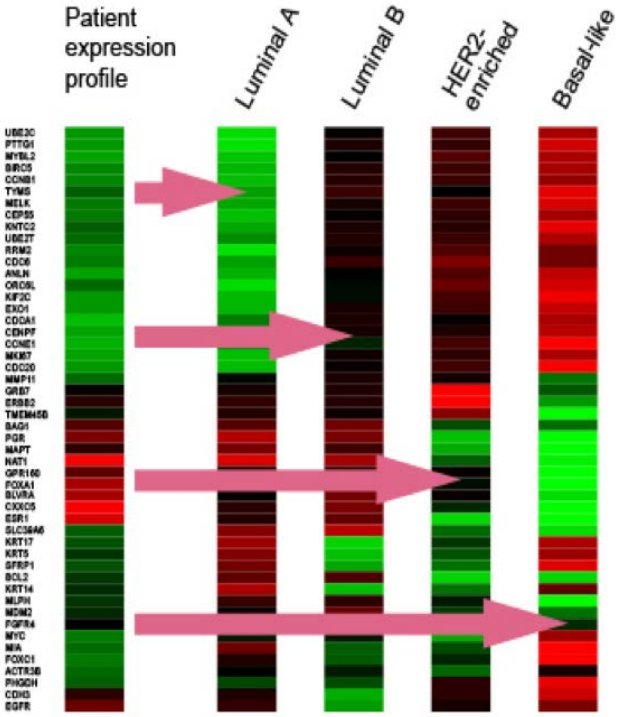
Gene expression – prognosis and treatment modality

Poor prognosis disease. Informative for treatment modality

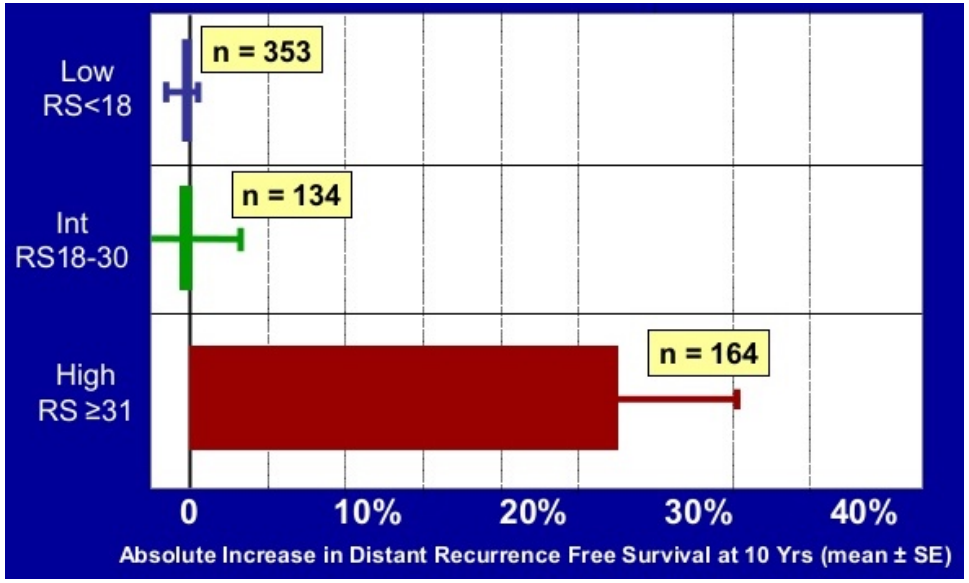
prosigna™

oncotype DX® Breast Cancer Assay

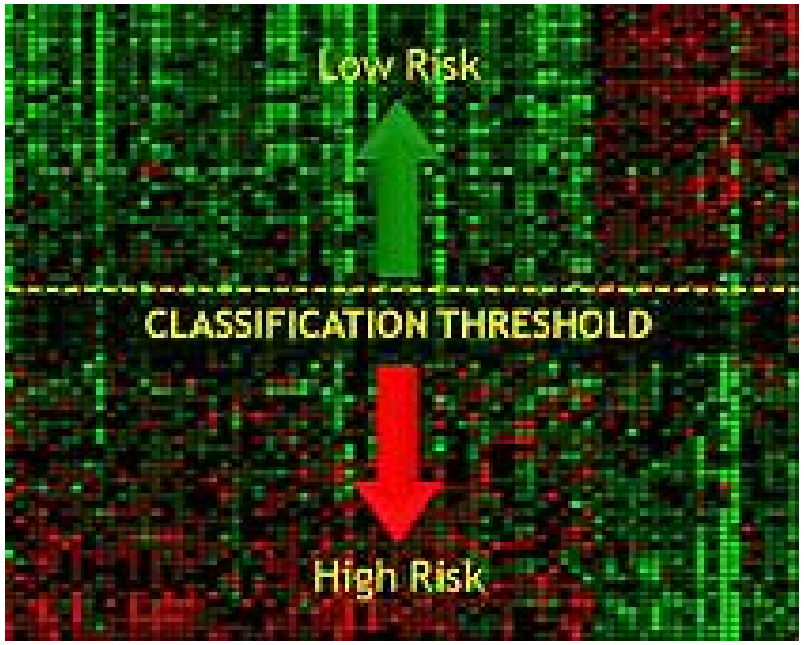
mammaprint®



Kelly *et al* Oncologist 2012



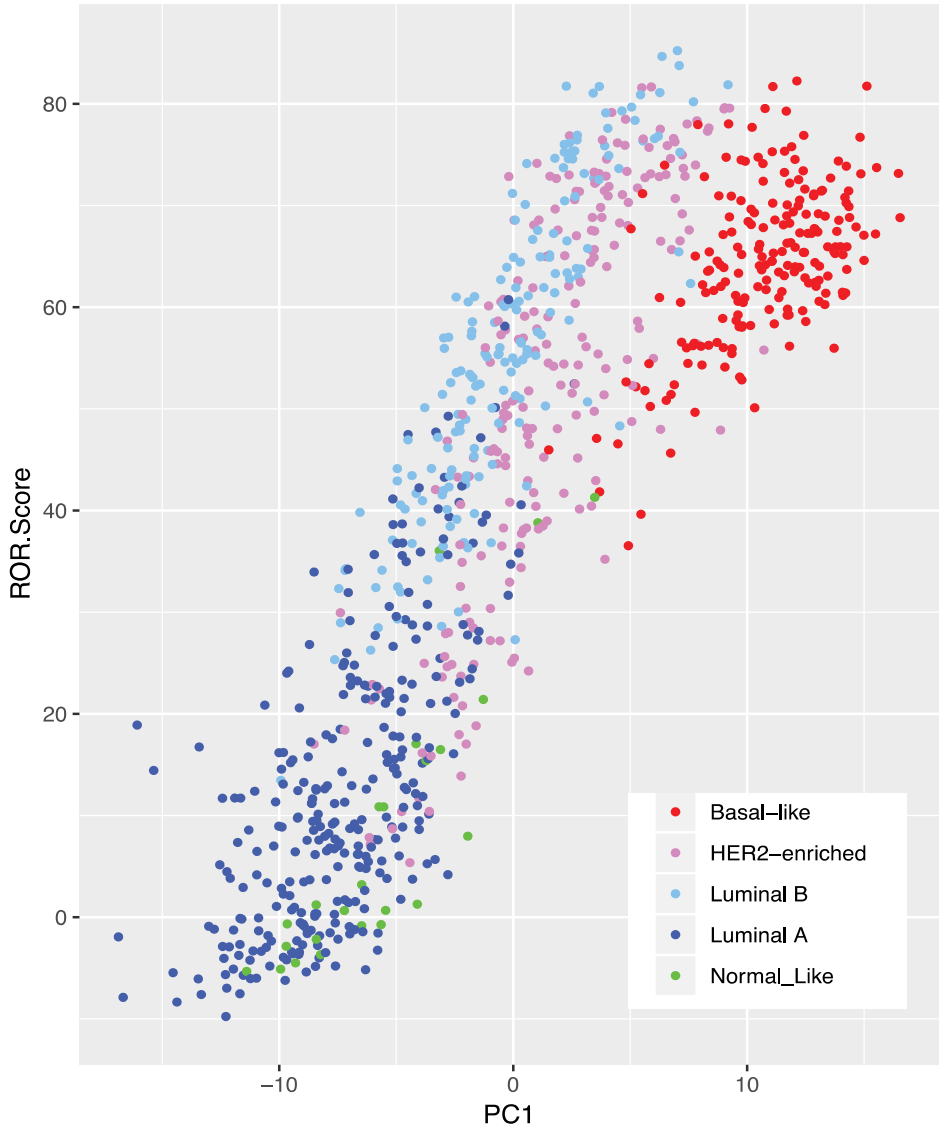
Paik *et al* NEJM 2004

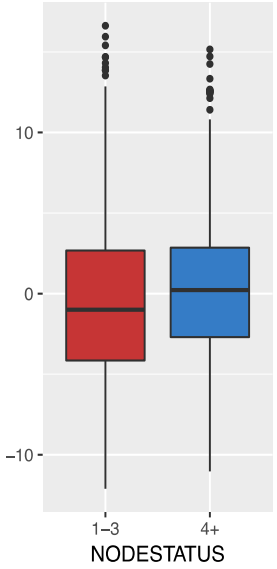


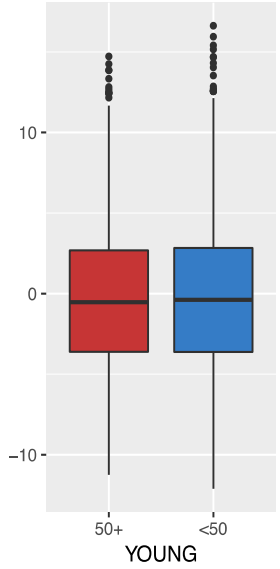
van 't Veer *et al* Nature 2002

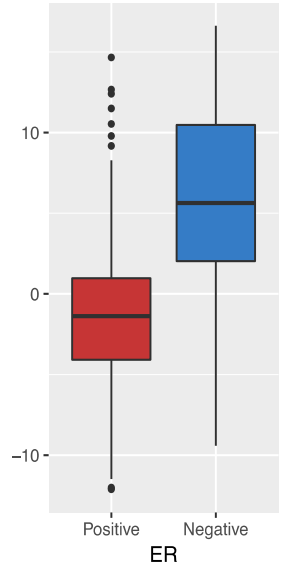
Precision therapy elusive Unable to identify interactions with specific drugs

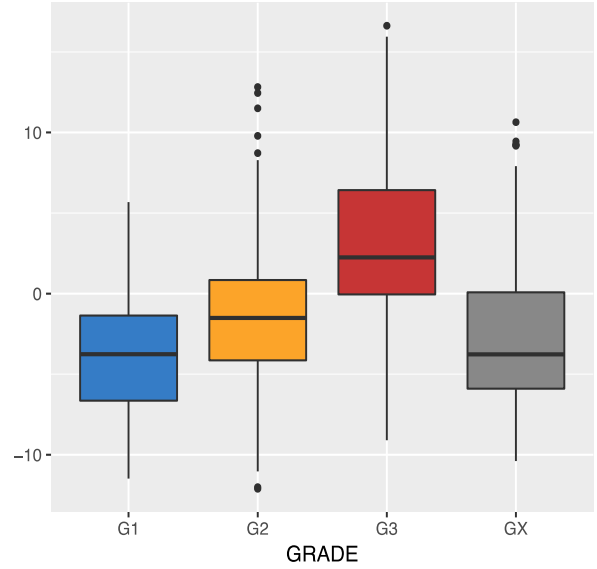
PC1 is recurrence risk… prognosis

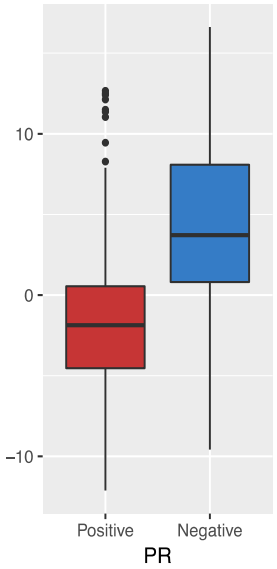


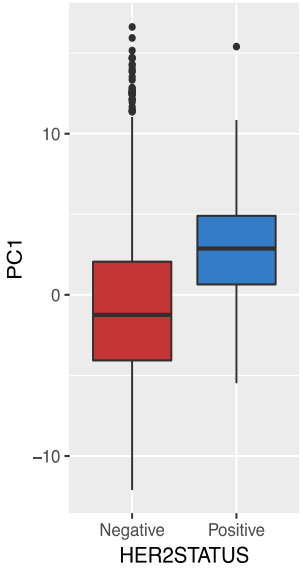


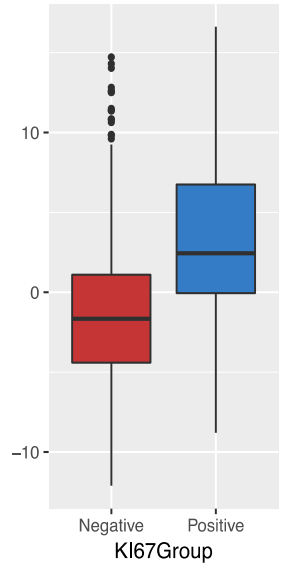


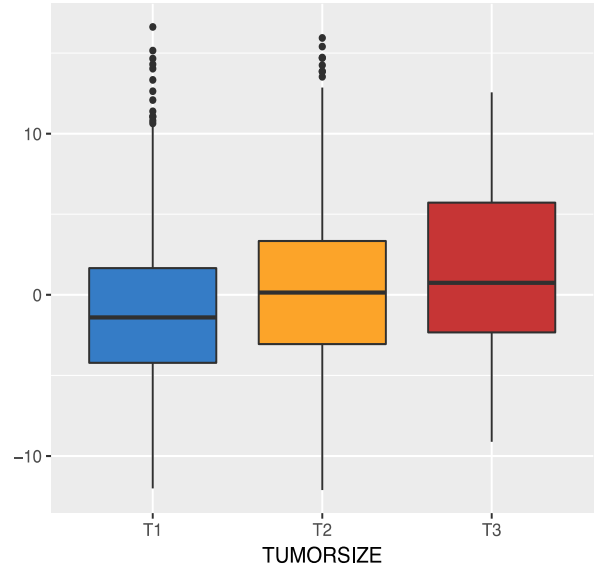






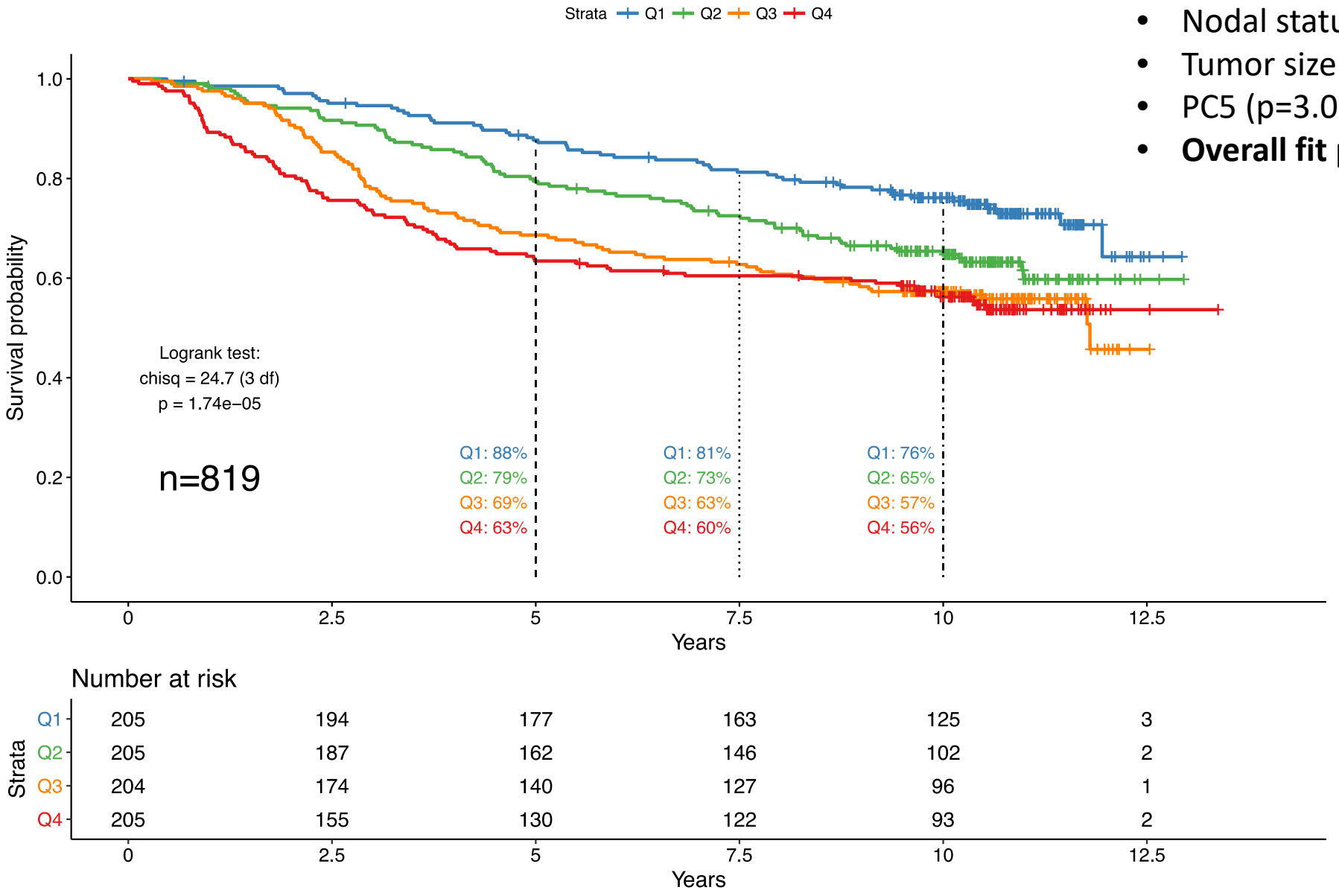






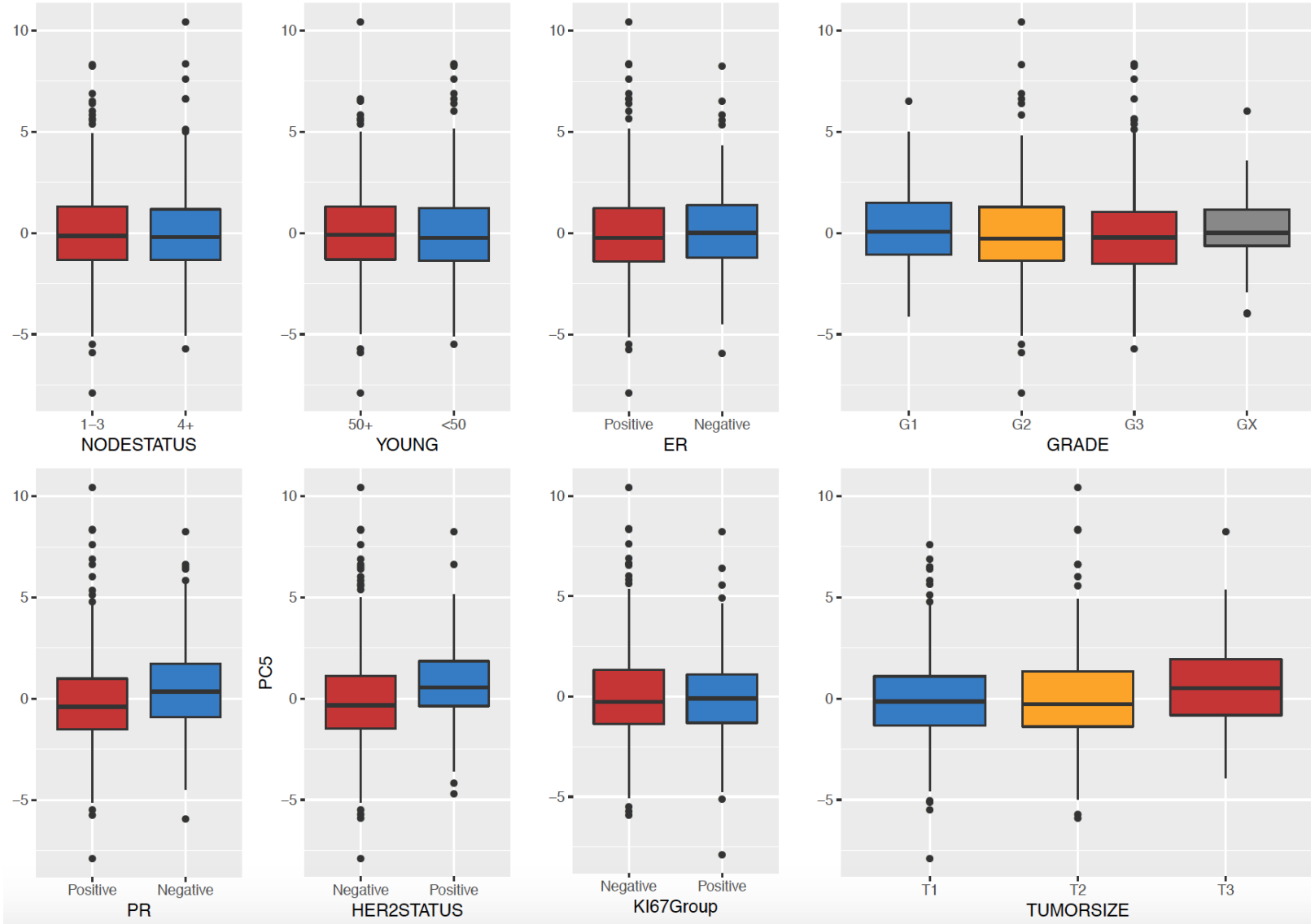
PC1 and Disease-Free Survival

- In a best fitting model
  - PC1 ($p=1.3\times10^{-6}$)
  - Nodal status ($p=2.7\times10^{-4}$)
  - Tumor size ($p=1.0\times10^{-3}$)
  - PC5 ($p=3.0\times10^{-3}$)
  - **Overall fit $p=2.5\times10^{-12}$**



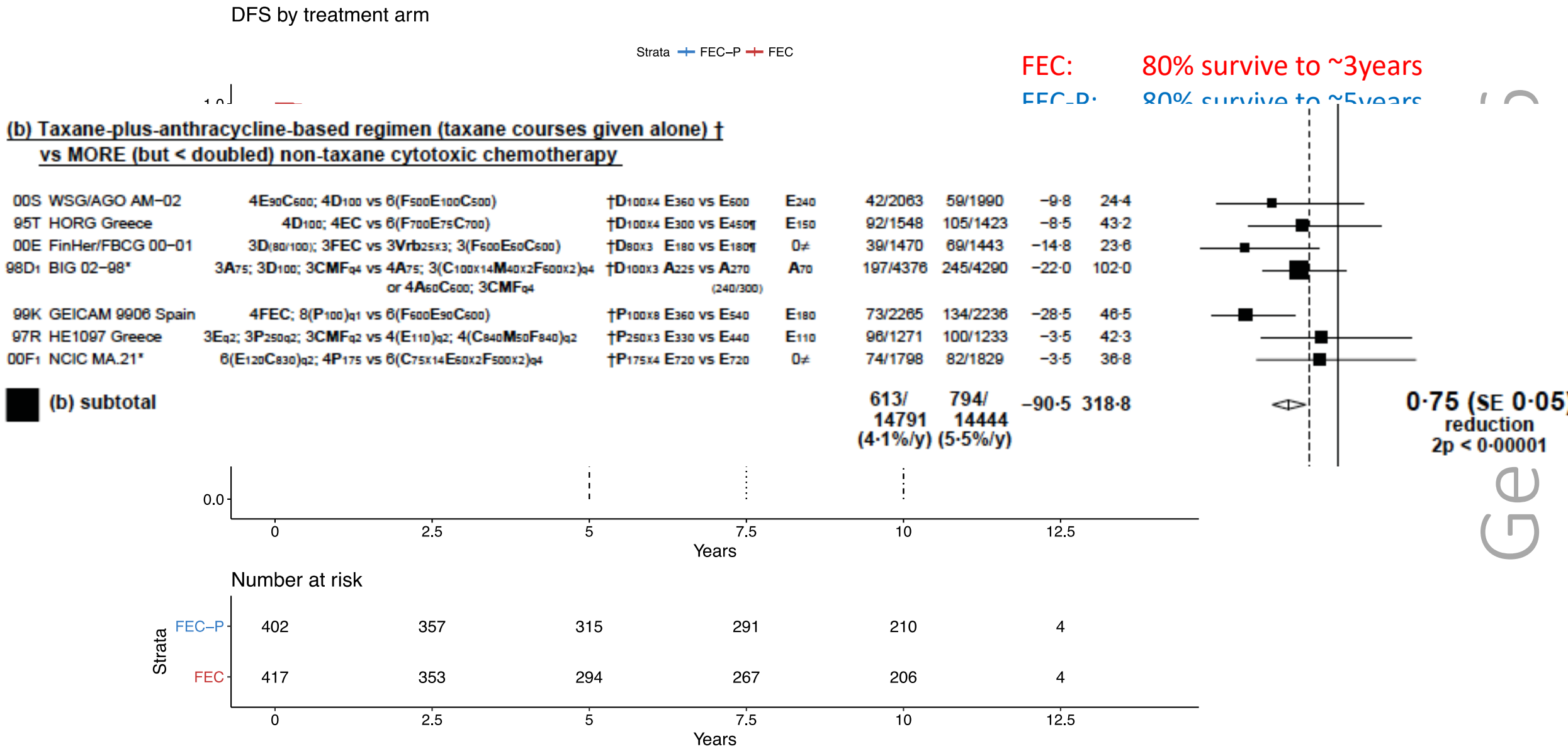
Geicam 9906

PC5 and clinical-pathological characteristics



More info for prognosis

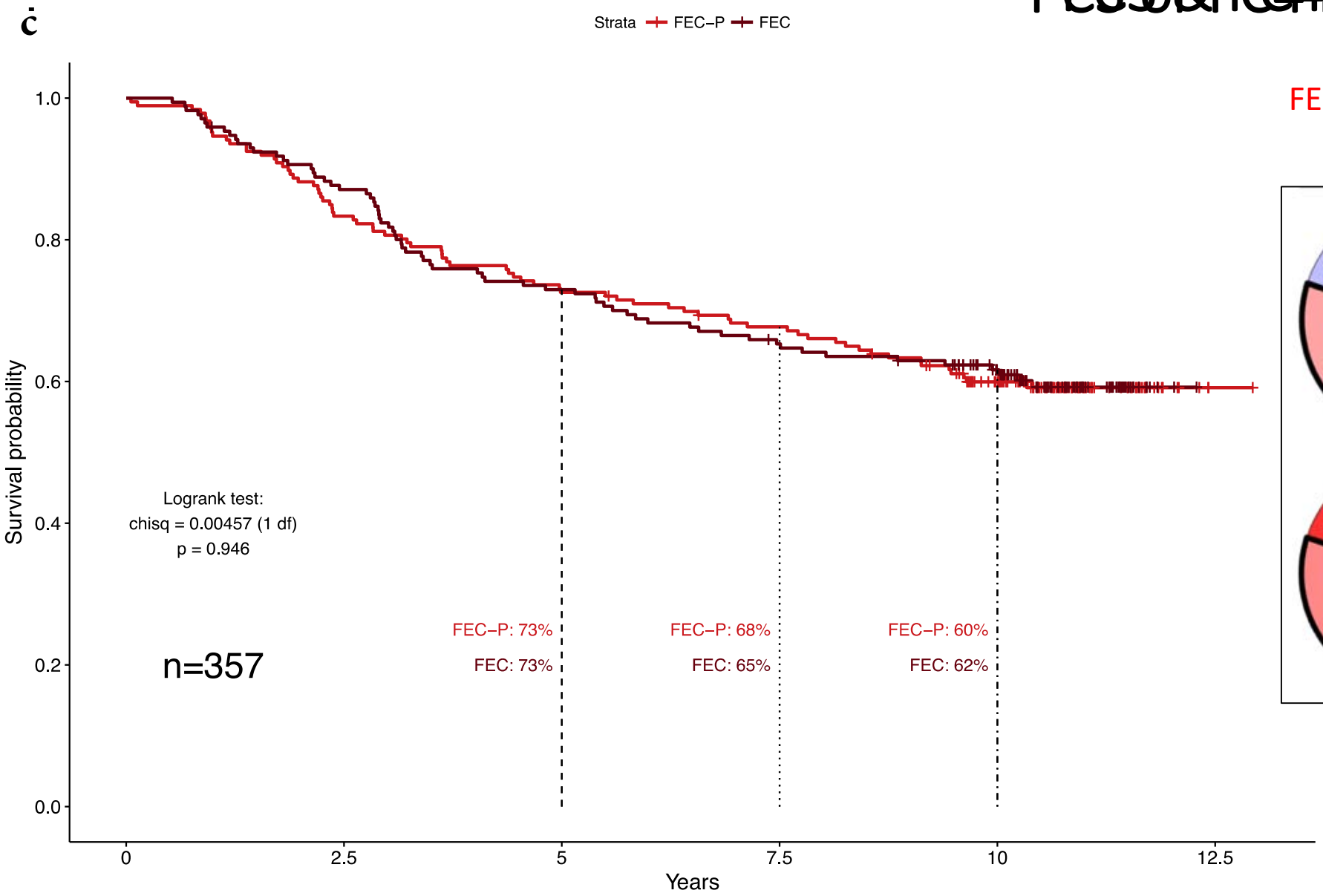
Main trial result: paclitaxel extends disease-free interval

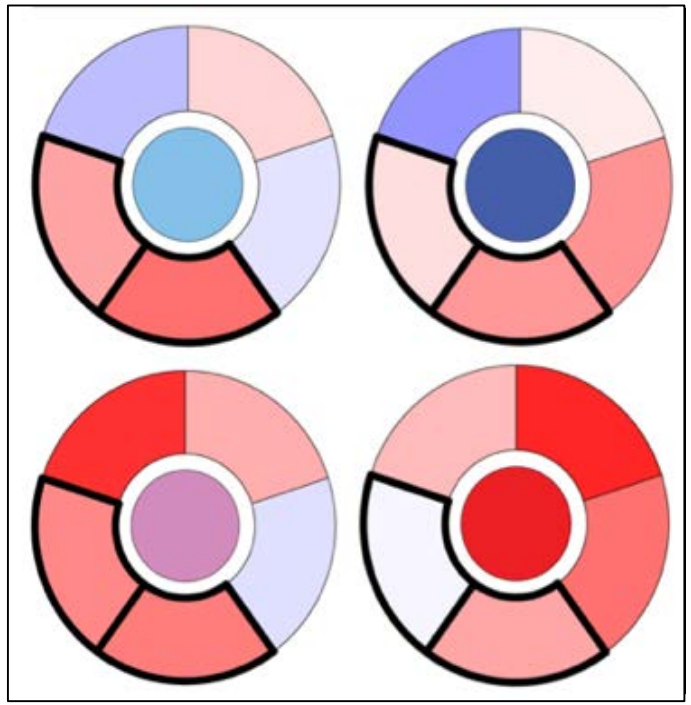


Dimension x Drug interactions?

PC3 & PC4 High (15.4% patients)

FEC & FEC-P: 80% survive to ~3 years



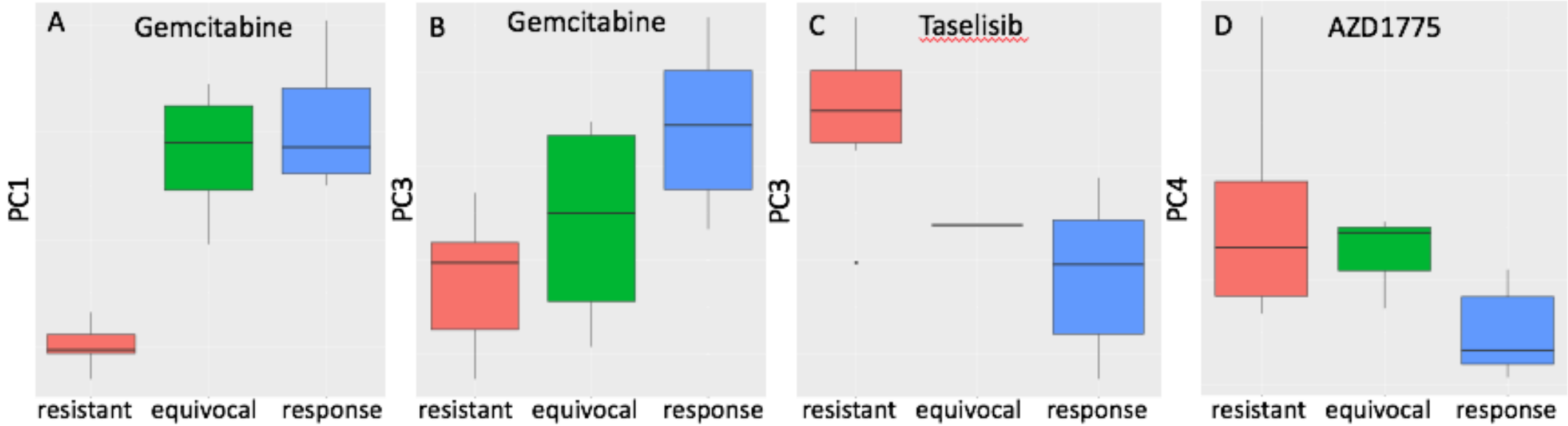


PC3 and PC4
Significant interactions with paclitaxel
Camp *et al* BCRT 2019

Patient-derived organoid models

- Preliminary utility as a framework for drug screens

Bryan Welm, PhD



Quantitative tumor dimension framework

- Dimensions add resolution
  - PC1-PC2-PC4 provides framework with increased resolution for categorical intrinsic subtypes

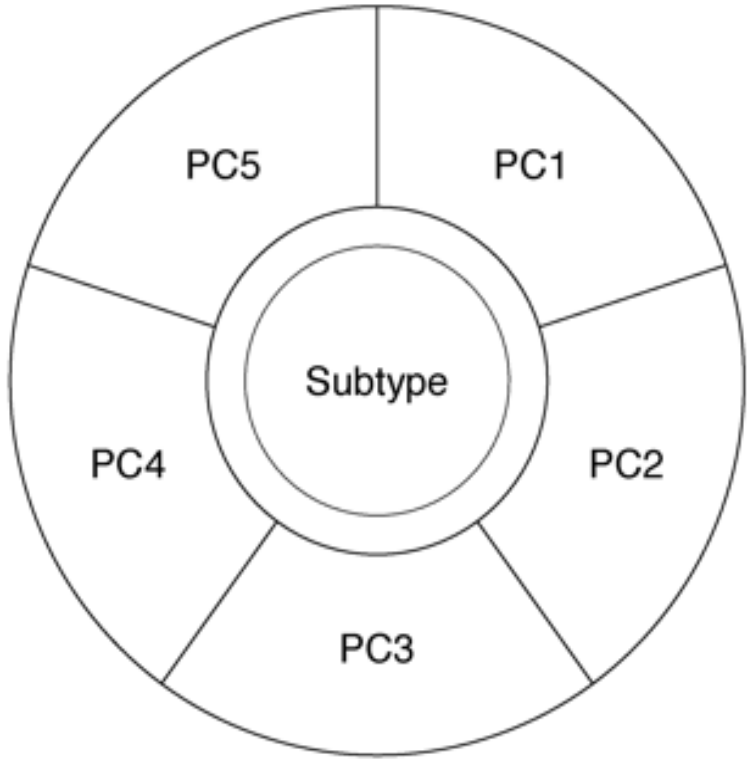
- Inherited susceptibility
  - Pedigree studies, PC3 and PC5 heritable
  - GWAS polygenic studies

- Precision risk
  - Precision prevention

- Survival analysis: Prognosis
  - PC1 and PC5 associated with prognosis
  - PC1 associated with risk of recurrence –Prosigna, Oncotype DX, Mammaprint

- Precision therapeutics
  - PC3 and PC4 proposed drug interaction with paclitaxel

- Preclinical models
  - Dimensions preserved in organoid and xenograft models



Waller, poster #30, 2:30pm

Thank you!

University of Utah / HCI

- Phil Bernard
- Rachel Factor
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