The Capital Region of Denmark

REGION

"Molekylære subtyper af brystkræft"

DBCG´s 40 års jubilæumsmøde, 18-19. Januar 2018
Hotel Marselis, Århus

- Maria Rossing, MD, PhD
- Enheden for Genomisk Medicine, GM4113, Rigshospitalet

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Genomisk Medicin, Rigshospitalet

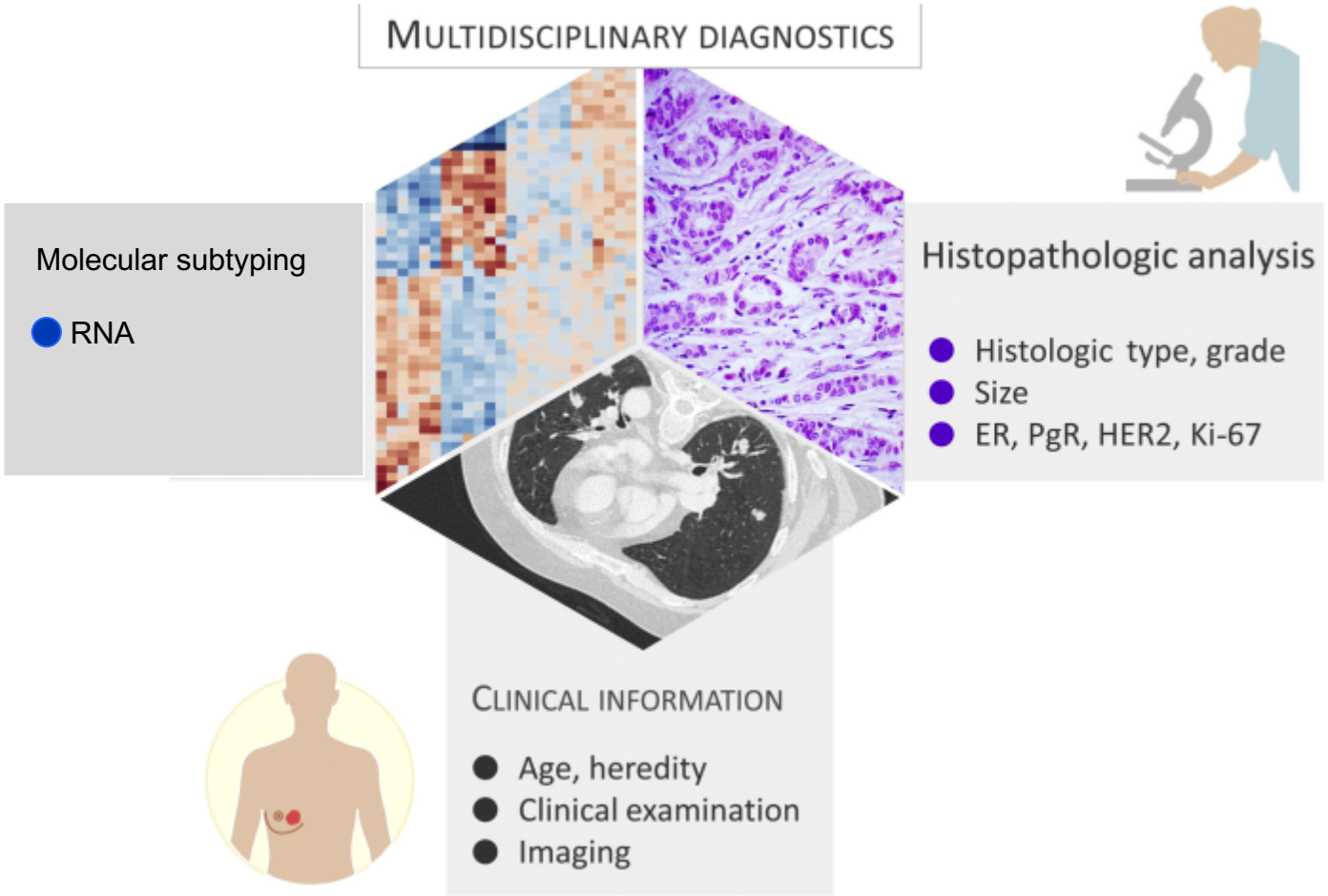
What is Genomic Medicine??

"an emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making) and the health outcomes and policy implications of that clinical use"

National Human Genome Research Institute

- sikre effektiv og præcis diagnostik og facilitere behandlingsbeslutninger
- skal være på forkant med molekylærgenetiske analyser
- sikre at de kliniske afdelinger har adgang til high-throughput teknologier

Brystkræftdiagnostik er blevet multidisciplinær



Russnes et al., AJP, 2017, with modifications

letters to nature

Molecular portraits of human breast tumours

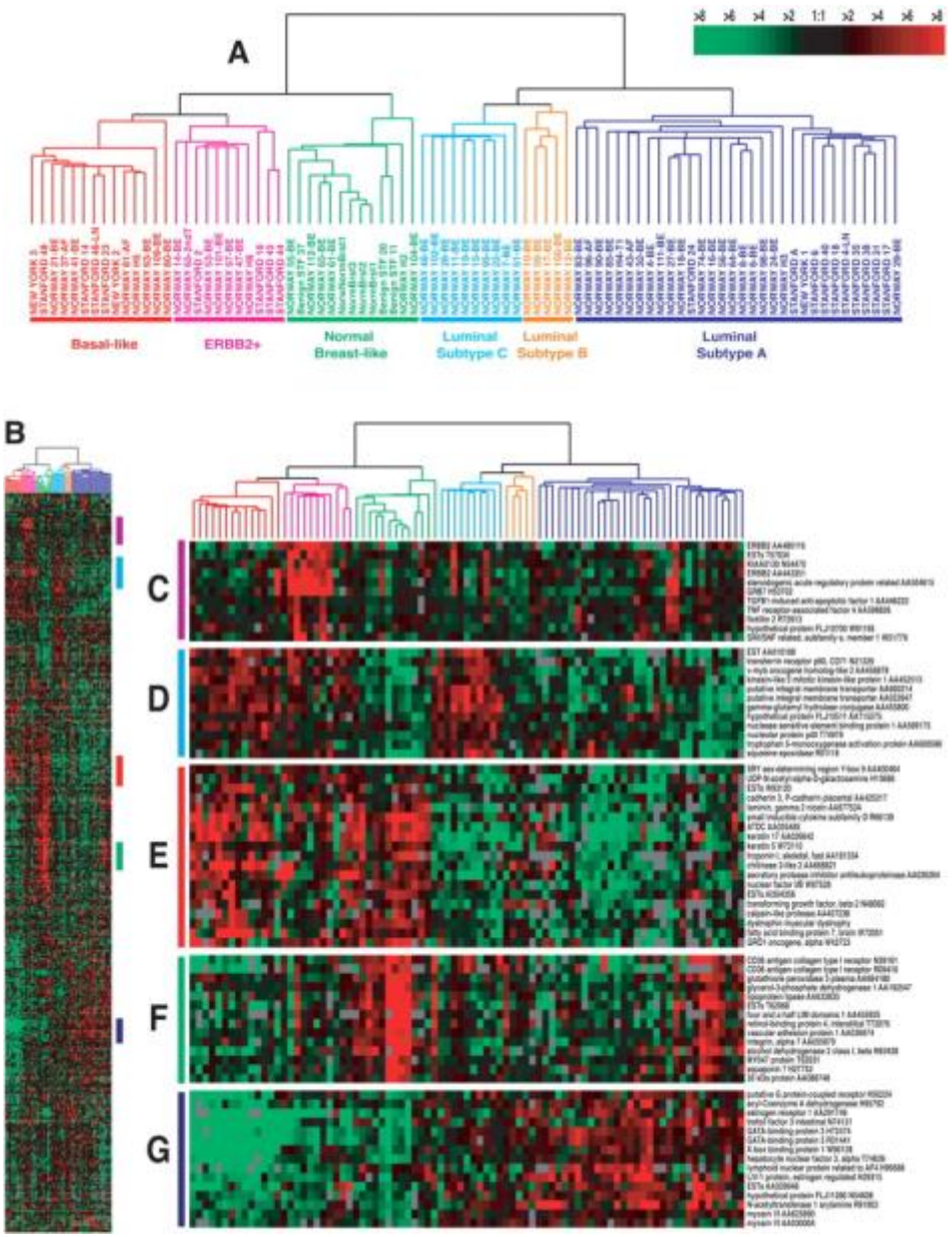
Charles M. Perou*†, Therese Sørlie†‡, Michael B. Eisen*, Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*, Jonathan R. Pollack¶, Douglas T. Ross¶, Hilde Johnsen‡, Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*, Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning**, Anne-Lise Børresen-Dale‡, Patrick O. Brown¶†† & David Botstein*

NATURE | VOL 406 | 17 AUGUST 2000 | www.nature.com

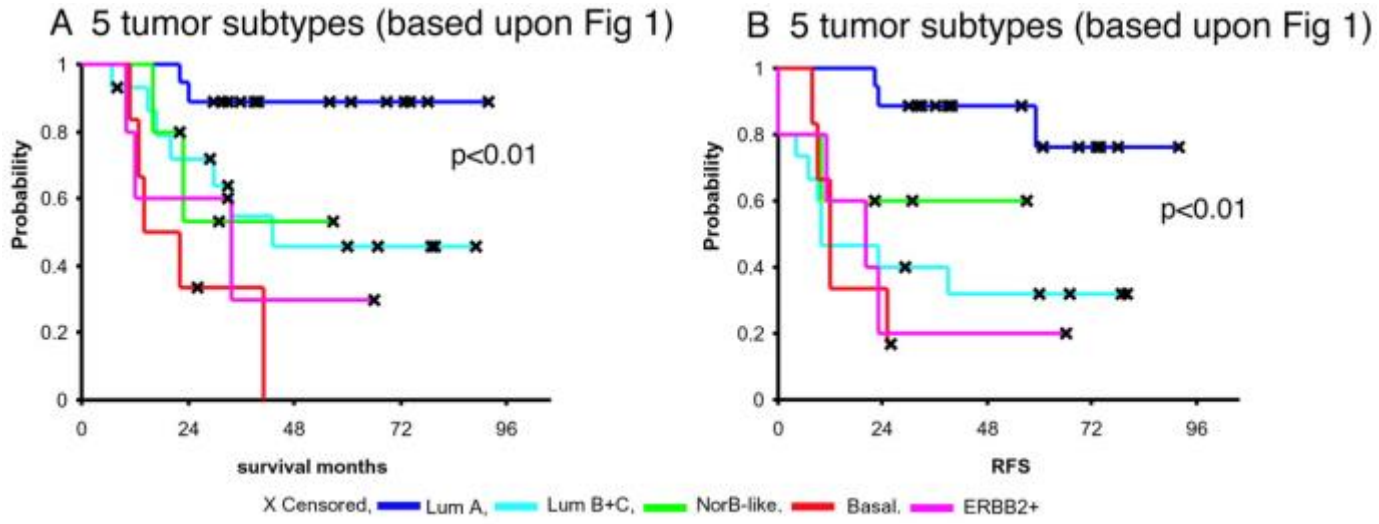
Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

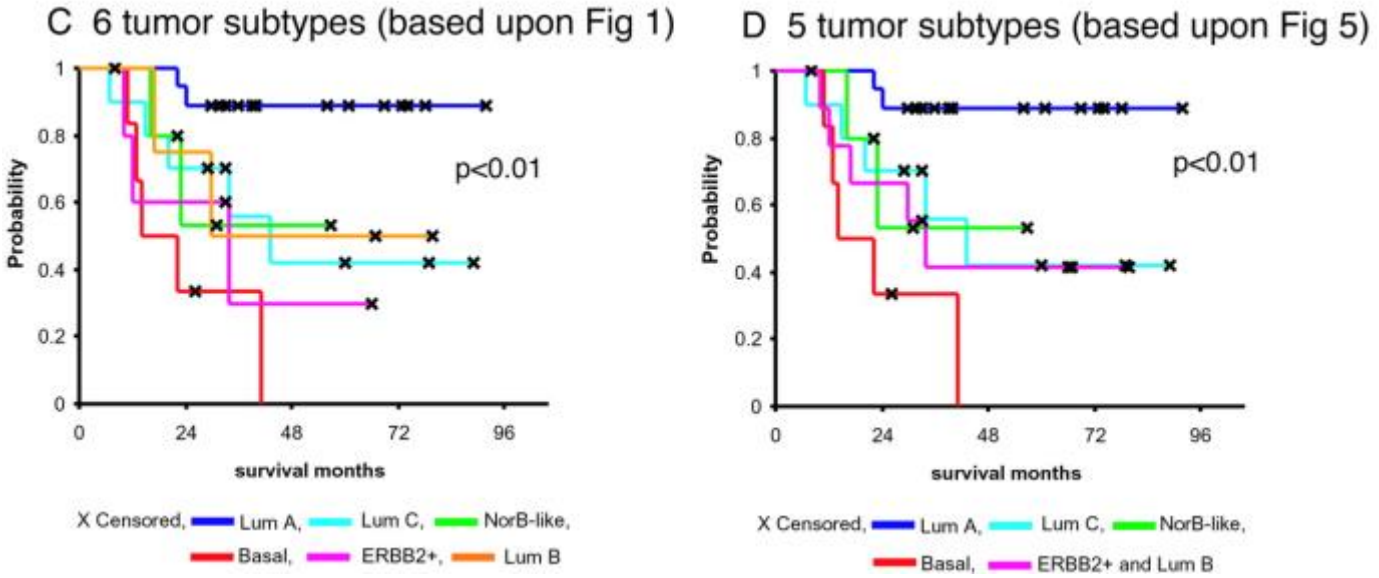
Therese Sørlie[a,b,c], Charles M. Perou[a,d], Robert Tibshirani[e], Turid Aas[f], Stephanie Geisler[g], Hilde Johnsen[b], Trevor Hastie[e], Michael B. Eisen[h], Matt van de Rijn[i], Stefanie S. Jeffrey[j], Thor Thorsen[k], Hanne Quist[l], John C. Matese[c], Patrick O. Brown[m], David Botstein[c], Per Eystein Lønning[g], and Anne-Lise Børresen-Dale[b,n]

PNAS | September 11, 2001 | vol. 98 | no. 19 | 10869–10874



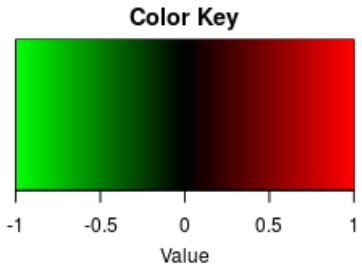
Therese Sørlie et al. PNAS 2001;98:10869-10874

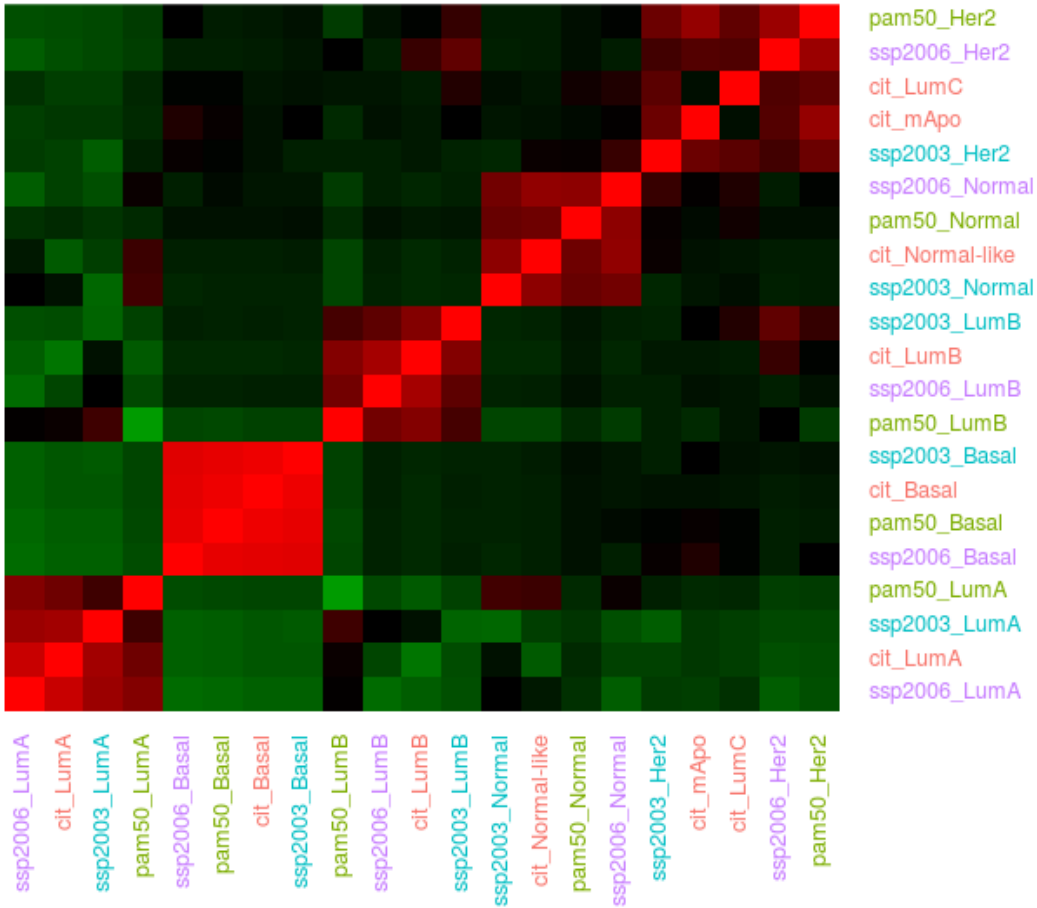




Therese Sørlie et al. PNAS 2001;98:10869-10874

Korrelation af subtyper; forskellige signaturer





Hirachical cluster analysis, unsupervised

- PAM50, 50
- SSP2006 (Hu, BMC)
- SSP2003 (Sørlie, PNAS)
- CIT (Guedj, Oncogene)

Molekylære subtyper; div. platforme

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 25, 2016 VOL. 375 NO. 8

70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer

mammaprint

oncotype DX® Breast Cancer Assay

Uncover the Unexpected™

prosigna™ Breast cancer gene signature assay

www.thelancet.com Vol 378 November 19, 2011

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Subtypeklassifikationsmodel på RH - 2014

Oncogene (2012) 31, 1196–1206

www.nature.com/onc

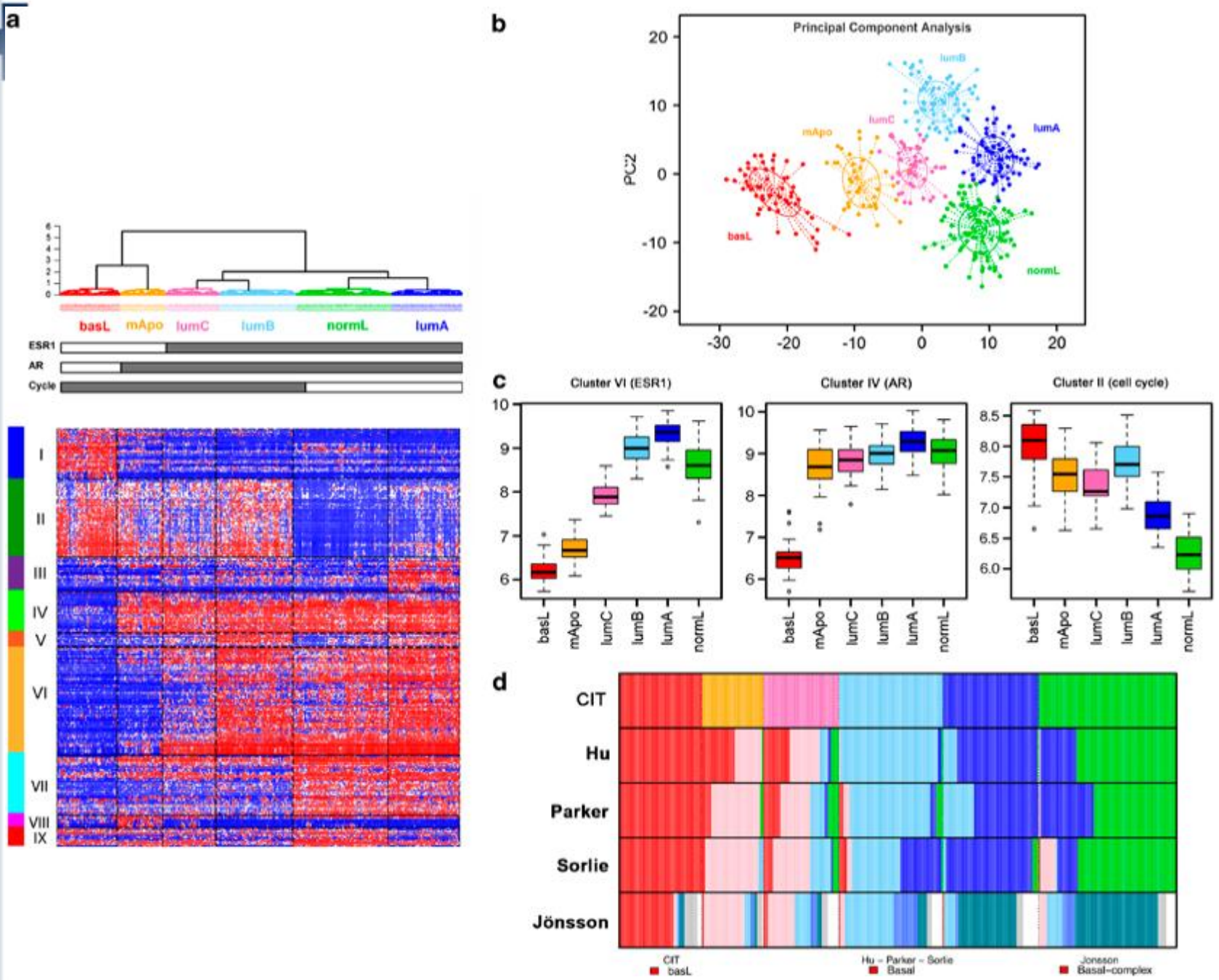
ONCOGENOMICS

A refined molecular taxonomy of breas

M Guedj[1,15], L Marisa[1,15], A de Reynies[1,15], B Orset, F Lerebours[6], P Finetti[7], M Longy[5], P Bertheau[8], JP Feugeas[10,11,12], I Bièche[6], J Lehmann-Che[10,11,12], H de Thé[10,11,12,15] and C Theillet[2,13,14,15]

[1]Ligue Nationale Contre le Cancer, Cartes d'Identité des Tumeurs pr… Cancérologie de Montpellier, Montpellier, France; [3]CRLC Val d'Aur… Pathology, CRLC Val d'Aurelle Paul Lamarque, Montpellier, France… Université Victor Segalen Bordeaux-2, Bordeaux, France; [6]Oncogenet… René Huguenin, St Cloud, France; [7]Department of Molecular Oncolog… Institut Paoli Calmette, Marseille, France; [8]Hopital St Louis APHP, Paris, France; [9]Fédération Nationale des Centres de Lutte Contre le Cu… Saint-Louis APHP, Paris, France; [11]INSERM/CNRS UMR 944/7212, Pu… Paris-7 Denis Diderot, Paris, France; [13]INSERM U896, CRLC Val d'Aurelle-Paul Lamarque, Montpellier, France and [14]Université Montpellier 1, Montpellier, France

- 256 gener
- 6 subklasser
- Genomisk data (incl.CNV)
- Korrelerer med kliniske karakteristika og prognose
- Robust (>3000 pt.)
- Affymetrix platform (open)
- *"In house"*


a
basL
mApo
lumC
lumB
normL
lumA
ESR1
AR
Cycle
I
II
III
IV
V
VI
VII
VIII
IX
b
Principal Component Analysis
PC2
c
Cluster VI (ESR1)
Cluster IV (AR)
Cluster II (cell cycle)
d
CIT
Hu
Parker
Sorlie
Jönsson
CIT
basL
Hu – Parker – Sorlie
Basal
Jonsson
Basal–complex

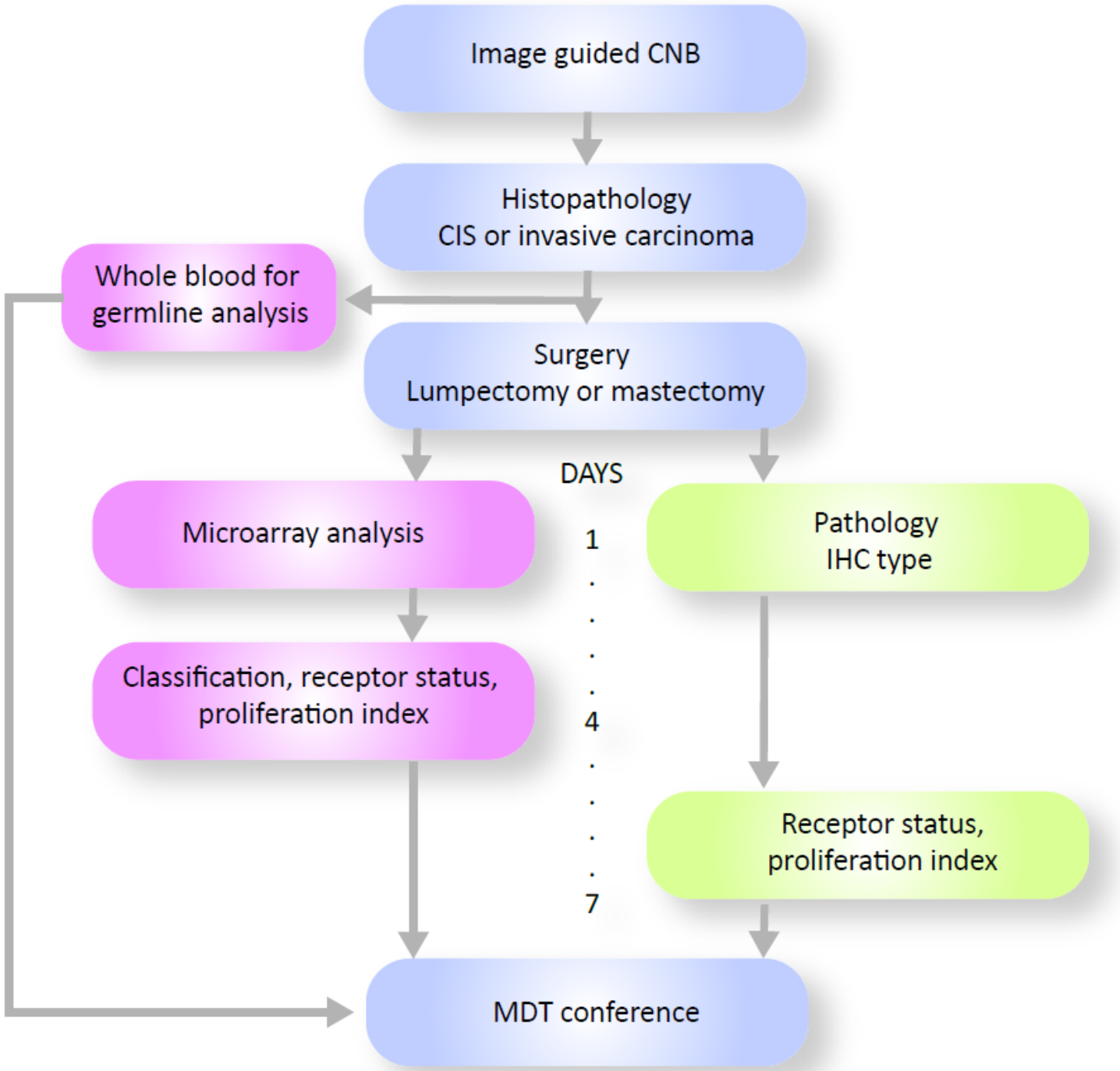


Image guided CNB
Histopathology
CIS or invasive carcinoma
Whole blood for
germline analysis
Surgery
Lumpectomy or mastectomy
DAYS
1
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4
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7
Microarray analysis
Pathology
IHC type
Classification, receptor status,
proliferation index
Receptor status,
proliferation index
MDT conference

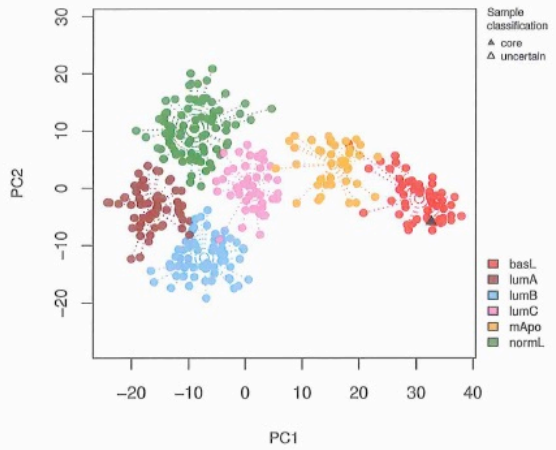


Figure 1: PCA on CIT data used to classify dataset & sample (black).

	Classification	Confidence	Mixed
CIT	basL	CORE	–
PAM50	Basal	HIGH	–

CIT: Possible confidences are: CORE, MIXED, and OUTLIER. If the confidence is MIXED, *Classification* lists the second of the two overlapping clusters under *Mixed*. In the case of an OUTLIER, the nearest cluster is listed under *Classification*.

PAM50: *Confidence* relates to the correlation coefficient (r) between the sample and the nearest cluster of PAM50 classification. Possible confidences are: HIGH ($r \geqslant 0.75$), LOW ($0.75 > r \geqslant 0.25$), and OUTLIER ($r < 0.25$).

Expression profiles

Her2	ERBB2	negative
Estrogen receptor	ESR1	negative
Progesterone receptor	PGR	negative

Proliferation Index(PI) score (tumor PI >5.5): 8.34

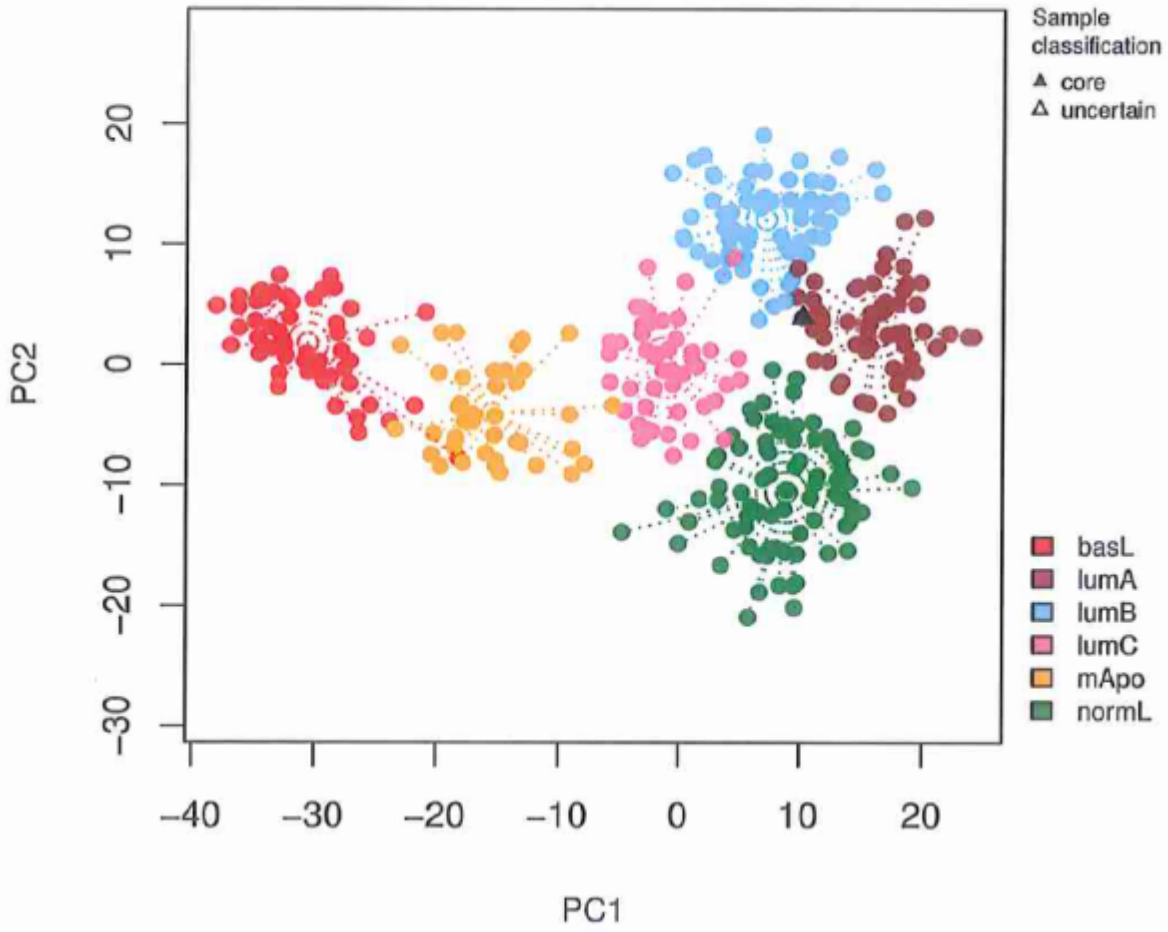
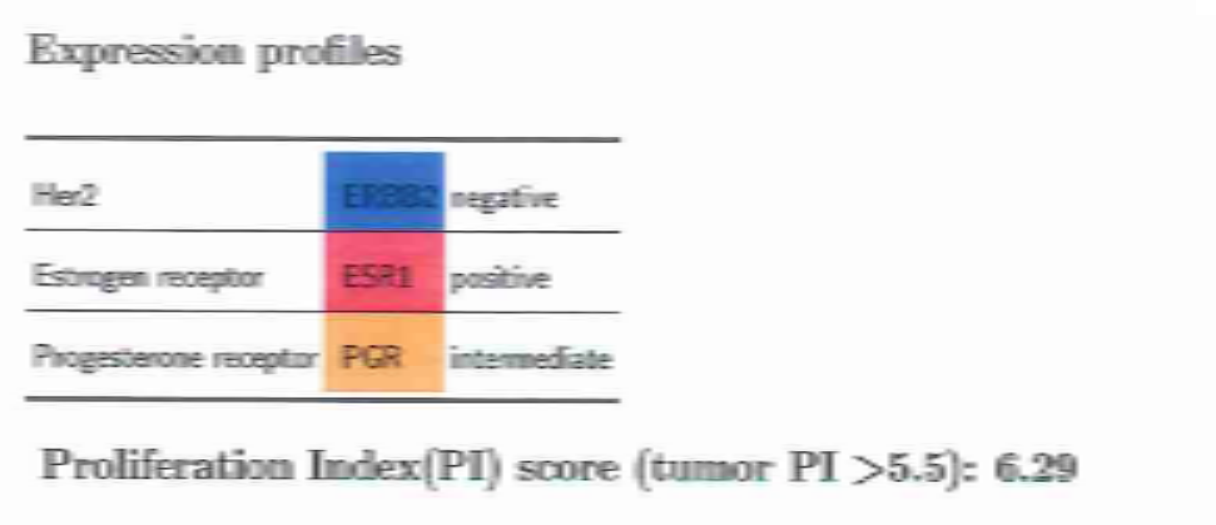


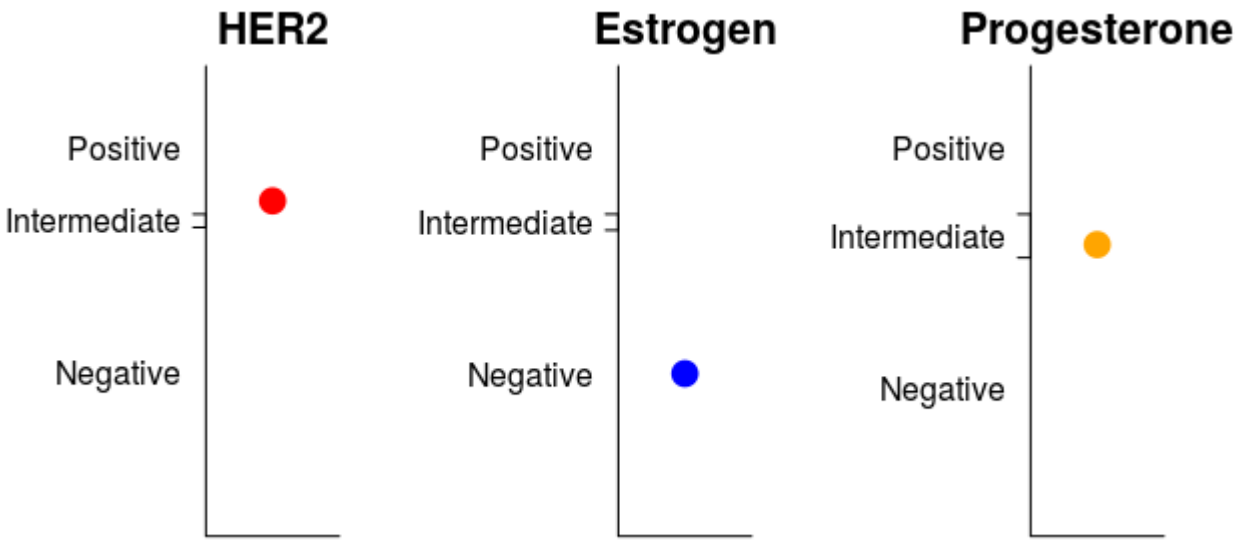
Figure 1: PCA on CIT data used to classify dataset & sample (black).

	Classification	Confidence	Mixed
CIT	lumA	CORE	–
PAM50	LumA	LOW	–

Receptorstatus og proliferation



Ny ”feature” på svar



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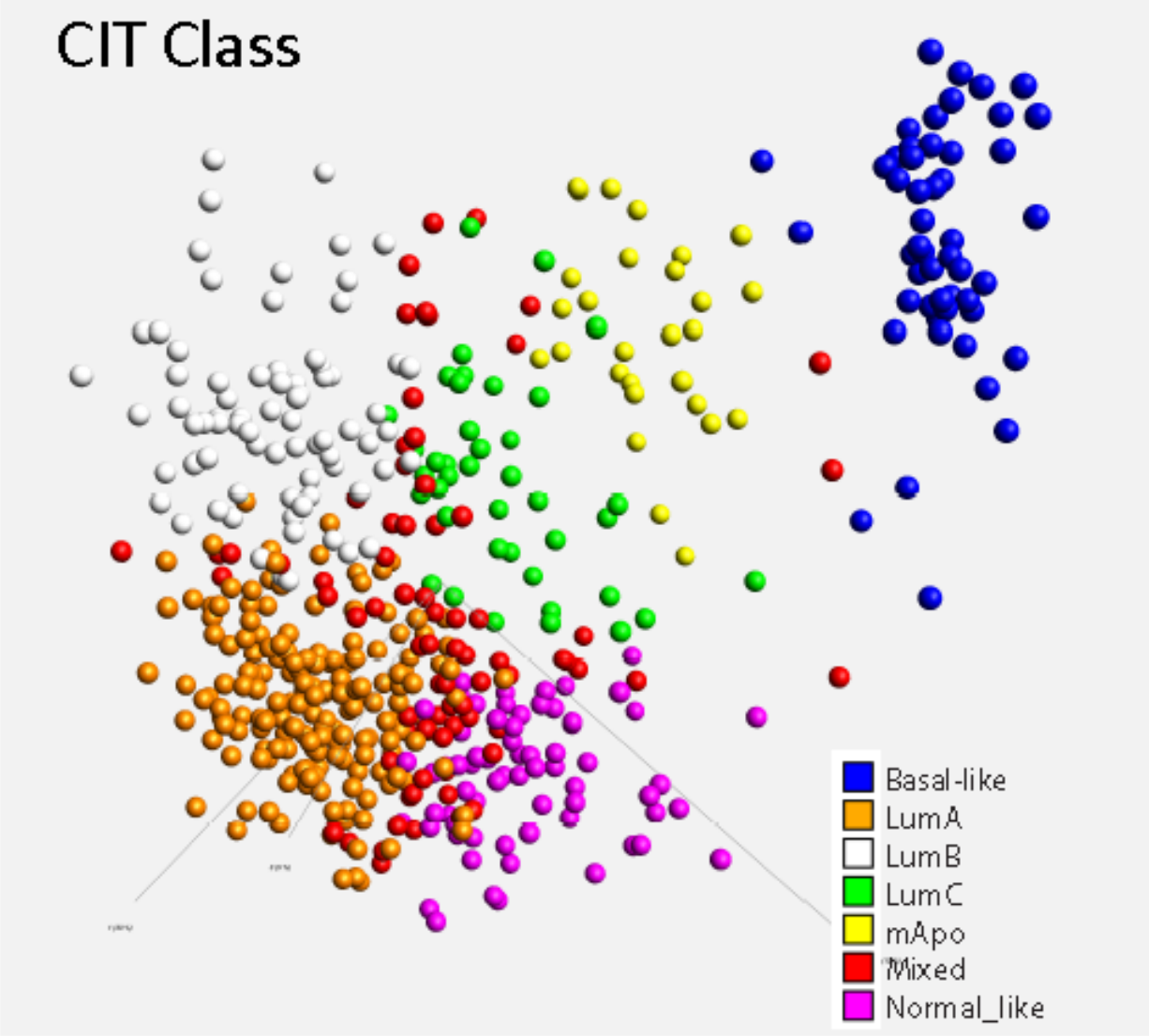
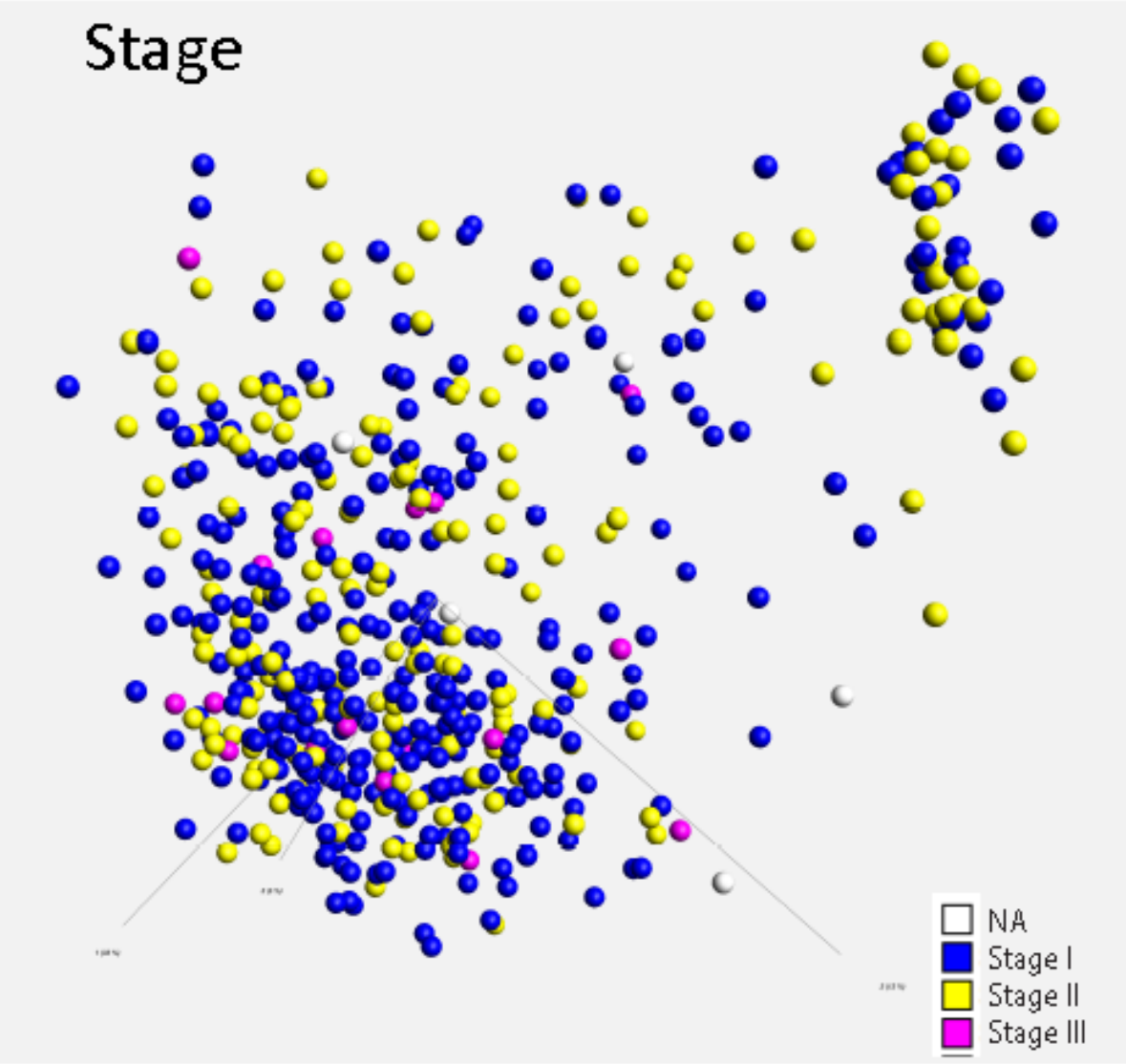
Status efter 1 år med molylære subtyper

- Opstart nov. 2014
- Succesrate
- Fordeling
- Receptor (mRNA vs IHC)
- Ki67 vs Prol. Index (PI)
- Genetisk disponering

- Stadie I-III: 524 vævsprøver
- 4 prøver udgik (1 QC af RNA og 3 normalvæv)
- I alt 520 til subtype (3-10 dage)



Rossing et al., Acta Oncol. 2018



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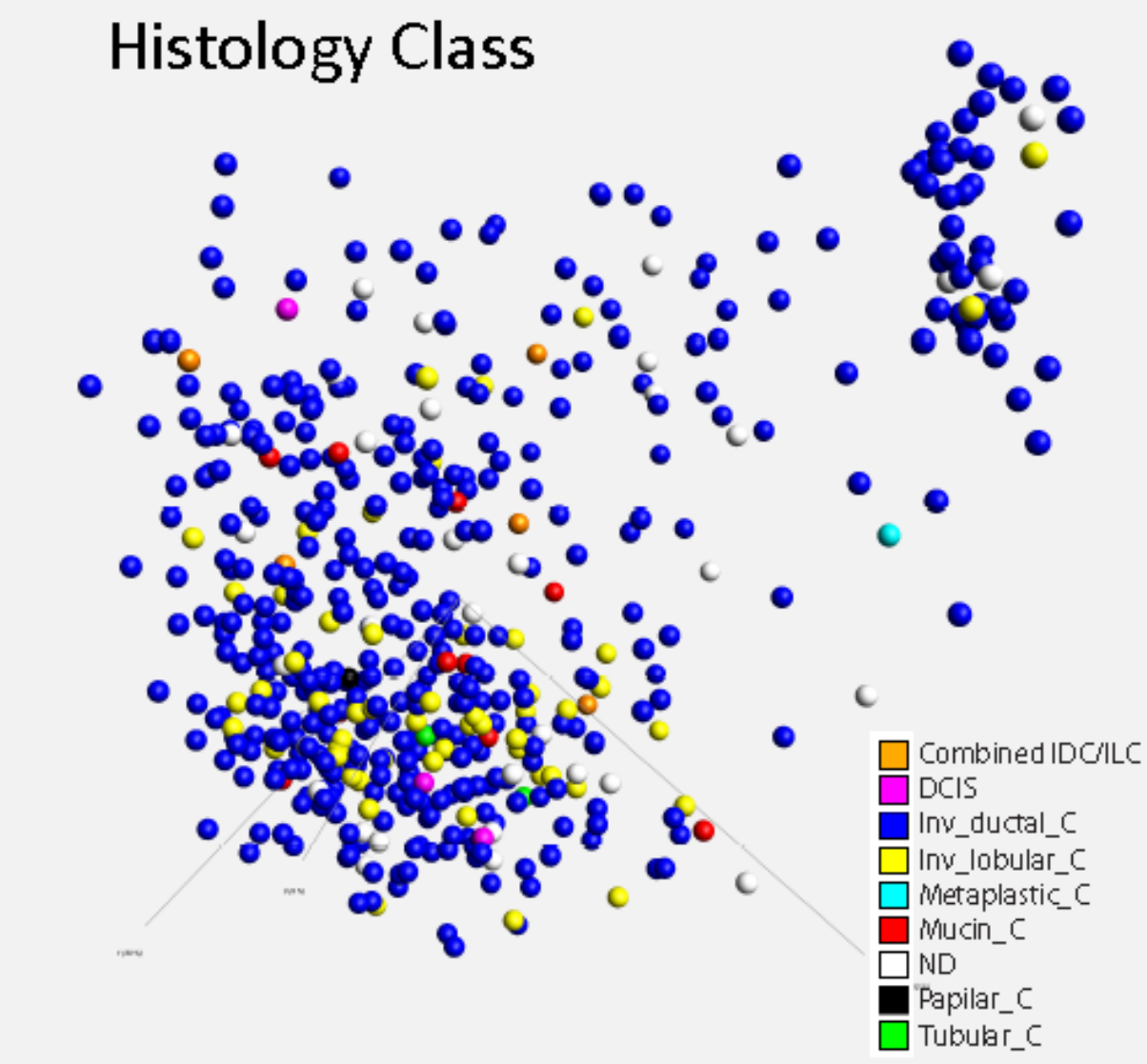


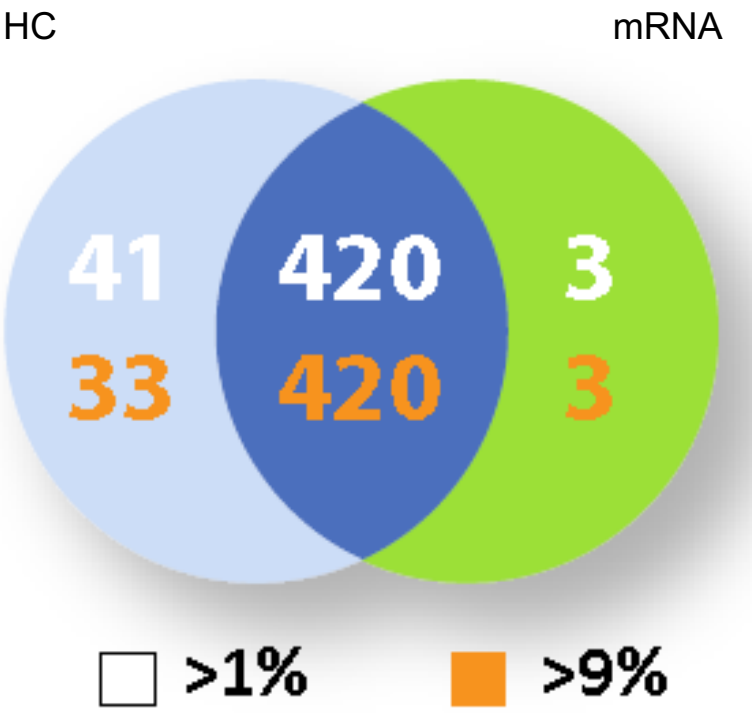
Rossing et al., Acta Oncol. 2018

Subtype fordeling

Subclass	BasL	mApo	LumC	LumB	LumA	NormL	Mixed
All (n=520)	50	28	40	76	182	68	76
	(9.6%)	(5.4%)	(7.7%)	(14.6%)	(35.0%)	(13.1%)	(14.6%)

Rossing et al., Acta Oncol. 2018

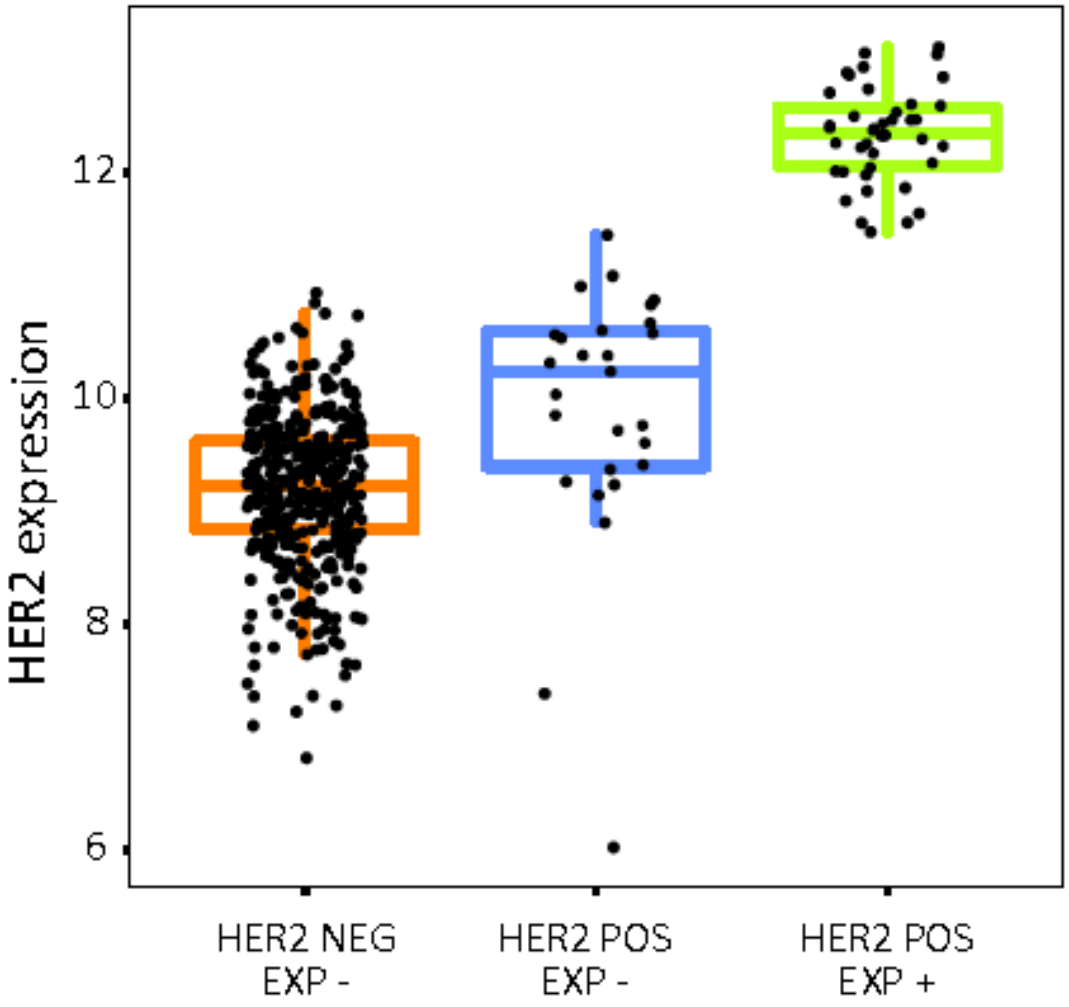
Receptorstatus_ER



91% overensstemmelse (420/461)

Rossing et al., Acta Oncol. 2018

Receptorstatus_HER2



Rossing et al., Acta Oncol. 2018

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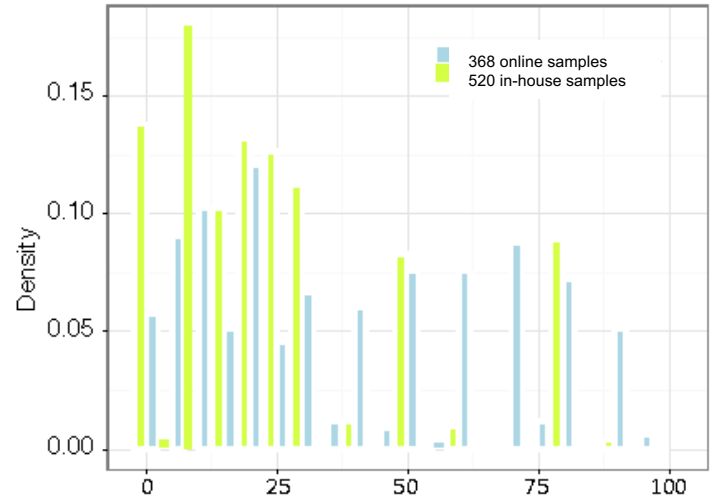
Receptorstatus_HER2

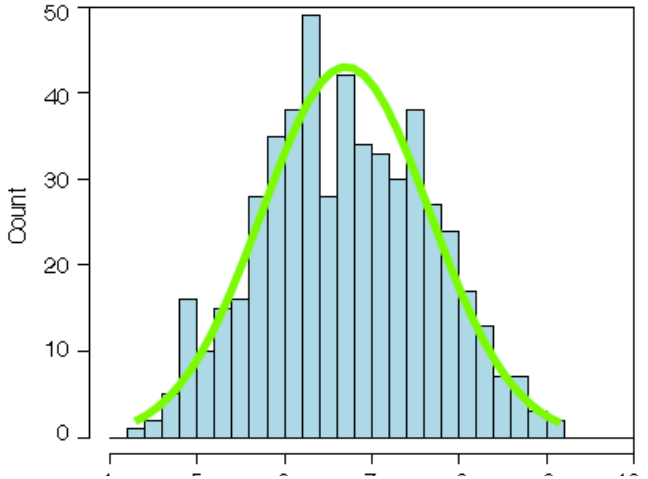
- HER2negativ (IHC (0-2) vs mRNA): ≈ 100% korrelation
- HER2+ status (IHC/FISH) vs mRNA: diskrepans 39% (27mRNA neg/69 HER2+)

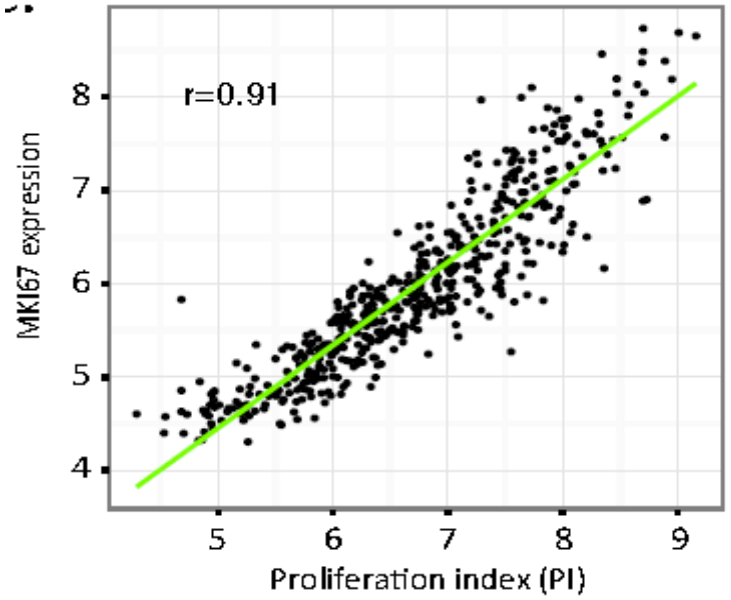
- Reevaluering v/spec. mammapatolog
- Forklaring i 70% af prøverne med diskrepans
- Forskellige tumorer, intratumor heterogenitet, borderline, ændring til HER2 neg. ved 2. gennemgang

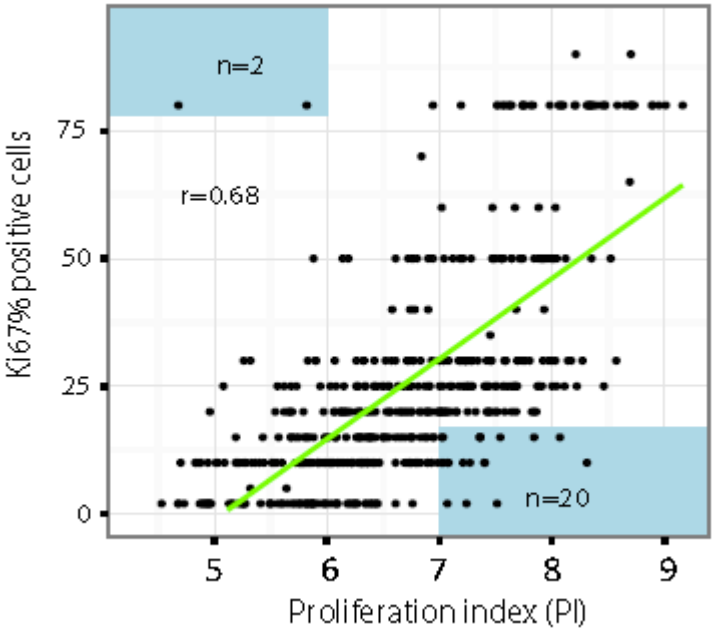
HER2-mRNA bestemmelse i kombination med subtypebestemmelse er et diagnostisk supplement til det eksisterende set-up.

Ki67_proliferative index









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- Diagnostisk rapport klar inden MDT

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- 39 patienter var i Q2/intermediær (prognostic standard mortality rate index (PSMRi)) udviklet af DBCG
- 16 (41%) klassificeret som LumA (+antiendokrin behandling, -chemotherapy)

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- Overvejende korrelation mRNA><IHC hormone receptor status
- IHC Ki67 proliferative index (PI) korrelerede ikke med mRNA PI index

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- Overvejende korrelation mRNA><IHC hormone receptor status
- IHC Ki67 proliferative index (PI) korrelerede ikke med mRNA PI index
- 41 patienter med basal-like subtype blev *BRCA1/2* testet uanset familieanamnese
- 17% var bærere af en patogen *BRCA1/2* mutation

ACTA ONCOLOGICA, 2018
VOL. 57, NO. 1, 51–57
https://doi.org/10.1080/0284186X.2017.1398837

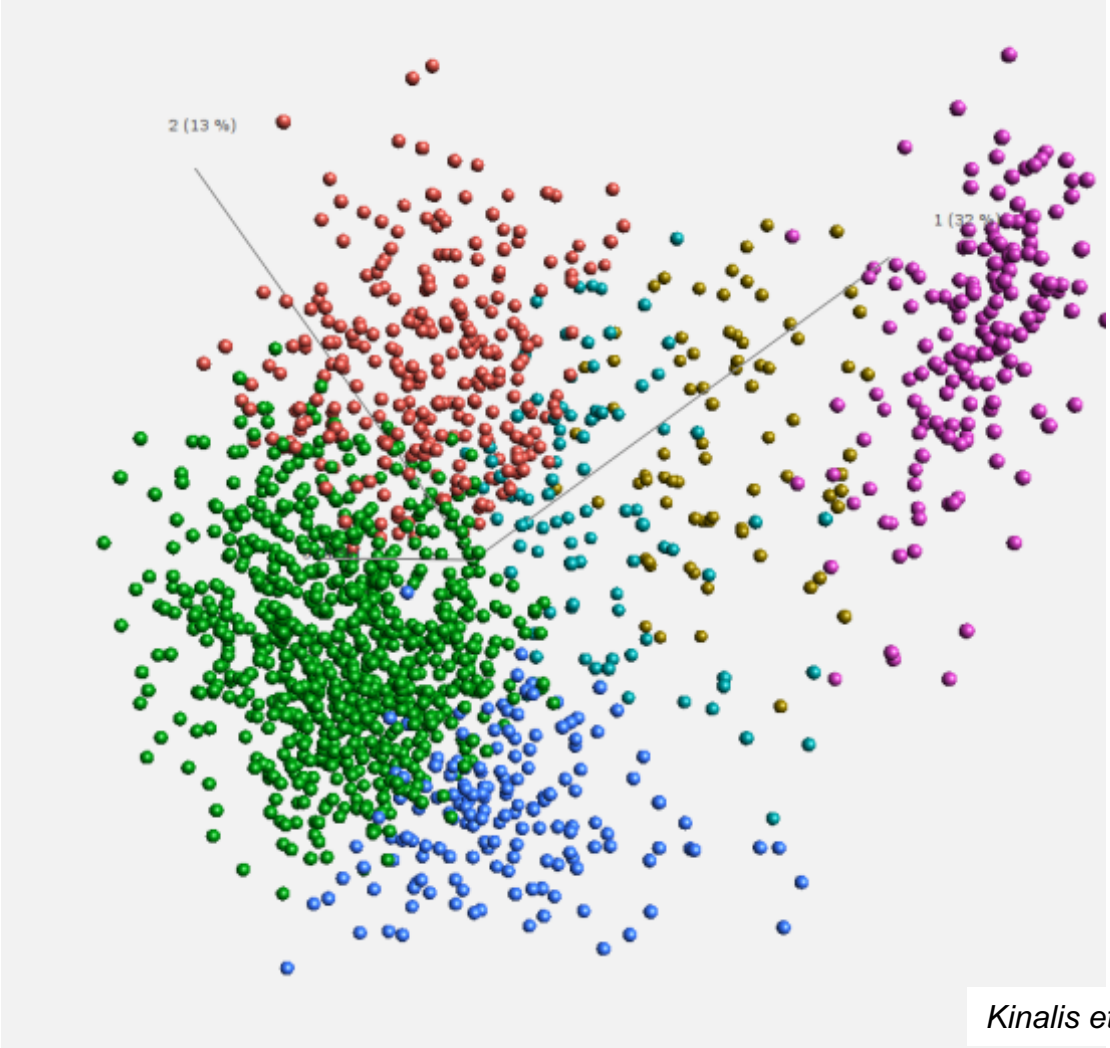
ORIGINAL ARTICLE

Characterization of basal-like subtype in a Danish consecutive primary breast cancer cohort

Savvas Kinalis[a], Finn Cilius Nielsen[a], Maj-Lis Talman[b], Bent Ejlertsen[c,d] and Maria Rossing[a]

[a]Center for Genomic Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [b]Department of Pathology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [c]Denmark Danish Breast Cancer Cooperative Group, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [d]Department of Clinical Oncology, Copenhagen University Hospital, Copenhagen, Denmark

Basal-like subtype



Kinalis et al., Acta Oncol. 2018

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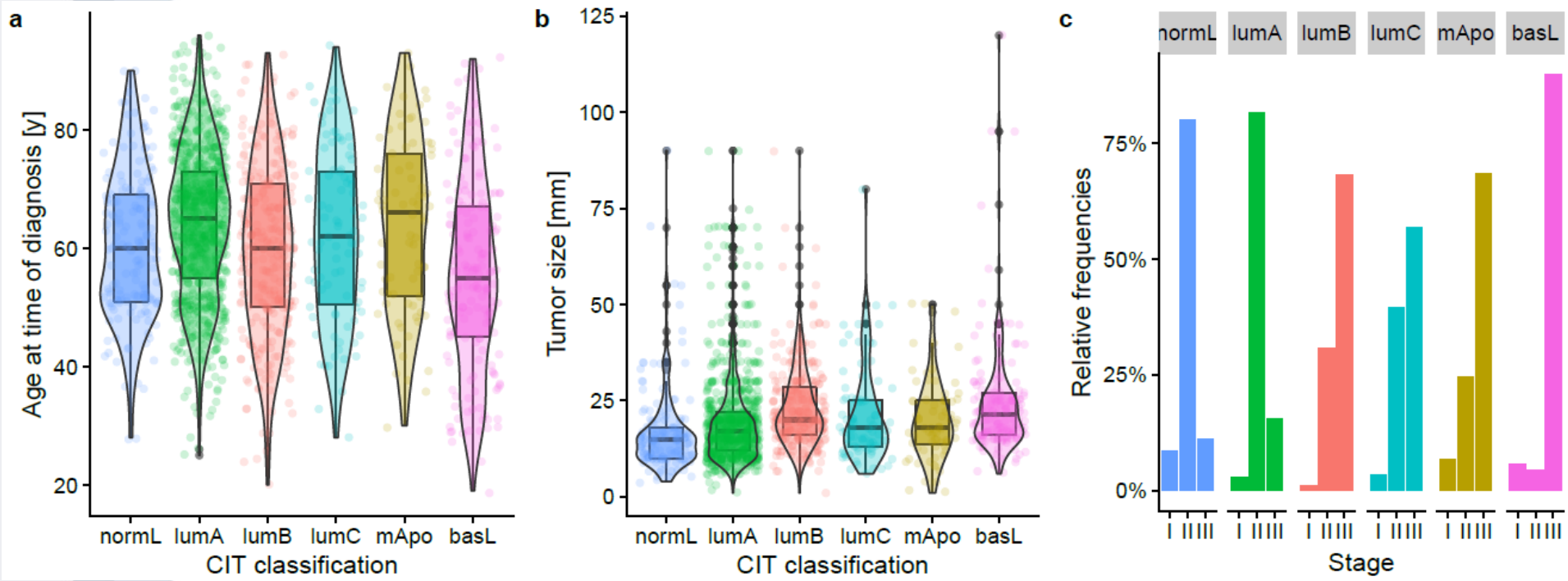
Basal-like subtype (n=168)



Kinalis et al., Acta Oncol. 2018

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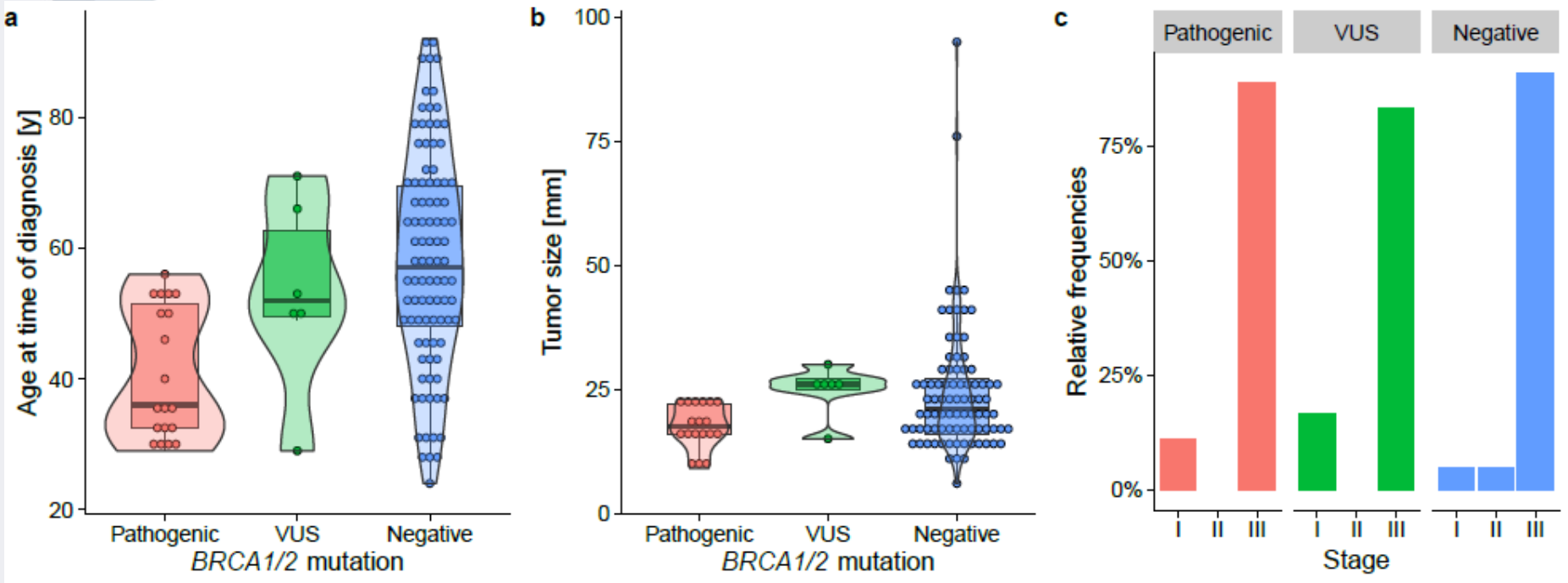
Basal-like subtype; *BRCA1/2* screenet



Kinalis et al., Acta Oncol. 2018

Konklusion Basal-like patienter

- Laveste mediane alder
- Højeste mediane tumor størrelse
- Flertal diagnosticeret i stadie III
- 120 screenet (19 *BRCA1/2*-bærere)
- *BRCA1/2*-bærere var signifikant yngre

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Tak til samarbejdspartnere

- Maj-Britt Jensen
- Ann Knoop
- Maj-Lis Talman
- Niels Kroman
- Finn Cilius Nielsen
- Bent Ejlertsen

DBCG DANISH BREAST CANCER GROUP