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REGION

Molekylær subtypning og identifikation af targets

DBCGs NACT Seminar,
Sandbjerg Slot 4.og 5. november 2019

- Maria Rossing, MD, PhD
- Center for Genomic Medicine, GM4113, Rigshospitalet, Copenhagen University Hospital

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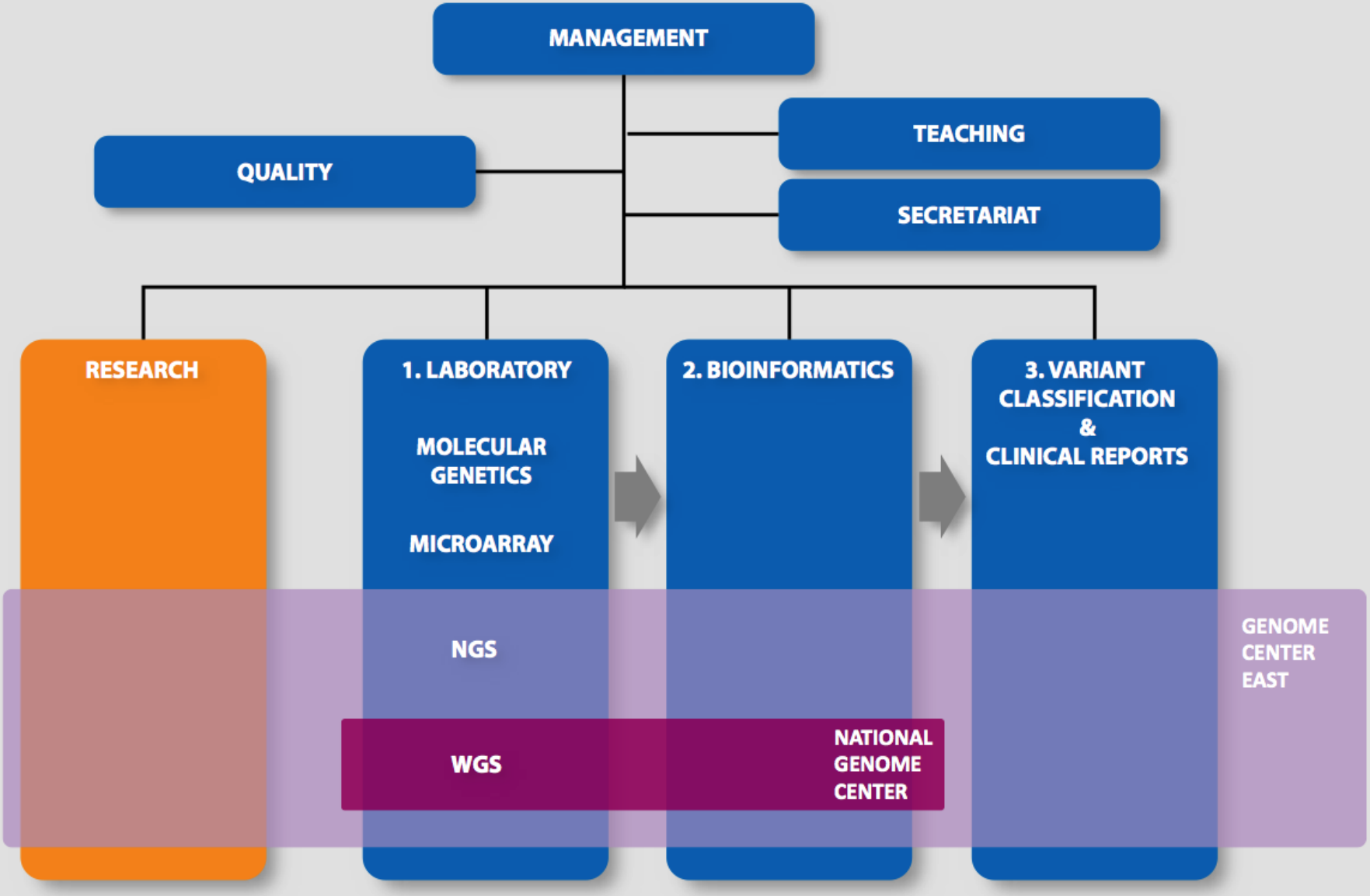
Genomic Medicine, Rigshospitalet

- Ensure precise diagnostics and facilitate targted treatment decisions
- Ensure that the clinical departments have access to high-throughput technologies and analyzes

GENOMIC MEDICINE - ORGANISATION



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NACT på RH

Radiologisk klinik

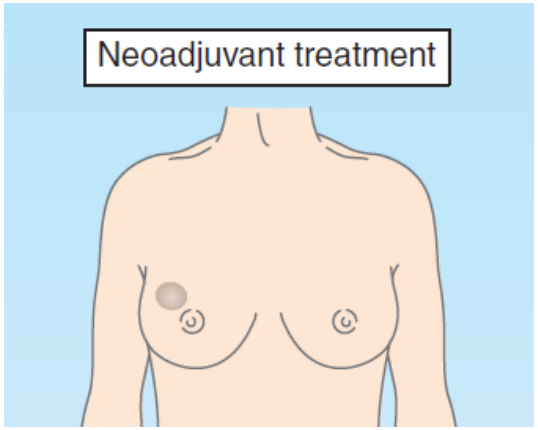
Onkologisk klinik

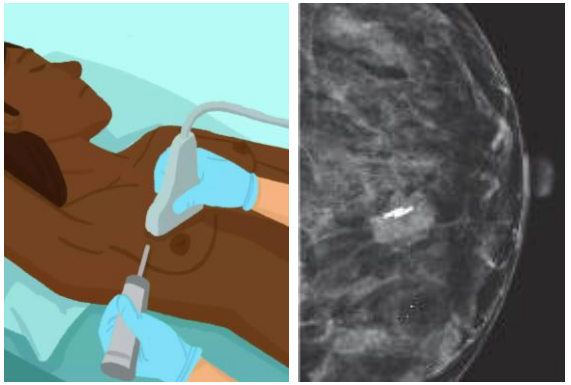
Kirurgisk klinik

Patologi Afdelingen

Genomisk Medicin

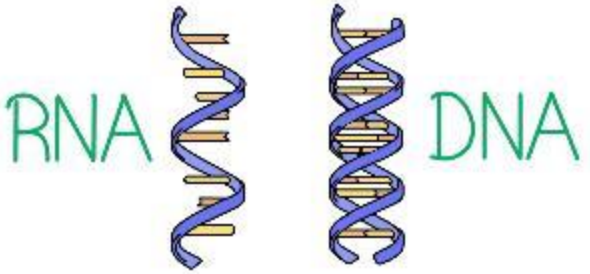
Genomiske analyser implementeret fra februar 2017 og frem


Neoadjuvant treatment



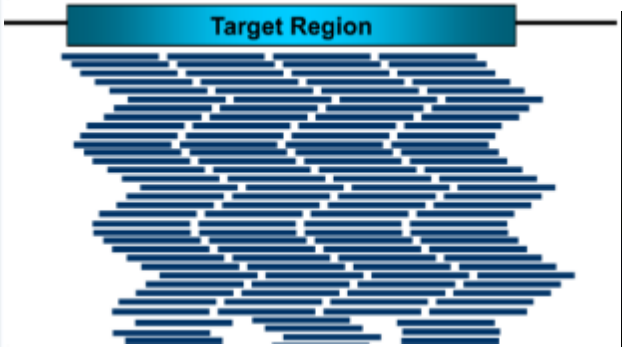

Whole blood

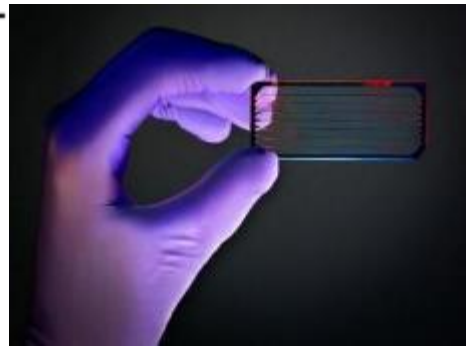

DNA

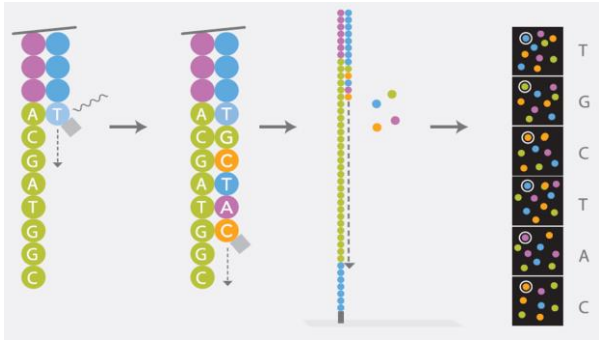

RNA
DNA

DNA fra tumorbiopsi

- NGS til somatisk mutations analyse
- Targeteret sekventering
- BC somatisk sequence capture GM-panel: 16 BC specifikke gener, incl. *TP53*, *AKT1*, *ERBB2*, *ESR1*, *BRCA1/2, PTEN*, m.fl.

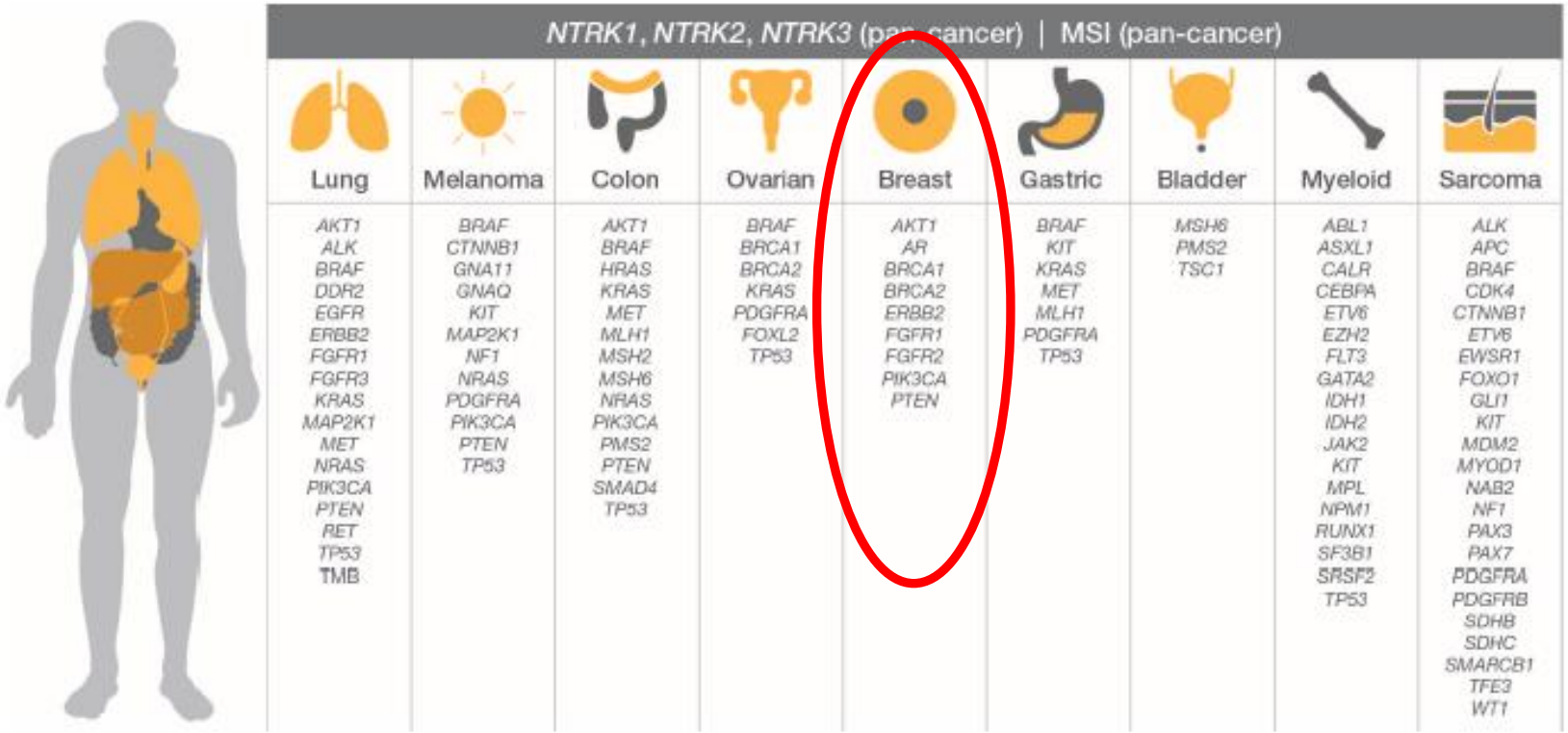






DNA

- TruSight Oncology 500
- Targeteret sekventering; samme metode, ”bare” 500 gener



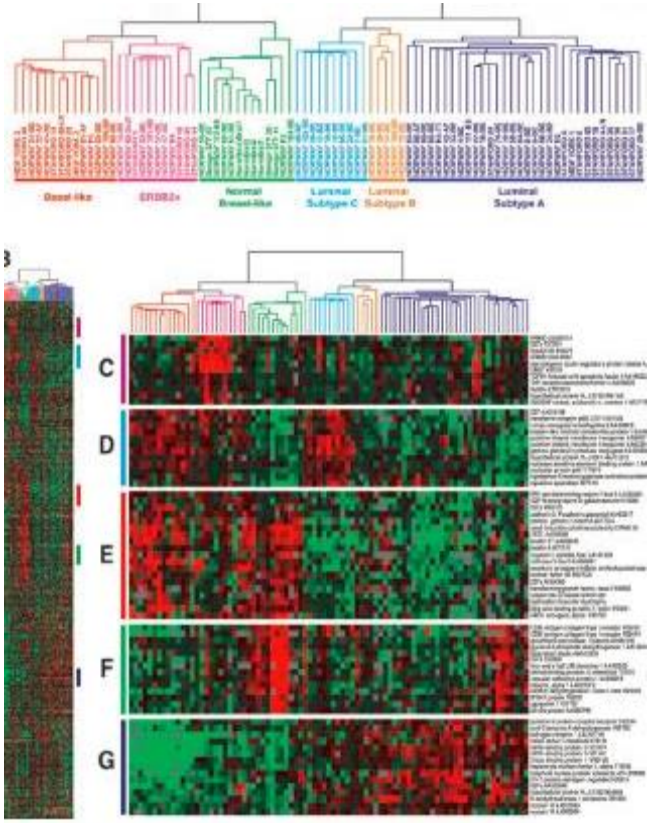
- Eksempel på somatisk BC mutationssvar

Mutation: *ERBB2*: Ingen mutation *ESR1*: Ingen mutation *PIK3CA*: c.3140A>T, p.His1047Leu	Acc.No. for reference cDNA-sekvens: *ERBB2:* NM_004448; *ESR1*: NM_000125; *PIK3CA*: NM_006218. Nukleotid nummer 1 er A i START-ATG
Vurdering og konklusion: Der er fundet en aktiverende mutation i *PIK3CA* (p.His1047Leu). Mutationen er velkendt blandt aktiverende *PIK3CA* mutationer (Dogruluk T. et al., Cancer Res. 2015). Der er ikke fundet mutationer i *ERBB2* og *ESR1* generne.	

Svardato: 31-10-19

RNA fra tumorbiopsi

- Bestemmer de fundamentale molekylær subtypebestemmelser baseret på signaturer fra transcriptomet.



- Genetic signatures have altered BC diagnostics
- ER+ and ER- are two separate entities
- Proliferation is a crucial prognostic factor in ER+ BC
- Specific patient risk score and LumA; chemotherapy can be omitted

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Oncogene (2012) 31, 1196–1206

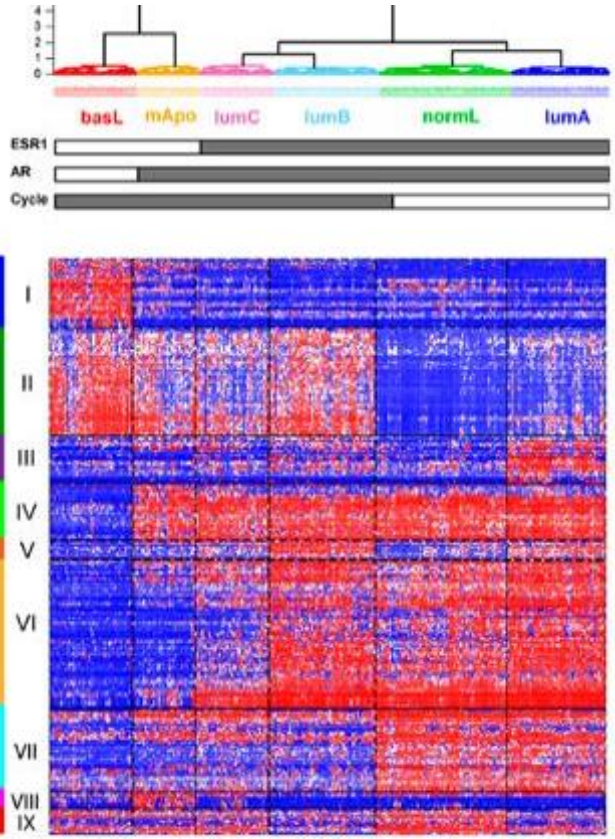
www.nature.com/onc

ONCOGENOMICS

A refined molecular taxonomy of breast cancer

M Guedj[1,15], L Marisa[1,15], A de Reyniès[1,15], B Orsetti[2,3], R Schiappa[1], F Bibeau[4], G MacGrogan[5], F Lerebours[6], P Finetti[7], M Longy[5], P Bertheau[8], F Bertrand[6], F Bonnet[5], AL Martin[9], JP Feugeas[10,11,12], I Bièche[6], J Lehmann-Che[10,11,12], R Lidereau[6], D Birnbaum[7], F Bertucci[7], 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 program, Paris, France; [2]IRCM, Institut de Recherche en Cancérologie de Montpellier, Montpellier, France; [3]CRLC Val d'Aurelle Paul Lamarque, Montpellier, France; [4]Department of Pathology, CRLC Val d'Aurelle Paul Lamarque, Montpellier, France; [5]Department of Pathology, Institut Bergonié; (EA 3669), Université Victor Segalen Bordeaux-2, Bordeaux, France; [6]Oncogenetics laboratory, INSERM U735, Institut Curie-Hôpital-Centre René Huguenin, St Cloud, France; [7]Department of Molecular Oncology, CRCM, Centre de Recherche en Cancérologie de Marseille, Institut Paoli Calmette, Marseille, France; [8]Hopital St Louis APHP, Department of Pathology, University Paris, Denis Diderot, Paris, France; [9]Fédération Nationale des Centres de Lutte Contre le Cancer, Paris, France; [10]Department of Biochemistry, Hopital Saint-Louis APHP, Paris, France; [11]INSERM/CNRS UMR 944/7212, Paris, France; [12]University Hematology Institute, University 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 molekylære subtyper
- Affymetrix platform (open)
- *"In house"*
- Overflytte til RNAseq.

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Molekylær subtypebestemmelse af brystkræft
mRNA microarray baseret klassifikation

Patientinformation

CPR: [redacted] **Prøvenr:** NABRB-255

Navn: **Labnr:** 103522-050008

Rekvirerende læge/hospital:

Afdeling:

Modtaget materiale: **Dato:** 18.09.19

Tumor biopsi: Tumorvæv fra operation

Undersøgelse: mRNA array baseret klassifikation af brysttumor

Array: Affymetrix U133plus2 **Klassifikationsmodel:** CIT* **Signatur:** 375

Array file: RH-NABRB-255-103522-050008-U133_Plus_2-a1.CEL

Resultat

Tumorvævet er triple-negativ. Klassificeres som basal-like*.

*Guedj et al., Oncogene, 2012, 31:1196-1206

Svardato: 25-09-2019

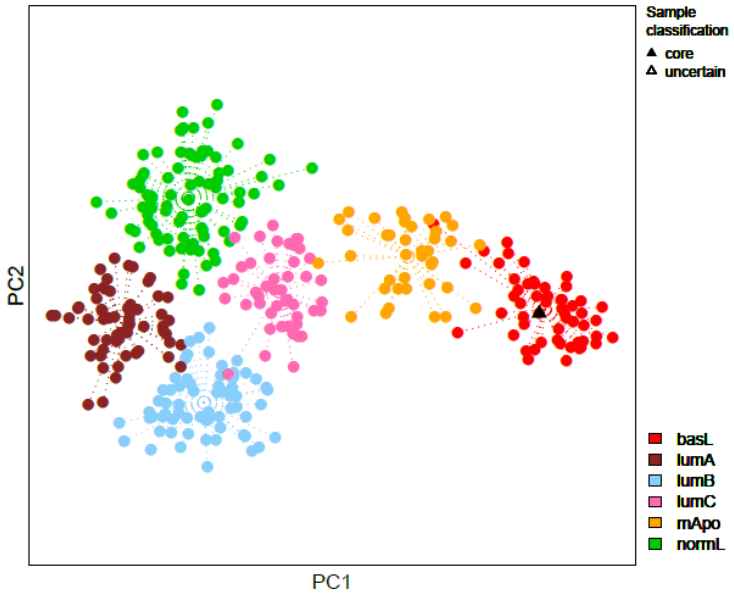
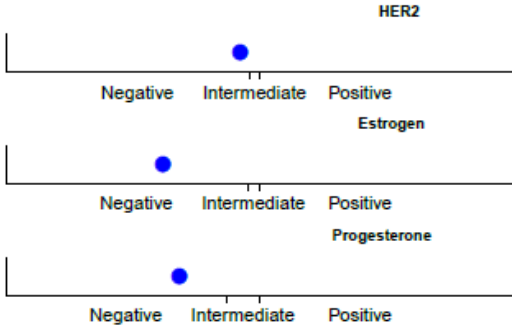


Figure 1: PCA on CIT data used to classify dataset & sample (black).

	Classification	Confidence	Mixed
CIT	**basL**	**CORE**	–
PAM50	Basal	HIGH	–

Expression profiles

Her2	ERBB2	negative
Estrogen receptor	ESR1	negative
Progesterone receptor	PGR	negative



Proliferation Index(PI) score (tumor PI >5.5): 7.74

Germline analyse

- Screener for prædisponerende varianter i kendte BC associerede gener

Bryst- og ovariekræft (DNABRYST) (EPC00098)

BRCA1, BRCA2, BRIP1, CDH1, PALB2, PTEN, RAD51C, RAD51D, STK11 og TP53 **(Stor pakke)**

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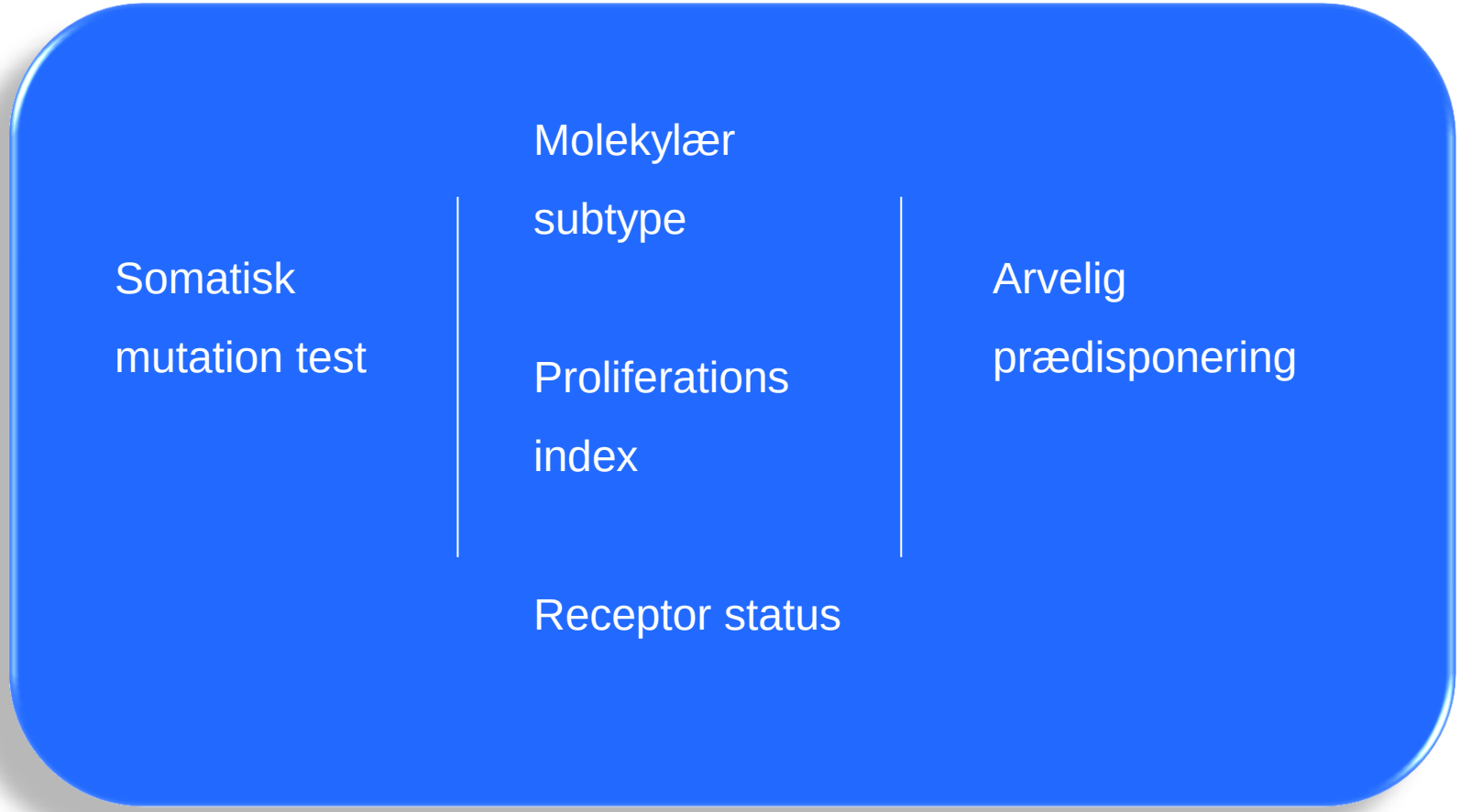
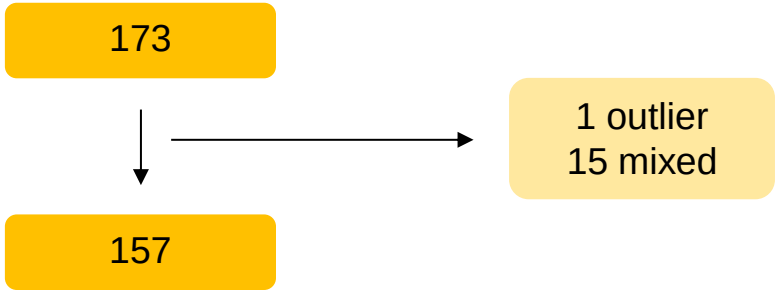
Genomisk analysepakke til NACT patienter



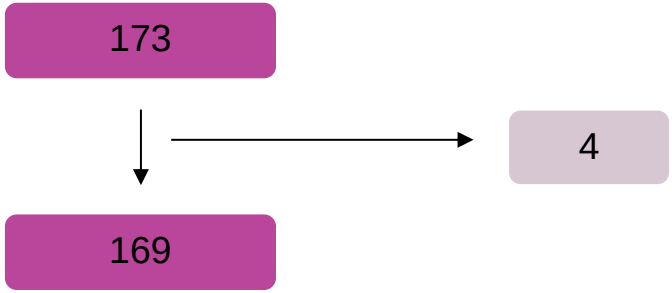
Resultater, subtyper + responsegrad (n=173)



Resp.grad	basallike	mAPO	lumC	lumB	lumA	normlike
	43	30	28	31	14	11
1	17 (40%)	18 (60%)	15 (54%)	4 (13%)	0	1 (9%)
2	7 (16%)	9 (30%)	6 (21%)	7 (23%)	1 (7%)	0
3	11 (26%)	1 (3%)	7 (25%)	15 (48%)	9 (64%)	3 (27%)
4	8 (18%)	2 (7%)	0	5 (16%)	4 (29%)	7 (64%)

1: Ingen invasive tumorceller; 2: >90% tab af tumorceller;
3: Mellem 30 og 90% tab af tumorceller; 4: < 30% tab af tumorceller

Resultater, ER/HER2 status + responsegrad



Resp.grad	HER2		ER (%)	
	normal	positiv	<9%	>9%
	98	71	64	105
1	21 (21%)	39 (55%)	33 (52%)	27 (26%)
2	14 (14%)	18 (25%)	14 (22%)	18 (17%)
3	38 (39%)	13 (18%)	9 (14%)	42 (40%)
4	25 (26%)	1 (1%)	8 (13%)	18 (17%)

1: Ingen invasive tumorceller; 2: >90% tab af tumorceller;
3: Mellem 30 og 90% tab af tumorceller; 4: < 30% tab af tumorceller

Resultater, ER/HER2 status + responsegrad

Resp.grad	HER2		ER (%)		ER (%)	
	normal	positiv	<9%	>9%	≤1%	>1%
	98	71	64	105	52	117
1	21 (21%)	39 (55%)	33 (52%)	27 (26%)	26 (50%)	34 (29%)
2	14 (14%)	18 (25%)	14 (22%)	18 (17%)	12 (23%)	20 (17%)
3	38 (39%)	13 (18%)	9 (14%)	42 (40%)	9 (17%)	42 (36%)
4	25 (26%)	1 (1%)	8 (13%)	18 (17%)	5 (10%)	21 (18%)

Pending…….

- Alder, tumorstørrelse, etc.
- Somatisk mutations resultater
- Germline variant resultater

Tak til Maj-Britt

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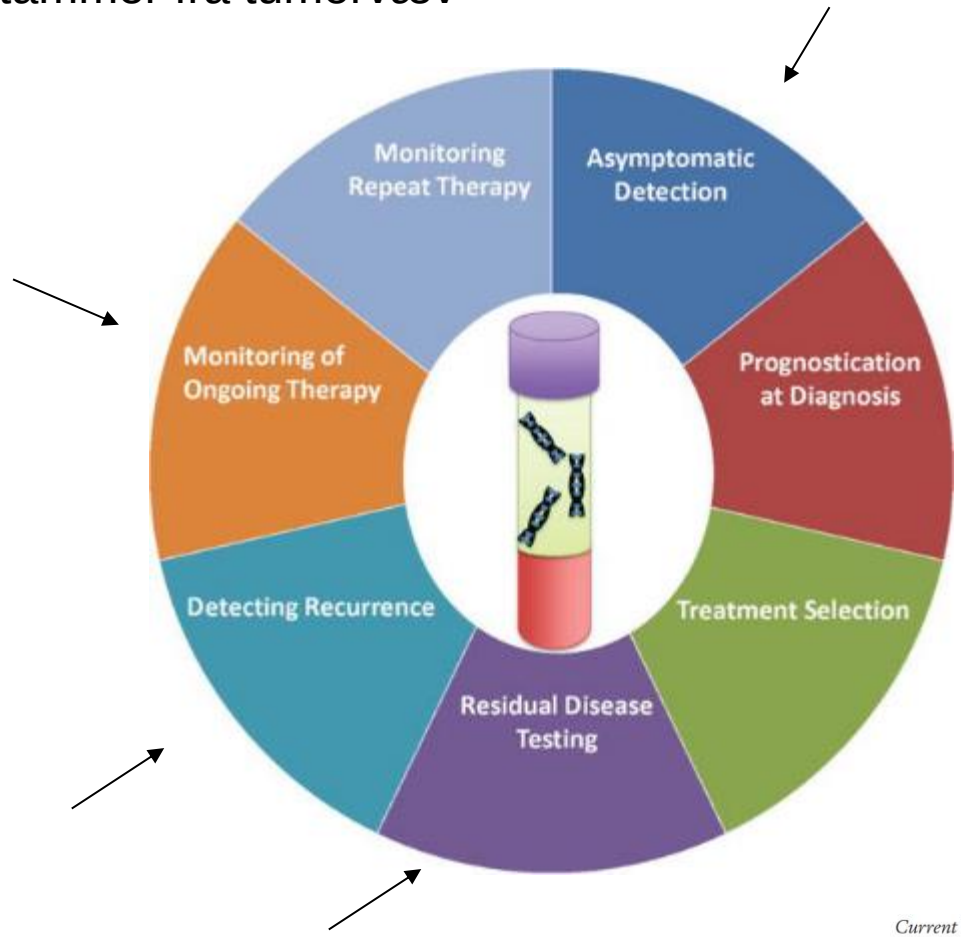
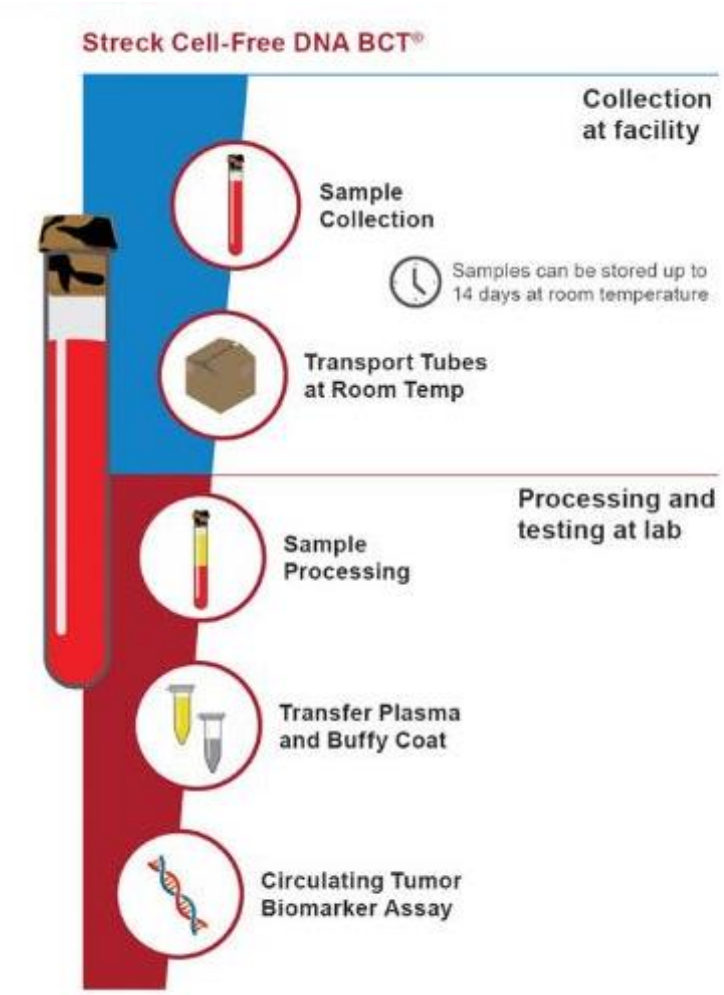
Cirkulerende tumor DNA (**ctDNA**)

- ctDNA repræsenterer det cellefrie DNA, der cirkulerer i blodbanen og stammer fra tumorvæv

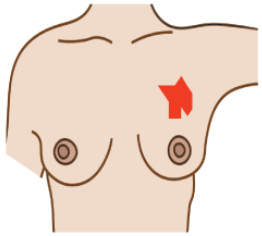


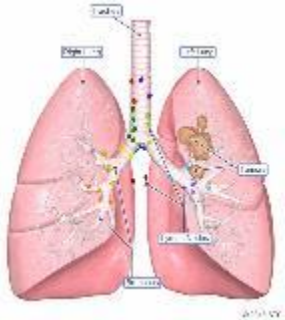
Current Utility and Future Applications of ctDNA in Colorectal Cancer
DOI: http://dx.doi.org/10.5772/intechopen.82316

ctDNA



- Oprenset ctDNA
- Gene panel (ex. TS500)
- Detekterer ned til 1% tumorDNA
- Kendt mutation





NordicHER2 Trial

- Molekylærsubtype
- Somatisk mutations bestemmelse
- Følge med ctDNA
- Germline status