Klinisk variant klassificering

Genomisk Medicin - Rigshospitalet

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MSc Biotech, PhD

Min rejse til personlig medicin

MSc Biotechnology (KVL, KU)

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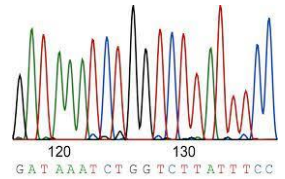
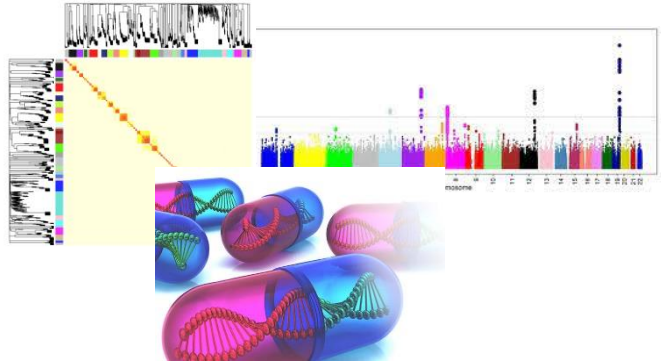
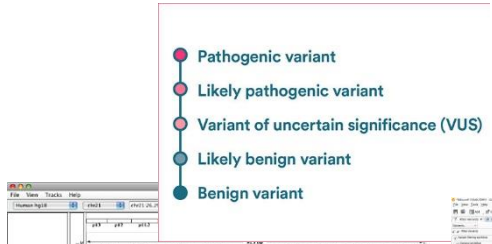
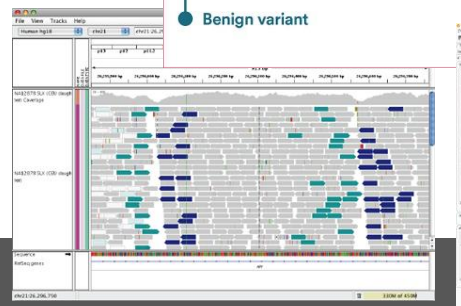
Sct. Hans Hospital

Klinisk akademiker
Genomisk Medicin
Rigshospitalet









Rigshospitalet
Afdeling for Genomisk Medicin

GENPANEL FOR ARVELIG KRÆFT

DANAK

PATIENT
Navn: Hans Hansen
CPR: 1234567890

PRØVE
Modtaget: 01-03-2022
Svarsdato: 01-04-2022
Prøvemateriale: Blod

KONKLUSION
Der er IKKE påvist patogene varianter i de undersøgte gener.

BEMÆRKNINGER

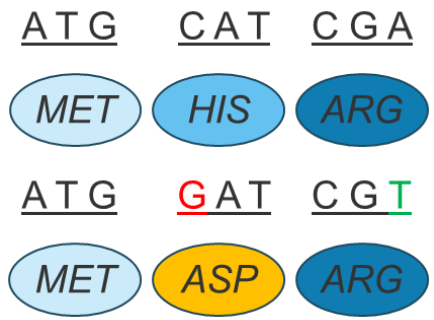
METODE

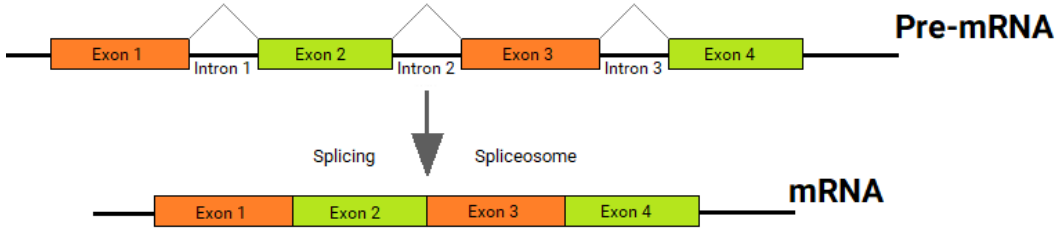
UNDERSKRIFTER
Majbritt Busk Madsen
Molekylærbiolog, ph.d.
Lisa Bartoba Ahlborn
Molekylærbiolog, ph.d.

Side 1 af 1

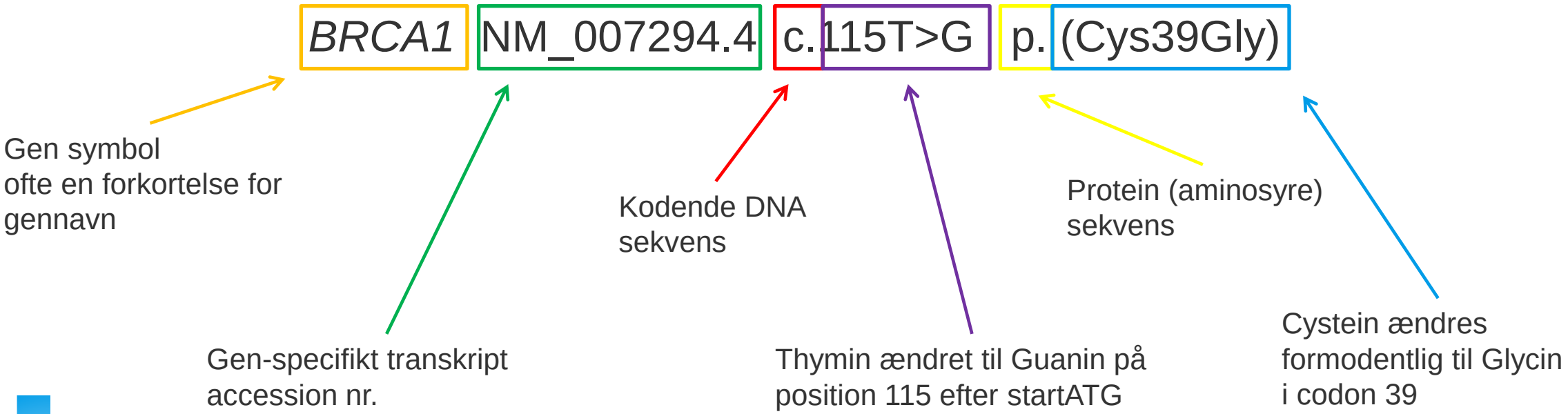
Typer af varianter

- Stop-codon og frameshift (præmaturt stop-codon)
  - trunkeret protein, Nonsense Medicated Decay
- Missense (aminosyre udskiftes)
  - ændret/nedsat protein funktion
- Synonyme og Intron
  - Mulig effekt på mRNA splejsning
- Større deletioner / duplikationer
  - for lidt / for meget protein





International standardiseret nomenklatur



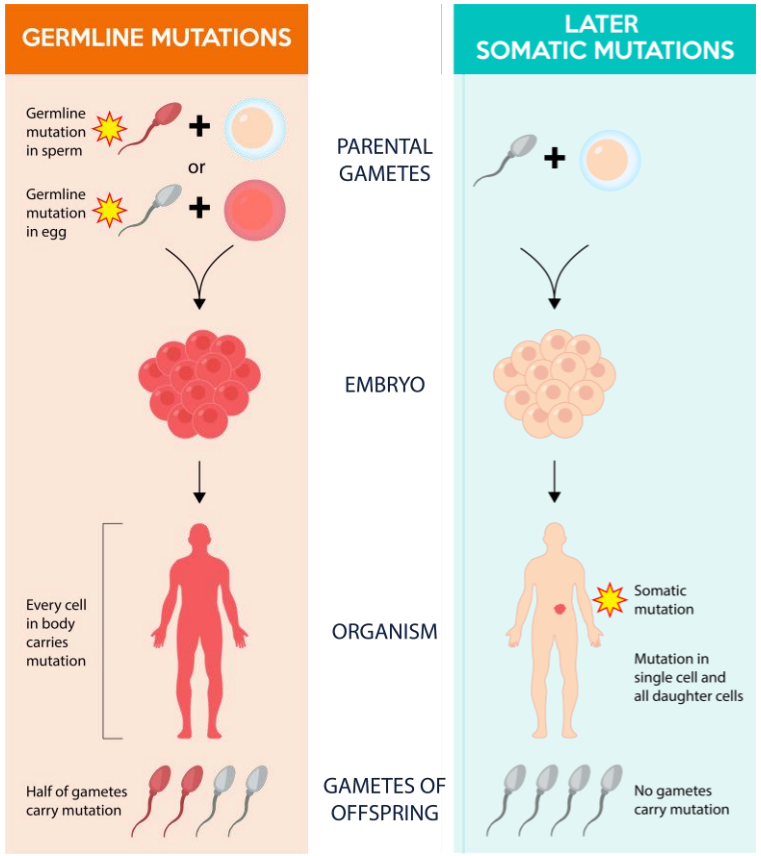
Germline og somatiske varianter

Germline varianter

Nedarvede eller nyopstået (de novo)

Findes i alle kroppens celler

Sekventeres oftest fra blodprøve



Variant filtering

- Find nålen i høstakken
- Filtering og annotering
  - Kvaliteten og dækningen af variantkaldet
  - Typen af variant (intron, exon, missense, deletion osv.)
  - Formodet effekt af varianten (ødelægger proteinet, påvirker mRNA splejsning osv.)
  - Hvad er patients fænotype?
  - Eventuel inddragelse af forældres genomer (trio)

Variant klassifikation - germline

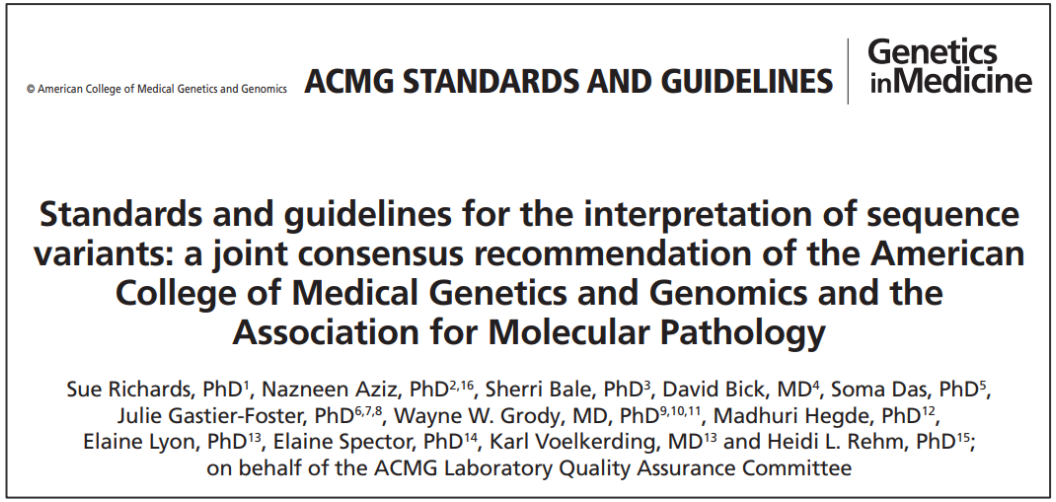
Klasse 1 – Benign

Klasse 2 – Formodentlig Benign

Klasse 3 – Variant af ukendt betydning (VUS)

Klasse 4 – Formodentlig Patogen

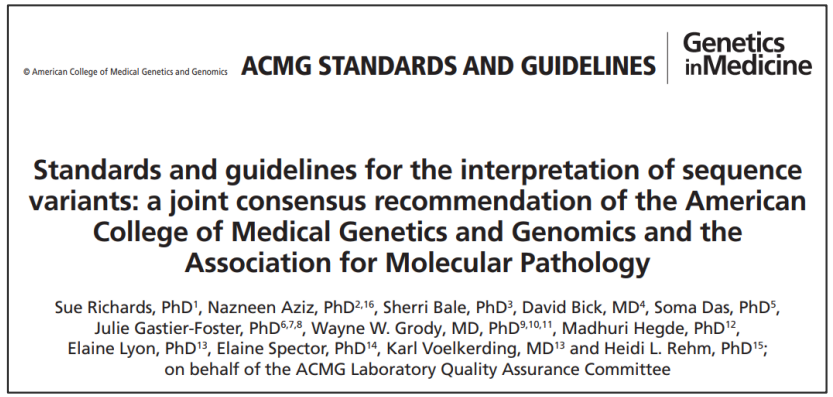
Klasse 5 – Patogen



Variant klassifikation

- Genet
  - Patientens fænotype
  - Biologisk funktion
- Varianten
  - Populationsfrekvens (gnomAD)
  - Litteratursøgning: funktionelle analyser, andre patienter, foundervariant, tilstedeværelse i databaser (fx ClinVar), fundet i andre laboratorier osv.
  - Intronic, missense, synonymous, nonsenes, deletion, splicesite
  - Formodet betydning for mRNA eller proteinet, bl.a. *in silico* prædiktioner

Klassifikationskriterier



	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Population Data	MAF is too high for disorder *BA1/BS1* **OR** observation in controls inconsistent with disease penetrance *BS2*			Absent in population databases *PM2*	Prevalence in affecteds statistically increased over controls *PS4*	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact on gene /gene product *BP4* Missense in gene where only truncating cause disease *BP1* Silent variant with non predicted splice impact *BP7*	Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3*	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5* Protein length changing variant *PM4*	Same amino acid change as an established pathogenic variant *PS1*	Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1*
Functional Data	Well-established functional studies show no deleterious effect *BS3*		Missense in gene with low rate of benign missense variants and path. missenses common *PP2*	Mutational hot spot or well-studied functional domain without benign variation *PM1*	Well-established functional studies show a deleterious effect *PS3*	
Segregation Data	Non-segregation with disease *BS4*		Co-segregation with disease in multiple affected family members *PP1*	Increased segregation data →		
De novo Data				*De novo* (without paternity & maternity confirmed) *PM6*	*De novo* (paternity & maternity confirmed) *PS2*	
Allelic Data		Observed in *trans* with a dominant variant *BP2* Observed in *cis* with a pathogenic variant *BP2*		For recessive disorders, detected in *trans* with a pathogenic variant *PM3*		
Other Database		Reputable source w/out shared data = benign *BP6*	Reputable source = pathogenic *PP5*			
Other Data		Found in case with an alternate cause *BP5*	Patient's phenotype or FH highly specific for gene *PP4*			

Summering af kriterier

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Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

Rules for Combining Criteria to Classify Sequence Variants

Pathogenic

1. 1 Very Strong (PVS1) *AND*
   - **a.** ≥1 Strong (PS1–PS4) *OR*
   - **b.** ≥2 Moderate (PM1–PM6) *OR*
   - **c.** 1 Moderate (PM1–PM6) and 1 Supporting (PP1–PP5) *OR*
   - **d.** ≥2 Supporting (PP1–PP5)
2. ≥2 Strong (PS1–PS4) *OR*
3. 1 Strong (PS1–PS4) *AND*
   - **a.** ≥3 Moderate (PM1–PM6) *OR*
   - **b.** 2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR*
   - **c.** 1 Moderate (PM1–PM6) *AND* ≥4 Supporting (PP1–PP5)

Likely Pathogenic

1. 1 Very Strong (PVS1) *AND* 1 Moderate (PM1–PM6) *OR*
2. 1 Strong (PS1–PS4) *AND* 1–2 Moderate (PM1–PM6) *OR*
3. 1 Strong (PS1–PS4) *AND* ≥2 Supporting (PP1–PP5) *OR*
4. ≥3 Moderate (PM1–PM6) *OR*
5. 2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR*
6. 1 Moderate (PM1–PM6) *AND* ≥4 Supporting (PP1–PP5)

Benign

1. 1 Stand-Alone (BA1) *OR*
2. ≥2 Strong (BS1–BS4)

Likely Benign

1. 1 Strong (BS1–BS4) and 1 Supporting (BP1–BP7) *OR*
2. ≥2 Supporting (BP1–BP7)

*Variants should be classified as Uncertain Significance if other criteria are unmet or the criteria for benign and pathogenic are contradictory.

ClinVar

https://preview.ncbi.nlm.nih.gov/clinvar/variation/54153/

Klinisk betydning af ACMG klassen (BRCA1 / BRCA2)

Benign / formodentlig benign

- Ingen klinisk betydning.
- Risiko beregnes kun vha. familiehistorik

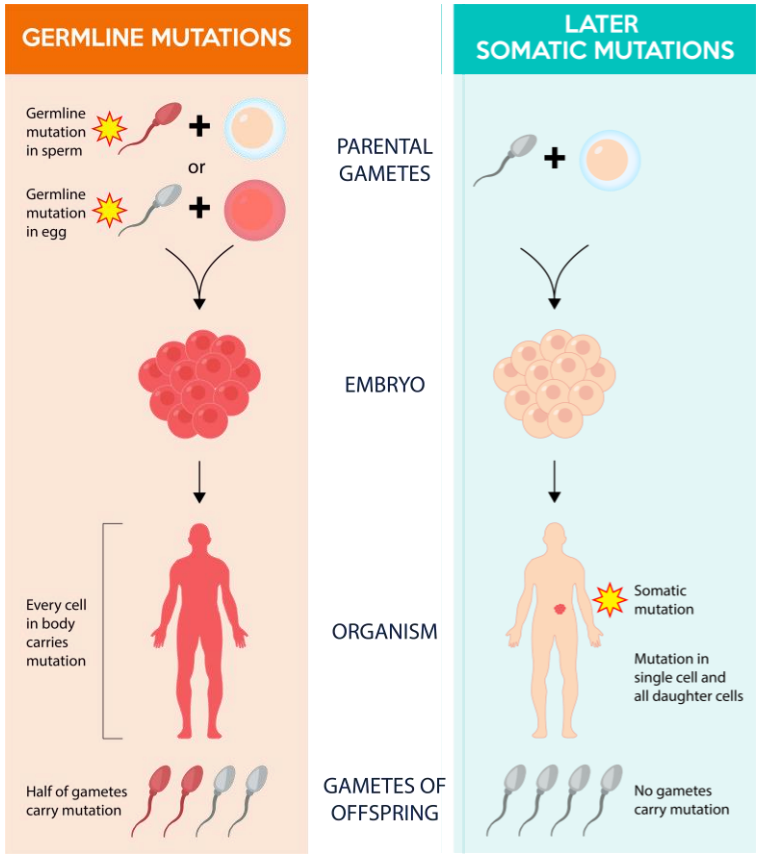
VUS (ukendt betydning)

- Ingen prædiktiv test af familiemedlemmer
- Ingen profylaktisk operation
- Risiko beregnes kun vha. familiehistorik

Patogen / formodentlig patogen

- Prædiktiv test af familiemedlemmer
- 80% livstidsrisiko
- Tilbud om profylaktisk operation af brystvæv (og/eller æggestokke)
- Tilbud om ekstra mammografi kontroller
- PARP-hæmmerbehandling ved kræft

Germline og somatiske varianter



Somatiske varianter

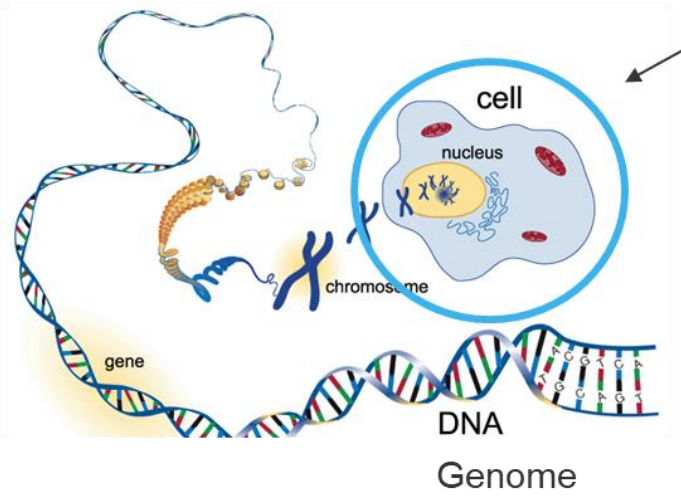
Spontant opståede varianter fx i kræftceller

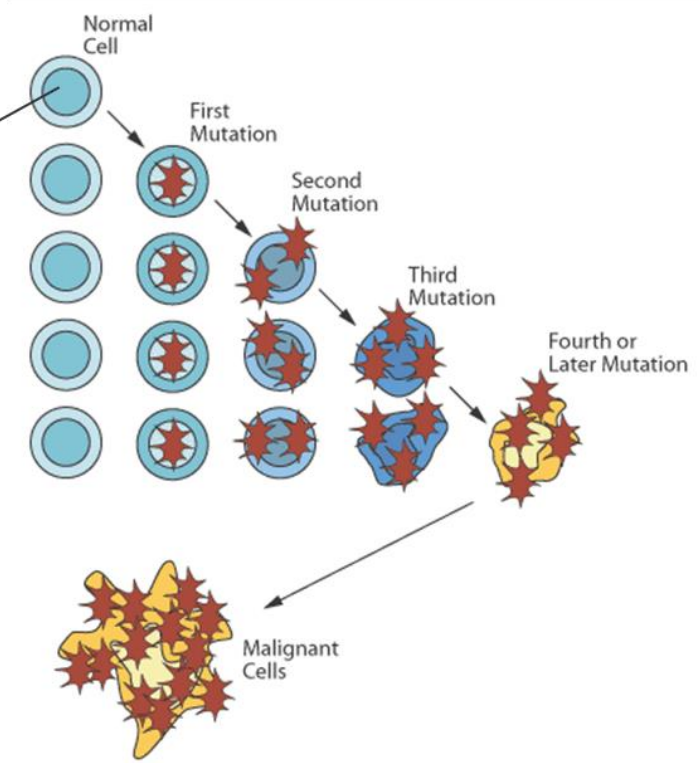
Findes derfor kun i nogle celler

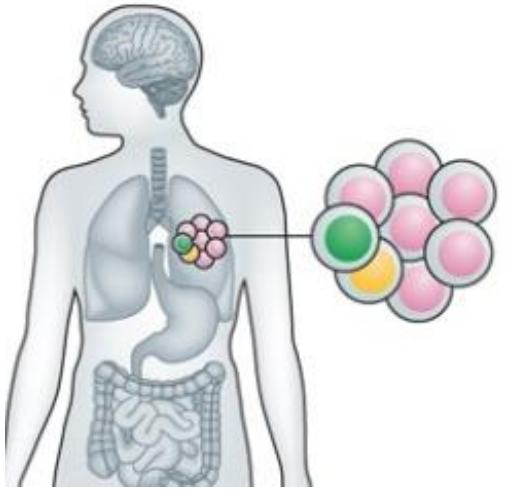
Sekventeres oftes fra en vævsbiopsi

Somatiske mutationer

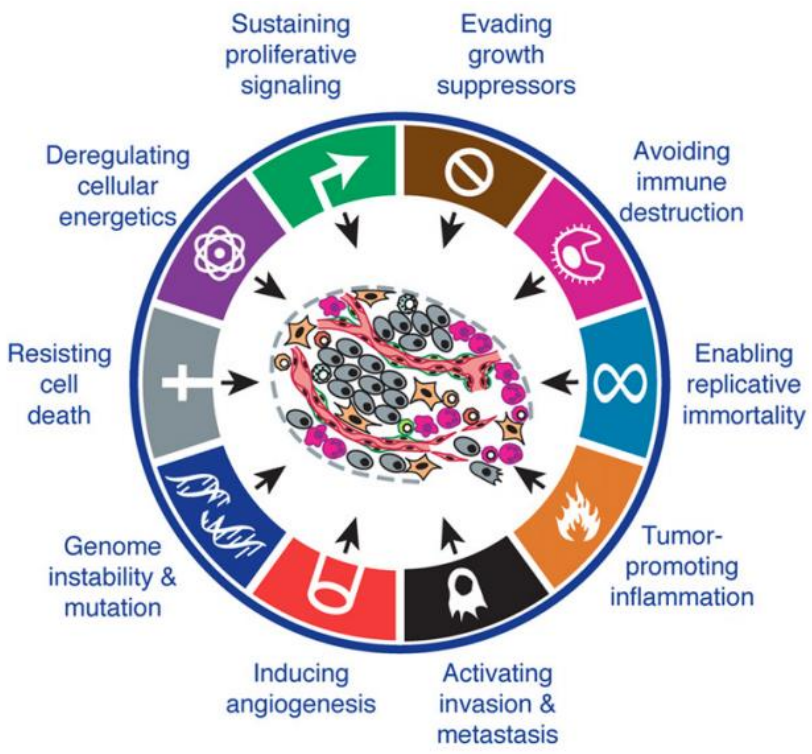
En cancercelle har mange flere varianter (mutationer) end normale celler

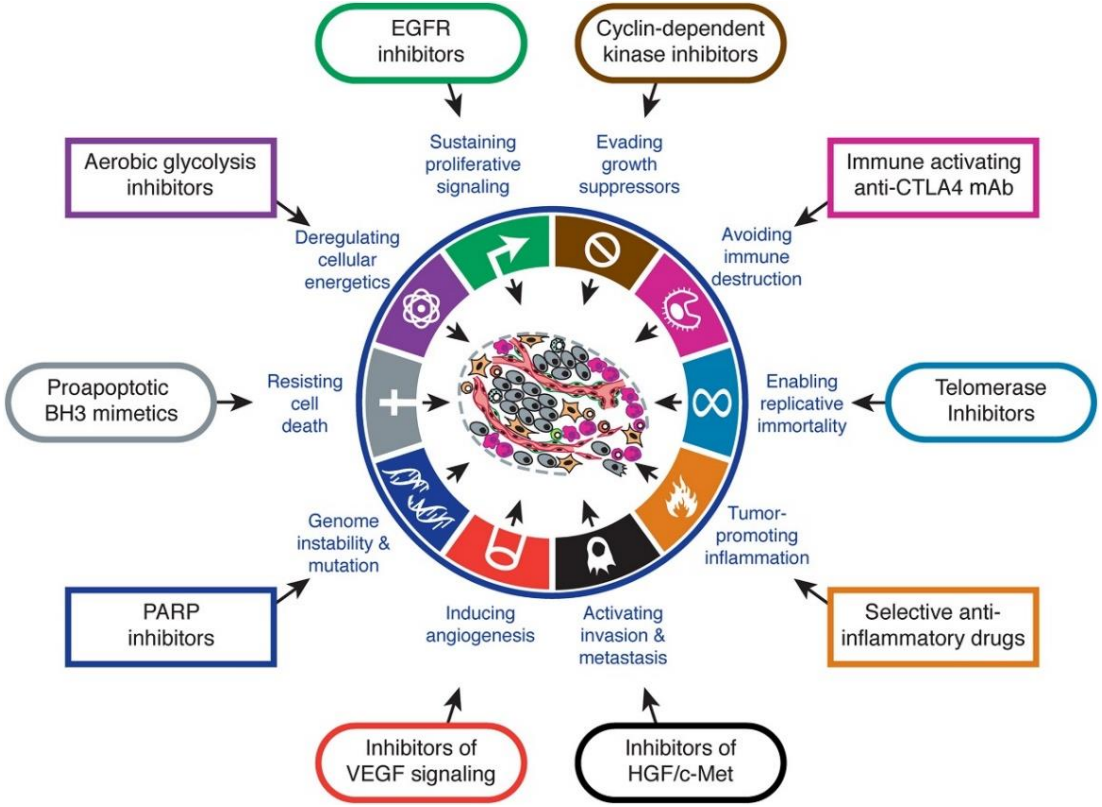




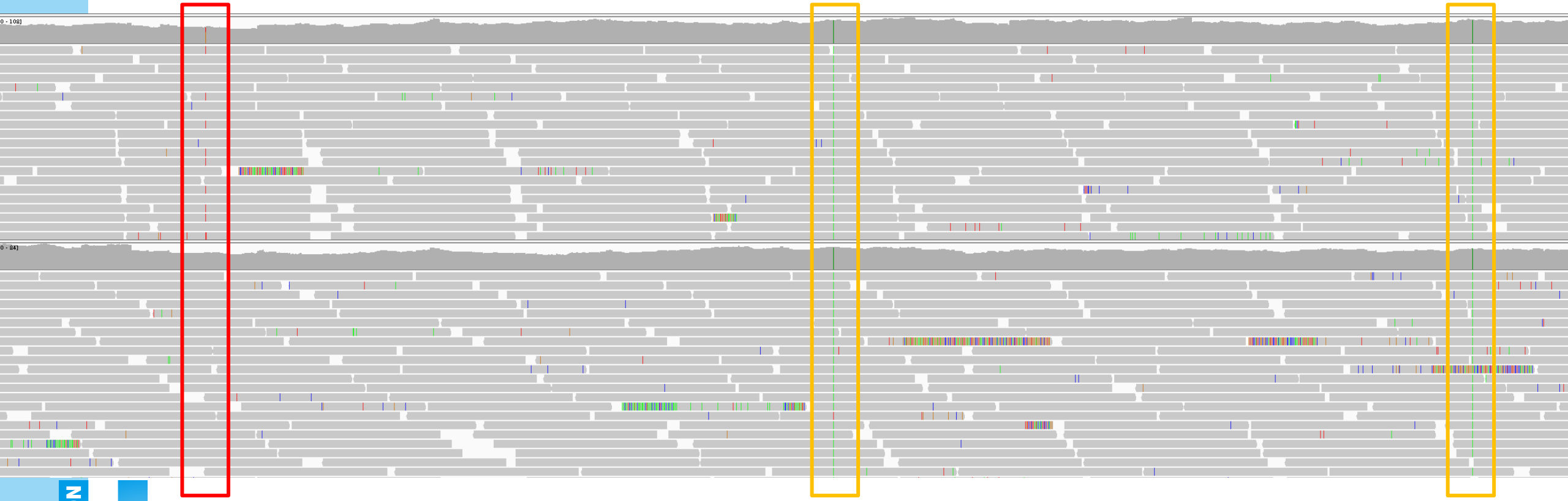


Målrettet cancerbehandling

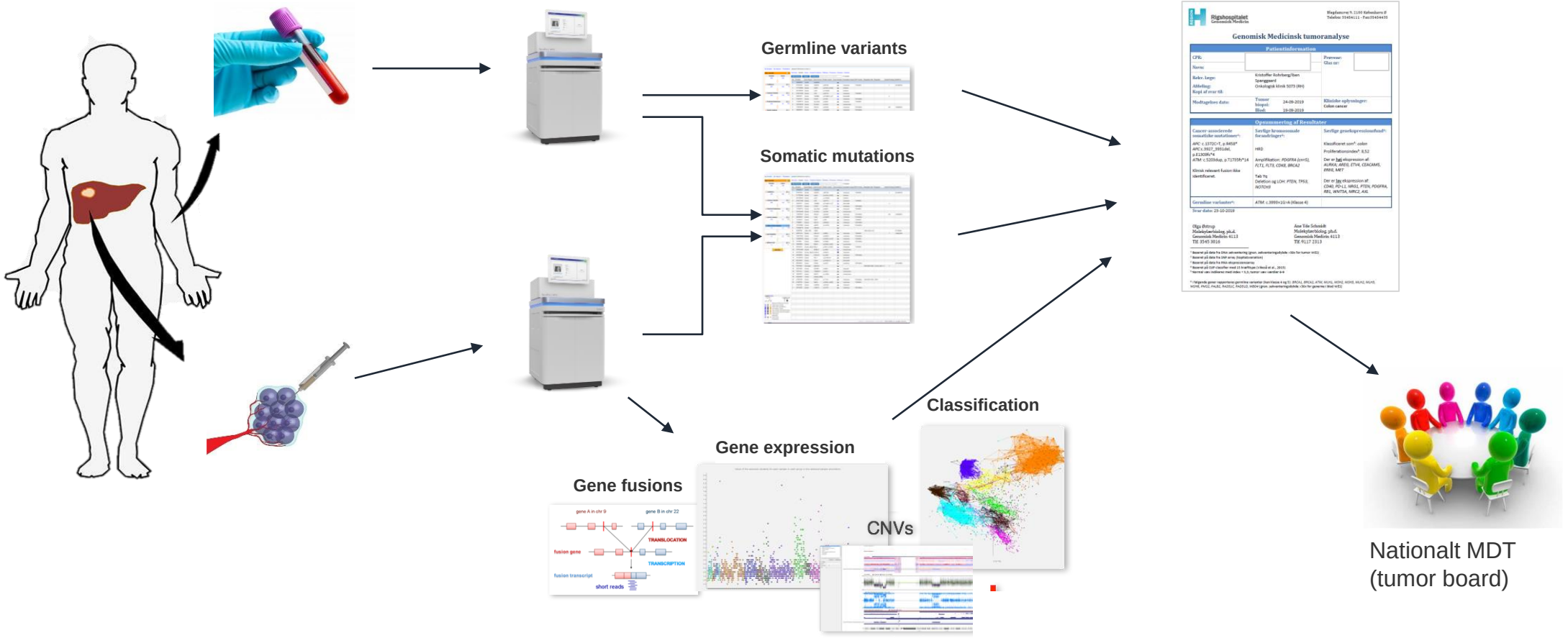




Cancer specifikke mutationer (Tumor minus blod)

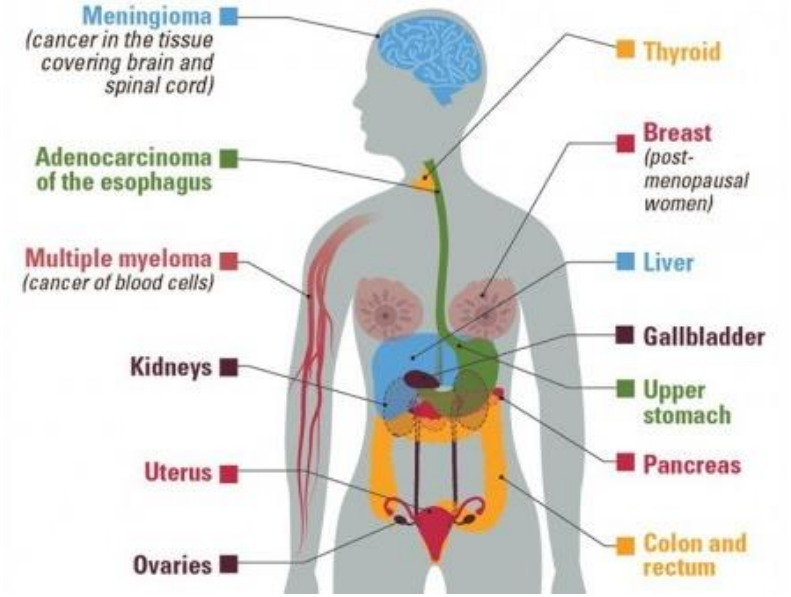


Fase1 projektet



Fase1 projektet

- Fase 1 enheden, Onkologisk Klinik, Rigshospitalet
- Afd. for Genomisk Medicin, Rigshospitalet
- Patienter der har udtømt standard cancerbehandling
- Genomisk tumor profil med henblik på målrettet (eksperimentel) behandling



Tak til Genomisk Medicin Rigshospitalet