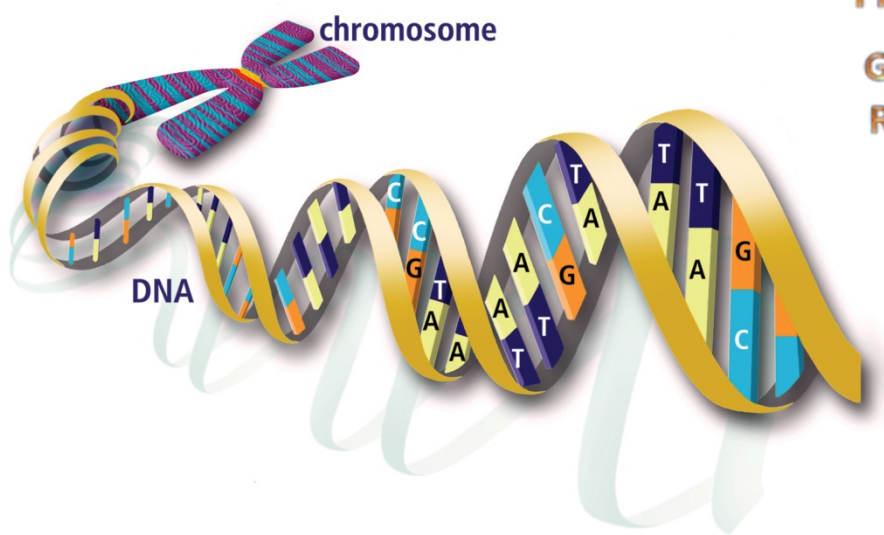
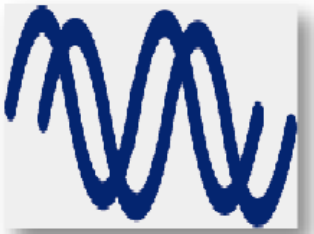
MOLECULAR CANCER DIAGNOSTICS



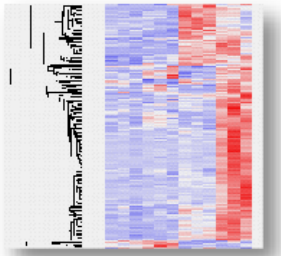
Finn Cilius Nielsen

Genomisk Medicin
Rigshospitalet

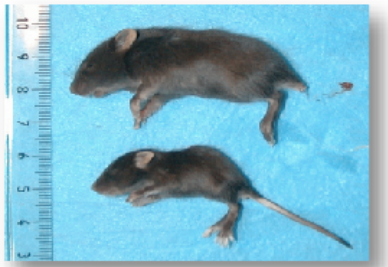
ill. Courtesy NIH.GOV



Genetics

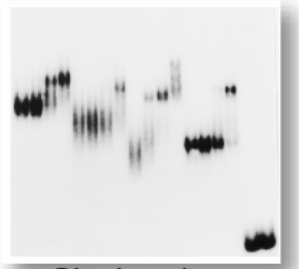


Bioinformatics

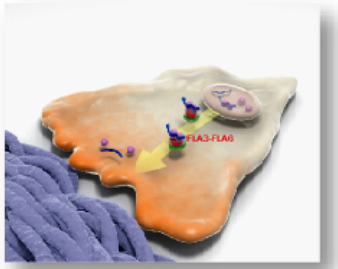


Disease models

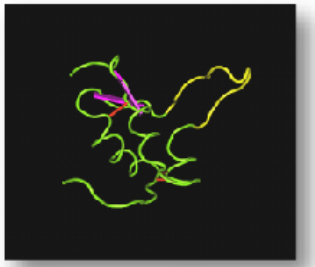
Molecular Medicine



Biochemistry



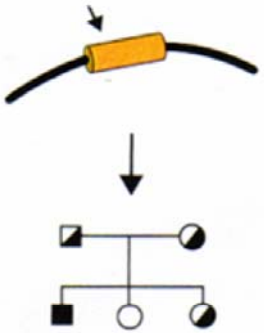
Cell Biology



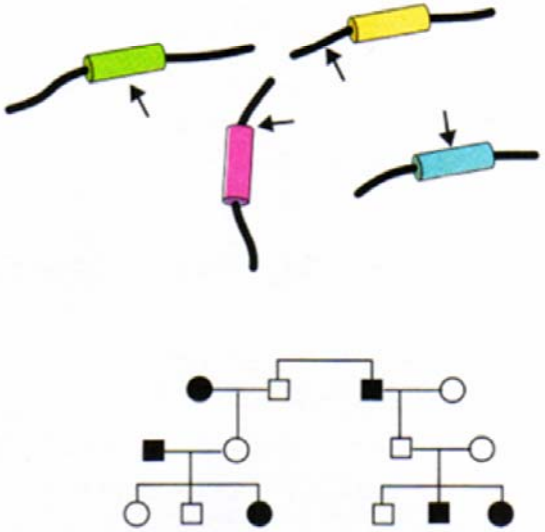
Structural Biology

Cancer Genetik

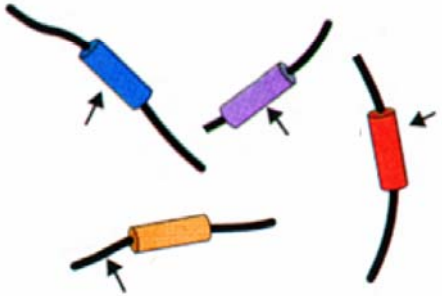
Monogen sygdom

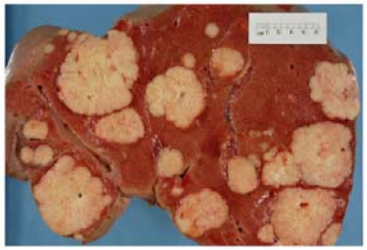


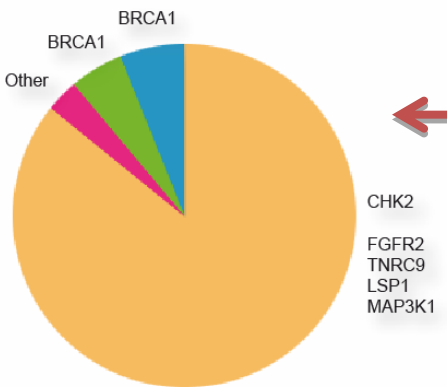
Kompleks sygdom



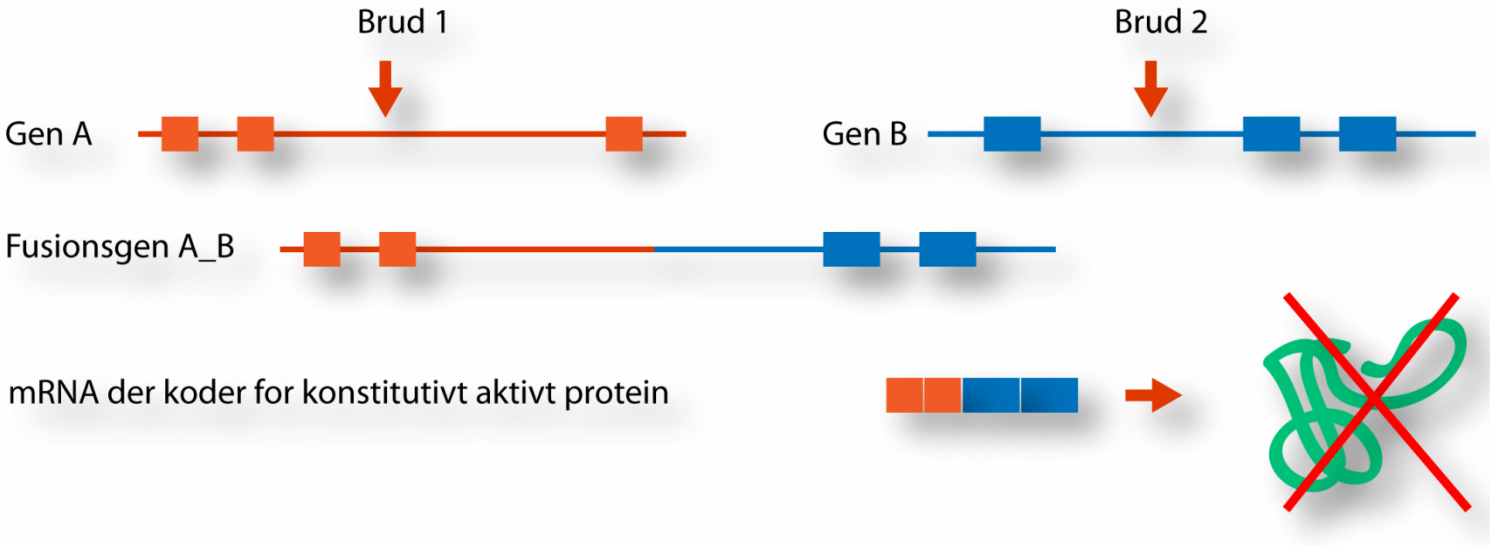
Somatisk mutation



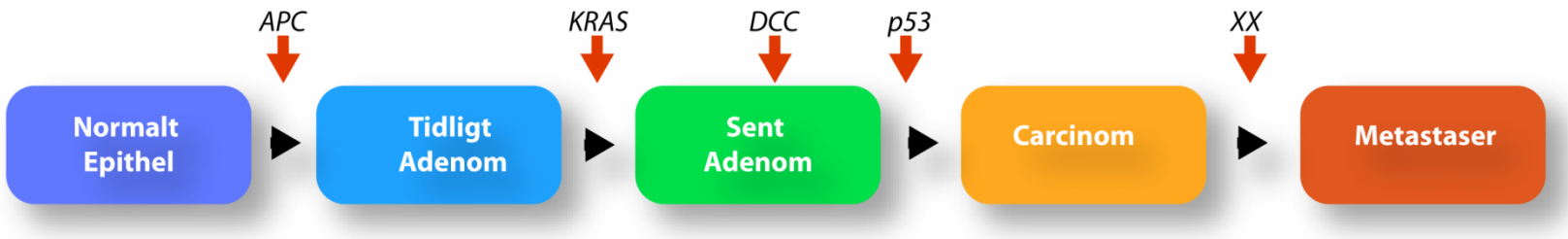




Transformation via enkelt mutation



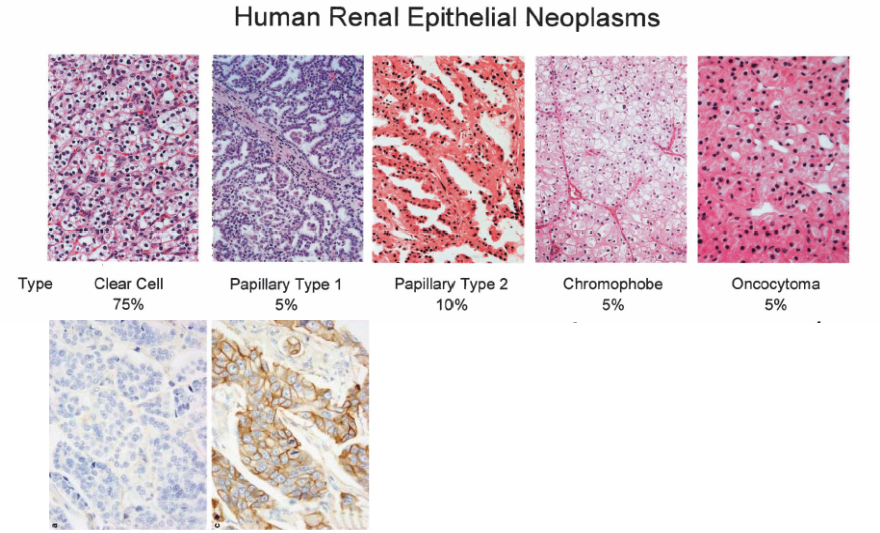
Transformation via konsekutive mutationer



Model for Colorectal Carcinogenese (Fearon & Vogelstein)

Cancer diagnostik

Histopatological examination of tissue by conventional staining or immuno-histochemistry only provides limited information about the causal defect in the cancer



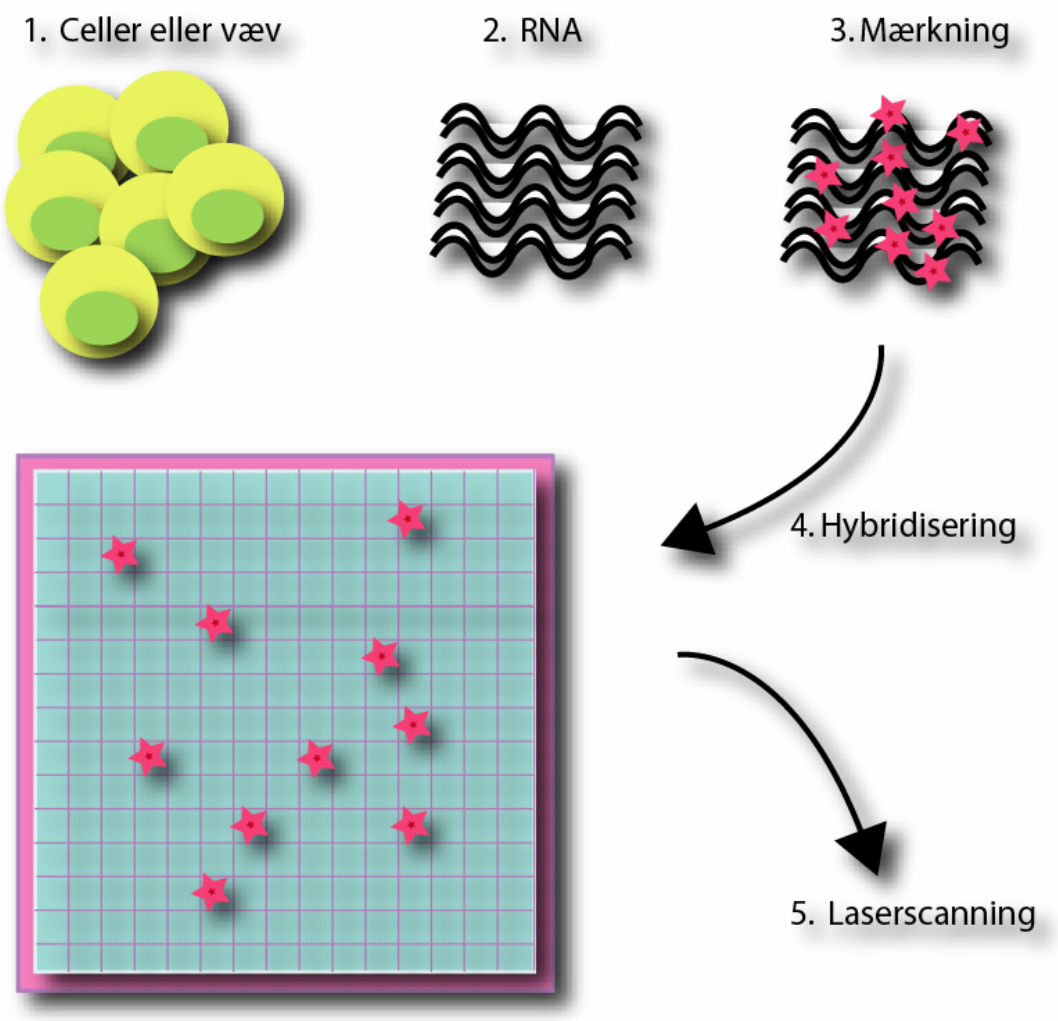
Cancer diagnostics should idealy seek to unravel the causal defects in the cells

Cytogenetiske og molekylære genetiske anomalier ved maligne solide tumorer hos børn.

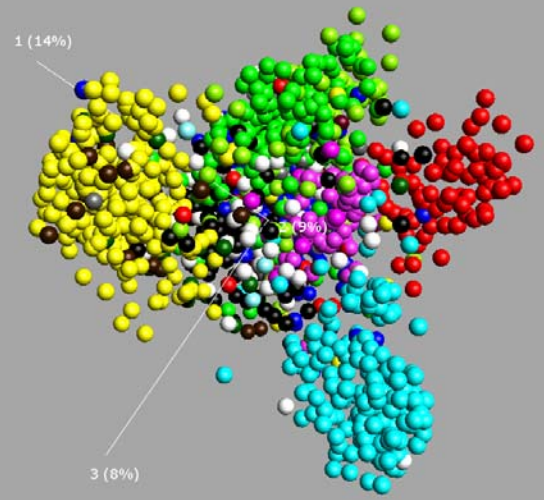
Tumor	Genetiske anomalier	Detektion af minimal residual sygdom
Neuroblastom	N-*myc*-amplifikation [2)]	RT-PCR for tyrosine-hydroxylase
	1p deletion (1p36.3, 1p 35-36,1) [2)]	
	17q +	
Wilms´ tumor	Mutation af *WT1*, 11p13, 11p15, 16q [1)]	
Rhabdomyosarkom (alveolær)	t(2;13) (q35;q14) [1)]	RT-PCR for *PX3-FKHR* fusionsprotein ved t (2;13)
	t(1;13) p3;q14) [1)]	
	mutation af p53 (17p13.1)	
Ewing´s sarkom	t (11;22) (q24;q12) [1)]	RT-PCR for *EWS-FLI* fusionsprotein ved t (11;22)
	t (21;22) [1)]	RT-PCR for *EWS-ERG* fusionsprotein ved t (21;22)
Osteosarkom	Mutation af *p53* (17p13.1)	
	Mutation af *RB*-genet (13q14)	
Retinoblastom	Mutation af *RB*-genet (13q14) [1)]	

1) Diagnostisk betydning
2) Diagnostisk og prognostisk betydning
3) RT-PCR:revers transkriptase polymerasekædereaktion

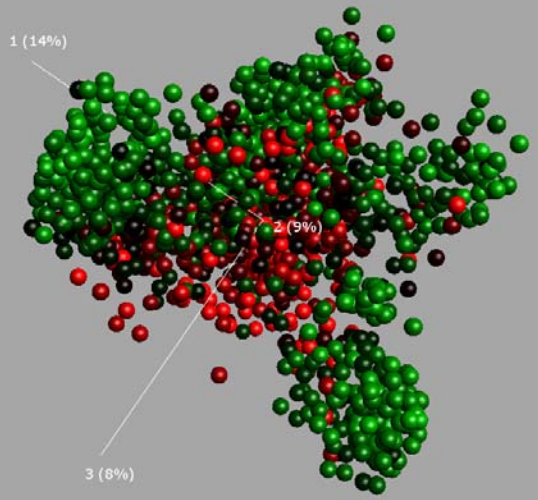
Rechnitzer & Nielsen
Ugeskr Laeger. 1999 Apr 12;161(15):2196-201.


1. Celler eller væv
2. RNA
3. Mærkning
4. Hybridisering
5. Laserscanning

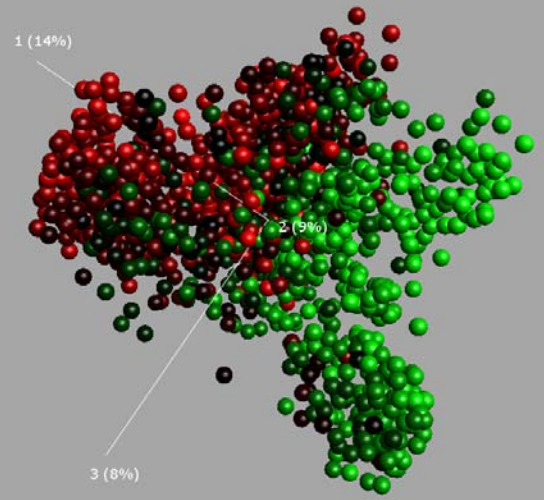
Classification



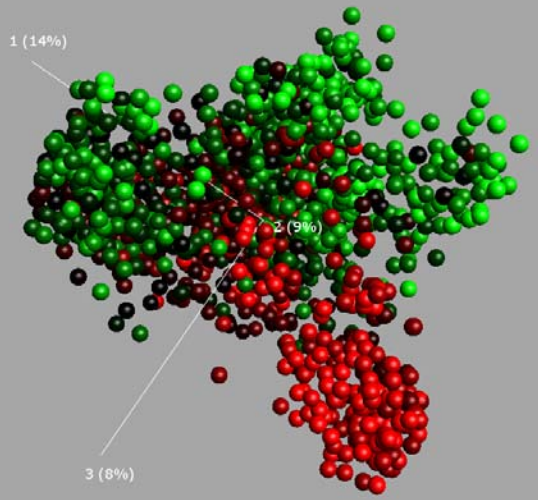
Claudin



ASP



Sorting nexin 10

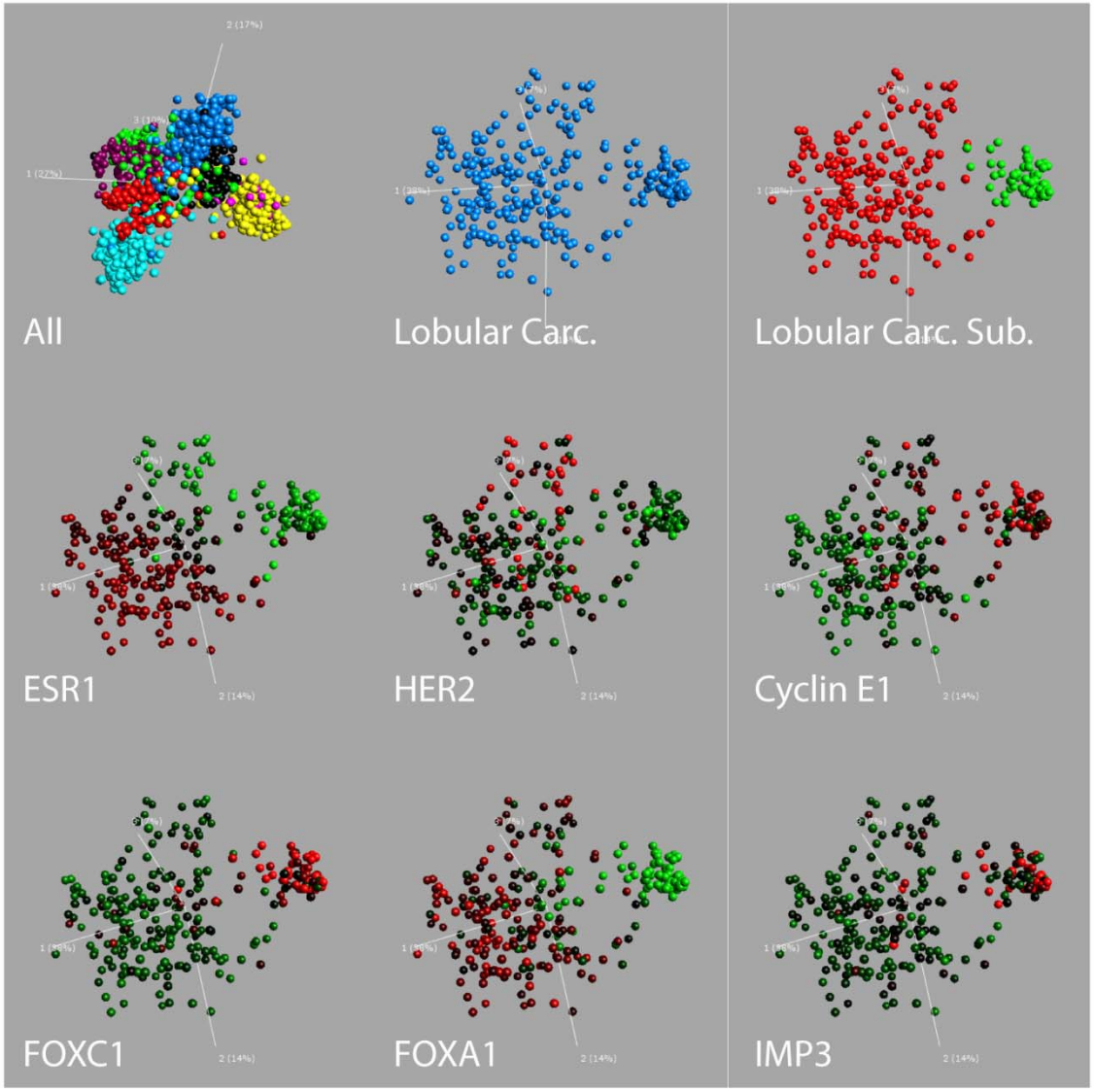


Prediction confusion matrix of primary cancers

e-160, cv error = 0.0906	Adrenal Gland	Bladder UT	Breast	Cervix_ Uteri	Cholangie_carcinoma	Colon	Esophagus	Fallopian Tube	Kidney	Liver	Lung	Melanoma	Normal	Ovary	Pancreas	Primary_Peritoneal	Prostate	Small_Intestine	Stomach	Testis	Thyroid	Uterus
Adrenal_Gland	2	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Bladder_UT	0	36	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Breast	0	0	255	2	0	4	0	1	5	2	2	0	0	3	1	0	0	0	0	0	2	4
Cervix_Uteri	0	2	0	15	0	2	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Cholangie_carcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Colon	0	2	4	1	0	270	2	0	0	0	1	0	0	1	2	0	2	2	4	1	3	0
Esophagus	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fallopian_Tube	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Kidney	1	0	4	1	0	0	0	0	193	0	1	0	0	1	0	0	0	0	0	0	0	0
Liver	0	0	0	0	2	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0
Lung	0	1	1	0	0	1	0	0	0	0	93	0	0	1	0	0	0	0	0	0	1	0
Melanoma	0	0	0	0	0	0	0	0	0	0	0	13	0	0	0	0	0	0	0	0	0	0
Normal	0	0	0	0	0	0	0	0	0	0	0	0	38	0	0	0	0	0	0	0	0	0
Ovary	0	0	2	0	0	1	0	2	1	1	2	0	0	94	0	6	0	0	0	0	1	8
Pancreas	0	0	0	0	0	0	0	0	0	0	1	0	0	0	16	0	0	1	2	0	0	0
Primary_Peritoneal_Cancer	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	5	0	0	0	0	0	1
Prostate	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	60	0	0	0	0	0
Small_Intestine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stomach	0	0	0	0	2	1	3	0	0	0	0	0	0	0	1	0	0	0	12	0	0	0
Testis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0
Thyroid	0	0	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	86	0
Uterus	0	1	1	1	0	0	0	0	0	0	2	1	0	4	0	0	0	0	0	0	0	110

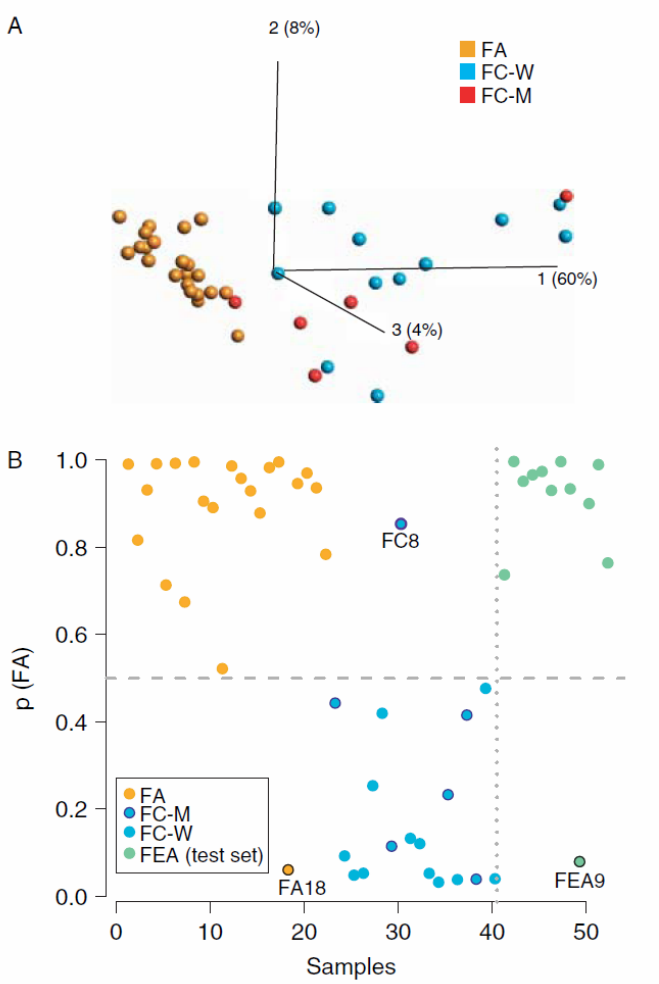
Metast. Predict Error: **0.88 = 46/211**

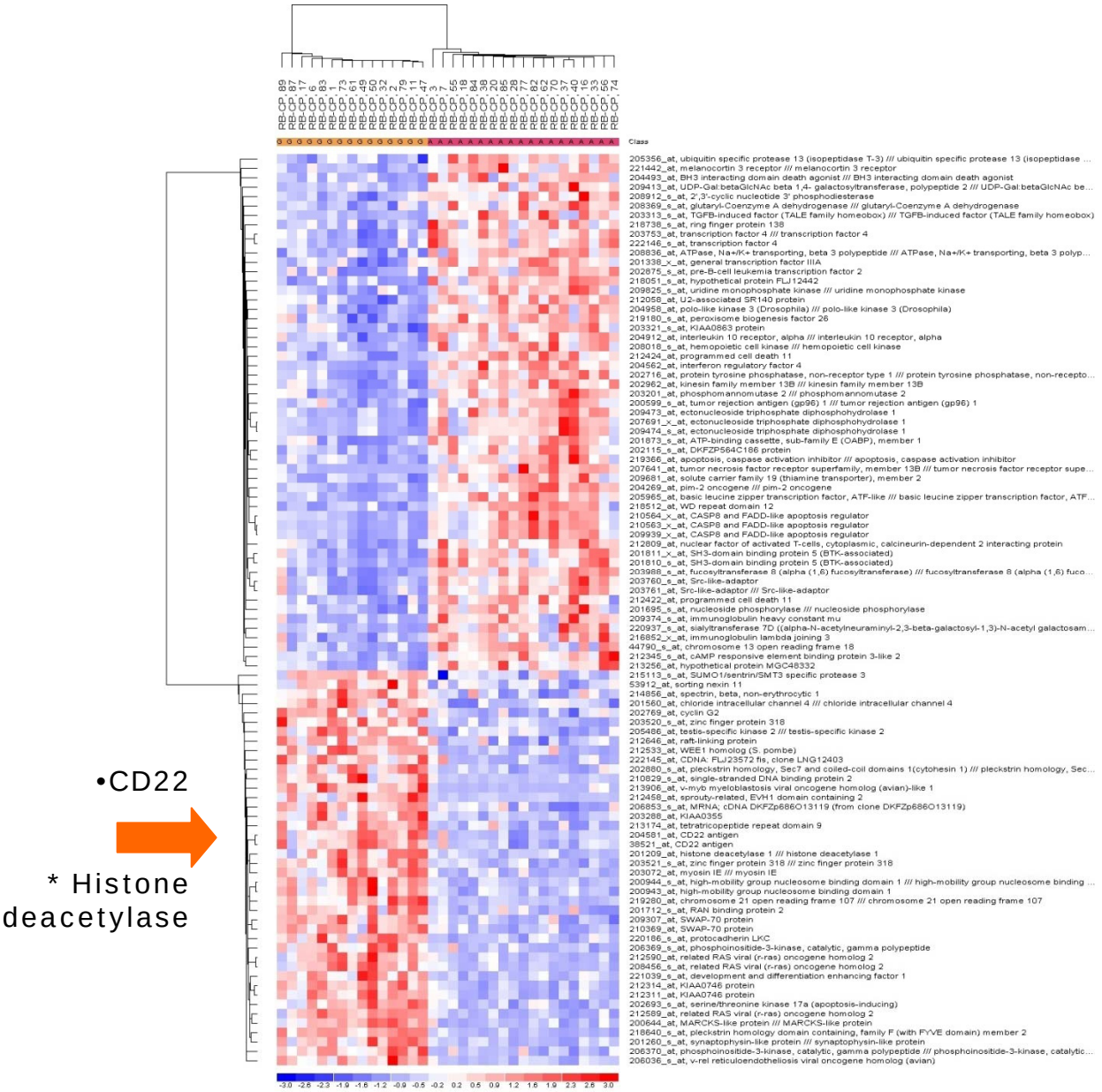
Defining Breast Cancers With Treatment Options or Poor Survival



Gene		Survival
Cyclin E1	↑	Poor
FOXC1	↑	Poor
FOXA1	↓	Poor
IMP3	↑	Poor

Global expression profiling distinguish thyroid adenoma from carcinoma





•CD22

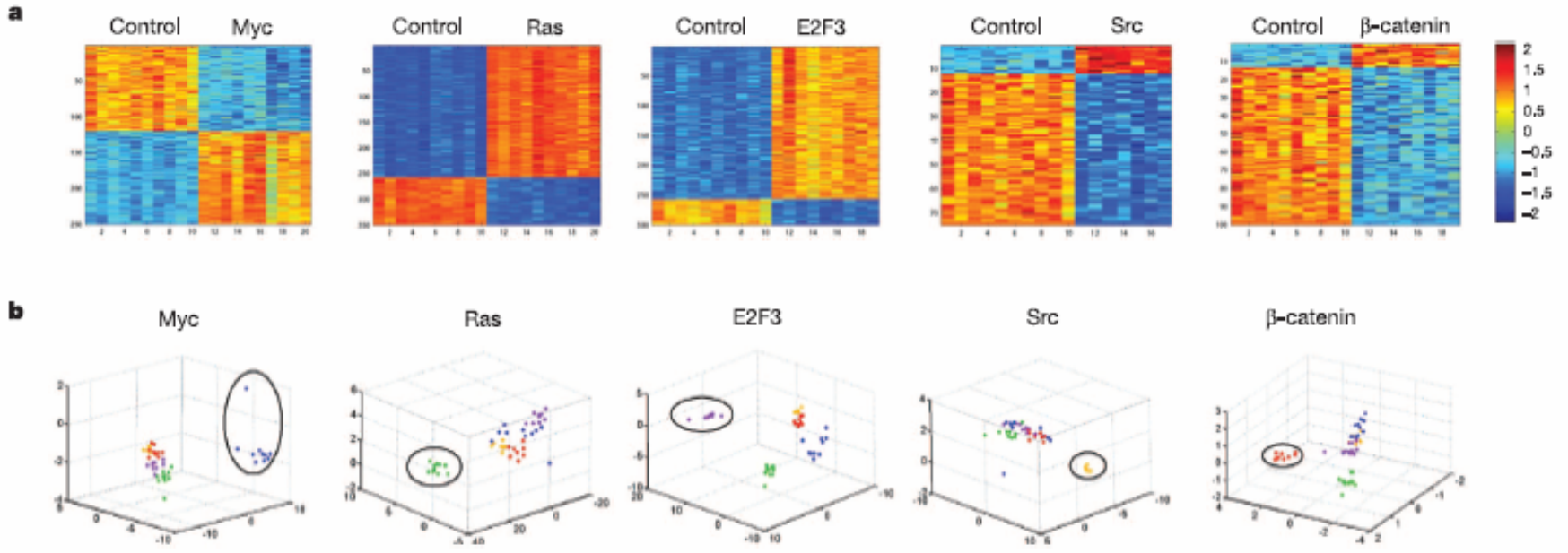
* Histone deacetylase

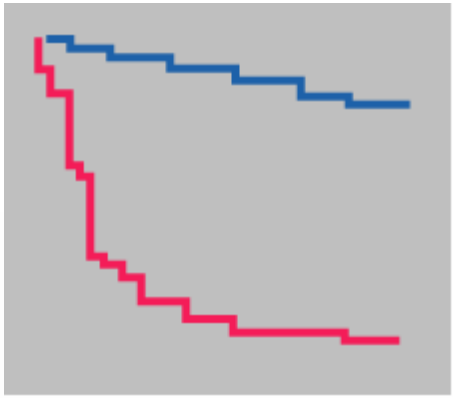
ABC **GCB** **DLBCL**

Bjørn et al. EJH

Oncogenic pathway signatures in human cancers as a guide to targeted therapies

Andrea H. Bild[1,2], Guang Yao[1,2], Jeffrey T. Chang[1,2], Quanli Wang[1], Anil Potti[1,4], Dawn Chasse[1,2], Mary-Beth Joshi[3], David Harpole[3], Johnathan M. Lancaster[7], Andrew Berchuck[5], John A. Olson Jr[1,3], Jeffrey R. Marks[3], Holly K. Dressman[1,2], Mike West[6] & Joseph R. Nevins[1,2]

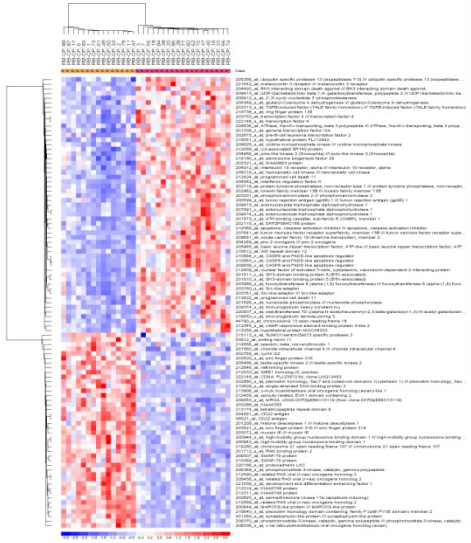




Discovery

Phase 1 - Pilot study

Phase 2 - Retrospective analysis

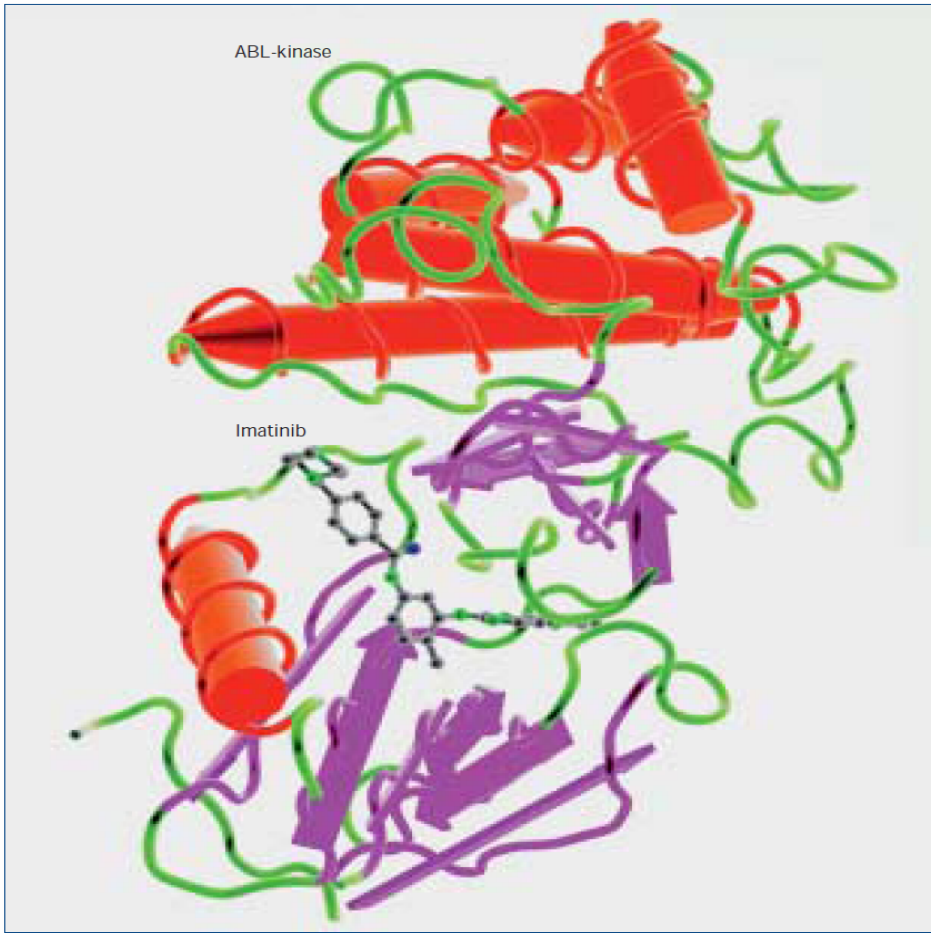


Phase 3 - Prospective study

Phase 4 - Multiinstitutional study

Standard of care

Chronic myeloid leukemia is caused by expression BCR-ABL fusion protein

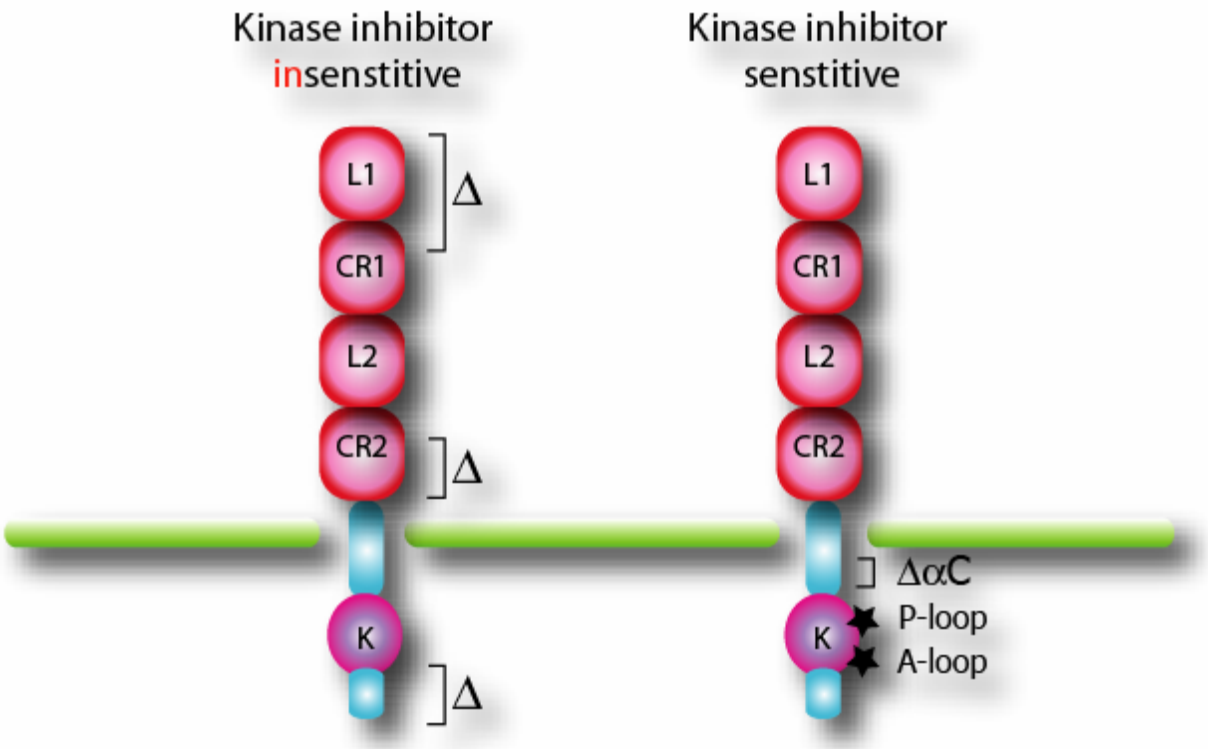


The activated ABL-kinase prevents cells from going into apoptosis.
The fusionsprotein is inhibited by Imanitib.

Tabel 1. Oversigt over nye små farmaka og deres kliniske status. Tabellen er adapteret fra [9].

Stofnavn	Handelsnavn	Målmolekyle	Klinisk status
FDA godkendt			
Anastrozole	Arimidex	ER	Godkendt til E
Bevacizumab	Avastin	VEGF	Godkendt til m
Cetuximab	Erbitux	EGFR	Godkendt til h
Erlotinib	Tarceva	EGFR	Godkendt til fr
Exemestane	Aromasin	ER	Godkendt til E
Geftinib	Iressa	EGFR	Godkendt til fr
Imatinib mesylate	Gleevec	BCR-ABL	Godkendt til k
Sorafenib	Nexavar	Raf, VEGF, KIT, FLT3	Godkendt til re
Tamoxifen	Nolvadex	ER	Godkendt til E
Trastuzumab	Herceptin	ERBB2	Godkendt til H
Klinsik afprøvning			
AMN 107	Nilotinib	BCR-ABL, KIT, PDGFR	Fase II
Roscovitine		CDK (E2F)	Fase II
ABX-EGF	Panitumumab	EGFR	Fase II
GW-572016	Lapatinib	EGFR, ERBB2	Fase III
BMS-214662 (FTI)		Ras	Fase I/II
Tipifarnib (FTI)	Zarnastra	Ras	Fase I/II
Everolimus	Rad001	mTOR	Fase II
Temsirolimus	CCI-779	mTOR	Fase II
Ly294002		PI3K	Fase I/II
FTS		Ras	Fase I/II
BMS-384825	Dasatinib	Src, BCR-ABL, KIT	Fase III
ZD-6474		RET, VEGF	Fase II/III
SU11248	Sunitinib maleate	VEGF, RET, FLT3	Fase III
PTK787/zk	Vatalanib	VEGFR1, VEGFR2	Fase III

DNA testing for Gefitinib sensitivity in non small cell lung cancer



Next generation - Deep – Sequencing

Next-generation sequencing transforms today's biology

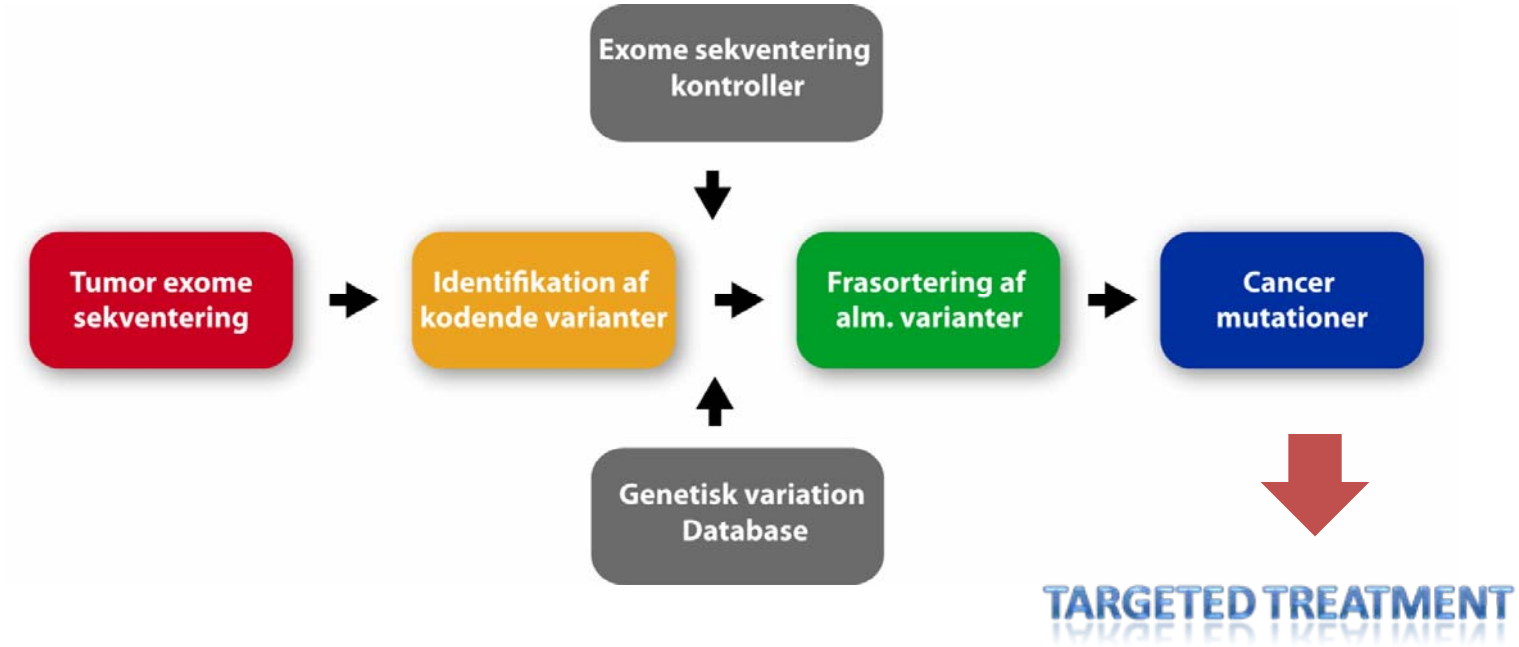
Stephan C Schuster

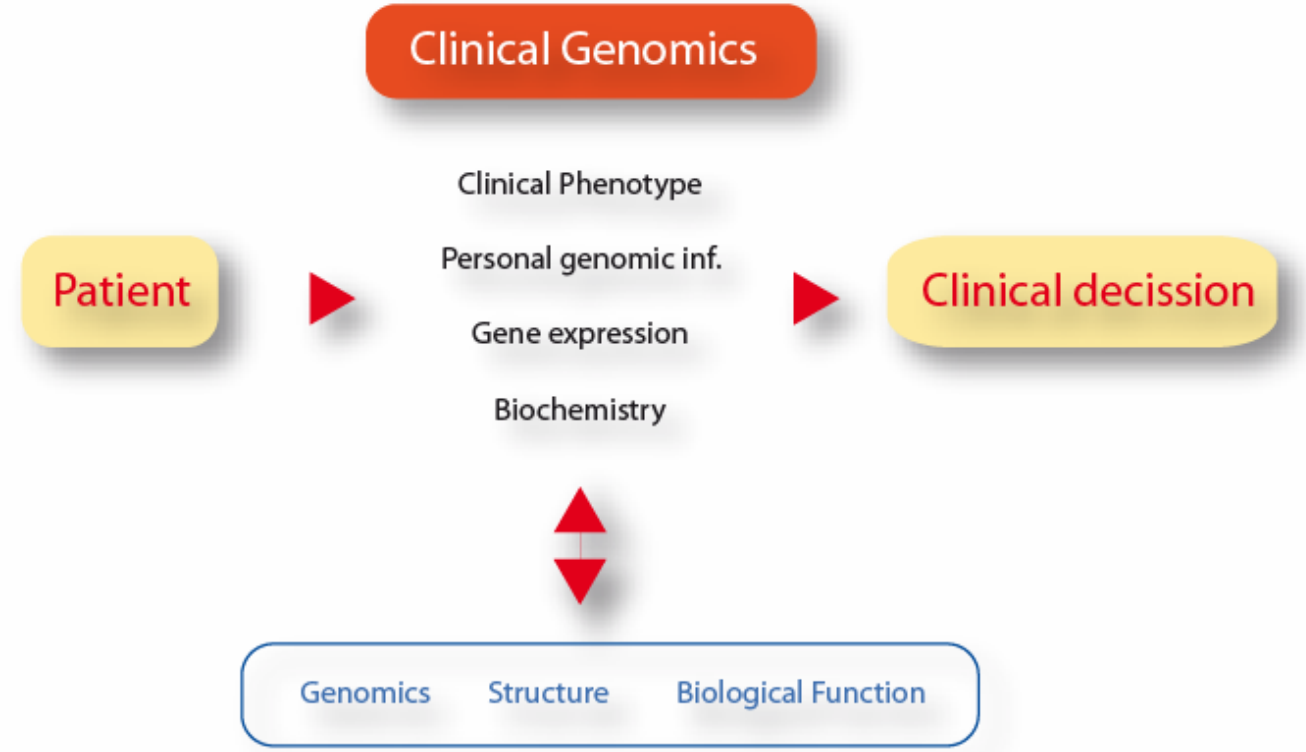
Technology, that allows parallel sequencing of massive amounts of DNA.

Deep sequencing is used to sequence whole genomes, transcriptome analysis and for identification of rare mutants.

Offer high troughput – 90 Gb per run
Can sequence complex mixtures of DNA

Next Generation Sekventering for Cancerdiagnostics




Clinical Genomics
Patient
Clinical Phenotype
Personal genomic inf.
Gene expression
Biochemistry
Clinical decission
Genomics
Structure
Biological Function