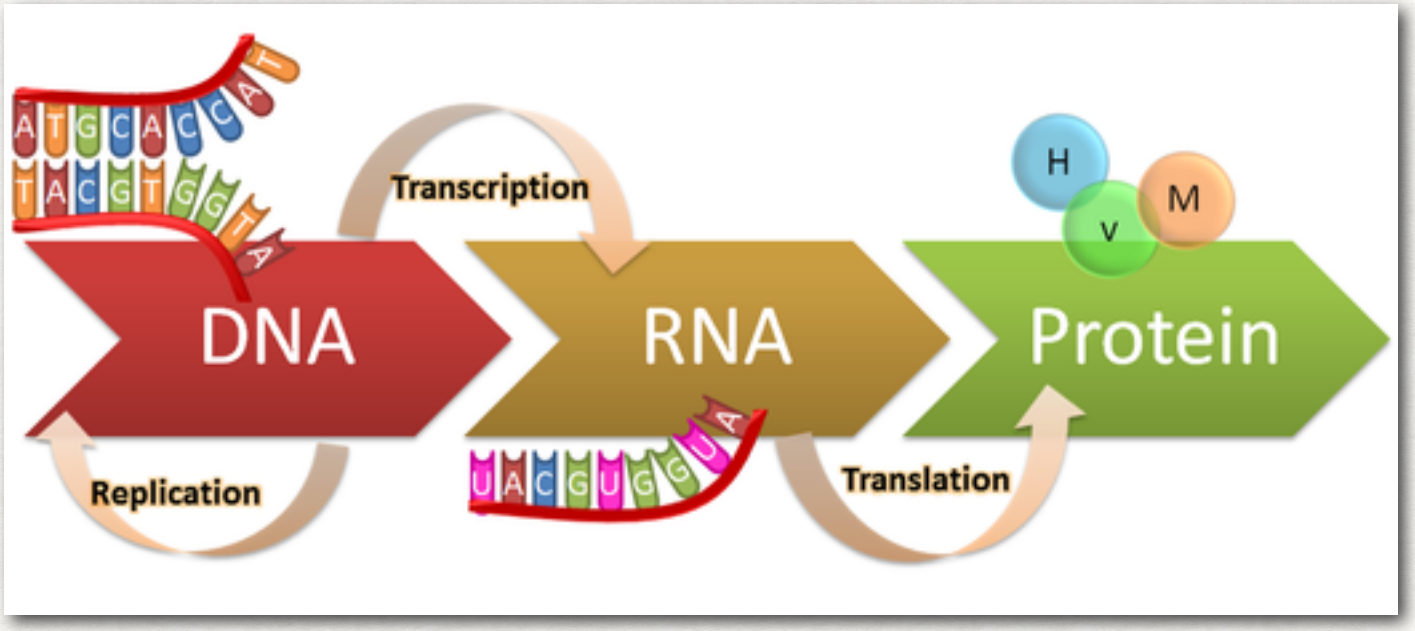
Predictive, diagnostic and prognostic markers

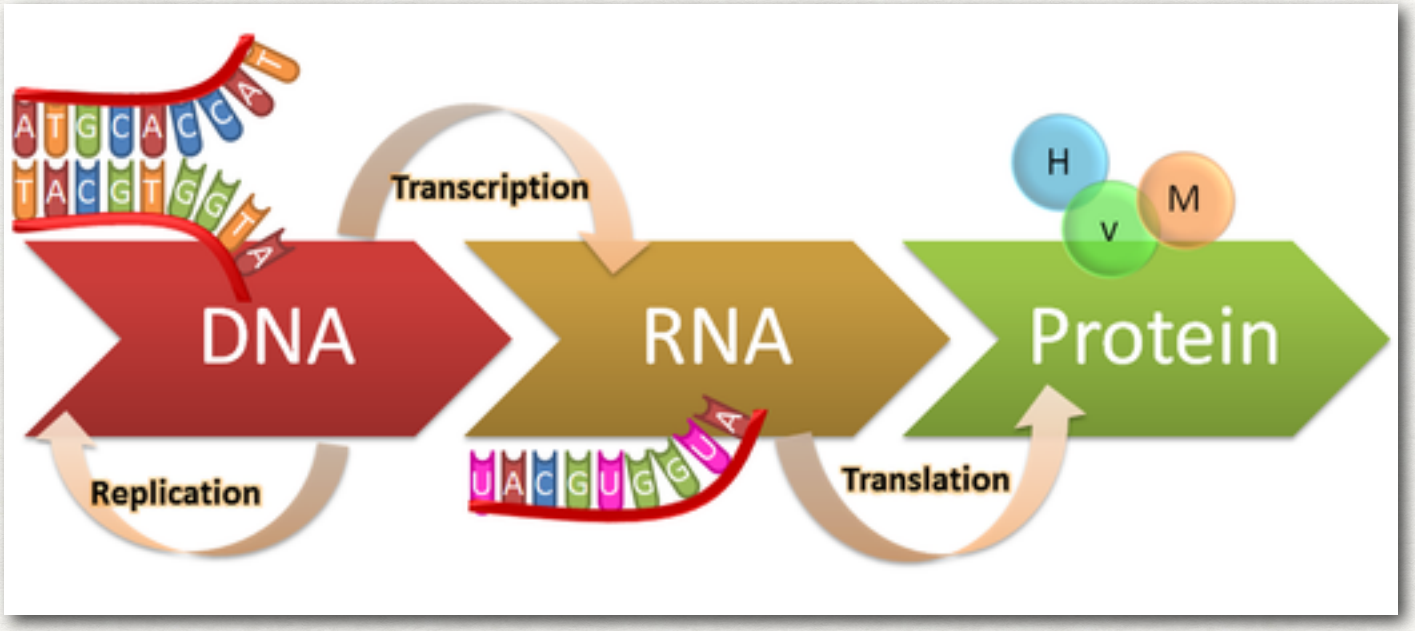
Predictive, diagnostic and prognostic markers

The central dogma



Predictive, diagnostic and prognostic markers

The central dogma

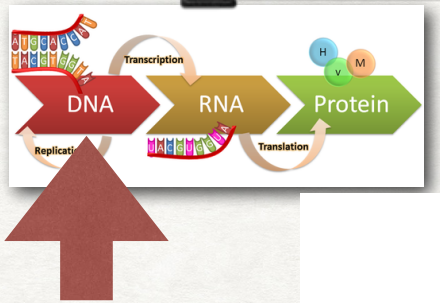


In-situ hybridization

Molecular methods (PCR, SEQ)

Immunohistochemistry

Predictive, diagnostic and prognostic markers



How do oncogenes and tumor suppressors work?

oncogene

(A) overactivity mutation (gain of function)

normal cell

single mutation event creates oncogene

activating mutation enables oncogene to stimulate cell proliferation

cells that proliferate abnormally

Tumor suppessor

(B) underactivity mutation (loss of function)

normal cell

mutation event inactivates tumor suppressor gene

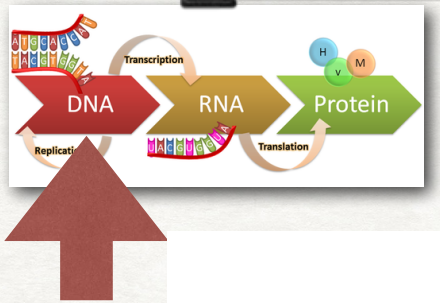
no effect of mutation in one gene copy

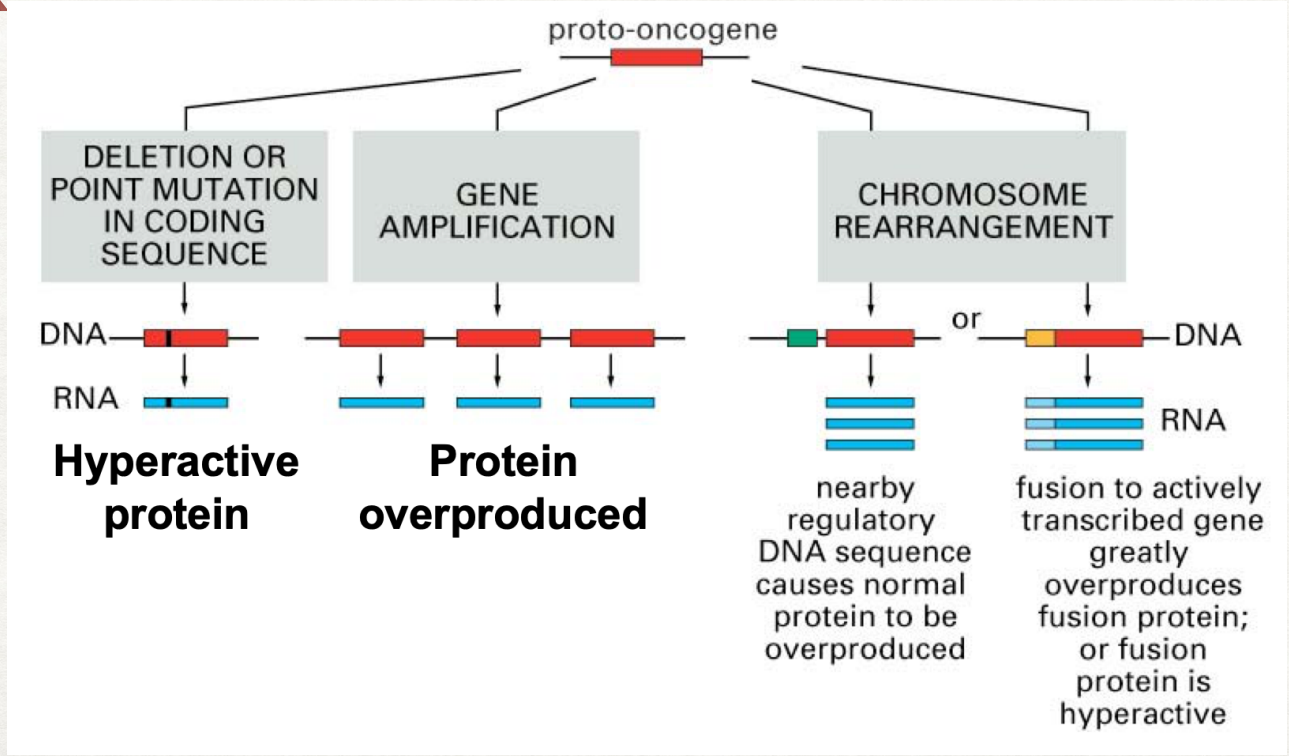
second mutation event inactivates second gene copy

two inactivating mutations functionally eliminate the tumor suppressor gene, stimulating cell proliferation

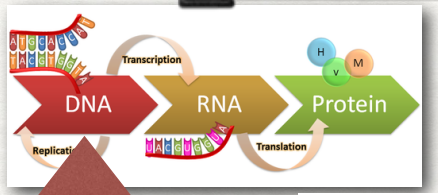
Figure 23–24. Molecular Biology of the Cell, 4th Edition.

Predictive, diagnostic and prognostic markers





Predictive, diagnostic and prognostic markers



How do oncogenes and tumor suppressors work?

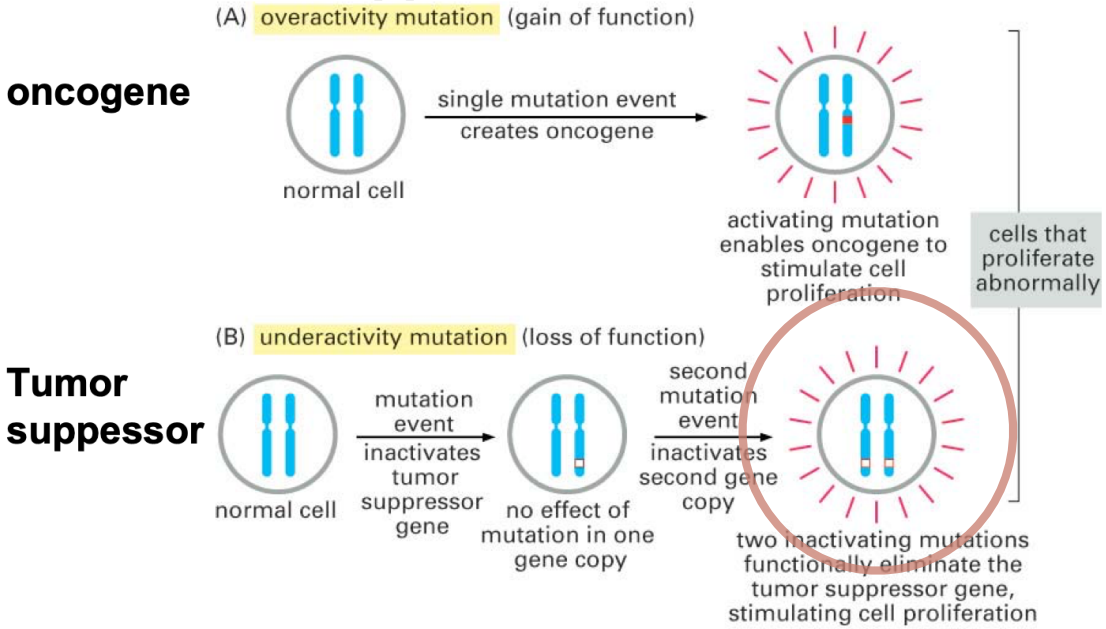
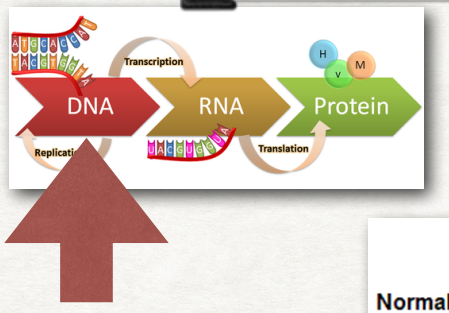
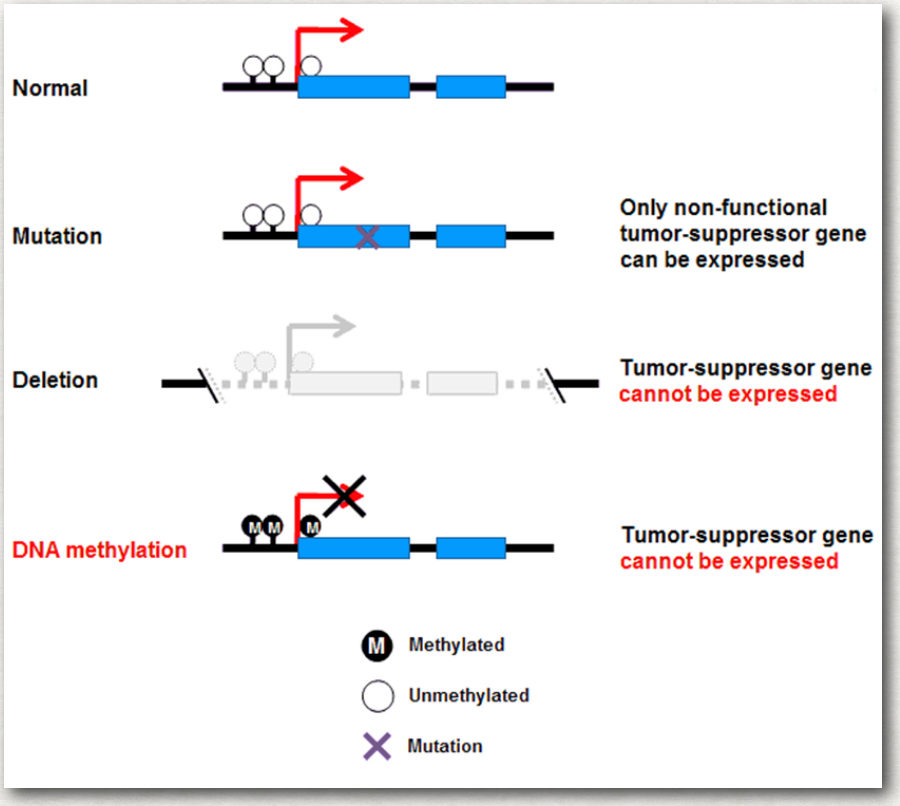


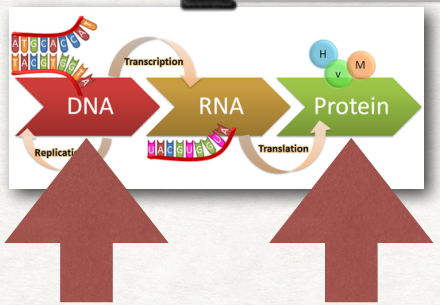
Figure 23–24. Molecular Biology of the Cell, 4th Edition.

Predictive, diagnostic and prognostic markers



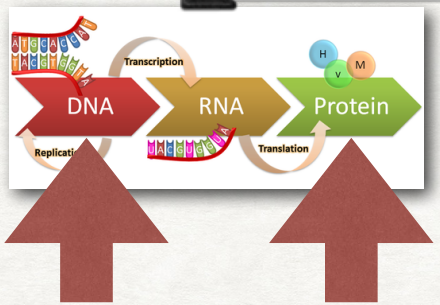


Predictive, diagnostic and prognostic markers



Mutation	Changed protein
Translocation	Absence of protein
Deletion	Abnormal localisation
Amplification	Over expression
Methylation	Fussion protein

Predictive, diagnostic and prognostic markers



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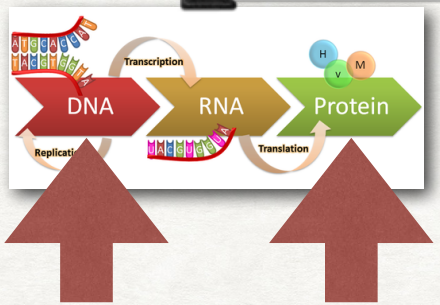
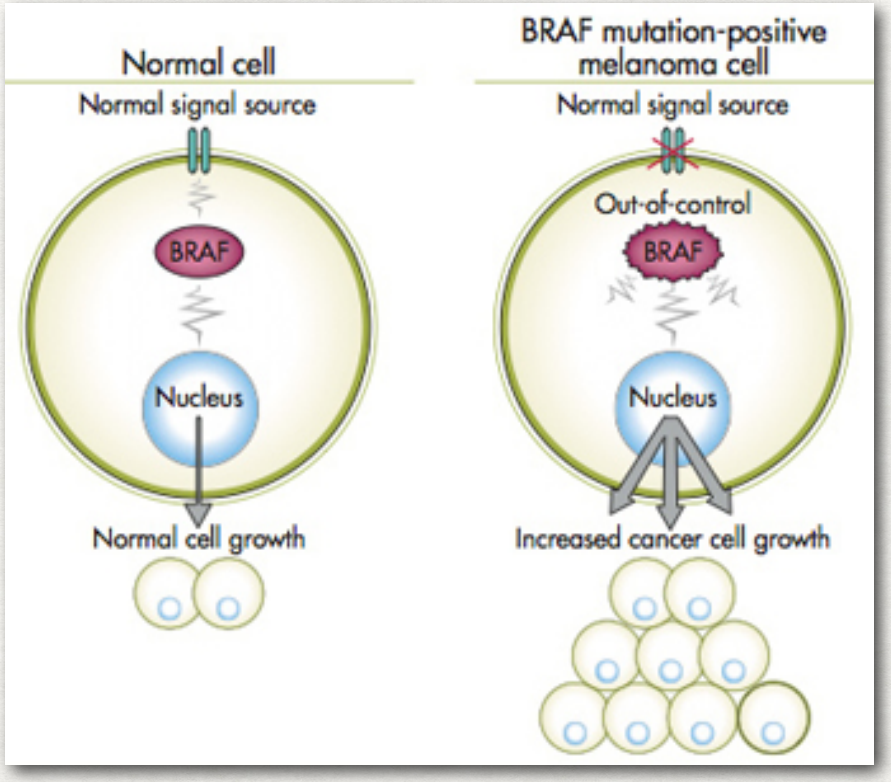
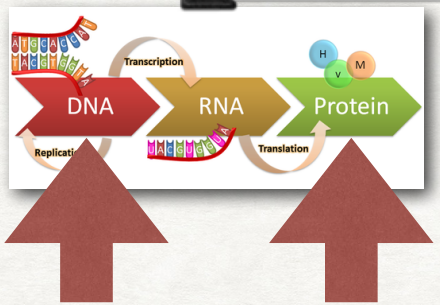


Mutated protein (auto activated)

Melanoma BRAF mutation

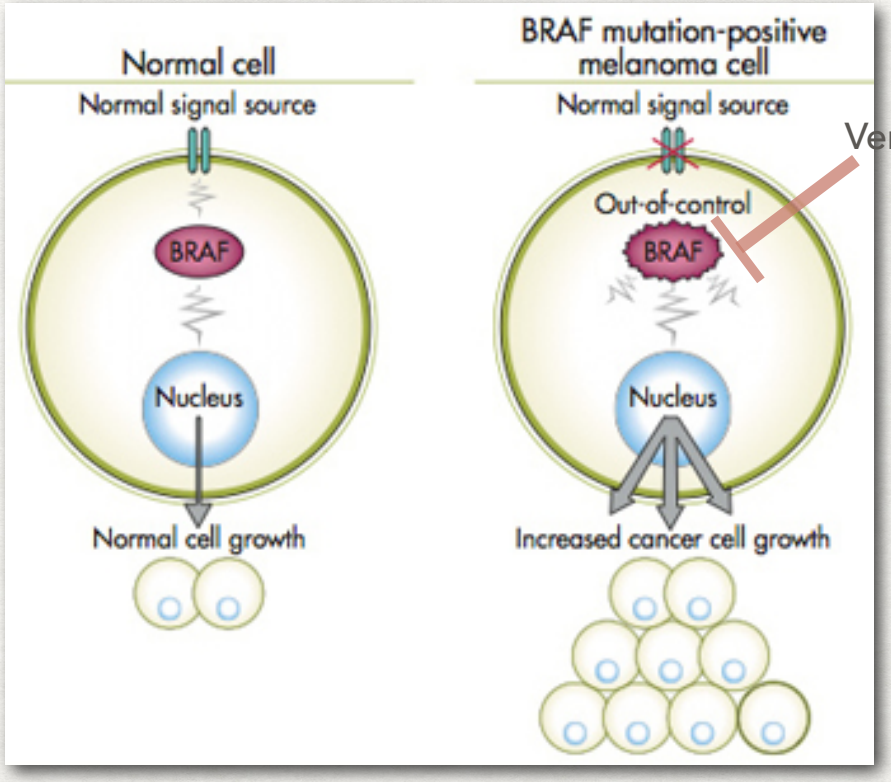


Predictive, diagnostic and prognostic markers

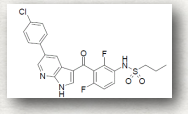


Mutated protein (auto activated)

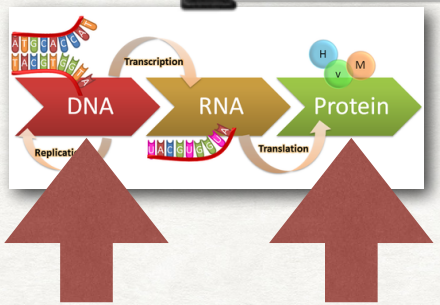
Melanoma BRAF mutation



Vemurafinib

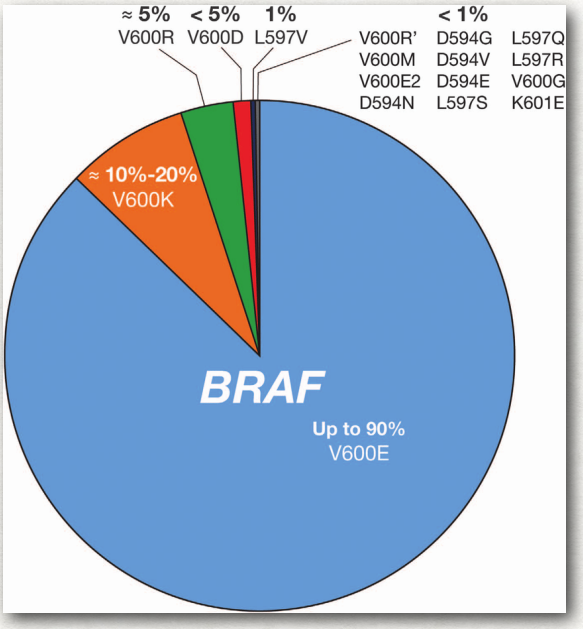


Predictive, diagnostic and prognostic markers



Mutated protein (auto activated)

Melanoma BRAF mutation



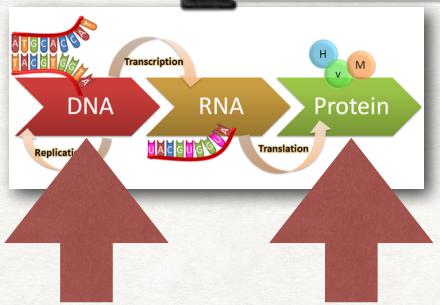
WT: GTG (valin)

V600E: GAG (glutamat)

V600K: AAG (lysin)

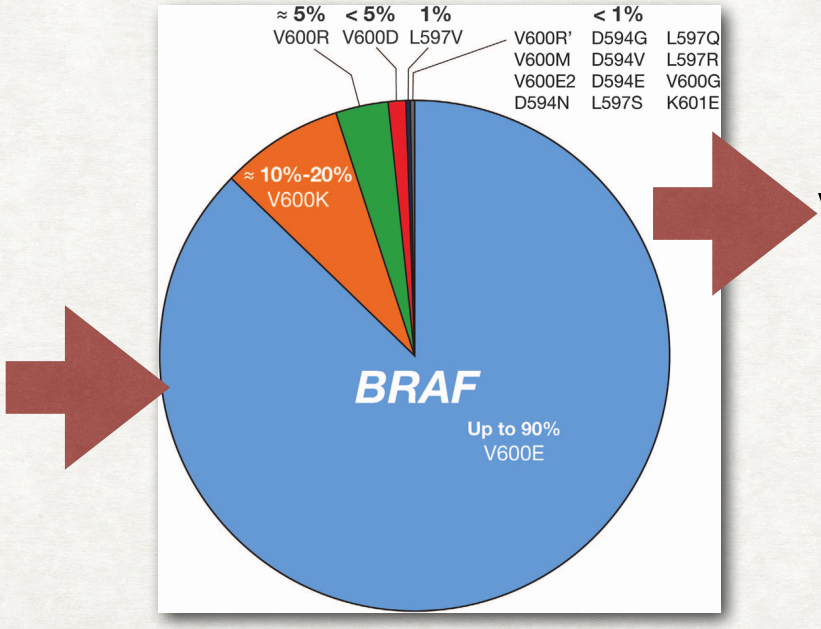
V600R: AGG (Arginin)

Predictive, diagnostic and prognostic markers



Mutated protein (auto activated)

Melanoma BRAF mutation



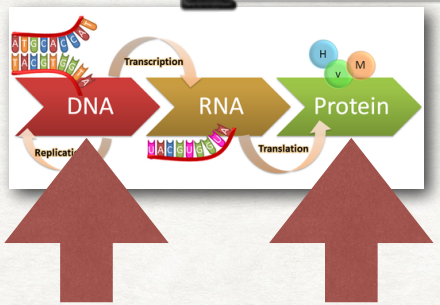
WT: GTG (valin)

V600E: GAG (glutamat)

V600K: AAG (lysin)

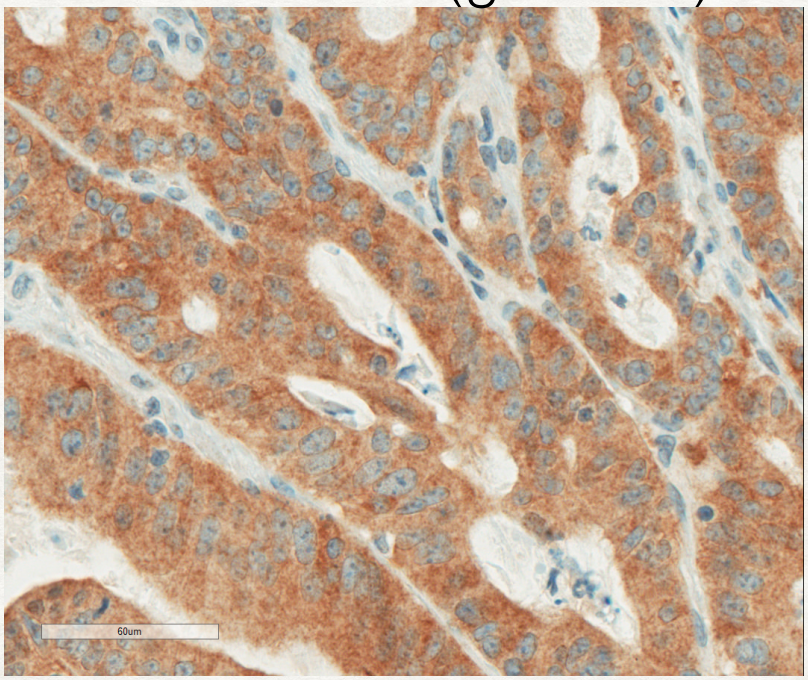
V600R: AGG (Arginin)

Predictive, diagnostic and prognostic markers



Mutated protein (auto activated)

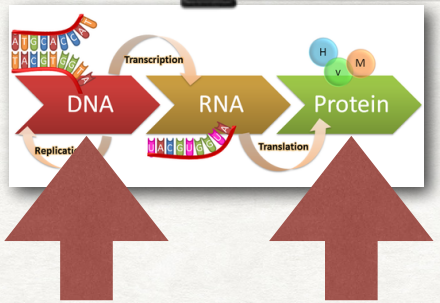
V600E: GAG (glutamat)



BRAF V600E (VE1)
Mouse Monoclonal Primary Antibode

VENTANA Roche

Predictive, diagnostic and prognostic markers



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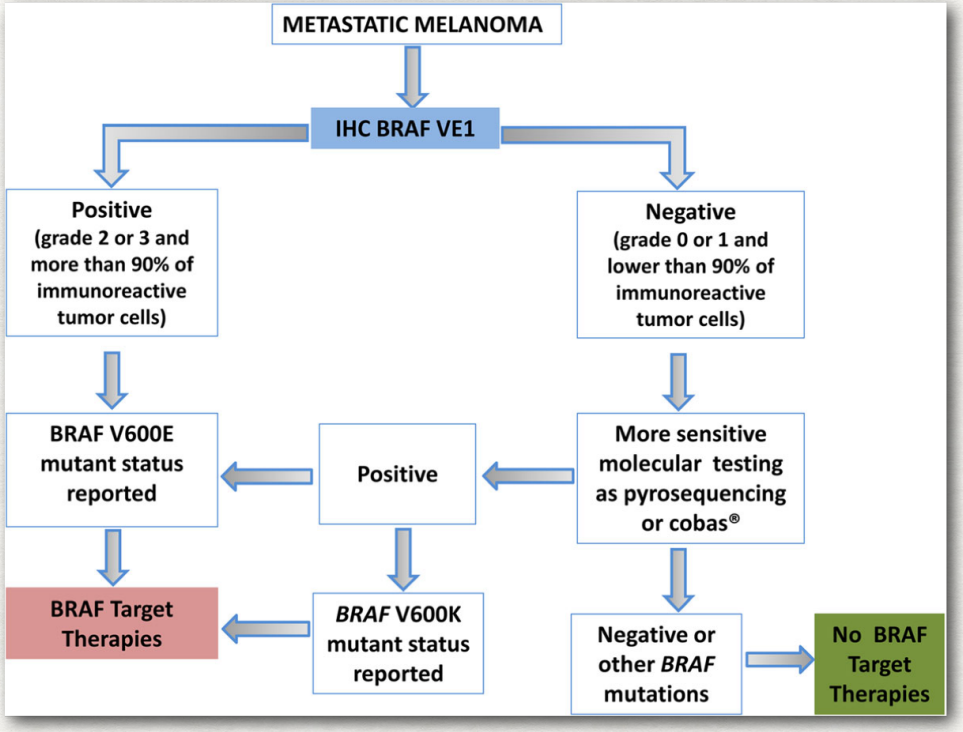
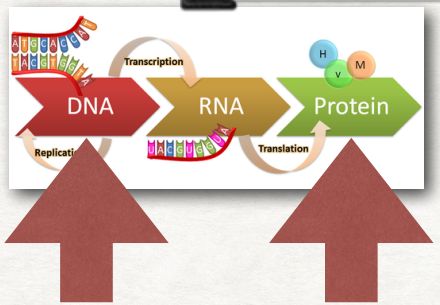


Schirosi *et al. BMC Cancer* (2016) 16:905
DOI 10.1186/s12885-016-2951-4

Predictive, diagnostic and prognostic markers

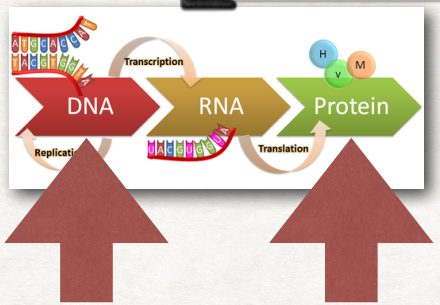


Mutated protein (auto activated)

Immunohistochemistry
BRAF V600E

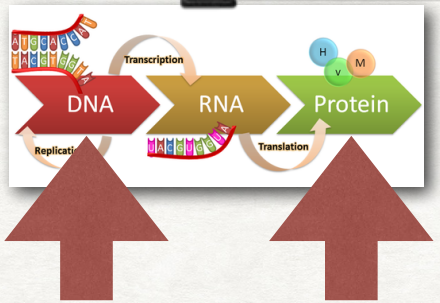
Mutation analysis of BRAF gene

Predictive, diagnostic and prognostic markers



Mutation	Changed protein
Translocation	Absence of protein
Deletion	Abnormal localisation
Amplification	Over expression
Methylation	Fussion protein

Predictive, diagnostic and prognostic markers



Often combination of
Deletion
Mutation
Methylation

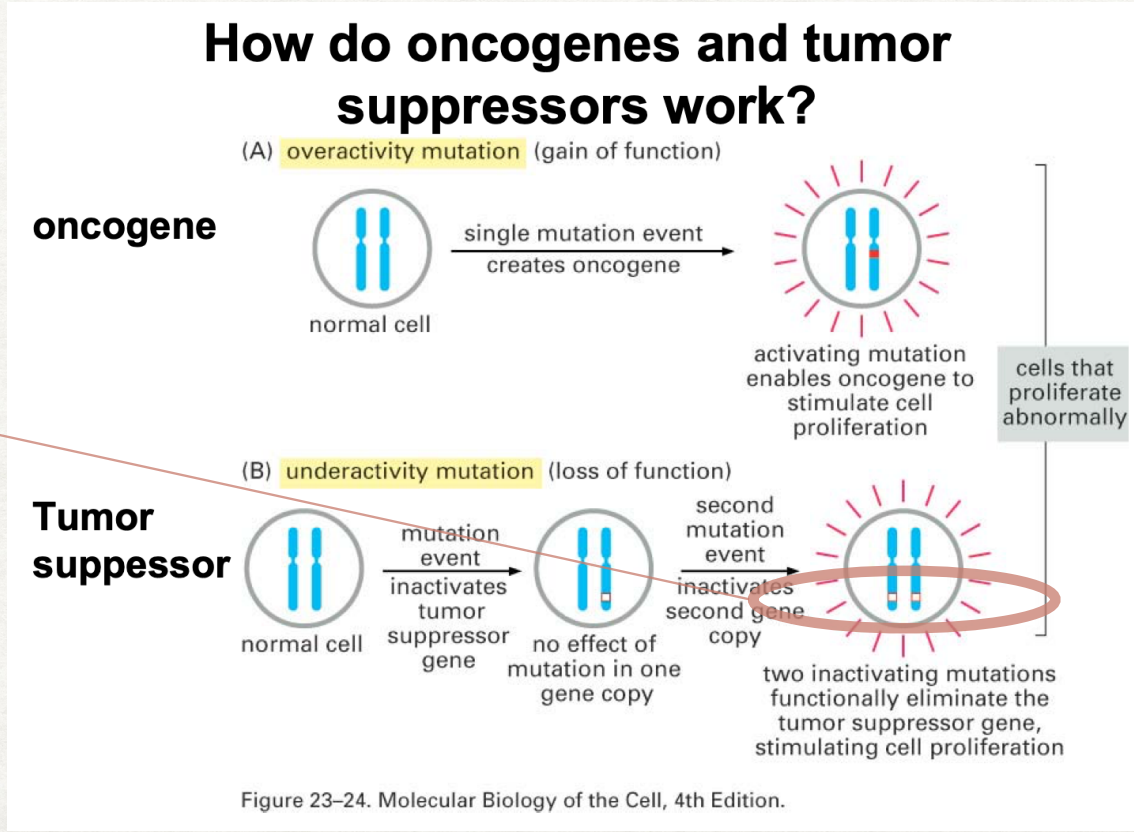
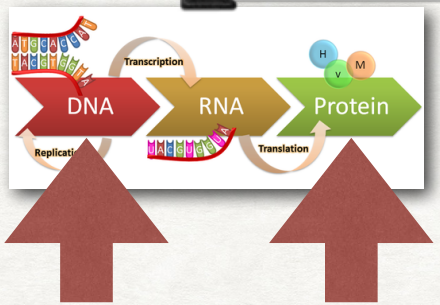
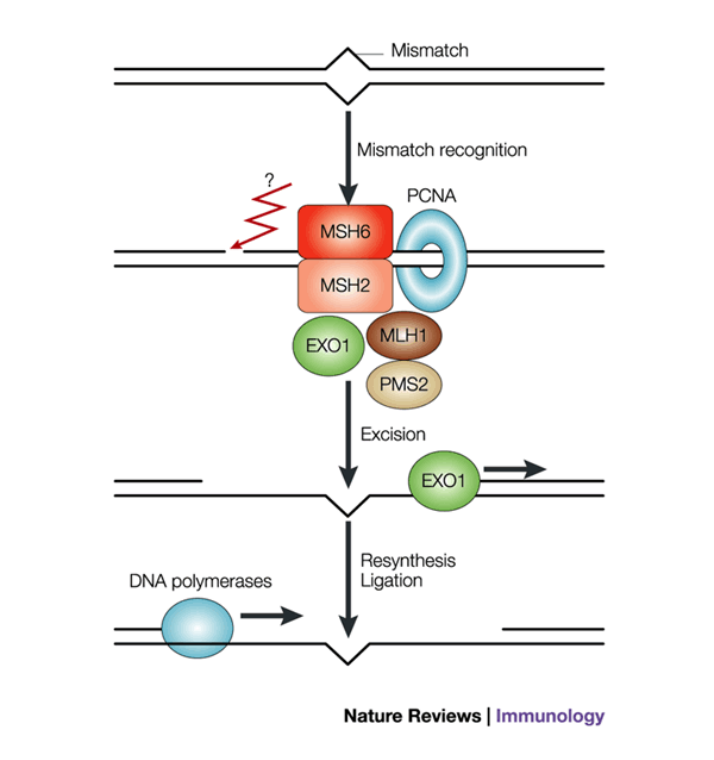


Figure 23–24. Molecular Biology of the Cell, 4th Edition.

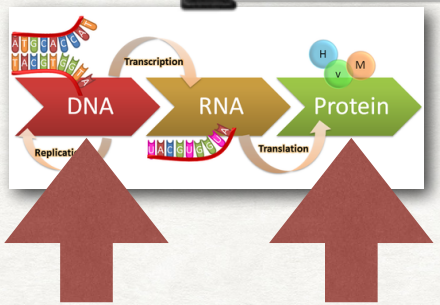
Predictive, diagnostic and prognostic markers



Absence of protein



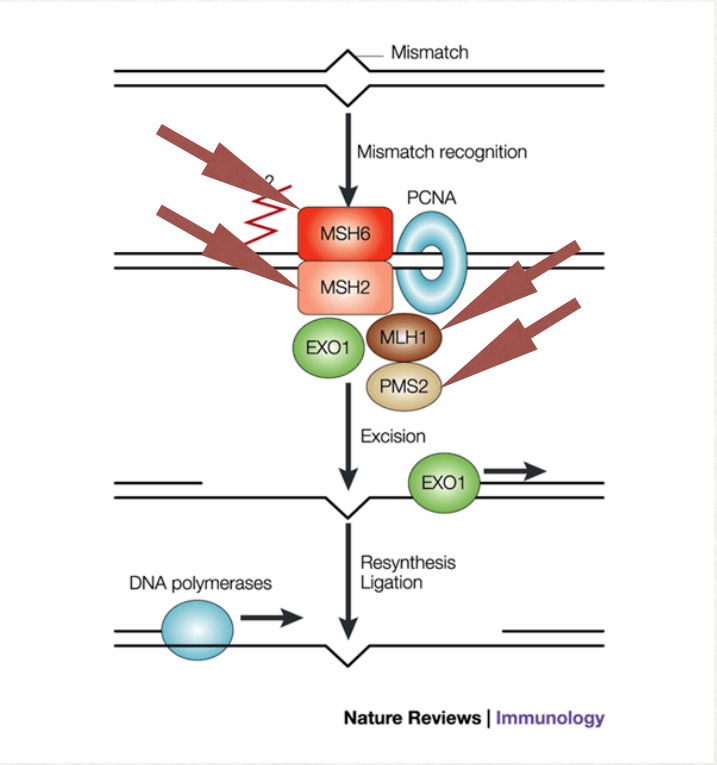
Predictive, diagnostic and prognostic markers



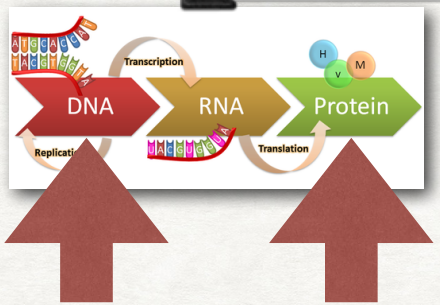
Absence of protein

Mutation
(Methylation)

Mismatch Repair deficiency
Microsatelite instability



Predictive, diagnostic and prognostic markers

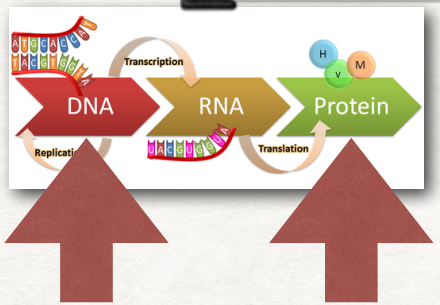


Absence of protein

Identify colon cancer patients with inherited colon cancer (Lynch syndrome)

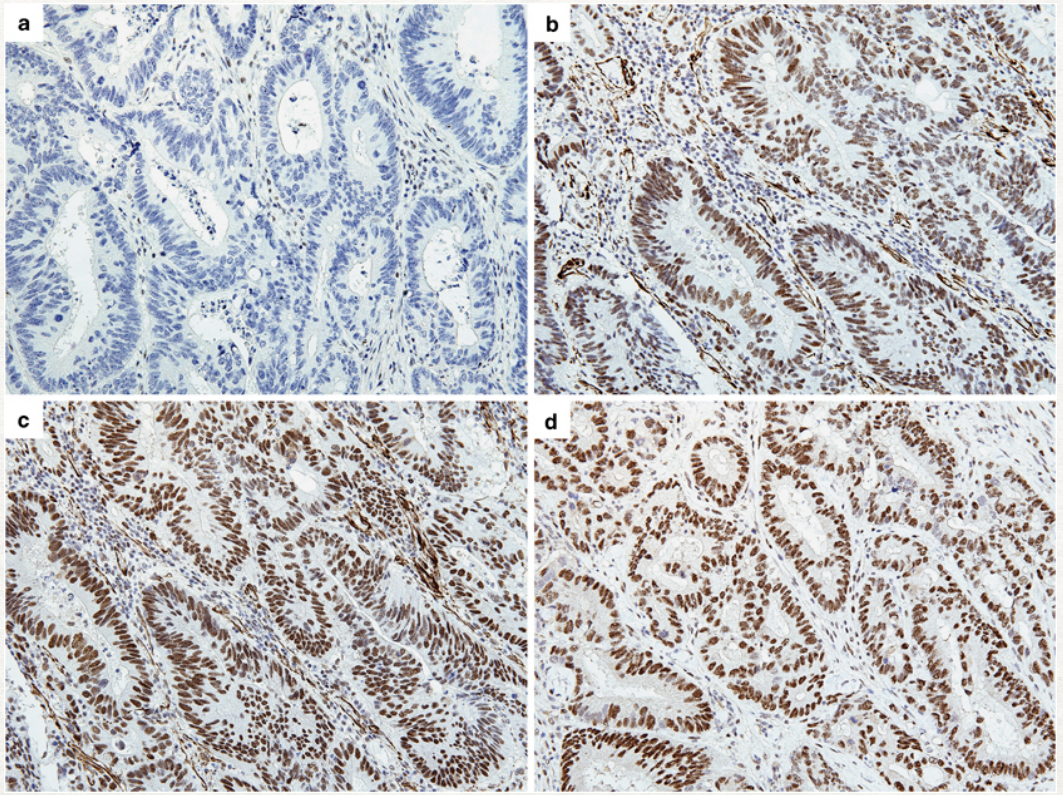
Identify patients with sporadic MSI colon cancers

Predictive, diagnostic and prognostic markers



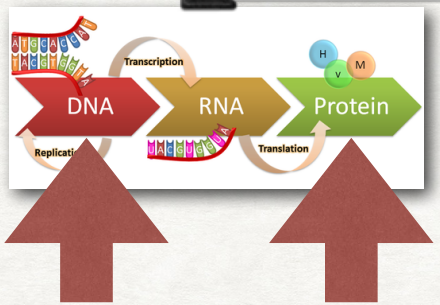
Absence of protein

MLH1 MLH6



PMS2 MSH6

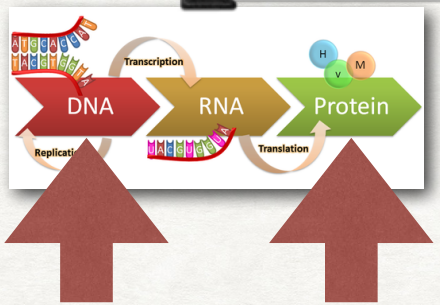
Predictive, diagnostic and prognostic markers



Immunohistochemistry
of MLH1, PMS2, MLH6 and MSH2

Mutation of MLH1, PMS2, MLH6 and MSH2 genes
Measurement of length of Microsatilites

Predictive, diagnostic and prognostic markers



Mutation	Changed protein
Translocation	Absence of protein
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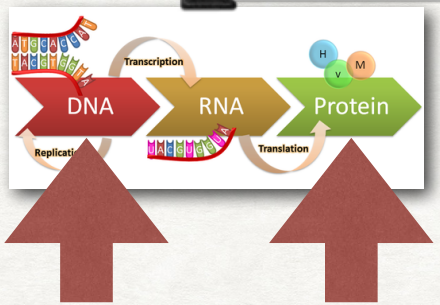
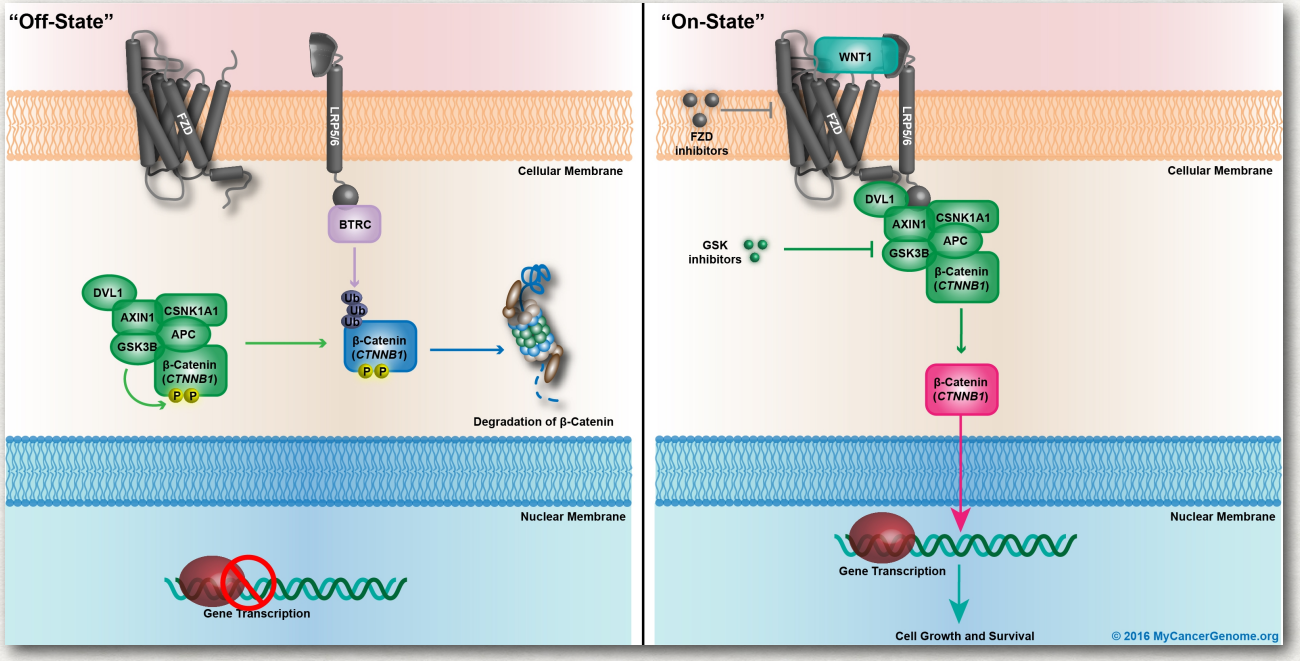
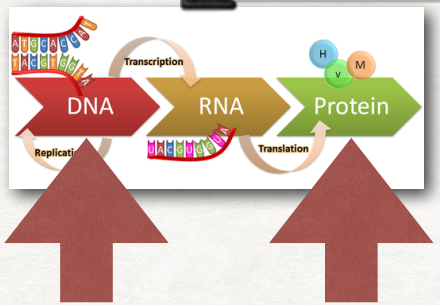
Predictive, diagnostic and prognostic markers



Abnormal localisation

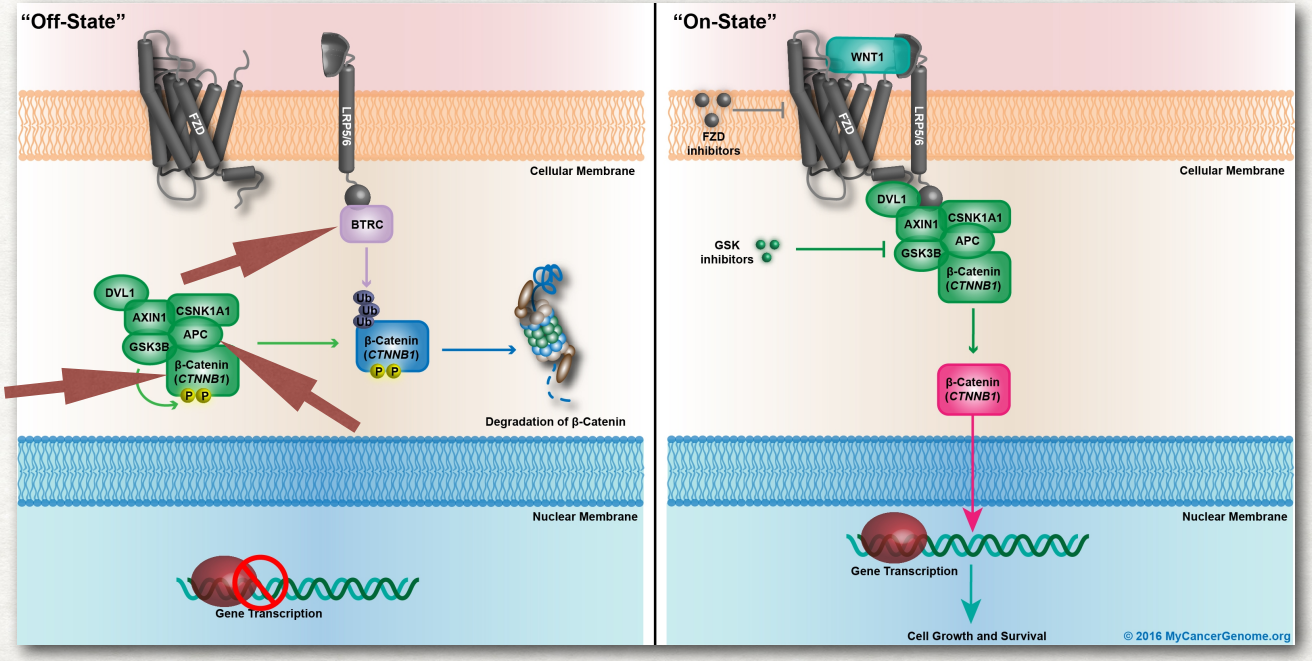


Predictive, diagnostic and prognostic markers

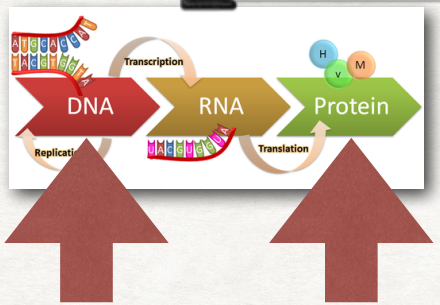


Abnormal localisation

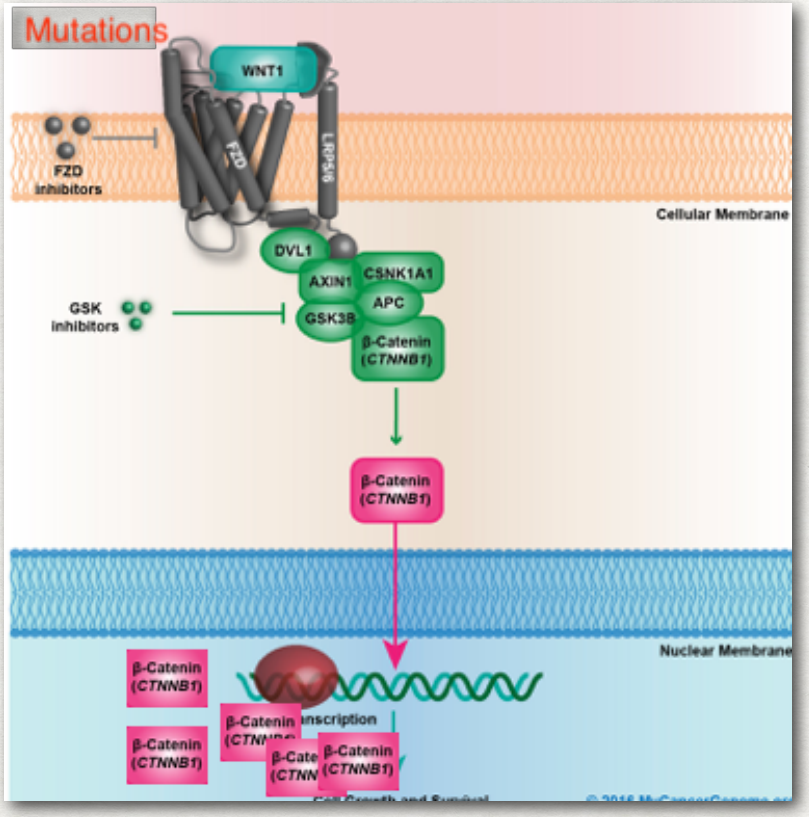
Mutations



Predictive, diagnostic and prognostic markers

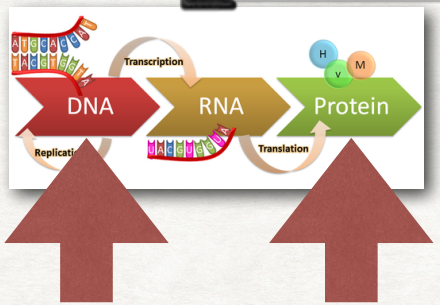


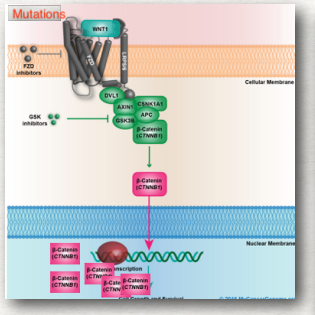
Abnormal localisation



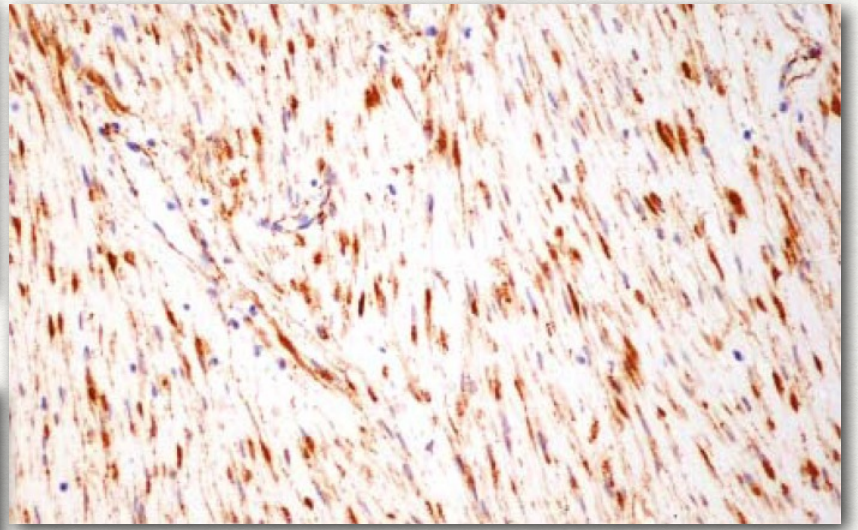
Mutations

Predictive, diagnostic and prognostic markers

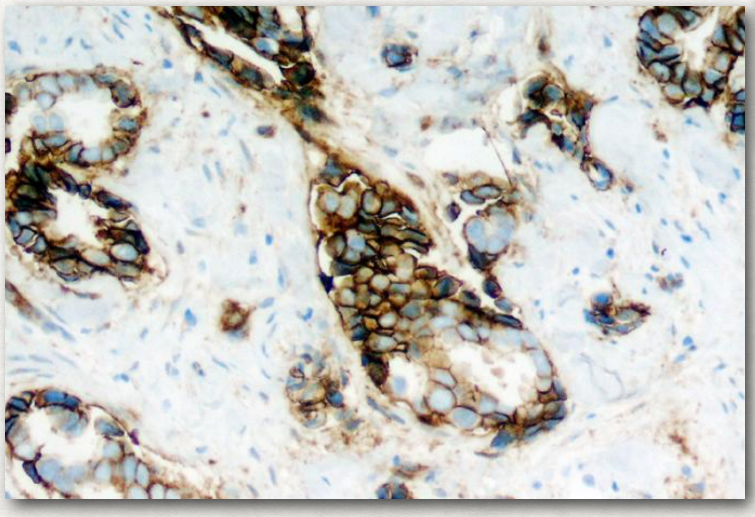


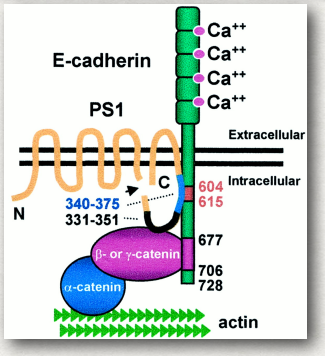


Abnormal localisation

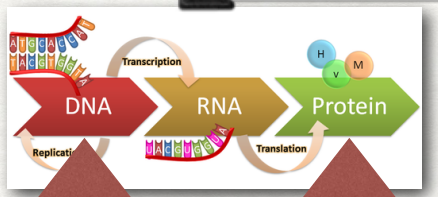


Normal lokalisation

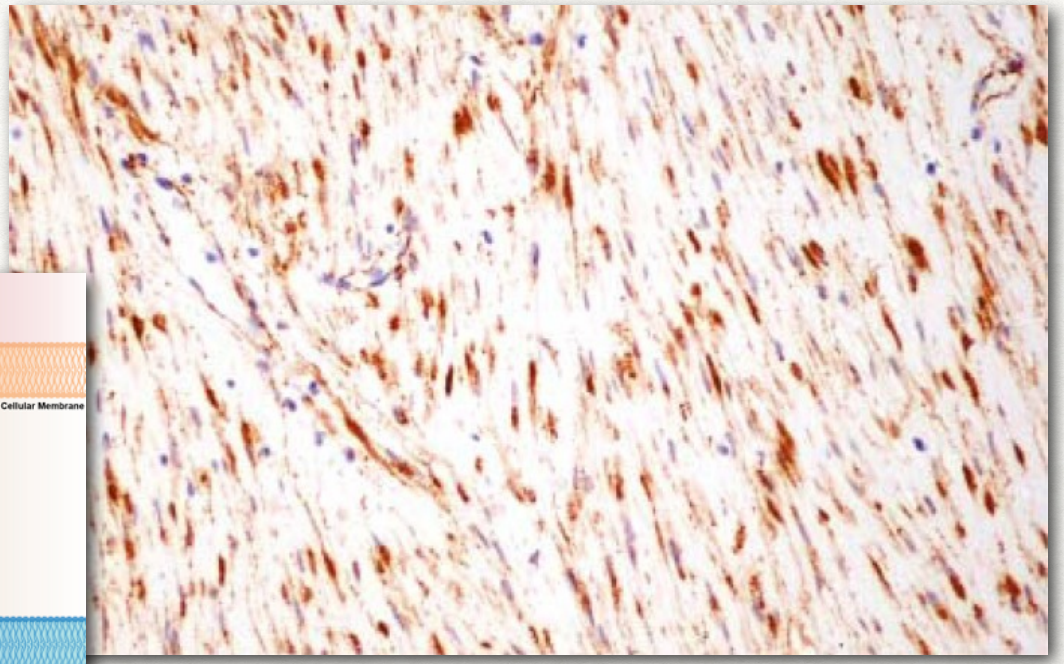




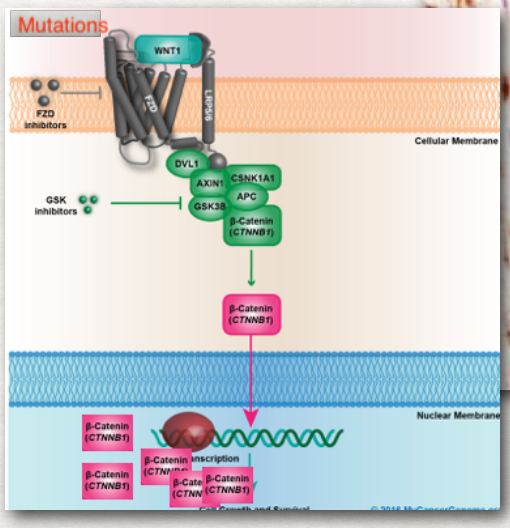
Predictive, diagnostic and prognostic markers



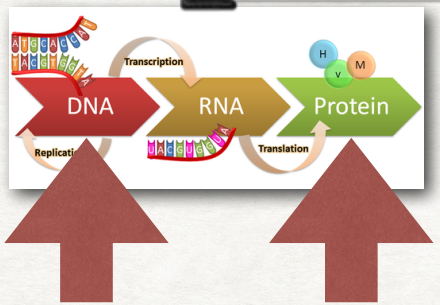
Abnormal localisation



Agressive fibromatosis



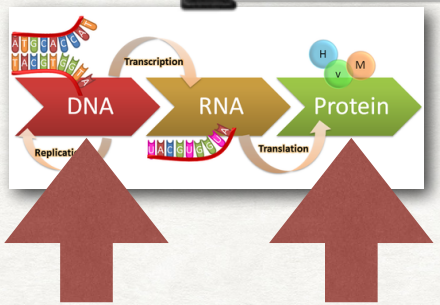
Predictive, diagnostic and prognostic markers



Immunohistochemistry
of B-cathenin

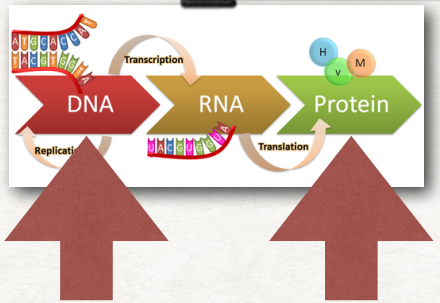
Mutations of B-cathenin, APC og BTRC

Predictive, diagnostic and prognostic markers

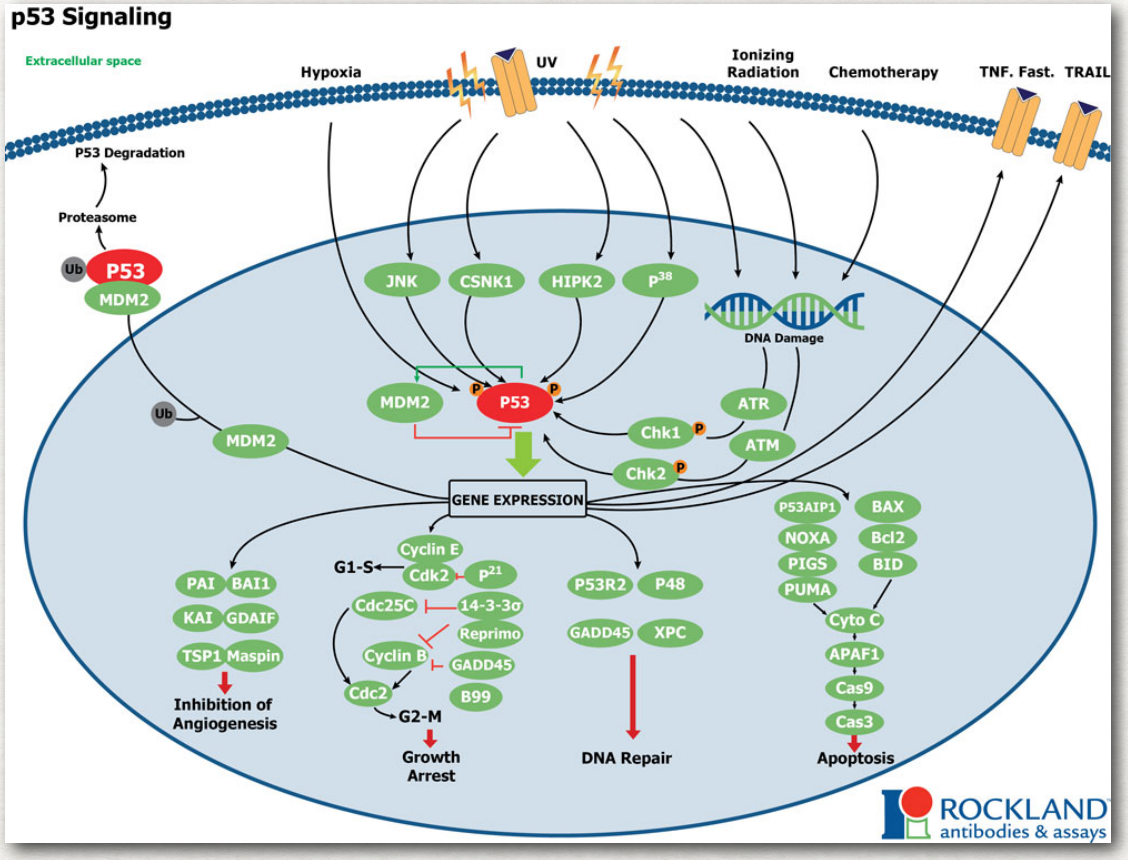


Mutation	Changed protein
Translocation	Absence of protein
Deletion	Abnormal localisation
Amplification	Over expression
Methylation	Fussion protein

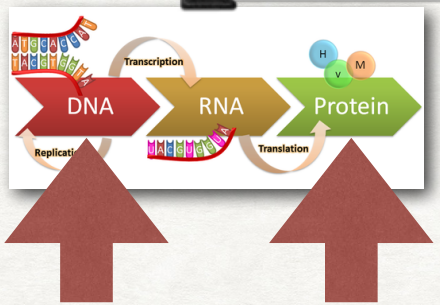
Predictive, diagnostic and prognostic markers



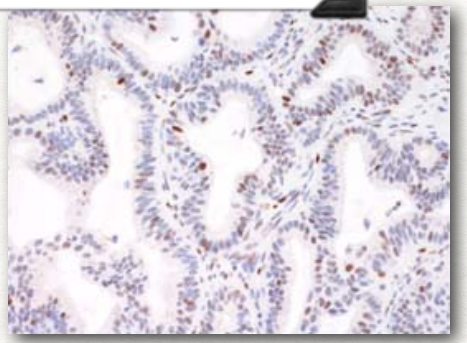
Over ekspression



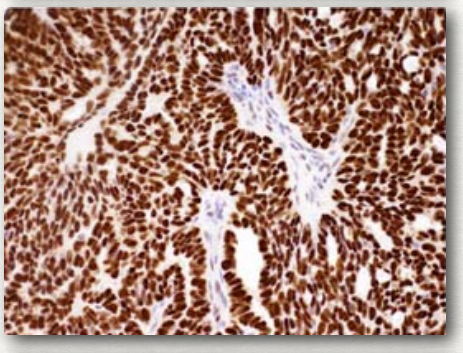
Predictive, diagnostic and prognostic markers



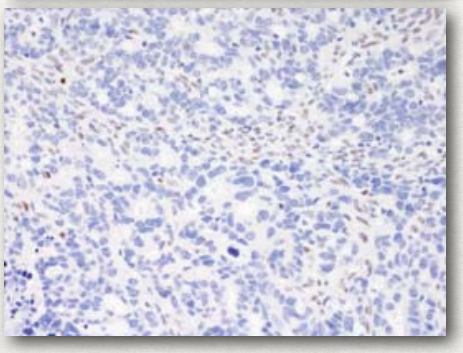
Normal expression



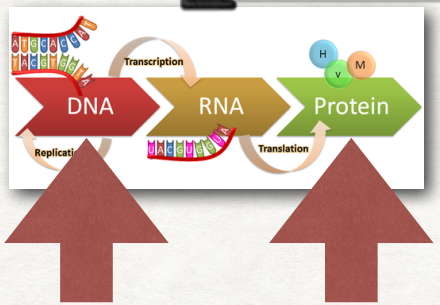
Some mutations cause (besides inactivation) that the P53 protein does not degrade and accumulates in the nucleus



Large deletions cause lack of protein expression



Predictive, diagnostic and prognostic markers



Journal of Pathology
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ORIGINAL PAPER

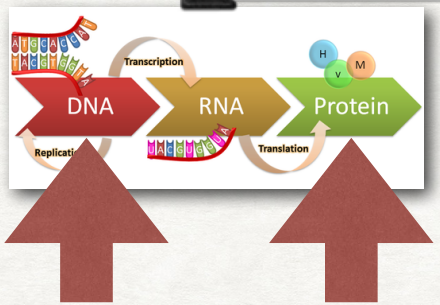
The biological and clinical value of p53 expression in pelvic high-grade serous carcinomas

Martin Köbel,[1] Alexander Reuss,[2] Andreas du Bois,[3] Stefan Kommoss,[3] Friedrich Kommoss,[3] Dongxia Gao,[4] Steve E Kalloger,[4] David G Huntsman[4] and C Blake Gilks[4]*

[1] *Department of Pathology and Laboratory Medicine, Calgary Laboratory Services/Alberta Health Services and University of Calgary, Canada*
[2] *Coordinating Centre for Clinical Trials (KKS), University Marburg (AGO-OVAR Statistical Centre), Germany*
[3] *Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe (AGO-OVAR), Germany*
[4] *Genetic Pathology Evaluation Centre of the Prostate Research Centre, Department of Pathology, Vancouver General Hospital and British Columbia Cancer Agency, Vancouver, BC, Canada*

stage, residual tumour, and stratification by cohort. The association of complete absence of p53 expression with unfavourable outcome suggests functional differences of *TP53* mutations underlying overexpression, compared to those underlying complete absence of expression.

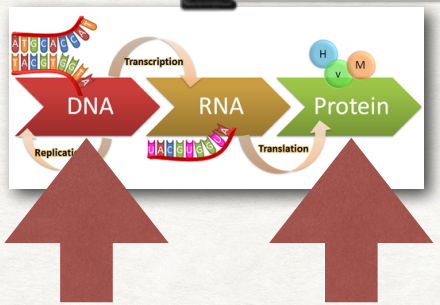
Predictive, diagnostic and prognostic markers



Immunohistochemistry of p53

NGS of the p53 gene

Predictive, diagnostic and prognostic markers



Mutation	Changed protein
Translocation	Absence of protein
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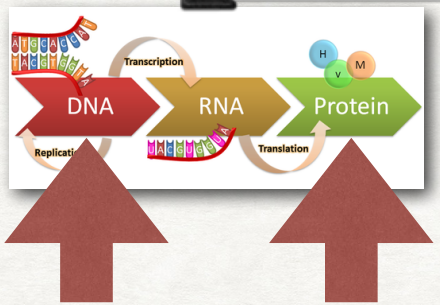
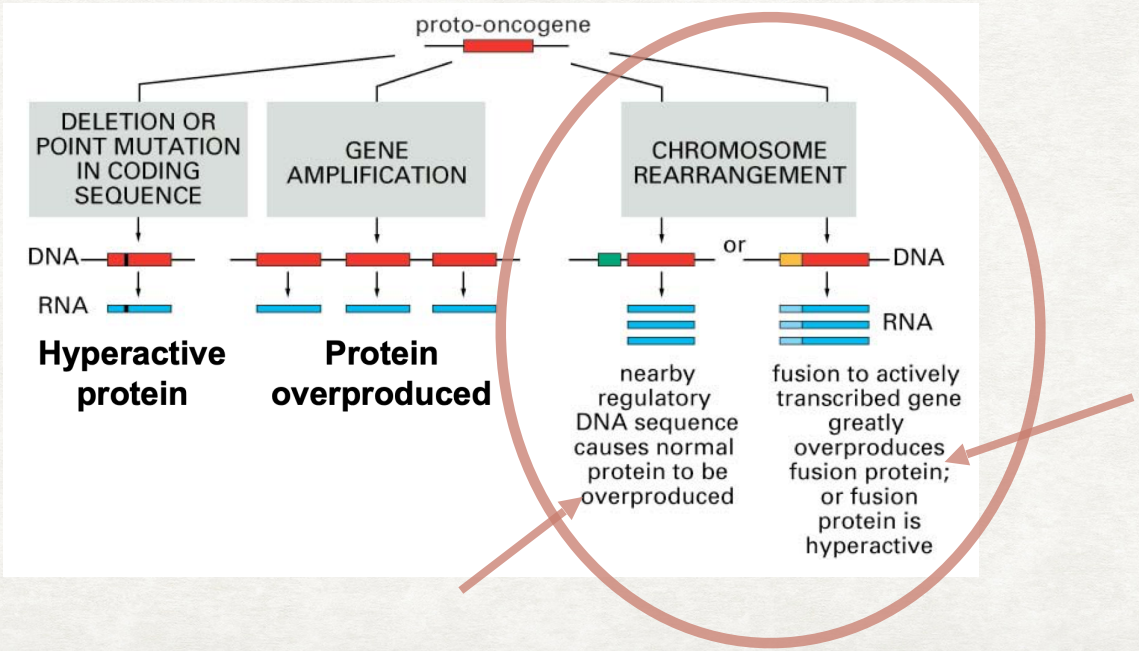
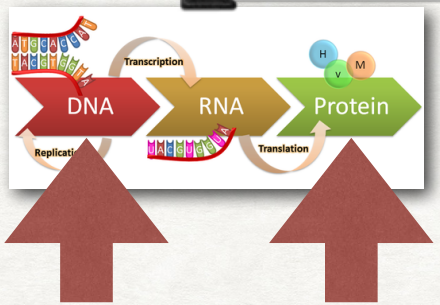
Predictive, diagnostic and prognostic markers

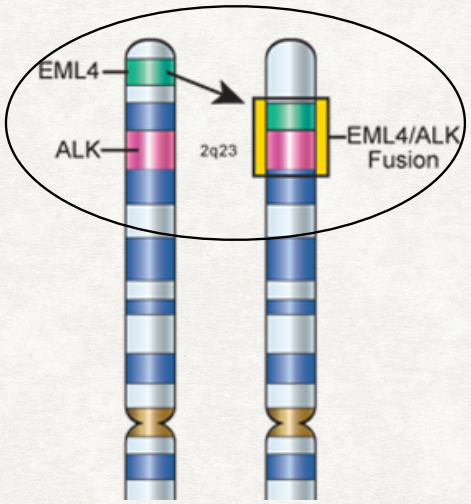


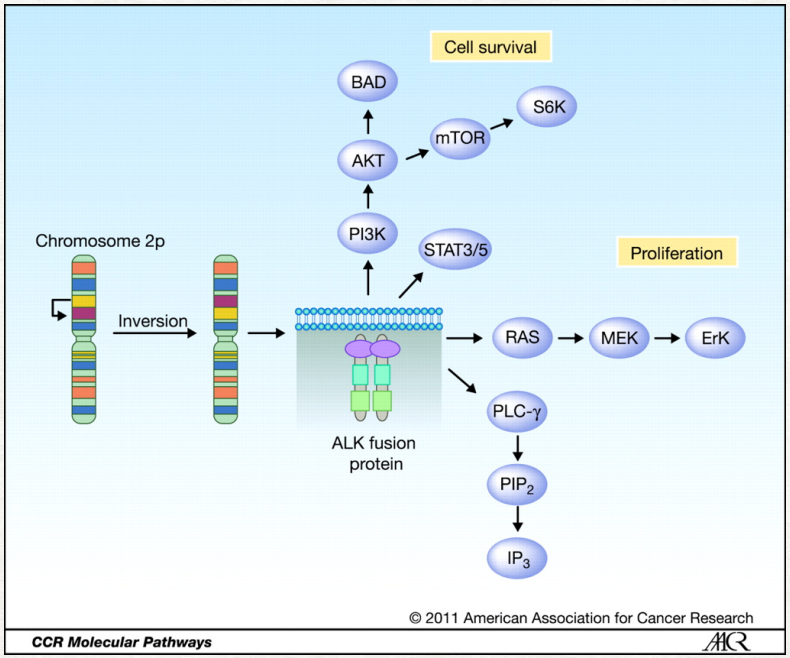


Predictive, diagnostic and prognostic markers

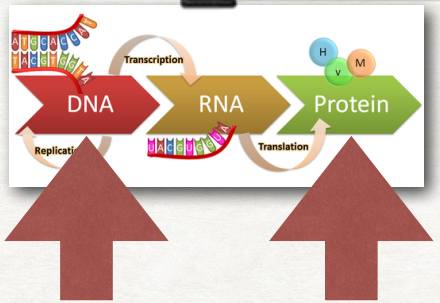


Lunge adenocarcinomer

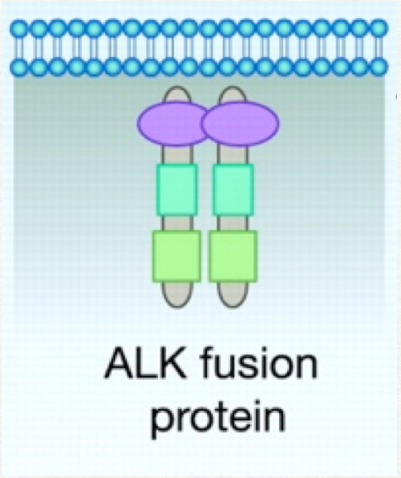




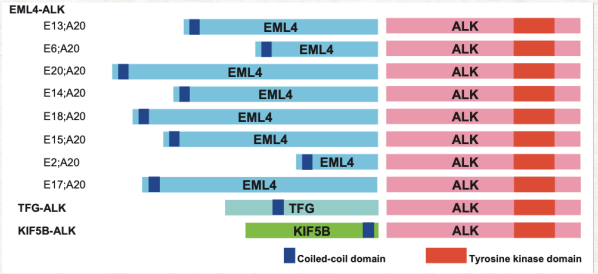
Predictive, diagnostic and prognostic markers



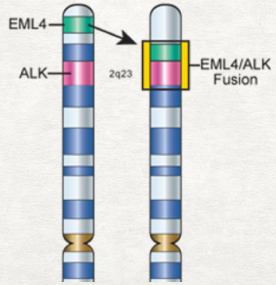
Detektion af fusion protein



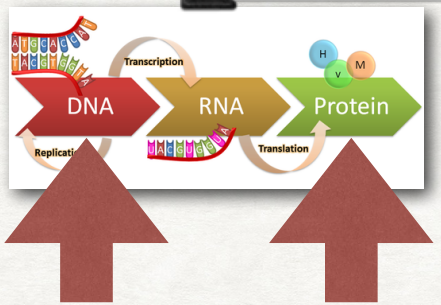
Detektion af fusions RNA

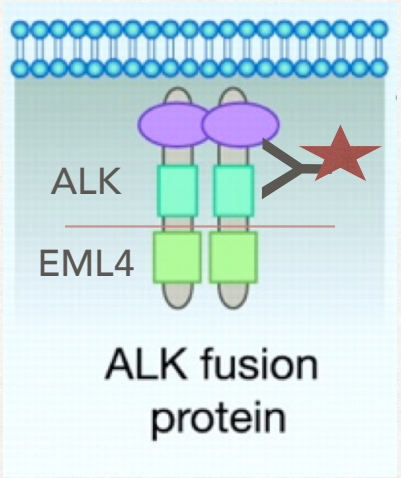


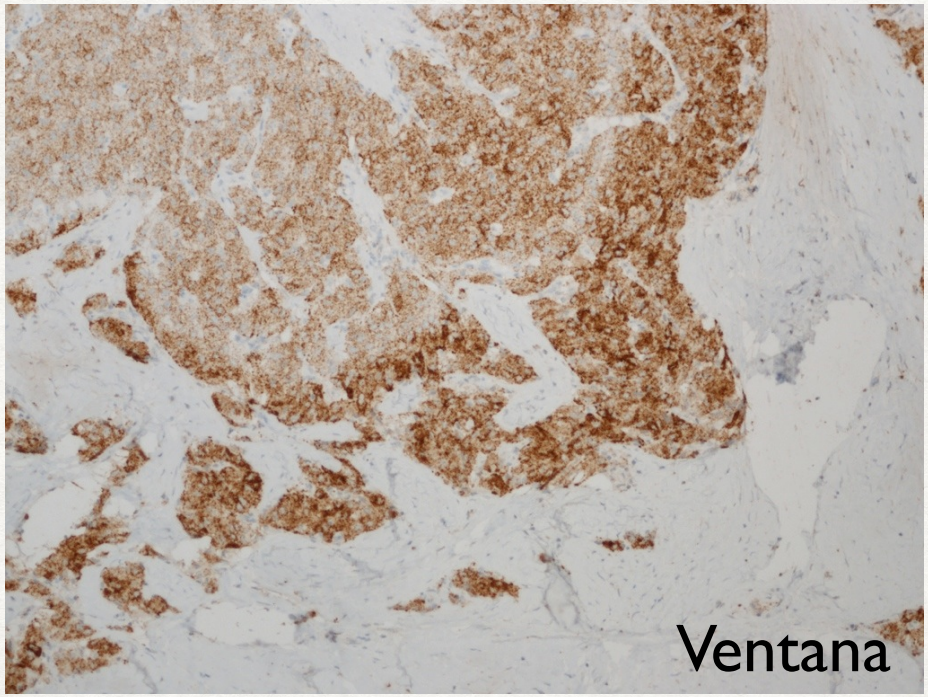
Detektion af chromosomale Forandringer



Predictive, diagnostic and prognostic markers

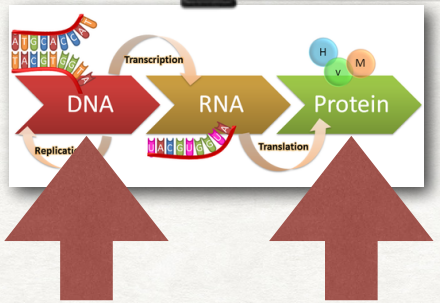






Detects ALK independent of fusion partner

Predictive, diagnostic and prognostic markers



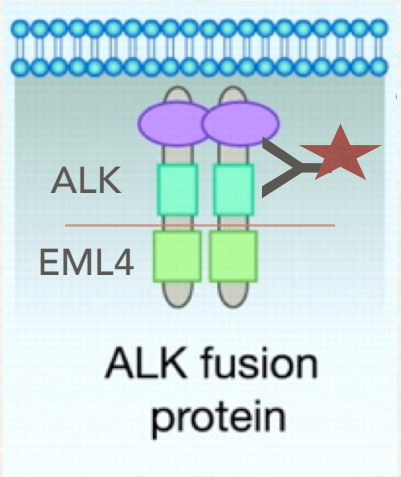
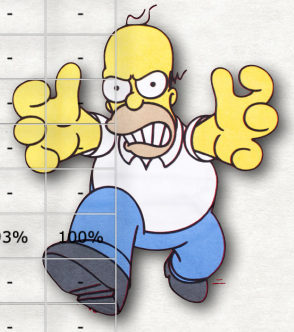


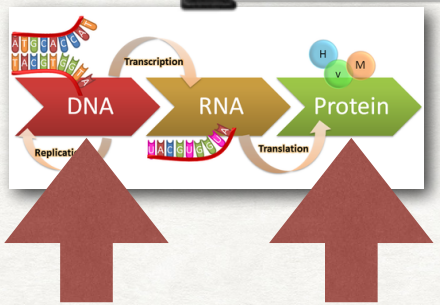
Table 1. **Antibodies and assessment marks for lu-ALK, run 51**

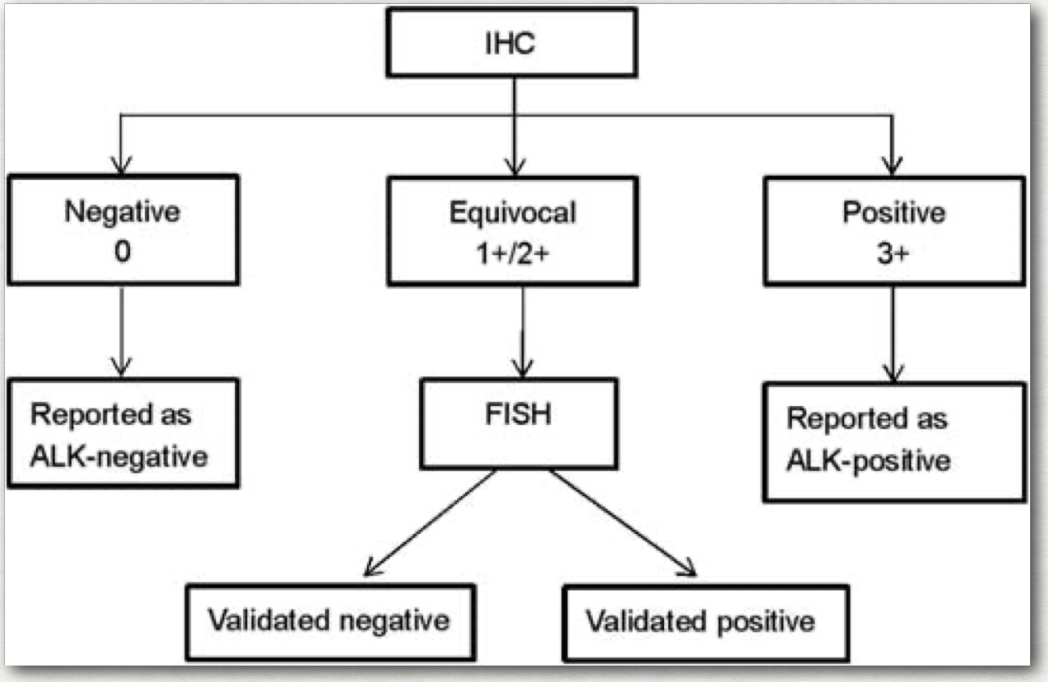
Concentrated antibodies	n	Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	Suff. OPS[2]
mAb clone **5A4**	43 1 1 1 1	Leica/Novocastra Abcam Biocare Monosan ThermoFisher	1	15	24	7	34%	22%
mAb clone **ALK1**	2 1	Dako Cell Marque	0	0	0	3	-	-
rmAb clone **D5F3**	23	Cell Signaling	6	12	3	2	78%	94%
mAb clone **OTI1A4**	13	ORIGENE	10	3	0	0	100%	100%
Ready-To-Use antibodies								
mAb clone **5A4** **PA0306**	6	Leica/Novocatra	0	0	6	0	-	-
mAb clone **5A4** **MAB-0281**	1	Maixin	0	0	1	0	-	-
mAb **5A4** **MAD-001720QD**	1	Master Diagnostica	0	0	1	0	-	-
mAb clone **5A4** **MS-1104-R7**	1	ThermoFisher	0	1	0	0	-	-
mAb **ALK1** **IR641**	9	Dako	0	0	1	8	-	-
mAb clone **ALK1** **GA641**	4	Dako	0	0	0	4	-	-
mAb clone **ALK1** **790/800-2918**	7	Ventana	0	0	2	5	-	-
rmAb clone **SP8** **AN770**	1	BioGenex	0	0	0	1	-	-
rmAb clone **D5F3** **790-4796**	70	Ventana	53	12	4	1	93%	100%
rmAb clone **D5F3** **790-4796**[3]	2	Ventana	1	0	1	0	-	-
mAb clone **OTI1A4** **8344-C010**	1	Sakura Finetek	1	0	0	0	-	-
Total	189		72	43	43	31	-	
Proportion			38%	23%	23%	16%	61%	

1) Proportion of sufficient stains (optimal or good).
2) Proportion of sufficient stains with optimal protocol settings only, see below. . 3) RTU system developed for the Ventana BenchMark systems (Ultra/XT) but used by laboratories on different platforms (e.g Dako Autostainer)



Predictive, diagnostic and prognostic markers



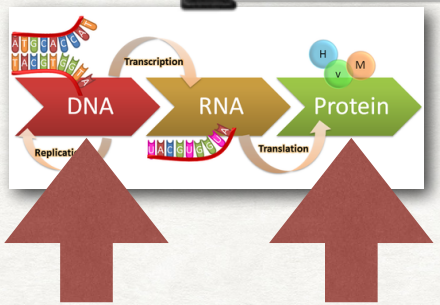


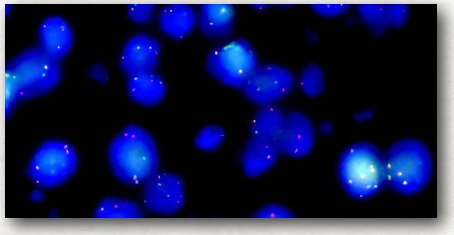
Improving Selection Criteria for *ALK* Inhibitor Therapy in Non–Small Cell Lung Cancer

A Pooled-Data Analysis on Diagnostic Operating Characteristics of Immunohistochemistry

Long Jiang, MD, PhD,† Haihong Yang, MD, PhD,‡ Ping He, MD, PhD,§ Wenhua Liang, MD, PhD,‡ Jianrong Zhang, MD,*† Jingpei Li, MD,*† Yang Liu, MD,*† and Jianxing He, MD, PhD, FACS*†*

Predictive, diagnostic and prognostic markers

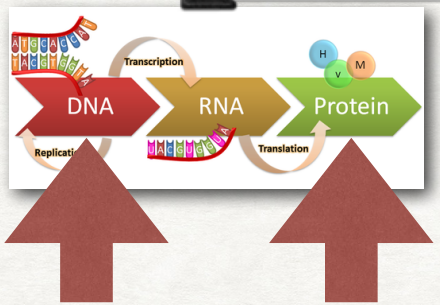




Immunohistochemistry of ALK

Fusions RNA analysis (PCR), NGS or FISH

Predictive, diagnostic and prognostic markers



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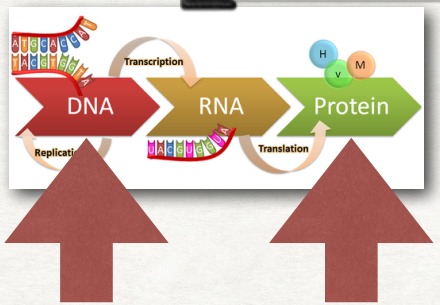
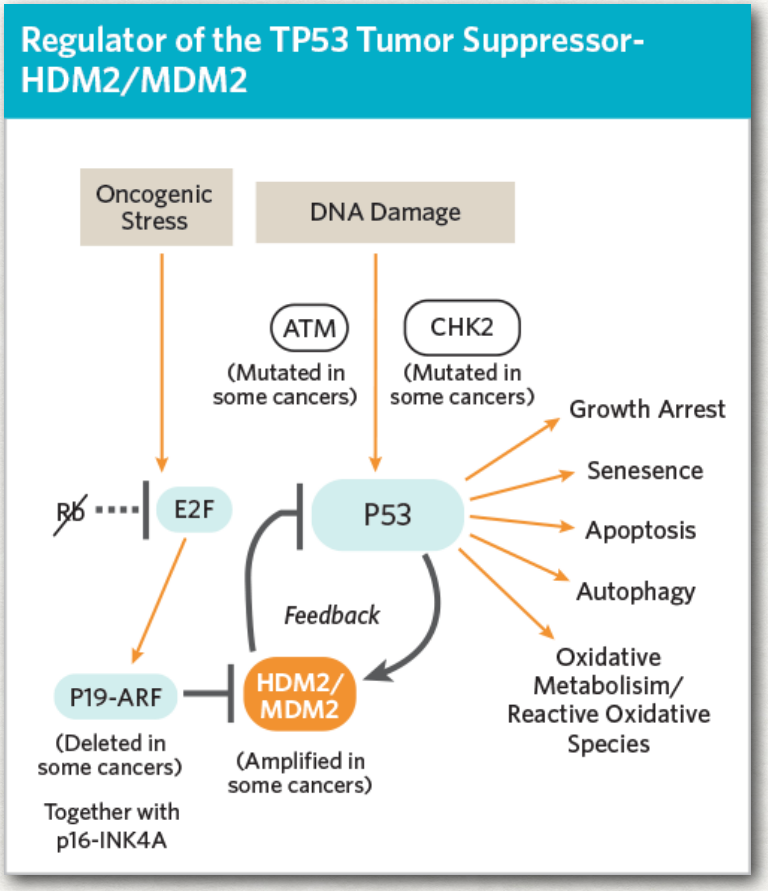
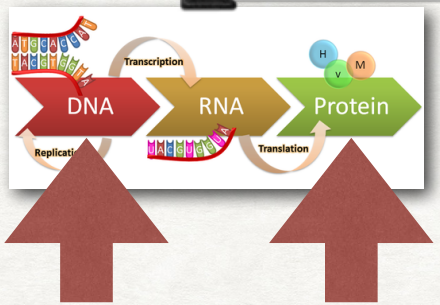
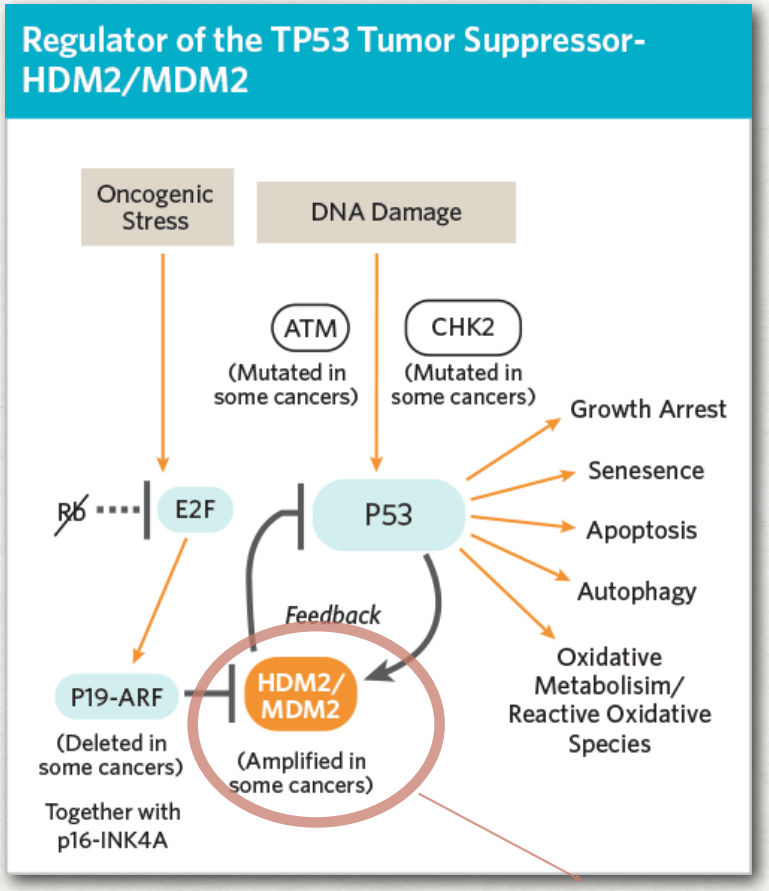
Predictive, diagnostic and prognostic markers





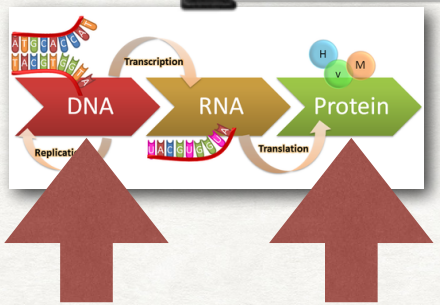
Predictive, diagnostic and prognostic markers



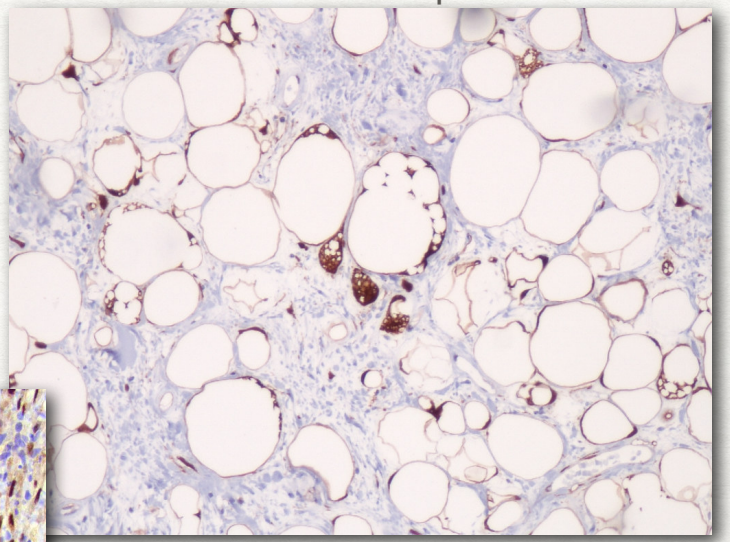


E.g. liposarcoma

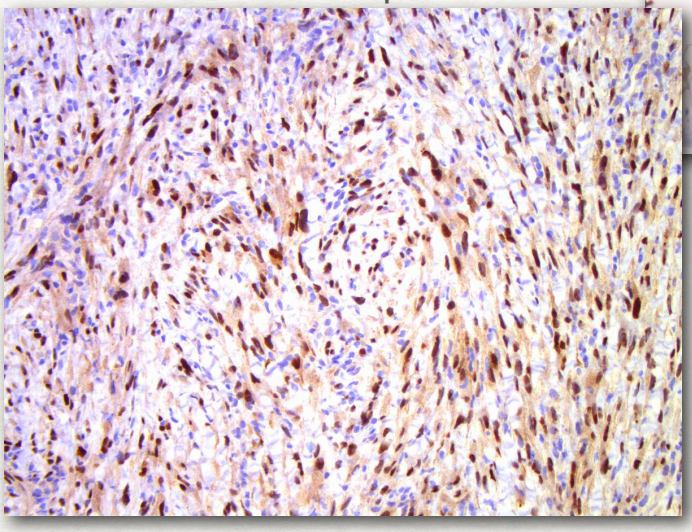
Predictive, diagnostic and prognostic markers



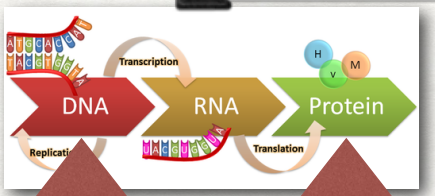
Well differentieret liposarcoma



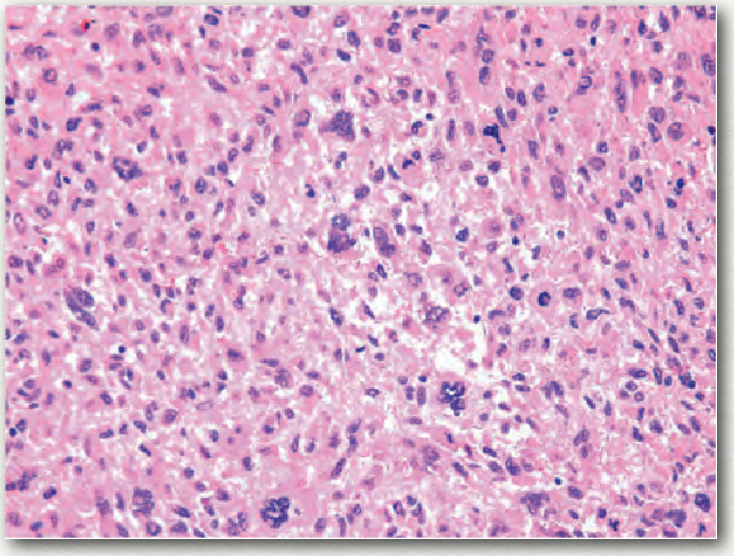
Dedifferentiated liposarcoma



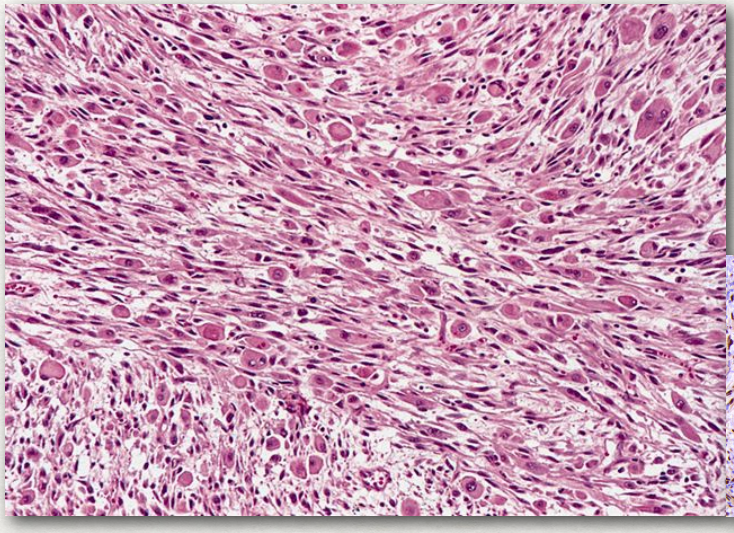
Predictive, diagnostic and prognostic markers



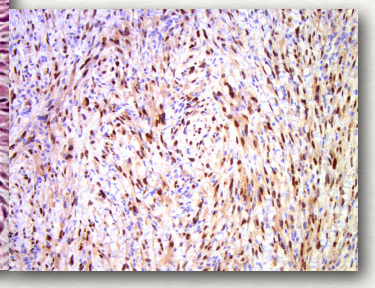
Pleomorph undifferentiated sarcoma



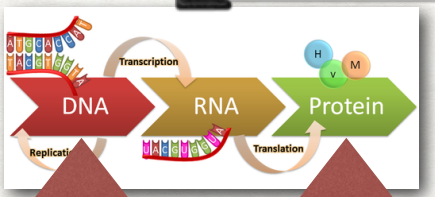
Dedifferentieret liposarcoma



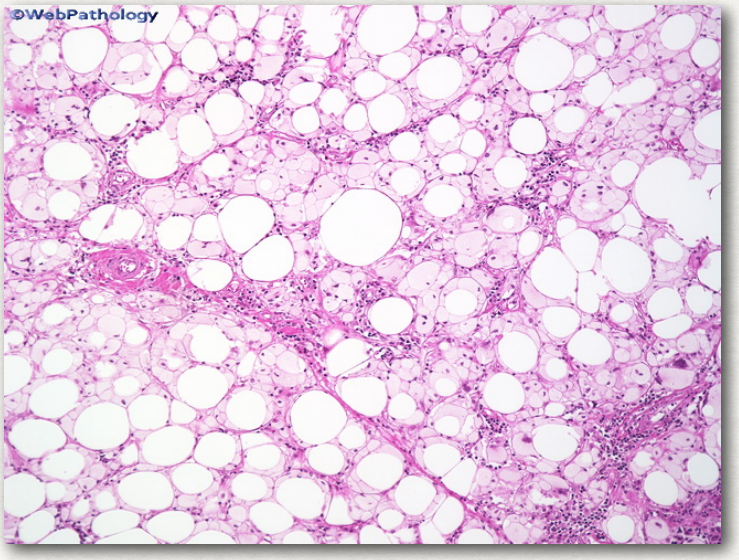
MDM2



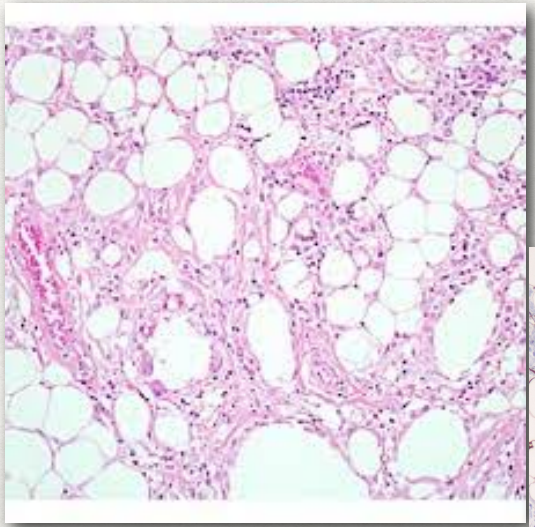
Predictive, diagnostic and prognostic markers



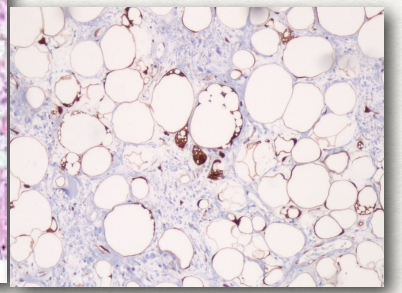
Lipoma



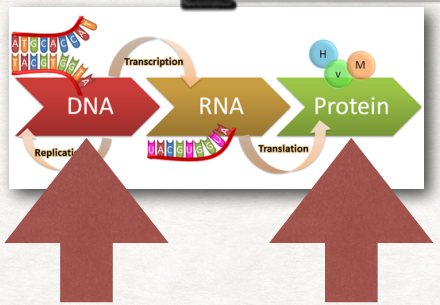
Well differentiated liposarcoma

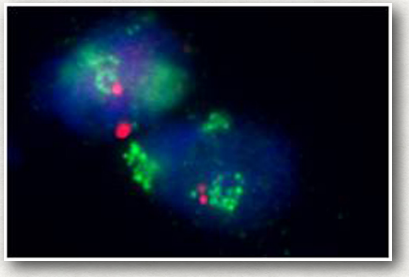


MDM2



Predictive, diagnostic and prognostic markers

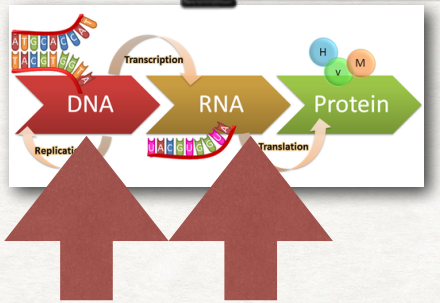




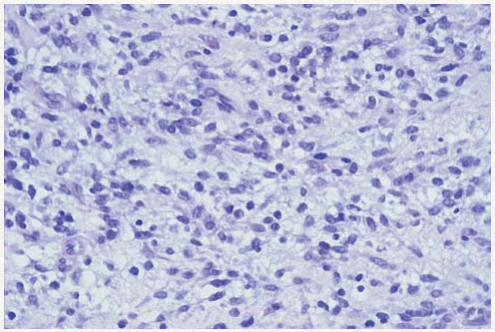
Immunohistochemistry of MDM2

NGS or FISH analysis of amplification of MDM2 gene.

Predictive, diagnostic and prognostic markers



Sarcoma



Comprehensive DNA- and RNA-NGS

Table 1. Chromosomal translocations in soft tissue sarcoma (STS).

Histological Subtype	Chromosomal Translocation	Fusion Gene
Ewing sarcoma	t(11;22)(q24;q12) t(21;22)(q22;q12) t(7;22)(q22;q12) t(17;22)(q12;q12) t(2;22)(q33;q12) t(16;21)(p11;q22)	*EWSR1-FLI1* *EWSR1-ERG* *EWSR1-ETV1* *EWSR1-ETV4* *EWSR1-FEV* *FUS-ERG*
Ewing sarcoma-like small blue round cell tumor	t(4;19)(q35;q13) t(X;19)(q13;q13)	*CIC-DUX4* *CIC-FOXO4*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWSR1-WT1*
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(1;13)(p36;q14)	*PAX3-FOXO1* *PAX7-FOXO1*
Alveolar soft part sarcoma	t(X;17)(p11;q25)	*ASPL-TFE3*
Synovial sarcoma	t(X;18)(p11;q11) t(X;18)(p11;q11) t(X;18)(p11;q11)	*SS18-SSX1* *SS18-SSX2* *SS18-SSX4*
Myxoid liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	*FUS-CHOP* *EWSR1-CHOP*
Clear cell sarcoma	t(12;22)(q13;q12)	*EWSR1-ATF1*
Inflammatory myofibroblastic tumor	t(1;2)(q21;p23) t(2;19)(p23;p13) t(2;17)(p23;q23)	*TMP3-ALK* *TMP4-ALK* *CLTC-ALK*
Infantile fibrosarcoma	t(12;15)(q13;q25)	*ETV6-NTRK3*