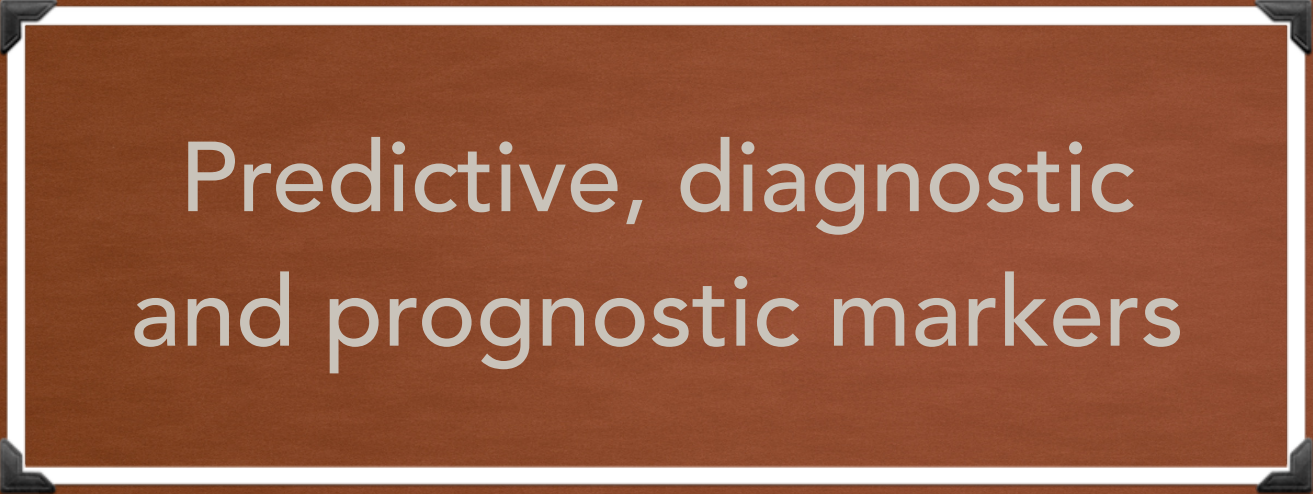
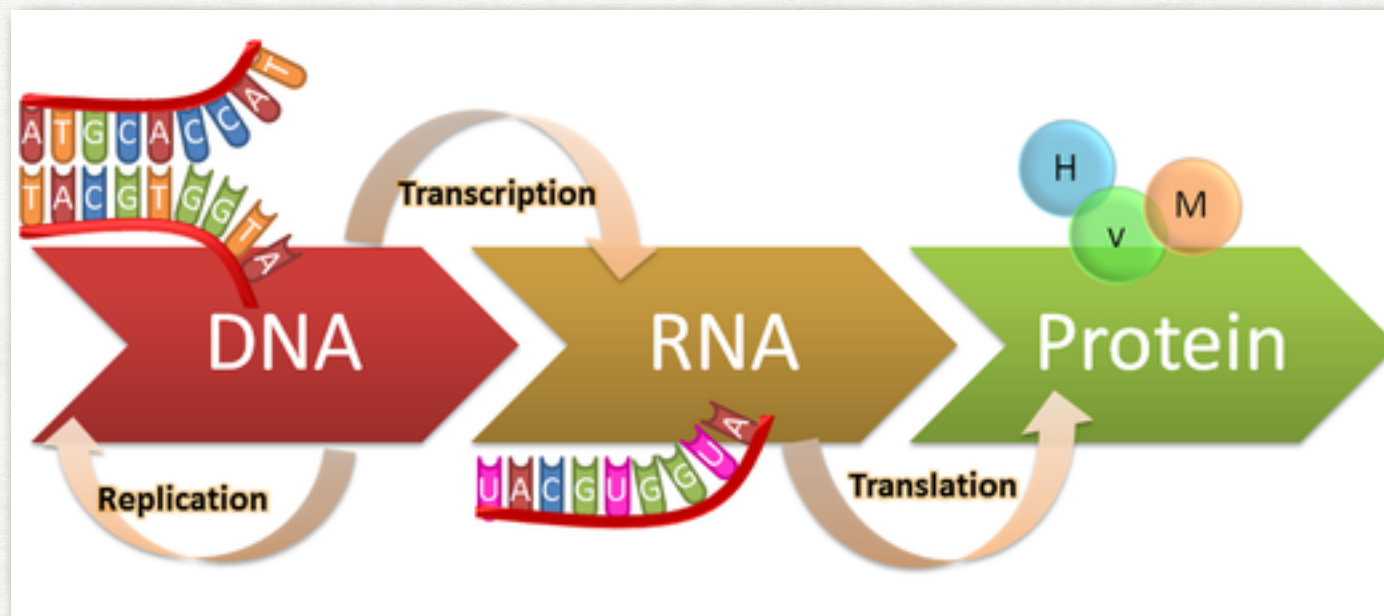




Predictive, diagnostic
and prognostic markers

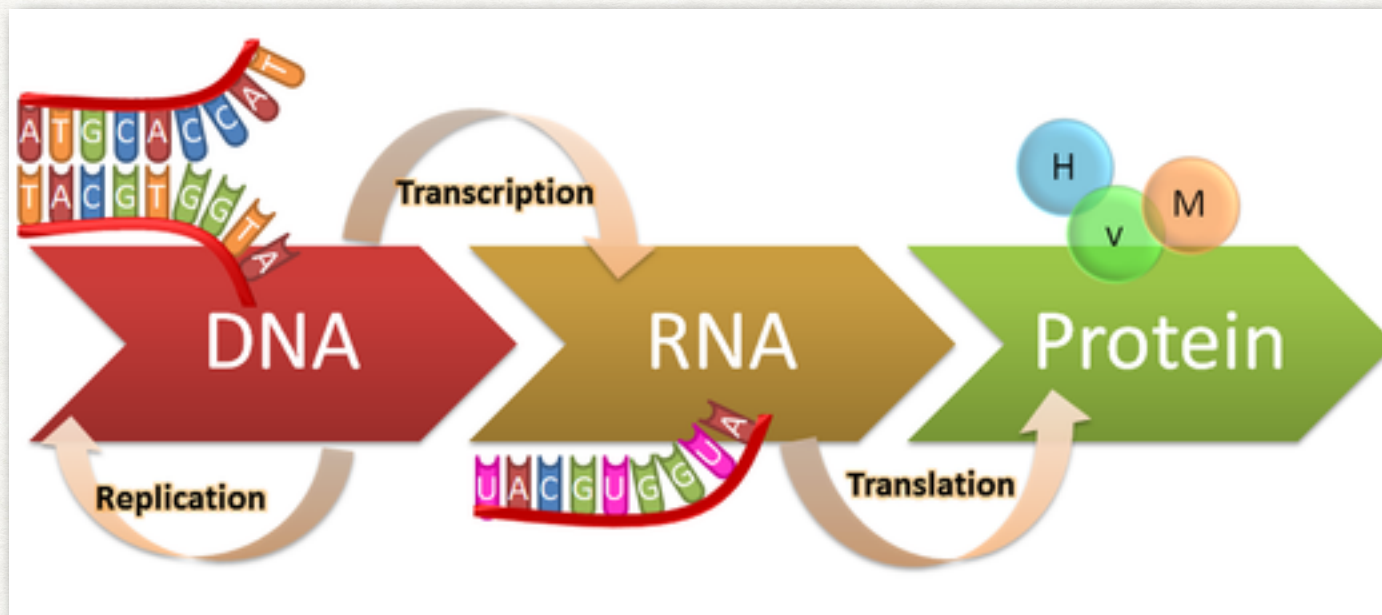
Predictive, diagnostic and prognostic markers

The central dogma



Predictive, diagnostic and prognostic markers

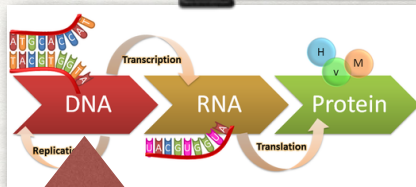
The central dogma



In-situ hybridization
Molecular methods (PCR, SEQ)

Immunohistochemistry

Predictive, diagnostic and prognostic markers



How do oncogenes and tumor suppressors work?

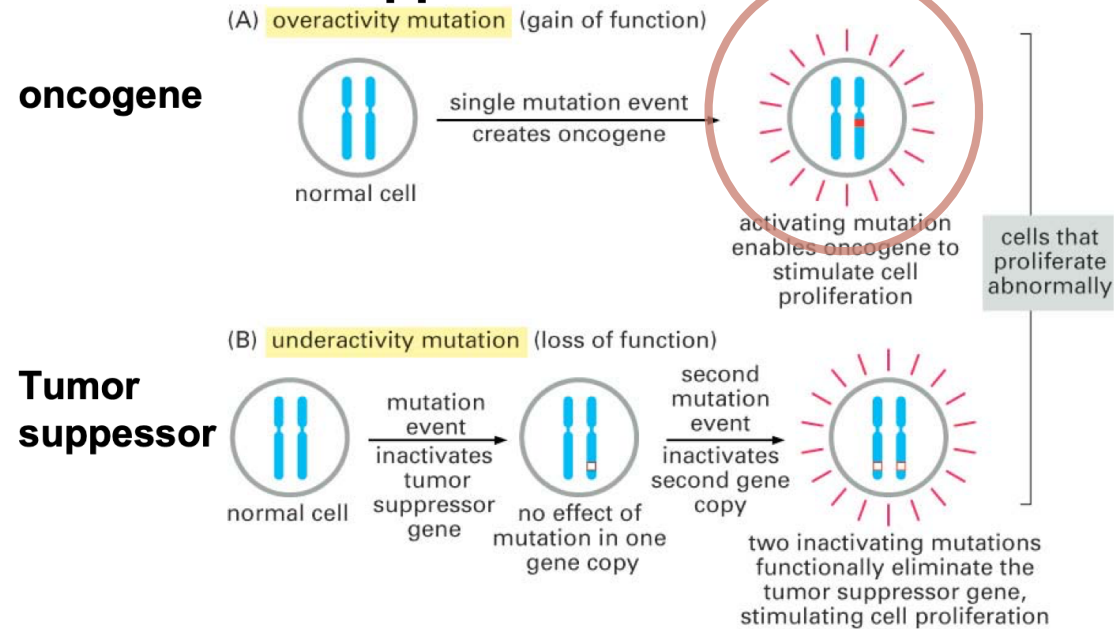
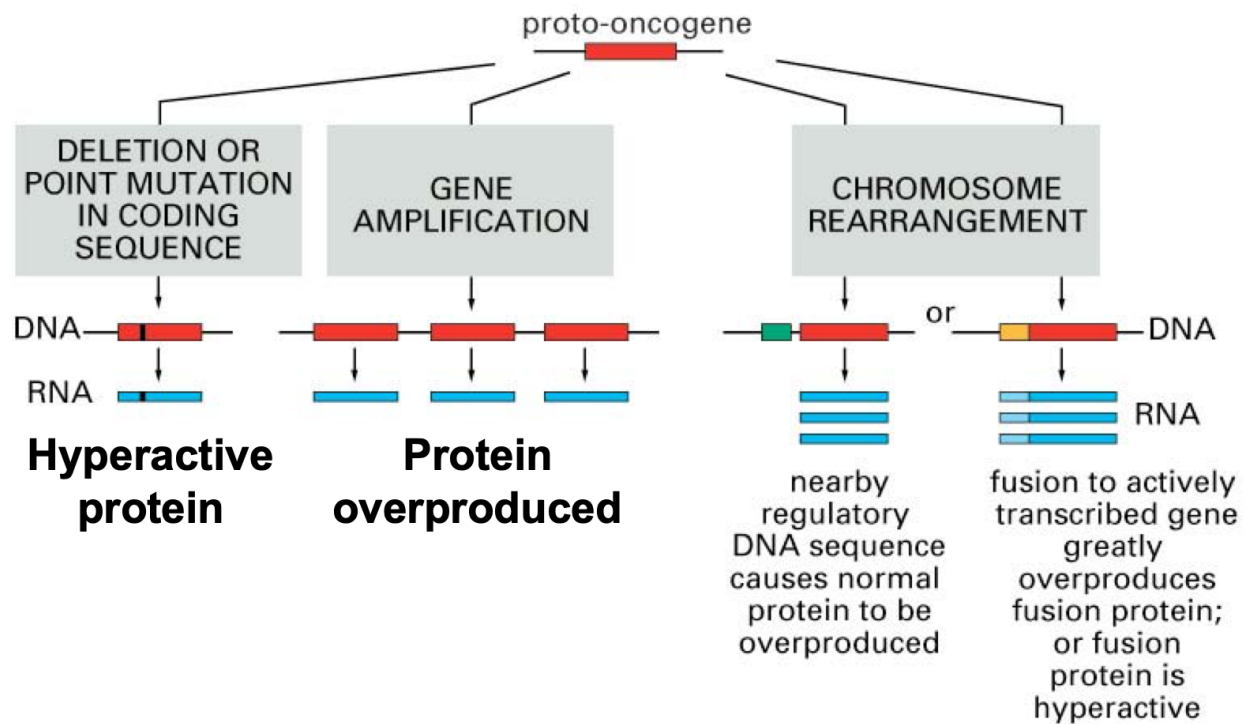
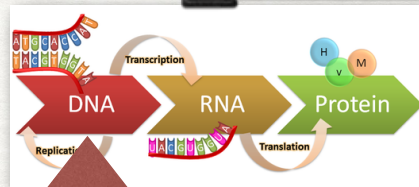
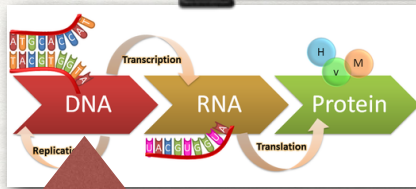


Figure 23–24. Molecular Biology of the Cell, 4th Edition.

Predictive, diagnostic and prognostic markers



Predictive, diagnostic and prognostic markers



How do oncogenes and tumor suppressors work?

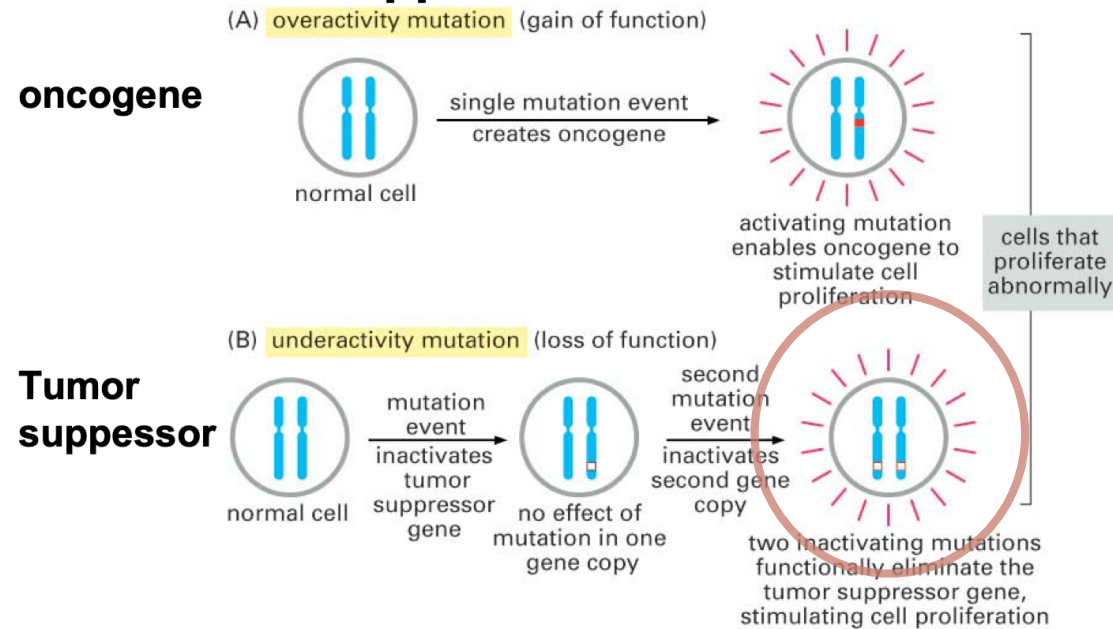
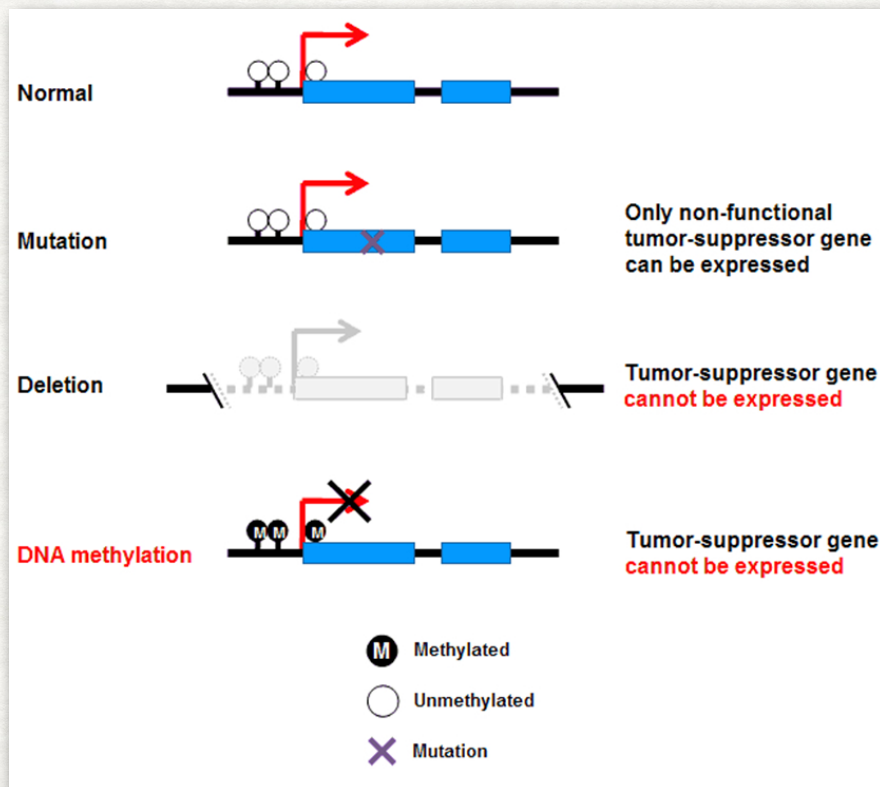
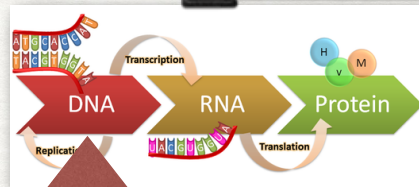
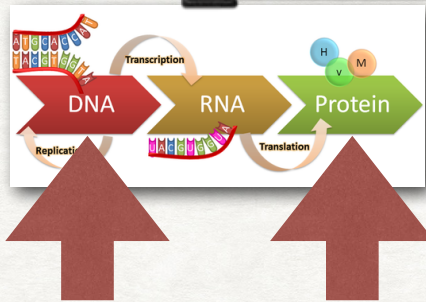


Figure 23–24. Molecular Biology of the Cell, 4th Edition.

Predictive, diagnostic and prognostic markers



Predictive, diagnostic and prognostic markers



Mutation

Translocation

Deletion

Amplification

Methylation

Changed protein

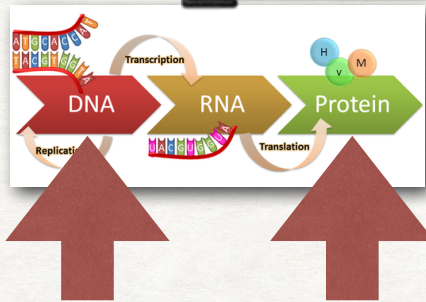
Absence of protein

Abnormal localisation

Over expression

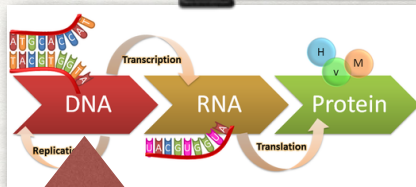
Fusion protein

Predictive, diagnostic and prognostic markers

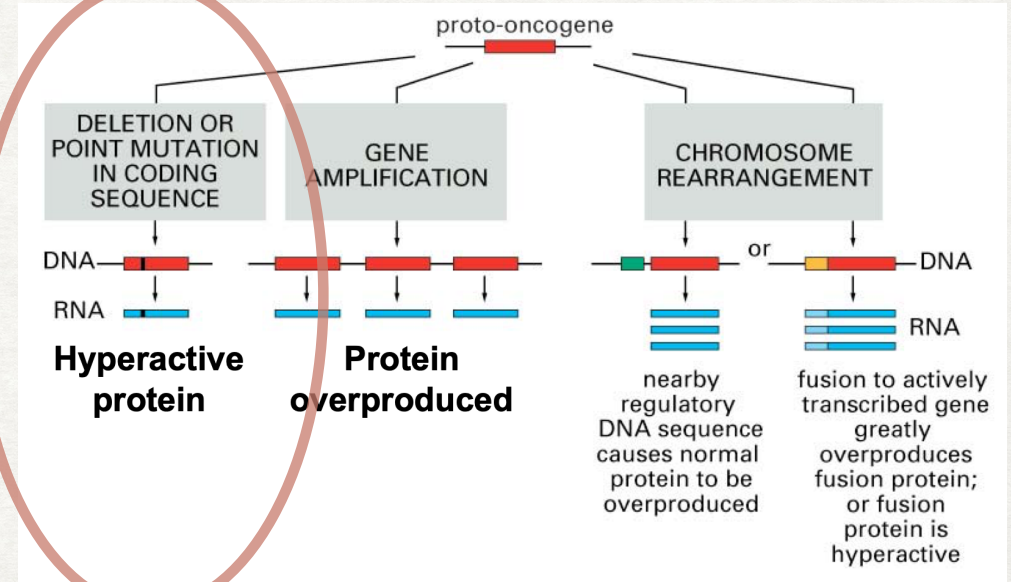
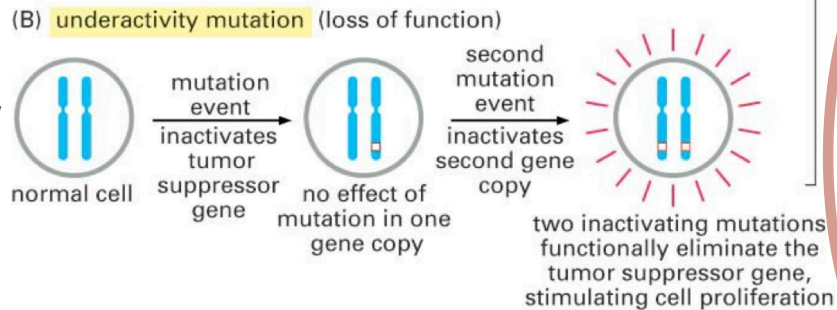


Mutation	→	Changed protein
Translocation		Absence of protein
Deletion		Abnormal localisation
Amplification		Over expression
Methylation		Fussion protein

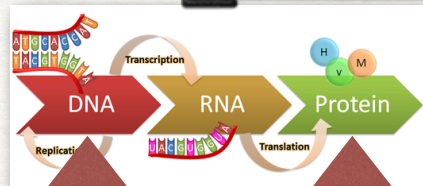
Predictive, diagnostic and prognostic markers



Tumor suppressor

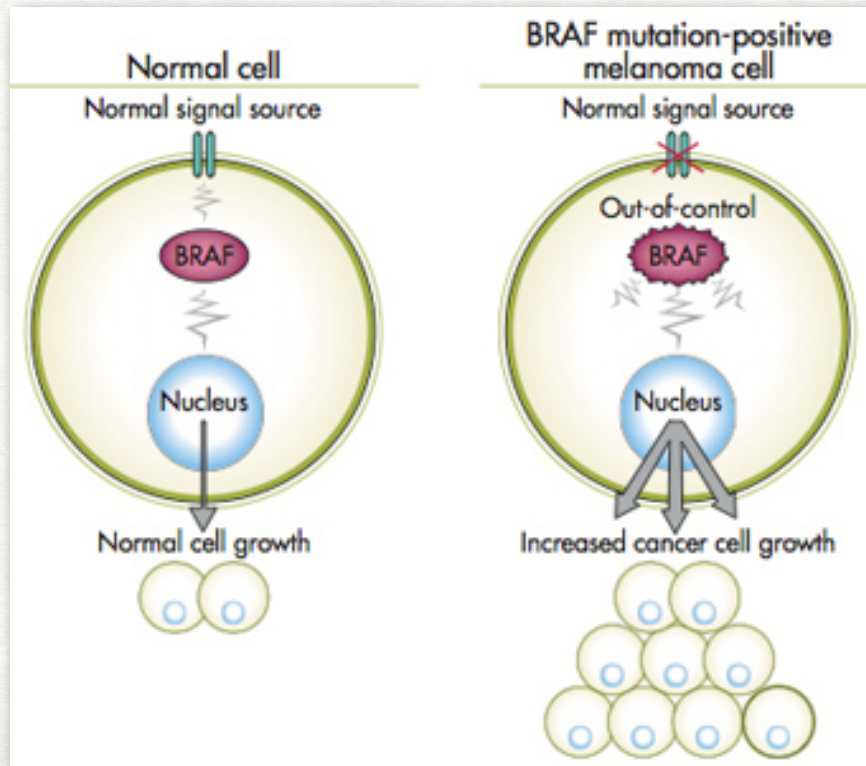


Predictive, diagnostic and prognostic markers

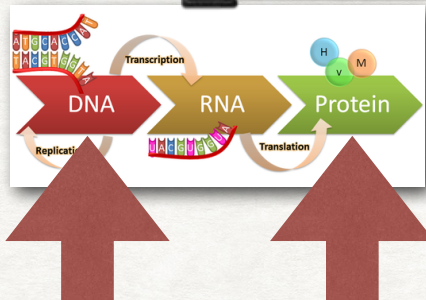


Mutated protein (auto activated)

Melanoma BRAF mutation

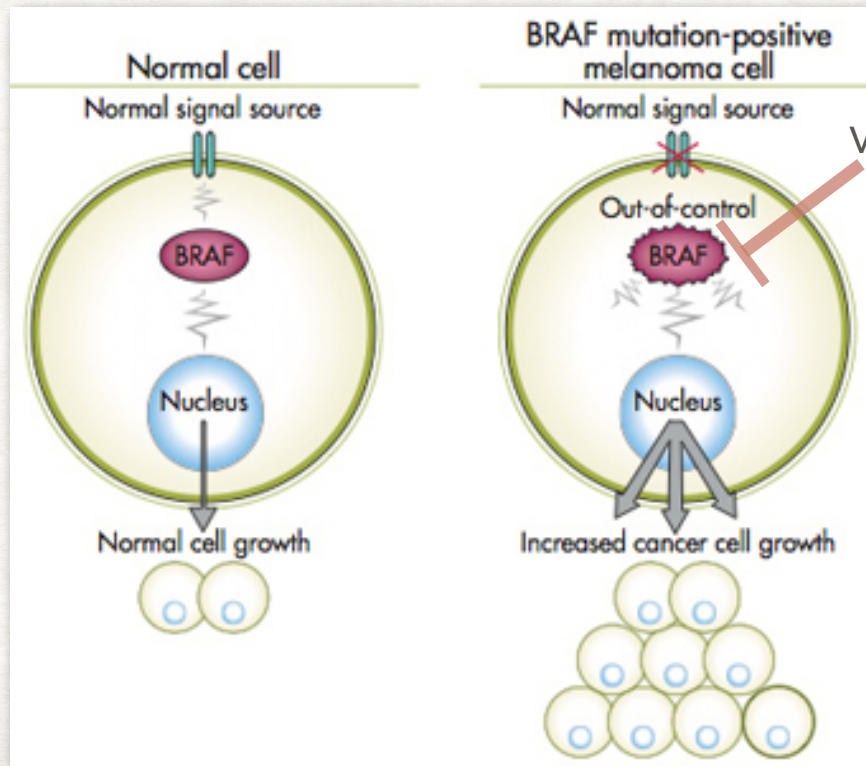


Predictive, diagnostic and prognostic markers

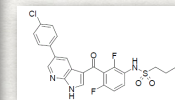


Mutated protein (auto activated)

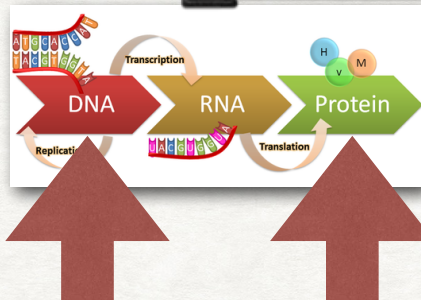
Melanoma BRAF mutation



Vemurafinib

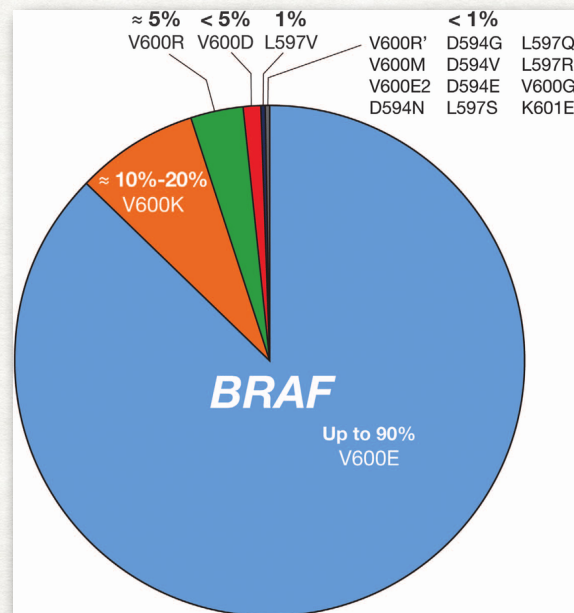


Predictive, diagnostic and prognostic markers



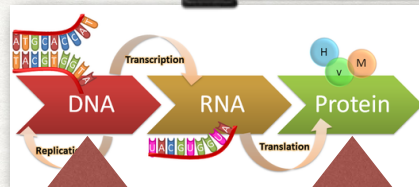
Mutated protein (auto activated)

Melanoma BRAF mutation



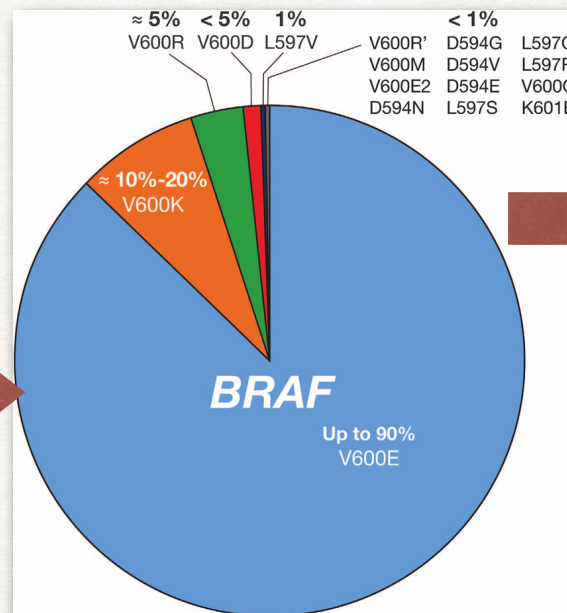
WT: GTG (valin)
V600E: GAG (glutamat)
V600K: AAG (lysin)
V600R: AGG (Arginin)

Predictive, diagnostic and prognostic markers



Mutated protein (auto activated)

Melanoma BRAF mutation



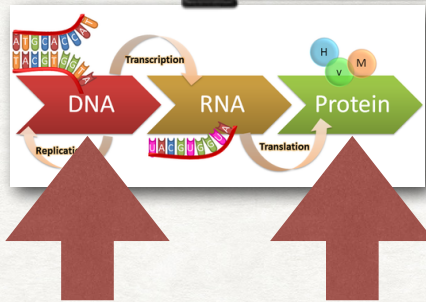
WT: GTG (valin)

V600E: GAG (glutamat)

V600K: AAG (lysin)

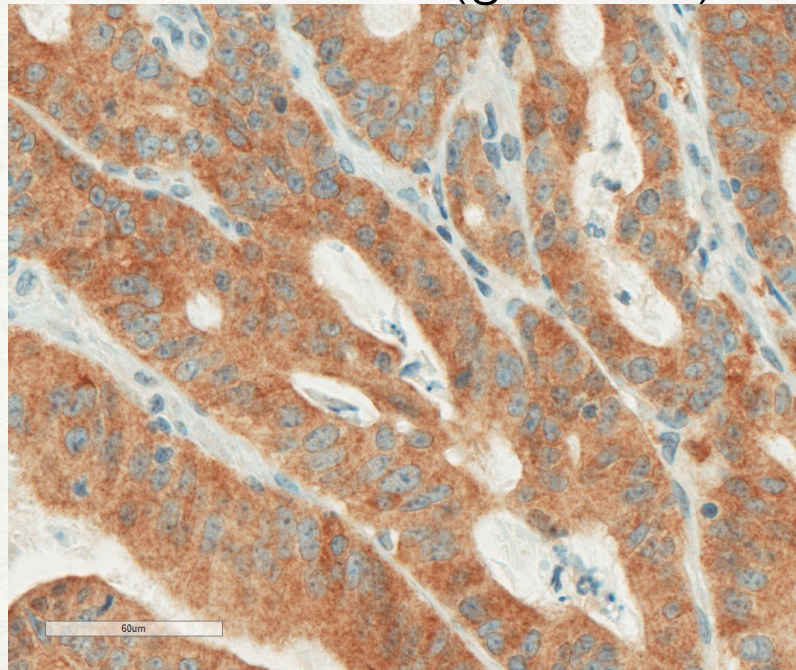
V600R: AGG (Arginin)

Predictive, diagnostic and prognostic markers



Mutated protein (auto activated)

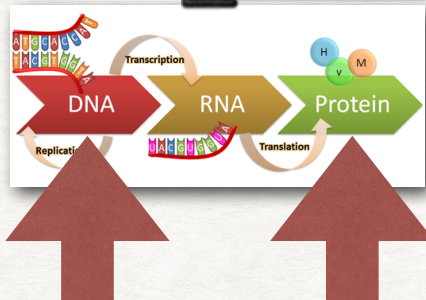
V600E: GAG (glutamat)



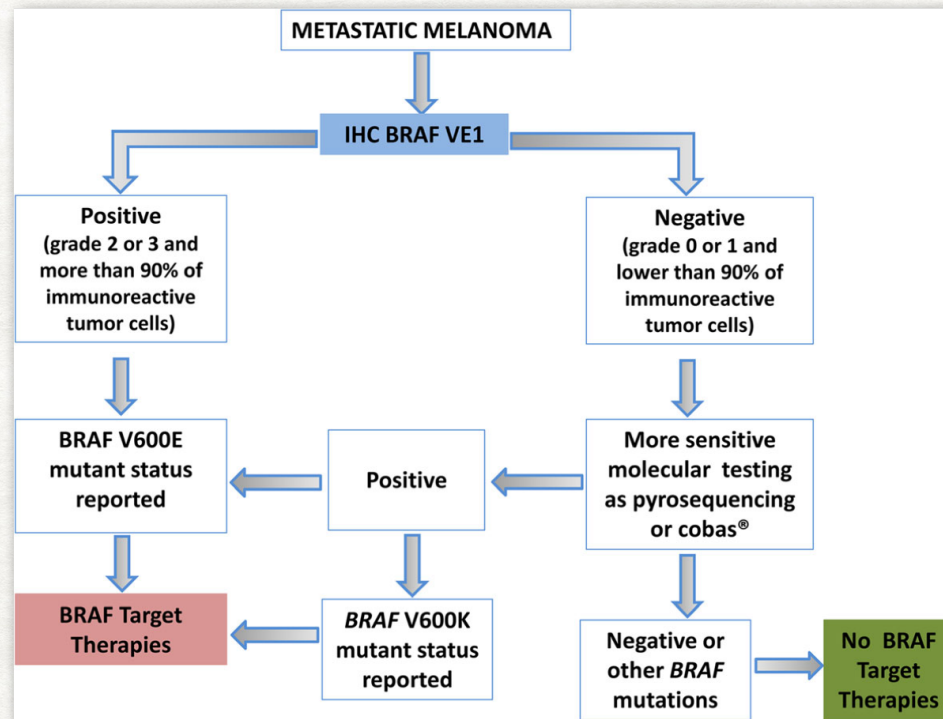
BRAF V600E (VE1)
Mouse Monoclonal Primary Antibody



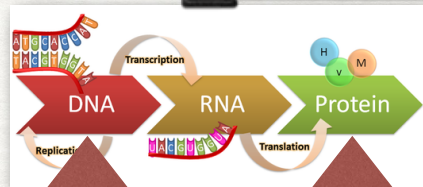
Predictive, diagnostic and prognostic markers



Mutated protein (auto activated)



Predictive, diagnostic and prognostic markers



Mutated protein (auto activated)

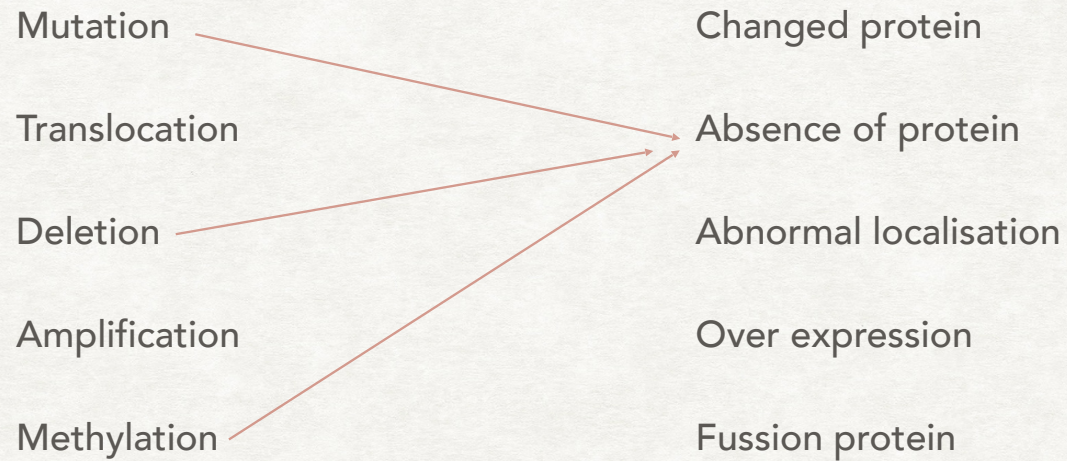
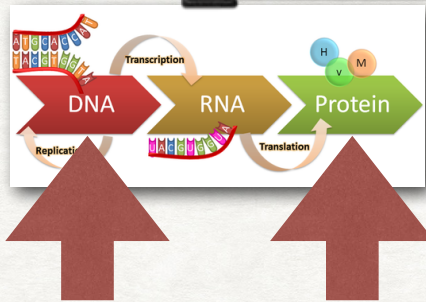


Immunohistochemistry
BRAF V600E

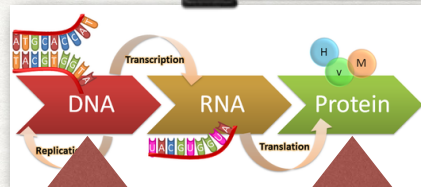


Mutation analysis of BRAF gene

Predictive, diagnostic and prognostic markers



Predictive, diagnostic and prognostic markers



Often combination of
Deletion
Mutation
Methylation

How do oncogenes and tumor suppressors work?

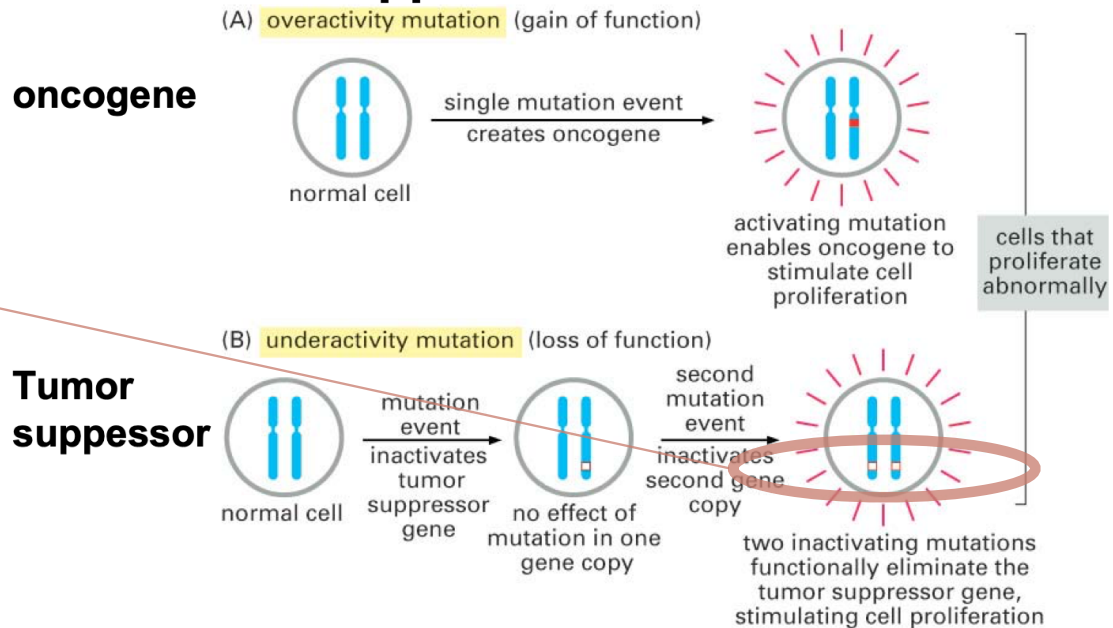
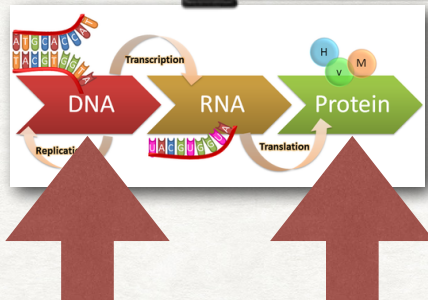
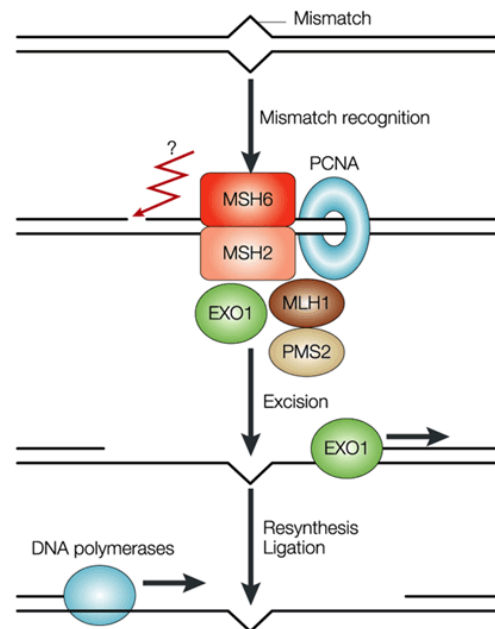


Figure 23-24. Molecular Biology of the Cell, 4th Edition.

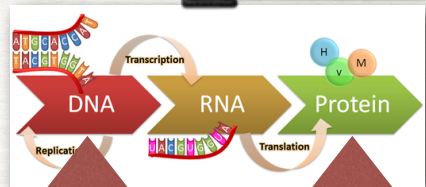
Predictive, diagnostic and prognostic markers



Mismatch repair deficiency



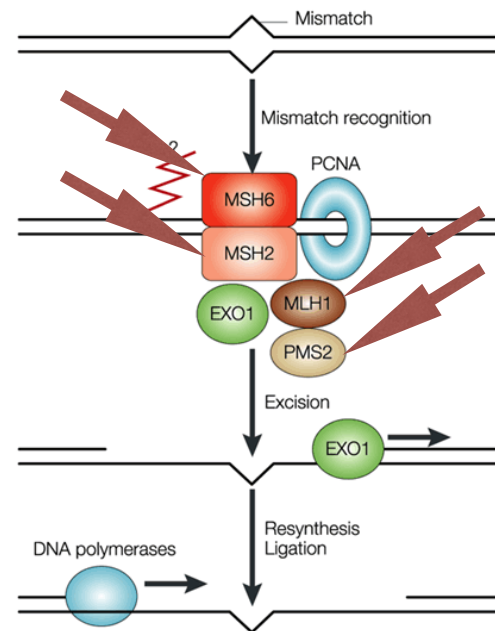
Predictive, diagnostic and prognostic markers



Absence of protein

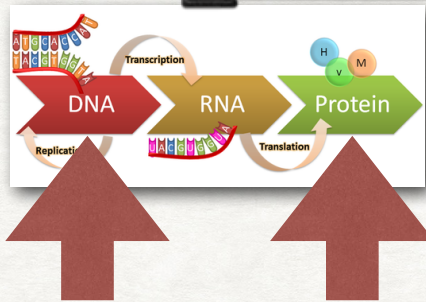
→
Mutation
(Methylation)

Mismatch Repair deficiency
Microsatellite instability



Nature Reviews | Immunology

Predictive, diagnostic and prognostic markers

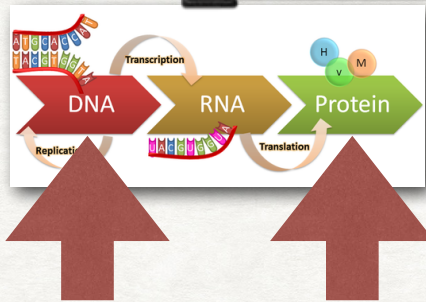


Absence of protein

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

Identify patients with sporadic MSI colon cancers (prognosis and predictive marker)

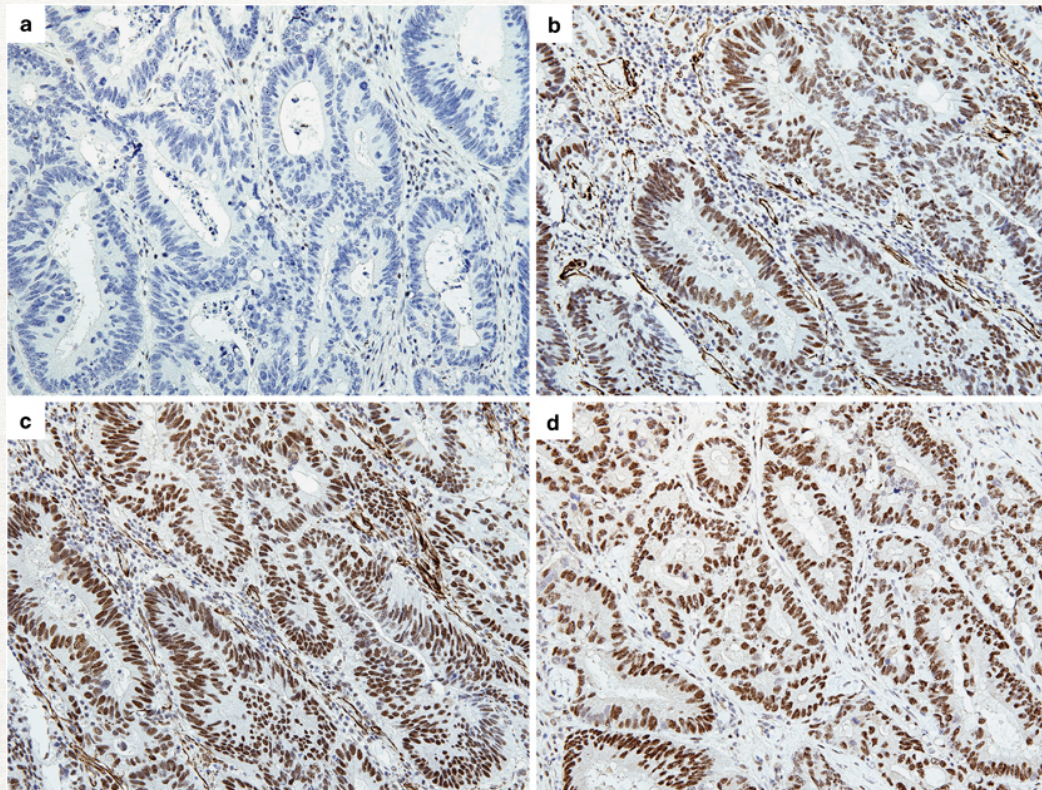
Predictive, diagnostic and prognostic markers



Absence of protein

MLH1

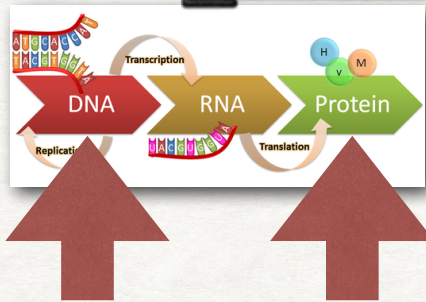
MSH6



PMS2

MSH6

Predictive, diagnostic and prognostic markers

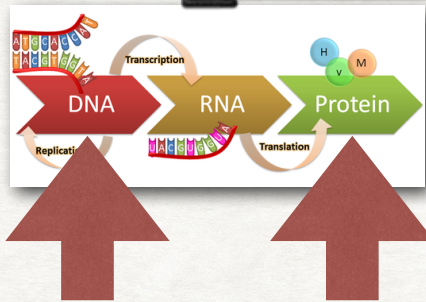


Immunohistochemistry
of MLH1, PMS2, MLH6 and MSH2
(Methylation of MLH1 Gene)



Mutation of MLH1, PMS2, MLH6 and MSH2 genes
Measurement of length of Microsatellites
(Methylation of MLH1 gene)

Predictive, diagnostic and prognostic markers



Mutation

Translocation

Deletion

Amplification

Methylation

Changed protein

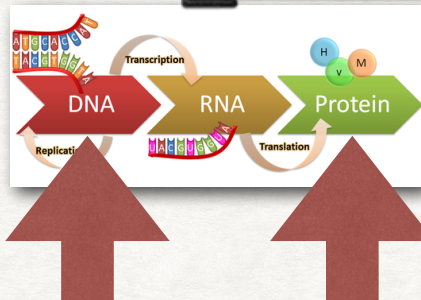
Absence of protein

Abnormal localisation

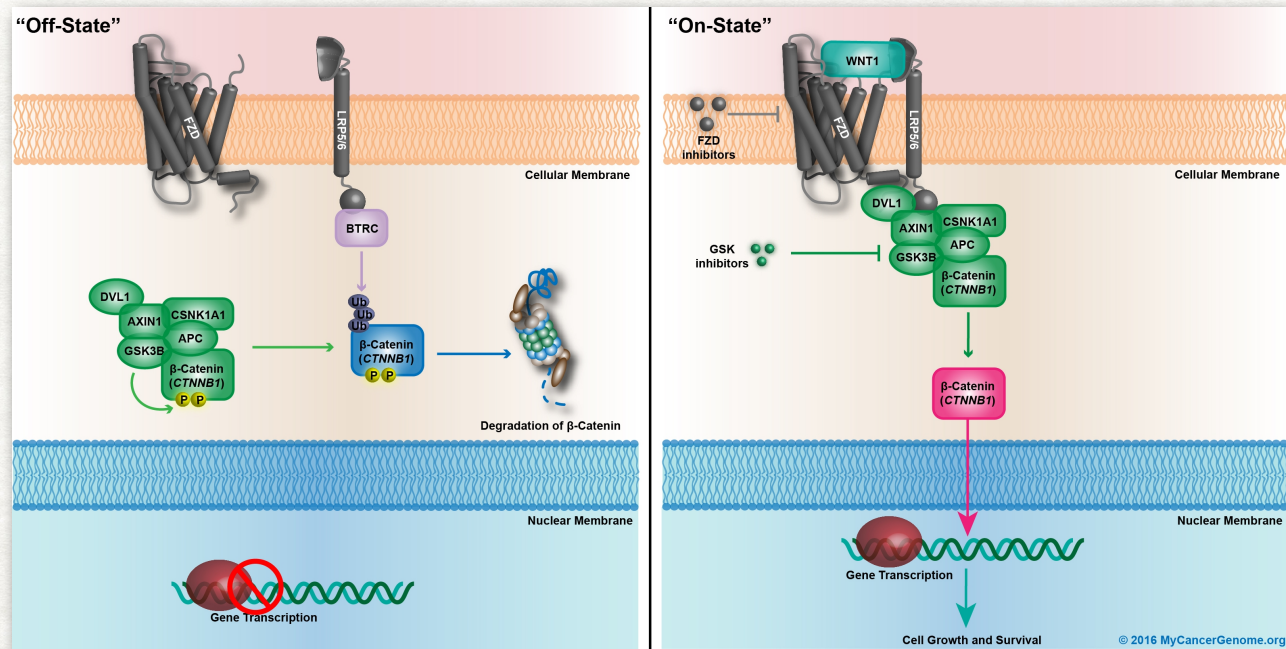
Over expression

Fusion protein

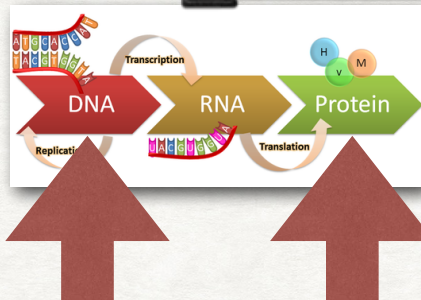
Predictive diagnostic and prognostic markers



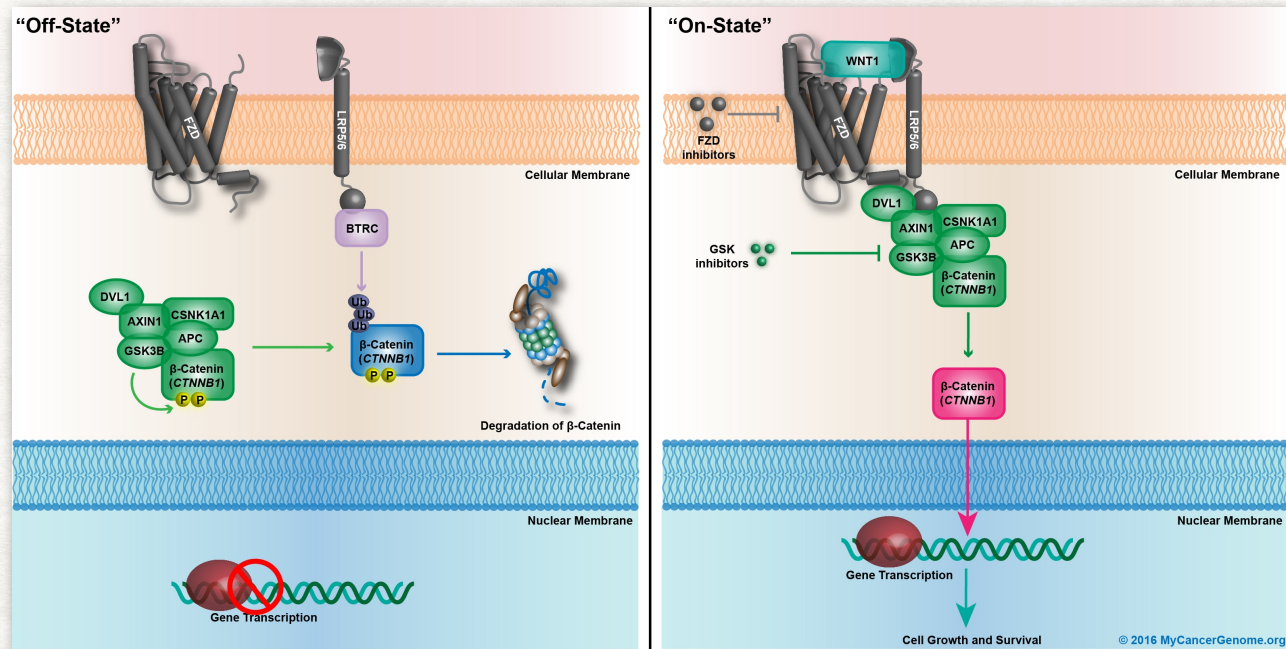
Abnormal localisation



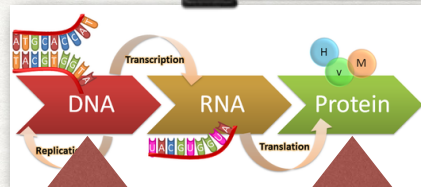
Predictive diagnostic and prognostic markers



Abnormal localisation

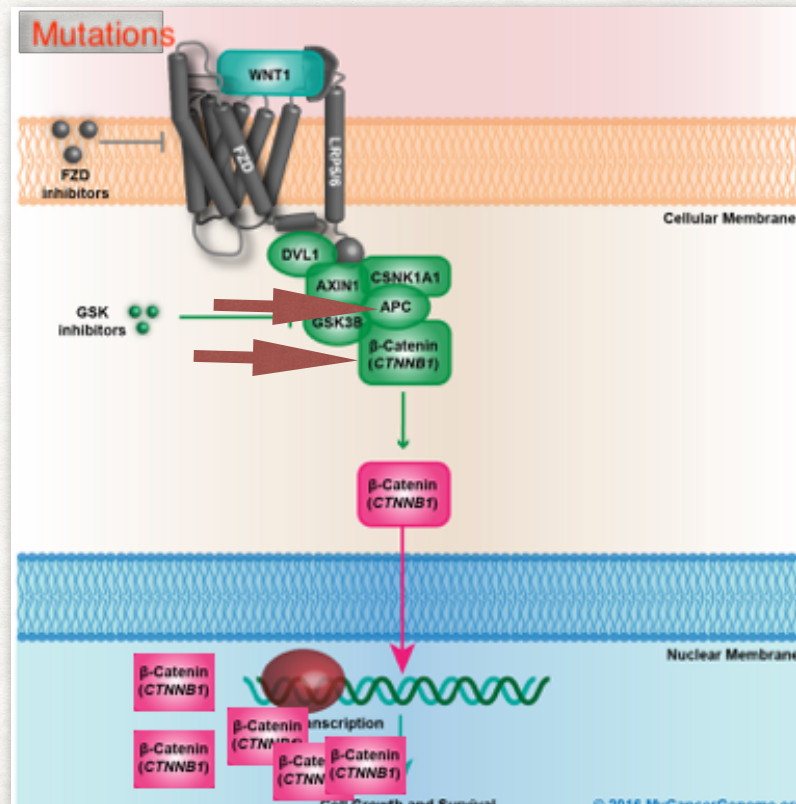


Predictive diagnostic and prognostic markers

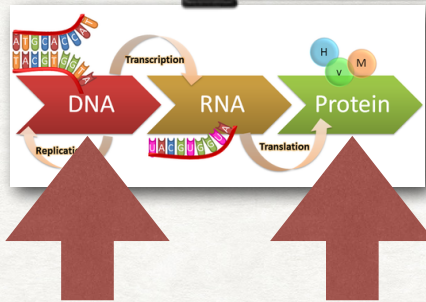


Abnormal localisation

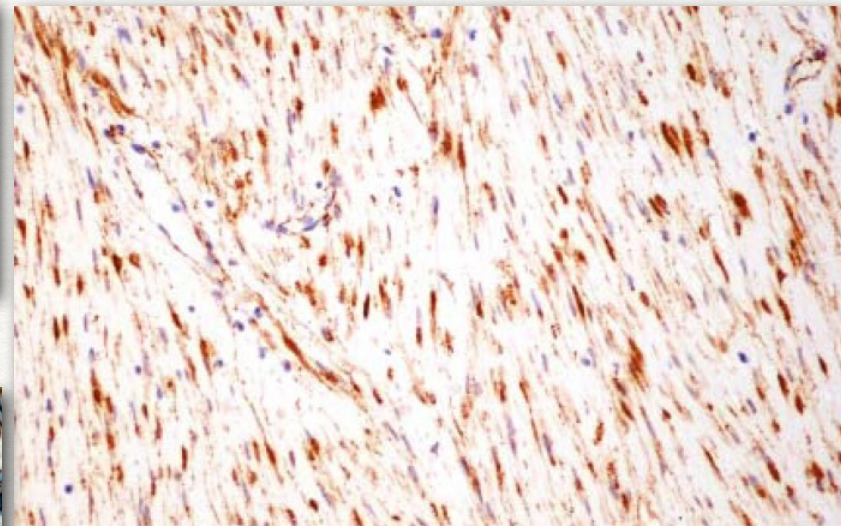
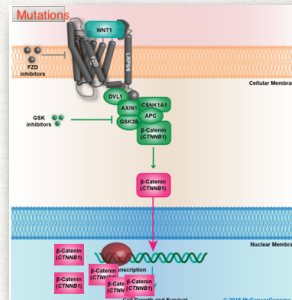
→
Mutations



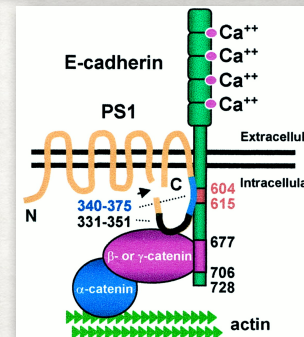
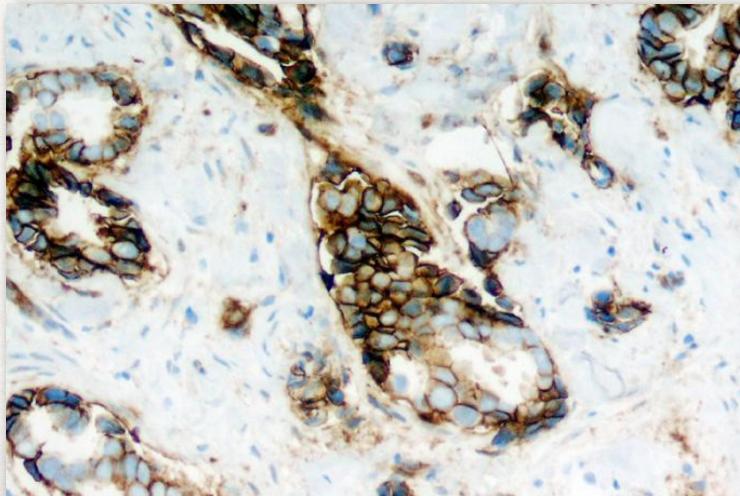
Predictive diagnostic and prognostic markers



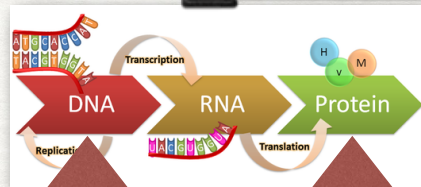
Abnormal localisation



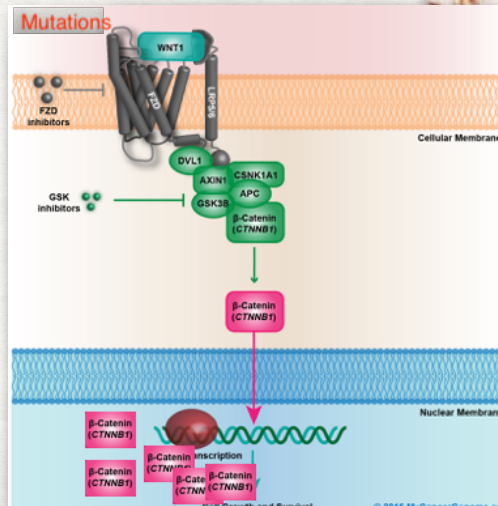
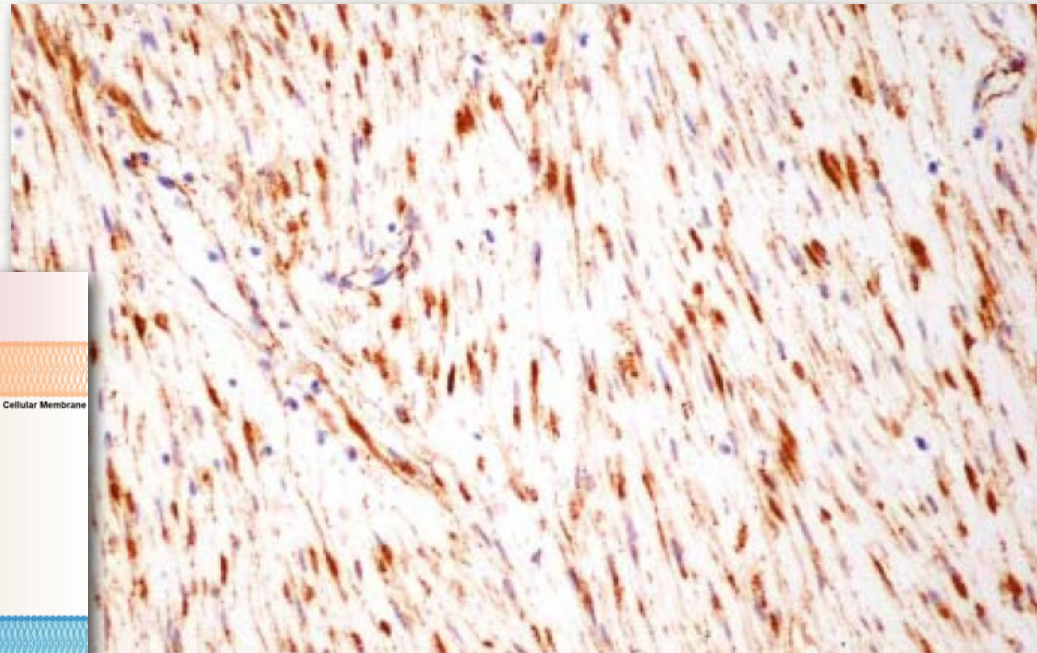
Normal lokalisation



Predictive diagnostic and prognostic markers

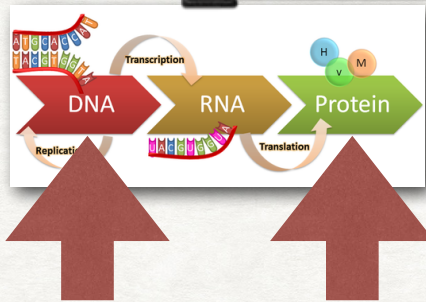


Abnormal localisation



Aggressive fibromatosis

Predictive diagnostic and prognostic markers

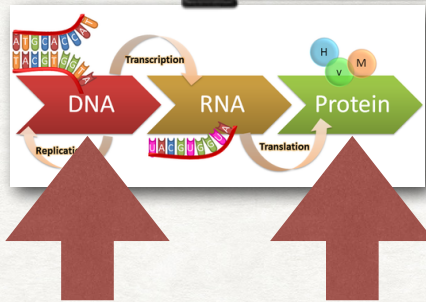


Immunohistochemistry
of B-catenin



Mutations of B-catenin or APC
(Somatic or genetic)

Predictive, diagnostic and prognostic markers



Mutation

Translocation

Deletion

Amplification

Methylation

Changed protein

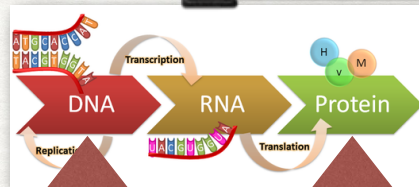
Absence of protein

Abnormal localisation

Over expression

Fusion protein

Predictive, diagnostic and prognostic markers



Often combination of
Deletion
Mutation
Methylation

How do oncogenes and tumor suppressors work?

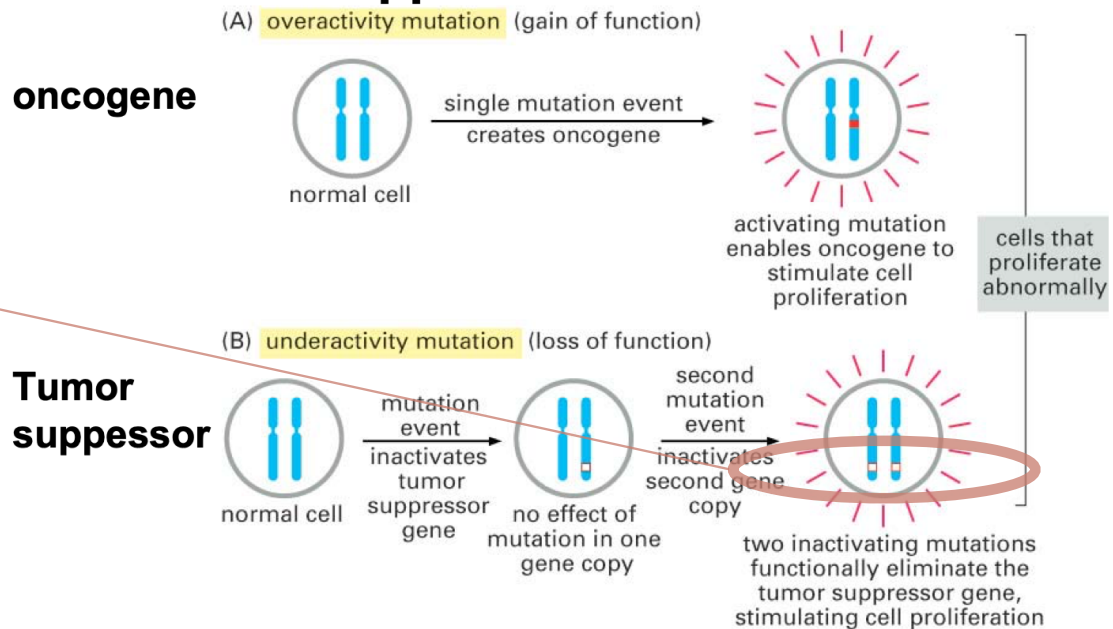
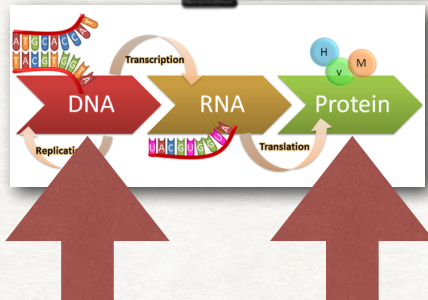
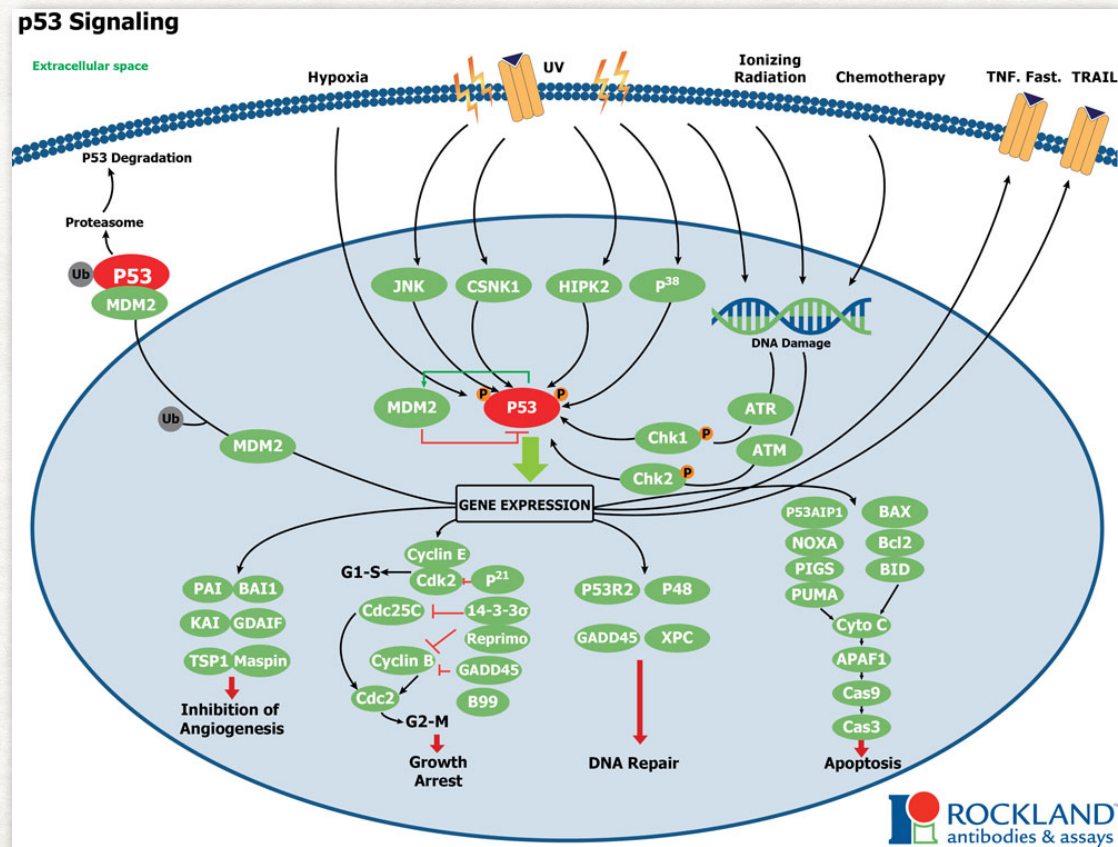


Figure 23-24. Molecular Biology of the Cell, 4th Edition.

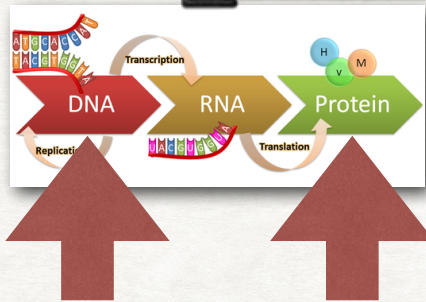
Predictive, diagnostic and prognostic markers



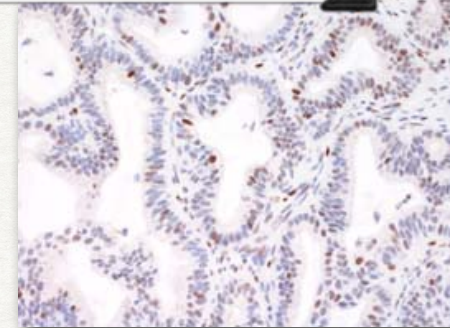
Over ekspression



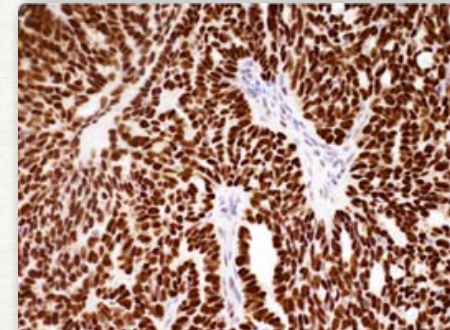
Predictive, diagnostic and prognostic markers



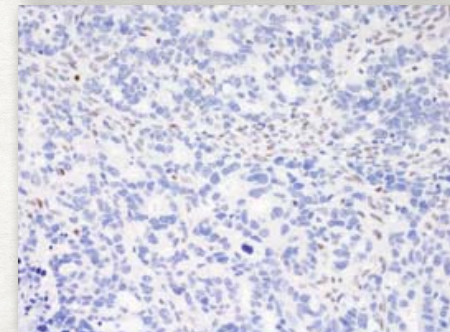
Normal expression



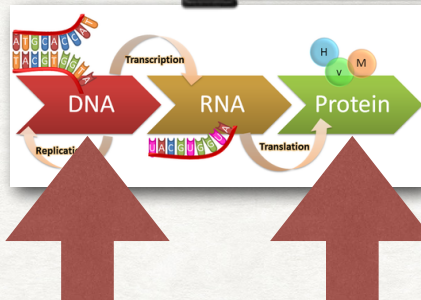
Some mutations cause (besides inactivation) that the P53 protein does not degrade and accumulates in the nucleus



Large deletions cause lack of protein expression



Predictive, diagnostic and prognostic markers



Journal of Pathology

J Pathol 2010; **222**: 191–198

Published online 13 July 2010 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/path.2744

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 Huntsman⁴ and C Blake Gilks^{1*}

¹ Department of Pathology and Laboratory Medicine, Calgary Laboratory Services/Alberta Health Services and University of Calgary, Canada

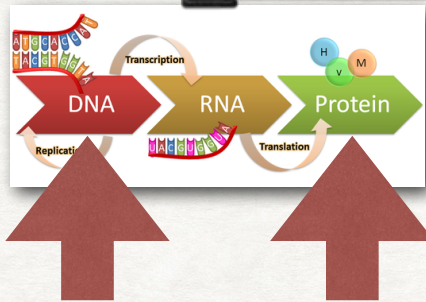
² Coordinating Centre for Clinical Trials (KKS), University Marburg (AGO-OVAR Statistical Centre), Germany

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

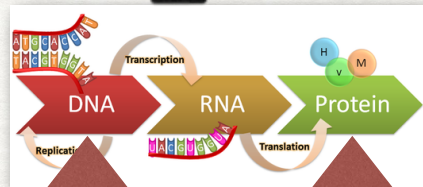


Immunohistochemistry
of p53



NGS of the p53 gene

Molekylærpatologi



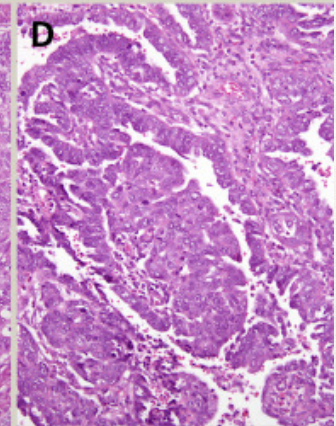
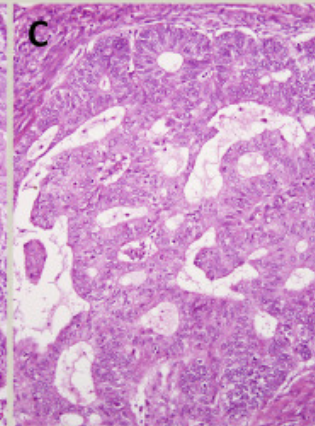
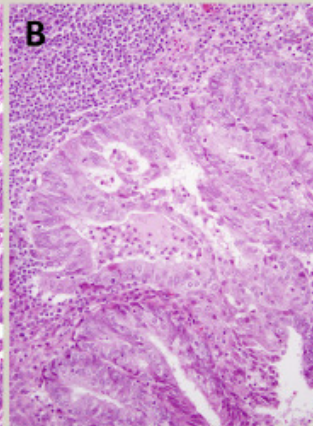
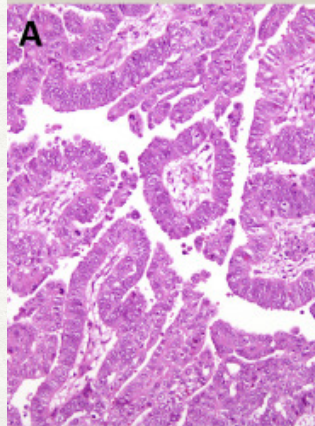
Endometrial carcinoma

***POLE* mutated**
(*POLE* EDM, *POLE*-mutant)

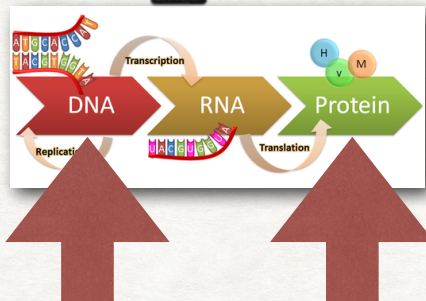
***MMR* deficient**
(*MMR*-D, MSI)

***p53* wild-type**
(*p53* wt, NSMP)

***p53* mutated**
(*p53* abn, *p53*-mutant)



Molekylærpatologi

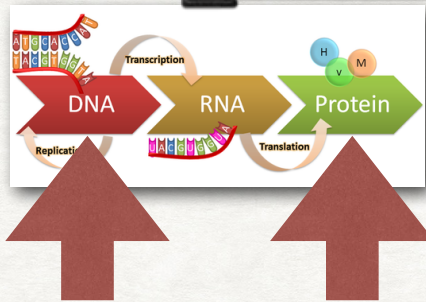


Immunohistochemistry
af p53 og MMR proteiner



NGS POLE, P53 og MMR gener

Predictive, diagnostic and prognostic markers



Mutation

Changed protein

Translocation

Absence of protein

Deletion

Abnormal localisation

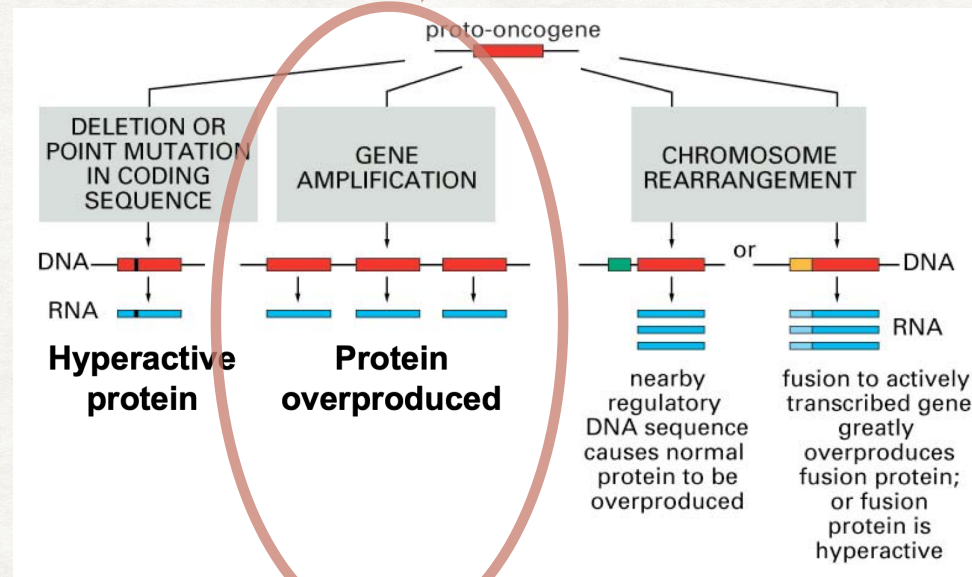
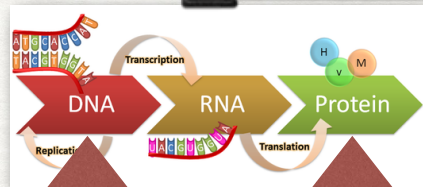
Amplification

Over expression

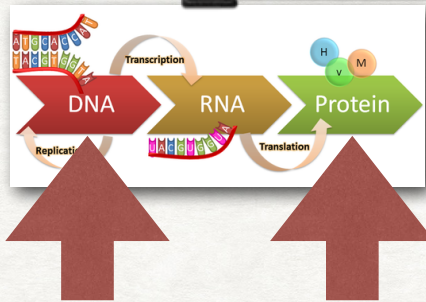
Methylation

Fusion protein

Predictive, diagnostic and prognostic markers

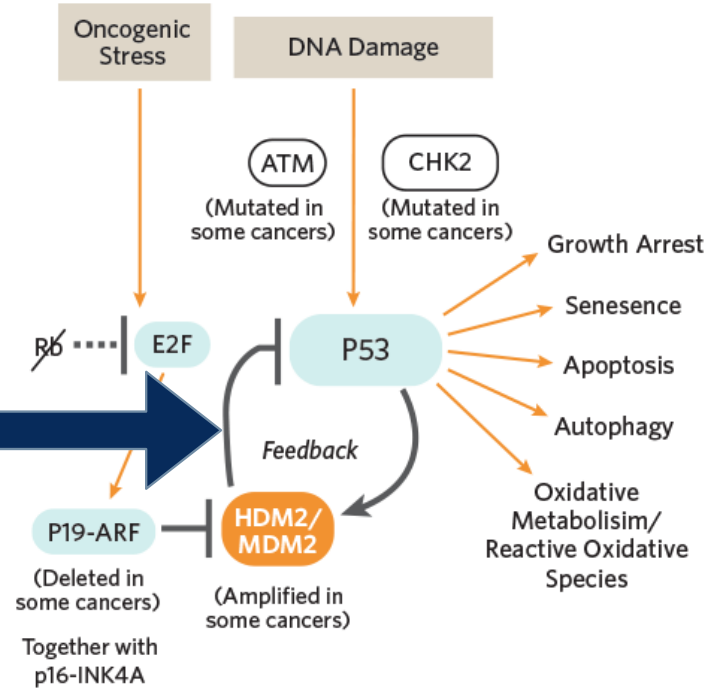


Predictive, diagnostic and prognostic markers

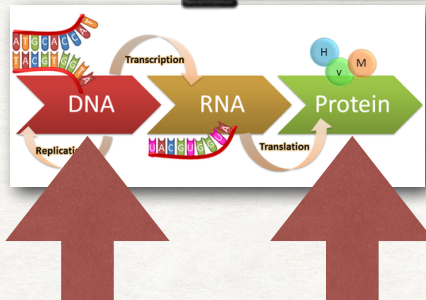


Amplification of oncogene MDM2
Destroys tumor suppressor function

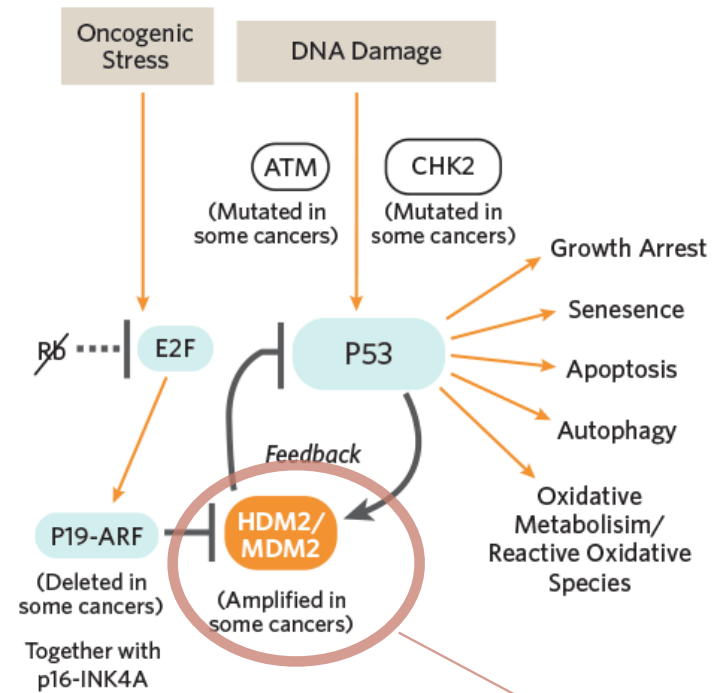
Regulator of the TP53 Tumor Suppressor- HDM2/MDM2



Predictive, diagnostic and prognostic markers

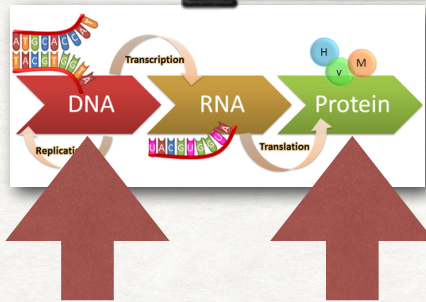


Regulator of the TP53 Tumor Suppressor- HDM2/MDM2

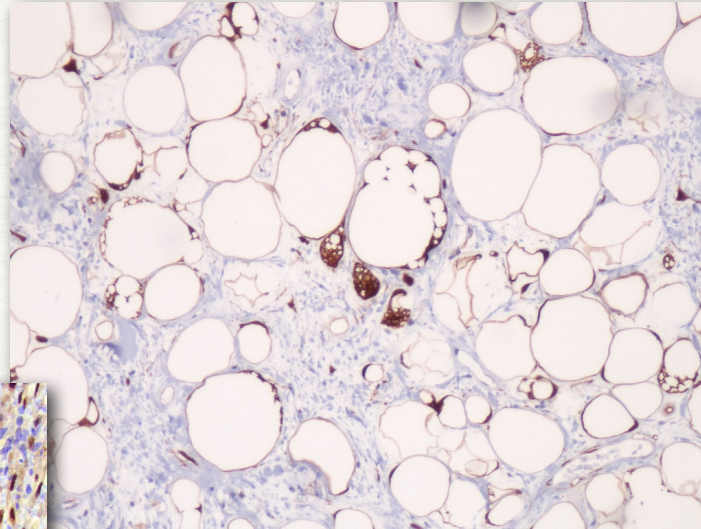


E.g. liposarcoma

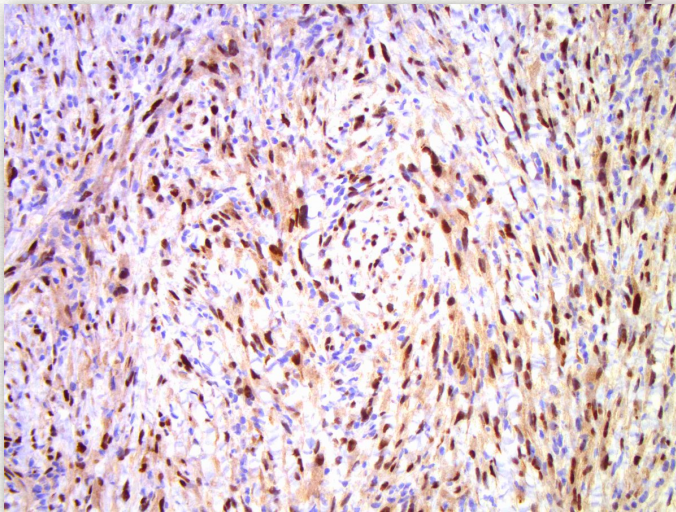
Predictive, diagnostic and prognostic markers



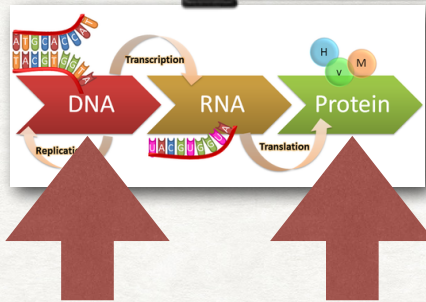
Well differentieret liposarcoma



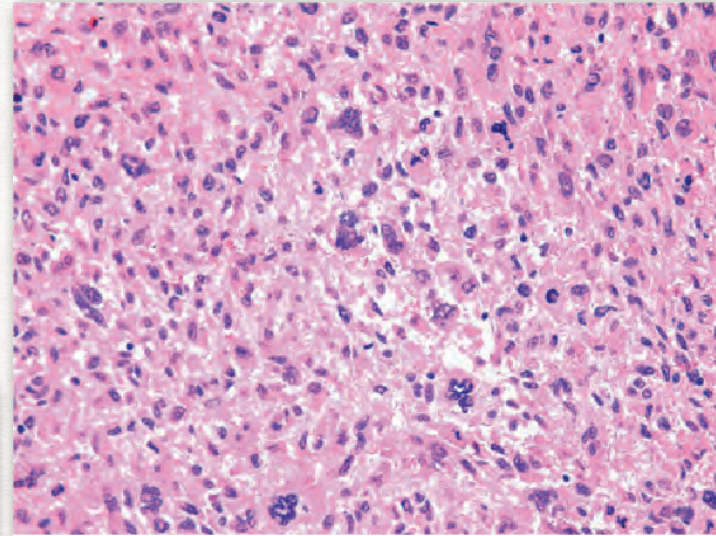
Dedifferentiated liposarcoma



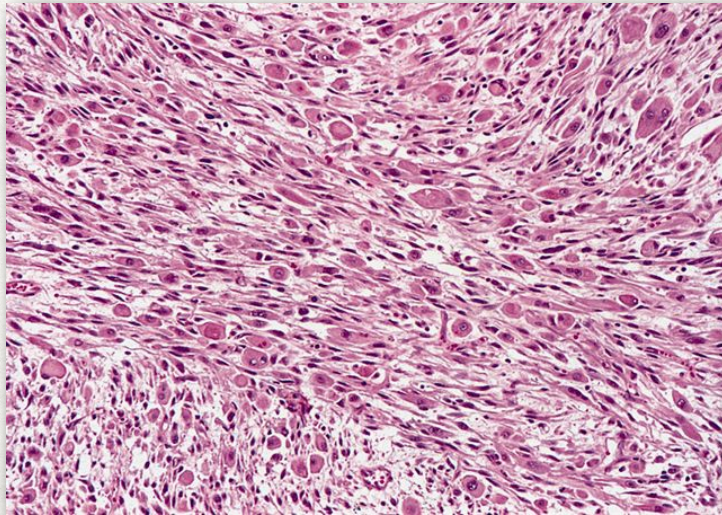
Predictive, diagnostic and prognostic markers



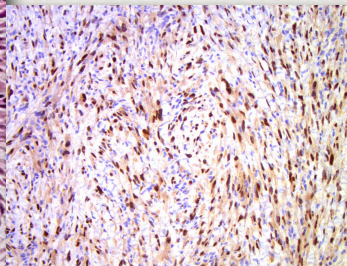
Pleomorph undifferentiated sarcoma



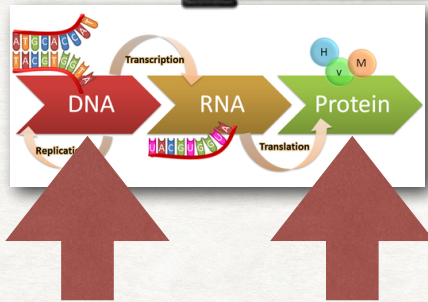
Dedifferentieret liposarcoma



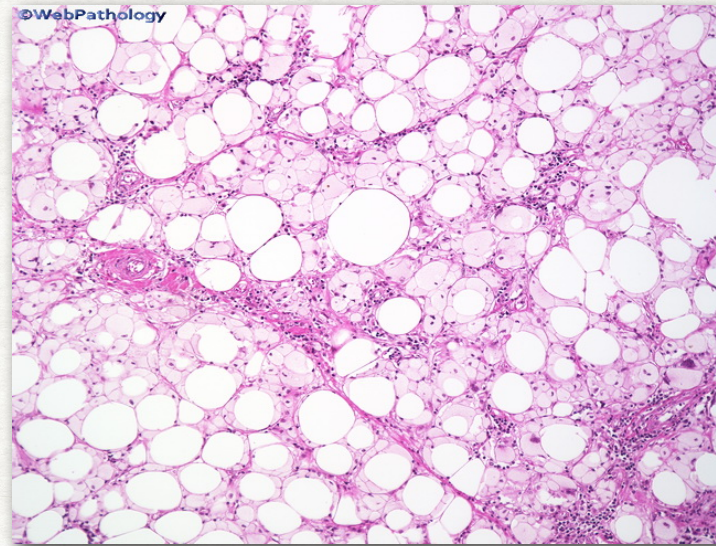
MDM2



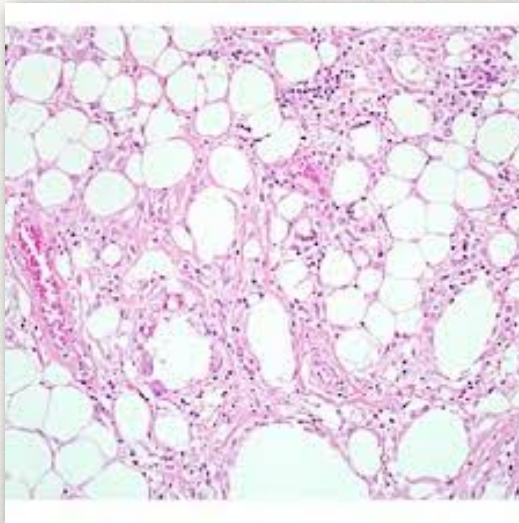
Predictive, diagnostic and prognostic markers



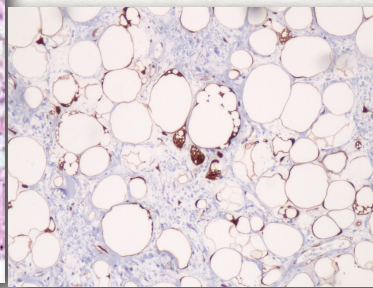
Lipoma



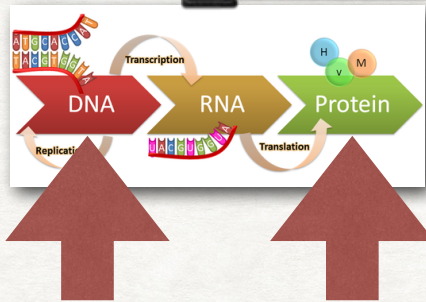
Well differentiated liposarcoma



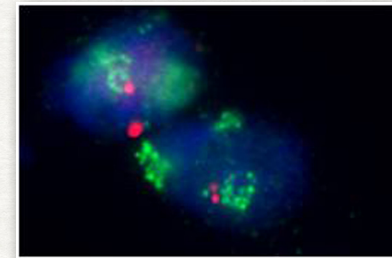
MDM2



Predictive, diagnostic and prognostic markers

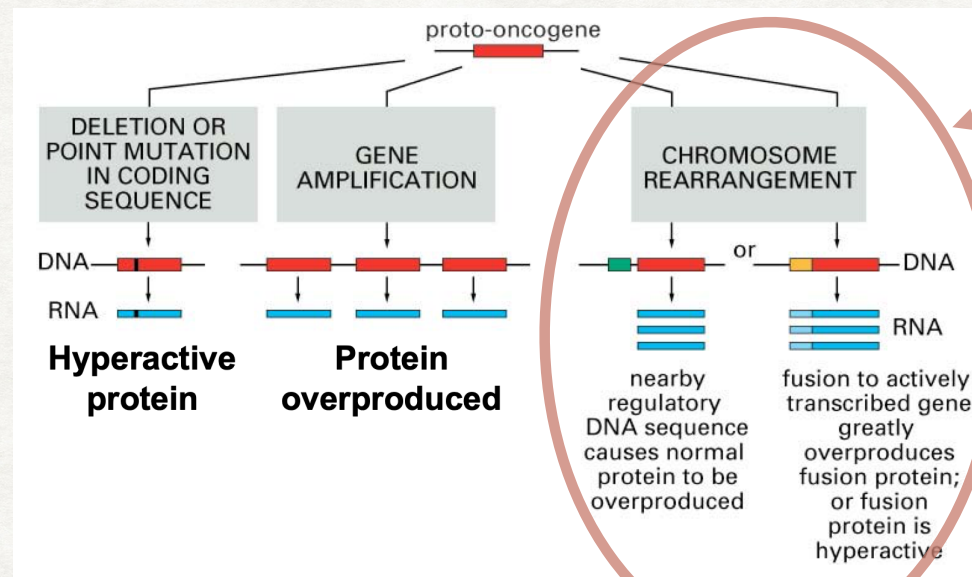
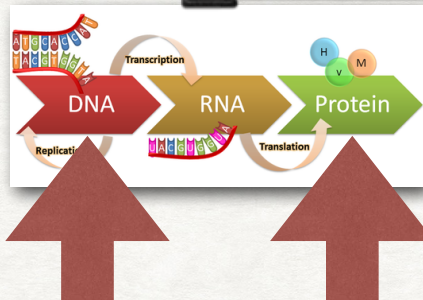


Immunohistochemistry
of MDM2

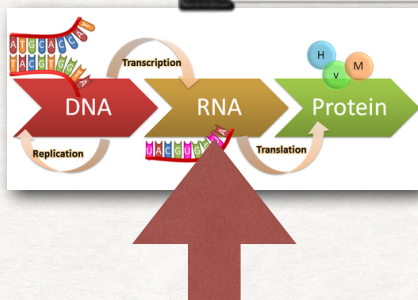


NGS or FISH analysis of amplification
of MDM2 gene.

Predictive, diagnostic and prognostic markers



Predictive, diagnostic and prognostic markers



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Molecular Sciences

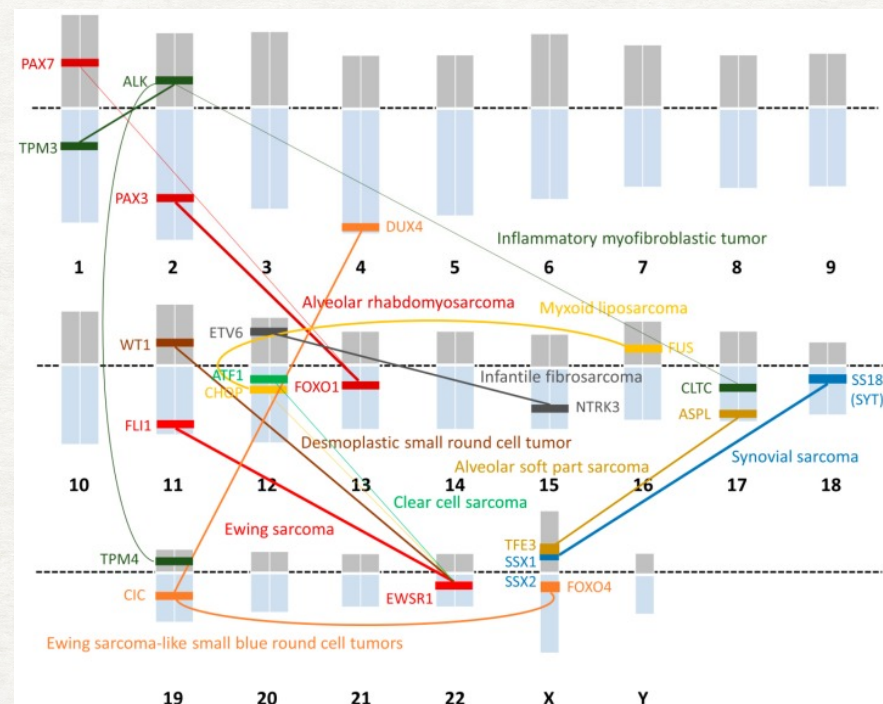
Review

Translocation-Related Sarcomas

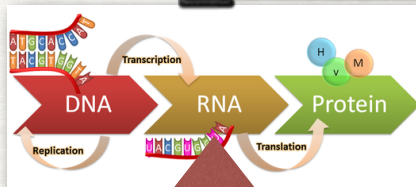
Kenji Nakano * and Shunji Takahashi

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

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



Predictive, diagnostic and prognostic markers



Big sarcoma RNA-seq panels