

Cell Signaling in Colorectal Cancer

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Topics

- Concepts of carcinogenesis
- Signaling pathways
- Growth factors
- Summary

Colorectal Cancer

- Second leading cause of cancer death
- 147,000 cases per year
- 50,000 deaths per year
- Medical treatment not curative

Concepts of Carcinogenesis



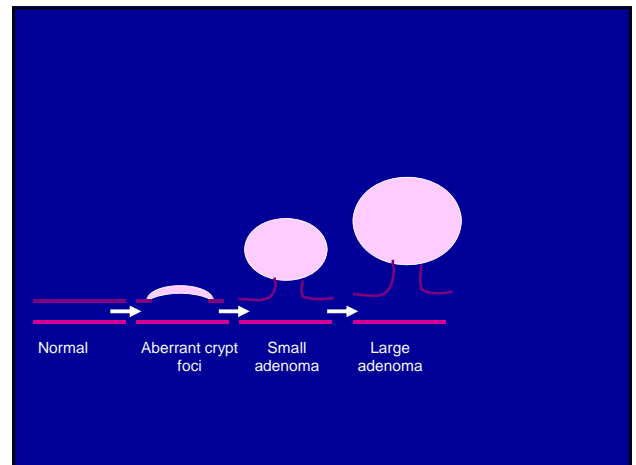
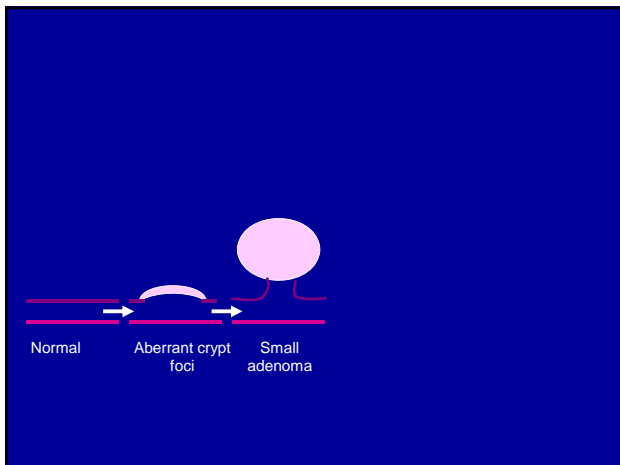
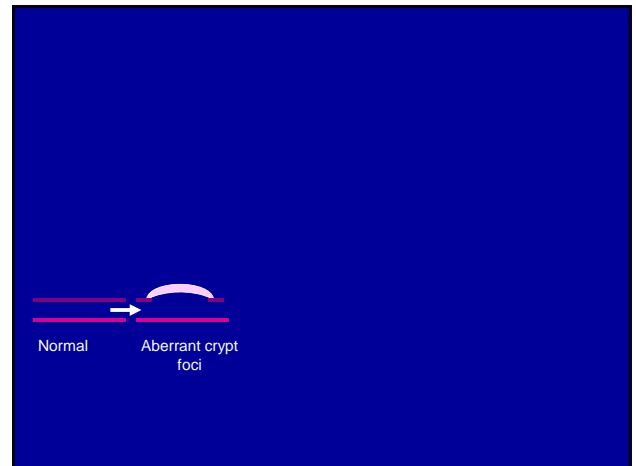
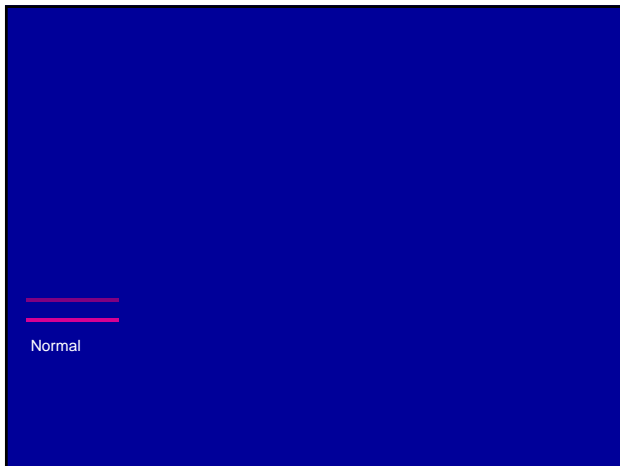
Bert Vogelstein

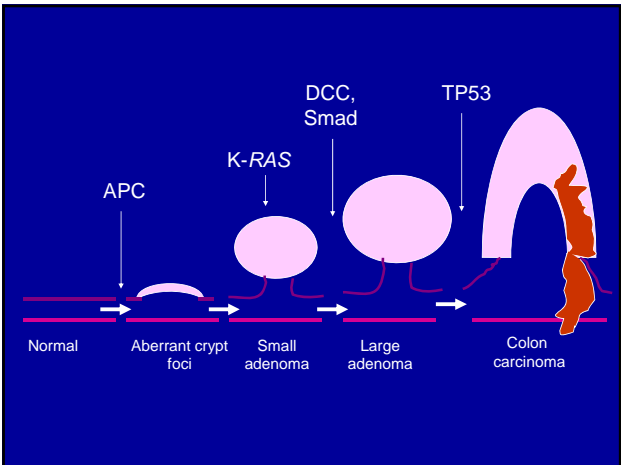
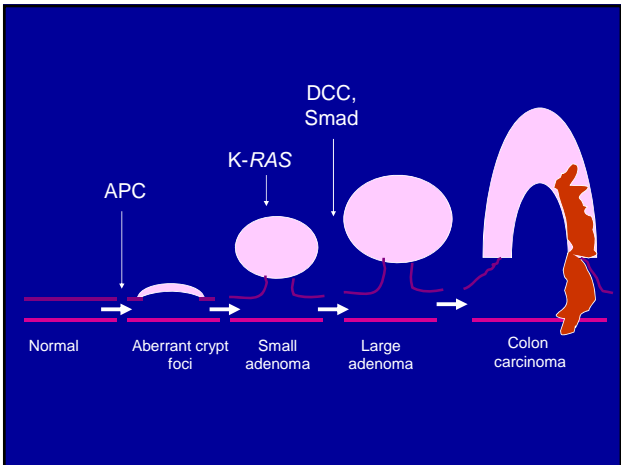
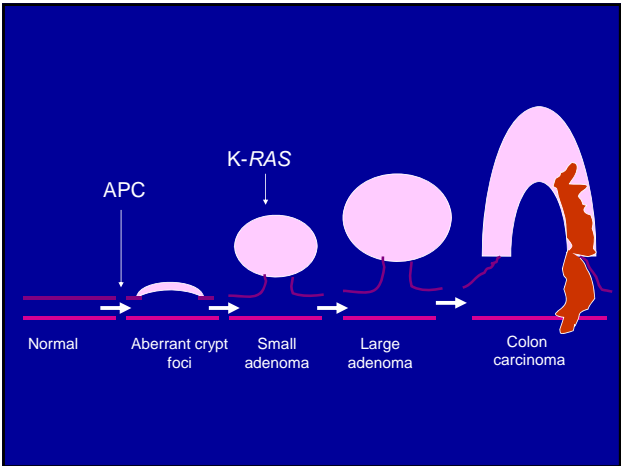
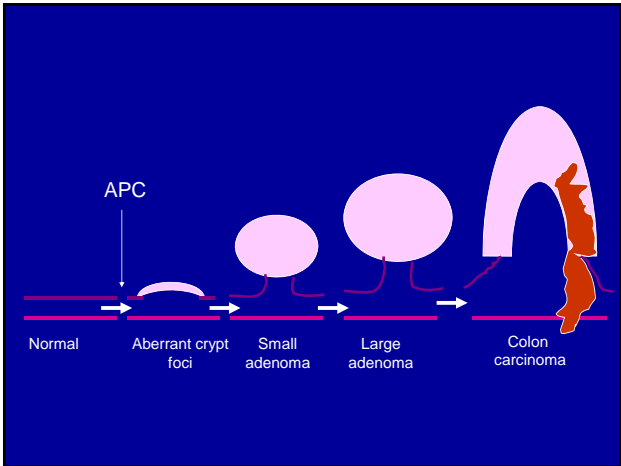
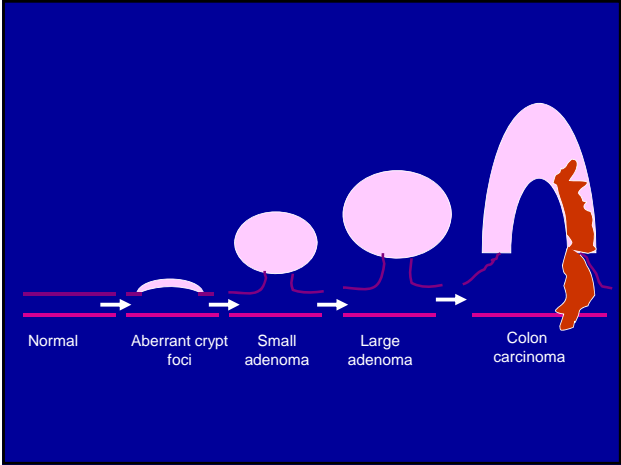
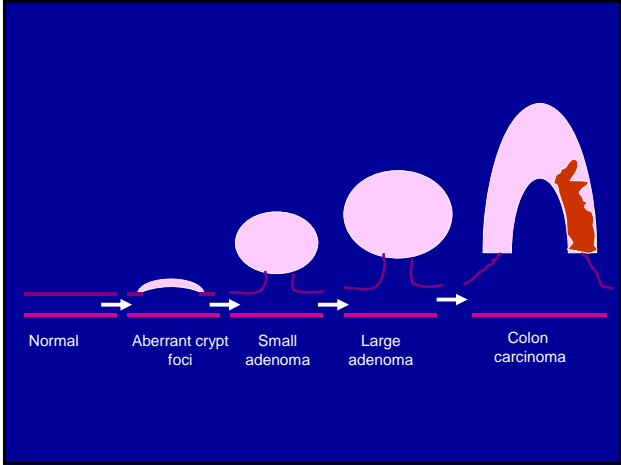
“Cancer is, in essence, a genetic disease”

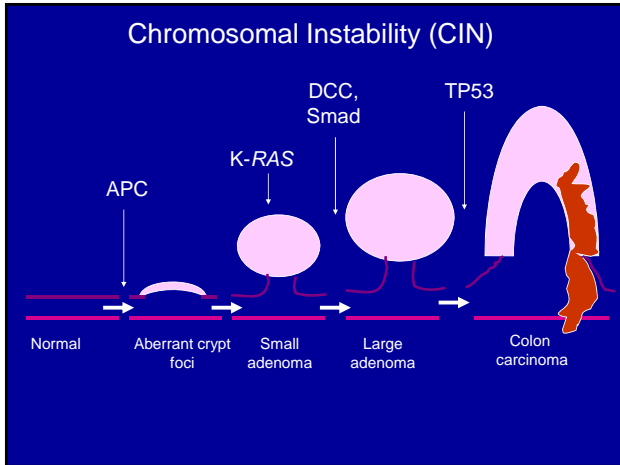
Carcinogenesis

- No single gene mutation
- Series of mutated genes
- Solid tumors- 3 to 8 genes
- Tumor suppressor, oncogene, caretaker

Adenoma-Carcinoma Sequence







Tumor Suppressor Genes

- Gene activity decreased by mutation
- Biallelic mutations necessary
- Defective brakes in auto
- APC, TP53

Oncogenes

- Gene activated by mutation
- Monoallelic mutation-growth advantage
- Stuck gas pedal in auto
- K-RAS gene

Caretaker Genes

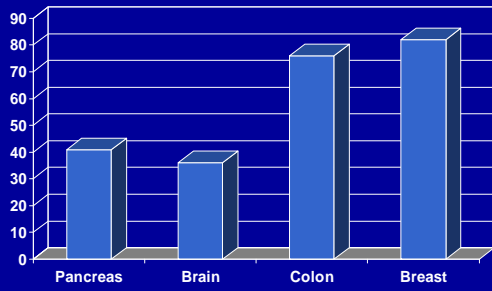
- Repairs mistakes- mutation more mistakes
- Inept auto mechanic
- Mismatch repair genes



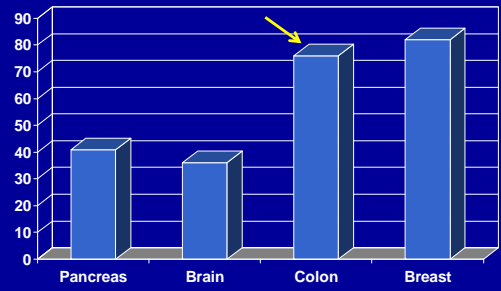
Analysis of Cancers

- Analyzed 20,000 genes in tumors
- Somatic mutation, amplification, deletion
- Validates findings in second set

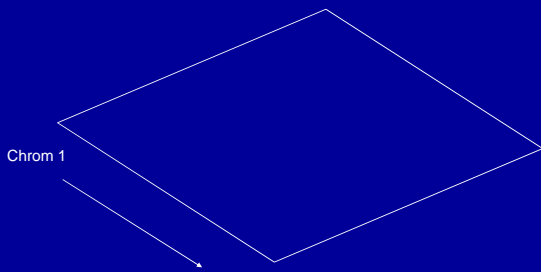
Gene Mutations in Tumors



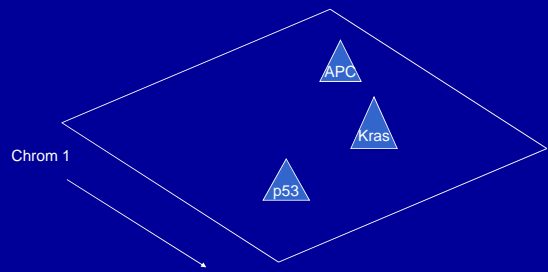
Gene Mutations in Tumors



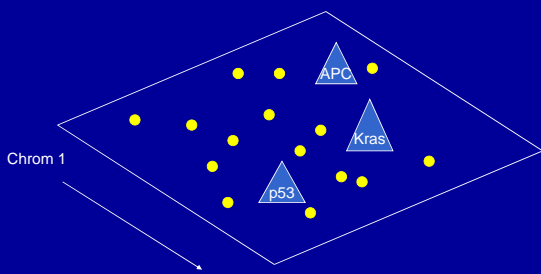
Genomic Landscape



Genomic Landscape



Genomic Landscape



Genomic Landscape

- Gene mountains
 - few frequently mutated genes- 20
 - driver gene mutations- causative
- Gene hills
 - many infrequently mutated genes- 60
 - passenger gene mutations- go for ride

Carcinogenesis

Carcinogenesis

Many Gene Alterations

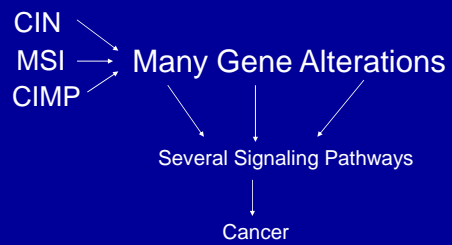
Carcinogenesis



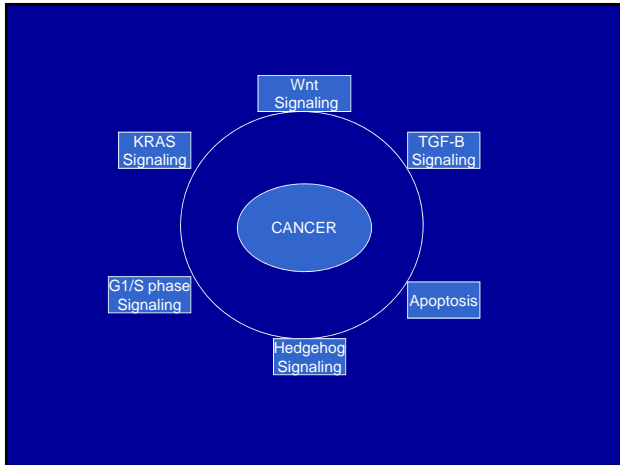
Carcinogenesis



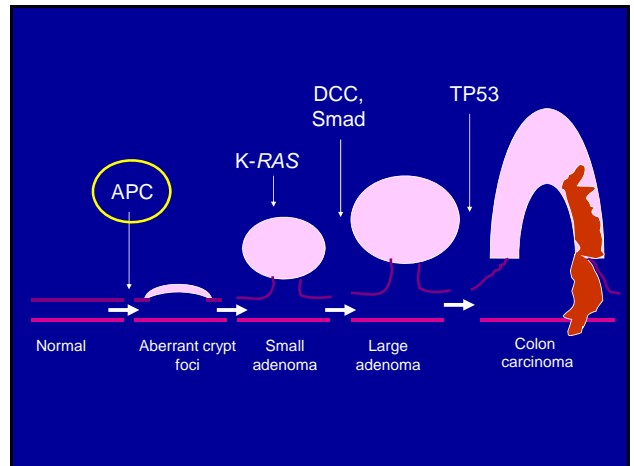
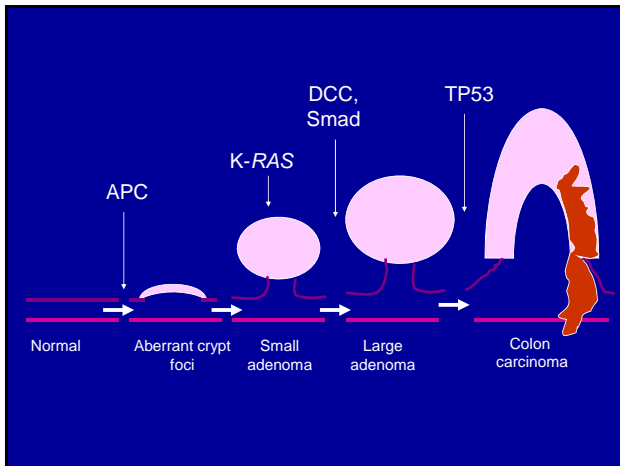
Carcinogenesis



CANCER



Signaling Pathways



APC Gene and Wnt Signaling

- ### APC Gene
- 1986- Herrera- pt with retardation & polyposis- deletion chromosome 5
 - Linkage in FAP families at 5q21
 - 1991 isolation of APC (Adenomatous Polyposis Coli) gene

APC Gene Functions

- Tumor suppressor
- Gatekeeper gene
- Cell adhesion
- Signal transduction
- Transcriptional activation
- Apoptosis

Clinical Correlations of APC Gene Mutations

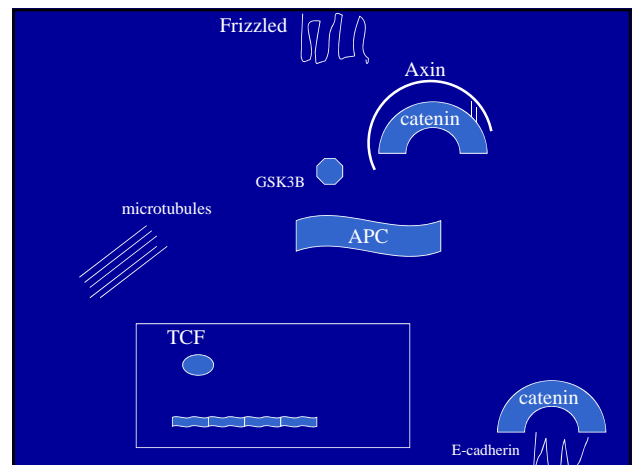
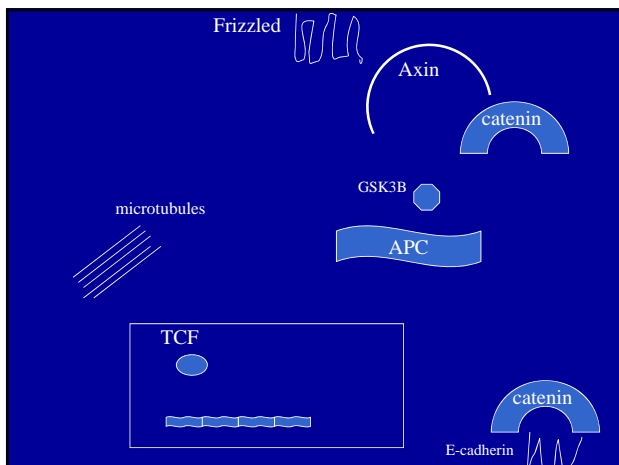
- Somatic mutations- sporadic CRC
- Germline mutations
 - Familial adenomatous polyposis (FAP)
 - Attenuated FAP

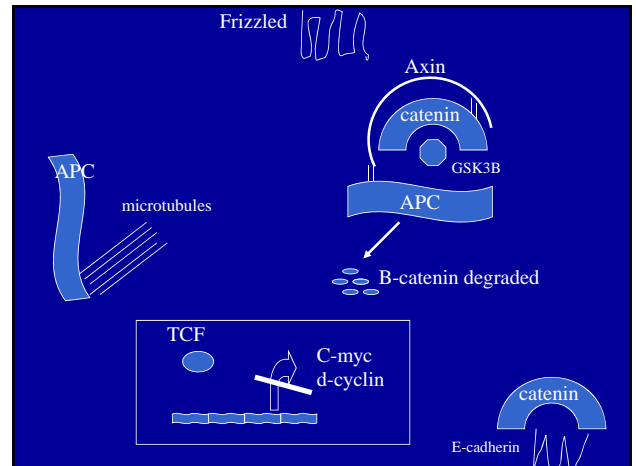
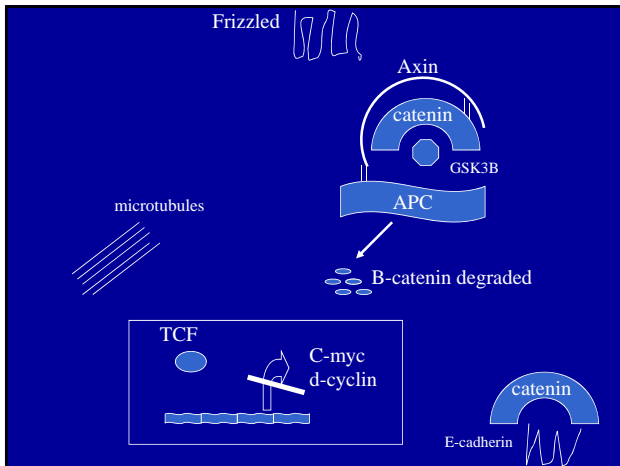
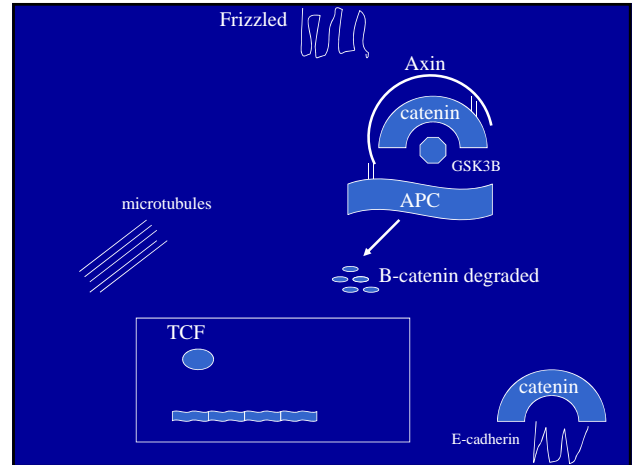
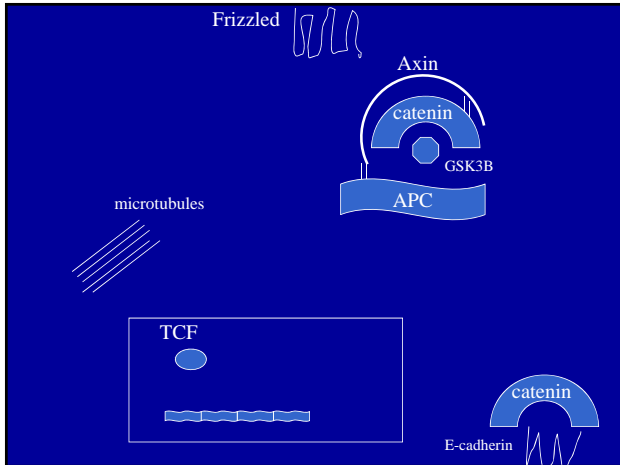
APC, B-Catenin, Wnt Signaling

- B-Catenin usually in cytoplasm, degraded by phosphorylation
- APC, axin complex facilitates degradation
- Not degraded, goes to nucleus stimulates transcription including oncogenes (c-myc, cyclin d)

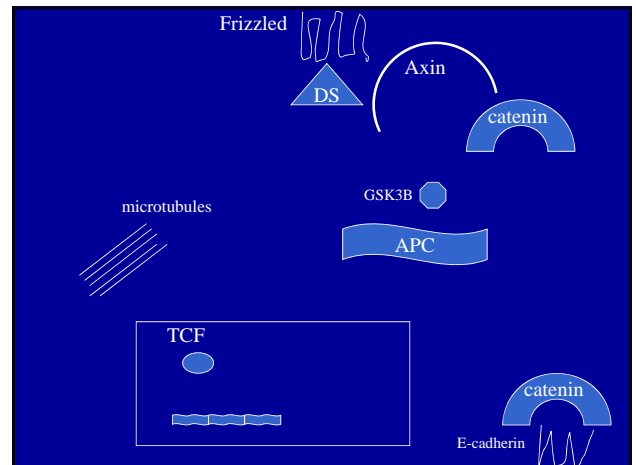
APC, B-Catenin, Wnt Signaling

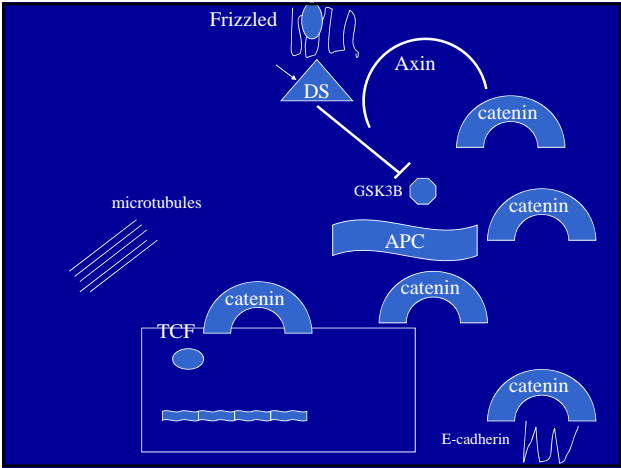
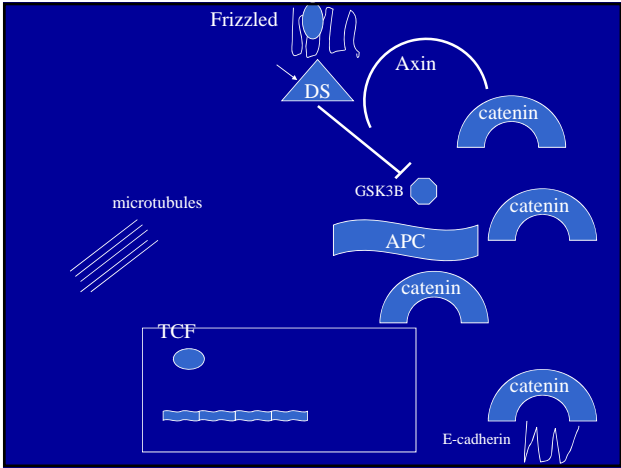
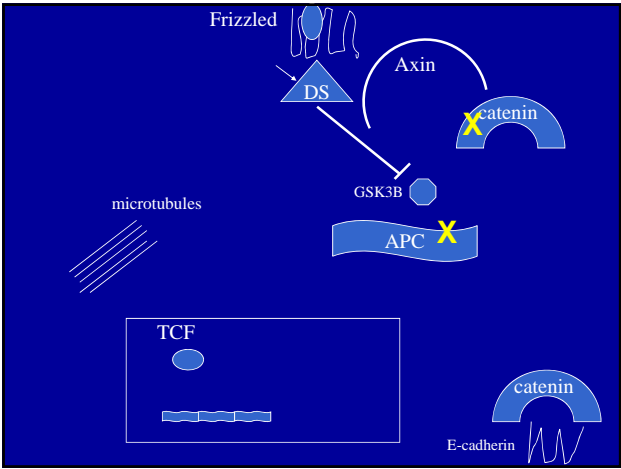
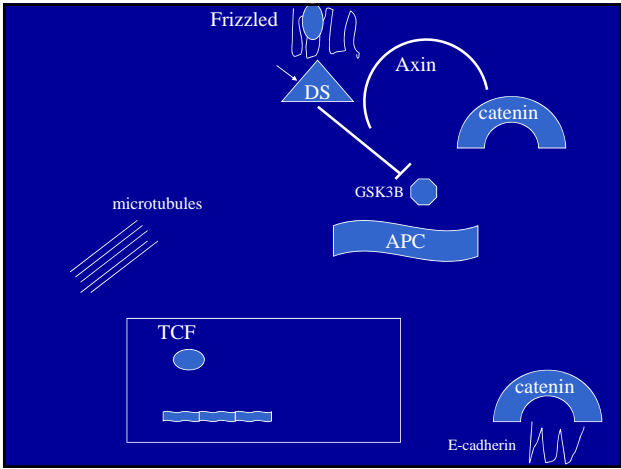
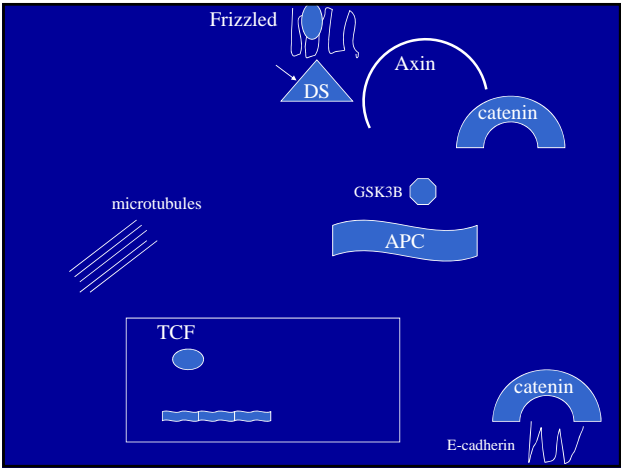
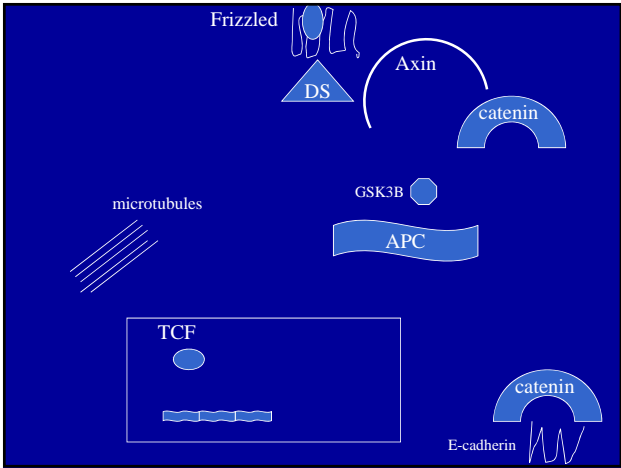
- Activation of WNT pathway through protein dishevelled interrupts APC, Axin, B-Catenin pathway
- Mutations in APC or B-catenin prevent phosphorylation and B-catenin activation

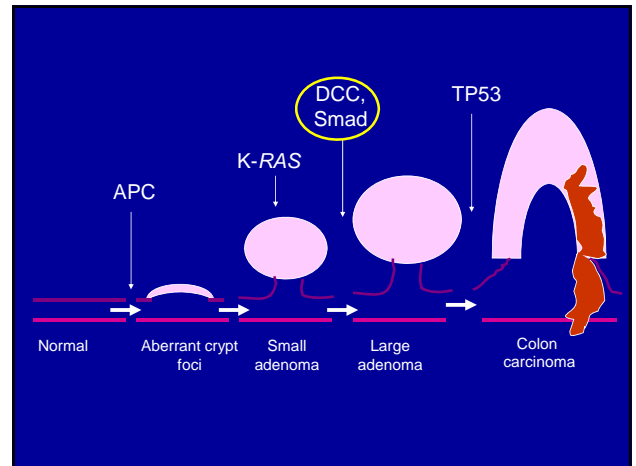
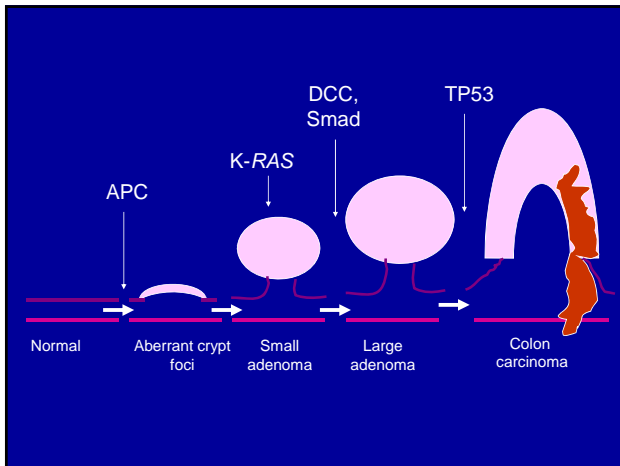
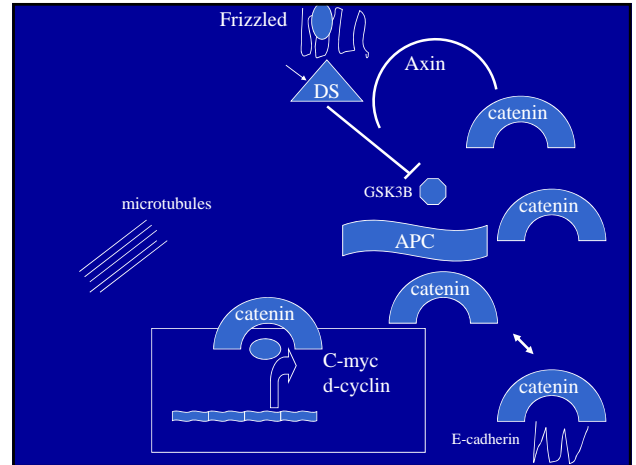
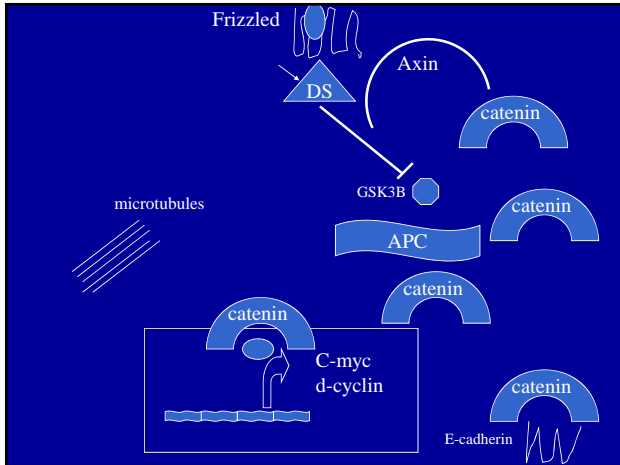




Wnt Signaling Activation

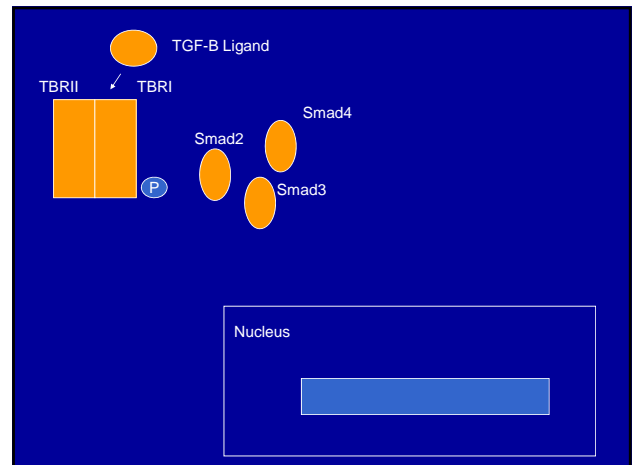


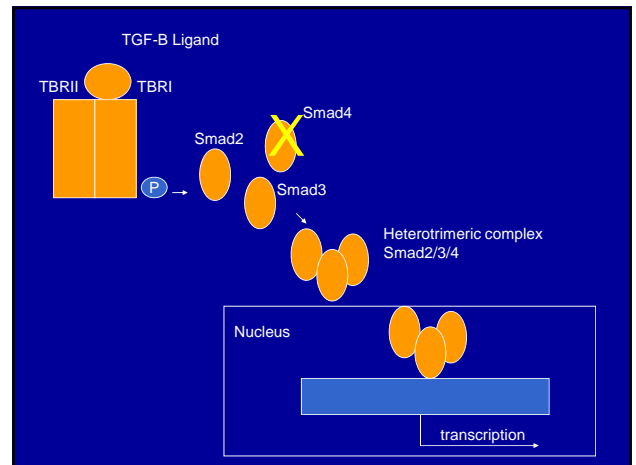
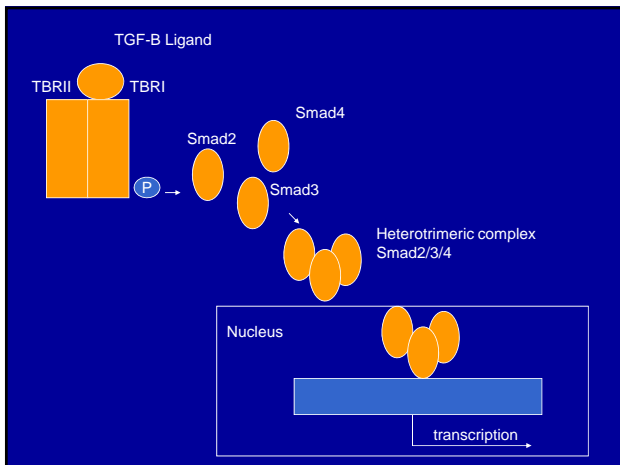
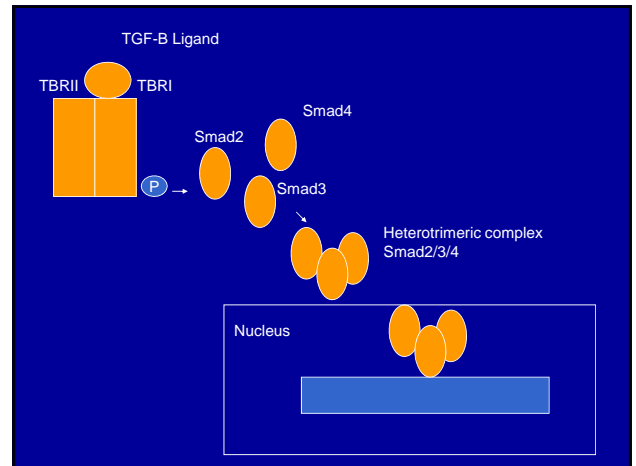
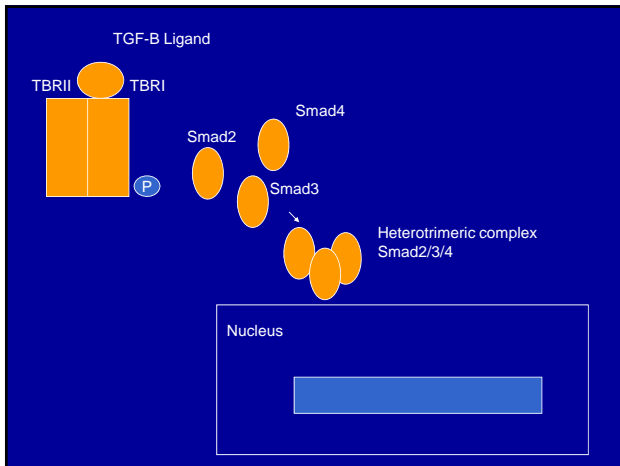
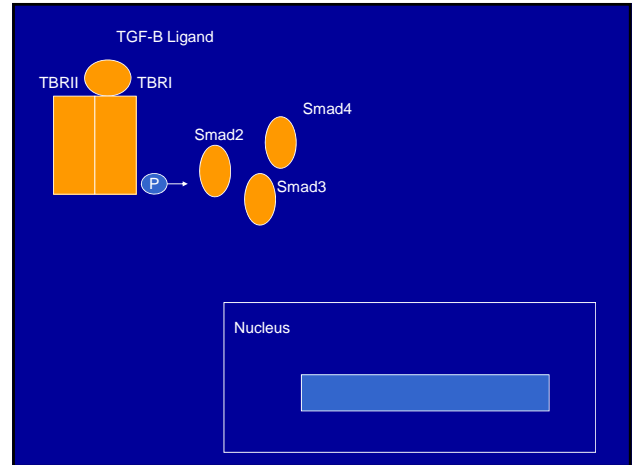
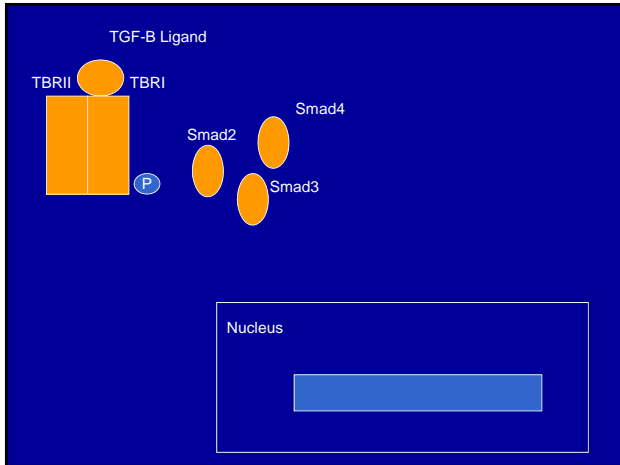


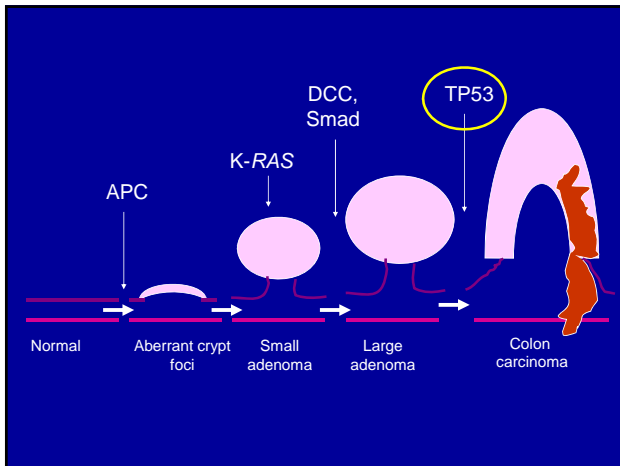
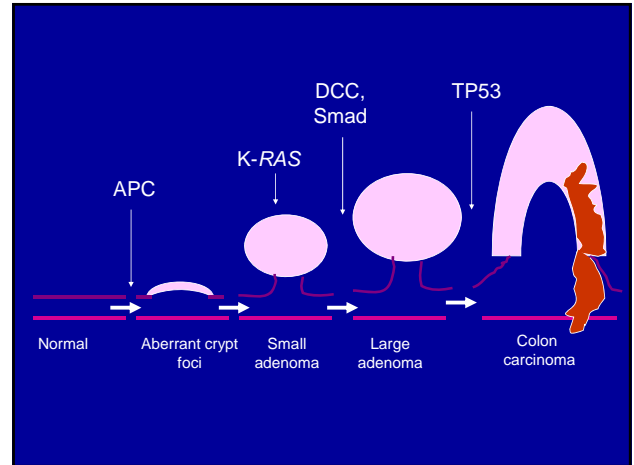
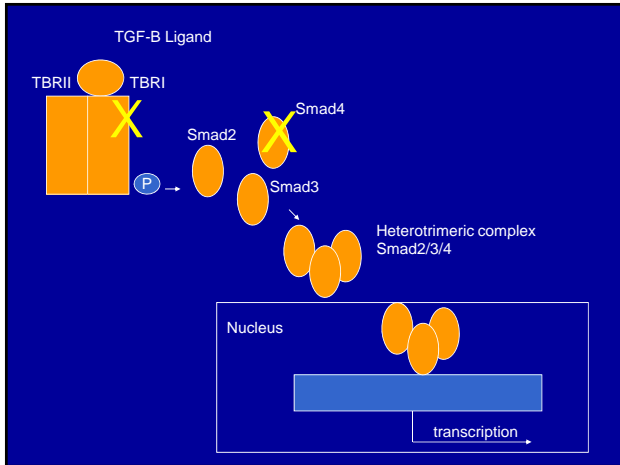


TGF-B Signaling Pathway

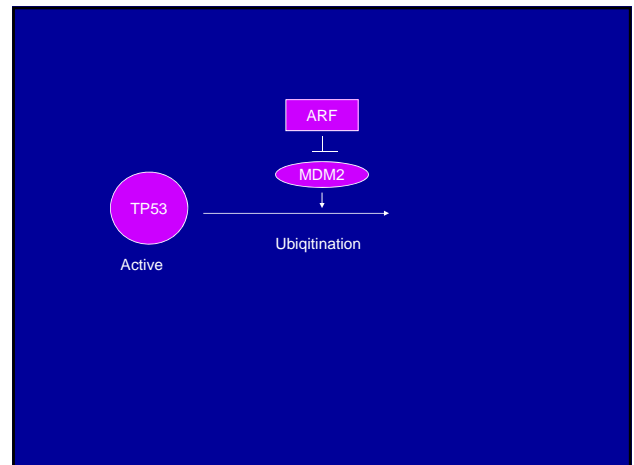
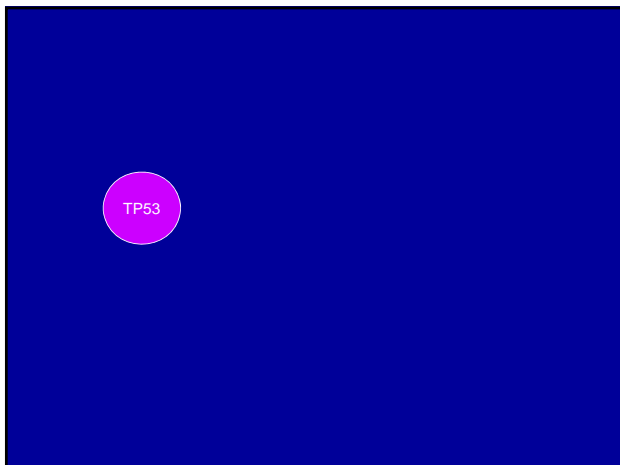
- Important in stem cell development
- Nearly all colon cancers have mutations inactivating components of pathway
- Tumor caused by loss of inhibitor effect
- Implicated in tumor invasion

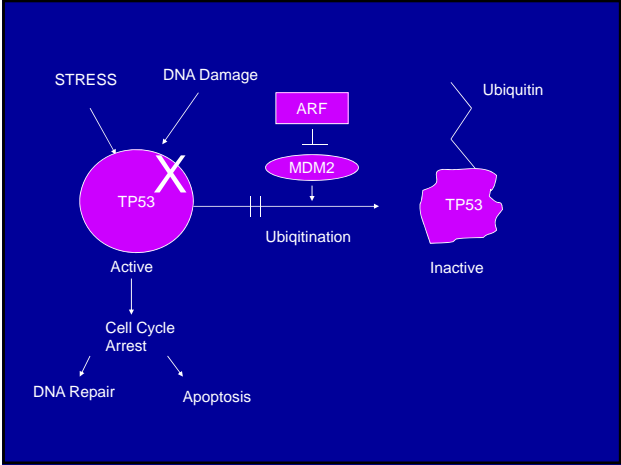
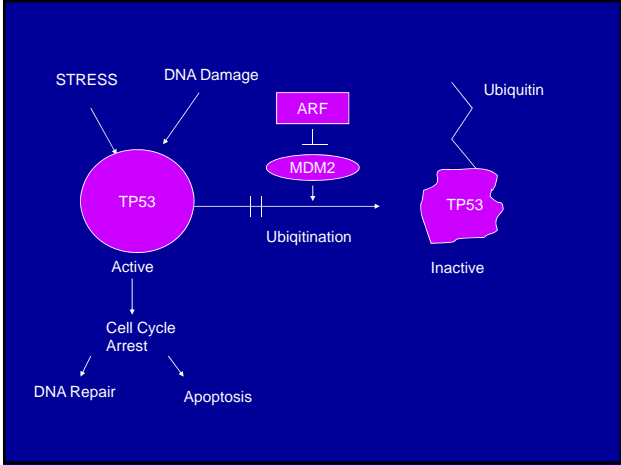
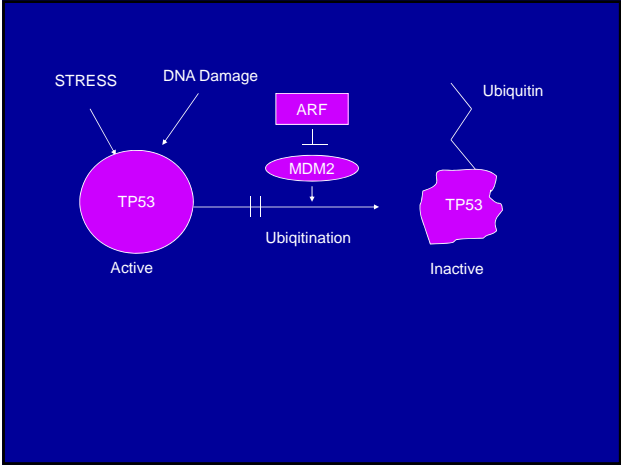
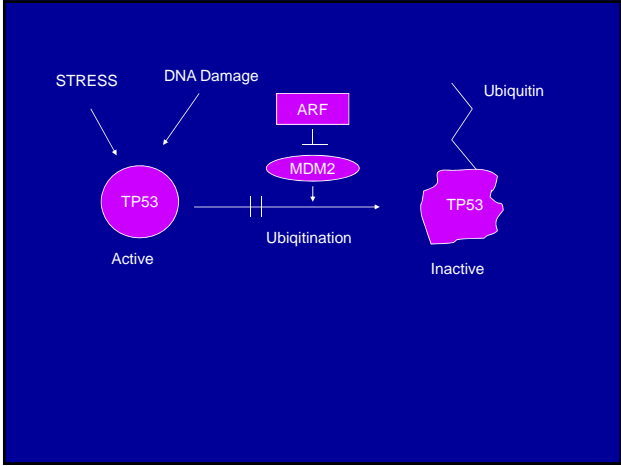
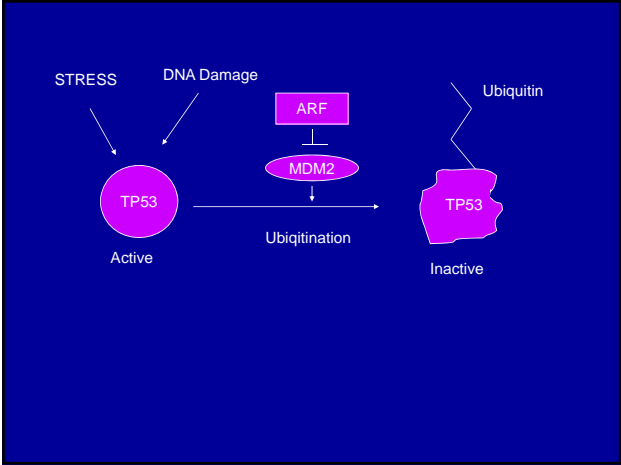
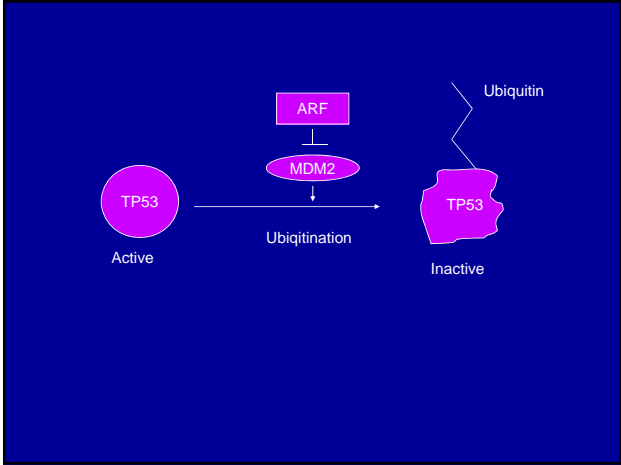






- ### TP53
- Tumor suppressor gene
 - Transition for late adenoma to cancer
 - Most common allelic loss in CRC
 - Anticancer effects-G1 cell cycle arrest, apoptosis

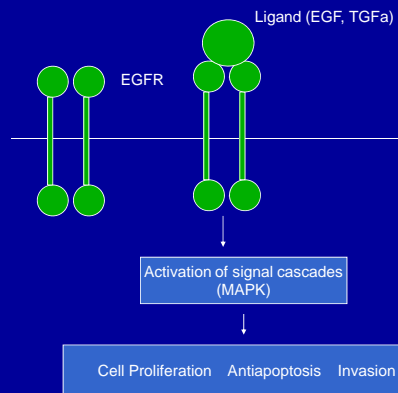
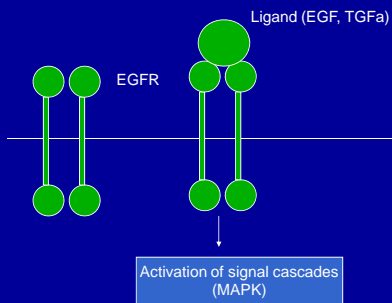
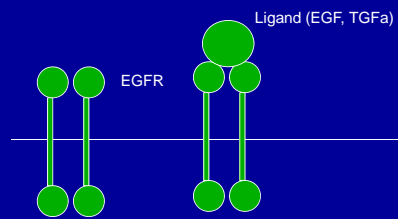
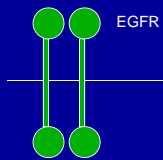


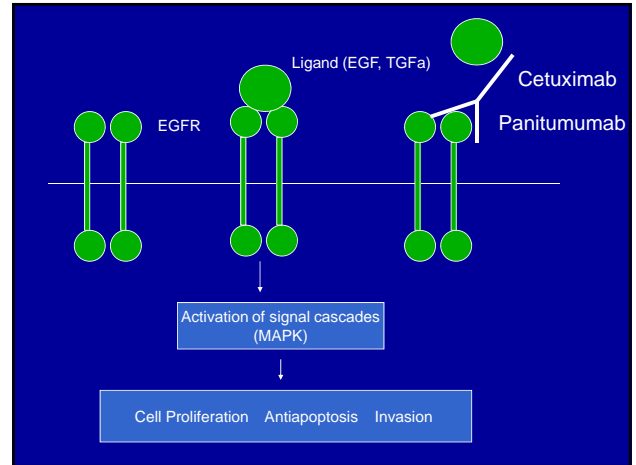
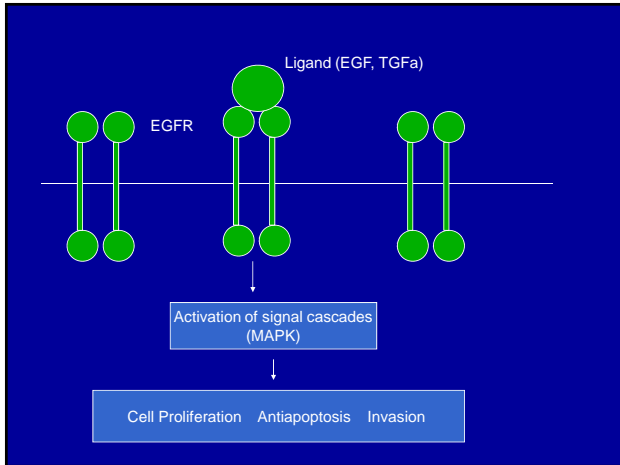


Growth Factors

Epidermal Growth Factor Receptor

- HER family of receptors
- Cell surface receptor
- Activated by ligand binding
- Receptor stimulates tyrosine kinase
 - Cell proliferation, angiogenesis, antiapoptotic
- Expressed in 60 – 80% of CRC

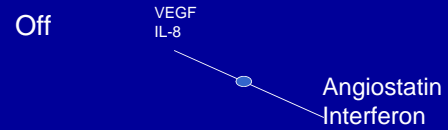




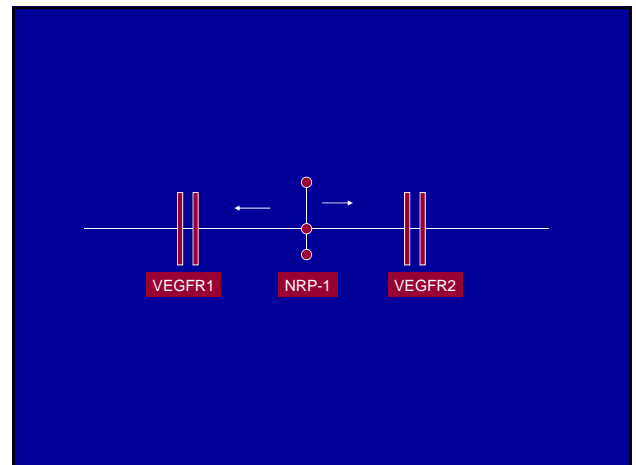
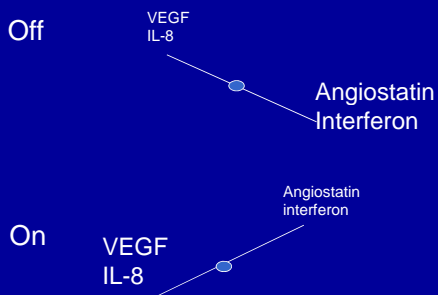
VEGF and Colorectal Cancer

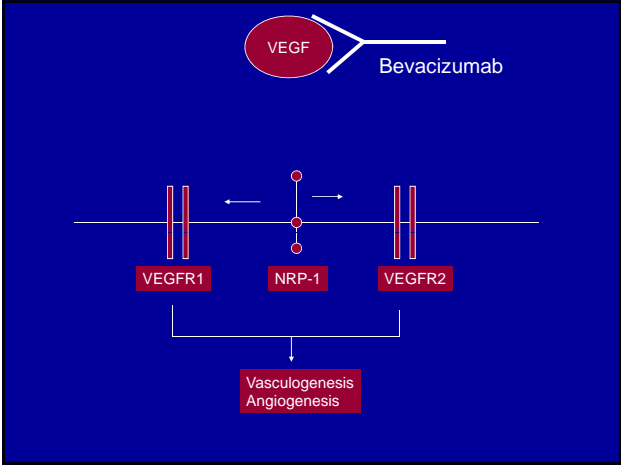
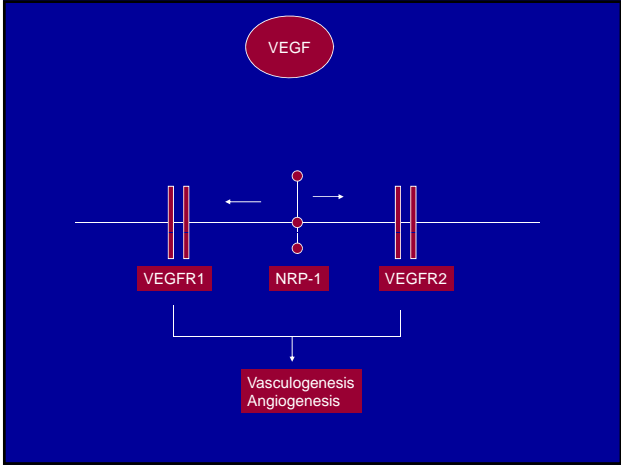
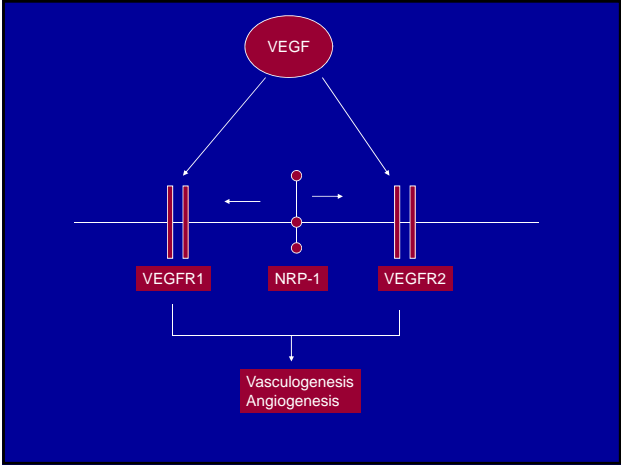
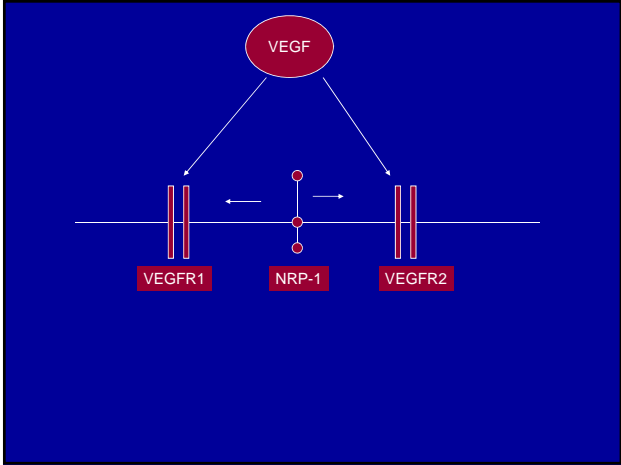
- VEGF associated with initiation and maintenance of angiogenesis
- Expressed from premalignant adenoma to metastatic cancer
- VEGF associated with poor outcomes, mets and patient survival

Angiogenic Switch



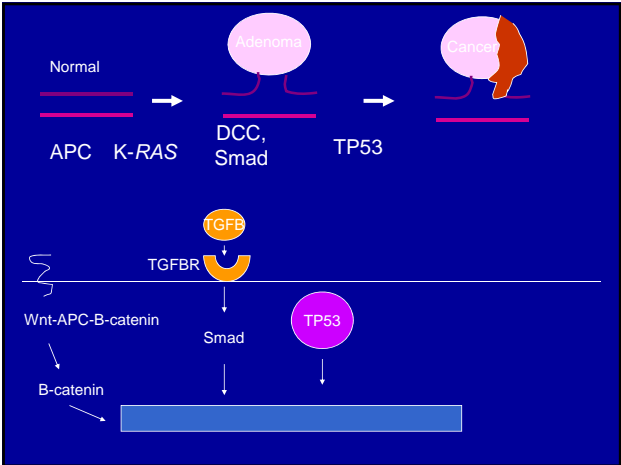
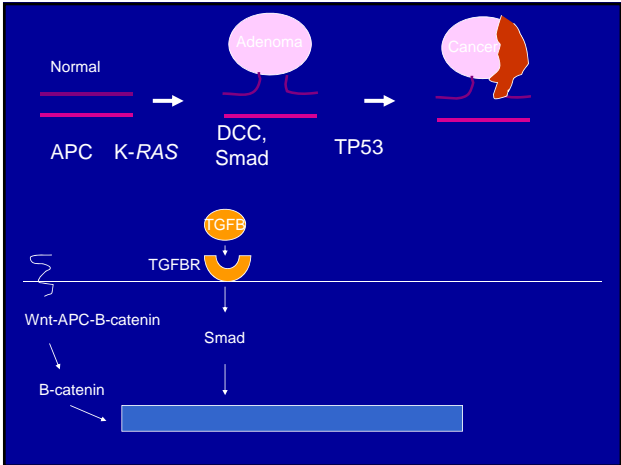
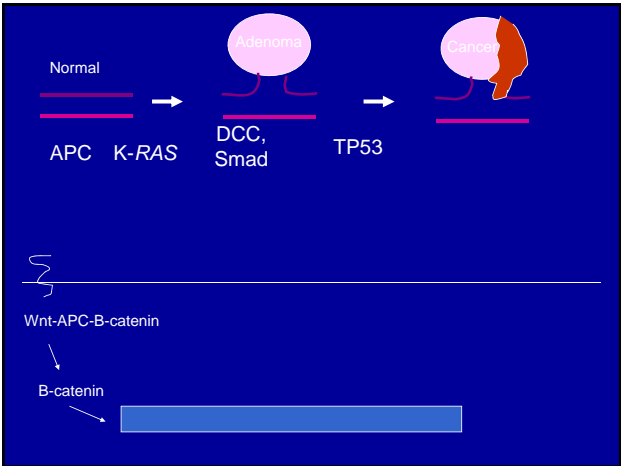
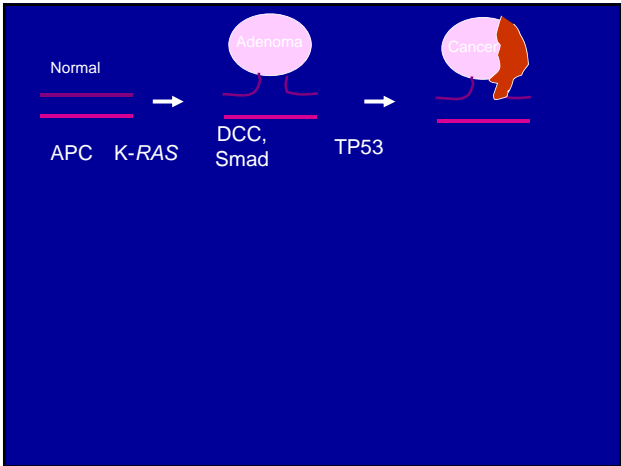
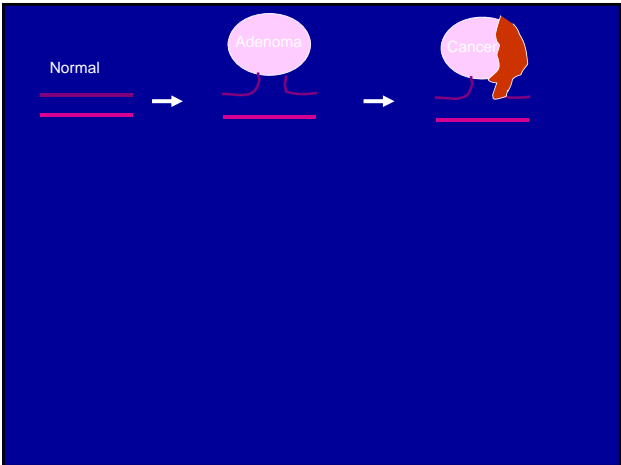
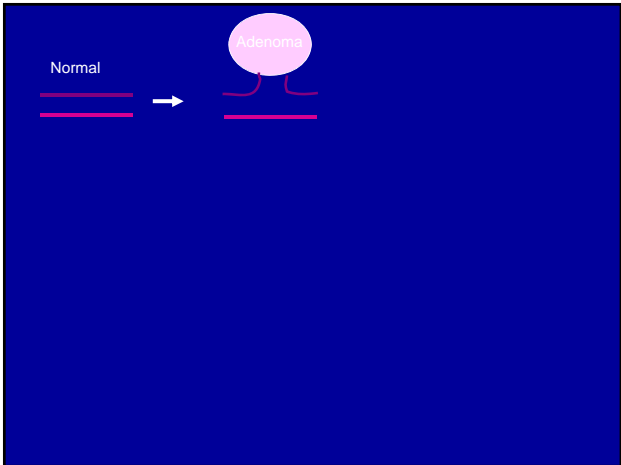
Angiogenic Switch

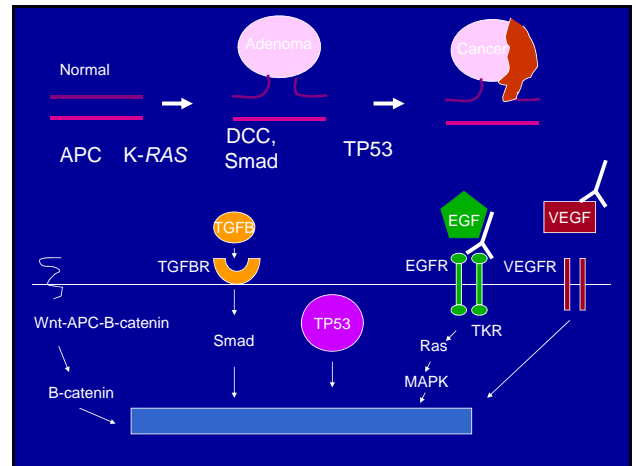
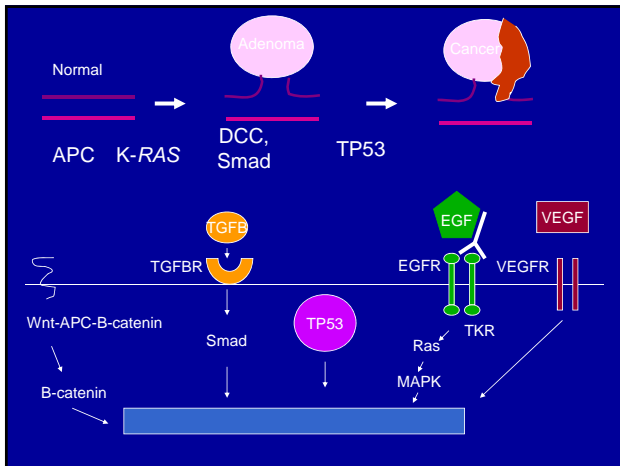
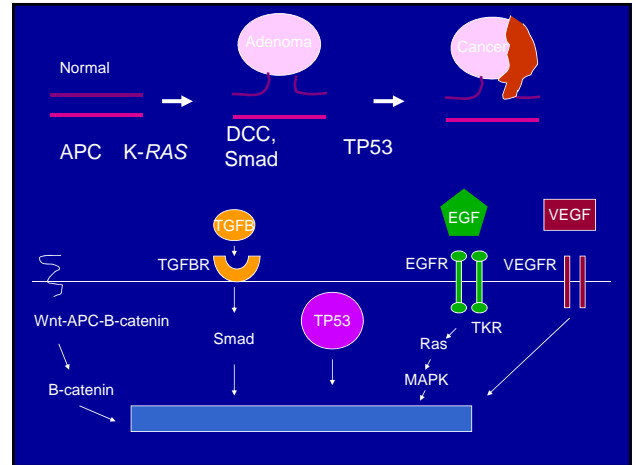
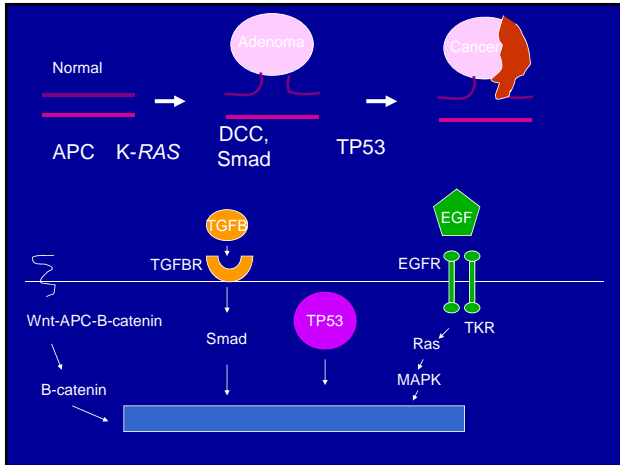




Summary

Normal

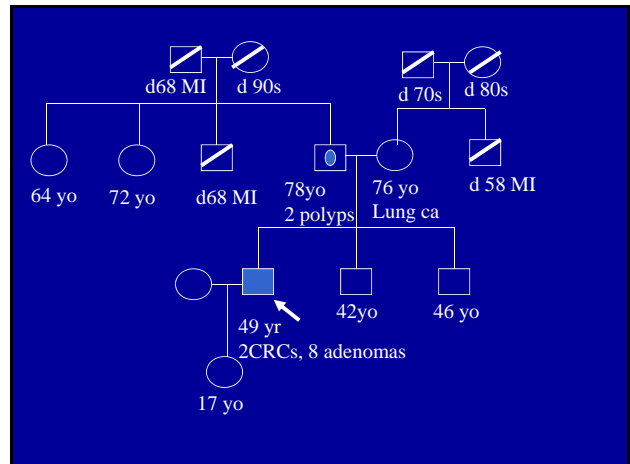
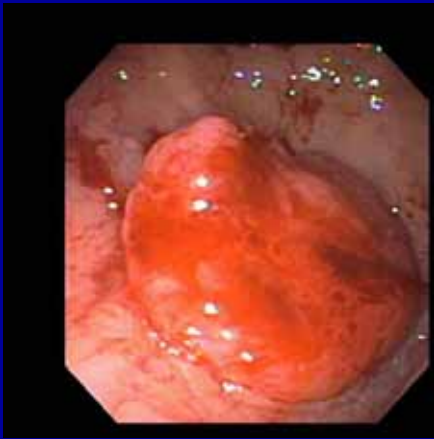




Case 1

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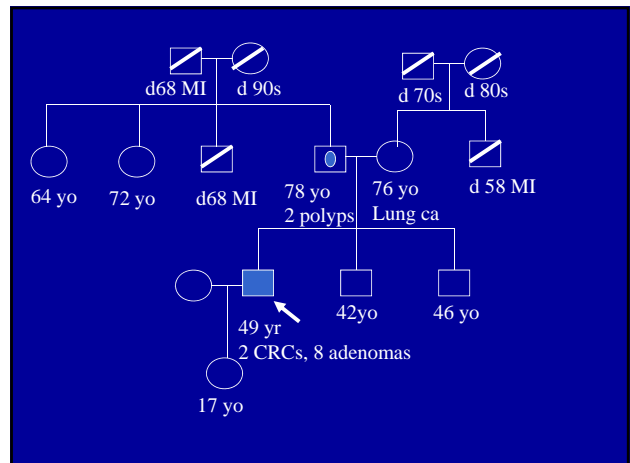
- 49 yo health white male
- 8 months of rectal bleeding
- PCP referred for colonoscopy



Question 1

All of the following are in the differential diagnosis of this family except?

- A. HNPCC
- B. Familial adenomatous polyposis
- C. Attenuated FAP
- D. MYH associated polyposis



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- D. MYH Associated Polyposis

Question 2

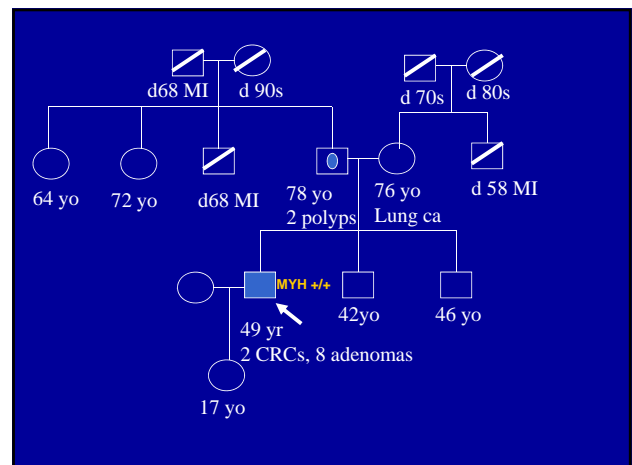
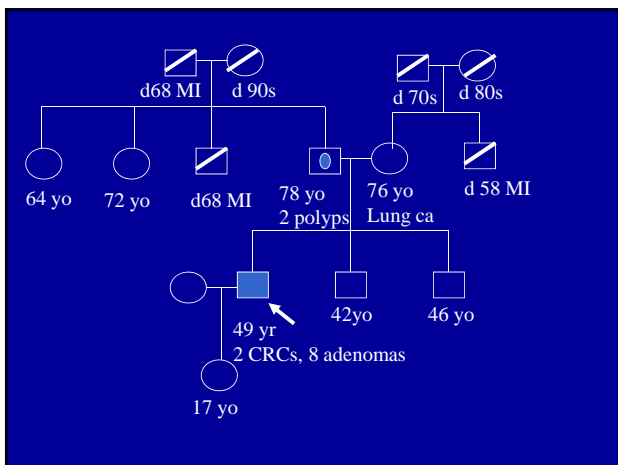
Which genetic testing would you order?

- A. MSI and IHC on rectal cancer
- B. MSH2 and MLH1 gene testing
- C. APC gene testing
- D. MYH gene testing
- E. APC and MYH gene testing

Question 2

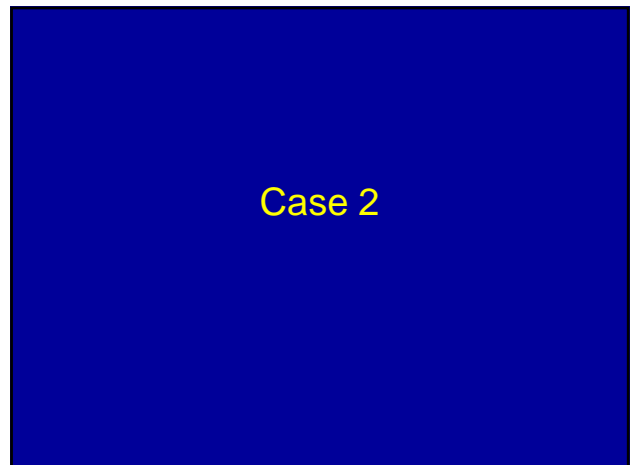
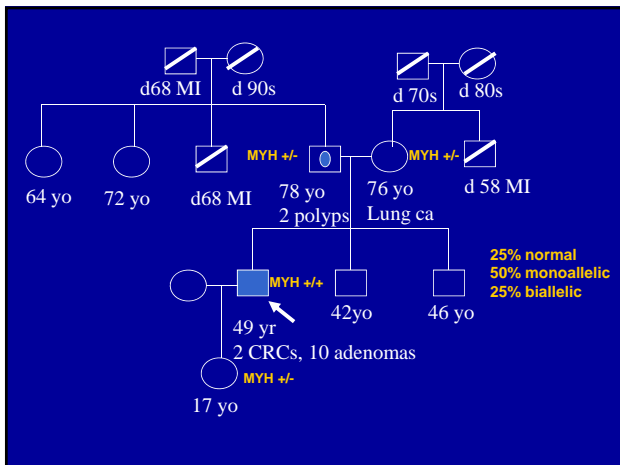
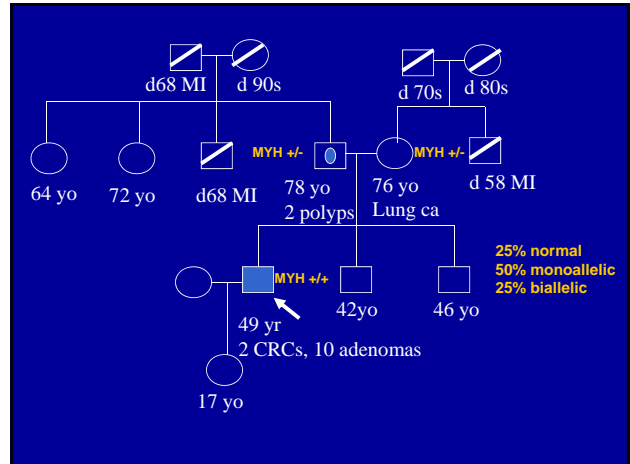
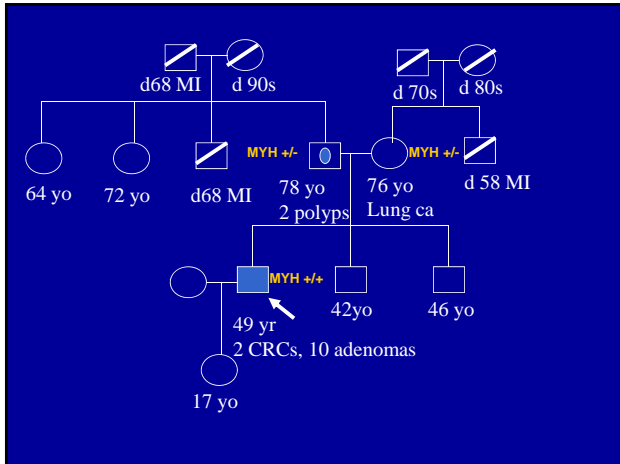
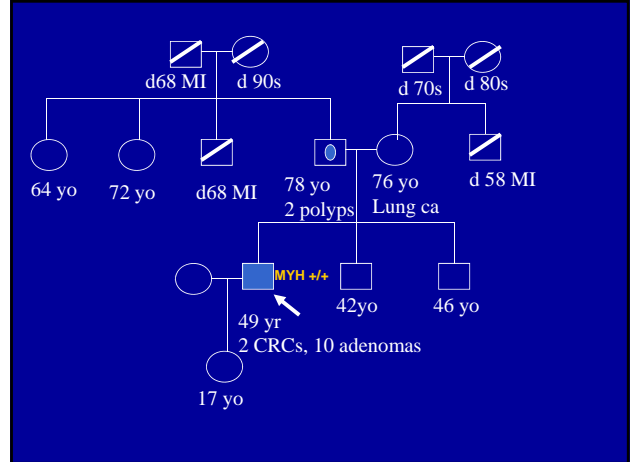
Which genetic testing would you order?

- A. MSI and IHC on rectal cancer
- B. MSH2 and MLH1 gene testing
- C. APC gene testing
- D. MYH gene testing
- E. APC and MYH gene testing



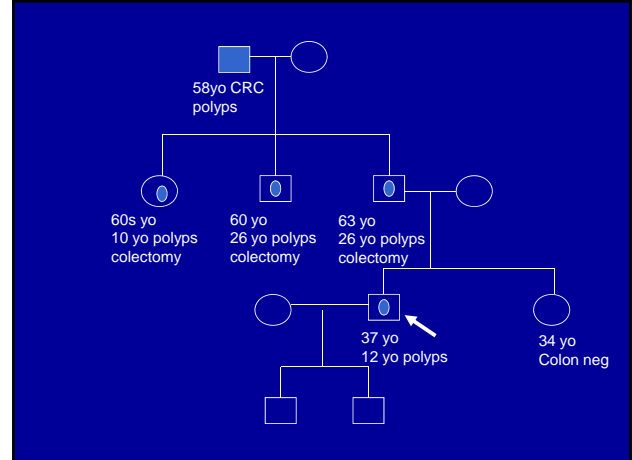
Question 3

- Based on the patient's gene test results what assumptions can be made about the risk status of the patient's first degree relatives?



Case 2

- 37 yo pt for gene testing for FAP
- Hematochezia age 12
- Multiple polyps -report adenoma/hyper
- 22 yo- colectomy ileorectal anastomosis
- 35 yo- polyps in gastric antrum
 - Bxs report acute and chronic inflammation
- 36 yo- rectal polyps- acute/chronic inflam.



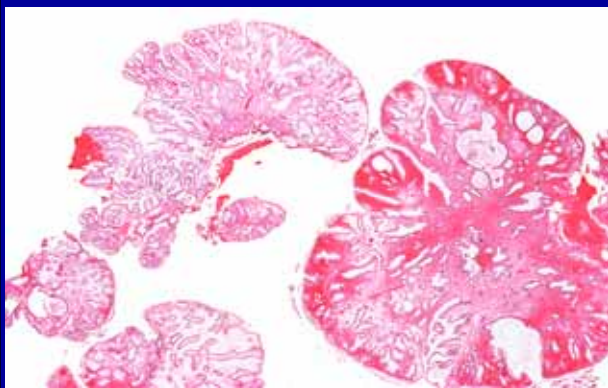
Question 1

What additional information do you need before proceeding with genetic testing?

Question 1

What additional information do you need before proceeding with genetic testing?

Answer: **Histology of polyps**



Question 2

The diagnosis in this family is?

- a. Hereditary nonpolyposis colorectal ca
- b. Familial adenomatous polyposis
- c. MYH associated polyposis
- d. Juvenile polyposis
- e. Peutz-Jeghers syndrome

Question 2

The diagnosis in this family is?

- a. Hereditary nonpolyposis colorectal ca
- b. Familial adenomatous polyposis
- c. MYH associated polyposis
- d. Juvenile polyposis
- e. Peutz-Jeghers syndrome

Question 3

What gene test would you select?

- a. MSH2 and MLH1
- b. APC and MYH
- c. HFE gene test
- d. STK 11 gene test
- e. SMAD4 and BMPR1A

Question 3

What gene test would you select?

- a. MSH2 and MLH1
- b. APC and MYH
- c. HFE gene test
- d. STK 11 gene test
- e. SMAD4 and BMPR1A

Question 4

The patient is at highest risk for what cancer?

- a. Colorectal
- b. Gastric
- c. Small bowel
- d. Pancreatic

Question 4

The patient is at highest risk for what cancer?

- a. Colorectal
- b. Gastric
- c. Small bowel
- d. Pancreatic

Cancers

Cancer	No.	Frequency (974)
Colon	115	12%
Gastric	11	1%
SB	12	1%
Panc.	4	0.4%

Colon Cancer Risk -PY Analysis

<u>Group</u>	<u>Relative Risk</u>	<u>CL</u>
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Colon Cancer Risk -PY Analysis

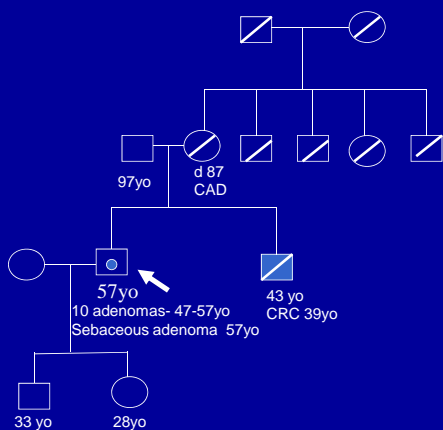
<u>Group</u>	<u>Relative Risk</u>	<u>CL</u>
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Males	36.3	13.0-77
Females	30.1	3.5-103
Combined	34.5	15.0-492

Absolute Risk

- Absolute risk CRC- 39.4% at 80 yrs
- Mean age of diagnosis 44 yo \pm 10
- No other GI tumors noted in cohort
- Metachronous cancer in rectum

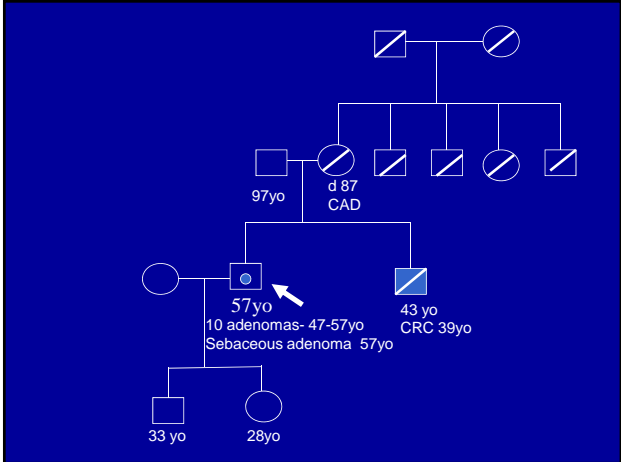
Case 3



Question 1

Which of the following is not in the differential diagnosis of this family?

- HNPCC
- Muir Torre syndrome
- Attenuated FAP
- Familial syndrome- unknown type



Question 1

Which of the following is not in the differential diagnosis of this family?

- A. HNPCC
- B. Muir Torre syndrome
- C. Attenuated FAP
- D. Familial syndrome- unknown type

Question 1

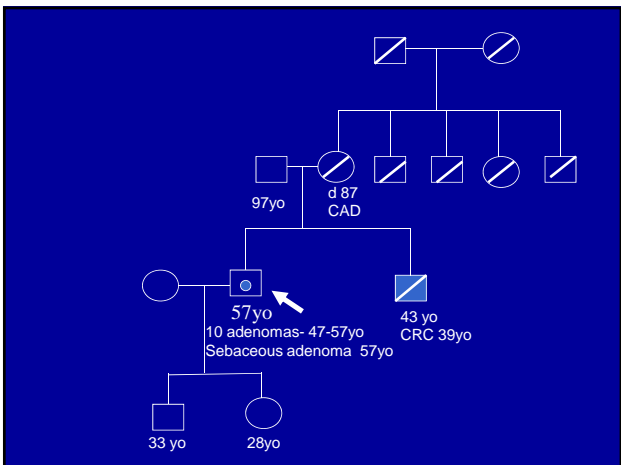
Which of the following is not in the differential diagnosis of this family?

- A. HNPCC
- B. Muir Torre syndrome
- C. **Attenuated FAP**
- D. Familial syndrome- unknown type

Question 2

What genetic testing would you do?

- A. MSI and IHC in the sebacious adenoma
- B. MLH1 and MSH2 gene testing
- C. APC gene testing
- D. MYH gene testing
- E. None



Question 2

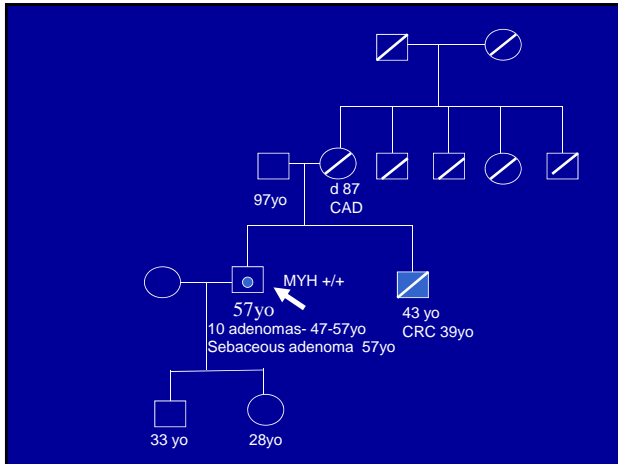
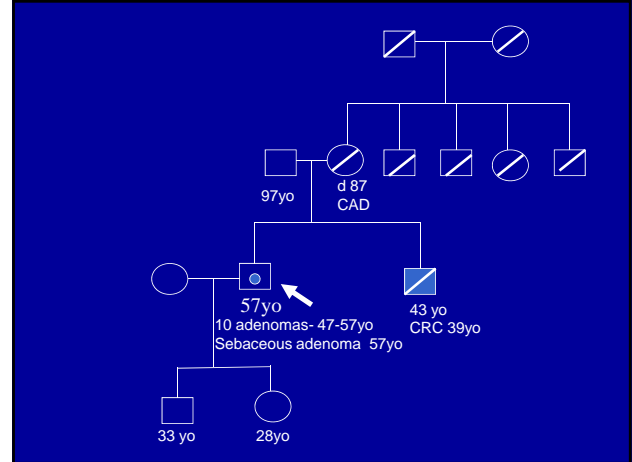
What genetic testing would you do?

- A. MSI and IHC in the sebacious adenoma
- B. MLH1 and MSH2 gene testing
- C. APC gene testing
- D. MYH gene testing
- E. None

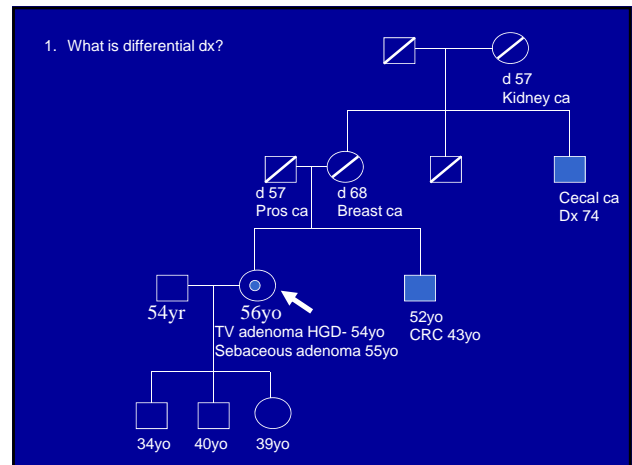
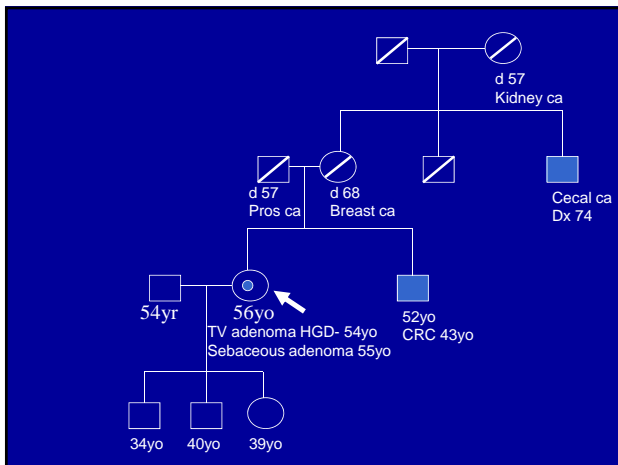
Question 2

What genetic testing would you do?

- A. MSI and IHC in the sebaceous adenoma
- B. MLH1 and MSH2 gene testing
- C. APC gene testing
- D. MYH gene testing
- E. None



CASE 4



1. What is differential dx?
HNPCC
Muir-Torre

56yo
TV adenoma HGD- 54yo
Sebaceous adenoma 55yo

54yr
34yo 40yo 39yo

d 57
Pros ca

d 68
Breast ca

d 57
Kidney ca

Cecal ca
Dx 74

52yo
CRC 43yo

1. What is differential dx?
HNPCC
Muir-Torre

2. What genetic testing?

56yo
TV adenoma HGD- 54yo
Sebaceous adenoma 55yo

54yr
34yo 40yo 39yo

d 57
Pros ca

d 68
Breast ca

d 57
Kidney ca

Cecal ca
Dx 74

52yo
CRC 43yo

1. What is differential dx?
HNPCC
Muir-Torre

2. What genetic testing?
MSH2, MLH1

56yo
TV adenoma HGD- 54yo
Sebaceous adenoma 55yo

54yr
34yo 40yo 39yo

d 57
Pros ca

d 68
Breast ca

d 57
Kidney ca

Cecal ca
Dx 74

52yo
CRC 43yo

1. What is differential dx?
HNPCC
Muir-Torre

2. What genetic testing?
MSH2, MLH1

56yo
TV adenoma HGD- 54yo
Sebaceous adenoma 55yo

54yr
34yo 40yo 39yo

d 57
Pros ca

d 68
Breast ca

d 57
Kidney ca

Cecal ca
Dx 74

52yo
CRC 43yo

MSH 2

1. What is differential dx?
HNPCC
Muir-Torre

2. What genetic testing?
MSH2, MLH1

3. What screen recommend?

56yo
TV adenoma HGD- 54yo
Sebaceous adenoma 55yo

54yr
34yo 40yo 39yo

d 57
Pros ca

d 68
Breast ca

d 57
Kidney ca

Cecal ca
Dx 74

52yo
CRC 43yo

MSH 2

1. What is differential dx?
HNPCC
Muir-Torre

2. What genetic testing?
MSH2, MLH1

3. What screen recommend?
colon, derm, Hx,pe, labs

56yo
TV adenoma HGD- 54yo
Sebaceous adenoma 55yo

54yr
34yo 40yo 39yo

d 57
Pros ca

d 68
Breast ca

d 57
Kidney ca

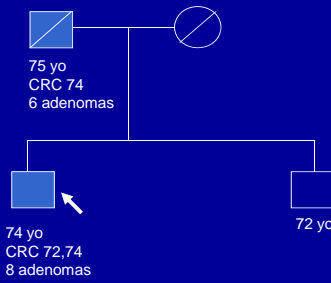
Cecal ca
Dx 74

52yo
CRC 43yo

MSH 2

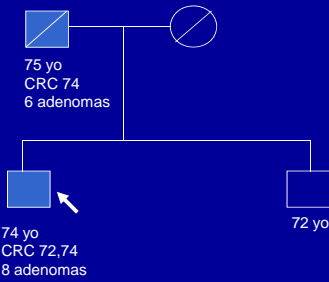
CASE 5

Family 14



Family 14

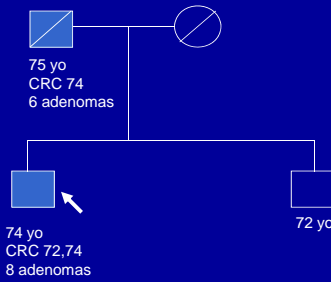
1 Differential Diagnosis?



Family 14

1 Differential Diagnosis?

- HNPCC
- AFAP
- MYH
- I1307K

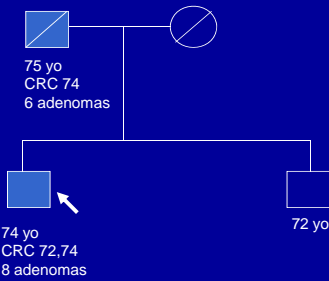


Family 14

1 Differential Diagnosis?

- HNPCC
- AFAP
- MYH
- I1307K

2 Genetic Testing?



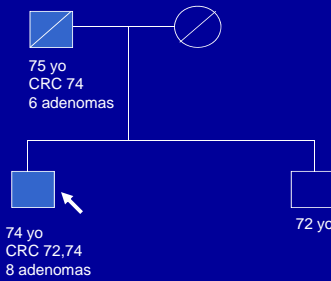
Family 14

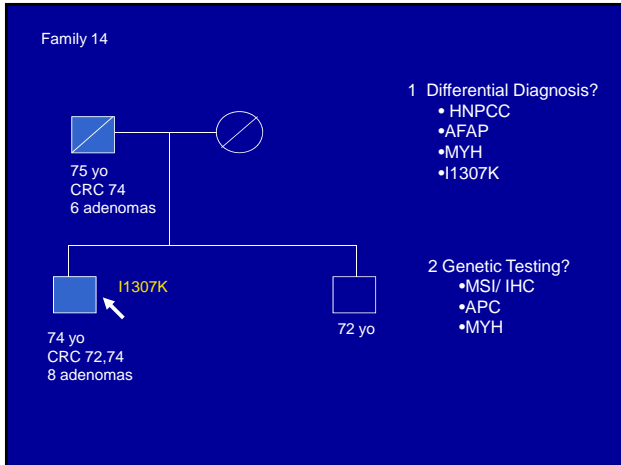
1 Differential Diagnosis?

- HNPCC
- AFAP
- MYH
- I1307K

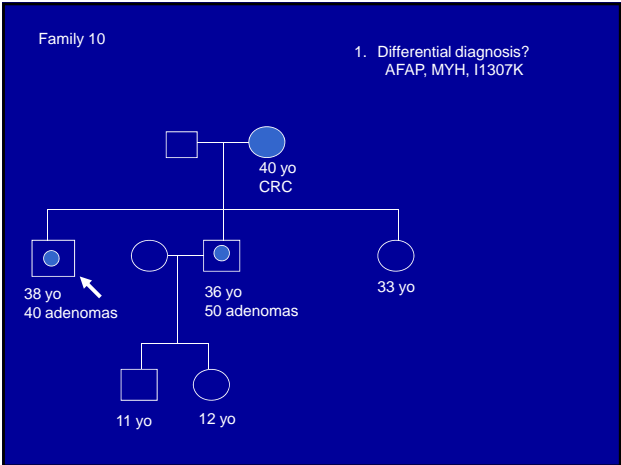
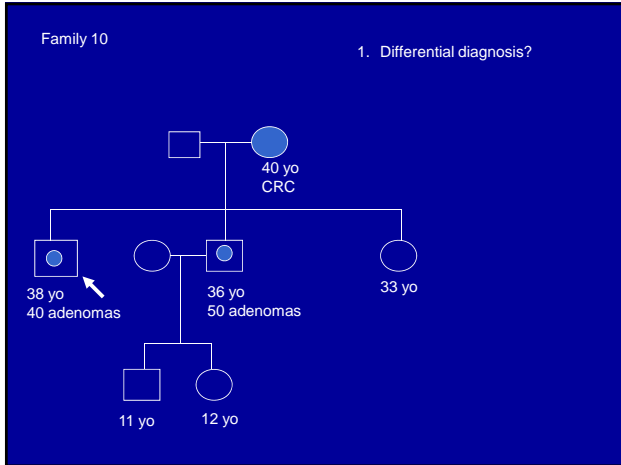
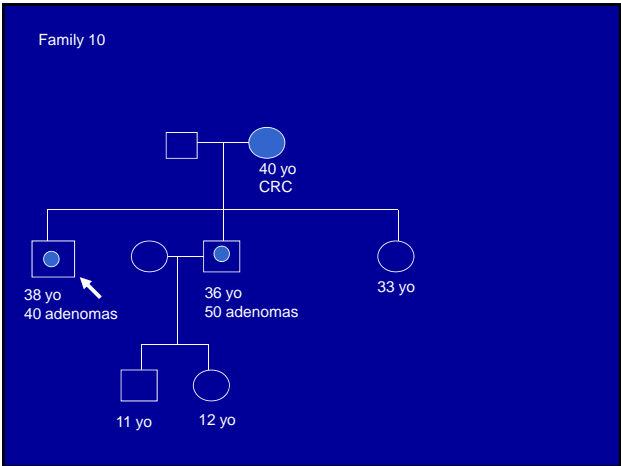
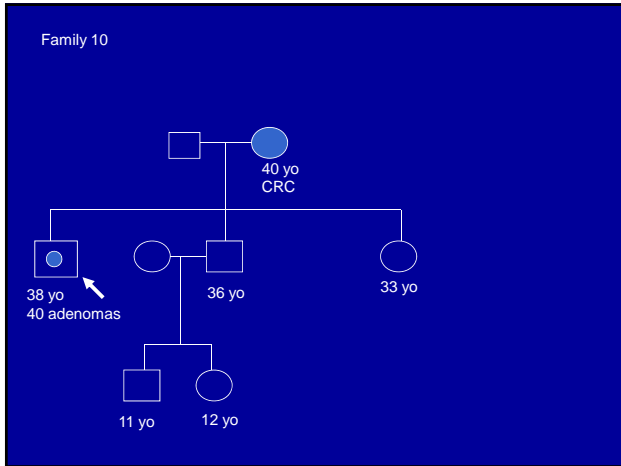
2 Genetic Testing?

- MSI/ IHC
- APC
- MYH





CASE 4



Family 10

1. Differential diagnosis?
AFAP, MYH, I1307K

2. Recommended treatment?

40 yo
CRC

38 yo
40 adenomas

36 yo
50 adenomas

11 yo

12 yo

33 yo

Family 10

1. Differential diagnosis?
AFAP, MYH, I1307K

2. Recommended treatment?
Colectomy

40 yo
CRC

38 yo
40 adenomas

36 yo
50 adenomas

11 yo

12 yo

33 yo

Family 10

1. Differential diagnosis?
AFAP, MYH, I1307K

2. Recommended treatment?
Colectomy

3. Recommended screening?

40 yo
CRC

38 yo
40 adenomas

36 yo
50 adenomas

11 yo

12 yo

33 yo

Family 10

1. Differential diagnosis?
AFAP, MYH, I1307K

2. Recommended treatment?
Colectomy

3. Recommended screening?
APC, MYH gene testing

40 yo
CRC

38 yo
40 adenomas

36 yo
50 adenomas

11 yo

12 yo

33 yo

Family 10

1. Differential diagnosis?
AFAP, MYH, I1307K

2. Recommended treatment?
Colectomy

3. Recommended screening?
APC, MYH gene testing

40 yo
CRC

38 yo
40 adenomas
APC+

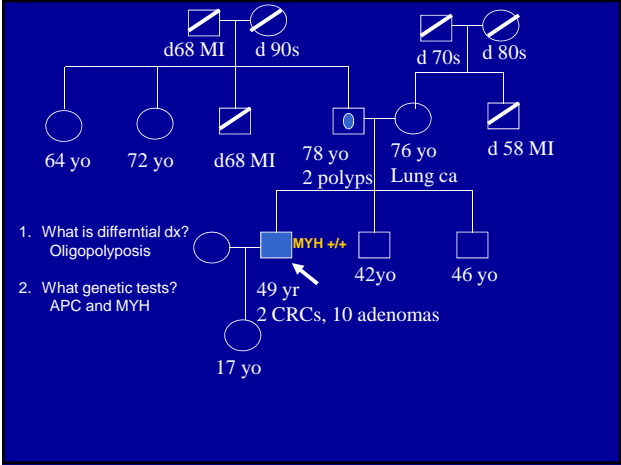
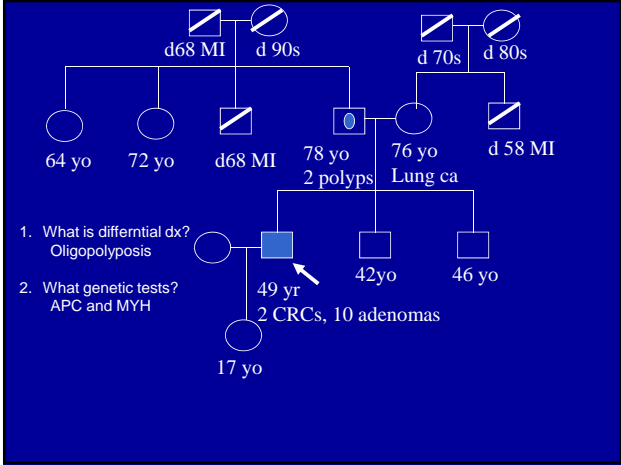
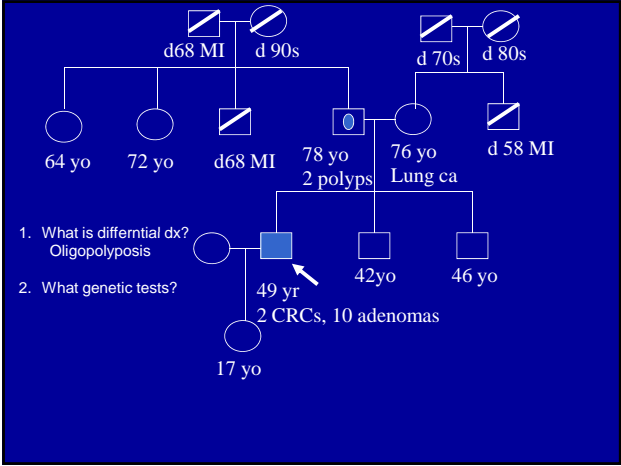
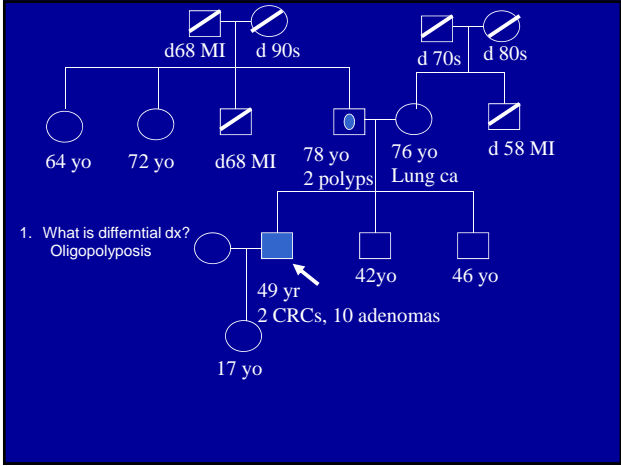
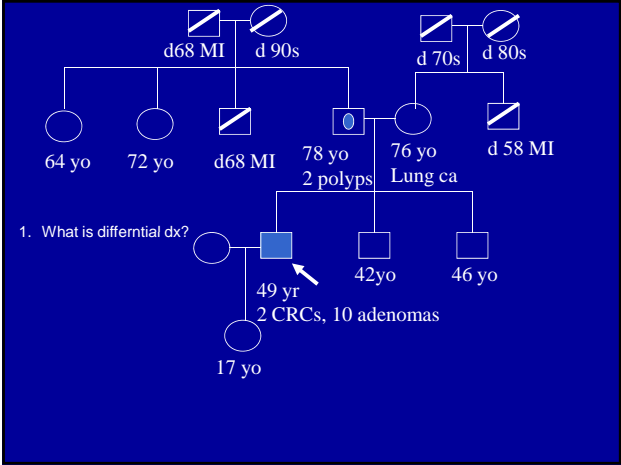
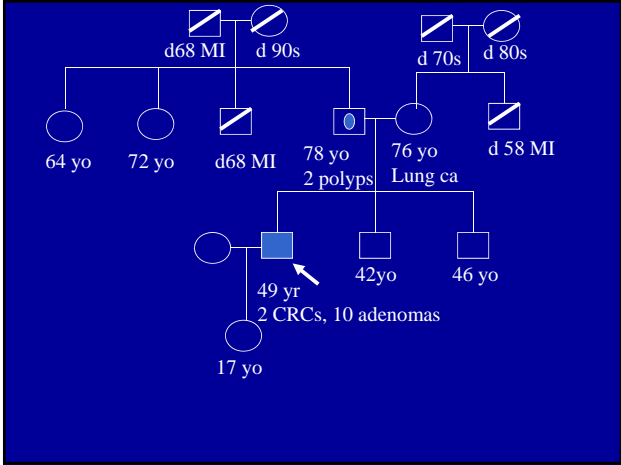
36 yo
50 adenomas
APC+

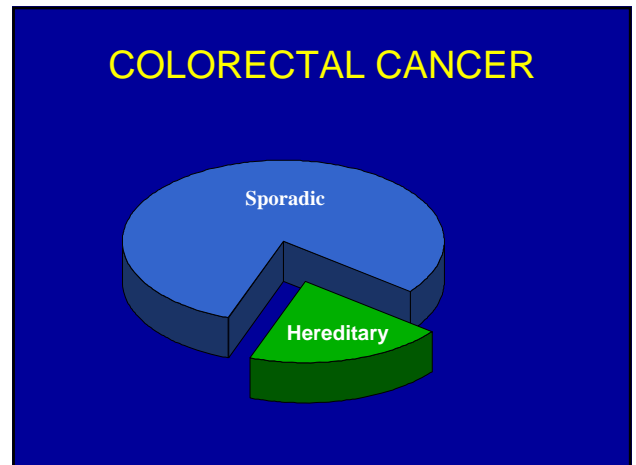
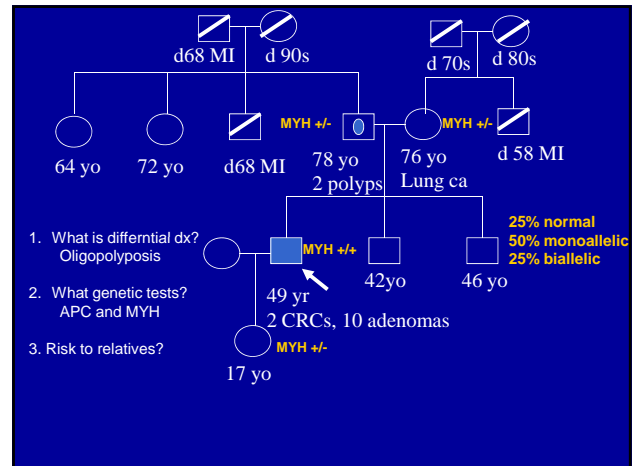
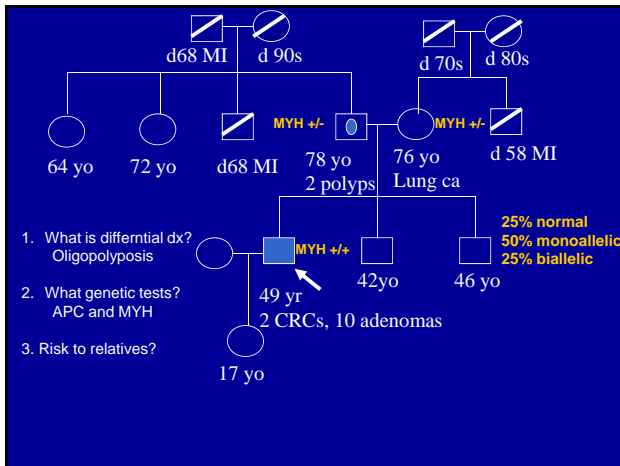
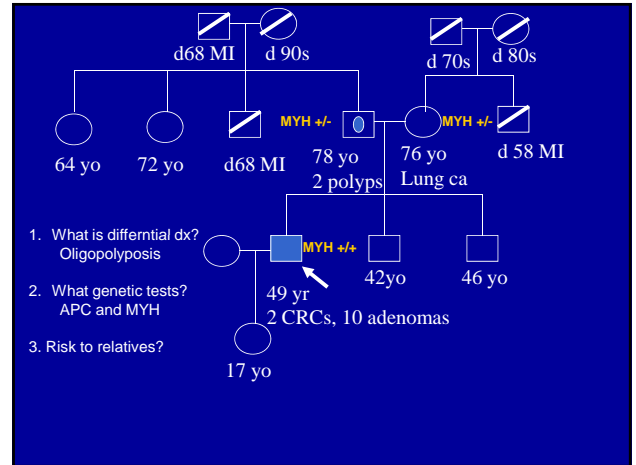
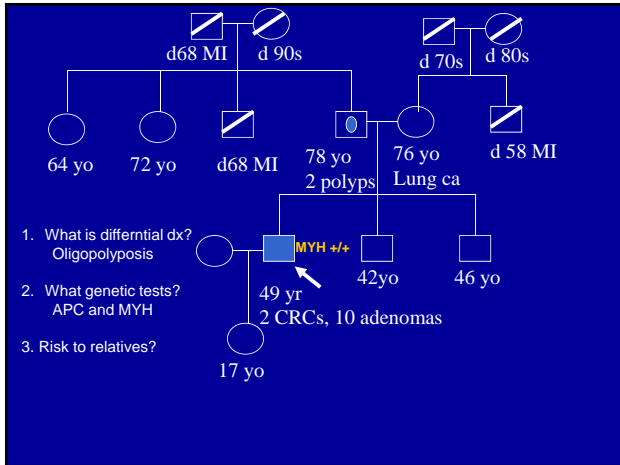
11 yo

12 yo

33 yo

CASE 1a





Cetuximab

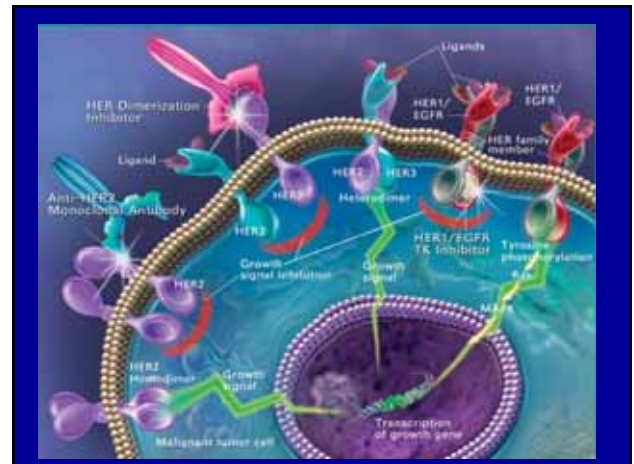
- Monoclonal antibody
- Binds to EGFR
- Blocks ligand binding
- Prevents receptor dimerization and induced phosphorylation
- Antiapoptotic or antiangiogenic

Sporadic Colorectal Cancer

- APC mutations in most sporadic CRC
- Occur early in tumorigenesis
 - crypts, small, large adenomas, cancer
- Most truncation mutations
- Inactivation of both alleles common

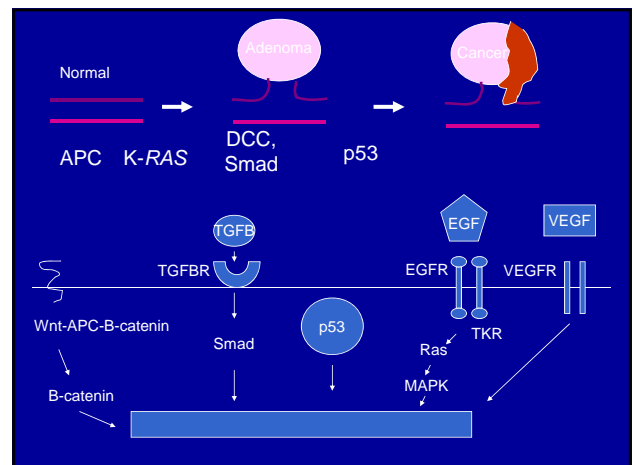
Mouse Model

- Min mouse model
- C57BL/6J mouse with ethylnitrosurea
- Nonsense mutation codon 850 mAPC
- 30-50 intestinal tumors at 90 days



DCC/MADH2/MADH4

- TGF-B pathway



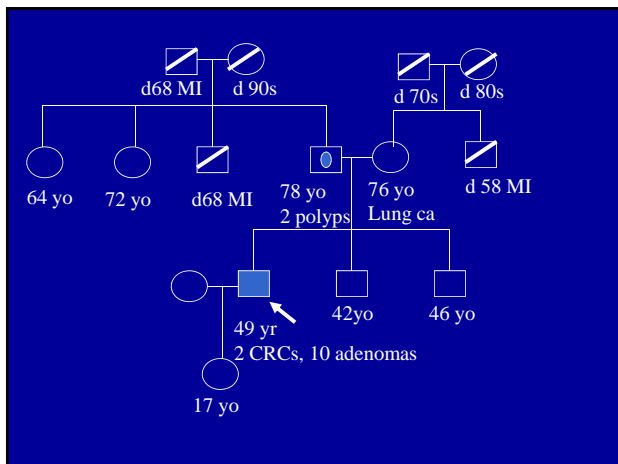
APC, B-Catenin, Wnt Signaling

- B-Catenin in nucleus activates transcription via TCF4/LEF complex

Question 3

Who would you test first?

- A. The patient
- B. The patient's father
- C. The patient's mother
- D. The patient's daughter



Question 3

Who would you test first?

- A. The patient
- B. The patient's father
- C. The patient's mother
- D. The patient's daughter

Question 3

Who would you test first?

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- B. The patient's father
- C. The patient's mother
- D. The patient's daughter



Colorectal Cancer

- Point mutations 76
 - Amplifications 4
 - Deletions 3
- total 83

