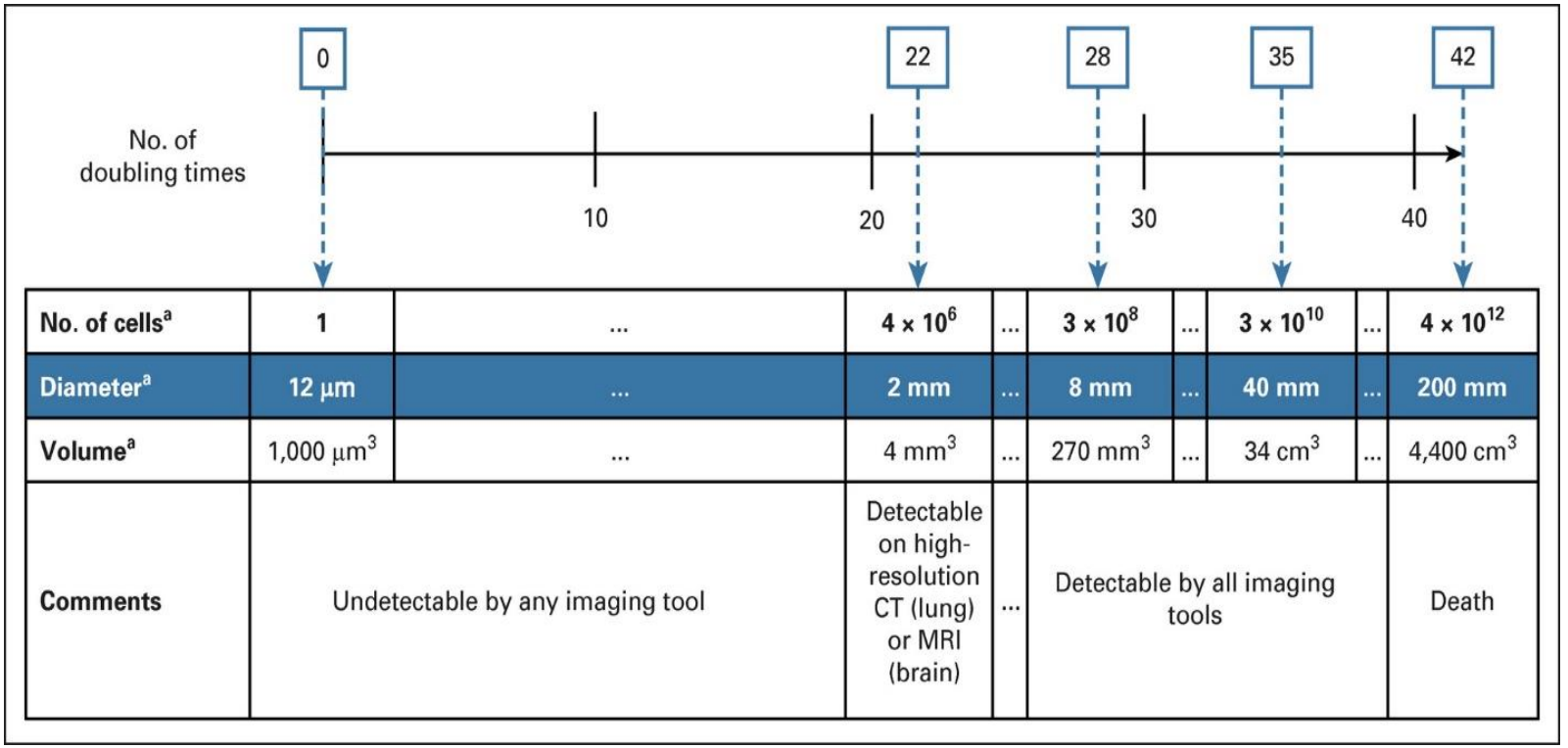
NEOPLASIA
CANCER EVOLUTION

Kenneth Alonso, MD, FACP



No. of cells[a]	1	...	4×10^6	...	3×10^8	...	3×10^{10}	...	4×10^{12}
Diameter[a]	12 μm	...	2 mm	...	8 mm	...	40 mm	...	200 mm
Volume[a]	1,000 μm^3	...	4 mm^3	...	270 mm^3	...	34 cm^3	...	4,400 cm^3
Comments	Undetectable by any imaging tool		Detectable on high-resolution CT (lung) or MRI (brain)	...	Detectable by all imaging tools				Death

https://ascopubs.org/doi/full/10.1200/JCO.21.00445?bid=86000281&cid=DM7933

Malignant transformation

- Steps to malignant transformation:
- Activation of RAS
- Inactivation of RB
- Inactivation of p53
- Inactivation of PP2A, a tumor suppressive phosphatase that is a negative regulator of many signaling pathways
- Constitutive expression of telomerase.

Colon cancer evolution

- Adenoma sequence
- APC gene (loss of 5q) encodes tumor suppressor gene that inhibits WNT function.
- Leads to hyperproliferation of colonic mucosal epithelium.
- KRAS activation (12p12) leads to dysplastic transformation
- SMAD4 lost on 18q21 (DCC, DPC4 genes).
- Loss of p53 (17p13) leads to adenocarcinoma
- Serrated adenoma sequence
- Critical step is loss of 8q (hMLH1, hMSH2 genes)
- With DNA hypermethylation, leads to adenoma formation

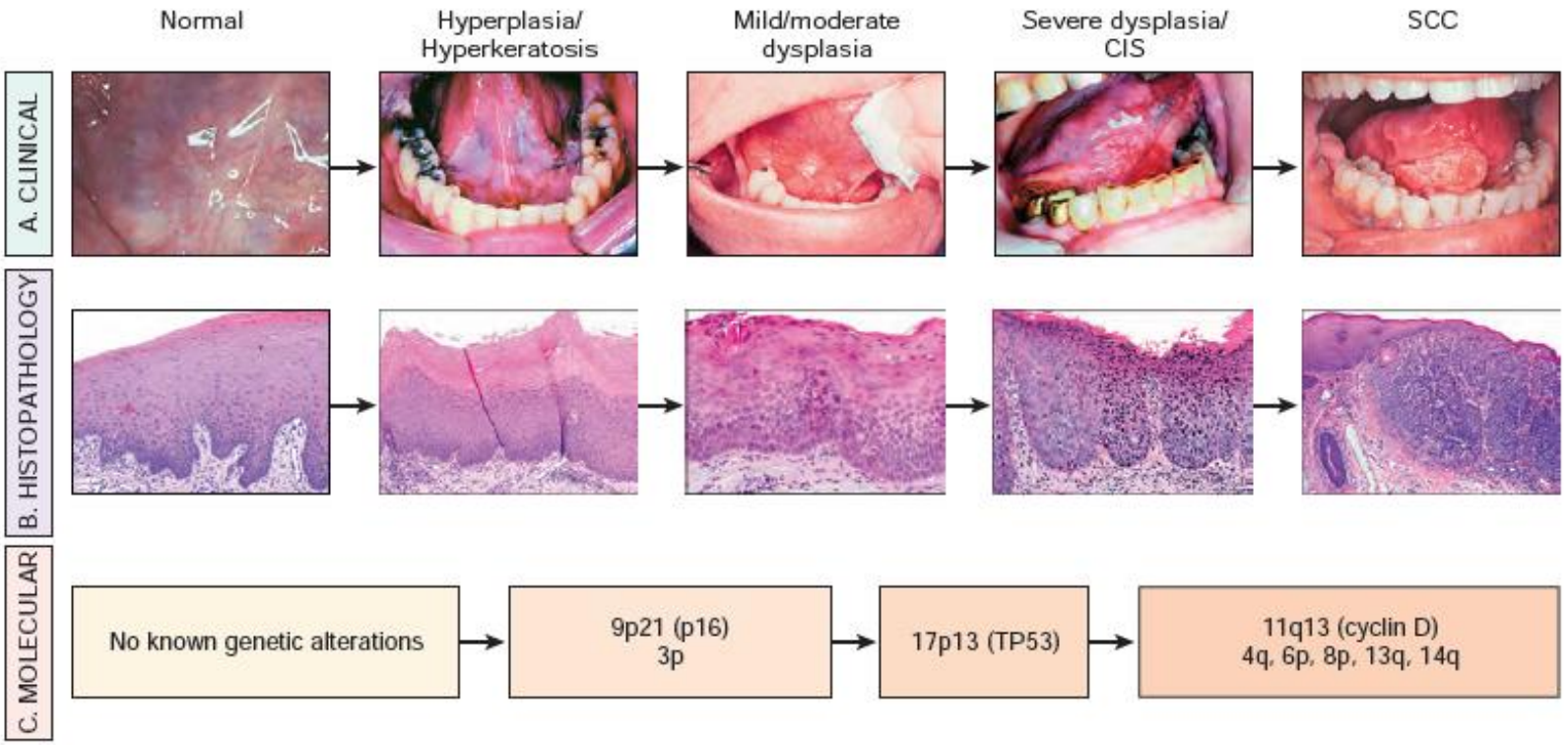


Figure 16-6 Clinical, histologic, and molecular progression of oral cancer. A, An idealized representation of the clinical progression of oral cancer. **B,** The histologic progression of squamous epithelium from normal, to hyperkeratosis, to mild/moderate dysplasia, to severe dysplasia, to cancer. **C,** The sites of the most common genetic alterations identified as important for cancer development. CIS, Carcinoma in situ; SCC, squamous cell carcinoma. (Clinical photographs courtesy of Sol Silverman, MD, from Silverman S: Oral Cancer. Hamilton, Ontario, Canada, BD Dekker, 2003.)

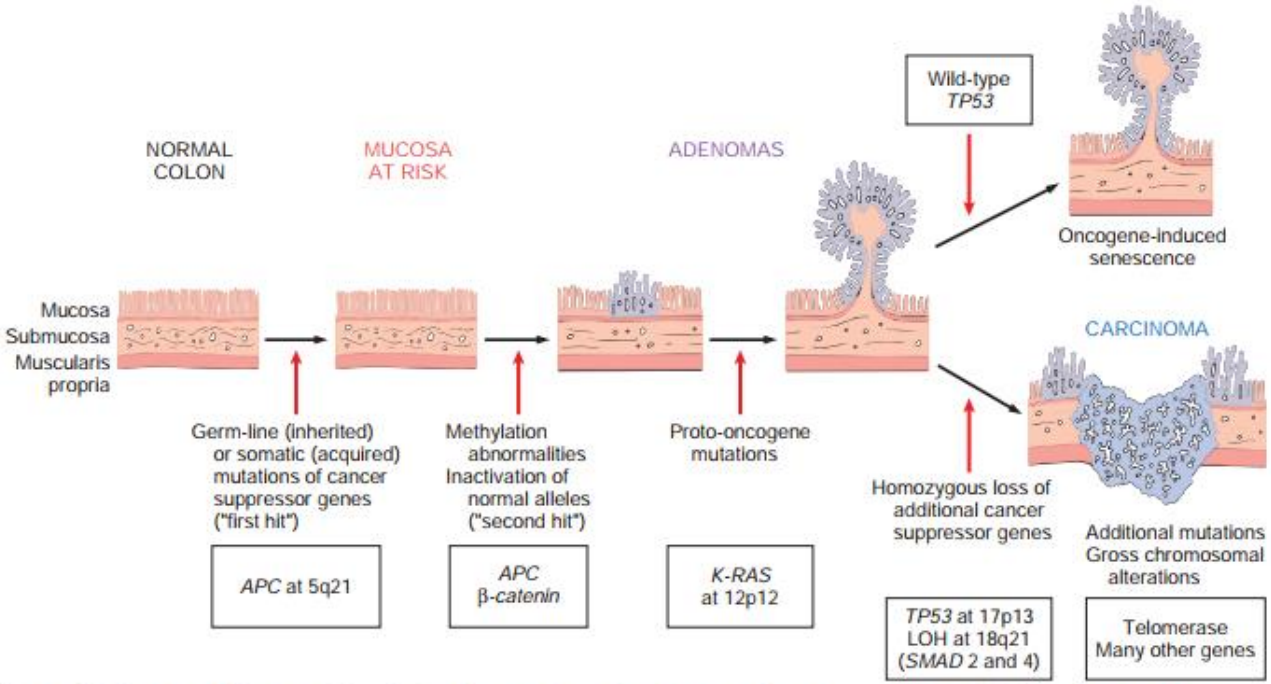


Figure 7-42 Molecular model for the evolution of colorectal cancers through the adenoma-carcinoma sequence. Although *APC* mutation is an early event and loss of *TP53* occurs late in the process of tumorigenesis, the timing for the other changes may be variable. Note also that individual tumors may not have all of the changes listed. *Top right*, cells that gain oncogene signaling without loss of *TP53* eventually enter oncogene-induced senescence. LOH, loss-of-heterozygosity.

Mis-match repair carcinogenesis

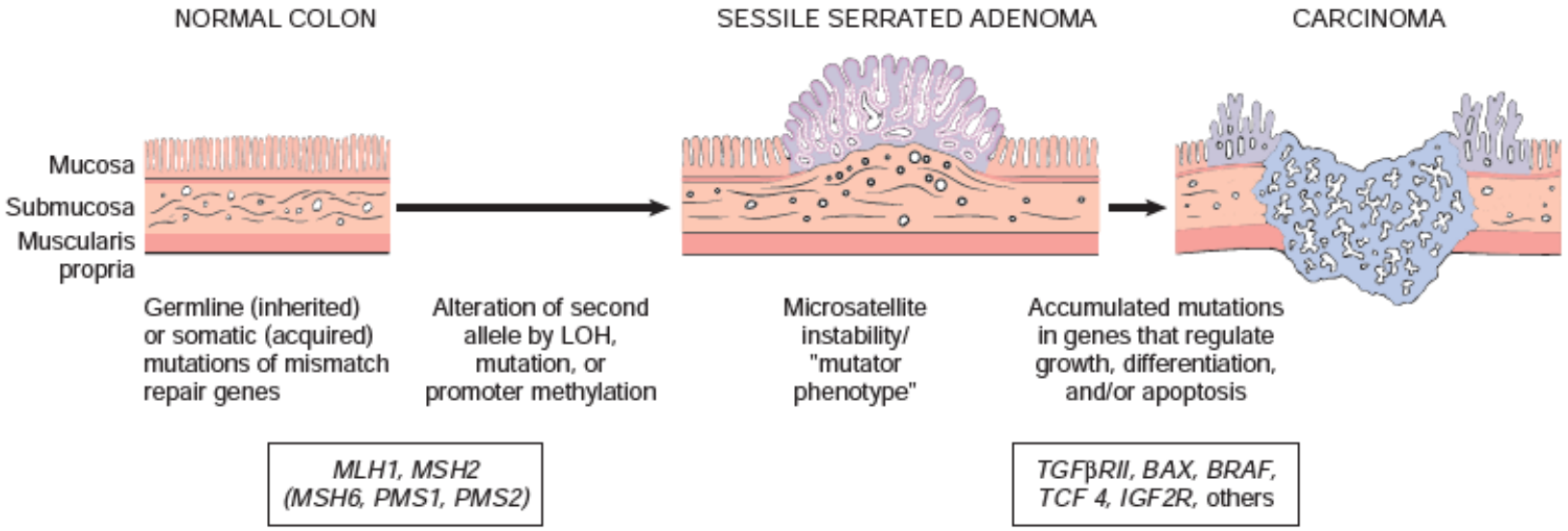


Figure 17-50 Morphologic and molecular changes in the mismatch repair pathway of colon carcinogenesis. Defects in mismatch repair genes result in microsatellite instability and permit accumulation of mutations in numerous genes. If these mutations affect genes involved in cell survival and proliferation, cancer may develop.

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES[j]

Tumor Testing[a]							Plausible Etiologies	Additional Testing[d,e]	NOTE: If younger than age 50 regardless of LS test results, consider genetic evaluation
IHC				MSI	*BRAF* V600E[b]	*MLH1* Promoter Methylation			
MLH1	*MSH2*	*MSH6*	*PMS2*						
NL	NL	NL	NL	MSS/~~Low~~	N/A	N/A	1) Sporadic cancer 2) Other (not LS hereditary CRC syndrome)	1) None[c]	
NL	NL	NL	NL	MSI-H	N/A	N/A	1) Sporadic cancer 2) Germline pathogenic variant in any of the LS genes	1) Germline MMR testing or paired germline MMR/somatic MMR tumor testing[f]; 2) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing[h]	
N/A	N/A	N/A	N/A	MSI-H	N/A	N/A	1) Sporadic cancer 2) Germline pathogenic variant in any of the LS genes	1) Consider IHC analysis and additional testing depending on IHC results 2) If IHC not performed, consider germline MMR testing or paired germline MMR/somatic MMR tumor testing 3) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing[h]	
AB	NL	NL	AB	N/A	N/A	N/A	1) Sporadic cancer 2) Germline *MLH1* pathogenic variant or rarely *PMS2*	1) *BRAF* pathogenic variant testing[b]/*MLH1* promoter methylation testing first 2) If *BRAF/MLH1* methylation testing normal, germline MMR testing or paired germline MMR/somatic MMR tumor testing[f]; 3) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing[h]	
AB	NL	NL	AB	N/A	Positive	N/A	1) Sporadic cancer 2) Rarely germline *MLH1* pathogenic variant or constitutional *MLH1* epimutation	1) None, unless young age of onset or significant family history; then consider constitutional *MLH1* epimutation testing[g] and/or germline MMR testing[f]	
AB	NL	NL	AB	N/A	Negative	Positive	1) Sporadic cancer 2) Rarely germline *MLH1* pathogenic variant or constitutional *MLH1* epimutation		

N/A = Either testing was not done or results may not influence testing strategy; NL = Normal presence of positive protein staining; AB-= Abnormal/Absence (negative) protein staining

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES[j]

Tumor Testing[a]							Plausible Etiologies	Additional Testing[d,e] NOTE: If younger than age 50 regardless of LS test results, consider genetic evaluation
IHC				MSI	*BRAF* V600E[b]	*MLH1* Promoter Methylation		
MLH1	*MSH2*	*MSH6*	*PMS2*					
AB	NL	NL	AB	N/A	Negative	Negative	1) Germline *MLH1* pathogenic variant or rarely *PMS2* 2) Sporadic cancer	1) Germline MMR testing or paired germline MMR/somatic MMR tumor testing[f]; 2) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing[h]
NL	AB	AB	NL	N/A	N/A	N/A	1) Germline *MSH2/EPCAM* pathogenic variant; or rarely germline *MSH6* pathogenic variant 2) Sporadic cancer	
NL	NL	NL	AB	N/A	N/A	N/A	1) Germline *PMS2* pathogenic variant 2) Germline *MLH1* pathogenic variant 3) Sporadic cancer	
NL	AB	NL	NL	N/A	N/A	N/A	1) Germline *MSH2/EPCAM* pathogenic variant 2) Sporadic cancer	
NL	NL	AB	NL	N/A	N/A	N/A	1) Germline *MSH6* pathogenic variant 2) Germline *MSH2* pathogenic variant 3) Sporadic cancer/Treatment effect[i]	1) Germline MMR testing or paired germline MMR/somatic MMR tumor testing[f]; 2) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing[h] 3) If applicable, consider MSI analysis or repeat IHC testing on nontreated tumor[i]
AB	NL	NL	NL	N/A	N/A	N/A	1) Sporadic cancer; 2) Germline *MLH1* pathogenic variant; 3) Germline *PMS2* pathogenic variant; 4) Somatic *MLH1* or *PMS2* pathogenic variant	1) *BRAF* pathogenic variant testing[b]/*MLH1* promoter methylation; 2) If *BRAF/MLH1* methylation testing normal, germline MMR testing or paired germline MMR/somatic MMR tumor testing[f]; 3) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing[h]
AB	AB	AB	AB	N/A	N/A	N/A	1) Germline pathogenic variant in *any* LS gene 2) Sporadic cancer	1) BRAF pathogenic variant testing[b]/*MLH1* promoter methylation AND Germline MMR testing or paired germline MMR/somatic MMR tumor testing (which often include *MLH1* methylation testing)[f]; 2) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing[h]

N/A = Either testing was not done or results may not influence testing strategy; NL = Normal presence of positive protein staining; AB = Abnormal/Absence (negative) protein staining

***MLH1* LYNCH SYNDROME: CANCER RISKS[a]**

Site	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y[b]	Cumulative Risk for Diagnosis Through Lifetime for General Population[c]
Colorectal	44 years	46%–61%	4.2%
Endometrial	49 years	34%–54%	3.1%
Ovarian	46 years	4%–20%	1.3%
Renal pelvis and/or ureter	59–60 years	0.2%–5%	--[d]
Bladder	59 years	2%–7%	2.4%
Gastric	52 years	5%–7%	0.9%
Small bowel	47 years	0.4%–11%	0.3%
Pancreas	No data	6.2%	1.6%
Biliary tract	50 years	1.9%–3.7%	0.2%
Prostate	63 years	4.4%–11.6%	11.6%
Breast (female)	No data	10.6%–18.6%	12.8%
Brain	No data	0.7%–1.7%	0.6%

***MSH2* AND *EPCAM* LYNCH SYNDROME: CANCER RISKS[a]**

Site	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y[b]	Cumulative Risk for Diagnosis Through Lifetime for General Population[c]
Colorectal	44 years	33%–52%	4.2%
Endometrial	47–48 years	21%–57%	3.1%
Ovarian	43 years	8%–38%	1.3%
Renal pelvis and/or ureter	54–61 years	2.2%–28%	--[d]
Bladder	59 years	4.4%–12.8%	2.4%
Gastric	52 years	0.2%–9.0%	0.9%
Small bowel	48 years	1.1%–10%	0.3%
Pancreas	No data	0.5%–1.6%	1.6%
Biliary tract	57 years	0.02%–1.7%	0.2%
Prostate	59–63 years	3.9%–15.9%	11.6%
Breast (female)	No data	1.5%–12.8%	12.8%
Brain	No data	2.5–7.7%	0.6%

***MSH6* LYNCH SYNDROME: CANCER RISKS[a]**

Site	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y[b,e]	Cumulative Risk for Diagnosis Through Lifetime for General Population[c]
Colorectal	42–69 years	10%–44%	4.2%
Endometrial	53–55 years	16%–49%	3.1%
Ovarian	46 years	≤1%–13%	1.3%
Renal pelvis and/or ureter	65–69 years	0.7%–5.5%	--[d]
Bladder	71 years	1.0%–8.2%	2.4%
Gastric	2 cases reported at age 45 and 81	≤1%–7.9%	0.9%
Small bowel	54 years	≤1%–4%	0.3%
Pancreas	No data	1.4%–1.6%	1.6%
Biliary tract	No data	0.2%–≤1%	0.2%
Prostate	63 years	2.5%–11.6%	11.6%
Breast (female)	No data	11.1%–12.8%	12.8%
Brain	43–54 years	0.8%–1.8%	0.6%

***PMS2* LYNCH SYNDROME: CANCER RISKS[a]**

Site	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y[b,e]	Cumulative Risk for Diagnosis Through Lifetime for General Population[c]
Colorectal	61–66 years	8.7%–20%	4.2%
Endometrial	49–50 years	13%–26%	3.1%
Ovarian	51–59 years	3%	1.3%
Renal pelvis and/or ureter	No data	≤1%–3.7%	--[d]
Bladder	71 years	≤1%–2.4%	2.4%
Gastric	Inadequate data	Inadequate data	0.9%
Small bowel	Single case - 59 years	0.1%–0.3%	0.3%
Pancreas	No data	≤1%–1.6%	1.6%
Biliary tract	No data	0.2%– ≤1%	0.2%
Prostate	No data	4.6%–11.6%	11.6%
Breast (female)	No data	8.1%–12.8%	12.8%
Brain	40 years	0.6%–≤1%	0.6%

Peutz-Jehgers

Site	% Lifetime Risk[d]
Breast (women)	32%–54%
Colon	39%
Stomach	29%
Small intestine	13%
Pancreas	11%–36%
Ovary (typically benign sex cord/Sertoli cell tumors)	18%–21%
Cervix (typically cervical adenoma malignum)	10%
Uterus	9%
Testes (typically sex cord/ Sertoli cell tumors)	9%
Lung	7%–17%

Juvenile polyposis

Site	% Lifetime Risk
Colon	40%–50%
Stomach	21% if multiple polyps
Small intestine	Rare, undefined
Pancreas	Rare, undefined
HHT	Undefined

Table 3: Evaluation of CRC Genes Commonly Included on Multi-Gene Panels

GENE	STRENGTH OF EVIDENCE	RISK LEVEL FOR CRC*	ASSOCIATION
APC	Well-established	Increased	FAP & AFAP
APC I1307K pathogenic variant	Well-established	Increased	Increased frequency in Ashkenazi Jewish individuals; increased risk for CRC
ATM	Not well-established	Uncertain	Increased risk for breast and pancreatic cancer; uncertain risk for CRC
AXIN2	Not well-established	Uncertain	Polyposis and oligodontia
BLM heterozygotes	Not well-established	Uncertain	Possible increased risk for CRC
BMPR1A	Well-established	Increased	JPS
CHEK2	Not well-established	Increased	Increased risk for breast, colon, and other cancers
EPCAM	Well-established	Increased	LS

Table 3: Evaluation of CRC Genes Commonly Included on Multi-Gene Panels (continued)

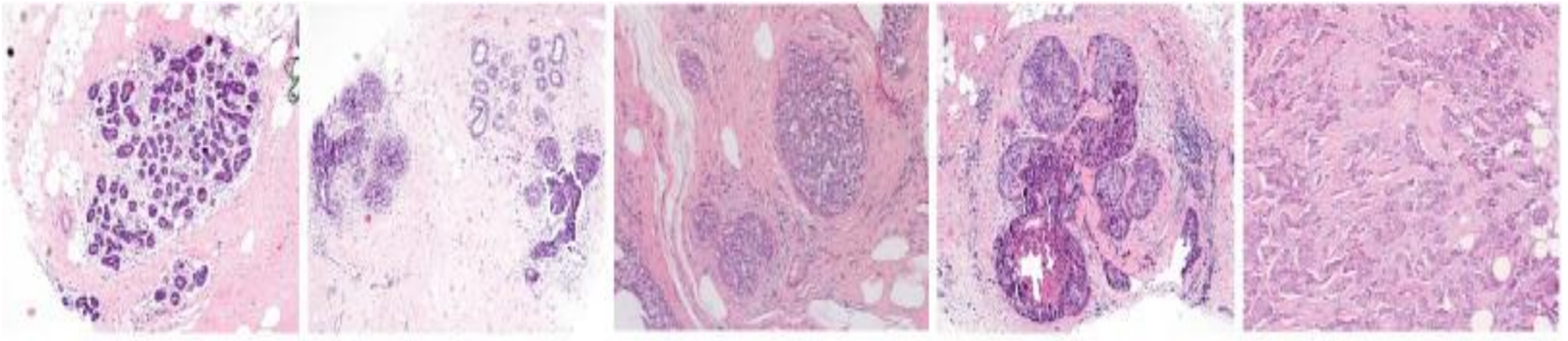
GENE	STRENGTH OF EVIDENCE	RISK LEVEL FOR CRC*	ASSOCIATION
GALNT12	Not well-established	Uncertain	Possible increased risk for colorectal cancer
GREM1	Not well-established	Uncertain	Hereditary mixed polyposis syndrome due to a 40kb duplication[f] upstream of *GREM1* in Ashkenazi Jewish ancestry only
MLH1	Well-established	Increased	LS
MSH2	Well-established	Increased	LS
MSH6	Well-established	Increased	LS
MSH3 biallelic pathogenic variants	Not well-established	Uncertain	Polyposis
MUTYH biallelic pathogenic variants	Well-established	Increased	MAP
MUTYH heterozygotes	Not well-established	Uncertain	Possible increased risk for CRC

Table 3: Evaluation of CRC Genes Commonly Included on Multi-Gene Panels (continued)

GENE	STRENGTH OF EVIDENCE	RISK LEVEL FOR CRC*	ASSOCIATION
NTHL1 biallelic pathogenic variants	Not well-established	Uncertain	Polyposis
POLD1	Not well-established	Uncertain	Polymerase proofreading-associated polyposis
POLE	Not well-established	Uncertain	Polymerase proofreading-associated polyposis
PMS2	Well-established	Increased	LS
PTEN	Well-established	Increased	Cowden syndrome/PTEN hamartoma syndrome
RNF43	Not well-established	Uncertain	SPS
RPS20	Not well-established	Uncertain	Possible increased risk for CRC
SMAD4	Well-established	Increased	JPS
STK11	Well-established	Increased	PJS
TP53	Well-established	Increased	Li-Fraumeni syndrome

*Risk level is based on panel consensus.

Progression to cancer



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

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Fig. 12-9 Accessed 08/01/2010

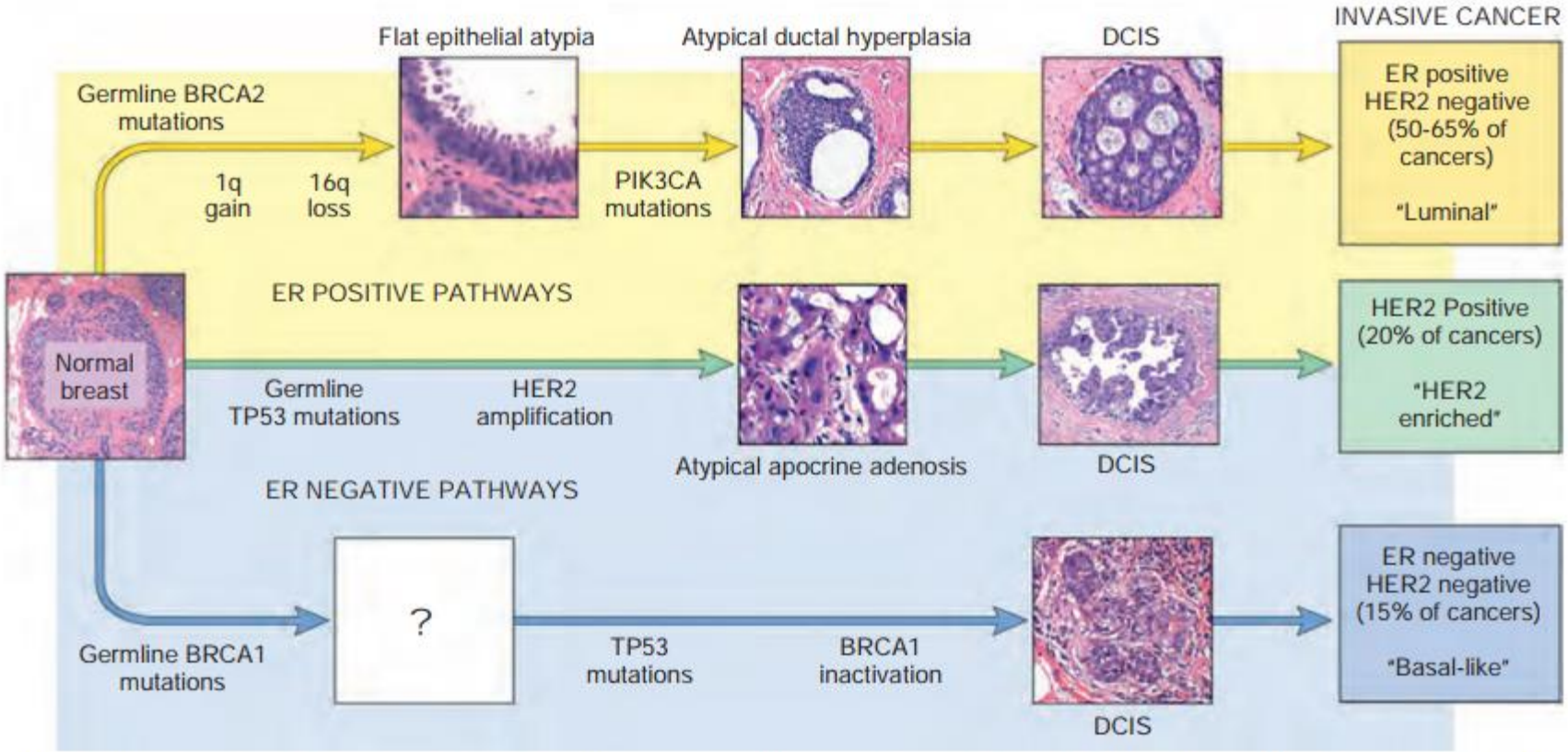


Figure 23-16 Major pathways of breast cancer development. Three main pathways have been identified. The most common pathway *(yellow arrow)* leads to ER-positive carcinomas. Recognizable precursor lesions include flat epithelial atypia and atypical hyperplasia. A less common pathway *(blue arrow)* leads to carcinomas that are negative for ER and HER2. The box with the question mark indicates that no precursor lesions have been identified—perhaps because lesions progress quickly to carcinoma. The third pathway *(green arrow)* consists of HER2-positive cancers, which may be ER-positive or ER-negative. Amplification of the *HER2* gene is also present in a subset of atypical apocrine lesions, which may represent a precursor lesion. Each molecular subtype has a characteristic gene expression profile termed luminal, HER2 enriched, and basal-like, respectively. See text for other details.

Breast Cancer

- Estrogen receptor positive (ER+) and progesterone positive (PR+) cancers are the most common subtype of breast cancer. Their proliferative index (Ki67) is low. They are HER2-. These are called luminal A subtype.
- Luminal B subtype are ER+, PR+ cancers with a high Ki67 proliferative index. They are HER2-.
- HER2+/ER- ,PR- subtype and triple-negative HER2−/ER- ,PR-subtype are known to be more aggressive and have poorer outcomes
- These molecular subtypes also correlate with a risk of local and regional recurrence and survival after distant metastasis.

Table 1

Summary of the breast tumor molecular subtypes

Intrinsic subtype	IHC status	Grade	Outcome	Prevalence[Δ]
Luminal A[*]	[ER+|PR+] HER2-KI67-	1|2	Good	23.7% [p1] [10]
Luminal B[*]	[ER+|PR+] HER2-KI67+	2|3	Intermediate	38.8% [p1] [10]
	[ER+|PR+] HER2+KI67+		|Poor	14% [p1] [10]
HER2 over-expression[*]	[ER-PR-] HER2+	2|3	Poor	11.2% [p1] [10]
Basal[*]	[ER-PR-] HER2-, basal marker+	3	Poor	12.3% [p1] [10]
Normal-like	[ER+|PR+] HER2-KI67-	1|2|3	Intermediate	7.8% [p2] [15]

[*]Subtypes with detailed expression patterns and clinical implications discussed in the text, which take the majority of the breast tumor cases and are most commonly referred to.

[Δ]The prevalence of each subtype is taken from the publication indicated in the square bracket.

Dai, X, Bai, Z, Yang, Y, Liu, X, Zhan, J, Shi, B, “Breast cancer intrinsic subtype classification, clinical use and future trends.” Am J Cancer Res 2015; 5(10): 2929-2943.
Accessed 02/20/2020

Breast Cancer

- HER2-/ER+,PR+ disease is less aggressive disease
- The three subgroups:
- HER2+/ER+,PR-; HER2+/ER-, PR-; or HER2−/ER-,PR- subgroups comprise 26% of the patients with stage I–III breast cancer
- But comprise 40% of patients with metastatic breast cancer.
- The highest frequency of bone metastatic disease is seen in the HER2−/ER+, PR+ patients
- ER− subtypes exhibit more metastases to the brain as a single site

Breast cancer

- SRC activation associated with bone metastases.
- Osteolytic because of the activation of osteoclasts in the metastatic site.
- Tumor cells secrete parathyroid hormone-related protein (PTHRP)
- Stimulates osteoblasts to make RANK ligand (RANKL).
- RANKL then activates osteoclasts, which degrade the bone matrix and release growth factors embedded within it, such as IGF and TGF-β

Breast Cancer

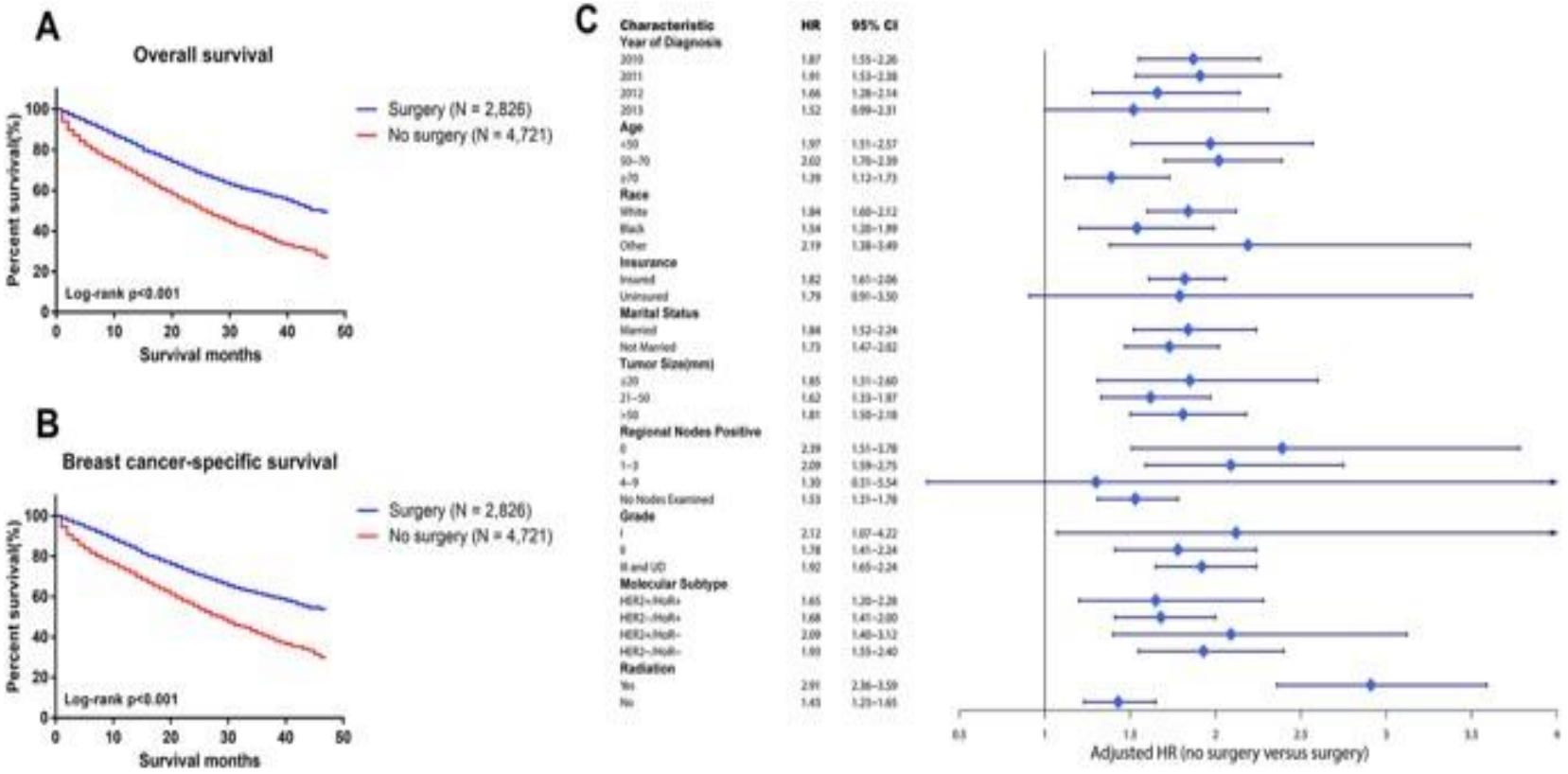
- HER2+ (over-expression of the growth factor receptor) increases the growth of metastatic breast tumor cells in the brain
- Active Wnt/β-catenin signaling has also been found to exert some effect on HER2−/ER− tumors that metastasize to the brain
- Liver only metastasis is most frequent in HER2+/ER−, PR- patients
- CXCR4, a chemokine receptor enhanced by HER2 activation, promotes the invasion of the liver

Breast Cancer

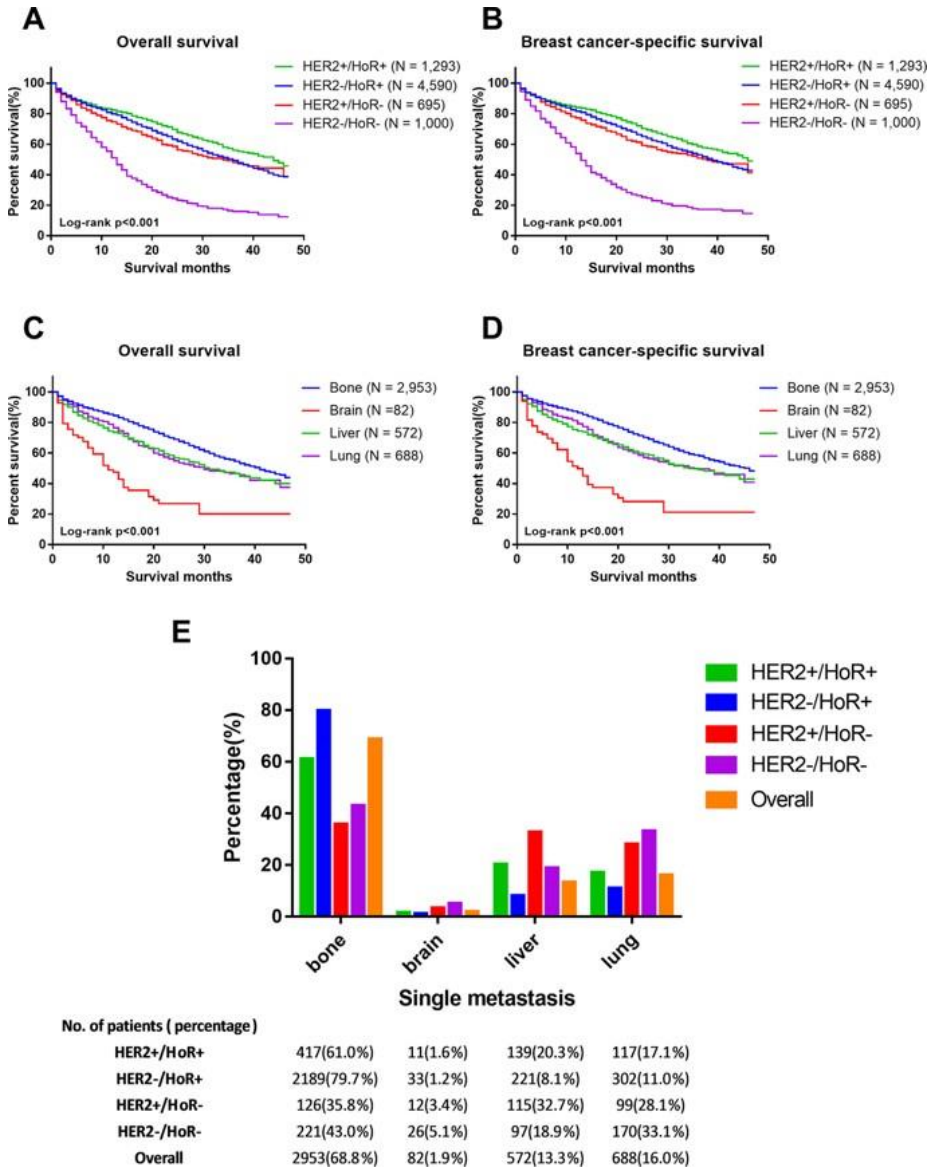
- Lung only metastasis is most common in triple negative breast cancer patients.
- The focal adhesion signaling cascade, which is down-regulated in these patients is an important modulator of lung-specific relapse.
- All subtypes have better outcomes if the primary tumor can be extirpated surgically.

Breast cancer

- Drugs that inhibit CYP2D6 are associated with increased cancer recurrence risk.
- Progesterone receptor activation is associated with resistance to microtubule agents.
- 30% have gain of function mutations of PI_3K/AKT
- BRCA mutation in 25% of cancers
- Occur at younger ages
- BRCA 1 at 17q21 Breast and ovarian cancer
- BRCA 2 at 13q12-13 Breast, pancreas and prostate cancer, melanoma



Gong, Y. *et al*. Impact of molecular subtypes on metastatic breast cancer patients: a SEER population-based study. *Sci. Rep.* **7**, 45411; doi: 10.1038/srep45411 (2017).



No. of patients (percentage)				
HER2+/HoR+	417(61.0%)	11(1.6%)	139(20.3%)	117(17.1%)
HER2-/HoR+	2189(79.7%)	33(1.2%)	221(8.1%)	302(11.0%)
HER2+/HoR-	126(35.8%)	12(3.4%)	115(32.7%)	99(28.1%)
HER2-/HoR-	221(43.0%)	26(5.1%)	97(18.9%)	170(33.1%)
Overall	2953(68.8%)	82(1.9%)	572(13.3%)	688(16.0%)

Gong, Y. *et al*. Impact of molecular subtypes on metastatic breast cancer patients: a SEER population-based study. *Sci. Rep.* **7**, 45411; doi: 10.1038/srep45411 (2017).

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a-e]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
ATM	**Increased risk of female breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[g,h] • RRM: Evidence insufficient, manage based on family history	**Potential increased risk of ovarian cancer** • RRSO: Evidence insufficient; manage based on family history	• **Pancreatic** ▸ See PANC-A • **Unknown or insufficient evidence for prostate cancer**
	Comments: Counsel for risk of autosomal recessive condition in offspring. Heterozygous ATM mutation should not lead to a recommendation to avoid radiation therapy at this time. See Discussion for information regarding the c.7271T>G variant.		
BARD1	**Limited emerging evidence to suggest increased risk of breast cancer, particularly ER, PR and HER-2 negative (triple negative disease)** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40y[g,h] • RRM: Evidence insufficient, manage based on family history	**Unknown or insufficient evidence for ovarian cancer risk**	**Unknown or insufficient evidence for other cancers**
BRCA1	**Increased risk of breast cancer (with predisposition to triple negative disease)** • See *BRCA* Pathogenic Variant-Positive Management	**Increased risk of ovarian cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Pancreatic** (See PANC-A), **Prostate** • See *BRCA* Pathogenic Variant-Positive Management
	Comment: There have been a few case reports of Fanconi-like conditions in individuals with two *BRCA1* pathogenic variants.[i]		
BRCA2	**Increased risk of breast cancer (with predisposition to ER+ disease)** • See *BRCA* Pathogenic Variant-Positive Management	**Increased risk of ovarian cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Pancreatic** (See PANC-A), **Prostate, Melanoma** • See *BRCA* Pathogenic Variant-Positive Management
	Comment: Counsel for risk of autosomal recessive condition in offspring.		

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
BRIP1	**Potential increase in female breast cancer (including triple negative) risk with insufficient evidence for risk management**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	**Unknown or insufficient evidence for other cancers**
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *BRIP1* appears to be sufficient to justify consideration of risk-reducing salpingo-oophorectomy. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset of ovarian cancer.		
CDH1	**Increased risk of female lobular breast cancer**[f] • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 30 y[g,h] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	**Diffuse gastric cancer** • See NCCN Guidelines for Gastric Cancer: Principles of Genetic Risk Assessment for Gastric Cancer
	Comments: There is controversy over how to manage gastric cancer risk in individuals with pathogenic/likely pathogenic variants in *CDH1* in the absence of a family history of gastric cancer. However, one small study found that >50% of such individuals had gastric cancer identified at the time of risk-reducing total gastrectomy (Jacobs MF, et al. Gastroenterology 2019;157:87-96). Cleft lip with or without cleft palate has been associated with *CDH1* pathogenic/likely pathogenic variants (Frebourg T, et al. J Med Genet 2006;43:138-142).		
CDKN2A	**No increased risk of breast cancer**	**No increased risk of ovarian cancer**	**Melanoma, Pancreatic cancer,** see PANC-A.
	Comments: General melanoma risk management is appropriate, such as annual full-body skin examination and minimizing UV exposure.		
CHEK2	**Increased risk of female breast cancer (with predisposition to ER+ disease)**[f] • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[g,h] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	**Colon** • See NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Colorectal
	Comments: Risk data are based only on frameshift pathogenic/likely pathogenic variants. The risks for most missense variants are unclear but for some pathogenic/likely pathogenic variants, such as Ile157Thr, the risk for breast cancer appears to be lower. Management should be based on best estimates of cancer risk for the specific pathogenic/likely pathogenic variant.		

RRM: Risk-reducing mastectomy RRSO: Risk-reducing salpingo-oophorectomy

Footnotes on GENE-A 5 of 5 Continued

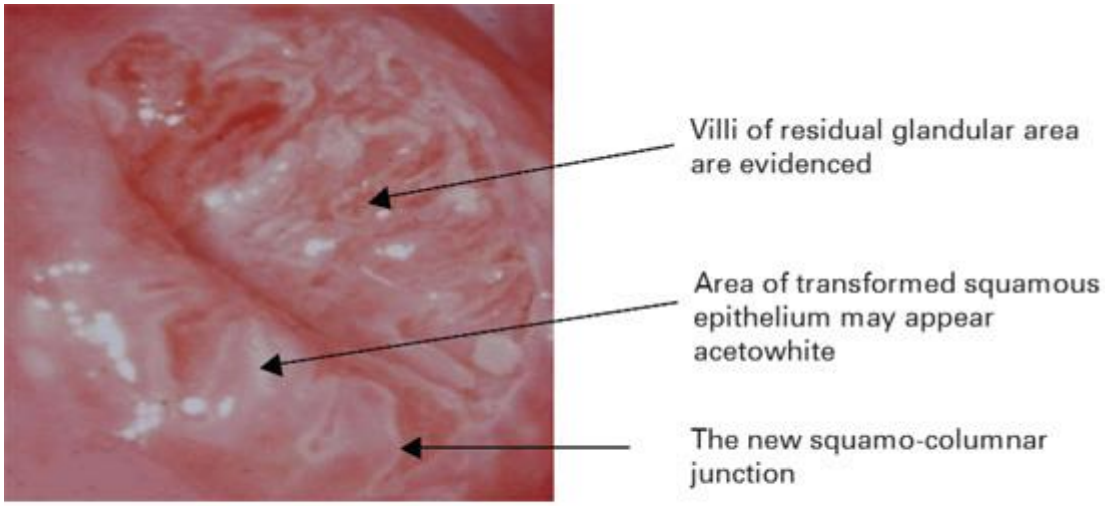
The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
MSH2, MLH1, MSH6, PMS2, EPCAM[i]	**Unknown or insufficient evidence for breast cancer risk**[g] • Manage based on family history	**Increased risk of ovarian cancer** • See NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Colorectal	**Colon, Uterine, Others** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal **Pancreatic (insufficient evidence for PMS2)** • See PANC-A
	Comment: Counsel for risk of autosomal recessive condition in offspring.		
NBN	**Current data suggest that breast cancer risks are not increased for pathogenic/likely pathogenic variants other than 657del5, for which there is mixed evidence for increased risk. Insufficient evidence for risk management**	**Mixed evidence for increased risk of ovarian cancer** • RRSO: Evidence insufficient; manage based on family history	**Unknown or insufficient evidence for other cancers**
	Comments: Counsel for risk of autosomal recessive condition in children.		
NF1	**Increased risk of female breast cancer**[f] • Screening: Annual mammogram with consideration of tomosynthesis starting at age 30 y and consider breast MRI with contrast from ages 30–50 y[g,h] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	• **Malignant peripheral nerve sheath tumors, GIST, others** • Recommend referral to *NF1* specialist for evaluation and management
	Comments: Screening recommendations only apply to individuals with a clinical diagnosis of NF. At this time, there are no data to suggest an increased breast cancer risk after age 50 y. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.		

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
PALB2	**Increased risk of female breast cancer**[f] • Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y[g,h] • RRM: Discuss option of risk-reducing mastectomy	**Increased risk of ovarian cancer** • RRSO: Evidence insufficient; manage based on family history	• **Pancreatic** ▸ See PANC-A • **Unknown or insufficient evidence for other cancers**
	Comments: Counsel for risk of autosomal recessive condition in offspring.		
PTEN	**Increased risk of female breast cancer** • See Cowden Syndrome Management	**No increased risk of ovarian cancer**	**Thyroid, colon, endometrial** • See Cowden Syndrome Management
RAD51C	**Potential increase in female breast cancer risk (including triple negative disease) with insufficient evidence for risk management**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	**Unknown or insufficient evidence for other cancers**
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51C* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
RAD51D	**Potential increase in female breast cancer risk (including triple negative disease) with insufficient evidence for risk management**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	**Unknown or insufficient evidence for other cancers**
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51D* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
STK11	**Increased risk of female breast cancer** • Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome • RRM: Evidence insufficient, manage based on family history	**Increased risk of non-epithelial ovarian tumors** • See NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome	• See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome • **Pancreatic**, see PANC-A
TP53	**Increased risk of female breast cancer** • See Li-Fraumeni Syndrome Management	**No increased risk of ovarian cancer**	• See Li-Fraumeni Syndrome Management • **Pancreatic,** see PANC-A

Normal cervix



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

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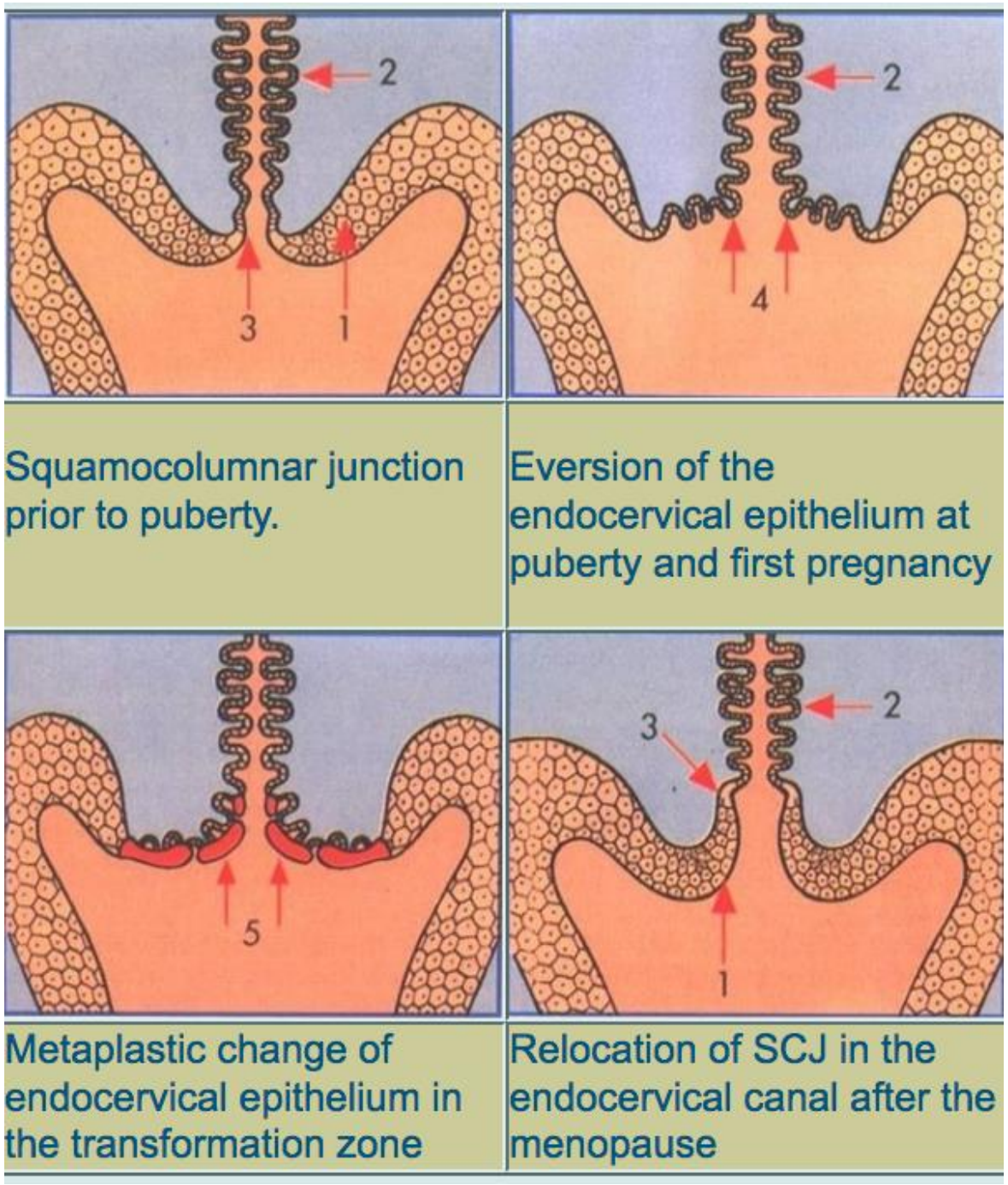
Colpophotograph of the cervix showing active transformation zone. The squamocolumnar junction, or "transformation zone" of the cervix, changes continually during a woman's reproductive life.

Fig. 24-7 Accessed 08/01/2010



Carcinoma of the cervix begins at the endocervical junction.

The routine Pap smear

- Screen throughout active sexual life
- False negative rate is up to 20% and largely represents error sampling of cervix.
- Risk factors for cervical cancer include:
- First intercourse earlier than 18 years of age
- More than six sexual partners
- Oral contraceptive use for more than 10 years
- Screen no more frequently than every 2-3 years if significant dysplasia is not found.

The routine Pap smear

- A negative liquid based Pap smear every 2 years until the age of 30 may then yield to less frequent screening (every 3 years) with concomitant HPV testing in patients at risk for HPV infection, not simply with condylomata.
- Terminate screening at age 70 or following hysterectomy if not performed for cancer.

The routine Pap smear

- History of genital warts is not an indication for HPV testing as the HPV strains are not associated with cervical cancer.
- Screen only if dysplasia found.
- Partner with penile cancer or whose previous partner has had cervical cancer
- Cis-gender sexual activity transmits HPV
- Chlamydia screens are only for those less than 24 years of age or pregnant and at high risk

Pap smear

- Atypical squamous cells of uncertain significance [ASUS] may represent HPV infection if no other abnormality present. HPV determination is indicated.
- Absence of cells from transformation zone may reflect inadequate scraping of endocervical canal.
- Presence of endometrial cells in the Pap smear of a woman older than 40 not on hormone therapy requires further investigation.

Pap smear

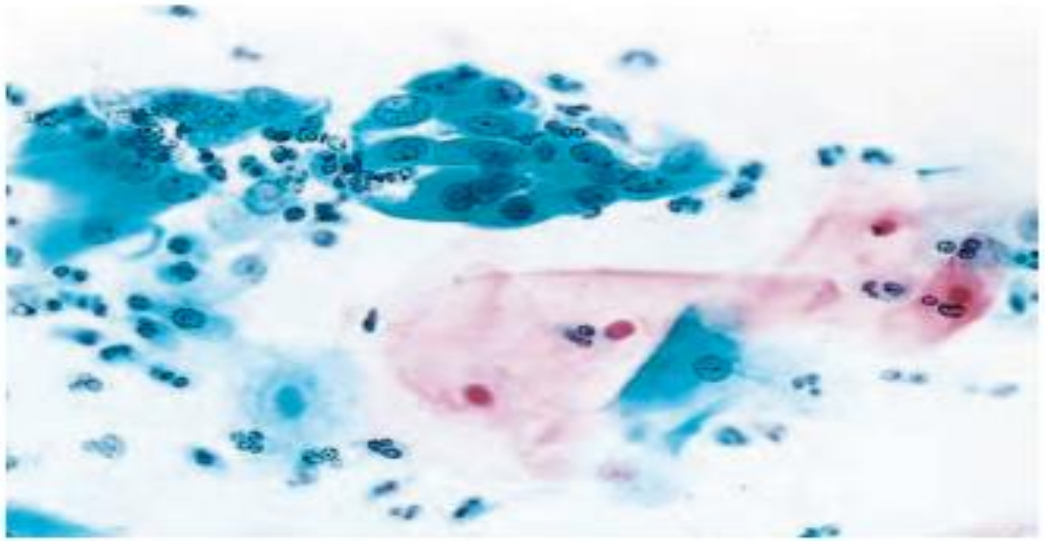
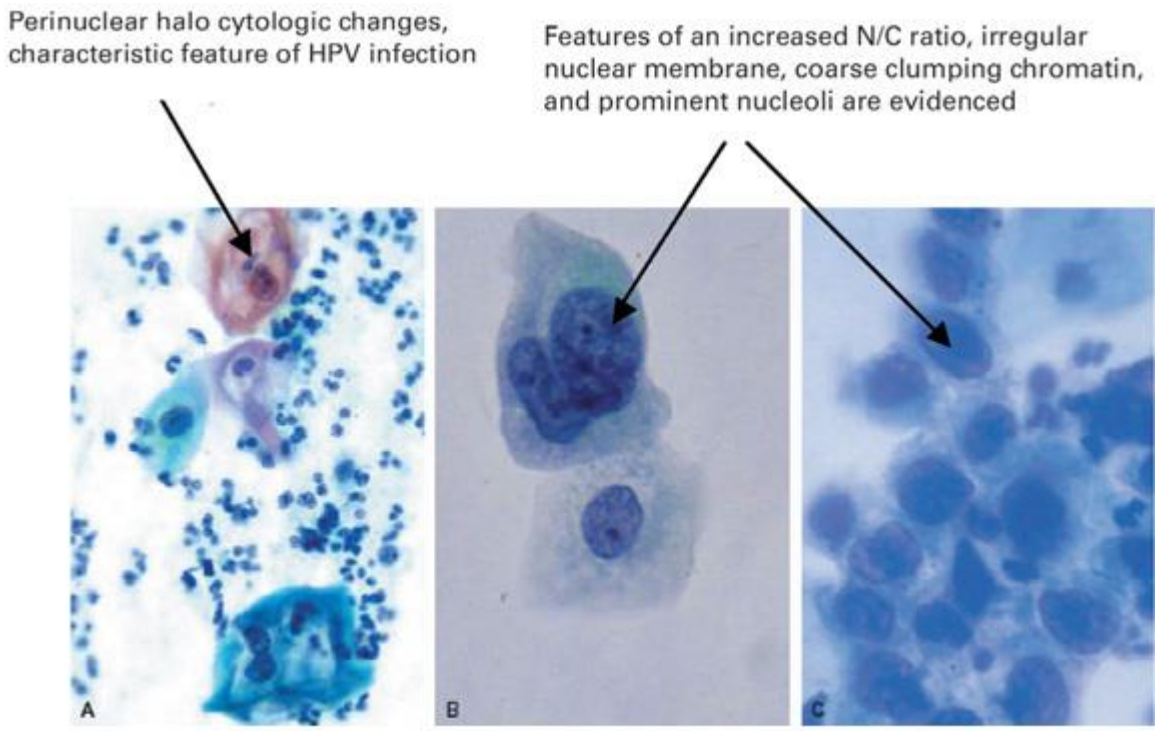


Figure 7-47 A normal cervicovaginal smear shows large, flattened squamous cells and groups of metaplastic cells; interspersed are neutrophils. There are no malignant cells. (Courtesy Dr. P. K. Gupta, University of Pennsylvania, Philadelphia, Pa.)

Pap smear



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

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Cytologic changes associated with cervical intraepithelial neoplasia (CIN), including CIN1 with koilocytotic feature of HPV infection A. x600 magnification, CIN2 B. x1000 magnification, and CIN3 C. x1000 magnification.

Fig. 24-10 Accessed 08/01/2010

Pap smear

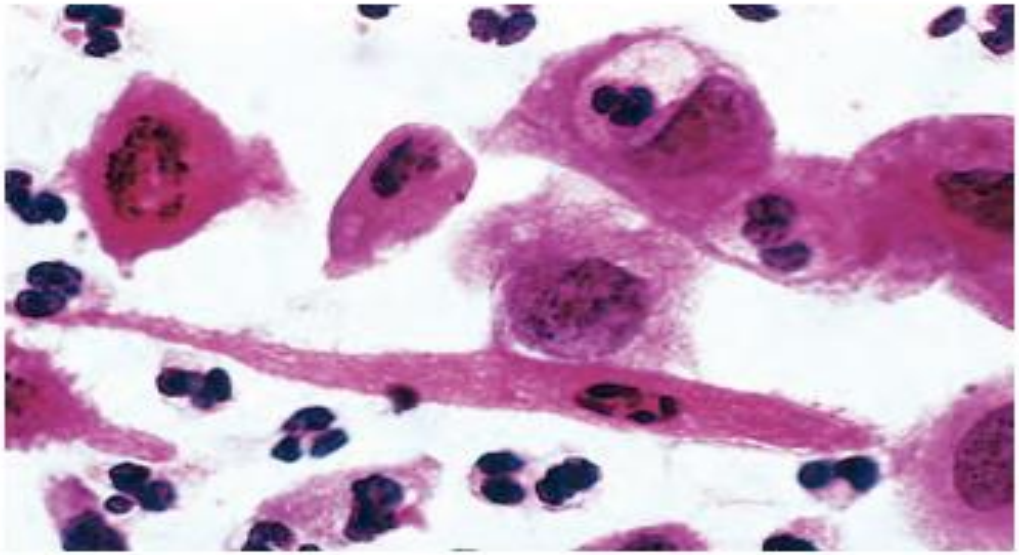
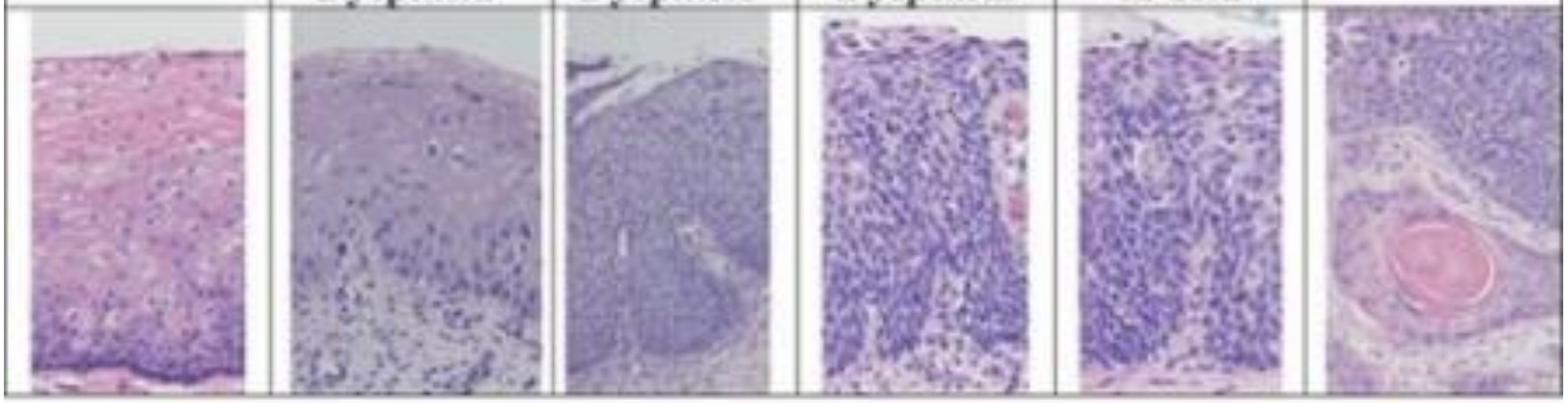


Figure 7-48 An abnormal cervicovaginal smear shows numerous malignant cells that have pleomorphic, hyperchromatic nuclei; interspersed are normal polymorphonuclear leukocytes. (Courtesy Dr. P. K. Gupta, University of Pennsylvania, Philadelphia, Pa.)

Non-Dysplastic Epithelium	LSIL	HSIL		Micro-Invasion
	CIN 1	CIN 2	CIN 3	
	Mild Dysplasia	Moderate Dysplasia	Severe Dysplasia	Carcinoma in Situ



Images courtesy of Chisa Aoyama, MD, David Geffen School of Medicine at UCLA.

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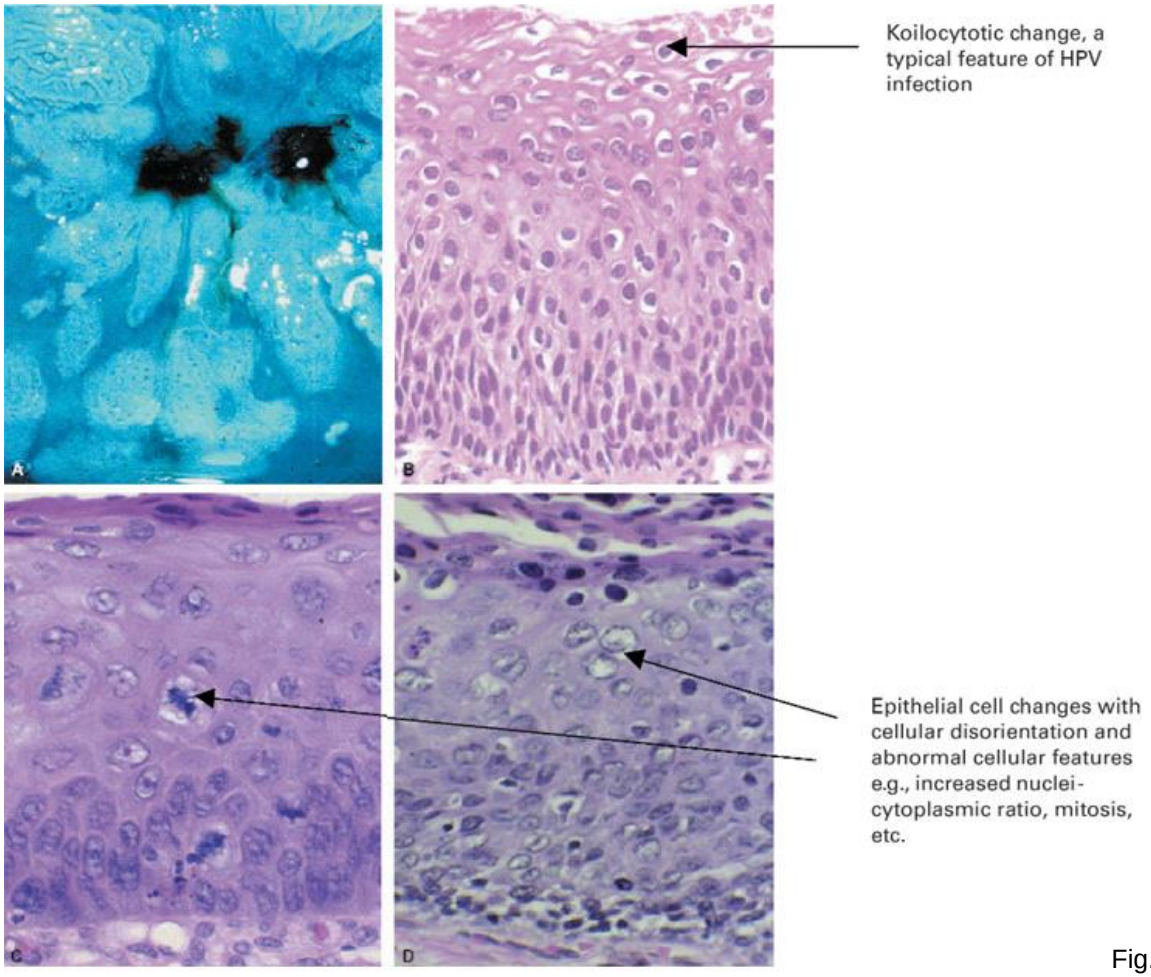
Accessed 05/05/2020

Grading



A. Colpophotograph illustrating a low-grade cervical intraepithelial neoplasia (CIN) in the transformation zone. B, C, and D. Histopathology of cervical intraepithelial neoplasia (CIN I, II, and III respectively) (H&E stain; x400 magnification).

Fig. 24-4 Accessed 08/01/2010

Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

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Cervical cancer

- The rate of progression from mild to moderate dysplasia is 1%/year, and can be followed on Pap smear.
- However, progression from moderate to severe dysplasia, the risk is 16% within 2 years and 25% within 5 years.
- Severe dysplasia if untreated leads to cancer in 12% of patients over a period of 20 years.
- Presents with abnormal vaginal bleeding (often postcoital). May complain of dyspareunia.

Bethesda grading system

Mild dysplasia CIN-I	Moderate dysplasia CIN-II	Severe dysplasia or carcinoma in situ CIN-III	Invasive
Atypical squamous cells of undetermined significance (ASC-US)	Low-grade squamous intraepithelial lesion (LGSIL or LSIL)	Atypical squamous cells – cannot exclude HSIL (ASC-H) High grade squamous intraepithelial lesion (HGSIL or HSIL)	Squamous cell carcinoma
Occupies lower third of mucosal thickness	Occupies at least 50% of mucosal thickness	Occupies entire mucosal thickness; basement membrane intact	Invades basement membrane

Bethesda grading system

Atypical Glandular Cells not otherwise specified (AGC-NOS)	Atypical Glandular Cells, suspicious for AIS or cancer (AGC-neoplastic)	Adenocarcinoma *in situ* (AIS)

- The absence of endocervical cells on the Pap smear should be noted as it likely indicates the specimen was not taken from the endocervical junction.
- The presence of endometrial cells apart from the menstrual period is an abnormality that warrants further examination.
- The cervical pap smear is not a screen for endometrial cancer.

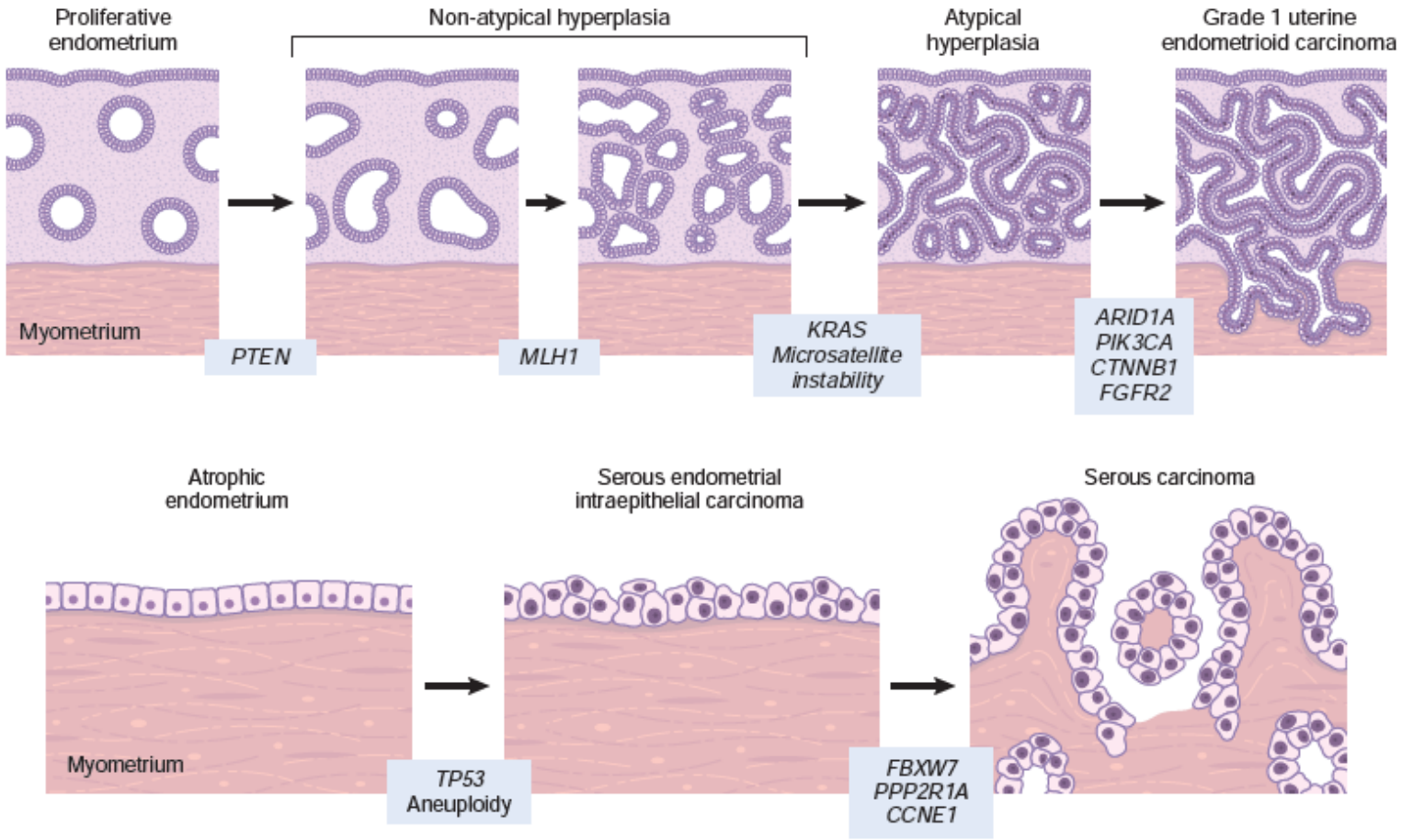

Figure 22-24 **A,** Schematic depicting the development of type I endometrial carcinoma arising in the setting of hyperplasia. **B,** Schematic diagram of the development of type II endometrial carcinoma. The most common molecular genetic alterations are shown at the time they are most likely to occur during the progression of the disease. *MI, Microsatellite instability. *CTNNB1*, beta-catenin gene; *PPP2R1A*, PP2A gene; *CCNE1*, cyclin E gene.

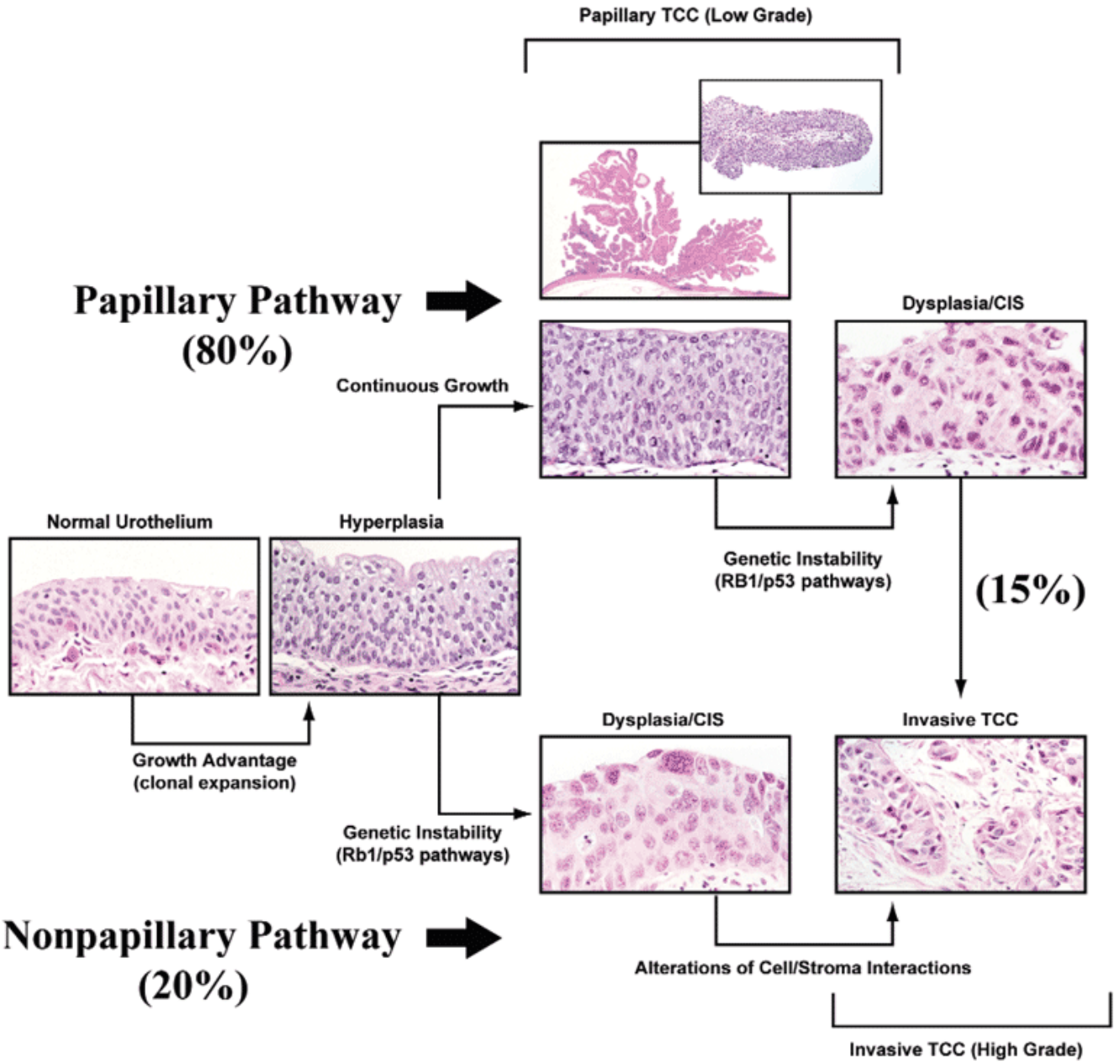

Fig. 28-1
Accessed
08/01/2010

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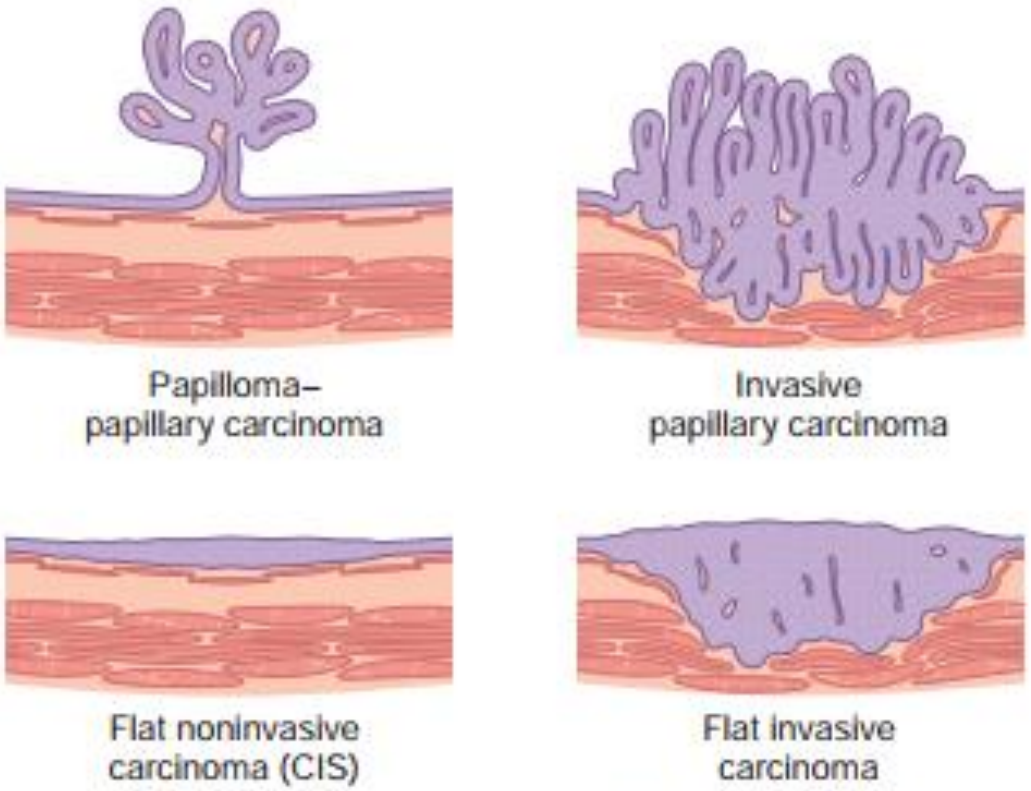
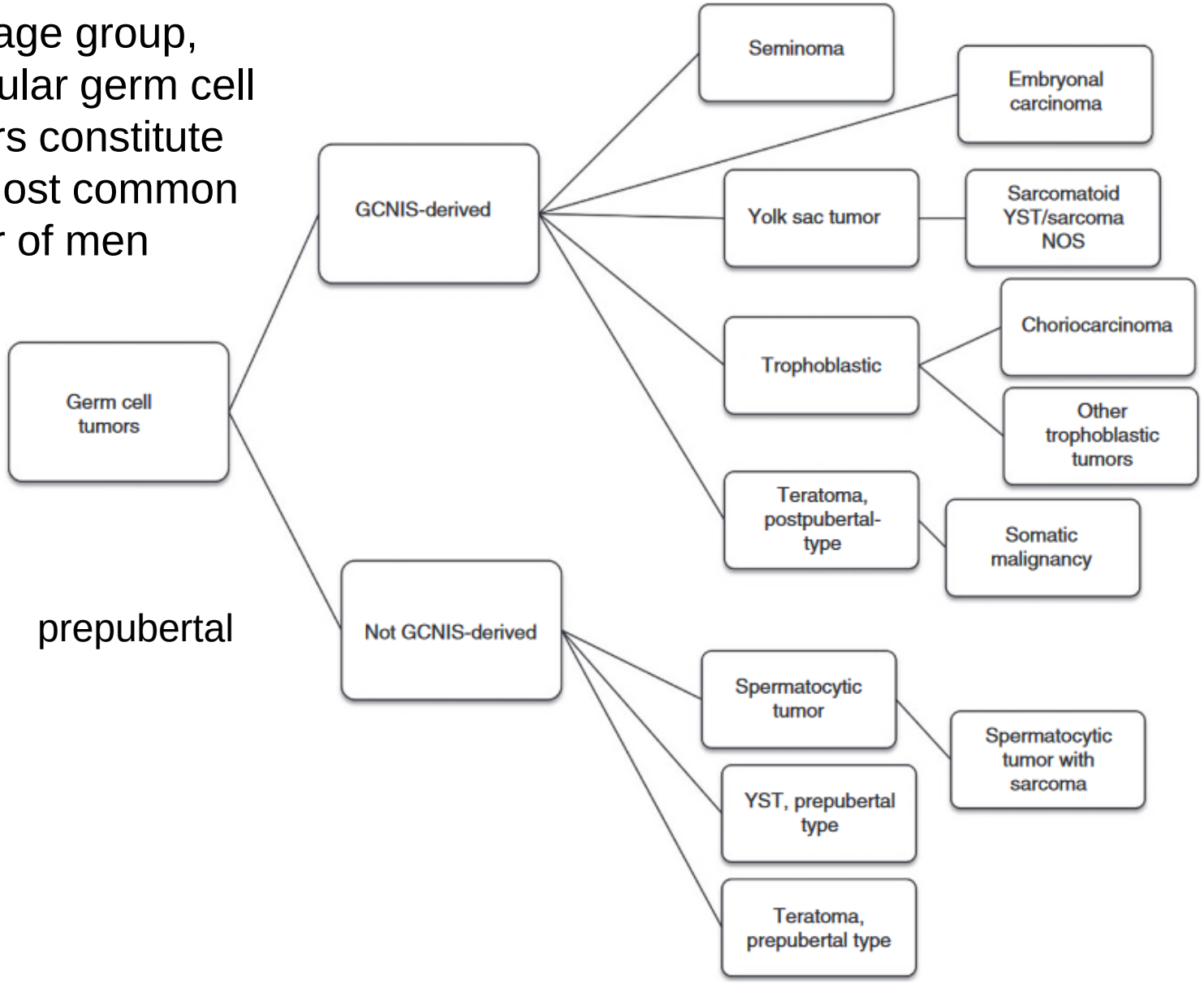


Figure 21-6 Four morphologic patterns of bladder tumors. CIS, Carcinoma in situ.

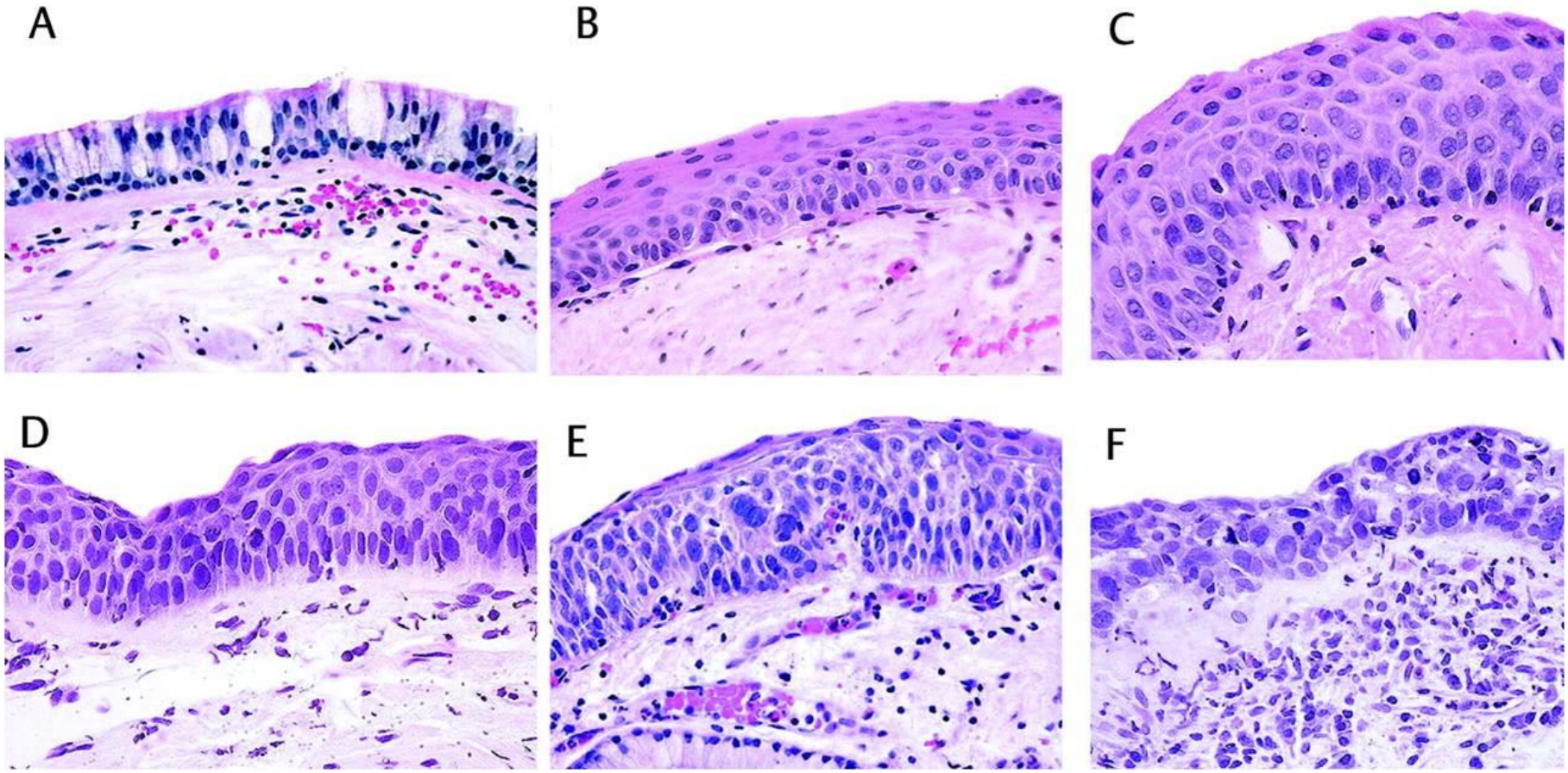
In the 15- to 34-year age group, testicular germ cell tumors constitute the most common tumor of men



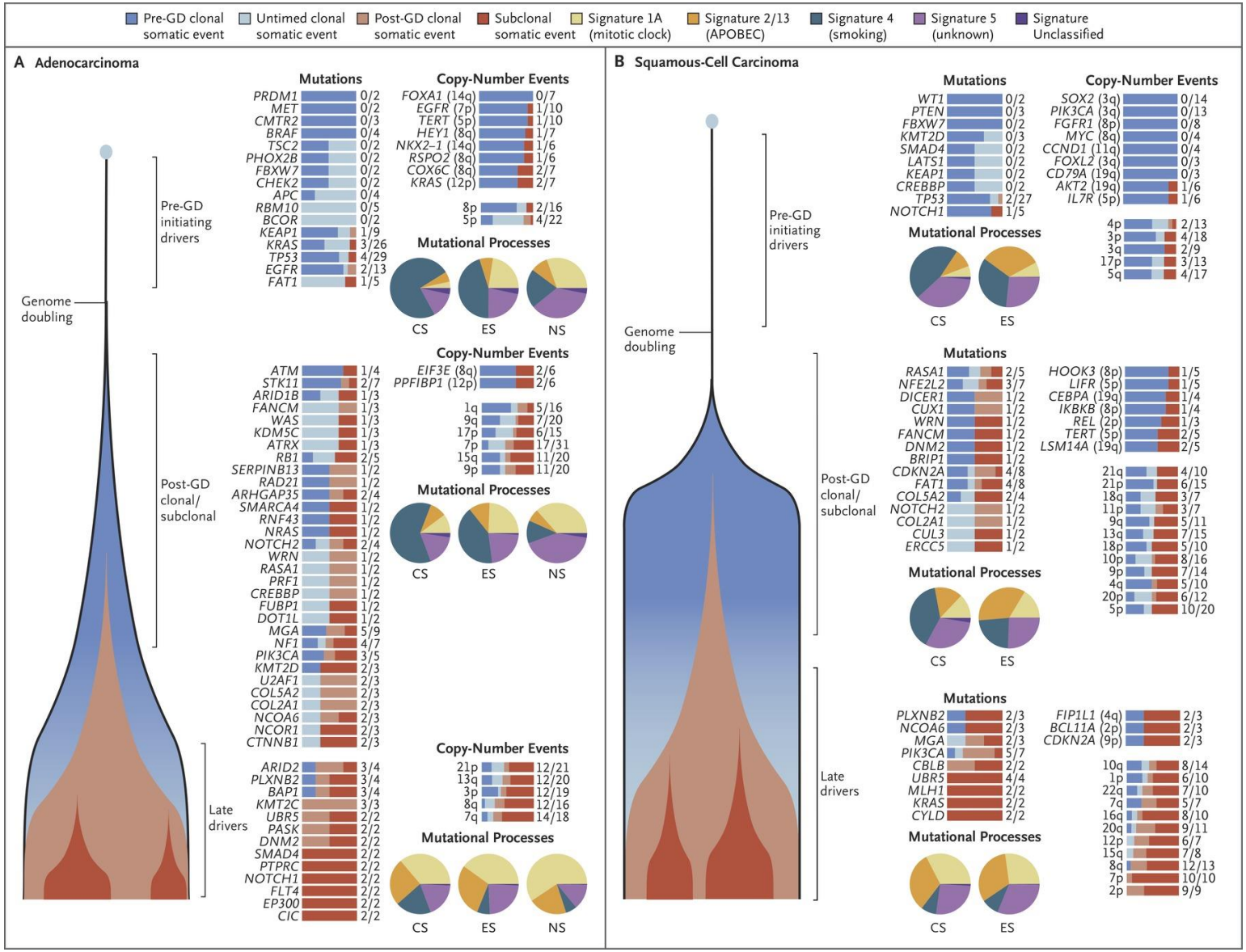
prepubertal

Figure 2. In the 2016 edition of the World Health Organization classification, germ cell tumour classification is restructured into tumours derived from germ cell neoplasia *in situ* (GCNIS) and those not derived from GCNIS. NOS, not otherwise specified; YST, yolk sac tumour.

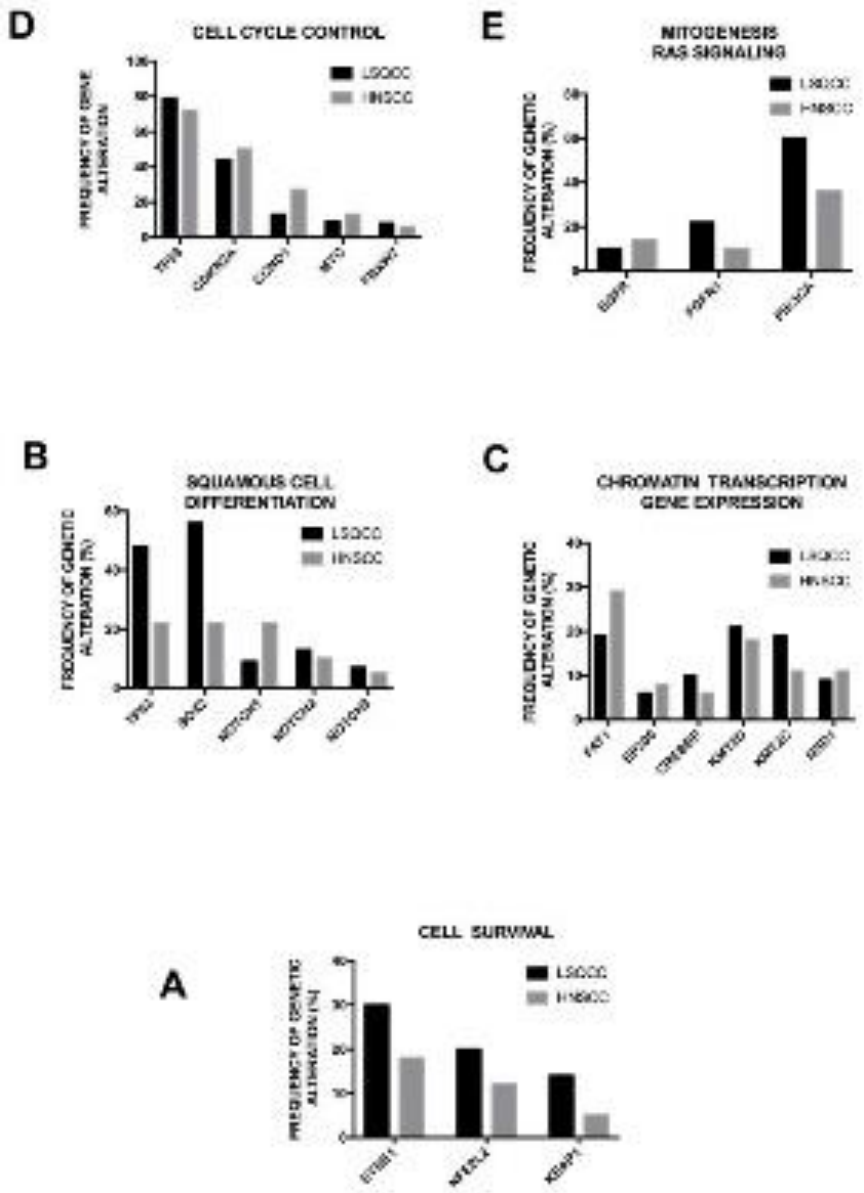
Histology of bronchial epithelium



(A) Normal two-layered epithelium; (B) squamous metaplasia; (C) mild dysplasia; (D) moderate dysplasia; (E) severe dysplasia; (F) carcinoma in situ. http://homepage.smc.edu/wissmann_paul/physiology/dysplasia.htm Accessed 12/10/2019



https://www.nejm.org/doi/10.1056/NEJMoa1616288 Accessed 05/05/2020



[Figure 3](#)

Pattern of frequently altered genes in Lung and Head and Neck squamous cell carcinoma subdivided according to their biologic function. A: Cell Survival; B: Squamous Cell Differentiation; C. Chromatin Transcription Gene Expression; D: Cell Cycle Control; E: Mitogenesis, RAS Signaling.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6116004/

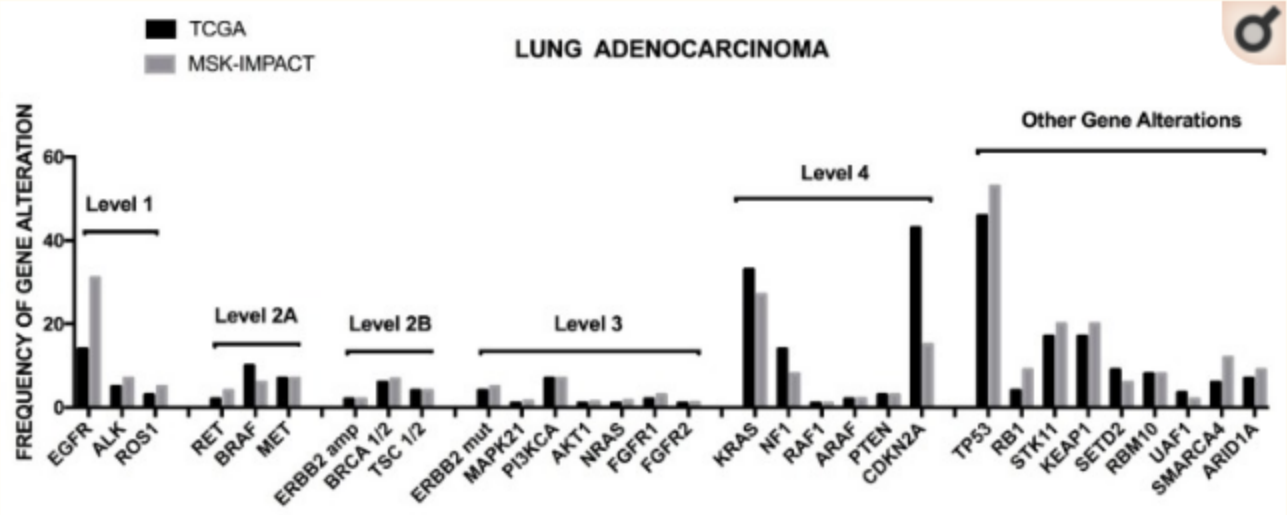


Figure 2

Frequency of main genetic alterations, subdivided into various levels according to the degree of therapeutic actionability of genetic events, in two groups of lung adenocarcinoma patients: TCGA data sets based on the analysis of non-metastatic patients and MSK-IMPAC data based on the analysis of recurrent/metastatic lung adenocarcinomas. Date are reported in [13,19].

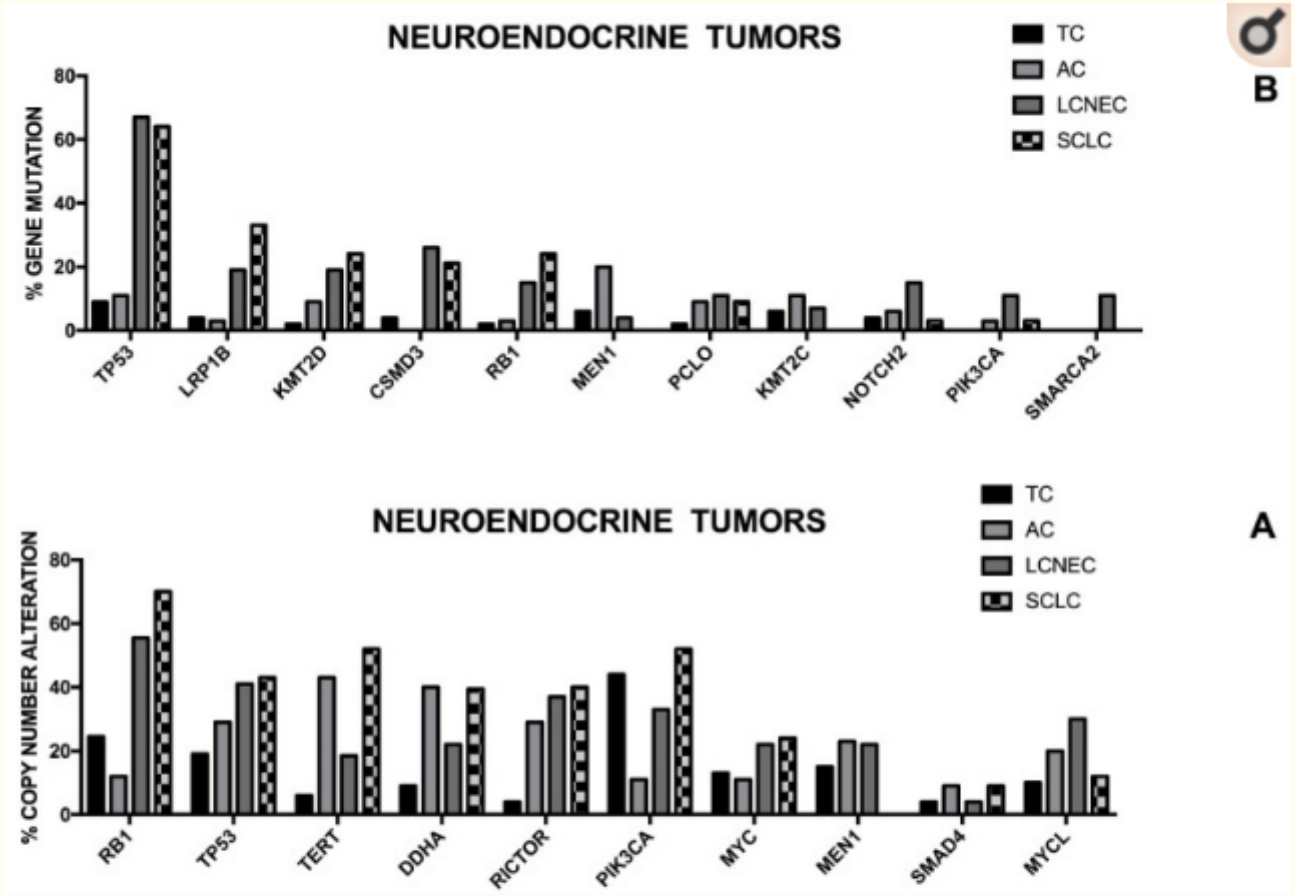


Figure 4

Genetic abnormalities observed in neuroendocrine lung cancers classified into four subtypes: TC (Typical Carcinoid); AC (Atypical Carcinoid); LCNEC (Large Cell Neuro Endocrine Carcinoma); SCLC (Small Cell Lung Carcinoma). A: Copy Number Alterations; B: Gene Mutations The data plotted in this figure were reported by Simbolo et al. [123].

Immunoglobulin switching

- Early B and T cells both express a pair of gene products, RAG1 and RAG2, that carry out V(D)J segment recombination, permitting the assembly of functional antigen receptor genes.
- In addition, after encountering antigen mature B cells express a specialized enzyme called antigen-induced cytosine deaminase (AID), which catalyzes both immunoglobulin gene class switch recombination and somatic hypermutation.
- Errors during antigen receptor gene assembly and diversification are responsible for many of the mutations that cause lymphoid neoplasms.

Esophageal adenocarcinoma

- The more common genetic and epigenetic (methylation) alteration is the inactivation of CDKN2A on chromosome 9p.
- Patients with LOH in TP53 are 16 times more likely to progress to adenocarcinoma
- Predominantly G:C to A:T transitions at CpG dinucleotides
- These changes are seen both in Barrett's as well as in adenocarcinoma of the cardia

Esophageal squamous carcinoma

- Loss of function early change in squamous cancer.
- Transversion G:C to T:A occurred preferentially at known sites of adduct formation on DNA.

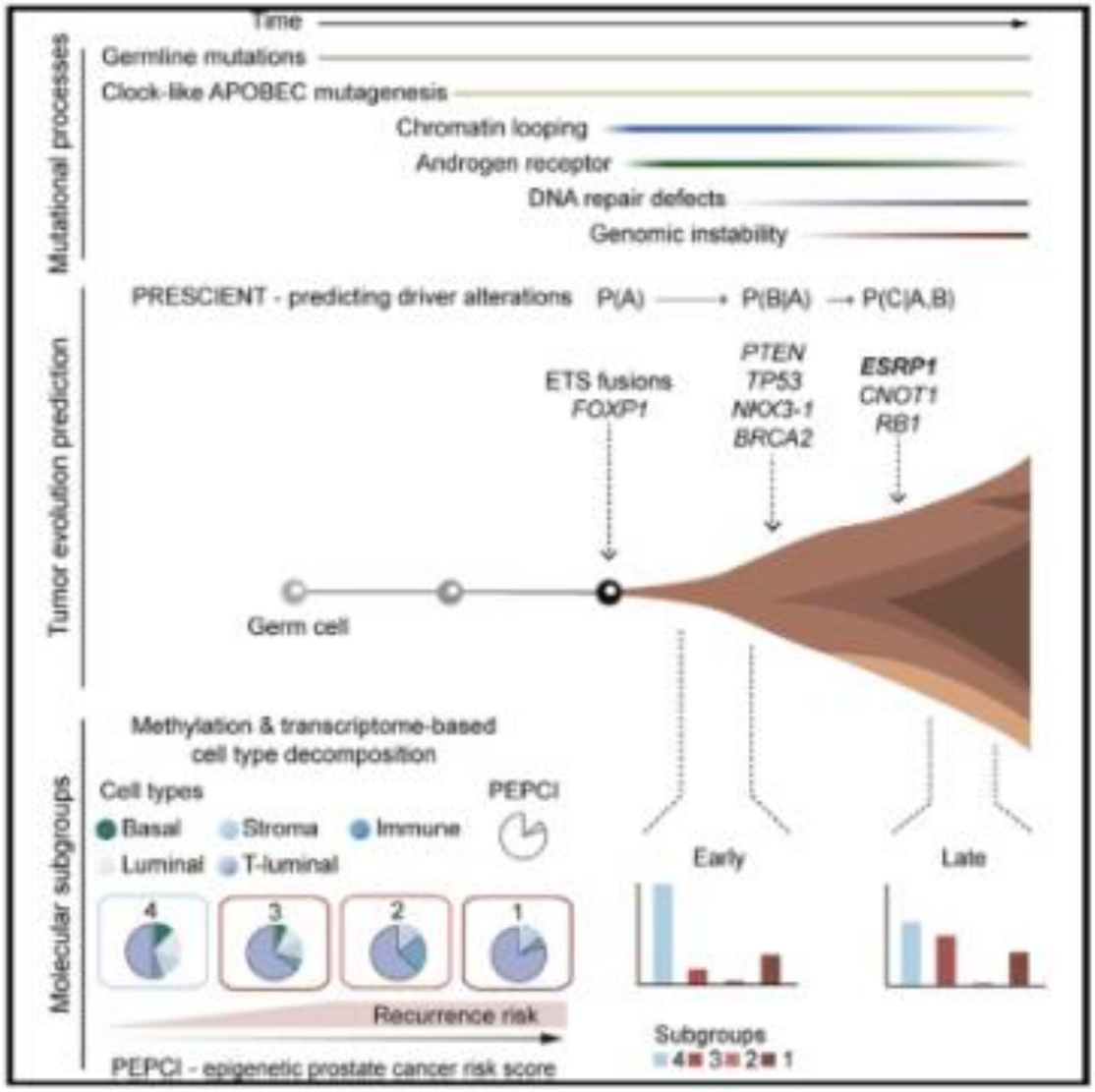
Table 1

Gastric adenocarcinoma classification systems

WHO (2010)	Lauren (1965)
Papillary adenocarcinoma Tubular adenocarcinoma Mucinous adenocarcinoma	Intestinal type
Signet-ring cell carcinoma And other poorly cohesive carcinoma	Diffuse type
Mixed carcinoma	Indeterminate type
Adenosquamous carcinoma Squamous cell carcinoma Hepatoid adenocarcinoma Carcinoma with lymphoid stroma Choriocarcinoma Carcinosarcoma Parietal cell carcinoma Malignant rhabdoid tumor Mucoepidermoid carcinoma Paneth cell carcinoma Undifferentiated carcinoma Mixed adeno-neuroendocrine carcinoma Endodermal sinus tumor Embryonal carcinoma Pure gastric yolk sac tumor Oncocytic adenocarcinoma	

Gastric adenocarcinoma

- There is a strong correlation between the expression of p53, BAX, and C-MYC, as well as with histological grade
- There is a reverse correlation between histological type and p53 expression
- Deregulation of p53 may result in uncontrolled proliferation in gastric cancer.
- p53 levels are elevated as it has a longer half-life than wt p53
- Epigenetic changes important in development (methylation)



Gerhauser et al., 2018, Cancer Cell *34*, 1–16
December 10, 2018 © 2018 Elsevier Inc.
https://doi.org/10.1016/j.ccell.2018.10.016

Some syndromes

- Hereditary nonpolyposis colon cancer (HNPCC) syndrome
- Autosomal dominant
- Carcinomas of the colon affecting predominantly the cecum and proximal colon.
- It results from failure of DNA mismatch repair.
- When a strand of DNA is being replicated, these proteins act as “spell checkers.” One of the hallmarks of patients with mismatch-repair defects is microsatellite instability.
- Microsatellites are tandem repeats of one to six nucleotides found throughout the genome.

Some syndromes

- In normal people the length of these microsatellites remains constant.
- In people with HNPCC, these satellites are unstable and increase or decrease in length in tumor cells, creating alleles not found in normal cells of the same patient.
- Germline mutations in the MSH2 and MLH1 genes each account for approximately 30% of cases. The remaining cases have mutations in other mismatch repair genes.
- 2% to 4% of all colonic cancers

Some syndromes

- Microsatellite instability can be detected in about 15% of sporadic colon cancers.
- The cancer genes that are mutated encode TGF-β receptor II as well as the TCF component of the β-catenin pathway

Some syndromes

- Li Fraumeni
- 20% occur “de novo”
- Median age of first cancer: 29, women; 40, men
- 25 times more likely to develop cancer before age 50 than is the general population
- Nearly all will develop cancer by age 70
- Breast cancer is the first presentation in women
- Often HER2/neu overexpressed

Some syndromes

- Germline mutation of TP53 at 17p13
- Associated with high incidence of post radiation sarcoma
- Highest risk if many TP53 mutations
- Myelodysplasia syndrome and acute myeloid leukemia
- Sarcomas, brain tumors, and carcinomas of the adrenal cortex as other commonly found neoplasms.

Some syndromes

- Familial adenomatous polyposis
- Germline mutation at 5q21 (APC)
- Loss-of-function
- Autosomal dominant
- Loss of second allele leads to adenoma formation.
- May have hundreds of colonic polyps by early teens. Progress to malignancy.
- Familial gastric adenocarcinoma
- Germline mutation at 16q22.1 (CDH1)
- E-cadherin
- Loss of function

Some syndromes

- Neurofibramotosis type 1
- Café-au-lait skin lesions
- Peripheral nerve sheath tumors
- May progress to malignancy
- 17q11 NF1
- Neurofibromin contains a GTPase domain that blocks RAS signaling

Some syndromes

- Neurofibromatosis 1
- Characterized by:
- Neurofibromas of peripheral nerve
- Gliomas of the optic nerve
- Pigmented nodules of the iris (Lisch nodules)
- Cutaneous hyperpigmented macules (café au lait spots).
- NF1 mutation at 17q11
- Neurofibromin contains a GTPase domain that blocks RAS signaling.
- May progress to malignancy

Some syndromes

- Neurofibromatosis type 2
- Bilateral acoustic schwannomas
- 22q12.2 NF2
- Neurofibromin 2 (merlin) resembles red cell cytoskeletal protein 4.1 (ERM family)
- Do not establish stable cell-cell junctions

Some syndromes

- Wilm's Tumor
- Most common kidney tumor in children
- Two-third found before age 5
- 5-10% are bilateral
- Also may occur at other sites in the genitourinary tract
- up to 50% may recur
- 11p13 WTI
- Genomic imprinting of IGF2, H19 genes at 11p15.5. Usually paternal copy is methylated. H19 is a non-coding gene.
- Transcriptional activator of genes involved in renal and gonadal differentiation; regulates mesenchymal-to-epithelial transition that occurs in development

Some syndromes

- Von Hippel Lindau
- Hereditary renal cell cancers, pheochromocytomas, hemangioblastomas of the central nervous system, retinal angiomas, and renal cysts.
- 3p25 VHL
- The VHL protein is a component of a ubiquitin ligase
- A critical substrate for the VHL ubiquitin ligase is the transcription factor HIF1α (hypoxia-inducible transcription factor 1α).
- In the presence of oxygen, HIF1α is hydroxylated and binds to VHL, leading to its ubiquitination and degradation.

Some syndromes

- In hypoxic environments the hydroxylation reaction does not occur, and HIF1α escapes recognition by VHL.
- As a result HIF1α accumulates in the nuclei of hypoxic cells and turns on many target genes:
- VEGF, PDGF, GLUT1 as examples
- Loss-of-function mutations in VHL also prevent the ubiquitination and degradation of HIF1α, even under normoxic conditions

Some syndromes

- Peutz-Jeghers syndrome
- Hamartomatous polyps predominate in small bowel but may also be found in colon and stomach.
- Mucosal pigmentation of buccal mucosa, lips.
- Germline mutation of the gene STK11 (LKB1) at 19p.13.3
- The gene encodes a protein with serine/threonine kinase activity that regulates cell polarization and growth.
- Autosomal dominant.
- 50% increased risk for colorectal, breast, gynecologic cancers

Some syndromes

- Xeroderma Pigmentosum.
- At increased risk for the development of cancers of the skin particularly following exposure to the UV light contained in sun rays.
- UV radiation causes cross-linking of pyrimidine residues, preventing normal DNA replication.
- POLH at 6p21.1 DNA polymerase-ε repairs same but is error-prone
- Such DNA damage is repaired by the nucleotide excision repair system.
- XPC at 3p25.1 initiates process
- ERCC at 19.13.32 acts as helicase in process

Some syndromes

- Fanconi anemia
- Bone marrow failure
- Hypopigmentation or café-au-lait spots
- Malformed thumbs or forearms as well as short stature
- Multiple organ abnormalities
- Small eyes
- Deformed ears and Hearing loss

Some syndromes

- 80-90% due to mutations in one of three genes, FANCA (at 16q24.3), FANCC (at 9q22.32), and FANCG (at 9p13.3).
- There are 15 genes involved in the FA core complex
- The FA core complex repairs inter-strand cross links (ICLs)
- Risk for acute myeloid leukemia

Some syndromes

- BRIP1 at 17q23.2
- DNA-dependent ATPase and 5' to 3' DNA helicase required for the maintenance of chromosomal stability.
- Acts late in the Fanconi anemia pathway, after FANCD2 ubiquitination.
- Involved in the repair of DNA double-strand breaks by homologous recombination in a manner that depends on its association with BRCA1.

Some syndromes

- Cowden syndrome
- Hamartomatous polyps in skin, oral as well as nasal mucosa, intestinal mucosa
- Macrocephaly
- Trichilemmoma.
- Males may have pigmented macules on the glans penis.
- Autosomal dominant.
- Increased risk of breast, endometrial, thyroid cancers
- Loss of function mutations in PTEN gene at 10p23.21 (inhibitor of $P1_3K$/AKT signaling pathway)

Some syndromes

- Retinoblastoma
- Most common ocular tumor in children.
- 70% sporadic
- Loss of light reflex; “red” eye
- Neuronal origin
- Primitive embryonal tumor characterized by small cells with large nuclei.
- Flexner-Wintersteiner pseudo-rosettes identified about vessel.
- 13q14 (Rb) germline mutation essential for development of tumor.
- Germline mutation associated with bilateral disease as well as pinealoblastoma.

Some syndromes

- Ataxia-telangiectasia
- This disorder is characterized by progressive difficulty with coordinating movements (ataxia) beginning before age 5.
- Later develop difficulty walking, chorea, myoclonus, oculomotor apraxia (inability to move eyes side to side)
- Multiple telangiectases (clusters of enlarged vessels) on skin and in the eyes
- High risk of lung infection as well as development of leukemia and lymphoma

Some syndromes

- Autosomal recessive
- Female carriers have increased risk of breast cancer
- ATM gene at 11q22
- Recognizes broken DNA strands

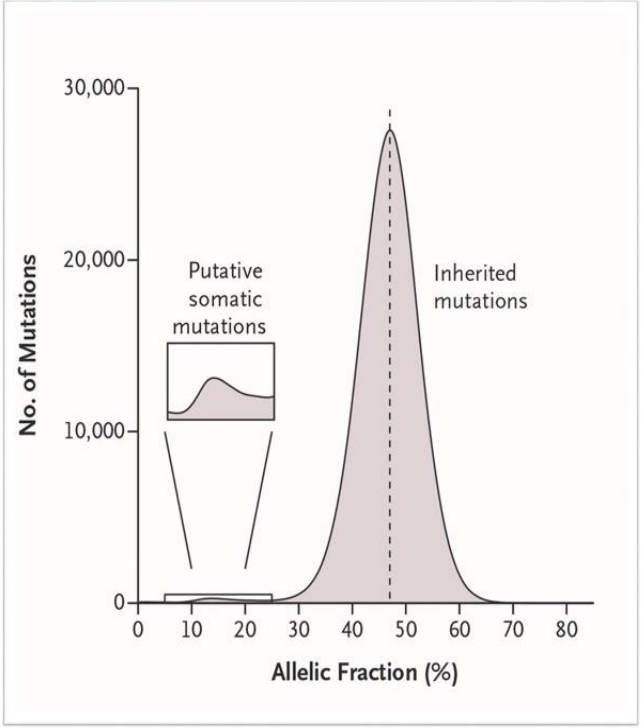
Some syndromes

- Familial melanoma
- 20% of melanoma
- All nevi have BRAF mutations
- Mutations in CDKN2A and ARF at 9p21
- Inhibit CDK4
- Mutations in CDK4 at 12q13
- BRCA 2 mutations at 13q12-13 also associated with increased risk of pancreatic adenocarcinoma

Germline/Inherited Genetic Variants

Remember that germline/inherited genetic variants are typically heterozygous

- **The variant allelic frequency (VAF) represents the fraction of alleles at any locus that carry that specific variant.**
- **An inherited, heterozygous variant associated with an autosomal dominant cancer syndrome (*BRCA1*, *TP53*, etc) should have a true VAF of 50%**
- **Due to technical considerations with NGS platforms, a range of 40-60% (or even 30-70%) can be reported with a heterozygous germline variant [1][2]**



[1]Judkins T et al, BMC Cancer 2015
[2]DiNardo CD et al, Cancer 2018
[3]Genovese G et al, NEJM 2014

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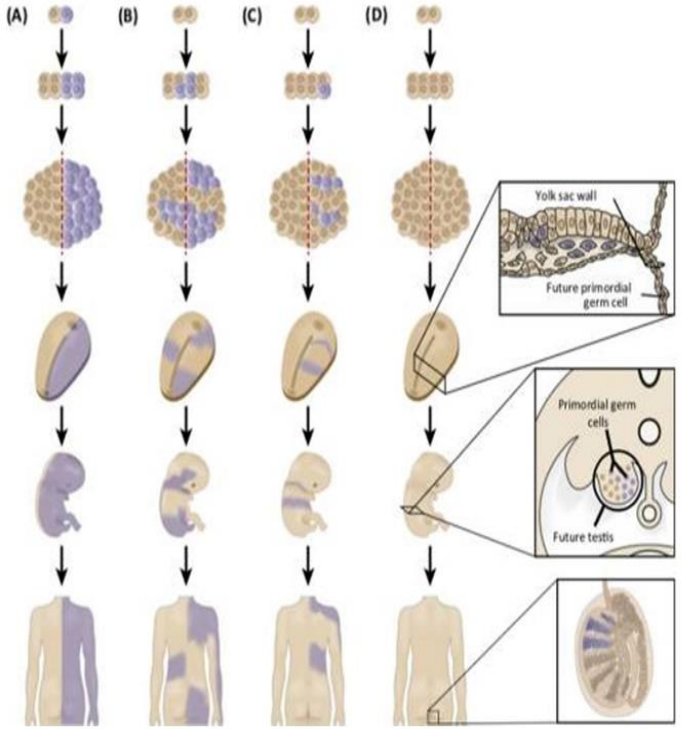
- Cell free DNA may detect clonal hematopoiesis (VAF <25%) but may also reflect underlying mutation.
- Not necessarily tumor related.
- Low level VAF in gene survey (TP53, ATM) probably clonal hematopoiesis.

Somatic Mosaicism

The term "mosaicism" is traditionally used in genetics to describe a disease-causing variant which occurs early in embryogenesis

(i.e. post-zygotic mosaicism)

Ex: a pathogenic variant classically seen throughout the mesoderm will be present in both the peripheral blood and in fibroblast analysis



Batalini et al, Breast Cancer Res 2019

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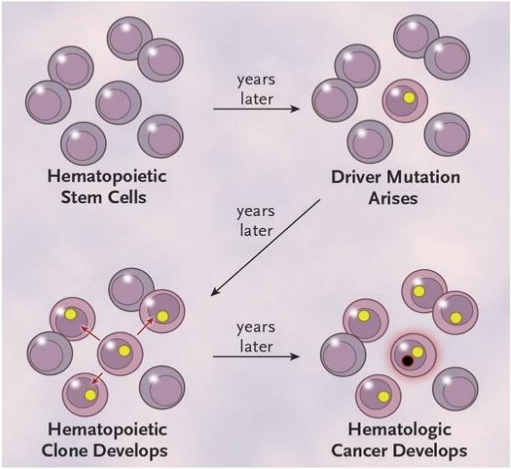
Somatic Mosaicism, continued

The term "mosaicism" is traditionally used in genetics to describe a disease-causing variant which occurs early in embryogenesis (i.e. post-zygotic mosaicism)

But variants can also develop later, in a more organ- or tissue- specific manner

Somatic variants developing in the hematopoietic system are now commonly referred to as clonal hematopoiesis (CH), clonal hematopoiesis of indeterminate potential (CHIP) or age-related clonal hematopoiesis (ARCH)



Jaiswal et al, NEJM 2014
Genovese G et al, NEJM 2014

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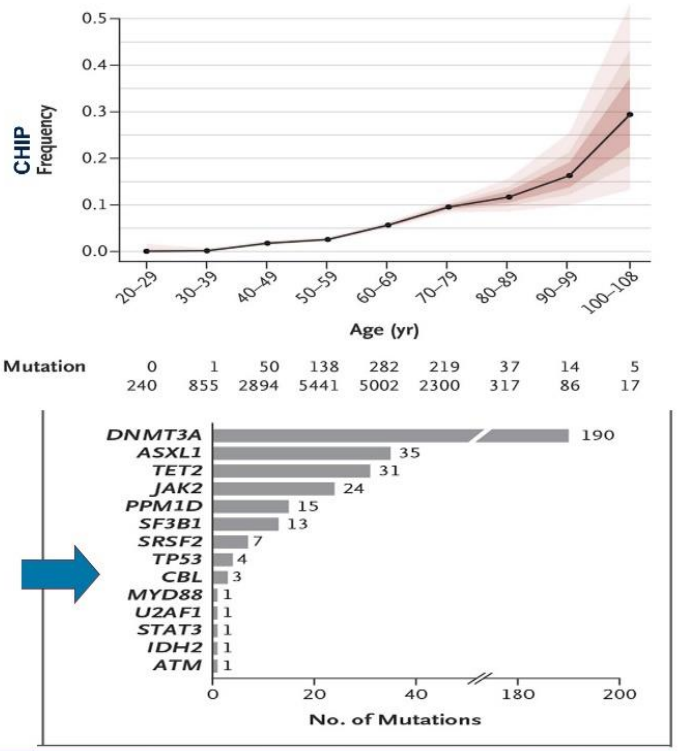
Clonal Hematopoiesis

- CH: Somatic variants in the hematopoietic system without an underlying heme malignancy
- Occurs in > 10% of healthy individuals over age 65 (using 2% VAF cutoff)
- The most common CH genes : *DNMT3A, TET2, ASXL1*
- Others include *TP53, PPM1D, CHEK2, ATM*



Jaiswal et al, NEJM 2014
Genovese G et al, NEJM 2014
Bolton K et al, Nat Gen 2020

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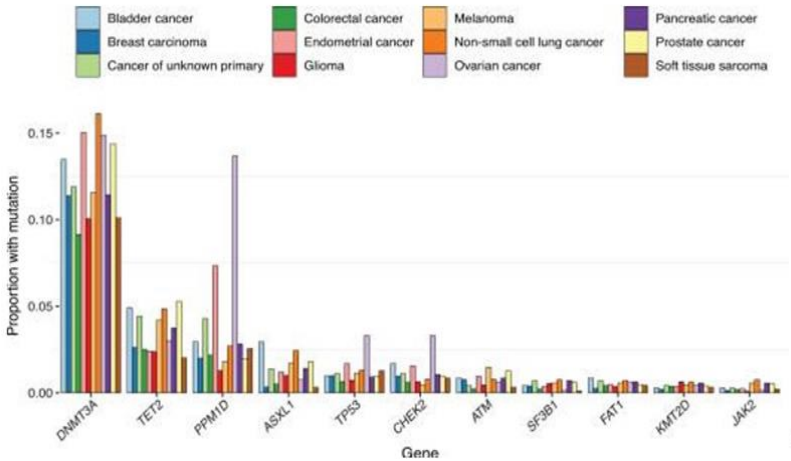
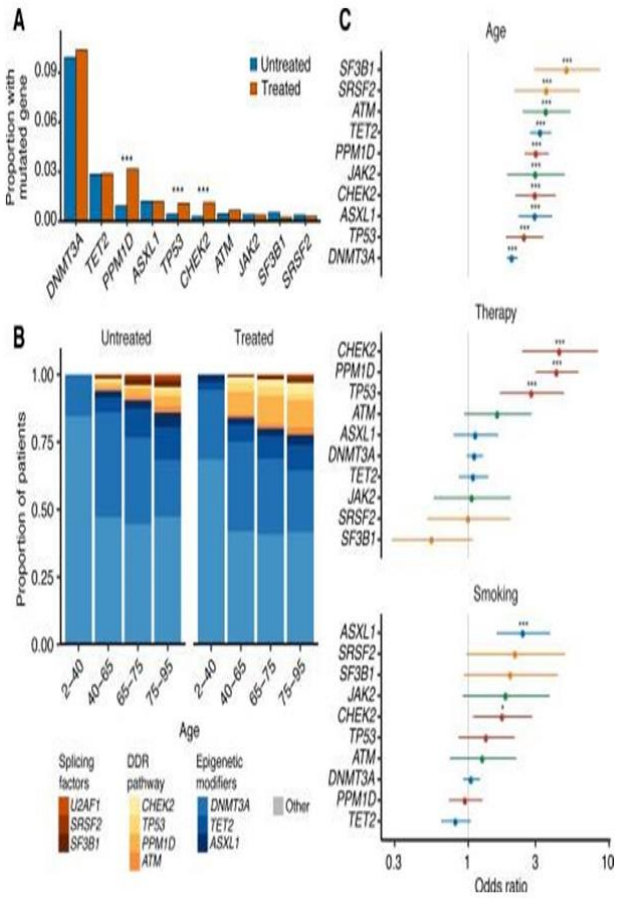
Clonal Hematopoiesis

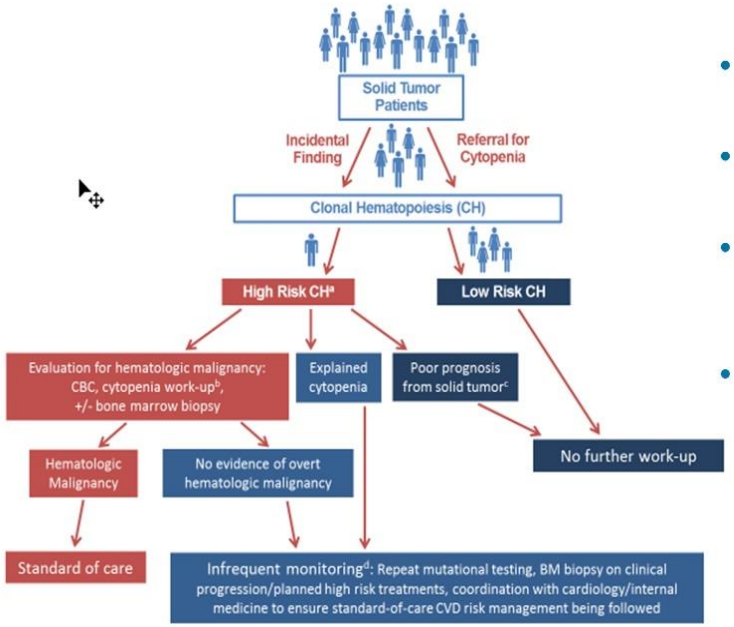
- CH is even MORE common in pts with cancer
- Among ~25,000 cancer patients, CH in 30% with median VAF 4.7% (range 2-87%)
- Increased incidence with history of prior XRT, platinum-based therapy and/or ovarian ca, increasing age and tobacco use





Bolton K et al, Nat Gen 2020

Clonal Hematopoiesis



- Increased risk of progression to hematologic malignancy
- Increased risk of cardiovascular disease and all-cause mortality
- ~ 1% of patients with CH will progress to a heme malignancy per year (similar to MGUS -> multiple myeloma)
- Recommendations include heme referral for surveillance and CBC monitoring; consideration of baseline bone marrow evaluation to rule out occult heme malignancy

Bolton K et al, Nat Gen 2020

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Table 7-11 Paraneoplastic Syndromes

Clinical Syndromes	Major Forms of Underlying Cancer	Causal Mechanism
Endocrinopathies		
Cushing syndrome	Small-cell carcinoma of lung Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate antidiuretic hormone secretion	Small-cell carcinoma of lung Intracranial neoplasms	Antidiuretic hormone or atrial natriuretic hormones
Hypercalcemia	Squamous cell carcinoma of lung Breast carcinoma Renal carcinoma Adult T-cell leukemia/lymphoma	Parathyroid hormone-related protein (PTHRP), TGF-α, TNF, IL-1
Hypoglycemia	Ovarian carcinoma Fibrosarcoma Other mesenchymal sarcomas	Insulin or insulin-like substance
Polycythemia	Renal carcinoma Cerebellar hemangioma Hepatocellular carcinoma	Erythropoietin
Nerve and Muscle syndromes		
Myasthenia	Bronchogenic carcinoma Thymic neoplasms	Immunologic
Disorders of the central and peripheral nervous system	Breast carcinoma	
Dermatologic Disorders		
Acanthosis nigricans	Gastric carcinoma Lung carcinoma Uterine carcinoma	Immunologic; secretion of epidermal growth factor
Dermatomyositis	Bronchogenic carcinoma Breast carcinoma	Immunologic
Osseous, Articular, and Soft Tissue Changes		
Hypertrophic osteoarthropathy and clubbing of the fingers	Bronchogenic carcinoma Thymic neoplasms	Unknown
Vascular and Hematologic Changes		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma Bronchogenic carcinoma Other cancers	Tumor products (mucins that activate clotting)
Disseminated intravascular coagulation	Acute promyelocytic leukemia Prostatic carcinoma	Tumor products that activate clotting
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability
Red cell aplasia	Thymic neoplasms	Unknown
Others		
Nephrotic syndrome	Various cancers	Tumor antigens, immune complexes

ACTH, Adrenocorticotropic hormone; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor.

Paraneoplastic syndromes

- Cushing syndrome is the most common endocrinopathy.
- Truncal obesity
- Facial plethora
- Proximal muscle weakness
- Hypokalemia
- It is caused by excessive production of corticotropin or corticotropinlike peptides.

Paraneoplastic syndromes

- The precursor of corticotropin is a large molecule known as pro-opiomelanocortin.
- Lung cancer patients with Cushing syndrome have elevated serum levels of both pro-opiomelanocortin and corticotropin.
- The former is not found in serum of patients with excess corticotropin produced by the pituitary.

Paraneoplastic syndromes

- Syndrome of inappropriate ADH secretion
- Often presents with confusion and delirium
- Na^+ <125 mEq/L
- U_{Osm} <275 mOsm/kg
- U_{Na+} >40 mEq/L
- Fractional Na^+ excretion >1%

Paraneoplastic syndromes

- Hypercalcemia of malignancy
- Parathyroid hormone-related protein (PTHRP), is a molecule that resembles PTH only in its N terminus.
- It has some biologic actions similar to those of PTH
- Both hormones share a G protein–coupled receptor, known as PTH/PTHRP receptor.
- PTHRP regulates calcium transport in the lactating breast and across the placenta, and modulates pulmonary development and remodeling.

Paraneoplastic syndromes

- In contrast to PTH, PTHRP is produced in small amounts by many normal tissues, including keratinocytes, muscles, bone, and ovary.
- Tumors most often associated with paraneoplastic hypercalcemia are carcinomas of the breast, lung, kidney, and ovary.
- Remember that the chief cause of hypercalcemia is excessive ingestion of Vitamin D and/or calcium.
- A serum Calcium level >12.0mg/dL may be life threatening. May respond to saline diuresis.

Paraneoplastic syndromes

- Cancer cachexia is associated with:
- Equal loss of both fat and lean muscle
- Elevated basal metabolic rate
- Evidence of systemic inflammation.
- Proteolysis inducing factor produced by tumor.

Table 1

Paraneoplastic syndromes and their associated antibodies and tumours. The most frequent antibodies and tumours are listed in bold

Neurological syndrome	Antibody	Tumour	References
Encephalomyelitis/limbic encephalitis	**Anti-Hu, anti-Ma2,** anti-CV2/CRMP5, anti-VGKC, anti-Ri, anti-amphiphysin, anti-GABA$_B$R, anti-AMPAR, anti-GAD	**SCLC, testicular tumour,** thymoma, neuroblastoma, prostate carcinoma, breast cancer, Hodgkin's lymphoma	[6,50,63,72–75]
Cerebellar degeneration	**Anti-Yo, anti-Hu,** anti-VGCC, anti-CV2/CRMP5, anti-Ma2, anti-Ri, anti-Tr, anti-GAD, anti-mGluR1-α	**SCLC, ovarian cancer, breast cancer, Hodgkin's lymphoma,** thymoma	[8,48,51,76,77]
Brainstem encephalitis/opsoclonus-myoclonus	**Anti-Ri, anti-Ma2,** anti-Hu, anti-amphiphysin	Breast cancer, ovarian cancer, testicular tumour, SCLC, neuroblastoma (children)	[50,78]
Encephalitis with psychiatric manifestations, seizures, dyskinesias, dystonia and autonomic instability	**Anti-NMDAR**	**Ovarian teratoma,** testis teratoma, SCLC	[5,79]
Neuromyotonia	**Anti-VGKC**	Thymoma, SCLC	[19]
Lambert-Eaton myasthenic syndrome	**Anti-VGCC**	**SCLC**	[80]
Myasthenia gravis	**Anti-AChR**	**Thymoma**	[81]
Subacute sensory neuronopathy	**Anti-Hu,** anti-CV2/CRMP5, anti-amphiphysin	**SCLC,** breast cancer, ovarian cancer	[6,82]
Subacute autonomic neuropathy	Anti-gAChR, anti-Hu	**SCLC,** thymoma	[82]
Stiff-person syndrome	**Anti-amphiphysin,** anti-GAD	**Breast cancer,** SCLC	[83–86]
Cancer-associated retinopathy	Anti-recoverin	**SCLC,** endometrium cancer	[87–89]

SCLC, small cell lung cancer.

doi: 10.1111/j.1468-1331.2010.03220.x
Accessed 02/20/2020

Paraneoplastic syndromes

- Lambert-Eaton syndrome
- Proximal muscle weakness
- Orthostatic change
- Diplopia but no ptosis (distinguish from myasthenia gravis)
- Improves during the day (distinguish from myasthenia gravis)
- Due to antibodies to presynaptic voltage gated (P/Q) calcium channel

Paraneoplastic syndromes

- Subacute cerebellar degeneration
- Presents with dizziness, nausea, and vomiting
- Ataxia
- Dysarthria
- Vertigo
- Diplopia
- Antibody to Purkinje cell
- May coincide with Lambert-Eaton syndrome
- Also seen in thiamine deficiency
- Optic neuritis
- Anti-CV2 antibody (to oligodendroglia)

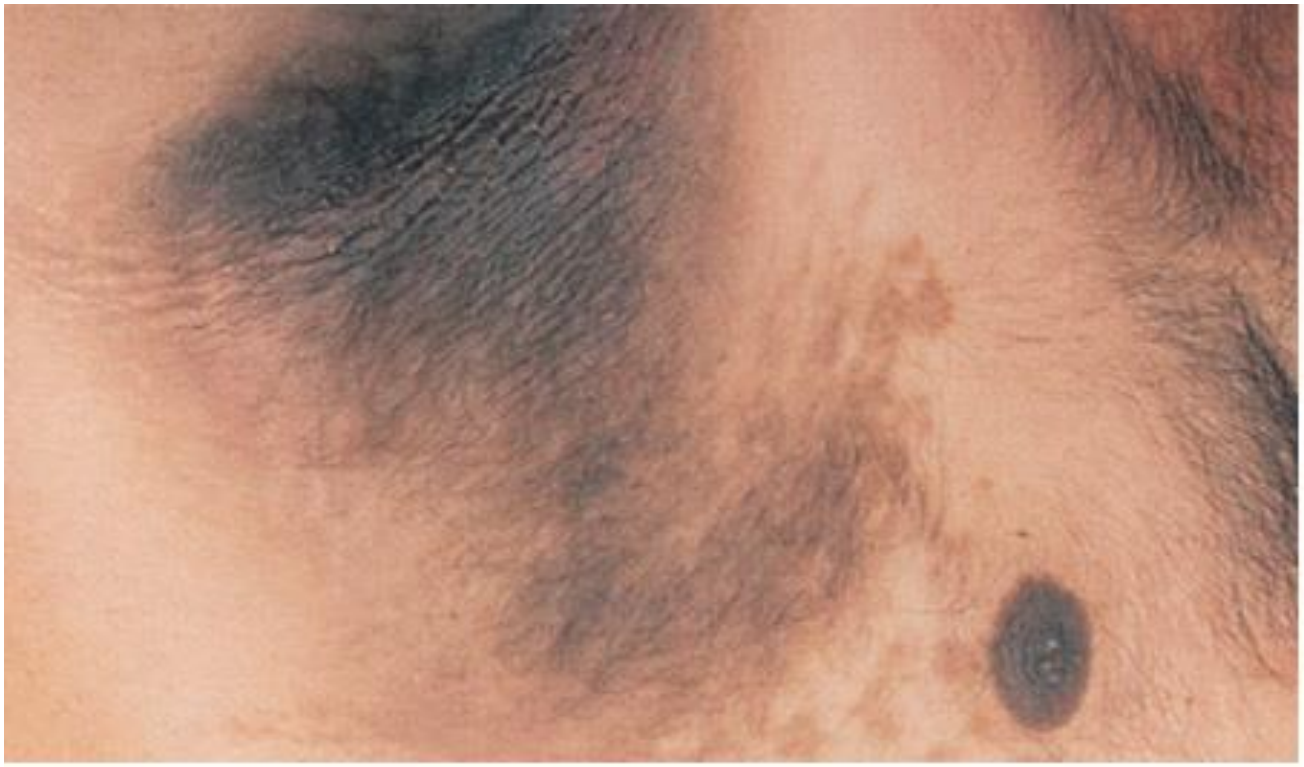
Paraneoplastic syndromes

- Limbic encephalitis
- Short-term memory defects
- Seizures
- Psychiatric disturbances
- Anti-Hu antibody
- May also be seen with germ cell tumor of testis (anti-Ma2) or ovarian teratoma (anti-NDAR)
- Indistinguishable from Herpes simplex or HSV-6 encephalitis
- (There are non-neoplastic variants associated with antibody to voltage gated potassium channels)

Acanthosis nigricans

- Develops gradually during childhood or puberty.
- Hyperplastic and hyperpigmented papules with “velvet” texture
- Flexor surfaces as well as posterior neck, axilla, groin.
- May be autosomal dominant.
- FGFR3 mutation
- Usually associated with insulin resistant diabetes
- IGFR1 activates same signalling pathways
- May see with pituitary or pineal tumors
- If arise in middle age, may be harbinger of GI cancer.

Acanthosis nigricans



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

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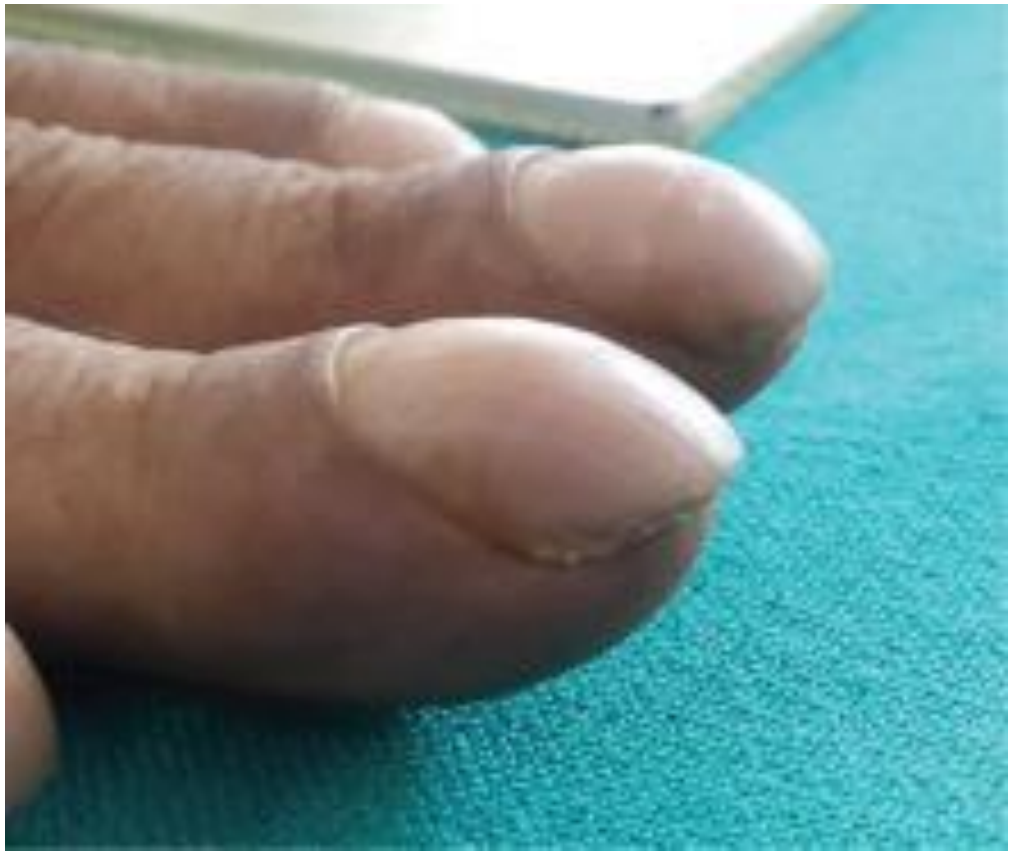
Fig. e-10 Accessed 07/16/2010

Hypertrophic osteoarthropathy

- Characterized by periosteal new bone formation, primarily at the distal ends of long bones, metatarsals, metacarpals, and proximal phalanges;
- Arthritis of the adjacent joints
- Nail changes associated with periostitis (on x-ray) are commonly associated with squamous carcinoma of the lung (in up to 5%) but may be seen in mesothelioma and liver cancer.
- Clubbing without periostitis is seen in cyanotic heart disease.

Hypertrophic osteoarthropathy



Digital clubbing.
Loss of normal nail angle.

https://www.mdedge.com/ccjm/article/134382/imaging/hypertrophic-osteoarthropathy-uncommon-presentation-lung-cancer Fig. 1 Accessed 12/10/2019

Paraneoplastic syndromes

- 10% of patients with pancreatic adenocarcinoma may have migratory thrombophlebitis (Trousseau syndrome)
- Patients at risk for venous thromboembolism:
- Stomach cancer (very high risk)
- Lung cancer
- Lymphoma
- GYN cancer
- Bladder cancer
- Testicular cancer
- Stratify with Khorana score

Predominant types of cancer	Pancreatic cancer, adenocarcinoma	Acute promyelocytic leukemia, metastatic prostate cancer	Many solid cancers
Predominant clinical symptom	Thrombosis	Bleeding	Neither
Different clinical presentations	Features of arterial ischemia, which can manifest as uneven, patchy discoloration of the skin, symptoms of poor digital circulation, cerebrovascular manifestations, peripheral neuropathy and ischemic colitis Venous thrombosis or pulmonary embolism An unusual form of non-infectious endocarditis has been noted to be a manifestation of cancer-related DIC	Widespread bruising, bleeding from mucosal surfaces, central nervous system, lungs, gastrointestinal tract and from sites of trauma Hemorrhage is the most common cause of induction mortality in acute promyelocytic leukemia, while catastrophic bleeding can occur before the diagnosis is made in some cases.	Only laboratory abnormalities, but no obvious clinical symptoms or signs of coagulation activation or fibrinolysis These abnormalities may include thrombocytopenia, hypofibrinogenemia and microangiopathic hemolytic anemia These features may remain long-standing due to the continuous thrombin generation as part of DIC, but may worsen or improve depending on the underlying malignancy
Treatment	That of underlying cancer Anticoagulation with heparin	That of underlying cancer Supportive care with blood products	That of underlying cancer Anticoagulation with heparin

Management of cancer-associated disseminated intravascular coagulation: guidance from the SSC of the ISTH
JTH 2015;13 (4) 671-675
https://doi.org/10.1111/jth.12838
Accessed 05/05/2020

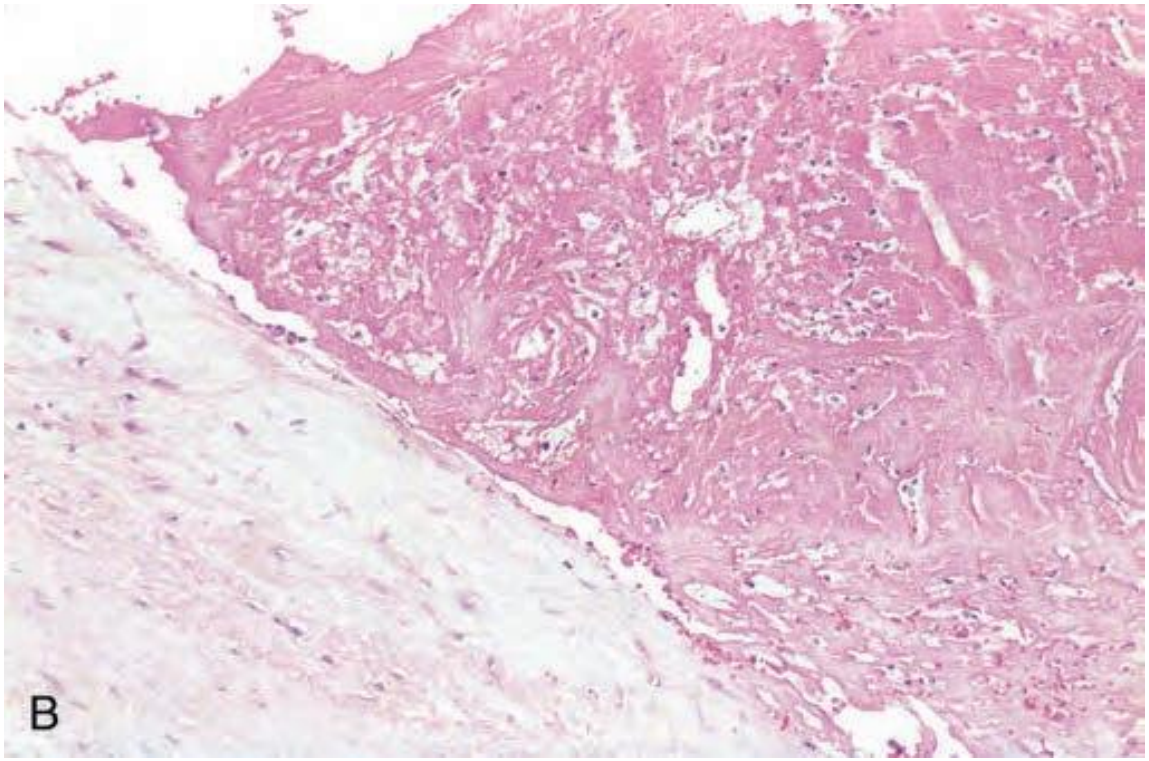
Paraneoplastic syndromes

- ITSH recommends against the routine use of tranexamic acid and recombinant FVIIa in patients with cancer-related DIC.
- If therapy-resistant bleeding dominates the picture in hyperfibrinolytic DIC, tranexamic acid may be considered.

Paraneoplastic syndromes

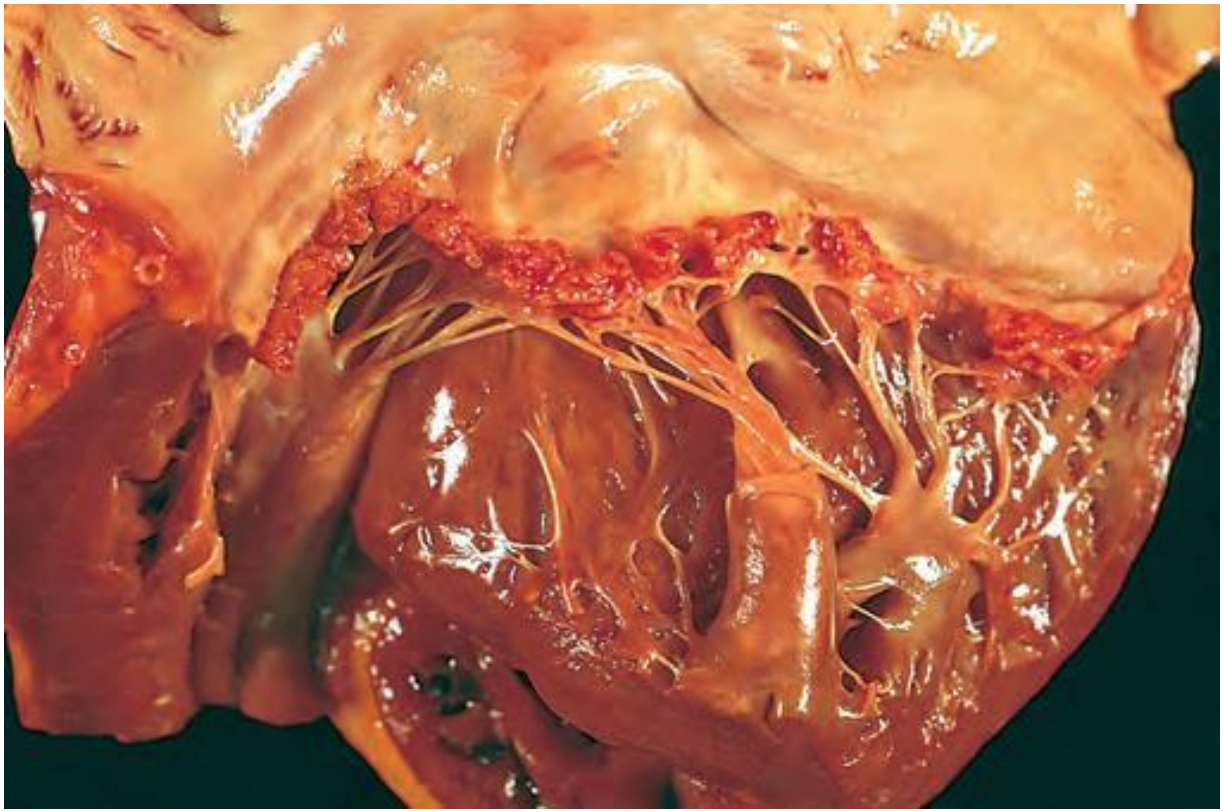
- Non-thrombotic bacterial (marantic) endocarditis
- Sterile verrucous vegetations (thrombus cap)
- No inflammatory infiltrate in tissue
- Procoagulant effect of circulating mucin from mucinous adenocarcinomas.
- Rarely embolize.
- Similar lesions are seen in antiphospholipid syndrome.
- Procoagulant effect.

Non-thrombotic bacterial (Marantic) endocarditis



Schoen, and FJ, Mitchell, RN, “Heart”, in Kumar, V, Abbas, AK, Aster, JC (eds.), Robbins and Cotran Pathologic Basis of Disease, 9th edition. 2015. Elsevier. Philadelphia. Fig. 12-26B.

Non-thrombotic bacterial (Marantic) endocarditis



Schoen, and FJ, Mitchell, RN, “Heart”, in Kumar, V, Abbas, AK, Aster, JC (eds.), Robbins and Cotran Pathologic Basis of Disease, 9th edition. 2015. Elsevier. Philadelphia. Fig. 12-26A.

Detection methods in tissue

- Detection, quantification, and characterization of tumors cells circulating in the blood has prognostic importance.
- Flow cytometry identifies cellular antigens expressed in leukemias and lymphoma.
- Immunohistochemistry to identify organ of origin.
- FISH to identify translocations

Detection methods in tissue

- PCR-based evaluation of rearranged T-cell receptor or immunoglobulin genes allows distinction between monoclonal (neoplastic) and polyclonal (reactive) proliferations.
- PCR amplification of nucleic acid sequences to establish/exclude presence of malignant disease
- DNA microarrays

Immunohistochemistry

Antibodies

- Breast
  - Estrogen Receptor
  - Herceptin Receptor
  - Progesterone Receptor
- Endothelial
  - Factor 13A
  - CD 31
  - CD 34
- Epithelial
  - Light
  - Heavy
  - pancytokeratin
- Lymphoid
  - T cell markers
  - B cell markers
  - CD 45
  - CD 68
  - Non-Hodgkins
- Muscle
  - Desmin
  - Myogenin
  - Smooth Muscle Actin
  - Vimentin
- Melanoma
  - HMB 45
  - Melan A
  - S100
- Mesothelial
  - Calretinin
  - CD 141
  - Carcinoembryonic antigen
  - CK 5/6
  - EP4
- Neuroendocrine
    - Chromogranin
    - CK20
    - Neurone specific elastase
    - Synaptophysin
  - Urological/Prostatic
    - CKHMW
    - Prostatic Specific Antigen
    - Prostatic Specific Acid Phosphatase

Cell surface markers

CELL	MARKER
Macrophage	CD14 (pattern associated molecular patterns) CD 40, CD33 CCR5 (HIV binding) MHC II B7 (binds CD28 on antigen presenting cell) Fc, C3b
B cells	CD19, CD20 CD21 (EBV binding) MHCII B& (binds CD28 on antigen presenting cell)
T cells	CD4, CD8 TCR (binds with MHC-antigen complex) CD3 (signals with TCR) CD28 (binds B7 on antigen presenting cell) CXCR4, CXCR5 (HIV binding)
Helper cells are CD4+	
Regulatory cells are CD4+ and CD25+	
Cytotoxic T cells are CD8+	MHC I CXCR4, CXCR5 (HIV binding)
NK cells	CD56 CD16 (binds Fc of IgG)
Dendritic cell (antigen processing cell)	CD11, CD40, CD 123

Cell surface markers

CELL	MARKER
Hematopoietic stem cells	CD34
Granulocyte	CD66
Erythrocyte	CD235
Platelet	CD41, CD61, CD62
Endothelial cell	CD146
Epithelial cell	CD326
PECAM adhesion molecule	CD31
Lymphocyte function associated antigen (LFA-3)	CD58
TNF Receptor	CD40

Table 7-12 Selected Tumor Markers

Tumor Markers	Tumor Types
Hormones	
Human chorionic gonadotropin	Trophoblastic tumors, nonseminomatous testicular tumors
Calcitonin	Medullary carcinoma of thyroid
Catecholamine and metabolites	Pheochromocytoma and related tumors
Ectopic hormones	See Table 7-11
Oncofetal Antigens	
α-Fetoprotein	Liver cell cancer, nonseminomatous germ cell tumors of testis
Carcinoembryonic antigen	Carcinomas of the colon, pancreas, lung, stomach, and heart
Isoenzymes	
Prostatic acid phosphatase	Prostate cancer
Neuron-specific enolase	Small-cell cancer of lung, neuroblastoma
Specific Proteins	
Immunoglobulins	Multiple myeloma and other gammopathies
Prostate-specific antigen and prostate-specific membrane antigen	Prostate cancer
Mucins and Other Glycoproteins	
CA-125	Ovarian cancer
CA-19-9	Colon cancer, pancreatic cancer
CA-15-3	Breast cancer
Cell-Free DNA Markers	
TP53, APC, RAS mutants in stool and serum	Colon cancer
TP53, RAS mutants in stool and serum	Pancreatic cancer
TP53, RAS mutants in sputum and serum	Lung cancer
TP53 mutants in urine	Bladder cancer