Cancer Genetics

Chapter 76 | Harrison's 22e

KEY CLINICAL POINTS

1. Cancer is a genetic disease resulting from somatic mutations that disrupt normal cellular proliferation control mechanisms.
2. Two primary classes of driver genes: oncogenes (activated) and tumor-suppressor genes (inactivated).
3. Multistep clonal expansion typically requires 3 cumulative mutations for common solid tumors, but only 2 for liquid tumors (leukemias/lymphomas).
4. Germline mutations in cancer predisposition genes lead to familial cancer clustering and hereditary syndromes.
5. Tumor heterogeneity (intratumoral, intermetastatic, intrametastatic, and interpatient) results from ongoing clonal evolution and genetic instability.
6. Genetic testing algorithms identify pathogenic mutations in an index patient to guide screening of asymptomatic relatives.
7. The 'Two-Hit Hypothesis' explains how tumor suppressor genes like RB1 require two hits (e.g., via Loss of Heterozygosity) for malignancy.
8. Specific translocations, such as t(9;22), create fusion proteins (e.g., BCR-ABL) that drive leukemia.
9. Genetic instability (MIN/CIN) accelerates the progression from benign to malignant states.
10. Negative genetic tests must be interpreted with caution due to limited sensitivity of current molecular assays.

1. DEFINITION & OVERVIEW

Cancer is a genetic disease arising from somatic mutations that disrupt normal cellular proliferation control mechanisms.

> ***Definition (Harrison's 22e):*** *Cancer driver gene: A gene containing a mutation that increases the selective growth advantage of the cell containing it.*

- **Clonal Origin of Cancer:**
  - Most cancers originate from a single cell through clonal expansion.
  - Multistep clonal development requires multiple cumulative mutations.
  - Each mutation provides an incremental growth advantage.
  - Tumor progression follows Darwinian microevolution principles.
  - Transformation to malignancy typically takes decades in most cases.
- **Mutation Requirements:**
  - Solid tumors: Typically require 3 cumulative mutations (Initiation, Expansion, Invasion).
  - Liquid tumors (leukemias/lymphomas): May require only 2 driver gene alterations.

– Benign tumorigenesis requires fewer mutations than malignant transformation.

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2. GENETIC BASIS OF CANCER

Cancer arises through somatic alterations in DNA that disrupt normal proliferation control mechanisms.

- **Mutational Processes:**
  – Initiation: First mutation provides growth advantage (e.g., APC inactivation).
  – Expansion: Second mutation enhances clonal expansion (e.g., KRAS/BRAF activation).
  – Invasion: Third mutation enables metastatic potential (e.g., TP53 loss).
  – Genetic instability (MIN/CIN) increases the likelihood of mutation at each step.
- **Genetic Basis of Cancer:**
  – Somatic mutations: Arise from replication errors, carcinogen exposure, or faulty DNA repair.
  – Germline mutations: Occur in cancer predisposition genes and cause familial clustering.
  – Oncogenes: Activated by mutations or aberrant regulation (e.g., RAS, MYC).
  – Tumor-suppressor genes: Inactivated by loss-of-function mutations (e.g., TP53, APC).

Key Driver Genes and Mechanisms

- **Oncogenes Commonly Altered in Human Cancers:**
  – AKT1: Serine/threonine kinase (Point mutation).
  – BRAF: Serine/threonine kinase (Point mutation).
  – CCND1: Cell cycle progression (Amplification) → Esophageal, head and neck.
  – CTNNB1: Signal transduction (Point mutation).
  – EGFR: Signal transduction (Point mutation) → Lung.
  – FLT3: Signal transduction (Point mutation).
  – IDH1: Chromatin modification (Point mutation) → Glioma.
  – MDM2/MDM4: Inhibitor of p53 (Amplification; MDM4 associated with Breast cancer).
  – MYC/MYCL1: Transcription factor (Amplification) → Ovarian, bladder.
- **Translocation-Driven Oncogenes:**
  – BCR-ABL: (9;22)(q34;q11) → Chronic myeloid leukemia (CML).
  – BCL2 (18q21.3)–IgH (14q32): (14;18)(q32;q21) → Follicular lymphoma.
  – LCK-TCRB: (1;7)(p34;q35) or (2;13)(q35;q14) → T-cell acute lymphocytic leukemia.
  – PAX8-PPARG: (2;3)(q13;p25) or (3;16)(q27;p11) → Thyroid.
  – TAL1-TCTA: (1;3)(p34;p21) → Acute T-cell leukemia.
- **Hereditary Cancer Syndromes:**
  – Ataxia telangiectasia (ATM, 11q22-q23): Breast.
  – Birt-Hogg-Dubé syndrome (FLCN, 17p11.2): Kidney (hybrid oncocytic, chromophobe).
  – Cowden syndrome (PTEN, 10q23): Breast, thyroid.
  – Familial melanoma (CDKN2A, 9p21): Melanoma, pancreatic.
  – Hereditary breast/ovarian cancer (BRCA1, BRCA2, 17q21; 13q12.3; 16q22).
  – Hereditary nonpolyposis colon cancer (HNPCC) (MSH2, MLH1, MSH6, PMS2): Colon, endometrial, ovarian, stomach, small bowel, ureter.
  – Juvenile polyposis syndrome (SMAD4, BMPR1A): Gastrointestinal, pancreatic.
  – Multiple endocrine neoplasia type 1 (MEN1): Parathyroid, endocrine, pancreas, pituitary.

  - Neurofibromatosis type 1 (NF1): Neurofibroma, neurofibrosarcoma, brain.
  - Gorlin's syndrome (PTCH1): Basal cell carcinoma, medulloblastoma.
  - Tuberous sclerosis (TSC1, TSC2): Angiofibroma, renal angiomyolipoma.
- **Signaling Pathways Altered in Cancer:**
  - Cell cycle regulation/apoptosis: RB1, BCL2.
  - RAS pathway: KRAS, BRAF.
  - PI3K pathway: PTEN, PIK3CA.
  - JAK/STAT: JAK2, FLT3.
  - MAPK: MAP3K, ERK.
  - TGF-β: BMPR1A, SMAD4.
  - Other pathways: Notch, Hedgehog, WNT/APC.
  - Genome maintenance: ATM, BRCA1.

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3. HISTORICAL PERSPECTIVE

- Otto Warburg's combustion theory (abnormal oxygen metabolism) was disproven.
  - Viral theories were partially validated (e.g., HPV in cervical cancer).
  - Retroviral studies identified first human oncogenes (V-SRC).
  - Molecular identification of somatic mutations established the genetic basis.

Evolution of Understanding

- 19th century: Tumors recognized as cellular masses.
  - Early 20th century: Warburg's oxygen metabolism theory.
  - Mid-20th century: Chemical mutagenesis and radiation studies.
  - Late 20th century: Molecular identification of driver genes.

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4. GENETIC TESTING ALGORITHM

The following steps outline the clinical decision-making process for genetic testing in a family with cancer predisposition (see Figure 2):

1. **Patient Selection:** Identify patients from three categories:
   - Family with a known cancer syndrome.
   - Family with a history of cancer.
   - Any recent cancer.
2. **Pre-test Workup:**
   - Provide pretest counseling.
   - Review family history.
   - Obtain informed consent.
3. **Index Patient Testing:** Perform molecular analysis on the cancer patient to identify specific disease-causing mutations.
4. **Decision Branch (Mutation Found):**

→ Identify mutation → Proceed to screening of asymptomatic family members.

5. **Decision Branch (No Mutation Found):**

→ No mutation identified → No basis for increased risk in family members based on that specific gene.

6. **Follow-up & Action:**

→ If relative tests positive: Implement increased screening or surgical intervention.

→ If relative tests negative: No greater risk than general population.

Clinical Implications

- **Positive test:** Indicates a specific mutation; requires increased screening or prophylactic surgery for at-risk relatives.
  - **Negative test:** No mutation identified in the index patient means no basis for risk in others. If a relative tests negative after an index positive, they are at no greater risk than the general population.
  - **Sensitivity Warning:** No molecular assay is 100% sensitive; negative results must be interpreted with caution as they do not rule out all risks if the correct gene was not targeted.

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5. TUMOR HETEROGENEITY

Tumor heterogeneity is the inevitable result of cell proliferation and clonal evolution.

- **Types of Heterogeneity:**
  - Intratumoral: Distinct subclones within a single tumor (e.g., primary tumor).
  - Intermetastatic: Genetic differences between different metastatic lesions in the same patient.
  - Intrametastatic: Genetic differences among cells within a single metastatic lesion.
  - Interpatient: Unique mutations in different patients; tumors are not monolithic.
- **Clinical Significance:**
  - Heterogeneity is critical for precision medicine.
  - Different clones may respond differently to treatment, explaining why a drug might work at one site but not another.

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6. GENETIC MECHANISMS OF MALIGNANCY

Specific mechanisms drive the transition from normal cells to malignancy:

- **The Two-Hit Hypothesis:**
  - Required for tumor suppressor genes (e.g., RB1) in hereditary syndromes.
  - Requires Loss of Heterozygosity (LOH).
  - LOH can occur via:

→ Mitotic crossing over.

→ Independent mutation or small deletion.

- **APC Mutation Dynamics:**
  - APC encodes a 2843-amino-acid protein with domains: O, ARM, 15 aa, 20 aa, B, and E/D.
  - All known pathogenic mutations result in truncation of the protein.
  - Mutation Hotspots: Positions 1061 and 1309 account for one-third of cases in Familial Adenomatous Polyposis (FAP).
- **Colorectal Cancer Progression:**

→ Normal epithelium → Early adenoma (Initiation) → Late adenoma (Expansion) → Carcinoma (Invasion) → Metastasis.

- Germline APC mutations place patients at Step 1 (Early adenoma).
- Genetic instability (MIN/CIN) accelerates progression through these steps.

7. KEY PEARLS & HIGH-YIELD POINTS

- **Mutation Thresholds:**
  - 3 mutations → common solid tumors.
  - 2 mutations → liquid tumors (leukemias/lymphomas).
- **Clinical Utility of Testing:**

→ Identifying a mutation in an index patient is the prerequisite for screening asymptomatic relatives.

- **Tumor Heterogeneity:**

→ Essential concept for precision medicine; tumors are not monolithic.

→ Different sites (e.g., primary vs. metastasis) may have different genetic profiles and respond differently to treatment.

REFERENCE TABLES

TABLE 76-1

Oncogenes Commonly Altered in Human Cancers

FUNCTION	ALTERATION IN CANCER	NEOPLASM
Serine/threonine kinase	Point mutation	Skin
Serine/threonine kinase	Point mutation	
Cell cycle progression	Amplification	Esophageal, head and neck
Signal transduction	Point mutation	
Signal transduction	Point mutation	Lung
Signal transduction	Point mutation	
Chromatin modification	Point mutation	Glioma
Inhibitor of p53	Amplification	
Inhibitor of p53	Amplification	Breast
Transcription factor	Amplification	
Transcription factor	Amplification	Ovarian, bladder
Transcription factor	Amplification	
Phosphoinositol-3-kinase	Point mutation	Multiple cancers
GTPase	Point mutation	
GTPase	Point mutation	Melanoma

TABLE 76-2

Representative Oncogenes at Chromosomal Translocations

GENE (CHROMOSOME)	TRANSLOCATION	MALIGNANCY
BCR-ABL	(9;22)(q34;q11)	Chronic myeloid leukemia
	(11;14)(q13;q32)	
BCL2 (18q21.3)–IgH (14q32)	(14;18)(q32;q21)	Follicular lymphoma
	(11;22)(q24;q12)	
LCK-TCRB	(1;7)(p34;q35)	T-cell acute lymphocytic leukemia
	(2;13)(q35;q14)	
PAX8-PPARG	(2;3)(q13;p25)	Thyroid
	(3;16)(q27;p11)	
TAL1-TCTA	(1;3)(p34;p21)	Acute T-cell leukemia
	Rearrangement on Chr21q22	

TABLE 76-3

Cancer Predisposition Syndromes and Associated Genes SYNDROME Ataxia telangiectasia Autoimmune lymphoproliferative...

SYNDROME GENE	CHROMOSOME INHERITANCE	TUMORS
Ataxia telangiectasia ATM	11q22-q23 AR	Breast
	10q24 1q23 AD	
Birt-Hogg-Dubé syndrome FLCN	17p11.2 AD	Kidney (hybrid oncocytic, chromophobe)
	15q26.1 AR	
Cowden syndrome PTEN	10q23 AD	Breast, thyroid
	5q21 AD 1p34.1 AR	
Familial melanoma CDKN2A	9p21 AD	Melanoma, pancreatic
	11p13 AD	
Hereditary breast/ovarian cancer BRCA1 BRCA2	17q21 AD 13q12.3	Breast, ovarian, prostate
	16q22 AD	

SYNDROME GENE	CHROMOSOME INHERITANCE	TUMORS
Hereditary multiple exostoses **EXT1** **EXT2**	8q24 AD 11p11-12	Exostoses, chondrosarcoma
	13q14.2 AD	
Hereditary nonpolyposis colon cancer (HNPCC) MSH2 **MLH1** **MSH6** **PMS2**	2p16 AD 3p21.3 2p16 7p22	Colon, endometrial, ovarian, stomach, small bowel, ureter carcinoma
	7q31 AD	
Juvenile polyposis syndrome **SMAD4** **BMPR1A**	18q21 AD	Gastrointestinal, pancreatic
	17p13.1 AD	
Multiple endocrine neoplasia type 1 MEN1	11q13 AD	Parathyroid, endocrine, pancreas, and pituitary
	10q11.2 AD	
Neurofibromatosis type 1 NF1	17q11.2 AD	Neurofibroma, neurofibrosarcoma, brain
	22q12.2 AD	
Nevoid basal cell carcinoma syndrome (Gorlin's syndrome) PTCH1	9q22.3 AD	Basal cell carcinoma, medulloblastoma, jaw cysts
	19p13.3 AD	
Tuberous sclerosis TSC1 **TSC2**	9q34 AD 16p13.3	Angiofibroma, renal angiomyolipoma
	3p25-26 AD	

TABLE 76-4

Signaling Pathways Altered in Cancer PROCESS Cell survival

PROCESS	PATHWAY	REPRESENTATIVE DRIVER GENES
Cell survival	Cell cycle regulation/ apoptosis	RB1, BCL2
	RAS	KRAS, BRAF
	PIK3CA	PTEN, PIK3CA
	JAK/STAT	JAK2, FLT3
	MAPK	MAP3K, ERK

PROCESS	PATHWAY	REPRESENTATIVE DRIVER GENES
	TGF-β	BMPR1A, SMAD4
	Notch	
	Hedgehog	
	WNT/APC	
	Chromatin modification	
	Transcriptional regulation	
Genome maintenance	DNA damage signaling and repair	ATM, BRCA1