# Cancer Genetics



### KEY CLINICAL POINTS

1. See source text for full details

### FIGURES IN THIS CHAPTER



## RAW CONTENT

[PAGE 519]

Cancer

Genetics

519

CHAPTER

76

Manson JE et al: Vitamin D supplements and prevention of cancer and THE CLONAL ORIGIN AND MULTISTEP

cardiovascular disease. N Engl J Med 380:33, 2019. NATURE OF CANCER

Mcneil JJ et al: Effect of aspirin on all-cause mortality in the healthy Nearly all cancers originate from a single cell; this clonal origin is a

elderly. N Engl J Med 379:1519, 2018. critical discriminating feature between neoplasia and hyperplasia.

Melnikow J et al: Screening for cervical cancer with high-risk human Multiple cumulative mutational events are invariably required for the

papillomavirus testing: Updated evidence report and systematic progression of a tumor from normal to fully malignant phenotype. The

review for the US Preventive Services Task Force. JAMA 320:687, process can be seen as Darwinian microevolution in which, at each

2018. successive step, the mutated cells gain a growth advantage resulting

Welch HG et al: Epidemiologic signatures in cancer. N Engl J Med in the expansion of a neoplastic clone (Fig. 76-1). Based on observa-

384:14, 2019. tions of cancer frequency increases during aging, the epidemiologists

Woloshin S et al: Breast-cancer mortality trends in four countries Armitage and Doll and Nordling independently proposed that cancer

with varied screening practices. N Engl J Med 389:1061, 2023. is a result of three discrete cellular changes. Remarkably, this early

Zeraatkar D et al: Effect of lower versus high red meat intake on model has been validated by extensive sequencing of cancer genomes.

cardiometabolic and cancer outcomes: A systematic review of ran- These studies revealed that just three causal mutations are required for

domized trials. Ann Intern Med 171:721, 2019. the development of several of the most common cancers. Overall, it is

currently believed that most common solid tumors require a minimum

of three mutated cancer driver genes (either oncogenes or tumor-

suppressor genes) for their development. One or two mutations are

sufficient for benign tumorigenesis, but not for the invasive capacity

that distinguishes cancers from benign tumors. Less common tumors,

such as liquid tumors (leukemias or lymphomas), sarcomas, and

76 Cancer Genetics childhood tumors, appear to require only two driver gene alterations

for malignancy. Note that a cancer driver gene is best defined as one

containing a mutation that increases the selective growth advantage of

Fred Bunz, Bert Vogelstein

the cell containing it. Normally, cell birth and cell death are in perfect

equilibrium; every time a cell is born, another in the same lineage dies.

Cancer driver gene mutations alter this equilibrium, so that more cells

CANCER IS A GENETIC DISEASE

are born than die. The imbalance is often slight, so that the difference

Cancer arises through a series of somatic alterations in DNA that result between cell birth and cell death can be less than 1%. This explains, in

in unrestrained cellular proliferation. Most of these alterations involve combination with the low rate of mutation, why tumorigenesis—the

subtle sequence changes in DNA (i.e., mutations). The somatic mutations journey from a normal cell to a typical malignant, solid tumor—often

may originate as a consequence of random replication errors or exposure takes decades.

to carcinogens (e.g., radiation) and can be exacerbated by faulty DNA We now know the precise nature of the genetic alterations respon-

repair processes. While most cancers arise sporadically, clustering of can- sible for nearly all malignancies and are beginning to understand how

cers occurs in families that carry a germline mutation in a cancer gene. these alterations promote the distinct stages of tumor growth. The

prototypical example is colon cancer, in which analyses of genomes

HISTORICAL PERSPECTIVE

from the entire spectrum of neoplastic growths—from normal colon

The idea that cancer progression is driven by sequential somatic muta-

tions in specific genes has only gained general acceptance in the past

30 years. Before the advent of the microscope, cancer was believed to

be composed of aggregates of mucus or other noncellular matter. By

the middle of the nineteenth century, it became clear that tumors were

masses of cells and that these cells arose from the normal cells of the

Initiation

tissue from which the cancer originated. The molecular basis for the

uncontrolled proliferation of cancer cells was to remain a mystery for

another century. During that time, a number of theories for the origin of

cancer were postulated. The great biochemist Otto Warburg proposed

the combustion theory of cancer, which stipulated that cancer was due

to abnormal oxygen metabolism. Others believed that all cancers were

caused by viruses and that cancer was in fact a contagious disease.

In the end, observations of cancer occurring in chimney sweeps, Expansion

studies of x-rays, and the overwhelming data demonstrating cigarette

smoke as a causative agent in lung cancer, together with Ames's work

on chemical mutagenesis, were consistent with the idea that cancer

originated through changes in DNA. However, it was not until the

somatic mutations responsible for cancer were identified at the molec-

ular level that the genetic basis of cancer was definitively established.

Although the viral theory of cancer did not prove to be generally

Invasion

accurate (with exceptions such as human papillomaviruses, which can

cause cervical and other cancers), the study of retroviruses led to the

discovery of the first human oncogenes in the late 1970s. Oncogenes

are one of the two major classes of cancer driver genes. The study of

families with genetic predisposition to cancer was instrumental to the

discovery of the other major class of cancer driver genes, called tumor- FIGURE 76-1 Multistep clonal development of malignancy. In this diagram, a series

of three cumulative mutations, each with a modest growth advantage acting alone,

suppressor genes. Current technologies permit the sequence analysis of

eventually results in a malignant tumor. Note that not all such alterations result in

entire cancer genomes and provide a comprehensive view of the genetic

progression. The actual number of cumulative mutations necessary to transform

changes that cause tumors to arise and become malignant. The field from the normal to the malignant state has been estimated to be three for several of

that studies the various types of mutations, as well as the consequences the most common types of cancer. (Adapted and modified from PC Nowell: The clonal

of these mutations in tumor cells, is now known as cancer genetics. evolution of tumor cell populations. Science 194:23, 1976.)

[TABLE]

Initiation

Expansion

Invasion

[/TABLE]

[PAGE 520]



promote tumor formation. The agent responsible

Microsatellite Instability (MIN) or

Chromosomal Instability (CIN) for the transmission of the cancer was a retrovirus

(Rous sarcoma virus [RSV]), and the oncogene

responsible was identified 75 years later as V-SRC.

Other oncogenes were also discovered through

APC inactivation KRAS or SMAD4 or TGFb II their presence in the genomes of retroviruses that

or b-catenin BRAF inactivation are capable of causing cancers in chickens, mice,

activation activation TP53 inactivation

and rats. The nonmutated cellular homologues of

these viral genes are called proto-oncogenes and

are often targets of mutation or aberrant regula-

tion in human cancer. Whereas many oncogenes

were discovered on the basis of their presence in

Normal Early Late

Carcinoma Metastasis retroviruses, other oncogenes, particularly those

epithelium adenoma adenoma

involved in translocations characteristic of par-

ticular leukemias and lymphomas, were identi-

Initiation Expansion Invasion

fied through genomic approaches. Investigators

FIGURE 76-2 Progressive somatic mutational steps in the development of colon carcinoma. The cloned the sequences surrounding the chromo-

accumulation of alterations

## FLOWCHARTS & ALGORITHMS — FROM HARRISON'S

carcinoma of the thyroid, and (in some pedigrees) pheochromocytoma, is due to gain-of-function mutations in the proto-oncogene *RET* on chromosome 10. Similarly, gain-of-function mutations in the tyrosine kinase domain of the *MET* oncogene lead to hereditary papillary renal carcinoma. Interestingly, loss-of-function mutations in the *RET* gene cause a completely different disease, Hirschsprung's disease (aganglionic megacolon **[Chaps. 339 and 400]**).

Although the heritable forms of cancer have taught us much about the mechanisms of growth control, most forms of cancer do not follow simple Mendelian patterns of inheritance. The majority of human cancers arise in a sporadic fashion, solely as a result of somatic mutation, and in the absence of any mutations in cancer-predisposing genes in their germlines.

## GENETIC TESTING FOR FAMILIAL CANCER

The discovery of cancer susceptibility genes raises the possibility of DNA testing to predict the risk of cancer in individuals of affected families. An algorithm for cancer risk assessment and decision making in high-risk families using genetic testing is shown in **Fig. 76-6**. Once a mutation is discovered in a family, subsequent testing of asymptomatic family members is crucial. A negative gene test in these individuals can prevent years of anxiety, providing comfort in the knowledge that their cancer risk is no higher than that of the general population. On the other hand, a positive test may lead to alteration of clinical management, such as increased frequency of cancer screening and, when feasible and appropriate, prophylactic surgery. Potential negative consequences of a positive test result include psychological distress (anxiety, depression) and discrimination, although the Genetic Information Nondiscrimination Act (GINA) makes it illegal for predictive genetic information to be used to discriminate in health insurance or employment. Testing should therefore not be conducted without counseling before testing is administered and during and after disclosure of the test result.

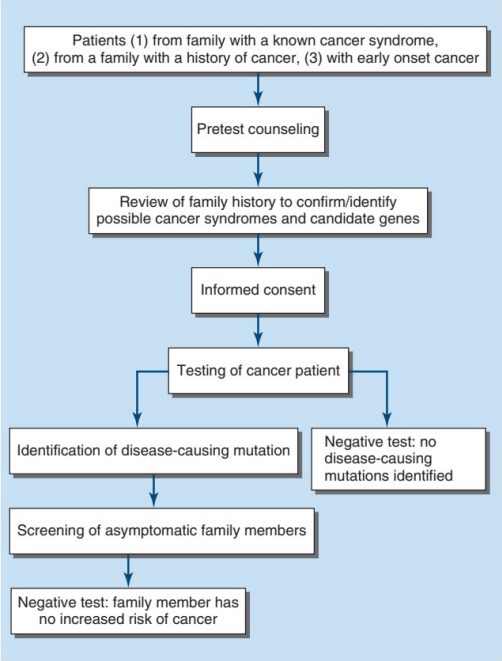



**FIGURE 76-6 Algorithm for genetic testing in a family with cancer predisposition.** The key step is the identification of a disease mutation in a cancer patient, which is an indication for the testing of asymptomatic family members. Asymptomatic family members who test positive may require increased screening or surgery, whereas those who test negative are at no greater risk for cancer than the general

It is now feasible to obtain high-quality sequence of all of the protein-coding DNA sequences, and even of the entire genome, in any given individual. In such studies, numerous variants in DNA sequences will inevitably be identified in every subject, but the significance of the vast majority of these DNA sequence findings will be unclear. Even mutations in tumor-suppressor genes can be difficult to interpret unless there is an obvious functional implication, such as the truncation of the open reading frame, or that particular mutation has previously been correlated with cancer in other individuals. Germline mutations associated with cancer predisposition are uncommon in individuals without a family history of cancer, though they do occur. Much more common are *variants of unknown significance* (*VUS*). VUS that are found during genetic testing cannot be used to evaluate the relative risk of cancer but may nonetheless cause anxiety because they represent a deviation from the reference allele that is established as "normal." Because of the low yield of informative mutations that modify cancer risk and the frequent identification of VUS, it is generally not appropriate to use DNA sequencing to assess cancer risk in individuals without a family history of cancer. However, there are exceptions. Testing may be appropriate in some subpopulations with a known increased risk, even without a personal family history. For example, two mutations in the breast cancer susceptibility gene *BRCA1*, 185delAG and 5382insC, exhibit a sufficiently high frequency in the Ashkenazi Jewish population that genetic testing based on ethnicity alone may be warranted.

It is important that genetic test results be communicated to families by trained genetic counselors. To ensure that the families clearly understand its advantages and disadvantages and the impact it may have on disease management and psyche, genetic testing should never be done *before* counseling. Significant expertise is needed to communicate the results of genetic testing to families.

## VIRUSES IN HUMAN CANCER

Several human malignancies are associated with viruses. Examples include Burkitt's lymphoma (Epstein-Barr virus; **Chap. 199**), hepatocellular carcinoma (hepatitis viruses), cervical cancer (human papillomavirus [HPV]; **Chap. 203**), and T-cell leukemia (retroviruses; **Chap. 207**). There are several types of HPV, including the high-risk types 16 and 18 that are strongly associated with the development of cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancer. The mechanisms of action of all these viruses involve inactivation of tumor-suppressor genes. For example, HPV proteins E6 and E7 bind to and inactivate cellular tumor suppressors p53 and pRB, respectively. This is the reason that HPV is such a potent initiator of cancer: infection with a virus is tantamount to having two of the three mutant driver genes required for cancer, that is, one viral oncogene inactivates p53 and the other inactivates Rb. Once these two inactivated gene products initiate tumorigenesis, only one additional mutant gene is required for these tumors to progress to malignancy.

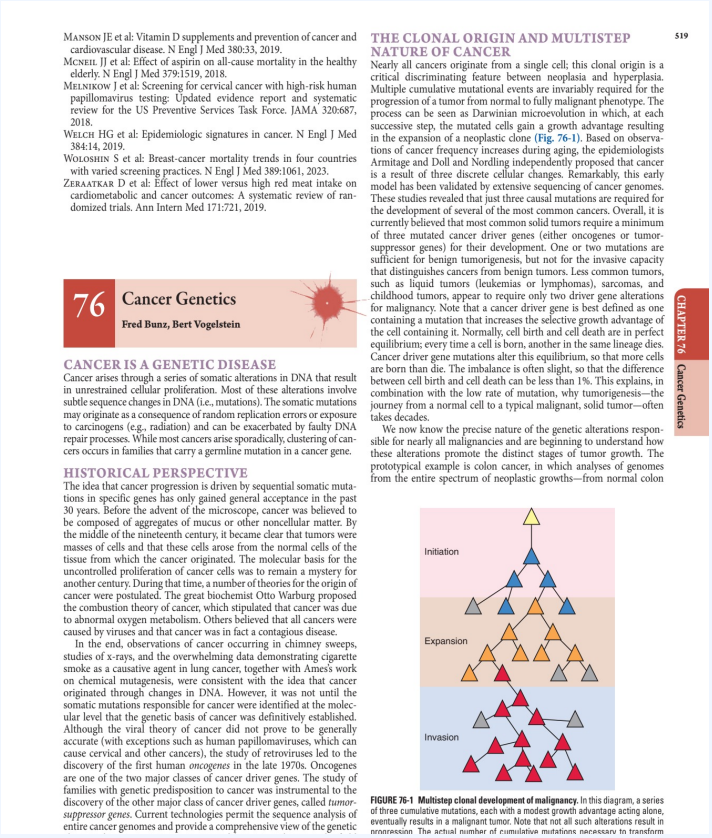
### CANCER GENOMES

The advent of relatively inexpensive technologies for rapid and high-throughput DNA sequencing has facilitated the comprehensive analysis of numerous genomes from many types of tumors. This unprecedented view into the genetic nature of cancer has provided remarkable insights. Most cancers do not arise in the context of a mutator phenotype, and accordingly, the number of mutations in even the most advanced cancers is relatively modest. Common solid tumors harbor 30–70 subtle mutations that are nonsynonymous (i.e., result in an amino acid change in the encoded protein). Liquid tumors such as leukemias, as well as pediatric tumors, typically have fewer than 20 mutations. The vast majority of the mutations detected in tumors are



Harrison's 22e · Flowchart 1

*FIGURE 76-6 Algorithm for genetic testing in a family with cancer predisposition. The key step is the identification of a disease mutation in a cancer patient, which in is an indication for the testing of asymptomatic family members. Asymptomatic as family members who test positive may require increased screening or surgery, whereas those who test negative are at no greater risk for cancer than the general population. It should be emphasized that no molecular assay used for this sort of testing is 100% sensitive; negative results must be interpreted with this caveat in mind.*



MANSON JE et al: Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med 380:33, 2019.
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76 Cancer Genetics

Fred Bunz, Bert Vogelstein

CANCER IS A GENETIC DISEASE

Cancer arises through a series of somatic alterations in DNA that result in unrestrained cellular proliferation. Most of these alterations involve subtle sequence changes in DNA (i.e., mutations). The somatic mutations may originate as a consequence of random replication errors or exposure to carcinogens (e.g., radiation) and can be exacerbated by faulty DNA repair processes. While most cancers arise sporadically, clustering of cancers occurs in families that carry a germline mutation in a cancer gene.

HISTORICAL PERSPECTIVE

The idea that cancer progression is driven by sequential somatic mutations in specific genes has only gained general acceptance in the past 30 years. Before the advent of the microscope, cancer was believed to be composed of aggregates of mucus or other noncellular matter. By the middle of the nineteenth century, it became clear that tumors were masses of cells and that these cells arose from the normal cells of the tissue from which the cancer originated. The molecular basis for the uncontrolled proliferation of cancer cells was to remain a mystery for another century. During that time, a number of theories for the origin of cancer were postulated. The great biochemist Otto Warburg proposed the combustion theory of cancer, which stipulated that cancer was due to abnormal oxygen metabolism. Others believed that all cancers were caused by viruses and that cancer was in fact a contagious disease.

In the end, observations of cancer occurring in chimney sweeps, studies of x-rays, and the overwhelming data demonstrating cigarette smoke as a causative agent in lung cancer, together with Ames's work on chemical mutagenesis, were consistent with the idea that cancer originated through changes in DNA. However, it was not until the somatic mutations responsible for cancer were identified at the molecular level that the genetic basis of cancer was definitively established. Although the viral theory of cancer did not prove to be generally accurate (with exceptions such as human papillomaviruses, which can cause cervical and other cancers), the study of retroviruses led to the discovery of the first human *oncogenes* in the late 1970s. Oncogenes are one of the two major classes of cancer driver genes. The study of families with genetic predisposition to cancer was instrumental to the discovery of the other major class of cancer driver genes, called *tumor-suppressor genes*. Current technologies permit the sequence analysis of entire cancer genomes and provide a comprehensive view of the genetic

519

THE CLONAL ORIGIN AND MULTISTEP NATURE OF CANCER

Nearly all cancers originate from a single cell; this clonal origin is a critical discriminating feature between neoplasia and hyperplasia. Multiple cumulative mutational events are invariably required for the progression of a tumor from normal to fully malignant phenotype. The process can be seen as Darwinian microevolution in which, at each successive step, the mutated cells gain a growth advantage resulting in the expansion of a neoplastic clone (Fig. 76-1). Based on observations of cancer frequency increases during aging, the epidemiologists Armitage and Doll and Nordling independently proposed that cancer is a result of three discrete cellular changes. Remarkably, this early model has been validated by extensive sequencing of cancer genomes. These studies revealed that just three causal mutations are required for the development of several of the most common cancers. Overall, it is currently believed that most common solid tumors require a minimum of three mutated cancer driver genes (either oncogenes or tumor-suppressor genes) for their development. One or two mutations are sufficient for benign tumorigenesis, but not for the invasive capacity that distinguishes cancers from benign tumors. Less common tumors, such as liquid tumors (leukemias or lymphomas), sarcomas, and childhood tumors, appear to require only two driver gene alterations for malignancy. Note that a cancer driver gene is best defined as one containing a mutation that increases the selective growth advantage of the cell containing it. Normally, cell birth and cell death are in perfect equilibrium; every time a cell is born, another in the same lineage dies. Cancer driver gene mutations alter this equilibrium, so that more cells are born than die. The imbalance is often slight, so that the difference between cell birth and cell death can be less than 1%. This explains, in combination with the low rate of mutation, why tumorigenesis—the journey from a normal cell to a typical malignant, solid tumor—often takes decades.

We now know the precise nature of the genetic alterations responsible for nearly all malignancies and are beginning to understand how these alterations promote the distinct stages of tumor growth. The prototypical example is colon cancer, in which analyses of genomes from the entire spectrum of neoplastic growths—from normal colon

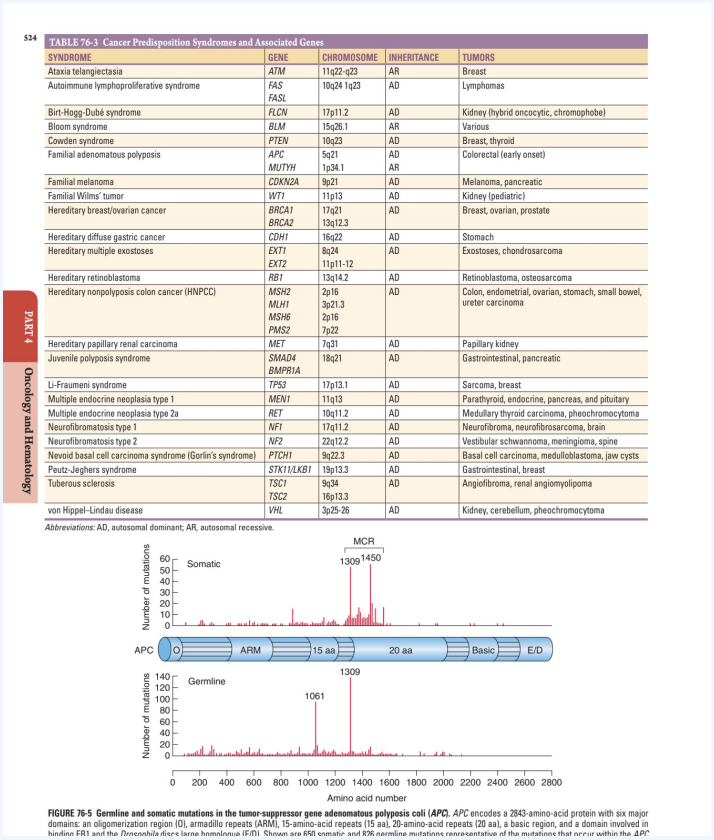
CHAPTER 76 Cancer Genetics



**FIGURE 76-1 Multistep clonal development of malignancy.** In this diagram, a series of three cumulative mutations, each with a modest growth advantage acting alone, eventually results in a malignant tumor. Note that not all such alterations result in progression. The actual number of cumulative mutations necessary to transform

**Harrison's 22e · Figure 1**

*FIGURE 76-1 Multistep clonal development of malignancy. In this diagram, a series of three cumulative mutations, each with a modest growth advantage acting alone, of eventually results in a malignant tumor. Note that not all such alterations result in progression. The actual number of cumulative mutations necessary to transform from the normal to the malignant state has been estimated to be three for several of the most common types of cancer. (Adapted and modified from PC Nowell: The clonal evolution of tumor cell populations. Science 194:23, 1976.)*



524

**TABLE 76-3 Cancer Predisposition Syndromes and Associated Genes**

| SYNDROME | GENE | CHROMOSOME | INHERITANCE | TUMORS |
|---|---|---|---|---|
| Ataxia telangiectasia | *ATM* | 11q22-q23 | AR | Breast |
| Autoimmune lymphoproliferative syndrome | *FAS*<br>*FASL* | 10q24 1q23 | AD | Lymphomas |
| Birt-Hogg-Dubé syndrome | *FLCN* | 17p11.2 | AD | Kidney (hybrid oncocytic, chromophobe) |
| Bloom syndrome | *BLM* | 15q26.1 | AR | Various |
| Cowden syndrome | *PTEN* | 10q23 | AD | Breast, thyroid |
| Familial adenomatous polyposis | *APC*<br>*MUTYH* | 5q21<br>1p34.1 | AD<br>AR | Colorectal (early onset) |
| Familial melanoma | *CDKN2A* | 9p21 | AD | Melanoma, pancreatic |
| Familial Wilms' tumor | *WT1* | 11p13 | AD | Kidney (pediatric) |
| Hereditary breast/ovarian cancer | *BRCA1*<br>*BRCA2* | 17q21<br>13q12.3 | AD | Breast, ovarian, prostate |
| Hereditary diffuse gastric cancer | *CDH1* | 16q22 | AD | Stomach |
| Hereditary multiple exostoses | *EXT1*<br>*EXT2* | 8q24<br>11p11-12 | AD | Exostoses, chondrosarcoma |
| Hereditary retinoblastoma | *RB1* | 13q14.2 | AD | Retinoblastoma, osteosarcoma |
| Hereditary nonpolyposis colon cancer (HNPCC) | *MSH2*<br>*MLH1*<br>*MSH6*<br>*PMS2* | 2p16<br>3p21.3<br>2p16<br>7p22 | AD | Colon, endometrial, ovarian, stomach, small bowel, ureter carcinoma |
| Hereditary papillary renal carcinoma | *MET* | 7q31 | AD | Papillary kidney |
| Juvenile polyposis syndrome | *SMAD4*<br>*BMPR1A* | 18q21 | AD | Gastrointestinal, pancreatic |
| Li-Fraumeni syndrome | *TP53* | 17p13.1 | AD | Sarcoma, breast |
| Multiple endocrine neoplasia type 1 | *MEN1* | 11q13 | AD | Parathyroid, endocrine, pancreas, and pituitary |
| Multiple endocrine neoplasia type 2a | *RET* | 10q11.2 | AD | Medullary thyroid carcinoma, pheochromocytoma |
| Neurofibromatosis type 1 | *NF1* | 17q11.2 | AD | Neurofibroma, neurofibrosarcoma, brain |
| Neurofibromatosis type 2 | *NF2* | 22q12.2 | AD | Vestibular schwannoma, meningioma, spine |
| Nevoid basal cell carcinoma syndrome (Gorlin's syndrome) | *PTCH1* | 9q22.3 | AD | Basal cell carcinoma, medulloblastoma, jaw cysts |
| Peutz-Jeghers syndrome | *STK11/LKB1* | 19p13.3 | AD | Gastrointestinal, breast |
| Tuberous sclerosis | *TSC1*<br>*TSC2* | 9q34<br>16p13.3 | AD | Angiofibroma, renal angiomyolipoma |
| von Hippel–Lindau disease | *VHL* | 3p25-26 | AD | Kidney, cerebellum, pheochromocytoma |

*Abbreviations:* AD, autosomal dominant; AR, autosomal recessive.



**FIGURE 76-5 Germline and somatic mutations in the tumor-suppressor gene adenomatous polyposis coli (*APC*).** *APC* encodes a 2843-amino-acid protein with six major domains: an oligomerization region (O), armadillo repeats (ARM), 15-amino-acid repeats (15 aa), 20-amino-acid repeats (20 aa), a basic region, and a domain involved in binding EB1 and the *Drosophila* discs large homologue (E/D). Shown are 650 somatic and 826 germline mutations representative of the mutations that occur within the *APC*

PART 4 Oncology and Hematology

**Harrison's 22e · Figure 2**

*FIGURE 76-5 Germline and somatic mutations in the tumor-suppressor gene domains: an oligomerization region (O), armadillo repeats (ARM), 15-amino-acid repeats binding EB1 and the Drosophila discs large homologue (E/D). Shown are 650 somatic and gene (from the APC database at www.umd.be/APC). All known pathogenic mutations of be relatively evenly distributed up to codon 1600 except for two mutation hotspots mutations found in familial adenomatous polyposis (FAP) families.*

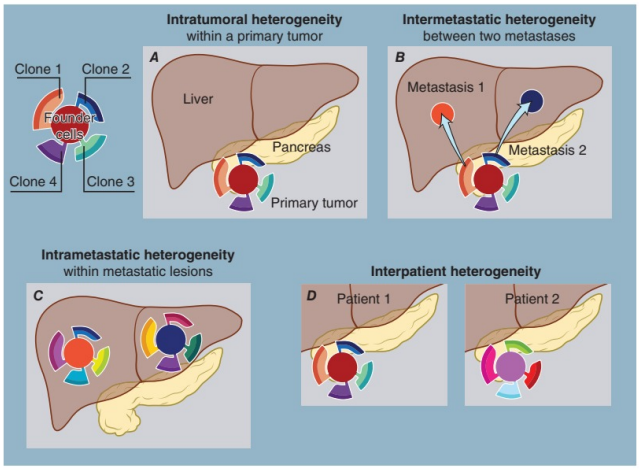



**FIGURE 76-7 Four types of tumor heterogeneity.** Tumor heterogeneity is the inevitable result of cell proliferation, as new mutations are introduced during clonal expansion. In a typical tumor (*upper left*), founder cells that harbor a large fraction of the total mutations give rise to subclones, which continue to evolve independently. The tumors of the founding populations are shown in the middle of each circle; the distinct subclones are shown around the periphery. ***A.*** Heterogeneity among the cells of a primary tumor is known as intratumoral heterogeneity. ***B.*** Heterogeneity among the founding cells of distinct metastatic lesions (marked as 1 and 2) that arise in the same patient is known



**Harrison's 22e · Figure 3**

*FIGURE 76-7 Four types of tumor heterogeneity. Tumor heterogeneity is the inevitable In a typical tumor (upper left), founder cells that harbor a large fraction of the total the founding populations are shown in the middle of each circle; the distinct subclones are is known as intratumoral heterogeneity. B. Heterogeneity among the founding cells of as intermetastatic heterogeneity. C. Heterogeneity among the cells of each metastatic The mutations in the tumors of two patients are almost completely distinct. 339(6127):1546, 2013.)*



to the diversity of mutations found in tumor-suppressor genes—most of the activated *KRAS* alleles contain point mutations in codons 12, 13, or 61. These mutations lead to constitutive activation of the mutant RAS protein. The restricted pattern of mutations observed in oncogenes compared to that of tumor-suppressor genes reflects the fact that gain-of-function mutations must occur at specific sites, while a broad variety of mutations can lead to loss of activity. Indeed, inactivation of a gene can in theory be accomplished through the introduction of a stop codon anywhere in the coding sequence, whereas activations require precise substitutions at residues that can somehow lead to an increase in the activity of the encoded protein under particular circumstances within the cell.

## DNA AMPLIFICATION

The second mechanism for activation of oncogenes is DNA sequence amplification, leading to overexpression of the gene product. This increase in DNA copy number may cause cytologically recognizable chromosome alterations referred to as *homogeneous staining regions* (HSRs) if integrated within chromosomes, or *double minutes* (dmins) if extrachromosomal.

Numerous genes have been reported to be amplified in cancer. Several of these genes, including *NMYC* and *LMYC*, were identified through their presence within the amplified DNA sequences of a tumor and their homology to known oncogenes. Because amplified regions

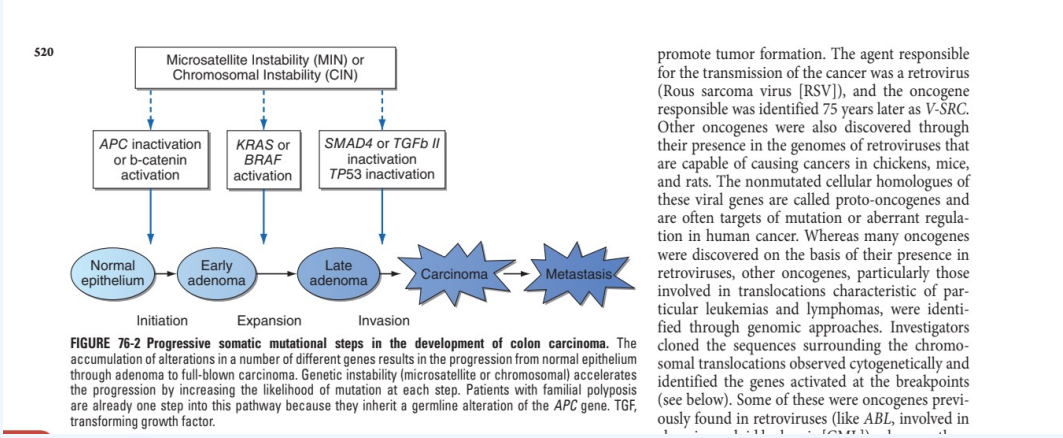
types have the capability to rearrange their DNA to generate antigen receptors. Indeed, antigen receptor genes are commonly involved in the translocations, implying that an imperfect regulation of receptor gene rearrangement may be involved in their pathogenesis. In addition to transcription factors and signal transduction molecules, translocation may result in the overexpression of cell cycle regulatory proteins or proteins such as cyclins and of proteins that regulate cell death. Recurrent translocations have more recently been identified in solid tumors such as prostate cancers. For example, fusions between *TMPRSS2* and *ERG*, which are normally located in tandem on chromosome 21, contribute to more than one-third of all prostate cancers.

The first reproducible chromosome abnormality detected in human malignancy was the Philadelphia chromosome detected in CML. This cytogenetic abnormality is generated by reciprocal translocation involving the *ABL* oncogene on chromosome 9, encoding a tyrosine kinase, being placed in proximity to the breakpoint cluster region (*BCR*) gene on chromosome 22. Figure 76-3 illustrates the generation of the translocation and its protein product. The consequence of expression of the *BCR-ABL* gene product is the activation of signal transduction pathways leading to cell growth independent of normal external signals. Imatinib, a drug that specifically blocks the activity of Abl tyrosine kinase, has shown remarkable efficacy with little toxicity in patients with CML. The successful targeting of *BCR-ABL* by imatinib is the paradigm for molecularly targeted anticancer therapies.



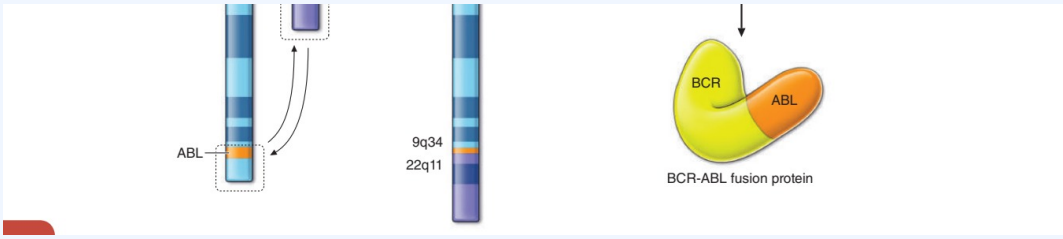
**Harrison's 22e · Figure 4**

*CHAPTER 76 22. Figure 76-3 illustrates the genera- its protein product. The consequence of gene product is the activation of signal to cell growth independent of normal drug that specifically blocks the activity remarkable efficacy with little tox- successful targeting of BCR-ABL by targeted anticancer therapies. IN SOLID*



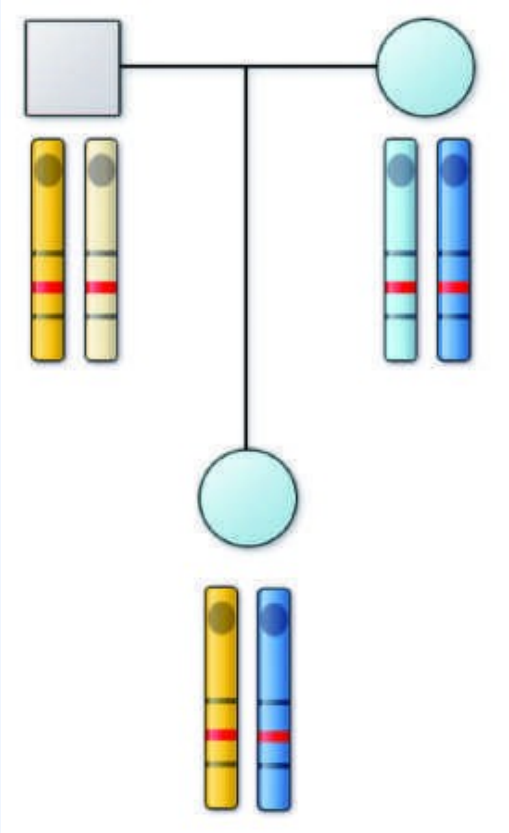

**Harrison's 22e · Figure 5**

*FIGURE 76-2 Progressive somatic mutational steps in the development of colon accumulation of alterations in a number of different genes results in the progression from through adenoma to full-blown carcinoma. Genetic instability (microsatellite or the progression by increasing the likelihood of mutation at each step. Patients with are already one step into this pathway because they inherit a germline alteration of transforming growth factor. epithelium through adenoma to carcinoma—have identified mutations that are highly characteristic of each type of lesion (Fig. 76-2).*




**Harrison's 22e · Figure 6**

*FIGURE 76-3 Specific translocation seen in chronic myeloid leukemia (CML). The chromosomes 9 and 22 with the breakpoint joining the sequences of the ABL oncogene entirely novel fusion protein with modified function.*



**Harrison's 22e · Figure 7**

*FIGURE 76-4 Diagram of possible mechanisms for tumor formation in an individual with hereditary (familial) retinoblastoma. On the left is shown the affected individual who has inherited the abnormal (Rb) allele from her affected mother. The normal allele is shown as a (+). The four chromosomes of her two drawn to indicate their origin. Flanking the retinoblastoma locus are genetic markers (A and B) also analyzed in this family. Markers A3 and B3 are on the carrying the retinoblastoma disease gene. Tumor formation results when the normal allele, which this patient inherited from her father, is inactivated. On the four possible ways in which this could occur. In each case, the resulting chromosome 13 arrangement is shown. Note that in the first three situations, the has been lost in the tumor tissue, which is referred to as loss of heterozygosity (LOH) at this locus.*