Rare, large families with multiple cases of early-onset cancer affecting several generations provide clear evidence that inherited factors are important causes of cancer. The range of cancers, the age at onset, and the number of generations affected all suggest familial risk. In this review, I discuss the five cancers in the United States that are associated with the highest number of deaths: lung, breast, colorectal, prostate, and pancreatic cancer.

In the late 1980s and early 1990s, numerous cancer susceptibility genes were identified, including those for breast and colorectal cancer (Glossary and Table 1). These genes confer high relative risks of cancer among carriers (i.e., they are highly penetrant). Thus, they could be detected by linkage analysis, wherein DNA obtained from many members of a family in which there are cases of cancer is collected and analyzed with the use of hundreds of anonymous, highly polymorphic DNA markers that are evenly spread across the genome. Family members are categorized in so-called liability classes, depending on their age and whether or not they have cancer, and a likelihood is assigned to putative gene carriers and noncarriers. With this information, the disease phenotype can be linked to one particular allele of a polymorphic marker, and a logarithm-of-odds (lod) score can be calculated for that allele. A high score (3.0 or higher) indicates a strong chance that the gene is located near the given marker (≥1000:1 in favor), whereas a low score (no higher than −2.0) means the gene is almost certainly not near that DNA marker locus.

Linkage analysis identified mainly tumor-suppressor genes. In hereditary cancer syndromes, one abnormal copy of the gene is inherited in the germ line from either parent, whereas the other copy is inactivated in a somatic cell, typically because of random processes whereby genes, chromosomes, or both are rearranged, deleted, or replaced. As a result, loss of heterozygosity is frequent at the position of the tumor-suppressor gene (Fig. 1), and in a tumor cell there is biallelic inactivation of the gene. Inherited biallelic mutations in tumor-suppressor genes are very rare and often result in a phenotype that differs from the phenotype of a monoallelic mutation (Table 2). In some genes, such as BRCA1 and APC, biallelic truncating mutations are incompatible with intrauterine development and are therefore lethal.

Family history is an important risk factor in almost all cancers, but most familial cancers are not caused by mutations in the rare tumor-suppressor genes described above. Other, lower-risk (less penetrant) genes must be present. Detecting them requires genetic strategies other than linkage analysis, because they do not confer a high enough risk of cancer to cause a noticeable accumulation of cancers in a family. One approach compares the frequency of alleles of genes in cases and controls. Initial case–control studies in cancer genetics used small samples (typically fewer than 500 cases and 500 controls), and relied on existing biologic knowledge as a basis for choosing candidate genes. Initial efforts on this scale were unsuccessful, partly because of the lack of an adequate sample size, but also...
because guessing which genes were relevant proved difficult.4–6 Recently, large-scale consortia examining thousands of cases and controls have identified 30 or more susceptibility loci for lung, prostate, breast, and colorectal cancer. These genomewide studies test hundreds of thousands of single-nucleotide polymorphisms (SNPs) for their association with cancer cases. The large number of subjects and the huge number of SNPs permit the detection of very small, but highly significant associations between any one SNP and disease.

Genes and loci identified by genomewide association studies bear little resemblance to the candidate genes previously associated with a hereditary risk of cancer (Table 1). The biologic relationship of many of these genetic markers to the pathogenesis of a tumor is not yet understood. For instance, one region of chromosome 8q24 harbors several (possibly five) independent loci, each of which is associated with an increased risk of breast, prostate, or colorectal cancer or all of these cancers, but no candidate genes have been identified in this “gene desert.”

### LUNG CANCER

Lung cancer is mainly attributable to tobacco use, and few large families with multiple cases of lung cancer are suitable for linkage analysis. Even if such families were available, it is not obvious that a single gene with a large effect would account for the cases observed. Nevertheless, one locus on chromosome 6q has been suggested by a traditional linkage study,28 though no gene has yet been identified. Some tumor-suppressor genes are associated with substantial increases in the risk of lung cancer, and in persons carrying mutations in these genes, tobacco smoking may be particularly dangerous. For example, in families with the Li–Fraumeni syndrome, smokers who carry a TP53 mutation are at much higher risk for lung cancer than nonsmokers who carry the same mutation,29 and carriers of RB1 mutations, which are associated with retinoblastoma, also have a high lifetime risk of lung cancer30,31 (see the table in the Supplementary Appendix, available with the full text of this article at www.nejm.org). Case reports of lung cancer occurring in the Bloom32 syndrome and in Werner’s33 syndrome, which are associated with a deficiency of DNA repair and DNA maintenance, respectively, suggest a possible hereditary risk of lung cancer.

Genes linked to the metabolism of tobacco carcinogens have been studied as hereditary risk factors in lung cancer, but they have not been readily linked to risk.34–37 Individual genes associated with DNA repair,38,39 inflammation,40 growth factors,41 vitamin metabolism,42 and the cell cycle43 have also been studied, but the results require confirmation in studies involving large populations. A problem encountered in genetic association studies is the “winner’s curse”: buyers in sealed-bid auctions tend to overpay because the true value is unknown, and those who most overestimate a commodity’s value win the prize.44
Similarly, the first genetic study to show a significant association is likely to have overestimated the size of the effect, which is one reason for the requirements for several thousand cases and a similar number of controls, with built-in replication, before the candidacy of any low-penetrance gene can be accepted. Recently, the risk of lung cancer has been closely linked to two markers, rs1051730 and rs8034191, which lie within or adjacent to the nicotinic acetylcholine receptor subunit genes CHRNA3, CHRNA5, and CHRNBN4. These genes are good candidates for low-penetrance, high-frequency lung-cancer susceptibility genes (Table 1). The two SNP markers have a combined odds ratio for lung cancer of approximately 1.30 for the rare allele (P<1×10−17). Notably, the effect of these genes on risk may be independent of any effect they may have on smoking behavior, and they may be important determinants of risk in persons with a family history of lung cancer.

**Breast Cancer**

Only a small proportion (≤10%) of breast cancers are due to hereditary mutations in single, dominantly acting genes, although models suggest that a larger fraction of so-called sporadic cases of breast cancer might be attributable to the action of multiple genes.

The two most important breast-cancer genes, BRCA1 and BRCA2, confer a risk of breast cancer among carriers that is 10 to 30 times as high as the risk among women in the general population. Other genes with a population frequency and risk profile similar to that of BRCA1 or BRCA2 are

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Table 1. Genes and Loci Implicated in the Inheritance of Common Cancers, According to the Risk among Heterozygotes (Monoallelic Carriers).*

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Relative Risk ≥5.0</th>
<th>Relative Risk ≥1.5 and &lt;5.0</th>
<th>Relative Risk ≥1.01 and &lt;1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>RB1 (&lt;0.1), TP53 (&lt;0.1)</td>
<td>No convincing examples</td>
<td>rs1051730, rs8034191, CHRNA3, CHRNA5 are candidate genes</td>
</tr>
<tr>
<td>Breast</td>
<td>BRCA1 (1–5),† BRCA2 (1–5),† TP53 (&lt;0.5), PTEN (&lt;0.5), STK11 (&lt;0.1), CDH1 (&lt;0.1)</td>
<td>CHEK2, ATM, PALB2, BRIP1</td>
<td>CASP8,‡ FGFR2,§ MAP3K1, loci on 8q24, 5p3, TOX3,§ 6q22,¶ LSP1</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>APC (0.5–1.0), MLH1 (1–2), MSH2 (1–2), MSH6 (&lt;1), PMS2 (&lt;1)</td>
<td>APC (I1307K), BLM (BLM*)</td>
<td>MUTYH,¶† CASP8,‡ 8q24 loci, 8q23 (EIF3H), 10p14, 11q23, CRAC1, SMAD7‡‡</td>
</tr>
<tr>
<td>Prostate</td>
<td>BRCA2 (&lt;0.1)</td>
<td>8q24 Loci††</td>
<td>rs6501455 (and other adjacent loci), rs721048, NBS1, EHB1, TCF2, CTBP2, JAZF1, MSMB, LMTK2, KLK3, SLC22A3‡‡</td>
</tr>
<tr>
<td>Pancreas</td>
<td>BRCA2 (&lt;0.5), CDKN2A (&lt;0.1), STK11 (&lt;0.1), TP53 (&lt;0.1), PRSS1 (&lt;0.1), SPINK1§§ (&lt;0.1)</td>
<td>BRCA1, MSH2, MLH1</td>
<td>No convincing examples</td>
</tr>
</tbody>
</table>

* In the high-risk category, risk alleles are rare (<0.1% to 0.01%) or very rare (<0.01%). In the moderate-risk category, most risk alleles are very rare and a few risk alleles are common. In the low-risk category, most risk alleles are common (>10%). The population attributable risk percentage is not indicated because it is a misleading number (i.e., it can sum to more than 100%).
† This percentage is closer to 1% in most populations and closer to 5% in the Ashkenazi Jewish population.
‡ Variants in CASP8 are associated with a decreased risk of breast, colorectal, and other cancers.
§ These loci only contribute to the risk of estrogen-receptor–positive breast cancer.
¶ The effects of this locus appear to be restricted to the Ashkenazi Jewish population.
† Bisallelic mutations in MUTYH result in a distinct syndrome, MUTYH–associated polyposis, which is akin to attenuated or classic familial adenomatous polyposis.
** The pooled odds ratio for the association between the SMAD7 intron 3 SNP rs4939827 and the risk of colorectal cancer is 0.87 (95% confidence interval [CI], 0.80 to 0.95). The rs12957171 is also in intron 3 of SMAD7 and is associated with an increased risk of colorectal cancer (odds ratio, 1.11; 95% CI, 1.03 to 1.20).
†† The alleles associated with increased risk are remarkably frequent in blacks (approximately 40% of blacks carry one or more of these variants). The allele at rs1447295 is also frequent in this population, but it does not appear to be associated with an increased risk of prostate cancer.
‡‡ Apart from NBS1, for all other cases in this group, the named gene is only the most likely candidate to be implicated in prostate cancer. The strength of each candidate varies. MSMB encodes a secreted protein. KLK3 encodes prostate-specific antigen, and therefore it may have nothing to do with prostate-cancer susceptibility itself. LMTK2 encodes a cyclin-dependent kinase.
§§ Mutations in STK11 cause Peutz–Jeghers syndrome, whereas PRSS1 and SPINK1 mutations are responsible for a sizable fraction of cases of hereditary pancreatitis.
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unlikely to exist. Less frequent mutations associated with a relative risk of breast cancer of 2.0 or greater have been identified (Fig. 2).

Multiple cases of early-onset breast cancer, which typically occurs in women younger than 50 years of age, and a high rate of bilateral breast tumors are characteristic of families with hereditary breast cancer. Serous papillary ovarian carcinoma, which is not described in this review, is a key feature of hereditary breast cancer caused by BRCA1 mutations, but it is less common in BRCA2 mutation carriers. Although BRCA1 and BRCA2 mutations are rare in most populations (occurring in approximately 1 of 400 persons), they are much more common in the Ashkenazi Jewish population in which 1 of 40 persons carries one of three main disease-causing mutations. Founder mutations exist in other populations as well, and their presence can aid genetic testing. Most pathogenic BRCA1 or BRCA2 mutations block protein production from the mutated allele. Missense mutations that interfere with critical regions of the gene, such as the RING finger motif or BRCT region of BRCA1 or the PALB2 gene–binding region of BRCA2, behave exactly like truncating mutations, whereas most missense mutations remain uncharacterized and hence are variants of unknown significance.

BRCA1-related breast cancers differ from other breast cancers in that they are usually high-grade, aneuploid carcinomas that do not express estrogen receptor, progesterone receptor, or HER2 (hence, they are called “triple negative”), but they often express cytokeratins 5 and 14, vimentin,
epidermal growth factor receptor (EGFR), and P-cadherin (CDH3). This phenotype is called “basal-like breast cancer.” These characteristics make BRCA1-related breast cancers difficult to detect by mammography. For this reason, as well as the increased prevalence among mutation carriers, screening for these cancers with magnetic resonance imaging (MRI) is warranted.

The risk of contralateral breast cancer among carriers of BRCA1 and BRCA2 is substantial (approximately 3% per year), warranting more vigorous breast surveillance with MRI or prophylactic mastectomies.

BRCA1 and BRCA2 are very large proteins with multiple functions, including repair of double-strand breaks in DNA by homologous recombination (see the table in the Supplementary Appendix). This cellular function may be exploited therapeutically with the use of agents that cause DNA strand breaks that require repair through homologous recombination. Compounds such as PARP1 protein inhibitors, which block alternative DNA repair mechanisms (in this case, base excision repair), may have a role in targeting cancers developing in BRCA1 and BRCA2 mutation carriers.

The other high-risk breast-cancer genes (Table 1 and Fig. 2) account for less than 1% of cases of breast cancer. Two rare hereditary cancer syndromes are linked to the risk of breast cancer. Mutations in PTEN cause a variety of inherited syndromes, including Cowden's syndrome and the Bannayan–Ruvalcaba–Riley–Smith syndrome. Mutations in TP53 cause the Li–Fraumeni syndrome, which includes early-onset sarcomas and cancer at any site diagnosed in persons younger than 45 years of age (see the table in the Supplementary Appendix).

A second class of breast-cancer susceptibility alleles includes genes, currently limited to four (CHEK2, ATM, BRIP1, and PALB2), which were originally referred to as low-penetrance genes but are now more properly referred to as moderate-risk alleles (Table 1 and Fig. 2). These alleles are rare in most populations, and they confer a risk of breast cancer that is two to three times as high as the risk among persons without these alleles, but the conferred risks may be higher in clinical settings. In selected populations, these alleles may be more clinically important: CHEK2 1100delC is carried by approximately 1% of the Dutch and Finnish populations; the S428F mutant of CHEK2 has a similar frequency in the Ashkenazi Jewish population, as does the found-

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**Table 2. Distinct Phenotypes in Monoallelic and Biallelic Mutation Carriers.**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Monoallelic Mutations</th>
<th>Phenotypic Effect</th>
<th>Biallelic Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>Lynch syndrome; cancers of colorectum, endometrium, small bowel, ureter, renal pelvis</td>
<td>CMMR-D syndrome (mainly in children and adolescents); parents may have Lynch syndrome</td>
<td></td>
</tr>
<tr>
<td>MSH2</td>
<td>Lynch syndrome; extracolonic cancers are frequent</td>
<td>CMMR-D syndrome (mainly in children and adolescents); parents may have Lynch syndrome</td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td>Lynch syndrome; endometrial cancer is common, other cancers are less common</td>
<td>CMMR-D syndrome (mainly in children and adolescents); parents may have Lynch syndrome</td>
<td></td>
</tr>
<tr>
<td>PMS2</td>
<td>Lynch syndrome; lower risk of colorectal and extracolonic cancers</td>
<td>CMMR-D syndrome (mainly in children and adolescents); cancer in previous generations uncommon</td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>Hereditary breast cancer; ovarian, fallopian-tube, peritoneal, and pancreatic cancer and melanoma</td>
<td>Fanconi’s anemia, type D1; early-childhood acute myeloid leukemia; medulloblastoma; Wilms’ tumor</td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td>Breast cancer, can be familial</td>
<td>Fanconi’s anemia, type N; early-childhood acute myeloid leukemia; medulloblastoma; Wilms’ tumor</td>
<td></td>
</tr>
<tr>
<td>BRIP1</td>
<td>Breast cancer, can be familial</td>
<td>Fanconi’s anemia, type J; solid tumors</td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td>Breast cancer, can be familial; T-cell leukemia</td>
<td>Ataxia–telangiectasia, childhood and adolescent lymphomas and T-cell leukemia; a wide variety of carcinomas may develop late</td>
<td></td>
</tr>
<tr>
<td>VHL</td>
<td>Inherited renal-cell cancer; retinal angiomas, cerebellar hemangioblastomas, endolymphatic sac carcinomas</td>
<td>Polycythemia, thrombosis, vertebral hemangiomas, low blood pressure; endemic in the Chuvashian population of Russia</td>
<td></td>
</tr>
</tbody>
</table>

*CMMR-D denotes constitutional mismatch repair deficiency.*
er mutation IVS2+1G→A in Slavic populations. Founder mutations in PALB2 occur in persons in Finland and Quebec, Canada.

Fanconi’s anemia is a rare disease of childhood that is characterized by skeletal defects, skin pigmentation, short stature, and microphthalmia. Among affected children who survive, early-onset acute myeloid leukemia and skin tumors in adulthood are common. In some subtypes of Fanconi’s anemia, medulloblastoma and Wilms’ tumors occur in infancy or childhood. Remarkably, three breast-cancer genes — BRCA2, PALB2, and BRIP1 — have all been found to be associated with Fanconi’s anemia, but only when they are present as biallelic mutations (Table 2 and Fig. 2).

Genomewide association studies have identified a third class of susceptibility genes in 15 to 40% of women with breast cancer (Table 1). One of these genes, FGFR2, encodes a growth factor receptor. The relative risk of breast cancer conferred by these genetic variants is minimal. The clinical usefulness of these findings may be in their suggestion of higher-order gene–gene interactions or multiplicative relationships that could account for a measurable fraction of population risk.

**COLORECTAL CANCER**

There are three classes of colorectal-cancer susceptibility genes (Table 1). Several of the most important genes — APC, MUTYH (familial forms of polyposis), and the Lynch syndrome genes (MLH1, MSH2, MSH6, and PMS2) — account for less than 5% of all cases of colorectal cancer, but they affect young people disproportionately (see the table in the Supplementary Appendix). Testing for mutations in these genes is recommended in patients with clinicopathological features that are suggestive of these syndromes (Table 2). The underlying defect in the Lynch syndrome is defective mismatch repair. Mismatches between DNA strands that occur naturally, but erroneously, during DNA replication are not repaired because the key genes have become inactivated, usually by two “hits” — one inherited, the other acquired later in life (Fig. 1). This lack of repair results in numerous DNA sequence errors, particularly in runs of tandemly repeated nucleotides such as (T)n or (CA)n, where n is usually 5 or more. Errors occurring in critical genes such as BAX or TGFBRII can initiate tumors. Since this mutator phenotype accelerates the rate of carcinogenesis and results in the rapid development of colorectal cancer once polyps have formed, frequent colonoscopic screening in carriers is warranted.

A more severe phenotype results if mutations are inherited on both parental alleles. This has recently been referred to as the constitutional mismatch repair-deficiency syndrome (CMMR-D). It consists of café au lait spots and childhood cancers, particularly leukemia, malignant brain tumors, and gastrointestinal neoplasia (Table 2).

APC causes familial adenomatous polyposis, the most common form of gastrointestinal polyposis. The colorectum in familial adenomatous polyposis is carpeted by hundreds to thousands of polyps (Fig. 3), and extracolonic neoplastic
and non-neoplastic manifestations such as adenocarcinoma of the ampulla of Vater, childhood medulloblastomas and hepatoblastomas, desmoid tumors, and sebaceous cysts are typical.\textsuperscript{71} \textit{APC} is a very large gene, and its product has several important functions, particularly with regard to regulation of \(\beta\)-catenin.\textsuperscript{72} Although it is considered to be a gatekeeper\textsuperscript{73} — a rate-limiting function in carcinogenesis — the \textit{APC} protein may also have some caretaker functions. The loss of \textit{APC} can induce chromosomal instability and subsequent aneuploidy, and thus it may cause widespread chromosomal changes\textsuperscript{74,75} (see the table in the Supplementary Appendix).

\textit{MUTYH} is the first base-excision repair gene to be associated with the risk of cancer, and the \textit{MUTYH}-associated polyposis syndrome is inherited as a recessive trait.\textsuperscript{76} The risk of colorectal cancer among carriers of biallelic mutations appears to be close to 100\% by 60 years of age,\textsuperscript{77} although the phenotype is variable, ranging from 10 or more polyps to widespread polyposis with associated colorectal cancer. Limited data suggest that heterozygotes have a slightly increased risk of colorectal cancer.\textsuperscript{78,79} The defect in base excision repair, caused by the absence of normally functioning \textit{MUTYH}, results in a specific target mutation, G-to-C transversion. When these mutations cause loss or inactivation of \textit{APC}, the resulting phenotype resembles familial adenomatous polyposis. Other high-risk polyp-related genes, such as \textit{SMAD4}, \textit{BMPR1A}, and \textit{STK11}, are quite rare.\textsuperscript{80}

A missense mutation in \textit{APC} known as I1307K (isoleucine changes to lysine) is associated both with polyps and risk of colorectal cancer that is 1.5 to 2 times as high as the risk among persons without this mutation.\textsuperscript{80} The mutation seems to increase the likelihood of DNA replication errors occurring locally because the mutation changes a T to an A (a transversion), resulting in a run of eight adenines in a row. Notably, this allele appears to be largely limited to Ashkenazi Jews, of whom approximately 6\% carry this variant.\textsuperscript{80,81} Another risk allele that is restricted to the Ashkenazi Jewish population, \textit{BLM}, has neither the frequency nor the penetrance to be of clinical use.\textsuperscript{82} Genomewide association studies confirm that a number of loci, including the chromosome 8q locus previously linked to prostate cancer, are associated with slightly increased risks of colorectal cancer\textsuperscript{14-17,23,24,83} (Table 1).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3}
\caption{An Operative Section of Colon with Polyps.}
\end{figure}

\textbf{PROSTATE CANCER}

Unraveling the genetics of prostate cancer has been difficult, and no high-risk, prostate-specific genes seem to exist. The closest candidate is \textit{BRCA2}, which confers a risk of prostate cancer that is as much as 20 times the risk in the general population.\textsuperscript{84} \textit{BRCA2}-associated prostate cancers are aggressive,\textsuperscript{85} suggesting the need for better screening in carriers. \textit{BRCA2} mutations are rare, however, in men with prostate cancer,\textsuperscript{84,86,87} and despite considerable collaborative efforts, no prostate-cancer genes have yet been conclusively identified by linkage analysis.\textsuperscript{88} Genomewide association studies have identified several new candidate genes and loci.\textsuperscript{79,18-21} None of these genes are associated with large risks, although some are of considerable interest. The variant near the gene \textit{MSMB} is the most promising because it encodes an immunoglobulin-binding factor that is present in seminal fluid.\textsuperscript{19} There are several different risk loci on chromosome 8q24,\textsuperscript{89} and some of them are very frequent, especially in blacks, a population with a high prevalence of prostate cancer (Table 1).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{A view of a small section of resected colon obtained from a patient with familial adenomatous polyposis is shown. Innumerable polyps are present. Most studies suggest that each polyp contains no fully functioning \textit{APC} protein. (Image courtesy of Dr. J.R. Jass.)}
\end{figure}

\textbf{PANCREATIC CANCER}

Elucidating the genetics of pancreatic cancer has also been difficult, but several genes already described have been implicated in its cause (Table 1). Again, the most important gene is \textit{BRCA2}, which
accounts for approximately 10% of cases of pancreatic cancer in Ashkenazi Jews, and carriers of the BRCA2 mutation, 6174delT (which is present in approximately 1 of 100 Ashkenazi Jews), have a 7% lifetime risk of pancreatic cancer. Carriers of other BRCA2 mutations also have a risk of pancreatic cancer that is three to five times the risk among persons without these mutations. Patients with BRCA2-associated pancreatic cancer may not have a family history of breast or ovarian cancer. The risk of pancreatic carcinoma is also significantly increased among carriers of mutations in BRCA1, MSH2, STK11, and probably both MLH1 and TP53. The highest risk of pancreatic cancer in association with a mutation in a tumor-suppressor gene is seen among carriers of mutations in CDKN2A; among such persons, the standardized incidence ratio may be as high as 52 (4 cases observed and 0.1 case expected in 811 person-years of follow-up). This gene encodes a cell-cycle–dependent kinase inhibitor (see the table in the Supplementary Appendix) that is associated with familial cutaneous malignant melanoma. It is very unusual to find pancreatic-cancer–associated mutations in CDKN2A other than in melanoma-prone families.

In rare cases, pancreatic cancer occurs in families with preexisting abnormalities of the pancreas. In some of these cases, the abnormalities lead to chronic pancreatitis, and in these families, pancreatic cancer is up to 50 times as frequent as it is in the general population. Many families with hereditary chronic pancreatitis carry mutations in PRSS1 or pancreatic SPINK1. Case reports have identified one or two families in which the risk of pancreatic cancer among persons with precursor lesions is almost 100%. PALLD, which encodes Palladin, appears to be the responsible gene in one family, although its candidacy has been questioned. The gene does not contribute significantly to familial pancreatic-cancer susceptibility. Screening by means of endoscopic ultrasonography or endoscopic retrograde cholangiopancreatography (and even preventive pancreatectomy) may be warranted in these exceptional kindreds.

The identification of high-risk cancer susceptibility genes means that physicians and persons at risk must understand the implications of the risk of genetic cancer; this identification has resulted in the blossoming of cancer genetics as a clinical subspecialty. Genetic counselors and other health specialists with expertise in cancer risk assessment are qualified to offer the kinds of services needed by persons with or at risk for hereditary cancer.

Genetic testing for the highly penetrant genes listed in Table 1 is widely available (see www.genetests.org for a list of testing laboratories). Despite the apparent simplicity of the genetic tests themselves, interpretation, particularly of unclassified variants, can be much more difficult. Such complexities, including genetic sites of low-impact or genetic variants of unknown significance, warrant appropriate pretest and post-test counseling for persons who undergo genetic testing.

Guidelines for deciding which patients should be tested and which tests should be performed are available. As with any test designed to identify risk factors or screen for relatively uncommon events in the general population, genetic tests for cancer present considerable social and ethical challenges. There are complex considerations to take into account before integrating the newer, less penetrant genetic markers into clinical cancer genetics because of the weak penetrance of individual alleles and the limited techniques of early detection and surveillance for certain cancers, including lung and pancreatic lesions. There is concern that direct marketing of genetic tests to the public plays on an often exaggerated fear of cancer.

Following the success of genomewide association studies, new forms of technology are emerging that may offer broader genetic testing to assess the risk of cancer. Grouping low-risk alleles could identify persons at the extremes of risk. However, in most cases, we lack sufficient information on the behavior of these risk panels in the clinical setting. Furthermore, the composition of these panels is likely to change with time as more alleles are detected and advances in computational biology are made. Important practical and ethical questions abound; these include the minimum level of risk associated with a panel of SNPs that would warrant their use. For instance, a change involving twice the risk or less is arguably not meaningful for most persons or societies, but specific populations or persons might feel justified in seeking...
genetic testing. It is not clear what thresholds of population-specific allele frequency and age-specific penetrance should trigger widespread consideration of genetic testing.

It is important to ensure that genetic testing, like cancer screening in general, does not become mainly a way for well people to buy reassurance, particularly when some reassurance is false and the findings are lacking in real evidence of benefit. Nevertheless, it would be a great loss if policymakers and the public were to tire of genes and gene-based medicine as a whole, because genetics has shown itself to be an enormously powerful tool in the discovery of new knowledge. If the new discoveries in the inherited basis of the common cancers can be effectively incorporated into other preventive and diagnostic strategies, and moreover, if these strategies can be cheaply and equitably delivered, then there is hope of real benefit for the entire population. High-throughput analysis of cancer genomes is revealing previously unrecognized complexity. Combined knowledge of inherited and acquired genetic changes is likely to result in significant advances in the prevention, diagnosis, and treatment of the five most common cancers, which are responsible for more than half of all cancer-related deaths in North America.

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I thank Dr. D.F. Easton for his assistance with the concept for Figure 2.

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the auction but I don’t want the prize. J Conflict Resolut 1983;27:618-34.


