the encoded protein may be a major contributing factor in approximately 10% of colorectal cancers in Ashkenazi Jews (*47*). The mutation generates a hypermutable tract in the APC sequence, and somatic mutations are presumed to arise at increased frequency in or near the tract. Other familial aggregations may reflect interactions between mutant alleles of inherited cancer genes and modifier genes. In some families and individuals, cancer risk may be attributable to variant alleles of genes that regulate cell metabolism or the response to environmental and dietary agents and toxins (*48*).

Research into the genetics of inherited cancer syndromes has provided fundamental insights into the cellular defects that subvert normal cell growth and lead to the insidious and destructive properties of cancer. Further identification and study of genes that influence cancer susceptibility will likely provide an ever clearer understanding of the origin and nature of cancer, as well as form the foundation for efforts to effectively prevent, detect, and treat it.

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Genetic Testing for Cancer Risk

Bruce Ponder

Genetic testing for cancer susceptibility is already part of the clinical management of families with some of the well-defined (but uncommon) inherited cancer syndromes. In cases where the risks associated with a predisposing mutation are less certain, or where there is no clearly effective intervention to offer those with a positive result, its use is more controversial. Careful evaluation of costs and benefits, and of the efficacy of interventions in those found to be at risk, is essential and is only just beginning. An immediate challenge is to ensure that both health professionals and the public understand clearly the issues involved.

With the cloning of cancer-predisposing genes over the past 10 years, it has become possible to offer predictive DNA testing to family members at risk. This procedure has been quietly and successfully applied by specialist clinics to several inherited cancers—for example, retinoblastoma, polyposis coli, and multiple endocrine neoplasia type 2 (MEN-2) (*1*). With the cloning of the *BRCA1* and *BRCA2* genes that predispose to breast and ovarian cancer, however, a small storm has blown up (*2*–*7*). The acceptance of testing for other inherited cancers suggests that there is nothing intrinsically contentious about testing for cancer genes. For breast cancer, the most important difference is that it is not clear whether it is necessarily helpful for a patient to know that she has a *BRCA1* or *BRCA2* mutation. In addition, breast cancer affects a very large number of people, and it seems probable that neither the patients nor their doctors fully understand what is involved in deciding to take

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the test, or the implications of a positive or negative result. Finally, the role of commercial interests, and the increased awareness of familial breast cancer risk because of the publicity surrounding the research, have raised concerns that women may be encouraged to seek testing without appropriate counseling and support. The arguments over genetic testing for breast cancer have been useful in focusing attention on these issues, which apply in some measure to all genetic testing for common adult-onset diseases. It would be a pity, however, if in a reaction against the uncritical application of testing, the potential benefits were thrown out with the bathwater.

What Can Genetic Testing Do?

Where the predisposing mutation in a family is known or is likely to be identifiable, and there is a clinical decision to be based on the information, genetic testing is likely to be helpful. For example, in familial polyposis of the colon, testing for mutation in the *APC* gene in childhood will indicate which individuals require regular surveillance by endoscopy and which do not; in MEN-2, testing for the inherited mutation in *RET* in early childhood will separate those individuals who require prophylactic thyroidectomy to prevent "C" cell tumors from those who require no further surveillance (*1*).

Although more contentious, genetic testing may also be justified in some families with strong histories of breast and ovarian cancer. This is illustrated by the family depicted in Fig. 1. The pattern of cancers suggests that this family harbors a *BRCA1* mutation, and indeed the mutation 1294del40 (in which a 40–base pair piece of the coding region has been deleted from the gene) has been detected in blood from individual III-8. Individual III-7 sought advice about her risks and what she should do. On the basis of the family history alone, she has a 50:50 chance of having inherited the putative predisposing gene. According to the International Breast Cancer Consortium (*8*), she has about a 40% chance of developing breast cancer by age 70 and a 25% chance of developing ovarian cancer. These are average risks, which probably vary between individuals, as discussed below. Nevertheless, on the basis of this information (she was seen before genetic testing was available), she decided to have prophylactic oophorectomy, but not mastectomy. Genetic testing, had it been available, might have changed her predicted risk up to 80% for breast and 45 to 60% for ovarian cancer by age 70, or down to the risk in the general population (about 6% and 1% by age 70, respectively) (Fig. 2). This information would have been helpful, because it would have given her a firmer basis for her decision about prophylactic surgery. Moreover, if she had not inherited the gene, she may have been reassured not only for herself, but for her children. It remains to be seen how many women will want genetic testing in this situation; presumably it will be related to how effective any resulting intervention (screening, surgery) is perceived to be (*9*). In a study of families with breast and ovarian cancer who were already taking part in genetic research, 43% of eligible family members requested *BRCA1* test results (*9*).

Genetic testing may also be useful in some cancers outside the family with a known mutation, to distinguish cancers that have an inherited basis from those that do not, and to select the cases where screening of family members for early detection of disease is needed. Examples are medullary thyroid carcinoma (MTC) in MEN-2 syndrome, and hereditary nonpolyposis colorectal cancer. About 5% of MTCs that present as isolated cases are in fact heritable, and in these cases biochemical screening of family members is important to pick up other affected family members at a curable stage (*10*). Unfortunately, there are no completely reliable clinical means to distinguish the heritable from the far more common sporadic cases. As a result, in the past many families have been subjected to regular screening for the sake of the few who would benefit, or clinicians have been unwilling to impose this burden and opportunities for early diagnosis have been missed. With genetic testing, almost all heritable cases can be detected by a simple mutation screen of a limited region of the *RET* gene, and screening can be effectively targeted. Genetic testing may similarly be helpful for familial colorectal cancer. Screening by flexible endoscopy is effective (*11*); however, the number of individuals with only slight indication of family history is very large, and the risks in most of these cases quite low. The balance of lives saved by early diagnosis against those damaged by serious complications from repeated endoscopy is not clear. In this situation, it has been suggested that genetic testing for mutations in the predisposing genes *MSH2* and *MLH1* will allow the families at highest risk to be selected out for screening, while the remainder, who are at relatively much lower risk, can be reassured (*12*).

Finally, genetic testing might in some circumstances be usefully applied as a screening procedure in whole populations. At present, for most genes, such an approach would be limited by technical feasibility to founder populations, where only one or a small number of mutations need be tested for. The most intensively studied population group is the Ashkenazi Jews, of whom some 2.5% carry one of three mutations in the *BRCA1* and *BRCA2* genes (*13*) and an estimated 6% have been reported in one study to carry a variant in *APC*, which confers increased risk of colon cancer (*14*). It is estimated that 20 to 25% of breast and ovarian cancer in young Ashkenazi women occurs in carriers of one of the three *BRCA* mutations, and that possibly 16% of colorectal cancer below the age of 66 years occurs in carriers of the *APC* mutation. Whether in fact it would be beneficial, either in human or economic terms, to offer screening to individuals in these populations is not yet known.

What Can Genetic Testing Not Do?

Although in the right circumstances genetic tests can be helpful, they have many limitations. It is these, and in particular the worry that the limitations are not sufficiently appreciated by doctors and the public, that have sparked the current concern. The problems center around the interpretation of the significance of a positive or negative test result.

With few exceptions, a negative result can provide reassurance only if the predisposing mutation in the family is already

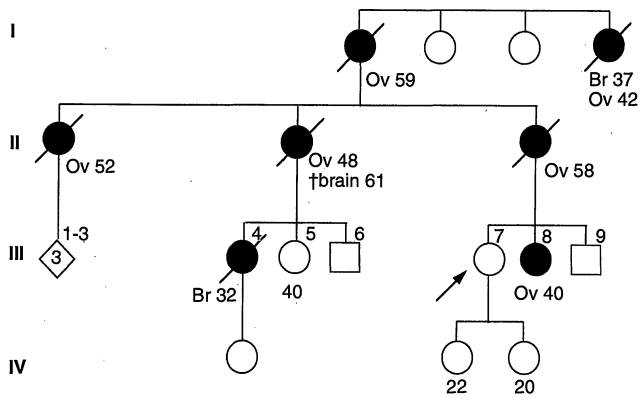

Fig. 1. A family with a mutation 1294del40 in the *BRCA1* gene, causing predisposition to breast and ovarian cancer. Individual III-7 sought medical advice about her risks and possible course of action in view of her family history.

known. Then, if the individual has not inherited it, he or she does not share the increased familial risk. This was the basis of testing in the breast or ovarian cancer family described in Fig. 1. In this situation, either a positive or a negative result is informative. However, it has been suggested by at least one commercial company that genetic testing for *BRCA1* and *BRCA2* mutations should be offered not just to women with very strong family histories, but to any woman whose family history includes one first- or second-degree relative diagnosed with breast cancer below the age of 40 or two relatives diagnosed below the age of 50 (*15*). In the United States there are several hundred thousand women aged 25 to 60 years with family histories of this sort. Current evidence suggests that perhaps 10 to 15% of affected women in such families will have detectable *BRCA1* or *BRCA2* mutations (*16*). The problem is that the failure to find *BRCA* mutations in the other 85 to 90% of families does not necessarily mean there is no familial risk (importantly, nor does it mean there is no breast cancer risk at all). The mutation may have been missed: Comparison of linkage with mutation data for the families in the International Breast Cancer Consortium suggests that—across a spectrum of research laboratories at least—up to 30% of mutations escape detection. Or there may be predisposition because of a strongly predisposing mutation in another gene that is yet to be discovered. Or the family cluster may reflect weaker genetic or environmental risks; or it may be chance with no risk implications at all. With a negative result, therefore, no conclusion about risk based on DNA analysis is possible unless there has already been a positive identification of the predisposing mutation elsewhere in the family. Two questions follow: (i) Given that the decision for genetic testing may have been associated with some thought and anxiety and will probably have drawn in other family members besides the individual who initiated it (*17*), how does the disturbance and the subsequent psychological "letdown" of no result in the majority balance against the possible benefits to the minority of families where testing is possible? (ii) How much explanation is needed to ensure that the decision for testing is well informed, and how should this be provided? The answer to neither of these is known.

The interpretation of a positive genetic test result also has limitations and some pitfalls. The genetic test assays for DNA sequence variation. One cannot always be certain that a particular variant is significant in terms of risk. A missense variation may be anything from a rare neutral polymorphism to a highly penetrant predisposing mutation; unless there is an assay for its effect on protein function, or it has established a "track record" by association with the disease in several families, it can be impossible to tell whether it is significant (*4*, *18*). On rare occasions, variants that produce a stop codon and truncated protein, and have therefore been assumed to be significant, have turned out not to be associated with greatly increased risk (*19*).

Even if it is known that a given variant is a predisposing mutation, accurate prediction of "the individual's cancer destiny by a simple blood test" (*5*, p. 70) is still not possible. This point has been forcefully made by critics of genetic testing, especially in relation to breast cancer, and is encapsulated by the title of a recent editorial, "*BRCA* genes: bookmaking, fortune telling and medical care" (*2*). There is the obvious point that risk inevitably has a dimension of time (Fig. 2); that is, even though the probability of cancer may be very high over a lifetime, it is still quite uncertain over the next 10 years, which may sometimes be the time frame with which an individual is concerned. On top of that, the effects of predisposing genes are modified by other genes—the hand of genes each individual is dealt at birth—and by lifestyle and environmental factors such as pregnancy or oral contraceptive use. The same mutation may therefore be associated with different quantitative levels of risk, and with predominant risks of different types of cancer, in different individuals even within the same family (*3*). We do not know enough about these modifying factors to make individual predictions. Even if we did, there would still be a substantial role for chance.

In the rare inherited cancer syndromes such as MEN-2, this problem is often deliberately disregarded. The argument in MEN-2 is that prophylactic total thyroidectomy based on a genetic test in childhood is simple and very effective. Although some gene carriers will not develop clinically significant disease by the age of 70, the small chance of an "unnecessary" operation that this implies is preferable to a lifetime of uncertainty and hospital visits waiting for biochemical signs of early thyroid cancer. In breast and ovarian cancer, because of the different clinical context, the problem presents differently. Surgical prevention by mastectomy or oophorectomy is perceived as a drastic step, and it is not certain that the surgery is effective (*20*). Before offering genetic testing that will lead to surgical decisions in this context, it seems important that the risks associated with a positive result should be accurately known. In particular, there is concern that the frequently quoted figures for lifetime risk of breast and ovarian cancer associated with *BRCA1* mutation are derived from the data of the International Breast Cancer Consortium (*8*), which deliberately set out to collect multiple case families with a high density of younger onset cases for gene-mapping studies. It seems likely that these families will also have, on average, more than their share of the other risk factors, so that the risks derived from them for the *BRCA* gene mutations will be overstated in relation to the risks for these mutations in the population as a whole. Some evidence to support this view has come recently from population-based studies of the Ashkenazi founder mutations (*13*). The confidence limits on the risks estimated from this study (and, it should be noted, on the risks from the Consortium studies) are wide (*21*), and there have been criticisms of the study design (*7*), but the results do suggest that, without a multiple-case family history, the risks of *BRCA1* and *BRCA2* mutations may

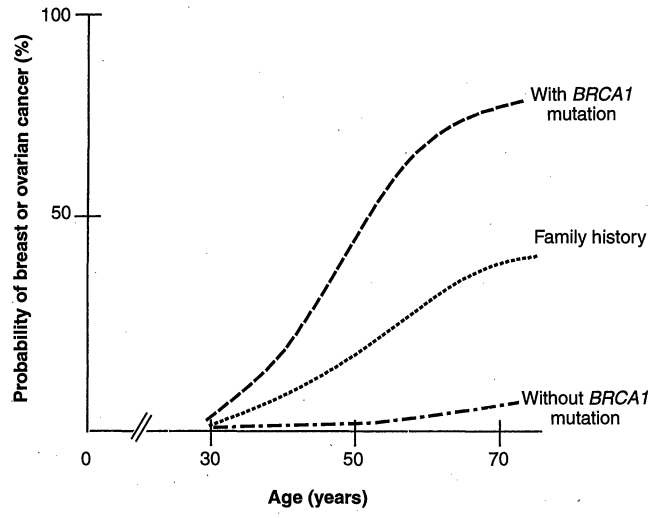

Fig. 2. Approximate chance of developing breast cancer by age in a woman in the family shown in Fig. 1, on the basis of family history alone or of *BRCA1* mutation status. Even in a woman who has the *BRCA1* 1294del40 mutation, the risk of developing breast cancer is not certain; the risk for a 40-year-old of developing breast cancer by age 50 is about 20 to 25%. Conversely, a woman who is shown not to have inherited the mutation still has the same risk as the rest of the population. Risks in mutation carriers may be lower if there is a weaker family history (see text).

be lower. The unresolved questions are how much lower, and whether this difference is of practical importance. Despite our emphasis on providing risk figures, the way in which individuals use risk information to make decisions is another aspect of genetic testing about which very little is known (*22*). Moreover, many members of the public and doctors misunderstand the process of mendelian inheritance, and so misinterpret risk information, or who in a family may be at risk (*23*).

Can Genetic Testing Be Harmful?

Most of the concern that has been expressed in print about genetic testing for cancer has focused on breast cancer, and on the potential adverse consequences for the individual and family. These fall under several headings.

First, the idea that this is "dangerous knowledge." Once given, it cannot be retrieved. Most clinicians who have dealt with *BRCA* gene testing can recount anecdotes of individuals who have been severely affected by the news that they had inherited the gene, and of individuals in whom the news that they had not inherited it produced not reassurance but agonies of guilt, perhaps toward a sister who was less fortunate. There may be particular problems with testing younger people. A 21-year-old can consent to a *BRCA1* test, but is it in her interest to do so? What are the possible effects of a positive result on decisions about career, marriage, childbearing; what is the benefit of knowing now rather than later, when her period of increased risk begins? Who should advise her, and who should decide? One has the impression that these issues are rarely a problem in genetic testing for MEN-2 or polyposis coli; for example, where the action to be taken on the test results is clearly defined, a negative result means effectively no risk, and the information is presented to the family as part of routine management. How common the problem really is with *BRCA* testing, to what extent it can be avoided by skillful pretest counseling, or whether it is unavoidable until simple and effective treatment is available for those who test positive is not clear. The little information we have comes mostly from "research families" who have lived with the idea of genetic risk for years, and may not accurately reflect the response in families newly recognized to have a mutation.

Second is the possibility that, especially in smaller families, where the chances of finding a mutation are quite low, the prospect of genetic testing may raise unrealistic expectations in the individual, and disturbances in the family, that serve only to increase anxiety when (as is probable) no prediction can be made. The failure to find a *BRCA* mutation may also be interpreted wrongly as a lack of risk, and women may fail to follow population screening programs as a result. Alternatively, the opposite may happen: In an atmosphere in which genetic testing is perceived as good simply because it can be done, individuals who test positive may find themselves impelled (despite the uncertainty of some of the risk estimates) toward screening or surgical prevention that may dramatically affect their lives, but for which the balance sheet of benefits and losses is far from clear (*20*, *24*).

Lastly, there are issues of privacy and discrimination, in particular relating to insurance and employment, which must be a serious concern (*25*, *26*). In the United Kingdom, where life insurance is the principal issue, the Association of British Insurers' position in early 1997 (*27*) was that for policies under £100,000 and associated with a mortgage on the principal residence of the life assured, although the results of genetic tests should be declared, they would not be taken into account if detrimental to the applicant. Family history must be declared and would be assessed, as previously. For other insurance, or sums greater than £100,000, the use of previous genetic test results would be at the discretion of the insurance company. The limit of £100,000 is consistent with actuarial calculations showing that this is the point at which there are significant adverse effects from individuals selectively buying insurance because they know themselves to be at risk. In the United States, where health and employment issues are more important, legislation varies from state to state. The National Action Plan on Breast Cancer–Ethical, Legal and Social Implications (NAPBC-ELSI) Working Group of the National Institutes of Health–U.S. Department of Energy (NIH-DOE) have presented recommendations on health insurance (*25*, *26*) that have had a major impact on the development of legislation in the United States. The Hereditary Susceptibility Working Group of the NAPBC together with the NIH-DOE and ELSI Working Group have also developed recommendations (*28*) that would preclude employers from requesting and using genetic information unless it could be shown that it was job-related and consistent with business necessity. It remains to be seen how these and similar proposals will be adopted and developed as legislation in the United States or other countries.

Apart from the potential costs of genetic testing to individuals, we should also consider the economic costs and benefits, including the opportunity costs—that is, within a system of limited resources, what else we could be doing if we were not doing genetic testing. The equations will be different for different cancers. The elimination of 50% of family members from the need for regular screening, and the ease of early and uncomplicated surgery, seem likely to ensure net benefits in well-defined syndromes such as MEN-2 and polyposis coli. The equation for widespread genetic testing for common cancers, such as colon cancer, is more difficult to solve (*29*). In the case of breast cancer, the need for information, counseling, and support, and possible large-scale changes in screening behavior in younger women brought about by awareness of familial risk, seem likely to be larger factors than the costs of the DNA tests themselves.

What Needs to Be Done?

The short answer is: research. There are too many questions to which we still do not know the answer; until we do, soundly based advice to the individual, and appropriate allocation of health care resources, will not be possible. In many countries, including the United Kingdom, health service provision is becoming decentralized as a response to the need for politically acceptable rationing of care. Here is a set of problems that require a centralized, or at least coordinated, approach to provide the data we need. A mechanism must be found by which this can be achieved. In the United States, the National Cancer Institute has set up the National Cancer Genetics Network for this purpose.

Even when the information is known, it still has to be applied. Several sets of principles and recommendations have been produced, not exclusively directed to cancer (*30*–*33*). They cover the areas of genetic test development; quality control and certification of laboratories; consent, privacy, and discrimination; and guidelines for the direct marketing of tests to the public. In the field of cancer genetic testing, and especially breast cancer testing, the priorities in the long term would seem to be better education of the medical profession as well as the public. Better understanding should ensure that demand more closely equates to need. In the short term, the priority must be to ensure that genetic tests are not offered unless validated, objective, and independent information and counseling is provided, and are not acted upon unless the results have been competently interpreted. A recent survey of the use of commercially available genetic testing for the *APC* gene in familial polyposis indicates that these

criteria are not being met (*34*). It is unrealistic to think that the specialist genetics services will expand to cope with this, so the burden will fall on primary care and on hospital surgical clinics. It is here that information and education must be targeted. Explicit guidelines have been published for the follow-up care of individuals found to have predisposing mutations for breast, ovarian, and colorectal cancer (*20*, *35*). A widely available consensus statement with similarly explicit guidelines for family history criteria that may merit specialist referral for genetic testing might also be helpful (at present, it seems the best-publicized criteria are those put forward by commercial laboratories). Such guidelines would provide reassurance to clinicians beset by demand and uncertain how to respond; and they will also encourage providers of health care that they will not be asked to meet an open-ended commitment.

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Nucleic Acid–Based Methods for the Detection of Cancer

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Continued elucidation of the genetic changes that drive cancer progression is yielding new and potentially powerful nucleic acid–based markers of neoplastic disease. Pilot studies indicate that these markers can be used to detect cancer cells in a variety of clinical settings with unprecedented precision. Nucleic acid–based markers may prove to be valuable tools for early detection of cancer in asymptomatic individuals, for confirmation or exclusion of a cancer diagnosis that is based on suspicious but nondiagnostic clinical material, for assessment of tumor burden in cancer patients, and for assessment of response to preventive approaches applied to healthy individuals who are at high risk of developing cancer. Examples of these markers, their potential applications, and the current practical limitations on their clinical use are reviewed here.

Recent discoveries in genetics and molecular biology have revolutionized our understanding of cancer initiation and progression. We now know that cancer is a heterogeneous group of diseases, each composed of a complex array of genetic changes driving uncontrolled growth and metastatic spread. Although this understanding has stimulated the development of innovative molecular therapies for cancer, successful introduction of these therapies into the clinical setting has been rare. Thus, a simple molecular cure for the most common cancers must still be viewed as a long-term goal. However, the war on cancer has many fronts. Identification of the genetic changes that drive cancer progression is also providing us with a variety of molecular markers and tests that may ultimately redefine the criteria for cancer diagnosis and provide new avenues for early detection. Long before molecular cures for cancer arrive, accurate molecular diagnosis may change our clinical approach to and management of cancer patients. Here I will review the status of promising molecular tests for cancer, focusing primarily on nucleic acid–based diagnosis of epithelial cell malignancies, which account for the overwhelming number of cancer deaths worldwide.

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Types of Molecular Markers

Strong evidence supports the concept that cancer is a genetic disease that involves clonal evolution of transformed cells (*1*). Cancer cells arise through the accumulation of mutations, either inherited (germline) or acquired (somatic), in critical proto-oncogenes and tumor suppressor genes. Each mutation may provide an additional growth advantage to the transformed cells as they dominate their normal counterparts (*2*, *3*). The genetic alterations that arise during tumorigenesis can be used as targets for detection of cancer cells in clinical samples. DNA is an ideal substrate for molecular diagnosis because it readily survives the adverse conditions experienced by many clinical specimens and it can be rapidly amplified by polymerase chain reaction (PCR)–based techniques, thus diminishing the amount of starting material needed.

In addition to specific mutations in oncogenes and tumor suppressor genes, changes in DNA repeat sequences, called microsatellites (*4*), can also be used as markers to detect the clonal evolution of neoplastic cells. Because they are highly polymorphic, microsatellite markers allow distinction of maternal and paternal alleles. Typically, paired samples of normal DNA (usually from blood lymphocytes) and DNA from a