UNDERWRITING DOMINANTLY INHERITED DISEASES

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Geneticists worry that their patients and the patients' families will be subject to unfair discrimination by medical underwriters when the results of DNA tests show that the patients are predisposed to certain diseases. They point out that these individuals may be healthy at the time the test is carried out and that, without the test, they would be considered standard insurance risks. This approach ignores the opportunities for antiselection. It talks of entitlement to insurance. Geneticists also worry about the appearance of a genetic underclass of people who, because they have one or more "genes," will be unable to find a job or to purchase insurance. Much of this concern centers on the problems of health insurance in the United States but it spills over into life insurance because distinctions between different segments of our business become artificial in the mind of the lay public.

As insurers, we tend to think that much of what geneticists, bioethicists, and consumer activist groups are saying is just so much rhetoric, seeking space in the media. We should listen, however, for many of their points have some validity and many may be the basis for restrictive legislation. The most dramatic stories that these groups bring to the press involve rare disorders like Huntington disease (which occurs only once in 3000 people) that is transmitted as an autosomal dominant– the children of an affected patient have a 50 percent chance of carrying the gene and expressing the disease.

Most adult onset diseases with genetic etiologies are the result of multifactorial processes involving both germline and somatic mutations– the mix of both nature and nurture. Heart disease, hypertension, and most cancers fall into this group. They are caused by both inherited genetic mutations and the effect of environmental factors that probably modify other genes. There will be no simple DNA tests to positively identify those at risk for multifactorial disease and no certain way to predict risk even if some genes prove to be informative.

At a recent series of conferences in Toronto,[1] the problem of a group of fairly common genes which transmit adult-onset diseases in an autosomal dominant (AD) manner, was considered. Breast, ovarian, and colon cancer can all be transmitted as a single gene, AD diseases resulting from mutations in one of BRCA1, BRCA2, AT< HNPCC, or APC genes. All transmit with a relatively high degree of penetrance and although these tests are only performed in the research lab today, we will soon be seeing test results in attending physicians' reports.

Each of these mutations may cause cancer and each carries an increased risk of early death, thus it would be simple to deny automatically an application for life insurance if the applicant was known to carry one of the mutant genes. That decision can be supported by data which show that the mortality from breast cancer is as high as 37 percent, that from ovarian cancer may reach 62 percent, and from colon cancer is over 45 percent.[2] These data, however, describe the risk for all individuals with tumors in each specified organ and include not only patients with far advanced tumors at diagnosis but also those identified in screening programs conducted on asymptomatic individuals. The cohort of people with dominant mutations who have any of these diseases varies from about five percent of all those women who have breast cancer to perhaps 10 percent for those with colon cancer. Breast, ovarian, and colon cancers can cause a significant percentage of tumor deaths and can impact on insurers' mortality experience.

Autosomal dominant diseases

In classical genetic dogma, single gene diseases are transmitted as recessives when germline mutations are found on both the maternally and paternally derived copies of the same gene. If disease results when a mutation only occurs on a single allele, while the allele on the other chromosome is normal or "wild type," the transmission is autosomal dominant. If mutation occurs on a gene on the X chromosome, in males, there is no paired matching gene on the Y chromosome and the disease is called X-linked. Recessive diseases are common in childhood while dominant diseases are more frequent in adults. X-linked diseases are usually present in young boys, although they may rarely be seen in girls who have both a mutant gene on one X chromosome and a deletion on the other.

Dominant diseases, with a pattern of delayed penetrance, are of concern to the insurer because an apparently healthy adult might develop signs and symptoms of disease in middle life and might die well before standard life expectancy. Family history usually provides the information to alert the underwriter to risk of a

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dominant disease because, by definition, the mutant gene must have been inherited from a parent who carried the same mutation. Adoption, unacknowledged alternate paternity and new mutations may confound this information but usually pedigree analysis will alert the underwriter to the risk.

Genetically determined breast and ovarian cancer can also prove confusing to the pedigree analyzer. Paternal transmission of a genetic defect that, like ovarian cancer, is only expressed in females, may occlude the pattern although the disease is a true dominant. Finally, the signs and symptoms of a disease may vary within members of the same family (variable expressivity) for reasons that may be the result of changes within the mutant gene itself or result from changes in other genes[3].

Table One lists several diseases that are transmitted as autosomal dominants and that have some interest for insurers. Some of these occur with fairly high frequency in the population (1:100 to 1:1000) and all can now be diagnosed using molecular genetic techniques. Each of these diseases present in adult life in individuals who had previously been apparently healthy and who, without the knowledge provided by family history or genetic tests would be considered as standard insurance risks. Bioethicists[4,5] and others[6,7] have made the point that it is "unfair" to discriminate against unaffected people with genes that predispose them to disease in the future. They maintain that these individuals were always in the pool of insureds which was covered by the pricing system in place before the new genetic era and that insurers should just accept added antiselective losses as part of doing business. They suggest that everyone should be entitled to some level of insurance coverage.

Insurers, on the other hand, are concerned about antiselection and the impact of excess early morbidity on corporate financial viability. What is to prevent the person who knows they carry a life-limiting gene from seeking excessive coverage? How does a company price an entitlement product, which will be more expensive than one with standard underwriting if the only purchasers are high risk people with genetic defects that lead to early morbidity? On first glance, as insurers, it seems easier to decline applicants at risk for dominantly inherited diseases.

All humans carry several mutant genes and some of these may be responsible for their final illness and death but most will achieve a normal life span and even if they succumb to a genetically determined disease, they have what is termed "expected mortality" and their insurance has been priced to pay their claims. It is the group who will die before they reach a normal life expectancy that concerns insurers. This paper examines a cohort of people who may die from an autosomal dominantly inherited disorder in middle age and who represent what appears to be an unacceptable insurance risk. New genetic technologies can identify these individuals and, in some instances, can direct defensive strategies which will not only prolong their otherwise shortened life expectancy but will also make them insurable.

GENETIC DEFECTS, MORBIDITY/MORTALITY IN CERTAIN DOMINANT DISORDERS

1. Breast and ovarian cancer genes

1.1 BRCA1 and BRCA2. It may be unreasonable to discuss these two different genes together but from the insurer's point of view they represent similar risks. It was long known that breast cancer occurred commonly in some families and, in 1990, work by King and others,[8] in the laboratories of Mary-Claire, indicated that some familial breast cancer could be linked to a mutation at 17q21. In families with at least three first degree relatives who had developed breast cancer under the age of 45, there were two distinct groups. Some families had a high incidence of associated ovarian cancer while others did not.[9] This difference and the failure to demonstrate linkage to BRCA1 in all familial breast cancers initiated a search for a second AD breast cancer gene, BRCA2, which was recently demonstrated on chromosome 13q12 to 13.[10]

BRCA1 and BRCA2 gene mutations account for at least five percent or more of all breast cancers and are usually associated with disease in younger women. The cancer risk for a woman with a BRCA1 mutation is estimated at 40 percent by age 50 years and 85 to 90 percent by age 70.[9,11,12] The gene is large and has many mutations[13,14] indicating that clinical BRCA1 testing may be technically difficult. The BRCA1 gene was characterized in 1994[15] and studies of the gene product from normal and mutant tissues indicate that over 80 percent of the mutations lead to a truncated protein. The wild type protein is probably a tumor suppresser.

1.2 Ataxia-telangiectasia. Ataxia-telangiectasia is an autosomal recessive disease occurring once in every 40,000 individuals. Affected patients are rare but the Hardy Weinberg equation indicates that 1:100 people are carriers. Both patients and carriers have an increased incidence of cancer. In the affected AT patient, the risk is estimated at 61 to 184 times higher than the general population. In 1991 Swift et al[16] reviewed 1599 blood relatives of patients with AT in 161 families and found a striking increase in the incidence of cancer compared to spouses in the same family who were not blood relatives.

The increase in risk for breast cancer in female obligate heterozygotes was 5.1 times the control group. Between the ages of 20 to 79, there is a 3.5 fold increased risk for all types of cancer for AT heterozygotes. When this figure is combined with the incidence of AT heterozygosity and the frequency of cancer in the general population, one can calculate that 4.7 percent of all cancer could result from AT gene mutations. The penetrance of the breast cancer risk in AT heterozygotes is only about 50 percent suggesting that some somatic mutations are also involved in the development of this form of breast cancer. Swift et al[16] also noted an increased risk of radiation induced cancers in heterozygotes. The AT gene has been localized to an approximately 500 kb interval of chromosome 11q23.1 by linkage studies and the gene appears to have several complementation groups suggesting that a simple test will not soon be available.[17]

2. Colon cancer genes

2.1 Hereditary non-polyposis colon cancer. Hereditary non-polyposis colon cancer (HNPCC) may occur at a frequency as high as 1:200 individuals and may cause five percent of all colon cancer. A common tumor site is in the ascending colon and, thus, these tumors are often not diagnosed until there has been extensive local spread or metastasis. Lynch et al[18] reviewed several kindreds and classified the hereditary disease into two types. Lynch syndrome one described only patients with site specific colon cancer while Lynch syndrome II included families with other tumors including those of urologic and endometrial origins. Mutations in at least four different DNA repair genes (hMLH1,[19] hMSH2,[20] hPMS1,[21] hPMS2[21]) have since been found in patients with HNPCC, and while each gene is known to have several mutations, the combined group of tests could have high predictive value when testing is confined to at-risk families.

The means by which these mis-match repair (MMR) genes cause cancer has only recently been characterized.[22] It appears that many genes are poorly repaired but when the gene for the receptor for transitional growth factor (TGF-B), which is located in the epithelial cells of the colon, does not repair properly, the control of growth provided by TGF-B is lost. Assays for the receptor may prove more useful in predicting cancer than the use of genetic tests for the MMR genes.

All carriers of HNPCC mutations will not develop colon cancer. Green et al[23] estimate the penetrance at only 25 percent in the 30 to 39 year age bracket but note that it rises to 80 percent by age 60. Penetrance for other cancers related to HNPCC genes was only 20 percent in their study but they suggest this frequency may vary with the nature of the DNA mutation.

As insurers, we can expect to see these assays appearing in attending physician's reports in the next few years. Risk will probably vary with the specific gene that is mutated and with the site of the mutation but, for the present, one can assume that 80 percent of all those with HNPCC-related gene mutations will develop colon cancer at some time in their middle life.

2.2 Familial adenomatous polyposis. Familial adenomatous polyposis (FAP) is a rare disease occurring once in every 5000 persons and it accounts for only about one percent of all colon cancers but gastroenterologists have long known that multiple polyps were associated with an increased risk of cancer. The gene responsible for the syndrome (adenomatous polyposis coli or APC) codes for a 300 kd protein that probably functions as a tumor suppressor.[24,25] The clinical course of the disease varies considerably between patients. Some develop colon cancer early in life and have a rapidly progressive disease, while others remain tumor free for many years. Caspari et al[26] examined 225 at-risk families and found the commonest mutation, a five base pair deletion in codon 1309, was also associated with the most aggressive tumors.

While only one percent of APC-related colon cancer results from dominantly transmitted germline mutations, as many as 60 percent of all colon cancers are associated with somatic mutations to APC that are confined only to the DNA extracted from the tumor.[27] While such analyses are somewhat more cumbersome than assays on leukocyte DNA, they could prove clinically useful in the management of patients with colorectal polyposis.

GENETIC INFORMATION IN PROTECTIVE STRATEGIES

Malignant tumors grow at differing rates, metastasize at differing rates, and may or may not lead to a fatal outcome. Advances in therapy bring better survival statistics and advances in diagnosis identify tumors at an earlier stage. Early diagnosis is associated with better survival (Table Two). Identification of a gene which predisposes to cancer should therefore improve the survival rate even further by indicating an increased risk before the tumor can be identified.

1. Breast and ovarian cancer

While mammography and breast self examination are widely supported as the best means to early diagnosis,[28] they have been employed in varying degree by different communities. The predictive value of mammography in young women has been questioned because of the low cancer incidence in that group and because the premenopausal breast is more radiodense than it is later.

Women who carry a BRCA1 mutation and do not yet have breast or ovarian cancer, however, are quite different from the general population. Most will get breast cancer at some time in the future. Their lifetime risk rises to nine in 10, from one in 10. The risk is 40 percent that they will develop a tumor before age 50 while that of all other women in that age bracket is less than two percent.[29] That 20-fold increase in probability makes the predictive value of mammography far higher and combined with a heightened awareness on the part of the woman, mammography should be used effectively in this high risk group.

Women who have BRCA1 mutations may consider high-fiber, low-fat diets which have been thought by some to provide less risk but primary preventions of this sort are probably more effective in multifactorial disease with somatic mutations. Some women have entered into long-term Tamoxifen trials in an attempt to lower their risk and others have had prophylactic mastectomy and/or oophorectomy; two rather dramatic "defensive" maneuvers.

2. Colon cancer

In this group of diseases both primary and secondary preventative measures are readily available to those who know they carry APC or HNPCC mutations. There is ample evidence to show that the nitrosamines in red meat, particularly barbecued red meat, are potent carcinogens. High dietary fat content delays bowel emptying time and increases the activity of coliforms which pro-

duce carcinogens. High fiber diets and antioxidants like Vitamins A, C, and E have a protective effect. Secondary prevention includes the frequent testing of stools for occult blood, colonoscopy, and polypectomy or colectomy. Colon cancer is a preventable disease, more particularly it is preventable in those who know they are at risk.

CALCULATING THE RISK

How will we underwrite this group of people at risk for AD disease? Can we predict the impact of a prophylactic mastectomy on mortality risk? Sound actuarial principles cannot be applied to these questions for many years because data for know carriers of BRCA1 and similar mutations have not been differentiated from the data for all breast cancers. Unfortunately, strong public support to restrict access to the genetic test data may make the collection of actuarially valid information impossible. In focus groups and market surveys, the ACLI have found that 80 percent of respondents thought insurers should not have the right to the results of genetic tests. I think it is time we begin to look for positive rather than negative responses to the legitimate concerns of the healthcare providers and their at-risk clients.

Let us make some general assumptions about cancer diagnosis and treatment. Firstly, if an individual is told they carry a lethal mutant gene which predisposes them to developing cancer, it is likely they will follow some of the defensive actions outlined above. Secondly, these people do not yet have the cancer but only the gene mutation which may give rise to a tumor. Mutations have variable penetrance and the tumor may not develop for many years, if at all. Thirdly, new forms of treatment are being developed and some, like the use of interleukin II for breast cancer, look very promising. The individual carrying the mutation may well be able to be treated before the tumor presents. As insurers, however, we cannot underwrite on future possibilities but must make use of known data.

1. Breast cancer mortality risk

Calculating mortality risk for breast cancer involves many assumptions. While breast cancer clearly results from differing causes, most registries lump all of these etiologies into a single cohort. BRCA1 mutations may have a somewhat better prognosis than some of the other forms 30 but these data are not firm. Survival data for breast cancer usually consider that a five-year survival is a "cure," but every underwriter knows that breast cancer carries a permanent extra risk as some recur many years later. Furthermore, if we are considering women with BRCA1 mutations, they are not cured by lumpectomy for they retain all the other breast tissue and both their ovaries. They continue to have high risk.

In order to consider the risk in spite of these data collection problems, I have taken a simplistic approach to compare the risk of dying with breast cancer with the risk of dying from all causes (Table Three) in various age groups. The analyses were based on ultimate female aggregate mortality (Canadian Institute of Actuaries 86-92) survival, and incidence statistics for breast cancer (Saskatchewan Cancer Foundation[31]) and the apparent penetrance of the gene.[9,11,12] The excess mortality falls with age because, by the seventh decade, the death rate for women from all causes approaches that from breast cancer.

In each age group, all women with BRCA1 mutations do not have breast cancer, but they are all presymptomatic in the Chambers[32] definition. With advancing age, the penetrance of the gene may reach 85 percent and one could consider all those with a mutant allele as potential cancer patients. Unfortunately, the Cancer Foundation statistics do not acknowledge any differences between death resulting from breast cancer associated with BRCA1 mutations and that from other causes because that information is not yet available.

Other data, however, make striking changes in the excess mortality for women who carry a BRCA1 mutation. Many women

Table One

Some autosomal dominant diseases

Disease	*Gene*	*Location*	*Reference*
Breast cancer	AT	11q23.1	16
Breast cancer	BRCA1	17q21	8
Breast cancer	BRCA2	13q12-13	10
Colon cancer	APC	5q21-22	24
Colon cancer	HNPCC		
	hMLH1		19
	hMSH2	2p16-15	20
	hPMS1		21
	hPMS2		21
Machado-Joseph	CAGrep	14q32.1	
Polycystic kidney	PKD1	16p13.3	37
Polycystic kidney	PKD2	4q13 23	38
Huntington	HD (CAGrep)	4p16.3	35

Table Two

Impact of cancer staging on survival; percent survivors five years after diagnosis

	Local	*Regional*	*Distant*
Site	*T*	*N*	*M*
Colon	91	60	6
Rectum	83	50	
Breast	92	72	19
Ovary	87	39	19

Table 3A

Extra mortality associated with BRCA (diagnosis in situ)

Age	*Penetrance*	*Prob. of cancer diag. in next year if mutation present*	*Prob. of death in next year if mutation present*	*Fem. agg. mortality 86-92 CIA*	*Extra mort. due to gene C/D*
	A	*B*	*C*	*D*	*E*
25	0.116	0.02290	0.00268	0.00034	788%
30	0.222	0.02830	0.00411	0.00057	721%
35	0.330	0.03040	0.00494	0.00075	659%
40	0.425	0.0290	0.00520	0.00124	419%
45	0.500	0.02510	0.00490	0.00187	262%
50	0.556	0.02110	0.00421	0.00274	154%
55	0.600	0.02160	0.00361	0.00417	87%
60	0.648	0.03340	0.00394	0.00654	60%
65	0.703	0.06090	0.00574	0.00958	60%

A. Extrapolated data from published penetrance figures (Refs. 9, 11, 12)

B. $\frac{A(t-1) - Ax}{1-At}$

C. Based on survival curves for in situ breast carcinoma Saskatchewan Cancer Foundation

D. Female aggregate mortality 1986 - 1992 Canadian Institute of Actuaries

Table 3B

Extra mortality associated with BRCA (diagnosis stage two)

Age	*Penetrance*	*Prob. of cancer diag. in next year if mutation present*	*Prob. of death in next year if mutation present*	*Fem. agg. mortality 86-92 CIA*	*Extra mort. due to mutation C/D*
	A	*B*	*C*	*D*	*E*
25	0.116	0.02290	0.00796	0.00034	2341%
30	0.222	0.02830	0.01153	0.00057	2023%
35	0.330	0.03040	0.01352	0.00075	1803%
40	0.425	0.0290	0.01396	0.00124	1126%
45	0.500	0.02510	0.01292	0.00187	691%
50	0.556	0.02110	0.01101	0.00274	402%
55	0.600	0.02160	0.00971	0.00417	233%
60	0.648	0.03340	0.01143	0.00654	175%
65	0.703	0.06090	0.01765	0.00958	184%

A. Extrapolated data from published penetrance figures (Refs. 9, 11, 12)

B. $\frac{A(t-1) - Ax}{1 - At}$

C. Based on survival curves for stage 2 b breast carcinoma Saskatchewan Cancer Foundation

D. Female aggregate mortality 1986 - 1992 Canadian Institute of Actuaries

with BRCA1 mutations will not develop breast cancer under the age of 50 when the cumulative risk is only 50 percent or less,[9,11,12] thus lowering the excess mortality. Furthermore, early diagnosis will lead to an even greater improvement in survival[33] which could be as high as 90 percent (i.e. of all women who develop breast cancer, over 25 percent will die; but early diagnosis could lower this figure to 10 percent: Table Two).

In Table 3A, I have estimated the excess mortality for women who know they carry BRCA1 mutations and who follow an active monitoring program which leads to early diagnosis (carcinoma in situ), as ranging from 262 percent at age 45 to only 60 percent at age 64. Many assumptions have been made in these calculations, but they do suggest that BRCA1 mutations probably represent a rateable, but an insurable risk. The data calculations in Table 3B, have been made for a diagnosis made at a later stage of tumor development (stage two) and clearly point out the importance of early diagnosis.

Similar calculations could also be made for BRCA2 but, at this point, there are not enough data on penetrance to complete the analysis. Ovarian cancer, resulting from BRCA1 mutations has a lower incidence and a lower penetrance but a higher death rate. The calculations used in Table Three can also be applied to ovarian cancer with similar results. Easton et al[9] have estimated the combined cumulative risk of breast and ovarian cancer as ranging from 34 percent at age 30 to 95 percent at age 70 but point out that there are at least two major allelic mutations and that the risk of breast or ovarian cancer varies with each. We now know there are over 80 to 100 mutations in this gene and based on clinical course, perhaps a wide clinical variability within the group. As more is learned about the molecular nature of these mutations and the clinical correlationship between disease risk and mutation, much more accurate predictions may be developed.

More importantly, the woman who knows she has a mutation that carries a high breast/ovarian cancer risk is clearly different from one who has harbored a presymptomatic ovarian cancer for many months or years before it is diagnosed. She will be expecting trouble and will, in most cases, be far more rigorous in surveillance than a woman who does not know her risk. These actions should further lower the risk of dying.

AT mutations, on the other hand, represent a different problem. The association of radiation sensitivity and cancer in AT heterozygotes[16] makes a monitoring mammography program the subject of much concern and may render those women who are AT heterozygotes and who have a family history of breast cancer, uninsurable. Until we have a clearer definition of the biology of AT mutations it will be difficult to predict risk.

2. Colorectal cancer mortality risk

Calculations of excess mortality for colorectal cancer can be completed like those for breast cancer. The excess risk will fall as the age increases due to the rising ultimate mortality figures. The calculations must be gender selected because cancer registries and life expectancy tables are constructed in that manner. Males have a somewhat greater incidence of colorectal cancer and a higher all-cause expected death rate in the later decades.

Individuals who know that they carry a colorectal cancer gene have a much better outlook than those with BRCA gene mutations because the prevention techniques are more rewarding and the tumor growth is usually slower. Death rates for those with colorectal cancer are high today because most patients are not diagnosed until there are signs of advanced disease. Early diagnosis (Table Two) has a highly significant impact on survival. Identification of those at risk by means of a genetic test provides the opportunity for early detection and should prevent colon cancer in that group. Dominantly inherited colon cancers represent a group of preventable tumors and preventable death. Based on this approach, carriers of mutations for AD colon cancer can be underwritten with modest ratings in the younger adults and may be taken as standard risks after they reach their 60s.

UNDERWRITING OTHER DOMINANT DISEASES

There are many forms of dominantly inherited disease which cannot be viewed as underwriting risks in the same manner as the BRCA, HNPCC and APC mutations. Huntington disease has an absolute risk but, like all impairments that underwriters consider, the prognosis for Huntington patients varies between different individuals. While the typical patient presents in their early fourth or fifth decade, some may not show signs until they reach 70 years of age[34] and thus could be offered rated insurance policies if they could be identified. Huntington disease results from an abnormal increase in tandem repeats (CAG triplets) and early suggestions that age of onset and severity would correlate with the number of repeats have not proven correct[35,36] but clearly there must be a genetic determinant that controls the course of the disease and it thus may be possible in the near future to offer insurance to some asymptomatic people with Huntington mutations.

Today, we know that the course of the illness is about 10 years thus individuals who are identified by triplet repeat studies can be offered non-renewable term contracts which could provide financial protection from death from other causes before the disease becomes terminal.

In like manner, two different forms of AD polycystic kidney disease have been described, resulting from mutations on two different chromosomes (PKD1 on 16p13.3[37] and PKD2 on 4q21.q23[38]). The age of onset varies within each of these different genes. Bear et al[39] noted that false negative ultrasound examinations were rare in patients over 30 years of age and the mean age of onset was 56 years. In the PKD2 group, the mean age of onset was 69 years. The PKD2 patients had a lower risk of progressing to renal failure, were less likely to have hypertension, and had fewer renal cysts. Genetic diagnosis in this disease should impact on the risk assessment. In fact, there are likely

many people with PKD2 mutations who are never diagnosed and have normal life expectancy.

We still have a great deal to learn about the molecular biology of dominant diseases and even more to learn about the clinical correlation with the various allelic mutations. Dominantly inherited diseases provide a window of opportunity for insurers to offer financial protection to those who presently think their genetic mutations will render them uninsurable. As we learn more about the risks associated with specific mutations in each of these genes, we will establish greater confidence in assessing individual ratings but it is important that we begin. The public image of our industry and its underwriting practices has fallen in the last few years. We do not need a new group of reasons to decline a cohort of applicants who are apparently healthy and have, in the past, been accepted as standard risks because their mutation status was unknown. We would do well to sharpen our pencils and get down to calculating the real increase in mortality that is associated with each of these so-called lethal genes.

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References

1. Petrillo A, Engel JV, Eds (1995) *Critical choices: ethical, legal and sociobehavioural implications of heritable breast, ovarian and colon cancer.* Univ. of Toronto Press (in press)
2. *Cancer in Ontario 1989,* Ontario Cancer Treatment and Research Foundation, Toronto, Ont.
3. Wallace DC (1995) Mitochondrial DNA variation in human evolution, degenerative disease and aging *Am. J Hum. Genet.* 57:201-223
4. Murray T (1992) Genetics and the moral mission of health insurance. *Hastings Center Reports* 22: 12-17
5. Capron A (1993) Hedging their bets, *Hastings Center Reports* 23: 30-31
6. Kass NE (1992) Insurance for the insurers. *Hastings Center Reports* 22 6-11
7. Billings PR, Kohn MA, deCuevas M, et al (1992) Discrimination as a consequence of genetic screening. *Am. J Hum. Genet.* 50:476482
8. Hall JM, Lee MK, Newman B, et al (1990) Linkage of early onset familial breast cancer to chromosome 17q21. *Science* 250:168-1689
9. Easton DF, Ford D, Bishop DT (1995) Breast and ovarian cancer incidence in BRCA1 mutation carriers. *Am. J Genet.* 56:265-271
10. Wooster R, Neuhausen SL, Mangion J, et al (1994) Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13 *Science* 265:2088-2090
11. Simard J, Tonin P, Durocher F, et al (1994) Common origins of BRCA1 mutations in Canadian breast and ovarian cancer families. *Nat. Genet.* 8:392-398
12. Goldgar DE, Fields P, Lewis CM et al (1994) A large kindred with 17q-linked breast and ovarian cancer: genetic, phenotypic and genealogical analysis. *J Nat. Cancer Inst.* 86:200 209
13. Castilla LH, Couch FJ, Erdos MR, et al, Mutations in the BRCA1 gene in families with early onset breast and ovarian cancer. *Nat. Genet.* 8:387-391
14. Shattuck-Eidens D, McClure M, Simard J et al (1995) A collaborative survey of 80 mutations in the BRCA1 breast and ovarian cancer susceptibility gene. Implications for presymptomatic testing and screening. *JAMA* 273:535-541
15. Miki Y, Swensen J, Shattuck-Eidens D, et al. (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1 *Science* 266:66-71
16. Swift M, Morrell D, Massev RB, Chase CL (1991) Incidence of cancer in 161 families affected by ataxia-telangiectasia. *N Eng. J Med.* 325:1831-1836
17. Lange E, Barresen A-L, Chen X. et al (1995) Linkage of an ataxia-telangiectasia gene to an ~500kb interval on chromosome 11q23.1: linkage analysis of 176 families by an international consortium. *Am. J Hum. Genet.* 57:112-119
18. Lynch HT, Lanspa S, Smyrk T, et al (1991) Hereditary nonpolyposis colon cancer (Lynch syndromes I and II): genetics, pathology, natural history and cancer control, Part 1 Cancer Genet. Cytogenet. 53:143-160
19. Bronner CE, Baker SM, Morrison PT, et al (1994) Mutation in the DNA match repair gene homologue hMLH1 is associated with hereditary non-polyposis colon cancer. *Nature* 368: 258-261
20. Fischel R, Lescoe MK, Rao MR et al (1993) The human mutator gene homolog MSH2 and its association with hereditary non-polyposis colon cancer. *Cell* 75:1027-1038
21. Nicolaides NC, Papadopoulos N, Liu B et al (1994) Mutations in two PMS homologues in hereditary non-polyposis colon cancer. *Nature* 371: 75-80
22. Markowitz S, Wang J, Myeroff L, et al (1995) Inactivation of type 11 TGF - B receptor in colon cancer cells with microsatellite instability. *Science* 268:1336-1338
23. Green RC, Narod SA, Morasse T-L, et al (1994) Hereditary nonpolyposis colon cancer: analysis of linkage to 2p15-16 places the COCA1 locus teleomeric to D2S123 and reveals genetic heterogeneity in seven Canadian families
24. Powell SM, Petersen GM, Krush AJ, et al (1993) Molecular diagnosis of familial adenomatous polyposis. *N Eng. J Med.* 329:1982-7
25. Myoshi Y, Ando H, Nagase H, et al (1992) Germline mutation of the APC gene in 53 familial adenomatous polyposis patients. *Proc. Nat. Acad. Sci.* USA 89:4452-6
26. Caspari R, Friedl W, Mandl M, et al (1994) Familial adenomatous polyposis: mutation at codon 1309 and early onset of colon cancer. *Lancet* 343:629-32
27. Powell SM, Zilz N, Beazer-Barclay Y, et al (1992) APC mutations occur early during colorectal tumorigenesis. *Nature* 359:235-7
28. Harris JR, Lippman ME, Veronesi U and Willett W (1992) Breast cancer. *N Eng. J Med.* 327:319-328
29. Bryant HE, Brasher PMA (1994) Risks and probabilities of breast cancer: short-term versus lifetime probabilities *Can. Med. Assoc. J* 150:211-216
30. Porter DE, Cohen BB, Wallace MR, et al (1994) Breast cancer incidence, penetrance and survival in probable carriers of BRCA1 mutation in families linked to BRCA1 on chromosome 17q12-21. *Br. J Surg.* 81:1512-1515
31. Snodgrass T (1995) Personal communication from Alberta Cancer Registry
32. Chambers D (1995) Defining genetic testing. *J Ins. Med.* (this issue)
33. Brescia FJ (1993) Specialized care of the terminally ill. in *Cancer: Principles and Practice of Oncology.* Lippincott. Philadelphia pp 2501-2507
34. Wiggins S, White P, Huggins M, Shelin A, et al (1992) The psychological consequences of predictive testing for Huntington's disease. *N Eng. J Med.* 327:1401-1405
35. Andrew SE, Goldberg YP, Kremer B, et al (1993) The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. *Nat. Genet.* 4:398-403
36. Andrew SE, Goldberg YP, Kremer B et al (1994) Huntington disease without CAG expansion: phenocopies or errors in assignment? *Am. J Hum. Genet.* 54:852-863
37. International polycystic kidney disease consortium (1994) The polycystic kidney disease 1 gene encodes a 14kb transcript and lies within a duplicated region on chromosome 16. *Cell* 77:881-894
38. San Millan JL, Viribay M, Peral B, et al. (1995) Refining the localization of the PDK2 locus on chromosome 4q by linkage analysis in Spanish families with autosomal dominant polycystic kidney disease type 2. *Am. J Hum. Genet.* 56:248-253
39. Bear JC, Parfrey PS, Morgan J et al (1992) Autosomal dominant polycystic kidney disease: new information for genetic counselling. *Am. J Med. Genet.* 43:548-553