

Genetic variation in nutritional requirements and susceptibility to disease: policy implications^{1,2}

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Introduction

Genetically determined differences in the ability to transport or metabolize certain dietary constituents (or their metabolites) contribute to variation in susceptibility to disease. The constituents of principal concern to us are those whose dietary intake can be reduced without—so far as is known—causing harm to anyone. Thus a policy debate is engendered: Should the genetically susceptible be identified so only their diets can be modified or should the dietary habits of the entire population be modified without regard to genetic differences. Critical issues in the debate include characteristics of the test and the disease as well as of the intervention intended to prevent the appearance of disease.

The prevention of rare single-gene disorders, such as phenylketonurea (PKU) and galactosemia, by placing everyone on a low phenylalanine, galactose-free diet is clearly untenable. Consequently, screening the entire population of newborns and treating affected infants is needed to prevent disability. The situation is different for genetic susceptibilities to coronary heart disease. The dietary changes needed to lower blood cholesterol can be applied to the entire population, presumably without risk, so it may not be necessary to identify those who are genetically susceptible.

Population-wide dietary modification beginning at age 2 y was advocated by the NIH consensus panel (1) in its statement "Lowering Blood Cholesterol to Prevent Heart Disease." It calls for a shift "from the current typical American diet to one that is lower in total fat, saturated fat, and cholesterol. . . . The recommended diet should be available to all family members except those younger than two years" regardless of blood cholesterol concentration." On the other hand, the Committee on Nutrition of the American Academy of Pediatrics (2) maintains, "There is no direct evidence from prospective studies that the diet now proposed by the NIH Consensus Development panel . . . will be effective in decreasing serum cholesterol during the first two decades of life or will adequately support growth and development, especially during the adolescent growth spurt . . . (Moreover,) there is no strong evidence that adolescent eating behavior generally persists into adulthood."

Rather than subject every child to an unproven and possibly dangerous diet, the academy committee recommended that in children > 2 y of age cholesterol testing be limited to those whose family history indicated an increased risk of future heart disease. A high yield of children at risk can be expected. In one recent study (3) half of the progeny of men with coronary artery disease angiographically diagnosed by age 50 y had lipid or lipoprotein concentrations above the 90th percentile. Another study showed that a history of coronary heart disease in one first degree relative (such as a parent) before age 55 confers a relative risk of 10.4 for early-onset coronary disease. The risk conferred by hypercholesterolemia alone, without regard to family history, is only 4.3 (4). It is not yet known, however, whether cholesterol lowering in these children will reduce their risk of heart disease.

Thus two different policy positions for dealing with a common disorder for which there are inherited predispositions have already emerged. The situation regarding coronary heart disease will not be unique. With recombinant DNA technology, we stand on the threshold of discovering genetic susceptibilities to a wide range of common disorders in which one or a few genes exert a major predisposing effect. Already, a small number of biotechnology companies are busy developing DNA-based tests (US Congress, Office of Technology Assessment, unpublished observations, 1988). As might be expected, they are more interested in common than in rare disorders. People identified by DNA-based tests as being susceptible to hypertension, colon cancer, adult-onset diabetes, gout, and peptic ulcer may benefit from diet modification. Alternatively, a general approach of modifying the American diet may apply to these disorders as well as to heart disease. The TV commercials of some cereal companies already urge everyone to incorporate more fiber in their diet to lower the risk of cancer.

The decision on whether the genetic approach makes the best policy—and whether the expenditure of public

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funds is appropriate—must be decided disease by disease. The basis for making this decision rationally rests on three criteria: the validity and reliability of the test, the efficacy of the intervention, and the effectiveness of the intervention. Unfortunately, policies are often adopted before data relevant to these criteria are gathered. For instance, the screening of newborns for PKU was mandated by many states before the validity of the screening test was determined and before the efficacy of early dietary intervention was established (5). (It was known that the low phenylalanine diet could reduce serum phenylalanine concentrations but not that it could prevent retardation.) Fortunately, the diet has proved successful in the most prevalent form of PKU. It is not effective in preventing disability in disorders involving bipterin cofactors. If these had been predominant, the dietary intervention would not have been of benefit. (At the time when screening started, there was no way of distinguishing the form of PKU responsive to diet from the others. Moreover, for the others, there was no effective treatment.)

More recently, the recommendation of the NIH consensus panel that “all physicians should be encouraged to include . . . a blood cholesterol measurement on every adult patient when that patient is first seen” was made without sufficient regard to the validity of the test and, as I have already discussed, the efficacy of interventions in the young. Data on whether a test satisfies these criteria can be collected—or systems for their concurrent collection established—before public policies are firmly promulgated.

The validity and reliability of the test

Is the test sufficiently sensitive and specific to warrant a policy of genetic screening? Is it reliable in laboratories performing the test routinely?

Population-wide screening is most appropriate when the test is sensitive, that is, when a large proportion of all those destined to suffer the disease in question will be detected, and when it is specific, that is, when almost all people who will never manifest the disease have negative test results. A third index of validity, but one which also depends on the prevalence of the disease in the population, is also important: the predictive value of a positive result, or the proportion of people with positive results who will eventually manifest the disease. Because trials to determine the sensitivity of screening for PKU by blood phenylalanine determinations were truncated by the passage of mandatory-screening legislation, it was only after several years of routine screening that sufficient data were collected retrospectively to indicate that ~8% of infants with PKU screening were being missed (6). Although very early screening—before the affected infant’s blood phenylalanine has a chance to rise above the cutpoint—accounts for part of this, poor laboratory quality was, and continues to be, a bigger problem (7). In the early days of PKU screening, infants with moderate

elevations of blood phenylalanine were also assumed to be at risk and were started on the low-phenylalanine diet. As a result of retrospective family studies, it became evident in a few years that these infants would not develop mental retardation (8). Approximately 10 times as many infants with initial elevations of phenylalanine do not have PKU as those that do. With appropriate follow-up none of the infants with false positive results need be treated.

Let us turn to cholesterol screening. Although the risks of coronary heart disease within 20 y after cholesterol determinations in men aged 33–49 y are 3.5 times higher in men in the highest quintile of cholesterol values than those in the lowest, they comprise only 30% of all those in this cohort who manifest coronary disease (Fig 1) (9). It should, moreover, be noted that deaths from coronary heart disease under age 65—essentially the only ones in which cholesterol-lowering diets have been claimed to have an effect—comprise only 19% of all deaths from this disorder (10). Cholesterol screening, therefore, detects a minority of those at risk. Moreover, 69% of the 33–49-y-old men in the upper quintile of cholesterol concentration will not manifest coronary disease in the next 20 y. There are over two false positives for every true positive; the predictive value is only 30%.

Reliability is also a problem. Forty-seven percent of 5000 clinical laboratories that voluntarily analyzed specimens provided by the College of American Pathologists in 1985 reported values that did not meet the desired goal of being within 5% of the true value. The values obtained by 15% of all labs were deemed unacceptable by the college (11). The college imposes no sanctions against these laboratories. They can continue to provide tests of poor quality.

Neither the blood phenylalanine test for PKU nor the cholesterol test for coronary heart disease detect the basic genetic defects associated with elevations of these low-molecular-weight molecules. Measurements of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol will probably enhance the validity of cholesterol screening but variations in their concentrations are undoubtedly determined by a variety of factors, not all of which will increase the risk of coronary heart disease. One of the difficulties is that the measurements of these substances are imperfect proxies for the underlying defects. Recombinant DNA research, however, promises to bring us tests for these underlying defects. Already, a DNA-based test that directly identifies the two most common alleles that cause PKU can be used for carrier testing (12).

Although the specificity and predictive value of DNA-based tests for a susceptibility-conferring allele will be higher than of tests for alterations removed from the basic defect, false positives will still occur when other genetic and environmental factors—in addition to the mutation—are needed in order for the disease to manifest itself. In other words, the deleterious effect of the susceptibility-conferring allele is not always expressed. Seldom is this the case for PKU but lack of expressivity occurs

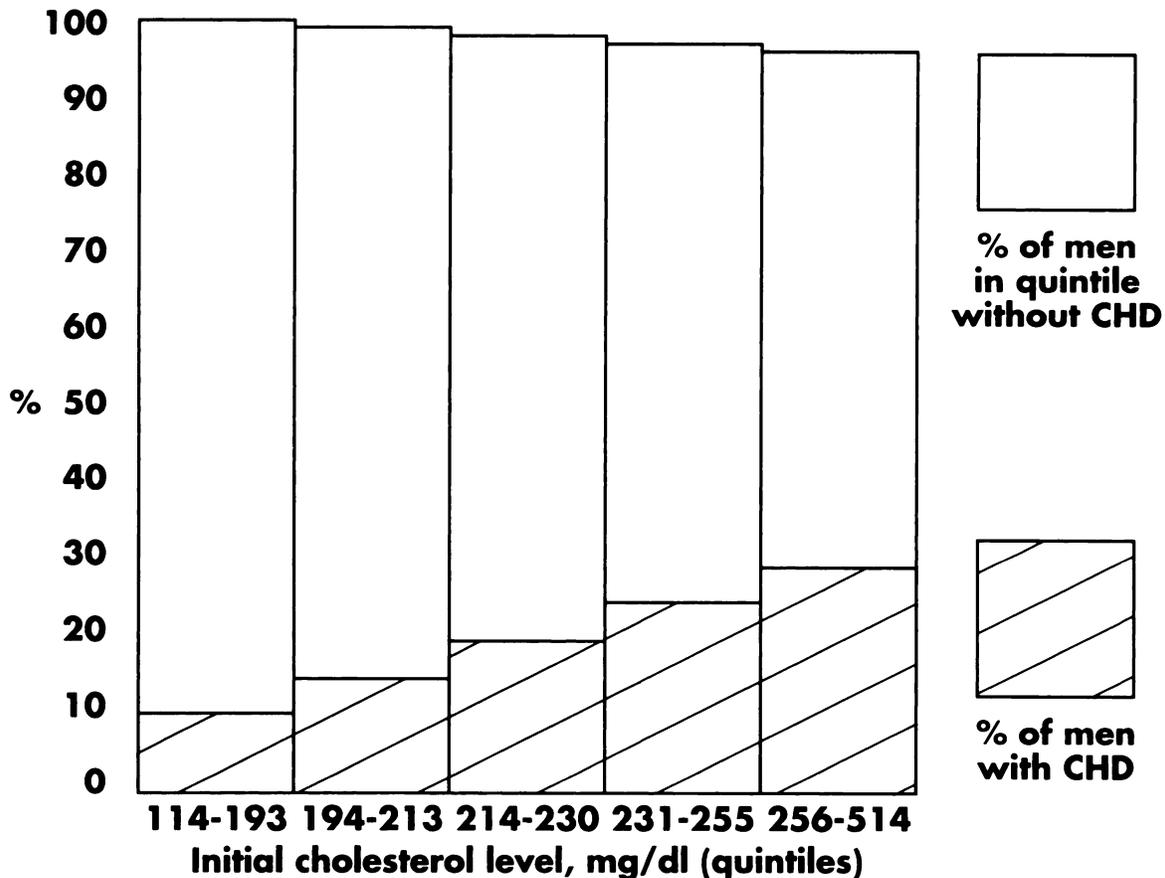


FIG 1. Distribution of cholesterol concentrations in healthy men aged 33–49 y. Data calculated from reference 9. (To convert mg cholesterol/dL to mmol/L, multiply by 0.02586.)

more often with mutations that increase the risk of coronary artery disease.

Despite their increased specificity and predictive value, DNA-based tests will be less sensitive. This is illustrated in Figure 2. A test that detects the alleles responsible for LDL receptor defects will have a predictive value of ~80% (13) whereas that for cholesterol testing will have a predictive value of only 30%. However, only ~5% of those destined to develop premature coronary heart disease will be detected by an LDL-receptor test compared with 30% with cholesterol screening. The diminished sensitivity reflects the etiologic heterogeneity of coronary heart disease. As more basic defects are identified and tests for multiple defects are devised, the combined sensitivity will increase. However, as the modes of inheritance of these as-yet-to-be detected genetic forms are not as clear as those for LDL-receptor defects, it is probable that their expressivity will be lower; the predictive value of a positive test result will not be as high as with LDL-receptor screening.

In general, we can expect that for common, late-onset disorders not everyone with a susceptibility-conferring genotype will suffer the disease; there will be false positives. Moreover, the more common the disease, the greater the chance that its etiology is heterogeneous.

Consequently, a test for one particular susceptibility-conferring genotype is unlikely to detect all or even most of the people destined to suffer that disease; there will be false negatives.

Thus with problems of sensitivity, specificity, and predictive value, the question of whether to screen for coronary heart disease at all reemerges. If screening detects only a small fraction of those who would benefit from diet modification, might not a policy of population-wide dietary reduction be more appropriate? The answer depends in good part on the efficacy and effectiveness of the interventions. These criteria will also be important in deciding whether a more specific or a more sensitive test should be used. If screening appears to be appropriate, then the reliability of laboratories performing the test must be ensured. At the present time the system of laboratory regulation is inadequate and variable from state to state. An increasing number of tests are being performed with semiautomated equipment in physicians' office laboratories. Very few states regulate these laboratories at all.

The efficacy of the intervention

Will people identified as at risk by genetic screening benefit from the intervention?

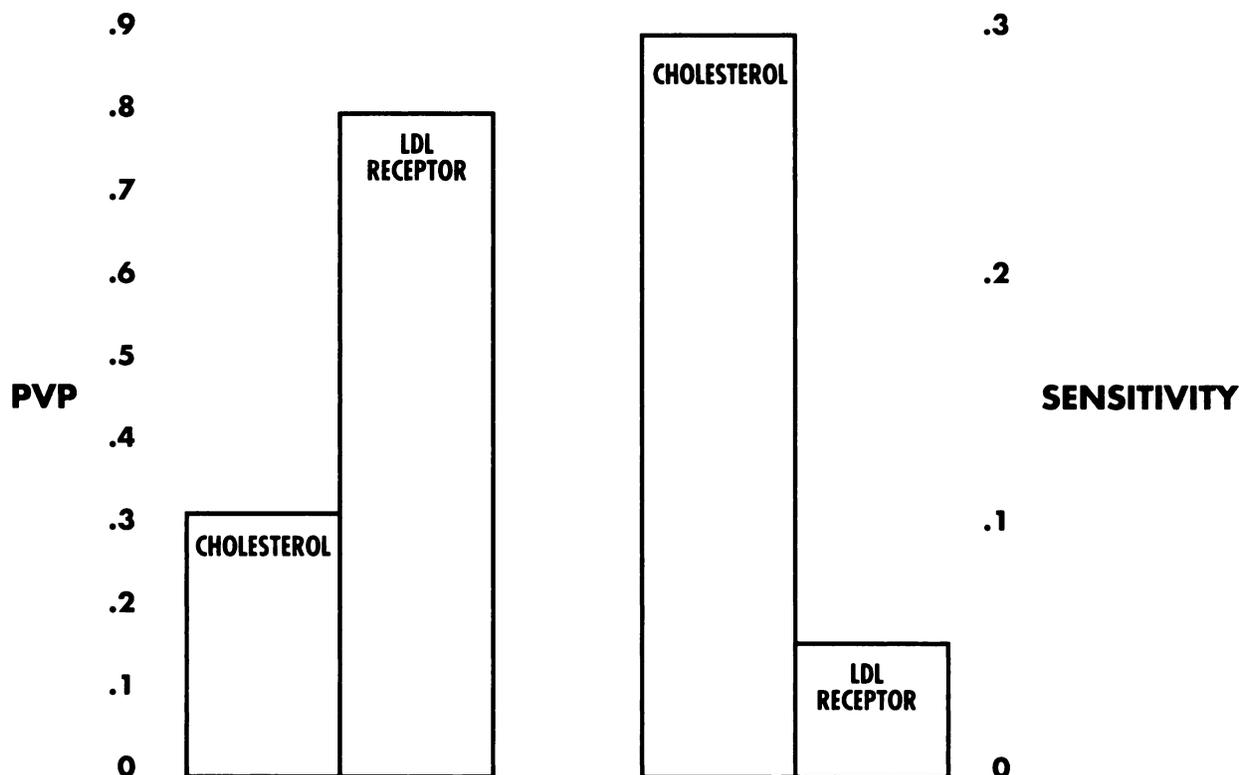


FIG 2. Left bars: Predictive value of positive test results (PVP) for serum cholesterol screening and, hypothetically, LDL receptor screening. (No test suitable for LDL receptor screening is available yet.) Right bars: Sensitivity of a test for serum cholesterol and, hypothetically, for LDL receptors. Data calculated from references 9 and 13.

As I have already mentioned, at the time that PKU screening became widespread, the efficacy of the intervention in preventing retardation was unknown. Had a randomized trial been conducted in which infants satisfying biochemical criteria for a diagnosis of PKU were assigned either to the special diet or to a regular one, only seven infants would have been needed in each arm. Moreover, the benefit of the diet would have been known in 2–3 y (14).

Efforts to determine the benefits of diet alone in the prevention of coronary artery disease by clinical trial have been equivocal at best. The NIH consensus panel noted that “no study (of dietary intervention) could be regarded as conclusive.” On the other hand, the age-adjusted mortality rate from coronary heart disease has fallen ~40% since 1968 in the United States. In analyzing factors that could account for this decline—including advances in the treatment of heart disease as well as dietary and smoking changes—Goldman (15) concluded that the largest single factor is reduction in serum cholesterol levels, as measured in the Health and Nutrition Examination Surveys. This drop accounted for about a third of the decline until 1976 and was in turn due to a decrease in the dietary intake of saturated fatty acids and cholesterol, a decrease that occurred before intensive cholesterol screening.

If we accept this finding, the question arises of what

can be accomplished by screening. It is possible that some people are lowering their saturated fatty acids and cholesterol intake unnecessarily. Although the manufacturers of beef and dairy products would like us to believe that (and hence can be counted on to encourage screening), recent data from the Framingham study suggest it is unlikely (16). The risk of coronary disease goes up continuously from the lowest cholesterol levels. For other disorders, however, there may be dietary changes that are unnecessary or even harmful for people with some genotypes but not for others. In those cases, screening would be advantageous.

Without knowledge of their particular risks and without medical guidance, some people may go overboard in modifying their diets. One recently reported cause of failure to thrive in infants is overzealous parental concern about the risk of obesity and heart disease in their offspring (17).

People whose risk is increased by a high serum cholesterol level may be more likely to change their diets when they are apprised of the results of screening. I will consider this in a moment under effectiveness. It is also possible that some genetically influenced forms of heart disease are refractory to the cholesterol-lowering effects of the prudent low-fat diet, but might respond to drugs. Using the more specific tests that will be available in the near future to screen for these forms, physicians could

promptly begin such drugs rather than wait to see if diet had an effect. Before such drugs are routinely used, the validity of the new test as well as the efficacy of the drug in those with positive results need to be determined. Both could be accomplished by a randomized controlled trial.

There is, as I have discussed, reluctance to place all children on cholesterol-lowering diets. Screening could identify the children whose elevated cholesterol levels suggest they are most at risk for heart disease so that dietary or other interventions could be started in them. This should be done as a randomized controlled trial. A child's cholesterol level is not a consistent predictor of his or her level as an adult. Only 43% of children with cholesterol levels above the 90th percentile on a single measurement were found to have similar elevations when they were 20–31 y old (18). (Tracking is much more consistent for children with a parent who had early-onset coronary disease.) Consequently, a reduction in cholesterol after long-term intervention might have occurred without the intervention. If it should turn out that the early-treated children developed heart disease less often than predicted by their initial cholesterol levels, without a randomized trial it would be uncertain whether this was due to the intervention or to spontaneous changes in cholesterol levels.

As new tests at the gene or gene-product level are developed to predict risks of future disease, their validity will have to be determined. The definitive proof that a positive result predicts future disease may have to wait for the appearance of the disease itself. The problem of waiting is compounded when a treatment—dietary or otherwise—is developed that may be efficacious in preventing the appearance of the disease. There may be considerable pressure to begin widespread treatment.

A randomized trial of the design shown in **Figure 3** can resolve the problems. Those with positive test results are randomized to receive the intervention. They, as well as a sample of those who test negative are followed past the age at which the disease usually appears. The sensitivity can be determined from the number of test-positive controls and those with negative test results who develop disease. The predictive value can be determined from the proportion of test-positive controls who become sick. The intervention will be efficacious if the proportion of treated individuals who remain disease free is significantly greater than the proportion of controls. The design will also indicate the proportion of people with positive test results who are being treated unnecessarily. The appearance of harmful reactions in these persons (such as nutritional deficiencies in the case of diet modifications) may mitigate the benefits of treatment and suggest the need for a test of higher predictive value.

Once a sufficient number of subjects are recruited into the trial to assure that it will have sufficient statistical power, the intervention can be made available to others. This is a departure from current drug policy but not from current policy for the manipulation of normal dietary constituents. In both cases, policies should be promul-

gated to warn potential users that the intervention is not yet of proven value and they proceed at their own risk.

The results from such trials should make it possible to determine whether screening is a better approach than population-wide efforts to change diet or other lifestyle behaviors. With data on validity and efficacy in hand, decisions can be made on the costs and benefits of the program. Although there is much talk about econometric analysis, seldom is health-care policy based on it. Aside from ethical reasons, it is unlikely that sufficient data—for instance on test validity—will be available when the policy is being promulgated. As data is accumulated, econometric analyses may be helpful in refining policies. However, by that time it may be too late to reverse policies. Cholesterol screening is so well entrenched in this country that at least one recent analysis on the costs of treating hypercholesterolemia does not even include the cost of screening (19). The makers of the equipment and the clinical labs performing the test have a vested interest in its continuation.

The effectiveness of the intervention

Will people at risk accept the intervention?

The people who enter a randomized trial may not be representative of the population from which they are drawn. Moreover, special efforts to get them to continue an intervention are often exerted. The question, then, is whether efficacious therapies will be routinely accepted by people at risk. If they are not, their effectiveness in improving health outcomes will be less than under the ideal conditions in which efficacy studies are conducted.

From the reductions in coronary heart disease mortality already mentioned as well as from the multiple-risk-factor intervention trial (MRFIT) (20), it is evident that people are altering their lifestyles in a healthful way without special interventions. Partly because of this, the MRFIT trial failed to show that intensive efforts to reduce risk factors had any significant effect in lowering coronary heart disease mortality.

An accurate perception of a person's risk would seem to be a logical prerequisite for taking appropriate action. Even geneticists, who specialize in presenting risk information, do not often succeed in improving understanding (**Table 1**) (21). In this collaborative study conducted in the late 1970s, 474 women were interviewed about their knowledge of the risk of disease in their offspring before and after genetic counseling. The largest number, 40%, had an inaccurate understanding before and after counseling. Ten women (2%) who had an accurate understanding before counseling had inaccurate understanding afterwards.

The question of whether apprising people of their personal risks—as would be accomplished by screening for genetic susceptibilities—would increase the chances that they would adopt healthful behaviors has not been rigorously studied. A recent review by Schoenbach et al (22) found only six studies reported through 1986 that used



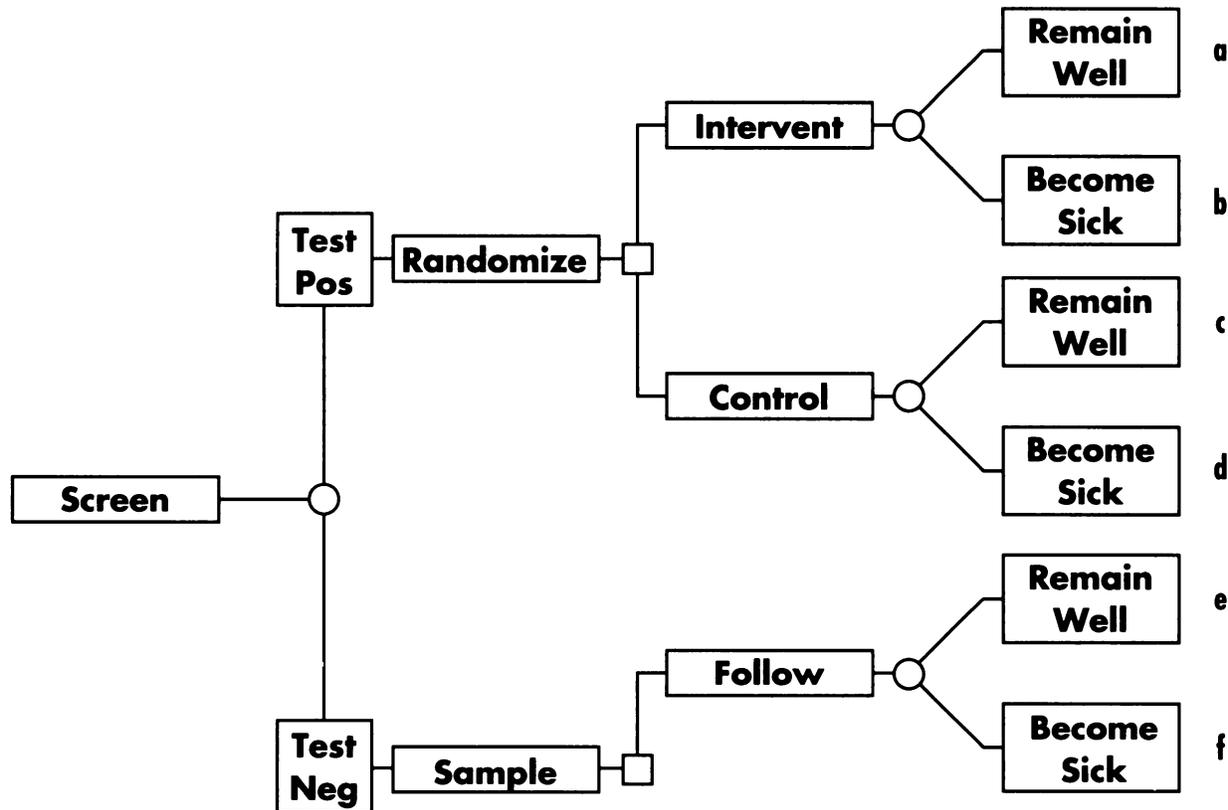


FIG 3. Prospective study of individuals screened with a new test to determine the validity of the test and the efficacy of an intervention in those with positive test results. After adjusting for the proportion of the total number screened in each group, sensitivity = $d/(d + f)$; specificity = $e/(e + c)$; PVP = $d/(d + c)$. The intervention is efficacious if the proportion of those with positive test results who remain well after treatment ($a/[a + b]$) is significantly greater than the proportion of those with positive test results who remain well after receiving the placebo ($c/[c + d]$).

comparison groups to assess the effectiveness of health risk appraisals. These appraisals present the client with a personalized mortality-risk projection and with recommendations for reducing that risk. The results of the studies were inconsistent; when outcomes were improved, considerable feedback and counseling were part of the program. The authors conclude that young people are less likely than middle aged people to respond to information regarding their risk of dying in what appears to them as the remote future. They also conclude that individualized risk appraisals are less effective in blue collar and minority groups. Yet it is low-income groups

that have the highest risk of dying at an earlier age from coronary heart disease and most other disorders (23). Schoenbach et al (22) suggest the incongruence of focusing on individual behavior modification for such groups when the “social-political system . . . restricts participation in decision making, economic gain, and educational opportunities.”

Summary and conclusions

I have considered several questions that should be answered in order to develop rational public policy for preventing disability and premature death for common disorders for which genes play a role and for which nutritional modification within the normal range can be effective. The sensitivity and predictive value of screening tests, the increment in improved outcomes from screening compared with population-wide changes in diet; the benefit, if any, to be derived from diet modification for those not identified by screening; and the reliability of the laboratories performing the test are some of the factors to be considered. We must bear in mind that many of the common disorders for which we will soon

TABLE I
Women’s knowledge of risk before and after counseling*

		Before		
		Accurate	Inaccurate	
After	Accurate	51	189	474
	Inaccurate	10	224	
	Totals	61	413	

* Derived from reference 21.

have tests at the gene or gene-product level result from the interaction of multiple factors, both environmental and genetic. Genetic screening will detect only a small proportion of all those destined to manifest a specific disorder, such as coronary artery disease or colon cancer. Dietary modification will also be only one of several interventions that will be efficacious for certain disorders. In some of these cases, genetic screening will prove to be an effective adjunct to general nutritional changes whereas in others it will have little utility and in still others it could play the predominant role in preventing or reducing the severity of the disorder. If we are to reduce the burden of disease most effectively, we cannot ignore factors in our environment and social structure that limit people's ability to control their own health. 

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