Editorial

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Screening to determine genetic susceptibility for common multifactorial diseases seems to be a good idea, at least when measures to prevent the development of full-blown pathology are available. On second thought, however, there are a number of problems that should be solved before genetic screening can be offered in a responsible way.

The first problem relates to the positive predictive value of the genetic predisposition [1]. This predictive value, or penetrance as it is mentioned by geneticists, tells us which percentage of those identified as genetically susceptible will indeed come to suffer from the disease. Since multifactorial diseases are caused by the combined effect of genes and environmental factors, the predictive value of a positive genetic test by definition will be less than 100%. Although useful testing will always result in a higher positive predictive value than the population prevalence of the disease, this value may not be more than 10 or 20%. This means that in this situation, in order to prevent the disease in one person, at least nine (or four) other persons have to be treated. These other persons would not have developed the disease, so in fact, from an individual point of view, they are treated for no good reason [2].

A second problem stems from the heterogeneity one may expect in individual susceptibility. Some people will have a higher genetic susceptibility, since they have more 'bad' genes. Others, who have less 'bad' genes, still may have an increased risk, compared to the population at large. This will lead to individualization of risk, and to the question who should be treated and who not. Such decisions are arbitrary, and will give rise to much criticism.

A third problem relates to the efficacy and efficiency of the preventive measures. Will they be able to prevent all cases or only part of them, even if all susceptible persons

are treated? Will everyone comply to the recommended treatment [3]? Will there be no adverse side effects for those treated? Epidemiologic measures as number needed to treat (NNT) and number needed to screen (NNS) are important parameters, since they summarize the predictive value of a positive test, efficacy and efficiency of treatment and prevalence of the susceptible genotypes [4]. This information should be requested from those who propose susceptibility testing for a genetic disease, together with information about the disadvantages of being labeled as a susceptible person, and the potential dangers of the treatment.

Perhaps we should wait with susceptibility testing till we have better predictors than genotypes. Intermediate phenotypes, for instance, may have a much better predictive value than genotypes alone, since they depend on environmental factors too. The disadvantage is that intermediate phenotypes are not stable, while genotypes are. A logical procedure then would be a multistep process: starting with genetic susceptibility testing at an early age, follow-up of susceptible individuals by regular observation of the intermediate phenotype and intervention only for those whose intermediate phenotype puts them at a much greater risk than other susceptible individuals.

References

- 1 Holtzman NA, Marteau TM: Will genetics revolutionize medicine? *N Engl J Med* 2000;343:141–144.
- 2 Motulsky AG, Beutler E: Population screening in hereditary hemochromatosis. *Annu Rev Public Health* 2000;21:65–79.
- 3 Marteau TM, Lerman C: Genetic risk and behavioural change. *BMJ* 2001;322:1056–1059.
- 4 Vineis P, Schulte P, McMichael AJ: Misconceptions about the use of genetic tests in populations. *Lancet* 2001;357:709–711.