EDITORIAL

Is cascade testing a sensible method of population screening?

Cascade testing is the identification of close relatives of an individual with a disorder to determine whether the relatives are also affected or are carriers of the same disorder. It is intended as a form of medical screening. Relatives of known cases are more likely to be affected or to be carriers of the disorder than members of the general population. It is therefore thought that more cases will be detected by testing fewer people than could be achieved using other approaches. However, the work involved in cascade testing is labour intensive, involving tracing relatives, asking them if they would be willing to have a DNA test and then asking them to reveal potentially sensitive information to other family members. It does not fit well into the general requirement that population screening needs to be simple, relatively automatic and able to reach everyone who stands to benefit. Cascade testing poses another special problem – a group of affected individuals must be identified before their relatives can be tested. It may take many years to identify enough cases in the population to be able to offer the intervention on a large enough scale to make a difference in the disease prevalence. As with all screening tests, the detection rates and false positive rates must be estimated and the potential harm assessed in relation to the benefits. These considerations need to be evaluated separately for autosomal dominant disorders, autosomal recessive disorders and X-linked disorders, because the consequences are different.

CASCADE TESTING FOR AUTOSOMAL DOMINANT AND X-LINKED DISORDERS

In autosomal dominant disorders, all heterozygotes are affected. Relatives are at a much higher risk of being affected than the general population and someone in each generation is likely to be affected. Similarly, for X-linked disorders all male relatives are at a much higher risk of being affected than the general population and some males in each generation are likely to be affected. Cascade testing for these disorders can theoretically achieve detection rates of 100%. Therefore cascade testing for autosomal dominant and X-linked disorders can in theory be an efficient method of screening if the costs of tracing relatives are less than those of testing greater numbers of people from the general population. This is the case in screening for familial hypercholesterolaemia, for example.[1,2] This is an autosomal dominant disorder occurring in about one in 500 people in Europe and North America. The characteristic clinical syndrome in adulthood comprises an increased serum cholesterol concentration, tendon xanthomas, and premature coronary heart disease at around 50 years of age. First-degree relatives are more than 300 times more likely to be affected than the general population and all of them can benefit from treatment at whatever age they are at diagnosis. Neither the study of Bhatnager *et al.*[2] nor that of Marks *et al.*[1] considered the problem of identifying the initial affected individuals. Bhatnager *et al.* identified only 262 affected individuals from two lipid clinics in over 12 years.[2] This suggests that there are practical problems in screening the whole population in a reasonable time scale using this method, in spite of theoretical advantages. The same conclusion affects screening for familial adenomatous polyposis (FAP). FAP arises from germline mutations of the APC gene and is inherited in an autosomal dominant fashion. At present DNA testing is recommended for all first-degree relatives of patients with known FAP, but not as a form of population screening.[3]

CASCADE TESTING FOR AUTOSOMAL RECESSIVE DISORDERS

In autosomal recessive disorders, screening is aimed at the detection of carrier couples with a view to offering preconception counselling or, more commonly, antenatal diagnosis. Therefore there is only an advantage to relatives knowing their status if they have a partner, know the partner's carrier status and are planning to have children or are already expecting a child. The knowledge is only useful at a particular time. Although relatives will be at a higher risk of being a carrier, these risks are not as high as for autosomal dominant disorders unless the marriage is consanguineous. Consequently more people need to be tested to find one affected individual. A recent paper demonstrated that, for cystic fibrosis (carrier frequency of 4%), testing all siblings and first cousins of all identified carriers would require locating and testing only 1.9% of the whole population, but would detect only 15% of all new cases.[4] Similarly, for congenital adrenal hyperplasia (carrier frequency of 1%), testing all siblings and first cousins of all identified carriers would require locating and testing only 0.1% of the whole population, but would detect only 3.1% of all new cases. The paper concluded that the performance of cascade testing is too poor to justify its introduction into practice as a screening test for any autosomal recessive disorder. A possible exception is in developing countries with high levels of consanguinity where it may have a limited role,[5] but even in this situation the case is not compelling.

CASCADE TESTING FOR FRAGILE X SYNDROME

Fragile X Syndrome is an exceptional example of an X-linked disorder, in that females may also be affected. The disorder is characterized by a mutation in the FMR1 gene located on the long arm of chromosome X, which involves the repeat of three nucleotide bases (CGG).[6] Males with over 200 CGG repeats have severe mental retardation. The number of repeats can increase in women during oogenesis from generation to generation.[7] It is not known what leads to the CGG expansion, but it appears that expansion is more common in families with a known case of Fragile X Syndrome compared to women identified through screening programs.[8] If this does occur then cascade testing has some advantage over population screening. Based on this assumption, a recent *Health Technology Assessment* report[8] concluded that compared with population-based prenatal screening, cascade testing was more efficient and cheaper, but that due to the problems of identifying the initial cases

over the first 10 years, cascade testing was less effective at reducing the total number of Fragile X Syndrome births. The report advised that large-scale trials of both methods of screening should be undertaken due to the uncertainties about the probability of CGG expansion. However, a recent review suggested that Fragile X Syndrome should only be screened for in male fetuses, in order to avoid the dilemma of having a prenatal diagnoses of a female fetus with over 200 CGG repeats.[9] Less than a quarter of females with over 200 CGG repeats are severely affected and there is no known method of determining which females will be affected and which will not. This dilemma will arise frequently in cascade testing, and phenotypically normal mothers will also find out that they themselves have over 200 CGG repeats.

In conclusion, there is evidence that cascade testing may be worthwhile for autosomal dominant and X-linked disorders if sufficient numbers of individuals with the disorder can be easily identified to start the cascade testing; it is not worthwhile for autosomal recessive disorders and there is a lack of evidence of its value in Fragile X Syndrome.

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