essentially no useful information to date, largely owing to the already low mortality rate from rectal and distal colon cancers in non-screened individuals. (The results of the randomised trial of sigmoidoscopy organised by the DCPC will probably not be available for at least another 10 years.)

If the study of Selby *et al* gets this sort of lukewarm reception, is it possible for the results of other, less definitive case-control studies of screening to have any credibility? Unfortunately, many persons do not have an appreciation of the contributions of non-randomised studies in general, and of case-control studies in particular, to our understanding of the cause of disease and of the efficacy and safety of therapeutic interventions. Undoubtedly, these persons will continue to view with skepticism even the most striking results of well done case-control studies that assess the efficacy of screening for cancer. But for the remainder of our audience—the size of which we can only hope grows with time!—we need to do what we can to enable our case-control studies of screening to provide as valid a result as possible. Although there is by no means unanimity about what should comprise the ingredients of a valid case-control study of screening efficacy, a consensus is beginning to form about some of these ingredients.[2 5 8] Certainly there will be instances in which the study group or data available for our case-control study of screening are suboptimal, and can lead only to an ambiguous interpretation no matter what the numerical results. In these instances, it is our responsibility as authors of such a study to issue a strong warning of caution to the reader.

By adhering to the principles underlying proper design and analysis when we conduct a case-control study of screening, and by recognising when circumstances prevent us from adhering to them, perhaps we can increase the chances that (*a*) those case-control studies of screening that yield valid findings will be heeded by a general audience and (*b*) the ones whose design has led to less easily interpretable findings will receive lesser attention, and then, primarily, from the afficionados of this corner of science.

NOEL S WEISS

Department of Epidemiology,
School of Public Health and Community Medicine,
Box 357236,
University of Washington,
Seattle, Washington 98195-7236,
USA

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Screening for Huntington disease and certain other dominantly inherited disorders: a case for preimplantation genetic testing

This invited article describes a new screening strategy with implications for families at increased risk for certain serious dominantly inherited, late onset genetic disorders. The approach has public health implications for disease prevention and the gradual elimination of the disease gene. It also shows the ability of preimplantation genetic testing (PGT) to do more than provide an earlier alternative to conventional methods of prenatal testing like amniocentesis and chorionic villus sampling. This summary is substantially derived from our recent article on this subject.[1] Huntington disease is used as the model disorder for purposes of this discussion.

In Huntington disease the natural desire of patients to avoid the transmission of a genetic disease to their children may conflict with the adverse effects of presymptomatic diagnosis in the parent at risk. This dilemma has led to the development of elaborate protocols to ensure that individuals at risk understand and are emotionally competent to accept all of the implications of presymptomatic diagnosis. In practice, only a minority of all adults who are at risk elect to have presymptomatic testing.[2 3] As a consequence, the potential of antenatal diagnosis to reduce the burden of genetic disease in the population, and the tragedy of recurrent cases within a family, is seldom realised. PGT now provides an approach in which antenatal diagnosis can be offered without incurring the adverse effects of the presymptomatic diagnosis. We believe this approach should be reviewed along with other relevant reproductive options when counselling patients at risk for Huntington disease and possibly other dominantly inherited traits as well.

We consider that PGT is far more desirable and ethical than an alternative approach involving prenatal testing, which is partially informative, and, while protecting parents from unwanted genetic information about themselves, results in pregnancy terminations in which 50% of the fetuses destroyed are genetically normal.

PGT refers to a group of related technologies in which in vitro fertilisation (IVF) is used to produce early embryos which are then biopsied, often as early as the four cell stage, to permit genetic testing of the embryos by polymerase chain reaction-based methods. Although the reliable amplification of target regions of the genome in single cells is still a technical challenge, prenatal diagnoses have been made accurately by this method without adverse effects on the fetus.[4] For patients who are at high risk (typically 50%) of carrying a gene for Huntington disease, PGT enables them to participate in antenatal genetic testing without incurring the emotional, social, and financial burdens that might result from the presymptomatic disclosure of their own carrier status. Such patients could be offered IVF with preimplantation biopsy and testing of their embryos without ever being informed of the specific test results. The couples would be told that embryos were formed and tested, and that only apparently disease free embryos were replaced in the uterus (and, if sufficient numbers were

available, *frozen* for subsequent pregnancy attempts). The parents would specifically not be given any information about the number of eggs obtained, the number of embryos formed, the number surviving biopsy, the number in which diagnosis was successful, etc. In other words, no information would be given which might provide a basis for inferring whether or not any embryos with the Huntington gene were ever identified. Hence, parents would derive no direct or indirect information about their own genetic risk, while PGT, if performed accurately, could reduce the fetal risk to zero.

This approach to the management of Huntington disease offers potential benefits, but it raises several issues. Firstly, IVF with PGT would be offered to some couples in whom the parent at risk was actually unaffected and this could be construed as an inefficient or wasteful use of an expensive technology. However, since presymptomatic diagnosis is not the goal of the testing, redundant testing must be regarded as part of the cost of the disease prevention by this approach. Secondly, accurate diagnosis on single cells removed from embryo biopsy specimens is technically difficult, especially for other triplet repeat disorders such as fragile X,[5-7] and for dominant disorders where allele dropout is a particular risk. These concerns may be addressed through rigorous methodology, such as the replacement of embryos only when the independent amplification of two blastomeres gives concordant normal results, or the possible use of blastocyst (multicell) biopsy. Thirdly, scrupulous attention to confidentiality and accuracy of communication would obviously be required. None of these issues, however, would seem to be insurmountable.

In principle, the same conceptual approach may be applicable to other late onset dominant disorders such as Charcot-Marie-Tooth disease, certain familial cancers, and possibly even Alzheimer's disease. IVF and PGT would emerge as important approaches for the management of such diseases.

This proposal has important public health implications. In Huntington disease nearly all cases arise in families with pre-existing Huntington disease rather than as new mutations. These procedures therefore constitute a potentially effective strategy for greatly reducing or even eliminating Huntington disease from the population. IVF is now a widely accepted reproductive option. Normally, about two to three IVF cycles are required to achieve a live birth in the best programmes. Hence, for a reasonable social cost, a couple containing one member at risk for having the Huntington gene could, on average, be assured of having two unaffected children, and the risk of the disease in all future generations would be eliminated.

If this opportunity were to be provided on a voluntary basis to all couples at risk, the gene frequency in the population could over several generations be dramatically reduced. The costs in any given generation and the cumulative benefits and cost saving to all future generations would be gradually realised.

Mankind has succeeded in eradicating certain infectious diseases such as smallpox, which is now considered officially to be absent world wide. Perhaps it is not too early to consider the strategy outlined above and make the elimination of Huntington disease and other extremely deleterious dominant traits a goal for the 21st century.

Both prenatal testing and PGT are services provided by the Genetics & IVF Institutes. Both authors are employees of the Institute.

JOSEPH D SCHULMAN
SUSAN H BLACK

Genetics & IVF Institute,
Fairfax, Virginia,
USA
and
Department of Human Genetics,
Medical College of Virginia,
Richmond, Virginia,
USA

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Systematic reviews of screening

Systematic reviews of screening for various disorders are being commissioned by health authorities, including the National Health Service in Britain. These are often necessarily long and comprehensive and there is a risk that because of their length they may not be published in full, so that the detail and the full list of references used to produce the report will not be made generally available. The *Journal of Medical Screening* thinks that it would be valuable if such reviews, if of sufficient quality, were published in their entirety. In this issue we publish such a review from Murray and her colleagues on screening for fragile X. The journal would welcome other systematic reviews of screening.

N J WALD

Department of Environmental and Preventive Medicine,
Wolfson Institute of Preventive Medicine,
St Bartholomew's and the Royal London School of Medicine and Dentistry,
Charterhouse Square,
London EC1M 6BQ,
United Kingdom