Letters to the Editor

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Population Screening for Cystic Fibrosis

To the Editor:

Dr. Gilbert's (1990) pessimistic attitude toward prospects for heterozygote screening for the cystic fibrosis (CF) gene in the United States is not widely accepted in the United Kingdom. The Research and Medical Advisory Committee of the Cystic Fibrosis Research Trust (UK) convened a meeting of experts in November and accepted the view that immediate pilot trials of CF screening were justified. An advertisement for appropriately designed and costed projects was placed in *Nature* in December.

Some of the reasons for this decision were dictated by the different pattern of health-care provision in the United Kingdom compared with the United States. This country has a strong tradition of providing prenatal care through hospital clinics and pioneered population-wide screening for neural tube defects by maternal serum alpha-fetoprotein measurement. Valuable lessons were learned from this exercise, and most health authorities have persisted with neural tube–defect screening even in the face of a natural (and unexplained) decline in the incidence of these disorders. Nonetheless, the Cystic Fibrosis Research Trust has invited projects for CF heterozygote screening which are based on general practitioner's offices as well as on hospital clinics.

I would take issue with Dr. Gilbert's assertion that, until all the CF mutations have been characterized, carrier screening would be a mistake and a disservice to the genetics community. Neural tube–defect screening began when the expected detection rate for spina bifida was about 70% and when that for anencephaly was about 80% (UK Collaborative Study 1977; Brock et al. 1987). If one is careful to specify that the objective of testing is to reduce rather than to abolish the risk of an affected child, unrealistic expectations can be minimized. The key to any prenatal screening program lies in the quality and skill of pretest counseling.

It is also necessary to pose another question. We currently have the ability to detect 81.5% of CF chromosomes through two defined mutations (McIntosh et al. 1989; I. McIntosh, personal communication)—and therefore to detect two-thirds of CF-homozygous affecteds. Do we have the right to withhold, largely because of our own unresolved worries about capacity to provide adequate counseling, screening from those who request it. Dr. Gilbert suggests that there is a potential nightmare in store for clinical geneticists and genetic counselors. This seems to be putting the cart before the horse; surely the profession's primary concern must be for its clients rather than for its counselors.

Of course we should not minimize the problems of delivering genetic screening to an entire population. Neural tube defect screening and Down syndrome screening need take no account of the male partners of pregnant women. Tay-Sachs programs are directed at identifiable subgroups within larger communities. However, there are useful lessons to be learned from the β-thalassemia screening experience in Mediterranean countries (Modell and Berdoukas 1984; Weatherall

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1985, p. 175). The most important of these is that if the medical profession is truly concerned about the well-being of the community in its care, and if it has the technical ability to offer some reduction in the risk of having an affected child, it will find the energy to overcome the inevitable organizational and social problems in delivering a suitably designed program.

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Risk Calculations under Heterogeneity: Comment on a Letter by D. E. Weeks and J. Ott

To the Editor:

The proposal of Weeks and Ott (1989) for estimating carrier risks in the presence of genetic heterogeneity is both sensible and practical. However, there must be strong reservations concerning their further suggestions for estimating "support intervals" of such risks. In effect, they require lay people to interpret statements such as the following: "The probability that you are a carrier of the gene for disease Y is about 1 in 10 and is probably somewhere between 1 in 4 and 1 in 25." Surely it is hard enough to understand the first part of the statement without having to wrestle with the concept of a "probability of a probability" embedded in the second. I would suggest that it is part of the duty of a genetic counselor to try to summarize, as a *single* probability, the uncertainties inherent in a particular set of circumstances. The only method of inference that is adequate to this task is a fully Bayesian one, in which all uncertainties regarding the values of model parameters are integrated over suitably defined distributions. The classic counterargument is that such distributions are often subjective; but this is not always the case, and, even where it is, it can be argued that the genetic counselor, as an expert whose advice is being sought and paid for, should be expected to evaluate and summarize the effects of prior knowledge to the best of his ability.

Consider the example given by Weeks and Ott in their figure 1, in which the risk that person 4 is a carrier is shown to be $(1-\alpha)/2$, where α (α_1 in the original notation) is the proportion of affected families linked to marker 1. Suppose that, although the exact value of α is unknown, our knowledge of it can be summarized as a distribution $\Pi(\alpha)$, say. When the above expression is integrated over Π, it becomes $[1-E(\alpha|\Pi)]/2$, showing that the Bayesian solution simply replaces α by its point expectation for a given Π. For example, if our entire knowledge of α came from a survey of N affected families, in which n were found to be linked to marker 1, we would have $\Pi(\alpha) \propto P(n|\alpha).\ P(\alpha)$, where $P(n|\alpha) = {}_NC_n\ \alpha^n(1-\alpha)^{(N-n)}$ and where $P(\alpha)$ denotes the initial prior distribution of α. If the latter is assumed to be uniform, it follows that $\Pi(\alpha)$ is a beta distribution with parameters $(n+1)$ and $(N-n+1)$ and expectation $(n+1)/(N+2)$. The assumption of a uniform prior is the only subjective element in the calculation and, in most practical situations, has little effect, since for any reasonably large values of n and N the expectation approximates the standard binomial estimate, n/N.

It is not my intention here to reopen the longstanding arguments between the contending schools of probabilistic inference; I merely wish to point out that different problems require different solutions. Confidence (or support) intervals may well be appropriate when estimating, say, the proportion of probands from a sample who carry a certain gene. However, where the problem is one of estimating the probability of a specific event—whether it be that a particular individual carries gene Y, that a particular horse will win a race, or that San Francisco will be struck by a major earthquake in the next 12 mo—only a single figure can form a rational basis for action, and only a fully Bayesian approach can in general supply it. No bookmaker would