**Table 1 (continued)**

| Location/Ethnic Group[a] | CF Chromosomes: Total No. Screened | CF Chromosomes: No. with ΔF508 (frequency) | Contributing Individual(s) (Affiliation) |
|---|---|---|---|
| Texas (Hispanic and other Caucasians) | 29 | 16 (.55) | S. Naylor, D. Barnett, and B. Bowman (The University of Texas Health Science Center at San Antonio) |
| United States (non-Jewish northern Europeans) | 26 | 19 (.73) | M. P. McGovern and R. J. Desnick (Mount Sinai School of Medicine, New York) |
| North America (Hutterite) | 20 | 7 (.35) | K. Klinger, G. Horn, and P. Locke (Integrated Genetics, Framingham, MA) and M. Fujiwara (McGill University, Montreal) |
| United States (Ashkenazic Jewish) | 12 | 6 (.50) | M. P. McGovern and R. J. Desnick (Mount Sinai School of Medicine, New York) |
| Total | 13,291 | 9,027 (.68) | |

[a] Geographic locations are listed as reported. The name of the ethnic group is included for comparative purposes; if unspecified, may be assumed to be Caucasian of European origin.

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## Carrier Screening for Cystic Fibrosis and Other Autosomal Recessive Diseases

*To the Editor:*

The February 1990 issue of the *Journal* contains "The American Society of Human Genetics Statement on Cystic Fibrosis Screening" (Caskey et al. 1990), as well as a letter to the editor on the same subject (Gilbert 1990). Both contributions agree that routine population screening for cystic fibrosis (CF) carriers should be postponed until the test detects a larger proportion of carriers and until more information is available regarding the issues surrounding the screening process.

Presently about 70% of CF carriers can be detected, but this percentage may vary significantly between populations. With a 70% detection rate of carriers, only 50% of couples at risk can be found. Moreover, under these circumstances, screening will reveal many couples in which one member is shown to carry a CF mutation, whereas for the other member the carriership cannot be excluded. Such couples are at significantly increased risk of having a child with CF but if they do not have the option of prenatal diagnosis or artificial insemination by donor (Ten Kate 1989).

In the near future comparable situations may occur for many other autosomal recessive diseases when they too are going through a phase of incompleteness of carrier detection. This makes it worthwhile to see what can be learned from present experience with CF.

**Table 1**

**Population Prevalence and Risk of Having an Affected Child for Different Mating Types in Screening Programs in Which Both Members of a Couple Are Tested**

| Type of Mating | Prevalence in Population | Risk of Having Affected Child |
|---|---|---|
| m × m | $a^2q^2$ | 1/4 |
| m × n | $2aq(1-aq)$ | (1/4)C |
| n × n | $(1-aq)^2$ | $(1/4)C^2$ |
| Overall | 1 | $(1/4)q^2$ |

**Table 2**

**Population Prevalence and Risk of Having an Affected Child for Different Mating Types in Screening Programs in Which the Second Member of a Couple Is Tested Only When the First is Shown to Be a Carrier**

| Type of Mating | Prevalence in Population | Risk of Having Affected Child |
|---|---|---|
| m × m ..... | $a^2q^2$ | 1/4 |
| m × n ..... | $aq(1-aq)$ | (1/4)C |
| n × ? ..... | $1-aq$ | $(1/4)C^2$ |
| Overall ..... | 1 | $(1/4)q^2$ |

One of the questions that will be asked repeatedly is, At which detection rate does screening becomes acceptable? Tables 1 and 2 give the necessary background information. These tables differ, in two ways, from calculations reported elsewhere (Ten Kate 1989). First, for persons in whom carriership cannot be demonstrated, the risk of being a carrier is calculated as a conditional probability (if it is given that the carrier test is negative). This may be important for some more frequent disorders. Second, table 2 has been added for screening programs in which both members of a couple are not tested routinely but in which the second member is tested only when the first is shown to be a carrier. Both tables give the population prevalences of the three different mating types, as well as their respective risk of having an affected child. m Denotes a person in whom the mutation is demonstrated; n denotes a person in whom the mutation is not demonstrated; ? denotes a person who is not tested; $q$ denotes the prevalence of carriers in the population; and $a$ denotes the proportion of carriers in which the mutation is demonstrable. For a person in whom the mutation is not demonstrated, the conditional probability of being a carrier is $q(1-a)/(1-aq)$, or $C$.

Suppose that ($a$) one has decided that screening should be postponed until the test is so sensitive that the risk for m × n couples is less than 1/1,000 and ($b$) one wants to know at which proportion of detectable mutations this can be achieved. From tables 1 and 2 it becomes clear that under these circumstances (1/4)C or $(1/4)q(1-a)/(1-aq)$, i.e., the risk for m × n couples, has to be less than .001. This is achieved when $a$ is greater than $(250\,q-1)/249q$. In CF (assume that $q$ = 1/25) this point is reached when the proportion of mutations detectable is more than 90.4%. At $a$ = 90.4% and $q$ = 1/25 the prevalence of m × n couples under the scenario of table 1 (both members are screened) is 7.0%, and under the scenario of table 2 (second member is screened if first member is positive) it is 3.5%.

Similarly, if one wants to restrict screening to situations in which the risk for m × n couples is less than the population risk for the disorder (so that no one other than m × m couples will have an increased risk), (1/4)C has to be less than $(1/4)q^2$. This is achieved when $a$ is greater than $(1-q)/(1-q^2)$. In CF this means that $a$ has to be greater than 96.2%. At $a$ = 96.2% and $q$ = 1/25 the prevalence of m × n couples under the scenario of table 1 becomes 7.4%, and under the scenario of table 2 it becomes 3.7%.

The consequences of other conditions, such as the maximum acceptable risk for n × n or n × ? couples, can be calculated in a comparable way. If multiple conditions are to be met, the one resulting in the higher value of $a$ determines the point beyond which screening is acceptable.

It should be noted that the formulas in the present tables ignore information from previous children and family history. If in an m × n marriage there are already $p$ unaffected children (and no affected ones), the probability that $n$ is a carrier reduces to $q(1-a)/[q(1-a)+(4/3)^p(1-q)]$, or $Cp$. With one unaffected child present, in the first example given above, with $a$ = 90.4% and $q$ = 1/25, $(1/4)Cp$ becomes 1/1,361 instead of 1/1,000. This difference in risk might plead in favor of models more complicated than those the tables provide, especially when one wants to assess the impact of carrier screening on society. On the other hand, it may be argued that, in most Western societies, first-born children represent a large proportion of all newborn infants; that couples without previous children may be more inclined to carrier testing than are couples who already have (unaffected) children; and that, for decisions at which detection-rate carrier screening becomes acceptable, the risk from false-negative tests in this special group may be more important than (or at least equally important as) the mean risk from false-negative tests in the population as a whole.

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