Carrier Screening for Gaucher Disease
Lessons for Low-Penetrance, Treatable Diseases

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Context The aim of carrier screening is to prevent severe, untreatable genetic disease by identifying couples at risk before the birth of an affected child, and providing such couples with options for reproductive outcomes for affected pregnancies. Gaucher disease (GD) is an autosomal recessive storage disorder, relatively frequent in Ashkenazi Jews. Carrier screening for GD is controversial because common type 1 GD is often asymptomatic and effective treatment exists. However, screening is offered to Ashkenazi Jews worldwide and has been offered in Israel since 1995.

Objective To examine the scope and outcomes of nationwide GD screening.

Design, Setting, and Participants All Israeli genetic centers provided data on the number of individuals screened for GD, the number of carriers identified, and the number of carrier couples identified, and the mutations identified in these couples between January 1, 1995, and March 31, 2003. Carrier couples were interviewed via telephone between January 21, 2003, and August 31, 2004, using a structured questionnaire for relevant outcome measures.

Main Outcome Measures Screening scope (number of testing centers, tested individuals, and carrier couples), screening process (type of pretest and posttest consultations), and screening outcomes (utilization of prenatal diagnosis and pregnancy terminations).

Results Between January 1, 1995, and March 31, 2003, 10 of 12 Israeli genetic centers (83.3%) offered carrier screening. Carrier frequency was 5.7%, and 83 carrier couples were identified among an estimated 28,893 individuals screened. There were 82 couples at risk for offspring with type 1 GD. Seventy of 82 couples (85%) were at risk for asymptomatic or mildly affected offspring and 12 of 82 couples (15%) were at risk for moderately affected offspring. At postscreening, 65 interviewed couples had 90 pregnancies, and prenatal diagnosis was performed in 68 pregnancies (76%), detecting 16 fetuses with GD (24%). Pregnancies were terminated in 2 of 13 fetuses (15%) predicted to be asymptomatic or mildly affected and 2 of 3 fetuses (67%) with predicted moderate disease. There were significantly fewer pregnancy terminations in couples who in addition to genetic counseling had medical counseling with a GD expert (1 of 13 [8%] vs 3 of 3 with no medical counseling [100%]; P = .007).

Conclusions In this study of GD screening among Ashkenazi Jewish couples in Israel, most couples did not terminate affected pregnancies, although screening was associated with a few pregnancy terminations. The main possible benefit was providing couples with knowledge and control. The divergence of these outcomes from stated goals of screening programs is likely to confront carrier screening programs for low-penetrance diseases.

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were gradually added, and the panel commonly offered to Ashkenazi couples now includes up to 14 autosomal recessive diseases.6,7

Gaucher disease is the most common of these disorders, with a carrier frequency of 6% in Ashkenazi Jews8 compared with an estimated 0.7% to 0.8% in non-Jewish populations.9,10 Testing for 4 mutations in the glucocerebrosidase gene (GBA) (N370S, 84insG [commonly denoted 84GG], L444P, and IVS2DS+1G-A [commonly denoted IVS2 +1]) detects at least 96% of carriers in Ashkenazi Jews11 and perhaps 75% of carriers in non-Jewish populations.8 Gaucher disease is caused by deficient glucocerebrosidase enzymatic activity, with subsequent accumulation of glucosylceramide in various organs.12 In type 1 GD, this mainly results in (1) visceral manifestations including hepatomegaly, splenomegaly, anemia, and thrombocytopenia causing fatigue, discomfort, infections, bleeding, and bruising; and (2) bone disease, including pain (acute or chronic), bone crises, and avascular necrosis. In type 2/3 GD, which is very rare, there is also progressive central nervous system disease.12

The most common GD mutation in Ashkenazi Jews, N370S, precludes the neurological disease and leads to type 1 GD with an extremely variable phenotype, from asymptomatic disease in early childhood to asymptomatic status throughout life.12 For simplification of terminology, the presence of 2 mild mutations is defined as leading to asymptomatic or mild disease and compound heterozygosity for 1 mild and 1 severe mutation is defined as leading to moderate disease. Mild mutations include N370S, RecTL, and R496H. Severe mutations include 84insG, L444P, IVS2DS+1G-A, and V394L. This is a generalization because genotype-phenotype correlations are inaccurate. Estimates suggest that up to 90% of N370S homozygotes are mildly symptomatic or even asymptomatic.13,14 The observed prevalence of patients with GD is much lower than expected based on carrier frequency in Ashkenazi Jews,13 and unsuspected N370S homozygotes are often detected during carrier screening.8,13 More significant GD expression is usually associated with compound heterozygosity for N370S and a severe mutation (eg, 84insG, L444P, IVS2DS+1G-A, or V394L).12,15 However, within type 1 GD, the genotype alone is an uncertain predictor of an individual’s clinical course. In symptomatic cases, intravenous enzyme replacement therapy is highly effective16,17 but very expensive ($75 000-$100 000 annually in Israel [approximately $200 000 annually in the United States])19, and oral substrate inhibitors have recently received clinical approval.19

Although type 1 GD is common and test sensitivity is high, carrier screening is controversial because the disease is usually not severe or untreatable, and the test performed does not fully predict disease severity. The World Health Organization criteria for carrier screening include elements such as that the disease be a significant health problem and the natural history of the disease be adequately understood.3,20,21 The divergence of GD screening from these criteria has clinical consequences: genetic counseling for carrier couples is complex and decisions regarding prenatal diagnosis and termination of pregnancy may be challenging. Couples may question why screening was ever performed for a mild, treatable disease and those couples whose older children were born before screening may become anxious regarding their up-to-now healthy children.22 Screening can also identify adults with asymptomatic GD, who then may experience unexpected medical evaluations.

Expert committees both in North America and in Israel have addressed these issues. The 1996 National Institutes of Health Technology Assessment Panel on Gaucher Disease concluded that “General population screening for carriers is not appropriate at this time,” and suggested that pilot studies of carrier screening programs may be valuable to determine their acceptability.23 The 2006 Ashkenazi screening guidelines of the Canadian Society of Obstetrics and Gynecology and College of Medical Geneticists recommend against GD screening because of “poor genotype/phenotype correlation.”24 A similar position was stated by an advisory committee for the Israel Ministry of Health,25 and a position paper reflecting this recommendation was subsequently adopted in 2004 by the Israeli Medical Geneticists’ Association. Nevertheless, despite formal positions against it, GD carrier screening continues to be widely offered both in the United States and in Israel.6,7,26-29

There is a paucity of data on GD screening outcomes with respect to prenatal diagnosis utilization and termination of affected pregnancies. We found no reports on GD screening outcomes in the clinical practice setting. Two pilot studies in New York,5,30 which assessed the expansion of Tay-Sachs carrier screening in Ashkenazi Jews to triple disease screening that included cystic fibrosis and GD, identified a total of 8 GD carrier couples: 1 couple (with an unaffected fetus) among 1000 screened individuals,2 and 7 couples in a clinical study of 1882 Ashkenazi Jewish couples performed in “a health-oriented and knowledgeable population,”30 who were presented with information about 3 diseases rather than the 12 or more offered today.

Herein, we present a nationwide study on the outcomes of essentially all clinical GD carrier screening performed in Israel. Our goals were to assess various aspects of GD screening: its scope, the screening process (pretest and posttest information and genetic counseling), and screening outcomes, especially utilization of prenatal diagnosis and pregnancy termination associated with type 1 GD. We discuss the implications of GD screening as a model for existing and future programs designed to screen for mild, low-penetrance, treatable diseases.

METHODS
Data Collection
Directors of all Israeli genetics centers were personally contacted between
January 2003 and June 2003 by 1 of the 2 principal investigators (M.S. and E.L.-L.). The study was described in detail, with the goals stated as noted above. Centers offering GD screening described their protocol, sent their information brochures, and provided details on topics discussed with carrier couples. Centers also provided data on the number of individuals screened for GD, the number of carriers identified, the number of carrier couples identified, and the mutations identified in these couples.

**Mutation Testing**

Four GBA mutations (N370S, 84insG, IVS2DS+1G-A, and L444P) account for at least 96% of GD carriers among Ashkenazi Jews and comprise the common GD testing panel worldwide. The L444P mutation occurs either as an isolated mutation or as part of the complex RecTL mutation, which includes 4 point mutations (D409H, L444P, A456P, and V460V). Thus, L444P testing detects both isolated L444P and RecTL carriers, which can be distinguished by testing for other RecTL-associated mutations (eg, D409H). Among 1208 healthy Ashkenazi individuals assessed in a prior study, N370S accounted for 90.8% of carriers, 84insG for 3.9% of carriers, RecTL for 1.3% of carriers, and isolated L444P and IVS2DS+1G-A were not observed. The IVS2DS+1G-A mutation has also not been observed in one study of 3764 healthy Ashkenazi Jewish individuals and in another study of 1256 healthy Ashkenazi Jewish individuals, demonstrating that IVS2DS+1G-A carriers are extremely rare (95% confidence interval, 0%-0.05%). Among Ashkenazi Jewish patients with type 1 GD, there are 2 additional recurrent mutations (V394L and R496H). The V394L mutation is found in 1.7% to 2.6% of Ashkenazi Jewish patients with type 1 GD, but is rare in controls (carrier frequency of 0 of 1208 healthy individuals, 95% confidence interval, 0%-0.2%). The R496H mutation is even milder than N370S and its carrier frequency is 0.44% (21 of 4734 healthy individuals), leading to recommendations against its inclusion in carrier screening.

**Classification of Type 1 GD Severity**

Based on their genotypes, type 1 GD couples and fetuses were classified by risk for asymptomatic or mild disease versus moderate disease. This classification is based on published studies, many of which used the Zimran Severity Score Index. Mild disease may be defined as a low severity score index, or in Israel, by not fulfilling even 1 of 10 criteria for enzyme replacement therapy. Moderate disease may be defined by a higher severity score, or in Israel, by fulfilling criteria for treatment. Approximately 90% of patients with moderate disease may require enzyme replacement therapy, usually in early adulthood.

**Participants**

Persons screened for GD are all self-reported as fully or partly Ashkenazi Jewish. At all centers, individuals recorded country of birth for all 4 grandparents, or grandparent ethnicity for Israeli-born grandparents. Fully Ashkenazi Jewish is defined as all 4 grandparents being European-born or of Ashkenazi origin, and partly Ashkenazi Jewish is defined as having 1 to 3 grandparents fulfilling these criteria.

Each center informed GD carrier couples if they identified (83 eligible couples between January 1, 1995, and March 31, 2003) of the study. Couples received a 2-page letter printed on the letterhead of the center where they were tested, and sent by that center to its carrier couples. The first page of the letter indicated that the letter was sent in regard to a national study on carrier screening for GD, for the purpose of examining the screening program and its outcomes and effects, personally signed by the center’s director. It stated in the letter that participants would all be couples found to be GD carriers at genetics centers throughout Israel, that the study would include a telephone interview, and that confidentiality would be maintained. It was also indicated in the letter that the study was being conducted by Shaare Zedek and Hadassah Hospitals in Jerusalem in collaboration with all the genetics centers in Israel, and was coordinated by the study coordinator (S.Z.).

Persons were invited to return the refusal form (the second page of the correspondence) and informed that if the form was not returned, they would be telephoned by the study coordinator (S.Z.) regarding participation in the study. It was indicated that even if the refusal form was not returned, they still retained every right to refuse participation when telephoned. The form was approved by 2 separate institutional review boards. It stated that, “If you are not interested in participating, please send this form to (contact information of the center),” and the individual was requested to note their name. This form was meant to be sent or faxed to the genetics center where the couple was tested. The genetics center then gave the study coordinator only the names and contact information of couples who received the letters and did not send refusal forms. Consenting couples (72 of 83 couples who did not return refusal forms and who had current addresses) were telephoned by the study coordinator (S.Z.), who further explained the study. No couples had returned refusal forms.

The nature of the information provided by the study coordinator (S.Z.) during the telephone call was similar to that described above (ie, persons were told they were being contacted regarding participation in a national study on the GD carrier screening program because they had been identified as a carrier couple). They were also told that participation would include a telephone interview and that they should feel free to refuse participation. Couples interested in participation received consent forms and were enrolled after giving individual, written informed consent for a telephone interview, for release of genetic testing and counsel-
ing information from the treating center, and for anonymous analysis of all data obtained. Telephone interviews were conducted by the study coordinator (S.Z.) between January 21, 2003, and August 31, 2004, using a structured questionnaire (available upon request). The questionnaire included items in 4 categories: (1) sociodemographic data (age, country of birth, ethnic origin, education, religiosity), (2) genetic data and reproductive history (type of mutations, number of pregnancies, number of children born before and after screening), (3) actions taken after knowledge of carrier status (genetic counseling, further counseling at the GD referral center, prenatal diagnosis utilization and results, and decisions made after detecting an affected fetus); and (4) testing of existing children. Couples who had children born before screening were asked about subsequent testing of these children, including test results and the health status of all their children.

Sixty-five of 83 couples (78%) were interviewed. Eleven couples (13%) could not be traced due to change in address or contact information, 5 couples (6%) refused participation after the initial telephone call, and 1 couple (1%) denied being a carrier couple. Data analysis was performed between September 2004 and April 2005. Data collection in this regard is not ongoing.

The study was approved by the ethics committees of Shaare Zedek Medical Center (Jerusalem) and Sourasky Medical Center (Tel Aviv). The positions of both institutional review boards that approved the study were that anonymous collection of genotype data was both possible and appropriate. Genotype data from nonparticipating couples was anonymized before being given to the study coordinator (S.Z.); therefore, we thought it was appropriate to present genotype data for all 83 eligible couples. The request for release of genetic information from the 66 participating couples (80%) was a request to receive identified genotypes.

**Statistical Analysis**

Comparison of termination of pregnancy and prenatal diagnosis rates and choice of prenatal diagnosis procedure was performed by using the χ² test for comparing dichotomy data and the Fisher exact test when the expected number in a cell was 5 or less. The threshold for significance was P ≤ .05. Analysis was performed by using Epi Info version 3.3.2 (US Centers for Disease Control and Prevention, Atlanta, Georgia, and the World Health Organization, Geneva, Switzerland).

**RESULTS**

**Survey of the Screening Process**

Ten of 12 genetic centers in Israel (all located in public hospitals) offered GD carrier screening during the study period (January 1, 1995, to March 31, 2003). Screening was initiated in 1995 at 3 centers, in 1999 at 5 centers, and in 2000 at 2 centers. In Israel, referral to carrier screening programs is routine in couples and women who are pregnant or planning a pregnancy to determine whether they are at risk for affected children. The Israeli Ministry of Health recommends carrier screening for all couples. This applies to all ethnic groups in Israel (eg, in non-Askenazi Jews and Arabs there is screening for cystic fibrosis, fragile X, thalassemia, and other ethnic-specific diseases). Thus, we did not note the referral reason, but only the referral source. To ascertain whether this is still the case in 2007, we contacted all centers included in our study and determined that GD screening is still widely offered in Israel (S.Z., unpublished data, 2007). Only 1 center, which serves a large non-Jewish population, has stopped offering GD screening. This center had the smallest screening volume and accounted for only 438 (of an estimated 28 893) screened individuals described herein. Thus, cessation of screening at this center will have had a negligible effect, if any, on the scope of the entire screening program. Carrier screening for GD is offered to all couples in which both partners are at least partly Ashkenazi Jewish, as part of the Ashkenazi screening panel. The Ashkenazi screening panel was the same across genetic centers. In 2003, this panel included testing for 8 diseases: fragile X, cystic fibrosis, Canavan disease, Bloom syndrome, Fanconi anemia, familial dysautonomia, GD, and Tay-Sachs (the latter offered through the Ministry of Health). Participation is voluntary and most individuals are screened during or just before pregnancy. Referral source was reported by 122 of 127 (96%) interviewed participants (members of carrier couples): 49 (38%) were referred by their gynecologist, 28 (23%) were informed by friends or family, 24 (19%) knew carrier screening to be routine in pregnancy planning, 8 (6.2%) were informed by pregnancy guides, 5 (3.9%) were informed by a genetic counselor, and 8 (6.2%) were informed through other resources. Of the 65 couples interviewed, for 3 couples, only 1 spouse was interviewed (2 women and 1 man).

Prescreening, all participants received information brochures. All the brochures included an explanation of autosomal recessive inheritance; the natural history, carrier frequency, and test sensitivity of each disease screened; and the option of prenatal diagnosis. Information on the variable expression of GD is mentioned in all the brochures, stating that GD can often be very mild or asymptomatic. In 3 of the 10 brochures, enzyme replacement therapy is mentioned. In 3 centers, which account for 21 430 of an estimated 28 893 persons screened (approximately 74%), a genetic counselor is available in person to give more detailed information upon request. Testing for each disease costs approximately 300 new Israeli sheqels (approximately US $70), and supplemental health insurance usually covers part of the cost. Screening is performed using the 2-step (sequential) approach: testing 1 partner first, and then offering testing only to partners of carriers. Testing a carrier’s partner is fully covered by National Health Insurance.

All centers tested for 4 GBA mutations (N370S, 84insG, IVS2D5+1G>A, and L444P). Four centers also tested...
for D409H and V394L. In Ashkenazi Jews, D409H testing does not identify additional carriers but only distinguishes between isolated L444P and RecTL carriers.8 The V394L mutation is rare in Ashkenazi Jewish controls with an upper frequency limit of 0.24%. Testing for 6 vs 4 GBA mutations, dictated by cost considerations, would at most increase capture of the carrier state from 90% to 96.24%. Carriers’ partners are offered testing for 7 mutations, all 6 noted above and the mild R496H mutation,12 which has a frequency of 0.44%.13 Once a carrier is identified, the sequential test (of the partner) is more extensive to provide for maximal detection of couples at risk; therefore, this further testing includes the R496H mutation.

In 2 centers, if a carrier’s partner is not fully Ashkenazi Jewish and is not found to carry any of 7 mutations, this partner is also offered enzymatic glucocerebrosidase testing to determine carrier status. Glucocerebrosidase enzymatic activity is measured in leukocytes using fluorescent substrates, and enzymatic testing is problematic due to enzyme instability and significant overlap between carriers and noncarriers.12 During the study period, 8 couples were identified in which the partly Ashkenazi Jewish or non–Ashkenazi Jewish partner of a mutation carrier was suspected to be a carrier based on enzymatic testing. These couples were excluded because enzymatic testing in couples of mixed ethnicity was not routinely performed, and those couples identified were counseled that their risk status was inconclusive, so their decisions were not comparable with those of true carrier couples.

Screening Outcomes

Scope of Screening. There were 22 692 persons screened in 9 of 10 centers that could provide exact data for the entire study period. The remaining center screened 3445 persons from January 1, 2000, but could not provide the exact number of people screened between January 1, 1995, and December 31, 1999. At this center, 10 couples were identified from January 1, 2000, and 8 couples were identified in the 1995-1999 period; therefore, assuming the rate of carrier couple detection was constant, we estimated that an additional 2756 persons were screened at this center in the first 5 years of the study period. Thus, the estimated total number of persons screened is 28 893.

Due to computerization issues, exact data on number of carriers was available in 4 of 10 centers for the entire study period and in 1 center starting on January 1, 2000. In this group, carrier frequency was 601 of 10 465 (5.7%). Based on this observed frequency, we estimate that approximately 1660 carriers were identified nationwide during the study period, consistent with prior reports.8,13,30

Carrier Couples. Centers reported a total of 83 carrier couples. Genotypes were known in all couples and follow-up information was obtained from 66 couples (80%), and 65 (78%) were interviewed. Eleven of 83 couples (13%) could not be traced due to change of address or contact information, 5 couples (6%) refused participation, and 1 couple (1%) denied being at risk. Sociodemographic data for 127 of 132 participants (96%) are shown in Table 1. Of these participants, 89% were of full Ashkenazi Jewish origin, 93% had post-high school education, and 88% defined themselves as secular. Genotypes of carrier couples are shown in Table 2. In 3 couples, 1 partner was identified as a N370S/N370S homozygote. Among the 83 carrier couples, 1 couple was at risk for offspring with neuronopathic type 2/3 GD and 82 couples were at risk for offspring with type 1 nonneuronopathic GD. Seventy of these 82 couples (85%) were at risk for offspring with 2 mild mutations and 12 couples (15%) were at risk for compound heterozygote offspring (1 mild and 1 severe mutation) (Table 2).

Among 66 participating couples, the couple at risk for type 2/3 GD was not interviewed and no pregnancy occurred in this couple. Of 65 couples at risk for type 1 GD offspring, 53 of 65 (82%) were at risk for offspring with asymptomatic or mild disease and 12 of 65 (18%) were at risk for offspring with moderate disease.

Genetic and Medical Counseling. Only 14 of 127 interviewed participants (11%) recalled receiving specific information regarding GD at the time of screening. This may be explained by low recall of written, brochure-based information, low recall of each specific disease when faced with a multidisease panel,30 and given the retrospective assessment of receipt of information, there is a possibility that pre-screening information is eclipsed by the extensive postscreening information carrier couples receive in person. Post-screening, 62 of 65 couples (95%) reported receiving genetic counseling in person at the screening center.

Nine of 10 carriers (in which 58 of 65 couples [89%] were identified) routinely referred carrier couples for medical consultation at the Israel GD Referral Center. All carrier couples were aware of the GD referral center’s existence, and 35 of 65 couples (54%) subsequently met with a GD expert who is not a medical geneticist (A.Z.). The

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Table 1. Individuals in Carrier Couples at Risk for Offspring With Gaucher Disease

<table>
<thead>
<tr>
<th>Sociodemographic Characteristics</th>
<th>No. (%) of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>36 (23-67)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>113 (89)</td>
</tr>
<tr>
<td>Partly Ashkenazi Jewish</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Non-Ashkenazi Jewish</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>High school (12 y)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Post-high school, no degree</td>
<td>13 (10)</td>
</tr>
<tr>
<td>College or university degree</td>
<td>105 (83)</td>
</tr>
<tr>
<td>Religiosity</td>
<td></td>
</tr>
<tr>
<td>Secular</td>
<td>112 (88)</td>
</tr>
<tr>
<td>Traditional</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Religious or Orthodox</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Ultra-Orthodox</td>
<td>0</td>
</tr>
</tbody>
</table>

aIncludes 127 individuals, because among the 65 couples interviewed, only 1 spouse was interviewed in 3 couples (2 women and 1 man).

bEthnicity is self-reported. Ashkenazi Jews are defined as Jews originating in Europe. Fully Ashkenazi Jewish is defined as all 4 grandparents being European-born or of Ashkenazi origin, and partly Ashkenazi Jewish as having 1 to 3 grandparents fulfilling these criteria.

cSelf-defined.
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information provided in this medical consultation includes information on reproductive risk for GD, predicted disease severity based on the couple’s genotypes, and available therapy. The GD expert also emphasized the high efficacy of enzyme replacement therapy and its coverage by National Health Insurance.

Pregnancy-Related Decisions. All 65 couples at risk for type 1 GD had at least 1 pregnancy during the study period. There were 90 singleton pregnancies (43 of 65 couples [66%] had 1 pregnancy, 19 of 65 couples [29%] had 2 pregnancies, and 3 of 65 couples [5%] had 3 pregnancies). A prenatal diagnosis procedure was performed in 68 of 90 pregnancies (76%); more commonly in pregnancies at risk for moderate disease (15 of 17 [88%]) than in pregnancies at risk for asymptomatic or mild disease (53 of 73 [73%]) (Table 3). Predicted severity also may have influenced choice of prenatal diagnosis procedure (chorionic villus sampling or amniocentesis). Chorionic villus sampling was performed in 16 of 53 (30%) pregnancies at risk for asymptomatic or mild disease vs 8 of 15 (53%) pregnancies at risk for moderate disease (P = .10). These differences in prenatal diagnosis rates and procedures were not significant. Fetuses with type 1 GD were diagnosed in 16 of 68 (24%) pregnancies at risk (13 with predicted asymptomatic or mild disease and 3 with predicted moderate disease). Four of 16 affected pregnancies (25%) were terminated (2 of 13 N370S/N370S homozygotes [15%] and 2 of 3 compound heterozygotes [67%]: 1 N370S/84insG and 1 L444P/R496H) (Table 3).

There was a significant association between consultation with the GD expert and pregnancy continuation. Among couples with fetuses with GD, only 1 (L444P/R496H) of 13 (11 with N370S/N370S, 1 with N370S/IVS2DS +1G-A, and 1 with L444P/R496H) who consulted with the GD expert terminated the pregnancy compared with 3 of 3 (100%) who had not (2 with N370S/N370S and 1 with N370S/84insG) (by Fisher exact test, P = .007). Consultation with the GD expert was also significant in the subgroup of fetuses with predicted asymptomatic or mild disease (termination of pregnancy in 0 of 11 fetuses vs 2 of 2 N370S/N370S fetuses; by Fisher exact test, P = .01). Participants were asked if they were tested for other conditions and if they or their spouse were found to be carriers, and also, if they had other reasons for prenatal diagnosis. No couple indicated being at risk for any other disease or condition. Thus, it would seem likely that decisions regarding pregnancy termination were related only to the GD genotype status of the fetus.

Testing Existing Children and Health Status of Children With GD Genotypes. A prenatal diagnosis procedure was not performed for 33 children who were born to at-risk couples (22 were children born before the parents knew they were at risk and 11 were children born after parents were identified as GD carriers). There were 12 of 16 couples (75%) who had child-

Table 2. Genotypes in Couples at Risk for Offspring With Gaucher Disease (GD)a

<table>
<thead>
<tr>
<th>Couples at Risk for Offspring With Mild or Asymptomatic Type 1 GD</th>
<th>No. (%)</th>
<th>Mild Mutation Carrier</th>
<th>Severe Mutation Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64 N370S/+</td>
<td>2 N370S/+</td>
<td>2 N370S/N370S</td>
<td></td>
</tr>
<tr>
<td>2 N370S/+</td>
<td>2 N370S/+</td>
<td>2 N370S/N370S</td>
<td></td>
</tr>
<tr>
<td>Total 70 (84)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Couples at Risk for Offspring With Moderate Type 1 GD</th>
<th>No. (%)</th>
<th>Mild Mutation Carrier</th>
<th>Severe Mutation Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 N370S/+</td>
<td>2 N370S/+</td>
<td>2 N370S/N370S</td>
<td></td>
</tr>
<tr>
<td>2 N370S/+</td>
<td>2 N370S/+</td>
<td>2 N370S/N370S</td>
<td></td>
</tr>
<tr>
<td>1 N370S/N370S</td>
<td>1 R496H/+</td>
<td>R496H/+</td>
<td></td>
</tr>
<tr>
<td>Total 12 (15)</td>
<td></td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Couples at Risk for Offspring With Severe Type 2/3 GD</th>
<th>No. (%)</th>
<th>Mild Mutation Carrier</th>
<th>Severe Mutation Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 84insG/+</td>
<td>1 L444P/+</td>
<td>L444P/+</td>
<td></td>
</tr>
<tr>
<td>Total 1 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a’= indicates wildtype (normal) allele. The sum of all couples at risk is 83 (100%).

Table 3. Outcome of Nationwide Gaucher Disease Screening Programa

<table>
<thead>
<tr>
<th>Both Carriers of Mild Mutation</th>
<th>1 Carrier of Mild Mutation and 1 Carrier of Severe Mutation</th>
<th>Both Carriers of Severe Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of carrier couples identified</td>
<td>70</td>
<td>12</td>
</tr>
<tr>
<td>No. of couples enrolled</td>
<td>53</td>
<td>12</td>
</tr>
<tr>
<td>No. of pregnancies</td>
<td>73</td>
<td>17</td>
</tr>
<tr>
<td>Prenatal diagnosis, No.</td>
<td>53</td>
<td>15</td>
</tr>
<tr>
<td>Affected fetus, No.</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Pregnancy termination, No.</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

aScreening of an estimated 28,893 persons led to identification of 83 couples at risk for Gaucher disease. Outcomes are shown for 66 participating couples.

bEnrolled and interviewed.

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CARRIER SCREENING FOR GAUCHER DISEASE

COMMENT

The expected practical benefit of carrier screening programs has traditionally been reduction in the birth prevalence of newborns affected with the disease through termination of pregnancies. Possible harms include the emotional impact on carriers and their families, including stigmatization and discrimination of individuals or the community. In this study, we addressed the practical outcomes of GD screening as a model of screening for a low-penetrance, treatable disease for which termination of pregnancy is controversial. To the best of our knowledge, this is the first study to evaluate the outcomes of a clinical, large-scale GD screening program.

Eighty-three carrier couples were identified, and because this is a complete, nationwide study, the sample size could not be enlarged to any extent. Only 1 couple was at risk for severe type 2/3 GD disease, which is too rare to justify screening. Thus, GD screening is essentially performed for type 1 GD, mostly (85%) identifying couples at risk for asymptomatic or mild disease, and less commonly (15%) identifying couples at risk for moderate, treatable disease.

Patient counseling specific to GD occurred at 2 points in the screening process (pretest, before individuals were tested, and posttest, if a couple was identified as being at risk for GD).

Pretest information was provided in written form, and in most cases (for approximately 74% of screened individuals), a genetic counselor was available to answer questions. The specific written information provided about GD included information on carrier frequency, mode of inheritance, variability of disease expression, imperfect prediction of severity, and treatability. This information differs from that given about severe diseases (eg, Canavan disease). Given the scope of screening in Israel, both in the number of persons and the number of different diseases screened, individual genetic counseling sessions before screening would overwhelm genetic services anywhere. The pretest process for couples is generally parallel to that in the United States, where it is also available on the Internet with written information but without genetic counseling (eg, http://www.labcorp.com/genetics/genetic_disorders/jewish_heritage_screening.html). Most couples choose to have all carrier tests available and expect to deal with specific diseases only if necessary (ie, only if they are found to be at risk).

The main purpose of our study was to describe posttest outcomes in at-risk couples, outcomes which have not been previously reported. Couples identified as carriers receive extensive, in-person genetic counseling, specifically focused on GD. Of 65 carrier couples with GD, 62 (95%) had such genetic counseling and 35 (54%) also had medical counseling at the GD referral center. These sessions included extensive discussion of the risk for GD, variability of disease, the expected severity (based on the couples’ genotypes), the existence and efficacy of treatment, and the implications for existing children. Options for prenatal testing (chorionic villus sampling or amniocentesis) as well as not having prenatal testing were also discussed. Evidence for the content and effectiveness of the posttesting counseling received is the high degree of knowledge about all of these issues demonstrated by interviewed couples in a manuscript in preparation on psychological impact of screening in carrier couples (S.Z., unpublished data, 2007). Couples’ decisions posttesting, which are the main focus of the study herein, were based on extensive counseling and adequate knowledge, irrespective of the written information received before testing.

We found that prenatal diagnosis was performed in 76% (68 of 90) pregnancies, and that terminations were performed in 25% (4 of 16) pregnancies of fetuses with GD (2 fetuses predicted to have asymptomatic or mild GD, and 2 fetuses predicted to have moderate GD). With respect to the stated goal of carrier screening programs, the main practical outcome of GD screening was a 66% reduction in birth prevalence for moderate type 1 GD, for which the estimated frequency is 1 in 27,000, and a 15% reduction in the birth prevalence of asymptomatic or mild type 1 GD for which the estimated frequency is 1 in 1300. This was achieved through termination of pregnancy of fetuses either treatable or likely to be asymptomatic, and it is debatable whether this represents a true benefit.

The 15% termination of pregnancy rate observed in asymptomatic or mild type 1 GD raises questions but may demonstrate couples’ comprehension of the special aspects of GD. It contrasts sharply with termination of pregnancy rates in couples identified to be at risk for offspring having severe disease in the same screening program for Ashkenazi Jews—Israel Ministry of Health registry data show that all Tay-Sachs carrier couples and 82% of cystic fibrosis carrier couples terminated pregnancies of affected fetuses (J. Zlotogora, MD, PhD, Department of Community Genetics, Israel Ministry of Health, unpublished data, 2007). Medical consultation with an expert from the GD referral center in addition to traditional genetic counseling was associated with a significantly
reduced termination of pregnancy rate in couples with fetuses with GD (P = .007).

Early recognition of genetic GD status did not appear to offer any medical advantage for the small number of GD cases (n=13) from continued GD pregnancies and previously unsuspected, older GD siblings, although follow-up was relatively short (mean of 5.6 years). Although future benefit of early diagnosis cannot be excluded, presymptomatic detection of childhood or adult disease is not a goal of carrier screening programs. Testing children at risk for type 1 GD may be medically justified to avoid unnecessary evaluations should symptoms develop later in childhood. However, because childhood onset is rare, presymptomatic diagnosis through a prenatal screening program raises the ethical concerns of testing children for adult-onset disease, including violation of the child’s future autonomy.40

Presymptomatic diagnosis in children is justified when there is evidence that early treatment improves outcomes, and this is the basis of newborn screening programs. When a severe disease is untreatable, carrier screening is performed with pregnancy termination as a reluctantly accepted outcome, but when there is postnatal treatment that is also more effective if given presymptomatically, newborn screening would be preferable. However, although there is effective treatment for type 1 GD, a large proportion of individuals with GD genetic status will never come to medical attention and we are not aware of convincing evidence that earlier diagnosis improves the disease outcome. A study of early treatment in newborns with type 1 GD has not shown added benefit,31 and the most important irreversible complication of type 1 GD, avascular bone necrosis, is very rare as an initial manifestation (A.Z., unpublished data, 2007). For type 1 GD, although the existence of treatment is an argument against carrier screening, the low rate of disease among individuals with GD status and the lack of evidence in favor of presymptomatic intervention is an argument against newborn screening.

Another approach to this issue is premarital screening, which is socially applicable to populations where arranged marriages are the norm. The purpose of premarital screening is to preclude marriage between persons who are both carriers of the same disease, and thus avoid the issue of prenatal diagnosis or pregnancy termination. In Israel, ultra-Orthodox individuals are almost universally screened when they reach marriageable age (approximately 18 years) through a separate program called Dor Yeshorim.42 Before suggesting a prospective marriage, the matchmaker confirms that persons to be matched are not carriers of the same genetic disease. Gaucher disease is one of the diseases in the Dor Yeshorim panel, so no couples at risk for GD are expected in this population. However, general social norms are more consistent with carrier or newborn screening.

Carrier screening for GD in Ashkenazi Jews was initiated because it is the most prevalent recessive disease in an accepting population, for which testing is simple and highly sensitive.31 Our results demonstrate realization of some of the concerns leading to professional recommendations against its continuation.43 However, factors favoring GD screening should be recognized. These include consumer-related competition between institutions, fear of litigation if affected children are born despite feasibility of prenatal diagnosis (wrongful birth), and a real concern that severity cannot be absolutely defined. Disease severity is considered an essential criterion for carrier screening,20 but there is no true consensus on what constitutes severe disease even among professionals.44 When treatment is very expensive, as for GD, severity may be affected by available resources, both personal and societal. Considerations by couples in Israel, where treatment is covered by National Health Insurance, may differ from those of couples facing less comprehensive coverage.36 There has been no substantial change in reimbursement or costs for GD screening, or for GD treatment since the time of the data collection and analysis herein.

Based on the right to autonomy, one could conclude that offering GD screening is justified, and participation should be left to couples’ discretion. In this vein, the Israeli Medical Geneticists’ Association decided to label GD screening as “not recommended” but to allow its continued availability. The association’s position paper on GD screening39 states that GD screening is widely offered, but that it does not meet World Health Organization criteria and is therefore not recommended. However, the position paper also includes recommendations for counseling in case screening is still offered, indicating awareness and consideration of the possibility of continued screening. Subsequent to the data collection and analysis herein, we surveyed 3 centers, which accounted for approximately 62% of tested individuals in the study period and which were able to provide exact data on GD carrier screening in 2006 and 2007, and we ascertained that there is not substantial change in the number of persons tested (S.Z., unpublished data, 2007). It may be that there is a cultural predilection to maximal screening in Israel, so that the fact that GD screening is still offered to couples probably carries greater weight than the statement by the Association recommending against GD screening. Thus, the screening process as described herein remains representative of current practice in Israel and is likely to be representative of current practices outside Israel (eg, in the United States).

Screening for GD illustrates the complexity of carrier screening for a relatively prevalent genotype with imperfect phenotype prediction, which may have little clinical implication. A similar situation already prevails for other conditions that are treatable, do not lead to mental retardation or decreased life expectancy, and are easily tested in specific populations (eg, familial Mediterranean fever),38,47 connexin 26 deaf-
ness,38,39 and albinism40). Although it would be important to compare our results with those of other screening programs, and in other social contexts, this study provides an initial evidence base for discussing the outcomes and ethics of carrier screening for low-penetrance, treatable disease. The history of GD screening suggests that availability, rather than utility, of a test could be the major determinant of its introduction.

CONCLUSIONS

Gaucher disease carrier screening resulted in a mild reduction in the birth prevalence of newborns with GD genetic status, through pregnancy termination of fetuses most likely to be asymptomatic or treatable. The main possible benefit of screening was allowing couples at risk to be identified and made an informed choice.

Applying the classic carrier screening paradigm to common, low-penetrance disease leads to inevitable dilemmas, and programs offering such screening should determine whether the true goal is knowledge and presymptomatic risk assessment or pregnancy termination of fetuses with a specified genetic status. Our results suggest that to avoid termination of pregnancies for generally mild conditions, even in a highly educated population, screening programs would require a combination of traditional, nondirective genetic counseling with medical counseling by professionals familiar with the specific conditions.

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