Hum Genet (2009) 126:247–253
DOI 10.1007/s00439-009-0669-y

REVIEW ARTICLE

Population programs for the detection of couples at risk for severe monogenic genetic diseases

Joël Zlotogora

Received: 23 September 2008 / Accepted: 8 April 2009 / Published online: 24 April 2009

Abstract Population genetic screening programs for carrier detection of severe genetic disorders exist worldwide, mainly for beta-thalassemia. These screening programs are either mandatory or voluntary. In several Arab countries and Iran, the state has made thalassemia carrier detection mandatory, while tests for detecting carriers are required by the religious authorities in Cyprus. In all the existing mandatory genetic screening programs, the couples have to get the information about the tests before marriage, but the decision whether or not to marry is left to them. Voluntary programs exist for instance in several Mediterranean countries for the prevention of thalassemia and for several genetic diseases among Jews. While voluntary programs leave the decision to be screened or not to the individual, a major problem is that in many cases awareness about the existence of screening tests is very sparse. Some programs, for instance in Canada or Australia, therefore provide education about genetic tests and screening at school in order to allow the individuals to be able to make an informed decision about their reproductive choices.

This article represents the opinions of the author and not necessarily those of the Ministry.

J. Zlotogora (✉)
Department of Community Genetics,
Public Health Services,
Ministry of Health, Building 67,
Sheba Medical Center,
Tel Hashomer, 52621 Ramat Gan, Israel
e-mail: joelz@cc.huji.ac.il

J. Zlotogora
Hebrew University Jerusalem,
Jerusalem, Israel

Introduction

Genetic carrier screening for reproductive choices is aimed at allowing couples to reach decisions before the birth of an affected child. Sickle cell anemia in the United States, Tay-Sachs disease among Ashkenazi Jews and thalassemia in the Mediterranean region were the first examples of severe diseases for which general screening programs were offered to delineated populations (Markel 1992; Kaback 2001; Cao et al. 2002). Since then, the molecular basis of many monogenic diseases has been defined, widening the possibilities of screening for reproductive purposes. Many studies have been made concerning the implementation of carrier genetic screening in the general population mainly for cystic fibrosis and fragile X syndrome, both being severe and relatively frequent.

For the purpose of this review, two types of carrier screening are distinguished. One is provided to the individuals who come to clinical care or advising based on professional recommendations. The other type of screening is the one provided to the general population that is recommended or made mandatory by the public health system and/or religious authorities. This review will cover only with the latter type of carrier genetic screening. Examples of population genetic screening programs, whether mandatory or voluntary, are reviewed in order to determine their advantages and problems.

Voluntary carrier population genetic screening programs

Thalassemia screening in Sardinia

In the island of Sardinia—population of 1,650,000—thalassemia is frequent with a carrier rate of 13%. From the late

1970s a public health voluntary screening program was developed for prospective parents and pregnant women (Cao et al. 1989, 2002). Education of the population and training of health personnel have been critical elements of the program. The addition of extended family screening allowed the identification of most of the couples at risk. Following counseling, the large majority of parents opted for prenatal diagnosis. This program resulted in a decline in 90% of thalassemia major births (from 1:250 live births to 1:4,000). The reasons for residual cases were mostly lack of information and, less frequently, misdiagnoses or refusal of fetal diagnosis. However, in the last decades an increasing number of young couples are not being screened since they are unaware of the disease. This observation led to design a pilot study implementing education on thalassemia early at school and to offer carrier screening to 13–14-year-old students (Cao et al. 2008). The uptake of the pilot study was high across the island, probably due to the interest of the Sardinian population for any initiative to improve the thalassemia prevention program. A total of 63,285 students were tested in the first 7 years of the screening, and 6,521 (10.3%) of them were beta thalassemia heterozygotes. In a preliminary survey of students 5 years after the test, 92% retained the information. While there has not been any formal evaluation, the first impression is that there were no negative effects of the screening (Cao et al. 2008).

Tay-Sachs screening among Ashkenazi Jews

The screening program for carrier detection of Tay-Sachs disease was initiated in the United States in 1970 (Kaback 2001). The program was developed together with the Jewish community, preceded by educational sessions in synagogues and Jewish cultural centers. The screening is voluntary and directed to reproductive-aged Ashkenazi Jewish individuals. In a summary of the first 30 years of the program around the world, 1,403,547 individuals were screened, and 1,379 couples at risk were identified. As a result the incidence of the Tay-Sachs disease has been dramatically reduced by 90% among Jews. While the Tay-Sachs screening was aimed at all the Ashkenazi Jewish population, the ultra-Orthodox Jews did not participate since the program implied termination of pregnancies in couples at risk. This led to the development of the Dor Yeshorim program adapted to the special needs of this community.

The national program for the detection of carriers of severe and relatively frequent genetic diseases in Israel

Tay-Sachs and thalassemia carrier screening

In Israel voluntary genetic screening for Tay-Sachs and thalassemia is a public health program provided free-of-charge to the populations at risk (Chemke and Zlotogora 1997). While it is recommended to have the screening tests before pregnancy, the instructions to the health-care providers are to inform every woman from the respective population at risk at the beginning of her pregnancy or before. The woman should know about the genetic screening program and be referred to have genetic tests as necessary (Zlotogora and Leventhal 2000).

Tay-Sachs carrier screening Up to September 2008, the Ministry of Health operated several regional clinics once a week in the evening offering Tay-Sachs screening. All the samples were transferred the next day to a central laboratory. In the last decade 25,000–27,000 tests were performed each year, and the disease almost disappeared among Jews. Since the beginning of the program, very few children with Tay-Sachs have been born among Jews, most being the result of misunderstanding or lack of knowledge of the parents.

Thalassemia carrier screening Thalassemia is relatively frequent among Arabs and Druze as well as some of the Jewish communities, in particular Jews originating from Kurdistan. The screening of the population at risk is based on the results of blood counts using MCV and MCH and, as needed, hemoglobin electrophoresis. In the last few years a part of the program in the northern region of Israel has used routine haemoglobin electrophoresis for screening, thus allowing the detection of carriers of sickle cell disease, which occurs relatively frequently in several villages of the region (Koren et al. 2002). While in the late 1980s the mean number of children affected with thalassemia born each year in Israel was 13 (mean 4 per 10,000 live births among Jews and 50 per 10,000 among Arabs), in the last decade the number is an average of 5 children each year (most being Arabs) out of approximately a total of 150,000 live births. Most importantly, almost all the affected children are born to parents who, although they were aware of their risk, chose not to use prenatal diagnosis/pregnancy termination (Department of Community Genetics 2009).

Targeted population carrier screening program

A national carrier screening program targeted at communities in which severe genetic diseases are present with a frequency higher than 1/1,000 live births (corresponding to 6% carrier frequency for autosomal recessive diseases) was added in 2002 to the existing Tay-Sachs and thalassemia population carrier screening program (Zlotogora et al. 2008). Since there are no known genetic diseases with such a high frequency in any of the Jewish communities, the program is in fact aimed at the non-Jewish population in Israel. The carrier screening includes genetic counseling

and testing, which are provided free of charge within the communities at risk. A total of 37 diseases are included in the program in 36 different localities/communities; in some of them more than one disease is screened for (Zlotogora et al. 2008).

Cystic fibrosis population carrier screening program

Since August 2008 population carrier screening has been offered to Israeli citizens, free of charge, aiming to discover couples at risk for cystic fibrosis (Zlotogora and Israeli 2009). Those couples have the possibility to make an informed choice, in the context of genetic counseling, between neonatal diagnosis and early treatment of an affected child or prevention. Prevention may be achieved by deciding not to have a family, adopting a child, having a child after preimplantation diagnosis (PGD) or prenatal diagnosis (with the possibility of termination of pregnancy), or deciding to separate. The screening is based on the fact that most of the mutations existing in the different Israeli communities are known. This type of screening was preferred to the neonatal screening that is offered in many western countries since it gives couples at risk the possibility to decide between the different options *before* the birth of an affected child.

In parallel to the introduction of the cystic fibrosis screening program, the Tay-Sachs regional clinics operated by the Ministry of Health were abolished. Nowadays the individuals/couples are referred to authorized screening centers (public or private) who offer all the tests recommended according to the origin either free of charge or not. The tests are those recommended by the Israeli association of Medical Geneticists, which has been adopted as a guideline of the Ministry of Health (Table 1). Gaucher disease, which is very frequent among Ashkenazi Jews, is not recommended for population carrier screening because of the variable phenotypes and the possibility of treatment (Zuckerman et al. 2007).

In all the components of the Israeli carrier screening program, most of the couples at risk are examined during pregnancy. In a survey of individuals who came to the Tay-Sachs carrier screening, 65% did so during a pregnancy (Fisher and Baram 2005). This often led to a late detection of the couples at risk at a period when abortion is often problematic. This observation is the result of an insufficient level of awareness of the population since many individuals first hear about the screening programs during a pregnancy. In order to improve the population's knowledge, a pilot education program was initiated. This program includes three to four lectures about genetic tests for high school students; in a second stage, there will be at least another meeting in the army, university or other framework later in life. The aim is that individuals will be able to decide whether and when genetic tests are relevant for them while already having heard about them at least once or better twice.

Table 1 The recommendations of the Israeli Ministry of Health for genetic screening for reproductive purposes

1. Screening recommended (carrier frequency >1:60 for autosomal recessive diseases)
Most of the population[a]
Cystic fibrosis (free of charge)
Fragile X (X-linked carrier frequency 1:157)
Spinal Muscular Atrophy (SMA)
Jews
Tay-Sachs Ashkenazi and North Africa (free of charge)
Familial dysautonomia Ashkenazi (free of charge)
Canavan disease Ashkenazi
Thalassemia, Jews from Iraq, Iran, Kurdistan, North Africa, Mediterranean countries (free of charge)
Metachromatic leukodystrophy, Yemen
Non-Jews
Thalassemia
Severe diseases in delineated populations (free of charge)[b]
2. Screening encouraged (severe diseases, carrier frequency >1:110 for autosomal recessive diseases)
Ashkenazi Jews
Niemann Pick (A,B), Fanconi C, Bloom syndrome, mucolipidosis IV, nemaline myopathy, MSUD, glycogen disease type 1, Usher syndrome and alpha 1 antitrypsin deficiency
North African Jews
Tay-Sachs (free of charge), Fanconi anemia A, ataxia telangiectasia and megalencephalic leukoencephalopathy with cortical cysts (Libyan Jews)

[a] In some delineated populations the screening is not recommended since the disease is very rare (as defined by the geneticist)

[b] Severe diseases with a frequency higher than 1:1,000 in a delineated population (in general a single village) for which the carrier screening including genetic counseling is provided free of charge (Zlotogora et al. 2008)

Premarital and preconceptional screening

Preconceptional counseling intends to minimize the maternal and fetal risk, to prevent birth defects and to provide high-risk women with information about the risk and available options. Very successful examples of preconceptional counseling have been reported in many different countries and cultures around the word, such as The Netherlands, Hungary, Hong Kong, South Korea, Belgium and Egypt (Czeizel et al. 2005; Ebrahim et al. 2006; Henneman et al. 2001; Rashed Khater and El Gazali 2003).

In societies where in general pregnancies occur after marriage and are not planned, premarital counseling based on the same principles may be more effective. Indeed, premarital counseling has been developed as a public health

program in several countries (Chaabouni-Bouhamed 2008; Ebrahim et al. 2006; Samavat and Modell 2004). In Iran and Tunisia the premarital consultations are mandatory, representing a means to help couples know about their risks and the possibilities of preventing severe diseases. In Tunisia, the mandatory premarital investigation has included genetic counseling since 1986, which is obligatory for all couples with a history of genetic problems and when the partners are consanguineous (Chaabouni-Bouhamed 2008). In couples found to be at risk for an affected child, the final decision whether to marry or not is left to the couples.

In China, the "Maternal and Infant Health Care Law," which came into effect in 1995, mandated that all persons must have a premarital medical examination to detect serious genetic diseases; if a disease was detected, the couple was not permitted to marry without committing to contraception or tubal ligation (Hesketh 2003). This policy was in accord with the views of more than 90% of the Chinese geneticists that believed that partners should know each other's genetic status before marriage and that carriers of the same recessive gene should not have children (Mao 1998). However, the law was seen by most outside of China as a violation of medical ethics and human rights, and the compulsory premarital medical examination was abolished in 2003, when it became voluntary (Ebrahim et al. 2006).

It should be emphasized that in western countries in particular, many couples are have children without formal marriage. It is evident that in such cases, preconceptional counseling cannot be mandatory and must be a choice of the women; it can be achieved only if they are aware of its advantages.

Population genetic programs mandatory by law

The national premarital screening program for carrier detection of thalassemia and sickle cell anemia in Saudi Arabia

Saudi Arabia has a population of almost 20,000,000 inhabitants, with a quarter being non-Saudis. A number of studies have demonstrated a very high prevalence of thalassemia and sickle cell disease mainly in the Eastern province of the country. After several discussions in various national and regional forums, the Ministry of Health decided on a mandatory national premarital screening program for carrier detection of thalassemia and sickle cell anemia. The program was launched in two stages; the first step was in 2002, when a royal decree was passed with emphasis on a health awareness program for premarital screening and the need for preparation of laboratories to be involved in the program. A second royal decree was issued 2 years later making the premarital screening tests mandatory for all those planning to marry. Accordingly, the couples applying for a marriage license are referred for the tests, and those found to be at risk receive a non-directive explanation of the significance of the results. While the premarital examination certificate is mandatory for the marriage, the decision about whether to proceed with the marriage or not is left to the couple. It must be emphasized that up to now, in Saudi Arabia the option of termination of pregnancy of an affected fetus is not available or is unacceptable for religious/social reasons, while treatment of the affected children is available free of charge. In the first 2 years of the program, 207,333 couples were screened. As expected, the observed carrier frequency for each of the diseases was high: 4.2% for sickle cell anemia and 3.2% for thalassemia trait; 2.1% of the couples were at risk for an affected child. In a telephonic survey including more than half of these couples at risk, in the first year of the program 90.8% married and in the second year 88.4%. Among several possible reasons for the choice of the large majority of the couples at risk to proceed with their marriage, the major one seems to have been the screening's timing, which was done after the marriage had already been decided upon and after the formal engagement. As a consequence, earlier screening is now planned so the issue of the risk for an affected child can be raised at an early stage of the marriage proposal (Alhamdan et al. 2007).

Similar mandatory programs exist in other Muslim countries in which abortions are prohibited, such as the United Arab Emirates, Bahrain, Qatar or Iran. However, in Iran the mandatory premarital screening led to the adoption of a law allowing for termination of pregnancy for medical causes in certain circumstances (Samavat and Modell 2004).

The national premarital screening program for carrier detection of thalassemia in Iran

The Iran the total population is approximately 65,000,000; 90% are Shiite Muslims. Since beta thalassemia is frequent and represents an important health problem, in 1997 screening to detect carriers of the disease was added to several premarital blood tests that were already mandatory. In the Iranian screening program marriage registrars refer prospective couples to a designated local laboratory for examination. At-risk couples are referred to non-directive genetic counseling and may attend as many sessions as needed. At the beginning of the program, the choice of the couples was limited since abortions were forbidden. However, the surveillance data demonstrated that most of the couples at risk supported the option of prenatal diagnosis and abortion of an affected fetus. This led to ethical and religious discussions about the adoption of a law allowing abortion based on the existing religious ruling (fatwa) that before 120 days after conception abortion is permitted if the fetus is affected

by a severe disease. In parallel, the infrastructures for DNA diagnosis and chorion villi sampling were developed so that in Iran the option of early prenatal diagnosis became progressively available to the couples at risk (Samavat and Modell 2004).

In the first 5 years of the program, 2,729,000 couples were tested and 10,298 (3.9%) were at risk. While in 1997, 45% of the couples at risk separated, in the following years a progressive reduction in the percentage of couples that separated was noted, and in 2001 they represented 24% of the couples. This change in the couples' decisions was parallel to the availability of prenatal diagnosis. Since the introduction of the program, the number of new patients with thalassemia has declined, and in 2002, it reached only 7% of the expected number of children that would have been born without the program.

Population genetic programs required by the religious authorities

Thalassemia and the Greek Orthodox Church in Cyprus

Cyprus has been divided since 1974 and has approximately 1,000,000 inhabitants. Thalassemia is frequent in both parts of the island, and approximately one in seven Cypriots carries a copy of the mutated gene. In the 1970s, physicians and parents' associations, both Greek and Turkish, began campaigns to improve thalassemia treatment on the island. By the end of the decade, both governments had begun free-of-charge programs for patients with thalassemia. A first effort toward prevention was made by a group of Greek-Cypriot physicians that began to screen young, unmarried people. Two events were central to the success of the program: one was the availability of prenatal diagnosis, and the other was that the Orthodox Church decided to support the program. The major argument that seems to have convinced the clergy, despite its opposition to abortion, was that screening would reduce human suffering and probably lower the number of abortions. In the first place, the program offers carriers to choose not to marry. In addition, without the program, parents who knew they were both carriers were often aborting all of their pregnancies, while only one-fourth of the pregnancies would have been afflicted and terminated if prenatal diagnosis had been performed. Since 1983, the church, which controls weddings in Greek Cyprus, requires a certificate in order to issue the marriage licenses. The certificate does not record the results of the tests, but confirms that the couple underwent premarital screening and received genetic counseling. The final decision, whether to marry or not, is left to the couple. Since then, most of the couples have proceeded with their marriages and utilized prenatal diagnosis when needed. In the following years, very few affected children were born, most to parents who declined to abort pregnancies for religious or other reasons. In parallel and together with the screening program, efforts were made to inform and educate about the disease, improve the well-being of affected individuals and allow their interaction in society. Indeed, nowadays, 25 years after its beginning, the program is well known and supported by all the sectors of Cypriot society—physicians, parents, public health officials and patients (Angastiniotis and Hadjiminas 1981; Kalokairinou 2007; Schwartz Cowan 2008).

Dor Yeshorim and carrier detection of genetic diseases among ultra-Orthodox Jews

With the beginning of the screening for carriers of Tay-Sachs disease in 1970, it became rapidly evident, as already mentioned, that the ultra-Orthodox Jews were not participating in the program. The main reason was that, since according to Jewish law termination of pregnancy is forbidden after 40 days of pregnancy, screening of married couples did not provide a solution. As a consequence, a program was developed within the community adapted to its particular needs. In 1983 the program started after obtaining the support of the major religious leaders of the ultra-Orthodox Jewish community. The Dor Yeshorim program is based on the community's custom of marriages though match-makers when the prospective spouses do not know one the other. The decision about a possible match is made according to various factors, and the program proposed that the first one should be whether or not the couple is at risk for Tay-Sachs disease. In a first stage, Dor Yeshorim representatives visit ultra-Orthodox high schools and draw blood samples from students, who are then issued a number. The samples are screened for genetic disease and the results stored in Dor Yeshorim offices. When young ultra-Orthodox men and women reach the age of marriage, the recommendation from the matchmaker about a potential mate should be based first on the results of the genetic tests. Dor Yeshorim receives the assigned numbers for each member of the potential couple and checks to see whether both are carriers or not of the same genetic disease. The matching procedure will continue only if the couple is not at risk, whether both partners are not carriers or only one is a carrier. The individuals do not receive any result, and the process is completely anonymous. Over the years, other tests have been added to the program, including those only for recessive traits that give rise to lethal or severely debilitating disorders. Nowadays, the screening includes, in addition to Tay-Sachs disease, cystic fibrosis, familial dysautonomia, Canavan disease, Fanconi anemia, Bloom syndrome, Niemann Pick disease, MSUD and mucolipidosis IV (Ekstein and Katzenstein 2001).

While the program is not mandatory, nowadays the ultra-Orthodox Jewish community will not allow a marriage to take place without the prospective spouses being screened.

The program has been effective within its own community, whose insularity, demand for privacy and rejection of abortion have made premarital screening accepted. In a recent study, it was shown that in spite of the recommendation of Dor Yeshorim that "the genetic compatibility check" should be done early in the matchmaking process, it is often done at a relatively late stage when the parents already have some knowledge of the potential mate (Raz and Vizner 2008).

Discussion

Programs for the detection of couples at risk for severe genetic diseases have been initiated with the aim to reduce suffering, with Tay-Sachs disease being a classical example.

The first experience with a population genetic screening program was the mandatory sickle cell disease screening in the United States. The failure of the program was mainly the result of the lack of appropriate knowledge about the disease and its carrier state by the medical personnel as well as the population. This failure allowed for a better understanding of the ways to implement genetic screening programs (Markel 1992). Genetic professional societies insist that genetic screening should be a personal and voluntary decision of the individual (Godard et al. 2003). However, one may wonder whether a free choice truly exists when an individual without familial history of genetic disorders does not have enough knowledge concerning the diseases that are frequent in the population, the possibility of genetic testing and the available alternatives. In many populations, the first time that a couple becomes aware of genetic diseases and the existing possibility of prevention is when an affected child is born. On the other hand, a mandatory program that does not interfere with the decisions of the individual gives an opportunity to learn about the genetic diseases that are relatively frequent in the population and to decide among the possible options. Voluntary screening programs, in order to provide an opportunity of choice and be a real alternative to mandatory programs, must include an educational component about genetic tests and screening. This was the basis for the success of the Tay-Sachs screening program among Ashkenazi Jews. However, in order to be truly relevant, the educational program must be aimed at a period in which the individual still has all options open, before the reproductive period. The largest amount of experience with a genetic carrier screening program directed at high school students has been accumulated in Montreal, Canada, since 1973 for Tay-Sachs among Ashkenazi Jews; it was later broadened to β-thalassemia screening in populations at risk (Mitchell et al. 1996; Zeesman et al. 1994). The program included first an educational session and then the possibility to perform a carrier test at school. A long-term follow-up demonstrated that good knowledge remained without stigmatization and that the screening led to a decrease of 90–95% in the incidence of Tay-Sachs disease and β-thalassemia (Mitchell et al. 1996).

Another large high school educational program including testing for Tay-Sachs disease and cystic fibrosis was developed in consultation with the local Jewish community in Australia (Barlow-Stewart et al. 2003; Gason et al. 2003, 2005). As already mentioned, the Sardinian screening program for thalassemia became implemented at school, and the test is offered to young students (Cao et al. 2008).

While high school offers a convenient setting for genetic screening and has many advantages for education, many questions have been raised about such genetic tests in adolescents (ASHG/ACMG report 1995). Since all the evaluations of these types of screening program in high schools found that education played a critical role in allowing informed decisions about testing, a better solution may be to include only the education component at school leaving to the students the decision, according to their own judgment, when to perform the test outside the school context. This may reduce the problems of such programs, in particular coercion (Frumkin and Zlotogora 2008).

In addition to the aim to lessen suffering, reducing the economical burden on the public health resources may be an additional purpose of the screening program. In Cyprus where thalassemia is frequent, it was calculated before the beginning of the program that if no measures were taken, in a 50-year period the Cypriots would not be able to supply the quantities of blood needed to treat the patients and that the cost of treatment would consume the entire budget of the health ministry (Kalokairinou 2007). This was a major factor in the development of the prevention program in Cyprus with the World Health Organization. It may be expected that similar problems will rise for other diseases since together with increasing knowledge of the basis of many metabolic diseases, effective and expensive drugs are becoming available. Already very expensive enzyme therapy for lysosomal diseases, such as Gaucher, Fabry or Pompe disease, is available (Beutler 2006). Since often these rare genetic diseases are found with a very high incidence in delineated populations, the availability of treatment may cause a locally unbearable economic burden. This may lead to ethical conflicts since a mandatory screening program for prevention is problematic when treatment allows for an almost normal healthy life.

The parallel development of mandatory and voluntary programs for thalassemia carrier screening in Cyprus and Sardinia demonstrates clearly that both approaches may be

very successful. In both cases, the number of affected children was considerably reduced by genetic screening either because of the exigence of the Orthodox Church or a voluntary program with a significant educational component. Today, some 30 years after the beginning of these programs screening mostly because of the involvement of the respective communities and their knowledge of the related problems, both populations are very supportive. This is evident by their support of the continuing efforts made to increase earlier use of the genetic tests so that the knowledge may be used in the choice of spouses.

References

Alhamdan NA, Almazrou YY, Alswaidi FM, Choudhry AJ (2007) Premarital screening for thalassemia and sickle cell disease in Saudi Arabia. Genet Med 9:372–377

Angastiniotis MA, Hadjiminas MG (1981) Prevention of thalassaemia in Cyprus. Lancet 1:369–371

ASHG/ACMG REPORT Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents. (1995) Am. J. Hum. Genet 57:1233–1241

Barlow-Stewart K, Burnett L, Proos A, Howell V, Huq F, Lazarus R, Aizenberg H (2003) A genetic screening programme for Tay-Sachs disease and cystic fibrosis for Australian Jewish high school students. J Med Genet 40:e45

Beutler E (2006) Lysosomal storage diseases: natural history and ethical and economic aspects. Mol Genet Metab 88:208–215 Epub 2006 Mar 3

Broide E, Zeigler M, Eckstein J, Bach G (1993) Screening for carriers of Tay-Sachs disease in the ultra orthodox Ashkenazi Jewish community in Israel. Am J Med Genet 47:213–215

Cao A, Rosatelli C, Galanello R, Monni G, Olla G, Cossu P, Ristaldi MS (1989) The prevention of thalassemia in Sardinia. Clin Genet 36:277–285

Cao A, Rosatelli MC, Monni G, Galanello R (2002) Screening for thalassemia: a model of success. Obstet Gynecol Clin North Am 29:305–328

Cao A, Congiu R, Sollaino MC, Desogus MF, Demartis FR, Loi D, Cau M, Galanello R (2008) Thalassaemia and glucose-6-phosphate dehydrogenase screening in 13- to 14-year-old students of the Sardinian population: preliminary findings. Community Genet 11:121–128 Epub 2008 Mar 26

Chaabouni-Bouhamed H (2008) Tunisia: communities and community genetics. Community Genet 11:313–323 Epub 2008 Aug 5

Chemke J, Zlotogora J (1997) Genetic services in Israel. Eur J Hum Genet 5(Suppl 2):105–111

Czeizel AE, Gasztonyi Z, Kuliev A (2005) Periconceptional clinics: a medical health care infrastructure of new genetics. Fetal Diagn Ther 20:515–518

Department of Community Genetics (2009) http://www.health.gov.il/genetics

Ebrahim SH, Lo SS, Zhuo J, Han JY, Delvoye P, Zhu L (2006) Models of preconception care implementation in selected countries. Matern Child Health J 105:S37–S42 Epub 2006 Jun 9

Ekstein J, Katzenstein H (2001) The Dor Yeshorim story: community-based carrier screening for Tay-Sachs disease. Adv Genet 44:297–310

Fisher N, Baram M (2005) Tay Sachs screening in Israel–is the consumer aware of the significance of the test results? Nurses Israel (in Hebrew) 172:40–44

Frumkin A, Zlotogora J (2008) Genetic screening for reproductive purposes at school: is it a good strategy? Am J Med Genet A 146:264–269

Gason AA, Sheffield E, Bankier A, Aitken MA, Metcalfe S, Barlow Stewart K, Delatycki MB (2003) Evaluation of a Tay-Sachs disease screening program. Clin Genet 63:386–392

Gason AA, Metcalfe SA, Delatycki MB, Petrou V, Sheffield E, Bankier A, Aitken M (2005) Tay Sachs disease carrier screening in schools: educational alternatives and cheekbrush sampling. Genet Med 7:626–632

Godard B, ten Kate L, Evers-Kiebooms G, Aymé S (2003) Population genetic screening programmes: principles, techniques, practices, and policies. Eur J Hum Genet 11(Suppl 2):S49–S87

Henneman L, Bramsen I, van der Ploeg HM, Adèr HJ, van der Horst HE, Gille JJ, ten Kate LP (2001) Participation in preconceptional carrier couple screening: characteristics, attitudes, and knowledge of both partners. J Med Genet 38:695–703

Hesketh T (2003) Getting married in China: pass the medical first. BMJ 326:277–279

Holtzman NA (1998) Eugenics and genetic testing. Sci Context 11:397–417

Kaback MM (2001) Screening and prevention in Tay-Sachs disease: origins, update, and impact. Adv Genet 44:253–265

Kalokairinou EM (2007) The experience of beta-thalassaemia and its prevention in Cyprus. Med Law 26:291–307

Koren A, Zalman L, Palmor H, Ekstein E, Schneour Y, Schneour A, Shalev S, Rachmilewitz EA, Filon D, Openhaim A (2002) The prevention programs for beta thalassemia in the Jezreel and Eiron valleys: results of fifteen years experience. Harefuah 141:938–943

Mao X (1998) Chinese geneticists' views of ethical issues in genetic testing and screening: evidence for eugenics in China. Am J Hum Genet 63:688–695

Markel H (1992) The stigma of disease: implications of genetic screening. Am J Med 93:209–215

Mitchell JJ, Capua A, Clow C, Scriver CR (1996) Twenty-year outcome analysis of genetic screening programs for Tay-Sachs and beta-thalassemia disease carriers in high schools. Am J Hum Genet 59:793–798

Rashed Khater RT, El Gazali S (2003) Premarriage checkup in Egypt. rapid response to: Hesketh T getting married in China: pass the medical first. BMJ 326:277–279

Raz AE, Vizner Y (2008) Carrier matching and collective socialization in community genetics: Dor Yeshorim and the reinforcement of stigma. Soc Sci Med 67:1361–1369 Epub 2008 Aug 11

Samavat A, Modell B (2004) Iranian national thalassaemia screening programme. BMJ 329:1134–1137

Schwartz CR (2008) Heredity and hope: the case for genetic screening. Harvard University Press, Cambridge

Zeesman S, Clow CK, Cartier L, Scriver CR (1994) A private view of heterozygosity: eight year follow-up on carriers of Tay-Sachs gene detected by high school screening. Am J Med Genet 18:769–778

Zlotogora J, Israeli A (2009) A comprehensive screening program for cystic fibrosis. IMAJ (in press)

Zlotogora J, Leventhal A (2000) Screening for genetic disorders among Jews: how should the Tay Sachs screening program be continued? IMAJ 2:665–667

Zlotogora J, Carmi R, Lev B, Shalev SA (2008) A targeted population carrier screening program for severe and frequent genetic diseases in Israel. Eur J Hum Genet December 24. [Epub ahead of print]

Zuckerman S, Lahad A, Shmueli A, Zimran A, Peleg L, Orr-Urtreger A, Levy-Lahad E, Sagi M (2007) Carrier screening for Gaucher disease: lessons for low-penetrance, treatable diseases. JAMA 298:1281–1290