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ARTICLE

A targeted population carrier screening program for severe and frequent genetic diseases in Israel

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A national carrier screening program targeted at communities in which severe genetic diseases are present with a frequency higher than 1/1000 live births, has been in existence in Israel since 2002. Within the communities at risk, carrier screening is voluntary whereas genetic counseling and testing is provided free of charge. During the first 5 years of the program more than 13 000 tests were performed, and at the end of 2007 it was offered in 35 different localities/communities for a total of 36 diseases. Many of the couples identified to be at risk opted for prenatal diagnosis and in two cases an affected pregnancy was terminated. In some cases the couples declined prenatal diagnosis and two of those families gave birth to an affected child. Based on the experience learnt from this targeted screening program it appears that a knowledge-based, voluntary screening program operated within the community is an effective way to provide genetic services and test referrals. The community program directed toward couples in their reproductive period does not seem to have led to stigmatization at either the individual or the community level.

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Introduction

The Israeli Ministry of Health sponsors a 'national program for the detection and the prevention of birth defects' established in 1980. The program is provided free of charge to all citizens and is multifaceted. It is comprised of a general newborn screening, prenatal diagnosis for women at increased risk for Down syndrome and genetic diseases and a carrier screening for populations at risk for Tay Sachs disease and beta thalassemia.[1] Although the newborn screening aims to prevent mental retardation, the other components of the program are aimed at giving reproductive choices to the population at risk. With the characterization of the molecular basis of many other relatively frequent genetic diseases in the population, a proposal was developed to expand the genetic screening program for reproductive purposes according to the criteria first developed by Wilson and Jungner for the World Health Organization.[2] Due to financial constraints, the program has not yet been incorporated into the national screening program. Currently more expansive genetic testing is being offered for a fee and the costs are partially covered by supplementary insurance plans of the Israeli health funds.

In 2002, the Ministry of Health[3] expanded the free-of-charge health basket to include a targeted carrier screening program directed at the communities in which severe genetic diseases are present with a frequency higher than 1/1000 live births. This was a major first step towards the expansion of the national genetic screening program.

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A general review of this program is presented here, based on the experience of the first 5 years. Some specific parts of this program have been previously published.[4–7]

The Israeli population and primary health care infrastructure

In 2006 the population of Israel numbered 7 116 700 citizens, of whom 75.8% were Jews and 16.5% Muslim Arabs.[8] The Bedouin-Arab, residing mostly in the Negev desert, represent one-fifth of the Muslims in the country. The other groups, including mainly Christian Arabs and Druzes, each represent less than 2% of the population. For the most part, the Arabs and Druzes live in villages/tribes that were founded less than 10 generations ago by only a few individuals. The population of each of those villages/tribes often numbers less than 10 000 inhabitants. The fertility rates are very high, and in the past half-century there has been a documented 6- to 7-fold natural increase in the population of most of those communities.[8] Currently in Israel there are more than 100 non-Jewish localities, with 88 having more than 2000 inhabitants. In addition, several of the large cities such as Jerusalem, Haifa and Tel Aviv-Yafo have a significant Arab population.

Middle-Eastern societies, specifically the Arab rural populations, are characterized by close family relationships. The preference of consanguinity is a result of a deeply rooted cultural custom, and even though the major religions officially discourage consanguineous marriages, they are highly prevalent in the region. In Israel more than 20% of Arab and Druze marriages are between first cousins whereas an additional 25% are between related individuals.[9] Among the Arab-Bedouin close to 70% of all marriages are consanguinous. Interreligious marriages are rare and in most localities the population is homogenous, either Muslim or Druze. When the inhabitants of a certain locality are of different religious faiths, most often they live in separate quarters.

Since the legislation of the 1995 bill of health, the entire Israeli population has been covered by national health insurance.[1] Four health funds are primarily responsible for the provision and delivery of health care to the population, either through a basket of services included in the national health insurance or through supplementary insurance plans. Primary care is provided in local family clinics. In addition, there is a large network of 'maternal and child health clinics' located all over the country. This service is primarily provided by the Ministry of Health and in few locations by the health funds or by the local municipalities. In these clinics a multidisciplinary team provides primary care to healthy pregnant women and infants.

Genetic diseases in Israel

Since the creation of the State in 1948, many efforts have been made to delineate the genetic diseases in the Israeli population.[1] Data about the genetic disorders present in the different communities, their clinical, metabolic and molecular basis and their frequencies were accumulated.[2,10] Although among Jews the differences in the frequencies of the genetic diseases are between the communities of origin, among the non-Jews differences exist not only between the religious communities but also between the different villages/tribes.[10] In the last decade, data on genetic diseases existing in Israel have been summarized and is constantly updated into current catalogs available online.[11]

Genetic screening

Genetic screening for Tay Sachs and thalassemia is a public health program provided free-of-charge to the Israeli populations at risk. Tay Sachs carrier screening is offered to Jews of Ashkenazi and North African descent. Thalassemia carrier screening is offered to all the Arab and Druze populations as well as to Jews originating in Iran, Iraq, Syria, Kurdistan, the Mediterranean countries and Asiatic countries of the former USSR. Although the official recommendation is to have genetic testing performed before pregnancy, many women are first made aware of the availability of genetic screening at the beginning of their pregnancy and are then referred as necessary. As a result of the screening program, Tay Sachs disease has almost disappeared among Jews in Israel, this is presumed to be due to the use of prenatal diagnosis by the general population and because of the discouragement of carrier couples' marriages within the ultra orthodox Jewish community.[12] As for thalassemia, a dramatic reduction in the prevalence of the disease has been observed.[13] In the late 1980s the mean number of children born each year in Israel with thalassemia was 13 among Arabs (mean 4 per 10 000 live births among Jews and 50 per 10 000). In the last decade the number has dropped to an average of 5 children each year (12 per 10 000 among Arabs).[14] Most importantly, most affected children born in the last decades were delivered to parents who, although were aware of their risk, chose not to use prenatal diagnosis and/or pregnancy termination.[14]

Based on the knowledge of the distribution of genetic diseases in the population, a targeted screening program for severe genetic diseases with a frequency higher than 1/1000 live births (corresponding to 6% carrier frequency for autosomal recessive diseases) was added in 2002 to the existing genetic screening program.[3] As 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 inclusion of diseases with a frequency of 1/1000 live births was a first step towards the implementation of the planned comprehensive program including severe diseases up to a

frequency of 1/15 000, as recommended by the Israeli Society of Medical Genetics.[2] The 1/1000 live births frequency was chosen so as to include most of the genetic diseases prevalent in small communities, where the program can be performed at a relatively low cost. In those delineated communities, less frequent diseases are usually limited to the close relatives of the affected individuals, therefore carrier testing, if available and indicated, is part of the genetic counseling given to the family and included in the basic services offered though the general medical insurance.

Implementation of the targeted program

The first step was the identification of the specific communities and the genetic diseases fulfilling the criteria for inclusion, namely, severe genetic diseases with early mortality or chronic severe disability and with a frequency equal to or more than 1/1000 live births.[3] Because of the limited experience with premarital genetic screening in the Israeli population, the screening was aimed mostly at married couples in their reproductive years. The aim of the carrier screening program was to offer reproductive choices to couples including prevention of the birth of affected children. In the case of cystic fibrosis or cerebrotendinous xanthomatosis, where early treatment significantly improves the course of the disease, an important option offered to the couples at risk was newborn diagnosis and early treatment of the disease. In two other specific cases, autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in a Bedouin community and hyperoxaluria in a village near Jerusalem, the primary goal of the screening program was to identify couples at risk and allow for the early diagnosis and treatment of their affected children.

Meetings with local medical personnel and influential public figures took place to explain the aims and terms of the screening program before the actual implementation of the program in each of the localities/communities.

Early in the course of the implementation of the targeted program, it became apparent that in several localities the set guidelines were not appropriately followed. The most significant problems encountered were the absence of regular/individual counseling sessions, screening of individuals outside the reproductive age period and, in several cases, a carrier frequency much lower than specified in the criteria. This led to the program's reorganization to assure consistent adherence to the guidelines.

In the first 3 years, the program was performed by eight separate genetic clinics and laboratories. Thereafter, the genetic counseling is being administrated regionally and is operated in five regions whereas the tests are performed in eight molecular genetics laboratories. A short explanatory movie and a pamphlet in Arabic were developed. The educational tools address the general concepts of genetic screening, using thalassemia as an example, and provide a short explanation of the respective disease(s) screened for within that particular community.

Genetic counseling and tests are provided in local clinics, by appointment and free of charge. When the screening involves a pregnant woman, the implications of a possible late diagnosis are explained to allow for an informed decision on the part of the couple as to whether to proceed with the screening. This is a two-step screening: one spouse is first examined and if found to be a carrier, he/she receives genetic counseling; and then the other spouse is examined. In the case of current pregnancy, if possible, the couple is examined simultaneously. If both spouses are found to be carriers, they receive genetic counseling that details all options available to them. A written report of the test results is sent to all individuals screened.

In each of the five regions a different geneticist is in charge of the program. This leads to minor local differences in the way the program is being implemented.

Results of the screening program

Since 2002 more than 13 000 tests were performed in concordance with the guidelines of the genetic screening program. At the end of the 5-year period, the program was fully implemented in 35 different localities/communities. Almost half of the communities screened were in the Arab-Bedouin population in the Negev, which represent less than one-fifth of the Israeli Muslim population. The screening was also provided in 6 different Druze localities and in fact included almost half of this community in Israel. The most probable explanation of overrepresentation of Bedouins and Druze in the screened population is that these are the two commununities with the highest rates of consanguineous marriages in Israel.[9] At the end of 2007, the program included a total of 36 diseases, in several cases the same disease was screened in different communities. For instance, screening for ataxia telangiectasia was provided in four different communities; in each a different founder mutation was responsible for the high prevalence of the disease. In nine of the communities more than one disease was screened with a maximum of four different diseases screened in one village (Table 1).

In almost all cases the first individual examined was a married woman, often during her pregnancy. Many couples that were both found to be carriers opted for prenatal diagnosis. In a heterozygous couple for a mutation causing spinal muscular atrophy-related disease and in another for an epidermolysis bullosa mutation, the foetuses were found affected and the pregnancies were terminated. Some carrier couples at 25% risk declined prenatal diagnosis, in particular when the screening results were obtained late in pregnancy. In one case of screened

Table 1 A list of the diseases for which the carrier screening program was fully implemented (more than 30 individuals screened) at the end of 2007

Disease[a]	*Gene*[15]	*OMIM*[15]
Albinism (1)	TYR	203100
Ataxia telangiectasia (2,3,4,B1)	ATM	208900
Bardet Biedl syndrome (B2)	BBS2	209900
Bardet Biedl syndrome (B3)	BBS4	209900
Bartter syndrome, with sensorineuronal deafness (B4)	BSND	602522
Cerebrotendinous xanthomatosis (5)	CYP27A1	213700
Congenital insensivity to pain (B5, B6)	NTRK1	256800
Corticotropin-releasing hormone deficiency (6)	CHR	122560
Cystic fibrosis (7,8)	CFTR	219700
Cystinuria hypotonia syndrome (B8)	2p16del	606407
Epidermolysis bullosa (9)	LAMA3; LAMB3	226700
Epidermolysis bullosa, pyloric atresia, aplasia cutis congenita (B9)	ITGB4	226730
Glycogen storage 1b (B10, B11, B12)	G6PT	232220
Hemolytic uremic syndrome (B5)	CFH	235400
Hyperinsulinemic hypoglycemia of infancy, persistent (B13)	ABCC8	256450
Hyperoxaluria (7,10)	AGTX	259900
Hypoparathyroidism, growth, mental retardation, dysmorphism (B12)	TBCE	241410
Infantile bilateral strial necrosis (B11)	NUP62	271930
Krabbe disease (11,12)	GALC	245200
Leber amaurosis (13)	CRB1	204000
Limb girdle muscular dystrophy LGMD2C (14)	SGCG	253700
Mental retardation (8)	CC2D1A	608443
Mitochondrial depletion (2)	DGUOK	251880
Molybdenum cofactor deficiency (15)	MOCS1	252150
Mapple syrup urine disease (B15)	BCKDHA	248600
Nephronophtisis (B14, B16, B12)	INVS	602088
Nephrotic syndrome (7)	NPHS1	256300
Niemann Pick C (B17)	NPC1	257200
Non ketotic hyperglycinemia (16,17)	AMT	605899
Osteopetrosis (B11)	TC1RG1	259700
Prolidase deficiency (5)	PEPD	170100
Pseudorheumatoid arthropathy of childhood (16)	WISP3	208230
Pychnodysostosis (15)	CTSK	265800
Spinal muscular dystrophy related disease SMARD (8)	SMARD1	604320
Spinal muscular dystrophy SMA (8)	SMN1	253300
Ventricular tachycardia, polymorphic catecholaminergic (18)	CASQ2	604772

[a]A different number was given for each of the communities where the screening was provided. For the Bedouin in the Negev a B appears before the number.

heterozygous parents, a child affected with congenital nephrotic syndrome was born. In another case of an epidermolysis bullosa-affected newborn, an early diagnosis was made by CVS but the couple decided nevertheless to continue the pregnancy. Although, in general, most spouses were examined on learning that their wives were carriers, in some of the localities a high percentage of men (up to 70% in one village[5]) did not come for further counseling and examination.

Case study: an example of one of the villages included in the program

In a village of approximately 5500 people, near Jerusalem (village 7 in Table 1), most of the inhabitants are descendants of a single Arab-Muslim family who settled in this site approximately 250 years ago. Meetings with local medical personnel and influential public figures took place in the village to explain the aims and terms of the screening program. Subsequently several lectures were given to the population at large and to the local high school students. The screening services are performed in the village 'Mother and Child Well Being Clinic' where all referred/interested individuals are seen by the same medical geneticist (JZ) and by appointment. The genetic testing is also available to individuals from the village that have been referred subsequent to hospitals based genetic clinics consultations. The initiation of the screening program in this village was based on a research study that identified a cystic fibrosis carrier frequency of 8.5% from a founder mutation.[16] Later, with the characterization of the molecular basis of congenital nephrotic syndrome and hyperoxaluria in this village, these tests were added to the screening.[17] The unique aim of the hyperoxaluria screening was to discover couples at risk to provide early diagnosis and treatment of affected children and thereby preventing complications. In this traditional religious community, termination of pregnancy with an affected foetus, particularly in the late stages of the gestation, is

generally not an acceptable option. In many cases the screening tests are being performed for early diagnosis and better treatment of an affected child. To date, 184 individuals were tested in this village. In 2003, 26% of the women giving birth had genetic counseling before or during the pregnancy (26 out of 100 women). This number increased in 2007 to 45.8% (54 out of 118 women). In most cases where the counseling and testing was performed during pregnancy, the women did not have any history of genetic problems in their first- or second-degree relatives. In addition, in 18 cases the genetic counseling was preconceptional and in 5 cases premarital. Among the 184 individuals screened, the carrier frequencies were 9.2% for cystic fibrosis, 9.3% for nephrotic syndrome and 8.1% for hyperoxaluria. In the 30 couples where the women were diagnosed as carriers of either cystic fibrosis or nephrotic syndrome, 10 husbands declined further screening. Two out of three couples heterozygous for cystic fibrosis had severe fertility problems and were referred for IVF. Infertility seems to be frequent in the village, in part probably due to a high frequency of the 5T allele of CFTR.[16] This polymorphism is not part of the mutations screened in the program but was examined in the two couples mentioned because of their infertility. The polymorphism was not found in either of the husbands. Because of the 25% risk for cystic fibrosis the two couples that underwent IVF, opted for preimplantation genetic diagnosis (PGD), and a healthy child was born in each case. The third heterozygous couple had a prenatal diagnosis and a healthy newborn.

In one case where the woman was found to be a carrier of congenital nephrotic syndrome, maternal serum α-fetoprotein was detected at a very high level, suggesting an affected foetus. The husband was subsequently also found to be a carrier. The couple declined prenatal diagnosis and an affected child was born.

Comparison between the targeted Israeli program and other genetic screening programs

With the decreased mortality and morbidity due to infectious diseases and prematurity, congenital malformations and genetic diseases have become a major cause of morbidity and mortality among infants and children. As a result, programs aimed at the prevention of genetic diseases, particularly for thalassemia were developed for the most part, in collaboration with the World Health Organization. In countries such as Iran, Saudi Arabia and other Muslim nations where thalassemia is highly prevalent, premarital screening is mandatory.[18–22] Although a premarital certificate that the tests have been performed is obligatory, the results are not taken into account when issuing a marriage licence. In Iran, most of the heterozygous couples decided to marry and the incidence of the disease was not significantly affected. This eventually lead to the enactment of a law, based on principles put forward by a religious decree (Fatwa), allowing for the termination of pregnancies before and up to the 120th day of pregnancy in cases of severe disease in the fetus.[22]

A different approach to premarital screening was adopted in Cyprus. Thalassemia screening is required but the results of the screening do not preclude a religious marriage within the church.[18] The Jewish ultra orthodox community also requires genetic screening before marriage. In this community, marriages are prearranged and the results of the genetic screening is one of the decisive factors as to whether the match-making will proceed (Dor Yeshorim).[12] In each of these two religious communities, the programs resulted in a highly significant reduction in the prevalence of the diseases screened: in Cyprus because of the use of prenatal diagnosis by couples at risk, and in the Ultra orthodox Jewish community by avoidance of marriages between carriers.

Several ethical questions may be raised concerning the mandatory screening programs, but experience seems to demonstrate that if the programs are confidential, culturally appropriate allowing individual freedom of choice as to how to proceed; the programs are well accepted by the screened population.

In addition to those carrier screening programs, pilot studies examined the feasibility of screening programs for relatively frequent diseases in the general population such as cystic fibrosis and fragile X syndrome.[23–27] In the United States, preconceptional cystic fibrosis carrier screening is recommended and performed using a consensus panel of mutations.[26]

For obvious reasons, it is expected that mandatory premarital genetic screening will be difficult or even impossible to implement in western societies in general and in particular if minorities are to be targeted. In addition, there is the contemporary secular problem of pregnancies that often precede formal marriages. A better alternative in such communities is a voluntary preconceptional screening together with an appropriate educational program targeting young adults. Examples of high school-based educational programs that included genetic testing have been reported to be very successful in Canada and in Australia.[28,29] Although high schools offer a convenient setting for genetic screening and it has many advantages, many questions have been raised about school-based blood testing in adolescents.[30,31] As all the evaluations of these high school screening programs found that education played a critical role in providing for informed testing decisions, a better solution would be to leave the student with the option of when to perform the test outside of the convenient school-binding context.[30]

In Israel, voluntary carrier genetic screening for Tay Sachs disease and thalassemia has been successfully provided for more than 25 years. This program has served as a model for the newly established targeted genetic

screening aimed at severe genetic diseases with a frequency higher than 1/1000 live births. In this new program pregnant women from the designated communities at risk are given the option of having genetic testing and when appropriate are referred for the actual performance of the test. A major difference between the screening program for Tay Sachs or thalassemia and the community-targeted program is that the later including genetic counseling is offered at the place of residence. The screening is offered to every couple in the designated at-risk community, regardless of whether any genetic disease actually exists in the family. This was purposely done to reduce possible stigmatization. Indeed, the program has been well accepted on both the individual and the community levels by different communities regardless of religions, traditions or socio-economical status. Over time we have observed improving knowledge of the genetic tests available, both among medical personnel and laymen in the communities. Although there has not been any systematic study, we are not aware of any program-related stigmatization. It has been our experience that the establishment of genetic clinics within the community increased awareness and accessibility and thus the demand for premarital counseling and preconceptional screening.[32]

As already noted, in several of the screened communities, husbands of screened women carriers did not come for counseling and testing. This may probably indicate a lack of thorough understanding of the aims of the program because initial participation infers the potential need to examine the spouse. Obviously, additional educational efforts are needed.

Many of the couples at risk that were discovered by the program opted for the prevention of the birth of an affected child. However, prenatal diagnosis and termination of pregnancy of an affected foetus is often very problematic. Two heterozygous couples with fertility problems used PGD within the framework of IVF and thus pregnancies with affected children were prevented. With the recent advancements in the use of PGD and the intention to include it in the Israeli basket of health services, this mode of genetic diagnosis is becoming a significant alternative for many families at risk for whom termination of pregnancy is not a religiously, traditionally or culturally acceptable option.

From the experience of the targeted screening program presented here it seems that voluntary screening within the community is an effective alternative to mandatory screening. However, for an individual to have a truly free choice of reproductive options she or he must be properly informed and knowledgeable of the program before the first pregnancy. Therefore, for such a voluntary program to be effective it must be accompanied by an extensive educational program that probably needs to start in high school and a concurrent community outreach program that includes as wide a circle in the community as possible[30]. As a first step toward this goal we began in 2007 to implement a pilot education program in high schools.

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