Cystic fibrosis is one of the most common severe and life-shortening genetic diseases. Now that advances in molecular genetics have made it possible to detect couples at risk, many families with an affected child use prenatal diagnosis to prevent the birth of more affected children. In 2001, the American College of Obstetricians and Gynecologists and the American College of Medical Genetics issued guidelines for preconceptive and prenatal carrier screening for CF [1]. As a result of this recommendation, CFTR mutation testing in the United States expanded the screening for CF into a routine service and the number of tests performed has increased to many thousands per week [2].

Alongside this screening for couples at risk, programs have developed for early detection by screening newborns. Several pilot programs have demonstrated that affected children diagnosed early in life have improved nutritional status, better growth, and fewer life-threatening complications [3]. Families also benefit substantially from CF screening of newborns, because it avoids the delay until the onset of symptoms and diagnosis as well as the anxiety, frustration and emotional distress that this causes. Today, CF newborn population screening is current in several countries – Australia, France, the UK, and almost all the states in the U.S.

**Cystic fibrosis is one of the most common severe and life-shortening genetic diseases**

**THE ISRAELI POPULATION AND HEALTH CARE INFRASTRUCTURE**

In 2007, Israel’s population of 7,243,600 comprised 75.6% Jews and 16.6% Muslim Arabs, while other groups, mainly Christian Arabs and Druze, each represented less than 2% of the population [4]. Since 1980 the Israel Ministry of Health has sponsored a nationwide program for the detection and prevention of birth defects. The program provides free prenatal diagnosis for all women over 35 at the beginning of pregnancy, as well as for those found by genetic counseling to be at increased risk for a genetic disease amenable to diagnosis [5]. This program includes neonatal screening for phenylketonuria and hypothyroidism, and carrier screening for populations at risk for Tay-Sachs disease (Ashkenazi Jews, i.e., Jews of European extraction, and Moroccan Jews) and beta-thalassemia (Arabs, Druze and several Jewish communities) [5]. Having established the molecular basis of many other diseases relatively prevalent in the Israeli population, additional screening tests have been recommended for the national program [6]. Although financial constraints have prevented this, the recommended tests, including for cystic fibrosis, are available privately and the costs are partially covered by supplementary insurance.

**CYSTIC FIBROSIS IN THE ISRAELI POPULATION**

The characterization of five mutations, which together account for 97% of the CF alleles in Ashkenazi Jews, made carrier screening possible for this community [7]. Since 1999, genetic screening for CF has been available privately to Israel’s Ashkenazi Jews. Subsequently, in each of the different religious communities and their subgroups a limited number of mutations was shown to be responsible for more than 80% of the CF cases. As a result, CF screening became part of the genetic screening tests that are offered privately to most of the population [8,9]. The tests are offered for a fee and the costs are partially covered by supplementary insurance plans of the Israeli health funds. Approximately 40% of the secular Jewish population undergo private genetic screening for carrier detection [10]. While among religious Jews the rate of utilization is lower (approximately 17%), among ultra-Orthodox Jews, it is almost 100% in a premarital context. Among Israeli Arabs utilization is lower still (less than 5%), probably because of the cost and the assumption that if the test is not covered by the national health insurance scheme it is not essential [11].
Israeli newborn screening for phenylketonuria began in the late 1960s and hypothyroidism was added in 1978. Since then 60–80 children with congenital hypothyroidism and 10–12 with phenylketonuria are diagnosed every year [5]. Although the possibility of expanding the program has been discussed several times, by the end of 2007 phenylketonuria and hypothyroidism remained the only two diseases screened for nationally. In 2006, with the complete renewal of the technical infrastructure of newborn screening, including the introduction of tandem mass spectrometry technology, the decision was taken to expand the program. Adding cystic fibrosis to newborn screening was considered since the disease is known to be relatively prevalent.

On the one hand, several studies have demonstrated that the secular Jewish population will do everything possible to avoid the birth of a child affected with a severe disease, including terminating the pregnancy [10]. Indeed, in recent years the utilization rate for prenatal CF diagnosis has been high, both for couples with an affected child and at-risk couples discovered through private screening. In the last decade 35–50 couples at risk underwent prenatal CF diagnoses each year, and on average 9 affected fetuses were diagnosed. In each of those cases the couples chose to terminate the pregnancy [12]. The added value of nationwide neonatal CF screening will therefore be small and may not justify the concomitant difficulties and costs. On the other hand, the Israeli population is particularly heterogeneous, and religious families, both Jewish and Arab or Druze – who constitute a significant portion of the population – reject the notion of terminating a fetus affected with a chronic disease, such as CF. In the case of Down syndrome, where prenatal diagnosis is recommended for all women over 35 and is available free of charge, about 65% of Jewish women and some 30% of non-Jewish women terminated the pregnancy of an affected fetus [12]. The main reason given for not taking the prenatal test was religious based; these were individual decisions made by couples based on informed choices [12].

In order to meet these very different needs it was decided to implement a new type of CF screening program. Since mid-2008 population screening is offered to all Israeli citizens free of charge with the aim of detecting couples at risk for cystic fibrosis. In parallel to the introduction of the CF screening program, the service offering only Tay-Sachs screening though regional clinics operated by the Ministry of Health was abolished. Since then, the individuals/couples are referred to authorized centers (public or private) that offer all the tests recommended according to the couple’s ethnic origin. The recommendations are those of the Israeli Association of Medical Geneticists, which were adopted as guiding principles by the Ministry of Health without regard to whether or not the test is free of charge. These measures were taken to improve the referral of couples and allow for a better coverage of the population for carrier screening [12].

In the context of genetic counselling, couples at risk discovered through the program have the possibility of making an informed choice even before the conception of a pregnancy, between neonatal diagnosis and early treatment or prevention, not marrying, using preimplantation diagnosis, or prenatal diagnosis available free of charge (with the possibility of termination of pregnancy). The main advantage of this type of screening is that it gives couples found to be at risk the possibility to decide between the different options before the birth of an affected child [13].

Another advantage of the proposed program is that it eliminates false positives, a major problem of newborn screening programs. When newborn screening for CF was first introduced, a second immunoreactive trypsinogen test of a second blood sample was needed to identify most of the affected children. More recently, a molecular test for the most frequent CFTR mutations is performed; however, in many cases only a single mutation is detected and a second blood sample for IRT testing is still required. Of these cases, most of the neonates prove to be unaffected, and counselling is needed only because they are carriers. The earlier diagnosis of couples at risk is obiously a solution to this problem since affected couples can receive genetic counselling before the birth.

In both types of screening, prenatal and neonatal, some CF-affected children will be missed. In a carrier screening program, the reason for false negatives is that the screening does not cover all the mutations present in the population. In the case of newborn screening, in some CF cases IRT levels are normal the first day after birth in children born with meconium ileus.

The uptake of the tests is expected to be high because of the experience in genetic population screening in Israel for Tay-Sachs and thalassemia. It is expected that most newborns will be born to couples who underwent cystic fibrosis screening. Following the percentage of newborns in whom the carrier status of the parents is known will allow us to determine whether the population screening is successful.

**The Israeli genetic screening program enables most of the couples at risk for cystic fibrosis to be detected**

**Couples at risk have the possibility to make an informed choice between neonatal diagnosis and early treatment or prevention**

IRT = immunoreactive trypsinogen
References

Capsule

Preparation for T cell war on infections

When T cells encounter an infection, they proliferate to create a larger army to fight the invader. The overall magnitude of the T cell response depends on the severity of infection and is determined by the number of T cells of a particular antigen specificity that are initially recruited, as well as the magnitude of the proliferative response. The extent to which these two components contribute to the response is unknown. By using DNA barcoding to track the responses of individual T cells, van Heijst and colleagues showed that the recruitment of T cells of a particular antigen specificity is similar and nearly complete, but that the extent of the proliferative response differed, and this determined the overall magnitude of the T cell response.

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Capsule

The flu pandemic in Mexico update

Data suggest that Mexico (population 110 million) has seen two waves of infection – the first, which peaked in late April, affected the Mexico City area, and the second, broader wave spanned June through August in southern states, including Chiapas, Yucatan and Quintana Roo. To prepare for a potentially larger wave this winter, Mexico is raising public awareness, standardizing timely diagnosis and treatment, and reinforcing equipment and management protocols in intensive care units throughout the country. To improve surveillance, Mexico has accelerated the upgrading of its public health laboratory network. The national reference laboratory and 28 states will soon have real-time polymerase chain reaction for running diagnostic tests. This builds on a restructuring of Mexico’s national surveillance and reporting systems, which started in 2007. As Mexico’s strategic reserve of antivirals would cover only 1% of the population for community cases and up to 80,000 hospitalized cases, the nation is implementing a central logistics and delivery system to assure their efficient allocation. The country also expects to have 20 million doses of the H1N1 vaccine available by December. As even this would cover only a fraction of the population, the government will prioritize health care workers, then individuals at risk of severe disease, such as pregnant women and people with chronic underlying illnesses.

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“By three methods may we learn wisdom; first by reflection, which is noblest; second by imitation, which is easiest; and third by experience, which is bitterest”

Confucius