

Compliance for Genetic Screening in the Arab Population in Israel

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ABSTRACT: **Background:** Genetic screening tests for cystic fibrosis (CF), fragile X (FRAX) and spinal muscular atrophy (SMA) have been offered to the entire Arab population of Israel in the last few years. Since 2008, screening for CF is provided free of charge, but for FRAX and SMA the screening is privately funded with partial coverage by complementary health insurance programs.

Objectives: To assess the compliance of Arab couples with regard to genetic screening tests, and the factors that affect their decisions.

Methods: We analyzed compliance for genetic screening tests at the Emek Medical Center Genetic Institute, and in outreach clinics in four Arab villages. We enquired about the reasons individuals gave for deciding not to undergo testing. We also assessed the compliance of these individuals for the triple test (a screening test for Down syndrome).

Results: Of the 167 individuals included in our study, 24 (14%) decided not to be tested at all. Of the 143 (86%) who decided to be tested, 109 were tested for CF only (65%) and 34 (20%) for SMA and FRAX (as well as CF). The compliance rate for the triple test was 87%. Technical reasons, mainly financial issues, were the most significant factor for not undergoing all three tests.

Conclusions: The compliance of the Arab community for genetic testing for SMA and FRAX is extremely low. We believe that this low utilization of screening is due to economic reasons, especially when a complementary health plan has not been acquired, and largely reflects the perception that these tests are less important since they are privately funded.

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national program funded by the Ministry of Health, followed by a national screening program for beta thalassemia for the populations at risk.

Due to the characterization of five mutations, which together account for 97% of the cystic fibrosis disease alleles in Ashkenazi Jews, this community is one of the first in which carrier screening for CF became possible [1]. Since 1999, genetic screening for CF has been available for Ashkenazi Jews, in addition to the national Tay-Sachs screening. Subsequently, with the discovery of the molecular basis of other diseases that are relatively frequent in this group, the list of tests offered to Ashkenazi Jews expanded. At the same time, the molecular basis of CF in non-Ashkenazi Jews along with several other diseases that are relatively frequent among non-Ashkenazi Jews, as well as among Arabs and Druze, was unraveled. Testing for some of these diseases was offered to the Israeli population according to the ethnic origin of the couples. Initially, testing for CF was privately funded, as was testing for other diseases included in the screening program. Later, the costs of these tests were partially covered by complementary insurance programs, and in recent years testing for CF (as well as Tay-Sachs and familial dysautonomia) has been funded by the Ministry of Health.

The Israel Society of Medical Genetics defined inclusion criteria for genetic screening tests according to the principles of Wilson and Jungner, including, in particular, the severity of the disease, its prevalence in the population, and sensitivity of the test [2-4]. It is common practice to offer couples testing for diseases that meet these criteria according to the couple's ethnic origin, whereas CF, FRAX and SMA are recommended to the entire population (except for a few groups in which CF testing is of low sensitivity).

In Israel, the triple test is offered to all pregnant women to screen for Down syndrome. The attending physicians and nurses, who are responsible for the follow-up and routine care of pregnant women, provide information and refer the women for testing. This screening program is highly efficient and successful in reaching the vast majority of pregnant women presenting within the relevant time frame to undertake the test.

Israel was one of the first countries to propose population genetic screening tests for reproductive purposes. The screening for Tay-Sachs disease was introduced in 1971 as a

In this study we assessed screening patterns for genetic diseases in the Israeli Arab population in order to compare them with this population's compliance with Down syndrome screening and to identify the factors that influence these patterns.

SUBJECTS AND METHODS

ISRAELI HEALTH INSURANCE

In 1995 the National Health Insurance Law was implemented, according to which all Israeli citizens are members of one of four health funds, each of which offers services included in the basket of services. These services are either entirely free of charge or require a small co-payment. In addition, a large proportion of the population has complementary insurance plans offering additional services, most of which require different levels of co-payment. However, there are significant differences in the rates of acquired complementary insurance according to the socioeconomic status of individuals.

POPULATION GENETIC SCREENING

Genetic screening tests are performed in medical centers approved by the Ministry of Health. As part of the routine follow-up of pregnant women, the relevant medical personnel must assure that every pregnant woman receives information about the recommended genetic screening tests and has made an informed choice. Couples are referred by physicians or nurses to designated centers for genetic testing on a regular basis before or during the pregnancy.

As mentioned earlier, the recommendations for genetic screening for the Arab and Druze population include testing for cystic fibrosis (free of charge) and for SMA and FRAX (offered at a relatively low cost for individuals with a complementary health plan, approximately US\$ 22 for each test). For individuals who do not have a complementary health plan the price is significantly higher (approximately \$80 for each test). Thalassemia screening is provided free of charge as part of the routine follow-up during pregnancy.

At the Emek Medical Center Genetic Institute individuals referred to genetic screening tests are scheduled for consultation with a genetic counselor. At this meeting the couple receives detailed information on the theoretical and practical aspects of the screening program. They are informed of the various tests that are offered based on their ethnic origin and accepted guidelines. In addition, during genetic counseling sessions conducted for medical indications, the issue of genetic screening is discussed routinely and the relevant tests are performed if the couple is interested. For these sessions, held in the Genetic Institute, all technical procedures are completed at the same meeting, including the drawing of blood and payment for the tests if required. Communication with the families in this setting is conducted in Hebrew.

The Emek Genetic Institute has community clinics in

Arab towns and villages located relatively close to the hospital. In these clinics, genetic counseling sessions are conducted by an Arabic-speaking genetic counselor. During these sessions, genetic screening tests are also discussed on a regular basis. Since the blood samples are taken at the clinic for individuals who are interested, testing for diseases recognized and funded by the Ministry of Health is conducted without further effort by the clients. However, for certain diseases (such as SMA and FRAX), testing that is privately funded requires additional steps on the part of the couple to complete the payment procedure – either by contacting the genetic institute to arrange payment by credit card over the phone or by visiting the hospital and paying cash.

THE POPULATION STUDY

We collected data from two different settings – the genetic institute at Emek Medical Center and community clinics in Arab towns and villages. The decisions of Muslim and Christian Arabs and the Druze regarding genetic screening for CF, SMA and FRAX were recorded. After receiving pertinent information, the counselees decided whether or not to be tested (or to be tested for certain diseases selected from the full recommended list). At the end of the counseling session they were asked to explain the reasons for their decision. The various reasons were then classified into four categories:

1. not convinced of the importance of genetic testing
2. not interested in genetic screening since they would not terminate a pregnancy in the event that the fetus is affected (mainly due to religious beliefs)
3. financial issues – either addressed directly during the interview or assumed by us to be the reason for not undergoing the tests, e.g., the couple stated that they were interested in testing for SMA and FRAX but did not proceed with the payment
4. other reasons.

DOWN SYNDROME SCREENING

The triple test, which is the main screening test for Down syndrome in low risk populations in Israel, is included in the basket of services with co-payment by the couple. We gathered information on compliance with the triple test among all the women in our study either during the current pregnancy or in a previous pregnancy. We excluded from this analysis women who had never been pregnant before, and cases for which we had no documentation. The study was approved by the Emek Medical Center Ethics Committee.

RESULTS

Our study group comprised 167 individuals of whom 139 were Muslim Arabs, 12 Christian Arabs and 16 Druze. Table 1 depicts screening rates for CF, SMA and FRAX in the

Table 1. Screening rates for CF, SMA and FRAX in the entire study population in community clinics and the Emek Medical Center Genetic Institute, according to the three religions

Reasons for refusing testing										
	Individuals included in the study		Individuals tested for CF		Individuals tested for FRAX & SMA		Financial reasons	Not convinced testing was important	Will not terminate	Other reasons
	No.		No.	%	No.	%	No.	No.	No.	No.
Total										
All	167		143	85.6%	34	20.4%	90	9	15	19
Muslims	139		119	85.6%	28	20.1%	74	7	12	18
Christians	12		11	91.7%	4	33.3%	7	1	0	0
Druze	16		13	81.3%	2	12.5%	9	1	3	1
Community clinics										
All	116	99		85.3%	19	16.4%	74	4	11	8
Muslims	91	78		85.7%	15	16.5%	58	3	8	7
Christians	11	10		90.9%	3	27.3%	7	1	0	0
Druze	14	11		78.6%	1	7.1%	9	0	3	1
Genetic Institute										
All	51	44		86.3%	15	29.4%	16	5	4	11
Muslims	48	41		85.4%	13	27.1%	16	4	4	11
Christians	1	1		100.0%	1	100.0%	0	0	0	0
Druze	2	2		100.0%	1	50.0%	0	1	0	0

*Jews of East European ancestry

entire study population, in the community clinics and at the genetic institute, as well as for the three religions. Of the 139 individuals who were offered screening for Down syndrome, 121 (87.1%) underwent the triple test.

Of the 167 individuals who were offered screening for CF, FRAX and SMA, 24 decided not to be tested at all (14.4%). Fifteen of these individuals stated that they were not interested in the tests since they would not consider abortion of an affected fetus. It is our opinion that the medical implications of testing for these conditions were fully understood. The other nine who decided not to undergo genetic testing stated that they were not convinced that testing is important. The remaining 143 individuals decided to be tested for CF (86.1%); only 34 (23.7%) were also tested for FRAX and SMA. In total, 20% of the individuals who were counseled (34 of 167) underwent the recommended testing for the three conditions.

Among the 139 Muslims, 20 did not undergo any test. Among the 119 (85.6%) who opted to be tested, only 28 (23.5%, 20% of the total group) were tested for FRAX and SMA in addition to testing for CF. Although there were differences in the compliance rates of the different groups classified according to their religion, conclusions could not be drawn because the number of individuals in the non-Muslim groups was too small [Table 1]. The highest rate of those who chose to be tested for all three diseases was among the Christian Arabs (33.3%) and the lowest was among the Druze (12.5%).

Similar rates of CF screening utilization were observed among Muslims in the two settings – the community clinics and the Genetic Institute (85.6% and 86.3% respectively).

While a majority of individuals who were counseled in the community clinics stated that they were interested in screening for SMA and FRAX, only 16.4% actually completed the required administrative procedures, and were tested subsequently for all three diseases. More people who were counseled at the Genetic Institute underwent the tests for the three diseases (29.4%); however, this difference did not reach statistical significance ($P = 0.06$). When analyzing these rates in the Muslim population only, the difference between the two settings was even smaller: 15 of 91 Muslims in the community clinics (16.5%) and 13 of 48 (27%) at the Genetic Institute underwent FRAX and SMA testing ($P = 0.1721$).

Financial reasons were noted by 44.4% of individuals who chose not to be tested for SMA and FRAX at the Genetic Institute (55.1% of those who were tested for CF but not for SMA and FRAX). In addition, 6.8% of those who decided not to be tested for FRAX and SMA stated that they were not convinced that screening for these diseases was important (4.1% in sessions in the community and 13.9% in sessions at the Genetic Institute). In the entire study population 9% stated that they were not interested in screening because they would not consider abortion of an affected fetus. The figures were approximately the same for the two settings (9.5% in the community and 7.8% at the Genetic Institute). "Other reasons" included explanations such as "our doctor referred us to be tested for CF only," "we are not planning a pregnancy soon" and "the pregnancy is too far advanced," or women who stated that they "need to consult with their husbands" but never contacted us again to complete the screening tests.

DISCUSSION

Most couples who were offered CF genetic screening decided to be tested (85.6%). These very high rates are almost similar to the compliance rates for the triple test that were observed in this same group of women (87.1%). It has been our experience that medical personnel routinely refer all pregnant women to tests that are included in the basket of services but only mention the existence of other tests. Some tests such as the triple test are considered by most caretakers as part of the routine prenatal workup. In a survey of 122 Israeli health care providers, only 9 (7.4%) presented screening for Down syndrome to pregnant woman as an option [4]. This could explain the high compliance rates for the triple test despite the fact that it is not free of charge and that most women with abnormal results in the Arab population ultimately do not have invasive tests, mostly since they oppose termination of pregnancy [5].

Since the introduction of cystic fibrosis population screening and inclusion of this test in the basket of services (i.e., available free of charge), most women are referred by their physicians for cystic fibrosis screening, even though the recommendation of the Israel Association of Medical Geneticists does not distinguish between screening for cystic fibrosis and spinal muscular atrophy or fragile X [3]. Indeed, it is our impression that several of the women who scheduled an appointment for genetic testing did so in order to be tested for cystic fibrosis without knowing that other tests are recommended with the same level of medical importance as cystic fibrosis according to accepted criteria. It seems that both for the patients and for a large proportion of the medical personnel, the perception of the importance and relevance of a test is largely determined by whether or not it is included in the basket of services.

Another issue that probably has a large impact on decision making is the financial difficulty of covering the costs of FRAX and SMA testing. Most of our studied population have a relatively low income. In addition, most of them do not have a complementary health program and are therefore required to pay the full price for SMA and FRAX testing, which is not negligible.

Our prediction was that there will be a lower utilization of genetic tests when the counseling session is held in the community, due to the additional effort required in order to complete the payment for these tests. However, a similar low rate of compliance for these tests was also observed in couples whose session was held in the genetic institute located in the medical center where administrative procedure is simple and easily accessible. Therefore, it seems that technical inconvenience or bureaucratic problems are relatively minor contributors to the final decision. We assume that many individuals who were counseled in the community

clinics and stated that they would complete the payment for the private tests did so to "please" the counselor but did not actually intend to do so.

It is interesting that only 9% of people stated that they were not interested in genetic screening due to cultural or religious beliefs, a rate that was not different between the two locations. These factors are considered important and influential in decision making in this community with regard to other tests performed for prenatal diagnosis that may lead to decisions of pregnancy termination [5-7]. We speculate that despite relatively detailed explanations by genetic counselors, testing for genetic diseases is not perceived in this context.

With regard to the role of communication and the benefit of an Arabic-speaking counselor to explain and deliver information to couples of Arab origin, our data are somewhat controversial. On one hand, we found that both in the community clinics and in the Genetic Institute only a few individuals stated that they were not convinced that genetic testing was important. On the other hand, this was only manifested in the high rates of testing for CF and not in the compliance rates for SMA and FRAX testing. Perhaps if testing for FRAX and SMA were mentioned by the primary caretakers on the same note as testing for CF, more individuals would accept our message and choose to be tested. Of course, among those for whom financial issues are the only factor, this probably would not change their decision.

In conclusion, we found that the compliance for genetic testing for SMA and FRAX, which is costly, was extremely low in the Arab Israeli community, when compared to CF testing, which is available free of charge. We assume that this finding can be attributed largely to the fact that these tests are perceived as private and therefore less important, as well as to the cost of these tests especially for individuals who do not have a complementary health program.

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Capsule

Zoonotic disease pathogens in fish used for pedicure

In a letter to the editor, Verner-Jeffreys et al. raise the question of infectious diseases in fish used for pedicure. "Doctor" fish might not be such good doctors after all. These fish are used for the increasingly popular spa treatment called fish pedicures. During these sessions, spa patrons immerse their feet in water, allowing the live fish to feed on dead skin, mainly for cosmetic reasons. However, examinations of doctor fish destined for these spas found that they can carry harmful bacteria. Thus, although reports of human

infection after fish pedicures are few, there may be some risks. Spa patrons who have underlying medical conditions (such as diabetes, immunosuppression, or even simple breaks in the skin) are already discouraged from undergoing such treatments. However, spas that offer fish pedicures should also consider using only disease-free fish reared in controlled facilities under high standards of husbandry and welfare.

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Eitan Israeli

Capsule

A periciliary brush promotes the lung health by separating the mucus layer from airway epithelia

Mucus clearance is the primary defense mechanism that protects airways from inhaled infectious and toxic agents. In the current gel-on-liquid mucus clearance model, a mucus gel is propelled on top of a "watery" periciliary layer surrounding the cilia. However, this model fails to explain the formation of a distinct mucus layer in health or why mucus clearance fails in disease. Button and colleagues propose a gel-on-brush model in which the periciliary layer is occupied by membrane-

spanning mucins and mucopolysaccharides densely tethered to the airway surface. This brush prevents mucus penetration into the periciliary space and causes mucus to form a distinct layer. The relative osmotic moduli of the mucus and periciliary brush layers explain both the stability of mucus clearance in health and its failure in airway disease.

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Eitan Israeli

Capsule

Cancer stem cells in color

One of the liveliest debates in contemporary cancer research centers on whether cancer stem cells (CSCs) exist and, if so, how these cells are defined phenotypically. CSCs are hypothesized to be a small population of cells within a tumor that are endowed with the unique capacity to drive tumor growth – a scenario that in principle would offer important therapeutic opportunities. By studying mice expressing multicolor reporter genes, Schepers and team were able to

visualize and monitor the fate of a candidate stem cell for intestinal adenomas, an early stage of cancer. This "lineage tracing" analysis suggests that tumor cells expressing the intestinal crypt stem cell marker Lgr5 (leucine-rich repeat containing G protein-coupled receptor 5) are the cells that fuel the growth of intestinal adenomas.

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