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Original Article

The impact of a national population carrier screening program on cystic fibrosis birth rate and age at diagnosis: Implications for newborn screening☆,☆☆

Patrick Stafler [a,b,*,1], Meir Mei-Zahav [1,a,b], Michael Wilschanski [c], Huda Mussaffi [a,b], Ori Efrati [d], Moran Lavie [d], David Shoseyov [c], Malena Cohen-Cymberknoh [c], Michal Gur [e], Lea Bentur [e], Galit Livnat [f], Micha Aviram [g], Soliman Alkrinawi [g], Elie Picard [h], Dario Prais [a], Guy Steuer [a], Ori Inbar [i], Eitan Kerem [c], Hannah Blau [a]

[a] *Kathy and Lee Graub Cystic Fibrosis Center, Schneider Children's Medical Center of Israel, Petach Tikva, Israel*
[b] *Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[c] *Cystic Fibrosis Center, Hadassah-Hebrew University Medical Centre, Jerusalem, Israel*
[d] *Cystic Fibrosis Center, Sheba Medical Center, Tel Aviv, Israel*
[e] *Cystic Fibrosis Center, Rambam Medical Center, Haifa, Israel*
[f] *Cystic Fibrosis Center, Carmel Medical Center, Haifa, Israel*
[g] *Cystic Fibrosis Center, Soroka Medical Center, Beersheva, Israel*
[h] *Cystic Fibrosis Center, Shaare Zedek Medical Center, Jerusalem, Israel*
[i] *Cystic Fibrosis Foundation of Israel, Israel*

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Abstract

Background: Population carrier screening (PCS) has been available in Israel since 1999 and universally subsidized since 2008. We sought to evaluate its impact.
Methods: A retrospective review of governmental databanks, the national CF registry and CF centers.
Results: CF rate per 100,000 live births has decreased from 14.5 in 1990 to 6 in 2011. From 2004–2011 there were 95 CF births: 22 utilized PCS; 68 (72%) had 2 known *CFTR* mutations; 37% were pancreatic sufficient. At diagnosis, age was 6 (0–98) months; 53/95 had respiratory symptoms, 41/95 failure to thrive and 19/95 pseudomonas. Thirty-four (36%) were Arabs and 19 (20%) orthodox Jews, compared to 20% and 8% respectively, in the general population.
Conclusions: PCS markedly reduced CF birth rates with a shift towards milder mutations, but was often avoided for cultural reasons. As children regularly have significant disease at diagnosis, we suggest a balanced approach, utilizing both PCS and newborn screening.

Keywords: Cystic fibrosis; Population carrier screening; Newborn screening

Abbreviations: CF, cystic fibrosis; CFTR, *cystic fibrosis transmembrane conductance regulator*; NBS, newborn screening; PCS, Population carrier screening

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* Corresponding author at: Graub CF Center and Pulmonary Institute, Schneider Children's Medical Center of Israel, 14 Kaplan Street, Petah, Tikva, 49202, Israel. Tel.: +972 39253654; fax: +972 39253308.
E-mail address: pstafler@hotmail.com (P. Stafler).

[1] Shared first authorship.

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1. Introduction

Cystic fibrosis (CF) is the most common life-limiting inherited disease amongst Caucasians [1]. In Israel, disease frequency and mutation distribution vary considerably between different ethnic groups [2]. In Ashkenazi Jews, who constitute the largest sector, testing for only five mutations can identify 97% of *cystic fibrosis transmembrane conductance regulator* (CFTR) alleles [3]. This extraordinarily high detection rate prompted the institution of population carrier screening (PCS) in Israel in 1999. However, the detection rates for non Ashkenazi Jews and Arabs are much lower at 75–91% and 92% respectively [4].

PCS targets a person who does not have the respective disease or a family history for that condition, in order to identify heterozygous carriers for disease mutations. Ideally, carrier screening is performed pre-conception, offering the widest possible range of choices including pre-implantation genetic diagnosis using in-vitro fertilization. However in practice, carrier screening is often performed during pregnancy, leaving only the options of chorionic villus sampling or amniocentesis to diagnose and possibly terminate the pregnancy of an affected fetus.

While initially targeting Ashkenazi Jews in 1999, the Israeli PCS program progressively expanded to include additional ethnic groups and eventually became fully funded for the entire Israeli population through the governmental health plan from 2008.

The PCS program is presented to couples in primary care settings by specialist nurses. Written information is provided via pamphlets and online resources. As far as we know, funding of such a program as a national public health strategy is unique to Israel. Existing PCS programs for CF in North America [5], Australia [6] and Europe [7] offer screening for selected regions or privately insured individuals [8].

PCS has been shown to reduce the proportion of CF live births by 50–75% as demonstrated in studies from the United States, United Kingdom and Italy [9–11]. It has been the impression that carrier screening similarly reduced the birth rate of children with CF in Israel since it commenced in 1999 and that it has shifted the spectrum of disease severity towards a milder phenotype by favoring the birth of children with milder mutations. Indeed, following government subsidization of PCS in 2008, this impression has led to a decision against the implementation of CF newborn screening (NBS) in Israel to date. As the question regarding the need for NBS remains open, we sought to examine the impact of PCS over the last decade on the rate of live births, mutation prevalence and clinical profile of children born with CF in Israel.

2. Methods

Date were collected retrospectively from a number of sources:

National birth rates were collected from the Central Bureau of Statistics of the Israeli government for the period 1990 till 2011, beginning with the discovery of the *CFTR* gene and a decade before the onset of population carrier screening. Data regarding annual CF births were collected from the 6 recognized Israeli CF centers over this period.

Israel CF patient registry data was only available since 2004. Thus, demographic and clinical data regarding children born with CF between January 2004 and December 2011 were accessed from the CF registry and corroborated directly with the 6 CF centers up until May 2013, allowing 17 months for the most recently born patients to manifest clinically and be diagnosed.

De-identified data from the PCS program were collected from the Israeli Ministry of Health from when it was available, in 2004. This included the annual number of participants in the PCS program (known since 2008), the number of couples with 2 PCS panel *CFTR* alleles who opted for invasive fetal CF diagnosis during pregnancy and the number of terminations. It should be noted that the second partner was screened only if the first partner screened positive. During the study period, the mutation panel consisted of 14 mutations for the Jewish population, supplemented with 3 additional mutations for Arab participants (Table 1).

Consensus criteria for CF diagnosis were adhered to [1]. Regarding children with CF, date of diagnosis was that of a positive sweat test. When sweat chloride was unavailable or was normal in the presence of other criteria satisfying the diagnosis of CF, the date of communicating the diagnosis to the parents was used. For individuals unequivocally diagnosed during pregnancy, the date of birth served as date of diagnosis.

We classified religious orientation as Arab, Jewish orthodox, Jewish non-orthodox or other, aiming to assess whether ethnic differences or the more stringent interpretation of religious law by orthodox Jews led to reduced PCS uptake. It should be noted that a subgroup of ultraorthodox Ashkenazi Jews test carrier status for CF and other genetic conditions in all secondary school children, in preparation for use by match makers for obligate arranged marriages [12]. Within this

Table 1
CFTR mutation panel for carrier screening.

Mutation
DF508
G542X
W1282X
N1303K
3849 + 10kbC- > T
D1152H
405 + 1G→A
G85E
S549R
W1089X
1717 + 1G→A
I1234V[a]
Y1092X[b]
3121-1G > A[b]
3120 + 1kbdel8.6 kb[c]
2183AA > G[c]
4010delTATT[c]

The first 14 mutations served as the panel used for Jewish population carrier screening program during the study period. Three additional mutations are added for Arab participants (*in italics*).

[a] Mutation in Jews of Yemenite origin.
[b] Mutations in Jews of Iraqi origin
[c] Mutations in Arabs.