Barriers to newborn screening for CF: Israel

ECFS Neonatal Screening Working Group
Annual meeting, Seville, 2017

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CF Newborn Screening globally

- NBS for CF has a positive effect on short and long-term clinical outcomes
- It is a cost effective public health strategy
- New emerging therapies for CF that correct the underlyging genetic defect highlight the importance of early diagnosis through NBS
- A bio-ethical model that incorporates cost-effectiveness should be used to establish best practicel

Newborn Screening for Cystic Fibrosis. A Review
Castellani C et al. Lancet Respir Med, 2016

So, why is there no CF NBS in Israel in 2017?

SUBMITTED ANNUALLY TO THE "HEALTH BASKET FOR NEW TECHNOLOGIES" SINCE 2013

EFFORTS HAVE INCLUDED MUCH EXPLANATION, LOBBYING OF ALL PARTIES (CF TEAMS, CF FOUNDATION , HEALTH MINISTRY, NATIONAL NBS PROGRAM (AN ADVANCED SERVICE), NATIONAL GENETICISTS, PUBLIC

(INCLUDING PROF. PHIL FARRELL MEETING WITH THE DIRECTOR OF THE HEALTH MINISTRY!)

Challenges to Instituting NBS in Israel:

The advanced Prenatal genetic carrier screening (PCS) program

Funding competes with all new treatments and services each year in the "National Health Basket New therapies and technologies"

DNA testing requires informed consent of both parents, by law

Population Carrier Screening (PCS) can impact performance of NBS

- May reduce CF births by 50-75% (shown in areas of UK, Italy) and decrease utility of NBS

- Shift the spectrum of disease severity, by favoring birth of children with milder mutations

Population carrier screening (PCS) for CF in Israel

- In Ashkenazi Jews, the largest sector, 5 mutations identify 97% CFTR alleles
- This extraordinarily high detection rate prompted population carrier screening (PCS) since 1999
- Since 2008, fully subsidized program for common genetic disease. All ethnic groups
- Couples informed in primary care setting. Supportive written and on-line brochures

CFTR MUTATION PANEL FOR PCS

Wide ethnic diversity of mutations

PCS panel increased (22 mutations today)

Despite this, up to 30% "unknown" mutations in CF population tested with this panel

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.

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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☆,☆☆

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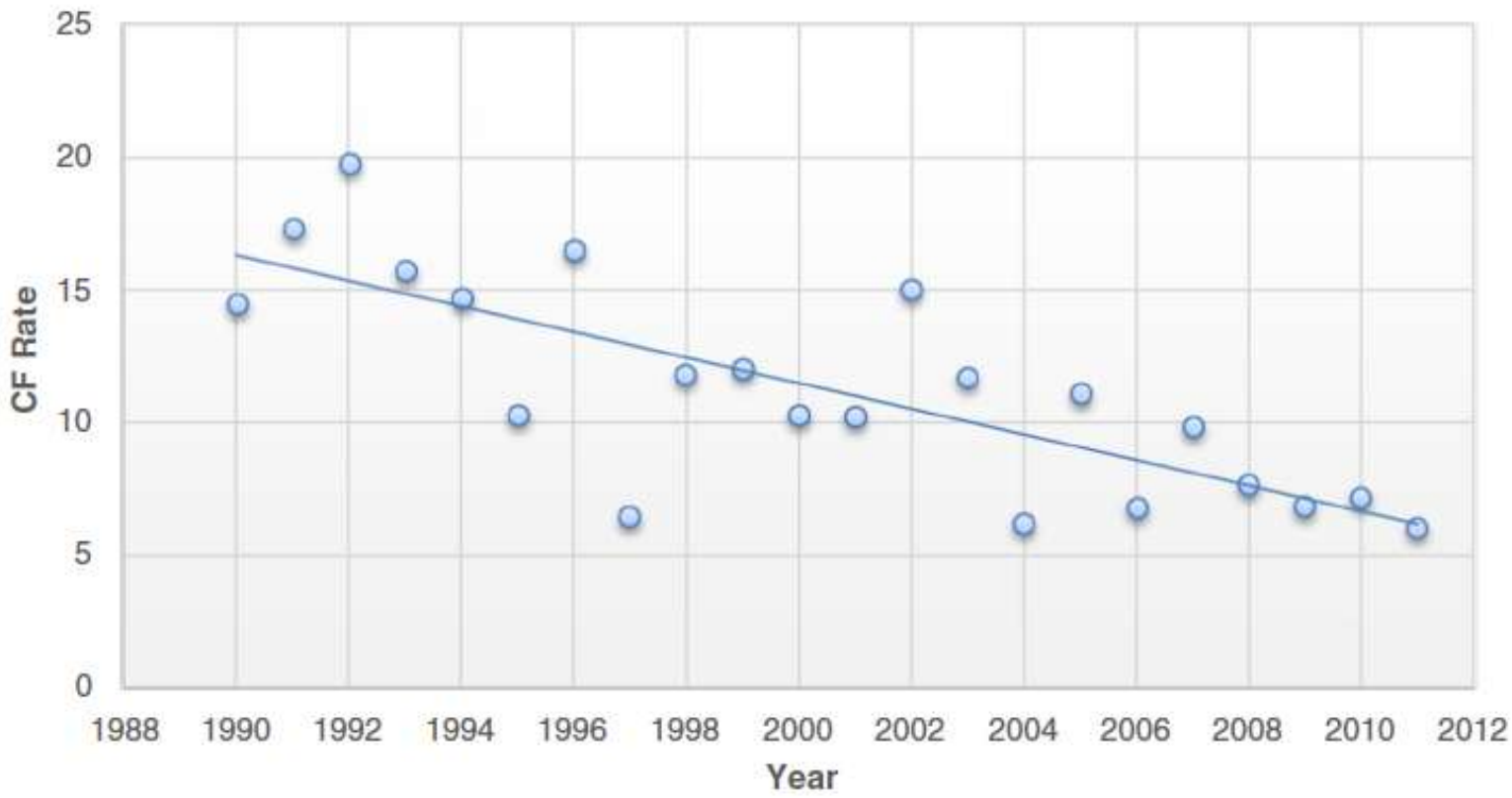

Fig. 1. Annual Rate of CF per 100,000 live births, 1990–2011. The figure shows the CF rate per 100,000 live births from the years 1990 to 2011 ($y = 977.1 — 0.48x$; $R^2 = 0.6$). Data according to National Bureau of Statistics and Ministry of Health.

Stafler P, et al
J Cyst Fibr 2016

Ethnic groups in children born with CF compared to general population 2004-2011

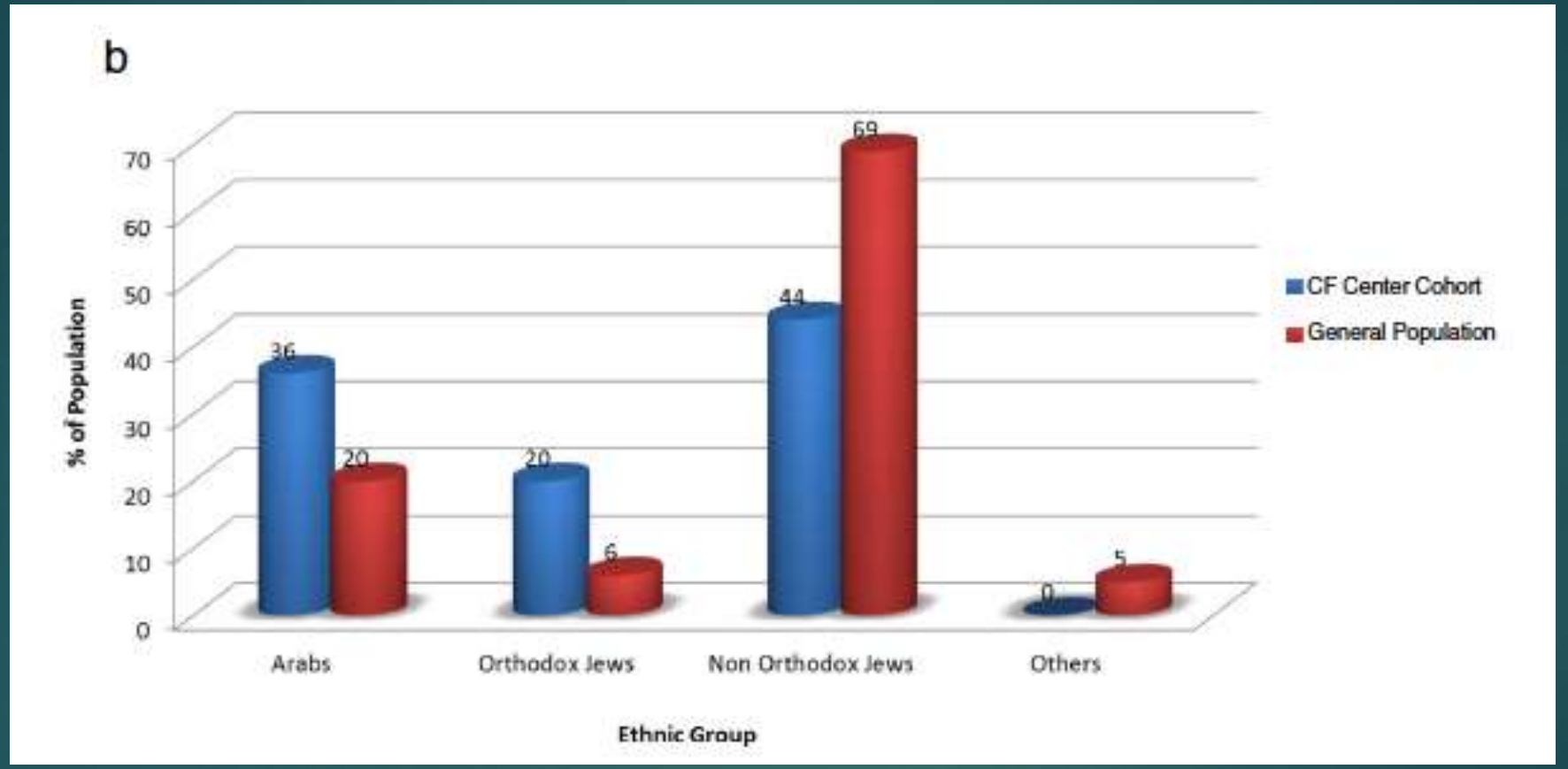

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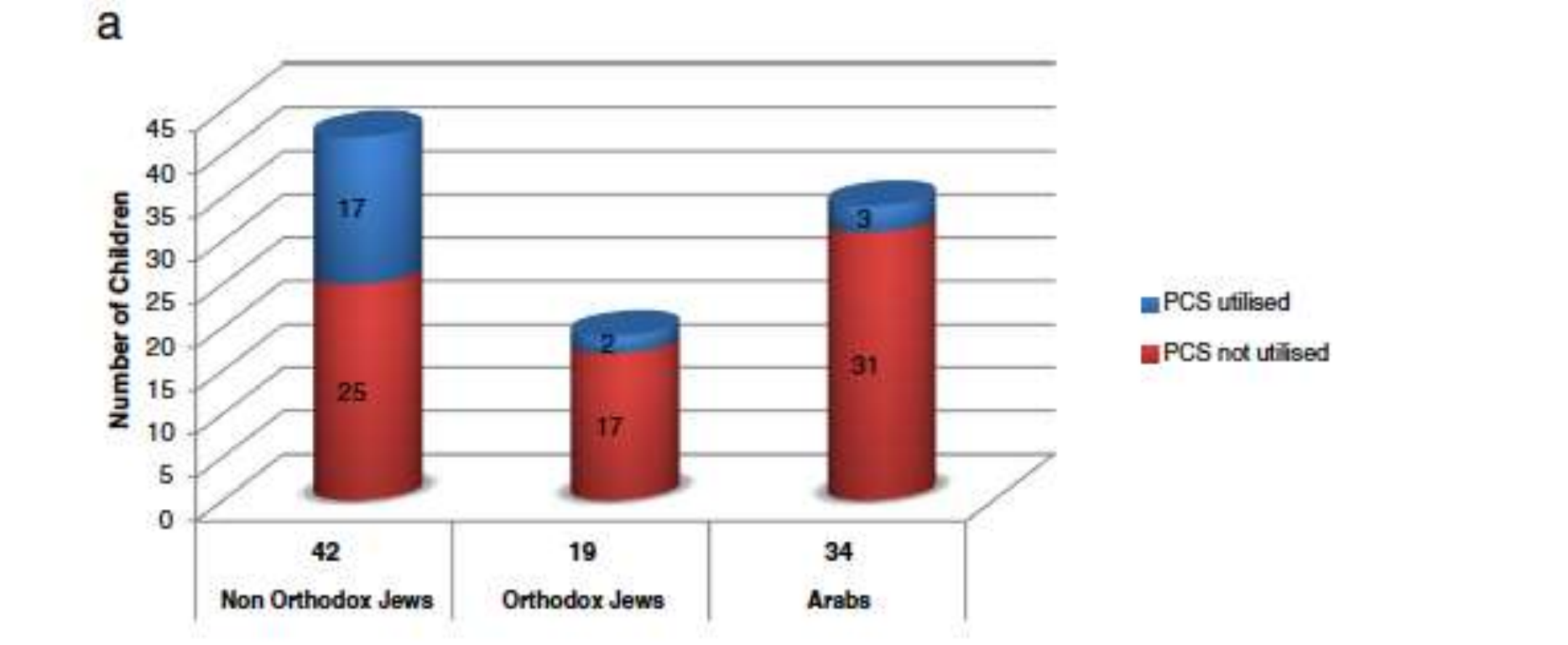
Fig. 2. a: Population carrier screening uptake in CF families from different ethnic/religious groups. The figure compares the population carrier screening uptake in families of children born with CF from different ethnic/religious groups. Patient data was collected from the 6 Israeli CF centers. b: Ethnic/religious make up of children born with CF compared to the general population, from 2004–2011. The figure compares the ethnic/religious make up of children born with CF from 2004–2011, to the general Israeli population as reported by the Israel Central Bureau of Statistics [14].

CF PCS utilization by ethnic group, 2004-2011



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Clinical features at diagnosis of CF, Israel 2004-2011

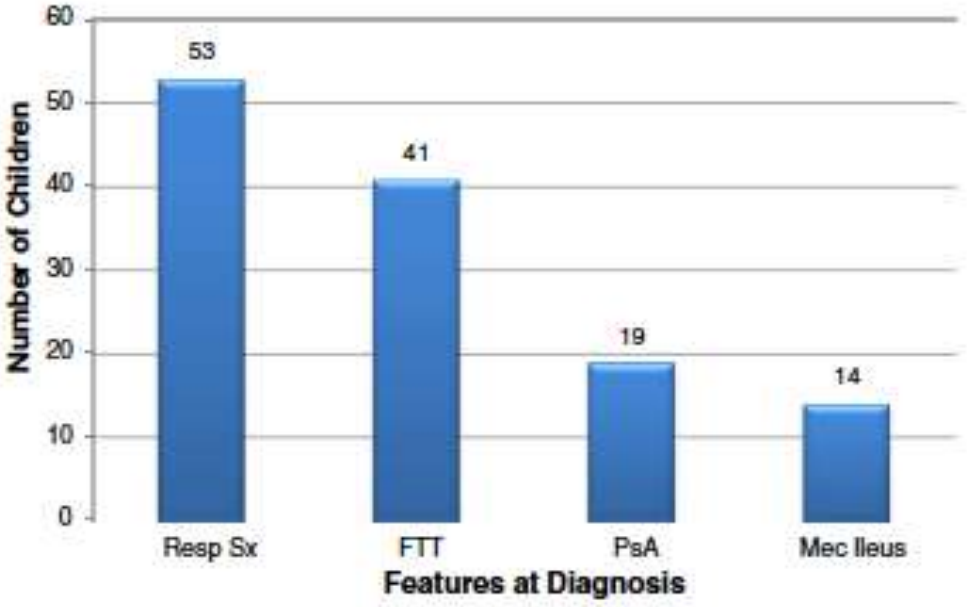

Fig. 3. Clinical features at diagnosis for Israeli children born with CF (n = 95). Data for 95 children born with CF in Israel, 2004–2011. When more than one feature was present at diagnosis, all were noted. PsA = *Pseudomonas aeruginosa*; Resp Sx = respiratory symptoms; FTT = failure to thrive; Mec Ileus = Meconium ileus.

This contrasts with countries where diagnosis is by NBS, usually prior to symptoms

Stafler P, et al
J Cyst Fibr 2016

Problems regarding PCS program in Israel

Rarer mutations not in PCS panel, lead to ‘false negative’

- 30% of the Israeli CF population
- Some choose not to utilize

Some choose not to utilize PCS

- Orthodox religious jews
- arabs

- Milder mutations not included but could cause significant disease

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www.elsevier.com/locate/jcf

Editorial

Newborn screening and population carrier screening for cystic fibrosis: Two ends of the same rope

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Department of Paediatrics, University of Melbourne, Australia

CF NBS will always be indicated:

- PCS will never detect all affected pregnancies

- Some parents will make the choice not to undergo PCS

Latest Israeli CF Data Registry Data: No. CF births

Year of Birth	Data Registry Year		
	2015	2014	2013
2015	3		
2014	7	2	
2013	5	5	4
2012	13	11	8
2011	14	13	10
2010	17	17	16
2009	17	17	17
2008	17	17	15

Israel CF data registry: Features of children born 2011-2015,

- 42 children
- 27 (64%) taking pancreatic enzymes
- 21 (50%) with 2 known severe mutations
- 11 (26%) with at least one unknown mutation
- 7 with at least one D1152H mutation
  - (no longer in prenatal screening panel)
- 6 meconium ileus
- 14 with chronic *Staphylococcus aureus* infection
- 4 with chronic *Pseudomonas aeruginosa* infection

Schneider Children's CF Center. Children born 2011-2017, n=24

	Pancreatic insufficient	Pancreatic sufficient
n	12	12
Diagnosed by:		
PCS	1	5
other prenatal	2	
sibling		2
resp	2	3
resp +FTT	5	
hypochloremic dehydration	1	2
anemia + edema	1	
age diagnosis, if postnatal mths, median (range)	4.5 (1-49)	19 (10-49)

2 meconium ileus, diagnosed late
4 nearly died,
PICU: 1 RSV, 3 dehydration

Nationwide genetic analysis for molecularly unresolved CF patients in a multiethnic society: implications for preconception and carrier screening.

Behar DM et al. Molecular Genetics and Genomic Medicine, 2017

176 (of 650 total) :

- Sanger sequencing for all exons and splice sites
- If negative: Multiplex ligation probe amplification (MLPA) and
- NGS of the poly –T/TG tracts

- 54 mutations identified (in 78 patients) -
  - 16 overlapped with PCS panel
  - 29 further mutations CF – causing , in CFTR2
  - 4 novel mutations
  - Prenatal diagnosis of 24/78 (30.8%) could been reached
    - if all CFTR2 mutations are included in the Israeli PCS panel

Conclusions

Our data reveal an overwhelming hidden abundance of *CFTR* gene mutations suggesting that expanded preconception carrier screening might achieve higher preconception detection rates.

Could improvements in PCS program eventually preclude need for NBS?

Population carrier screening has an important role:

- Making carrier couples aware of their reproductive risk
- Informing them of possible options:
- PGD with IVF, CVS or amniocentesis and termination of pregnancy, or continuing a pregnancy and early CF care

BUT infants born with CF without PCS diagnosis are disadvantaged

parents not performing PCS

With false negative PCS

(rare mutations, mild mutations not in the panel)

Without NBS these will have a delayed diagnosis

These two strategies are complementary rather than mutually exclusive

ECFS Standards of Care: Best Practice Guidelines Smyth AR et al J Cyst Fibros 2014

- Suggest a careful evaluation of the validity of NBS when the cystic fibrosis incidence is less than 1 in 7000
- The incidence decline connected with carrier screening might generate an unfavourable ratio between CF cases and unwanted effects, such as false positives and inconclusive diagnoses

- In Israel today:
  - Incidence of CF < 1:20,000
  - Of those born since 2011, 40% have pancreatic sufficient CF

- Still, the question of the need for NBS in Israel remains open
- Annual cost estimated at 1.5 million euro/y
- Has been resubmitted this year, again, for inclusion in funding of the 2018 'National health basket'.

- We hope for a balanced, public health strategy combining population/prenatal CF screening with IRT/IRT screening of newborns, followed by sweat test and DNA for those found positive

muchas gracias

In Israel:
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THANK YOU!!

תודה רבה!!