8vo Congreso argentino
de neumonologia
Buenos Aires 2018

Hospital de Pediatria
"J. P. Garrahan"

PESQUISA NEONATAL: FALSOS POSITIVOS Y NEGATIVOS. ¿CÓMO SEGUIR CON LOS RESULTADOS?

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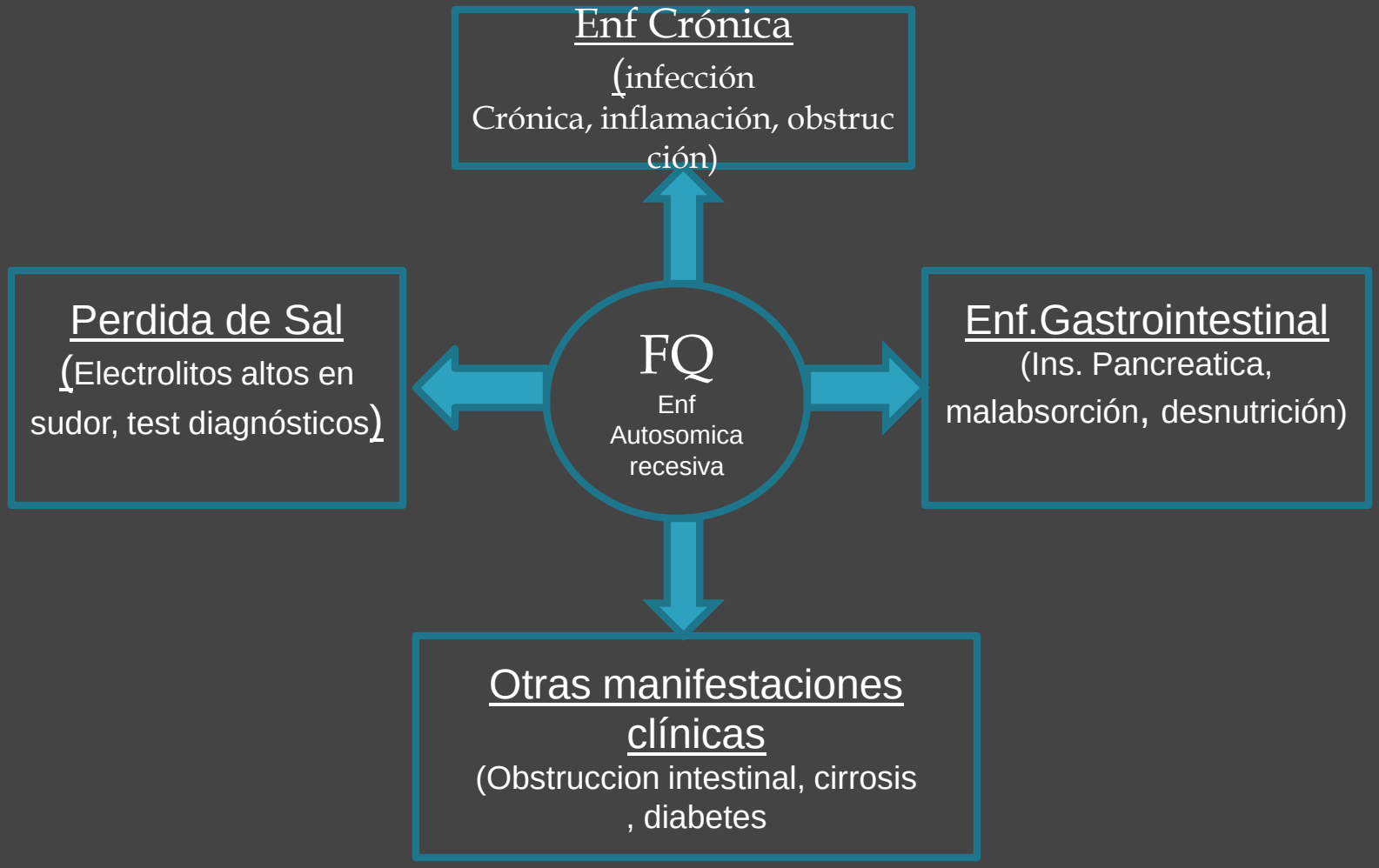
CONFLICTO DE INTERESES PARA DECLARAR

- Ninguno

Objetivos

- Objetivos de la pesquisa neonatal en FQ
- Mostrar los diferentes métodos de pesquiza y como interpretar los resultados
- Revisar las ventajas y las desventajas de los diferentes métodos de pesquiza
- Resultados falsos positivos y negativos
- Seguimiento de los pacientes pesquizados en los centros de FQ. Intervención temprana para obtener mejores resultados.


Enf Crónica
(infección
Crónica, inflamación, obstruc
ción)
Perdida de Sal
(Electrolitos altos en
sudor, test diagnósticos)
FQ
Enf
Autosomica
recesiva
Enf.Gastrointestinal
(Ins. Pancreatica,
malabsorción, desnutrición)
Otras manifestaciones
clínicas
(Obstruccion intestinal, cirrosis
, diabetes

“Pesquisa neonatal” Para que sirve

- *La Pesquisa Neonatal son programas de salud publica creados para detectar en recién nacidos una serie de enfermedades tratables pero sin evidencia clínica de la misma al momento del nacimiento.*
- *Algunas de las enfermedades incluidas en los programas de pesquisa serían solamente detectadas después que ya se han producido daños irreversibles siendo incluso en algunos casos la muerte súbita la primera manifestación de la enfermedad.*

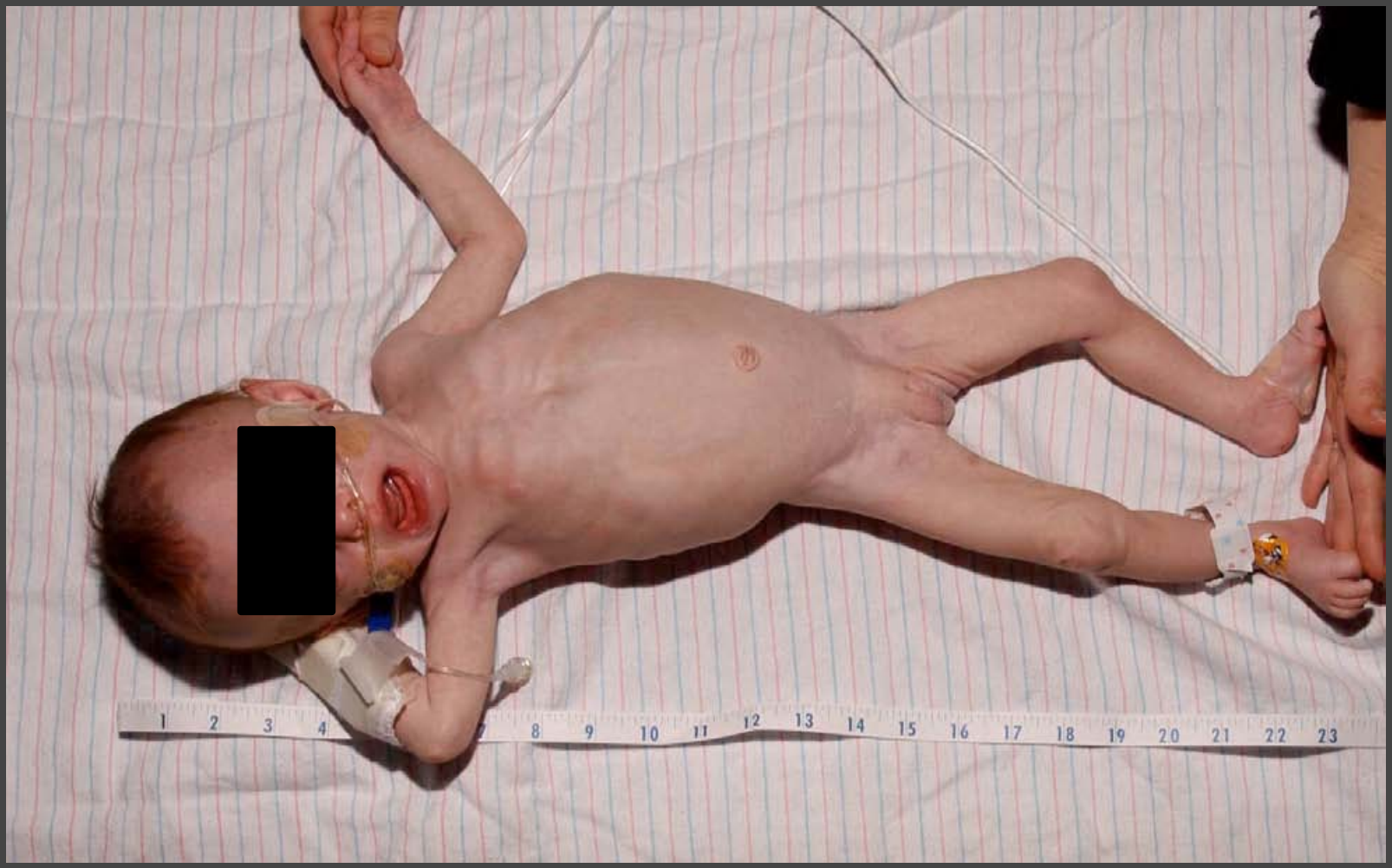
Programas de Pesquisa neonatal

- Los programas de pesquisa neonatal fueron creados con el objetivo de prevenir la detección tardía de la enfermedad.
- La Pesquisa consiste en la realización de test, exámenes y procedimientos que puedan ser aplicados rápidamente.
- Trata de separar aquellos individuos que pueden estar enfermos o en riesgo de padecer una determinada enfermedad de aquellos que no lo están .

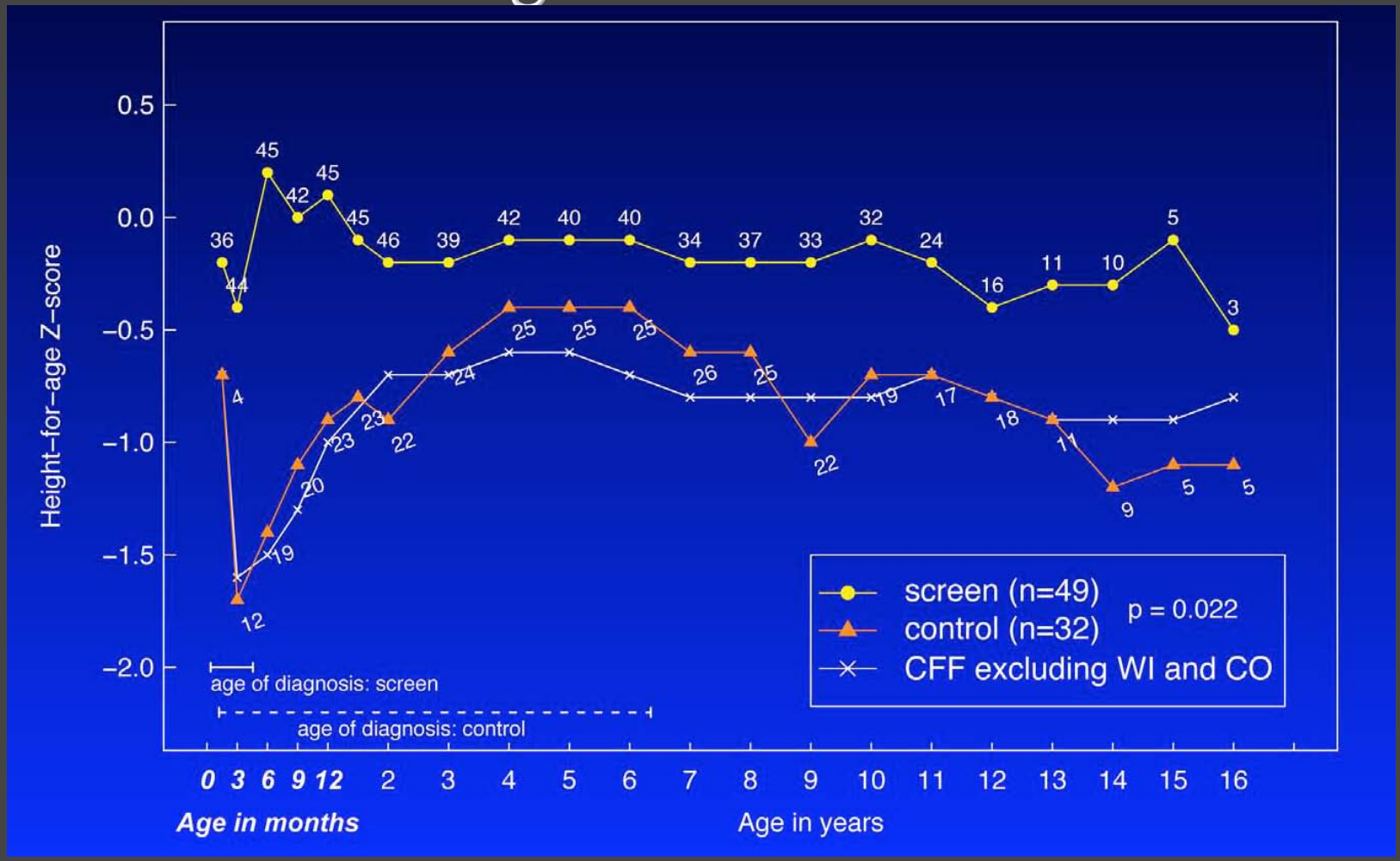
PROBLEMAS ASOCIADOS A UN DIAGNÓSTICO TARDIO EN FQ

- Muertes potencialmente prevenibles
- Desnutrición severa con trstornos hidroelectrolítica
- Complicaciones pulmonares
- Ansiedad familiar
- Retraso en el consejo genetico

Malnutrición severa

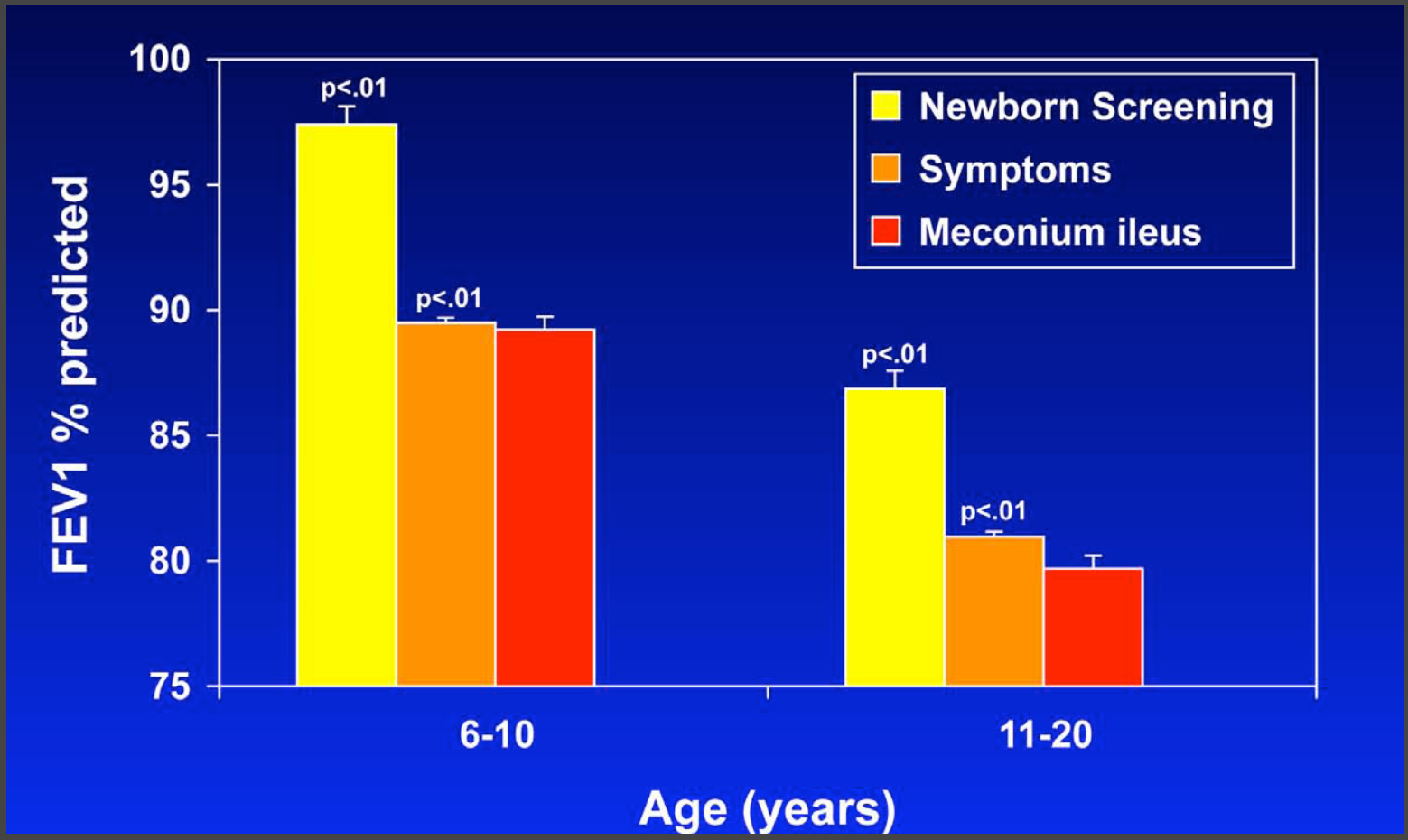


Pesquisa neonatal en Winsconsin RCT crecimiento de pacientes con pesquisa o con diagnostico tradicional.



Farrell y col, J Pediatrics 2005; 147.S30-36

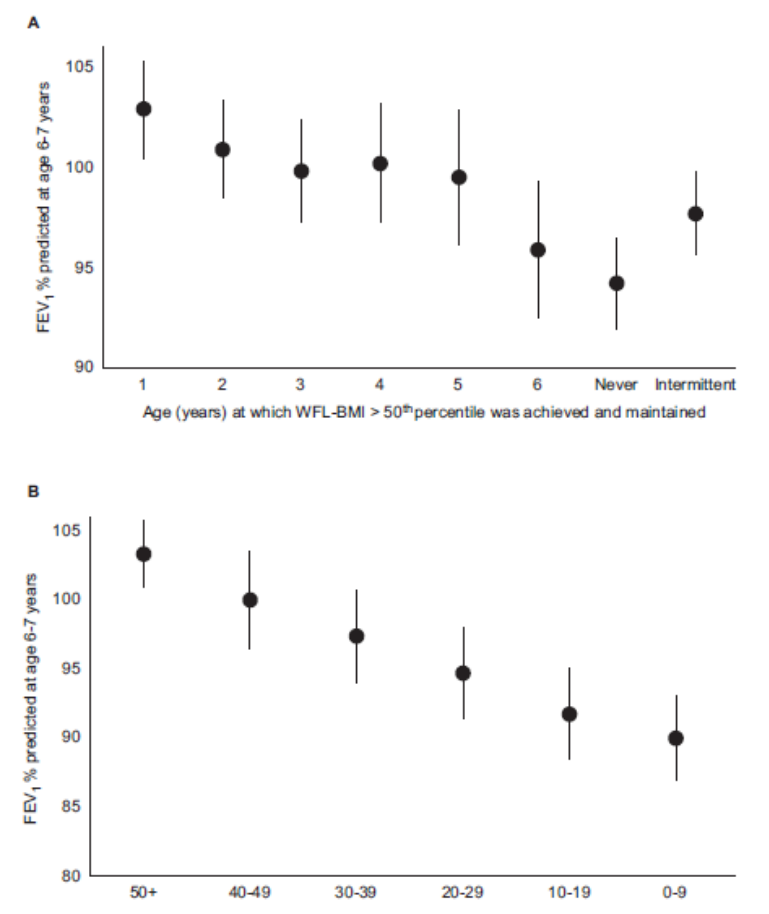
Funcion pulmonar de los niños con FQ diagnosticados por diferentes metodos según el registro americano de FQ 2002



Accurso y col J . Pediatrics 2005

Early Life Growth Trajectories in Cystic Fibrosis are Associated with Pulmonary Function at Age 6 Years

Don B. Sanders, MD, MS[1], Aliza Fink, DSc[2], Nicole Mayer-Hamblett, PhD[3,4], Michael S. Schechter, MD, MPH[5], Gregory S. Sawicki, MD, MPH[6], Margaret Rosenfeld, MD, MPH[4], Patrick A. Flume, MD[7], and Wayne J. Morgan, MD[8]

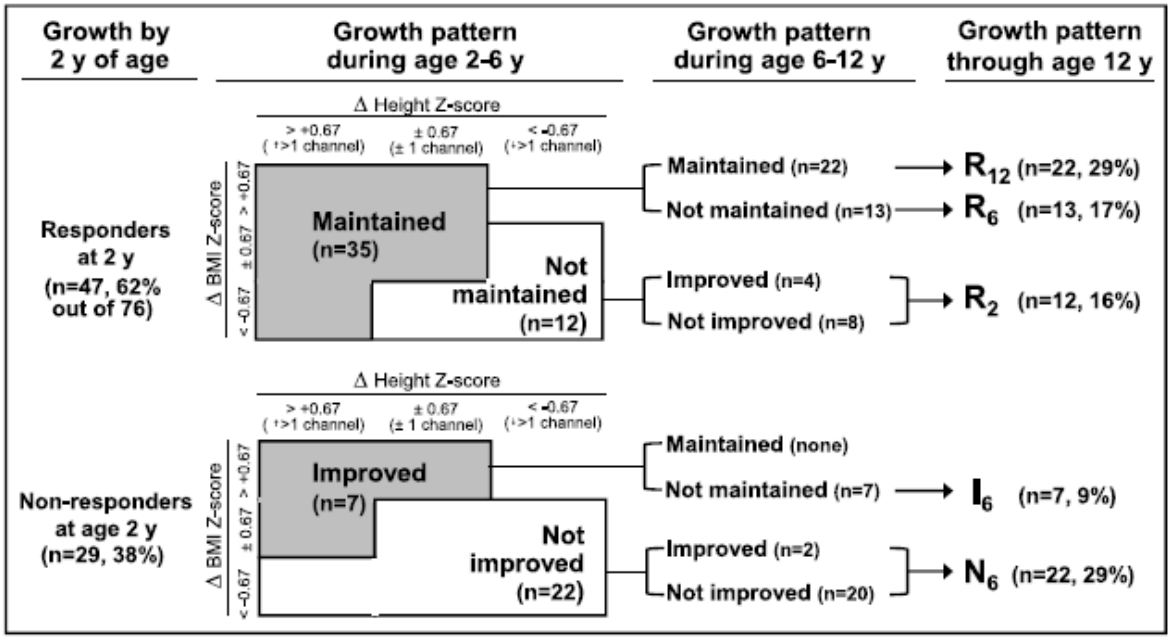


Conclusión: entre pacientes cambios del estado nutricional en los primeros 6 años de vida estan asociados con el VEF1 a los 6-7 años.
Hay una clara relación entre intervenciones nutricionales tempranas y la función pulmonar.

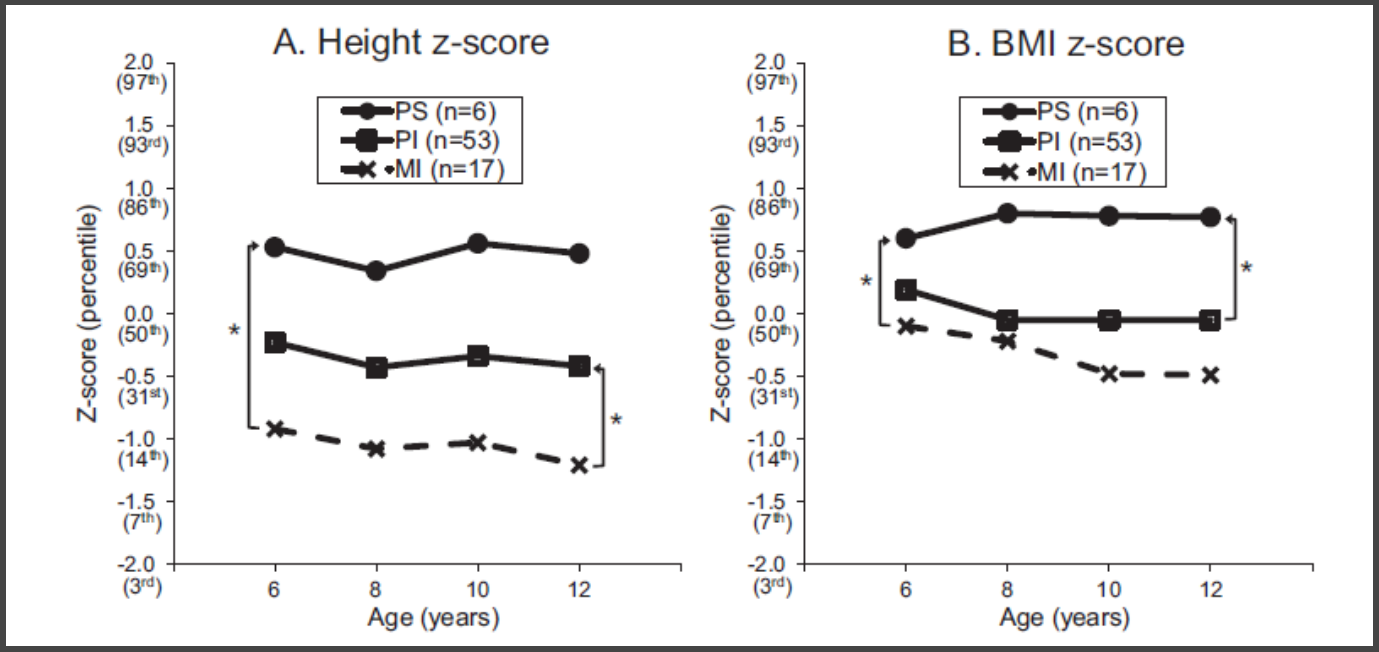
J. Pediatrics 2015;167:1081-8

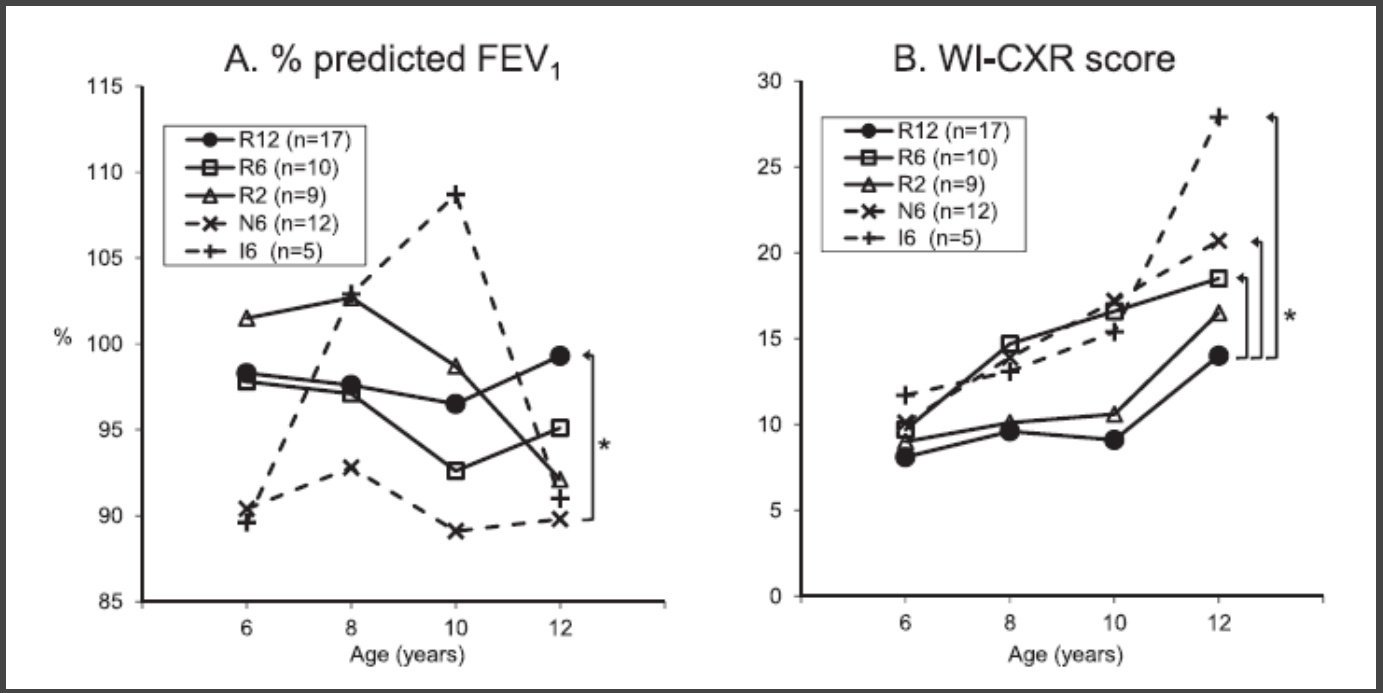
Early life growth patterns persist for 12 years and impact pulmonary outcomes in cystic fibrosis☆,☆☆,★

Don B. Sanders [a,1], Zhumin Zhang [b], Philip M. Farrell [c,d], HuiChuan J. Lai [b,c,d,*], on behalf of the Wisconsin CF Neonatal Screening Group



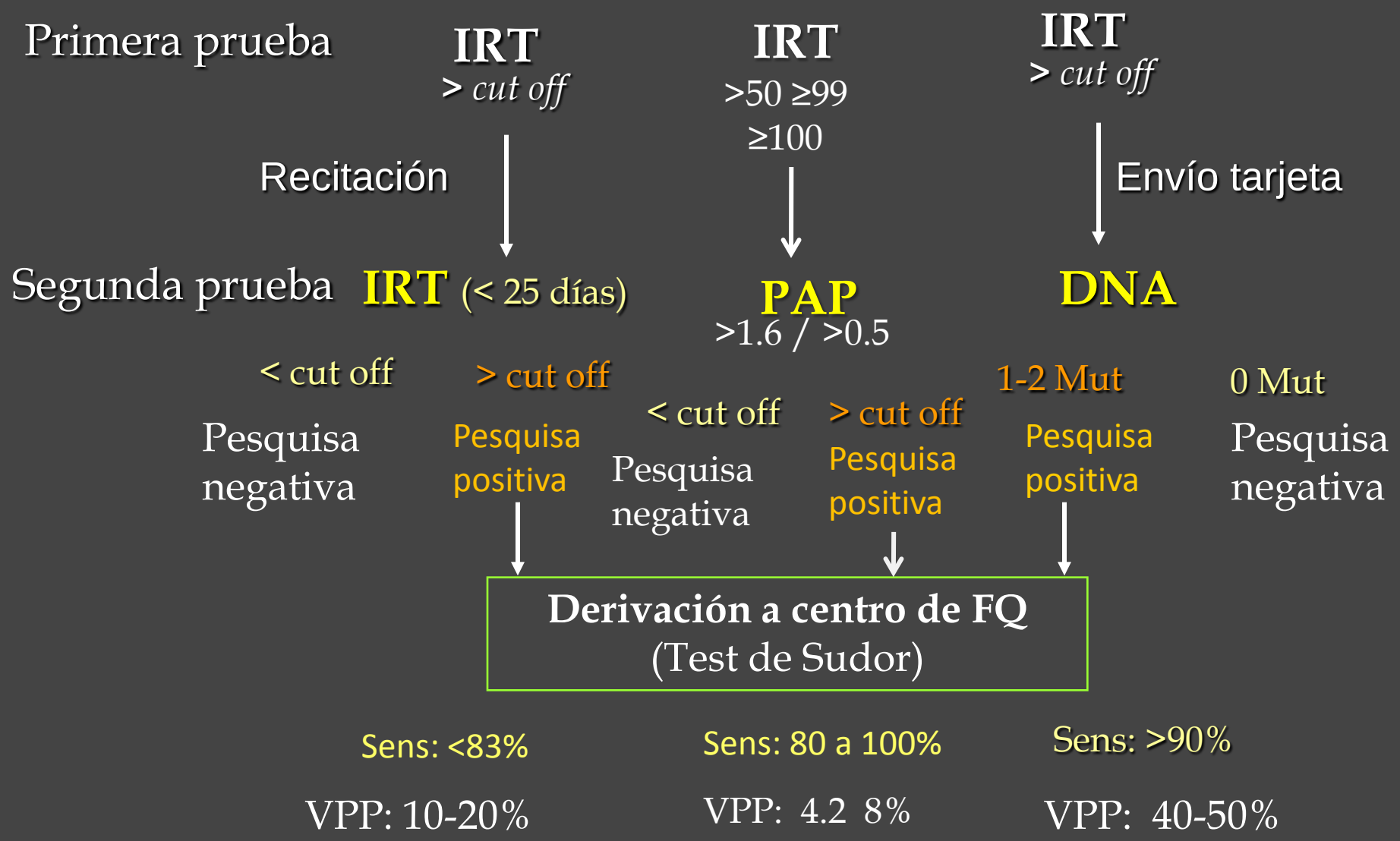
Sandres,D y col . J of CF 2018 in press





Sandres,D y col . J of CF 2018 in press

Estrategias para la pesquisa de Fibrosis Quística



Pesquisa Neonatal

	TIR/TIR	TIR/ADN	TIR/PAP
Sensibilidad	< 83%	> 90% población / mutaciones analizadas	80 a 100%
VPP	10 a 20%	40 a 50%	4 a 8 %
Ventajas		Alto VPP No requiere recitación	No requiere recitación
Desventajas	Alta tasa de recitación	Detecta portadores sanos y mutaciones que pueden no tener significado clinico Costo	

Original Article

Neonatal screening for cystic fibrosis: Comparing the performances of IRT/DNA and IRT/PAP☆

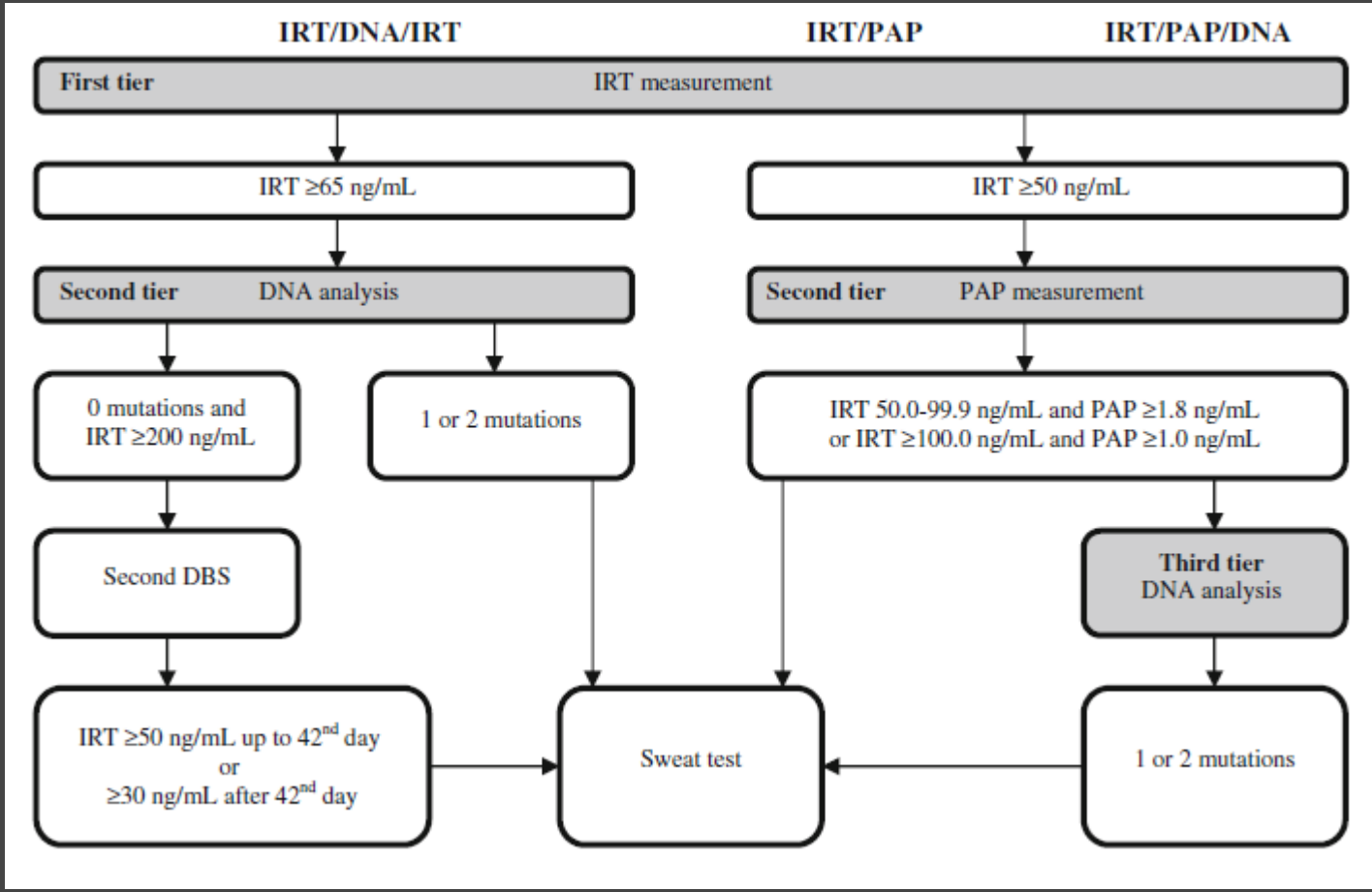
Jacques Sarles [f,i,*], Roch Giorgi [a,b], Patrice Berthézène [c,d], Anne Munck [f,g], David Cheillan [f,h], Jean-Charles Dagorn [c,d], Michel Roussey [e,f]

IRT >50 and mean PAP >	IRT>100 and mean PAP >	Detection rate* (%)	Sweat tests n	% Suspects	TP				FP	FN			
					n	Classical forms**	AF§	MI$		n	Classical forms**	AF	MI
1.2	0.6	86.7	1706	0.308	84	70	6	8	1622	11	4	6	1
1.3	0.6	86.7	1502	0.271	84	70	6	8	1418	11	4	6	1
1.4	0.6	86.7	1344	0.243	84	70	6	8	1260	11	4	6	1
1.5	0.6	84.9	1210	0.219	83	69	6	8	1127	12	5	6	1
1.6	0.6	84.9	1111	0.201	83	69	6	8	1028	12	5	6	1
1.7	0.6	84.9	1021	0.184	82	69	5	8	939	13	5	7	1
1.8	0.6	84.9	951	0.172	82	69	5	8	869	13	5	7	1
1.9	0.6	84.9	904	0.163	82	69	5	8	822	13	5	7	1
2.0	0.6	83.2	845	0.152	81	68	5	8	764	14	6	7	1

	IRT d3	Ctrl IRT	PAP	Cl^-	Mut 1	Mut 2
1	66	68	0.4	80	ΔF508del	ΔF508del
2	87.8	106.5	0.5	137	E1104X	E1104X
3	93.2	105.8	0.8	82	G91R	ΔF508del
4	71.1	56.7	0.3	80.0	ΔF508del	ΔF508del
5	67.9	54.4	1.5	99.0	ΔF508del	ΔF508del
6	87.1	82.9	4.5	70.0	E1104X	D110H
7	61.5	62	5.0	88.0	R553X	A455E
8	62.4	63.0	14.6	110.0	2183AA>G	907delCins11
9	117.0	81.5	15.6	130.0	S466X	S466X

Sarles y col JCF 2014

Prospective and parallel assessments of cystic fibrosis newborn screening protocols in the Czech Republic: IRT/DNA/IRT versus IRT/PAP and IRT/PAP/DNA



	IRT/DNA[a]/IRT	IRT/PAP	IRT/PAP/DNA[a]
Newborns screened (*N*)	106,522	106,522	106,522
IRT positives (*N*; %)	1,158 (1.09)	3,155 (2.96)	3,155 (2.96)
PAP positives (*N*; %)	–	260 (0.24)	260 (0.24)
Median age (range) at the availability of DNA-testing[a] results (days)	36 (9–222[b])	–	36 (9–222[b])
1 and/or 2 CF mutations detected (*N*; %)	76 (0.07)	–	27 (0.03)
Recalled newborns for repeated IRT examination (*N*; %)	47 (0.04)	–	–
Positive CF NBS (*N*; %)	123 (0.12)	260 (0.24)	27 (0.03)
Positive IRT in newborns recalled for repeated examination (*N*)	1	–	–
ST indicated (*N*; %)	77 (0.07)	260 (0.24)	27 (0.03)
ST carried out (*N*; % of indicated ST)	72[c] (93.51)	204[c] (78.46)	24[c] (88.89)
CF carriers (*N*)	55	–	12
Prevalence of CF carriers	1 in 21	–	1 in 22
Diagnosed CF patients (*N*)	19	16	15
False positives based on performed ST (*N*; % of all cases screened)	99[d] (0.09)	188 (0.18)	9 (0.01)
Newborns with equivocal diagnosis [F508del/R117H-IVS-8 T(7) and ST<30 mmol/L; *N*]	2	–	0
False negatives (*N*)	2	5	6
Total of CF patients detected (*N*)	21[c]		
Median age (range) at diagnosis (days)	36 (9–57)[e]		
CF prevalence	1 in 5,072[e]		
Sensitivity (TP/TP+FN)	0.9048	0.7619	0.7142
Specificity (TN/TN+FP)	0.9991	0.9982	0.9999
PPV (TP/TP+FP)	0.1610	0.0784	0.625

NO HAY NINGUN SISTEMA DE PESQUISA PARA FQ QUE SEA PERFECTO

- Ninguno de los sístemas actuales de pesquisa es ideal y detecta todos los casos de FQ, pudiendo haber falsos negativos
Pediatrics 2009
- Hay una variedad de algoritmos de pesquisa alrededor del mundo, en Europa en el 2016 habia 16, en 16 países. A causa de que no existe un programa perfecto.
Archdischild 2017
- Los pediatras deben saber que la pesquisa no es un test diagnóstico y como toda pesquisa pierde pacientes por lo cual se debe mantener un alto indice de sospecha.
Pediatr Pulmonol 2011

Pacientes con Pesquisa negativa

DIAGNOSTICO DE FIBROSIS QUÍSTICA EN PACIENTES CON PESQUISA NEONATAL NORMAL.

OBJETIVOS: Alertar sobre probabilidad diagnóstica de FQ en pacientes con el antecedente de pesquisa neonatal normal.

RESULTADOS:
De 169 pacientes con diagnóstico de fibrosis quística, en seguimiento en el Hospital Garrahan, 89 pacientes fueron incluidos en el estudio, 80 pacientes no lo fueron por no presentar pesquisa neonatal al nacimiento o por presentar diagnóstico de FQ fuera del periodo de estudio. Las edades al diagnóstico fueron de entre 4 y 21 meses.De los 89 pacientes incluidos, 78 (87,6%) presentaron pesquisa positiva y 11 (12,4%)negativa

Congreso argentino de Neumonologia 2018
(trabajo 83)

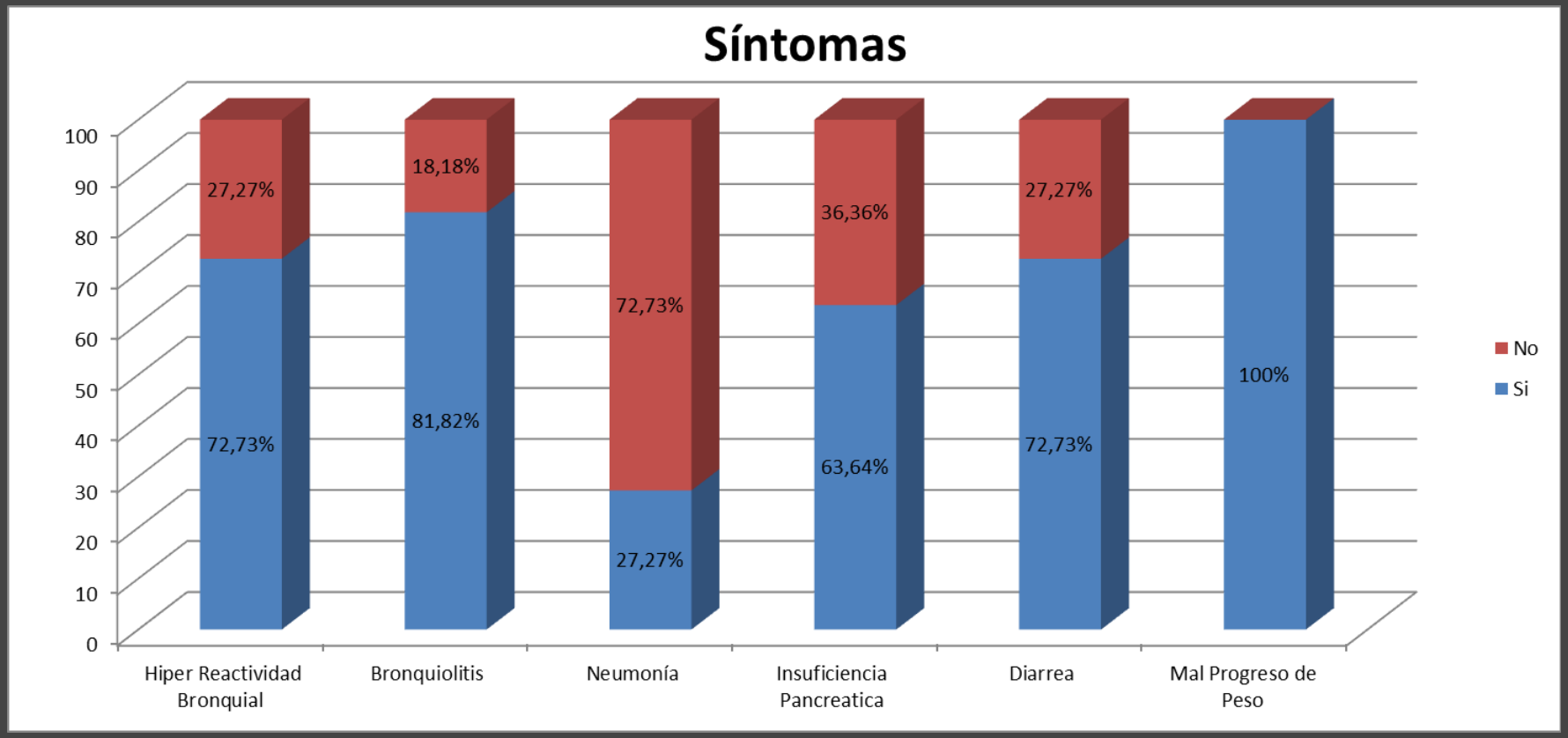
Pesquisa negativa en pacientes con FQ

DIAGNOSTICO DE FIBROSIS QUÍSTICA EN PACIENTES CON PESQUISA NEONATAL NORMAL.

Paciente	Sexo	Edad Dx	Diagnóstico		Síntomas					Insuf. Pancreatica	Cultivo de Secreciones		
			Test del Sudor	Molecular	HRB	BQL	NMN	MPP	Di		SAM	PA	BC
1	F	4 Meses	X2	-	No	Si	No	Si	Si	No	Si	No	No
2	F	8 Meses	X2	DF508/R334W	Si	Si	Si	Si	No	No	No	No	No
3	F	9 Meses	X2	DF508/ -	No	No	No	Si	No	No	No	No	No
4	F	6 Meses	X2	DF508/DF508	Si	Si	No	Si	No	Si	Si	No	No
5	M	3 Meses	X2	R117H/R117H	No	No	No	Si	Si	No	No	No	Si
6	M	4 Meses	X1/3 Dudosos	DF508/ -	Si	Si	No	Si	Si	No	Si	Si	No
7	F	11 Meses	X2	DF508/-	Si	Si	Si	Si	No	Si	Si	Si	No
8	M	10 meses	X2	DF508/DF508	SI	Si	No	Si	Si	Si	Si	Si	No
9	F	7 meses	X2	DF508/DF508	Si	Si	No	Si	Si	Si	Si	Si	Si
10	M	6 Meses	X2	DF508/R553X	Si	Si	No	Si	Si	Si	Si	Si	No
11	F	21 Meses	X2	DF508/-	Si	Si	Si	Si	Si	Si	No	Si	No

Trabajo N 83

Síntomas que presentaron al diagnóstico



Factors Accounting for a Missed Diagnosis of Cystic Fibrosis After Newborn Screening

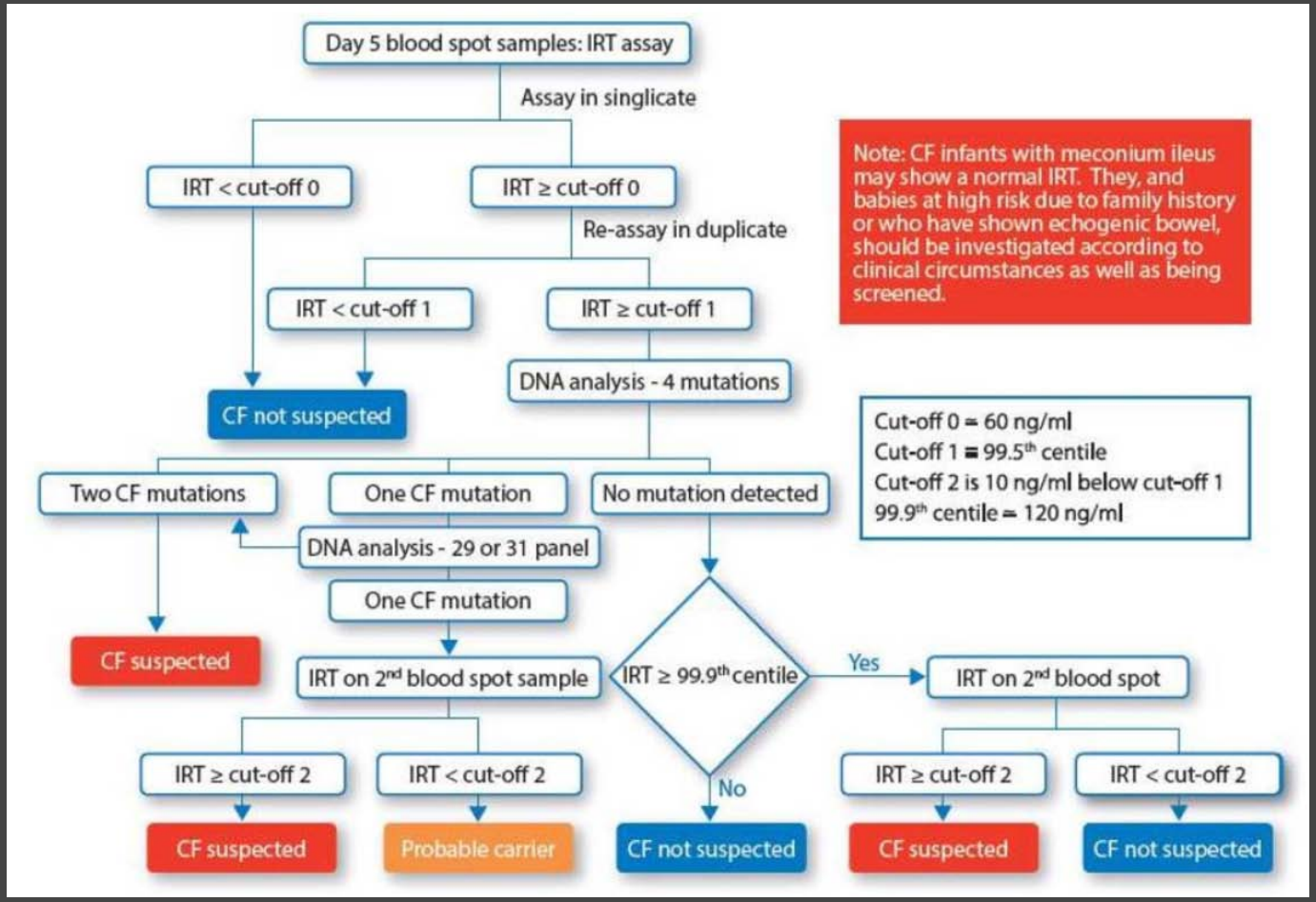
Michael J. Rock, MD[1,*], Hara Levy, MD[2], Christina Zaleski, MS, CGC[3], and Philip M. Farrell, MD, PhD[1]

In the newborn nursery	
1	Newborn screening specimen is not obtained
2	Newborn screening specimen quality is unacceptable
3	Newborn screening specimen labeling error in the neonatal nursery
In the centralized testing laboratory	
4	Newborn screening specimen mix-up in the centralized testing laboratory
5	Initial immunoreactive trypsinogen (IRT) cutoff level is inappropriate
6	Infant's IRT level is below the cutoff (biologic false negative)
7	In IRT/IRT method, a second specimen is not obtained and there is no follow-up
8	In IRT/IRT method, the second IRT is not above the cutoff
9	In IRT/DNA method, uncommon mutation(s) is(are) present
10	Lab errors (e.g., errors measuring IRT, or DNA mutation analysis)
11	Clerical error in reporting the newborn screen result to the primary care provider
Follow-up	
12	Miscommunication of newborn screen result between primary care provider and family (e.g., sweat test not performed)
13	Error in measurement of sweat chloride
14	Inappropriate cutoff value of sweat chloride

Rock, M y col Pediatr.Pulmon 2011

Cystic fibrosis newborn screening: outcome of infants with normal sweat tests

Claire Edmondson,[1] Christopher Grime,[1] Ammani Prasad,[2] Jacqui Cowlard,[3] Chinedu E C Nwokoro,[3] Gary Ruiz,[4] Colin Wallis,[2] Ian M Balfour-Lynn[1]



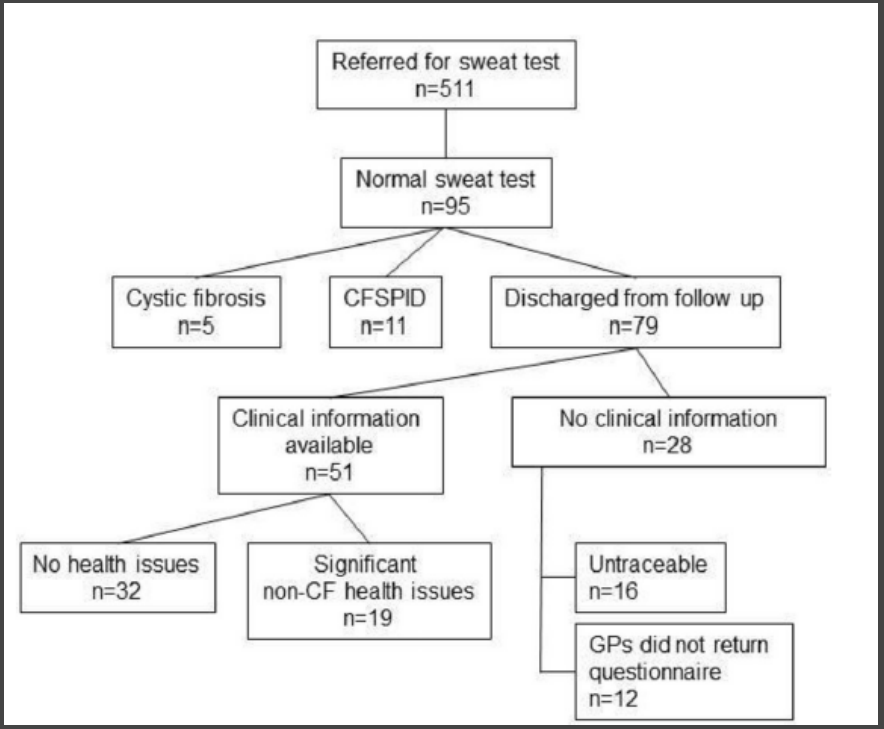


Table 1 Genetic results for children with CF mutations and CFSPID

(n)	Children with two mutations believed to cause CF disease	
1	p.Phe508del	Duplication part of CFTR gene from promotor to exon 10
1	p.Gly542X	p.Tyr1073Cys
1	p.Phe508del	3489+10kbC>T
1	p.Phe508del	p.Leu206Trp
1	p.Phe508del	p.Arg117His (7T)*
(n)	Children with one or two CFTR gene mutations of uncertain or variable significance (CFSPID)	
5	p.Phe508del	p.Arg117His (7T)
4	p.Phe508del	p.Asp1152His
1	p.Gly524X	p.Leu997Phe
1	p.Glu1124del	p.Glu1124del

Original Article

Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID): A new designation and management recommendations for infants with an inconclusive diagnosis following newborn screening

A. Munck [a,b], S.J. Mayell [c], V. Winters [d], A. Shawcross [c], N. Derichs [e], R. Parad [f,g], J. Barben [h], K.W. Southern [c,d,*]

- Grupo A:

  Test del sudor normal y dos mutaciones para el gen de la FQ , con almenos una con consecuencia fenotipica desconocida

- Grupo B:

  Test del sudor dudoso y una o ninguna mutacion del gen de la FQ

J ournal of Cystic Fibrosis 2014

Group A, normal sweat chloride value (<30 mmol L^{-1}) and two *CFTR* mutations, at least one of which has unclear phenotypic consequences	
A1	Infants should be followed up in specialist CF clinic. If they are seen in a non-CF clinic they should be reviewed by a CF physician (or a physician with an interest in CF).
A2	For infants attending a specialist CF clinic, policies should ensure that the infant is not exposed to any increased risk of cross infection.
A3	Infants should undergo a repeat sweat test aged 6–12 months. Depending on genotype, a further sweat test may be considered in the second year of life.
A4	Infants should be reviewed in clinic between 6 and 12 months of age, and thereafter annually (or more frequently, as indicated by clinical concerns or family anxieties).
A5	Annual review should clinically assess growth, weight gain and respiratory condition. Biochemical or radiological investigations should only be undertaken if clinically indicated.
A6	Families should be fully informed regarding their child's genetic and biochemical results. They should understand that their child does not have a definitive diagnosis of cystic fibrosis and that this will be reviewed annually.
A7	Reflecting the absence of a clear diagnosis, the term "Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID)" should be used to describe these infants.
A8	Clinicians should review the CFTR-2 website at the annual review for new information regarding the infant's genotype and discuss these findings with the family.
A9	Families and the primary care physician should be given clear information as to how to contact the CF team in the following situations; failure to gain weight adequately, persistent loose stools or persistent respiratory symptoms (more than 2 weeks).
A10	Children should receive routine childhood immunizations.
A11	Children should not be exposed to cigarette smoke.
A13	Children and their families should be encouraged to adopt a healthy lifestyle consistent with national guidance on exercise, nutrition and other aspects of public health policy.
A14	Families should be offered a referral for genetic counselling.
A15	Details of infants in this group should be kept on an appropriate national database.
A12	Did not reach consensus (79% agreement). Respiratory cultures should be taken routinely at annual review and when clinically indicated.

Group B, intermediate sweat chloride value (30–59 mmol L^{-1}) and one or no *CFTR* mutations	
B1	Infants should be followed up in a specialist CF clinic. If they are seen in a non-CF clinic they should be reviewed by a CF physician (or a physician with an interest in CF).
B2	For infants attending a specialist CF clinic, policies should ensure that the infant is not exposed to any increased risk of cross infection.
B3	Infants should undergo a repeat sweat test aged 6–12 months.
B4	Clinic follow-up may be 3-monthly, or less frequently depending on clinical assessment. The frequency of follow-up appointments may lessen with time, but children should be followed up annually as a minimum standard.
B5	Annual review should clinically assess growth, weight gain and respiratory condition. Biochemical or radiological investigations should only be undertaken if clinically indicated.
B6	Families should be fully informed regarding their child's genetic and biochemical results. They should understand that their child does not have a definitive diagnosis of cystic fibrosis and that this will be reviewed annually.
B7	Reflecting the absence of a clear diagnosis, the term "Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID)" should be used to describe these infants.
B8	Clinicians should review the CFTR-2 website at the annual review for new information regarding the infant's genotype and discuss these findings with the family.
B9	Families and the primary care physician should be given clear information as to how to contact the CF team in the following situations; failure to gain weight adequately, persistent loose stools or persistent respiratory symptoms (more than 2 weeks).
B10	Oral antibiotics should be provided when the infant has a cough (lower threshold than for the general population). The Primary care physician should be provided with clear guidance to this effect. If the cough persists for more than 2 weeks, the infant should be reviewed by the CF team, respiratory cultures taken and further investigation considered.
B11	Children should receive annual influenza vaccine in addition to all routine childhood immunisations.
B12	Children should not be exposed to cigarette smoke.
B13	Respiratory cultures should be taken routinely at annual review and when clinically indicated.
B14	Children and their families should be encouraged to adopt a healthy lifestyle consistent with national guidance on exercise, nutrition and other aspects of public health policy.
B15	Parents should be informed of the sweat test result and advised that during periods of high sweat loss*, dietary salt intake should not be restricted. (* hot weather, increased physical activity, fever etc.).
B16	Families should be offered a referral for genetic counselling.
B17	Details of all children in this group should be kept on an appropriate database.

Conclusiones

- Hay suficientes evidencias que muestran los beneficios de la pesquisa neonatal en FQ
- Ninguno de los sistemas de pesquisa actuales es perfecto
- Existen falsos positivo y negativos en todos los sistemas
- Debe mantenerse alto nivel de sospecha en pacientes con síntomas de FQ a pesar que la pesquisa sea negativa.
- Los pacientes en los cuales la pesquisa es inconclusa deben ser controlados periódicamente en centros de FQ

Muchas Gracias

II CURSO ANUAL

MEDICINA DEL SUEÑO EN PEDIATRÍA

Mayo - Noviembre 2018

> **Inicio:** Lunes 7 de Mayo

Un encuentro presencial el primer lunes de cada mes

+ Actividad web complementaria
Workshops en cada encuentro

Hospital Garrahan

Temas Principales

- Fisiología del sueño y fisiopatología respiratoria durante el sueño
- Estudios diagnósticos y equipamiento del laboratorio de sueño
- Síndrome de apnea obstructiva del sueño
- Hipoventilación Alveolar Periférica
- Control central de la ventilación
- Trastornos no respiratorios del sueño
- Ventilación
- Monitoreo de la ventilación

Dirigido a:

Pediatras, Neumonólogos, Neurólogos, Kinesiólogos, Técnicos en Polisomnografía, Personal de Salud Especializado en Medicina del Sueño.

Organizadores:

Directora: Dra. Vivian Leske
Coordinadora: Dra. María José Guerdile

Docentes:

Nacionales e Internacionales

Actividad Acreditada
Inscripción Arancelada
Cupos limitados

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ORGANIZA:

Hospital de Pediatría Garrahan | Servicio de Neumonología

AUSPICIA:

Sociedad Argentina de Pediatría

Asociación Argentina de Medicina del Sueño