

Risk Factors for Age at Initial *Pseudomonas* Acquisition in the Cystic Fibrosis EPIC

Observational Cohort

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ONLINE SUPPLEMENT

## **METHODS**

**CFNPR Replication Cohort:** After approval by the CF Foundation Registry Review Committee and the Seattle Children's Hospital IRB. Eligibility criteria mimicked those of the EPIC OBS cohort. Thus, participants in the CFNPR replication cohort had an established diagnosis of CF, were born between July 1992 and September 2006, were not enrolled in the EPIC OBS Study, and had at least one encounter between November 2004 and October 2006 (the enrollment period for the EPIC OBS Study), of which one was randomly selected as the entry date. Further criteria were no Pa-positive respiratory cultures recorded in the CFNPR prior to and within 120 days after the entry date.

**Analysis:** Categorization of CFTR function was based on CFTR mutation functional class: "minimal," both alleles with mutations resulting in minimal CFTR function (class 1, 2 or 3); "residual," at least one allele with a mutation resulting in partial CFTR function (class 4 or 5); "unclassified," both alleles with unknown functional class, or 1 allele in class 4 or 5 and the second with unknown functional class. Individuals without recorded CFTR genotype were not included in analyses involving functional class. . Robust variance estimates were used in all models to account for clustering due to 37 sibling sets (78 siblings) in the EPIC OBS cohort. The proportional hazards assumption was assessed by regressing scaled Schoenfeld residuals on functions of time and testing for non-zero slopes. Analyses were performed using Stata 10.0 (StataCorp LP, College Station, TX).

## RESULTS

To address concerns that older study participants might represent an unusual population by virtue of having survived without acquiring Pa up to the age at enrollment, we divided the cohort by age at enrollment  $\leq 3.6$  or  $> 3.6$  years, the median age at Pa acquisition in the CFNPR replication cohort. We then repeated our analyses limited to the participants  $\leq 3.6$  years of age at enrollment. As expected, the younger participants did acquire Pa at a greater rate than participants  $> 3.6$  years of age at enrollment (19 cases per 100 person-years, 95% CI 17, 22) vs 13 cases per 100 person-years, 95% CI 11, 15) (Figure E1). However, the effects of risk factors on age at Pa acquisition among the younger participants (Tables E1, E2 and E3) were very similar to those observed in the entire cohort.

## Figure Legends

Figure E1: Kaplan Meier survival curves by age at enrollment  $\geq 3.6$  years vs.  $< 3.6$  years, the median age at Pa acquisition in the CFNPR replication cohort.

**Table E1. Univariate Cox Models for Demographic Characteristics<sup>1</sup>**

<b>Age Enrolled ≤3.6 years</b>				
<b>Risk Factor</b>	<b>N in Model</b>	<b>Hazard Ratio</b>	<b>95% CI</b>	<b>P Value</b>
Female	412	1.17	.90, 1.53	0.24
Non-white race	410	1.30	0.82, 2.08	0.27
Hispanic ethnicity	390	1.13	0.57, 2.21	0.73
CFTR function: Minimal	401	2.81	1.62, 4.88	<0.001
CFTR function: Unclassified		1.37	0.64, 2.90	0.42
Genotype: both alleles ΔF508	401	1.45	0.83, 2.53	0.19
Genotype: one allele ΔF508		1.30	0.74, 2.29	0.36
Diagnosis age (years)	412	0.91	0.71, 1.17	0.45
Meconium ileus	397	1.01	0.74, 1.39	0.93
Diagnosis by screening <sup>2</sup>	338	0.90	0.67, 1.20	0.47

<sup>1</sup> Separate Cox models were developed for each characteristic. The reference groups are: male sex, white race, non-Hispanic ethnicity, residual CFTR function, neither allele deltaF508, no history of meconium ileus, and not diagnosed by prenatal or newborn screening. The number of children contributing observations to each model varied due to missing data.

<sup>2</sup> Diagnosis by prenatal or newborn screening: the reference group excludes children with a family history of CF.

**Table E2. Multivariate Cox Models for Baseline Clinical Characteristics<sup>1</sup>**

Risk Factor	Age Enrolled ≤3.6 years			
	N in Model	Hazard Ratio	95% CI	P Value
Pancreatic enzymes	297	1.69	0.76, 3.77	0.20
DNase	312	0.91	0.67, 1.24	0.55
Any inhaled medication	312	0.94	0.70, 1.26	0.67
Weight percentile	290	1.00	0.996, 1.01	0.68
Height percentile	285	1.00	0.996, 1.01	0.56
BMI percentile <sup>2</sup>	95	1.00	0.99, 1.01	0.77
S. aureus	300	0.90	0.67, 1.21	0.47
MRSA	300	1.10	0.56, 2.16	0.79
H. influenzae	300	0.89	0.65, 1.22	0.48
S. maltophilia	300	0.77	0.41, 1.43	0.41
A. xylosoxidans	300	1.46	0.39, 5.46	0.58

<sup>1</sup> Each row in the table shows results for a separate Cox model. The number of children contributing observations to each model varied due to missing data. Each model was adjusted for CFTR risk group, race, ethnicity, gender, and diagnosis by screening.

<sup>2</sup> Children age 2 years or older at enrollment.

**Table E3. Univariate Cox Models for Time-Varying Risk Factors Reported on Annual Family Surveys in EPIC Obs Cohort**

Risk Factor	Age Enrolled ≤3.6 years			
	N in Model	Hazard Ratio	95% CI	P Value
Influenza vaccine during past year	398	0.82	0.58, 1.18	0.29
Household member smokes cigarettes	399	1.01	0.77, 1.34	0.92
Wood-burning stove used in home	399	1.13	0.73, 1.77	0.58
Hot-tub use during past year	399	0.79	0.51, 1.23	0.30
Swimming pool use during past year	399	0.74	0.54, 1.01	0.06
Social event with others with CF during past year	398	1.26	0.87, 1.81	0.22
Daycare or preschool during past year <sup>2</sup>	397	0.89	0.66, 1.19	0.43
Breastfed during past year <sup>3</sup>	261	0.85	0.60, 1.21	0.38
Received palivuzimab during past year <sup>4</sup>	284	1.02	0.75, 1.40	0.89
Maternal education beyond high school <sup>5</sup>	384	0.89	0.67, 1.19	0.44
Annual household income: ≥ \$80,000 <sup>5</sup>	330	1.01	0.71, 1.43	0.97
Annual household income: \$40,000-\$79,000 <sup>5</sup>		0.85	0.59, 1.21	0.37

<sup>1</sup> From separate Cox model for each risk factor, modeled as a time-varying covariate. The number of children contributing observations to each model varied due to missing data.

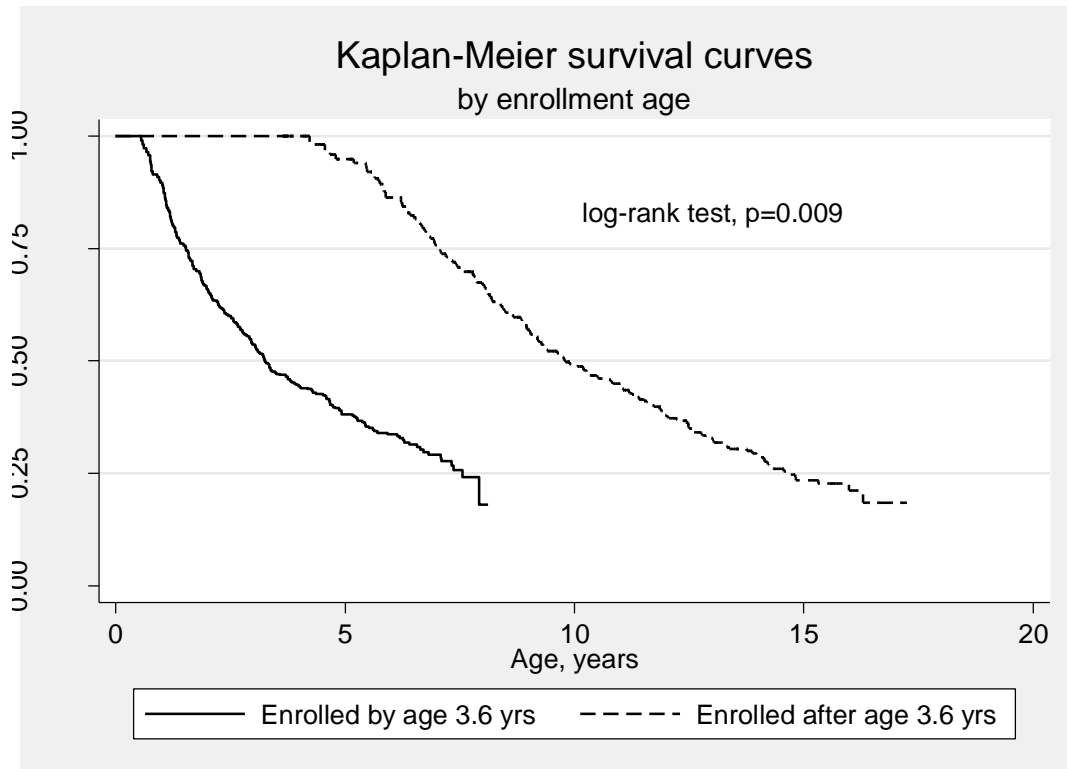
<sup>2</sup> Children younger than 6 years.

<sup>3</sup> Children younger than 2 years.

<sup>4</sup> Children younger than 2.5 years.

<sup>5</sup> As reported at enrollment; the reference group for annual income is < \$40,000.

**Figure E1: Kaplan Meier survival curves by age at enrollment  $\geq 3.6$  years vs.  $< 3.6$  years, the median age at Pa acquisition in the CFNPR replication cohort**





## **Appendix 1: The EPIC Study Group**

Albany Medical College, Albany, NY, Paul Comber, MD, PhD and Terese Evens; All Children's Hospital CF Center, St. Petersburg, FL, Magdalen Gondor, MD, Kathy Hosler and Stasia Lehmann; Baylor College of Medicine, Houston, TX, Peter Hiatt, MD and Charlene Hallmark; Brown University Medical School – Rhode Island Hospital, Providence, RI, Karen Daigle; Cardinal Glennon Children's Medical Center, St. Louis, MO, Blakeslee Noyes, MD and Vikki Kociela; Children's Hospital, Boston, MA, Henry Dorkin MD, Ashish George, Erin Leone Thakkallapalli and Jane Solomon; Children's Hospital & Clinics, Minneapolis, MN, John McNamara, MD, Sandy Landvik and Mary Sachs; Children's Hospital Colorado, Aurora, CO, Frank Accurso MD, Meg Anthony and Shelley Mann; Children's Hospital of Los Angeles, Los Angeles, CA, Arnold Platzker MD; Children's Hospital Medical Center of Akron, Akron, OH, Gregory Omlor MD and Deborah Ouellette; Children's Hospital of Michigan, Detroit, MI, Ibrahim Abdulhamid, MD and Catherine Van Wagnen; Children's Hospital of Milwaukee, Milwaukee, WI, Diana Quintero MD, MaryEllen Freeman and Tami Miller; Children's Hospital – University of Birmingham, Birmingham, AL, Hector Gutierrez, MD, Heather Hathorne and Gina Sabbatini; Children's Hospital of Pittsburgh , Pittsburgh, PA, David Orenstein MD, Caitlin Clarke, Judy Fulton, Elizabeth Hartigan and Sandra Hurban; Children's Hospital at Westchester Medical Center, Valhalla, NY, Allen Dozor MD, Ingrid Gherson and Madelint Heydendael; Children's Medical Center of Dayton, Dayton, OH, Robert Fink, MD and Sandy Bartosik; Children's Mercy Hospital, Kansas City, MO, Philip Black MD, Karie Robinson and Candy Schmoll; Children's Specialty Center, FAHC, Burlington, VT, Thomas Lahiri MD and Sandra Diehl; Cohen Children's Hospital, Great Neck, NY, Joan DeCelie-Germana MD, Lynn Bonitz and Susan Galvin; Cook Children's Medical Center, Fort Worth, TX, Maynard Dyson MD and Sara Scott; Dartmouth Hitchcock Clinic – Lebanon, Lebanon, NH, H. Worth Parker MD, Dana Dorman, Pamela Hofley and Lisa Moulton; DuPont Hospital for Children, A.I., Wilmington, DE, Aaron Chidekel MD and Sandra Budd; Emory University School of Medicine, Atlanta, GA, Michael Schechter MD, Monica Haughton, Eric Hunter and Jeannette Peabody; Helen DeVos Women & Children's Center, Grand Rapids, MI, Susan Millard MD, Hollie Bonnema and Teri Crumb; Intermountain CF Center, Salt Lake City, UT, Barbara Chatfield MD, Heather Oldroyd and Jane Vroom; Kaiser Permanente Medical Care Program, Oakland,

CA, Gregory Shay MD, Julie Lee and Erika Marmolejo; Le Bonheur Children's Medical Center, Memphis, TN, Robert Schoumacher MD and Barbara Culbreath; Medical College of Georgia, Augusta, GA, Kathleen McKie MD and Heidi Stapp; Milton S. Hershey Medical Center – Penn State University, Hershey, PA, Gavin Graff MD, Lisa Allwein and Diane Kitch; MMC Cystic Fibrosis Center, Portland, ME, AnneMarie Cairns DO, Mary Ellen Corrigan and Carrie Milliard; Monmouth Medical Center, Long Branch, NJ, Robert Zanni MD and Bridget Marra; Nationwide Children's Hospital, Columbus, OH, Karen McCoy MD, Barbara Butera, Diana Gilmore, Mary Terri Johnson, Veronica Lowell, Patricia Olson and Laura Raterman; Nemours Children's Clinic, Jacksonville, FL, David Schaeffer MD and Rena Sprinkle; Northwestern University, Chicago, IL, Adrienne Prestridge MD, Jennifer Milam and Catherine Powers; Oregon Health Sciences University, Portland, OR, Michael Wall MD, Aaron Guzik and Ben McCullar; Rainbow Babies and Children's Hospital, Cleveland, OH, Michael Konstan MD, Colette Bucur, Ellen Divoky, Kate Hilliard, Jeanne Krenicky and Cheryl Velotta; Riley Hospital for Children, Indianapolis, IN, Michelle Howenstine MD, Terry Barclay and Lisa Bendy; Seattle Children's Hospital, Seattle, WA, Margaret Rosenfeld MD, MPH, Judy Gabrysiak and Sharon McNamara; St. Christopher's Hospital for Children; Philadelphia, PA, Laurie Varlotta MD and Marcella Aramburo; St. Louis Children's Hospital, St. Louis, MO, Thomas Ferkol MD, Mary Boyle, Patricia Burks and Jane Quante; Stanford University Medical Center, Palo Alto, CA, Richard Moss MD, Zoe Davies, Colleen Dunn and Cassie Everson; SUNY Upstate Medical University, Syracuse, NY, Ran Anbar MD, Donna Lindner and Valoree Suttmore; UMass Memorial Health Care, Worcester, MA, Brian O'Sullivan; University of California at San Francisco, San Francisco, CA, Dennis Nielson MD and Courtney Moreno; University of Iowa Hospital and Clinics, Iowa City, IA, Richard Ahrens MD, Jean Frauenholtz, Tom Santacroce and Mary Teresi; University of Kentucky, Lexington, KY, Jamshed Kanga MD, Brittany Fuller, Tammy Taylor and Tammy Watts; University of Michigan Health System, Ann Arbor, MI, Samya Nasr MD and Dawn Kruse; University of Mississippi Medical Center, Jackson, MS, Suzanne Miller MD, Kim Adcock and Linda Bonham; University of Nebraska Medical Center, Omaha, NE, John Colombo MD, Diane Acquazzino, Shandalle Fertig and Sandra Strizek; University of North Carolina at Chapel Hill, Chapel Hill, NC, George Retsch-Bogart MD, Carol Barlow, Paul Jones and Caroline LaFave; University of Rochester

Medical Center, Rochester, NY, Clement Ren MD, Nancy Jenks and Mary Platt; University of Virginia Health System, Charlottesville, VA, Deborah Froh MD, Mary Alice Blackwell and Patricia Moss; University of Wisconsin, Madison, WI, Michael Rock MD and Linda Makhholm; Vanderbilt Children's Hospital, Nashville, TN, Rebekah Brown MD and Alice Bray; Women & Children's Hospital of Buffalo, Buffalo, NY, Daniel Sheehan MD, Jameelah Ali and Nadine Caci

## APPENDIX 2: EPIC OBSERVATIONAL STUDY –ANNUAL FAMILY SURVEY

When answering the questions below, “this survey year” refers to the period January 1 to December 31 of the survey year.

Thank you for taking the time to complete this survey.

**Date family completed survey:** \_\_\_\_\_ (mm/dd/yyyy)

**Did this child receive the influenza vaccine during this survey year?** The influenza vaccine (flu shot) is generally available between October and January. Answer “yes” if the child received the vaccine as a shot (injection) or a nasal spray (i.e., FluMist™).

- Yes
- No
- Don’t know

**Does anyone this child lives with smoke cigarettes, even occasionally?** Please include all households where this child routinely spends time (once per week or more). Answer “yes” even if the smoking is done outdoors.

- Yes
- No

**If yes, whom?** (Please check all that apply)

**Mother**

- About how many years has she been smoking? \_\_\_\_\_  Don’t Know
- About how many cigarettes a day has she smoked on average over the past week? \_\_\_\_\_  Don’t Know
- How many of these are smoked at home (indoors and outdoors)? \_\_\_\_\_  Don’t Know
- How many of these are smoked in the car? \_\_\_\_\_  Don’t Know

**Father**

- About how many years has he been smoking? \_\_\_\_\_  Don’t Know
- About how many cigarettes a day has he smoked on average over the past week? \_\_\_\_\_  Don’t Know
- How many of these are smoked at home (indoors and outdoors)? \_\_\_\_\_  Don’t Know
- How many of these are smoked in the car? \_\_\_\_\_  Don’t Know

**Other, Specify** (e.g., grandmother, brother, aunt, cousin): \_\_\_\_\_

- About how many years has he/she been smoking? \_\_\_\_\_  Don’t Know
- About how many cigarettes a day has he/she smoked on average over the past week? \_\_\_\_\_  Don’t Know
- \_\_\_\_\_

ANNUAL FAMILY SURVEY – (cont)

**Is there anyone living with this child who smoked cigarettes when this child was younger, but has since quit smoking?**

- Yes
- No

**If yes, whom?** (Please check all that apply)

- Mother
- Father
- Other

**During the past 3 months, how frequently has this child been around people who are smoking? Would you say:** (Please choose *only one*)

- Daily
- Several times a week
- Several times a month
- Rarely
- Never

**Is a wood-burning stove or fireplace used in any home in which this child routinely spends time (once per week or more)?**

- Yes
- No

**Did this child get in a hot tub or jacuzzi in this survey year?**

- Yes
- No

**If yes, approximate number of times:** (Please choose *only one*)

- 1 to 10
- 11 to 30
- More than 30

**Did this child get in a swimming pool in this survey year?**

- Yes
- No

**If yes, approximate number of times:** (Please choose *only one*)

- 1 to 10
- 11 to 30
- More than 30

**ANNUAL FAMILY SURVEY – (cont)**

**Did this child attend a camp or other social event attended by other children with CF during this survey year?** (Please check all that apply)

- Camp
- Other social event (e.g., birthday party, fundraising events)
- None

**Do other people with CF live in the same home as this child?** Please include all households where this child routinely spends time (once per week or more).

- Yes
- No

**How often did this child play with other children with CF (NOT including siblings) during this survey year?**

- Never
- Less than once per month
- Once per month
- More than once per month

**What was the combined total income of the household (before taxes) where this child resided for the majority of this survey year?** If the child's time was shared equally between households, use the mother's household income.

- <\$20,000
- \$20,000-\$39,000
- \$40,000-\$59,000
- \$60,000-\$79,000
- \$80,000-\$99,000
- ≥\$100,000
- Don't know
- Prefer not to answer

**What is the mother's education level?**

- Less than high school
- High school diploma or equivalent
- Some college but no bachelor's degree
- Bachelor's degree or higher
- Prefer not to answer or don't know

**ANNUAL FAMILY SURVEY – (cont)**

**If this child was 5 years old or younger at any time during this calendar year, please answer the following questions:**

**Did this child spend nine or more hours per week during this survey year with children other than siblings, such as with a babysitter (including family members) or in day care or preschool?**

- Yes
- No

**If yes, please answer the following three questions:**

**About how many other children are there in this setting?**

- 1-3
- 4-6
- 7-10
- Greater than 10
- Don't know

**Approximately how many hours per week did this child spend in this setting?**

Select the greatest number of hours per week.

- 9 to 15 hours
- 16 to 30 hours
- More than 30 hours

**Does anyone who cared for this child in any of these settings smoke cigarettes?**

- Yes
- No
- Don't know