Advisory Committee on Heritable Disorders in Newborns and Children

Rare Disease Registries Panel

April 23, 2019

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Disclosures

The CF Foundation has business relationships with Abbvie, Allergan, Digestive Care, Mylan, Vertex and Vivus for the conduct of post-approval research studies.

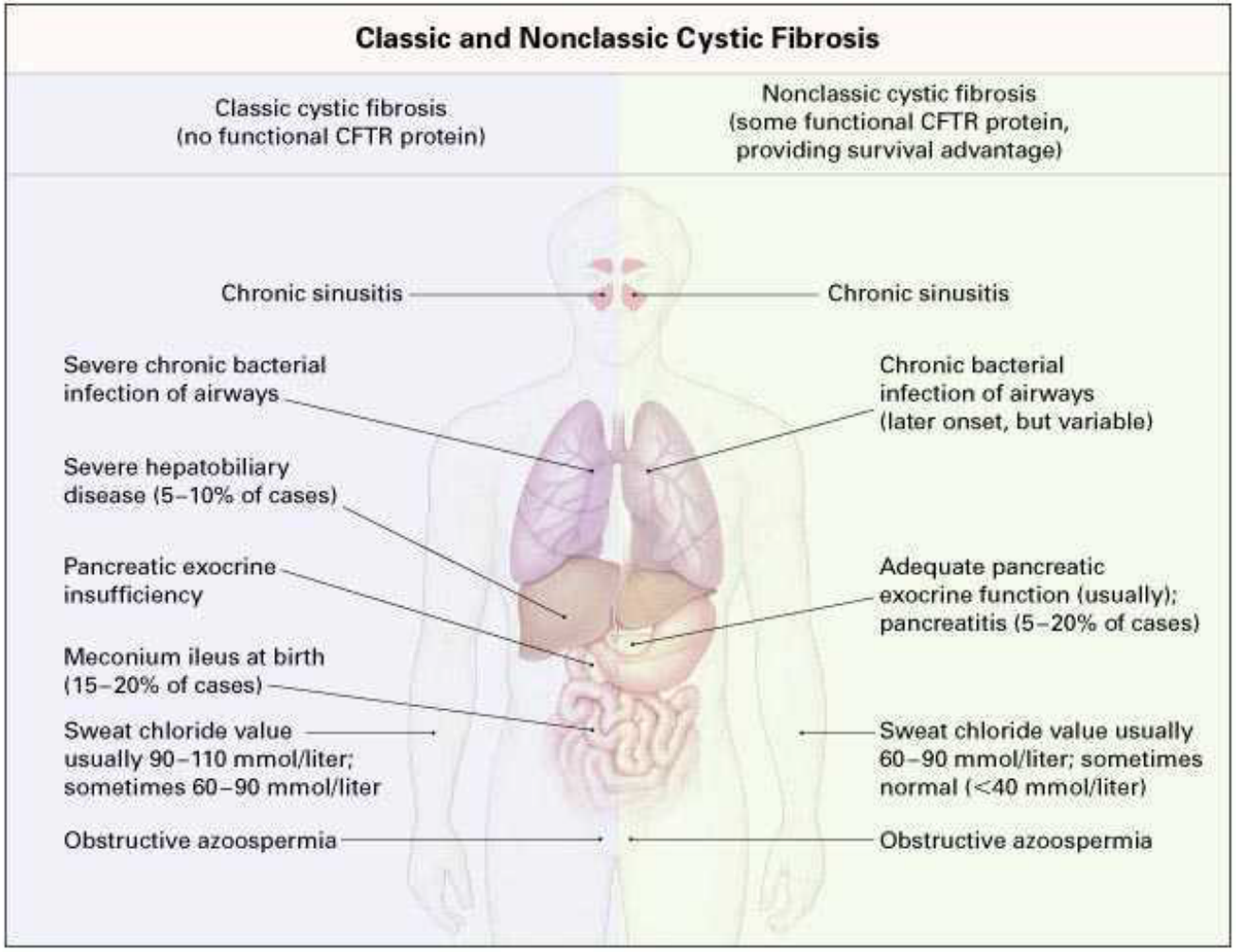
Outline

- Context
- Patient registry - the basics
- How the registry data is used
- Intersection of registry and CF NBS
- Q & A

Cystic Fibrosis

- Autosomal recessive disease
  - ± 35,000 US patients (± 100,000 worldwide)
- Most common life-shortening inherited disease of Caucasians
- Complex, multisystem chronic disease
  - Majority of deaths due to lung disease

CF: Complex, Multisystem Chronic Disease



<u>Other important co-morbidities</u>

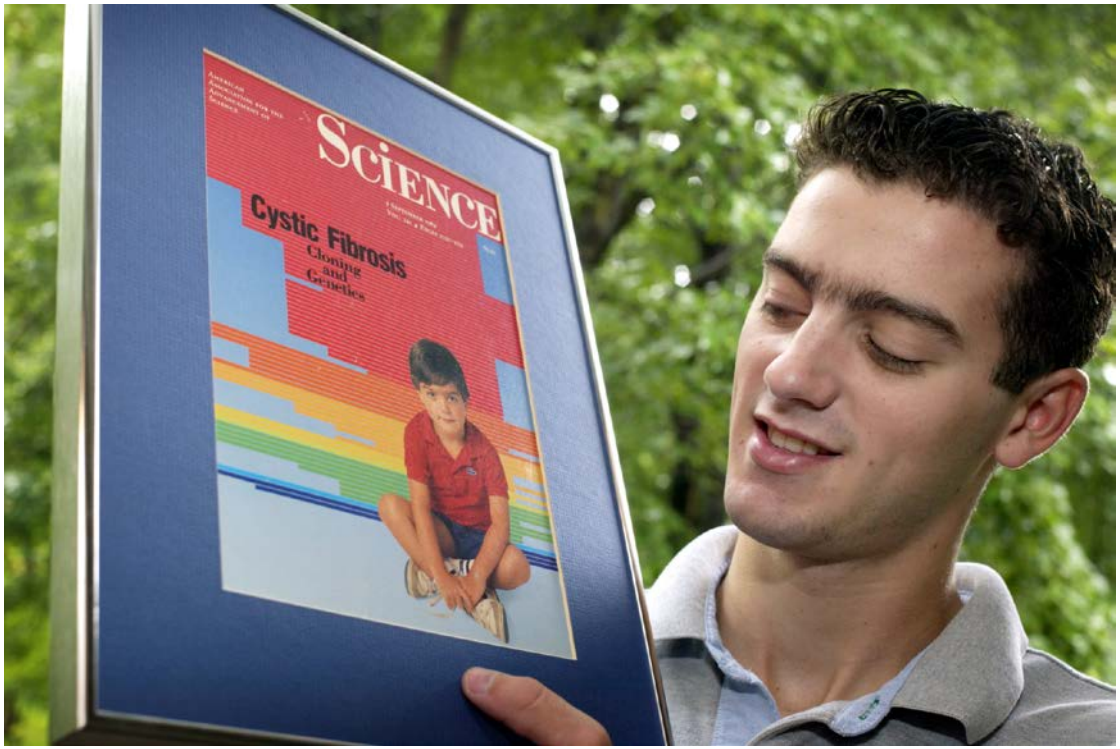
CF-related diabetes
Anxiety/depression

ABPA
Pulmonary NTM

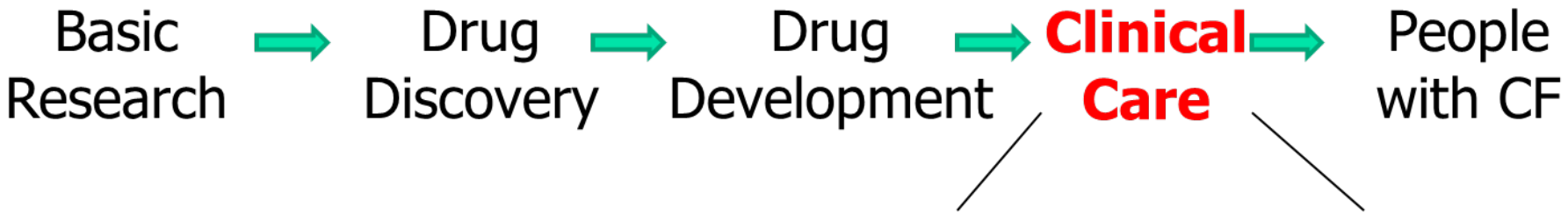
Identification of the Cystic Fibrosis Gene: Genetic Analysis

Bat-sheva Kerem, Johanna M. Rommens, Janet A. Buchanan, Danuta Markiewicz, Tara K. Cox, Aravinda Chakravarti, Manuel Buchwald, Lap-Chee Tsui

Science; 1989; 245(4922): 1073-1080

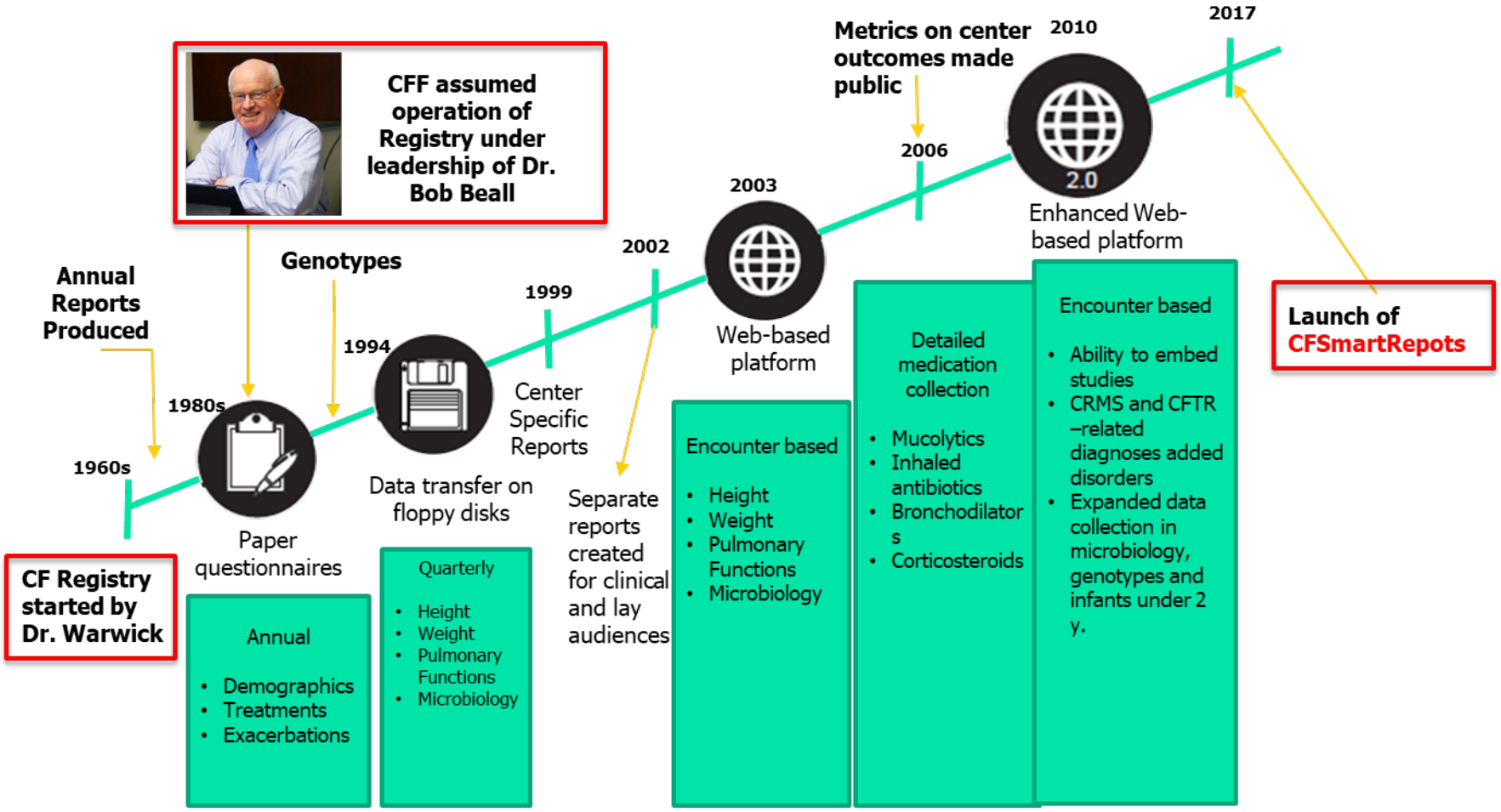


CFF Medical and Scientific Activities



- Center Network
- Peer review accreditation
- **Patient Registry**
- Quality Improvement
- Practice Guidelines

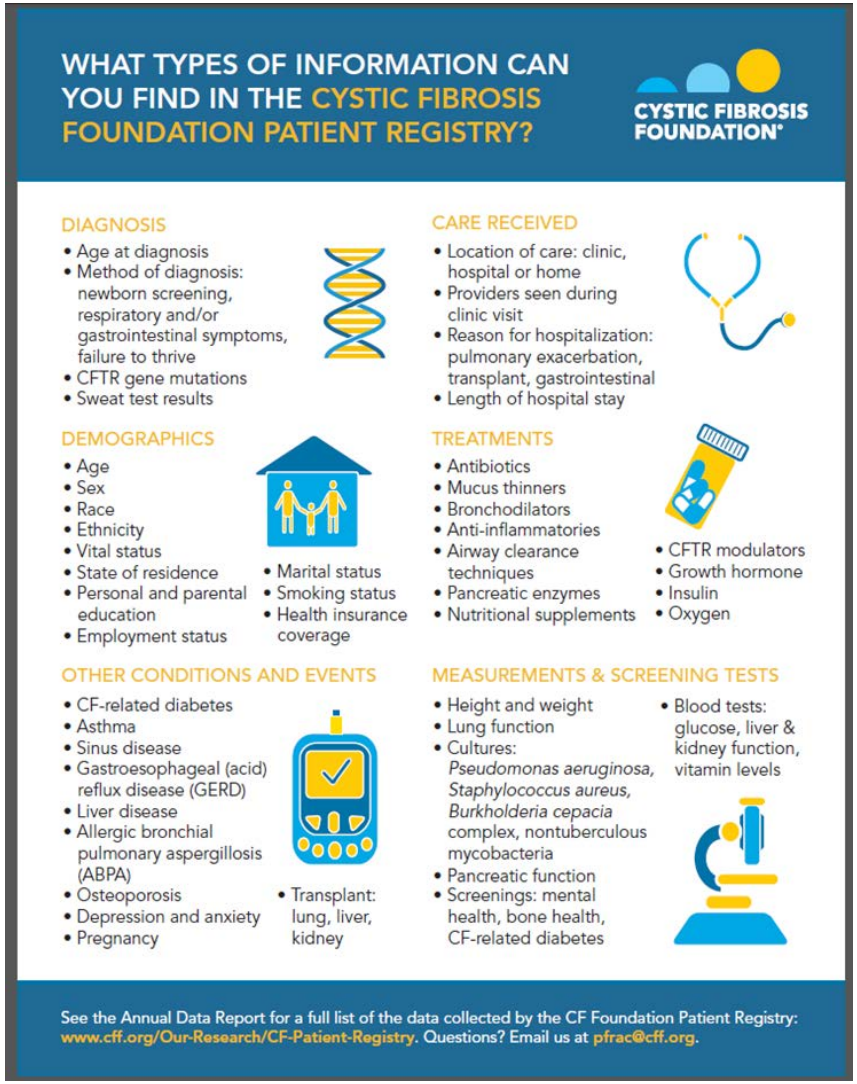
CFF Patient Registry History



Approximately 85% of individuals with CF in the US enrolled

Ann Am Thorac Soc Vol 13, No 7, pp 1173–1179, Jul 2016

CF Foundation Patient Registry: IRB-Approved, Patient-Consented Observational Study



Data entered by: Care center teams

Data entry incentivized by:

- User and financial support by CFF
- Broad use of registry data

Data quality facilitated by:

- Data entry guidelines
- Annual data validations of key variables
- Annual “deduping” of records
- Educated and dedicated stakeholders

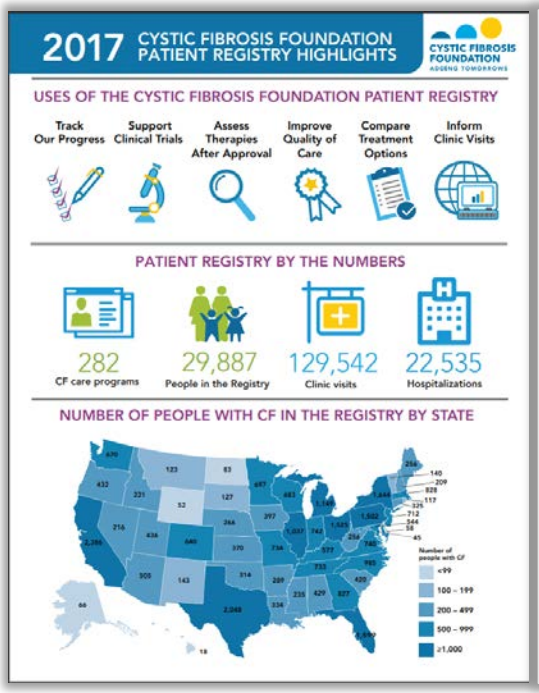
Data quality is confirmed by:

- Selective audits of registry data

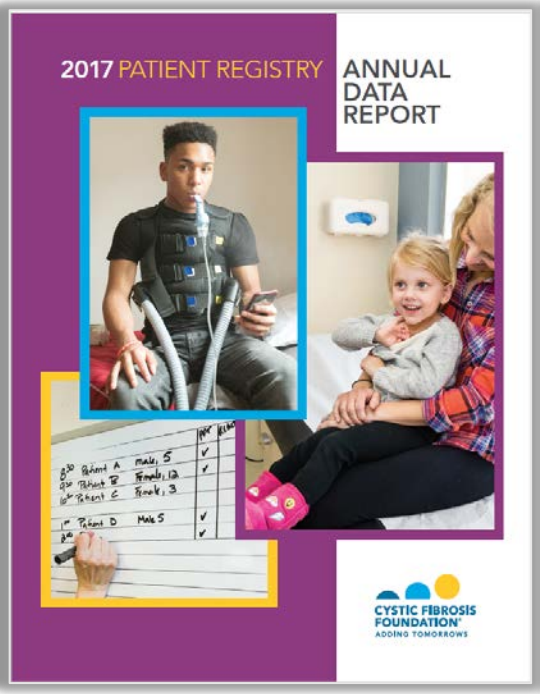
Uses of the Cystic Fibrosis Foundation Patient Registry

DISEASE SURVEILLANCE	FRAMEWORK FOR CLINICAL TRIALS	POST-MARKETING SURVEILLANCE STUDIES	QUALITY IMPROVEMENT	COMPARATIVE EFFECTIVENESS RESEARCH
				
Track progress in curing CF and the impact of treatments	Test promising new therapies	Ensure safety and effectiveness of approved products	Provide all patients with high-quality care	Promote evidence-based clinical decision making

CF Foundation Registry Annual Reports



Highlights Report



Annual Data Report

Center-Specific Report

CF SmartReports: Driving Improvements in Care

~~ONE YEAR~~ → 24 hours or less

CF Clinic

Data Collection in PortCF

January, 2017

CFSmartReports with patient–level data deployed!

Data Reporting

Data Transfer to CFF

Data Processing

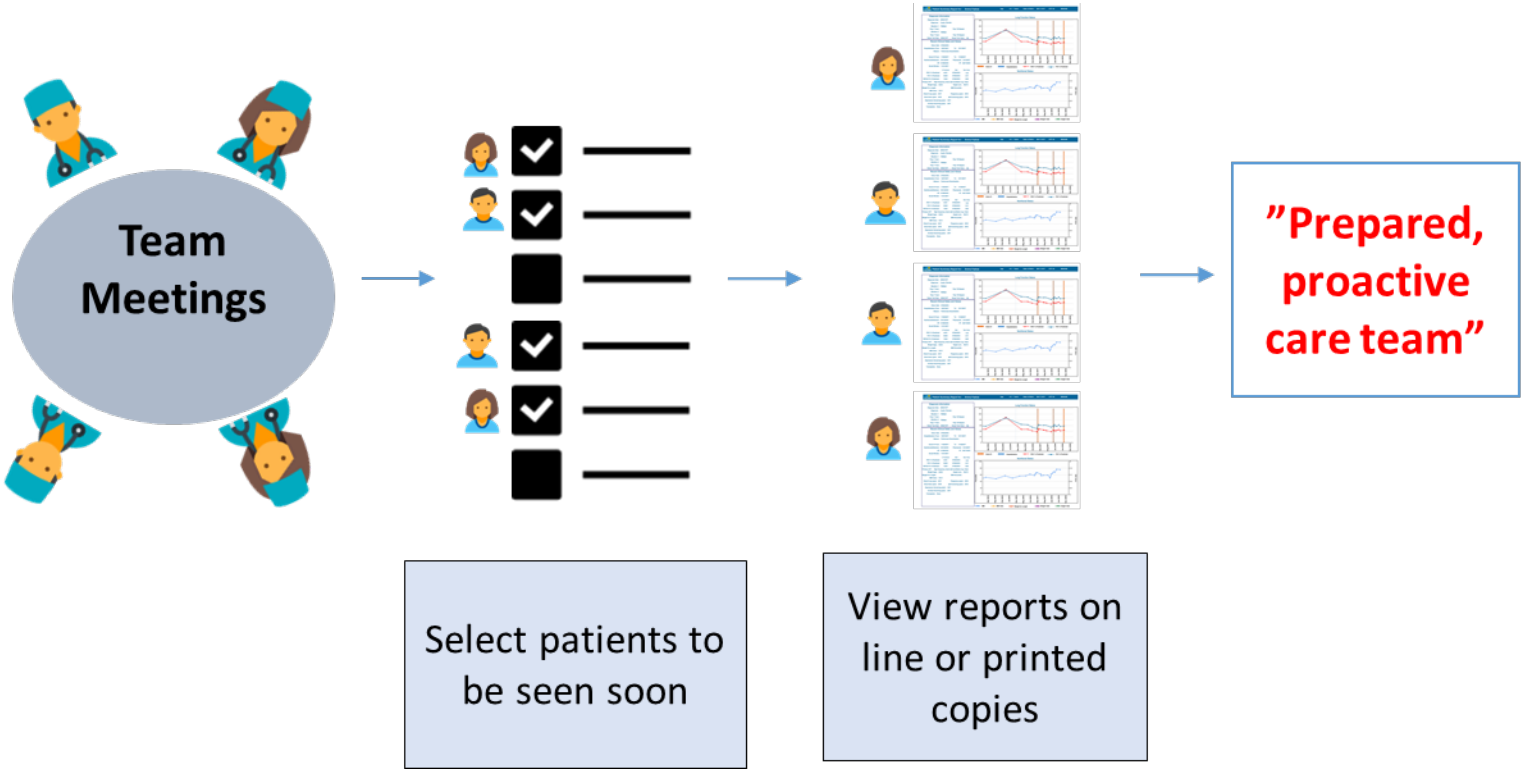
Patient Summary Report

Hospitalizations and home IV's on FEV1 trend chart

Microbiology and other key data

... and much more on other three pages!

Pre-visit planning using CFSmartReports



Screening for Clinical Trials

Uses of the Cystic Fibrosis Foundation Patient Registry

DISEASE SURVEILLANCE	FRAMEWORK FOR CLINICAL TRIALS	POST-MARKETING SURVEILLANCE STUDIES	QUALITY IMPROVEMENT	COMPARATIVE EFFECTIVENESS RESEARCH
				
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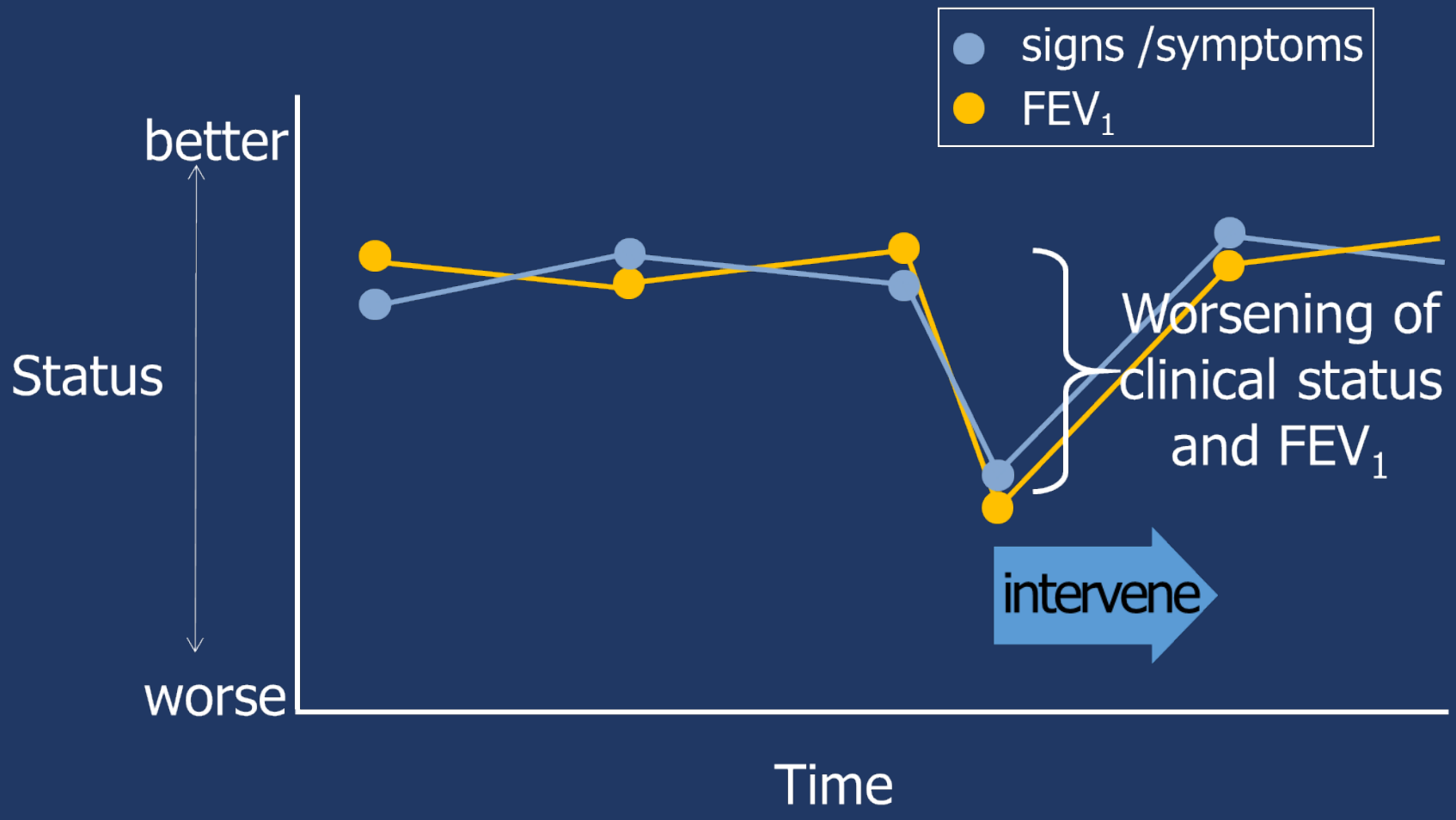
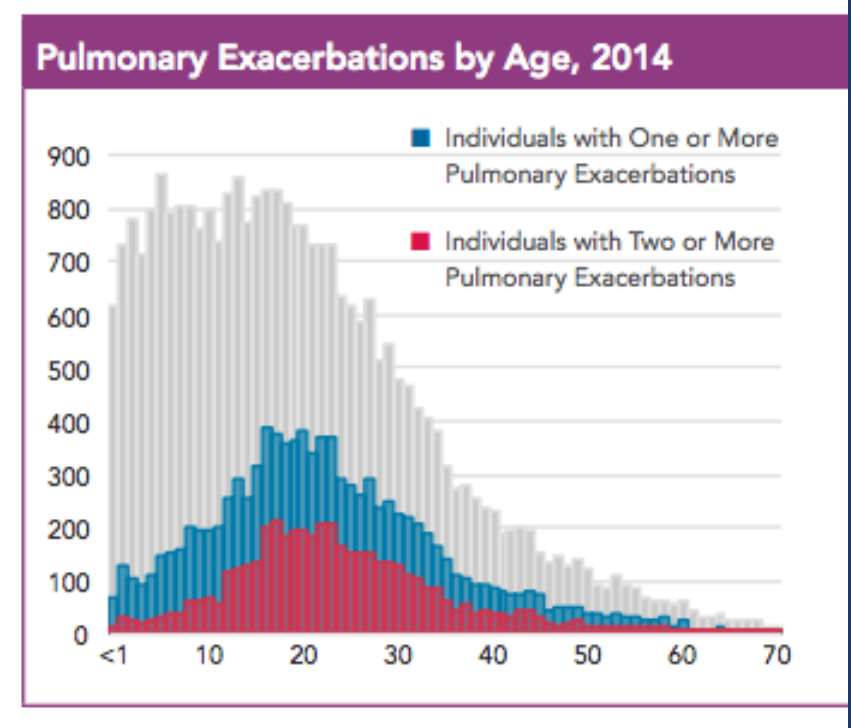
What is a Pulmonary Exacerbation?



Why are exacerbations important?

- Common events



- Major driver of cost
- Negative impact on quality of life
- Associated with decreased survival

Am J Epidemiol. 2001 February 15; 153(4): 345–352.

Predictive 5-Year Survivorship Model of Cystic Fibrosis

Theodore G. Liou[1,2], **Frederick R. Adler**[3,4], **Stacey C. FitzSimmons**[5,9], **Barbara C. Cahill**[1,2,6], **Jonathan R. Hibbs**[7], and **Bruce C. Marshall**[1,2,8]

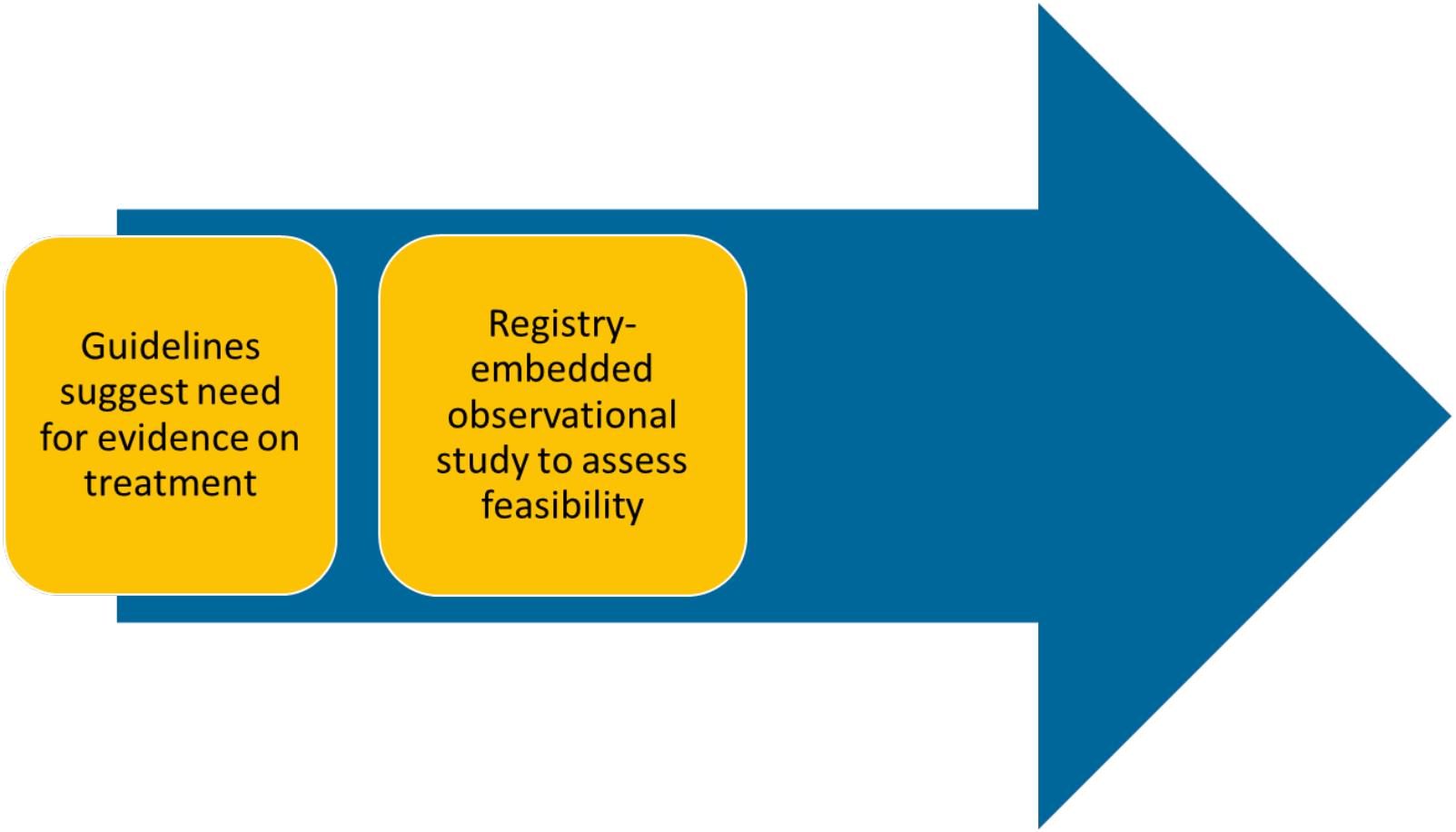
Validated 5-year logistic regression survivorship model for cystic fibrosis,* Cystic Fibrosis Foundation Patient Registry, United States, 1993

Covariate† (x_{0-10})	Coefficient		Odds ratio	FEV_1%‡ equivalence§
	β_{0-10}	SE‡		
(Intercept)	1.93	0.27	6.88	50
Age (per year)	−0.028	0.0060	0.97	−0.7
Gender (male = 0, female = 1)	−0.23	0.10	0.79	−6
FEV_1% (per %)¶	0.038	0.0028	1.04	1
Weight-for-age *z* score	0.40	0.053	1.50	10
Pancreatic sufficiency (0 or 1)¶	0.45	0.31	1.58	12
Diabetes mellitus (0 or 1)¶	−0.49	0.15	0.61	−13
Staphylococcus aureus (0 or 1)¶	0.21	0.12	1.24	6
Burkerholderia cepacia (0 or 1)¶	−1.82	0.30	0.16	−48
No. of acute exacerbations (0–5)¶	−0.46	0.031	0.63	−12
No. of acute exacerbations × *B. cepacia*	0.40	0.12	1.49	10

* Hosmer-Lemeshow *p* value = 0.54; no significant difference between predicted and actual survivorship of the validation group of patients (31).

"Each pulmonary exacerbation had an unexpectedly large negative impact on 5-year survival equivalent to subtracting 12% from the measured FEV1% value."

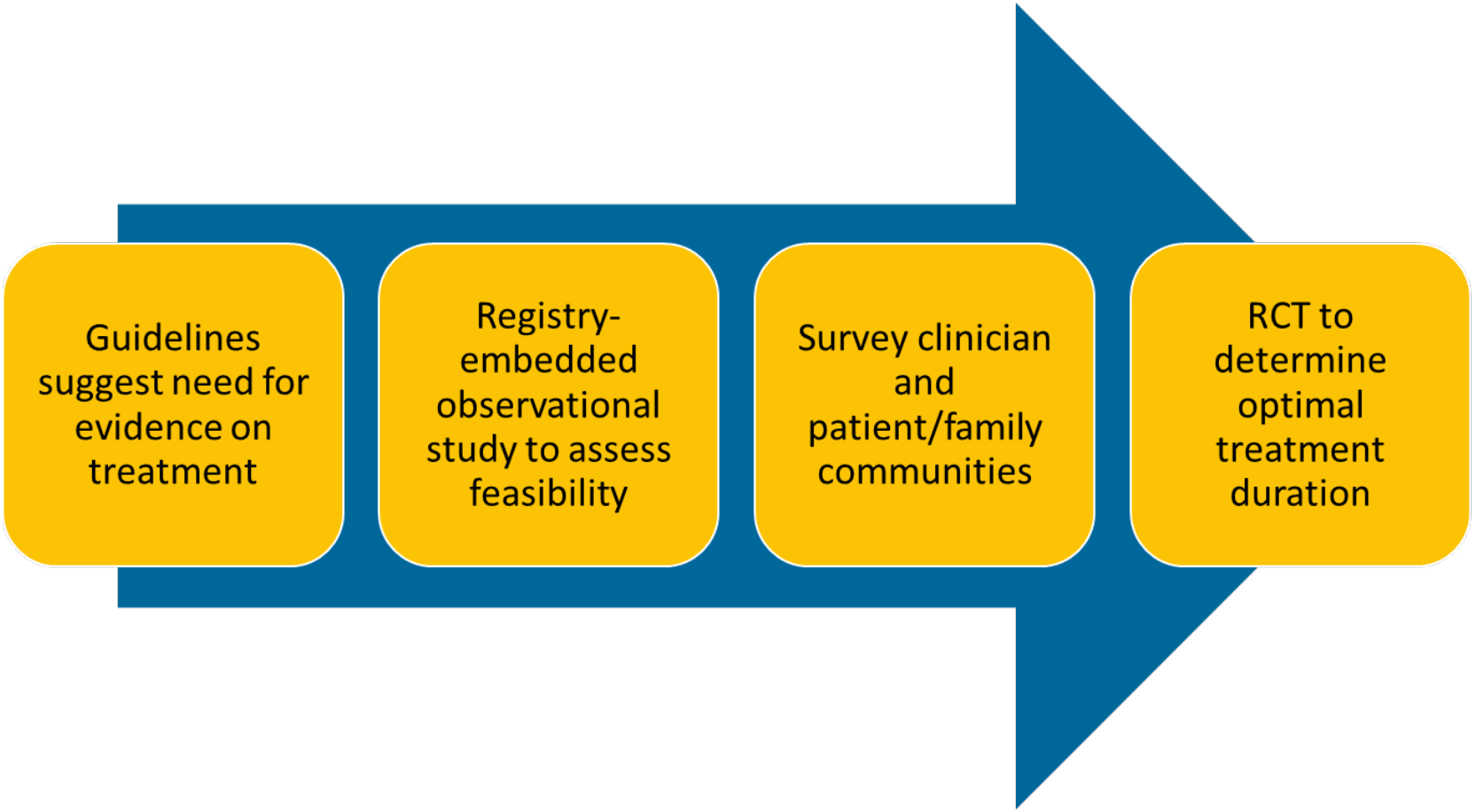
Standardized Treatment Of Pulmonary Exacerbations



STOP Trial: Achievement of Aims

Aim	Findings
Expand capability of registry	• Registry was successfully used to conduct study
Establish equipoise for future interventional studies	• Willingness of sites to participate in most (but not all) trial designs
Inform the design of future research of exacerbations	• Established variance for key outcome measures
Build consortium of centers to enable design and conduct of interventional trials	• High degree of engagement • Significant enthusiasm from wider CF community

Standardized Treatment Of Pulmonary Exacerbations



Intersection of CF NBS and Registry

- Assess performance of NBS (e.g., false negatives)
- Track time from birth to entry into the CF care delivery system to facilitate improvement efforts
- Clinical follow-up of CF cases and CF Screen Positive, Indeterminant Diagnosis (CF-SPID) cases

CF NBS Metrics Derived from Registry Data

	2010-2012	2013-2016	P Value
Age at first care center event (days) Median (n)	11 (1825)	8 (2333)	0.003*
Age at first care center event (days) Mean (SD)	17.6 (24.31)	15.1 (22.73)	<0.001*
Patients with false negative NBS, n (%)*	79 (4.1%)	98 (4.0%)	0.995

* Patients diagnosed with CF, but not detected through NBS

Slide courtesy of Susanna McColley, MD

PEDIATRICS Volume 135, number 6, June 2015

Outcomes of Infants With Indeterminate Diagnosis Detected by Cystic Fibrosis Newborn Screening

Clement L. Ren, MD[a], Aliza K. Fink, DSc[b], Kristofer Petren, BS[b], Drucy S. Borowitz, MD[c], Susanna A. McColley, MD[d], Don B. Sanders, MD, MS[e], Margaret Rosenfeld, MD, MPH[f], Bruce C. Marshall, MD[b]

	CFF Guideline Diagnosis	
Registry Diagnosis	**CF**	**CRMS**
CF	1,532	126
CRMS (i.e., CFSPID)	8	183
Total	1,540	309
% of Total	83.2	16.7

41% with CFSPID cases entered with CF diagnosis
Misclassification Bias?

CF Foundation Patient Registry: Summary

Highly impactful asset used effectively for multiple purposes. Developing and operating the registry is labor and resource intensive, but the value to the CF community continues to increase over time.

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