CF ATLANTA Research & Development Program at Emory University and Georgia Tech (CF@LANTA)

Clinical & Translational Research Core

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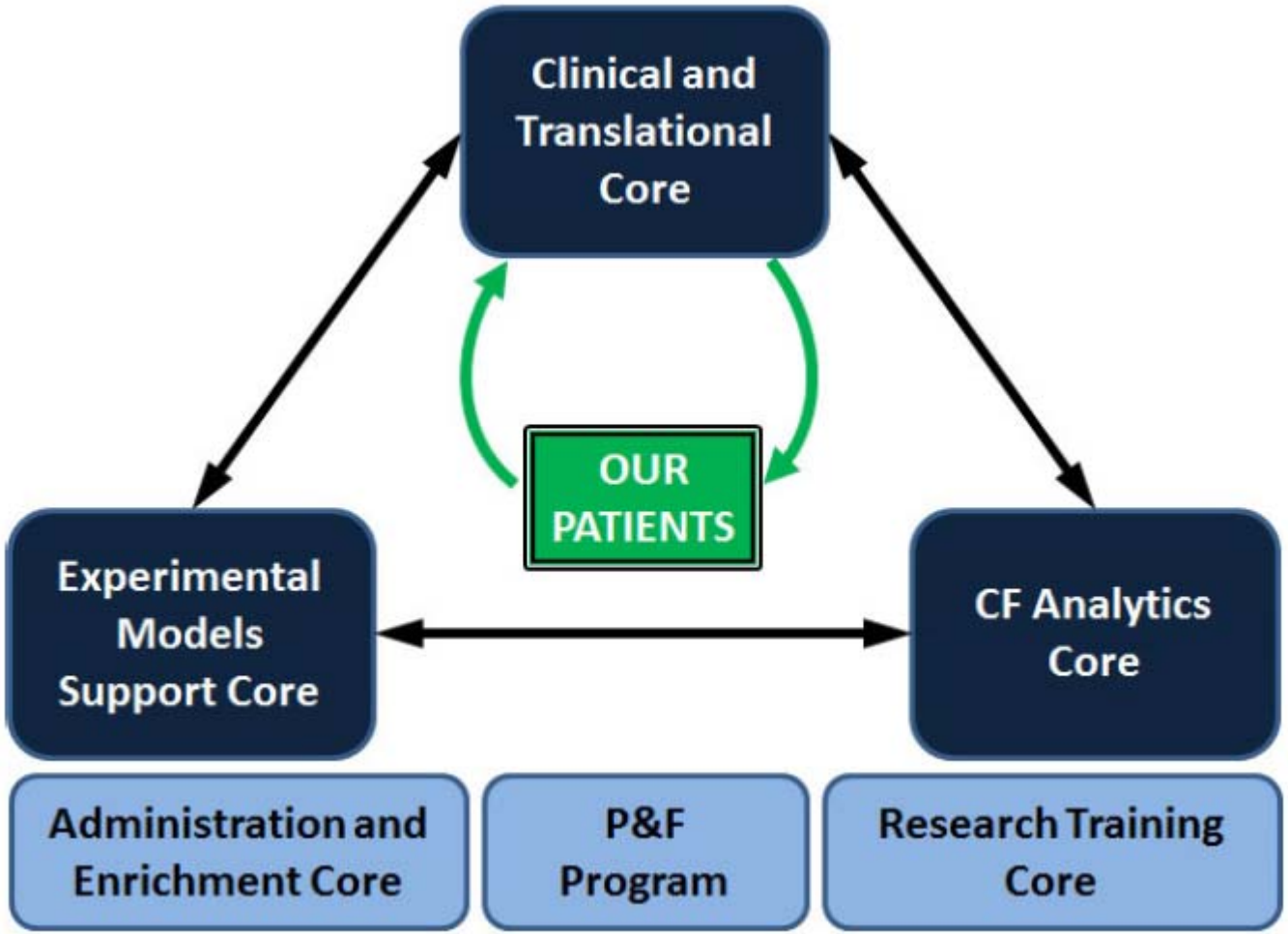
Director, Clinical & Translational Research Core for CF@LANTA RDP
November 4, 2015

Overarching Goal CF@LANTA

- Promote interdisciplinary research in CF pathogenesis & translate new knowledge into improved preventive & personalized therapies
- Centered around 700 CF patients followed at our care center

Overall Organization of CF@LANTA



Overall Goals of Clinical & Translational Research Core

- Promote human subjects research in CF, with an emphasis on CF diabetes and on acute pulmonary exacerbations
  - **Banking:** Develop a biospecimen repository where each biologic sample has a complimentary & detailed description of the clinical phenotype at the time of collection
  - **Prospective:** Provide tailored specimen collection to match specific investigators needs
  - **Creativity:** Stimulate new ideas. Bring new investigators to CF

Specific Aims

1. Develop Standard Operating Procedures (SOPs) for Biospecimen Collection
2. Manage CF Biospecimen Repository (CFBR) & Build Portfolio of Banked Specimens
3. Manage CFF Clinical Data Registry & Enhance Depth/Quality of Data Collected
4. Provide Translational & Clinical Research Support/Consultation for Human Studies
5. Provide Biostatistics & Data Management

Aim 1. Develop Standard Operating Procedures (SOPs) for Biospecimen Collection

- Four SOPs Refined: Exhaled breath condensate (EBC), sputum (microbes & supernatant), serum & platelet poor plasma
- Collection & storage personalized for current core investigators needs as well as future needs
- Dr M. Brown trained all research staff for Emory Adult CF & Emory+Children's Pediatric CF programs on processing
- Dedicated lab space on third floor identified and being equipped with all needed equipment and supplies
- To do site visit at Scottish Rite CF Pediatric program

Format SOPs

SPUTUM PROCESSING **STANDARD OPERATING PROCEDURE** **Version 1**

Cystic Fibrosis Biospecimen Registry

APPROVALS

RDP Clinical and Translational Research Core Director	**Arlene Stecenko, MD**	Date: 8/12/2015
Scientific Advisor	**Joanna Goldberg, PhD & John Varga, PhD**	Date: 8/8/2015
Scientific Advisor	**Rabin Tirouvanziam, PhD**	Date: 8/8/2015
Scientific Advisor	**Nael McCarty, PhD**	Date: 8/12/2015

Prepared by: Maret Maliniak, Julie Flores, and Arlene Stecenko

1. **PURPOSE**
   1.1 This procedure describes a standardized method for processing expectorated and induced sputum for use by scientific researchers for measurement of metabolomics, bacterial quorum sensing molecules, the microbiome, metagenomics, cytokines, chemokines, proteases, and other assays that may be shown to be useful in the future. Although not described herein, this procedure is designed such that viable host cells could be retrieved if needed.

2. **SCOPE**
   2.1 This procedure applies to all three programs of the Emory University and Children's Healthcare of Atlanta Adult and Pediatric Cystic Fibrosis Clinics and hospitals that are processing sputum for the Cystic Fibrosis Biospecimen Registry (CFBR).

3. **DEFINITIONS**
   3.1 Expectorated sputum: sputum produced spontaneously by coughing
   3.2 Induced sputum: non-invasive procedure to induce a sputum specimen by having a subject inhale 4-5 mL of 7% hypertonic saline through a nebulizer and coughing at intervals to collect sputum.

4. **REFERENCES**
   4.1 Tirouvanziam, R., Gernez, Y., Conrad, C. K., Moss, R. B., Schrijver, I., Dunn, C. E., Herzenberg, L. A. (2008). Profound functional and signaling changes in viable inflammatory neutrophils homing to cystic fibrosis airways. Proc Natl Acad Sci U S A, 105(11), 4335-4339. doi: 10.1073/pnas.0712386105
   4.2 Hector, A., Jonas, F., Kappler, M., Feilcke, M., Hartl, D., Griese, M. (2010). Novel method to process cystic fibrosis sputum for determination of oxidative state. Respiration, 80(5):393-400. doi: 10.1159/000271607. Epub 2009 Dec 23.

- Collaborative effort core investigators, CFBR research staff, CFBR Director
- Once approved, only CFBR Director can make changes
- Format – purpose, equipment, supplies, solutions, processing, labelling, storage, clinical state at time of collection (stable vs APE vs recovering from APE, oral intake, FEV1 – baseline and at time sample taken, what inhaled antibiotic when sample taken)

Aim 2. Manage CFBR: Study Methods for CFBR

1. Identify eligible patients attending the adult or pediatric CF clinics at Emory or Children's
2. Approach patients in clinic, explain the study, and consent if willing to participate
3. Ask participating patients each time they are in clinic or the hospital if they want to donate samples
4. Collect blood, sputum, bronchoalveolar lavage fluid, and/or nasal scrapings from the subject
5. Process samples immediately and store
6. Link each sample to clinical data

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Aim 2. Manage CFBR & Build Portfolio of Banked Specimens

- Build on work done since CFBR started in Aug 26, 2010
- With additional resources from the RDP, recruited more research coordinators and replaced data manager
- Emory/Children's team → Jane Wei, Julie Flores, Chris Driggers, Miti Gandhi, Joy Dangerfield, Eric Hunter

Aim 2. Manage CFBR & Build Portfolio of Banked Specimens – cont'd

- Prioritized work flow based on currently funded research studies requiring specimens. Realized needed samples when clinically stable (cross sectional studies) and also during an acute pulmonary exacerbations (APE)
- Identified 220 high value CF patients at Emory (adult and pediatric) based on having 1 to 3 APEs per year.
- Focus: collecting every time in clinic and when hospitalized → clinically stable, pre-APE (no symptoms, clinically stable, and about to have an APE within the next 3 months), APE severe enough to require hospitalization, response to treatment for APE, recovery from APE

Aim 2 Results: Inception in Aug 2010 to October 2015

- 497 adult and pediatric CF patients enrolled
  - Emory Adult CF Clinic – 194 out of 280 patients (69%) enrolled
  - Emory Pediatric CF Clinic – 114 out of 230 patients (50%) enrolled
  - Scottish Rite Pediatric CF Clinic – 138 out of 170 patients (81%) enrolled
- 3,321 specimens collected
- 7,589 aliquots banked

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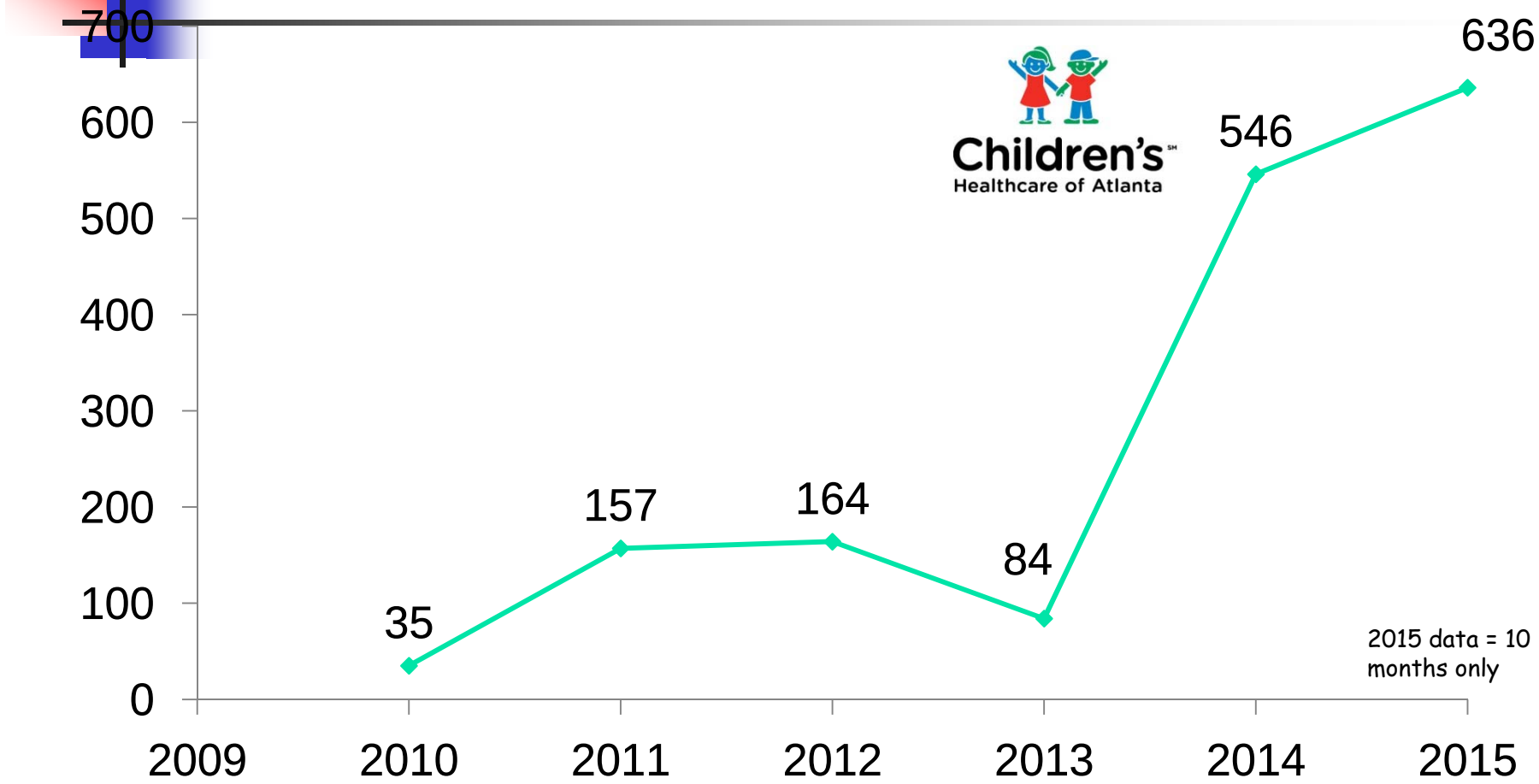
Number of Specimens Collected Per Year
Excluding bacterial isolates



Aim 3. Manage CF Clinical Data Registry & Enhance Depth/Quality of Data Collected

- CFF Registry
  - Clinical data on each patient at clinic and during hospitalization
  - Includes demographics, health outcomes (lung function, nutrition, pulmonary exacerbations), airway microbiology, adherence to CFF care and prevention guidelines, treatments, and complications
  - Problem – data cross sectional by group and not longitudinal by cohort or individual

Aim 3. Manage CF Clinical Data Registry & Enhance Depth/Quality of Data Collected – cont'd

- Importing key data from CFF Clinical Registry each year from 2010 onward for each patient to CFBR
- Longitudinal clinical data on Master Sheet
  - Demographics
  - Baseline FEV1 each year
  - OGTT each year
  - Airway microbiology each year

Aim 3. Manage CF Clinical Data Registry & Enhance Depth/Quality of Data Collected – cont'd

- Enhanced CFF Registry data in CFBR
  - Longitudinal data in individual or cohorts of subjects from 2010
  - Follow disease progression with aging or development of complication (CFRD, APE)
  - Follow disease improvement with intervention - Quality improvement, new therapies

Aim 3. Manage CF Clinical Data Registry & Enhance Depth/Quality of Data Collected – cont'd

- Linkage between CFF Registry & CFBR
  - Basic CFBR linkage = Cross sectional by sample and clinical state at time of sample
  - Advanced CFBR linkage = Longitudinal by clinical progression

Combination of CFF Clinical Registry & CF Biospecimen Repository: A Powerful Tool

Co-infection with *Staph aureus* and *Pseudomonas aeruginosa*

A Longitudinal Analysis of Chronic MRSA and *P. aeruginosa* Co-infection in Cystic Fibrosis: A Single-Center Study

Maret L. Maliniak, Arlene A. Stecenko, Nael A. McCarty

- 354 CF patients at Emory Adult CF clinic and Emory+Children's Pediatric CF clinic followed from 2007 to 2013
- Classified according to whether had chronic co-infection with MRSA and pseudomonas, chronic infection with either, or neither
- Correlated infection status with rate of decline in FEV1 and in rate of APE needing intravenous antibiotics

Results: Maliniak

- **Rate of Decline in % FEV1.0**
  - Adjusted for age, sex, baseline FEV1, CFRD, B cepacia, average rate of decline significantly greater with co-infection compared to either alone, or neither
  - Co-infection = 2.77% decrease/year
- **Rate of APE**

AVERAGE NUMBER OF APEs NEEDING IV ANTIBIOTICS PER YEAR BY INFECTION STATUS

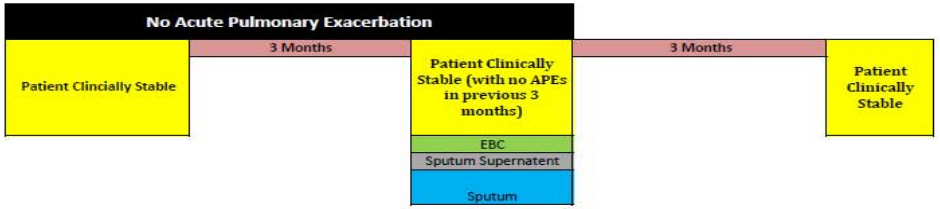
Infection Status*	Adjusted IRR†	95% CI	P Value
Chronic Co-infection vs. Chronic PA alone	1.24	1.01, 1.52	0.04
Chronic Co-infection vs. Chronic MRSA alone	1.34	1.03, 1.74	0.03
Chronic Co-infection vs. Intermittent infection	1.56	1.21, 2.01	<0.001
Chronic Co-infection vs. No MRSA/PA	2.00	1.54, 2.61	<0.001

Aim 4. Provide Translational & Clinical Research Support/Consultation for Human Studies

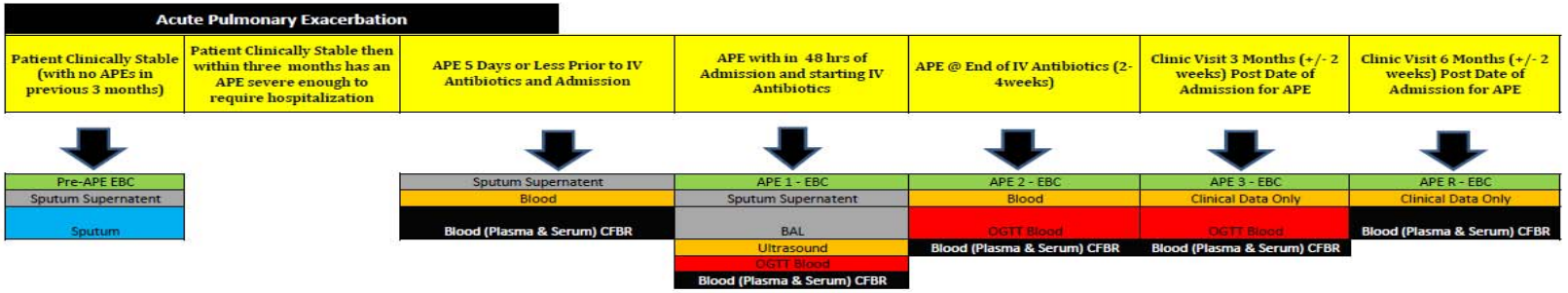
- Support both cross sectional and longitudinal studies
- Increase efficiency – one patient may provide samples for more than one study at the same time
- Consistency of definitions
- Decrease misclassification of clinical state
  - Defining CF without diabetes as absence of clinical diagnosis of diabetes and treatment with insulin
  - Defining clinical stable CF as absence of clinical diagnosis of APE

Roadmap for APE Studies

VERSION September 3, 2015



APE Definition = increase in symptoms (cough, sputum production) and/or new findings on chest exam PLUS decrease in Baseline FEV1 by 10% or more
Definition of Baseline FEV1 represents the avg of the best % FEV1 for each quarter in the previous calendar year
Definition of Clinically Stable = no increase in symptoms, lung exam at baseline, FEV1 within 10% of baseline, AND not placed on oral antibiotics



Inclusion Criteria
- Clinically Stable for 2 clinic visits in a row OR
- Clinically Stable then subsequent 3 month APE
- Normal OGTT w/in 6 months OR
- Prediabetic OGTT w/in 6 months OR
- CFRD on insulin
- CF or Healthy controls
- No APE in previous 3 months
- APE severe enough to require admission
- Complete at least 14 days of iv antibiotics
- APE severe enough to require admission
- Normal OGTT done in previous 12 months prior to enrollment
CF, healthy controls, disease controls

PI	Age Group	Sample Size
Facundo	≥ 7yrs	50
Joanna	10-39	30
Rabin	All	280
Jay	8-18yrs	20
Stecenko	8-21yrs	20
CFBR	All	All

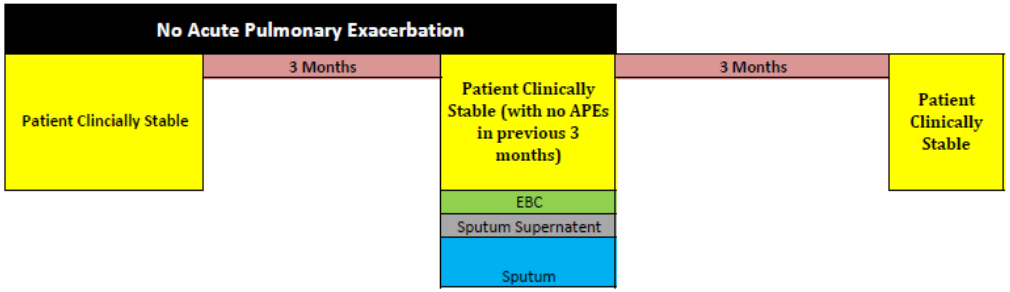
Roadmap for APE Studies: Definitions

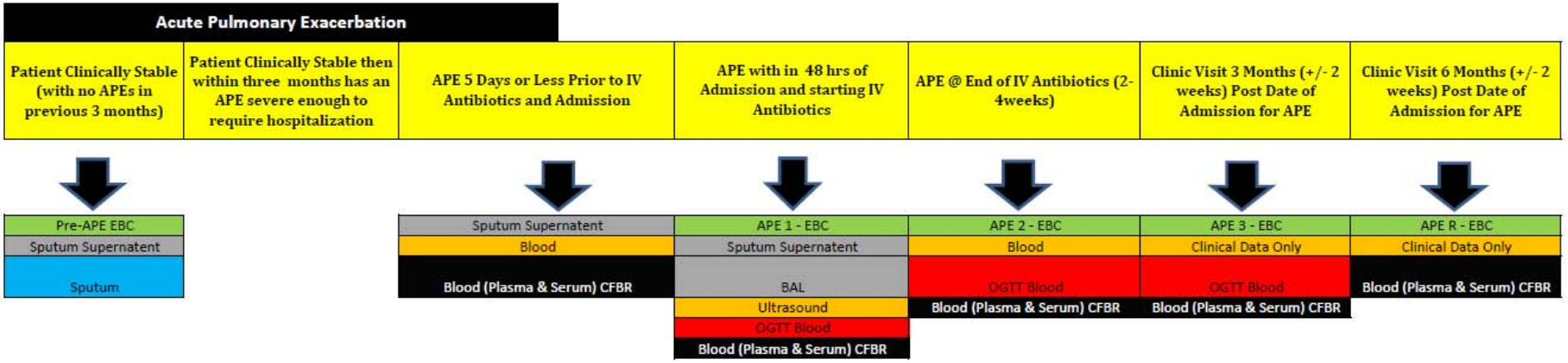
APE Definition = increase in symptoms (cough, sputum production) and/or new findings on chest exam PLUS decrease in Baseline FEV1 by 10% or more
Definition of Baseline FEV1 represents the avg of the best % FEV1 for each quarter in the previous calendar year
Definition of Clinically Stable = no increase in symptoms, lung exam at baseline, FEV1 within 10% of baseline, AND not placed on oral antibiotics

Roadmap for APE Studies: Funded Studies

PI	Age Group	Sample Size	Inclusion Criteria
Facundo	≥ 7yrs	50	- Clinically Stable for 2 clinic visits in a row OR - Clinically Stable then subsequent 3 month APE
Joanna	10-39	30	- Normal OGTT w/in 6 months OR - Prediabetic OGTT w/in 6 months OR
Rabin	All	280	- CFRD on insulin
Jay	8-18yrs	20	- CF or Healthy controls
Stecenko	8-21yrs	20	- No APE in previous 3 months - APE severe enough to require admission - Complete at least 14 days of iv antibiotics
CFBR	**All**	**All**	- APE severe enough to require admission - Normal OGTT done in previous 12 months prior to enrollment **CF, healthy controls, disease controls**

Roadmap for APE Studies: Specimen Collection





Additional Goals for Next 8 Months

- Develop joint services with other Cores in RDP
  - Cell Models Core -> nasal epithelial cells & airway epithelial cells from lung transplant
  - Analytic Core → human samples for measures of redox balance/oxidative stress
- Start Director's Fund
- Market Clinical Core's expertise
- Other suggestions ?