Children's Hospital Colorado
Breathing Institute

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Overview of Rare Lung Diseases: Challenges and Research Opportunities

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School of Medicine
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ANSCHUTZ MEDICAL CAMPUS

Faculty Disclosures: *ATS 2016 San Diego*

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<Robin Deterding, MD>

- **Relevant financial relationships with a commercial interest:**
  - **No financial disclosures**

Key areas of challenge and opportunities

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- Phenotypes
- Omics & big data
- Treatment
- Outcomes
- Development
- Prevention
- It takes a village!

RARE LUNG DISEASE IS…..
PEDIATRIC PULMONARY DISEASE

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- Rare disease is one that affects fewer than 200,000 people in the United States
- Nearly 7,000 rare diseases
- More than 25 million Americans have one
- Often have no treatment or not very effective treatment
- Are frequently not diagnosed correctly
- Are often very complex
- Hard to find a specialist
- Are often caused by changes in genes

Rare Disease Pardigm: CF story

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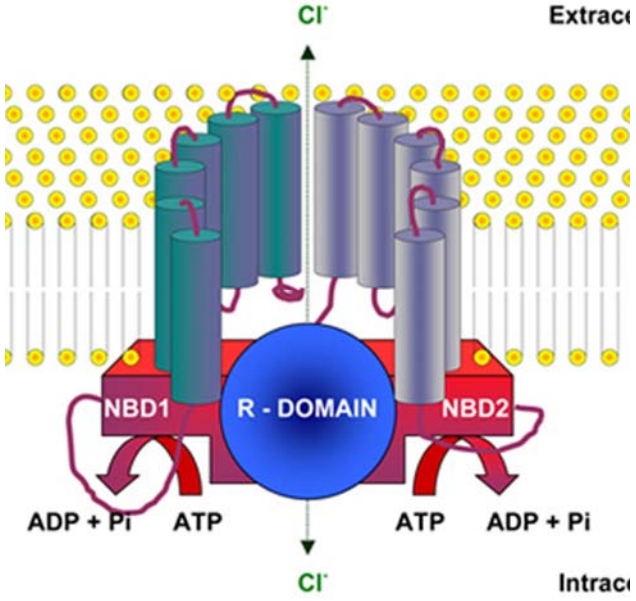

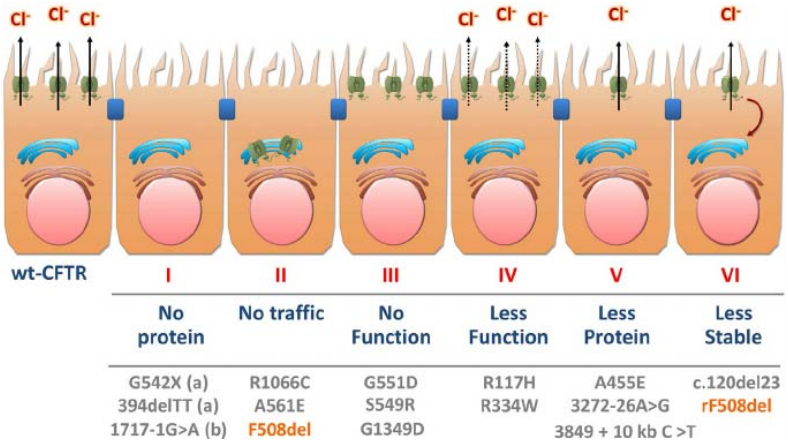

1989 opened the path to mechanisms & understanding

No cure but improved mortality

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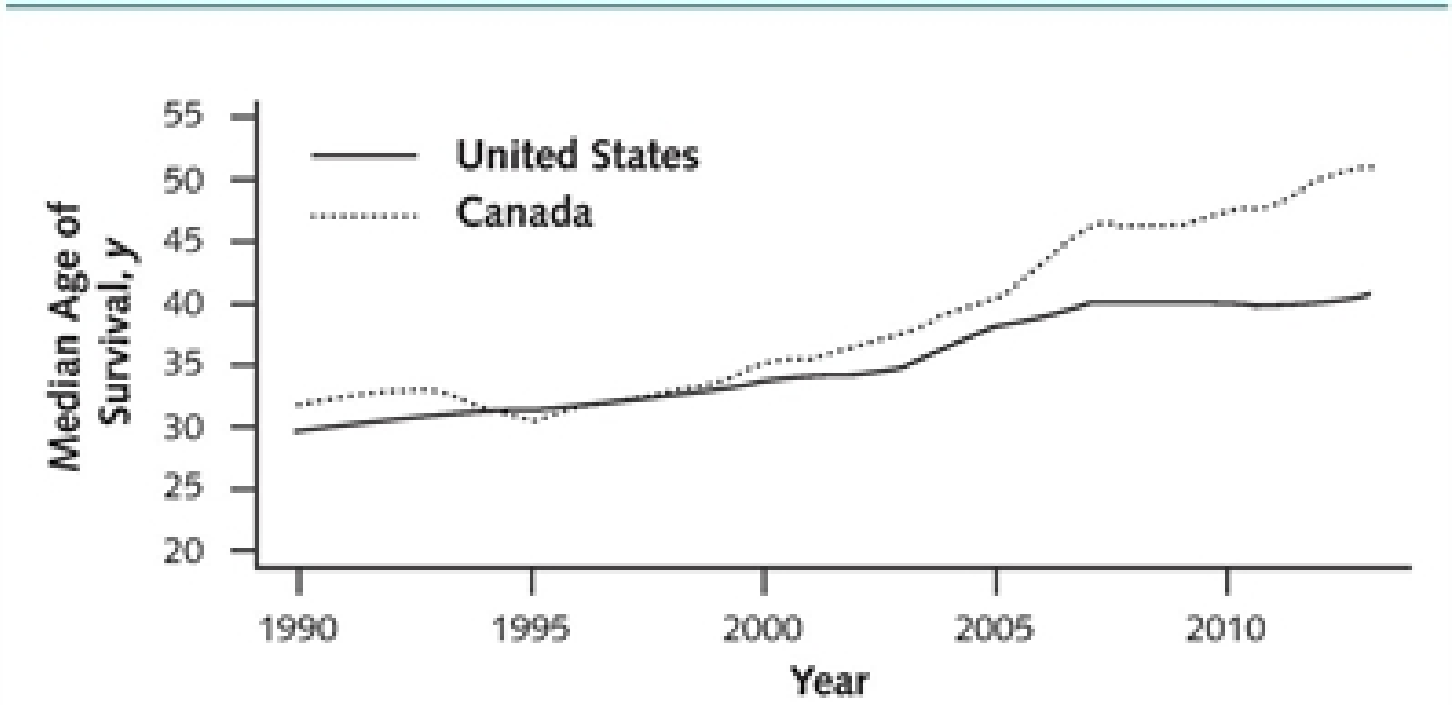
More than the gene - Many variables



Annals of Internal Medicine, 4/18/2017, Vol. 166 Issue 8, p537-546, 11p, 4 Charts, 2 Graphs; Graph; found on p539

Genes alone aren't the whole story:

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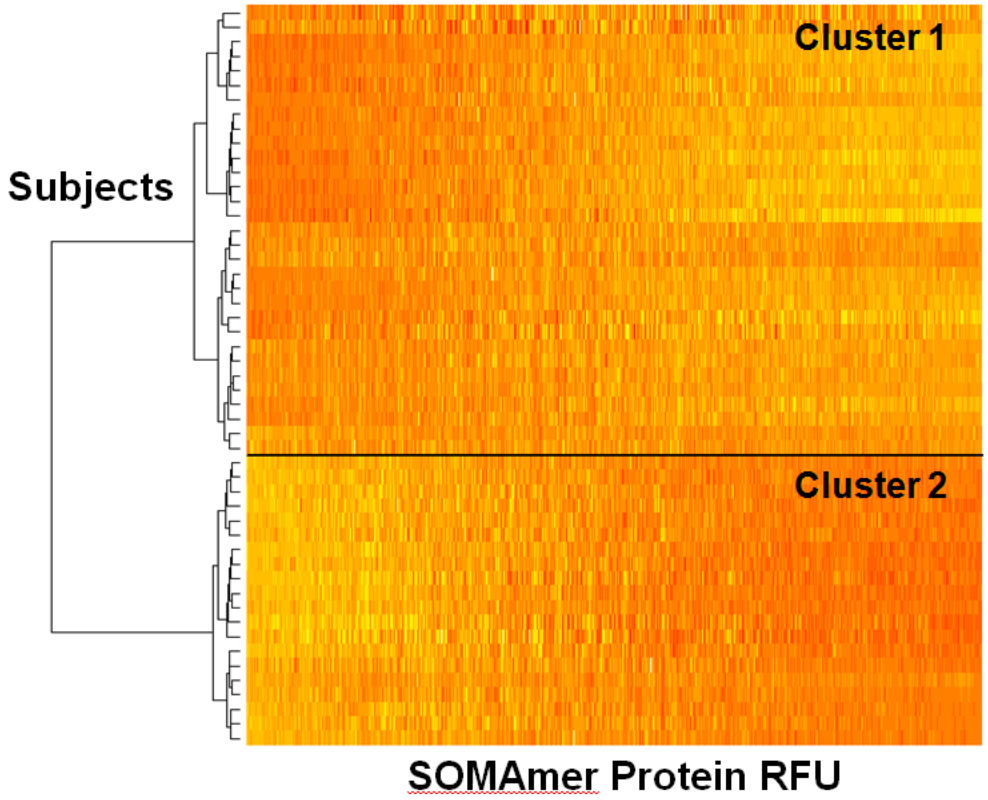
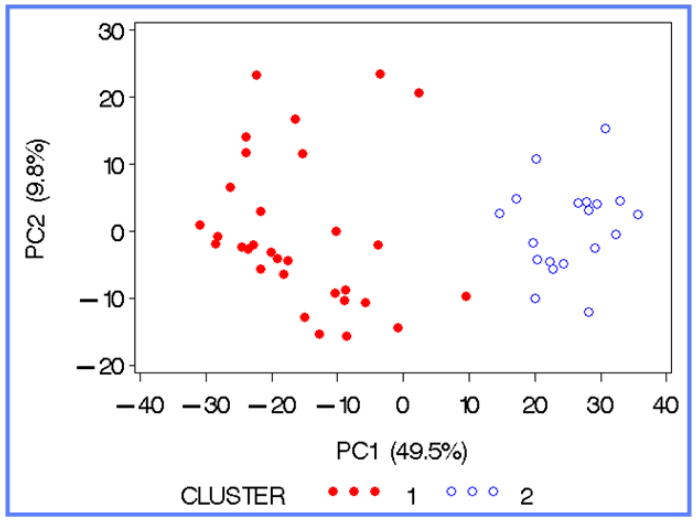
Unbiased Protein Analysis BALF





Heatmap showing 2 distinct clusters for CF samples across all measured proteins (**red low**; **yellow high** RFU)

Clinical metadata -
To understand differences

But what about Sickle Cell and Others

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- Clinically discovered in 1910
- A single gene mutation on chromosome 11 that codes for the beta subunit of the hemoglobin protein – discovered 1956
- Most common among people from Africa, India, the Caribbean, the Middle East, and the Mediterranean

New Genetic Disease

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Disease	Genetic Defect
Lethal Cystic Lung disease	FLNA (filamin A, alpha) mutations
Severe pediatric PAP	MARS (Methionyl-tRNA synthetase) mutations
Autoimmunity with arthritis, vasculitis and chILD	COPA (Coatomer subunit alpha) mutations
Immunodeficiencies with monocytopenia, infections, lymphatic abnormalities, chILD and PAP	GATA-2 transcription factor mutations
Immune mediated lung disease – GLILD/ CVID like	LRBA (lipopolysaccharide-responsive and beige-like anchor protein) mutations
Immune mediated lung disease – GLILD/ CVID like	CTLA 4 haploinsufficency

The list will grow exponentially

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Genes are important ….
So is phenotype

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Rare Disease Phenome –is critical!

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"Getting ready for the Human Phenome Project"

Rare Disease Phenome Definition:

set of all phenotypes expressed by a cell, tissue, or organ. Just as the genome and proteome signify all of a childs genes and proteins, the phenome represents the sum total of a child's phenotypic traits

Hum Mutat. 2013 Apr;34(4):661-6. doi: 10.1002/humu.22293

Rare Disease Phenome –is critical!

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- Defining chILD diseases
- Finding chILD patients
- Capturing chILD the Phenome
- Phenome/ genome
- Phenome/ mechanisms
- Phenome/ stem cells
- Outcomes for chILD

Progress in chILD since the 2004 RLDC meeting

2004	→ 2016
Case reports or small series	Multicenter publications
Inconsistent terminology	Consensus terminology
No standard case definitions	Pathology classification system
Genetic testing on research basis only	Genetic testing clinically available in CLIA certified labs
No multicenter studies	chILD Research Network National registry
No clinical standards	ATS clinical guideline
No ICD codes	ICD10 codes
No physician training	Inclusion in board exams
No organized family support or educational resources	Children's ILD Foundation; Annual conferences

Classification Spectrum of chILD**

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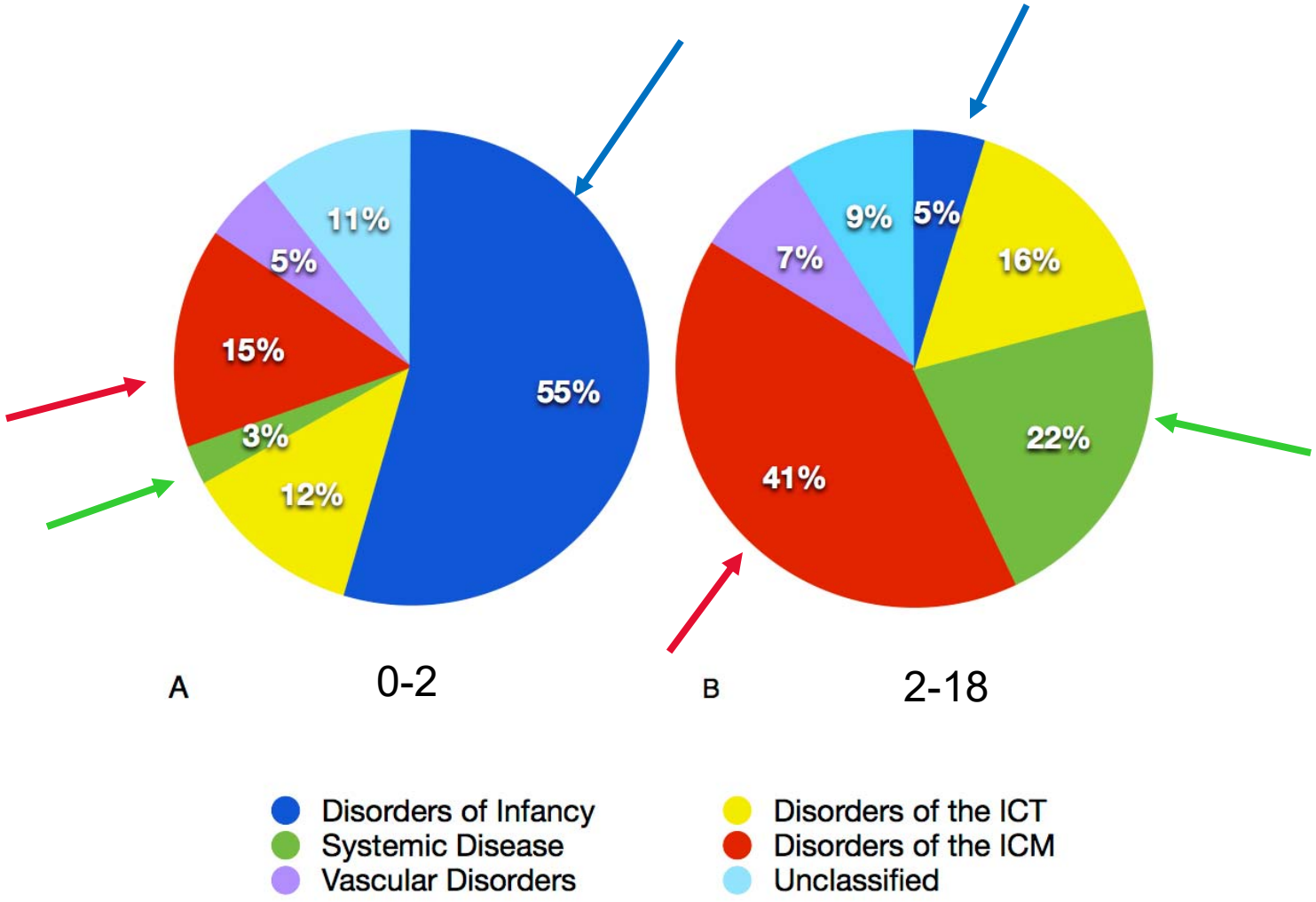

** Deterding, Ann Am Thorac Soc Vol 12, No 10, pp 1451–1457, Oct 2015

USE THE DIAGNOSTIC CODES!

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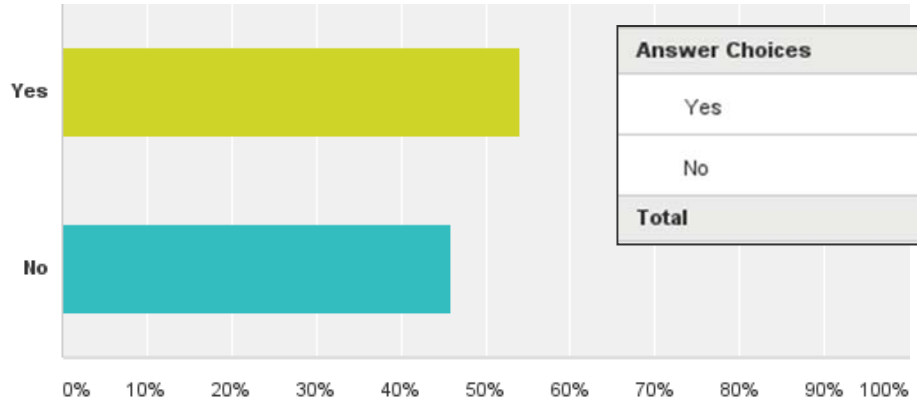
- **516.6 Interstitial lung diseases of childhood**
  - 516.61 Neuroendocrine cell hyperplasia of infancy
  - 516.62 Pulmonary interstitial glycogenosis
  - 516.63 Surfactant mutations of the lung
  - 516.64 Alveolar capillary dysplasia with vein misalignment
  - 516.69 Other interstitial lung disease of childhood

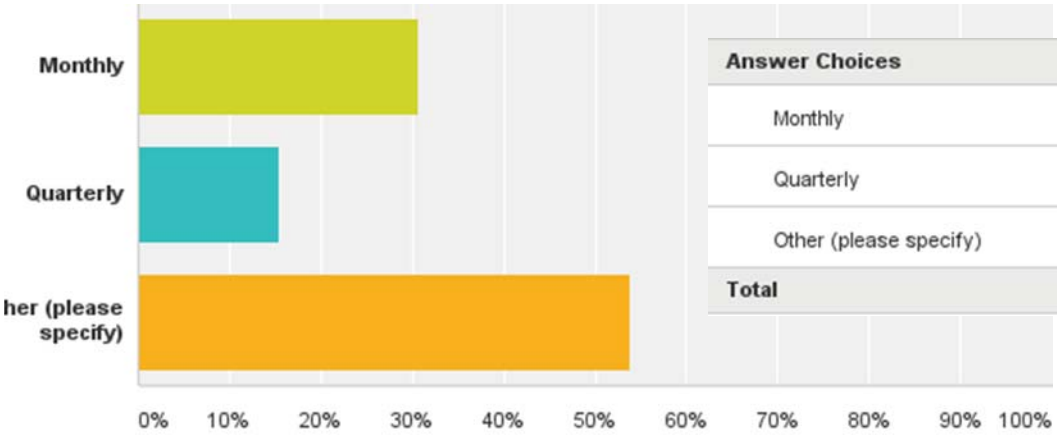
Rare Disease is a team sport!

Multidisciplinary review of chILD patients is part of clinic practice

Answered: 24 Skipped: 2



Answer Choices	Responses	
Yes	54.17%	13
No	45.83%	11
Total		24



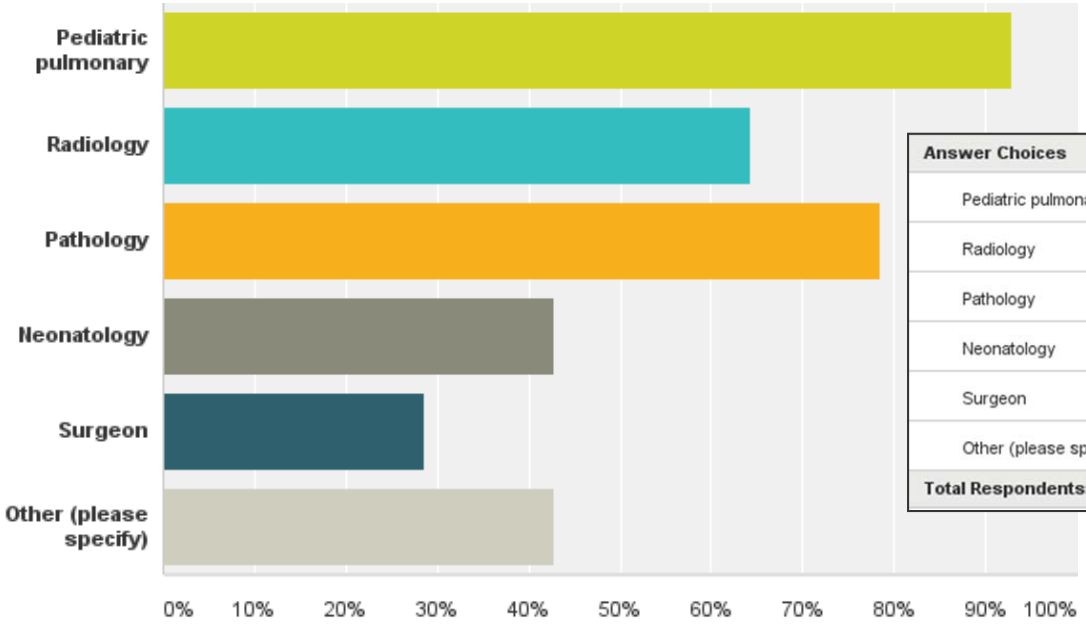
Answer Choices	Responses	
Monthly	30.77%	4
Quarterly	15.38%	2
Other (please specify)	53.85%	7
Total		13

State of chILDRN US
- chILD Center Survey, 2016

Rare Disease is a team sport!

If yes, who attends these meetings? (check all that apply)

Answered: 14 Skipped: 12



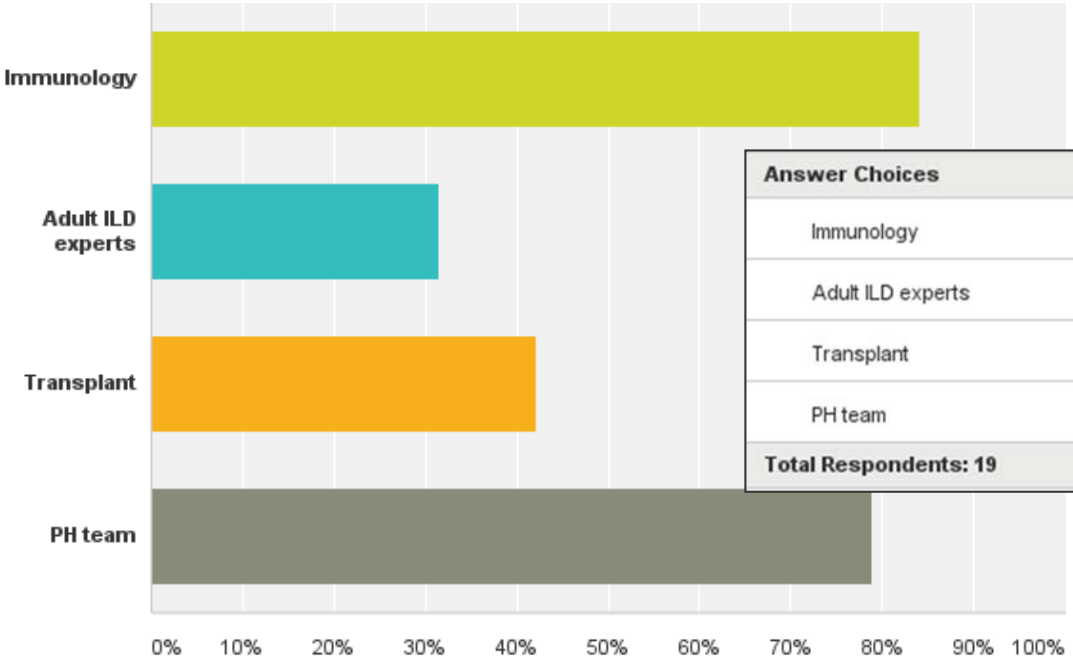
Answer Choices	Responses	
Pediatric pulmonary	92.86%	13
Radiology	64.29%	9
Pathology	78.57%	11
Neonatology	42.86%	6
Surgeon	28.57%	4
Other (please specify)	42.86%	6
Total Respondents: 14		

State of chILDRN US
- chILD Center Survey, 2016

Rare Disease is a team sport!

Do you have interaction with the following on chILD patients as part of your team? (check all that apply)

Answered: 19 Skipped: 7



Answer Choices	Responses	
Immunology	84.21%	16
Adult ILD experts	31.58%	6
Transplant	42.11%	8
PH team	78.95%	15
Total Respondents: 19		

State of chILDRN US
- chILD Center Survey, 2016

Objectives: National chILD Registry

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- To advance knowledge on the prevalence, clinical features, management, and outcomes of children with these rare lung diseases
- To facilitate scientific discovery and additional research in this field

Initial Motivation: To reduce the regulatory and operational barriers to our collaboration and work as a network

chILD Approach

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- **IRBChoice** platform for reliance agreements
- Vanderbilt as coordinating center
- Children's Interstitial and Diffuse Lung Disease Research Network sites
- Prospective Longitudinal, observational study
- REDCap database – minimal data set
- Virtual repository

Beyond Genes: Big Data for Patients

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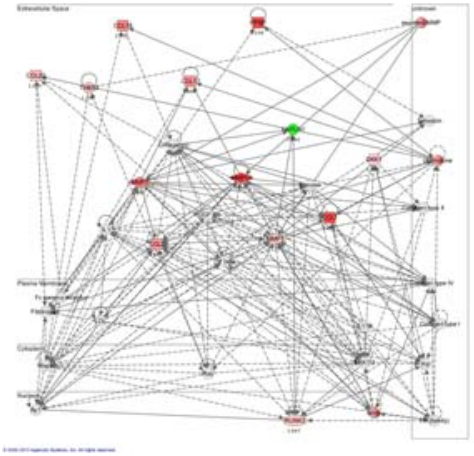
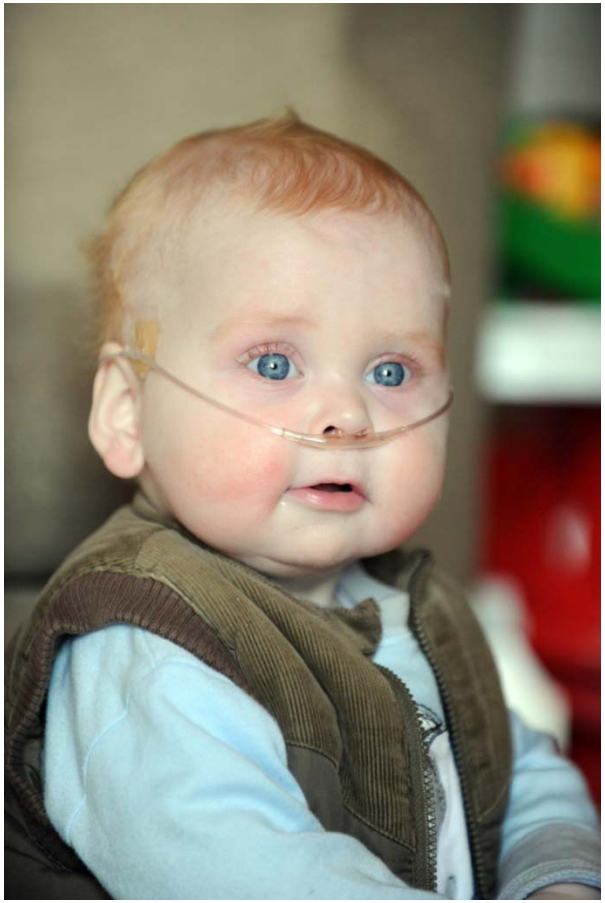
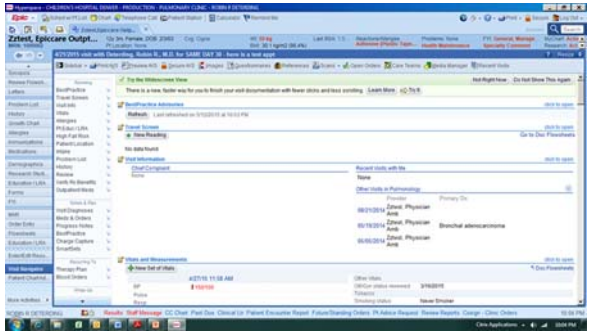
Proteins



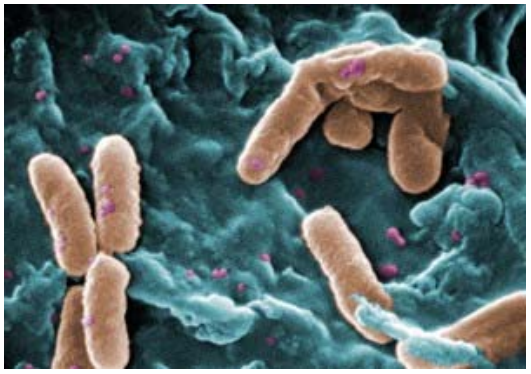
Genes



Phenotype



Microbiome



Treatment: Most NOT FDA or Studied

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Medication	Condition
Glucocorticoids; Pulse Solumedrol	Most – NOT NEHI
Azithromycin	Airway based disease; Surfactant?
IVIG	Immunodeficiency, Immune dysregulation, DAH
Hydroxychloroquine	Immune Modulation; Surfactant, Autophagy
Rituximab (Anti - CD20)*	Autoimmune; AAV*, APS-1
Cyclophosphamide	Autoimmune, AAV- DAH
Rapamycin	Immune dysregulation, Autophagy
Cyclosporine/ Tacrolimus	Autoimmune, Immune dysregulation
DMARDS: Disease Modifying Anti-Rheumatic drugs (Steroids, MTX, Azathioprine, etc)	Autoimmune, RA, JIA,

* FDA approved

Treatment: Most NOT FDA or Studied

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Newer Medication	Condition
Anti-IL-1; Anakinra (Kineret)/ Canakinra (Ilaris)	Macrophage activation Syndrome (MAS); sJIA, others?
Anti- IL-6; Tocilizumab (Actemra)	Macrophage activation Syndrome (MAS); sJIA, others?
Ofev (Nintedanib)*	IPF – not in children
Esbriet (pirfenidone)*	IPF – not children
Anti-IL-5; NUCALA (mepolizumab)	Eosinophilic pneumonia/ churg strauss syndrome
Abatacept (Orencia)*; Cytotoxic T Lymphocyte Antigen 4 (CTLA4)	sJIA*, LRBA (Lipopolysaccharide – responsive and beige- like anchor protein) – type of Common Variable Immunodeficiency (CVID)

* FDA approved

iPS - Inducible Pluripotent Stem Cells

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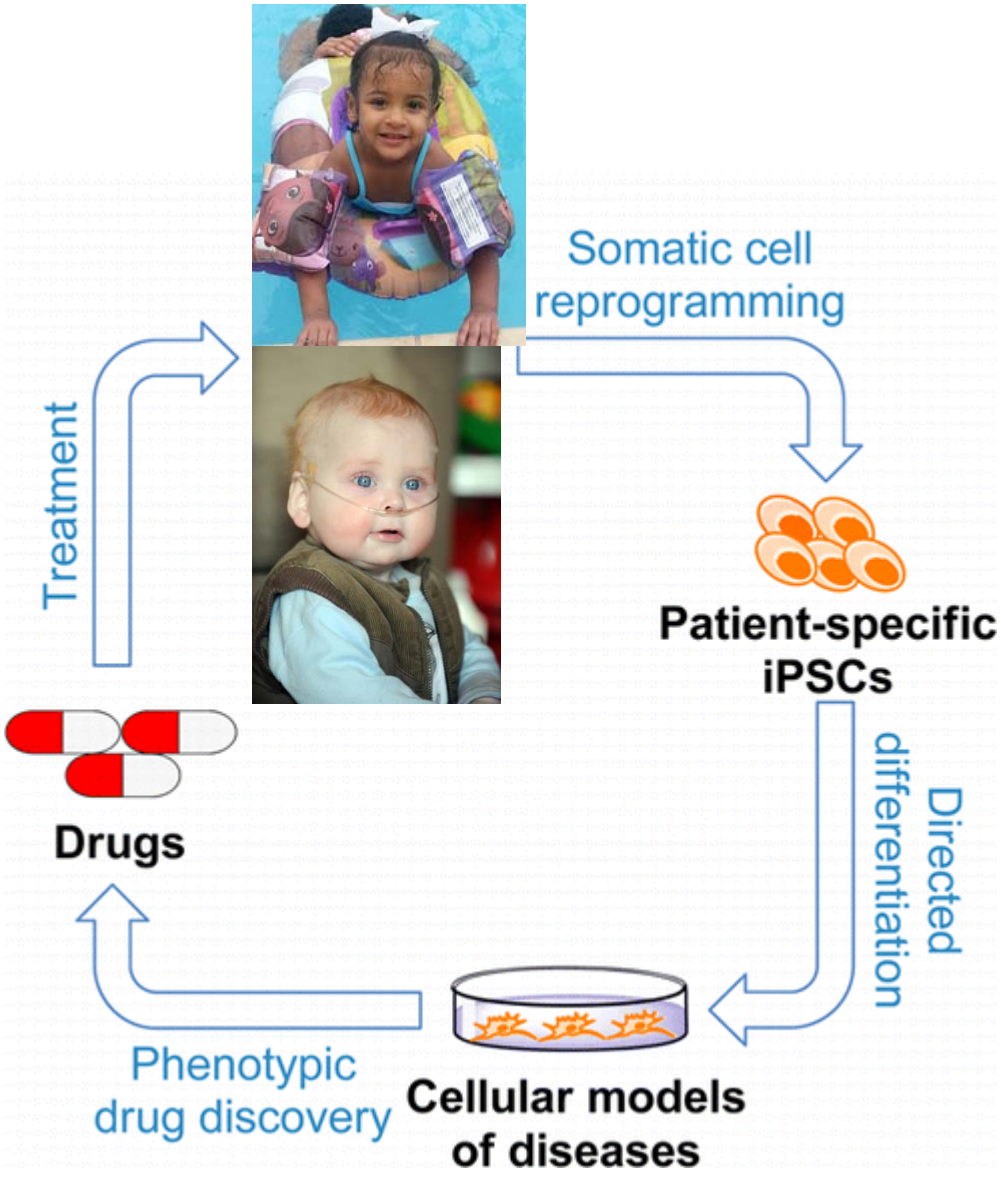

Gene editing

Tang, *J. Med. Chem.*, **2016**, *59* (1), pp 2–15

Regenerative strategies

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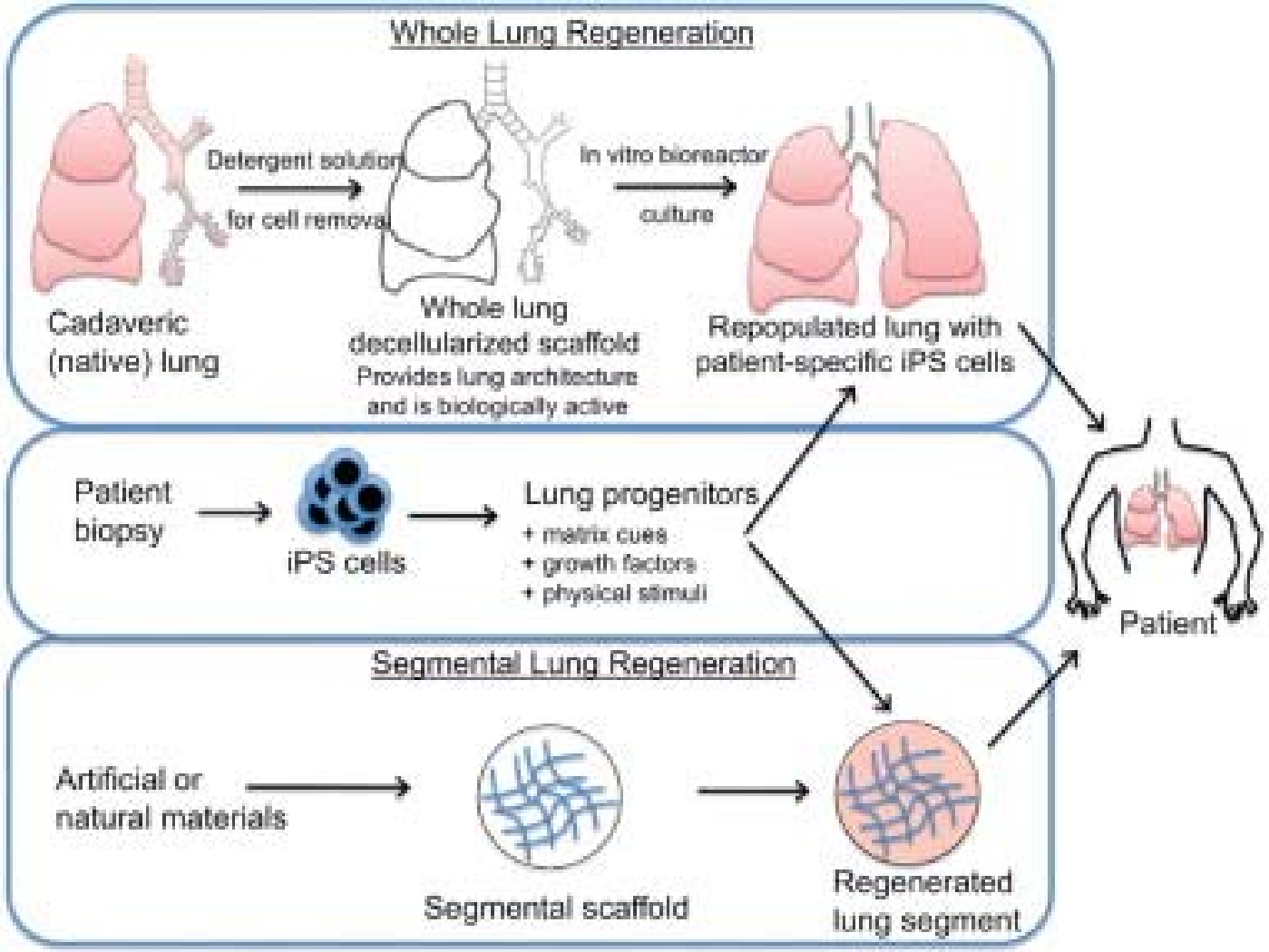

Petersen, Materialstoday, 6 MAY 2011 | VOLUME 14 | NUMBER 5

Novel transplantation: Macrophages

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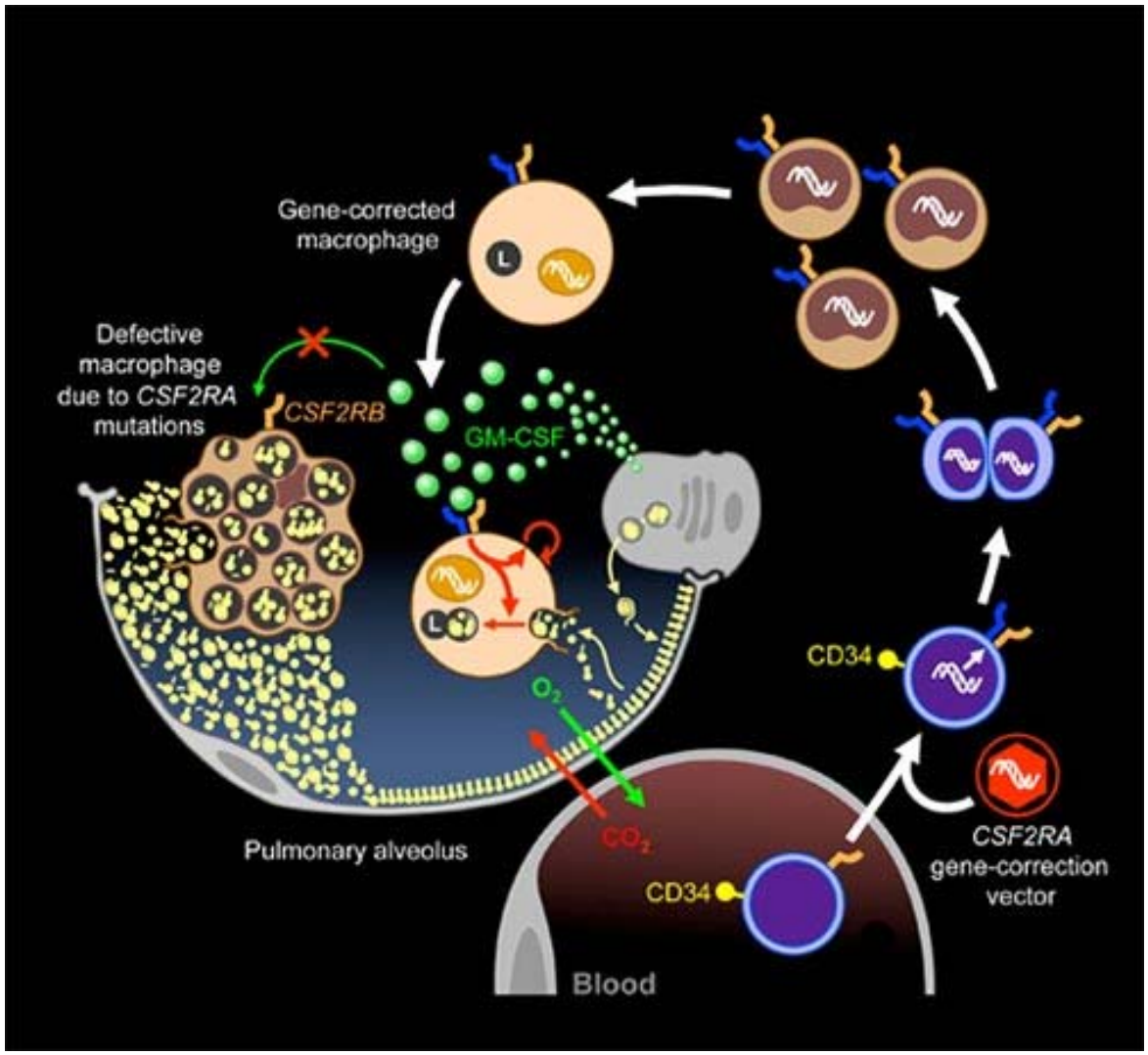

Suzuki T, Arumugam P, Sakagami T, Lachmann N, Chalk C, Sallese A, Abe S, Trapnell C, Carey B, Moritz T, Malik P, Lutzko C, Wood RE, Trapnell BC. Pulmonary macrophage transplantation therapy . Nature. 2014;514(7523):450-454.

Clinical Trials for Children

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- Patient Selection
- Novel Outcomes
  - Biomarkers – mechanism
  - Technology- Clinical outcomes
    - Remote monitoring
    - New devices

Pulmonary function measures derived from functional electrical impedance tomography in children with cystic fibrosis☆

Peter A. Muller, PhD, Jennifer L. Mueller, PhD*, Michelle M. Mellenthin, PhD, Rashmi Murthy, Michael Capps, Brandie D. Wagner, PhD, Melody Alsaker, PhD, Robin Deterding, MD, Scott Sagel, MD, PhD, Jordana Hoppe, MD

Lung Development – Critically important

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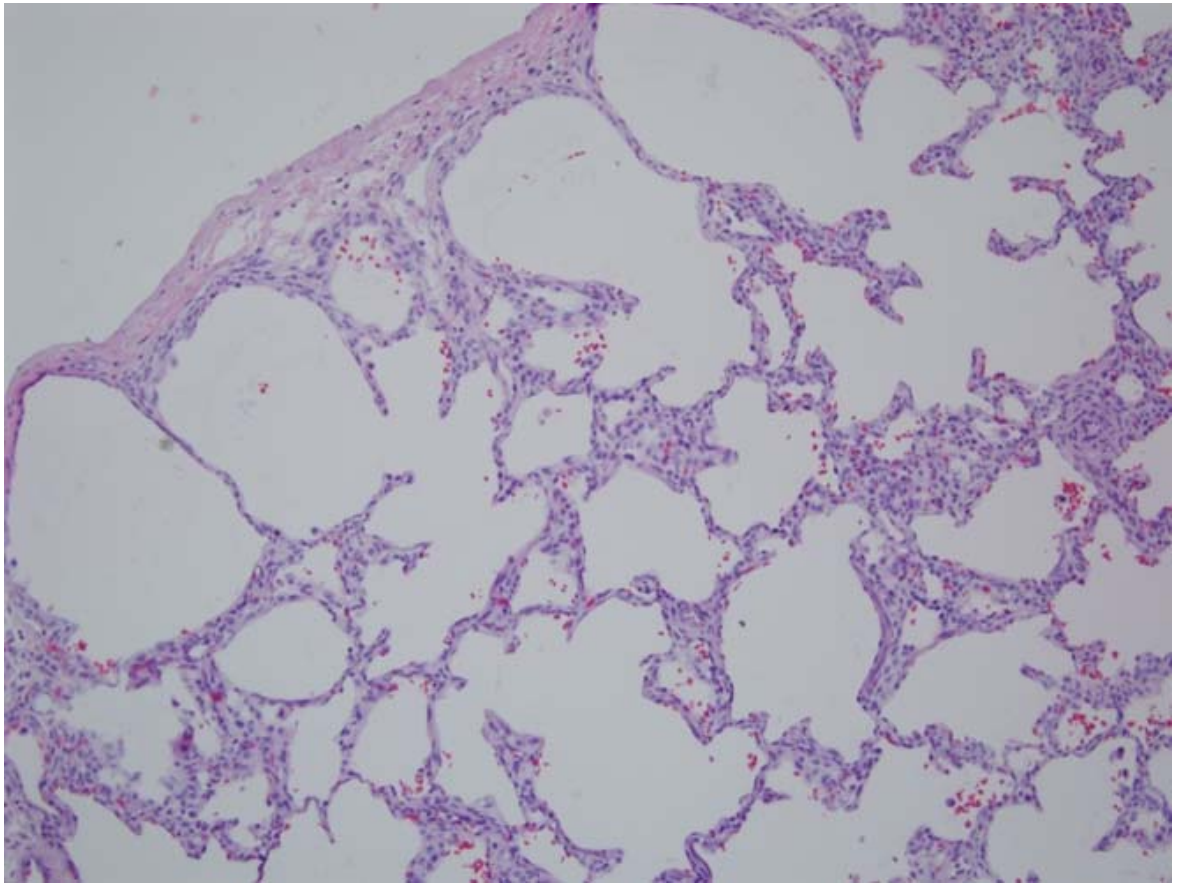
* Background of any pediatric disease
* Rare Disease Disorders Await Discovery



Lung Function is critical

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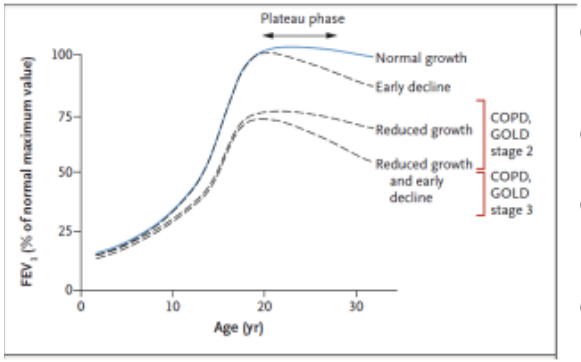
Long Term Risk for Lung Disease (asthma) in Adulthood

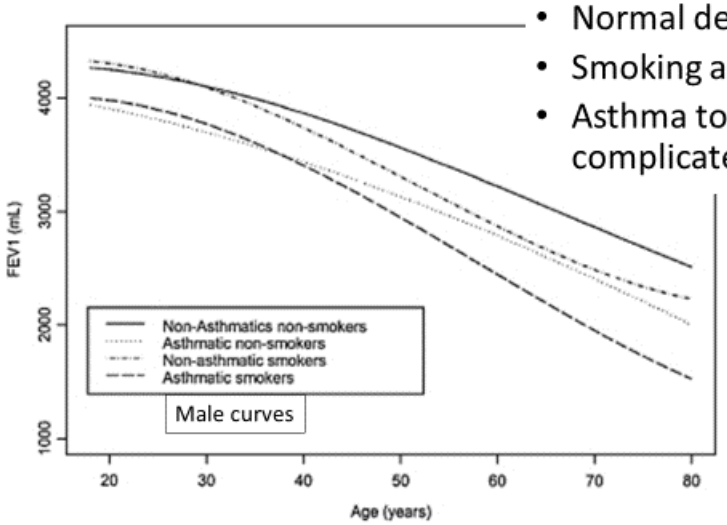


- Diagnosed with COPD, based on which pattern of reduced growth pattern:
- Only 1% with normal lung function developed COPD in adulthood.
- Normal growth but early decline — 5% developed COPD
- **Reduced growth** but no ea decline — 16% developed COPD
- **Reduced growth** and early decline — 21% developed COPD

McGeachie MJ. N Engl J Med 2

Normal lung function declines slowly over time after in your 20's

- Normal decline
- Smoking accelerates
- Asthma too – but more complicated



Brusselton Health Study: James AL. Am J Respir Crit Care Med. 2005 Jan 15;171(2):109-14.

Exposures and Prevention

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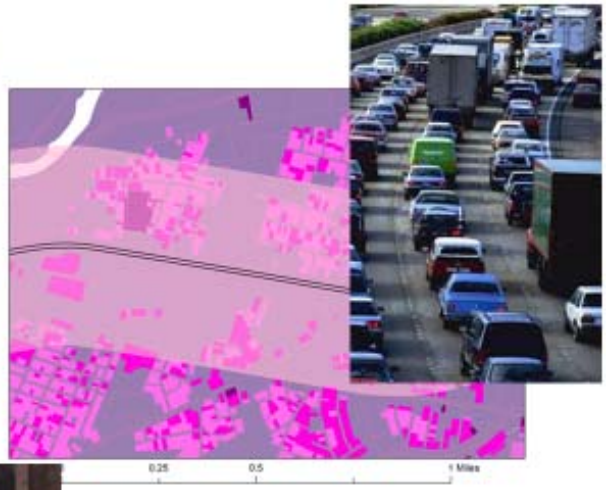

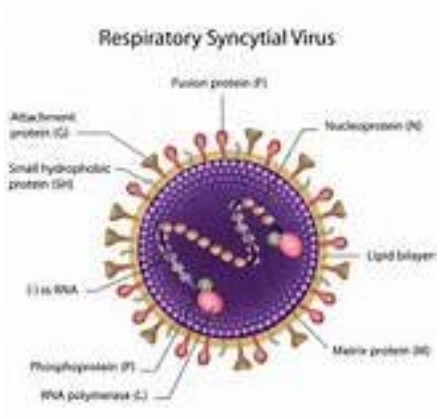

New innovations

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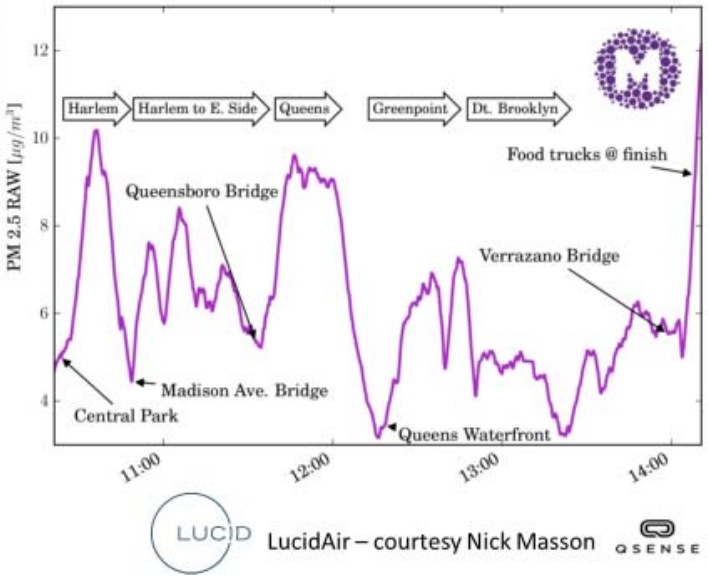
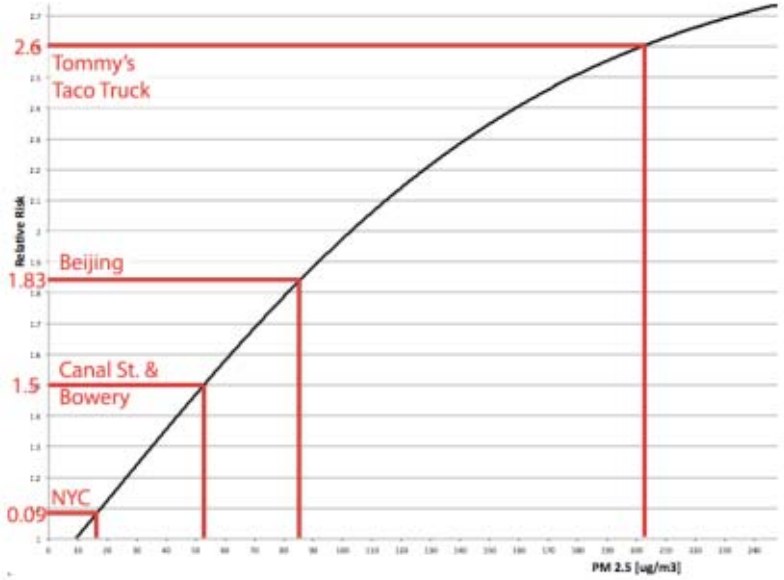
Personalized Environmental monitoring



LUCID LucidAir – courtesy Nick Masson QSENSE



LucidAir – courtesy Nick Masson

Common Prevention Strategies

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All chILD/ RARE DISEASE patients:

- Trial of pharmacological therapy closely monitored for side effects.
- Receive supportive and **preventive care**: (treatment of hypoxemia, nutritional failure, and comorbidities, as well as interventions to prevent infection)
- Receive education & support
- Genetic counseling should be made available to the family members of patients with genetic chILD
- Takes center structure and resources

Kurland, Deterding, Hagood, Young, et al., ATS Guideline, 2013

Patient and Family Powered!!!

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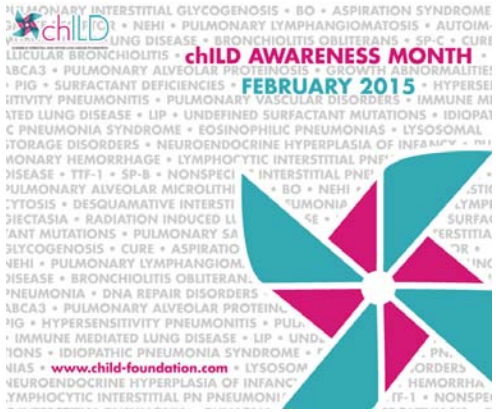
chILD Foundation 2004

- Advocacy
- Research
- Fund raising
- Get to Clinical Trials
- BE THE POWER!



chILD: Big Umbrella for Success

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- Similar presentations
- Similar physicians
- Parallel discovery
- Common experiences
- Stronger together
  - Organizationally
  - Fund raising
  - Education
  - Resources

- chILD Foundation – support it!

  http://www.child-foundation.com/
- chILD Research Network (chILDRN)
- EU chILD
- AUS chILD

Opportunities to Transform Rare Disease

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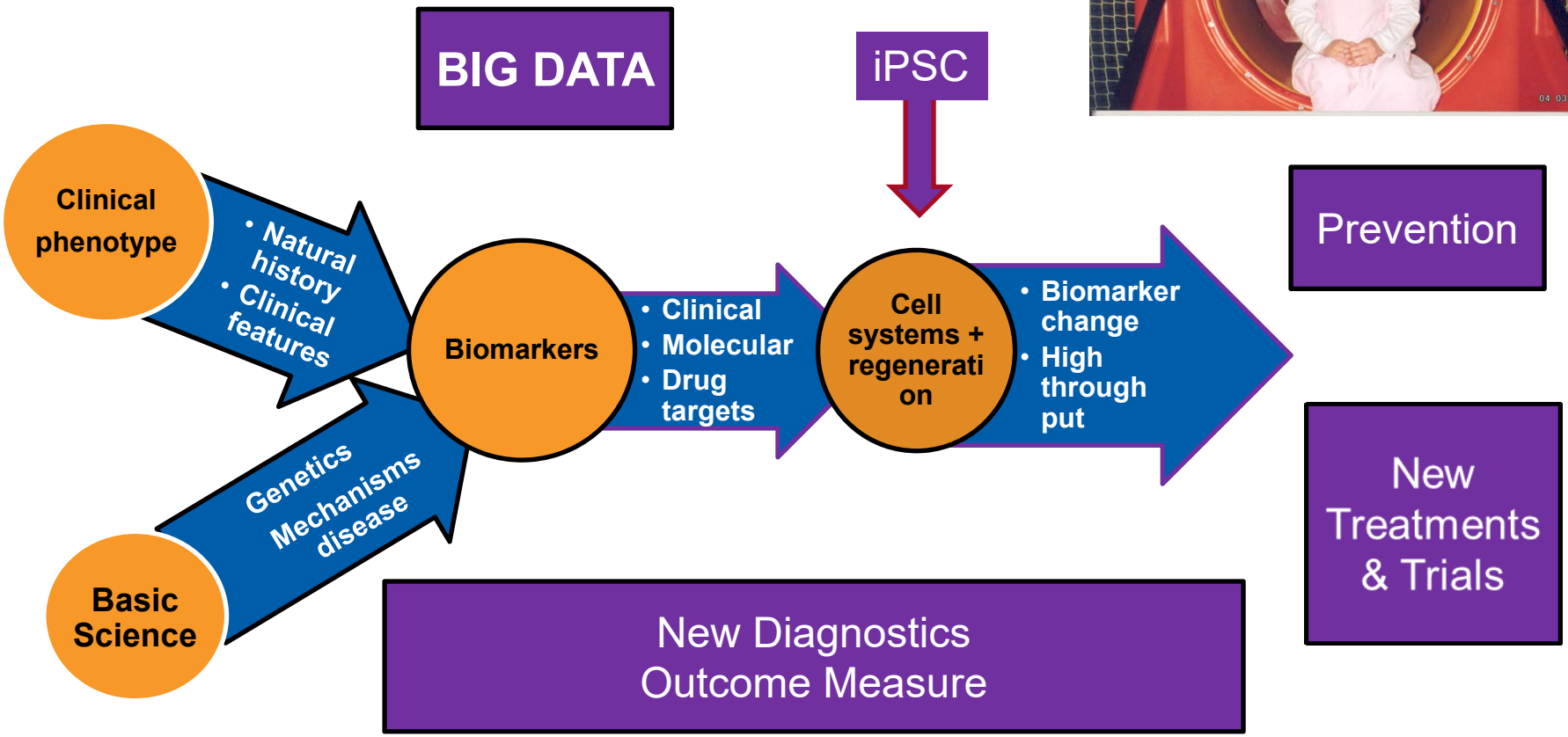
Patient Foundation + Physician & Scientific Collaboration



Future

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- It takes everyone!
- National prospective registry
- Many new genetic diseases – exome/ genomics
- IPS Stem cell banks – “no chILD left behind”
- Drug testing systems
- Clinical trials
- Novel outcome measures
- Gene correction strategy for mono-genetic disease