Advancing Endpoint Development for Preterm Neonates with Pulmonary Morbidities

The Duke-Margolis Center for Health Policy

October 2, 2018

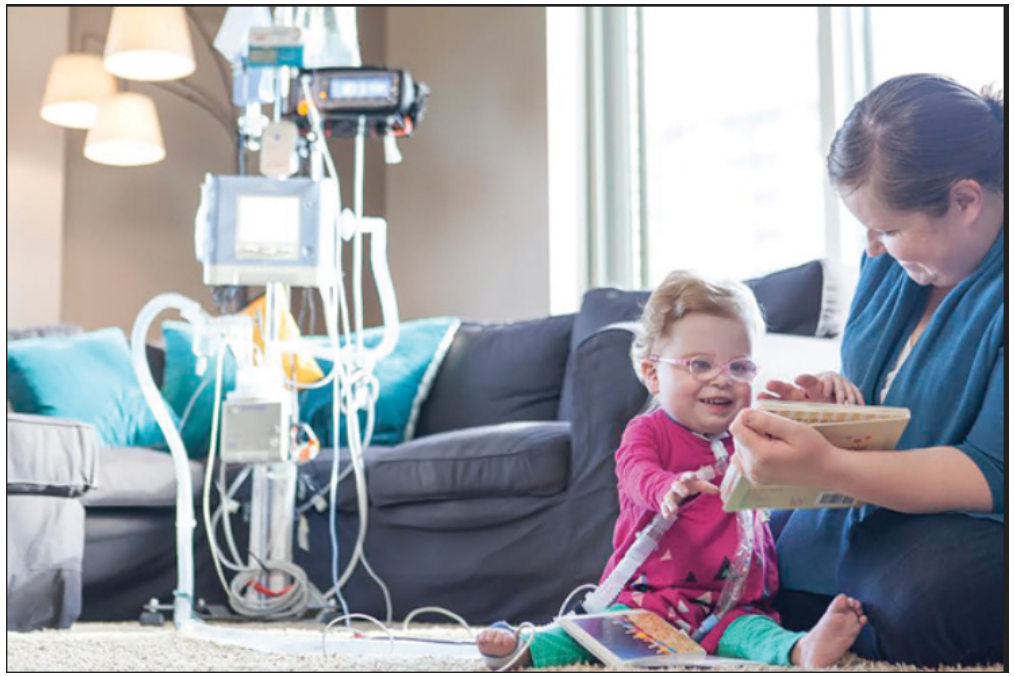
OPENING REMARKS FROM FDA

Susan McCune, M.D.
Director, Office of Pediatric Therapeutics
Office of the Commissioner, FDA

Advancing Endpoint Development for Preterm Neonates with Pulmonary Morbidities
October 2, 2018

Disclaimer

- The views presented here are personal and do not necessarily reflect the views of the Agency
- All specific drug development questions should be discussed with the relevant review division



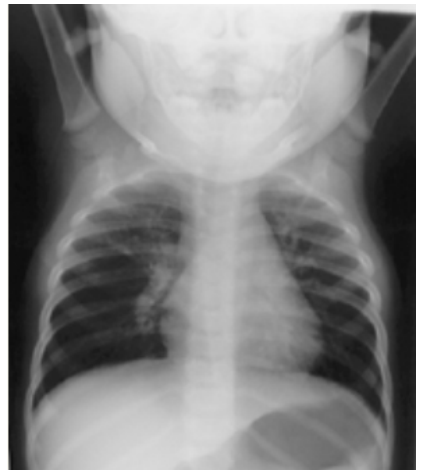
https://www.homecaremag.com/features/october-2015/future-pediatric-homecare

http://www.keranews.org/post/rsv-respiratory-virus-can-send-infants-and-kids-hospital

https://infusionnurse.org/2015/01/08/qa-blood-draw-from-piv/

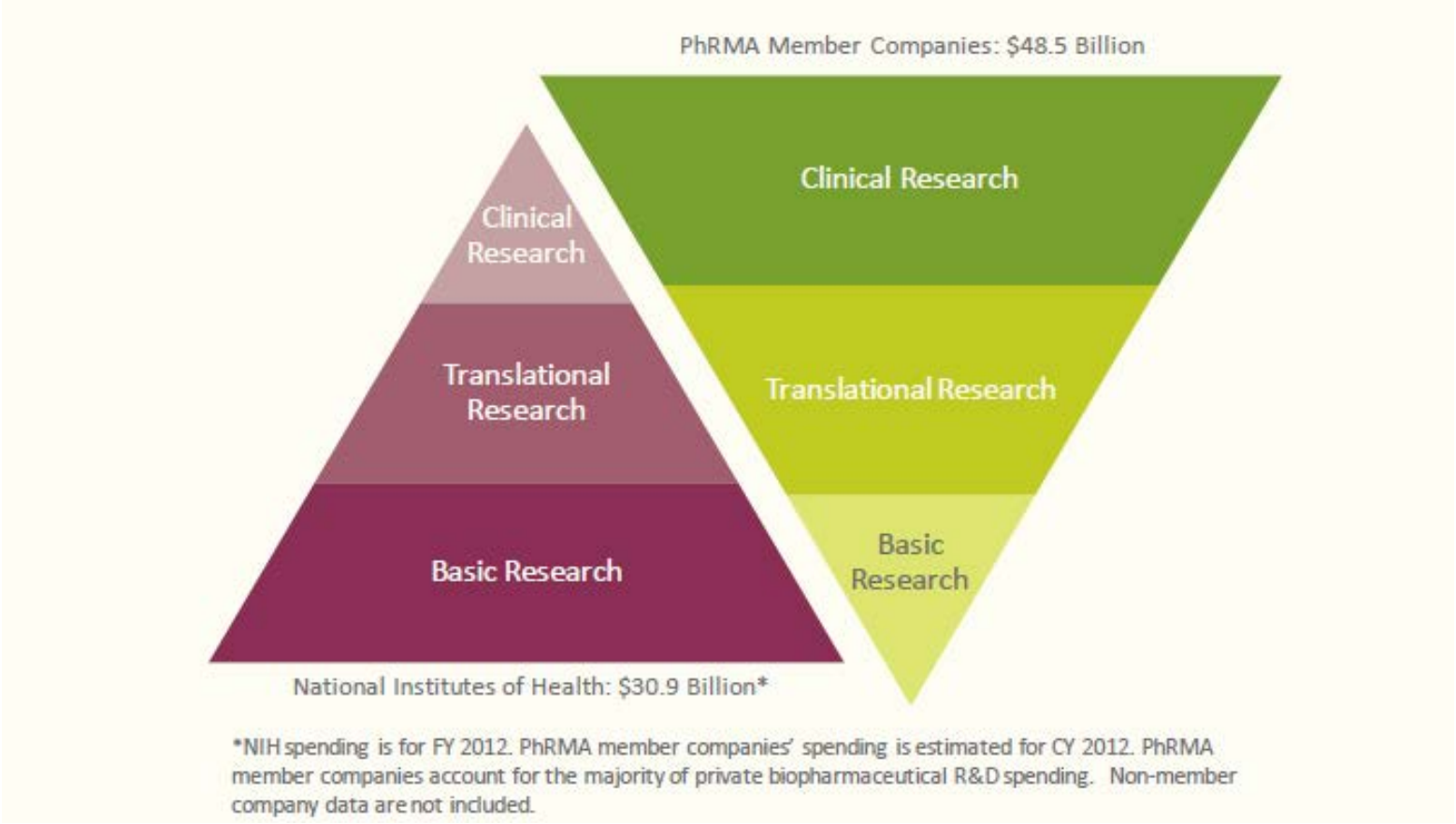
https://www.practicelink.com/JobBoard/FacilityDetail.aspx?facilityId=16809

https://adorablekidsemporium.wordpress.com/2015/10/03/is-my-child-too-sick-for-school/



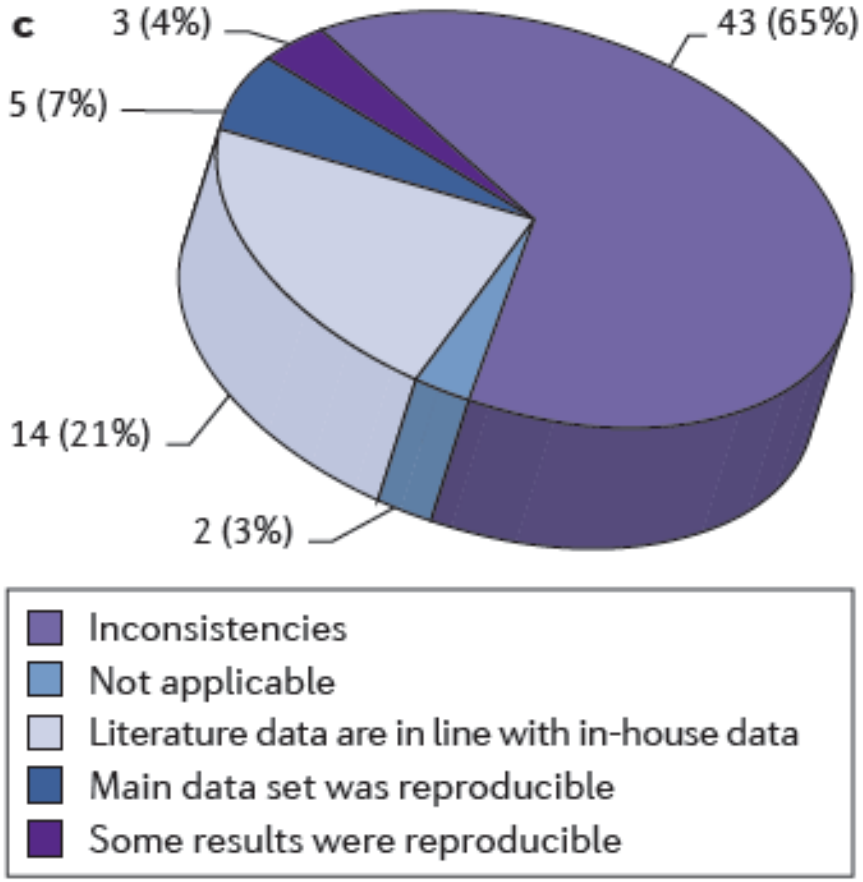
https://pedclerk.uchicago.edu/page/rsv-bronchiolitis

Research Spending



SOURCES: Pharmaceutical Research and Manufacturers of America. "PhRMA Annual Membership Survey." 2013; National Institutes of Health (NIH), Office of Budget. "History of Congressional Appropriations, Fiscal Years 2000–2012." Bethesda, MD: NIH, 2012. http://officeofbudget.od.nih.gov/pdfs/FY12/Approp.%20History%20by%20IC)2012.pdf (accessed February 2013); Adapted from E. Zerhouni. "Transforming Health: NIH and the Promise of Research." Transforming Health: Fulfilling the Promise of Research. Washington, DC. November 2007. Keynote address.
www.researchamerica.org/transforming_health_transcript (accessed January 2013).

Reproducibility of Published Data



Relationship of published data to in-house data (Bayer HealthCare) for drug targets

Prinz F, Schlange T, and Asadullah K. 2011. Believe it or not: how much can we rely on published data on potential drug targets? Nature Reviews Drug Discovery. 10:712-713.

Considerations in Designing a Development Program

- What is the quality and robustness of the evidence of an effect (including the totality of the evidence)?
- Given that it exists, how meaningful will this effect be in the overall context of the disease? How much will it matter to patients?
- If it matters, what would be the impact of failing to provide this benefit, if real?
- This reasoning has to be weighed against the potential harms of the intervention

Innovative Trials in Rare Diseases

- Carglumic acid for N-acetylglutamate synthase (NAGS) deficiency
  - Rare urea cycle disorder (~ 10 patients in U.S.)
  - Retrospective review of a 23 patient case series in Europe
  - Short-term (ammonia) and long-term (neurocognitive) outcomes
  - Compared to historical control (not formally conducted)
- Deferiprone for transfusional iron overload in patients with thalassemia syndromes not responding to other therapies
  - Planned pooled analysis of patients from several studies (n=236)
  - Endpoint was change in serum ferritin, not a clinical outcome
- Cysteamine bitartrate for nephropathic cystinosis
  - 2 open-label studies (n=94) children treated with product or innovator cysteamine HCl
  - Largely a pharmacodynamic comparison based on WBC cystine levels vs. historical control pharmacokinetic/pharmacodynamic levels

What Did These Have in Common?

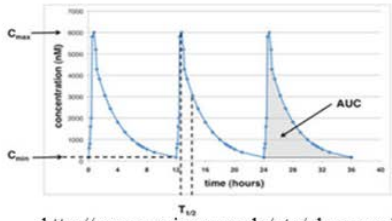
- Highly plausible mechanistic hypothesis
- Natural history data on untreated patients
- Highly plausible biomarkers; most could be measured in a standard manner
- Serious unmet medical need
- Relatively large treatment effect

Drug Development Paradigm

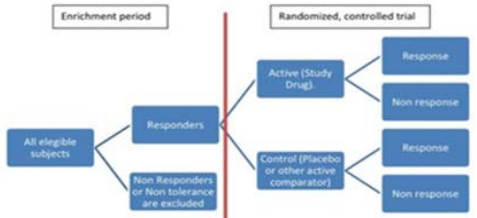
Right Drug

Right Population

Right Dose

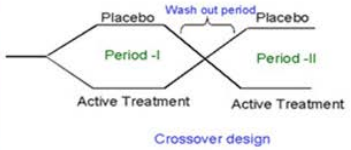


http://www.upci.upmc.edu/ctp/pharmacokinetics.cfm

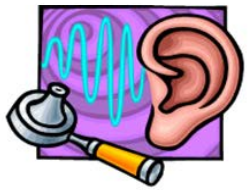


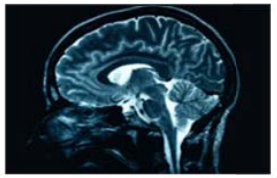
http://www.wfsbp.org/activities/feature-forum-current-issue/archive-single/should-we-accept-enrichment-designs-in-psychiatry/ac3a3fb97cf270c48b2ecd25c825ee9b.html

Right Trial Design



http://accp1.org/pharmacometrics/theory.htm





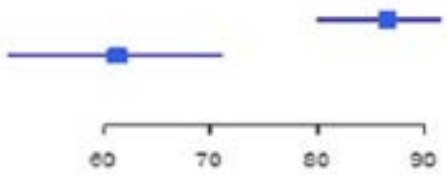
Right Endpoints

Right Endpoints

- Clinically meaningful endpoints
- Surrogate endpoints
- Safety endpoints
  - Short-term
  - Long-term

Pediatric Trial Outcome by Whether the Pediatric & Adult Endpoint Were the Same

	Success	Failure	Lower 95% CI	Upper 95% CI
Same	122	19	80	91.4
Different	57	36	51.1	71.2
Total	179	55		



Examples – Failed Trials Where the Adult & Pediatric Endpoints Were Not the Same

Indication	Ped Age Grp	Ped Endpoint	Time of Measurement	Adult Endpoint	Time of Measurement
Pulmonary Arterial Hypertension	1 - 17 yrs	Percent change in VO2 peak	16 wks	6-minute walk	12 wks
Chronic HBV	2 – 17 yrs	HBV DNA <1000 copies/mL & ALT normalization	48 wks	Histological improvement (biopsy)	48 wks
Bronchospasm	0 - 5 yrs	Daily asthma SS; Ped Asthma Caregiver Assessment	4 wks	FEV1	12 wks

Green DJ, Burnham JM, Schuette P, et al. Primary Endpoints in Pediatric Efficacy Trials Submitted to the US FDA. The Journal of Clinical Pharmacology 2018; DOI: 10.1002/jcph.1109

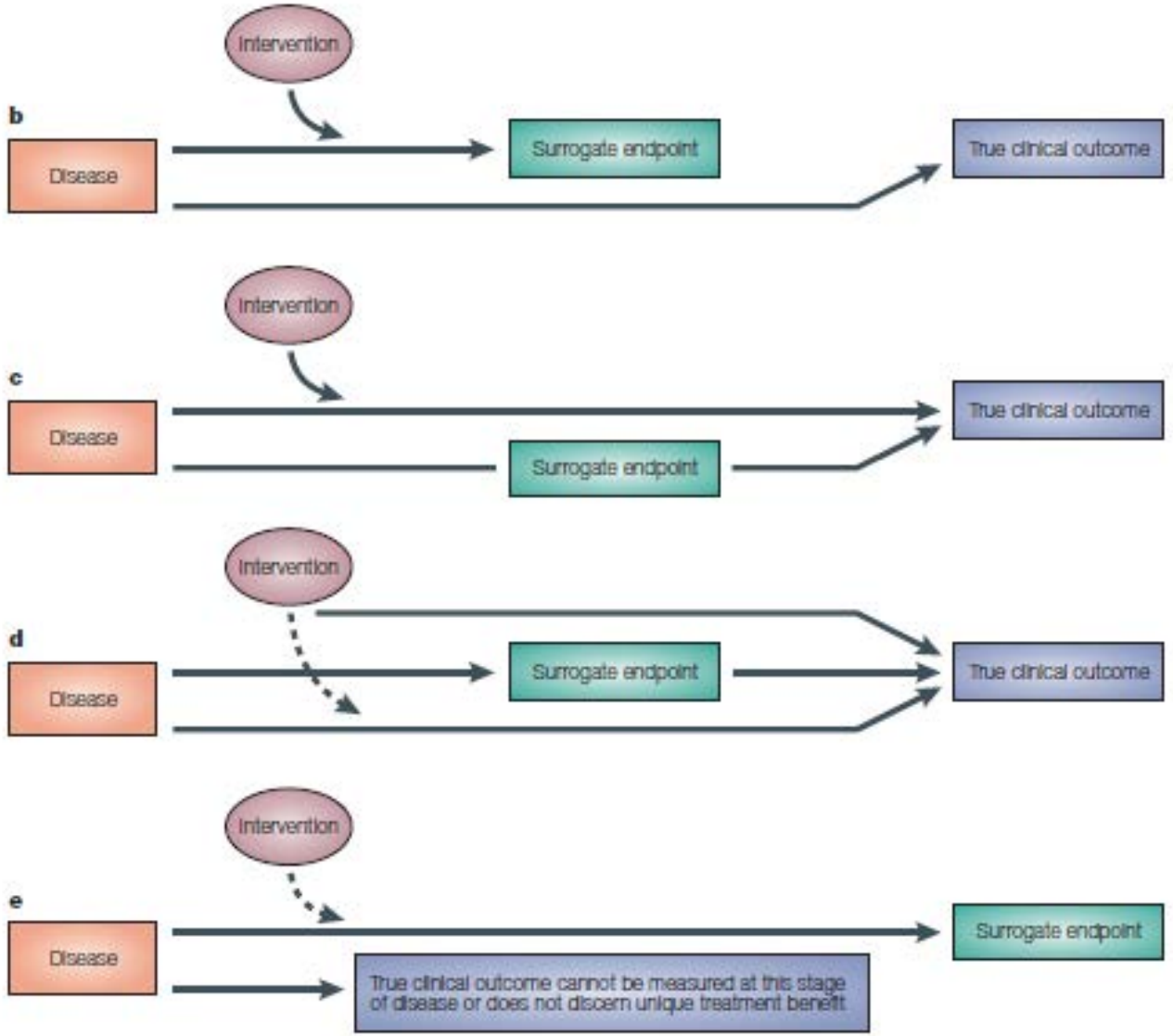
Support for Use of Surrogate Markers

Table 1. Support for Surrogates

Factor	Favors Surrogate	Does Not Favor Surrogate
Biological plausibility	Epidemiologic evidence extensive and consistent	Inconsistent epidemiology
	Quantitative epidemiologic relationship	No quantitative epidemiologic relationship
	Credible animal model shows drug response	No animal model
	Well-understood disease pathogenesis	Pathogenesis not clear
	Drug mechanism of action well understood	Novel actions not previously studied
	Surrogate relatively late on biological path	Surrogate remote from clinical outcome
Success in clinical trials	Effect on surrogate has predicted outcome with other drugs of same pharmacologic class (supports surrogate in class)	A negative outcome without clear explanation
	Effect on surrogate has predicted outcome in several classes (supports more general use)	Inconsistent results across classes
Risk-benefit, public health considerations	Serious or life-threatening illness and no alternative therapy	Nonserious disease and alternative therapy with different pharmacologic action known to affect outcome
	Large safety database	Little safety data
	Short-term use	Long-term use
	Difficulty of studying clinical end point (rare, delayed)	Easy to study clinical end point (short-term study)
		Long-delayed, small effect in healthy people

Temple R. Are surrogate markers adequate to assess cardiovascular disease drugs? JAMA 282:790-795, 1999.

Surrogate Endpoint Challenges



The Voice of the Patient: Neurological Manifestations of Inborn Errors of Metabolism

- FDA Patient Focused Drug Development Initiative meeting 6/10/14
- Wide spectrum of neurological signs and symptoms including seizures, cognitive or behavioral problems, language delay, sleep problems, weakness, difficulty swallowing, balance problems, bowel or bladder problems, pain and other symptoms
- “While each day we deal with the obvious hurdles [like the inability to speak], it’s really the secondary sensory, behavioral, and cognitive symptoms that seem to most impact [my son’s] daily stresses and struggles.”

https://www.fda.gov/downloads/drugs/newsevents/ucm436454.pdf


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Advancing Endpoint Development for Preterm Neonates with Pulmonary Morbidities

Session I: Current State of Research and Challenges in Developing Endpoints for Preterm Neonates with Pulmonary Morbidities

Overview of preterm respiratory disease in the NICU and limitations of our current endpoints for pulmonary morbidity

Judy Aschner, MD

Advancing Endpoint Development for Preterm Neonates with Pulmonary Morbidities

Washington, DC

October 2, 2018

Duke | MARGOLIS CENTER for Health Policy

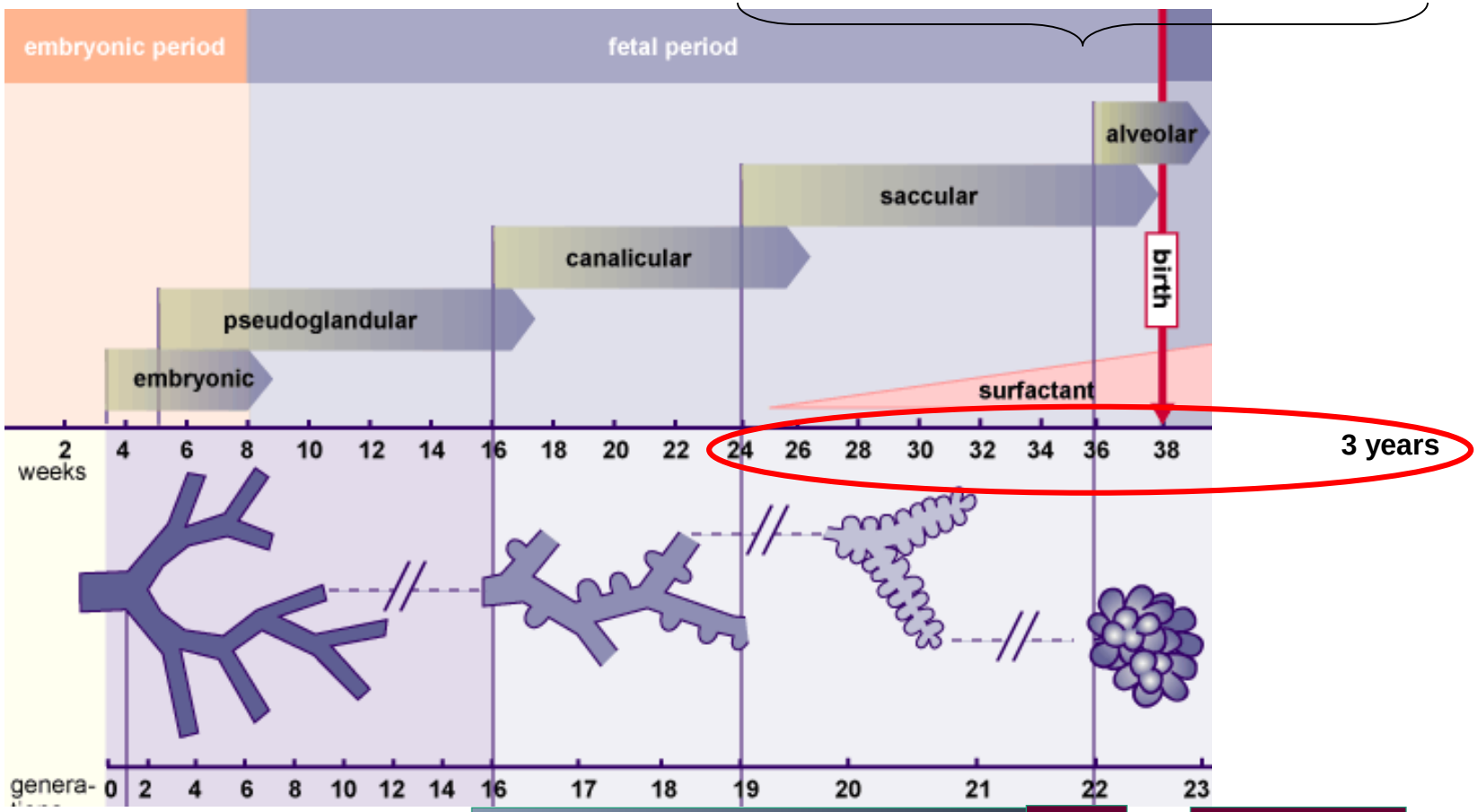
EINSTEIN
Albert Einstein College of Medicine

Objectives

- Review pathobiology, incidence and health relevance of BPD
- Examine why so many clinical trials have yielded negative or inconsistent results
- Discuss the limitations of our current definitions of BPD as a clinical trials endpoint

Stages of Lung Development

Rapid increases in vessel growth
Septation of the distal air spaces



Preterm birth can disrupt normal lung alveolar and vascular growth

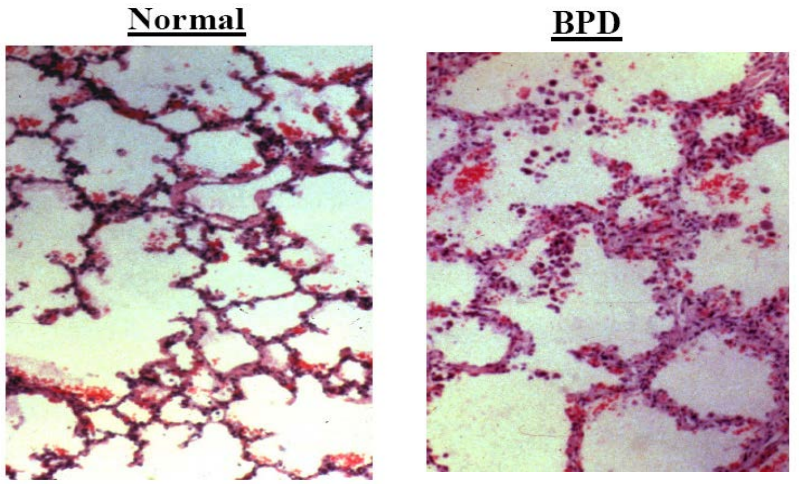
Disrupted lung development → BPD → Persistent pulmonary disease

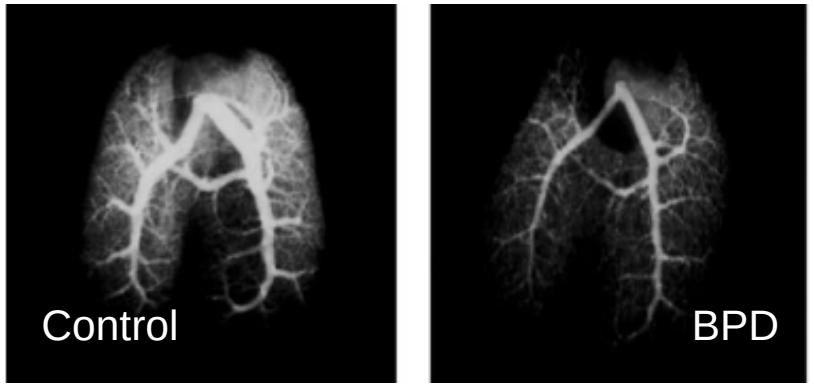
BPD: Health Significance

- Most common complication of extreme preterm birth
  - 30% incidence among infants <1500 g
  - >50% incidence among infants <750 g
- Increasing prevalence as more ELBW infants survive
- Important cause of morbidity and mortality
  - prolonged and recurrent hospitalizations
  - higher rates of other serious complications of prematurity

BPD: Lung injury during a critical window of lung development

- Impaired Alveolar Septation
  - Reduction of lung surface area → abnormal gas exchange
- Impaired Blood Vessel Growth
  - Vascular dysplasia characterized by remodeling, increased vasomotor tone and reduced alveolar-capillary coupling → Pulmonary hypertension

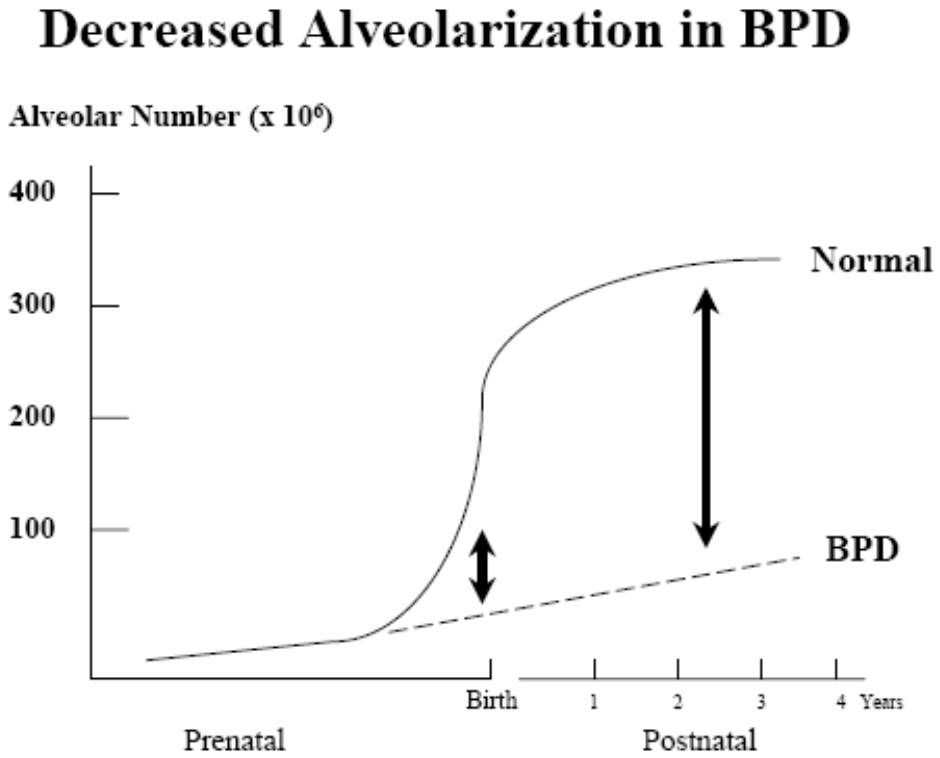




BPD: persistent alterations in lung structure and function

- Abnormalities of lung structure can persist into adulthood
- Long-term pulmonary follow-up
  - small airway damage, hyperinflation - age 8-10
  - airway obstruction in adult life
  - risk of cor pulmonale

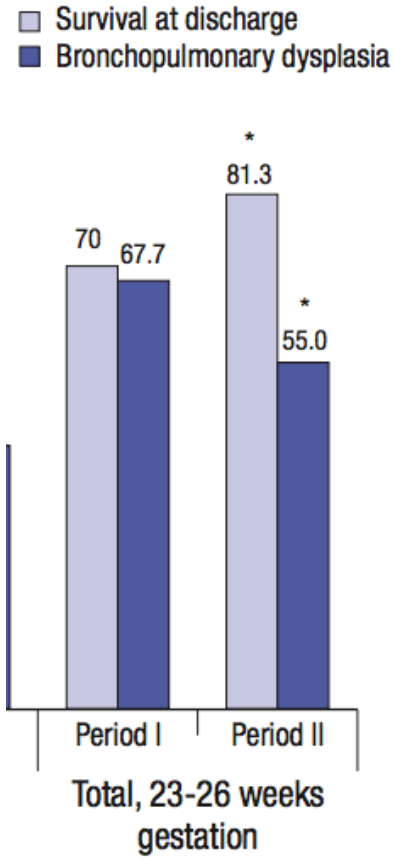
  - lung function is normal in at least some premature infants w/o BPD



Curtesy of Steve Abman

So many studies, so little progress…..

- Despite decades of promising research, prevention of BPD has proven elusive.
- There is an alarming lack of evidence to support the use of any pharmacologic agent in the management of infants at risk of developing or with established BPD… with the exception of caffeine and vitamin A.
- Little change in the incidence of BPD in the past 20 years.

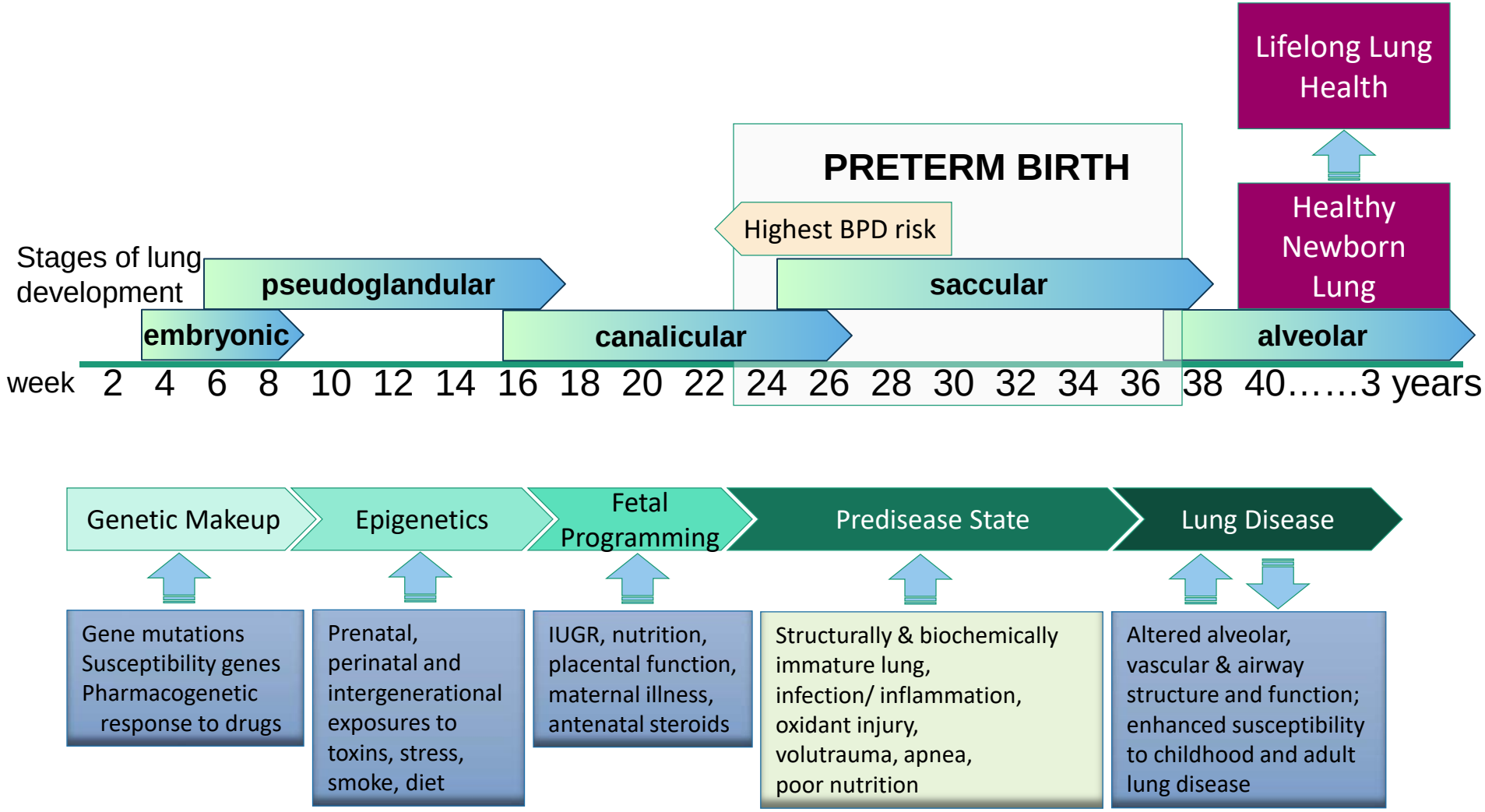


Kim et al, JKMS, 2016

Why have so many clinical trials to prevent or treat BPD yielded negative or inconsistent results, despite promising preclinical studies?

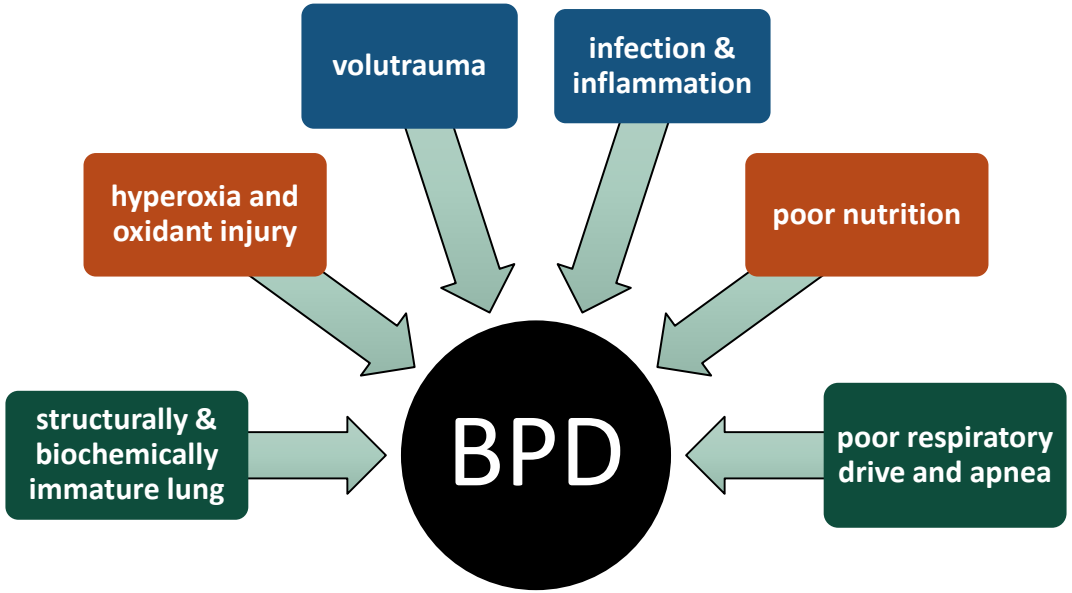
- BPD has a more complex pathogenesis in human infants, i.e. multiple endotypes
  - Infection/inflammation
  - Intermittent hypoxia and hyperoxia
  - Free radicals/oxidant injury
  - Nutrition
  - Genetics

Windows of opportunities for BPD prevention and Rx



Adopted from McEvoy CT, Jain L, Schmidt B, Abman S, Bancalari E, Aschner JL
Ann Am Thorac Soc Vol 11, Supplement 3, pp S146–S153, Apr 2014

Modulating and Host Response Factors



- Responses of individual patients to these insults are modulated by genetic, epigenetic and antenatal factors
- While not mutually exclusive, distinct causal factors may dominate in different patients

Different physiological disorders are associated with use of oxygen and can contribute to continuing pulmonary disease

- *alveolar simplification with reduced gas diffusion*
- *immature/disordered control of breathing*
- *increased airways resistance/reactivity*
- *bronchial/tracheal stenosis/malacia*
- *parenchymal inflammation/scarring*
- *pulmonary hypertension*

BPD Endotypes

- Failure to identify subpopulations with distinct mechanisms of disease (endotypes) contributes to:
  - exposures to therapies unlikely to benefit individual patients
  - negative trials
  - skepticism about biologically plausible therapies that may benefit a subset of at-risk infants

Why have many clinical trials yielded negative or inconsistent results, despite promising preclinical studies?

- BPD has a complex pathogenesis in human infants, i.e. multiple endotypes
- BPD is a non-specific diagnosis based on a supplemental oxygen requirement at 36 weeks
- Variable approach to the intervention: dose, timing, duration

BPD: We have a definition problem!!!

- Inherent shortcoming of defining a disease by how we treat it!
- Current definition of BPD provides no information about pathophysiology, disease progression or phenotype variability
  - Multiple definitions: Shennon, NIH workshop, Physiologic
- Poor negative predictive value for longer term respiratory morbidity

McEvoy, Jain, Schmidt, Abman, Bancalari, Aschner, *Annals ATS* 2014

Limitations of Existing Definitions of BPD

- Fails to account for respiratory deaths before 36 weeks
- Most studies have used a dichotomous BPD outcome, reducing study power
- Does not account for recent changes and variation in clinical practice
  - Room-air–high flow NC (to provide positive airway pressure)
  - Extremely low flow with 100% oxygen
  - Use of respiratory medications that can temporarily impact the need for oxygen
  - Unclassifiable and misclassified babies

Limitations of Existing Definitions of BPD

Recent changes in clinical practice lead to missclassifications or unclassifiable infants

At 36 wks PMA:	Workshop	Shennan	Physiologic
5 cm CPAP - RA	severe	No	Yes*

*Not eligible for RA/flow reduction challenge

Limitations of Existing Definitions of BPD

Relevance of 36 weeks as the outcome time point?

- Lung development continues through childhood
- Definition based on one day in a NICU stay that lasts for many weeks or months
- Many reasons for oxygen use at 36 weeks are not related to parenchymal lung disease….and mature as infants approach term
  - Control of breathing
  - Feeding/breathing coordination
  - Chest wall stability

Summary

Commonly used definitions for BPD

- encompass a number of endotypes and distinct pathophysiological entities that are unlikely to respond similarly to a given intervention
- do not take into account current care practices in our NICUs

Existing large research datasets can be used to develop a more nuanced assessment of respiratory status at term equivalence (or discharge) with greater prognostic value and that may provide a statistically more powerful surrogate outcome for therapeutic trials.

Overview of long-term pulmonary insufficiency outcome data for preterm neonates: Related to BPD definition

Prakesh S Shah

Professor, Department of Pediatrics and

Institute of Health Policy, Management and Evaluation

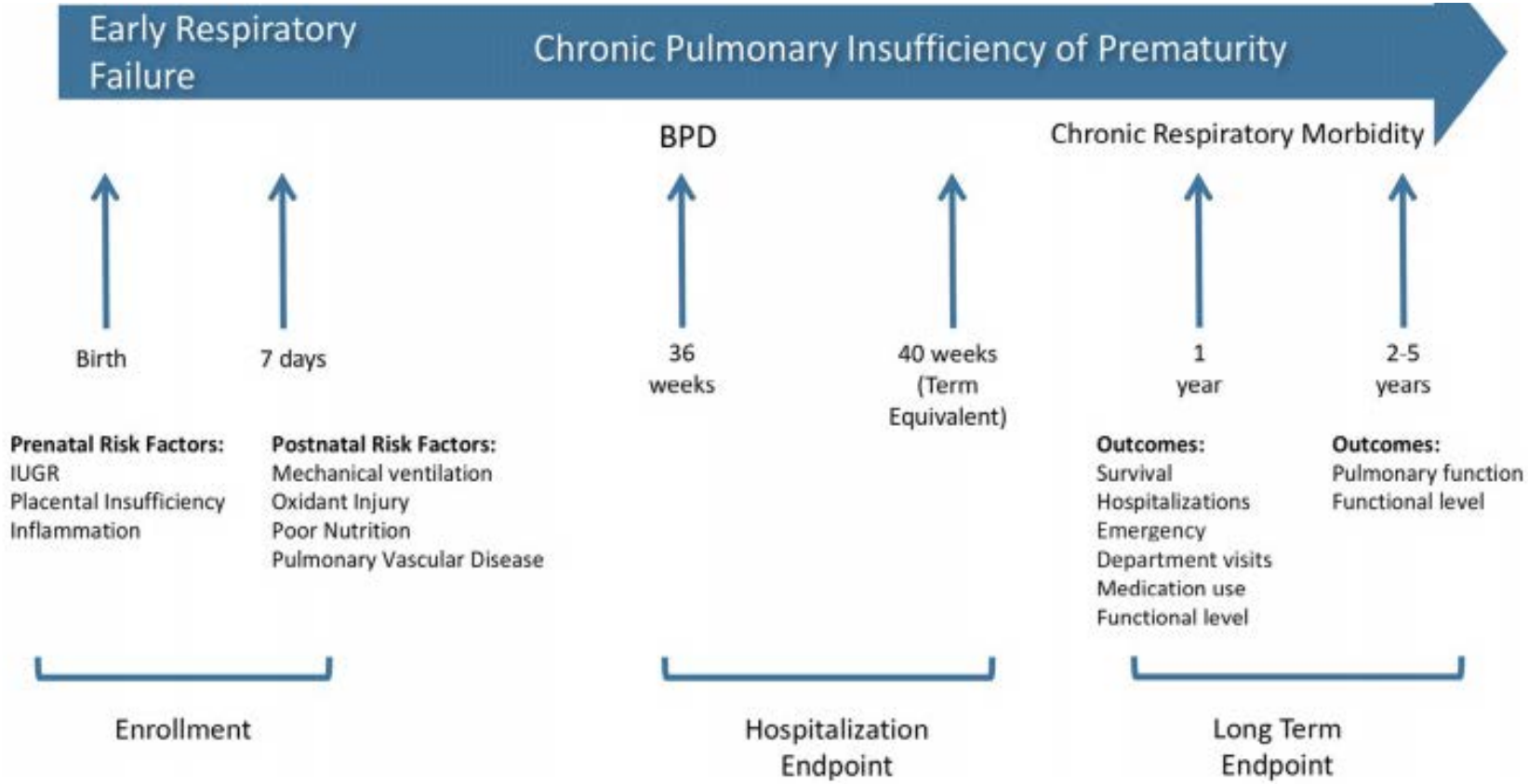
Mount Sinai Hospital and University of Toronto, Toronto, Canada

Conflict of interest

Nothing to declare except that I will show results from couple of papers that we have published.

Chronic Pulmonary Insufficiency of Prematurity: Developing Optimal Endpoints for Drug Development

Robin Steinhorn, MD[1], Jonathan M. Davis, MD[2], Wolfgang Göpel, MD[3], Alan Jobe, MD[4], Steven Abman, MD[5], Matthew Laughon, MD[6], Eduardo Bancalari, MD[7], Judy Aschner, MD[8], Roberta Ballard, MD[9], Anne Greenough, MD[10], Linda Storari[11], Merran Thomson, MBChB[12], Ronald L. Ariagno, MD[13], Laura Fabbri, PhD[11], and Mark A. Turner, MD[14], for the International Neonatal Consortium



Long-term consequences of BPD

Lung structural alterations

LRT functional abnormalities

Clinical issues

- Re-hospitalization
- RTI and/or wheeze
- Pulmonary hypertension
- Prolonged need for respiratory support
- Mortality
- Neurodevelopmental abnormalities

Lung structural alterations

Auckland et al (Thorax 2009;64:405–10)

- HRCT on <29 weeks and <1Kg at 10-18 years of age
  - Moderate or severe BPD had significantly higher total HRCT scores (mean 3.0 vs 5.2; p = 0.009), as well as more opacities (p = 0.035) and hypo-attenuated areas (p = 0.007).

Wong et al (Eur Respir J. 2008;32:321–8)

- Adults who were born preterm and diagnosed with BPD
  - Pulmonary emphysema was the most common and was detected in 71%

Mahut et al (ADCFN 2007;92:F459–64)

- VLBW children who were 10-20 months old
  - All of the CT scans were abnormal, with linear and triangular subpleural opacities and hyperlucent areas seen on the vast majority of scans

Lung structural alterations

Yee et al (Am J Physiol Lung Cell Mol Physiol 2009;297(4):L641–9)

- Helium magnetic resonance (3HeMR)
- Despite lower FEV1 values in preterm-born children, alveolar dimensions were not different to term-born children
  - ?catch-up alveolarisation

Functional abnormalities

Abnormal spirometry parameters

- lower FEV1, lower FEF25–75 with normal FVC

Airway obstruction partially reversible with bronchodilators (1/3rd responsive)

Functional abnormalities

Reduced RV/TLC in preterm children at school-age

Increased respiratory system resistance and altered elastic properties of the respiratory system (reactance)

Gas exchange (DLCO) provide conflicting results

- some studies suggesting decreased alveolar-capillary membrane function throughout childhood and adolescence while others fail to detect a difference

Rehospitalization

Lamarche-Vadel (Acta Paediatr 2004;93:1340–5)

- 9 months after discharge and found that 47.3% were readmitted at least once
- BPD (OR 2.2; 95% CI 1.3–3.7)

Ralser (Acta Paediatr. 2012;101:e1–5)

- Among <32 weeks GA - 40% in first year and 25% in second year
- 40-50% of rehospitalization due to respiratory causes

Greenough (Arch Dis Child. 2002;86:40–3)

- Median GA 27 weeks
- Median 2 readmissions - esp. those discharged home on oxygen

RTI and asthma like symptoms

Most common reason was RSV

- RSV occurred in 60% and 70% of them required hospitalization for >7 days
- Groothuis et al
  - RSV related hospitalization reduced by 50% between 1998 and 2008
- Also at higher risk of other LRTI

Among EPT, incidence of asthma is ~25%

- BPD related illness is different from atopy related
- BPD related with higher inflammation
- Less exacerbations due to fixed airway narrowing

RTI and asthma like symptoms

Karila (Rev Mal Respir. 2008;25:303–12)

- Children with BPD at 7–14 years old had ventilatory limitations during exercise, with greater use of the ventilatory reserves ($p < 0.01$) and lower maximal ventilation ($p < 0.01$) and tidal volume ($p = 0.01$)

Bronchopulmonary dysplasia and pulmonary hypertension: a meta-analysis

G Al-Ghanem[1], P Shah[2], S Thomas[3], L Banfield[1], S el Helou[1], C Fusch[1] and A Mukerji[1]

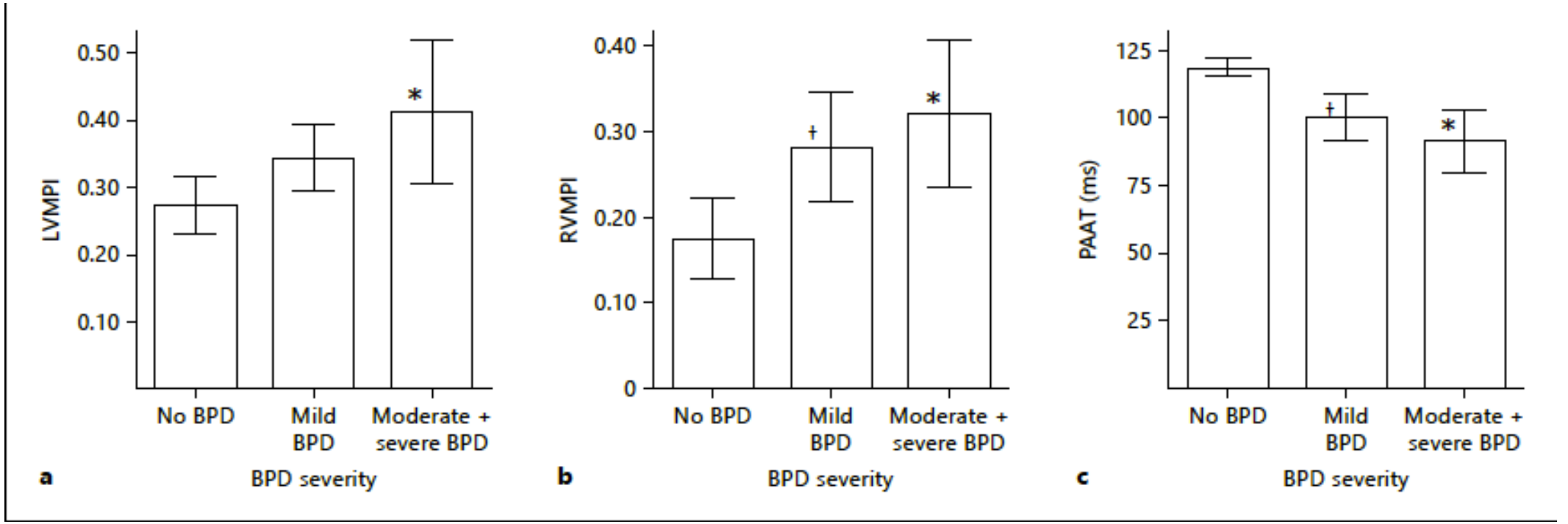
Table 2. Pooled incidence and comparative analyses of PH in BPD

BPD severity	*Studies (n)*	*Subjects (n)*	*I^2(%)*	*Pooled incidence (%; 95% CI)*	*Comparison*	*Studies (n)*	*Subjects (n)*	*I^2(%)*	*OR (95% CI)*
Mild BPD	6	455	74	4 (1,7)	vs no BPD	4	426	0	1.03 (0.38, 2.80)
Mild-mod BPD	5	706	75	5 (2,8)	vs no BPD	4	604	0	1.41 (0.59, 3.36)
Mod BPD	5	289	66	6 (2,11)	vs no or mild BPD	4	604	76	2.80 (0.51, 15.43)
Mod-severe BPD	9	1079	87	24 (17,30)	vs no or mild BPD	6	1351	69	8.11 (2.91, 22.58)
Severe BPD	6	431	85	33 (21,44)	vs no or mild-mod BPD	4	838	14	6.67 (4.01, 11.11)

CONCLUSIONS: PH occurs in one out of 4 to 5 preterm neonates with BPD. Patients with BPD and PH may have higher odds of mortality; however, there is urgent need for high quality studies that control for confounders and provide data on long-term outcomes.

Cardiovascular Consequences of Bronchopulmonary Dysplasia in Prematurely Born Preschool Children

Ozge Altun Koroglu[a] Mehmet Yalaz[a] Erturk Levent[b] Mete Akisu[a]
Nilgun Kültürsay[a]



Neonatology 2013;104:283–289

Prolonged need for respiratory support

Prevalence of respiratory symptoms, hospitalisation and medication use is reported to significantly decrease between 2 and 6 years of age

Some studies reporting persistent need for respiratory support in early and mid-childhood

Longitudinal data are lacking from recent cohort

Neurodevelopmental outcomes

Prediction of Late Death or Disability at Age 5 Years Using a Count of 3 Neonatal Morbidities in Very Low Birth Weight Infants

Barbara Schmidt, MD[1,2], Robin S. Roberts, MSc[2], Peter G. Davis, MD[3,4], Lex W. Doyle, MD[3,4], Elizabeth V. Asztalos, MD[5], Gillian Opie, MD[6], Aida Bairam, PhD[7], Alfonso Solimano, MD[8], Shmuel Arnon, MD[9], and Reginald S. Sauve, MD[10], on behalf of the Caffeine for Apnea of Prematurity (CAP) Trial Investigators*

Table I. Univariate relationships between individual neonatal morbidities and poor outcome at 5 years

	Death or disability at 5 y					
	No./total no. (%)					
Neonatal morbidity	Morbidity absent	Morbidity present	Observed OR (95% CI)	*P* value	Model estimated OR (95% CI)	*P* value
BPD	110/857 (12.8)	187/657 (28.5)	2.7 (2.1-3.5)	<.001	2.3 (1.8-3.0)	<.001
Brain injury	222/1318 (16.8)	75/196 (38.3)	3.0 (2.2-4.2)	<.001	2.6 (1.9-3.6)	<.001
Severe ROP	254/1421 (17.9)	43/93 (46.2)	4.0 (2.6-6.1)	<.001	2.5 (1.6-3.9)	<.001

(J Pediatr 2015;167:982-6).

Bronchopulmonary dysplasia—impact of severity and timing of diagnosis on neurodevelopment of preterm infants: a retrospective cohort study

Anna Maria Malavolti,[1,2] Dirk Bassler,[1] Romaine Arlettaz-Mieth,[1] Giacomo Faldella,[2] Beatrice Latal,[3] Giancarlo Natalucci[1,3]

BPD severity	36 weeks		40 weeks	
	NDI (OR, 95% CI	MDI (MD, 95% CI)	NDI (OR, 95% CI	MDI (MD, 95% CI)
Mild	1.1 (0.6-2.1)		1.2 (0.6-2.1)	
Moderate	1.5 (0.7-3.4)		2.2 (0.6-8.1)	
Severe	5.6 (2.0-15.9)	-11 (-19, -4)	16.6 (4.6-59.9)	-26 (-36, -16)

BMJ Paediatrics Open 2018;**2**:e000165.

Relationship to definitions of BPD

Scoping review shows wide variation in the definitions of bronchopulmonary dysplasia in preterm infants and calls for a consensus

Delaney Hines[1], Neena Modi[2], Shoo K. Lee[1,3], Tetsuya Isayama[1], Gunnar Sjörs[4], Luigi Gagliardi[5], Liisa Lehtonen[6], Maximo Vento[7], Satoshi Kusuda[8], Dirk Bassler[9], Rintaro Mori[8], Brian Reichman[10], Stellan Håkansson[4], Brian A. Darlow[11], Mark Adams[9], Franca Rusconi[12], Laura San Feliciano[7], Kei Lui[13], Naho Morisaki[8], Natasha Musrap[1], Prakesh S. Shah (pshah@mtsinai.on.ca)[1,3], for the International Network for Evaluating Outcomes (iNeo) of Neonates

Table 2 Characteristics of studies included in the review

Characteristic	Category	BPD not defined (n = 192) n (%)	BPD defined (n = 628) n (%)	P
Continent of study	Europe	73 (22)	253 (78)	0.44
	North America	76 (26)	217 (74)	
	Asia	26 (19)	108 (81)	
	Oceania	8 (22)	28 (78)	
	Transcontinental	4 (25)	12 (75)	
	South America	3 (25)	9 (75)	
	Africa	2 (67)	1 (33)	
Study sites	Multicenter	74 (24)	232 (76)	0.73
	Single	118 (23)	396 (77)	
Year of publication	2010	26 (24)	82 (76)	0.57
	2011	34 (27)	92 (73)	
	2012	25 (18)	115 (82)	
	2013	35 (25)	104 (75)	
	2014	35 (24)	108 (76)	
	2015	37 (23)	127 (77)	
Type of study*	Retrospective cohort	92 (24)	290 (76)	<0.01
	Prospective cohort	38 (23)	129 (77)	
	Randomised controlled trial/Clinical trial	40 (30)	91 (70)	
	Case–control	13 (14)	83 (86)	
	Cross-sectional	2 (10)	18 (90)	
	Survey/questionnaire	7 (54)	6 (46)	
	Case series (including before–after design)	0 (0)	11 (100)	
Primary outcome BPD in report	Yes	73 (17)	348 (83)	<0.01
	No	119 (30)	280 (70)	

Acta Paediatrica 2017;106:366-74

Scoping review shows wide variation in the definitions of bronchopulmonary dysplasia in preterm infants and calls for a consensus

Delaney Hines[1], Neena Modi[2], Shoo K. Lee[1,3], Tetsuya Isayama[1], Gunnar Sjörs[4], Luigi Gagliardi[5], Liisa Lehtonen[6], Maximo Vento[7], Satoshi Kusuda[8], Dirk Bassler[9], Rintaro Mori[8], Brian Reichman[10], Stellan Håkansson[4], Brian A. Darlow[11], Mark Adams[9], Franca Rusconi[12], Laura San Feliciano[7], Kei Lui[13], Naho Morisaki[8], Natasha Musrap[1], Prakesh S. Shah (pshah@mtsinai.on.ca)[1,3], for the International Network for Evaluating Outcomes (iNeo) of Neonates

Table 3 Characteristics of studies that defined BPD (n = 628)

Characteristic	Type	Frequency	Per cent
Definition used	Oxygen at 36 weeks of PMA	284	45.2
	NICHD criteria	188	29.9
	Oxygen at 28 days	53	8.4
	Oxygen/respiratory support at 36 of weeks PMA	37	5.9
	Oxygen at 36 of weeks PMA and/or oxygen at 28 days	22	3.5
	Modified NICHD	20	3.2
	Other	8	1.3
	Vermont Oxford Network definition	7	1.1
	Combination of definition	4	0.6
	ICD code 770.7	3	0.5
	Oxygen/respiratory support at 28 days	2	0.3
Incorporation of physiological test	No	588	93.6
	Yes	37	5.9
	Partly	3	0.5
Accounting of death before definition criteria met	No	596	94.9
	Yes	32	5.1
Severity of BPD categorised	No	440	70.1
	Yes	188	29.9

Acta Paediatrica 2017;106:366-74

Scoping review shows wide variation in the definitions of bronchopulmonary dysplasia in preterm infants and calls for a consensus

Delaney Hines[1], Neena Modi[2], Shoo K. Lee[1,3], Tetsuya Isayama[1], Gunnar Sjörs[4], Luigi Gagliardi[5], Liisa Lehtonen[6], Maximo Vento[7], Satoshi Kusuda[8], Dirk Bassler[9], Rintaro Mori[8], Brian Reichman[10], Stellan Håkansson[4], Brian A. Darlow[11], Mark Adams[9], Franca Rusconi[12], Laura San Feliciano[7], Kei Lui[13], Naho Morisaki[8], Natasha Musrap[1], Prakesh S. Shah (pshah@mtsinai.on.ca)[1,3], for the International Network for Evaluating Outcomes (iNeo) of Neonates

Table 4 Studies comparing different definitions of BPD incidences

Author	Population	Definition	Incidence
Palta (22)	Neonates ≤1500 g (n = 272)	Tooley (7)	37.9%
		Shennan (8)	23.0%
Gregoire (23)	24–28 weeks' gestation who survived to discharge and were followed (n = 217)	Tooley (7)	65%
		Shennan (8)	43%
Bancalari (24)	Alive at 28 days, 500–1000 g; GA 23–32 weeks (n = 1266)	Oxygen during all of first 28 days	5.9%
		On oxygen at 28 days	57.2%
		On oxygen for ≥28 days	47.1%
		Shennan (8)	25%
		NICHD (12)	22.8%
Sahni (25)	For neonates <1251 g BW (27.3 ± 2.3 weeks of GA) (n = 230 studied at 28 days, n = 237 studied at 36 weeks PMA)	Tooley (7)	21.1%
		Shennan (8)	7.4%
		Mild BPD (12)	13.5%
		Moderate BPD (12)	4.8%
		Severe BPD (12)	2.6%

Acta Paediatrica 2017;106:366-74

Table 5 Studies comparing different definitions of BPD and their correlation to long-term adverse outcomes

Author, follow-up age, study population	Definition	Long-term outcome measure	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Other statistics
Palta (22), 5 years of age, N = 272	Tooley (7)	Diagnosis of asthma	52	66	29	83	AOR 1.3; 95% CI: 0.6–2.8
	Shennan (8)		43	82	40	84	AOR 2.7; 95% CI: 1.3–5.7
	Tooley (7)	Respiratory hospitalisation	58	68	37	83	AOR 2.8; 95% CI: 1.4–5.8
	Shennan (8)		38	82	40	80	AOR 3.6; 95% CI: 1.7–7.6
Gregoire (23), 18.5 months of age, N = 217	Tooley (7)	Hospitalisation due to respiratory cause	69	37	33	72	
	Shennan (8)		53	62	39	74	
	Tooley (7)	Developmental quotient ≤ 82	72	37	20	86	
	Shennan (8)		58	60	24	86	
	Tooley (7)	Severe cerebral palsy	69	36	16	38	
	Shennan (8)		50	58	17	87	
Davis (28), 18 months of age, N = 809	Tooley (7)	Pulmonary outcome*	67	54	62	58	Accuracy: 61%
		Neurosensory outcome**	67	47	39	74	Accuracy: 54%
	Shennan (8)	Pulmonary outcome*	46	82	75	57	Accuracy: 68%
		Neurosensory outcome**	45	72	45	72	Accuracy: 63%
Ehrenkranz (14), 18–22 months of age, N = 3848	Tooley (7)	Use of diuretics or bronchodilators	82	26	38	73	
	Tooley (7) + X-ray changes		68	44	40	72	
	Shennan (8)		54	62	44	71	
	Shennan (8) + X-ray changes		49	67	45	71	
	NICHD (12)		82	26	38	73	
	Tooley (7)	Rehospitalisation due to pulmonary causes	82	25	32	76	
	Tooley (7) + X-ray changes		67	43	34	75	
	Shennan (8)		52	60	36	74	
	Shennan (8) + X-ray changes		47	65	37	74	
	NICHD (12)		82	25	32	76	
Parad (27), 24 months corrected age, N = 76; N = 227	Bancalari (9)	Respiratory hospital admission	NC	NC	NC	NC	AOR 3.89; 95% CI: 0.45–33.6; AUC 0.55
	Shennan (8)		NC	NC	NC	NC	AOR 1.58; 95% CI: 0.5–5.0; AUC 0.55
	Bancalari (9)	Any cough, wheeze, and/or use of respiratory medications	NC	NC	NC	NC	AOR 0.94; 95% CI: 0.38–2.32; AUC 0.5
	Shennan (8)		NC	NC	NC	NC	AOR 1.41; 95% CI: 0.69–2.9; AUC 0.54

Acta Paediatrica 2017;106:366-74

Bronchopulmonary Dysplasia and Perinatal Characteristics Predict 1-Year Respiratory Outcomes in Newborns Born at Extremely Low Gestational Age: A Prospective Cohort Study

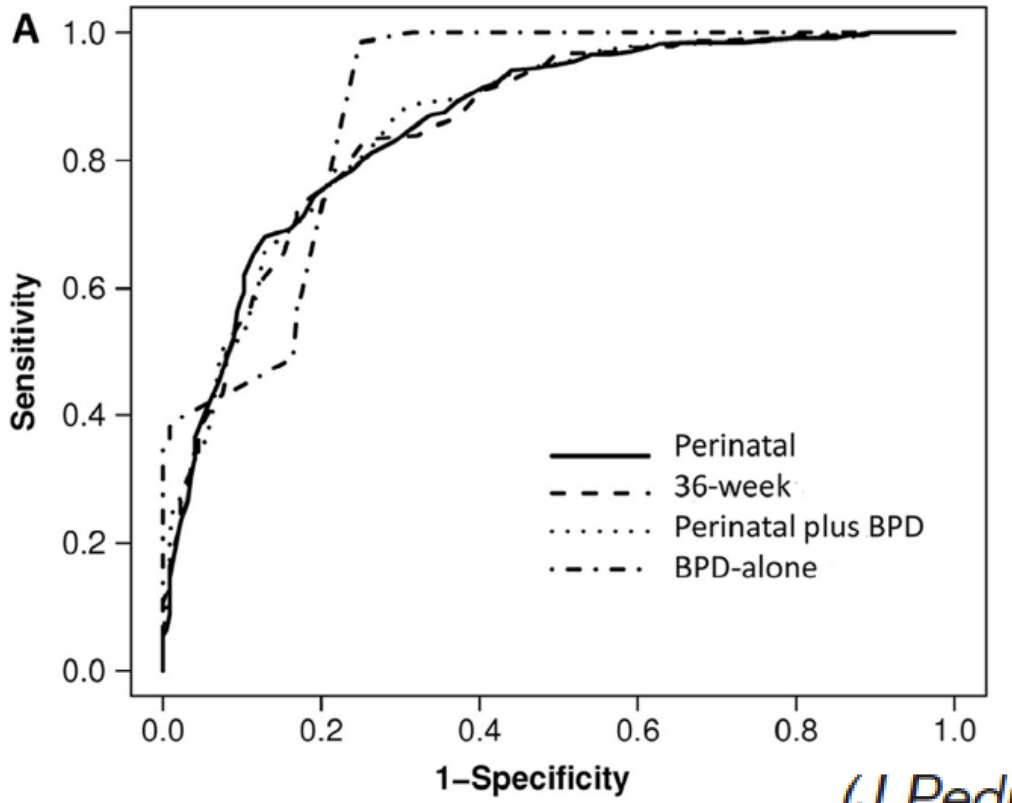
Roberta L. Keller, MD[1], Rui Feng, PhD[2], Sara B. DeMauro, MD, MSCE[3], Thomas Ferkol, MD[4], William Hardie, MD[5], Elizabeth E. Rogers, MD[1], Timothy P. Stevens, MD, MPH[6], Judith A. Voynow, MD[7], Scarlett L. Bellamy, PhD, ScD[2], Pamela A. Shaw, PhD[2], and Paul E. Moore, MD[8], for the Prematurity and Respiratory Outcomes Program*

- Post-prematurity respiratory disease (PRD)
  - An infant was classified with PRD if there were positive responses indicating respiratory morbidity on at least 2 caregiver questionnaires.
  - Respiratory morbidity was defined as mentioned previously: hospitalization for respiratory indication, home respiratory support, respiratory medication administration, and respiratory symptoms.

(J Pediatr 2017;187:89-97)

Bronchopulmonary Dysplasia and Perinatal Characteristics Predict 1-Year Respiratory Outcomes in Newborns Born at Extremely Low Gestational Age: A Prospective Cohort Study

Roberta L. Keller, MD[1], Rui Feng, PhD[2], Sara B. DeMauro, MD, MSCE[3], Thomas Ferkol, MD[4], William Hardie, MD[5], Elizabeth E. Rogers, MD[1], Timothy P. Stevens, MD, MPH[6], Judith A. Voynow, MD[7], Scarlett L. Bellamy, PhD, ScD[2], Pamela A. Shaw, PhD[2], and Paul E. Moore, MD[8], for the Prematurity and Respiratory Outcomes Program*



(J Pediatr 2017;187:89-97)

JAMA Pediatrics | Original Investigation

Revisiting the Definition of Bronchopulmonary Dysplasia
Effect of Changing Panoply of Respiratory Support for Preterm Neonates

Tetsuya Isayama, MD; Shoo K. Lee, MBBS, PhD; Junmin Yang, MSc; David Lee, MD; Sibasis Daspal, MD; Michael Dunn, MD; Prakesh S. Shah, MD, MSc; for the Canadian Neonatal Network and Canadian Neonatal Follow-Up Network Investigators

Research question

When is the optimal PMA for diagnosis and definition of BPD for predicting adverse respiratory /neurodevelopmental outcomes later in life?

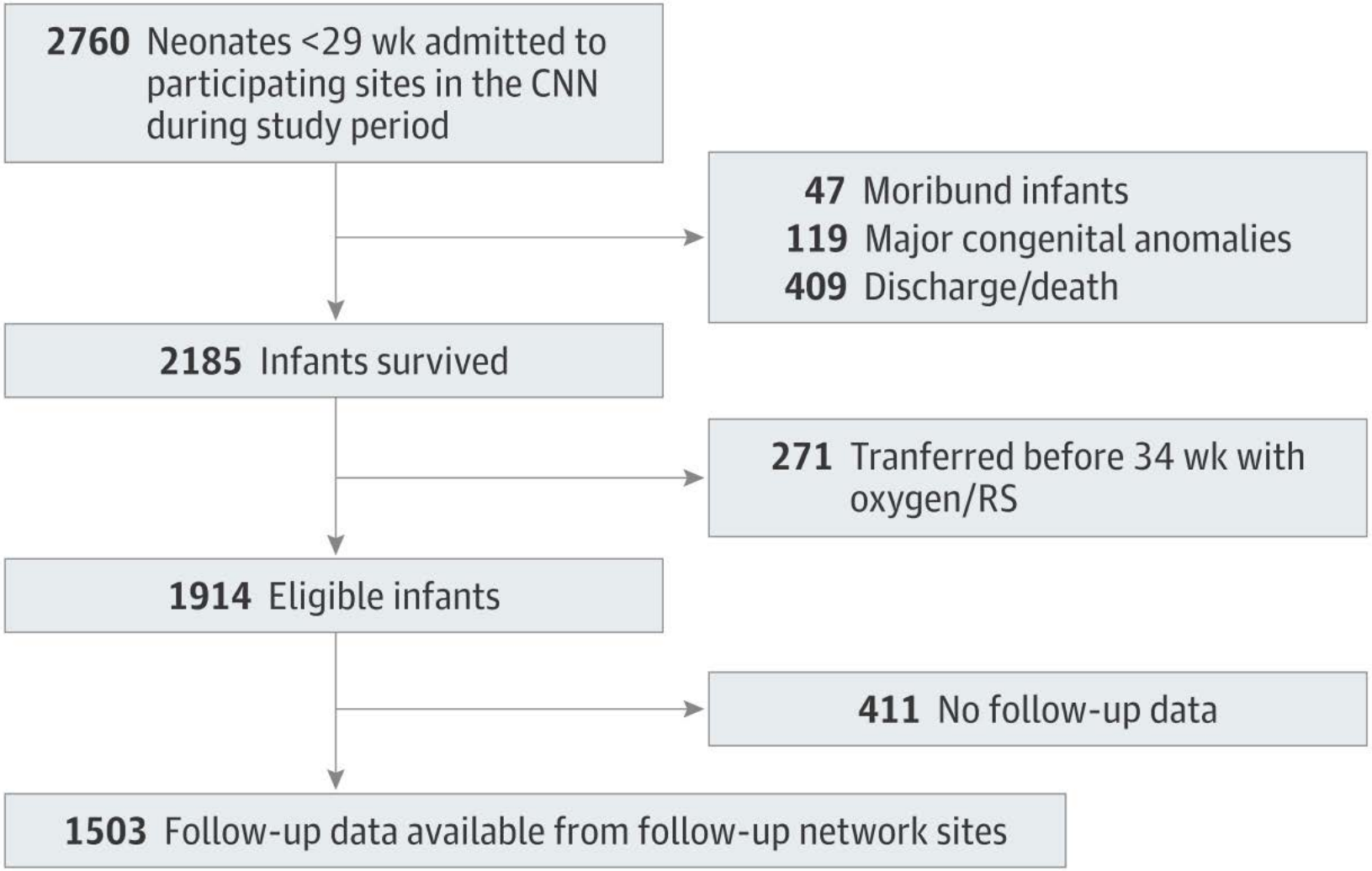
JAMA Pediatr. 2017 Mar 1;171(3):271-279.

Design/Methods

- **Data sources:**
  - CNN and CNFUN in Jan 2009-Sep 2011
- **Inclusion:**
  - Infants at < 29 wk GA who survived and discharged after 34 wk PMA
- **Exposures of interest:**
  - **Oxygen use and/or respiratory support (Oxygen/RS) at 34-40 wk PMA**
- **Potential confounders:**
  - Maternal factors (maternal age, PIH, antenatal steroids, delivery modes, multiple births)
  - Infant factors (sex, GA, BW, SGA, 5min Apgar < 4, SNAP II > 20, severe IVH/PVL NEC, PDA, late onset sepsis)
  - Socioeconomic factors (maternal education, ethnicity).
- **Outcomes at 18-24 months:**
  - Respiratory: Re-hospitalizations (≥ 3 times) for respiratory problems, respiratory monitoring, home oxygen, CPAP, tracheostomy
  - Neurosensory: CP (GMFCS 3-5), Bayley III <70, severe hearing/visual impairment
  - Composite: Respiratory or neurosensory

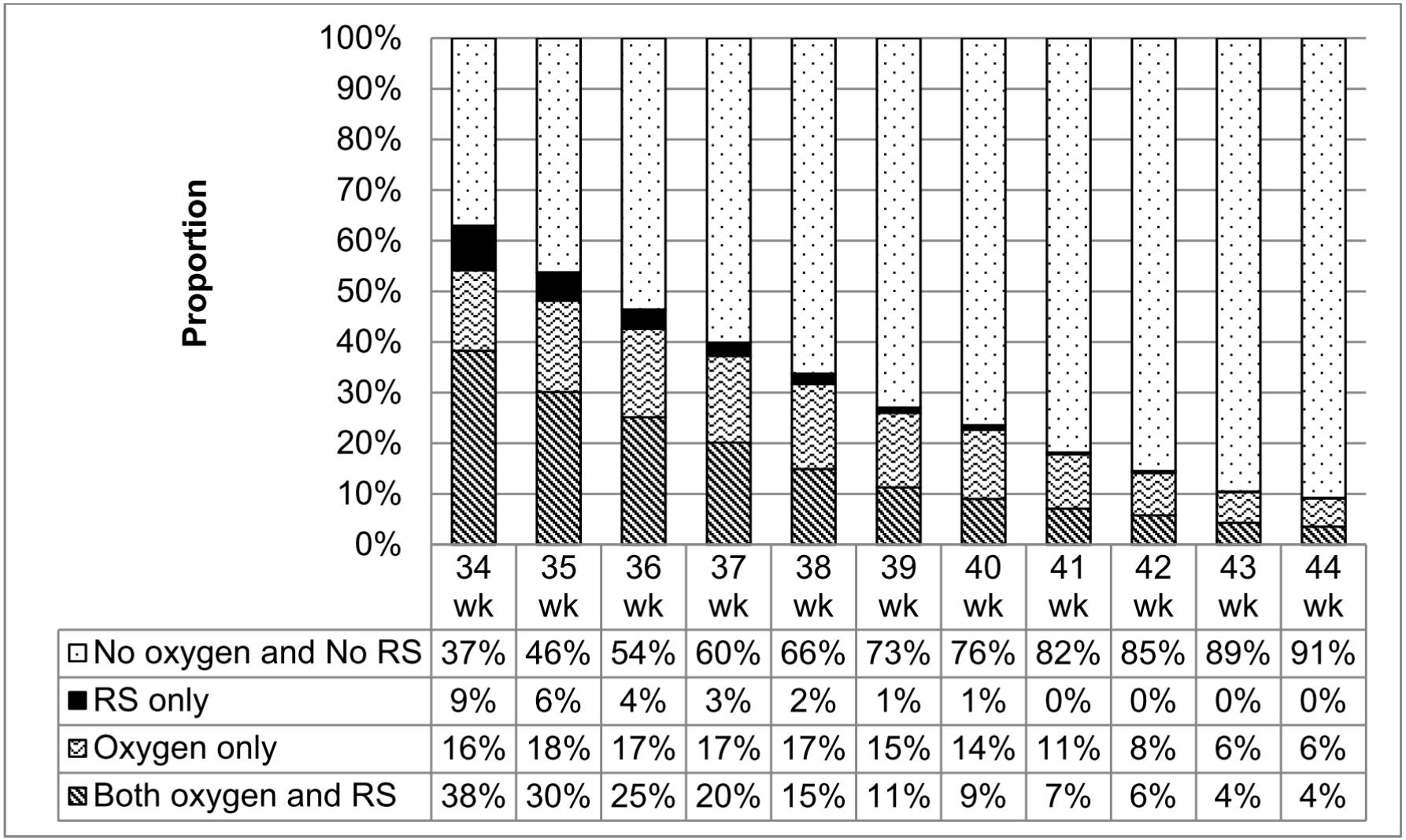
JAMA Pediatr. 2017 Mar 1;171(3):271-279.

Study Population



JAMA Pediatr. 2017 Mar 1;171(3):271-279.

Proportions of infants receiving oxygen and/or RS at each PMA



	34 wk	35 wk	36 wk	37 wk	38 wk	39 wk	40 wk	41 wk	42 wk	43 wk	44 wk
No oxygen and No RS	37%	46%	54%	60%	66%	73%	76%	82%	85%	89%	91%
RS only	9%	6%	4%	3%	2%	1%	1%	0%	0%	0%	0%
Oxygen only	16%	18%	17%	17%	17%	15%	14%	11%	8%	6%	6%
Both oxygen and RS	38%	30%	25%	20%	15%	11%	9%	7%	6%	4%	4%

JAMA Pediatr. 2017 Mar 1;171(3):271-279.

Adverse Outcomes at 18-24 m CA

Outcome	No. (%)
Serious respiratory morbidity	88 (6)
≥3 Rehospitalizations owing to respiratory problems	58 (4)
Use of respiratory monitoring or support devices	44 (3)
Serious neurosensory impairment	257 (17)
Moderate to severe cerebral palsy, GMFCS ≥3	91 (6)
Bayley-III<70 in cognitive, language, or motor	208 (14)
Bayley-III composite score	
<70 in cognitive	47 (3)
<70 in language	157 (11)
<70 in motor	87 (6)
Hearing aid or cochlear implant	35 (2)
Bilateral severe visual impairment	20 (1)
Death after initial discharge	12 (1)
Composite outcome[a]	321 (21)

JAMA Pediatr. 2017 Mar 1;171(3):271-279.

Maternal and Infant Characteristics

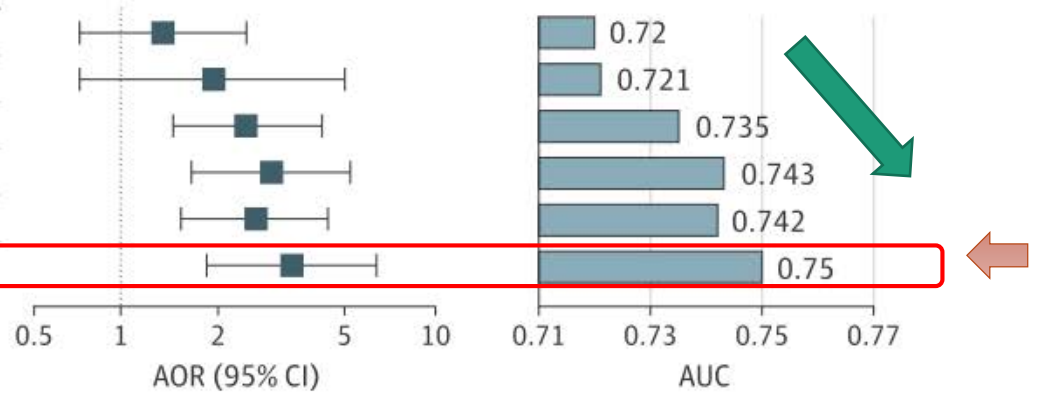
Characteristics	No. (%)						
	All Infants (n = 1503)	No Serious Respiratory Morbidity (n = 1459)	Serious Respiratory Morbidity (n = 44)	*P* Value	No Serious Neurosensory Impairment (n = 1230)	Serious Neurosensory Impairment (n = 257)	*P* Value
Maternal age, mean (SD), y	30.7 (6)	30.7 (5.9)	30.8 (5.0)	.88	30.8 (5.9)	30.2 (5.8)	.12
Hypertensive disorders of pregnancy	267 (18)	262 (18.2)	5 (11.4)	.24	216 (17.8)	48 (19.0)	.67
Antenatal steroids	1349 (92)	1310 (91.6)	39 (90.7)	.83	1112 (92.2)	222 (88.5)	.05
Rupture of membrane >24 h	325 (22)	314 (22.0)	11 (25.6)	.58	173 (22.7)	50 (19.9)	.34
Chorioamnionitis	320 (27)	303 (26.2)	17 (48.6)	<.001	261 (26.7)	55 (27.4)	.84
Multiple birth	415 (28)	404 (27.7)	11 (25.0)	.69	342 (27.8)	65 (25.3)	.41
Cesarean section	876 (58)	850 (58.4)	26 (59.1)	.93	721 (58.8)	145 (56.4)	.48
Race/ethnicity							
White	853 (68)	829 (67.9)	24 (60.0)	.56	730 (69.7)	123 (57.8)	<.001
Black	112 (9)	108 (8.9)	4 (10.0)		83 (7.9)	29 (13.6)	
Other	296 (23)	284 (23.3)	12 (30.0)		235 (22.4)	61 (28.6)	
Maternal education, ≥complete college	729 (53)	707 (53.2)	22 (55.0)	.82	624 (54.6)	104 (46.0)	.02
Male	775 (52)	750 (51.4)	25 (58.1)	.39	606 (49.3)	162 (63.3)	<.001
Gestational age, mean (SD), wk	26.3 (1)	26.3 (1.4)	25.3 (1.4)	<.001	26.4 (1.4)	25.8 (1.5)	<.001
Birth weight, mean (SD), g	929 (226)	933 (225)	777 (169)	<.001	944 (225)	861 (213)	<.001
Small for gestational age	116 (8)	111 (7.6)	5 (11.6)	.33	92 (7.5)	22 (8.6)	.55
SNAP II score >20	410 (27)	387 (26.6)	23 (54.8)	<.001	293 (23.9)	109 (42.9)	<.001
Severe cerebral injuries	160 (11)	153 (10.6)	7 (16.7)	.21	90 (7.4)	68 (26.7)	<.001
Necrotizing enterocolitis	120 (8)	112 (7.7)	8 (19.1)	.01	84 (6.8)	34 (13.3)	<.001
Patent ductus arteriosus	903 (60)	868 (59.6)	35 (83.3)	<.001	712 (58.0)	179 (69.9)	<.001
Late onset sepsis	429 (29)	410 (28.1)	19 (43.2)	.03	313 (25.5)	109 (42.4)	<.001

JAMA Pediatr. 2017 Mar 1;171(3):271-279.

Six traditional BPD definitions with adverse outcomes at 18 to 24 months CA

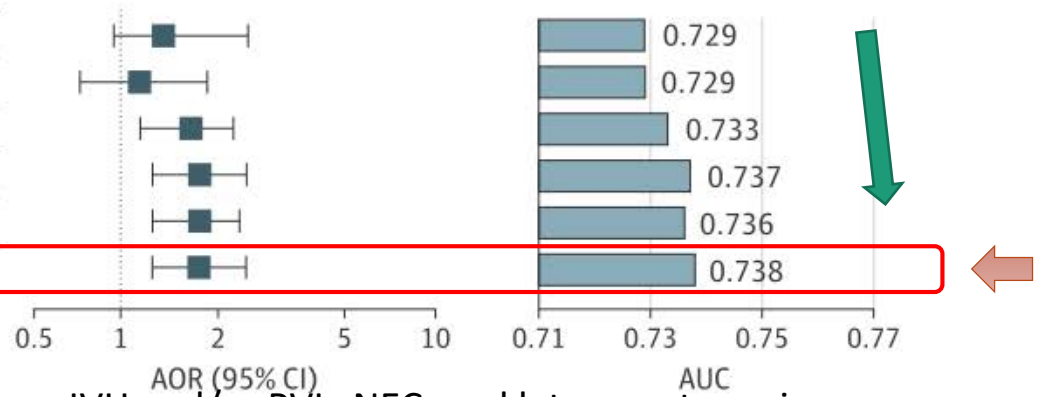
A Serious respiratory morbidity

Traditional BPD Definitions	Adverse Outcome in BPD (+) Infants	Adverse Outcome in BPD (−) Infants	AOR (95% CI)[a]
Oxygen, 28 d	71/893 (8.0)	17/513 (3.3)	1.3 (0.7-2.4)
Oxygen/RS, 28 d	81/1123 (7.2)	7/283 (2.5)	1.9 (0.7-5.0)
Oxygen, 28 d and Oxygen/RS 36 wk PMA	62/579 (10.7)	26/827 (3.1)	2.4 (1.4-4.2)
Oxygen/RS, 28 d and 36 wk PMA	66/620 (10.7)	22/786 (2.8)	2.9 (1.6-5.2)
Oxygen, 36 wk PMA	61/548 (11.1)	27/858 (3.2)	2.6 (1.5-4.4)
Oxygen/RS 36 wk PMA	69/652 (10.6)	19/754 (2.5)	3.4 (1.8-6.3)



B Serious neurosensory impairment

Traditional BPD Definitions	Adverse Outcome in BPD (+) Infants	Adverse Outcome in BPD (−) Infants	AOR (95% CI)[a]
Oxygen, 28 d	192/892 (21.5)	55/511 (10.8)	1.3 (0.9-1.9)
Oxygen/RS, 28 d	217/1120 (19.4)	30/283 (10.6)	1.1 (0.7-1.8)
Oxygen, 28 d and Oxygen/RS 36 wk PMA	145/578 (25.1)	102/825 (12.4)	1.6 (1.1-2.2)
Oxygen/RS, 28 d and 36 wk PMA	153/619 (24.7)	94/784 (12.0)	1.7 (1.2-2.4)
Oxygen, 36 wk PMA	134/547 (24.5)	113/856 (13.2)	1.7 (1.2-2.3)
Oxygen/RS 36 wk PMA	158/651 (24.3)	89/752 (11.8)	1.7 (1.2-2.4)

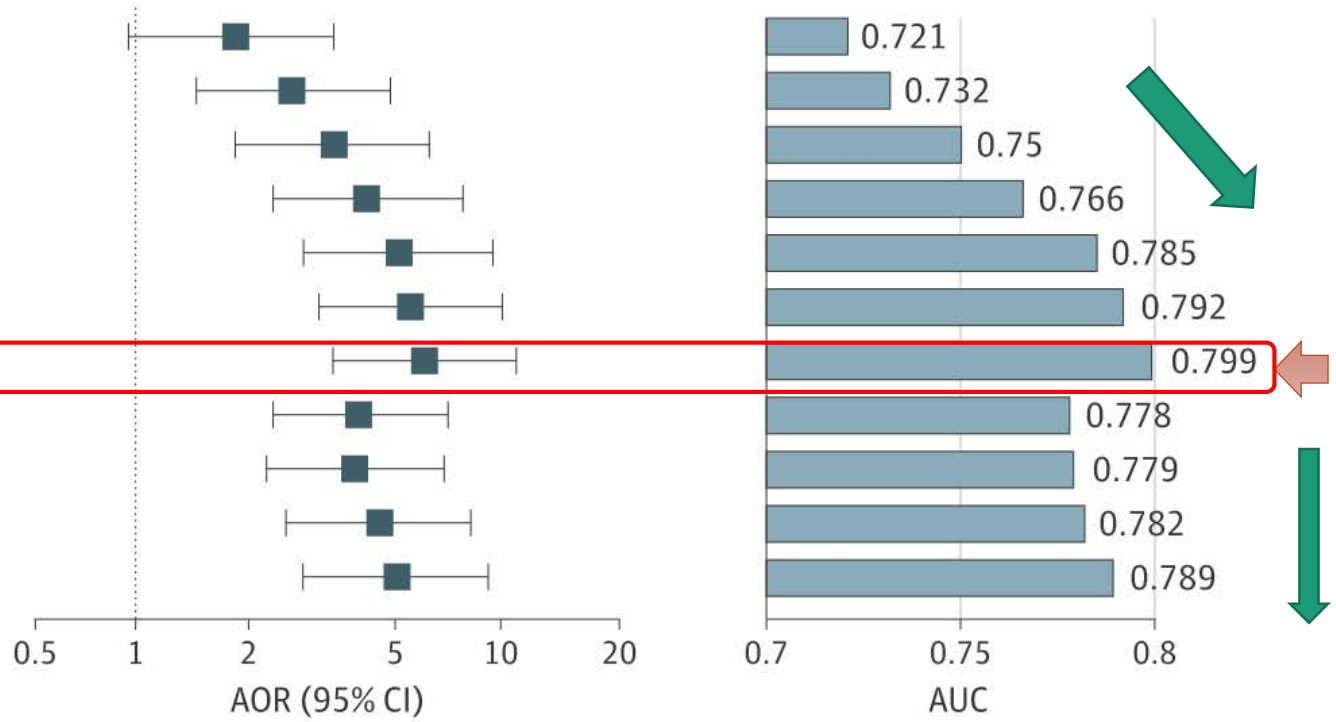


Adjusted for gestational age, sex, SGA, SNAP II score >20, maternal education, severe IVH and/or PVL, NEC, and late-onset sepsis.

JAMA Pediatr. 2017 Mar 1;171(3):271-279.

O_2/RS at 34-40 wk PMA and long-term respiratory morbidity at 18-24 months CA

Traditional BPD Definitions	Adverse Outcome in BPD (+) Infants	Adverse Outcome in BPD (−) Infants	AOR (95% CI)[a]
34 wk PMA	72/939 (7.7)	16/552 (2.9)	1.8 (0.9-3.4)
35 wk PMA	70/780 (9.0)	18/673 (2.7)	2.6 (1.4-4.9)
36 wk PMA	69/652 (10.6)	19/754 (2.5)	3.4 (1.8-6.3)
37 wk PMA	67/555 (12.1)	19/821 (2.3)	4.2 (2.3-7.8)
38 wk PMA	65/467 (13.9)	20/879 (2.3)	5.2 (2.8-9.5)
39 wk PMA	60/392 (15.3)	22/928 (2.4)	5.6 (3.1-10.1)
40 wk PMA	59/362 (16.3)	23/942 (2.4)	6.1 (3.4-11.0)
41 wk PMA	45/315 (14.3)	30/966 (3.1)	4.0 (2.3-7.1)
42 wk PMA	43/294 (14.6)	32/974 (3.3)	3.9 (2.2-6.9)
43 wk PMA	40/272 (14.7)	29/981 (3.0)	4.6 (2.5-8.2)
44 wk PMA	41/269 (15.2)	28/980 (2.9)	5.1 (2.8-9.2)



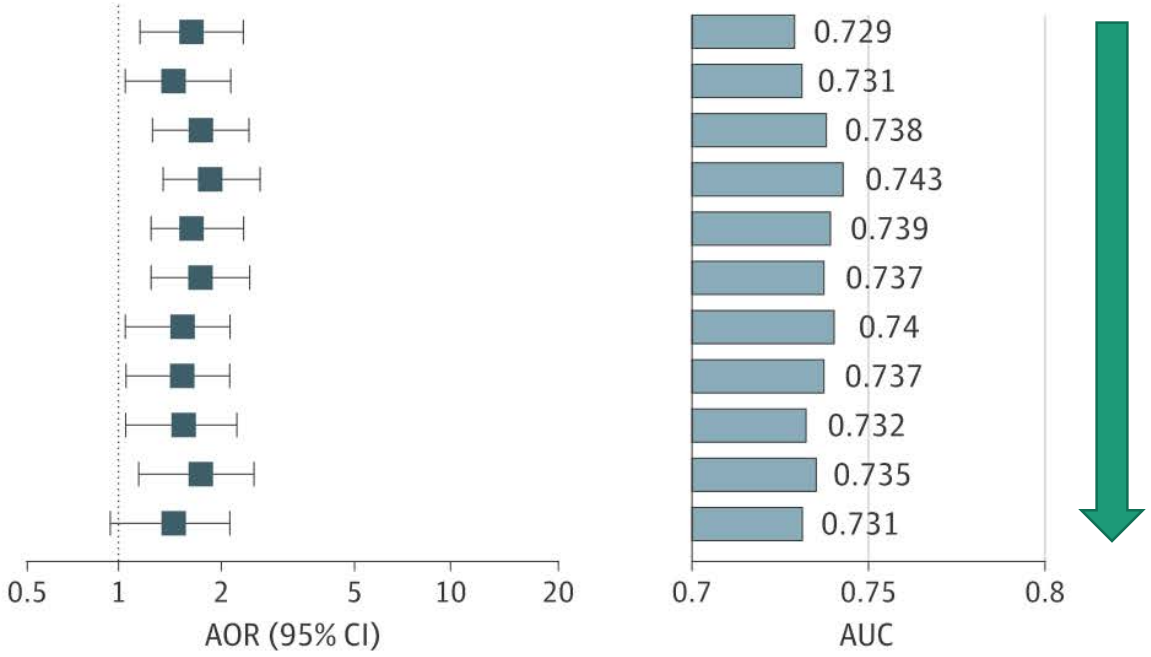
Adjusted for gestational age, sex, SGA, SNAP II score >20, maternal education, severe IVH and/or PVL, NEC, and late-onset sepsis.

JAMA Pediatr. 2017 Mar 1;171(3):271-279.

O_2/RS at 34-40 wkPMA and NDI at 18-21 months CA

B Serious neurosensory impairment

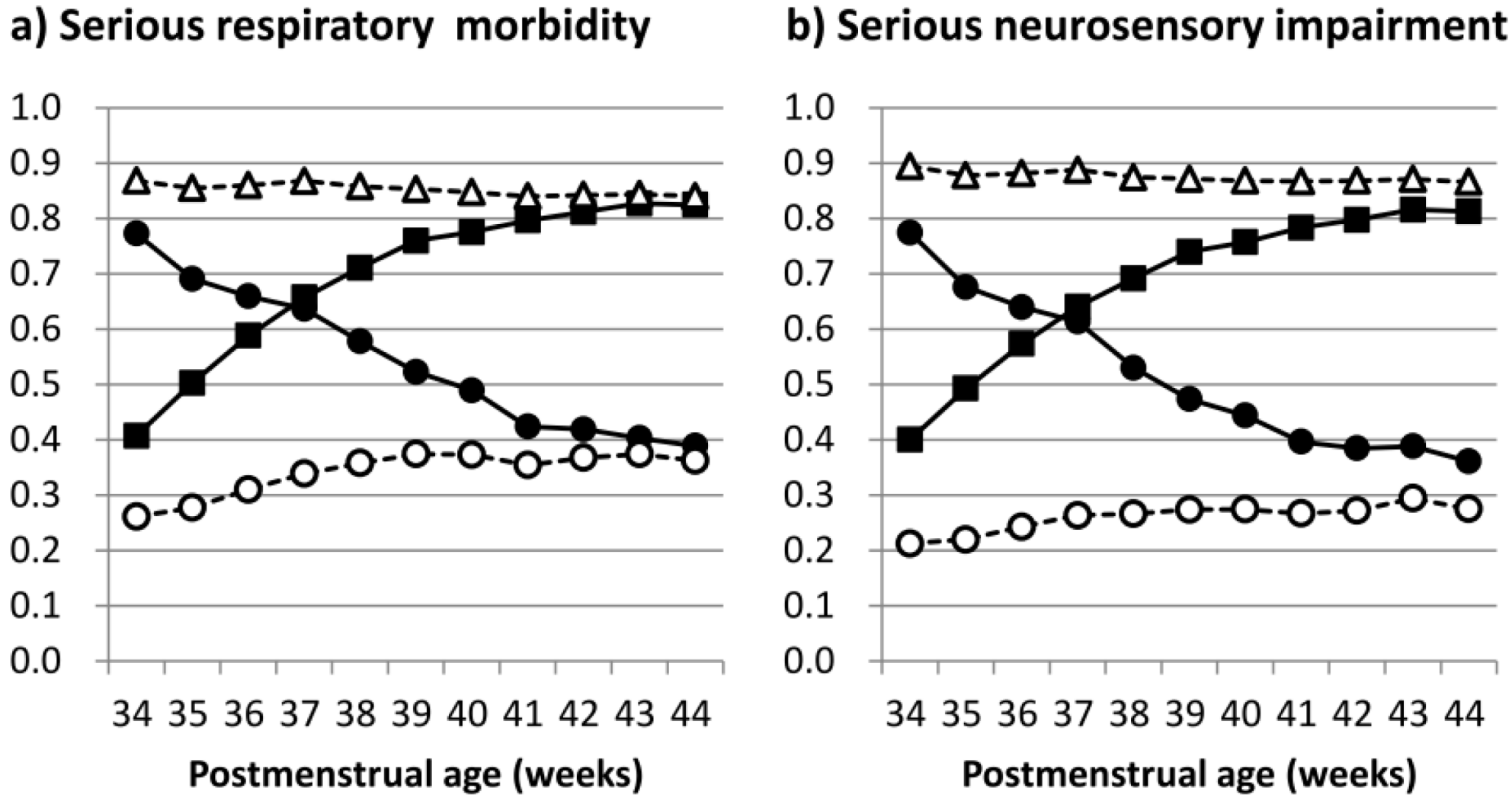
Traditional BPD Definitions	Adverse Outcome in BPD (+) Infants	Adverse Outcome in BPD (−) Infants	AOR (95% CI)[a]
34 wk PMA	199/937 (21.2)	58/550 (10.6)	1.6 (1.1-2.3)
35 wk PMA	171/778 (27.0)	82/671 (12.2)	1.4 (1.0-2.1)
36 wk PMA	158/651 (24.3)	89/752 (11.8)	1.7 (1.2-2.4)
37 wk PMA	146/554 (26.4)	92/819 (11.2)	1.8 (1.3-2.6)
38 wk PMA	124/466 (26.6)	110/877 (12.5)	1.6 (1.2-2.3)
39 wk PMA	107/391 (27.4)	119/926 (12.9)	1.7 (1.2-2.4)
40 wk PMA	99/361 (27.4)	124/940 (13.2)	1.5 (1.0-2.1)
41 wk PMA	84/315 (26.7)	128/963 (13.3)	1.5 (1.0-2.1)
42 wk PMA	80/294 (27.2)	128/971 (13.2)	1.5 (1.0-2.2)
43 wk PMA	80/272 (29.4)	126/978 (12.9)	1.7 (1.1-2.5)
44 wk PMA	74/269 (27.5)	131/977 (13.4)	1.4 (0.9-2.1)



The oxygen/RS at 40 wk PMA was identified as BPD definition or diagnosis for predicting long-term significant respiratory problems.

JAMA Pediatr. 2017 Mar 1;171(3):271-279.

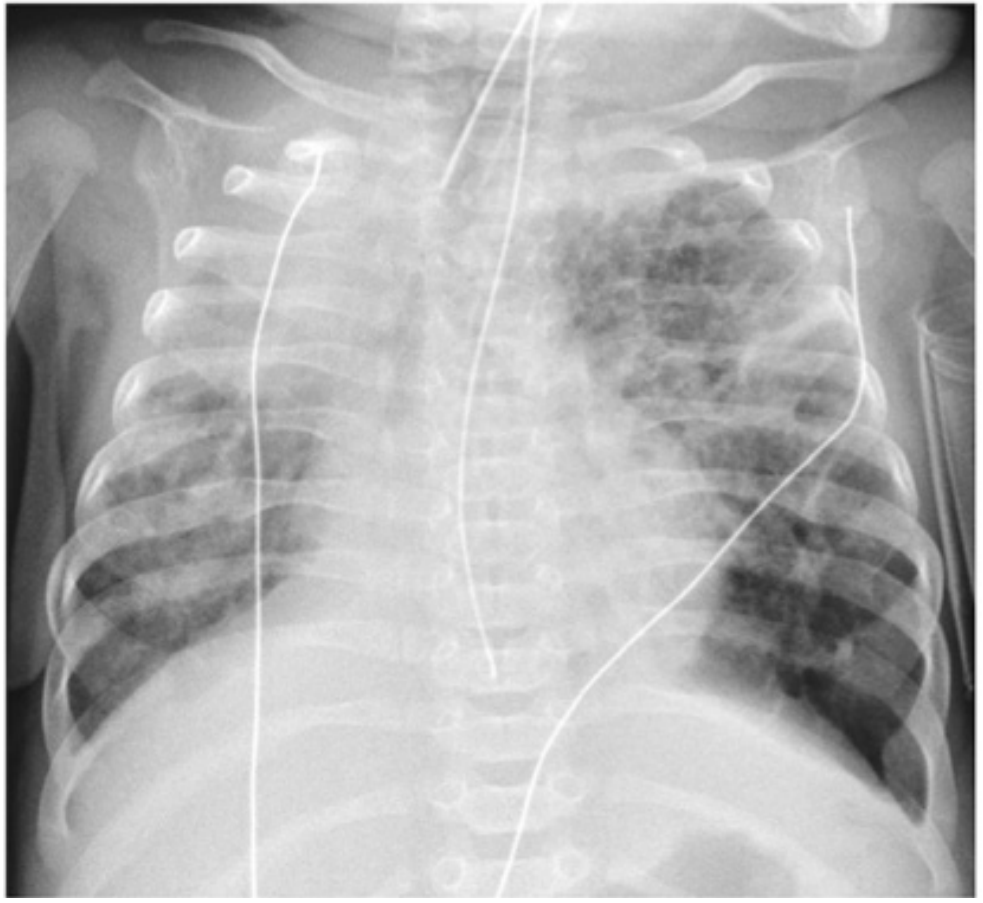
eFigure 2: Sensitivity, specificity, and positive and negative predictive values of oxygen/RS at 34-40 weeks postmenstrual age to predict serious respiratory morbidity and/or neurosensory impairment at 18-24 months corrected age



What happened to radiological changes?

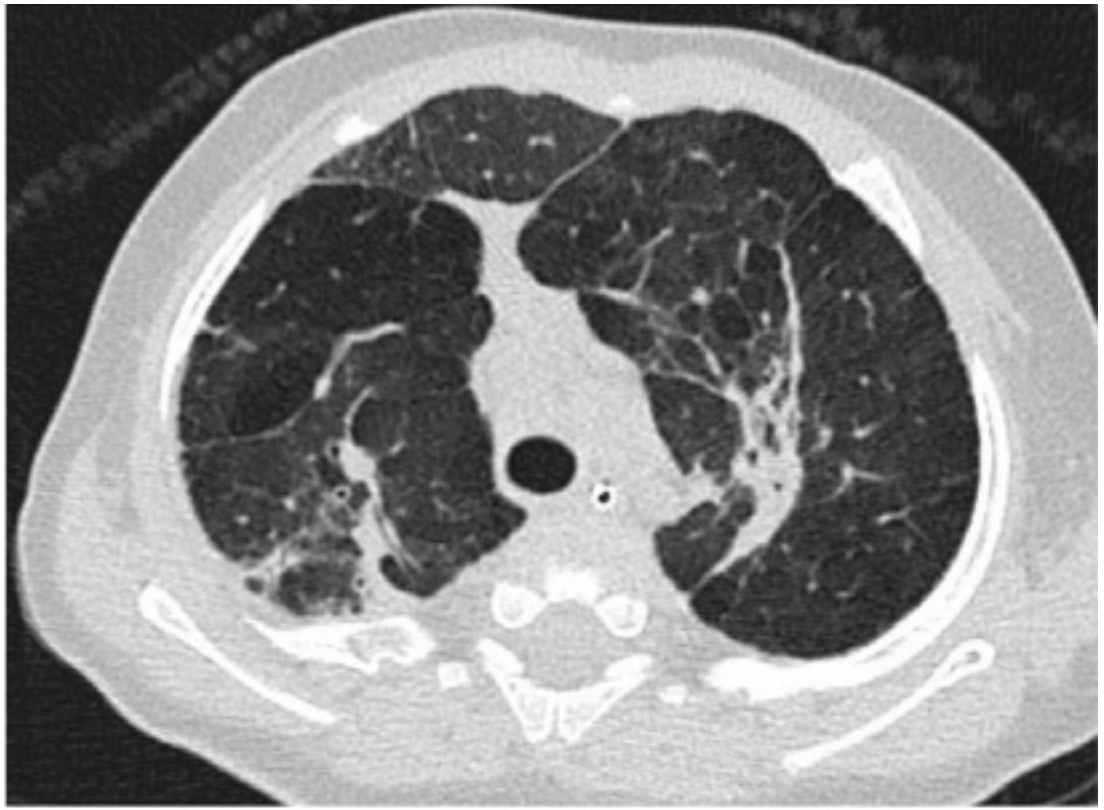
Imaging Bronchopulmonary Dysplasia—A Multimodality Update

*Thomas Semple[1,2], Mohammed R. Akhtar[3] and Catherine M. Owens[2]**



Imaging Bronchopulmonary Dysplasia—A Multimodality Update

*Thomas Semple[1,2], Mohammed R. Akhtar[3] and Catherine M. Owens[2]**

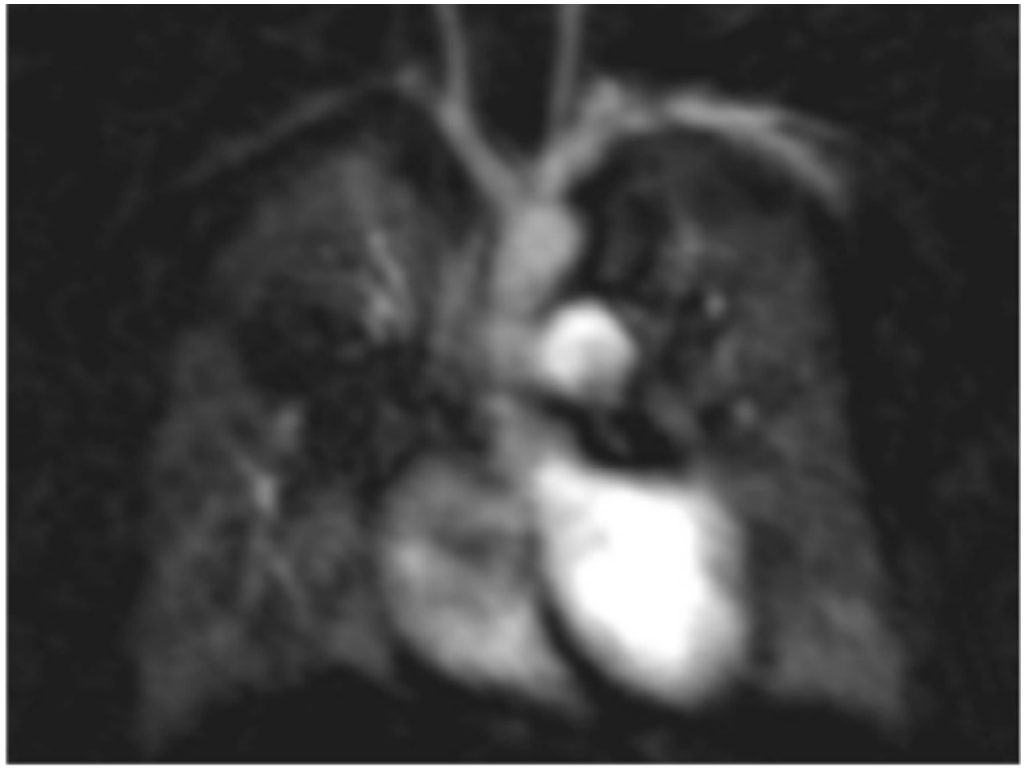


Linear and subpleural opacities, Bronchial wall thickening, and areas of low attenuation

Imaging Bronchopulmonary Dysplasia—A Multimodality Update

*Thomas Semple[1,2], Mohammed R. Akhtar[3] and Catherine M. Owens[2]**

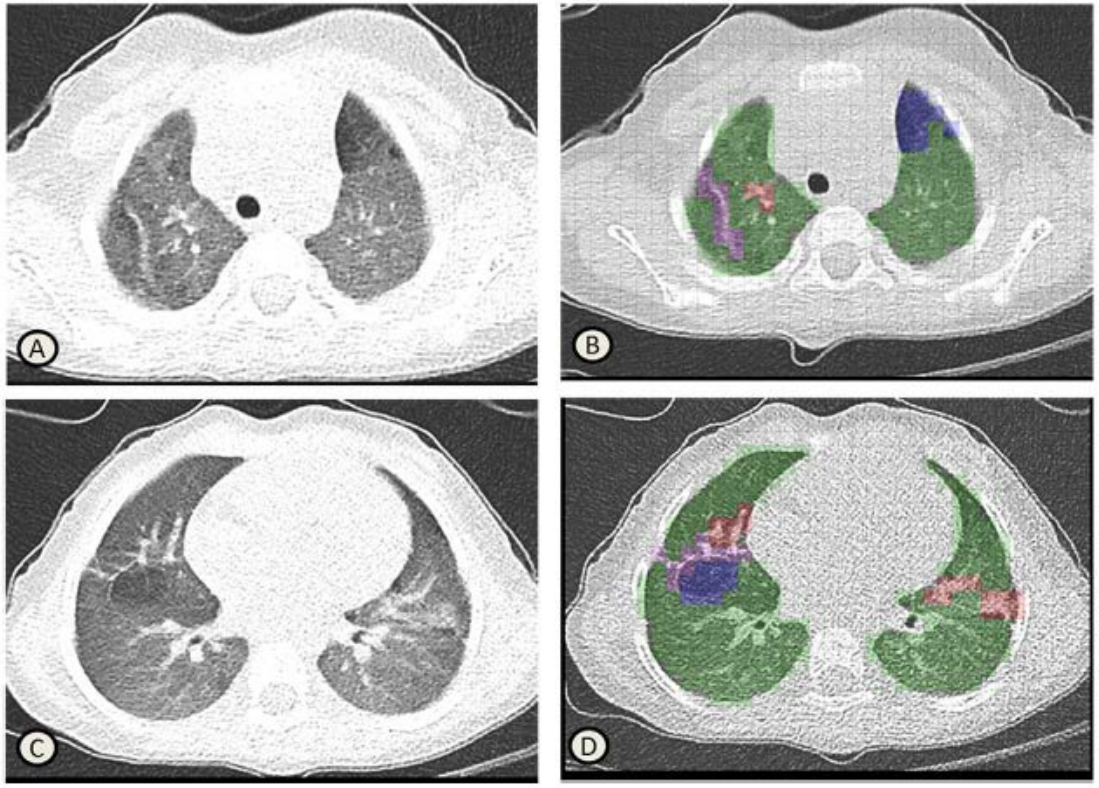
MRI



Poor perfusion of the right upper lobe related to severe small airways disease and reflex vasoconstriction

Lung CT Imaging in Patients With Bronchopulmonary Dysplasia: A Systematic Review

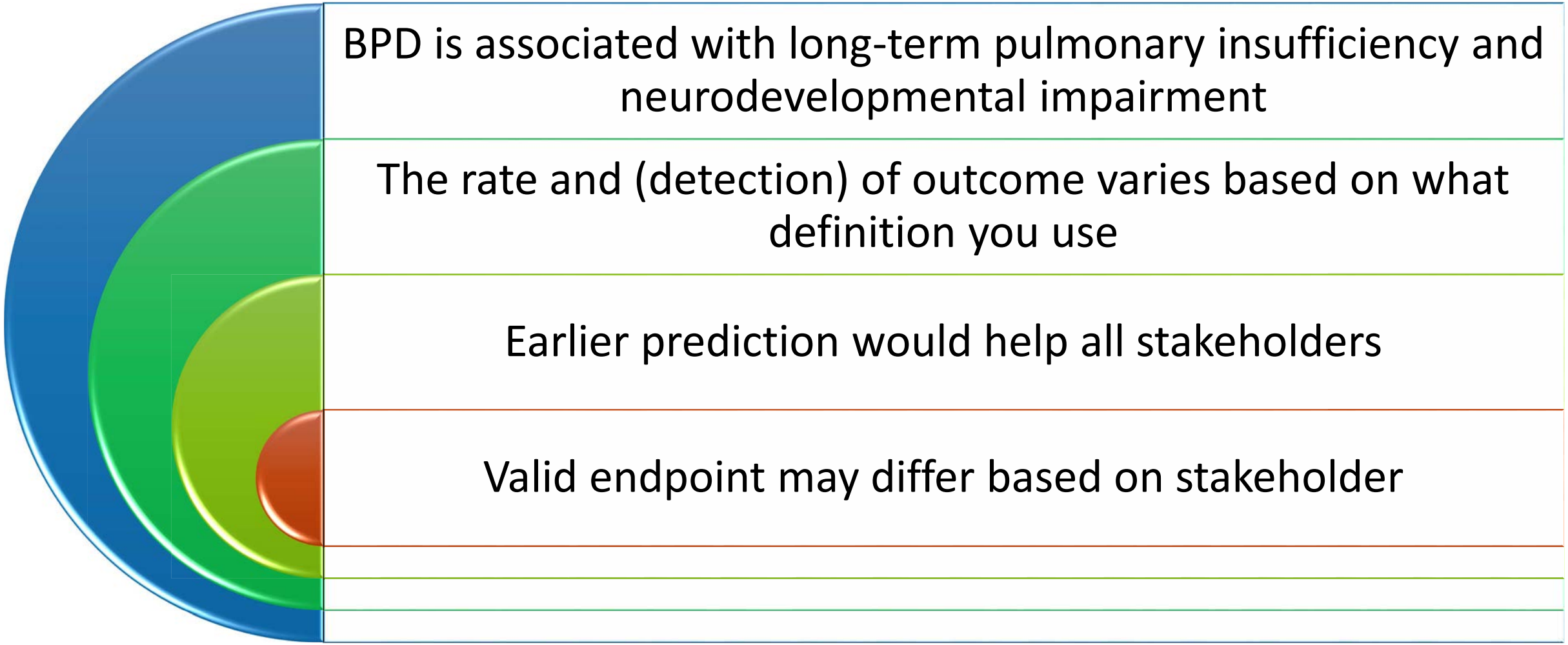
Pediatric Pulmonology 51:975–986 (2016)



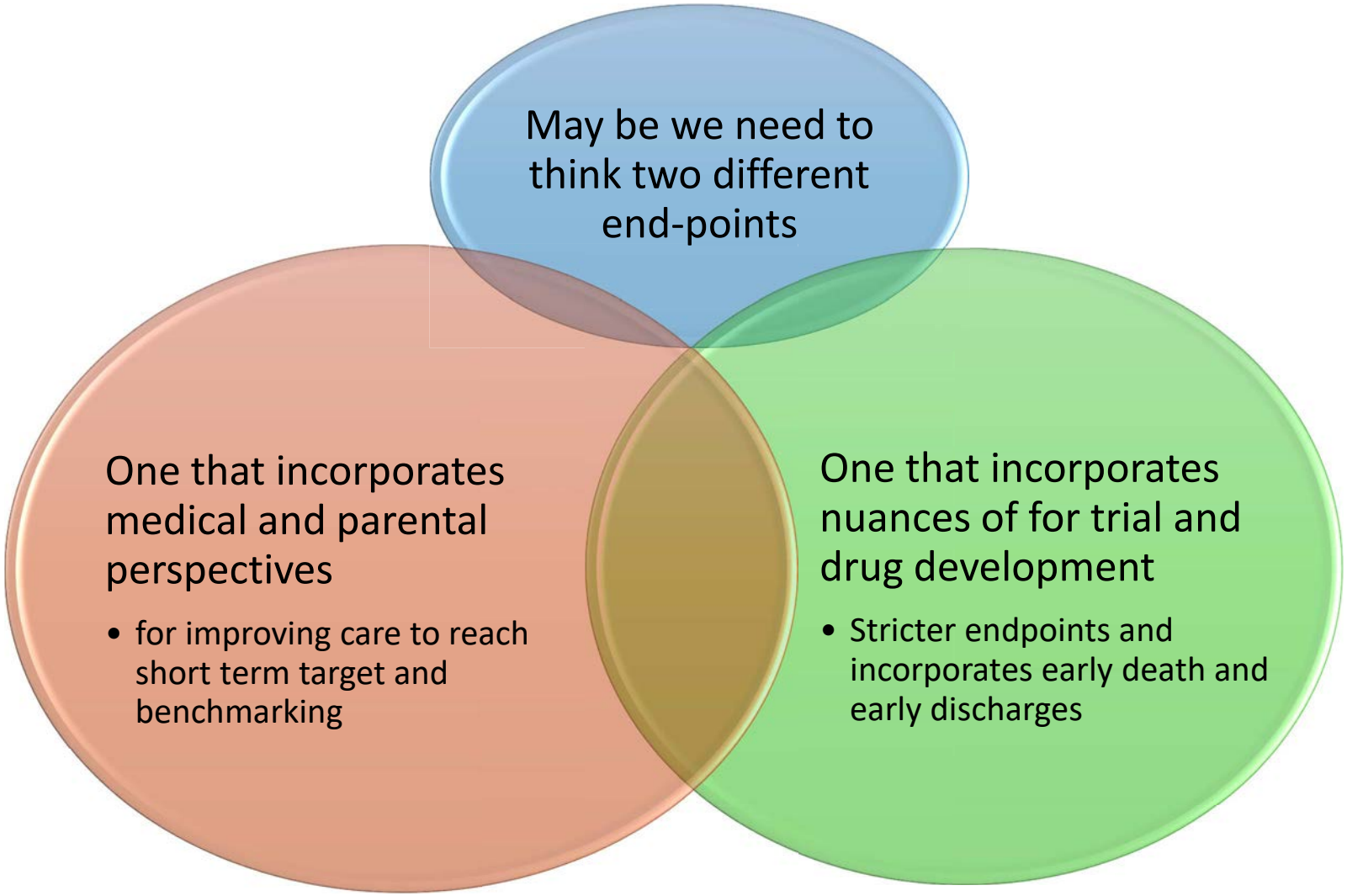
PRAGMA-BPD SCORE

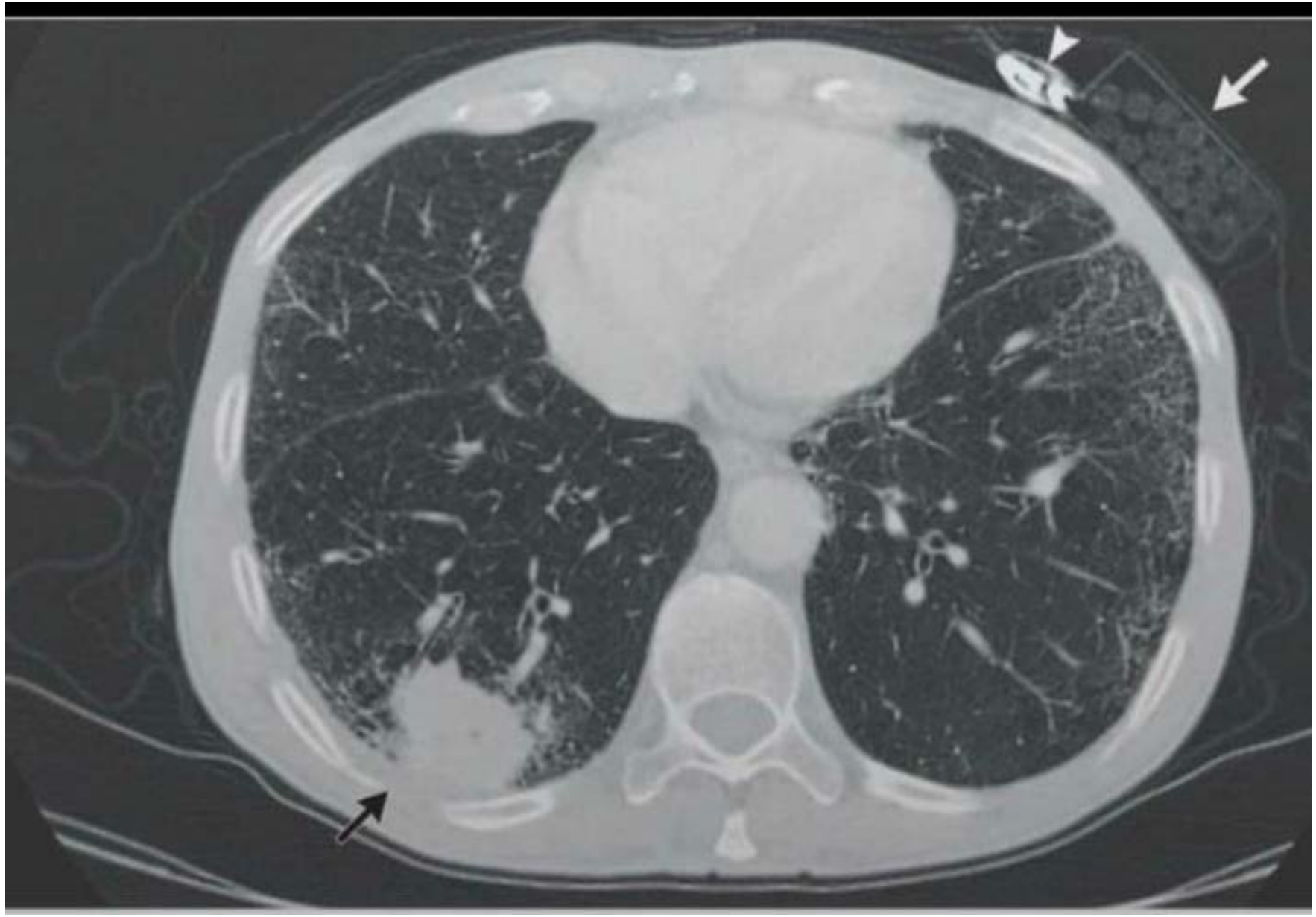
1) Red; opacities (linear and subpleural triangular) and consolidation;
2) Purple: bronchial wall thickening;
3) Blue: decreased pulmonary attenuation (bullae, emphysema, mosaic perfusion, trapped air);
4) Green: no abnormality seen.

Conclusions



Personal thought





Bronchopulmonary Dysplasia: Executive Summary of a Workshop

Rosemary D. Higgins, MD[1], Alan H. Jobe, MD[2], Marion Koso-Thomas, MD[1], Eduardo Bancalari, MD[3], Rose M. Viscardi, MD[4], Tina V. Hartert, MD[5], Rita M. Ryan, MD[6], Suhas G. Kallapur, MD[7], Robin H. Steinhorn, MD[8], Girija G. Konduri, MD[9], Stephanie D. Davis, MD[10], Bernard Thebaud, MD[11,12,13], Ronald I. Clyman, MD[14,15], Joseph M. Collaco, MD[16], Camilia R. Martin, MD[17], Jason C. Woods, MD[18], Neil N. Finer, MD[19], and Tonse N. K. Raju, MD[1]

Table I. Suggested refinements to the definition of BPD

A premature infant (<32 weeks' gestational age) with BPD has persistent parenchymal lung disease, radiographic confirmation of parenchymal lung disease and at 36 weeks PMA requires 1 of the following FiO_2 ranges/oxygen levels/O_2 concentrations for ≥3 consecutive days to maintain arterial oxygen saturation in the 90%-95% range.

Grades	Invasive IPPV*	N-CPAP, NIPPV, or nasal cannula ≥ 3 L/min	Nasal cannula flow of 1-<3 L/min	Hood O_2	Nasal cannula flow of <1 L/min
I	—	21	22-29	22-29	22-70
II	21	22-29	≥30	≥30	>70
III	>21	≥30			
III(A)	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (eg, necrotizing enterocolitis, intraventricular hemorrhage, redirection of care, episodes of sepsis, etc).				

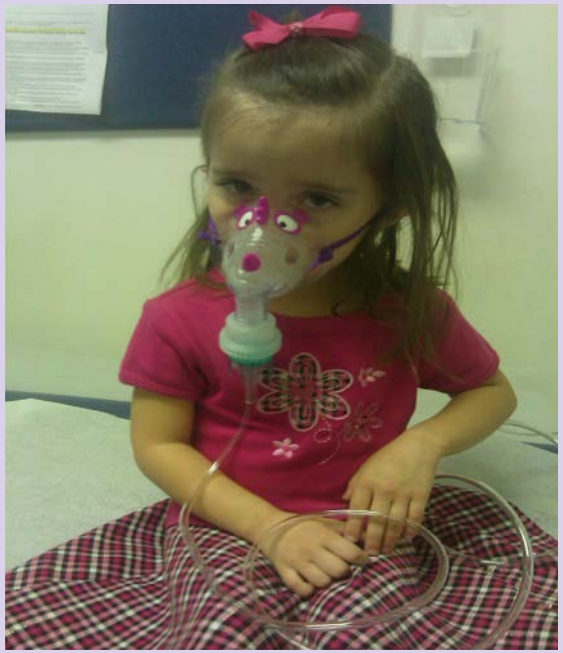
J Pediatrics 2018;197:300-08

Advancing Endpoint Development for Preterm Neonates with Pulmonary Morbidities

Session II: Identifying What is Clinically Meaningful to Stakeholders in Endpoint Development for Preterm Neonates with Pulmonary Morbidities

Faces of Chronic Lung Disease

A complication of prematurity



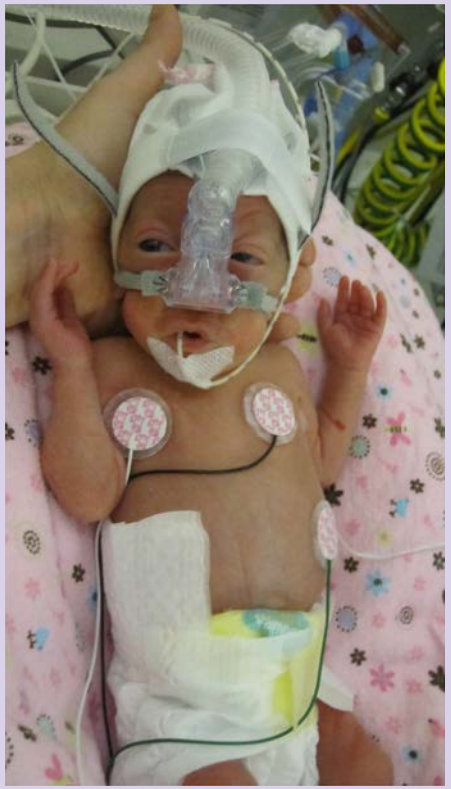
Triplets- Avery, Lily and Zoe were born at 25 weeks, 5 days. Although they all suffered lung complications from their premature birth, sweet Zoe lost her battle with Bronchopulmonary dysplasia at 13 month old.

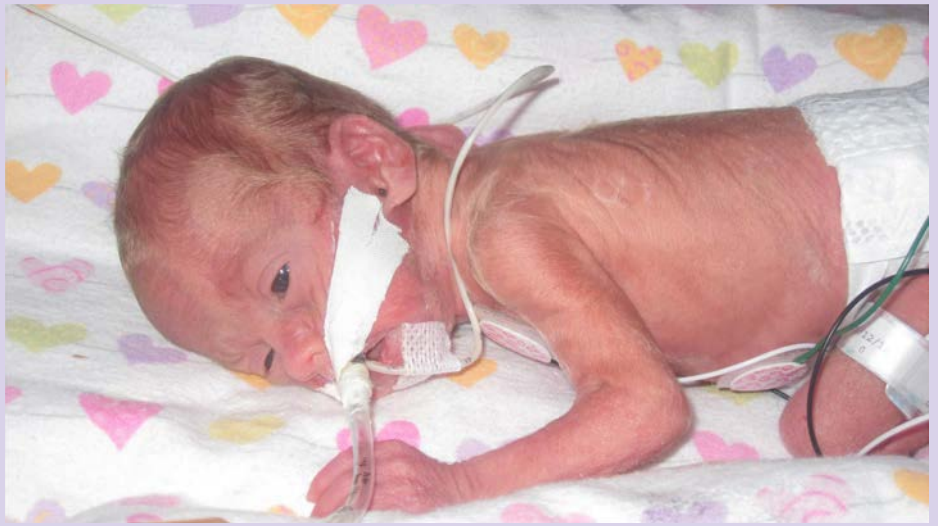
What Preemie Parents Feel We Should Focus On

- Specialists Follow-Ups
- Trach/Vent Infants and the Increased Needs/Supports
- Home Health Care Nursing - prescribed vs. reality

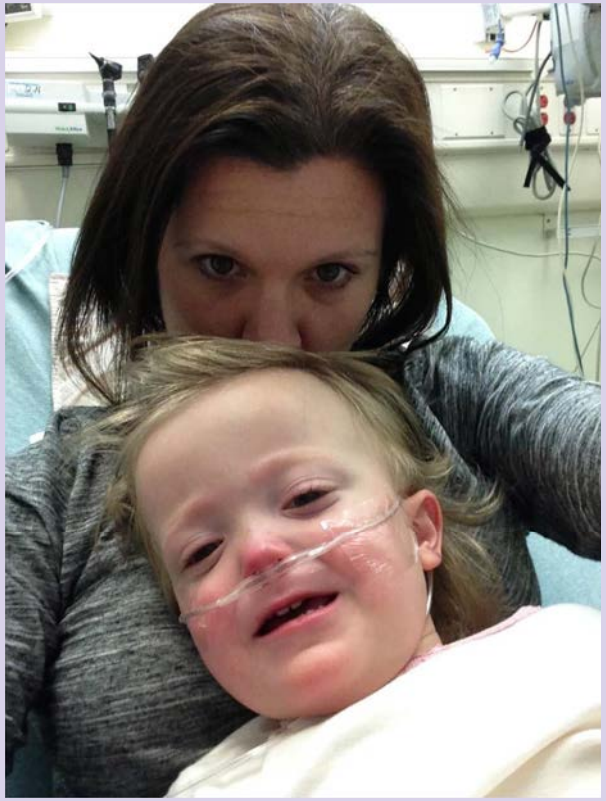
Having to pull over just to suction my son out(he has a trach) alarms going off,his food is done(Gtube) ...Trying to figure out what's hurting him as he's fussy(can't hear his cry due to trach) constant jumping up to make sure his airway is clear..or out in the stores and having to stop just to suction

Meds, and waking up in the middle of the night to hear the pulse o2 monitor alarming. With her desating. Watching her have "blue episodes" and not be able to take a deep breath to help her breath. Fear of one of my other children getting a cold and sharing the germs. I could go on and on....





Joy ~ born at 23 weeks, spent 121 days in the NICU, sent home on O2 with severe BPD, was rehospitalized 8 times due to complications from respiratory viruses, takes inhaled steroids 2x daily at 6 years old. Colds last forever...



What Preemie Parents Feel We Should Focus On

- Use of Durable Medical Equipment (DME) post-NICU & Gestational Age
- Severity of illnesses (length of time, ER visits)
- Types of meds needed (steroids, bronchodilator)

My poor nugget gets sick for 3 weeks at a time constantly. We usually get a two week reprieve and then he's sick again.

How difficult it is to get out of the house, even just for doctor's appointments. Change to portable o2, cart around the canister and the pulse ox, make sure the tubing's not stuck anywhere, jam it in the car seat, pulse ox goes off constantly in the back seat.

Becky, 30 weeks, now 15. - “She’s doing great!” baby. Severe reflux/feeding/breathing issues. Discharged with oxygen/monitor w/feedings. Peds unit 5 days later due to stopping eating + alarms. Full-time oxygen at home. Inhaler 18 mos-Present. Measuring: Oxygen need; severe episode.

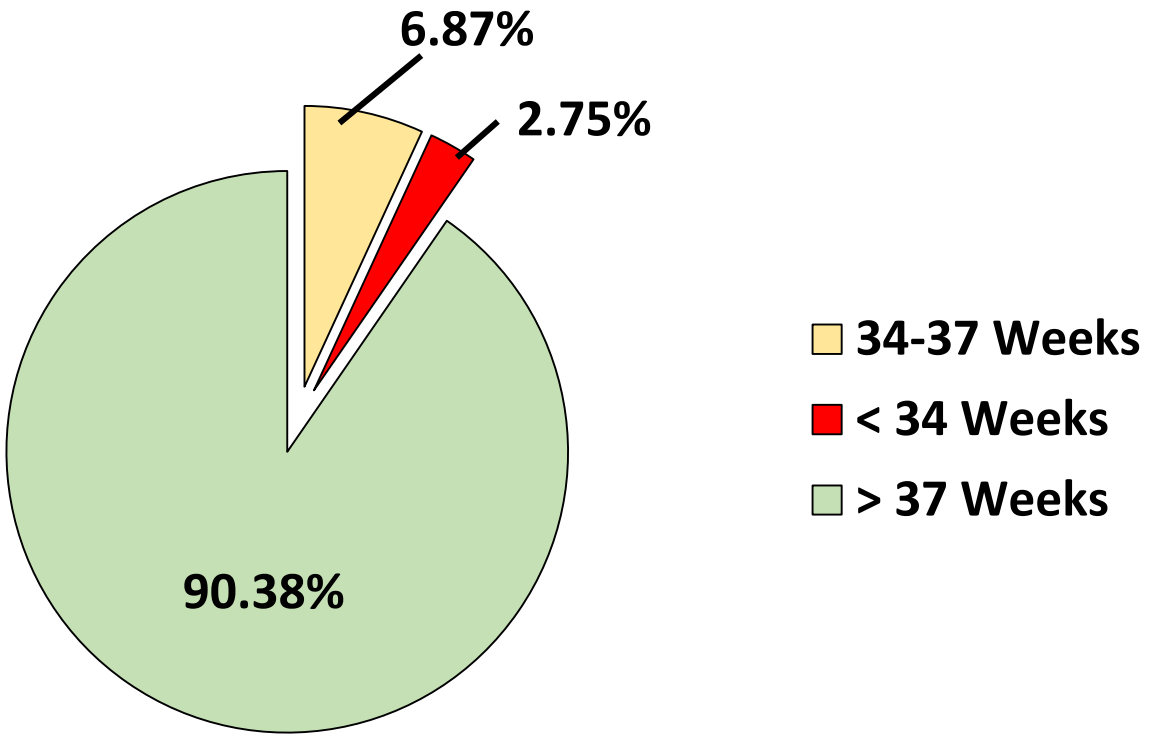
What Preemie Parents Feel We Should Focus On

- Factors to Susceptibility to Illness
- Hospitalization
- Insurance Coverage Lacking + Financial Burden
- Parental Stress

The anxiety related to every sneeze and sniffle - will this be a two-day cold, or a three-week knock-her-down flare up? How many times to the ped/urgent care/ED before admission?

Worrying about every little sniffle and cold impacting his breathing. My son has been off of oxygen since February, but every cold terrifies me still

- In 2015, their were about 4 million live births in the US
- Of these ~ 382,600 births were delivered at <37 wks gestation. Very low birth weight infants at highest risk for developing chronic lung disease



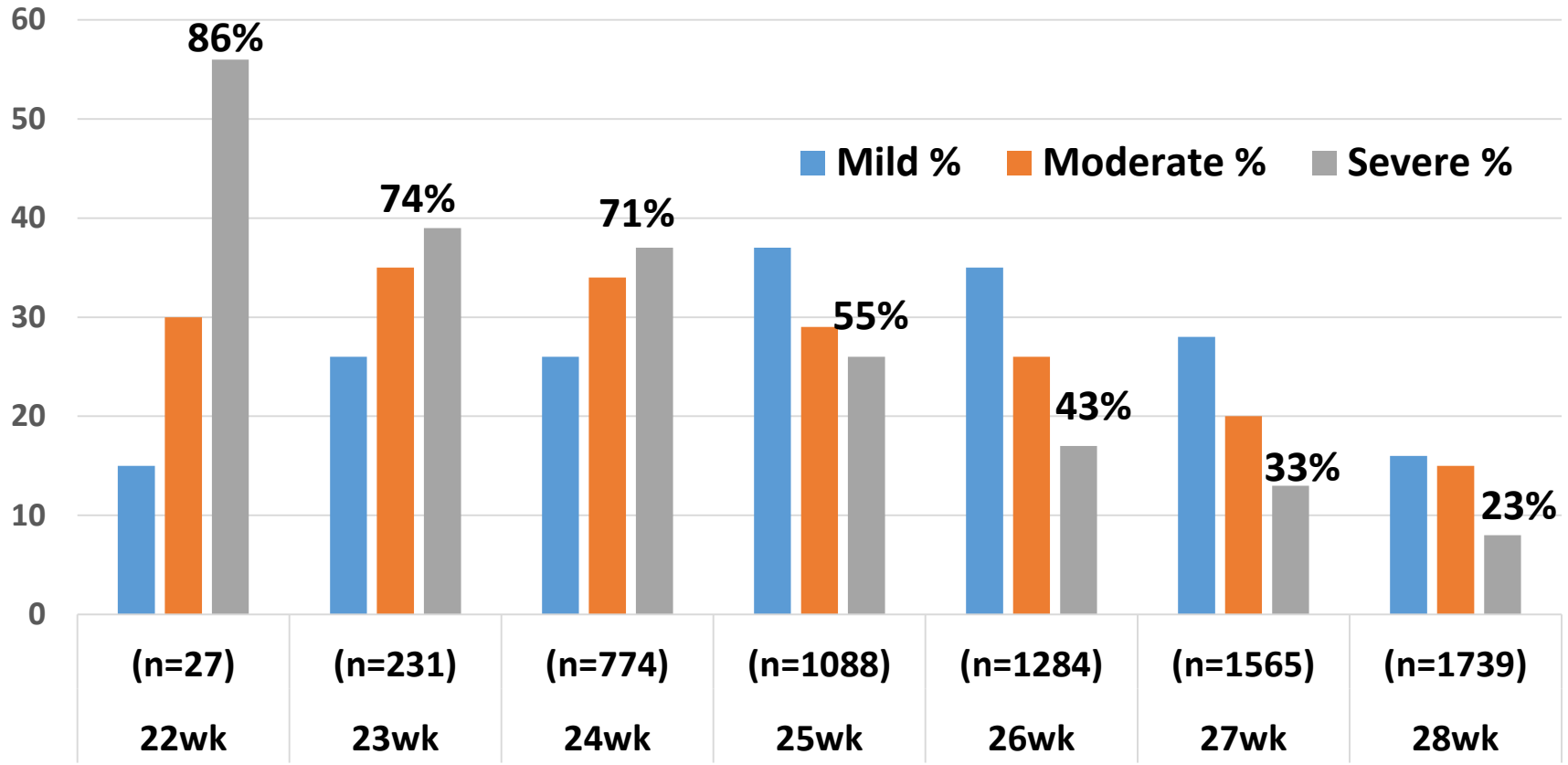
National Vital Statistics Reports, Vol. 65, No. 3, June 2, 2016

- **Bronchopulmonary dysplasia (BPD)-** is the most common chronic lung disease of infancy, and usually occurs in infants born < 32 weeks gestation and < 1500 grams

  - ~ 12,000 infants diagnosed with BPD <u>each year</u>* in the US
  - In contrast ~ there are 30,000 people (all ages) in the US who have cystic fibrosis-
    - Net assets of CF foundation- 4.2 billion in 2017
  - BPD research- “limited funding and lack of pharmaceutical industry support have delayed translation into early-phase clinical trials, ”
    (Bronchopulmonary Dysplasia: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases, McEvoy et. al, 2014)

***American Lung Association Lung Disease Data: 2008**

Likelihood of being diagnosed with BPD by gestational age

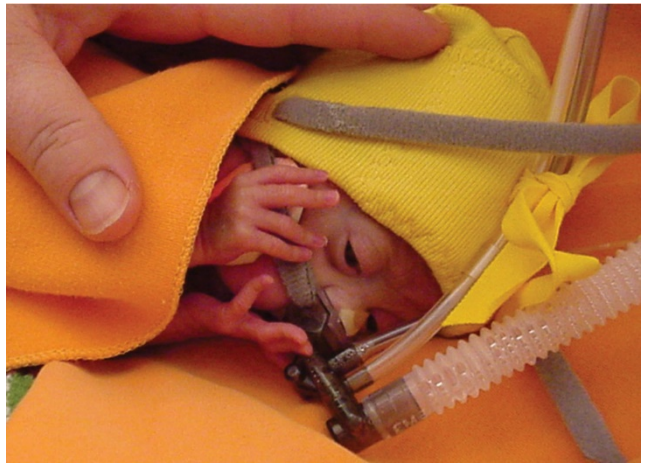


Data from the NICHD Neonatal Research Network

Stoll et. al., Pediatrics, 2010

Infants with BPD can have some or all of the following conditions:

• Upper airway lesions -vocal cord injury -subglottic stenosis • Large airway disease -Bronchomalacia Tracheomalacia • Small airway disease -Wheezing, intermittent, chronic, with exercise	• Alveolar growth impairment -Gas exchange anomalies, hypoxia and hypercarbia • Impaired angiogenesis -Pulmonary hypertension • Control of breathing issues -Apnea- central and obstructive



After discharge to home respiratory symptoms often persist in BPD infants and children

- Up to 40-50% of infants diagnosed with BPD are re-hospitalized for respiratory illnesses in the first two years of life
- Higher rates of asthma-like symptoms
- Higher use of respiratory medications

Ehrenkranz et.al., Pediatrics 2005, Dombkowski KJ et.al.,. Ann Epidemiol 2008;18:290-297. Smith et., al. J Peds, 2004

Estimates of Preterm Respiratory Disease

Preterm Respiratory Disease	Disease Phenotype (and preterm source data)	General Population Data	Preterm Population Data	Individuals at Risk	Estimated Number of Affected Individuals Born Annually in U.S.
Alveolar Disease	2001 NHLBI Bronchopulmonary Dysplasia Definition	N/A	Mild: 30.3% Moderate: 30.2% Severe: 16.4%	<32 weeks gestation: 63,258	Mild: 19,149 Moderate: 19,123 Severe: 10,374 **TOTAL: 48,646**
	Home Supplemental Oxygen	N/A	23-28 weeks gestation: 27.5% 29-33 weeks gestation: 2.8% 34-36 weeks gestation: 0.8%	<28 weeks gestation: 27,054 28-33 weeks gestation: 82,753 34-36 weeks gestation: 273,323	7452 2324 2162 **TOTAL: 11,938**
	Home Ventilator for BPD	N/A	Live Births: 4.77 per 100,000	Live Births: 3,978,497	**190**
Obstructive Lung Disease	Childhood Asthma	8.4%**	≤32 weeks gestation: 3.9 OR compared to general population 33-36 weeks gestation: 1.7 OR compared to general population	<32 weeks gestation: 63,258 32-36 weeks gestation: 319,871	20,723 45,678 **TOTAL: 66,401**
Large Airway Malacia	Airway Malacia	N/A	≤28 weeks gestation: 2%	<28 weeks gestation: 27,054	**541**
	Airway Malacia Requiring Tracheostomy	N/A	≤28 weeks gestation: 0.6%	<28 weeks gestation: 27,054	**162**
Obstructive Sleep Apnea	Sleep-Disordered Breathing	0-5.7%	School-Age: 6.6-11.0%	≤36 weeks gestation: 383,129	**25,287 – 42,144**
Pulmonary Vascular Disease	Pulmonary Hypertension (at 36 weeks PMA)	N/A	~≤28 weeks gestation: 4.2-24.0%	<28 weeks gestation: 27,054	**1136 - 6493**

Collaco JM; *Ann Am Thorac Soc.* 2018 May;15(5):530-538.

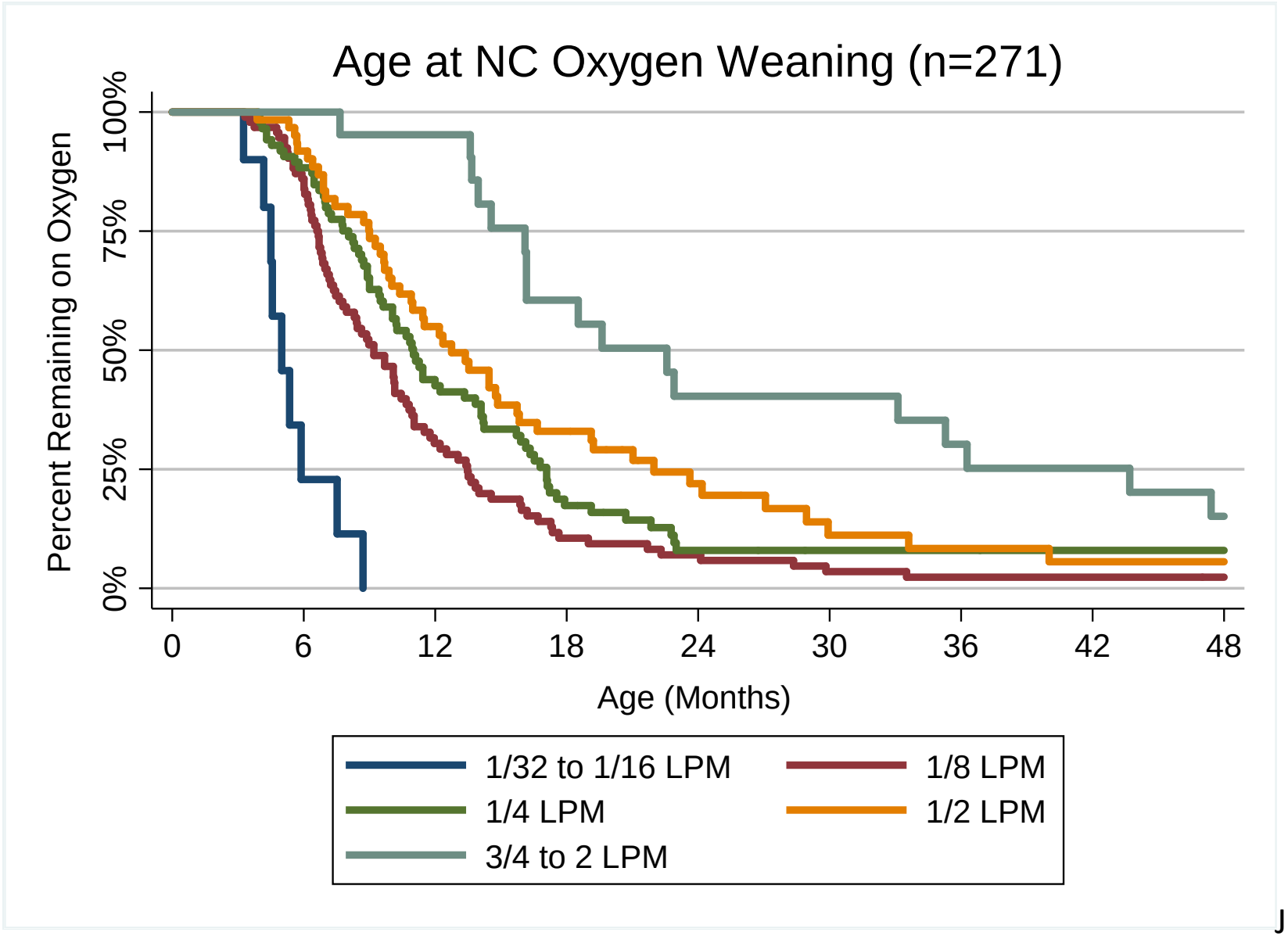
BPD Registry at Johns Hopkins

n= 728 ≤ 32 week

(as of April 2018)

Characteristic	Mean ± S.D.
Sex (% male)	**60.1**
Race/Ethnicity (% non-white)	**64.4**
Gestational Age (weeks)	**27.2 ± 3.0**
Birth Weight (grams)	**996 ± 493 (n = 768)**
Home Supplemental Oxygen (%)	**36.9**
Tracheostomy (%)	**4.3**
Home Ventilator (%)	**3.3**
GT (%)	**26.8**
Nissen (%)	**16.8**
Ventricular Shunt (%)	**8.2**
Pulmonary Hypertension after 2 months of age (%)	**15.9**

Duration of Home Oxygen Use



JHU BPD Registry: Unpublished

Daycare exposure positively associated with more acute care usage in BPD children

	Attends daycare (n = 211)	
	Odds Ratio	*P* value
ED Visit	**3.74** [1.14 – 9.91]	**0.02**
Admission	3.22 [0.97 – 10.72]	0.10
Prednisone	**2.22** [1.10 – 4.49]	**0.01**
Antibiotics	**2.40** [1.10 – 5.30]	**0.01**

McGrath-Morrow et.al., Pediatrics ,2010

Higher hair nicotine levels associated with greater likelihood of inpatient hospitalization and activity limitation in children with moderate to severe BPD

Outcome	All Subjects (n = 114)	P	Subjects on Home Respiratory Support[a] (n = 50)	P
Emergency department visit	1.75 (0.83–3.67)	.14	2.06 (0.53–7.99)	.29
Inpatient hospitalization	1.82 (0.78–4.23)	.16	6.42 (1.35–30.62)	.020
Systemic steroid use	1.09 (0.46–2.59)	.84	0.54 (0.11–2.78)	.46
Antibiotic use	0.43 (0.16–1.16)	.10	0.32 (0.06–1.78)	.19
Cough or wheeze	1.57 (0.81–3.02)	.18	0.77 (0.24–2.46)	.66
Rescue β-agonist use	1.00 (0.50–2.03)[b]	.99	2.89 (0.71–11.88)[c]	.14
Activity limitations	1.33 (0.50–3.50)[b]	.57	7.52 (1.59–35.60)[c]	.011
Nighttime symptoms	0.80 (0.38–1.66)[b]	.55	1.36 (0.33–5.51)[c]	.67

Collaco et. al., Pediatrics, 2015.

Adherence (Medication Refill Rates)

- **Each 10% increase in adherence was associated with**:
  - Decreased ED visits (**OR: 0.75)**
  - Fewer activity limitations (**OR: 0.71**)
  - Less rescue medication use (**OR: 0.84**)

Collaco JM *et al. Pediatr Pulmonol* 2012

Future Directions

- Develop strategies to optimize lung growth and limit lung insults in preterm infants
- Develop personalized treatments
- Understand the impact of BPD on long-term pulmonary function
- Create guidelines for the management of BPD
- Educate caregivers

Session II: Identifying What is Clinically Meaningful to Stakeholders in Endpoint Development for Preterm Neonates with Pulmonary Morbidities

Questions to address:

- What does the disease process look like and what are you trying to prevent/improve?
- What is important to you, your child, and your family?

Advancing Endpoint Development for Preterm Neonates with Pulmonary Morbidities

Session III: Defining the Potential for Endpoint Development for Preterm Neonates with Pulmonary Morbidities

Session III: Defining the Potential for Endpoint Development for Preterm Neonates with Pulmonary Morbidities

Questions to address:

- What should the timing of endpoints be? 1 year, 2 years, or some other time frame?
- What type of endpoint(s) would best serve the needs of all the stakeholders? (These include COA, clinical endpoint, biomarker, among others)

Advancing Endpoint Development for Preterm Neonates with Pulmonary Morbidities

Session IV: Exploring Endpoint and COA Development

Exploring Endpoint and COA Development

Carole A Tucker , PhD

Advancing Endpoint Development for Preterm Neonates with Pulmonary Morbidities

Washington, DC

October 2, 2018

Duke | MARGOLIS CENTER for Health Policy

TEMPLE UNIVERSITY
College of Public Health

Objectives

- Review key concepts in measurement science and instrument development
- Overview of FDA COA development process
- Provide overview of parallel resources for COA development

Measurement Properties

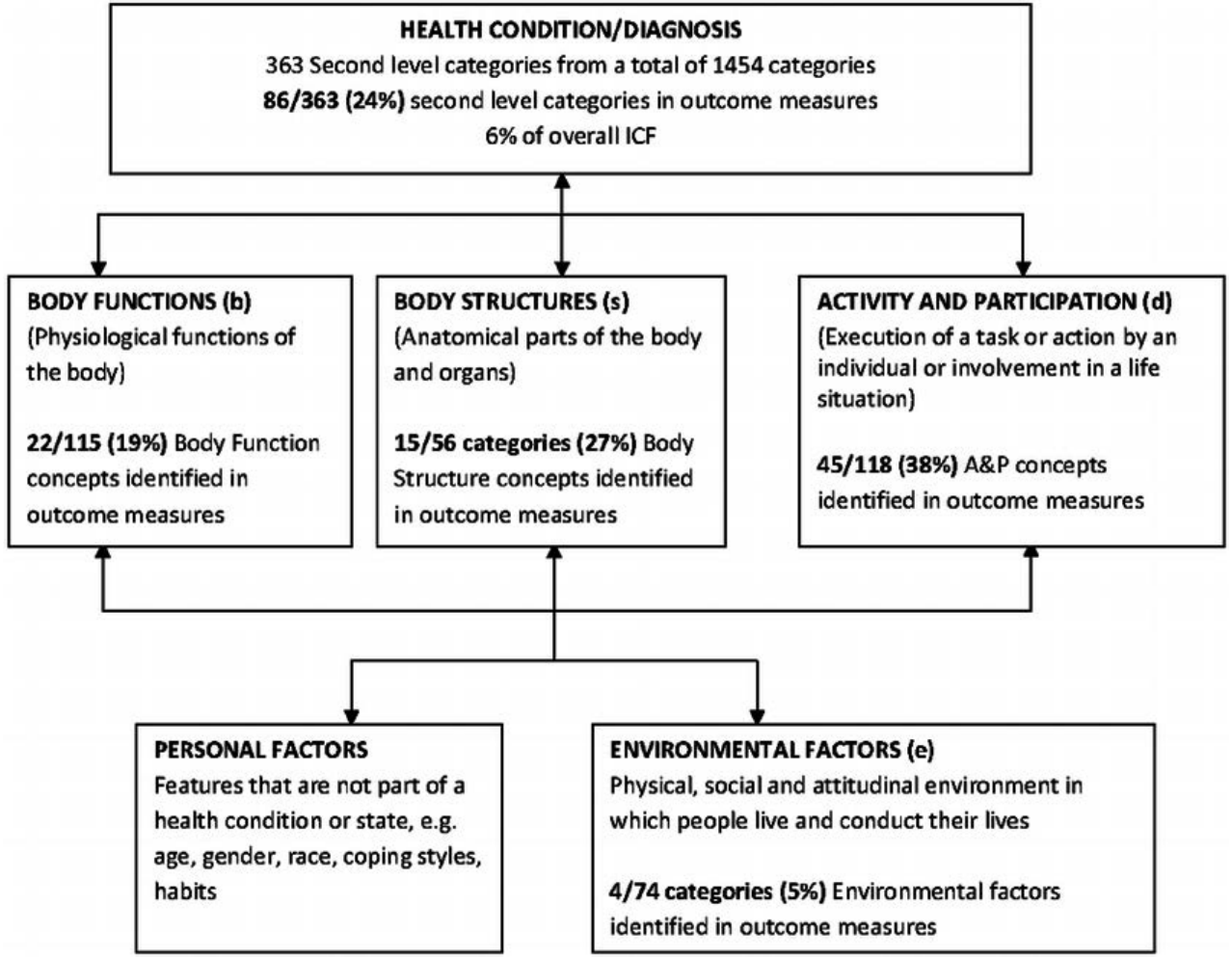
- Reliability – consistent, reproducible estimates of treatment effects
  - Test-retest, Internal consistency, Inter-rater
- Content validity –measures the concept of interest
- Construct Validity – relationship among items and concepts are logically related
  - Convergent, Discriminative, Factor analysis, Known groups
- Longitudinal
  - Responsiveness – ability to detect change
  - Individual patient change
- Meaningfulness – YIKES
  - Meaningful to what group and in what context?
- Interpretability (communicate results to stakeholders/patients)

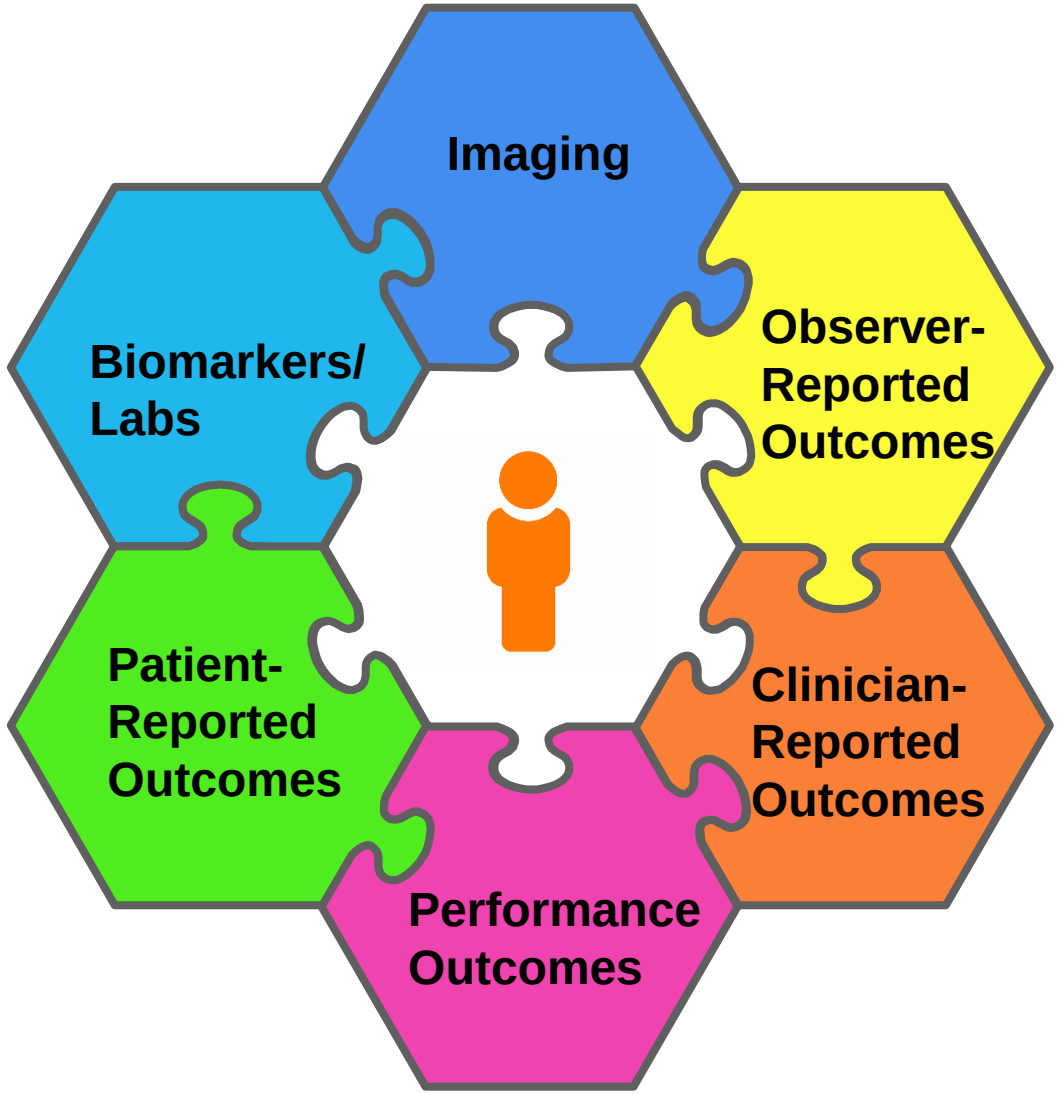
Treatment benefit

- The impact of treatment as measured by survival or a COA of how patients feel or function.
- Direct evidence of treatment benefit is derived from clinical trial effectiveness endpoints that measure survival or a meaningful aspect of how a patient feels or functions in daily life.
- All other effectiveness endpoint measures provide indirect evidence of treatment benefit (e.g., performance assessments).
- Treatment benefit can be demonstrated by an advantage in either effectiveness or safety, or both.

Concept of Interest for meaningful treatment benefit

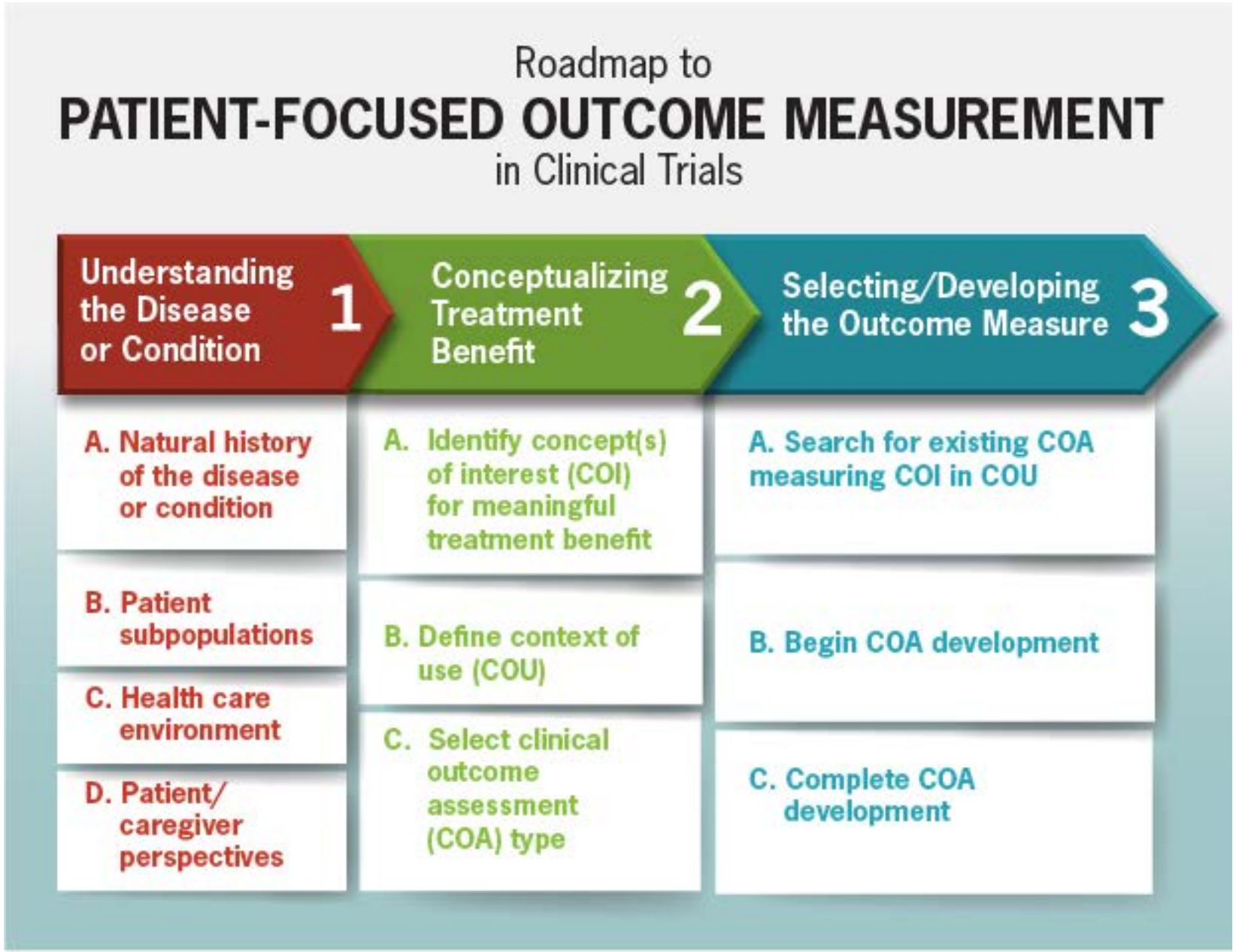
- The meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., the specific symptom and/or sign presence or severity or limitations in performance or daily activities relevant in the targeted context of use)
  - Body Structure -Imaging
  - Body Functions – Biomarkers
  - Activity & Participation - Outcomes

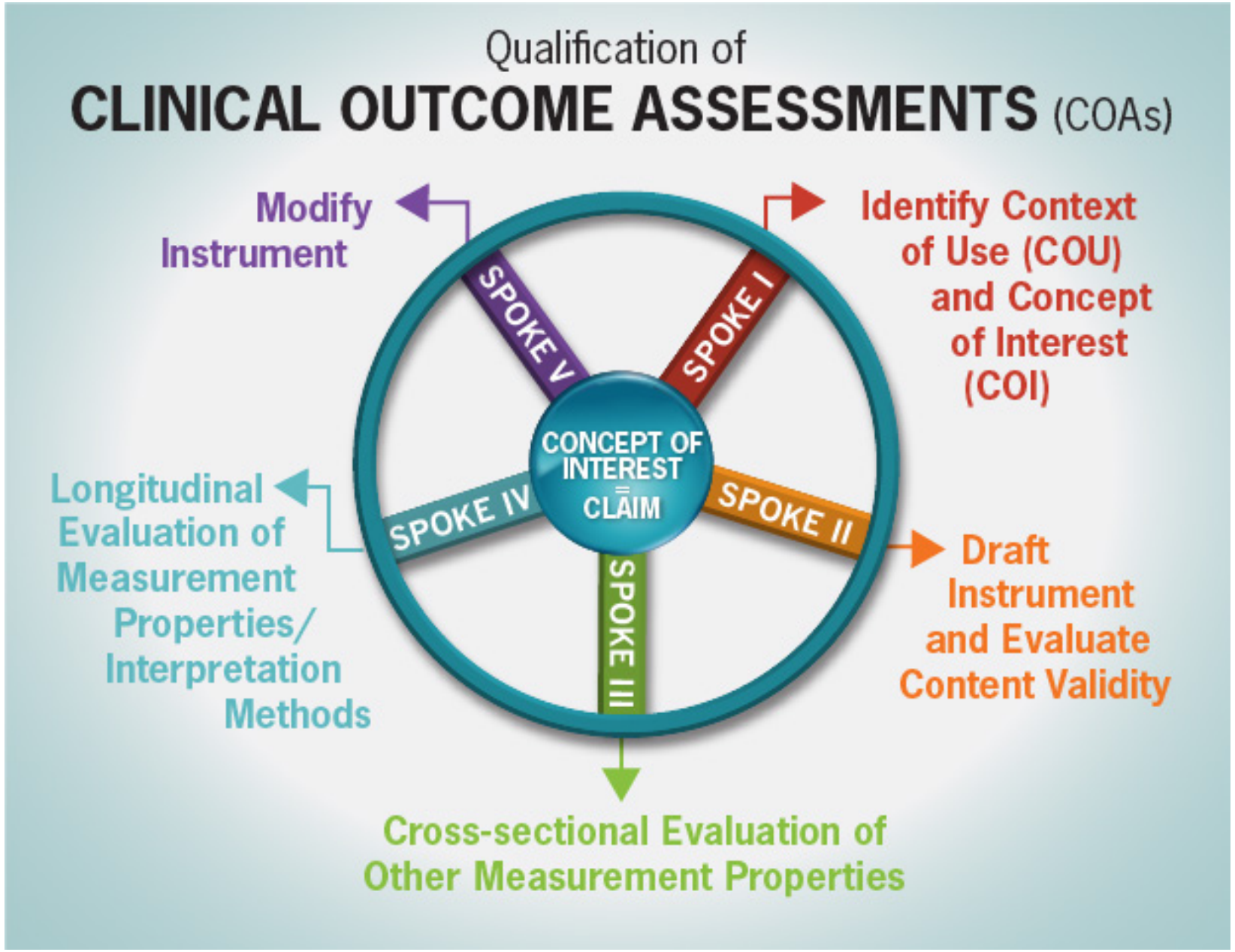



Imaging
Observer-Reported Outcomes
Clinician-Reported Outcomes
Performance Outcomes
Patient-Reported Outcomes
Biomarkers/ Labs

Definitions

- **Concept of interest** — The thing measured by an assessment (e.g., pain intensity).
- **Context of Use** — A comprehensive statement that fully and clearly describes the way the COA is to be used and the drug development-related purpose of the use. The context of use defines the boundaries within which the available data adequately justify use of the COA and describes important criteria regarding the circumstances under which the COA is qualified.
- **Effectiveness** — An essential component of the basis for marketing approval of a drug; drugs must be safe and effective to justify approval. Effectiveness is defined as a benefit to patients in how they feel, function, or survive due to treatment with the drug.


Roadmap to
PATIENT-FOCUSED OUTCOME MEASUREMENT
in Clinical Trials
Understanding the Disease or Condition
1
Conceptualizing Treatment Benefit
2
Selecting/Developing the Outcome Measure
3
A. Natural history of the disease or condition
B. Patient subpopulations
C. Health care environment
D. Patient/ caregiver perspectives
A. Identify concept(s) of interest (COI) for meaningful treatment benefit
B. Define context of use (COU)
C. Select clinical outcome assessment (COA) type
A. Search for existing COA measuring COI in COU
B. Begin COA development
C. Complete COA development


Qualification of
CLINICAL OUTCOME ASSESSMENTS (COAs)
Modify Instrument
Identify Context of Use (COU) and Concept of Interest (COI)
Longitudinal Evaluation of Measurement Properties/ Interpretation Methods
Draft Instrument and Evaluate Content Validity
Cross-sectional Evaluation of Other Measurement Properties
SPOKE I
SPOKE II
SPOKE III
SPOKE IV
SPOKE V
CONCEPT OF INTEREST = CLAIM

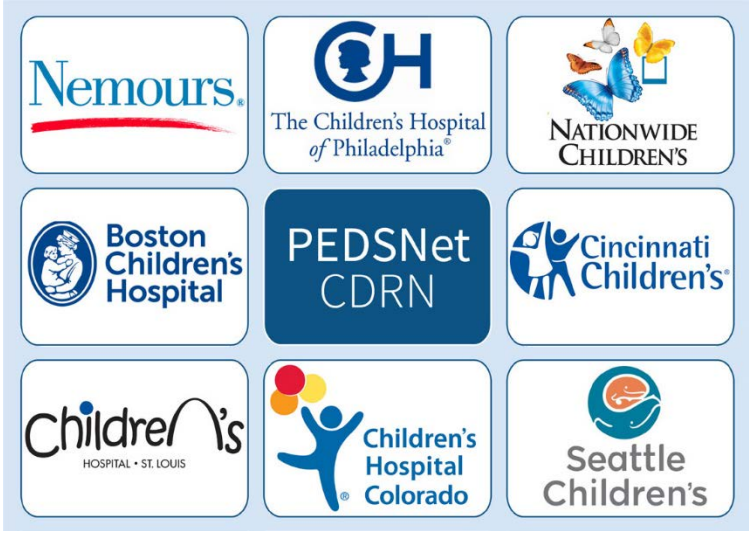
COA Qualification Process

- Qualitative Evidence & Conceptual Framework
- Quantitative Analysis Plan
  - Item level description
  - Dimensionality
  - Scoring & Subscales
  - Reliability
    - Test-retest, Internal consistency, Inter-rater
  - Construct Validity
    - Convergent, Discriminative, Known groups
  - Longitudinal
    - Responsiveness – ability to detect change
  - Language & Cultural Harmonization
  - Clinical Meaningfulness
  - Interpretability (communicate results to stakeholders/patients)

Parallel Efforts in Pediatric Outcome Measures

- Environmental Influences on Child Health Outcomes (**ECHO**)
- Health Measures (PROMIS) www.healthmeasures.org
- Validation of Pediatric Patient Reported Outcomes in Chronic Diseases (PEPR) Consortium (U19)
- PCORI-based Early Intervention Networks
  - PEDSnet
- Patient generated data
  - ShowMe.Health

ShowMe.Health



What do PROMs measures?

Quality of Life

Fatigue

Global Health

Asthma Impact

Participation

Positive Affect

Mobility

Anger

Anxiety

Health Related Quality of Life

Wellbeing

Pain

School Performance

Dexterity

Depression

Functioning

Activity

Symptoms

Sleep Disturbance

Physical Activity

Life Satisfaction

Friendships

Self-Report and Parent/Proxy Report

Meaningfulness…

Content validity *(physiological)*

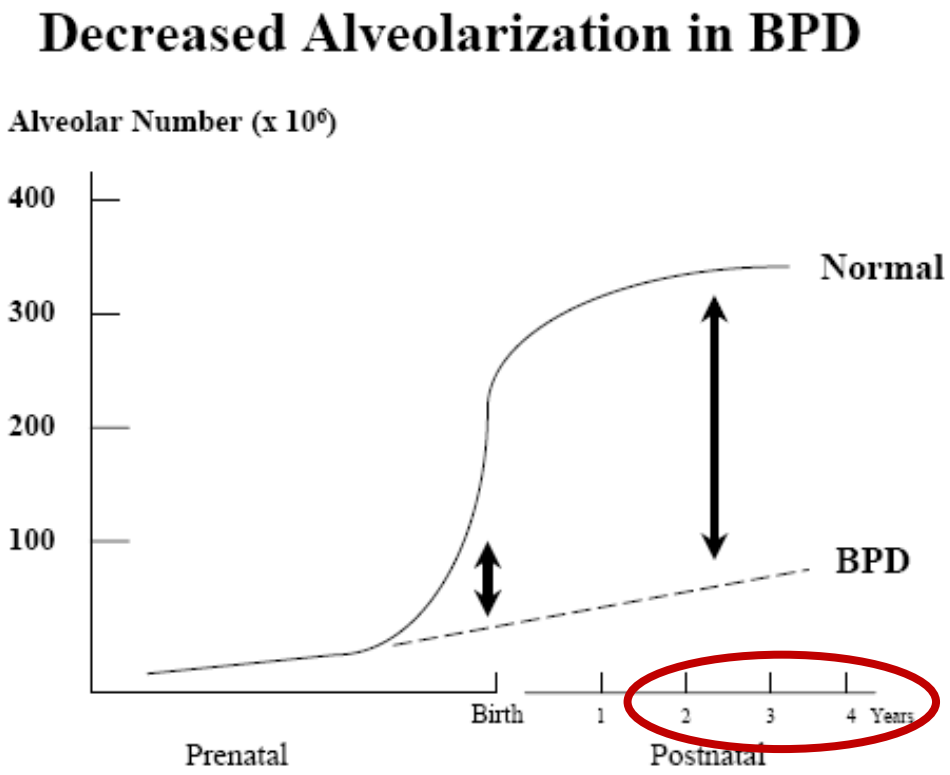
≠

Meaningfulness (*person/family*)

Meaningful at "birth"

≠

Meaningful at > 1 yr



Efficiency & Personalization

IRT-based PROMs:

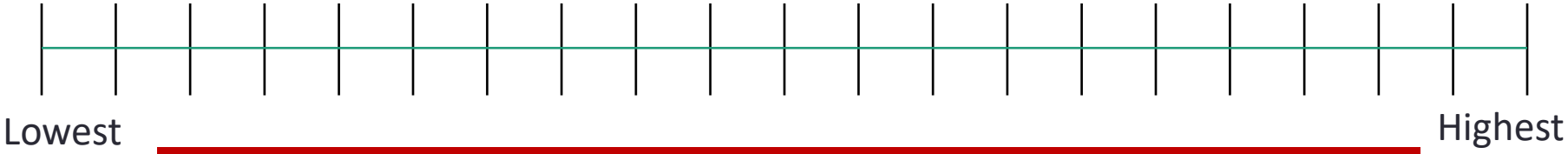
unique forms → same metric

Forms can be tailored to:

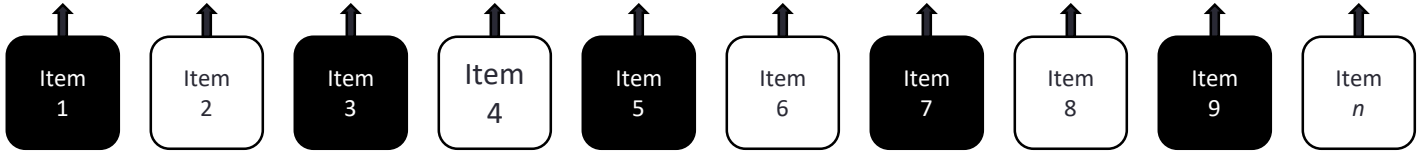
- *Person's item responses (CATs)*
- *Condition or other characteristic*
- *Purpose of the assessment*

SHORT FORM

Equiprecision Method



MOBILITY ITEM BANK



Advantages	Disadvantages
• Administration of “key” items • Detection of change	• Not as tailored to the individual • Loss of efficiency

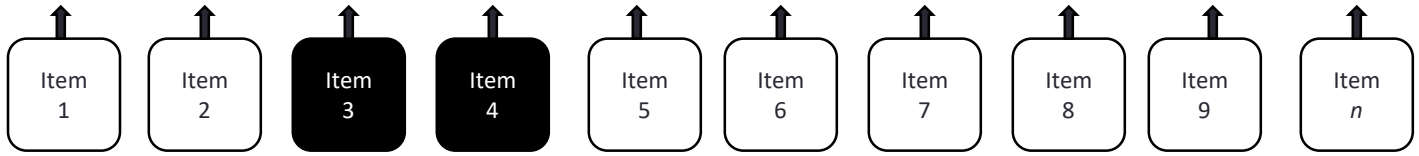
SHORT FORM

Targeted Method

Lowest

Highest

MOBILITY ITEM BANK



Advantages	Disadvantages
• Good for screening • Efficient	• Less sensitive to change • Don't always know what level to target

Interpretability

- Need PROM score cut-points for:
  - Classifying people into meaningful categories
  - Determining whether change is meaningful
- For PROMs with T-scores: M = 50, SD = 10
  - What does a score of 60 mean?
  - How much change in the score indicates that the person is actually “better” or “worse?”

Defining Cut-points

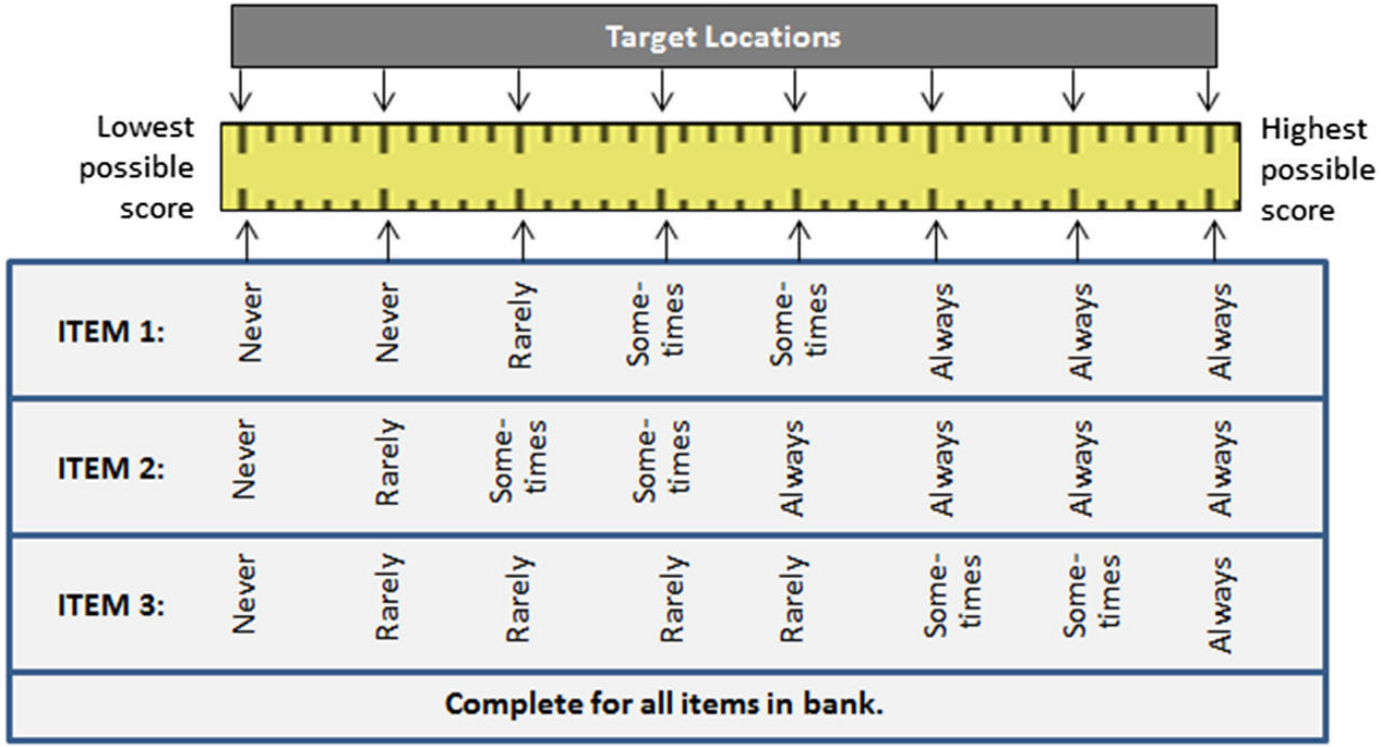
Standard empirical approach:

Calculate mean scores for people categorized according to an external criteria (e.g., clinician global assessment)

- PROM cut-points = mid-points between PROM means for people in adjacent categories
- Minimally important difference (MID) = mean change in PROM scores among “responders” (change over time)

Bookmarking

Development of classification system for multi-item measures calibrated using IRT



In the last 7 days, Ms. Ross often felt exhausted and often was so tired she needed to rest during the day. She was often too tired to take a short walk or do household chores. Sometimes she needed to sleep during the day.

Consensus-development approach through which patients and clinicians placed "bookmark" between vignettes that described mild, moderate, and severe fatigue.

Cook et al. Creating meaningful cut-scores… *Qual Life Res*; 2015, 24: 575-589.

Need anchors that are valid and meaningful

Best-Practice Approach to Content Validation

Elicit PRO concepts

1. Determine target population and context
2. Develop qualitative concept elicitation protocol
3. Conduct concept elicitation interviews and/or focus groups
4. Analyze qualitative data
5. Document concept development, methods, and results

Generate item expressions

1. Develop items based on concept elicitation
2. Design cognitive interview process for context of use
3. Conduct cognitive interviews with members of the target population
4. Revise and re-test items
5. Document cognitive interview methods and results

Patrick et al. Content validity…Part 1-Eliciting concepts for a new PRO Instrument. Value in Health, 14, 967-977, 2011

Patrick et al. Content validity…Part 2-Assessing respondent understanding. Value in Health, 14, 979-988, 2011

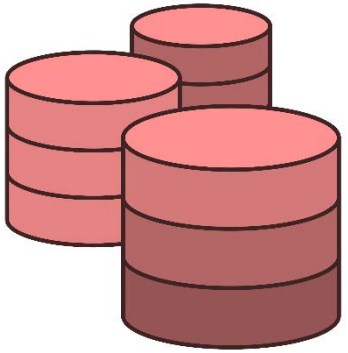
Ecological Momentary Assessment

Ecological momentary assessment (EMA): repeated sampling of subjects' current behaviors and experiences in real time, in people's natural environments.

Examples: Diaries, Behavioral Observations, Self-Monitoring, Time Budget Studies, Experience Sampling Method, Ambulatory Monitoring (physiological or behavioral data)

SHOnet

A Pediatric Learning Health System



Databases

EHR

ShowMe.Health

Research

Quality Improvement

These 3 things…

- Leverage existing measures and techniques whenever possible
  - Generic (vs Condition specific) for family, participation level endpoints
  - Or at least pull in measurement scientists
- Measures across breadth of concepts of interest
  - Clinical versus surrogate measures
- Meaningfulness – dynamic (time & perspectives)
  - Markers of lung disease/maturation?
  - Measures of pulmonary “function”?
  - What is the “job” of a 1 year old ?
  - Functioning, Activity & Participation
    - Sleep
    - Global & general health
    - Neurodevelopment
    - Activity limitations
    - Social functioning
    - Emotional regulation
    - Caregiver /family stress, health & impact

Session IV: Exploring Endpoint and COA Development

Questions to address:

- What are the most important components in endpoint development and how are these incorporated when developing new endpoints?
- Do you foresee particular measurement areas that could hinder endpoint development in this space?
- Are there exemplar COAs that could be helpful as we begin to develop COAs for neonates with pulmonary insufficiency?
- What is the feasibility of follow-up programs and how do we address family, researcher, and sponsor concerns?

Advancing Endpoint Development for Preterm Neonates with Pulmonary Morbidities

Session V: Characterizing Data Sources for Endpoint and COA Development Opportunities

Data Sources for Bronchopulmonary Dysplasia

October 2, 2018

Rosemary D. Higgins, MD
NICHD

NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development

NIH Data Sources

- NHLBI – Biologic Specimen and Data Repository Information Coordinating Center (https://biolincc.nhlbi.nih.gov/home/)

- **Prematurity and Respiratory Outcomes Program (PROP) Core Database Protocol**
- **High Frequency Ventilation in Premature Infants**
- **Trial of Late Surfactant for Prevention of Bronchopulmonary Dysplasia: A Study in Ventilated Preterm Infants Receiving Inhaled Nitric Oxide (TOLSURF)**

NIH Data Sources

https://dash.nichd.nih.gov/

Studies related to:

- Pregnancy
- Neonatology
- Prematurity
- Stillbirth
- Global health

Hydrocortisone for BPD Trial NCT01353313

Randomized trial – 10 day tapering course of hydrocortisone vs. placebo

Inclusion Criteria:

- infants <30 weeks estimated gestational age
- inborn at an NRN site or were admitted to an NRN site before 72 hours postnatal age
- have received at least 7days of mechanical ventilation;
- are receiving mechanical ventilation through an endotracheal tube

Primary outcome – death or BPD at 22-26 months of age

Extended follow up – 5-6 years of age – functional developmental and respiratory outcomes

BPD Workshop - NICHD

Table I. Suggested refinements to the definition of BPD

A premature infant (<32 weeks' gestational age) with BPD has persistent parenchymal lung disease, radiographic confirmation of parenchymal lung disease, and at 36 weeks PMA requires 1 of the following FiO_2 ranges/oxygen levels/O_2 concentrations for ≥3 consecutive days to maintain arterial oxygen saturation in the 90%-95% range.

Grades	Invasive IPPV*	N-CPAP, NIPPV, or nasal cannula ≥ 3 L/min	Nasal cannula flow of 1-<3 L/min	Hood O_2	Nasal cannula flow of <1 L/min
I	—	21	22-29	22-29	22-70
II	21	22-29	≥30	≥30	>70
III	>21	≥30			
III(A)	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (eg, necrotizing enterocolitis, intraventricular hemorrhage, redirection of care, episodes of sepsis, etc).				

*Excluding infants ventilated for primary airway disease or central respiratory control conditions.
Values are percents.
CPAP, continuous positive airway pressure; *IPPV*, intermittent positive pressure ventilation; *N-CPAP*, nasal continuous positive airway pressure; *NIPPV*, noninvasive positive pressure ventilation.

Higgins et. al., 2018

Characterizing Data Sources for Endpoint and COA Development Opportunities: *An Assessment of Available Data Sources*

Alexandra Mangili
Global Development Lead, Shire

October 2, 2018

Shire has experience working with US and International databases

1. **Premier Perspectives Database**
   US hospital-based claims data; limited outpatient claims
2. **MarketScan Commercial Claims Database**
   Claims data inclusive of inpatient, outpatient and ER visits
3. **Kaiser Permanente Research Bank**
   Closed cohort claims data from Northern and Southern California; similar to commercial claims
4. **PHARMO (Netherlands)**
   National registry linkages available for pharmacy and hospitalization episodes
5. **National Neonatal Research Database (UK)**
   NICU dataset comprising of data from England, Scotland and Wales
6. **PROP Study**
   Prospective multicenter (US) longitudinal follow-up study of premature infants

ER = Emergency Room; NICU = Neonatal Intensive Care Unit; PROP = Prematurity and Respiratory Outcomes Program; UK = United Kingdom; US = United States

Are the Currently Available Datasets Suitable for Validating Endpoints?

Strengths

- Resource utilization data availability
  - Most datasets are good for economic analyses for payers and funding agencies
    - Charges, costs, copays, etc. available in claims data
    - Limited clinical outcomes are available in NICU-focused data sources
  - Resource utilizations, procedures and medications covered in administrative claims data
    - Hospitalizations, outpatient visits, inpatient visits and pharmacy claims are available
- Longitudinal outcomes not well collected
  - Short-term outcomes (1 to 2 years) can be evaluated for resource utilization and costs
  - Need to access national registries for long-term clinical outcomes

Weaknesses

- Clinical outcomes are not well captured
  - Reliance on ICD-9/10 codes rather than physician diagnoses and notes
    - For example, BPD is diagnosed by ICD-9/10 codes; no data on severity levels 36-week oxygen challenge tests
- Dwindling sample sizes
  - Difficult to study long-term outcomes as the sample sizes start decreasing year after year
    - Continuous eligibility requirement may not be satisfied with publically funded databases like CMS Medicaid; patients move in and out of coverage
- Neurocognitive outcomes, such as Bayley or VABS scores are not accessible
- Generalizability is limited

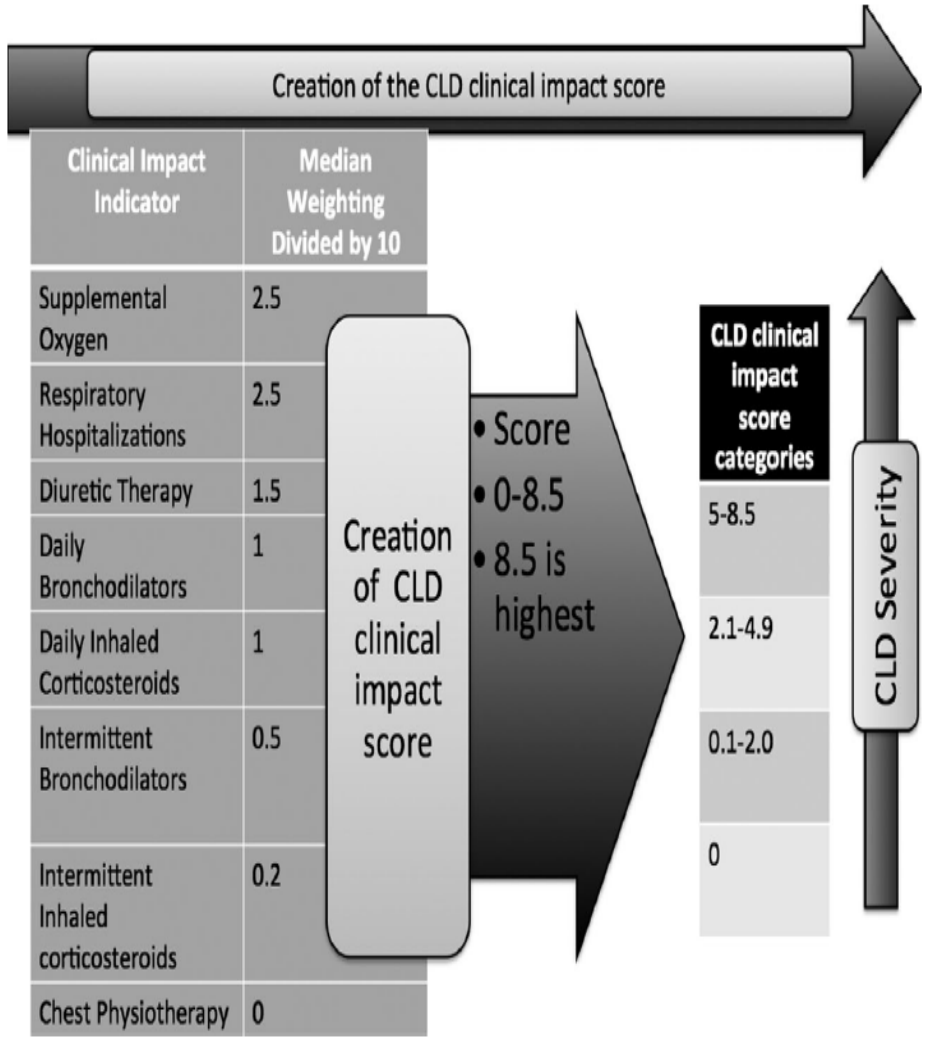
There is no 'One Size Fits All' database that can support the development and validation of various endpoints (continuous, weekly measures, time to event/competing risk). Most researchers need to rely on expensive time-consuming prospective studies.

Shire

BPD = Bronchopulmonary Dysplasia; CMS = Centers for Medicare and Medicaid Services; ICD = International Classification of Diseases; VABS = Vineland Adaptive Behavior Scale

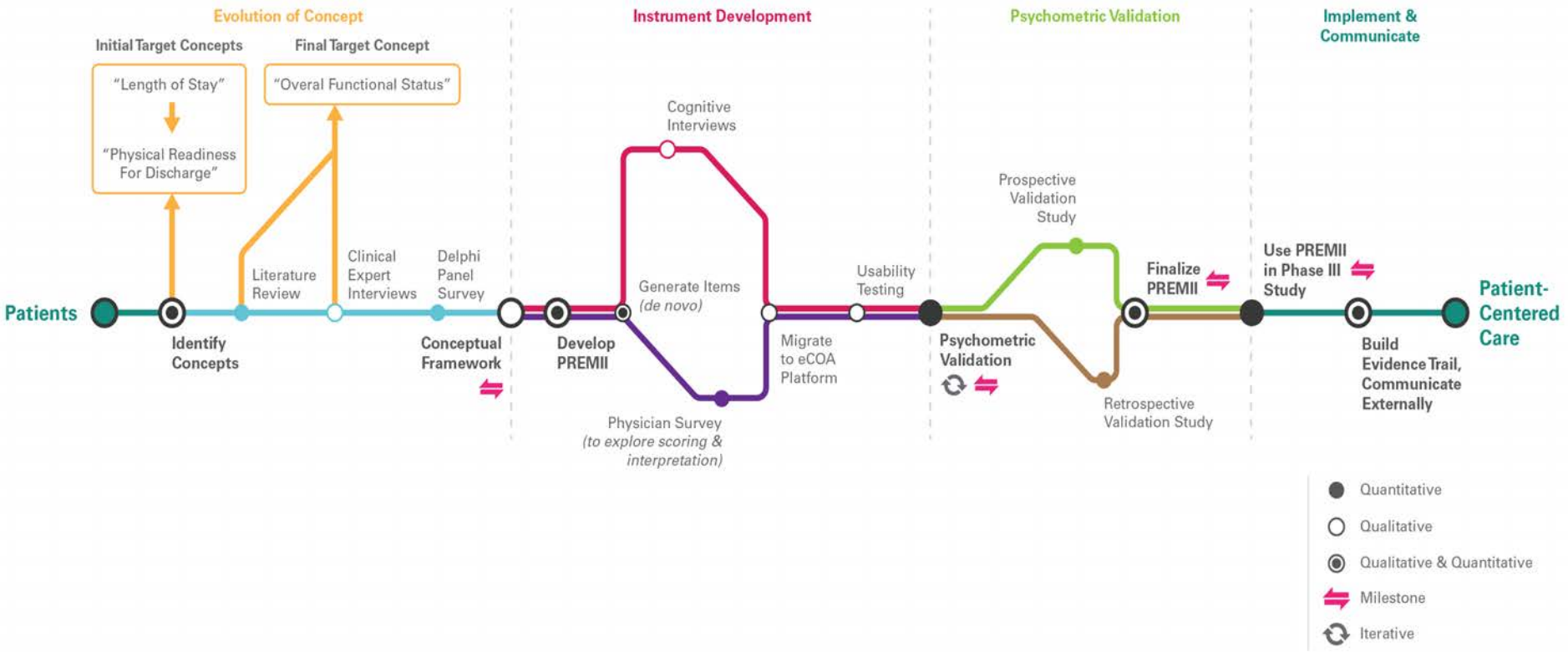
Shire is Modifying The Chronic Lung Disease of Infancy Severity Score (CLDiSS) for Global Clinical Trial Use

- CLDiSS was developed by Dr. Susan Gage and colleagues[1]
- Objective: To assess the comprehensiveness and relevance of CLDiSS factors and weighted scoring
- Outcome: A modified CLDiSS for use in a global clinical trial
- Methods: Delphi panel survey amongst pediatric pulmonologists (majority), pediatricians and neonatologists
- Additional Factors: Mechanical ventilation, systemic corticosteroids, and pulmonary vasodilators, etc.



1. Gage S, Kan P, Oehlert J, Gould JB, Stevenson DK, Shaw GM, and O'Brodovich. Determinants of Chronic Lung Disease Severity in the First Year of Life: A Population Based Study. *Pediatric Pulmonology* 2015;50:878-888.

A Road Map of Development of the PREMature Infant Index (PREMII)

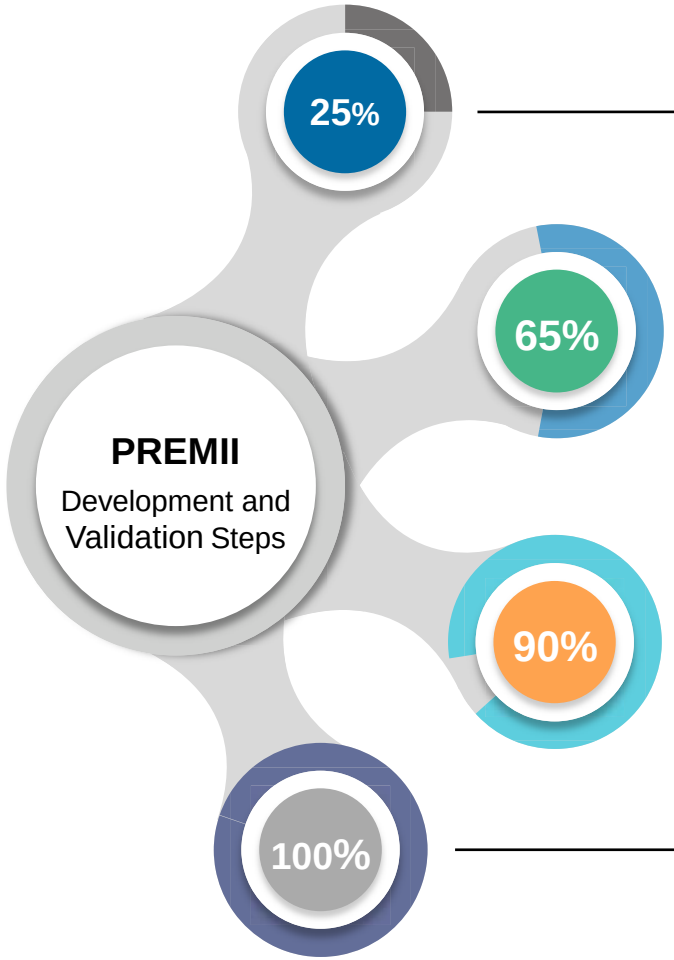


Shire has developed PREMII, a clinician-reported outcomes (COA) tool to evaluate overall functional status of extremely preterm infants. PREMII assesses how premature infants grow and mature on a day to day basis in the NICU. There are 8 factors in the PREMII – Respiratory Status, Oxygen Administration, Apnea, Bradycardia, Desaturation, Thermoregulation, Weight Gain and Feeding.

Shire

Shire is following FDA guidance to validate PREMII

Steps to ensure PREMII is valid and reliable



Prospective Validation Study
A prospective validation study is underway with Imperial College London and Beth Israel Deaconess Medical Center in Boston to evaluate psychometric properties of the PREMII for real-world use.

Retrospective Validation Study
Shire is working with Imperial College London to access the National Neonatal Research Database (NNRD) to retrospectively validate PREMII based on the variables available.

eCOA (ERT SitePad) Conversion
Conversion of PREMII to an electronic format is almost final. Shire estimates that it will take the nurses less than 5 minutes to fill out PREMII on electronic devices, such as tablets.

Instrument Development
Shire has completed the instrument development for PREMII based on the guidance provided by FDA. PREMII is intended to be filled out by the primary NICU nurse near the end of the shift.

Shire

Unmet Needs: What Can We Do?

Clinical Outcomes

Availability of long-term clinical outcomes such as pulmonary function tests and neurocognitive assessments could greatly enhance the efforts to develop and validate novel endpoints

Long-term Follow-Up

Outcomes measured over a long-term follow-up period are critical for regulatory and reimbursement success to ensure that the treatment under development have continued benefits

Larger Sample Sizes

Larger sample sizes are vital in ensuring that the endpoints are reliable and consistently as well as precisely measured accounting for the variability in the population

PROs

Patient-reported outcomes (PROs) such as quality of life, health status, activities of daily living, etc. are essential in evaluating the overall benefits of a new treatment under development

Shire

KAISER PERMANENTE NORTHERN CALIFORNIA (KPNC) DATA RESOURCES

ALLEN FISCHER MD – REGIONAL DIRECTOR OF NEONATOLOGY KPNC

MICHAEL KUZNIEWICZ MD MPH – DIRECTOR, PERINATAL RESEARCH UNIT KPNC

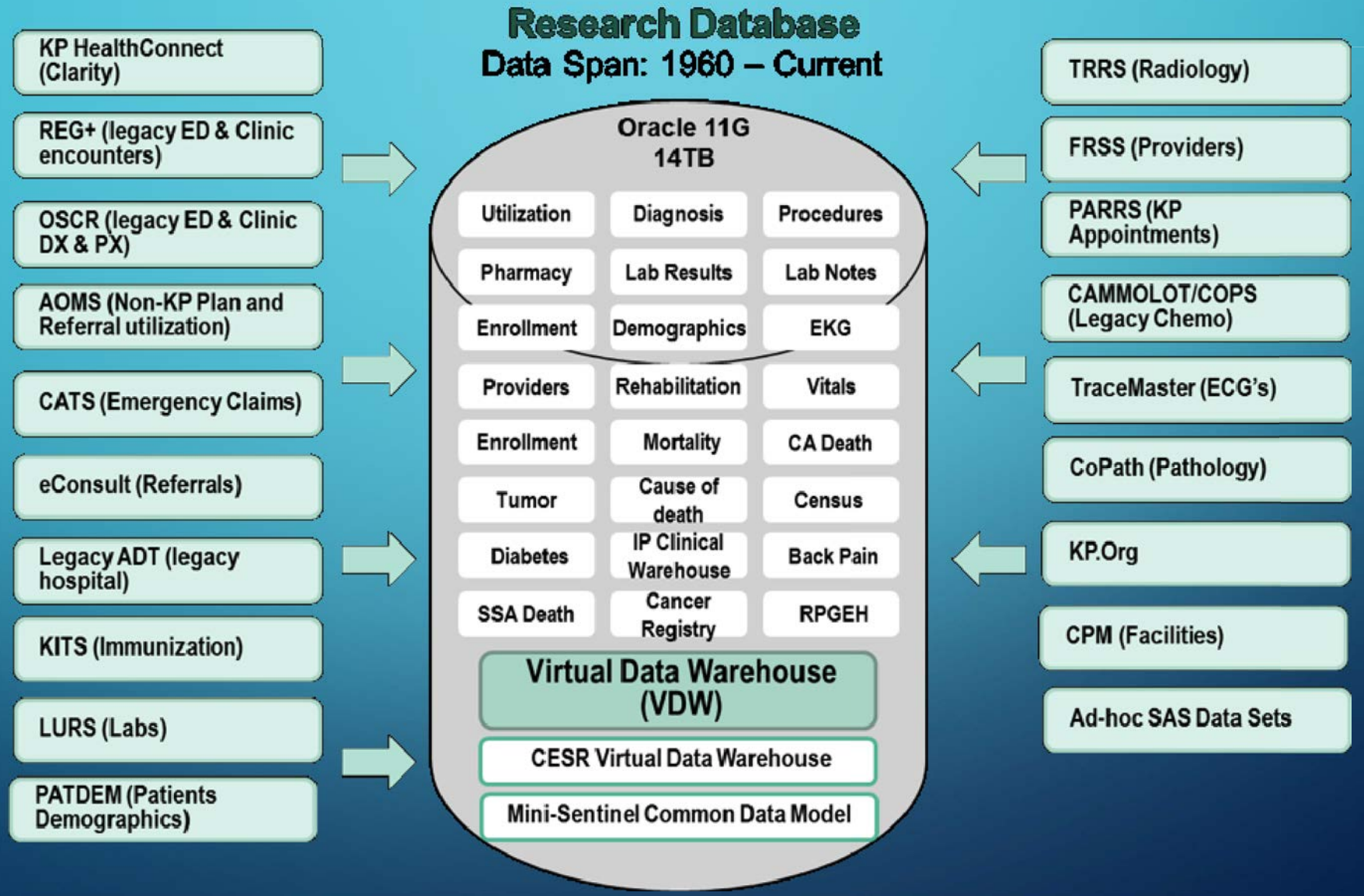
KAISER PERMANENTE NORTHERN CALIFORNIA

- ~4million members
- Serves ~40% of population
- 15 L&D facilities
- ~40,000 births/yr
- 7 Level III NICUs
- 10% Live Births CA

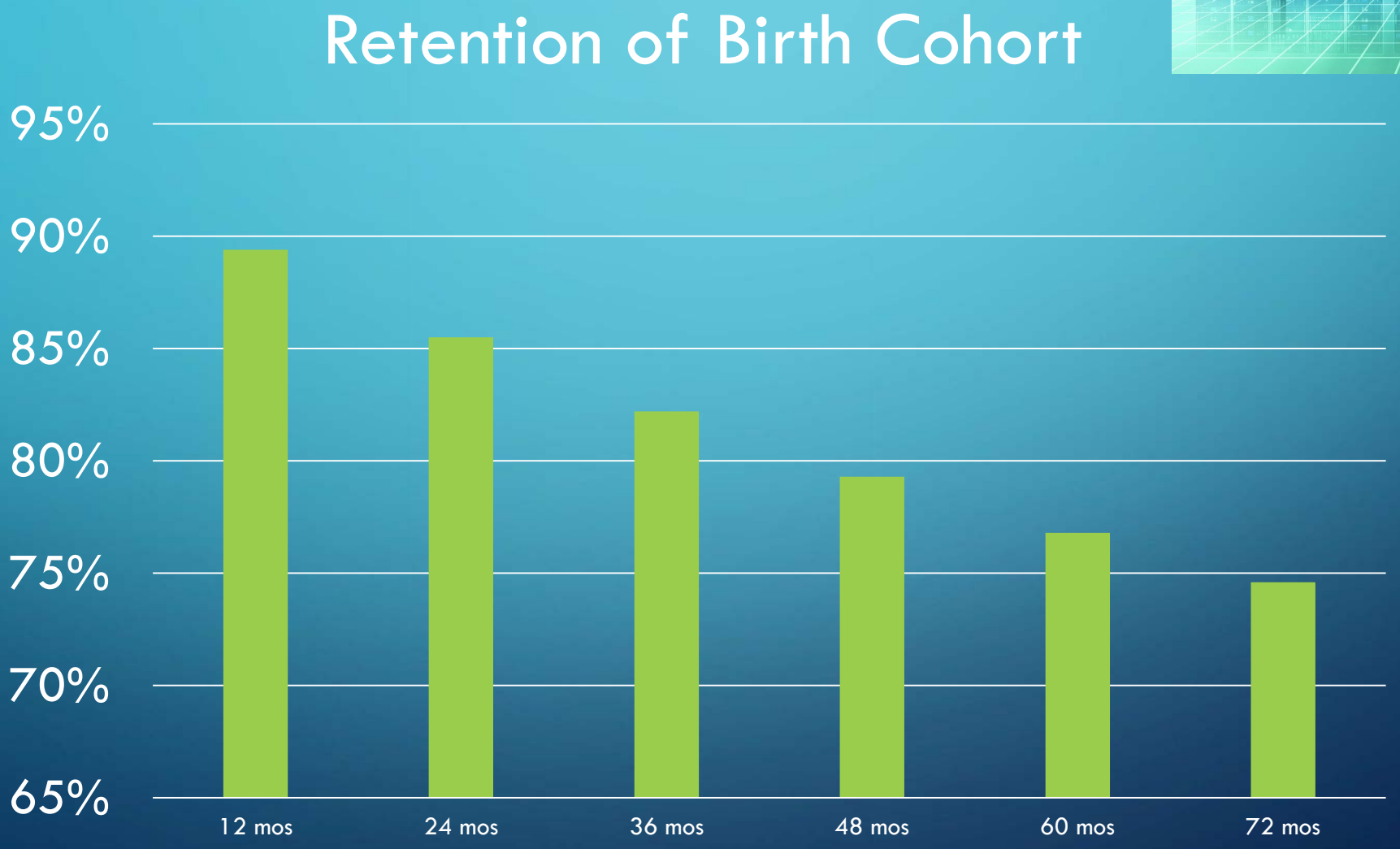
KPNC POPULATION

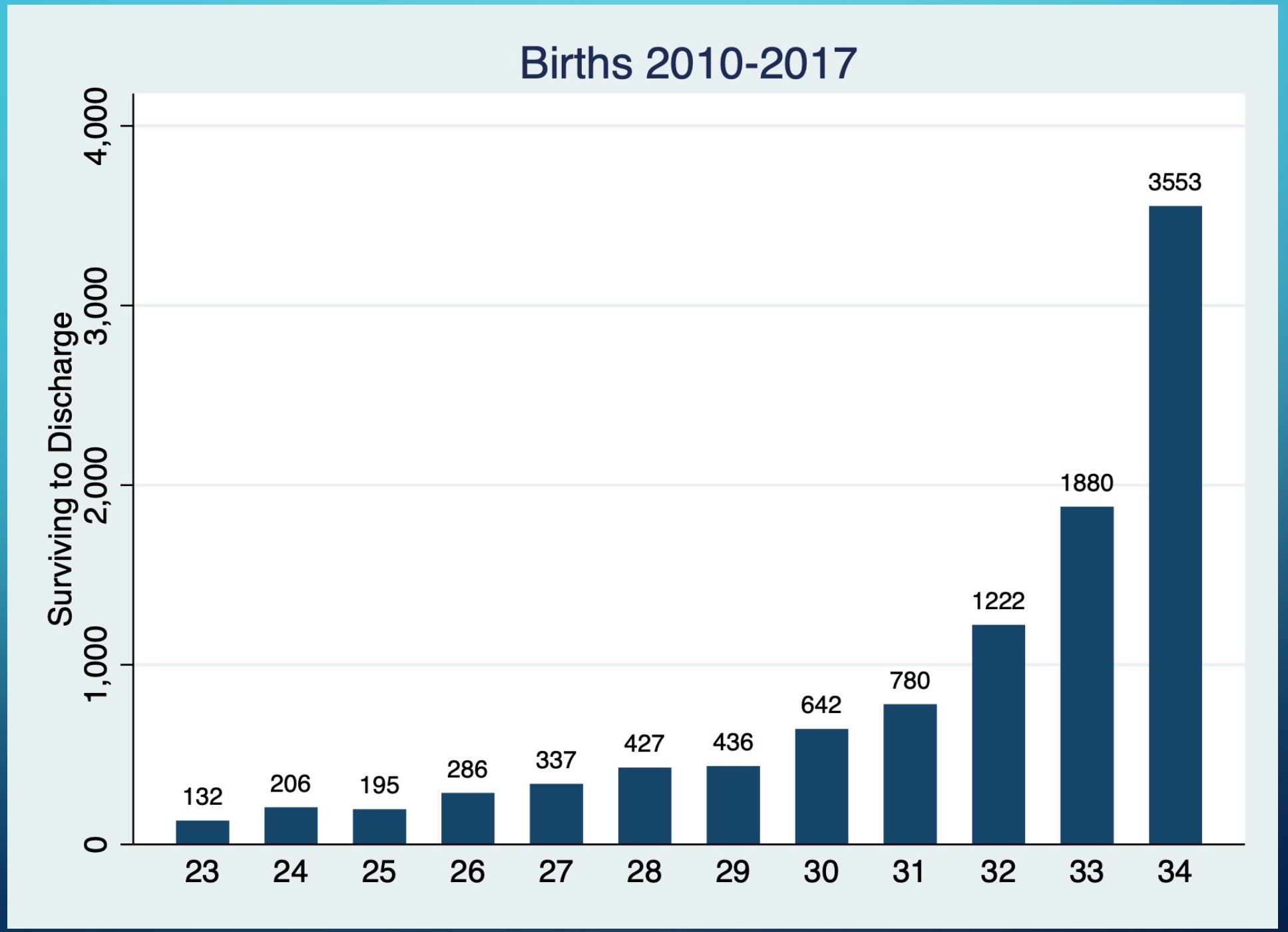
- Pseudo- population based sample
- Economically and racially diverse
- Longitudinal follow-up
- Integrated care
  - Inpatient Data, Outpatient Data, DME, Pharmacy, Lab, Referring and Referral Hospital
- Multi-center
  - Regional centers, Teaching Facilities, Community-Based
  - Variation in practice

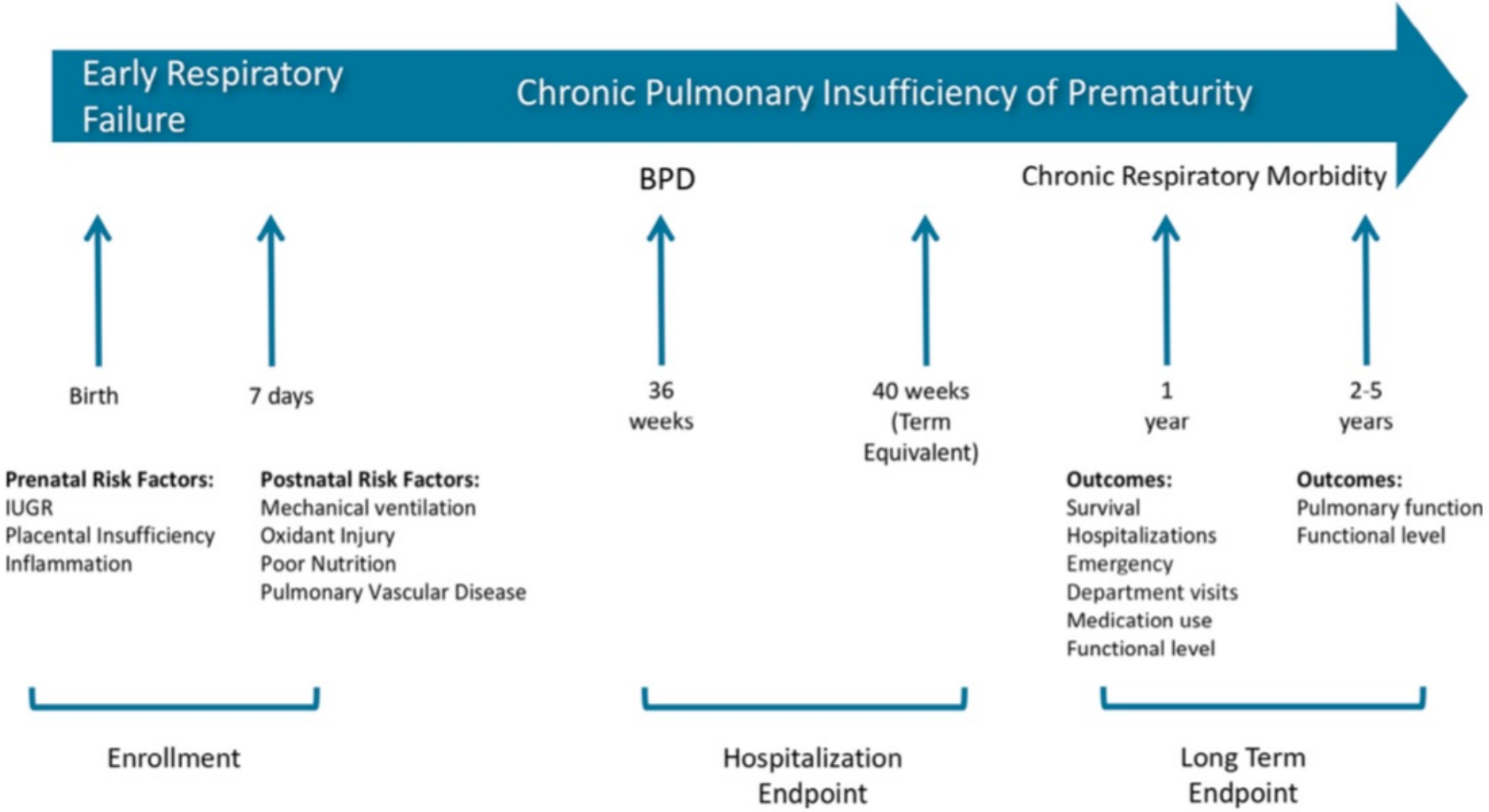
KPNC VIRTUAL DATA WAREHOUSE



LONGITUDINAL DATA IN FOLLOW-UP




Births 2010-2017
Surviving to Discharge
0
1,000
2,000
3,000
4,000
132
206
195
286
337
427
436
642
780
1222
1880
3553
23
24
25
26
27
28
29
30
31
32
33
34


Early Respiratory Failure
Chronic Pulmonary Insufficiency of Prematurity
BPD
Chronic Respiratory Morbidity
Birth
7 days
36 weeks
40 weeks (Term Equivalent)
1 year
2-5 years
Prenatal Risk Factors:
IUGR
Placental Insufficiency
Inflammation
Postnatal Risk Factors:
Mechanical ventilation
Oxidant Injury
Poor Nutrition
Pulmonary Vascular Disease
Outcomes:
Survival
Hospitalizations
Emergency Department visits
Medication use
Functional level
Outcomes:
Pulmonary function
Functional level
Enrollment
Hospitalization Endpoint
Long Term Endpoint

Session V: Characterizing Data Sources for Endpoint and COA Development Opportunities

Questions to address:

- What is possible with existing sources?
- What data are needed and how might they be obtainable?
- Is there an instrument/endpoint ready for testing? If not, what would be needed to make it ready for testing?