Current NEC definitions and considerations in redefining NEC

Ravi Mangal Patel, MD MSc

Associate Professor of Pediatrics

Emory University School of Medicine, Atlanta, GA, USA

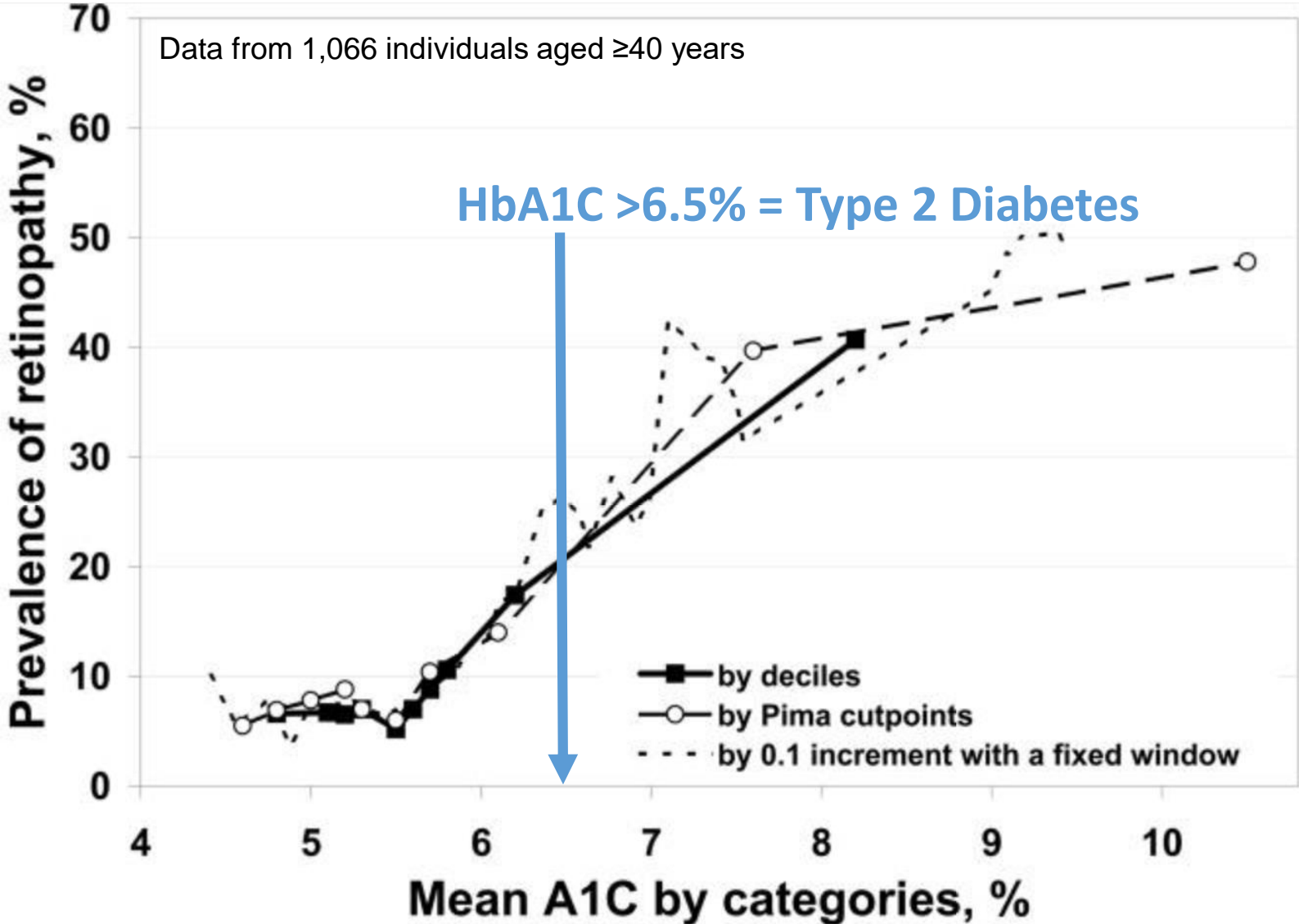#preventNEC #SIGNEC18

@ravimpatelmd

Objectives

- Review existing definitions for NEC reported in the literature

- Highlight key similarities and differences

- Discuss considerations regarding redefining and diagnosing NEC, utilizing lessons from efforts to redefine BPD and diagnose and treat early-onset sepsis

Definitions matter

"Type 2 diabetes is a disease in search of a definition. It has no hallmark clinical features … has very heterogeneous pathophysiological features, and varies widely between populations in clinical presentation and consequences. Despite this obvious heterogeneity, laboratory and clinical research is typically done as if type 2 diabetes were one disease entity with uniform characteristics, thus assuming standard causal mechanisms and universal treatment pathways."

-Edwin Gale (Lancet, 2013)

Definitions matter

Data from 1,066 individuals aged ≥40 years

HbA1C >6.5% = Type 2 Diabetes

- by deciles
- by Pima cutpoints
- by 0.1 increment with a fixed window

Prevalence of retinopathy, %

Mean A1C by categories, %

Cheng et al. *Diabetes Care.* 2013

SIGNEC

Definitions matter

Cheng et al. *Diabetes Care.* 2013
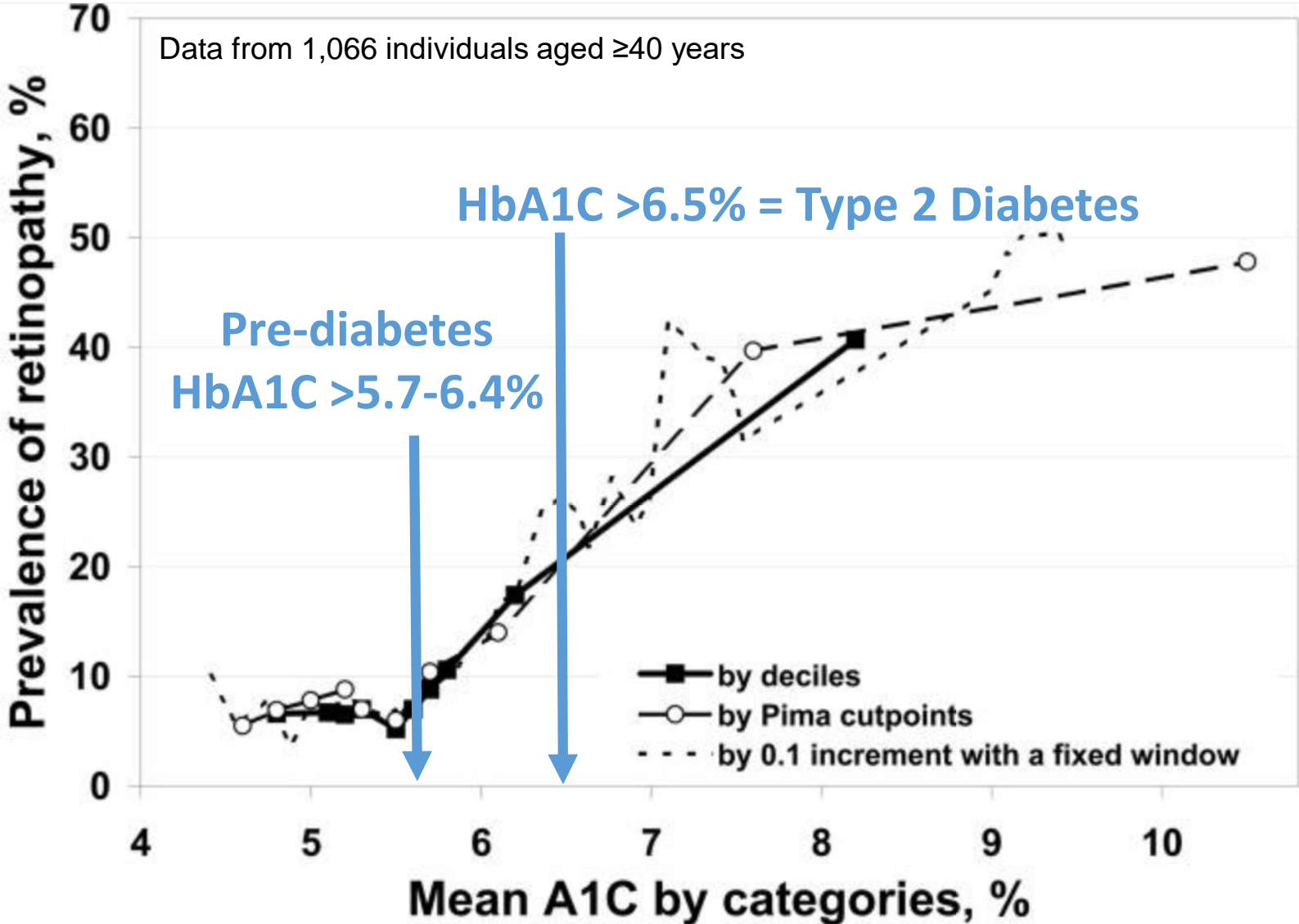
#preventNEC
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Outcomes often exist across a spectrum
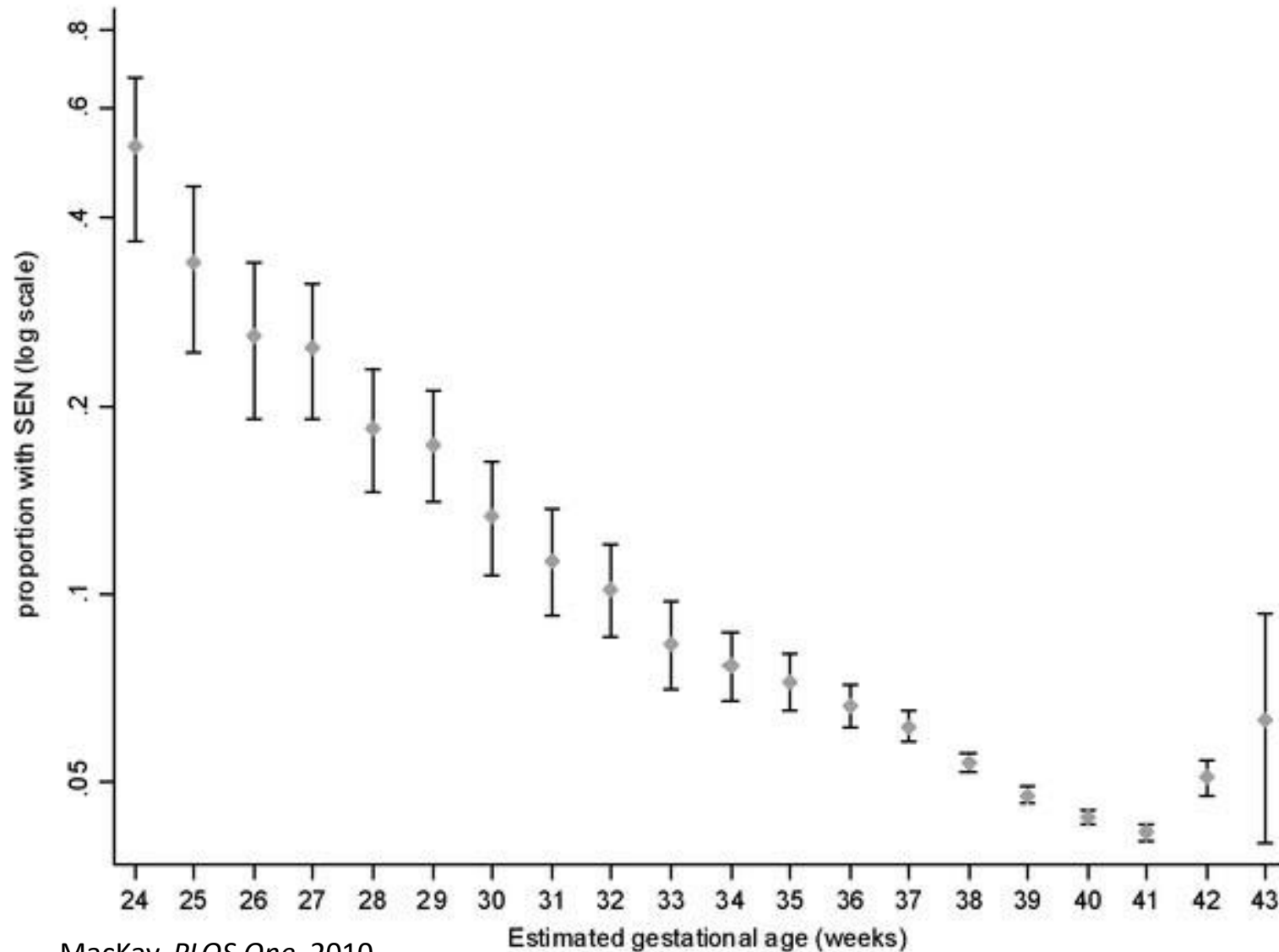
N=407,503
School age children
In 19 Scottish Local
Authority areas

MacKay. *PLOS One.* 2010

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SIGNEC

Initial report of NEC staging

Neonatal Necrotizing Enterocolitis

Therapeutic Decisions Based upon Clinical Staging

MARTIN J. BELL, M.D., JESSIE L. TERNBERG, M.D., RALPH D. FEIGIN, M.D., JAMES P. KEATING, M.D.,
RICHARD MARSHALL, M.D., LESLIE BARTON, M.D., THOMAS BROTHERTON, M.S., M(ASCP)

Initial report of NEC staging

"Necrotizing enterocolitis can be recognized at various stages; a spectrum exists between a fulminant form, progressing to intestinal necrosis in 12-24 hours, and a more slowly evolving and benign form. In fact, in its earliest stages NEC may resemble a number of other conditions prevalent in the neonatal population."

Bell et al. *Ann Surg.* 1978.

Initial report of NEC staging

"Comparison of the results of various treatment programs for NEC is hampered by the lack of a uniformly accepted set of diagnostic criteria and failure to delineate precisely the stage of the disease at the time of diagnosis."

TABLE 1. *NEC Staging System Based upon Historical, Clinical and Radiographic Data*

STAGE I (Suspect)

a. Any one or more historical factors producing perinatal stress.
b. Systemic manifestations—temperature instability, lethargy, apnea, bradycardia.
c. Gastrointestinal manifestations—poor feeding, increasing pregavage residuals, emesis (may be bilious or test positive for occult blood) mild abdominal distension, occult blood may be present in stool (no fissure).
d. Abdominal radiographs show distension with mild ileus.

STAGE II (Definite)

a. Any one or more historical factors.
b. Above signs and symptoms plus persistent occult or gross gastrointestinal bleeding; marked abdominal distension.
c. Abdominal radiographs show significant intestinal distension with ileus; small bowel separation (edema in bowel wall or peritoneal fluid), unchanging or persistent "rigid" bowel loops, pneumatosis intestinalis, portal vein gas.

STAGE III (Advanced)

a. Any one or more historical factors.
b. Above signs and symptoms plus deterioration of vital signs, evidence of septic shock or marked gastrointestinal hemorrhage.
c. Abdominal radiographs may show pneumoperitoneum in addition to others listed in II c.

Bell et al. *Ann Surg.* 1978.
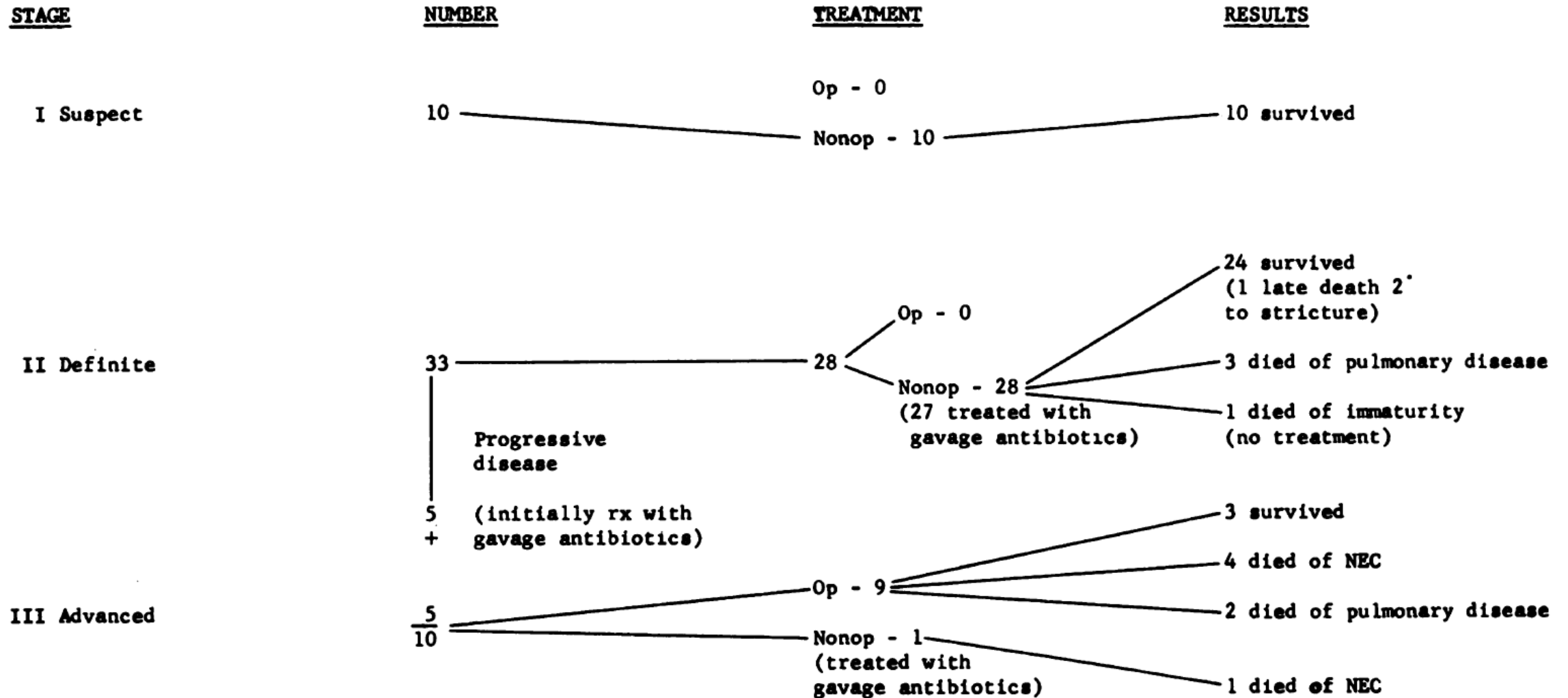
Bell stage and outcomes

STAGE	NUMBER	TREATMENT	RESULTS

I Suspect — 10 — Op - 0 / Nonop - 10 — 10 survived

II Definite — 33 — 28 — Op - 0 / Nonop - 28 (27 treated with gavage antibiotics) — 24 survived (1 late death 2° to stricture) / 3 died of pulmonary disease / 1 died of immaturity (no treatment)

Progressive disease

5 + (initially rx with gavage antibiotics)

III Advanced — 5/10 — Op - 9 / Nonop - 1 (treated with gavage antibiotics) — 3 survived / 4 died of NEC / 2 died of pulmonary disease / 1 died of NEC

FIG. 1. Results of treatment.

Bell et al. *Ann Surg.* 1978.

Initial report of NEC staging

	Stage		
	I	II	III
Number of patients	10	33	5
Signs and Symptoms			
Abdominal distension	60	66	100
Increased pregavage aspirate	60	30	40
Emesis	20	42	40
Gastrointestinal bleeding	60	69	60
Lethargy, cardiopulmonary or temp. instability	30	33	60
Radiographic Findings			
Ileus and distension	100	42	80
Interloop thickening	20	18	0
Pneumatosis intestinalis	0	78	60
Portal vein gas	0	9	0
Pneumoperitoneum	0	0	60

Bell et al. *Ann Surg.* 1978.

Modified Bell Staging

Necrotizing Enterocolitis: Treatment Based on Staging Criteria

Michele C. Walsh, M.D.,* and Robert M. Kliegman, M.D.†

"The true nature or clinical course that NEC will follow is usually not known until 24 to 48 hours of onset."

"Studies of the pathogenesis and treatment of NEC have been hampered by the failure to define the stage of the disease at the time of diagnosis."

Walsh and Kliegman. *Pediatr Clinics N Am.* 1984.

Modified Bell Staging

Table 1. *Purported Risk Factors*

1. Prematurity
2. Perinatal asphyxia
3. Respiratory distress syndrome (RDS)
4. Umbilical catheterization
5. Hypothermia
6. Shock
7. Hypoxia
8. Patent ductus arteriosus (PDA)
9. Cyanotic heart disease
10. Polycythemia
11. Thrombocytosis
12. Anemia
13. Exchange transfusion
14. Congenital gastrointestinal anomalies
15. Chronic diarrhea
16. Non-breast milk formula
17. Nasojejunal feedings
18. Hypertonic formula
19. Too much formula—too fast
20. Hospitalization during epidemic
21. Colonization with "necrogenic" bacteria

Table 2. *Initial Signs and Symptoms of Necrotizing Enterocolitis*

SIGNS	PERCENTAGE OF PATIENTS*
Abdominal distention	73
Bloody stool	28
Apnea, bradycardia	26
Abdominal tenderness	21
Retained gastric contents	18
Guaiac-positive stool	17
"Septic appearance"	12
Shock	11
Bilious emesis	11
Acidosis	10
Lethargy	9
Diarrhea	6
Cellulitis of abdominal wall	6
Right lower quadrant mass	2

Modified Bell staging criteria for NEC

STAGE	SYSTEMIC SIGNS	INTESTINAL SIGNS	RADIOLOGIC SIGNS	TREATMENT
IA—Suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Elevated pre-gavage residuals, mild abdominal distention, emesis, guaiac-positive stool	Normal or intestinal dilation, mild ileus	NPO, antibiotics $\times$ 3d pending culture
IB—Suspected NEC	Same as above	Bright red blood from rectum	Same as above	Same as above
IIA—Definite NEC Mildly ill	Same as above	Same as above, *plus* absent bowel sounds, $+/-$ abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis	NPO, antibiotics $\times$ 7–10d if exam is normal in 24–48 hours
IIB—Definite NEC Moderately ill	Same as above, *plus* mild metabolic acidosis, mild thrombocytopenia	Same as above, *plus* absent bowel sounds, definite abdominal tenderness, $+/-$ abdominal cellulitis or right lower quadrant mass	Same as IIA, *plus* portal vein gas, $+/-$ ascites	NPO, antibiotics $\times$ 14d NaHCO$_3$ for acidosis
IIIA—Advanced NEC Severely ill, bowel intact	Same as IIB, *plus* hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, neutropenia	Same as above, *plus* signs of generalized peritonitis, marked tenderness, and distention of abdomen	Same as IIB, *plus* definite ascites	Same as above, *plus* 200 + ml/kg fluids, inotropic agents, ventilation therapy, paracentesis
IIIB—Advanced NEC Severely ill, bowel perforated	Same as IIIA	Same as IIIA	Same as IIB, *plus* pneumoperitoneum	Same as above, *plus* surgical intervention

Walsh and Kliegman. *Pediatr Clinics N Am.* 1984.

Bell staging predominant definition used

Country	Case-definition
Australia / New Zealand	Bell stage ≥ 2
Canada	Bell stage ≥ 2
Finland	Bell stage 1-3
Germany	At least 1 radiologic and 2 clinical findings
Italy	Bell stage ≥ 2
Japan	Bell stage ≥ 2
South Korea	At least 1 radiologic and 2 clinical findings
Poland	At least 2 of a list of clinical/radiologic findings
Spain	Bell stage ≥ 2
Sweden	ICD-9 code
Switzerland	Bell stage ≥ 2
USA	At least one clinical and one radiologic finding (VON definition)

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Battersby et al. *Arch Dis Child Fetal Neonatal.* 2018

Limitations of Bell staging

- Presence of pneumoperitoneum may be from spontaneous intestinal perforation
- High incidence of Stage I
- Uncertainty of presence of pneumatosis
- Case definition not explicit
- Baseline risk not accounted for
  - Degree of prematurity

TABLE 1. *NEC Staging System Based upon Historical, Clinical and Radiographic Data*

STAGE I (Suspect)

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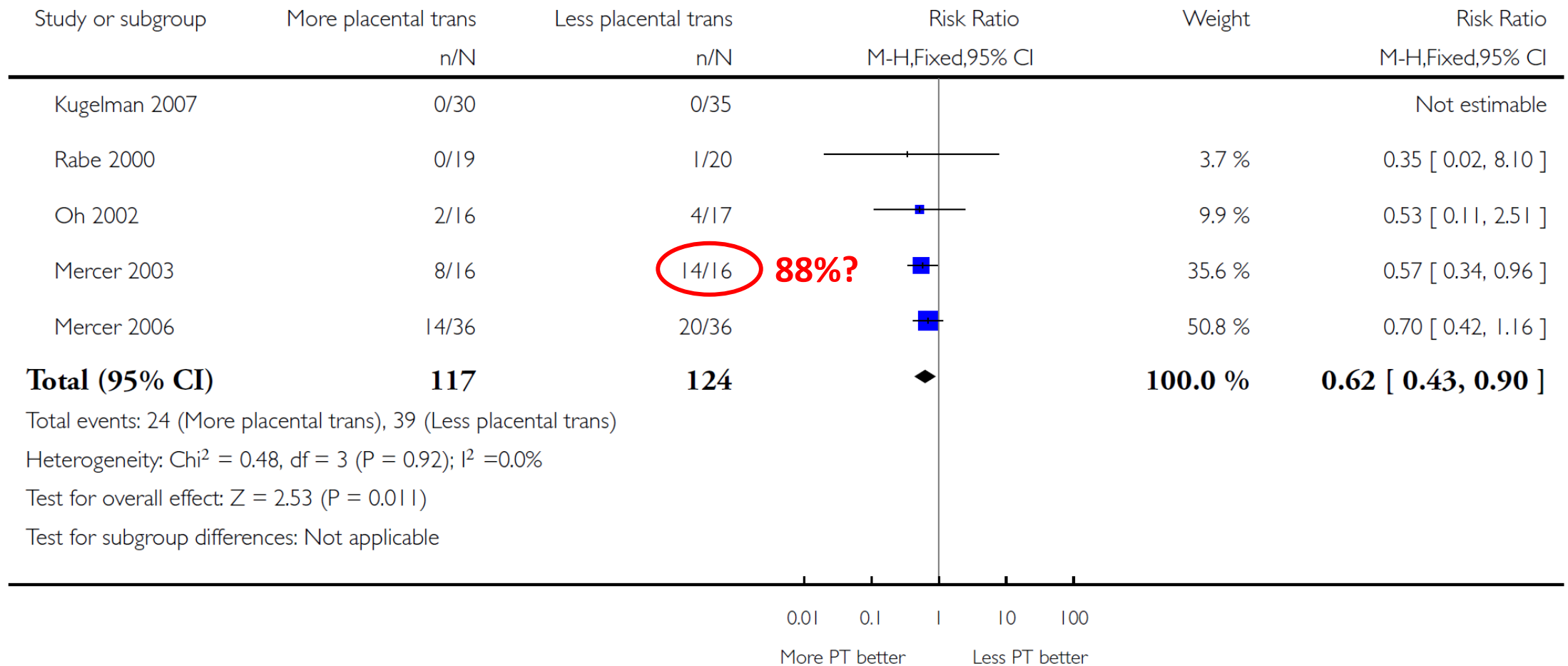
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Limitations of Bell staging

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  - Degree of prematurity

Inclusion of Bell Stage I into Cochrane for DCC

Outcome: 22 Necrotising enterocolitis

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kugelman 2007	0/30	0/35			Not estimable
Rabe 2000	0/19	1/20		3.7 %	0.35 [0.02, 8.10]
Oh 2002	2/16	4/17		9.9 %	0.53 [0.11, 2.51]
Mercer 2003	8/16	14/16 **88%?**		35.6 %	0.57 [0.34, 0.96]
Mercer 2006	14/36	20/36		50.8 %	0.70 [0.42, 1.16]
Total (95% CI)	**117**	**124**		**100.0 %**	**0.62 [0.43, 0.90]**

Total events: 24 (More placental trans), 39 (Less placental trans)

Heterogeneity: Chi^2 = 0.48, df = 3 (P = 0.92); I^2 =0.0%

Test for overall effect: Z = 2.53 (P = 0.011)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

More PT better   Less PT better
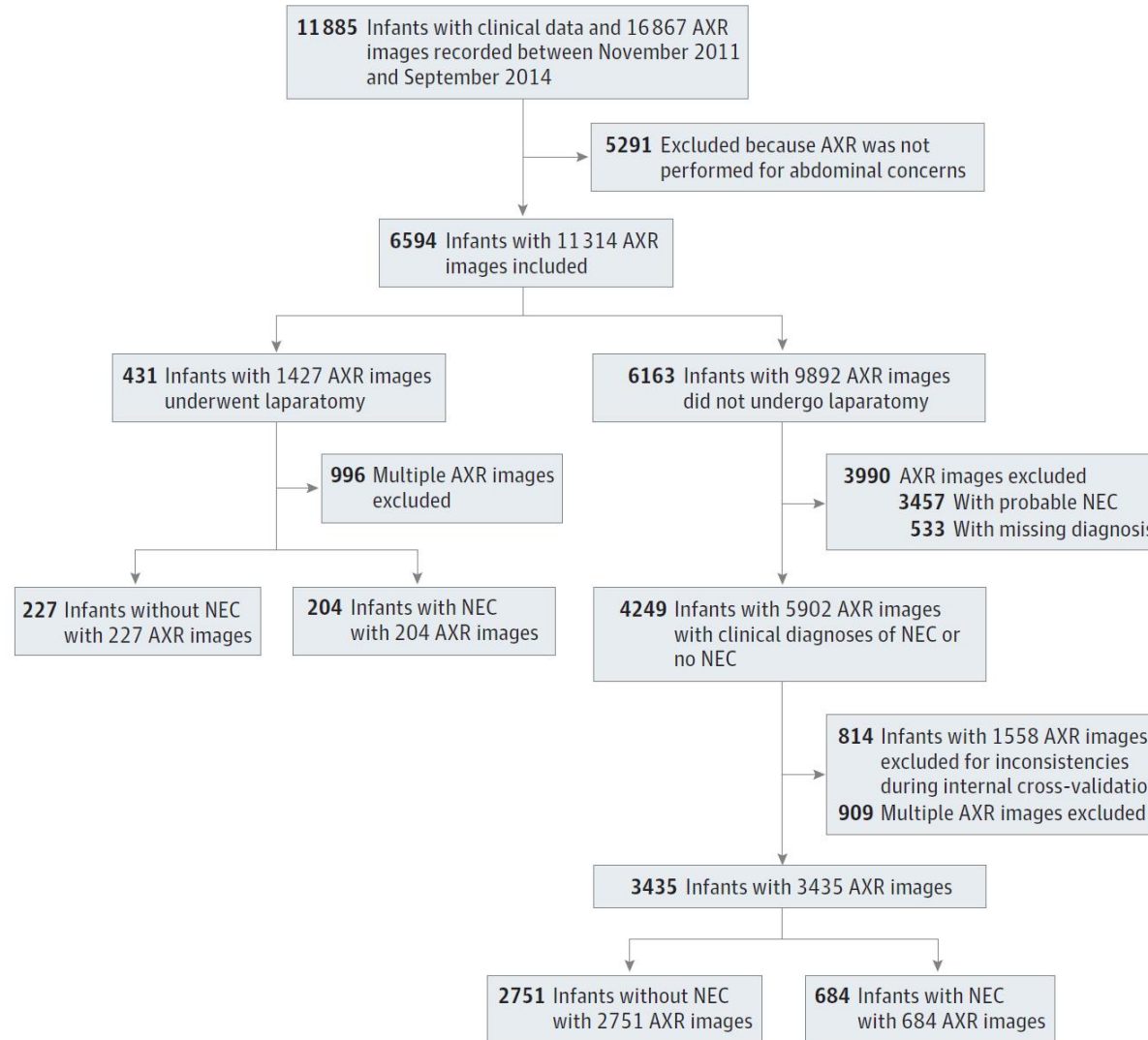
Rabe et al. *Cochrane Database Syst Rev.* 2012

Additional definitions

- Gestational age-specific case definition

- Severe NEC

- VON

- CDC

- Two of 3 rule

- Stanford NEC score

- Not discussed: INC definition (working)

Gestational age specific case definition (UK)

11885 Infants with clinical data and 16 867 AXR images recorded between November 2011 and September 2014

→ 5291 Excluded because AXR was not performed for abdominal concerns

6594 Infants with 11 314 AXR images included

431 Infants with 1427 AXR images underwent laparatomy

6163 Infants with 9892 AXR images did not undergo laparatomy

→ 996 Multiple AXR images excluded

→ 3990 AXR images excluded
3457 With probable NEC
533 With missing diagnosis

227 Infants without NEC with 227 AXR images

204 Infants with NEC with 204 AXR images

4249 Infants with 5902 AXR images with clinical diagnoses of NEC or no NEC

→ 814 Infants with 1558 AXR images excluded for inconsistencies during internal cross-validation
909 Multiple AXR images excluded

3435 Infants with 3435 AXR images

2751 Infants without NEC with 2751 AXR images

684 Infants with NEC with 684 AXR images

The final data set included 3866 infants with 3866 abdominal radiography (AXR) images, with 888 infants with necrotizing enterocolitis (NEC) (204 confirmed by laparotomy) and 2978 infants without NEC.

Battersby et al. *JAMA Pediatr.* 2017

Gestational age specific case definition (UK)

Table 1. Diagnostic Characteristics for Clinical and Radiological Signs of NEC

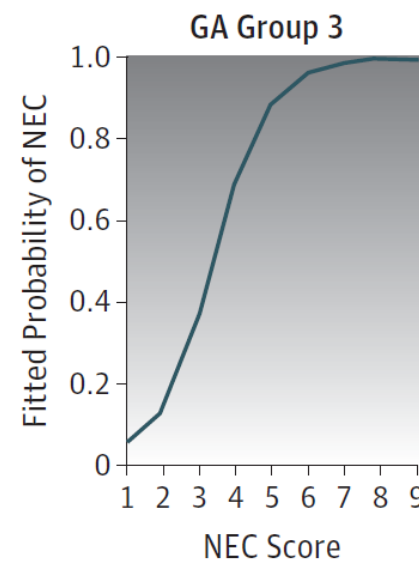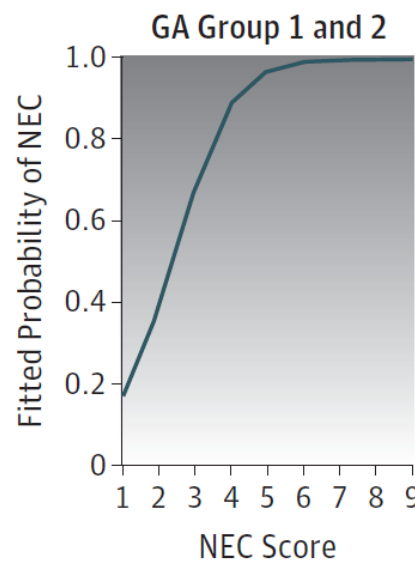| Clinical and Radiological Findings	No. of Infants (%)		NEC, Odds Ratio (95% CI)	P Value	%			
	No NEC (n = 2978)	NEC (n = 888)			Sensitivity	Specificity	PPV	AUC
Clinical signs								
Abdominal distension	1444 (48.5)	740 (83.3)	5.3 (4.4-5.4)	<.001	83.3	51.3	33.9	67.0
Abdominal tenderness	175 (5.9)	369 (41.6)	11.4 (9.3-14.0)	<.001	41.6	94.1	67.8	68.0
Increased and/or bilious aspirates	1060 (35.6)	370 (41.7)	1.3 (1.1-1.5)	<.001	41.7	64.4	25.9	53.0
Abdominal discoloration	71 (2.4)	182 (20.5)	10.6 (8.0-14.1)	<.001	20.5	97.6	71.9	59.0
Abdominal mass	32 (1.1)	12 (1.4)	1.3 (0.6-2.4)	.50	1.4	98.9	27.3	50.0
Blood in stool	72 (2.4)	187 (21.1)	10.8 (8.1-14.4)	<.001	21.1	97.6	72.2	59.0
Mucus in stool	20 (0.7)	44 (5.0)	7.7 (4.6-13.4)	<.001	5.0	99.3	68.8	52.0
Radiological signs								
Pneumatosis	30 (1.0)	387 (43.6)	75.9 (52.6-113.6)	<.001	43.6	99.0	92.8	71.0
Portal venous gas	4 (0.1)	22 (2.5)	18.9 (6.5-55.0)	<.001	2.5	99.9	84.6	51.0
Pneumoperitoneum	57 (1.9)	70 (7.9)	4.4 (3.1-6.3)	<.001	7.9	98.1	55.1	53.0
Fixed loop	79 (2.7)	62 (7.0)	2.8 (2.0-3.9)	<.001	7.0	97.3	44.0	52.0
Gasless abdomen	95 (3.2)	40 (4.5)	1.3 (1.0-2.1)	.06	4.5	96.8	29.6	51.0

Abbreviations: AUC, area under the receiver operating characteristic curve; NEC, necrotizing enterocolitis; PPV, positive predictive value.

Battersby et al. *JAMA Pediatr.* 2017

Gestational age specific case definition (UK)

NEC score	
Finding	**Point**
Abdominal discoloration	1
Abdominal tenderness	1
Both increased and/or bilious aspirates and abdominal distension	1
One or more of pneumoperitoneum, fixed loop, and portal venous gas	1
Blood in the stool	2
Pneumatosis	3
Total	**1-9**

GA-specific case definition	
GA	**Cutoff score for NEC**
<30 wk (GA groups 1 and 2)	≥2
30 to <37 wk (GA group 3)	≥3
≥37 wk (GA group 4)	≥4

GA-specific probability of NEC

GA Group 1 and 2

GA Group 3

GA Group 4

Fitted Probability of NEC vs NEC Score

Battersby et al. *JAMA Pediatr.* 2017
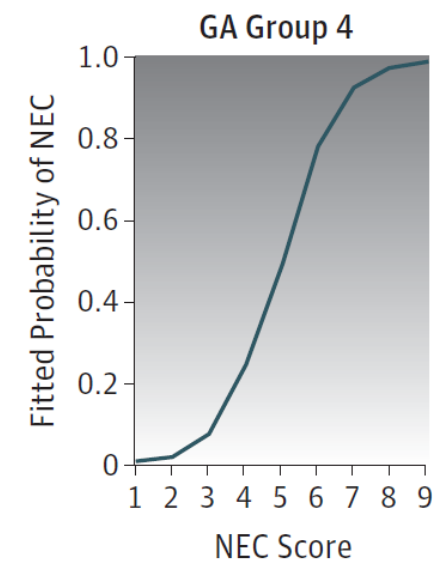
Severe NEC definition (UK population based study)

- Disease confirmed by laparotomy, histology, or autopsy

- If no tissue evidence was available, the reported primary cause of death on the death certificate.

- Infants who received a diagnosis of spontaneous intestinal perforation at laparotomy were excluded.

Battersby et al. *Lancet Gastroenterol Hepatol.* 2016

VON NEC definition

- NEC diagnosed at surgery or at postmortem examination

- OR diagnosed clinically and radiographically using following criteria:

- At least one of the following clinical signs present:
  - Bilious gastric aspirate or emesis
  - Abdominal distension
  - Occult or gross blood in stool (no fissure)

And at least one of the following radiographic findings present:
  - Pneumatosis intestinalis
  - Hepato-biliary gas
  - Pneumoperitoneum

Note: Infants who satisfy the definition of NEC but are found at surgery or post-mortem examination for that episode to have a "Focal Intestinal Perforation" should be coded as having "Focal Intestinal Perforation", not as having NEC.

CDC NEC definition

- Definition used by the US Centers for Disease Control and Prevention (CDC) for surveillance (up to 1 year of age)

1. Infant has at least _**one**_ of the clinical and _**one**_ of the imaging test findings from the lists below:
   At least _one_ clinical sign:
   a. bilious aspirate** (see **Note**)
   b. vomiting
   c. abdominal distention
   d. occult or gross blood in stools (with no rectal fissure)

   And at least _one_ imaging test finding which if equivocal is supported by clinical correlation (specifically, physician documentation of antimicrobial treatment for NEC):
   a. Pneumatosis intestinalis
   b. Portal venous gas (Hepatobiliary gas)
   c. Pneumoperitoneum
   Note: Bilious aspirate from a transpyloric feeding tube should be excluded

2. Surgical NEC: Infant has at least _**one**_ of the following surgical findings:
   a. surgical evidence of extensive bowel necrosis (>2 cm of bowel affected)
   b. surgical evidence of pneumatosis intestinalis with or without intestinal perforation

Two of three rule

The two out of three rule for bedside diagnosis of preterm NEC.[14]

Patients may be given a diagnosis of Preterm NEC if they have abdominal distension, ileus and/or bloody stools and meet at least 2 of the criteria below:

1. Pneumatosis and/or portal air by ultrasound or abdominal x-ray at presentation
2. Persistent platelet consumption ($< 150,000 \times 3$ days after diagnosis)
3. Post-menstrual age at disease onset is more consistent with NEC than spontaneous intestinal perforation (SIP)[*]

Patients excluded from a diagnosis of Preterm NEC:

1. Infants known to have SIP
2. Infants with complex congenital anomalies
3. Infants being fed < 80 ml/kg/day
4. Infants ≥ 36 weeks gestation

*See published figures describing timing differences for NEC versus SIP.[18]
Preterm is defined in this instance as < 36 weeks gestational age at birth.

Gordon et al. *Sem Perinatol.* 2017
Gephardt et al. *Sem Ped Surg.* 2018

Stanford NEC score

Ji et al. *PLOS One.* 2014

Stanford NEC score

Ji et al. *PLOS One.* 2014
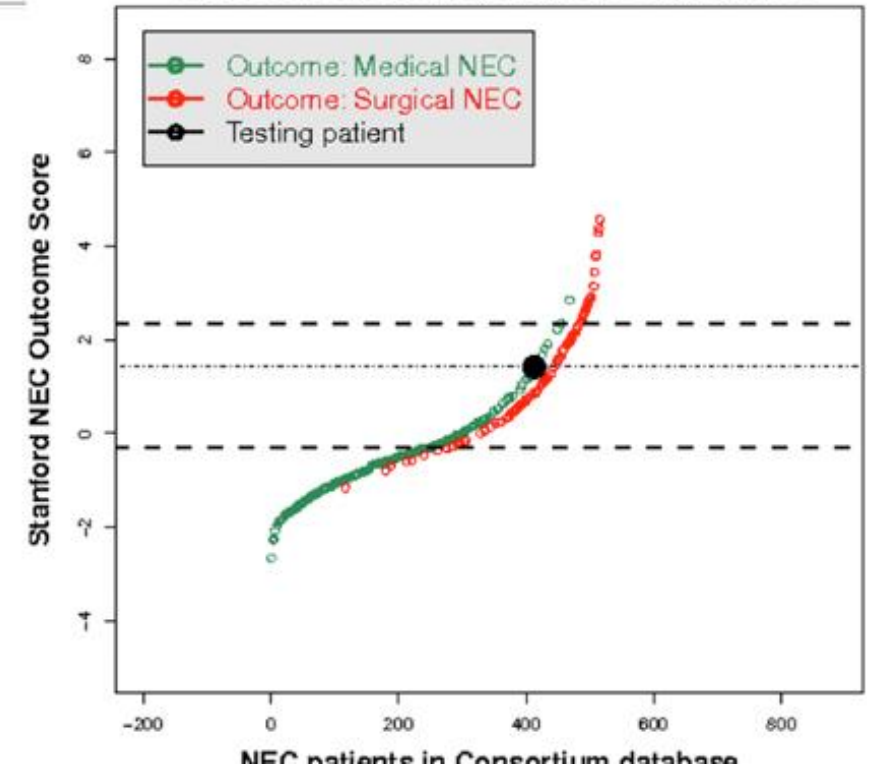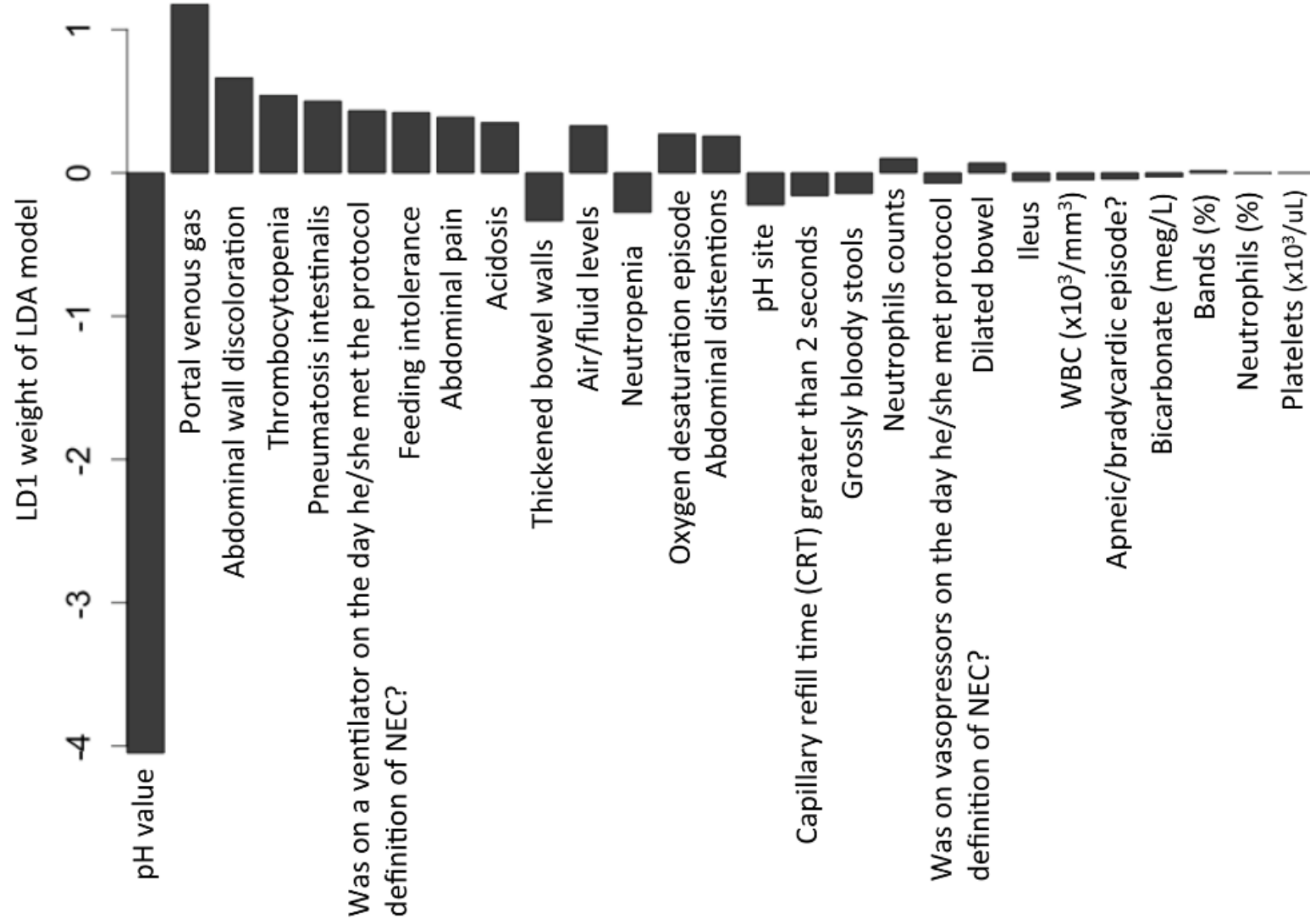
Stanford NEC score
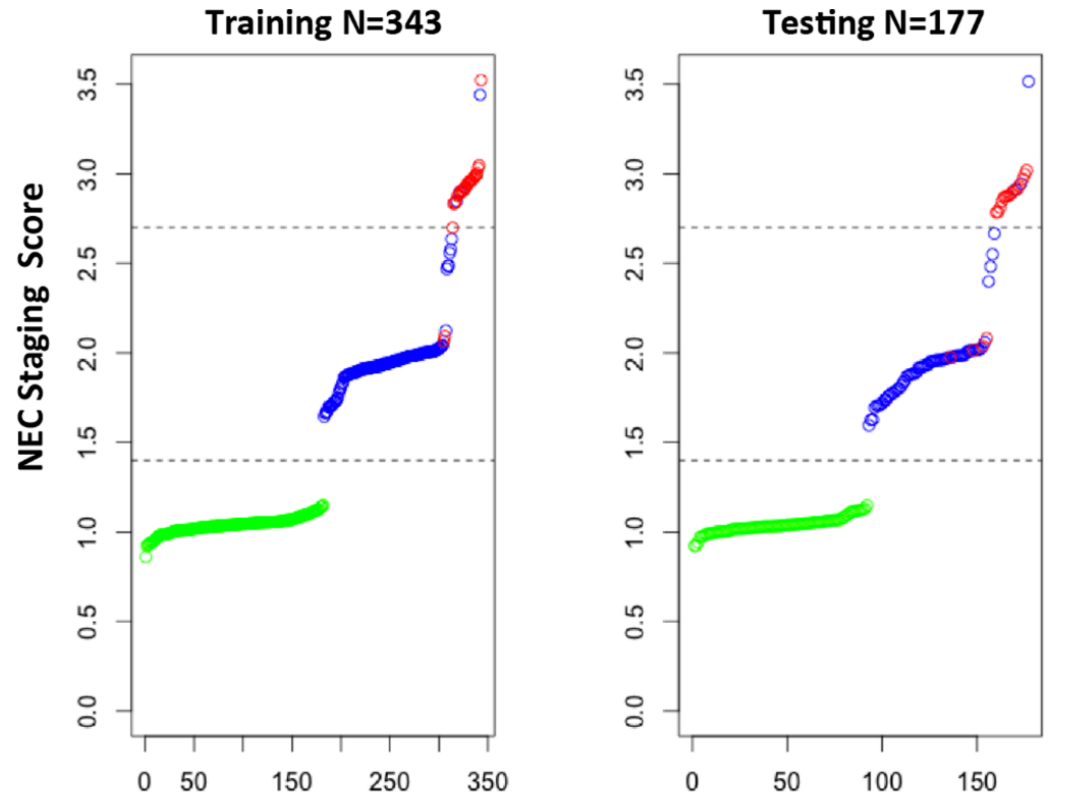
|		Bell's stage					
		Training (N=343)			Testing (N=177)		
		● I	● II	● III	● I	● II	● III
Computed	I	180 (177, 184)	0 (0, 0)	0 (0, 0)	94 (90, 97)	0 (0, 0)	0 (0, 0)
	II	0 (0, 0)	126 (123, 130)	4 (4, 5)	0 (0, 0)	65 (61, 69)	2 (1, 3)
	III	0 (0, 0)	4 (4, 5)	28 (26, 30)	0 (0, 0)	3 (2, 3)	14 (12, 16)

Ji et al. *PLOS One.* 2014
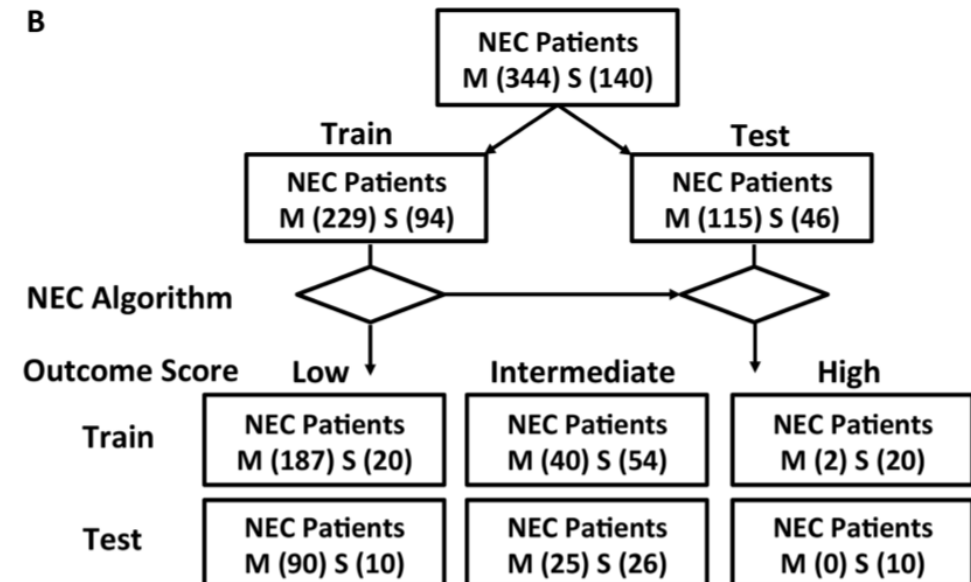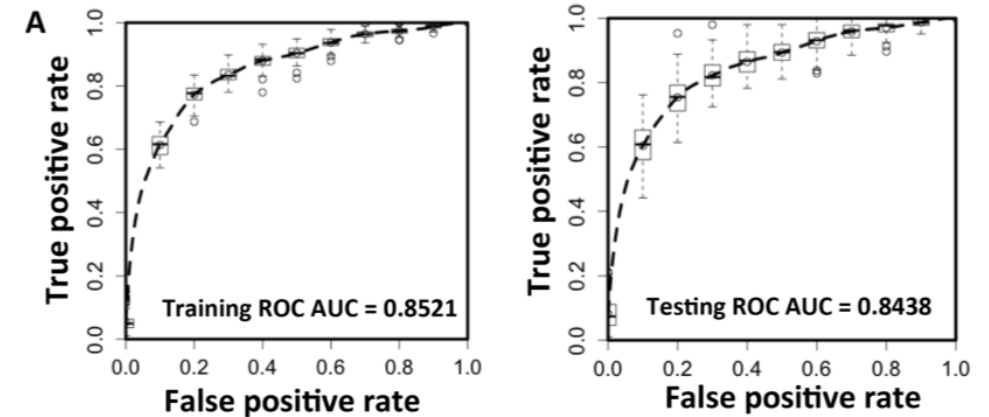
Comparisons of definitions

- Only 2 variables consistent across all definitions: presence of pneumatosis intestinalis and portal venous gas

- Two definitions stratify baseline risk by gestational-age grouping

- Two of 3 rule, severe NEC and VON definitions provide explicit guidance regarding exclusion of SIP

When is the diagnosis being determined

"The true nature or clinical course that NEC will follow is usually not known until 24 to 48 hours of onset."

Walsh and Kleigman. *Pediatr Clinics N Am.* 1984

When is the diagnosis (onset) being determined

Gephardt et al. *Sem Ped Surg.* 2018
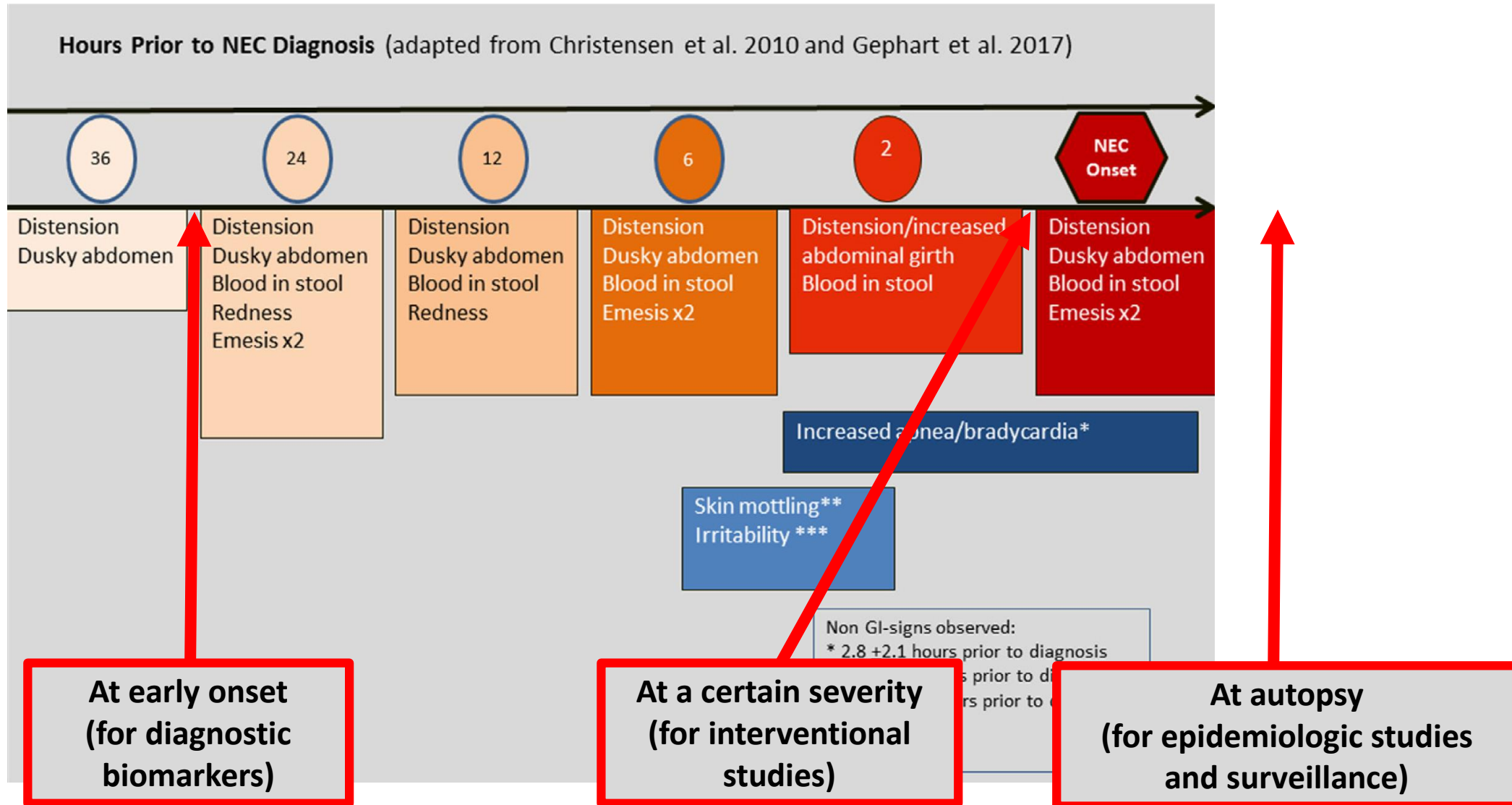
Seven considerations regarding redefining NEC

1. Address possible contamination by spontaneous intestinal perforation

2. Avoid inclusion of Bell stage I

3. Risk-stratification incorporated into definitions

4. Assessment of predictive ability of measures to guide inclusion

5. Need to compare performance of case-definitions in classifying an important set of outcomes among infants with NEC

6. Describe how uncertainty addressed (e.g. findings of questionable or possible pneumatosis)

7. Better tools to estimate pre-test probability of NEC before diagnostic testing

#preventNEC
#SIGNEC18   SIGNEC

Thank you !