

**JOURNAL CLUB:**  
**TWO ARTICLES THAT SHOULD  
CHANGE YOUR PRACTICE**

Alfonso Vargas, MD  
Practice Medical Director  
Pediatrix Medical Group  
Tampa, FL

FANNP's National Neonatal Nurse Practitioner Symposium: Clinical Update and Review, 2025 ©




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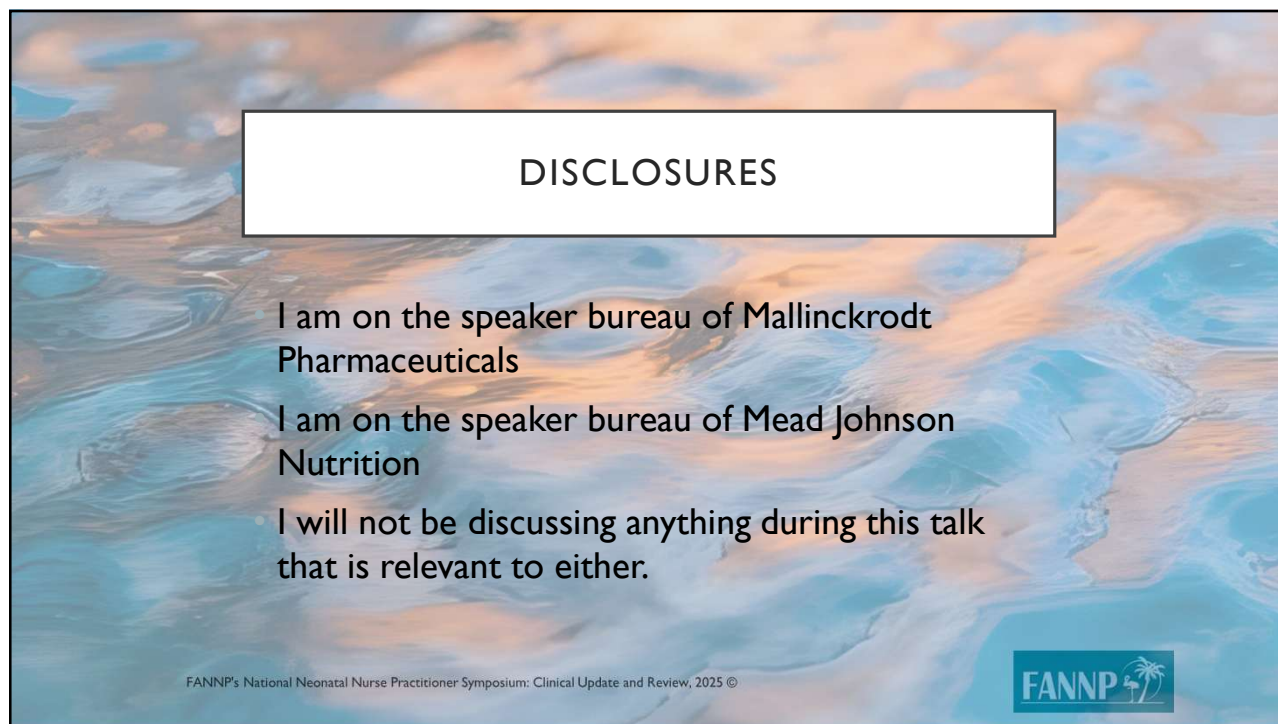
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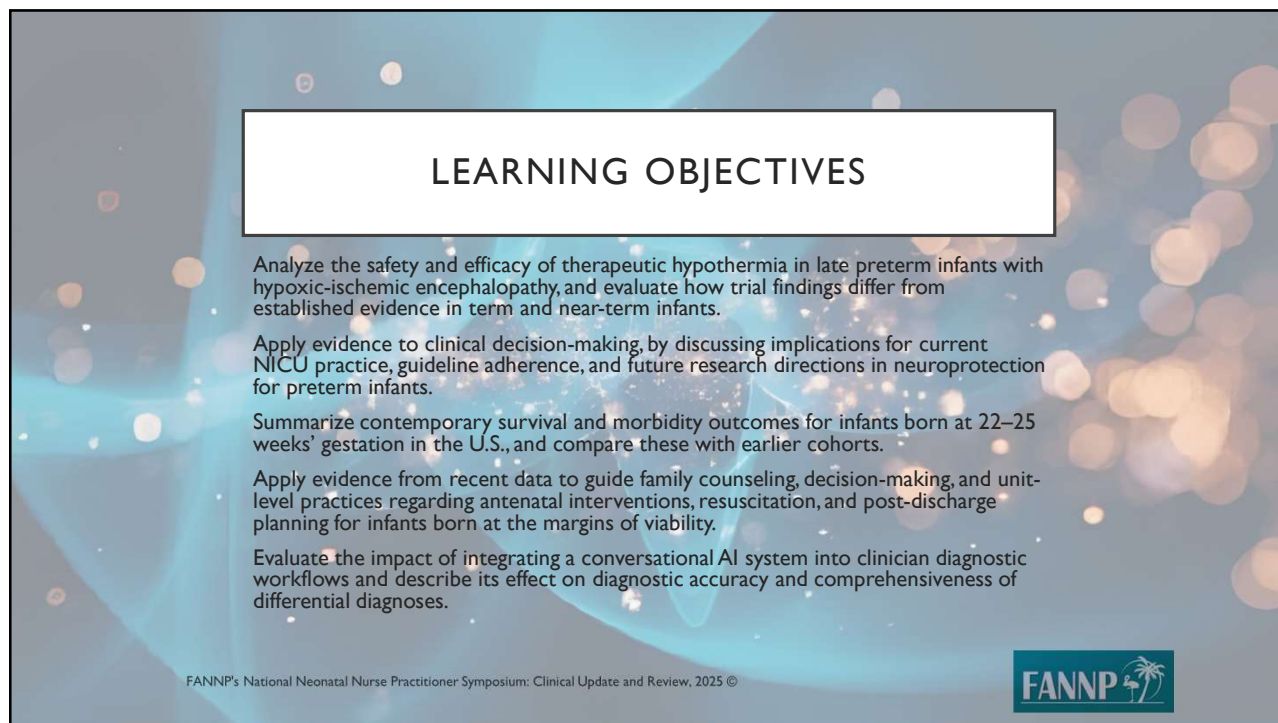
## DISCLOSURES

- I am on the speaker bureau of Mallinckrodt Pharmaceuticals
- I am on the speaker bureau of Mead Johnson Nutrition
- I will not be discussing anything during this talk that is relevant to either.

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## LEARNING OBJECTIVES

- Analyze the safety and efficacy of therapeutic hypothermia in late preterm infants with hypoxic-ischemic encephalopathy, and evaluate how trial findings differ from established evidence in term and near-term infants.
- Apply evidence to clinical decision-making, by discussing implications for current NICU practice, guideline adherence, and future research directions in neuroprotection for preterm infants.
- Summarize contemporary survival and morbidity outcomes for infants born at 22–25 weeks' gestation in the U.S., and compare these with earlier cohorts.
- Apply evidence from recent data to guide family counseling, decision-making, and unit-level practices regarding antenatal interventions, resuscitation, and post-discharge planning for infants born at the margins of viability.
- Evaluate the impact of integrating a conversational AI system into clinician diagnostic workflows and describe its effect on diagnostic accuracy and comprehensiveness of differential diagnoses.

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JAMA Pediatrics | Original Investigation

## Whole-Body Hypothermia for Neonatal Encephalopathy in Preterm Infants 33 to 35 Weeks' Gestation

### A Randomized Clinical Trial

Roger G. Faix, MD; Abbot R. Laptook, MD; Seetha Shankaran, MD; Barry Eggleston, MS; Dhuly Chowdhury, MS, MBA; Roy J. Heyne, MD; Abhik Das, PhD; Claudia Pedroza, PhD; Jon E. Tyson, MD, MPH; Courtney Wusthoff, MD, MS; Sonia L. Bonifacio, MD; Pablo J. Sánchez, MD; Bradley A. Yoder, MD; Matthew M. Laughon, MD, MPH; Diana M. Vasil, MSN, BSN, RNC-NIC; Krisa P. Van Meurs, MD; Margaret M. Crawford, BS, CCRP; Rosemary D. Higgins, MD; Brenda B. Poindexter, MD, MS; Tarah T. Colaizy, MD, MPH; Shannon E. G. Hamrick, MD; Lina F. Chalak, MD, MSCS; Robin K. Ohls, MD; Michele E. Hartley-McAndrew, MD; Kevin Dysart, MD; Carl T. D'Angio, MD; Ronnie Guillet, MD, PhD; Stephen D. Kicklighter, MD; Waldemar A. Carlo, MD; Gregory M. Sokol, MD; Sara B. DeMauro, MD, MSCE; Anna Maria Hibbs, MD, MSCE; C. Michael Cotten, MD, MHS; Stephanie L. Merhar, MD, MS; Roopali V. Bapat, MD, MSHQS; Heidi M. Harmon, MD, MS; Elizabeth Sewell, MD; Sarah Winter, MD; Girija Natarajan, MD; Ricardo Mosquera, MD, MS; Susan R. Hintz, MD, MSEpi; Nathalie L. Maitre, MD, PhD; Kristen L. Benninger, MD, MSc; Myriam Peralta-Carcelen, MD, MPH; Abbey C. Hines, PsyD; Andrea F. Duncan, MD, MSClinRes; Deanne E. Wilson-Costello, MD; Andrea Trembath, MD, MPH; William F. Malcolm, MD; Michele C. Walsh, MD, MS; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

<https://jamanetwork.com/journals/jamapediatrics/article-abstract/2830701>

Published February 24, 2025

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### MAJOR STUDIES

- **CoolCap trial [2005]** selective head cooling within 5.5 h of age for 72 hrs showed independent protective effect on outcome of **death** or **disability** in **term infants**.
- **NICHD trial [2005]** whole body cooling showed a significant reduction in the risk of **death** and **moderate to severe disability** at 18 months in **≥36 week infants**.
- **TOBY trial [2008]** whole body cooling showed improvement in **neurologic outcome** in **term infants**.

**Systematic review of all three trials showed a significant reduction of combined rate of death and severe disability.**




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## AHA GUIDELINES

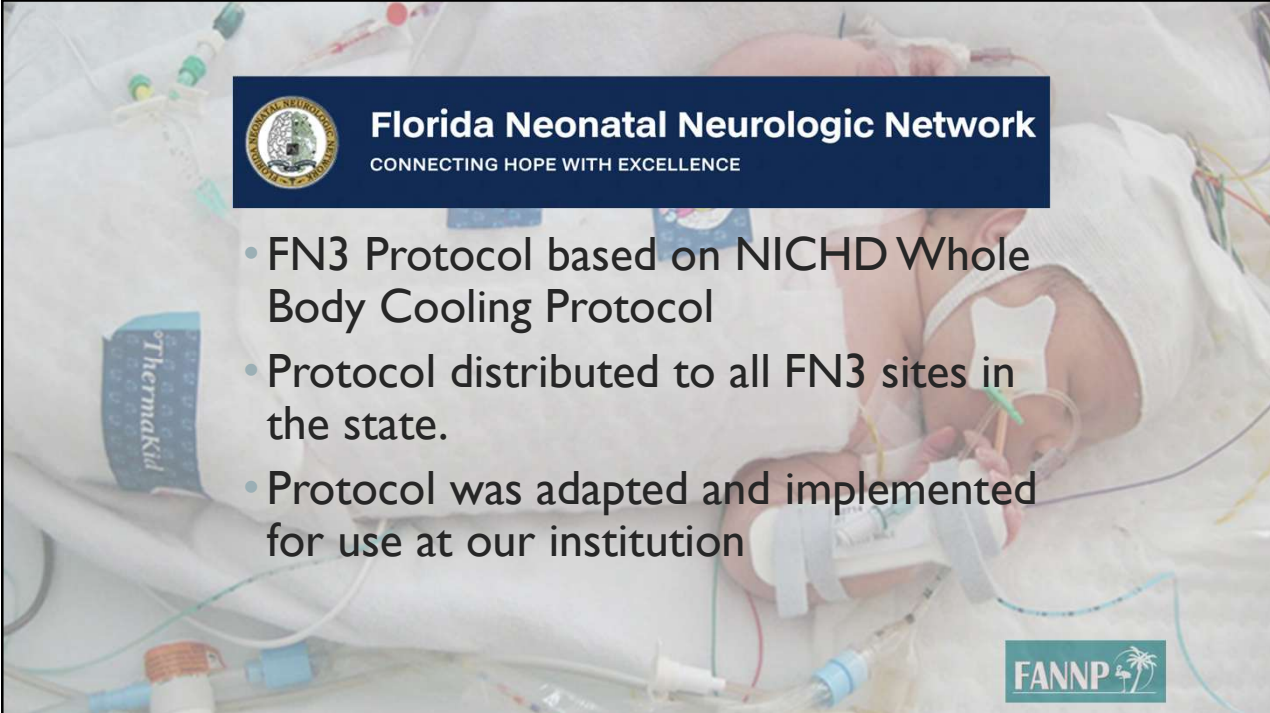
**2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science**


- It is recommended that *infants born at  $\geq 36$  weeks gestation with evolving moderate to severe HIE should be offered therapeutic hypothermia.*

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### Florida Neonatal Neurologic Network

CONNECTING HOPE WITH EXCELLENCE

- FN3 Protocol based on NICHD Whole Body Cooling Protocol
- Protocol distributed to all FN3 sites in the state.
- Protocol was adapted and implemented for use at our institution

FANNP

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THERAPEUTIC  
HYPOTHERMIA AT SJWH

Gestational Age greater than or equal to 35 weeks gestation

Birth weight greater than or equal to 1800 g

Less than or equal to 6 hours since insult occurred

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01

Therapeutic hypothermia (TH) is proven to reduce death and disability in term and near-term infants (≥36 weeks) with hypoxic-ischemic encephalopathy (HIE).

02

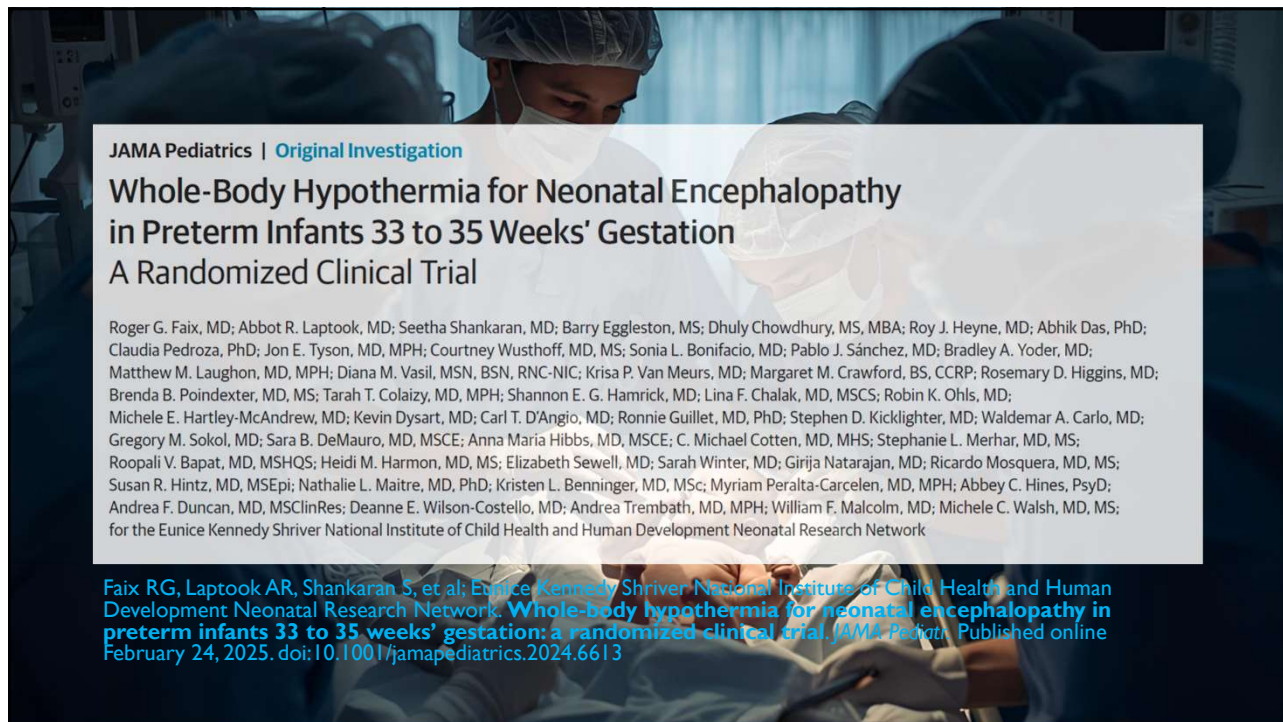
Despite lack of randomized trial data, TH has been increasingly used off-label in infants <36 weeks' gestation.

03

Preterm infants may be more vulnerable to complications of cooling, such as intracranial hemorrhage, NEC, coagulopathy, or hemodynamic instability.

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JAMA Pediatrics | Original Investigation

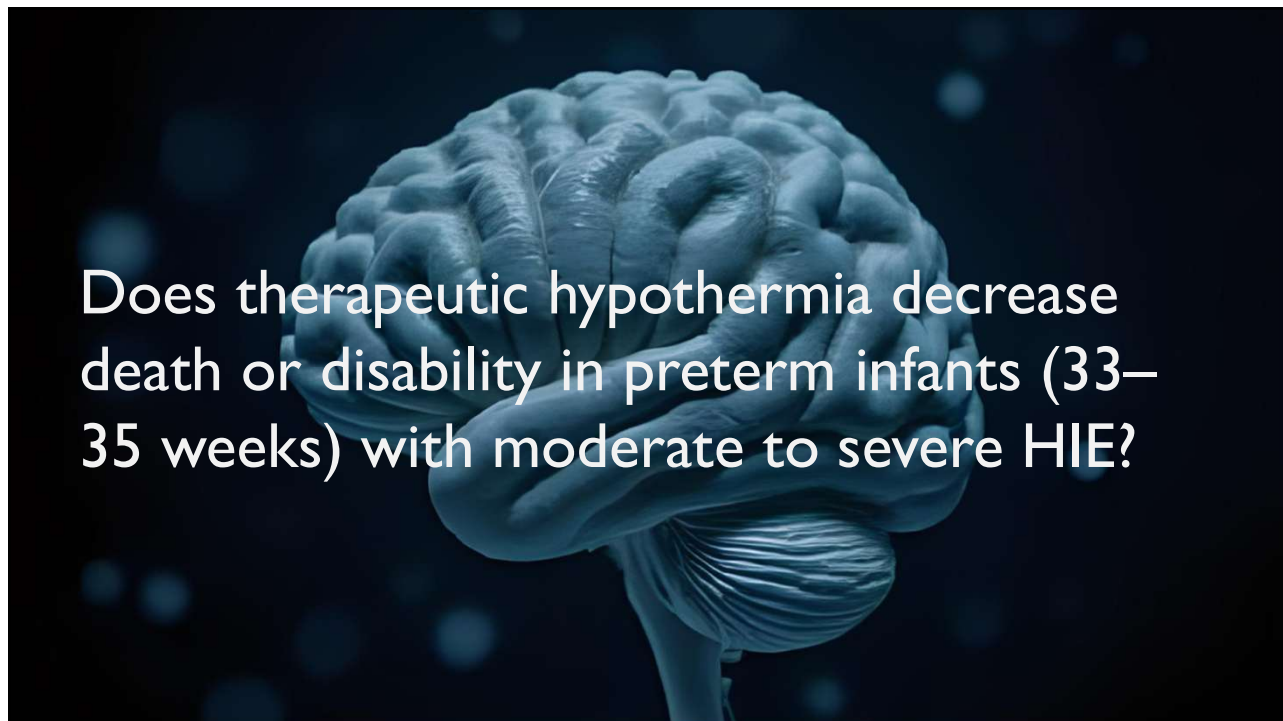
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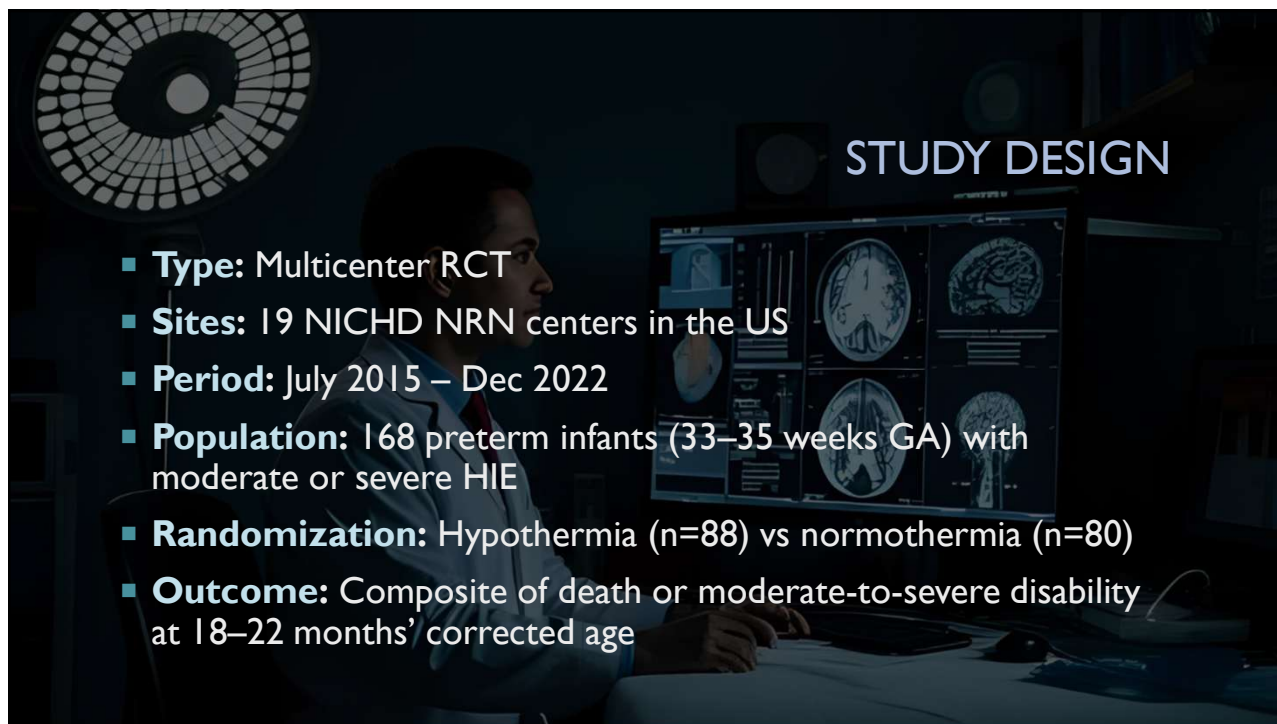
Faix RG, Laptook AR, Shankaran S, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. **Whole-body hypothermia for neonatal encephalopathy in preterm infants 33 to 35 weeks' gestation: a randomized clinical trial.** JAMA Pediatr. Published online February 24, 2025. doi:10.1001/jamapediatrics.2024.6613

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## Does therapeutic hypothermia decrease death or disability in preterm infants (33–35 weeks) with moderate to severe HIE?

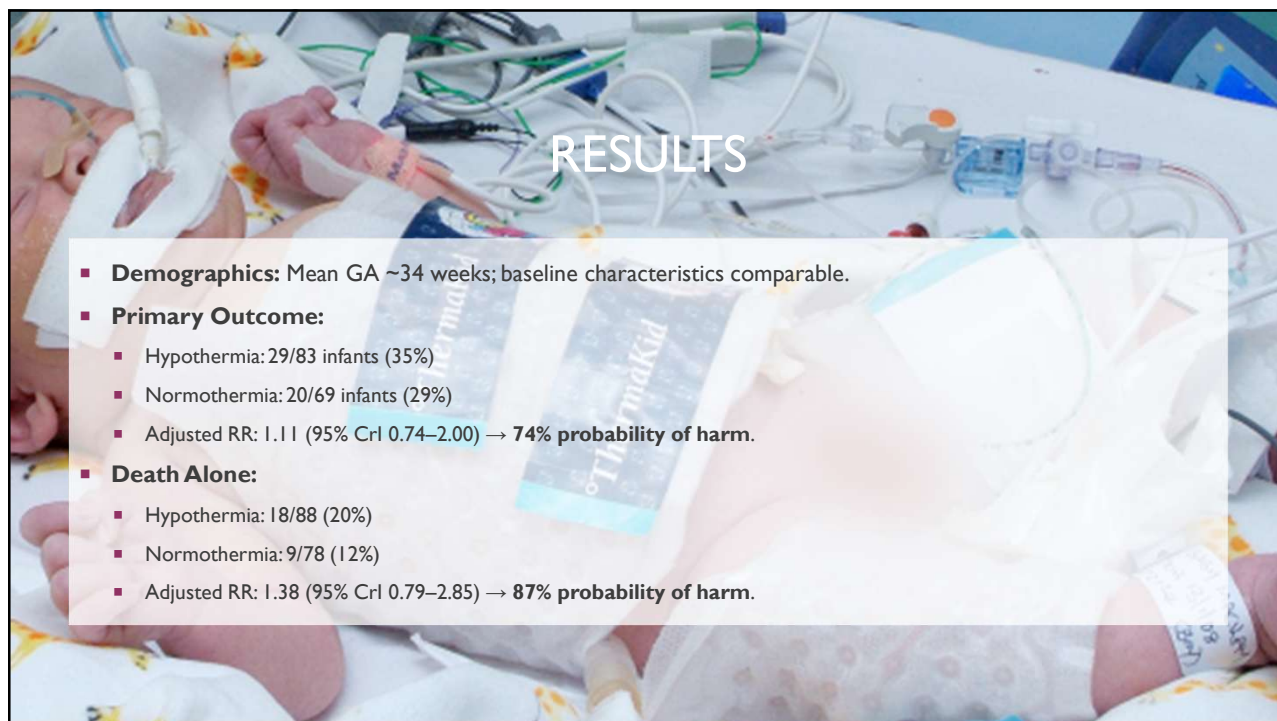
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## STUDY DESIGN

- **Type:** Multicenter RCT
- **Sites:** 19 NICHD NRN centers in the US
- **Period:** July 2015 – Dec 2022
- **Population:** 168 preterm infants (33–35 weeks GA) with moderate or severe HIE
- **Randomization:** Hypothermia (n=88) vs normothermia (n=80)
- **Outcome:** Composite of death or moderate-to-severe disability at 18–22 months' corrected age

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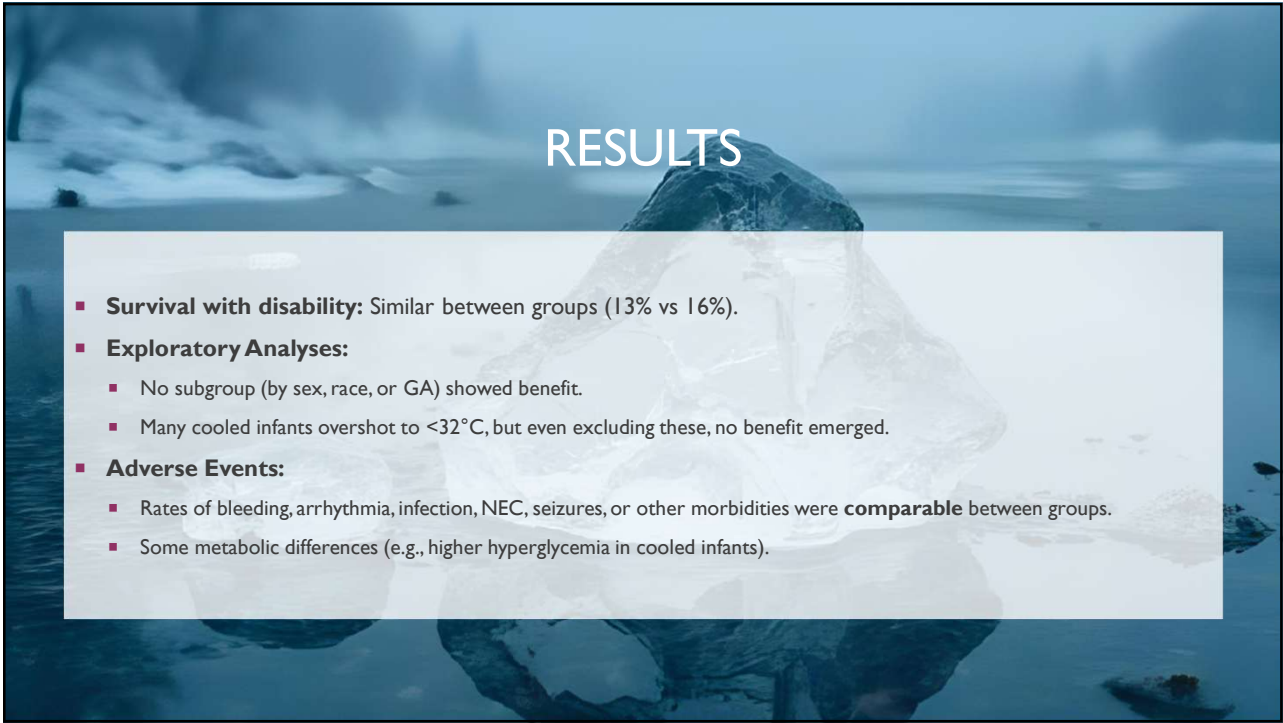


## RESULTS

- **Demographics:** Mean GA ~34 weeks; baseline characteristics comparable.
- **Primary Outcome:**
  - Hypothermia: 29/83 infants (35%)
  - Normothermia: 20/69 infants (29%)
  - Adjusted RR: 1.11 (95% CrI 0.74–2.00) → **74% probability of harm.**
- **Death Alone:**
  - Hypothermia: 18/88 (20%)
  - Normothermia: 9/78 (12%)
  - Adjusted RR: 1.38 (95% CrI 0.79–2.85) → **87% probability of harm.**

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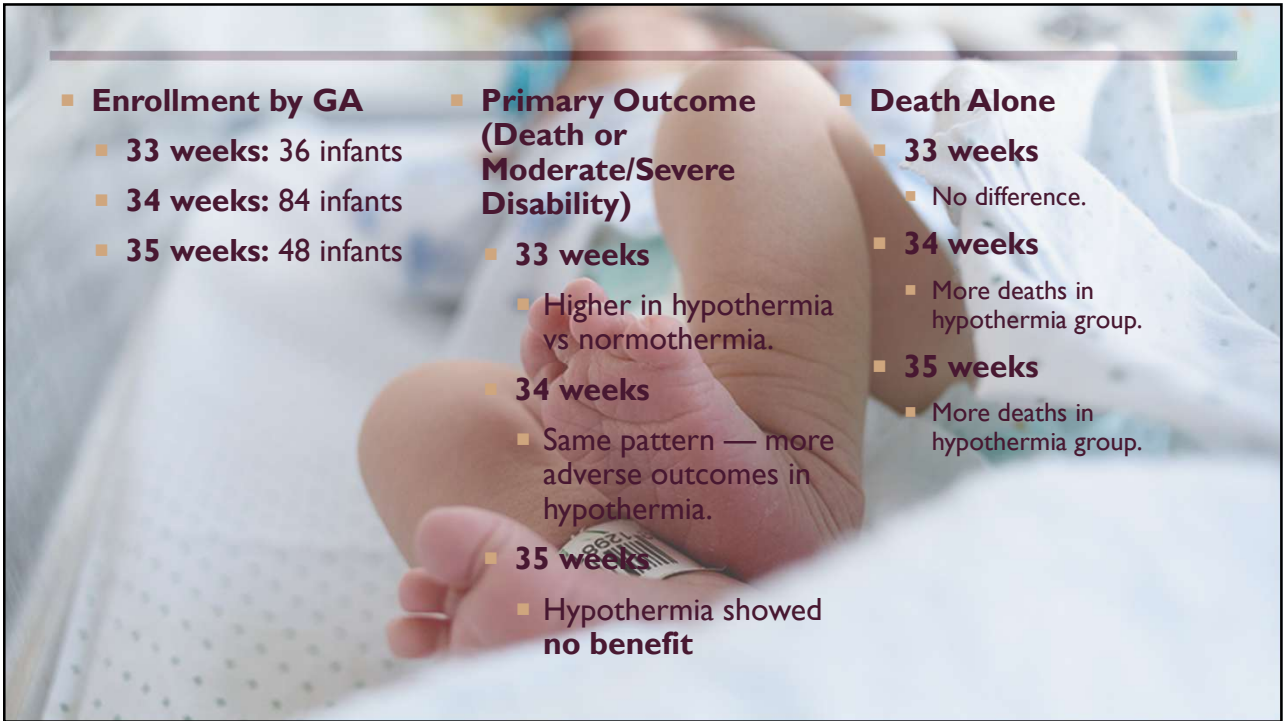




## RESULTS

- **Survival with disability:** Similar between groups (13% vs 16%).
- **Exploratory Analyses:**
  - No subgroup (by sex, race, or GA) showed benefit.
  - Many cooled infants overshot to <32°C, but even excluding these, no benefit emerged.
- **Adverse Events:**
  - Rates of bleeding, arrhythmia, infection, NEC, seizures, or other morbidities were **comparable** between groups.
  - Some metabolic differences (e.g., higher hyperglycemia in cooled infants).

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- **Enrollment by GA**
  - **33 weeks:** 36 infants
  - **34 weeks:** 84 infants
  - **35 weeks:** 48 infants
- **Primary Outcome (Death or Moderate/Severe Disability)**
  - **33 weeks**
    - Higher in hypothermia vs normothermia.
  - **34 weeks**
    - Same pattern — more adverse outcomes in hypothermia.
  - **35 weeks**
    - Hypothermia showed **no benefit**
- **Death Alone**
  - **33 weeks**
    - No difference.
  - **34 weeks**
    - More deaths in hypothermia group.
  - **35 weeks**
    - More deaths in hypothermia group.

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## STRENGTHS

- First large RCT in late preterm infants with HIE
- Multicenter, standardized design with blinded outcome assessors
- Careful measures to avoid hyperthermia in the control group.

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## LIMITATIONS

- Moderate sample size (n=168); limited power to detect small effects.
- Some loss to follow-up (11% normothermia, 6% hypothermia).
- Intervention unblinded to clinicians (though outcome assessors were blinded).
- 47 eligible infants were excluded because clinicians opted for hypothermia outside trial.

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KEY TAKEAWAY

Across all **GA**, hypothermia did **not reduce disability** and tended to increase mortality. The only exception: at **33 weeks**, mortality was not worse with hypothermia, but disability outcomes still were not improved.

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CONCLUSIONS

01

Hypothermia should not be used for HIE in infants <36 weeks' gestation outside of strict protocols.

02

For 33–35 week infants, cooling may increase mortality without reducing disability.

03

Future research should explore alternative neuroprotective therapies for this vulnerable population.

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PRACTICE IMPLICATIONS	
Re-evaluate	hypothermia use in <36 week neonates—current evidence does not support it
Develop	NICU guidelines to align hypothermia eligibility strictly with evidence
Educate	staff and align practice with new risk data to ensure safety
Highlight	importance of stratifying by GA in neuroprotection trials

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www.nature.com/jpp

Journal of Perinatology

ARTICLE

Check for updates

# Therapeutic hypothermia for preterm infants 34–35 weeks gestational age with neonatal encephalopathy

Seh Hyun Kim<sup>1</sup>, Hoda El-shibiny<sup>1</sup>, Terrie Inder<sup>1,2</sup> and Mohamed El-Dib<sup>1</sup>✉

© The Author(s), under exclusive licence to Springer Nature America, Inc. 2024

**OBJECTIVE:** To evaluate the short-term outcomes and safety of therapeutic hypothermia (TH) for neonatal encephalopathy in preterm infants at 34–35 weeks of gestation.

**STUDY DESIGN:** A matched retrospective cohort study of 20 preterm infants at 34–35 weeks of gestation and 40 infants at 36 weeks of gestation or more who received TH between the years 2015–2021.

**RESULT:** Short-term outcomes of preterm infants at 34–35 weeks of gestation who received TH were comparable with infants at 36 weeks or more of gestation who received TH regarding seizures, intraventricular hemorrhage, blood transfusions, subcutaneous fat necrosis, brain injury on magnetic resonance imaging, and mortality. These findings were consistent when short-term outcomes were adjusted for birthweight.

**CONCLUSION:** TH in preterm infants at 34–35 weeks of gestation is feasible and safe in our study population.

FANNP 36th National Neonatal Nurse Practitioner Symposium, Clinical Update and Review, 2024 ©  
Journal of Perinatology (2024) 44:528–531; <https://doi.org/10.1038/s41372-024-01874-x>

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### Survival of Infants Born at 22 to 25 Weeks' Gestation Receiving Care in the NICU: 2020–2022


Enika M. Edwards, PhD, MPH<sup>1,2,3</sup> Danielle E. Y. Ehret, MD, MPH<sup>1,2,3</sup> Roger F. Soll, MD<sup>1,2</sup> Jeffrey D. Horbar, MD<sup>1,2</sup>

**OBJECTIVE:** To provide contemporary data on infants born at 22 to 25 weeks' gestation and receiving care at level 3 and 4 neonatal intensive care units in the United States.

**SETTING:** Vermont Oxford Network members submitted data on infants born at 22 to 25 weeks' gestation at a hospital with a level 3 or 4 NICU from 2020 to 2022. The primary outcome was survival to hospital discharge. Secondary outcomes included survival without severe complications, length of stay, and technology dependence.

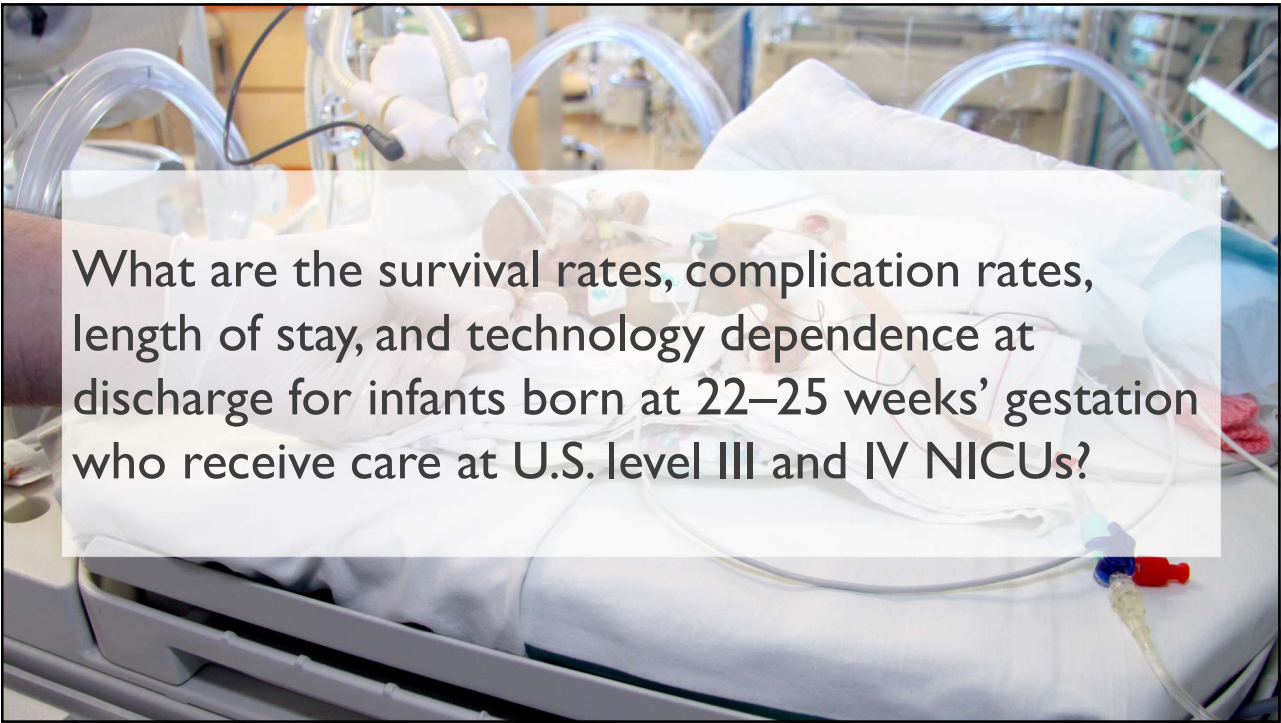
**RESULTS:** Overall, 22 953 infants at 636 US hospitals were included. Postnatal life support increased from 68.0% at 22 weeks to 99.8% at 25 weeks. The proportion of infants born at 22 weeks receiving postnatal life support increased from 61.6% in 2020 to 73.7% in 2022. For all infants, survival ranged from 24.9% at 22 weeks to 82.1% at 25 weeks. Among infants receiving postnatal life support, survival ranged from 35.4% at 22 weeks to 82.0% at 25 weeks. Survival without severe complications ranged from 6.3% at 22 weeks to 43.2% at 25 weeks. Median length of stay ranged from 160 days at 22 weeks to 119 days at 25 weeks. Among survivors, infants born at 22 weeks had higher rates of technology dependence at discharge than infants born at later gestational ages.

**CONCLUSIONS:** Survival ranged from 24.9% at 22 weeks to 82.1% at 25 weeks, with low proportions of infants surviving without complications, prolonged lengths of hospital stay, and frequent technology dependence at all gestational ages.



Edwards EM, Ehret DEY, Soll RF, Horbar JD. **Survival of Infants Born at 22 to 25 Weeks' Gestation Receiving Care in the NICU: 2020–2022.** *Pediatrics*. 2024;154(4):e2024065963. doi:[10.1542/peds.2024-065963](https://doi.org/10.1542/peds.2024-065963)

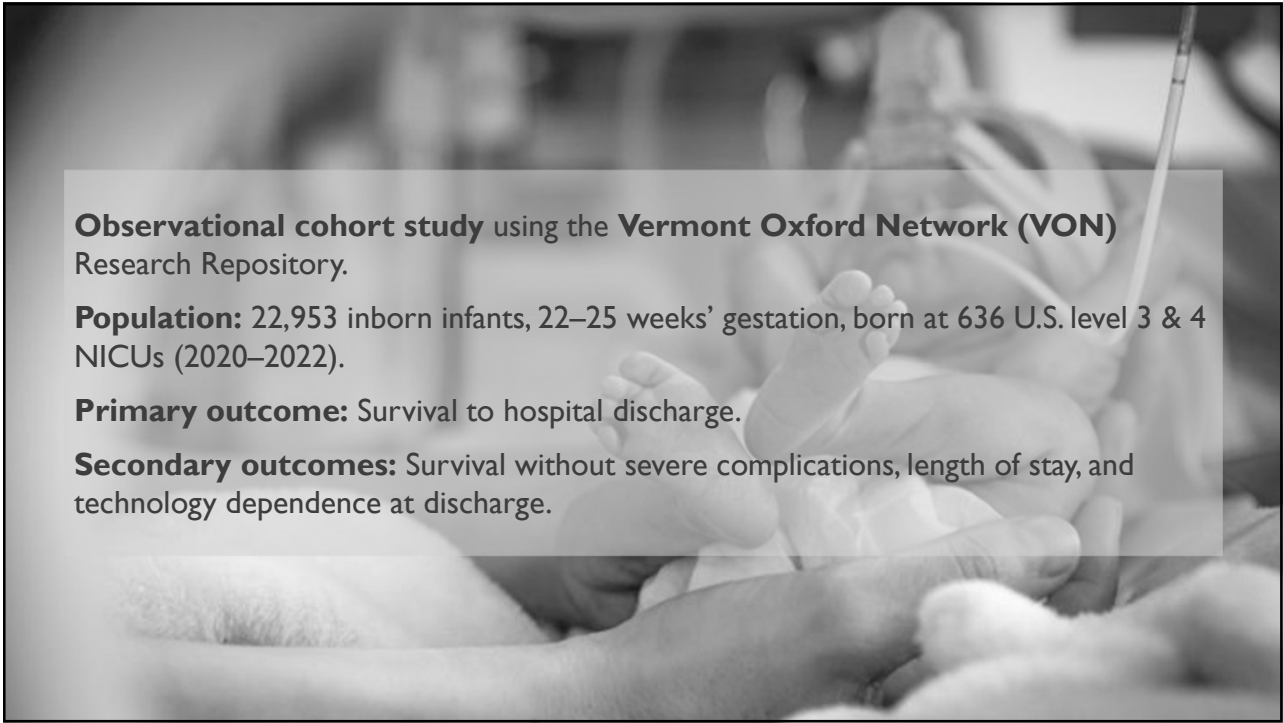
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What are the survival rates, complication rates, length of stay, and technology dependence at discharge for infants born at 22–25 weeks' gestation who receive care at U.S. level III and IV NICUs?

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**Observational cohort study** using the **Vermont Oxford Network (VON)** Research Repository.

**Population:** 22,953 inborn infants, 22–25 weeks’ gestation, born at 636 U.S. level 3 & 4 NICUs (2020–2022).

**Primary outcome:** Survival to hospital discharge.

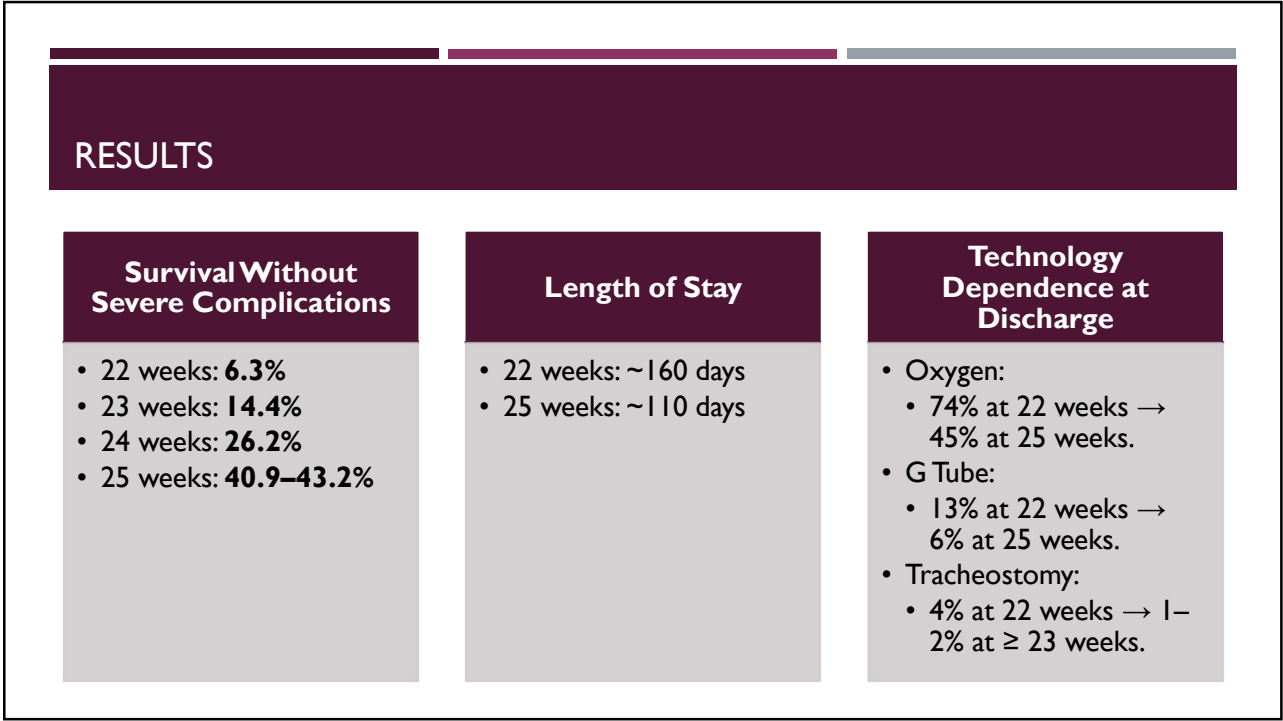
**Secondary outcomes:** Survival without severe complications, length of stay, and technology dependence at discharge.

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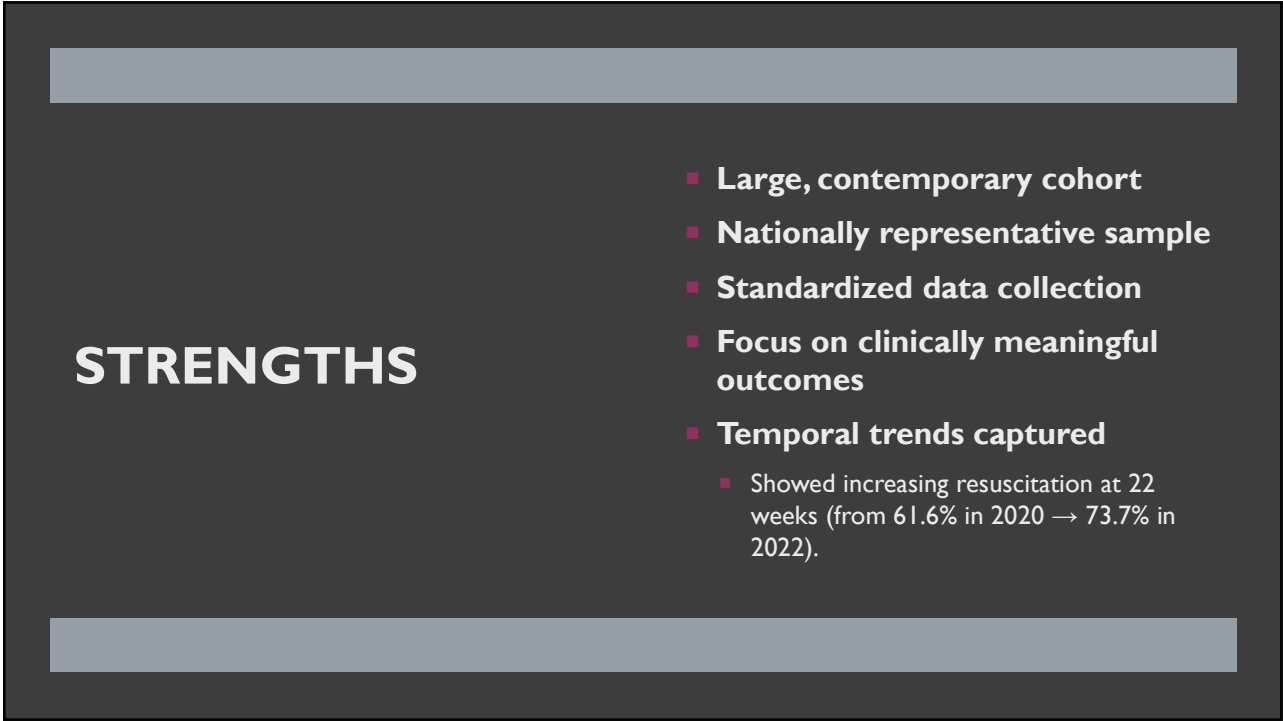
RESULTS

Active Resuscitation	Overall Survival	Survival If Active Resuscitation
<ul style="list-style-type: none"><li>• 22 weeks: 68% (61.6% in 2020 → 73.7% in 2022)</li><li>• 25 weeks: 99.8%</li></ul>	<ul style="list-style-type: none"><li>• 22 weeks: <b>24.9%</b></li><li>• 23 weeks: <b>52.8%</b></li><li>• 24 weeks: <b>71.1%</b></li><li>• 25 weeks: <b>82.1%</b></li></ul>	<ul style="list-style-type: none"><li>• 22 weeks: <b>35.4%</b></li><li>• 23 weeks: <b>55.1%</b></li><li>• 24 weeks: <b>71.5%</b></li><li>• 25 weeks: <b>82.0%</b></li></ul>

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35



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## **LIMITATIONS**

- **Restricted to level III/IV NICUs**
- **Observational design**
  - No randomization
  - Causality between interventions (e.g., steroids, magnesium, delivery mode) and outcomes cannot be firmly established.
- **No long-term neurodevelopmental outcomes**
- **Limited detail on decision-making factors**
  - Hospital-level and provider-level variations in resuscitation practices not fully explained.
  - Parental preferences and counseling strategies not captured.
- **Study period included the COVID-19 pandemic**

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## **KEY TAKEAWAYS**

- **Survival at 22 weeks is higher than previously reported**
- **Survival without severe complications remains low at the earliest gestations.**
- **Hospital stay is long and resource-intensive.**
- **Maternal interventions matter.**
  - At 22 weeks, only 41% received both antenatal steroids and magnesium sulfate, compared with ~80% at 25 weeks.
- **Care is shifting toward greater intervention at the margins of viability.**

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WHY FOCUS ON SMALL BABIES?

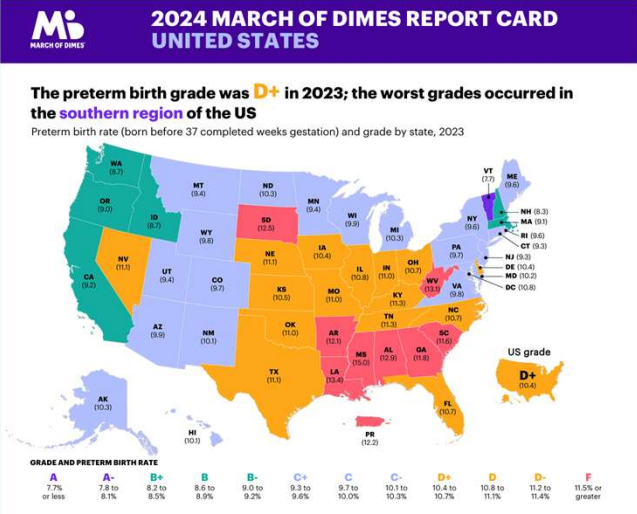


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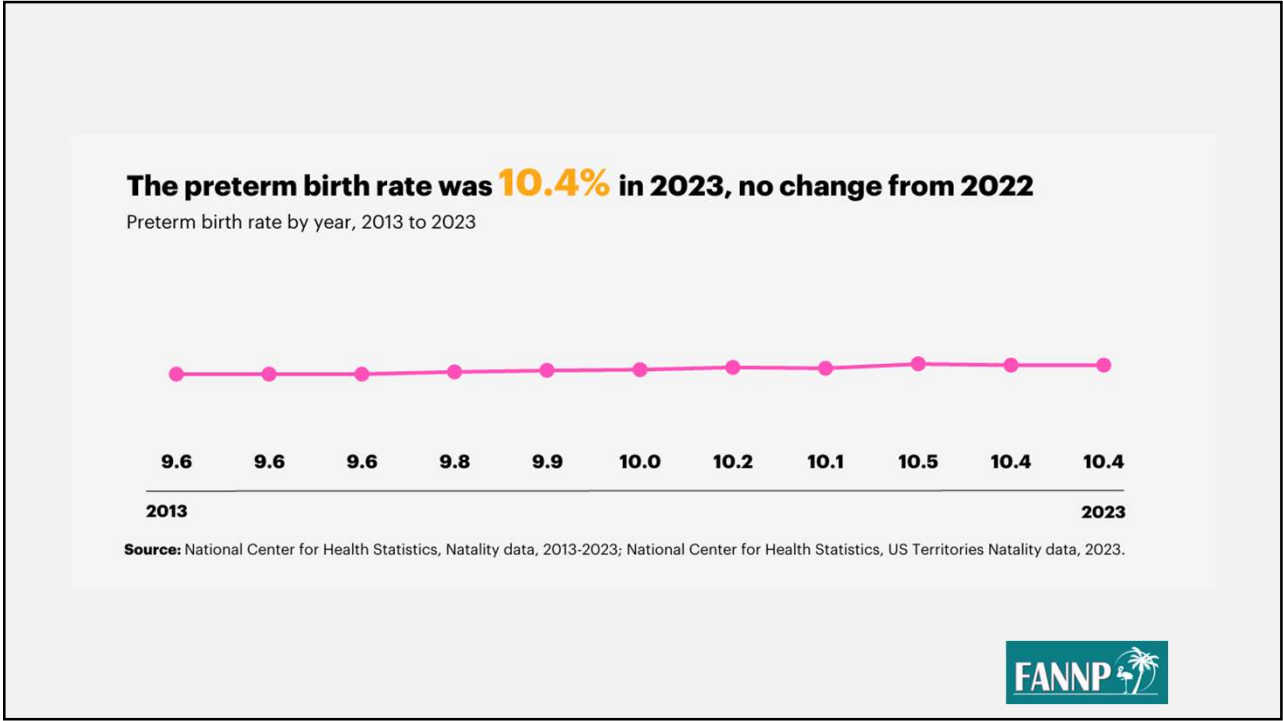
PRETERM BIRTH IN THE US

3.6 million births in 2024  
Approximately 10% preterm  
Extremely preterm infants (<28 wks)  
contribute disproportionately to both neonatal  
and infant mortality

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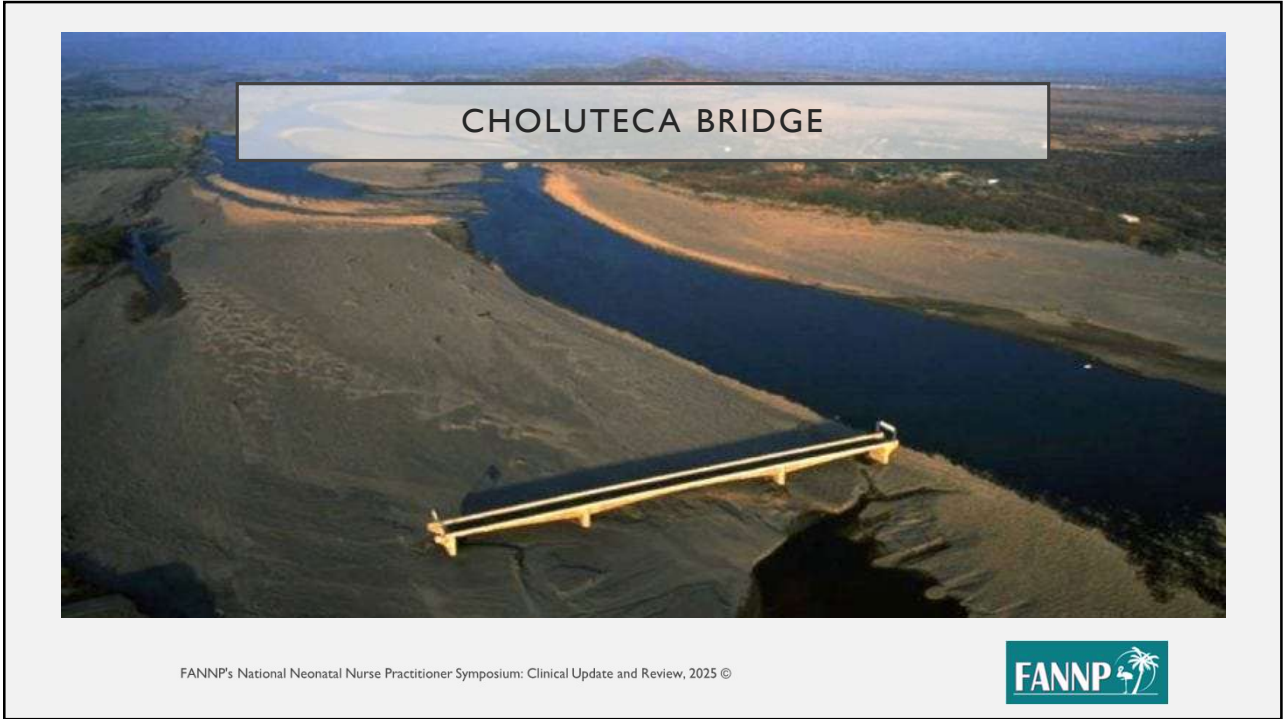
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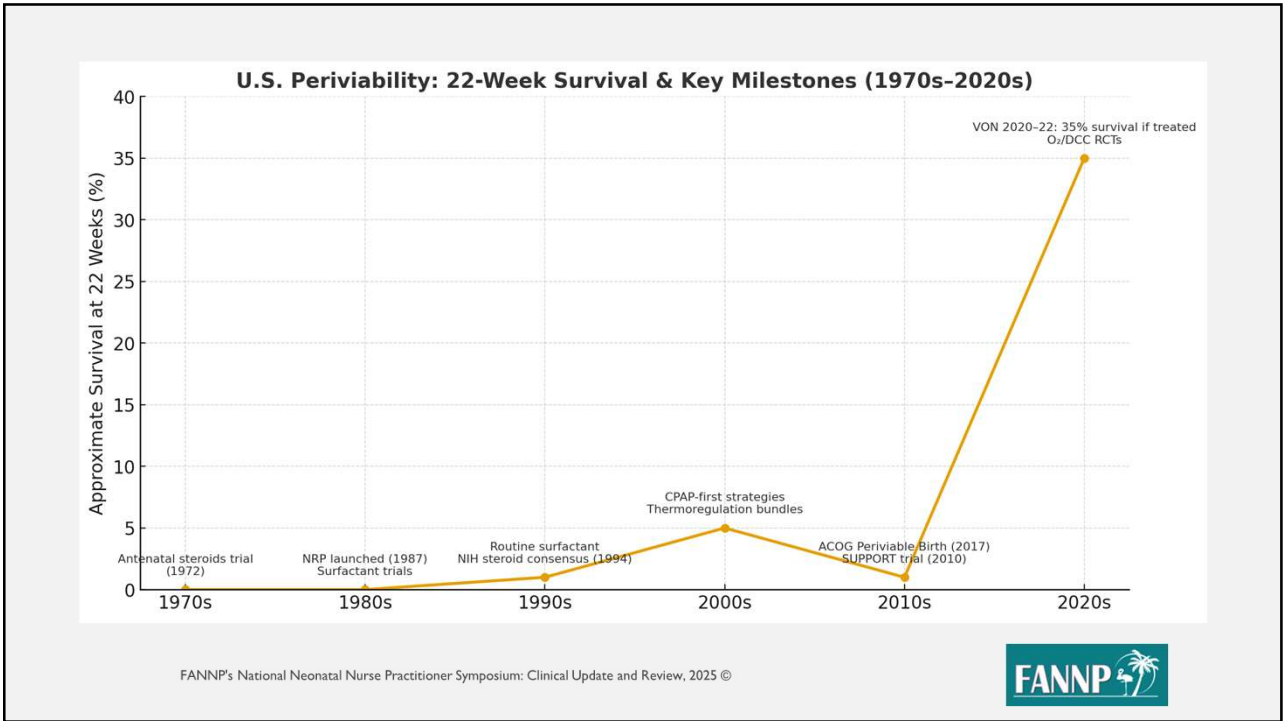
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Decade	Definition of Periviability	Resuscitation / NICU Practice Trends	Survival at Threshold (22–24 wks)
1970s	Viability cited around 26–28 wks; 'perivable' not yet a standard term.	First RCT of antenatal corticosteroids (1972).  No surfactant. Resuscitation inconsistent and center-dependent.	Survival ≤24 wk essentially 0%; survival expected at 26–28 wk in select centers.
1980s	Lower limit ~24–25 wks in tertiary centers.	NRP launched 1987.  Surfactant trials late decade. Antenatal steroid use expanding.	23–24 wk survival rare, highly center-specific; 22 wk almost universally non-survivable.
1990s	Emerging 'periviability' concept, usually 23–24 wks.	Surfactant routine by early 1990s.  1994 NIH consensus drives routine antenatal steroids. NRP uptake expands.	NRN data (1993+): survival at 23–24 wk improving, still uncommon at 22 wk.
2000s	Active care considered at 23–24 wks; 22 wk still rarely resuscitated.	CPAP-first strategies emerge; gentle ventilation; thermoregulation bundles.	NRN 2006–2011: median survival ~5% at 22 wk (if treated), higher at 23–24 wk.
2010s	ACOG 2017 defines perivable birth as 20 0/7–25 6/7 wk.  Active care often 22–24 wk.	SUPPORT trial (2010) validates CPAP at birth. NRP/ILCOR updates emphasize titrated O <sub>2</sub> and deferred cord clamping.	NRN (2000–2011): deaths 97–98% at 22 wk, ~1% survived without NDI (reflects low treatment rates).
2020s	Many centers now offer active care at 22 wk with shared decision-making.	Active treatment at 22 wk rising nationally. DCC standard. 2020 NRP guidelines emphasize targeted O <sub>2</sub> . New RCTs on FiO <sub>2</sub> during DCC.	VON 2020–2022: 22 wk survival 24.9% overall, 35.4% if treated; survival without severe complications 6.3%.

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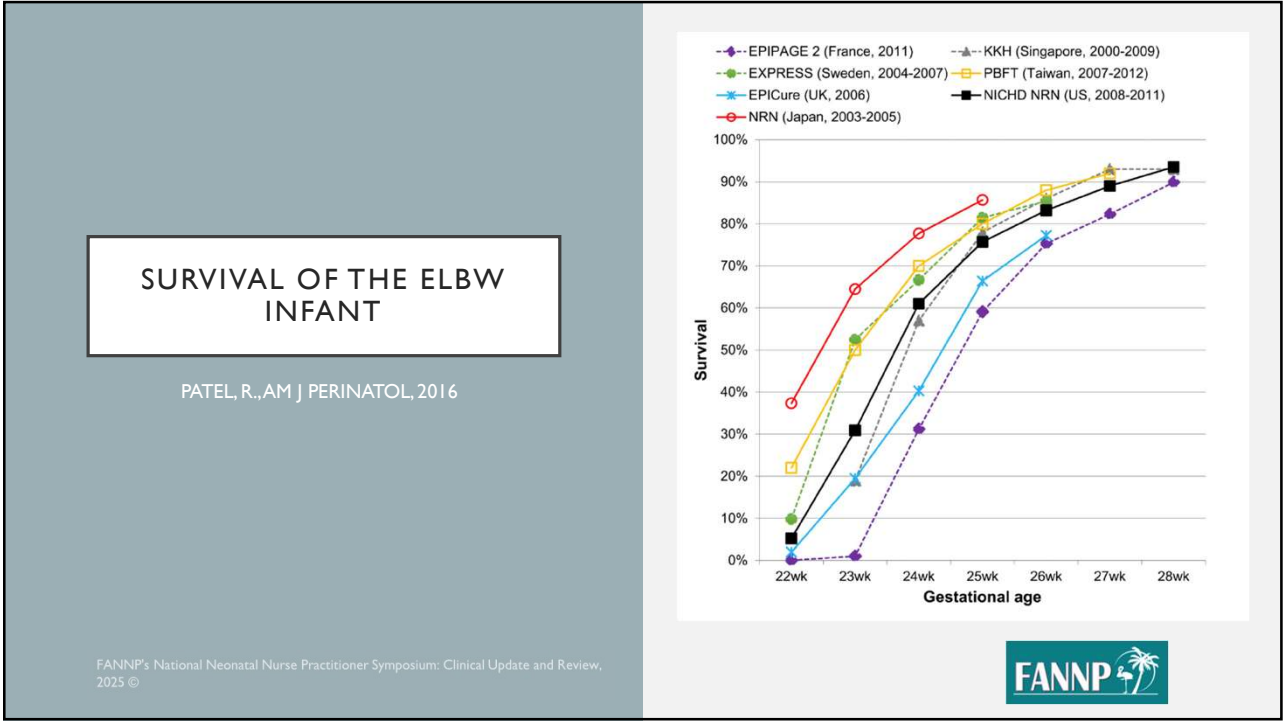


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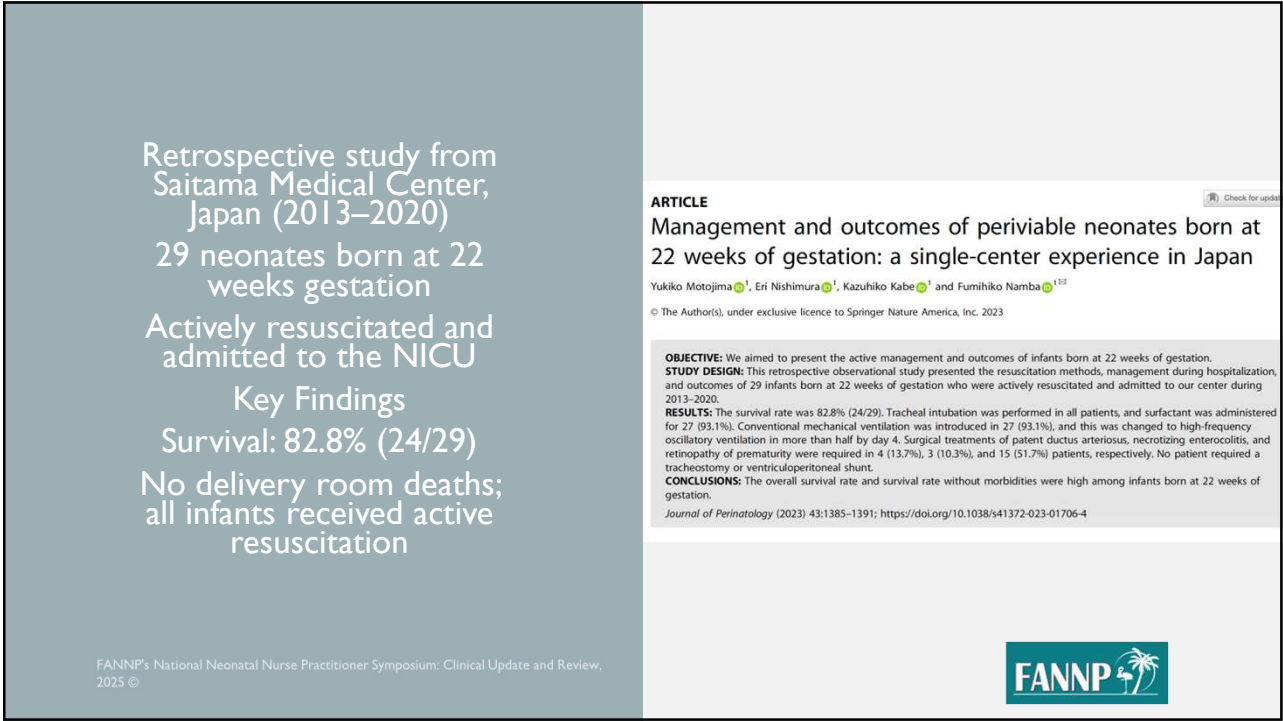


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### Doctors Can Now Save Very Premature Babies. Most Hospitals Don't Try.


Babies born 22 weeks into pregnancy have increasingly better odds of survival—but parents often don't know what's possible

“After her water broke early, doctors told Fatima Goines to prepare for her newborn’s death. Goines was 22 weeks into her pregnancy, just past the halfway mark. Doctors at Methodist Hospital in suburban Minneapolis said **they couldn’t save such a premature baby and that no hospital could**. They told her that once the baby girl was born, Goines could hold her until the infant died.

Goines didn’t want to give up. She checked herself out of Methodist Hospital and, on the recommendation of a fellow mom on [Facebook](#), went to a birthing center connected to Children’s Minnesota hospital, 7 miles away from Methodist. After Goines gave birth, doctors there immediately intubated the baby to help her breathe and placed her in an incubator.

Me’Lonii is now a **healthy 4-year-old**, and **has surpassed all the developmental milestones for her age**. “She’s doing wonderfully well,” said Dr. Thomas George, who directs the Children’s Minnesota neonatal intensive care unit.”

[Wall Street Journal, 8/7/2024](#)



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EXCLUSIVE

HEALTHCARE

### Bill Would Force Hospitals to Warn If They Aren't Equipped to Save Premature Babies

A Wall Street Journal investigation found parents were told nothing could be done for their infants even when other nearby hospitals could offer care

By Liz Essley Whyte

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July 23, 2025 8:00 pm ET

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- “...would require hospitals to **disclose publicly whether there is a minimal gestational age at which they offer active care for infants**, rather than comfort measures before their death. While many hospitals require lifesaving measures to be given at 25 weeks’ gestational age or above, decisions on whether to attempt to save younger premature infants can vary by hospital or even doctor.”

[Wall Street Journal, 7/23/2025](#)

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10/16/2025

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S.2433 - Neonatal Care Transparency Act of 2025

119th Congress (2025-2026) | Get Alerts

BILL

Help Overview R

Sponsor: Sen. Collins, Tom (R-ME) (Introduced 07/24/2025)

Committees: Senate - Health, Education, Labor, and Pensions


Latest Action: Senate - 07/24/2025 Read twice and referred to the Committee on Health, Education, Labor, and Pensions. (GA) (All Actions)

Tracker: Introduced → Passed Senate → Passed House → To President → Became Law

- (a) HOSPITAL REQUIREMENT.—Each hospital shall publicly disclose the policy of such hospital regarding the provision of life-saving care to an infant in the case of a premature birth, including—
  - (1) whether there is a minimum gestational age at which life-saving care will be provided to an infant in the case of a premature birth;
  - (2) whether the decision to provide life-saving care to an infant in the case of a premature birth is made on a case-by-case basis; and
  - (3) the process by which the hospital, in the case of a premature birth or expected premature birth, would transfer the infant and mother to the nearest facility with a neonatal intensive care unit that would provide life-saving care to the infant, if the hospital does not have the capacity to provide life-saving care to such infant.
- (b) PRACTITIONER REQUIREMENT.—Each obstetrician, or other health care practitioner who provides obstetric services to patients, shall, at the first prenatal visit of a patient, disclose to the patient the policy of any hospital at which the obstetrician or practitioner has admitting privileges regarding the provision of life-saving care to an infant in the case of a premature birth, including—
  - (1) whether there is a minimum gestational age at which life-saving care will be provided to an infant in the case of a premature birth;
  - (2) whether the decision to provide life-saving care to an infant in the case of a premature birth is made on a case-by-case basis; and
  - (3) the process by which the hospital, in the case of a premature birth or expected premature birth, would arrange for the transfer the infant and mother to the nearest facility with a neonatal intensive care unit that would provide life-saving care to the infant, if the facility in which the practitioner is providing services does not have the capacity to provide life-saving care to such infant.

<https://www.congress.gov/bills/119th-congress/senate-bill/2433/text>

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SMALL BABY TEAMS



ACTA PÆDIATRICA

NURTURING THE CHILD

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REGULAR ARTICLE

# Implementation of a multidisciplinary guideline-driven approach to the care of the extremely premature infant improved hospital outcomes

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EVIDENCE BASED  
PRACTICE GUIDELINES

- Single center; Ohio State University
- 37 infants <27 wks in first week of life to Small Baby Guideline Group vs 40 controls
- **Survival without BPD and severe IVH was greater in the SBG Group**
- **Length of stay shorter in SBG Group**

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DEDICATED ELBW TEAMS

Single center 67 bed Level IV NICU

28 weeks or < 1000 grams.

Pre- intervention 117 infants, post 232 infants over 3 year period.

Core team with EB guidelines, and checklists.

Care in a distinct unit by a consistent multidisciplinary SBU team

**Decrease in BPD, sepsis, and improved growth.**

Comparative Study > Pediatrics. 2015 Oct;136(4):e1007-15. doi: 10.1542/epub.2015.Sep.7.

## Small Baby Unit Improves Quality and Outcomes for Extremely Low Birth Weight Infants

Mindy Morris<sup>1</sup>, John Patrick Cleary<sup>2</sup>, Antoine Soliman<sup>3</sup>

Affiliations + expand  
PMID: 26347427 DOI: 10.1542/peds.2014-3918

### Abstract

**Objective:** The survival rates for extremely low birth weight (ELBW) infants have improved, but many are discharged from the hospital with significant challenges. Our goal was to improve outcomes for this population by using a multidisciplinary team-based quality improvement approach.

**Methods:** A unique program called the Small Baby Unit (SBU) was established at our hospital to care for the ELBW infant born at 28 weeks or less and weighing less than 1000 g at birth. These patients were cared for in a separate location from the main neonatal intensive care unit by a multidisciplinary team that participates in ongoing educational and process-improvement collaboration provides care. Evidence-based guidelines and checklists standardize care.

**Results:** Data from the 2 years before and 4 years after opening the SBU are presented.

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## PRACTICE IMPLICATIONS

Counseling Families

- Provide updated, data-driven survival and morbidity rates.
- Stress differences between survival *with* vs. *without* complications.
- Discuss prolonged hospitalization, technology needs at discharge, and long-term developmental risks.

Standardization of Care

- Develop Small Baby Teams.
- Align obstetric and neonatal management (antenatal steroids, magnesium sulfate use, delivery planning).

Quality Improvement & Equity

- Focus on shared decision-making, clear communication, and family-integrated care.
- Address regional disparities: ensure deliveries occur at level 3/4 NICUs.

Policy Considerations

- Support risk-appropriate perinatal regionalization to reduce care variability.
- Address social determinants of health, parental stress, and financial burdens associated with prolonged NICU stays.

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## BOTTOM LINE

Survival for infants born at 22–25 weeks has improved substantially, particularly at high-level NICUs, but survival without severe morbidity remains low—especially at 22–23 weeks. NICUs must balance aggressive care with realistic counseling, structured “small baby” care programs, and ongoing family-centered, equitable approaches to improve both survival and long-term outcomes.

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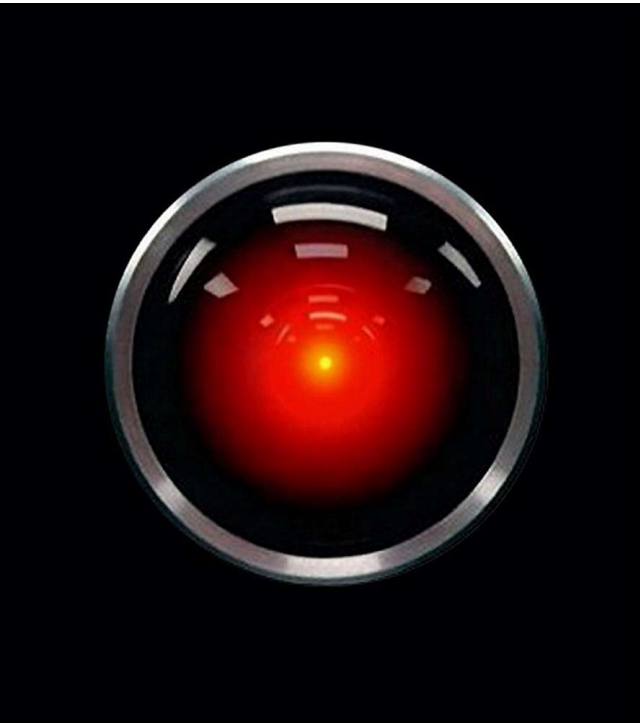


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**Artificial Intelligence (AI):**  
Computer systems designed to perform tasks requiring human-like intelligence (e.g., pattern recognition, reasoning).

**Large Language Models (LLMs):**  
A type of AI trained on massive text datasets. They “predict the next word” in context, which allows them to answer questions, write summaries, and even reason through medical cases.

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A glowing red sphere with a metallic ring around it, set against a black background. The sphere has a bright yellow-orange light source in the center, creating a lens flare effect. The metallic ring is silver and has some reflections.

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Article

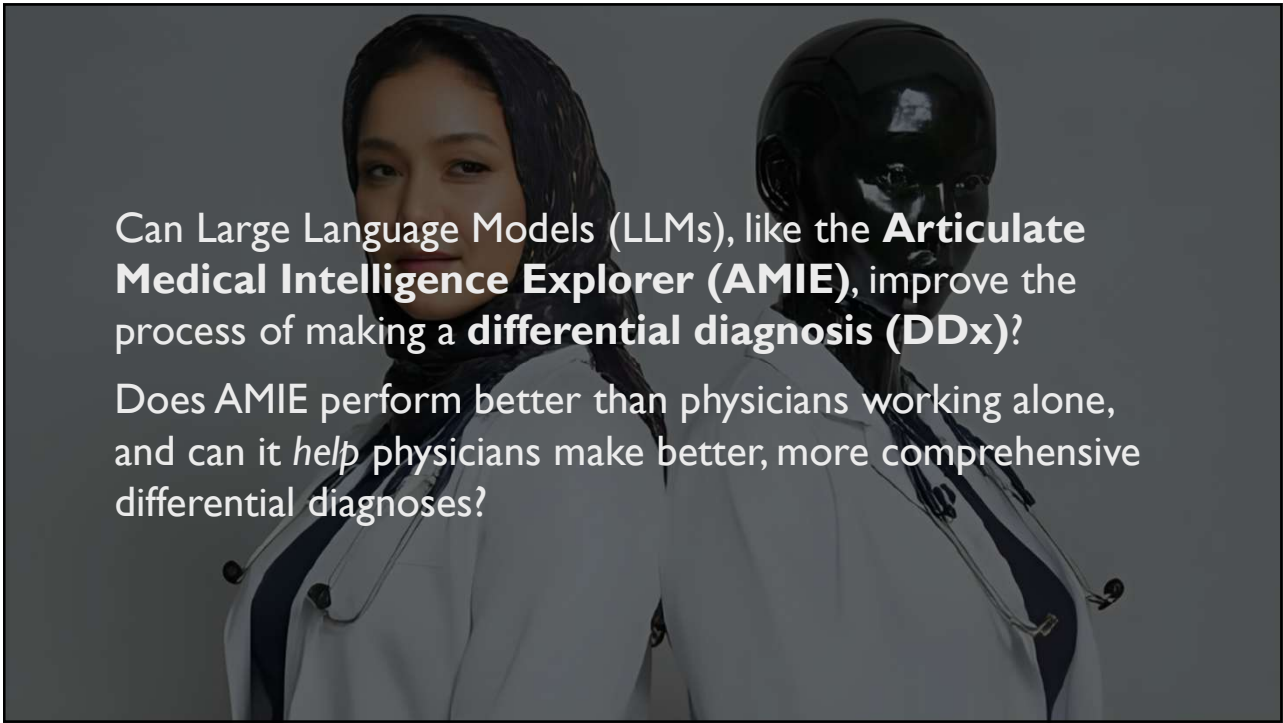
## Towards accurate differential diagnosis with large language models

<https://doi.org/10.1038/s41586-025-08869-4>  
Received: 19 January 2024  
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Check for updates

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A comprehensive differential diagnosis is a cornerstone of medical care that is often

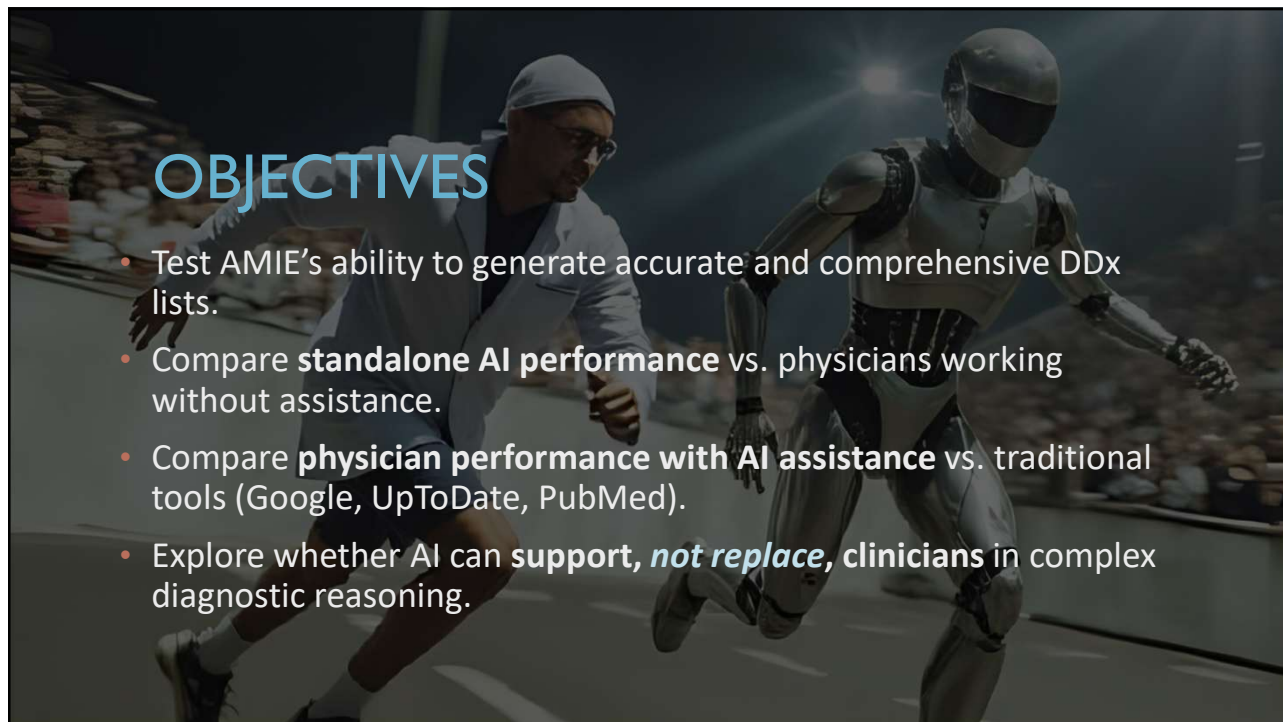
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Can Large Language Models (LLMs), like the **Articulate Medical Intelligence Explorer (AMIE)**, improve the process of making a **differential diagnosis (DDx)**?

Does AMIE perform better than physicians working alone, and can it *help* physicians make better, more comprehensive differential diagnoses?


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## OBJECTIVES

- Test AMIE's ability to generate accurate and comprehensive DDx lists.
- Compare **standalone AI performance** vs. physicians working without assistance.
- Compare **physician performance with AI assistance** vs. traditional tools (Google, UpToDate, PubMed).
- Explore whether AI can **support, *not replace*, clinicians** in complex diagnostic reasoning.

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## METHODS

- **Cases:** 302 challenging real-world cases from the *New England Journal of Medicine* Clinicopathological Conferences.
- **Participants:** 20 board-certified internal medicine physicians.
- **Study design:**
  - Physicians first gave an **unassisted DDx**.
  - Then they were randomized to receive help from:
    - **Traditional resources** (search, UpToDate, PubMed).
    - **AMIE (LLM)**, with or without additional searches.

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## EVALUATION

Expert raters scored DDx lists on:


- Accuracy** (did it contain the final diagnosis?).
- Quality** (how close was the DDx to the correct diagnosis?).
- Comprehensiveness** (did it cover all reasonable options?).
- Appropriateness** (fit with the case context).

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## RESULTS




**AMIE alone:**  
Top-10 accuracy of **59.1%** vs. **33.6%** for unassisted physicians



**Physicians assisted by AMIE:**  
Accuracy improved significantly (top-10 accuracy **51.7%**) compared to physicians with search tools (**44.4%**)



AMIE helped clinicians build **more comprehensive and appropriate DDx lists.**



**Efficiency:**  
Using AMIE took about the same time as search tools (~7 minutes), despite being new to clinicians.

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WHY I LIKED THIS PAPER

- **Head-to-head design**
  - It directly compares clinician-alone vs. clinician+AI vs.AI-alone.
- **Nuanced findings**
  - Shows that **AI can surpass clinicians in isolation**, but **clinician+AI is best**—emphasizing partnership.
- **Future relevance**
  - It captures the complexity we face:AI as an augmentation tool, not a wholesale replacement.
- **Practical message for providers**
  - The value of AI lies not in replacing us, but in re-shaping workflows to let us practice at the top of our license while AI handles breadth, recall, and pattern-spotting.


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Study	Setting	Who/What Compared	Primary Finding	Limitation
1) AMIE (Nature, 2025)	302 NEJM CPC cases (simulated)	AI alone vs Clinicians vs Clinicians+AI	Clinicians+AI > clinicians alone;AI alone strong	Simulated, text-only; no outcomes
2) LLM RCT (JAMA NO, 2024)	Physician vignettes (randomized)	Physicians w/LLM vs without; LLM-alone benchmark	LLM access didn't boost MD accuracy; LLM-alone highest	Vignettes; short exposure; small N
3) GPT-4 (NEJM AI)	Complex case challenges (text)	GPT-4 vs aggregate physician readers	GPT-4 exceeded nearly all readers	Self-selected benchmark; no real-world data

WHAT OTHER STUDIES ARE OUT THERE?

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### IMPLICATIONS FOR HEALTHCARE



#### Promise:

LLMs can help clinicians broaden their diagnostic thinking, reduce missed possibilities, and support education.

Could be especially valuable in **time-sensitive settings** (NICU, ER) or **resource-limited areas**.




#### Cautions:

AI may still “hallucinate” or mislead.

AI should be viewed as an **assistant, not a replacement**.

**Human** clinical judgment, context, and responsibility remain central.



#### Future Directions:

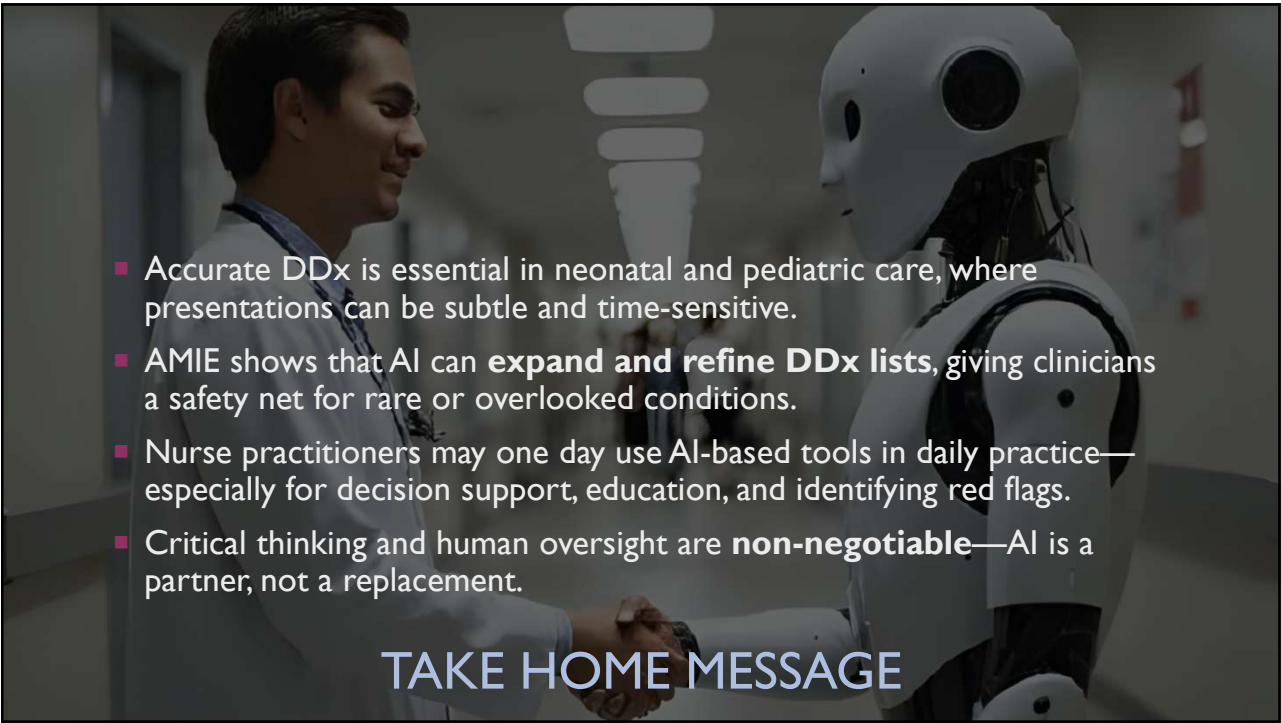
Integrating multimodal data

Training clinicians to interact effectively with AI.

Ensuring fairness and avoiding health disparities in AI use.

Exploring educational uses—“upskilling” junior staff with broader DDx thinking.

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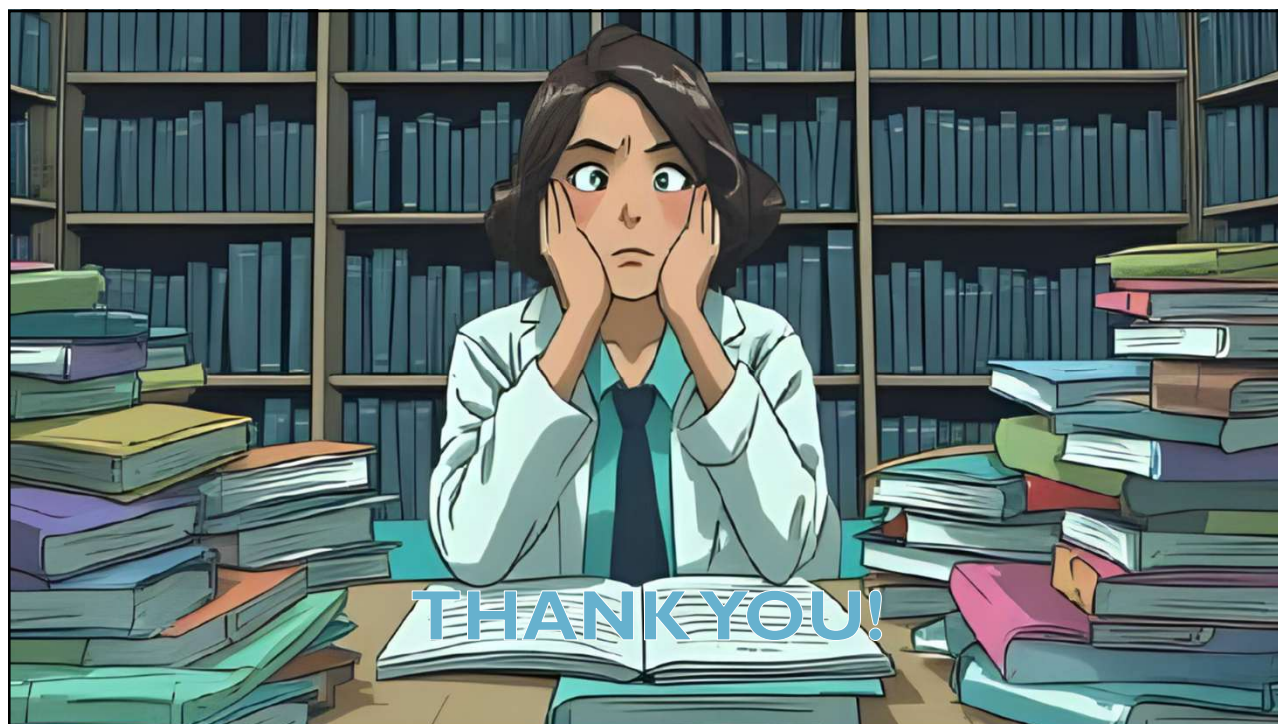
- Accurate DDx is essential in neonatal and pediatric care, where presentations can be subtle and time-sensitive.
- AMIE shows that AI can **expand and refine DDx lists**, giving clinicians a safety net for rare or overlooked conditions.
- Nurse practitioners may one day use AI-based tools in daily practice—especially for decision support, education, and identifying red flags.
- Critical thinking and human oversight are **non-negotiable**—AI is a partner, not a replacement.

### TAKE HOME MESSAGE

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10/16/2025

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