Practice Changing Articles from the Past Year

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Disclosures

Neither Dr. Vellody nor Dr. Bulova have any financial interests or relationships that could potentially bias the presentation

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Our Goals

- To bring our audience up to date on literature that is:
  - Relevant
  - Practice changing
  - Rigorous
  - Key take home points
  - Variety of ages/topics

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Our Process

- Recommendations from colleagues
- Pub med review of articles with title or abstract MESH term “Down syndrome”, “Trisomy 21” or “Down’s syndrome” since 6/1/2021
  - 1003 Articles
  - Reviewed for clinical applicability: 147 articles
- Presented as different chapters in the life of a person with Ds
  - Given time constraints, will be only a surface-level, high-yield overview of the studies discussed

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Chapter 1

Maya and Derek are first-time parents whose son Elijah was born at 29 weeks gestation and is now in the NICU. On day 3 of life, the neonatology team notices some subtle facial features and hypotonia that seem beyond what is typical for his degree of prematurity. They are uncertain whether these findings represent Down syndrome or simply related to his extreme prematurity. The team sends a karyotype. On day 8 of life, expedited chromosome results return confirming trisomy 21. You are called to discuss the diagnosis with his parents. They ask why it took so long to find out, and whether Elijah's prematurity made it harder to recognize. They also want to know how prematurity might impact his long-term outcome.

PEDIATRICS | OPEN SCIENCE

ORIGINAL RESEARCH ARTICLE

Prematurity and Delayed Diagnosis of Down Syndrome

Emily A. Messick, DO,[1] Austin A. Antoniou, PhD,[2] Bimal P. Chaudhari, MD, MPH[1,3,4,5]

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Background

- Prenatal screening (like NIPS) has increased
- Postnatal phenotypic recognition of genetic conditions remains essential
  - Confirmation of diagnosis
  - Management strategies
  - Outcomes
- Few resources include images showing features of genetic conditions in premature infants
- Prematurity alters baseline facial appearance
  - And care may also involve respiratory apparatus that obscures face

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Study

- Retrospective cohort study of NICU admissions from 2010-2021 at Nationwide Children's Hospital
  - 8 total NICUs, >3000 infants per year
  - 33,315 NICU admissions in the study period
- Excluded infants with antenatal suspicion or confirmed diagnoses
- Days to karyotype confirmed diagnosis of Ds in 3 groups
  - ≤34 weeks gestation
  - 34-36 weeks gestation
  - ≥37 weeks gestation

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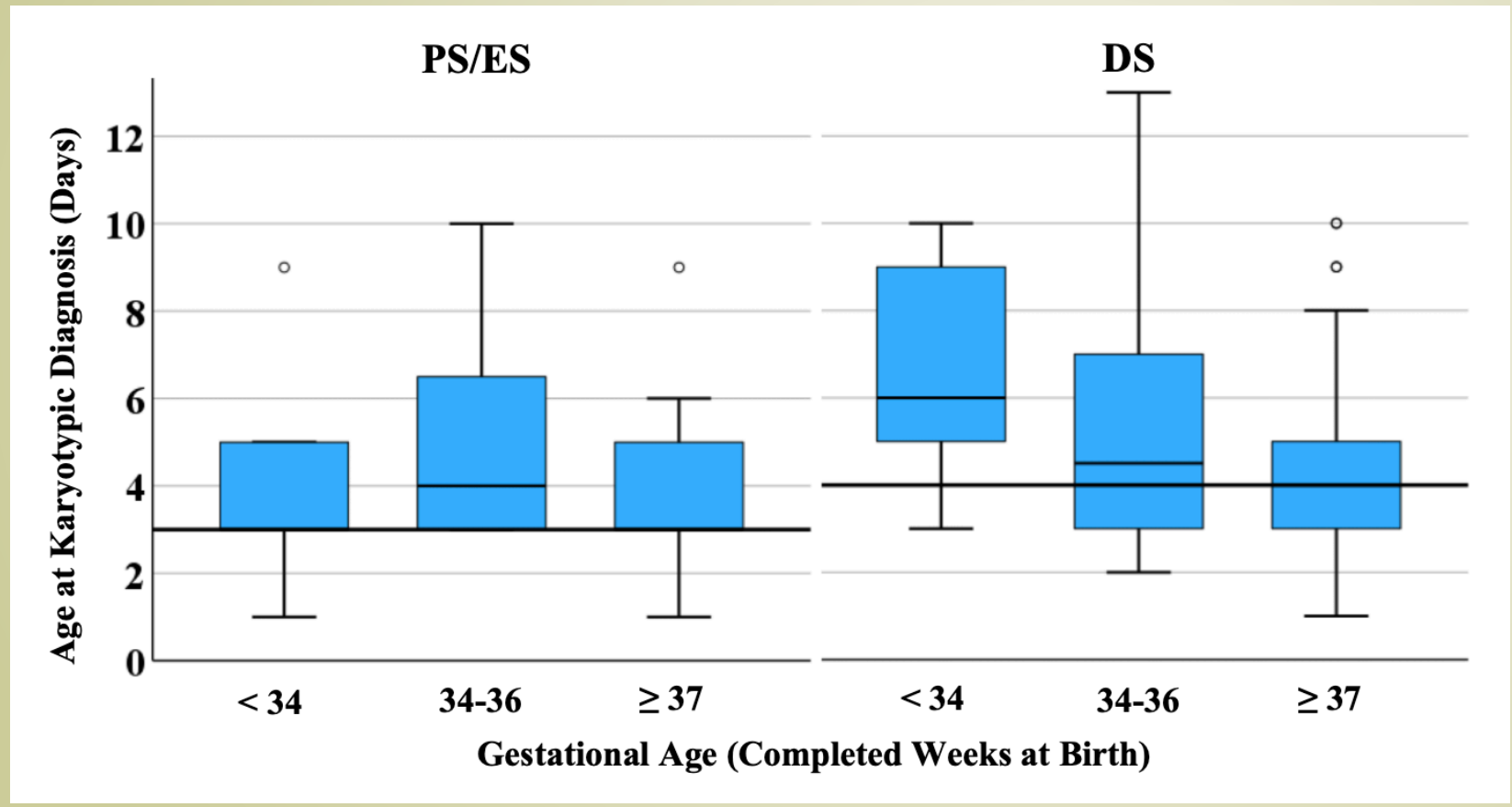
111 DS analyzed
12% (n=13) < 34 weeks GA (preterm)
20% (n=22) 34-36 weeks GA (late-preterm)
68% (n=76) ≥ 37 weeks GA (term/post-term)



Median age at diagnosis

- Preterm (< 34wk)
  - 6 days (IQR 5-9/10)
- Late preterm (34-36 wk)
  - 5 days (IQR 3-7)
- Term (> 37 wk)
  - 4 days (IQR 3-5)

Take Home Points

- In this large study, the diagnosis of Down syndrome was significantly delayed with increasing prematurity:
  - Preterm infants (under 34 weeks) received karyotypic diagnosis at a median of 6 days versus 4 days for term infants ($p < .01$)
- 25% of preterm DS infants didn't receive a diagnosis until after 10 days of life.
- Genetic training material should include images of premature infants with Ds

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Journal of Perinatology

www.nature.com/jp

ARTICLE OPEN

Check for updates

Gestational age-based outcomes of neonates with Down syndrome in the neonatal intensive care unit (NICU): review of pediatric health information system (PHIS) database

Emily A. Messick[1,2]✉, Stephen A. Hart[1,3], Julie Strominger[4], Sara Conroy[4,5], Carl H. Backes[1,2,3,4] and Clifford L. Cua[1,3]

Background

- 20% of infants with Ds are born prematurely (<37 weeks gestation)
  - 65-85% require NICU admission
- Prematurity in Ds has been linked with increased mortality in prior publications
  - Single center or regional studies
  - Often dichotomizing prematurity as “yes/no”
- Pediatric Health Information System (PHIS) database contains extensive medical records and billing data for >50 freestanding (85%) U.S. children’s hospitals

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Methods

- Retrospective analysis of PHIS database
- 7037 neonates with Ds admitted to a NICU <30 days of age between January 2008-December 2022
- 4 gestational age groups
  - 95 (1%) - extremely preterm (≤28 weeks gestation)
  - 304 (4%) - very preterm (28-31 weeks gestation)
  - 2168 (31%) - moderate/late preterm (32-36 weeks gestation)
  - 4470 (64%) - term (≥37 weeks gestation)
- Evaluated diagnoses, medical utilization, complications

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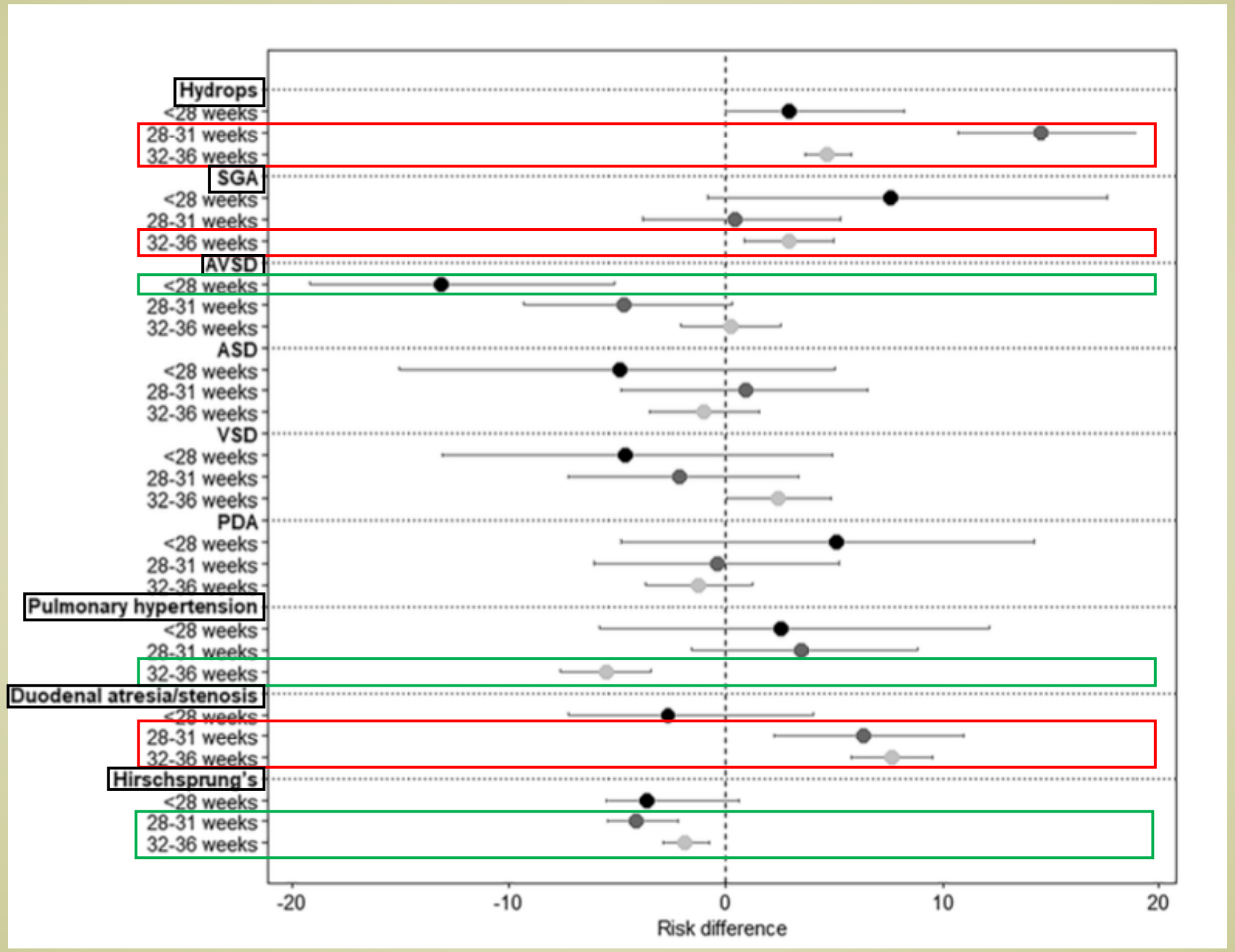
Hydrops
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PDA
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Pulmonary hypertension
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Duodenal atresia/stenosis
<28 weeks
28-31 weeks
32-36 weeks
Hirschsprung's
<28 weeks
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-20
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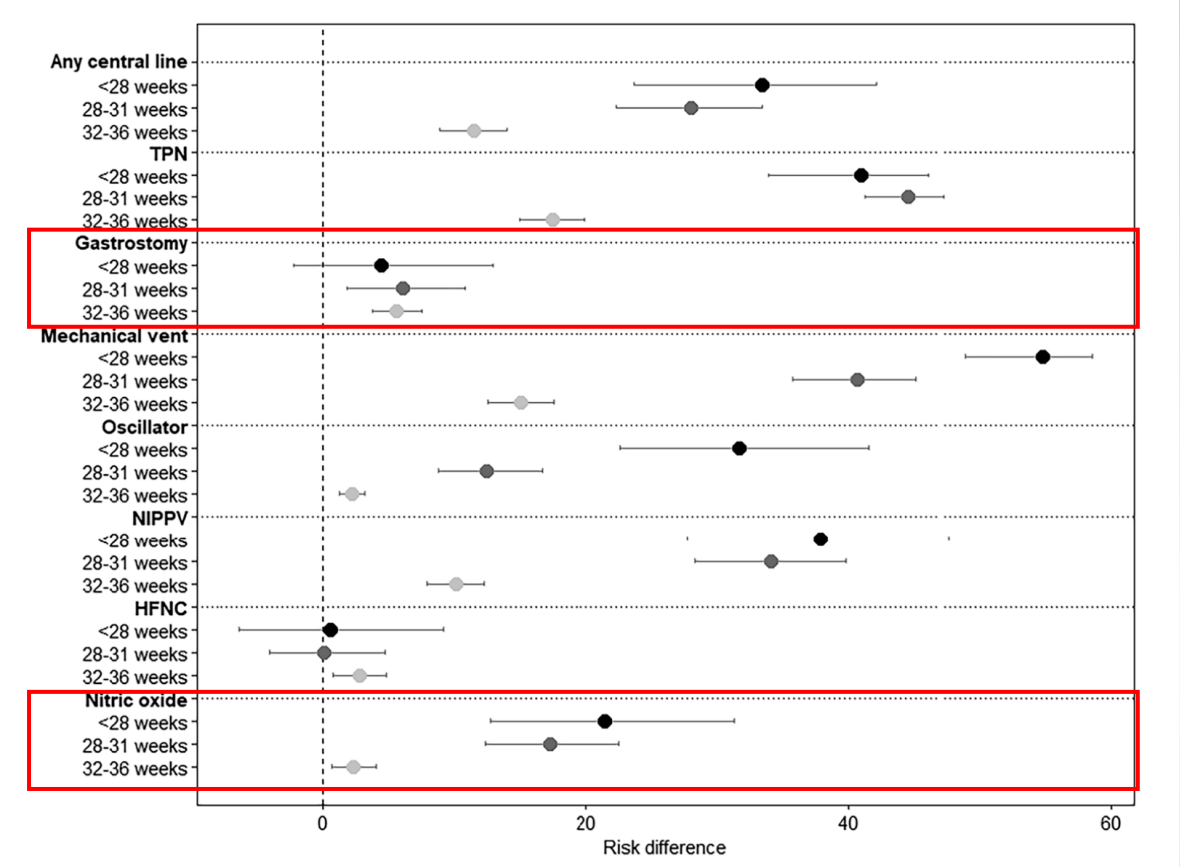
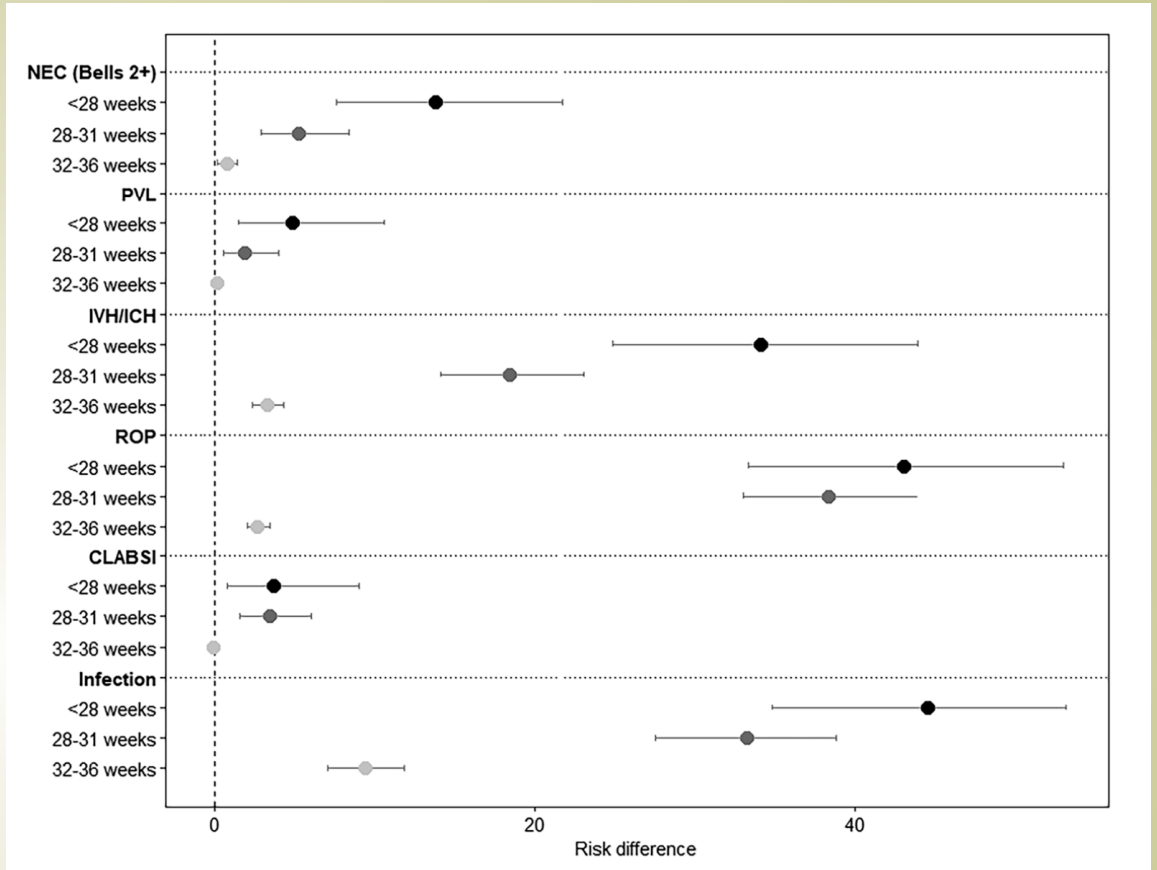
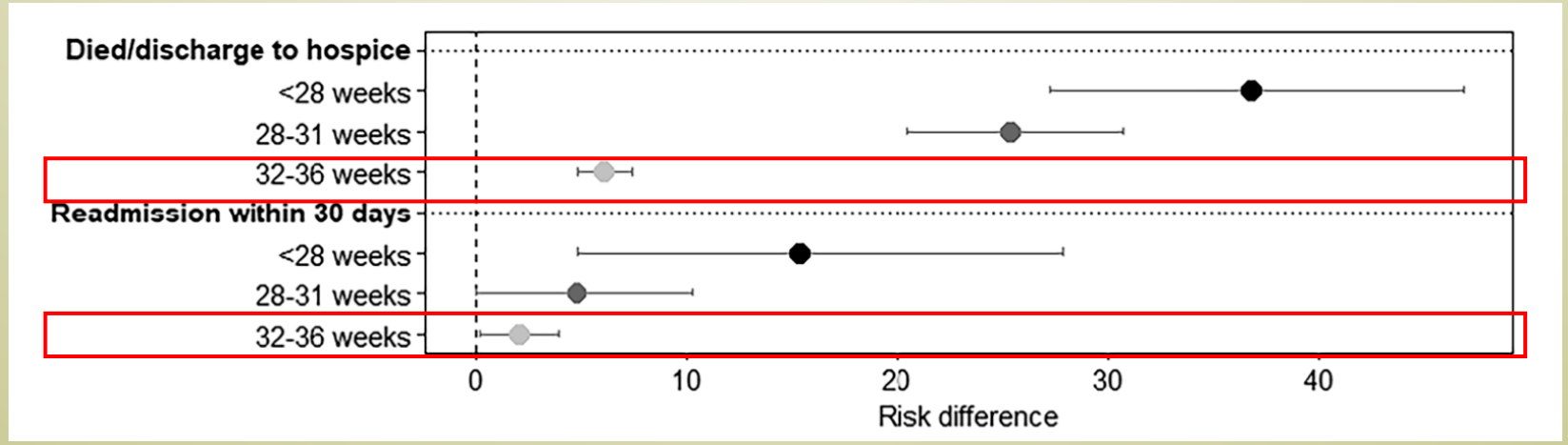
20
Risk difference







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Take Home Points

- Prematurity significantly and dramatically worsens outcomes for neonates with Ds in a clear dose-dependent fashion — the more premature the infant, the worse the outcomes across nearly every measure examined
- NICU mortality in neonates with Ds increases with prematurity
  - Including those in the 32-36 week gestational age
- G-tube placement, pulmonary hypertension/nitric oxide utilization, infection rates are high across all levels of prematurity
  - Ds specific factors contributing in addition to prematurity

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Chapter 2

8-year-old Elijah moves to Denver with his family to be closer to the site of the 2027 NDSC Convention and DSMIG Symposium. At his initial visit at the clinic, the family is first surprised that some doctors taking care of children with Down syndrome have hair! They are also surprised that they screen all children with Down syndrome for celiac disease starting by age 3, regardless of symptoms. Elijah has no GI symptoms, is growing well, and by all accounts seems to be doing fine. The screening tTG-IgA returns positive, and subsequent workup confirms celiac disease. They ask how long he may have had it, whether it has caused any harm, and why no one had ever tested him before.

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American Journal of Medical Genetics Part A

WILEY

AMERICAN JOURNAL OF medical genetics PART A

ORIGINAL ARTICLE

Impact of a Pediatric Down Syndrome Clinic on the Identification of Celiac Disease in the Patient Population

Francis Hickey[1,2] | Kristine Wolter-Warmerdam[2] | Liz Maastricht[2] | Dee Daniels[1,2] | Karen Kelminson[1,2]

[1]Department of Pediatrics, University of Colorado, School of Medicine, Aurora, USA | [2]Anna and John J. Sie Center for Down Syndrome, Children's Hospital Colorado, Aurora, USA

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Background

- Celiac disease (CD) is a chronic immune-mediated enteropathy triggered by gluten ingestion
  - ~1% in the general population
  - Anywhere from 1.6-18.6% reported in Ds literature
    - Recent meta-analysis of biopsy proven CD in Ds found overall 5.8% prevalence
      - 6.6% in children, 5.1% in mixed age samples
- 20-48% of children with Ds are asymptomatic with CD at time of diagnosis
  - Leading to 2.5-2.85 year diagnostic delay
  - Is there value in diagnosing asymptomatic CD in Ds?
- AAP Guideline
  - 1994, 2001 – no mention of celiac disease
  - 2011, 2022 – serologic screen for celiac disease only if symptomatic
- Adult Guideline (2020) - serologic screen for celiac disease only if symptomatic

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Method

- At the time of the study, Sie Center for DS (SCDS) at Children's Colorado (CHCO) did universal celiac screening at age 3
- 3 different groups compared
  - 2164 seen between 2011-2024 at SCDS
  - 924 seen at CHCO between 2011-2024 but not seen at SCDS
  - 1070 seen at hospital 1998-2010 before SCDS existed

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Results

TABLE 3 | Incidence of celiac disease[a] in children with and without Down syndrome.

	2011–2024 Sie Center for Down Syndrome (SCDS) patients with DS and routine testing	2011–2024 Children's Hospital Colorado (CHCO) patients with DS not seen at the SCDS	2011–2024 CHCO patients not seen at the SCDS, no DS	1998–2010 CHCO patients with DS receiving care at CHCO before the SCDS	1998–2010 CHCO patients before the SCDS, no DS
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Total	2164 (100.0)	924 (100.0)	199,854 (100.0)	1070 (100.0)	176,353 (100.0)
Celiac disease	160 (7.4)	22 (2.4)	3085 (1.5)	26 (2.8)	654 (0.4)

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TABLE 4 | Symptoms present at celiac diagnosis.

Characteristics	SCDS patients *n* (%)	Sie Center for Down Syndrome (SCDS) patients with documented diagnosis type ($n=95$)	
		Clinically identified *n* (%)	Screening identified *n* (%)
Total patients	95 (100.0)	16 (16.8)	79 (83.2)
Symptoms present			
Asymptomatic	30 (31.6)	0 (0.0)	30 (38.0)
Symptomatic	65 (68.4)	16 (100.0)	49 (62.0)
Symptoms present at diagnosis			
Diarrhea	18 (18.9)	4 (25.0)	14 (17.7)
Abdominal pain	14 (14.7)	2 (12.5)	12 (15.2)
Weight loss/failure to thrive	6 (6.3)	3 (18.8)	3 (3.8)
Gassiness	5 (5.3)	1 (6.3)	4 (5.1)
Vomiting	5 (5.3)	2 (12.5)	3 (3.8)
Fatigue	5 (5.3)	1 (6.3)	4 (5.1)
Rash	4 (4.2)	2 (12.5)	2 (2.5)
Behavior problems	4 (4.2)	1 (6.3)	3 (3.8)
Short stature	3 (3.2)	0 (0.0)	3 (3.8)
Swollen belly	3 (3.2)	0 (0.0)	3 (3.8)
Neurological symptoms	2 (2.1)	1 (6.3)	1 (1.3)
Other	16 (16.8)	4 (25.0)	12 (15.2)

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JPGN

REVIEW ARTICLE

Gastroenterology: Celiac Disease

Toward harmonized guidelines: A systematic review of celiac disease recommendations for children with Down syndrome

Vanessa Nadia Dargenio[1] | Marina Attolico[1] | Alessia Cafforio[1] | Fernanda Cristofori[1] | Federico Schettini[2] | Costantino Dargenio[1] | Stefania Paola Castellaneta[1] | Giovanni la Grasta[1] | Ruggiero Francavilla[1]

AAP, American Academy of Pediatrics

ACP, American College of Gastroenterology

AGA, American Gastroenterological Association

BSPGHAN, British Society of Paediatric Gastroenterology, Hepatology and Nutrition

DSMIG, Down Syndrome Medical Interest Group

ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition

ESsCD, European Society for the Study of Coeliac Disease

NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

NICE, National Institute for Health and Care Excellence

Guideline	Increased risk	Clinical presentation	Screening recommendations	Timing of screening	Role of intestinal biopsy	Management	Follow-Up and Monitoring	Recommended Tests	Frequency of Screening	Indications for Further Testing	HLA Testing
AAP (2022)[14]	CD prevalence in DS ~ 1–5%; immune-mediated risk	Overlap with DS symptoms: constipation, FTT, anemia	No screening for asymptomatic DS; screen if symptoms	After age 2 if symptomatic	Serology + possible biopsy if positive	Standard CD management with GFD	Annual visit; TTG monitoring	TTG-IgA, total IgA	Only when symptomatic	Clinical suspicion persists post-negative test	Not addressed
ACG (2022)[15]	DS identified as high-risk population	Similar to general population; may be masked in DS	Screen symptomatic DS individuals; no mass screening	When symptoms/lab signs present	Required unless TTG-IgA >10× + EMA+	Strict GFD with dietitian support	Initial at 3–6 months, then annually	TTG-IgA, total IgA; EMA if weakly positive	Initial at symptoms; repeat if new symptoms	Positive serology; persistent antibodies or symptoms	Specialist setting only (e.g., biopsy-sparing)
AGA (2019)[16]	DS identified as high-risk; screen if symptomatic or at-risk	GI and extra-GI symptoms; often non-specific in DS	Targeted screening in symptomatic/risk groups like DS	When clinically indicated	Recommended unless non-biopsy criteria met	Strict lifelong GFD; multidisciplinary care	Clinical + serological every 6–12 months	TTG-IgA, total IgA; IgG-based if IgA deficient	As clinically indicated	Persistent symptoms; positive serology	Not routinely recommended
BSPGHAN (2013)[17]	DS identified as high-risk population	Symptomatic (GI and non-GI); asymptomatic with associated condition	Universal screening recommended; use TTG-IgA and HLA-DQ	After gluten introduced; ≥3 months exposure required	Mandatory for confirmation	Strict lifelong GFD	6-12 month and then annual clinic and laboratory assessment	HLA; TTG-IgA, total IgA; EMA; TTG-IgG if IgA deficient	At least 3 months challenge with adequate gluten intake; repeat after 3 years or if new symptoms	HLA positive	Initial screening in at risk population
DSMIG (2016)[17]	DS identified as high-risk population	Symptomatic (GI and non GI); asymptomatic	Consider screening in DS; gluten exposure prerequisite; use TTG-IgA	Screening at 3 years; upon symptom development; at diagnosis of autoimmune thyroid disease and type 1 diabetes	Mandatory for confirmation	Strict lifelong GFD	Clinical and serological every 6–12 months	TTG-IgA, total IgA; EMA; TTG-IgG if IgA deficient; HLA	Repeat every 3 years in HLA positive	HLA positive or symptoms	HLA testing early in life, at birth if possible
ESPGHAN (2020)[18]	DS identified as high-risk population	Classic and non-classic symptoms; can be atypical in DS	Serologic screening if symptomatic/risk groups like DS	Upon symptom development	Biopsy required unless non-biopsy pathway applies	Strict GFD with dietitian support	Clinical and serologic monitoring; biopsy if persistent issues	TTG-IgA, total IgA; EMA; IgG-DGP if IgA deficient	When symptomatic; no defined intervals	Persistent serology; biopsy for non-responders	HLA testing is not obligatory criteria for a serology based diagnosis without biopsies.
ESsCD (2019)[19]	DS identified as high-risk population	Symptomatic (GI and non GI); asymptomatic	Serologic screening in symptomatic/risk groups like DS	In childhood, symptomatic and asymptomatic	Serology + possible biopsy if positive	Strict lifelong GFD + dietist/nutritionist	Clinical and serologic monitoring every 3–6 months during the first year, then annual follow-up	TTG-IgA, total IgA; EMA; TTG-IgG if IgA deficient; HLA	No defined intervals	HLA positive or symptoms	Initial screening in at risk population
NASPGHAN (2005)[20]	Prevalence in DS 5–12%; HLA-DQ2 nearly universal in DS + CD	1/3 asymptomatic; anemia, low height/weight more common	Universal screening recommended; use TTG-IgA	After age 3 with ≥1 year gluten intake	Mandatory for confirmation; ≥4 duodenal biopsies	Lifelong strict GFD; do not start before biopsy	Monitor growth TTG at 6 months then yearly	TTG-IgA, total IgA; TTG-IgG if deficient	Initial after 3 years + gluten; repeat if needed	Positive serology; abnormal growth or labs	Not standard; HLA-DQ2 found in most DS + CD
NICE (2020)[21]	DS included as a high-risk group	Wide range from GI to extra-GI; often subclinical	Consider serological screening in DS; gluten exposure prerequisite	After gluten introduced; ≥6 weeks exposure required	Referral to pediatric GI for biopsy if serology positive	GFD with full dietary education and psychosocial support	Annual review: growth, GFD adherence, nutrition	TTG-IgA, total IgA; EMA if needed	No fixed interval: repeat if new symptoms arise	Persistent symptoms; serologic elevation post-GFD	Only in specialist setting or if gluten challenge refused

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Take Home Points of Discussion

Screen Universally!

- Untreated CD has consequences like poor weight gain, anemia, osteoporosis, decreased quality of life
- 31-48% of children with Ds are asymptomatic at diagnosis and will be missed
- Communication challenges limit symptom recognition
- Other high risk groups (first degree relatives, type 1 DM, etc) are routinely screened

Screen Symptomatically!

- Limited cost effectiveness of universal screening
- Symptoms such as poor weight gain, anemia, behavioral changes should trigger screening
- Long-term risks of solid organ tumors (such as small intestinal lymphomas) are lower in Ds
- Gluten-free diet is restrictive on palates that are often already selective

Take Home Points of Agreement

- People with Ds have a much higher risk of celiac disease
- Universal screening will increase diagnosis rate
- tTG IgA + total IgA are first line tests
- Screening should not be done until gluten introduction to diet
- Repeat testing will identify people who were previously screened negative
- Life-long gluten-free diet is the treatment for celiac disease
- HLA-DQ2/DQ8 can help when negative and reduce need for other serologic monitoring

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Chapter 3

Elijah is now 14 years old and has returned to Pittsburgh (because nobody every leaves Pittsburgh forever). Over the past few months, Elijah has seemed stiffer in the mornings and has been slower to get going after sitting for long periods. He has also become less interested in his favorite activities. His teacher has noted a decline in his participation at school. On exam, you find that Elijah has limited range of motion in several joints and swelling with warmth over those joints. You refer him to pediatric rheumatology. Elijah's parents wonder if there were screening labs or tests that could have been done to diagnose this earlier.

American Journal of Medical Genetics Part A

WILEY

AMERICAN JOURNAL OF medical genetics PART A

ORIGINAL ARTICLE

The Detection of Down Syndrome Arthritis in Clinical Practice: A Multicenter, International Pilot and Feasibility Study of a Down Syndrome-Specific Musculoskeletal Screening Tool

Jordan T. Jones[1,2,3] | Nasreen Talib[1] | Emily Cramer[1] | Diletta Valentini[4] | Nicole Baumer[5] | Sabrina Sargado[6] | Nicolas M. Oreskovic[7,8] | Stephanie L. Santoro[7,8] | Kavita Krell[7,8] | Jonathan D. Santoro[9,10] | Kishore Vellody[11] | Andrew McCormick[11] | Catherine Franklin[12,13] | Priya Kishnani[14] | Sarah Hart[14] | Gail Spiridigliozzi[15] | Jacqueline Kitchen[1] | Brian G. Skotko[7,8]

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Background

- Down Syndrome-Associated Arthritis (DA) is an inflammatory arthritis related to immune dysregulation
  - Prior small studies show 1% prevalence in Ds
- More common and different clinical profile that juvenile idiopathic arthritis (JIA)
- Difficult to diagnose due to no defining lab findings and overlap of symptoms with other Ds related conditions (hypotonia, laxity)
- No AAP guideline advice on diagnosis of DA

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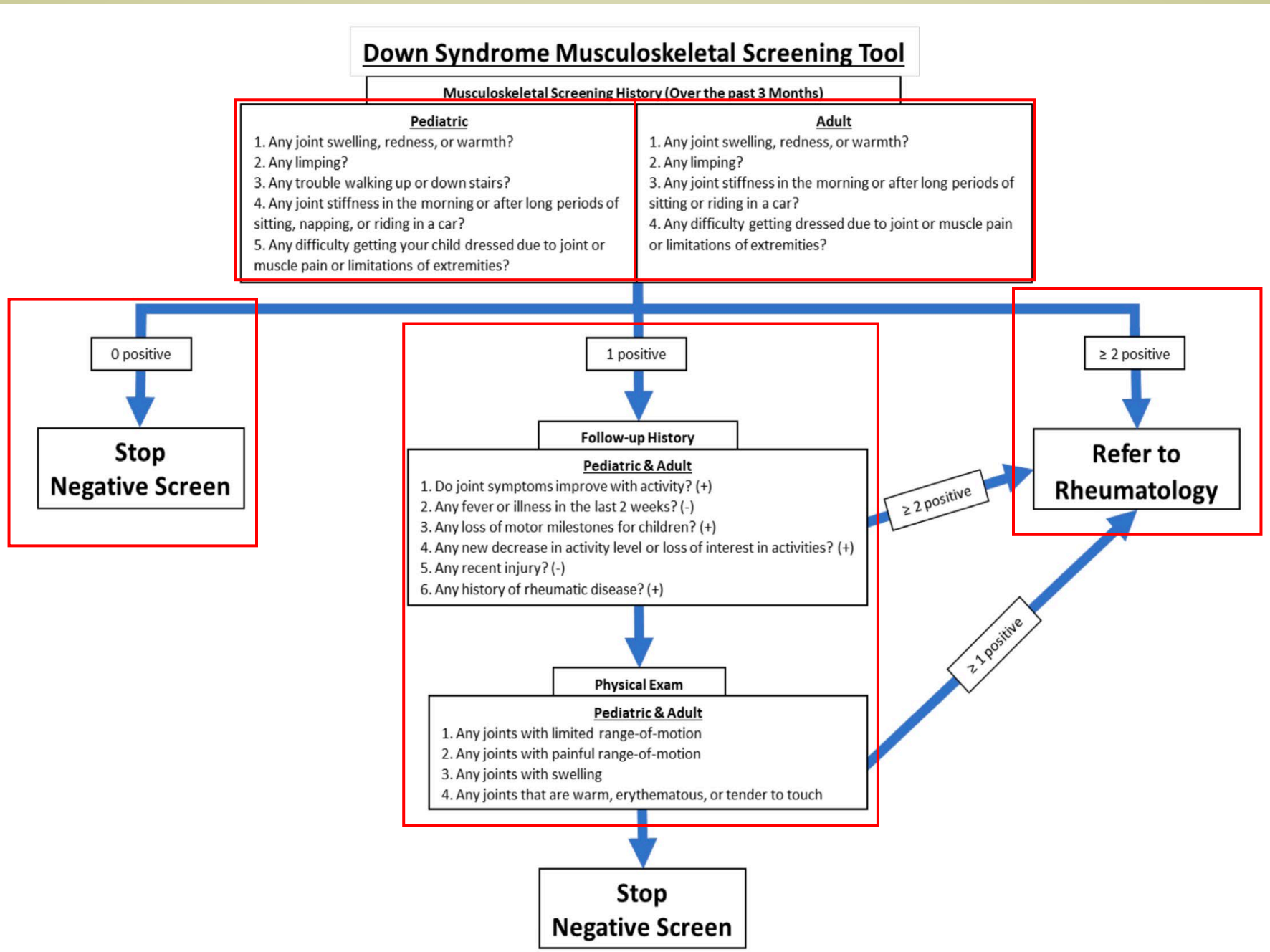

FIGURE 1 | Musculoskeletal screening tool.

TABLE 2 | Positive screen and diagnosis rate[c] of Down syndrome-associated arthritis.

Site	*n*	Positive screen rate, *n* (%)	Diagnosis rate, *n* (%)
University of Queensland	12	3 (25.0%)	1 (33.3%)
Bambino Gesù Children's Hospital	427	16 (3.8%)	2 (12.5%)
Boston Children's Hospital[a]	306	7 (2.3%)	1 (14.2%)
Children's Hospital Los Angeles	107	24 (22.4%)	16 (66.7%)
Children's Mercy Kansas City	76	2 (2.6%)	1 (50.0%)
Duke University Medical Center	8	1 (12.5%)	0 (0%)
Massachusetts General Hospital[b]	115	9 (7.8%)	0 (0.0%)
Children's Hospital of Pittsburgh	60	0 (0.0%)	0 (0.0%)
Total	1111	62 (5.6%)	21 (33.9%)

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Take Home Points

- DA may have a higher prevalence than previously described
- Average age of diagnosis 13 years old
- Most predictive history
  - Joint stiffness
  - Joint swelling/redness/warmth
- Most predictive exam
  - Painful range of motion
  - Joint swelling
- Total time for history/exam question – 15 minutes (even shorter if only most predictive history and exam are used)

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Chapter 4

16-year-old Elijah has nails that have ridges, especially his big toe. His family is convinced that it is because of nutritional deficiencies from his gluten-free diet. They have looked online to find supplements that could help. They wonder if you have ever seen this before. You mention that nail changes (and a love for 90's boy bands) are very common features in Down syndrome.

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Pediatric Dermatology

WILEY

Pediatric Dermatology

ORIGINAL ARTICLE

Nail Disorders in Children With Down Syndrome: A Multicenter Study

Sezgi Sarikaya Solak[1] | Filiz Cebeci Kahraman[2] | İsa An[3] | Hilal Kaya Erdogan[4] | Selma Emre[5] | Rukiye Yasak[6] | Ilkin Zindanci[7] | Ferdi Ozturk[8] | Sevilay Kilic[9] | Eda Oksum Solak[10] | Sevil Savas Erdogan[11] | Tugba Kontbay Cetin[12] | Kursad Bora Carman[13] | Mehmet Boyraz[14] | Nurullah Celik[15] | Ozlem Akgun Dogan[16,17] | Tugberk Akca[18] | Durmuş Dogan[19] | Ülkü Gül Şiraz[20] | Suna Kilinc[21]

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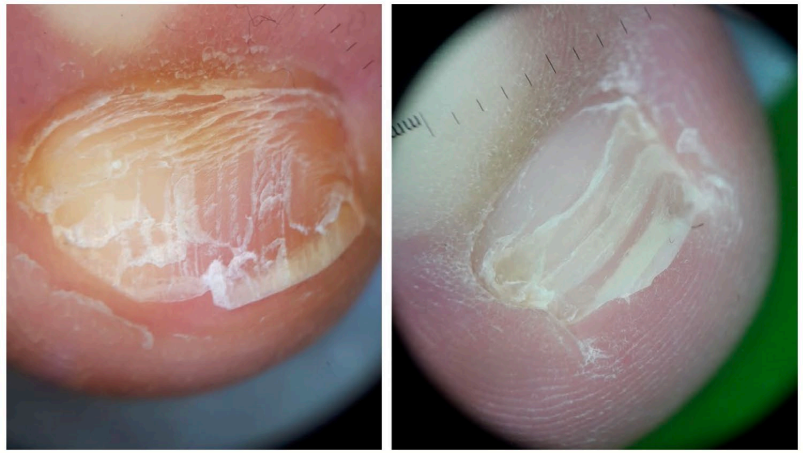

FIGURE 1 | Brittle nail in a child with Down syndrome, demonstrating onychoschizia (horizontal, lamellar splitting of the free nail margin), and Beau's lines (transverse grooves that typically occur due to temporary interruption of nail matrix activity, often associated with infections, trauma, systemic diseases, or certain medications).

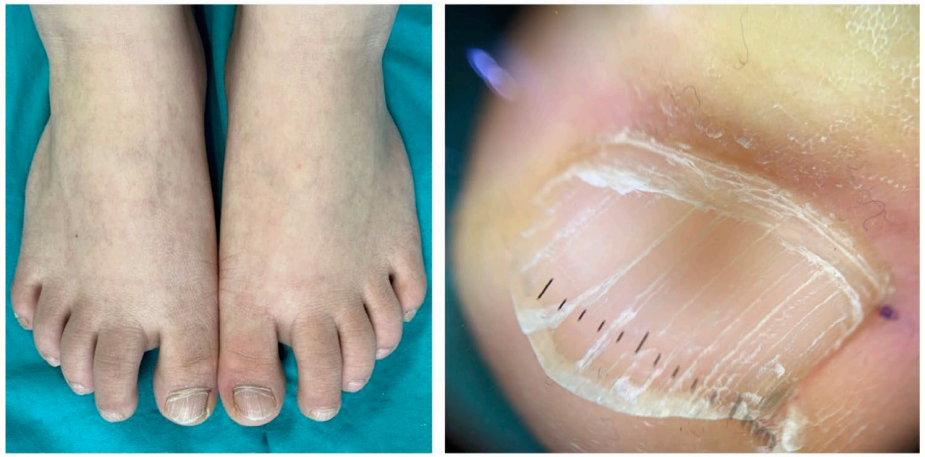

FIGURE 2 | Longitudinal ridging in toenails of a child with Down syndrome.

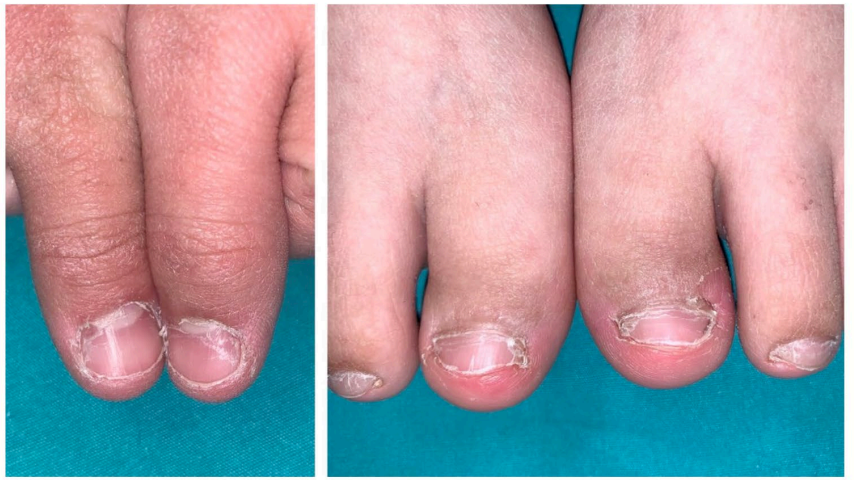

FIGURE 3 | Onychophagia and onychotillomania in fingernails and toenails of a child with Down syndrome (short nail plate with irregular distal nail margins, ragged cuticle, erythema, and periungual skin peeling).

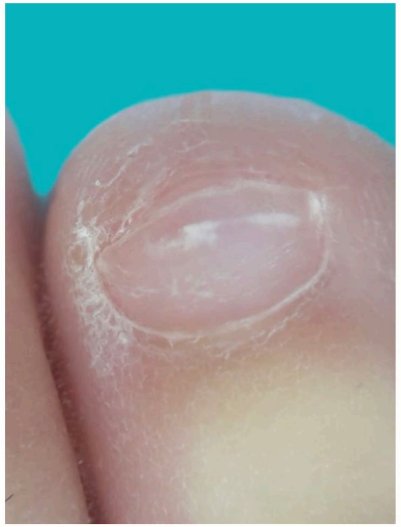

FIGURE 4 | Leukonychia in a toenail of a child with Down syndrome.

TABLE 2 | Characteristics of nail disorders in children with Down syndrome and healthy controls.

	Down syndrome ($n=221$)		Healthy controls ($n=160$)		
	n	**%**	***n***	**%**	***p***
Presence of nail disorder	126	57.0	21	13.1	<0.001*[a]
Localization of nail disorder					
Fingernail	31	24.6	11	52.4	0.03*[b]
Toenail	62	49.2	7	33.3	
Fingernail and toenail	33	26.2	3	14.3	
Types of nail disorders					
Brittle nails	42	19	2	1.3	<0.001[a]*
Beau lines and/or onychomadesis	36	16.3	1	0.6	<0.001[a]*
Longitudinal ridging	28	12.7	2	1.3	<0.001[a]*
Self-induced nail disorders	22	10.0	7	4.4	0.04*[b]
Leukonychia	8	3.6	3	1.9	0.37
Trachyonychia	3	1.4	3	1.9	0.7

TABLE 3 | Multivariate logistic regression analysis of factors associated with nail disorders in children with Down syndrome compared to healthy controls.

Variable	OR (95% CI)	*p*
Presence of nail disorders	3.0 (2.3–3.9)	<0.001
Fingernail involvement (ref: toenail)	0.4 (0.2–0.8)	0.01
Fingernail and toenail involvement (ref: toenail)	1.7 (0.7–4.0)	0.23
Brittle nails	4.3 (2.1–8.7)	<0.001
Beau lines and/or onychomadesis	5.6 (2.1–8.8)	<0.01
Self-induced nail disorders	1.6 (1.0–2.4)	0.05
Longitudinal ridging	3.4 (1.6–7.0)	<0.01
Leukonychia	1.4 (0.7–2.7)	0.32
Trachyonychia	0.8 (0.4–1.9)	0.69

Note: Values are presented as odds ratios (ORs) with 95% confidence intervals.

Chapter 5

Elijah is now 23 years old and has moved on to the boring, beige-walled world of adult medicine. His parents have noticed that he has developed a dramatic decrease in social interactions and loss of ability in dressing, bathing, and eating. You diagnose Down Syndrome Regression Disorder (DSRD) and talk through the treatment options with his family.

Neurol Ther (2026) 15:1099–1120
https://doi.org/10.1007/s40120-026-00906-2

ORIGINAL RESEARCH

A Comparative Effectiveness Study of Lorazepam or IVIg Versus no Treatment for Down Syndrome Regression Disorder

Jonathan D. Santoro · Saba Jafarpour · Panteha Hayati Rezvan · Mellad M. Khoshnood · Benjamin N. Vogel · Lina Nguyen · Lilia Kazerooni · Noemi A. Spinazzi · Nidhiben Anadani · Kristen S. Fisher · Robyn A. Filipink · Melanie A. Manning · Cathy Franklin · Eileen A. Quinn · Michael S. Rafii

Received: December 29, 2025 / Accepted: February 17, 2026 / Published online: March 8, 2026

Study design

Prospective observational cohort (natural history study) N = 212 patients with DSRD 3 groups:

- Lorazepam (n=85)
- IVIg (n=68)
- No therapy (n=59)

Follow-up: **24 weeks**

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Methods

- Not a randomized controlled trial – treatment decision by clinician and caregiver
- No treatment if:
  - Delay in insurance to get therapy
  - Caregiver preference
  - Patient met criteria, but didn't complete the full work up
- Still, no baseline criteria were statistically significant between groups
- Average Symptom onset age 16.3,
- 18.3 for diagnosis,
- 18.8 for initiation of therapy

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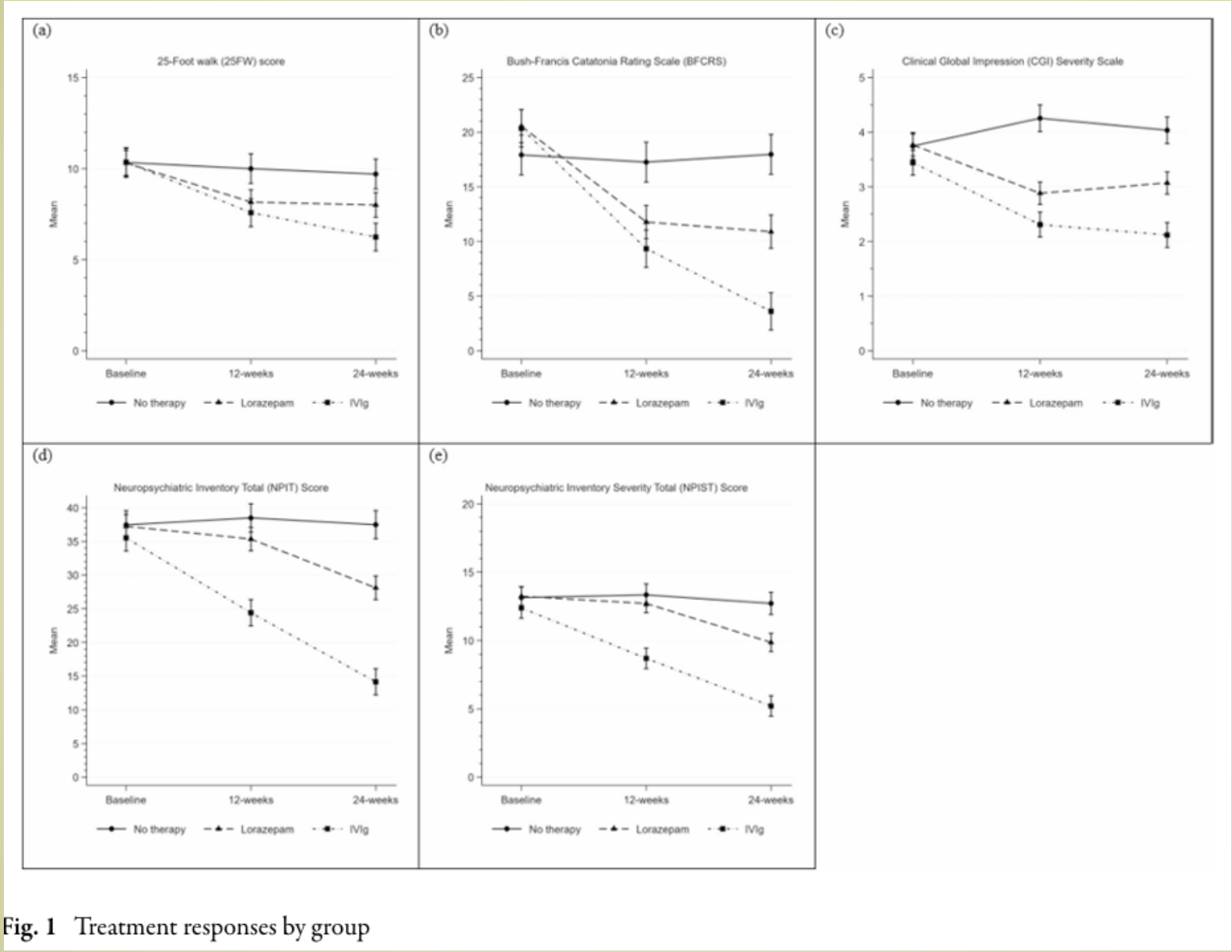
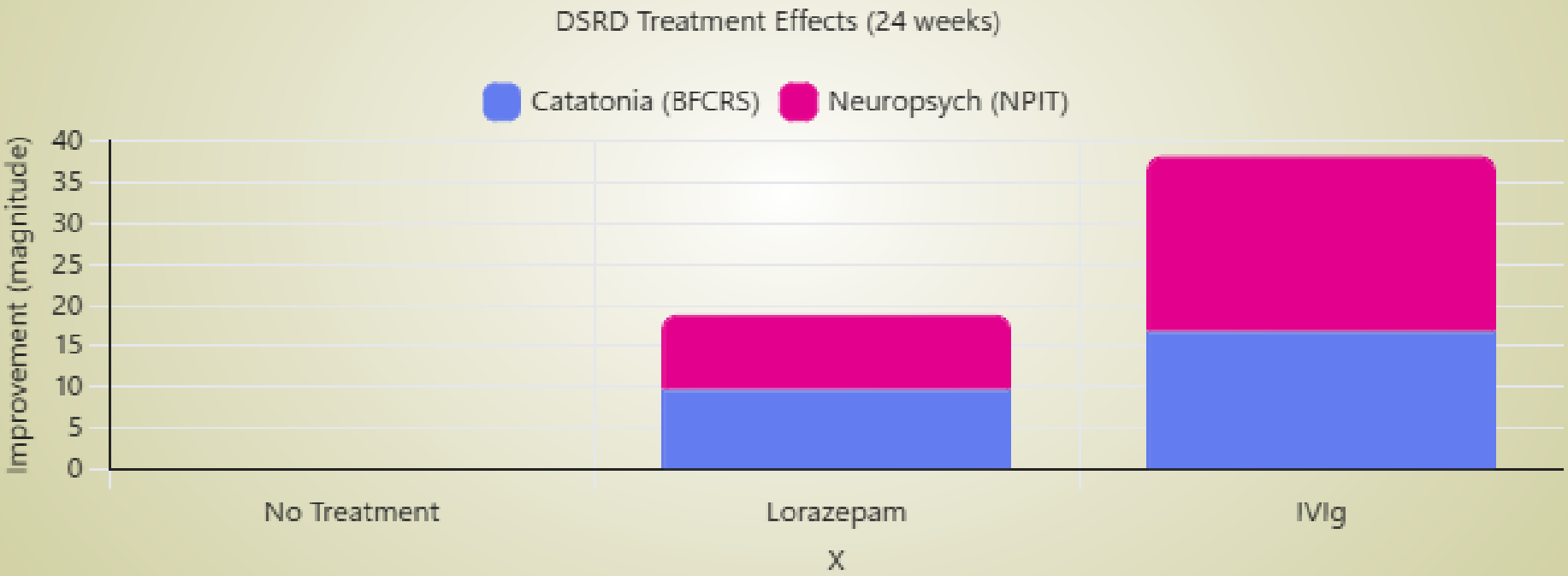


Fig. 1 Treatment responses by group

Results


DSRD Treatment Effects (24 weeks)
Catatonia (BFCRS)
Neuropsych (NPIT)
Improvement (magnitude)
40
35
30
25
20
15
10
5
0
No Treatment
Lorazepam
IVIg
X

Take home

- Both therapies work
- IVIG superior in all scales
- Gives more data to get IVIG coverage for this condition.
- Among those without neurodiagnostic abnormalities, lorazepam showed comparable benefit to IVIG

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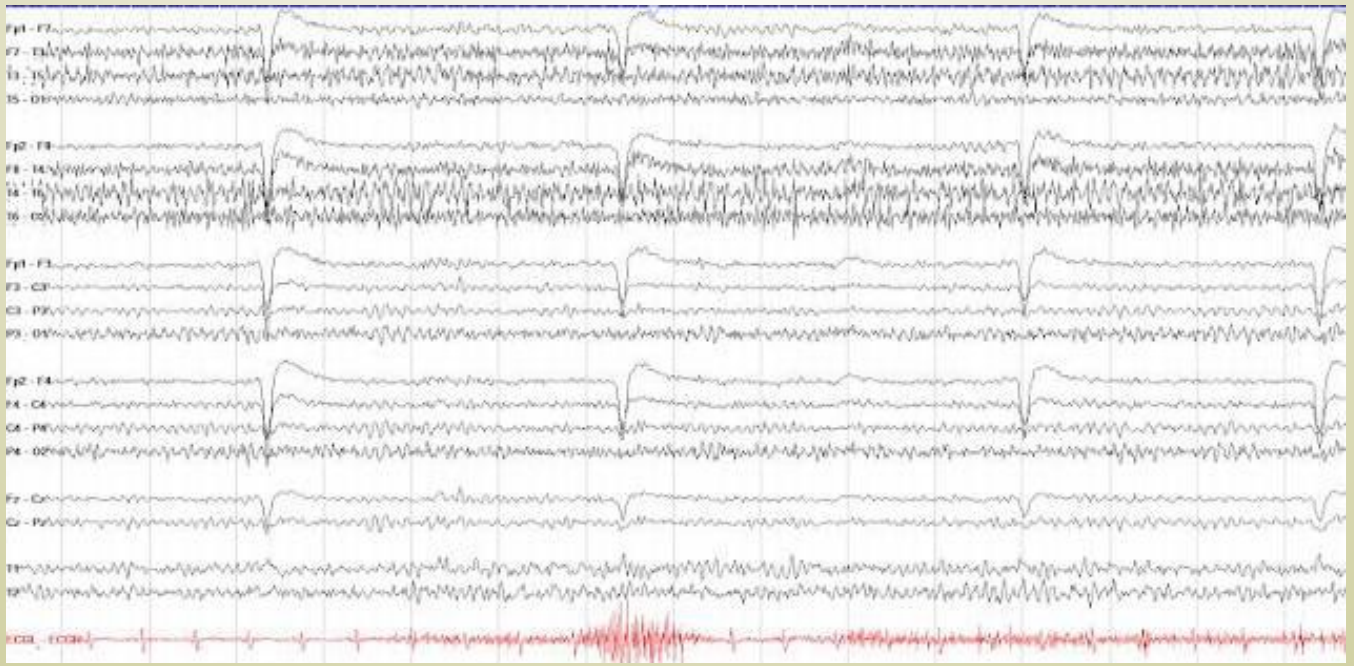
Chapter 6

Elijah's parents are thrilled by his clinical improvement after receiving IVIG. They wonder if there is any role in repeating any of the prior testing to see if those findings have improved.



Annals of Clinical and Translational Neurology

RESEARCH ARTICLE OPEN ACCESS

Electroencephalographic Normalization as a Biomarker of Clinical Recovery in Down Syndrome Regression Disorder

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Received: 15 April 2026 | **Accepted:** 18 May 2026

Background

- EEG is routinely obtained during evaluation, but whether EEG abnormalities represent a dynamic, modifiable marker of disease activity — rather than a static finding — has been unclear.

- Prior work showed EEG is abnormal in ~30–38% of DSRD cases at baseline, but longitudinal EEG data linked to treatment and clinical outcomes were lacking.

Methods

- **Design:** Retrospective longitudinal cohort study from a DSRD database
- **Participants:** 181 individuals with DSRD who had EEG within 2 months of symptom onset plus repeat EEGs at 6 and 12 months after undergoing treatment

- Any normalization of EEGs?.....

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- At baseline 69 (38%) had an abnormal EEG

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EEG ABNORMALITY TYPES OVER TIME

Abnormality Type	Baseline (n=69)	6 Months (n=37)	12 Months (n=30)
Diffuse slowing	82.6%	100%	100%
Focal slowing	13.0%	0%	0%
Diffuse epileptiform	2.9%	0%	0%
Focal epileptiform	1.4%	0%	0%

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How much of this was due to the IVIG group?

- 89%!

- Among participants with abnormal baseline EEG, normalization at 6 months occurred in 32/36 (88.9%) with immunotherapy versus 2/33 (6.1%) without immunotherapy

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- Non-immunotherapy treatments may address symptoms without modifying the underlying encephalopathic process.

- EEG normalization was associated with greater improvement in clinical severity.

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Chapter 7

You are seeing 35-year-old Elijah in clinic, and the EMR pops up a warning that he is due for his Tdap vaccine. As an internist, you have to Google what the EMR means by the term “vaccine.” In the process of doing this search, you discover that there may be benefit in Tdap immunization beyond only preventing illness.

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Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

Tetanus, diphtheria and pertussis vaccination and risk for incident dementia among adults with down syndrome

Kimberly Schiel [a,*], Joanne Salas [b,c], Anjani Urban [a], Daniel F. Hoft [d,e], Jeffrey F. Scherrer [a,b,f]

Background

- Adults with Down syndrome are at a high risk for Alzheimer's type dementia
- Studies in those without Down syndrome suggest that multiple vaccines (flu, zoster, Tdap) are associated with a lower risk of dementia
- There are no prior studies in adults with Down syndrome

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Design

Retrospective cohort review of 74,827 people with DS (American)

- 5,591 adults with Down syndrome over age 40 without a diagnosis of dementia, regular health care users
- Followed for 5-10 years (median 67 months)
- 9.5% had documented Tdap in adulthood.
- How many developed dementia?

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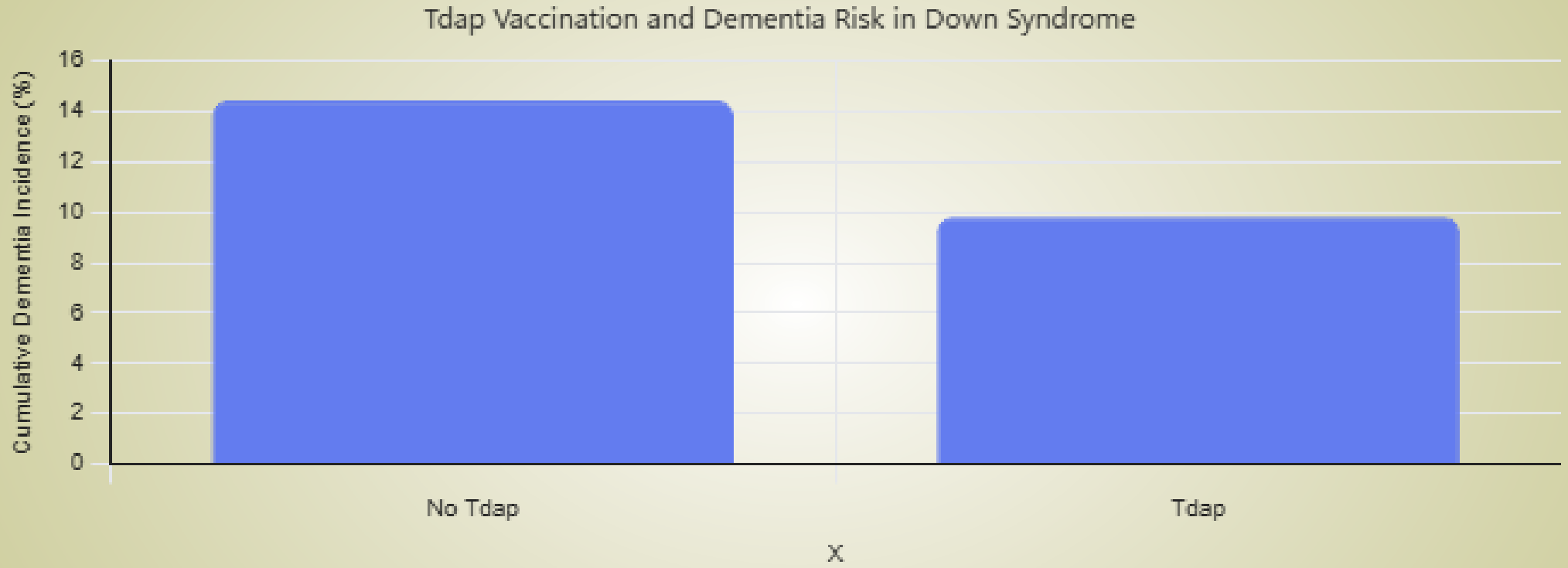
Results


Tdap Vaccination and Dementia Risk in Down Syndrome
Cumulative Dementia Incidence (%)
16
14
12
10
8
6
4
2
0
No Tdap
Tdap
X

- No Tdap 14.4%
- Tdap 9.8%
- Adjusted risk: HR 0.74
- 26% relative risk reduction

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Take home points

- First evidence linking vaccination to lower dementia risk
- 26% is a clinically meaningful reduction
- Builds on the signal that immune modulation/inflammation may influence neurodegeneration

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Chapter 8

53-year-old Elijah is starting to get more forgetful, including things that have been lifelong routines for him. While he still knows all the lyrics to every *NSYNC song, you think he may be developing Alzheimer disease. You head to your secret underground lab and ponder any lab tests that could help support an AD diagnosis.

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Prediction of amyloid and tau brain deposition and cognitive decline in people with Down syndrome using plasma biomarkers: a longitudinal cohort study

Shorena Janelidze*, Lyduine E Collij*, Niklas Mattsson-Carlgren, Alex Antill, Charles M Laymon, Ira Lott, H Diana Rosas, Davneet S Minhas, Weiquan Luo, Shahid Zaman, the Alzheimer's Biomarker Consortium–Down Syndrome investigators†, Mark Mapstone, Elizabeth Head, Florence Lai, Sigan L Hartley, Beau M Ances, Sharon J Krinsky-McHale, Joseph H Lee, Rik Ossenkoppele, Bradley T Christian, Benjamin L Handen, Oskar Hansson

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Background

- Plasma biomarkers are in use in people without Down syndrome
- This group aimed to identify the biomarkers that most accurately predict longitudinal changes in Alzheimer's disease related pathology and cognitive functioning in individuals with Down syndrome.
- First longitudinal study of adults with Down syndrome comprehensively assessing the potential of the most promising plasma Alzheimer’s disease biomarkers (p-tau217, GFAP, NfL, total tau, amyloid β)

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- Analyzed data collected at seven university sites in the USA and UK. This study included 258 adults (aged ≥25 years) with Down syndrome who were followed up prospectively every 16 months as part of the Alzheimer Biomarker Consortium-Down Syndrome (ABC-DS) study

- The study followed adults with Down syndrome for up to 4.7 years and compared five plasma biomarkers (p-tau217, GFAP, NfL, total tau, Aβ42/40).

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Results

- Baseline and longitudinal plasma p-tau217 were associated with subsequent decline in global cognition, and progression to dementia

- **Plasma p-tau217 was the only standalone biomarker** that independently predicted future cognitive decline, progression to dementia, and longitudinal tau accumulation — no other biomarker added meaningful prognostic value when combined with p-tau217

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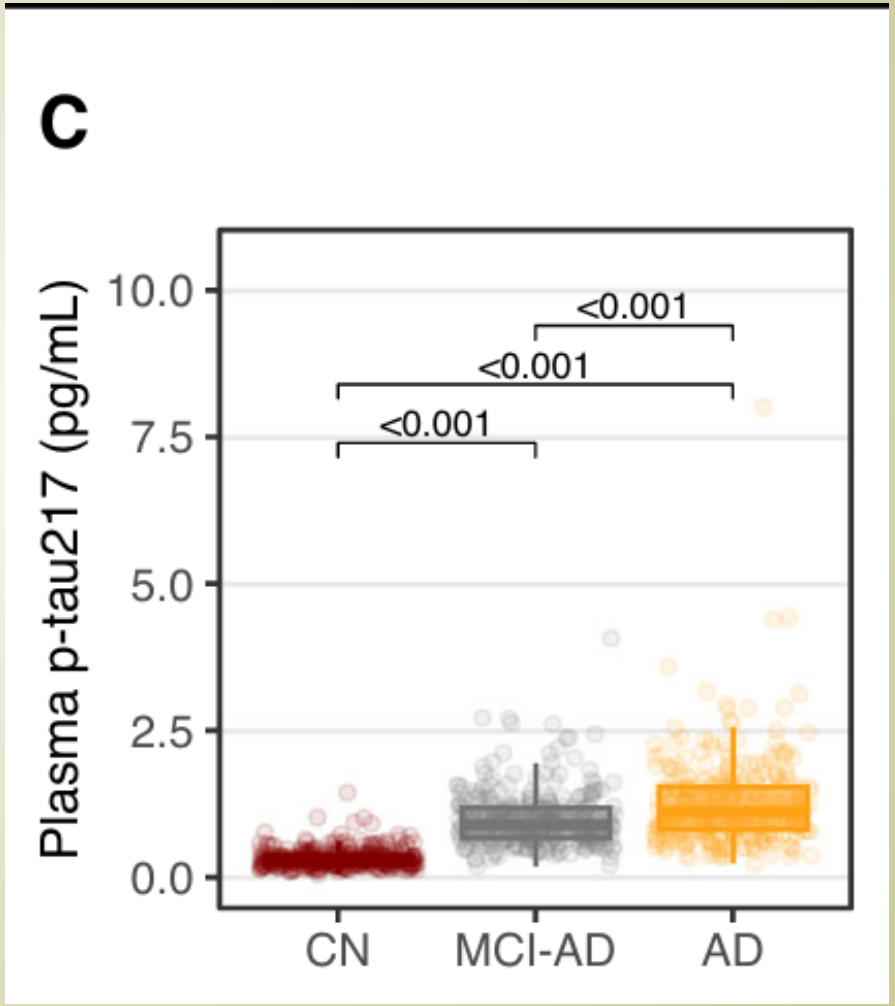
- For Down syndrome, p-tau217 shows comparably excellent diagnostic accuracy (AUC 0.95–0.96), but **population-specific cutoffs, age-adjusted reference ranges validated in this population are still needed**

Plasma p-tau217- can it be used in adult with Down syndrome?

- A result in the **positive zone** in a patient with Down syndrome who has clinical cognitive decline is highly suggestive of AD pathology, given the very high prior probability in this population.
- A result in the **negative zone** in a younger adult with Down syndrome (<35–40 years) is reassuring but does not exclude early preclinical pathology.
- **Do not use the test result alone to diagnose dementia** — it detects AD pathology, not the clinical syndrome of dementia, which still requires clinical assessment of functional and cognitive decline.



nature medicine

Article

https://doi.org/10.1038/s41591-025-04080-0

A minimally invasive dried blood spot biomarker test for the detection of Alzheimer's disease pathology

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Chapter 9

As you are humming the song “Bye Bye Bye” while wrapping up your visit with Elijah, your EMR pops up a message that your next patient has arrived. Zoe is a young woman with Down syndrome who has been medically well but, as a huge fan of former Steelers safety Troy Polamalu, she becomes particularly nervous around bald people, causing her to pick compulsively at her fingernails.

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JOURNAL ARTICLE

Skin picking in Down syndrome: a patient speaks out

Zoe Epstein, Lisa Epstein, Jillian Rork, John Koo, Allison Kranyak ✉ Author Notes

British Journal of Dermatology, Volume 193, Issue 5, November 2025, Pages 998–999,
https://doi.org/10.1093/bjd/ljaf264

Published: 07 July 2025 **Article history** ▾

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- **Zoe** — a young woman with Down syndrome who uses skin picking as coping mechanism or to give her hands something to do when she is bored.
- She shares her experience and **what she wishes doctors knew** when treating patients with Down syndrome

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In Zoe's own words

- I do not believe that DS has anything to do with skin picking, I think it has more to do with increasing anxiety over what I cannot control and doing it subconsciously- without me realizing it.
- I wish doctors would understand that I am not trying to hurt myself by picking at my skin, but trying to do what I can in stressful situations – ones I have no control over.

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Epilogue

You are attending the world's greatest Down Syndrome Medical Conference. You have a question or comment about something you've just heard, and you boldly raise your hand for the microphone to ask …