Extra-Axial Cerebrospinal Fluid as a Potential Biomarker in Infants Who Develop ASD and Insights into the Role of Early Behavior

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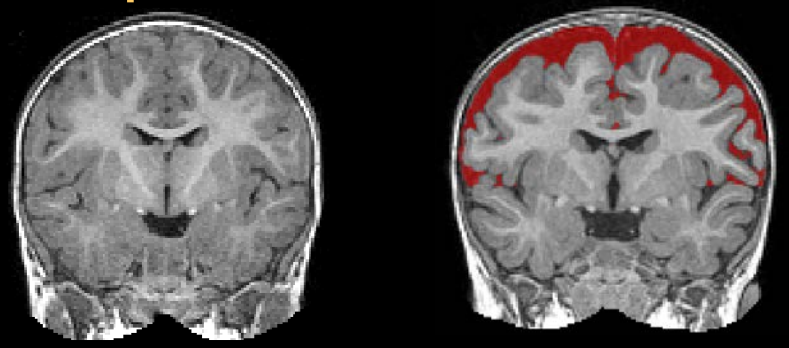
IACC Meeting
April 26, 2017

Initial Report of Extra-Axial CSF



- 2013: Published ini1al finding at UC Davis MIND Ins1tute

BRAIN
A JOURNAL OF NEUROLOGY

Early brain enlargement and elevated extra-axial fluid in infants who develop autism spectrum disorder

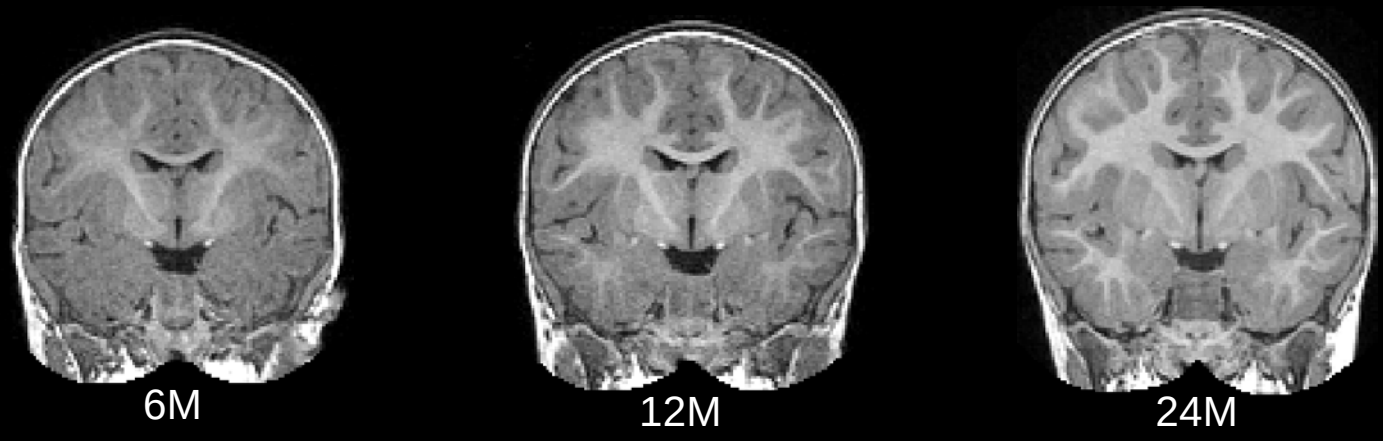
Mark D. Shen,[1] Christine W. Nordahl,[1] Gregory S. Young,[1] Sandra L. Wootton-Gorges,[2] Aaron Lee,[1] Sarah E. Liston,[1] Kayla R. Harrington,[1] Sally Ozonoff[1] and David G. Amaral[1]

- Total sample: **N=55 (ASD=10)**

Shen et al., 2013

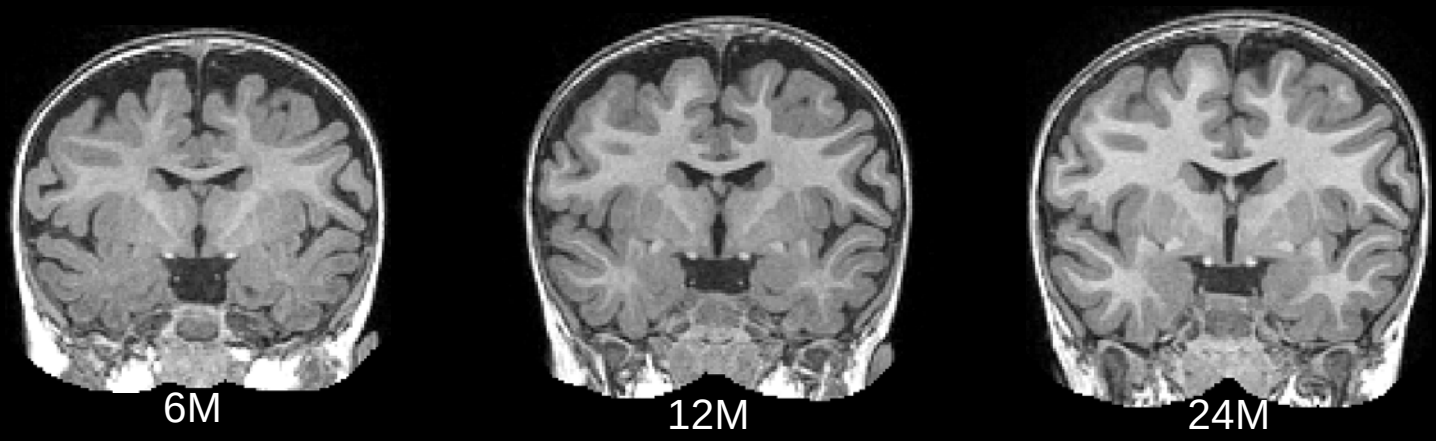
Extra-Axial CSF from 6-24 months

Low-Risk Infant with Normal MRI; ASD-negative



6M 12M 24M

High-Risk Infant with Increased Extra-Axial CSF; Diagnosed with ASD



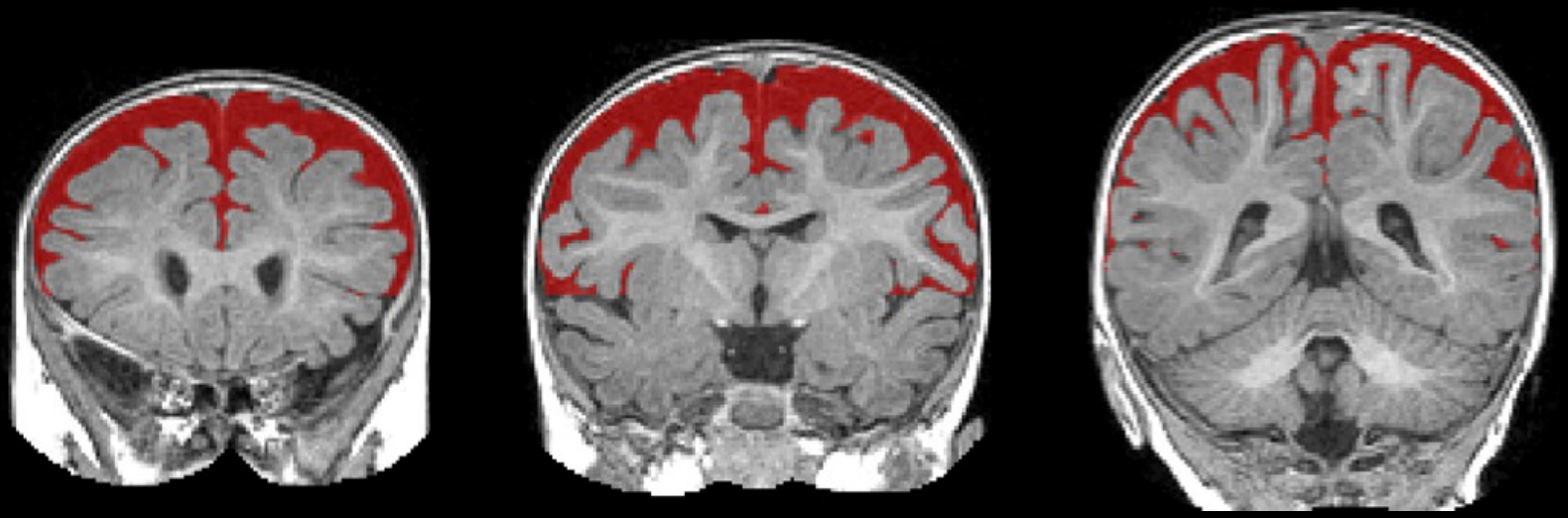
6M 12M 24M

(Shen et al., 2013, Brain)

Infant Brain Imaging Study (IBIS) Network

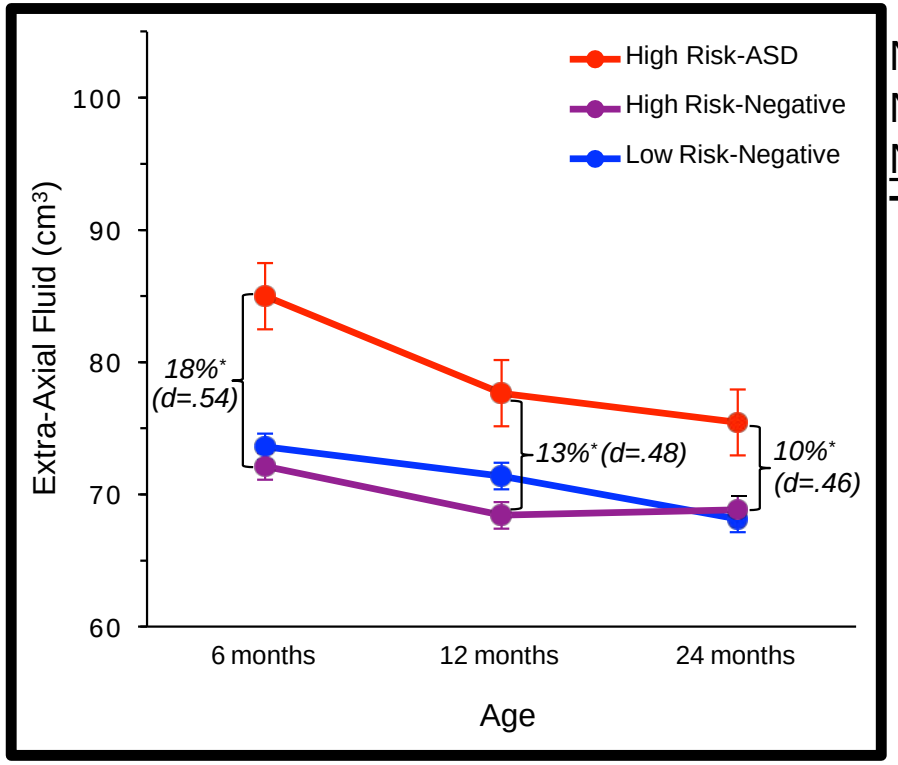
- MRI Scans at 6, 12, 24 months; Diagnosis at 24M
- 4 clinical data collec1on sites
- **N=343 infants** (804 total scans)

Automatic Segmentation of Extra-Axial CSF:



(Shen et al., 2017, Biol Psych)

HR infants later diagnosed with ASD had increased Extra-Axial CSF by 6 months, persistently elevated through 24 months



N=47
N=174
N=122
Tot = 343

%diff vs. HR-negaBve (Cohen's d effect size)

Covariates: Age, Sex, Site, Total Cerebral Volume

**p<0.005 vs. LR-neg, HR-neg*

(Shen et al., 2017, Biol Psych)

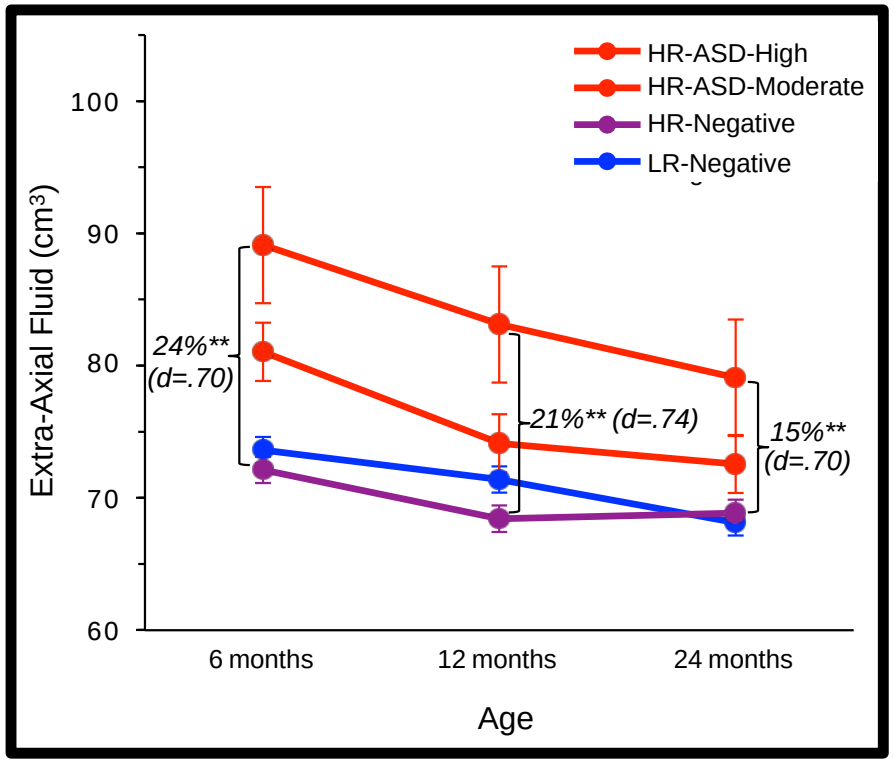
Large ASD group (n=47)

…

Examine subgroups based on symptom severity

(Gotham & Lord, 2007)

More pronounced increase of Extra-axial CSF in more severe ASD subgroup



N=23
N=24
N=174
N=122
Tot = 343

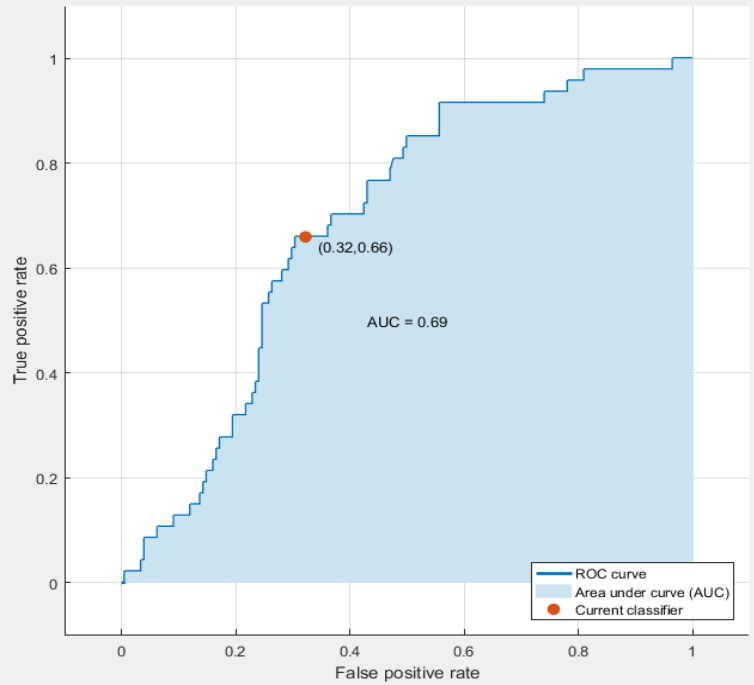
Covariates: Age, Sex, Site, Total Cerebral Volume

***p<0.05 vs. all other groups*

(Shen et al., 2017, Biol Psych)

Extra-axial CSF as a single brain measure at 6 months has modest prediction accuracy of ASD diagnosis at 24 months

25-fold cross-validation
Logistic regression (ROC curve)



IBIS 2017 sample:
- Overall accuracy =69%
- Sensitivity at 6 months = 66%
- Specificity at 6 months = 68%

Externally validated in MIND 2013 sample:
- Overall accuracy = 72%
- Sensitivity at 6 months = 80%
- Specificity at 6 months = 67%

1. Observable, reliable brain anomaly
2. Detectable w/ any structural MRI
3. Replication is rare

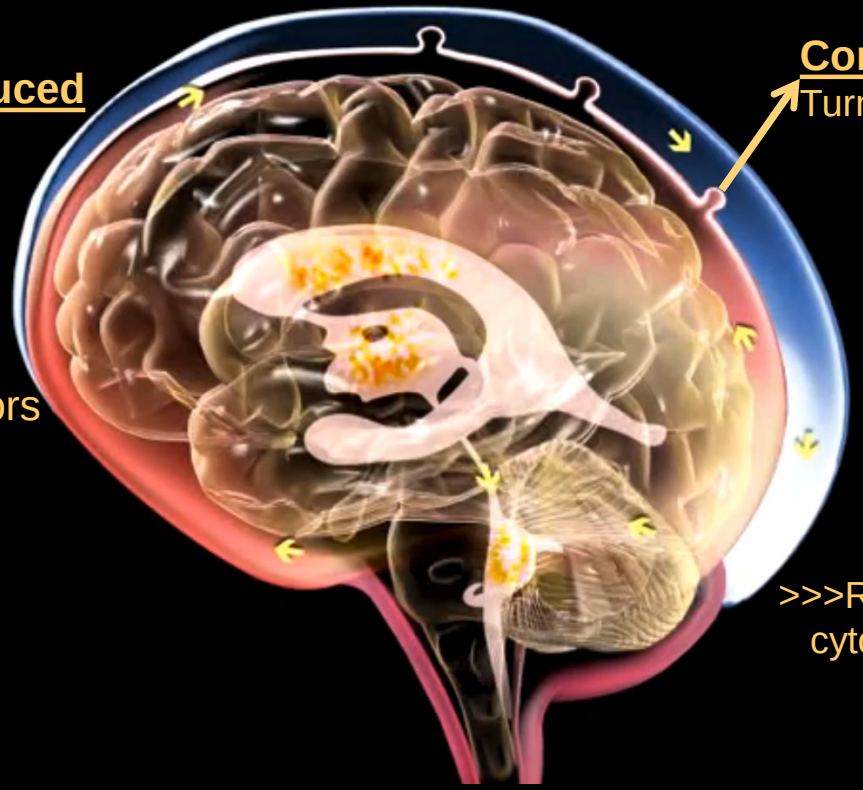
(Shen et al., 2017, Biol Psych)

CSF: Filtration System of Brain

Xie, 2013 (Science)
Iliff, 2012 (Science Transl Med)
Louveau, 2015 (Nature)

Continuously produced

Delivers growth factors
>>>developing brain



Continuously absorbed
Turns over every 6 hours

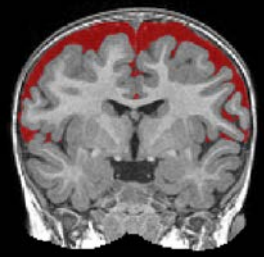
>>>Removes inflammatory cytokines, metabolites (Aβ)

Neuroinflammation?

Cytokine accumulation?

4/26/2017
video: medical-animations.com

Current follow-up studies
(unpublished)



1) ***What is the specificity?***
   - Is it present in monogenic subtypes of ASD?
     Or in other neurodevelopmental disorders?

2) ***What is the pathogenic mechanism?***
   - **Using mouse models to test hypothesized mechanism of neuroinflammation**

3) ***Are there genetic variants associated with extra-axial CSF?***
   - DNA in family quads (infant, parents, older ASD sibling)
   - Genome-wide SNP genotyping, Whole-exome sequencing, Polygenic risk scores

4) ***Combined with other brain/behavioral measures to improve prediction?***

(Collaborators: David Amaral, Joseph Buxbaum, Dani Fallin, Patrick Sullivan, John Gilmore, Ben Philpot)

Integrating behavior & early language environment

(Meghan Swanson et al., 2017)

Brain development doesn't occur in avacuum

LENArecorder = "Language Pedometer"

-Whole-day recordings @ 9 months
-NaturalisBc, home environment

Automated detection of “Hyper-vocalizers”

CHILD DEVELOPMENT

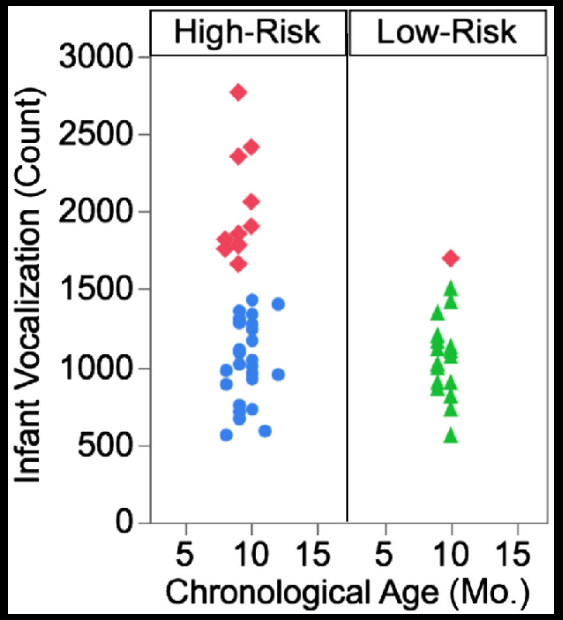
Child Development, xxxx 2017, Volume 00, Number 0, Pages 1–14

Naturalistic Language Recordings Reveal “Hypervocal” Infants at High Familial Risk for Autism

Meghan R. Swanson

University of North Carolina at Chapel Hill

Meghan Swanson
Postdoc (K99/R00)



- **20% of HR infants were “hyper-vocal” at 9 mos.**
  - Parents of high- and low-risk infants provided equally rich language environments
- Hyper-vocalizers had lower social babbling (AOSI)
  - **Early stereotyped behavior?**
- **To be continued… 24 month diagnosis?**

Example of the added value of behavior:

Hyper-vocalizaBon as an early marker for heterogeneous outcomes?

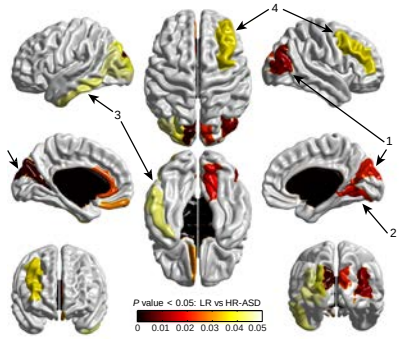
Meghan Swanson
Postdoc (K99/R00)

- Moving beyond dichotomous outcomes (ASD, not ASD) to understanding an early trajectory of heterogeneous outcomes
  - More/less social, language delay

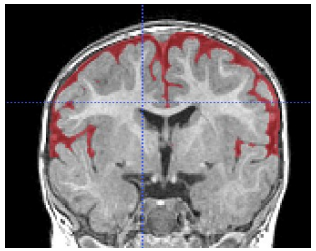
- Benefits:
- Scalable, high-throughput, quantifiable, and objective
  - Attributes that are critical for a potential early marker

- Cost-effective:
  - Easily implemented by sending recorders in mail
  - Data is automated

Mul1-dimensional Approach to Early Markers of Au1sm

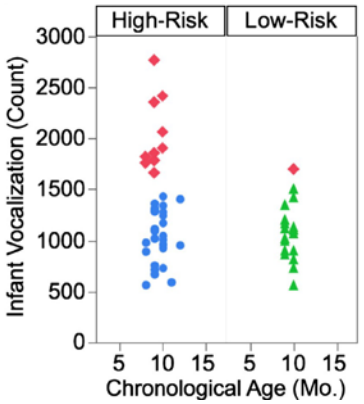


Brain surface area/volume:
increased proliferaBon of progenitor cells

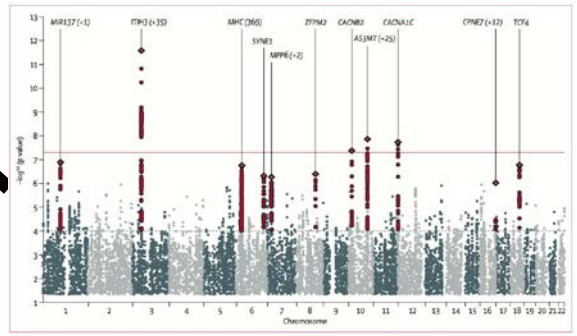


Extra-axial CSF
AccumulaBon of inflammatory cytokines

1. Improve predicCon in infancy
2. Develop personalized treatments



Early language/ psychological environment



Molecular gene1cs

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IBIS Network

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Rebecca Knickmeyer

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