The Stories Behind the Spots: Successes and Struggles of Universal Newborn Screening for Congenital Cytomegalovirus

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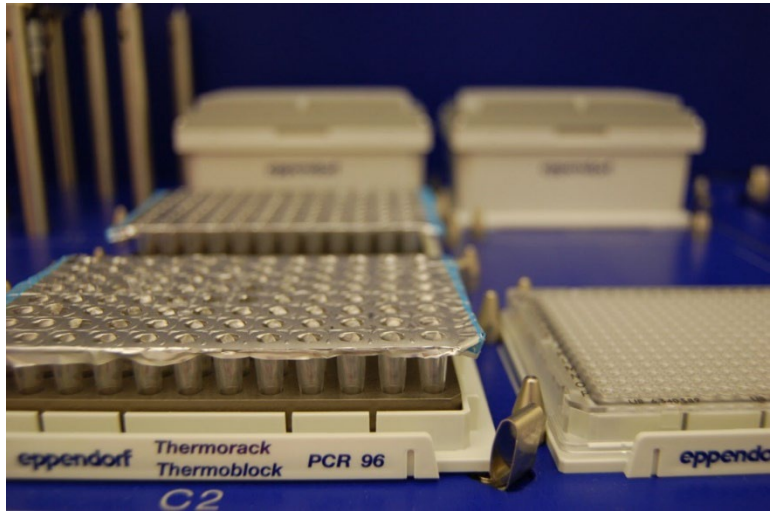
Overview of Newborn Screening

CMV Screening

- Performed via qualitative real-time PCR
- Assay detects CMV DNA extracted from 2 dried blood spot punches
- Results that flag are tested in triplicate
- Final result typically available around 3 days of age and sent to follow-up team for call-out



CMV Follow-up – Notification

- Abnormal result notifications made to primary care clinic/provider, midwife, or NICU if baby is admitted
- Provide “just-in-time” education
- Recommend urine CMV PCR for confirmation by 21 days of age
- Fax screening report, informational fact sheets for both provider and the family, and contact list for infectious disease specialists

CMV Follow-up – Recommended Evals for Confirmed Cases

Laboratory testing: liver function tests (AST/ALT) and complete blood count (CBC) with differential

Pediatric diagnostic audiologic evaluation (even if baby passed their newborn hearing screen) with continued regular audiologic monitoring

Pediatric ophthalmology examination; follow-up as recommended

Cranial ultrasound; a brain MRI may be recommended to clarify nonspecific findings

Developmental assessments and referral to Early Intervention

Stories behind the spots…

Value of CMV Newborn Screening

Story #1

- 39-week gestation, 2830g, female
- Notification on DOL 5
- Urine CMV PCR on DOL 5 = CMV detected
- Physical exam was normal at birth and at initial well child visit.
- Only intrauterine growth restriction; maternal factors could have also been a cause
- CMV infection could have been missed

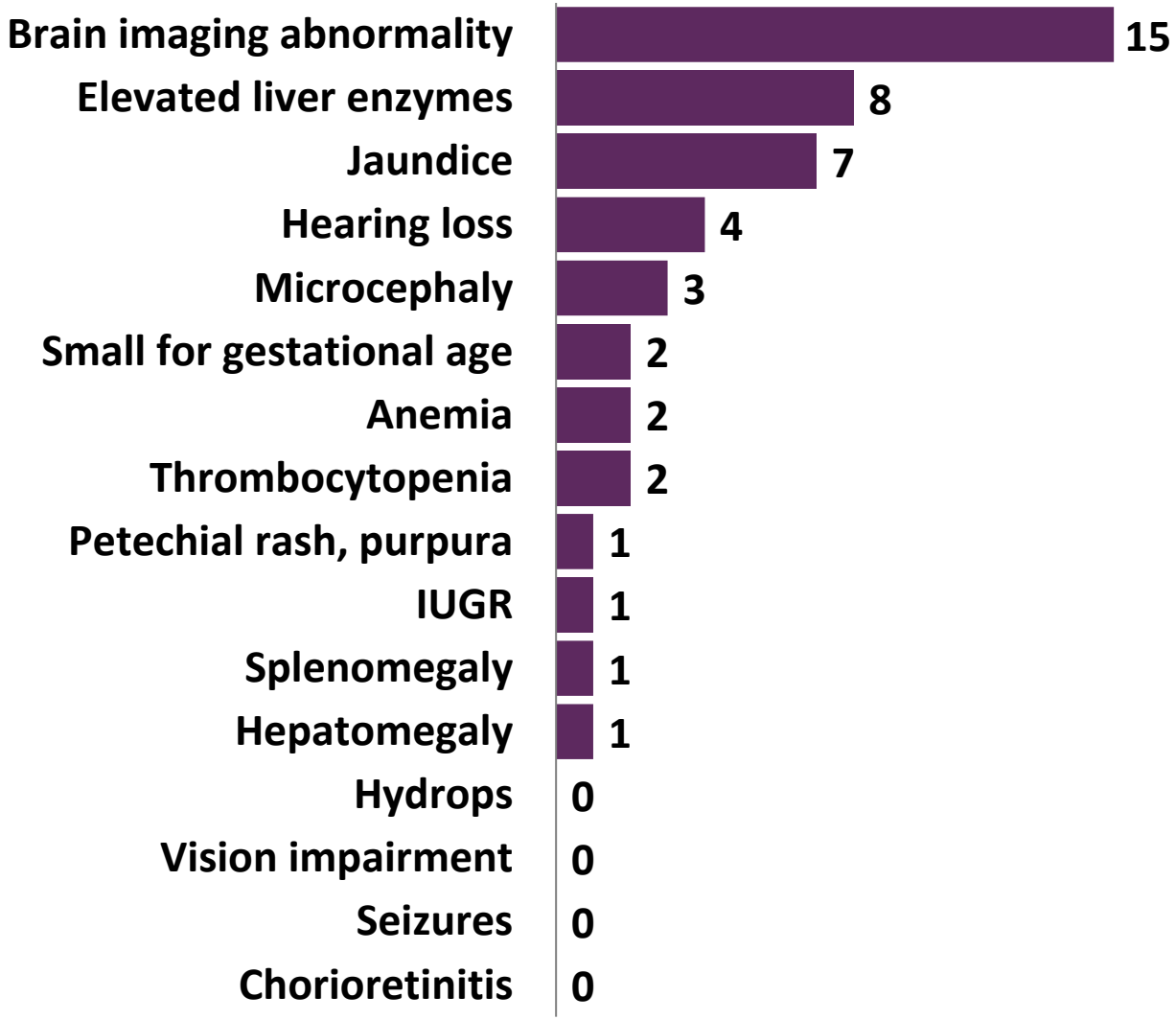
Story #2

- 33-week gestation, 1620, male
- Baby was jaundiced and anemic
- Baby had multiple other health concerns at birth that would not have necessarily indicated cCMV involvement
- Maternal TORCH panel after birth indicated CMV IgG (negative for everything else)
- Despite symptoms (albeit non-specific) of cCMV, baby was not tested and would have been missed if it weren't for newborn screening

Story #3

- 36-week gestation, 3470, female
- In NICU for apnea and episodes of bradycardia
- Notification on DOL 10
- Urine CMV PCR on DOL 10 = CMV detected
- Physical exam was normal, no anemia, no elevated transaminases
- Audiology exam (DOL 24): non-permanent conductive hearing loss
- Head U/S and MRI (DOL 39): calcifications, cysts, vasculopathy
- ID consulted (DOL 39) and valganciclovir started
- Ophthalmology exam (DOL 42) within normal limits
- Had this baby not been screened, the brain findings may not have been found, which could have delayed treatment

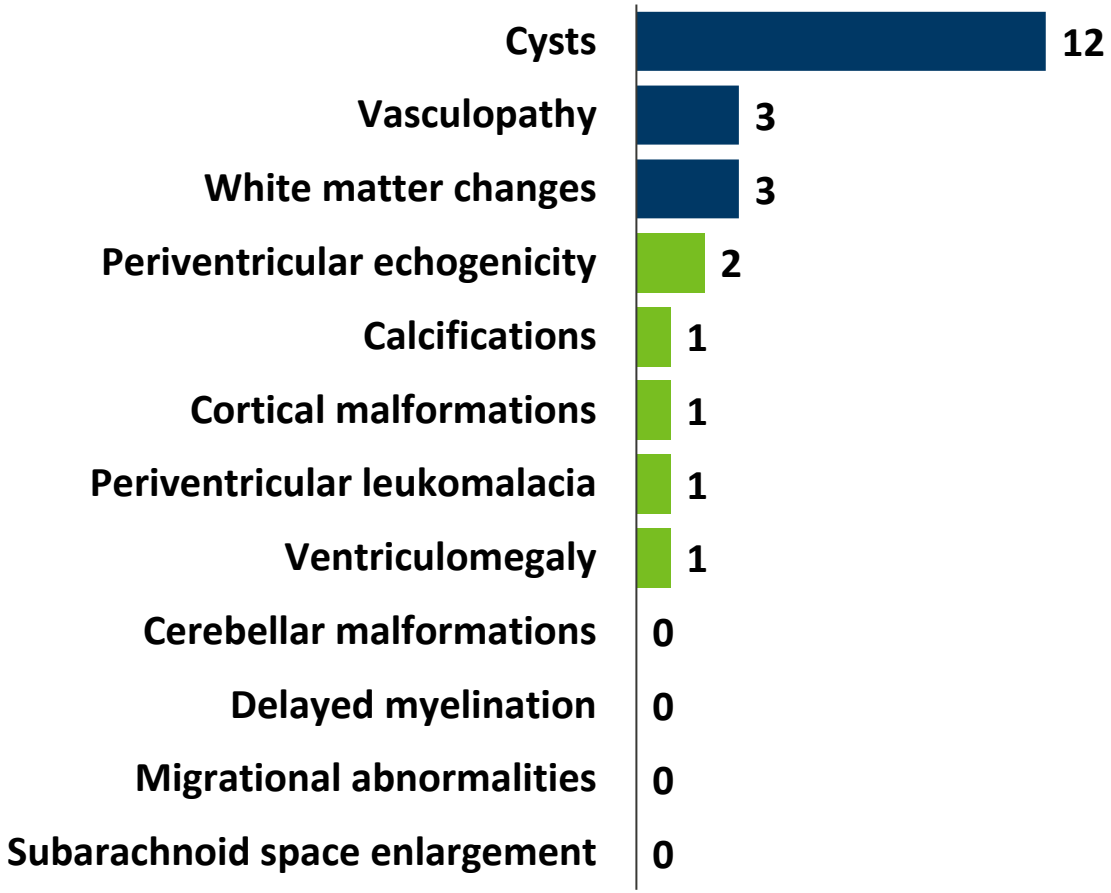
cCMV Symptom Distribution



- A total of 23 infants with cCMV have clinical findings that may be related to their infection
- Of the 15 with brain imaging abnormalities:
  - 8 (53%) have no other signs/symptoms noted
  - Only 4 babies have brain abnormalities known to be consistent with cCMV the remaining are of unknown clinical relevance

Cranial Imaging Findings

Ultrasound findings among infants with no other signs/symptoms



- Among infants with cCMV that have brain imaging abnormalities, cysts were the most commonly noted abnormality (12, 92%).

Factors Impacting Follow-up

Story #4

- Baby's parent's native language is K'iche
- Translator was unavailable for this language, however an older daughter speaks Spanish and K'iche, so CMV information was translated from English to Spanish (provider → translator →daughter), then Spanish to K'iche (daughter →parent)
- Urine sample, eye and hearing exams completed same day, however head ultrasound was not completed due to time constraints and transportation
- Barriers (whether language, transportation, coverage, etc) will impact follow-up and may be more exaggerated with CMV follow-up due to the sheer number and frequency of evaluations recommended

Evaluation Completion

Audiology	Ophthalmology	Head Ultrasound	Number (%)
✓	✓	✓	53 (72%)
✓	✓	✗	2 (3%)
✓	✗	✗	2 (3%)
✓	✗	✓	7 (9%)
✗	✓	✓	3 (4%)
✗	✗	✓	4 (5%)
✗	✗	✗	3 (4%)

Total Incomplete	**10 (14%)**	**16 (22%)**	**7(9%)**

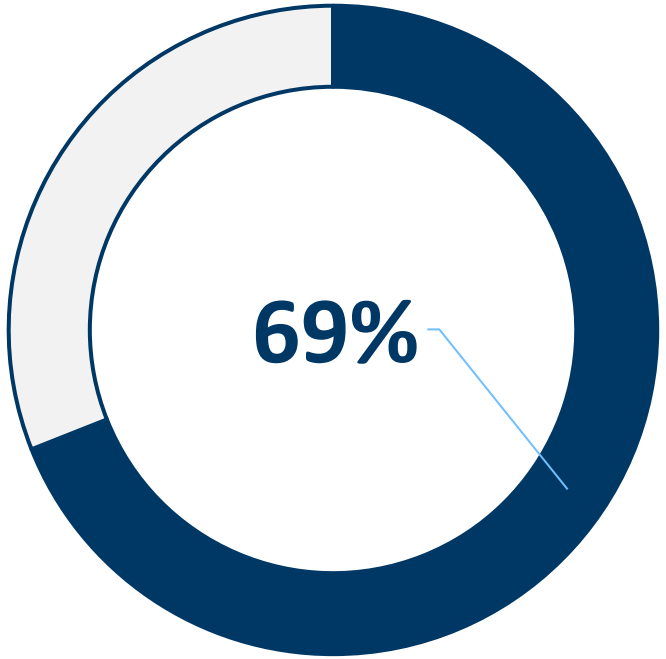
Of 74 infants with confirmed cCMV, a total of 21 (28%) did not complete all evaluations

Story #5

- Immigrant family that primarily speaks Somali at home.
- Family attends well child visits regularly
- Family completed initial confirmatory urine test, CBC and LFT labs, and head ultrasound before baby was 1 month old.
- Baby has no noticeable symptoms at well child physical exams (no rash, baby responds to sound/visual stimuli as expected).
- Ophthalmology and audiology appointments were not completed (only hearing re-screen, was normal).
- Providers and/or families not understanding importance of diagnostic audiology evals and monitoring, especially when babies are “asymptomatic”

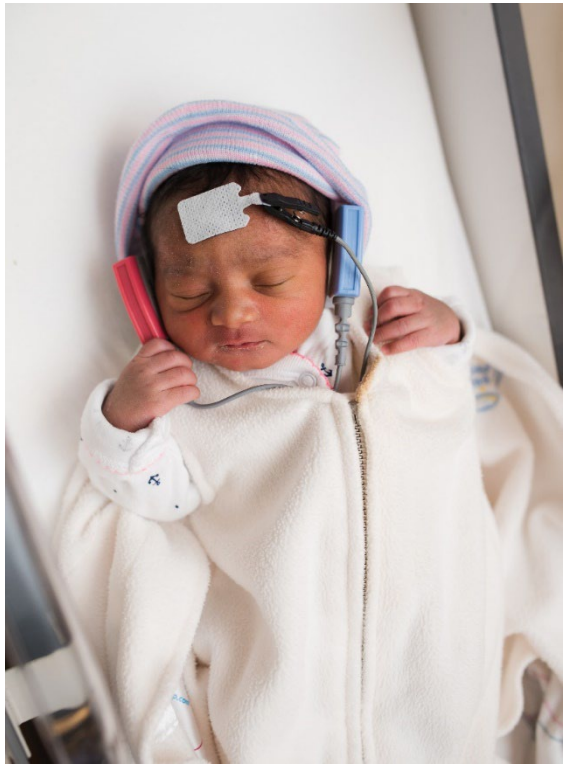
Asymptomatic vs symptomatic

Most have **no clinical findings**



Story #6

- Notification on DOL 9
- Clinic nurses tried calling mom repeatedly but were getting a signal as if it was disconnected
- No other number on file
- PCP sent message to mom via MyChart; no response
- Response received from mom on DOL 31
- Urine collected (positive) on DOL 52
- Missed 21-day window so confirmatory testing could be from acquired infection; still recommend evaluations?



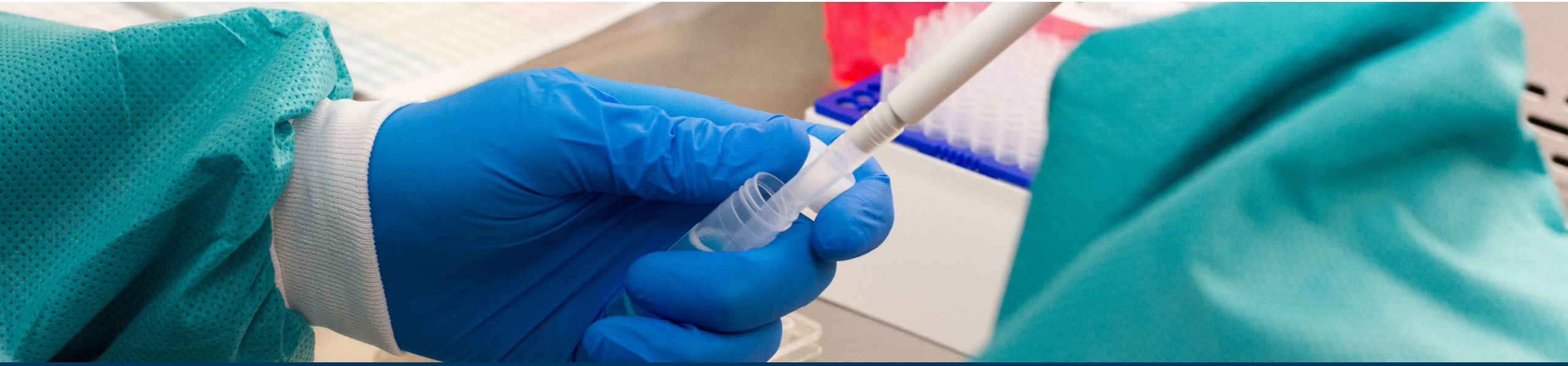
Clinical Lab Matters

Story #7

- Notification on DOL 5
- Multiple attempts to get urine PCR test results
- Response on DOL 18
  - "After careful discussion with the family, they have opted not to have a urine PCR test performed and proceed with the blood test as a presumptive positive. [He] has already had a comprehensive hearing screen done, and parents are scheduling a full cranial ultrasound in the near future."
  - Family declined ophthalmology
- Suspect we may have more of these situations as providers get used to screening results confirming

Story #8

- Initial results – HIGHLY VARIABLE; reported as CMV detected
- Notification on DOL 9
- Urine PCR result on DOL 10 = NEGATIVE
- First and currently ONLY false positive result
  - Expected to be minimal; investigation prompted
  - Retested specimen – HIGHLY VARIABLE
  - Checked for contamination by testing white of card – NOTHING
- Why would this happen? Possible that urine test is wrong? Should we have tested urine a second time?



Investigations

Story #9

- 27-week gestation, 470g, female, di-di twin
- NICU for prematurity and respiratory failure
- Anemia, thrombocytopenia, neutropenia, and intrauterine growth restriction
- No elevated transaminases
- Physical exam: No jaundice, rash/petechia/purpura, or hepatosplenomegaly and normal neurologic exam

Story #9 Cont.

- Results:
  - 3hr (pre-transfusion) screen – CMV NOT detected
  - 24hr (post-transfusion) screen – CMV NOT detected
  - **Quantitative CMV urine PCR (DOL#7): POSITIVE (viral load=10,969 IU/mL) – peds ID consulted and valganciclovir started**
  - **Quantitative CMV blood PCR (DOL#8): NEGATIVE**
  - 13d 20h screen – CMV NOT detected
  - 29d 16h screen – CMV NOT detected
  - **Quantitative urine CMV PCR (3 months of age, while on valganciclovir): NEGATIVE**
  - **At 4 months of age, off antiviral therapy, quantiative urine CMV PCR: POSITIVE**

Story #9 Cont.

- Thanks to wonderful partnerships with our peds ID docs, this case was brought to our attention
- False negative result prompted investigation
  - Tested all specimens multiple times to see if we missed it – NO CMV DNA
- Possible explanations?
  - 3h specimen – viral load too low; issue with sensitivity?
  - 24h specimen – 490g baby; transfusion impacting results?
  - 14d and 30d expected to be normal given antiviral treatment
- Would we have picked it up if we used 3 punches instead of 2?

Story #10

- 33-week gestation, 1620g, female
- SGA, but not microcephalic
- 1st screen collected at DOL 1 = no CMV detected
- 2nd screen collected at DOL 13 = CMV detected (inconsistent levels – tested 5 times – 2 spots had CMV detected and 3 spots were WNL)
- Result reported at DOL 22
- Urine CMV collected at DOL 26 = CMV detected
- Normal hearing and cranial imaging
- Ophthalmology not yet completed

Story #10 Cont.

- Internal staff curiosity prompted investigation
  - Tested all 5 spots on the initial specimen to see if we missed it – NO CMV DNA
- Possible explanation?
  - Viral load too low on initial screen; issue with sensitivity?
  - Acquired infection even though DBS was collected <21 days of age?
- Newborn screens are collected between 24-48 hours. We are lucky this baby had a 13d screen.
  - Are the babies we're missing (~25% per the literature), because they are not viremic enough in that timeframe for us to detect them? Perhaps 24-48 hours of age is not the best timeline for CMV screening? Would our sensitivity using dried blood be better if the specimen was collected a little later?

Conclusions

- Have detected CMV in newborns that otherwise would have been missed, which has resulted in connection with early interventions/treatment
- Vast majority of confirmed cases are pursuing the recommended evaluations, but there are barriers and misunderstandings that we need to continue to address
- Screening for CMV using dried blood spots is not perfect, but the infrastructure is there, and we are continuously looking to better understand our results and identify opportunities to improve

DEPARTMENT OF HEALTH

Questions?

Newborn Screening Program
https://www.health.state.mn.us/people/newbornscreening/index.html
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