SMA NBS in Wisconsin:

Considerations For Clinical Follow-up

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Objectives

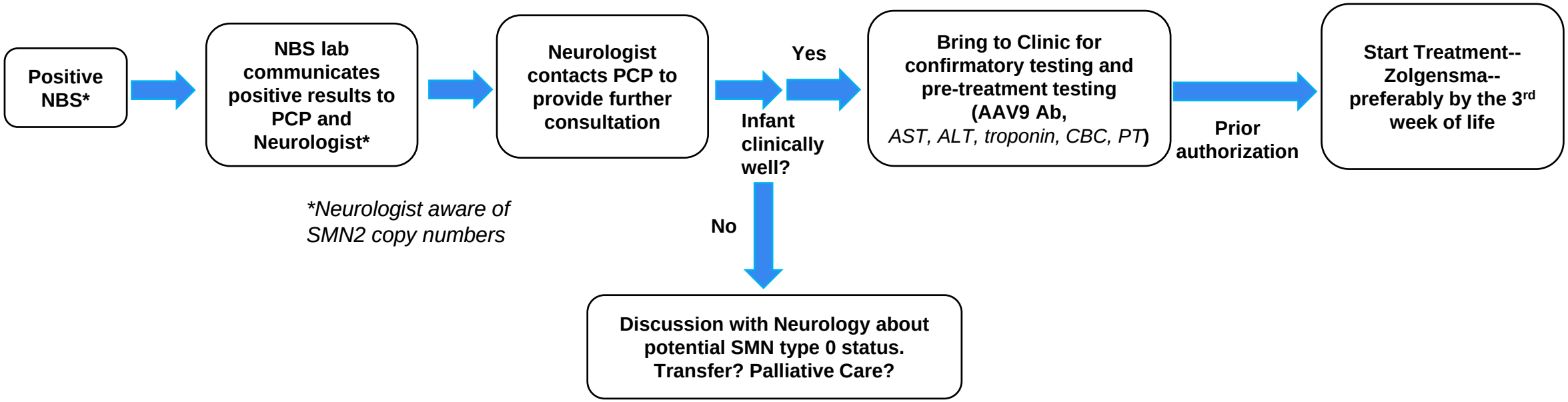
- Describe Wisconsin's clinical follow-up plan for infants identified with SMA by NBS
- Understand the challenges and barriers to providing presymptomatic SMA treatment, even with NBS

Disclosure

- The University of Wisconsin is a site for Avexis gene therapy trials and I am the site PI
- I will be using the trade names, **Spinraza** (nusinersen) and **Zolgensma** (onasemnogene abeparvovec-xioi) in this talk

Feel free to contact me at kwon@neurology.wisc.edu

Clinical Management After Screening



Neurologist aware of SMN2 copy numbers

Wisconsin SMA NBS Program

Why 3 weeks?

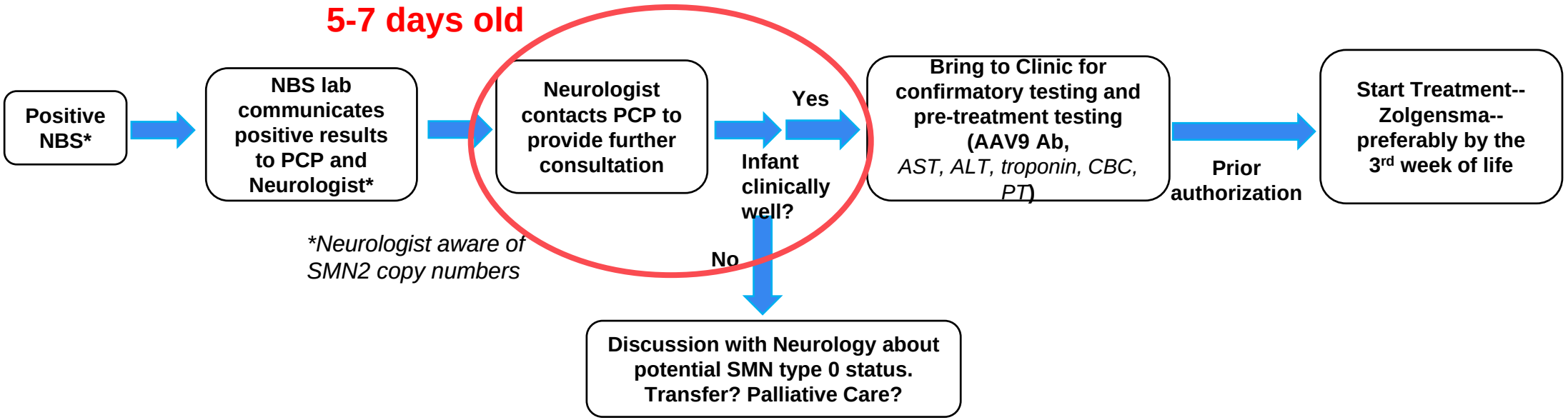
YOUTUBE: Evelyn tested positive for spinal muscular atrophy, the disease that claimed her sister's life.

https://www.abc.net.au/news/2019-05-25/worlds-most-expensive-drug-spinal-muscular-dystrophy/11149788

https://www.nationsonline.org/oneworld/map/USA/wisconsin_map.htm

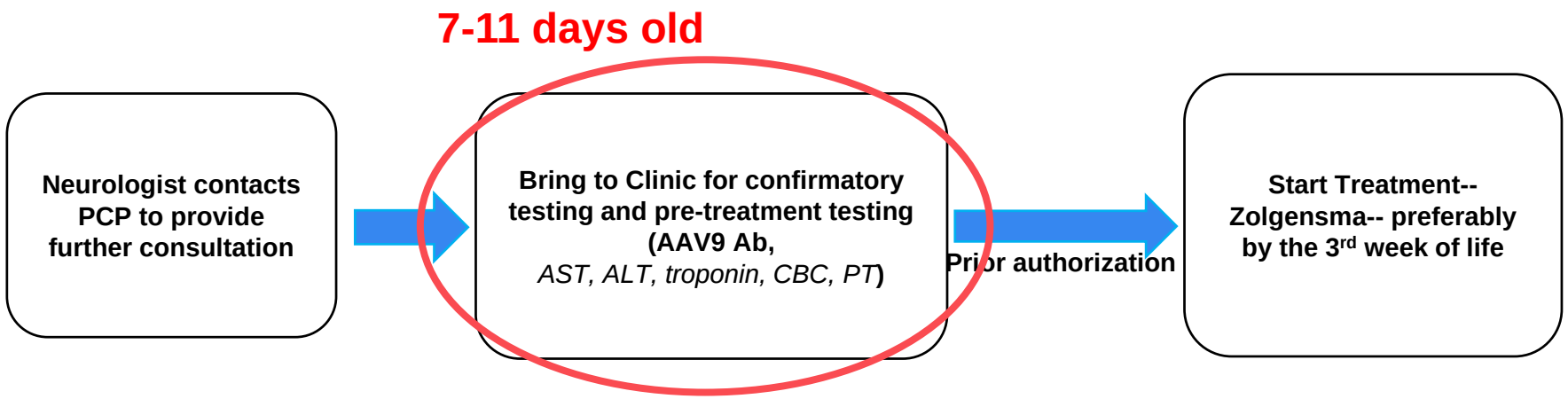
Neurologist contacts PCP…

- PCP may not have seen the infant
- How best to quickly contact the family and arrange for:
  - Clinic Visit: confirmatory testing and counselling?
  - Admission? If infant is sick, transfer to a medical center?
  - In both cases, we have to be able to convey the seriousness and urgency of the disorder, by phone, to a family of a new infant



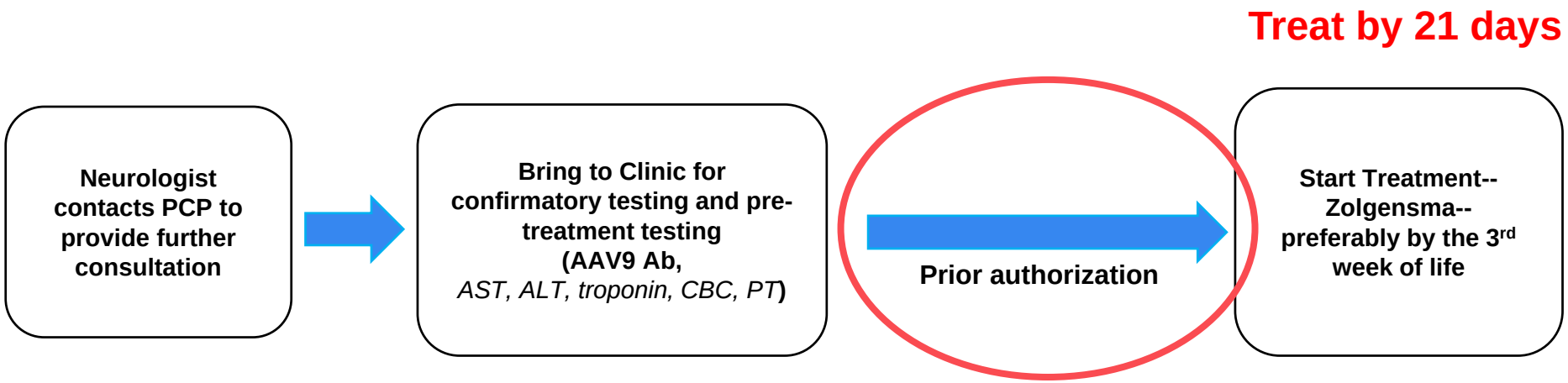
First Visit: Counselling & Testing

- Discuss SMA and treatment
- Patient assessment (CHOP-INTEND?, HINE?)
- Even before the visit, prior authorization team notified
- Blood is drawn for
  - SMN1, SMN2 copy numbers (WI lab will do this)
  - AAV9 Ab titers (eligibility for Zolgensma)
  - “pre-Zolgensma labs”: CBC, AST, ALT, troponin, PT/INR



Authorizing Treatment(s)

- Ensure prompt prior authorization
  - WI Medicaid – will provide urgent PA for Zolgensma for SMA
  - Other payers?– this is still a work in progress
- Does every infant need a prompt response?
  - Those with 2 or 3 SMN2 copies should be treated quickly
  - Those with 4 SMN2 copies?
    - Recommendation is to follow closely.
    - Treat with Zolgensma before age 2 yr?



Authorizing Treatment(s): choice of treatment?

In Wisconsin, treatment after NBS will be with Zolgensma. But,

- In other states, clinicians may look to starting Spinraza first
- It is likely that some who have received Zolgensma will also receive Spinraza as ongoing treatment

Treatment and associated follow-up

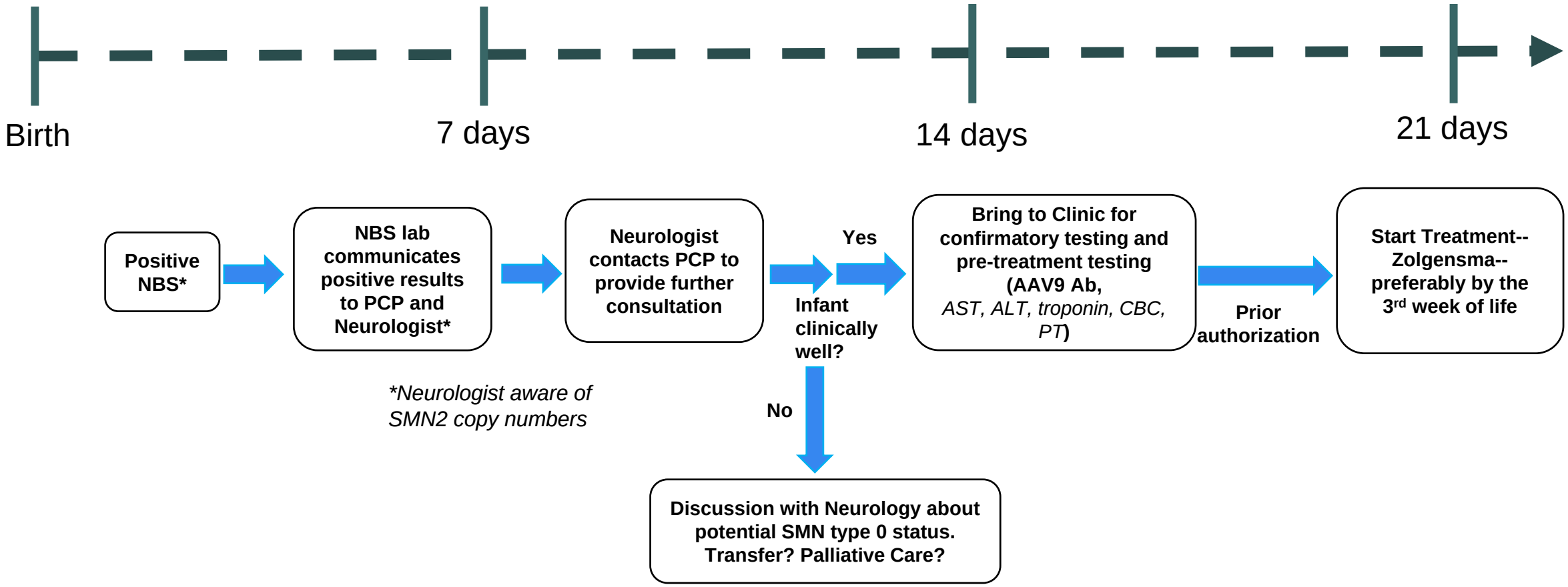
- Infusion of Zolgensma
  - Before infusion, pre-treatment labs are obtained (during initial visit)
  - Prednisolone (1 mg/kg/day) is started the day before infusion, to be continued for a month
- After infusion, infants will have their blood drawn at least 8 times over the next 12 weeks and will have frequent clinical assessments

What if the infant is sick?

- A symptomatic infant with SMA may need support to breath and eat
  - A gastrostomy tube placement may be recommended urgently because of the need for respiratory support makes nasogastric feeds more complicated
  - These interventions may delay treatment
- Zolgensma and Spinraza are generally not given to inpatients

Photo from: https://www.cpapxchange.com/wisp-pediatric-cpap-bipap-mask-respironics-nasal.html

Clinical Management After Screening



Wisconsin SMA NBS Program

SMA NBS and Timeliness

In Wisconsin…

- Insurance authorization (assuming the infant has insurance) has been a barrier to providing prompt treatment for SMA
- To allow infants identified by NBS to have the best outcomes, insurers must agree to authorize this treatment promptly
  - We have started to work with our hospital's payers
  - If an insurer refuses or delays authorization, our only option is to recommend transfer to Medicaid
- I have seen my institution and state invest time and other resources so we can provide these innovative treatments for SMA. Now they are working make sure that treatment starts as soon as possible so that the outcomes are as good as possible.
- I hope that other states considering the addition of SMA NBS understand the value of prior planning to prevent delays related to insurance authorization.

Feel free to contact me at kwon@neurology.wisc.edu

NEWBORN SCREENING FOR SMA IN UTAH

Spinal Muscular Atrophy (SMA) Webinar Series Part 2: SMA Treatment and Outcomes

Russell Butterfield MD, PhD

November 21, 2019

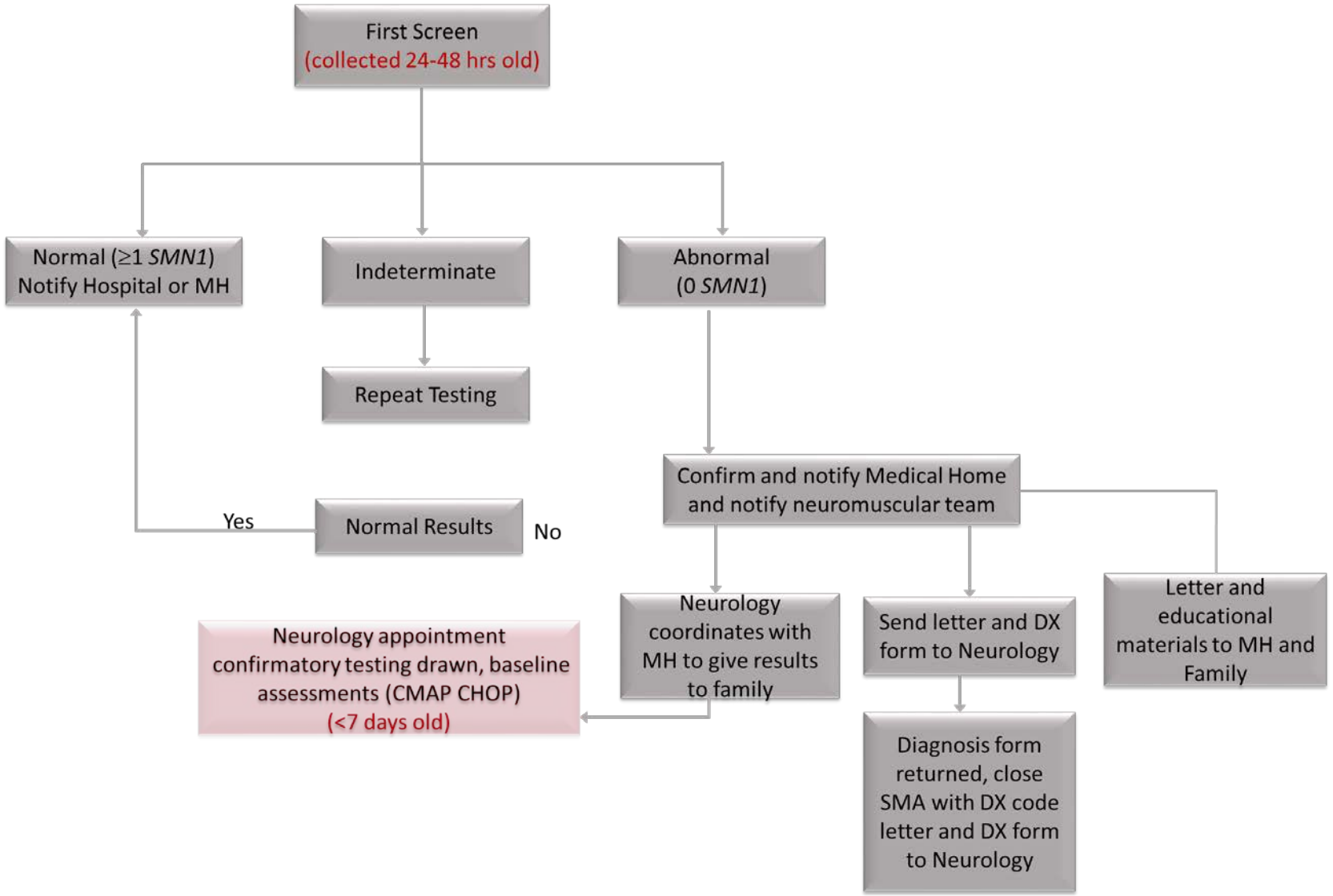
DISCLOSURES

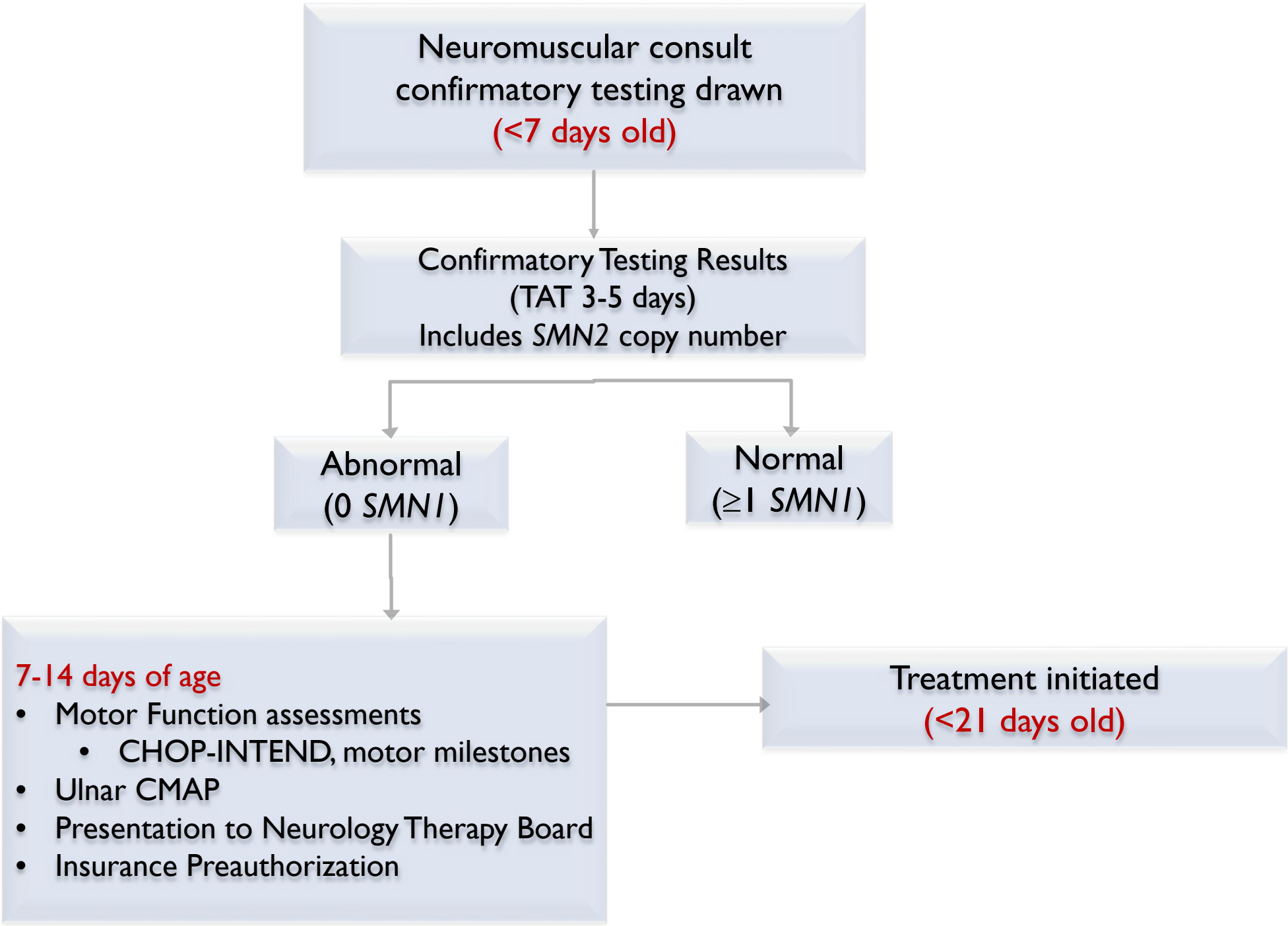
- Scientific advisory board: Sarepta Therapeutics, Biogen, Avexis
- Investigator on clinical trials funded by PTC Therapeutics, Sarepta Therapeutics, Pfizer, Biogen, Avexis, Catabasis, Capricor Therapeutics, and Acceleron Pharma

NBS FOR SMA IN UTAH

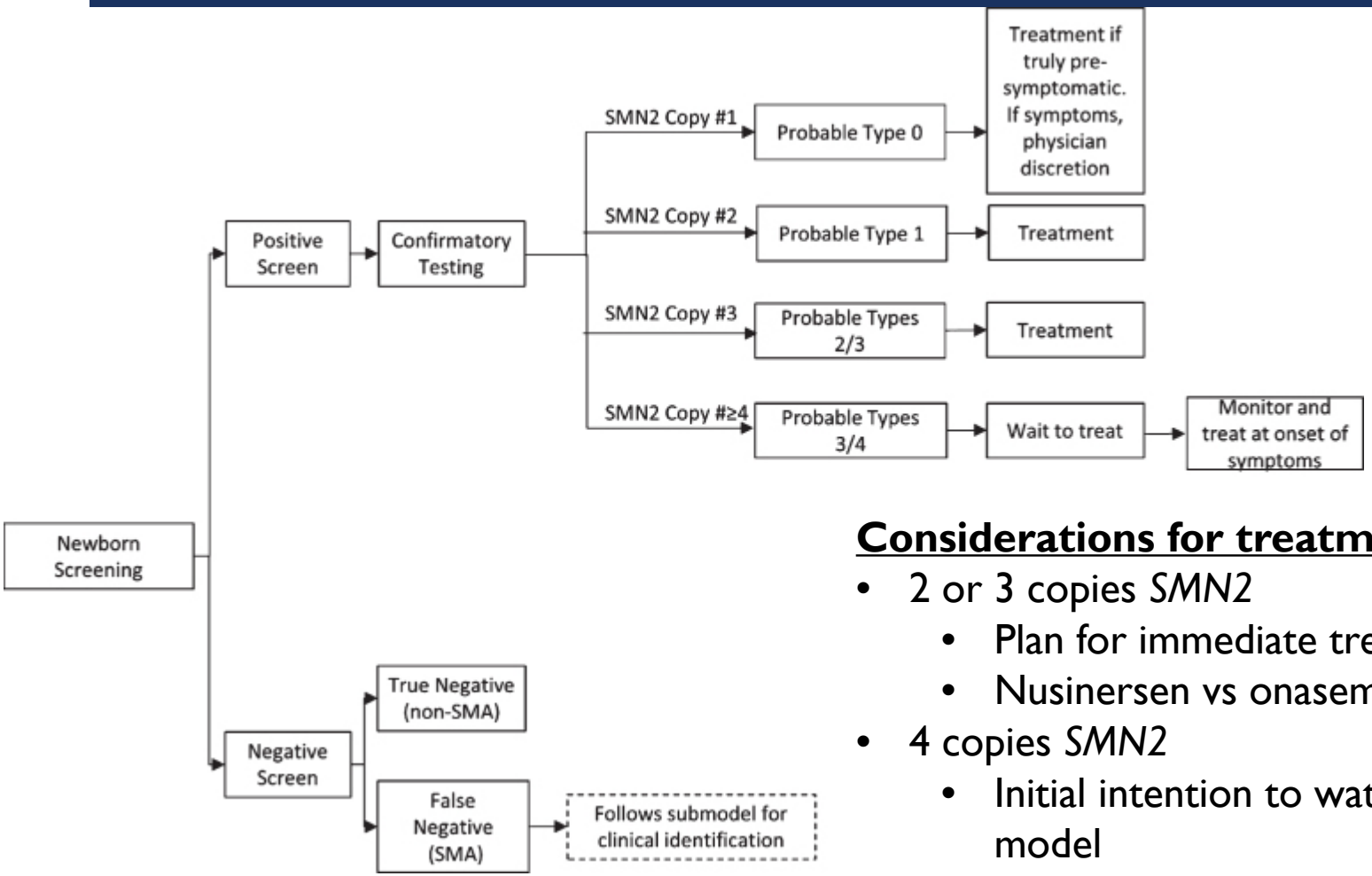
- Start for statewide screening Jan 28, 2018
  - qPCR
  - *SMN1* only
    - Carrier status and *SMN2* copy number not assayed
- Key points that helped lead to early adoption
  - Early data supporting treatment efficacy was strong (ENEAR, NURTURE)
  - Technology for qPCR already in state lab for SCID
  - Published assay for multiplex with SCID testing
  - Recommendation from NBS Advisory Committee to adopt new disorder is by medical review, not legislative process
    - Some concerns about cost of treatment, but acknowledgement that we are treating either way.
  - Funding from CureSMA for the first 6 months of screening
  - Funding for new disorders is legislative process, added $3 to kit fee

NBS FOR SMA—DEPT. OF HEALTH PROCESS




Neuromuscular consult
confirmatory testing drawn
(<7 days old)
Confirmatory Testing Results
(TAT 3-5 days)
Includes SMN2 copy number
Abnormal
(0 SMN1)
Normal
(≥1 SMN1)
7-14 days of age
• Motor Function assessments
• CHOP-INTEND, motor milestones
• Ulnar CMAP
• Presentation to Neurology Therapy Board
• Insurance Preauthorization
Treatment initiated
(<21 days old)

DECISION TO TREAT



Considerations for treatment

- 2 or 3 copies *SMN2*
  - Plan for immediate treatment
  - Nusinersen vs onasemnogene abeparvovec-xoio
- 4 copies *SMN2*
  - Initial intention to watch and wait with nusinersen model
  - Revised model, consider treatment at diagnosis with gene therapy model

Glascock et al. J Neuromuscul Dis. 2018. 5:145-158. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening

SMA THERAPIES NUSINERSEN IN UTAH

- Nusinersen (Spinraza)
  - 31 patients dosed to date
  - 9 type 1; 13 type 2; 9 SMA type 3
  - One type 1 patient declined treatment
  - 2 treated pre-symptomatic
  - 15 patients on long term open label extensions of phase2 and phase3 trials
- Onasemnogene abeparvovec-xioi (Zolgensma)
  - 3 commercial patients, all pre-symptomatic
  - 4 on clinical trials

INFANTS SCREENED FOR SMA IN UTAH 2018-2019

2019	Number Screened	Indeterminate Result	Abnormal Result
January	3868	6	0
February	3611	2	0
March	4047	1	1
April	3906	0	0
May	4262	3	1
June	4071	1	0
July	4522	5	0
August	4247	7	1
September	4060	1	0
2019	36,594	26	3
2018	48,180	42	3
TOTAL screened	**84,774**	**68**	**6**
Positive SMA			**5**

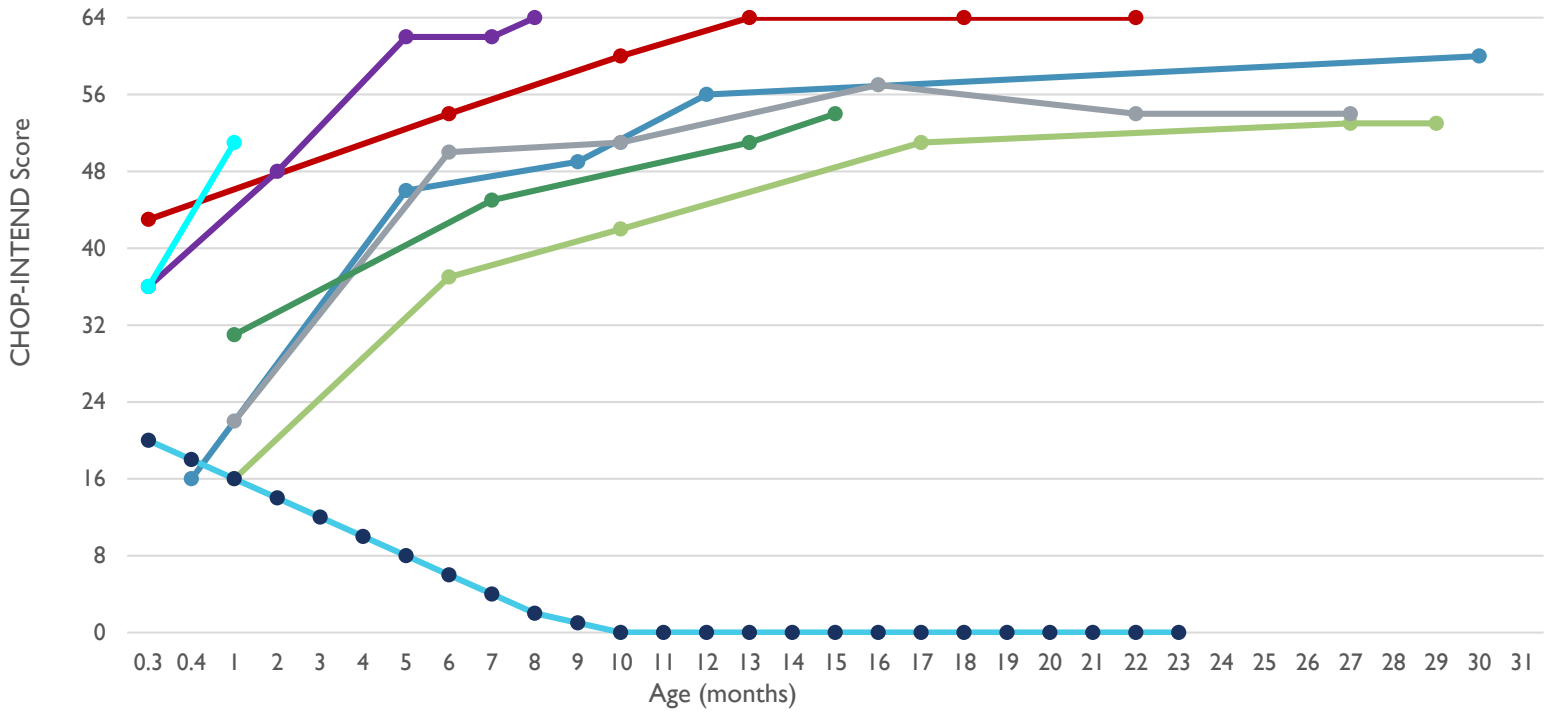
NBS RESULTS IN UTAH

- Five positive screens to date (from Jan 2018 launch):
  - All positive screens seen within 2 days of notification and evaluations completed within 1 week
  - 1with 2 copies *SMN2*
  - 4 with 3 copies of *SMN2*
  - One false positive
    - Optimization of qPCR in DOH lab, case now would correctly screen as failed test
  - No known false negative to date

OUTCOMES IN PRE-SYMPTOMATIC SMA

Notification	Clinic visit (days)	Confirmation (days)	Treatment initiated	*SMN2* copy	Treatment	Outcome to date
pre-natal	13	8	21 days	2	nusinersen (AAV9 positive)	4 month old, completed loading doses, concern for feeding, OSA
pre-natal	4	7	12 days	2	nusinersen	2.5 years old, walked at 21 months, mild proximal weakness, G-tube placed at 5 months
pre-natal/10 days	4	8	15 days	2	nusinersen (AAV9 positive), onasemnogene at 7 months	8 months old, symptomatic at birth with absent DTR, hypotonia. Rolls to get around, sits when placed for a few seconds, eats well
6 days	8	11	22 days	3	onasemnogene	3 months old, normal development, no complications
7 days	8	12	6 weeks	3	onasemnogene	5 months old, normal development, no complications
6 days	8	21	6 months	3	AVXS-101 trial	-
6 days	7	13	5 weeks	3	AVXS-101 trial	-
prenatal	20	7	21 days	2	nuisnersen trial	-

MOTOR FUNCTION ASSESSMENT IN TREATED INFANTS WITH SMA ~NEW ONSET OR PRE-SYMPTOMATIC, 2 COPIES OF *SMN2*



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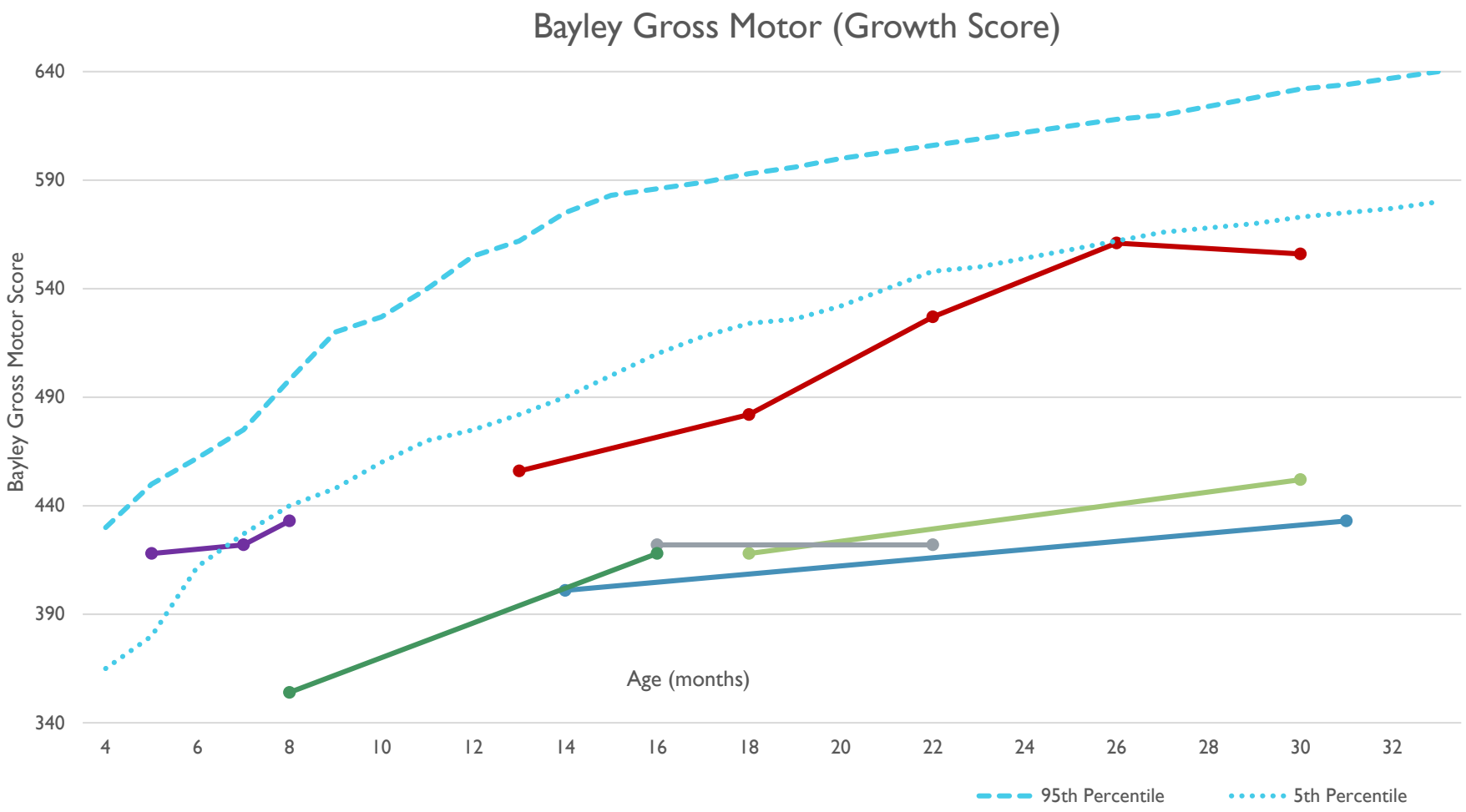

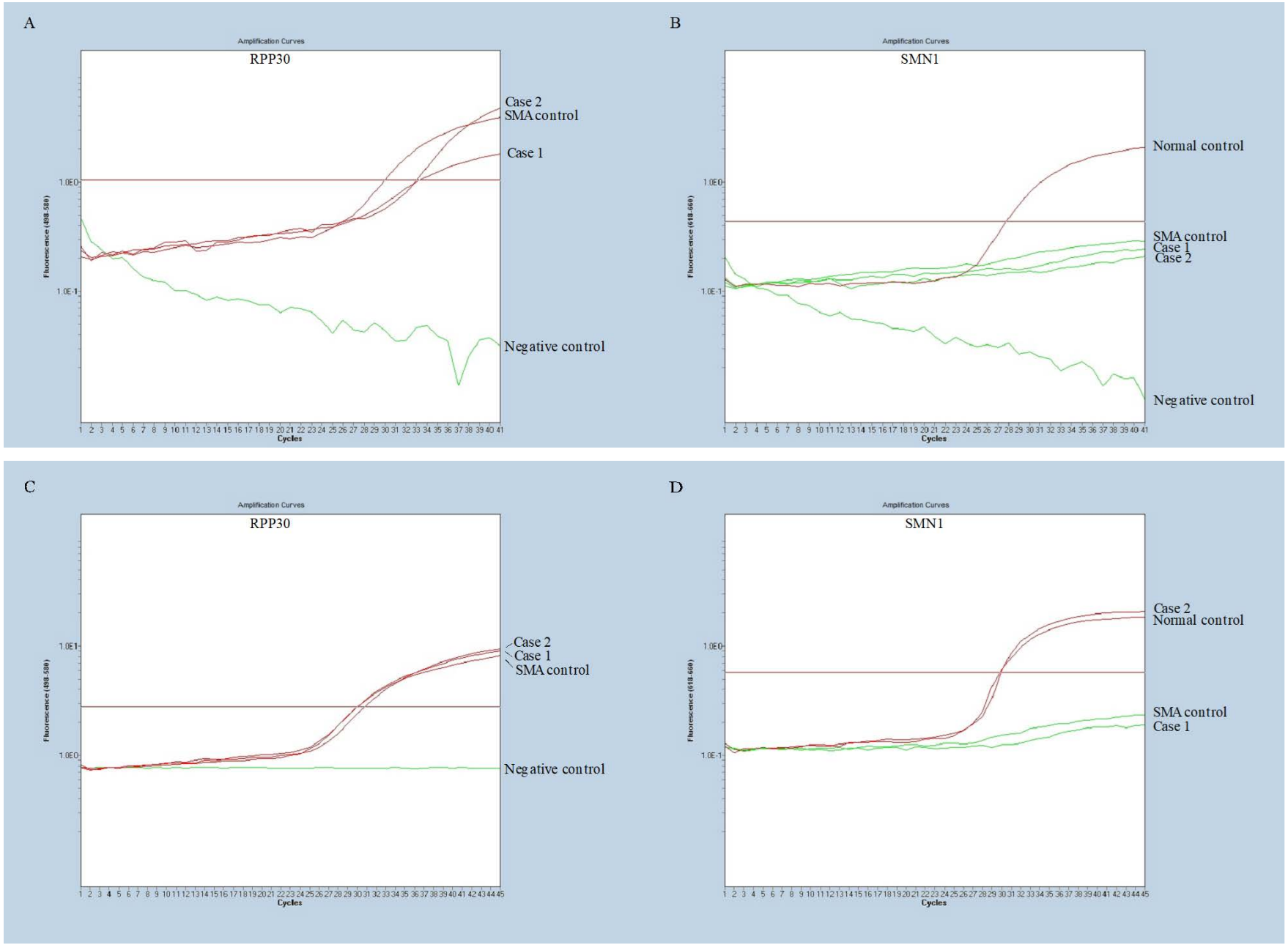

qPCR results from two subjects with positive initial screens for absent *SMN1*

QUESTIONS/DISCUSSION