Spinal Muscular Atrophy Screening in New York State

Feasibility and Prospective Pilot Study

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Disclosures

Biogen, Idec funded this study (screening, recruitment).

Biogen had no role in data analysis, interpretation, or decisions regarding patient counseling or care.
Spinal Muscular Atrophy (SMA)

- Progressive degeneration & loss of spinal cord & brainstem motor neurons
- Muscle weakness, atrophy
- Difficulty breathing, poor weight gain, pneumonia, scoliosis, joint contractures
Spinal Muscular Atrophy (SMA)

Most common genetic cause of infant & toddler death
- Incidence: 1 in 6,000 to 1 in 10,000
- Carriers: 1 in 50 to 1 in 60

95%–98% homozygous deletion of Survival of Motor Neuron 1 exon 7

$SMN1$ (5q)

↑ $SMN2$ ≈ less severe, later onset
SMA newborn screening

- Natural Hx
- Recognizable latent stage
- Important health problem
- Biomarker & test
- Acceptable Tx
- Demonstrated benefit of early detection, intervention & Tx

photo: March of Dimes
SMA newborn screening

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ACHDNC: No evidence review


Rebecca Buckley, MD read the summary report of the Internal Review Workgroup in the absence of the chairperson, Piero Rinaldo, M.D., Ph.D. The report, based primarily from the nomination form and also from submitted references and other publicly available materials, was distributed in advance of the meeting. The review was conducted October 20, 2008. SMA, or Werdnig-Hoffman disease in its more severe form, is a very serious condition that is characterized by progressive degenerative motoneuron disease and has an expected lifespan of less than 3 years. Its incidence is approximately 1 per 10,000 births. Prospective pilot data from population-based assessments are available. Analytical and clinical validation has been pursued in a single laboratory. It remains to be seen how effectively the screening method can be implemented in public health laboratories. The proposed screening method is one of the first examples of a primary screening test based on genotyping. Those individuals that could benefit from treatment are easily identifiable. Nutritional support and respiratory care are the only treatments currently available. Drug treatments are being investigated. In summary, Dr. Buckley noted that critical elements are missing from both the test characteristics, such as reproducibility outside of an academic lab, and treatment efficacy beyond the relatively limited benefits of palliative measures.

According to the Internal Review Workgroup, “The nomination of SMA might be premature for evaluation at this time as judged by the evidence...there are critical elements missing for both the test characteristics (reproducibility outside of an academic lab) and treatment efficacy beyond the relatively limited benefits of palliative measures.”

“The Internal Nomination and Prioritization Workgroup recommends no evidence review at this time and further recommends a nominator to conduct prospective pilot studies in one or more traditional public health laboratories in order to show reproducibility of the preliminary findings in Dr. Prior’s laboratory. The time frame required to collect the analytical evidence mentioned above could also lead to a better assessment of the efficacy of novel treatment modalities under investigation.”
Pilot SMA newborn screening

NYS Newborn Screening Program and Columbia University Medical Center

Major Goals
- Develop $SMN1$ assay and demonstrate NBS feasibility
- Offer screening, assess uptake and outcomes

Morgan Stanley Children’s Manhattan
4,400 births/yr

Allen Hospital
Upper Manhattan/Bronx
2,000 births/yr

Weill-Cornell Medical Center
Manhattan
5,800 births/yr
Recruitment – opt-in model

Hospitals - 3 NYC hospitals, 12,000 births/yr
Materials - video & brochure
Coordinators - describe study, answer questions, obtain consent on tablet (REDCap), mark Guthrie card

Year 1: 93% opt-in
**SMA assay**

DNA: 3-mm DBS (96-well plate)

TaqMan real-time PCR assay (384-well plate)
- *SMN1* exon 7 (Anhuf, 2003, Hum Mut)
- *RPPH1* (internal control gene; RNaseP)

ABI 7900HT / QuantStudio 12K Flex

\( \Delta \Delta C_t \) to calculate *SMN1* copy number, estimated from Relative Quantity (RQ)

Controls: 0-copy, 1-copy, 2 copies, NTC

*RPPH1* amplifies
*SMN1* does not amplify

- **Hom del**
  - RQ = 0.300-0.599
  - Normal

- **Het del**
  - RQ ≥ 0.800
SMA assay validation

45 Positive Controls

- ≥1 copy SMN1
- (1-2 copies SMN2)
- 0 copies SMN1
  (2-4 copies SMN2)

RPPH1 amplification

SMN1 amplification

4,028 DBS

*each point=mean RQ, 3 replicates

- Screen neg (3,929)
- Borderline (14)
- Fail (34)
- Het del (51)
NYS SMA algorithm

SMN1 Exon 7 Deletion Assay

≥2 copies
SCREEN NEGATIVE
No Further Action Required

1 copy
REPORT
Carrier

0 copies
SCREEN POSITIVE
Referral for Evaluation & Diagnostic Testing

Turnaround time (2017)
Screen Neg: 3 days (98% w/in 2–5)
Carriers: 4 days (98% w/in 3–5)
business days, day 1=receipt, includes late consents
Follow-up, 82 carriers

17% (14/82) agreed to genetics referral
   – 71% (10/14) made appt
   – 70% (7/10) maintained appt

Most parents expressed concern; after speaking with counselor, expressed understanding of "carrier" status versus "affected"

48% (39/82) knew they were carriers
   – less concerned, better understanding
Results

Morgan Stanley and Allen: January, 2016
Weill-Cornell: July, 2016

January 15, 2016 – August 30, 2017
Infants screened: 7,317

False positives: 0% (0/7,317)
False negatives: 0% (0/7,317)
Results

Affected Infant

Tested: day 1-2*
Confirmed: 2-3*
Reported: 2-3*
Clinic: DOL 7 (normal neuro, phys exam)
Genetics: DOL 12 (SMN1=0; SMN2=2)
Treatment: NURTURE (open-label, pre-sx, 2-3 SMN2): DOL 13
Dose 1: DOL 15

*business days

@ 19 months – tolerates medication, meeting milestones on time, walking, running, talking
Considerations

Assays, platforms (Taiwan, CDC, PE, ...)

Carriers – To report or not report?
• RPPH1 Y/N and SMN1 Y/N
• 2+0 genotype → missed carriers

Late onset SMA

Non-deletion mutations → false negatives
• 2 – 5%
Current status

ACHDNC – SMA evidence review & recommendation (Feb, 2018)

New York – Pilot, 3 hospitals, opt-in, ≥ June, 2018

Taiwan – Pilot, parent consent, Nov, 2016 – present (Chien, 2017, J Peds)

Massachusetts – Pilot, full population, opt-in, Fall 2017

Missouri – Legislature approved bill to add SMA by Jan 1, 2019 (subject to appropriations)
Future directions

Population-wide screening in NYS?
- Regulation
- Identify specialty care centers, neuromuscular specialists
- Revisit carrier reporting
- Technical
  - Multiplex with SCID TREC assay
  - Eliminate triplicate testing
  - 10 µl → 8 µl rxn
  - Possible elimination of sequencing (primer-probe binding sites sequenced in carriers to rule out allelic dropout)
- SMN2 dosage (digital droplet PCR)
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