Newborn Screening Pilot Studies

Presented to the ACHDNC

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- The NBSTRN is an NICHD funded contract, awarded to ACMG in September 2008 and after open recompete in September 2013 and 2018.

- The NBSTRN will maintain, administer and enhance resources to support investigators with projects related to newborn screening for:
  - New technologies
  - New Conditions
  - New treatments and management approaches

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Research Areas Related to Newborn Screening Pilot Studies

- Obtaining an unbiased understanding of **rare** genetic conditions
  - Population-based pilot testing of new NBS tests
- Validating new tests and treatments in asymptomatic newborns that allows for NBS expansion

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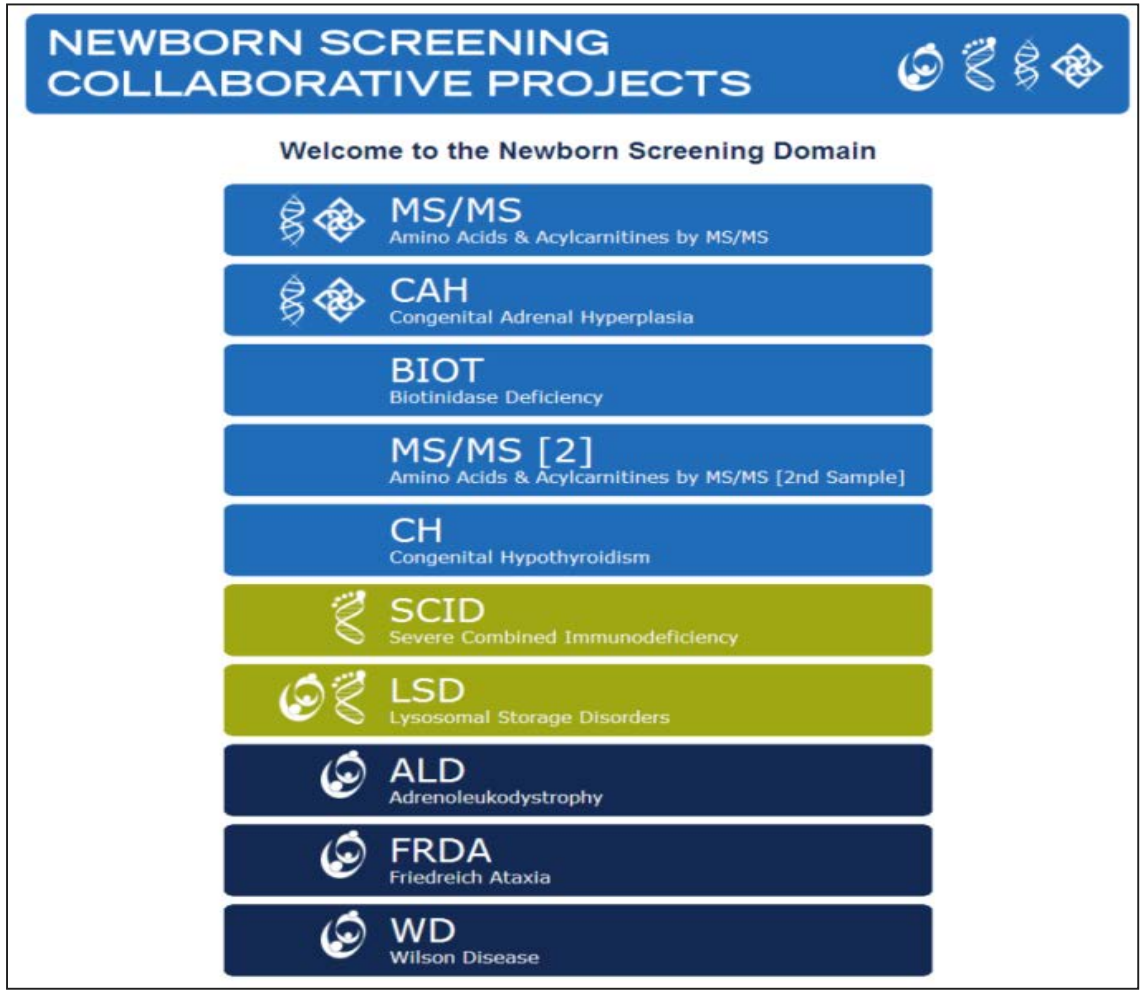
Much Learned from Ongoing NBS Pilot Studies

- Currently coordinating multistate pilots for:
  - SCID (Complete)
  - Pompe (Complete)
  - MPS1 (Complete)
  - X-ALD
  - SMA
  - Duchenne Muscular Dystrophy +
  - Next??



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Pilot Study Systems

- Sue Berry, Piero Rinaldo, Amy Brower, Bob Currier, NBSTRN Steering and Pilot Study workgroup
- What are the Measures of Progress of a Pilot Study?
  - Sufficient data for ACHDNC to make informed decisions
- What's coming, what's changing, what's needed to deal with challenges?
  - Understand statistics around rare diseases at the population level
  - How to meet the capacity needs
    - Systems
    - Workforces

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Problems Emerging in the NBS Pilot Study System

- The R & D pipeline is full
  - Several conditions are ready for pilot studies
  - New drug pipelines are growing
  - NBS and medical genetics workforces are strained
  - Funding is limited
- Targets of newborn screening are changing
  - Pharmaceutical pipeline full of treatments that target a disease subgroup
  - Systems are overloaded with off target services
    - false positives impact individuals
    - carrier rates can be very high for some conditions
- Rare diseases at the populational level challenge our current clinical trial ‘system’ for genetic screening.
  - Very hard to know when you know enough

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Conditions Ready for Clinical Follow-up Pilot Studies

- Disorders with already available analyte data (e.g., amino acids, often low)
  - proximal urea cycle disorders (OTC, CPS, NAGS)
    - Low citrulline and ratios by MS/MS; treated by medical foods and drugs
  - remethylation disorders (MTHFR, Cbl E, G)
    - low methionine and other intermediate pathway related biomarkers
  - Conditions with low valine, leucine, and isoleucine like branched chain kinase
  - Conditions with low serine/glycine like 3-phosphoglycerate dehydrogenase def.
  - Several formerly “secondary conditions” may be candidates for RUSP
- More LSDs

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More Molecularly Screened Target Conditions are Emerging

- Cancer predispositions
  - RB (retinoblastoma)
  - TP53 (Li-Fraumeni)
- Infectious diseases
  - HIV
  - TOXO
  - CMV
- Molecular phenotypes, yes/no questions, or targeting genes

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Targets of NBS and Treatment are Changing

- Severe and early onset forms of conditions are often the impetus for considering screening for a condition
- New therapeutics aimed at subtypes of diseases are growing
- Individualized treatments are coming fast

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Treatments for Disease Subgroups Redefine Targets of NBS

Treatment Type	Disease Patient Subgroup
Chaperones	Change conformation of a defective protein
RNA-directed exon skipping	Brings out of frame mutations leading to premature stop codons back into frame for more complete protein
Readthrough	Allows RNA to read through a premature stop codon due to nonsense variants (e.g. DMD)
Pre-mRNA splicing modifiers	Increases amount of functional protein (e.g. SMN2 to generate more functional SMN protein)
RNA interference	siRNA silences or downregulates genes via mRNA
Substrate reduction therapy	Enzymatic modification of specific enzyme substrates

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Targets of Treatment are Changing

- New therapeutics aimed at subtypes of diseases
  - Exon 51 skipping (read-through) for DMD
  - Chaperone therapies
- Gene therapies
  - AAV and Lenti virus treatments are coming fast
    - Safety profiles are very positive
- Ultimately, primary targets should be the forms for which treatment outcome is assessed in pilots

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The Challenge of Assessing Clinical Validity of Rare and Clinically Variable Diseases

- Rare diseases in prospective population-level pilot studies require latitude in statistical power
  - Incidence of disease, proportional distribution of mutations, and genomic background on which variants operate vary across populations
  - Requires extensive data sharing to maximize
- Variability in time of treatment and disease onset requires ongoing data collection
- Monitoring of performance of screening tests over time requires ongoing data collection
- Curating genetic variation before formal screening begins

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Goals of Pilot Study: Statistical Considerations

- Generate sufficient data such that:
  - there is a high likelihood that the screen for the condition will perform as it did in the pilot study.
- Generate statistically robust data to make a well-informed decision of whether to add the condition to the RUSP
  - Measures of the progress of the pilot study over time
  - Should there be a minimum PPV that is acceptable for NBS conditions?
  - Should the incidence of the treatable form of the condition be considered?

All while accommodating the unique needs of rare diseases to ensure access when data is limited

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Statistical Perspectives

- How Much Pilot Study Data Do We Need
  - How likely is that the test performs in routine use as it did in pilot studies?
  - Are there criteria by which a proposed screening test fails?
- Statistical perspective in coming slides
  - Confidence intervals (CI) provide a measure of the uncertainty of a result
    - A 10% difference between lower and upper CIs is a general target
  - Coefficient of variation (CV) is a measure of the spread of data (standard deviation) around the average
    - A CV of 10% or less is a general target

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Relatively Small Pilots Define False Positive Rate

Incidence:1:10,000; Detection rate100%;PPV 20%, False positive rate 0.05%

PILOT STUDY SIZE	95% CI	CV
25,000	(0.022%, 0.078%)	28.3%
50,000	(0.030%, 0.070%)	20.0%
75,000	(0.034%, 0.066%)	16.3%
100,000	(0.036%, 0.064%)	14.1%
150,000	(0.039%, 0.061%)	11.5%
200,000	(0.040%, 0.060%)	10.0%

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Determining Detection Rate Requires Very Large Pilots

Incidence:1:10,000; Detection rate100%; PPV 20%;

False positive rate 0.05%

Cases Detected	95% CI	Population Size
10	(70%, 100%)	100,000
30	(90%, 100%)	300,000
60	(95%, 100%)	600,000
120	(97.5%, 100%)	1,200,000
300	(99%, 100%)	3,000,000

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Larger Numbers are Needed to Define PPV

Incidence:1:10,000; Detection rate100%; PPV 20%,

False positive rate 0.05%

PILOT STUDY SIZE	95% CI	CV
100,000	(7.2%, 26.1%)	28.3%
150,000	(9.0%, 24.4%)	20.0%
200,000	(10%%, 23.2%)	16.3%
250,000	(10.7%, 22.6%)	14.1%
300,000	(11.2%, 22.1%)	11.5%
350,000	11.6%, 21.7%)	10.0%

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As Incidence Decreases, the PPV Decreases

- Incidence:1:10,000; Detection rate100%; PPV 20%,
- False positive rate 0.05% (125 cases), Pilot Study Size 250,000

INCIDENCE	TRUE POSITIVE CASES	PPV
1 in 5,000	50	28.57%
1 in 10,000	25	16.67%
1in 25,000	10	7.41%
1 in 50,000	5	3.85%
1in 125,000	2	1.57%
1 in 250,000	1	0.79%

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PPV is Maintained as False Positive Rate Decreases

Pilot size 250,000; Incidence:1:10,000; Detection rate100%;
False positive rate 0.05%, **PPV 20%**

INCIDENCE	TRUE POSITIVE CASES	FALSE POSITIVE CASES	FALSE POSITIVE RATE
1 in 5,000	50	200	0.080%
1 in 10,000	25	100	0.040%
1 in 25,000	10	40	0.016%
1 in 50,000	5	20	0.008%
1 in 125,000	2	8	0.0032%
1 in 250,000	1	4	0.0016%

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Managing False Positive and Off-Target Rates

- Carriers can be important to a screened individual for some conditions (e.g. X-linked)
  - Can be confounded when variants are associated with a wide range of disease severity
  - Can be less individually important for others (autosomal recessives)
    - Need functional EHRs to make it useful for infants eventual family planning
- 2nd tier biochemical vs. molecular tests can minimize carrier identification family recontact
- Use of alternative risk assessment tools (e.g., CLIR)

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Workforces Misaligned

- Medical Geneticist and Newborn Screening Program shortages
- Limited comfort with genetics services among non-genetics trained providers
- Analytical and clinical complexity of screening results are separating

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How Can we Meet the Capacity Demands?

- Delegate responsibilities for off-target results after Public Health mandate is met
- Multiplex pilot studies
- Virtual pilot studies
- Ensure adequate workforces to meet growing demands
- Evolve a system in which the limited data available for screening for rare diseases can be developed in an controlled and organized way
- Consider alternative financing models that involve a broader range of stake holders.

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Systems for Enhancing Capacity When Rare Disease Science is Moving Rapidly

- Regulatory Mechanisms
  - Models systems such as for ensuring rare disease treatment development and availability
    - Orphan Drug Act provided incentives for rare disease drugs
      - Postmarket surveillance to ensure that expected performance is maintained (i.e., DATA SHARING)
    - Need similar model for rare disease diagnostics and screening
- Reimbursement Systems
  - Maximizing evidence development
    - Coverage with evidence development (what's not covered)
- Distribution of responsibilities to minimize duplication of effort and meet stakeholder needs

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Resources to Enhance Translational Capacity

- Public funding limited
- Centralized data sharing in the absence of robust clinical EHRs is limited without incentives

- Public Private Partnership models
  - Risk sharing models (e.g., PPMD-funded DMD pilot in NY)
  - Patient driven data sharing works for those clinically affected but is limited for asymptomatic people with risks
  - Managed Entry Agreements (MEAs) to share the cost of uncertainty as in Europe for oncology drugs

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