Point-of-care screening and clinical considerations for OTC deficiency: Is NBS ready?

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NBS and UCDs

Why and how NBS?

What do we do now?

What is missing?

Screening for proximal disorders

Challenges

Newborn Screening: why and how

- Newborn screening is one of the nation's most successful public health programs
- Newborn screening programs test babies for disorders that are not apparent at birth
- The majority of conditions are identified using analytical techniques in public health laboratories

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Classic criteria for inclusion in NBS panels

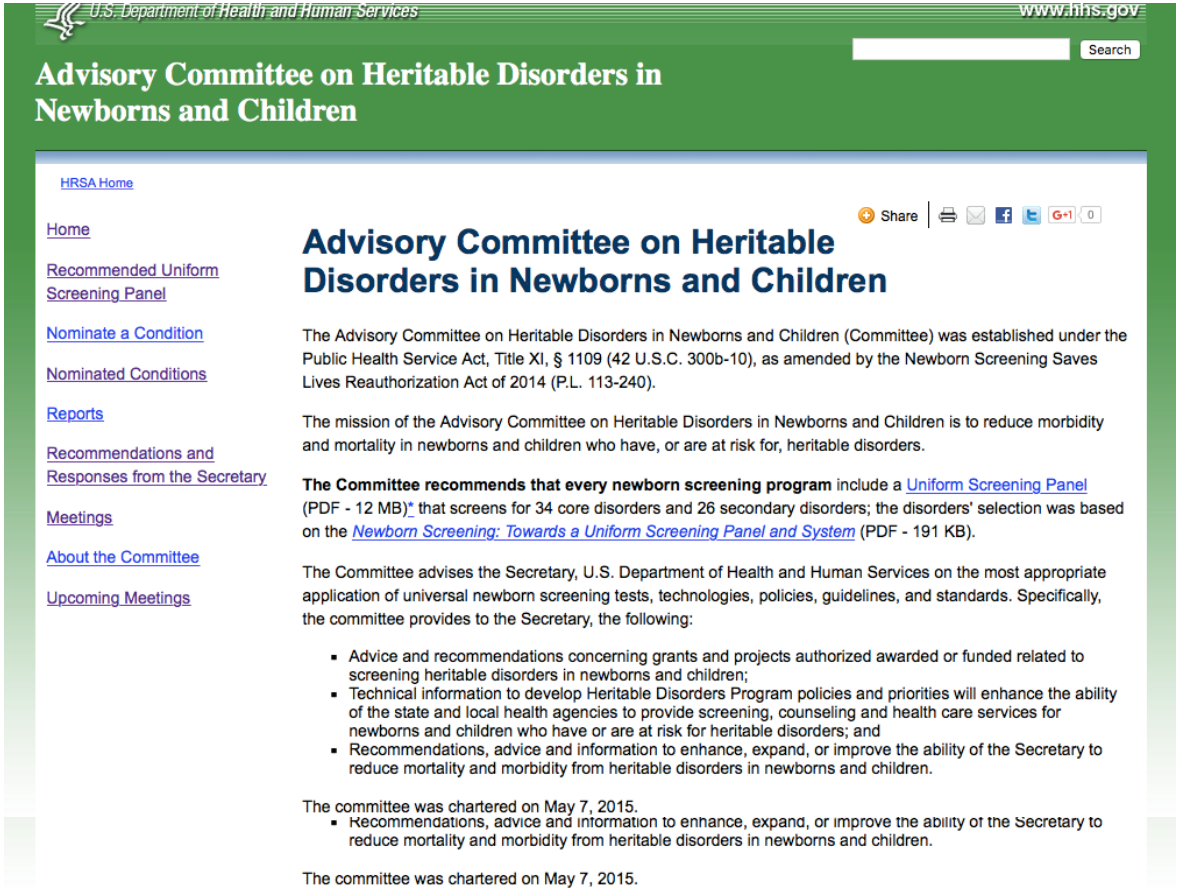
- Treatment available for disorder screened
- Early treatment improves outcome
- Routine exam will not yield Dx (testing necessary to diagnose in asymptomatic person)
- Rapid, highly sensitive test available
- Screening is cost-effective
- Infrastructure exists to help families, medical homes connect with specialists for confirmation, treatment, and follow-up

Fundamental assumption for testing:

To be a PRIMARY screening target a condition should fit these criteria:

- It can be identified at a phase (24 to 48 hours after birth) at which it would not ordinarily be clinically detected;
- A test with appropriate sensitivity and specificity is available for it;
- There are demonstrated benefits of
  - early detection,
  - timely intervention and
  - efficacious treatment of the condition being tested.

Process



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Advisory Committee on Heritable Disorders in Newborns and Children

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Recommended Uniform Screening Panel

Nominate a Condition

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Advisory Committee on Heritable Disorders in Newborns and Children

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) was established under the Public Health Service Act, Title XI, § 1109 (42 U.S.C. 300b-10), as amended by the Newborn Screening Saves Lives Reauthorization Act of 2014 (P.L. 113-240).

The mission of the Advisory Committee on Heritable Disorders in Newborns and Children is to reduce morbidity and mortality in newborns and children who have, or are at risk for, heritable disorders.

The Committee recommends that every newborn screening program include a Uniform Screening Panel (PDF - 12 MB)* that screens for 34 core disorders and 26 secondary disorders; the disorders' selection was based on the *Newborn Screening: Towards a Uniform Screening Panel and System* (PDF - 191 KB).

The Committee advises the Secretary, U.S. Department of Health and Human Services on the most appropriate application of universal newborn screening tests, technologies, policies, guidelines, and standards. Specifically, the committee provides to the Secretary, the following:

- Advice and recommendations concerning grants and projects authorized awarded or funded related to screening heritable disorders in newborns and children;
- Technical information to develop Heritable Disorders Program policies and priorities will enhance the ability of the state and local health agencies to provide screening, counseling and health care services for newborns and children who have or are at risk for heritable disorders; and
- Recommendations, advice and information to enhance, expand, or improve the ability of the Secretary to reduce mortality and morbidity from heritable disorders in newborns and children.

The committee was chartered on May 7, 2015.

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Current NBS for UCDs

On the RUSP as primary targets

- Citrullinemia
- Argininosuccinic aciduria

On the RUSP as secondary targets

- Arginase deficiency
- Citrin deficiency

All based on ELEVATIONS of metabolites

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What is missing?

- Proximal UCD (OTC, CPS1, NAGS deficiencies)
- Why?
  - Do we have the right test?
  - Are there issues of secondary targets?
  - Can timing be right?

Update on screening: proximal UCDs

- Selected states indicate that they screen
- Citrulline is the foundational metabolite
  - New England: 0.4/100000 (9y)
  - California: 0.37/100000 (11.5y)
- Ratios and data tools used to enhance utility
- (Second tier used/tried: orotic acid)

NewSTEPS Report: States screening for proximal UCDs

Condition	Not Screened	Universally Screened	Likely to be detected and reported due to universal screening of another disorder
Carbamoyl phosphate synthetase I deficiency	42	10	1
Ornithine transcarbamylase deficiency	42	8	3

NewSTEPs
A Program of the Association of Public Health Laboratories™

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Potential Secondary Targets: Low Citrulline

- Mitochondrial disorders
  - MT-ATP6 at high heteroplasmy levels (+C5OH)
- OAT (Ornithine aminotransferase deficiency)
  - gyrate atrophy of the choroid and retina, elevated ORN
- Delta-1-pyrroline-5-carboxylate synthetase (P5CS)
  - intellectual disability, joint hypermobility, skin hyperelasticity, cataract plus metabolic abnormalities: hyperammonemia, low PRO, **CIT**, and ORN hypoornithinemia
- (low in premature infants)

OTC Deficiency: Variable Presentations

- X-linked so most presenting patients are male
  - ~20% of female heterozygotes have symptoms
- Null variants = neonatal onset in males
- Hypomorph variants ->any age (including life-long asymptomatic state)
- Sequencing identifies ~80-90% of alleles

Potential challenges

- Unknown rate and detection of milder forms of disorders
- X-linked disorder for OTC deficiency
- *Typical acute presentation will often precede availability of NBS*

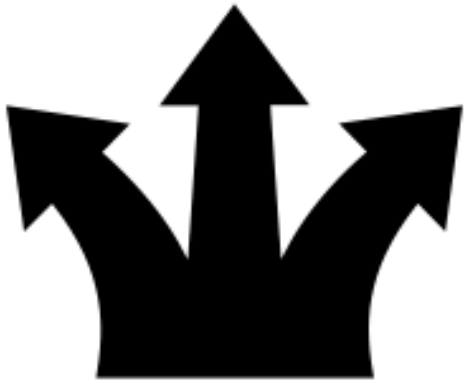
It will be hard to be fast enough

- Male infant, term, discharged at 24h
- Returns to ED <24 h, moribund. Active resuscitation fails. (No ammonia measured)
- NBS results with low CIT (after death)
  - CLIR significant for proximal UCD
- Postmortem:
  - DBS used to remeasure CIT (low) and orotic (high)
  - DBS used for OTC sequencing -> VUS present: classified as pathogenic based on presentation

Conclusion: OTC deficiency, severe neonatal

Alternative Options???

- Point-of-care testing (Handheld NH3 meter)
  - Advantages
    - Immediate info
    - Has broader care applicability
  - Disadvantages
    - There isn't one (yet)
    - We know little about cadence of rise
- Prenatal screening???
  - Could we do this?
  - Would we find the variants?



Summary

- NBS available already for selected UCDs
- NBS is likely technically feasible for proximal UCDs
  - Timing a challenge!!
  - Degree to which testing will detect attenuated forms unknown
- Other options?