Examining Cut-offs in Follow-Up Practices

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OVERVIEW AND RECAP OF FOLLOW-UP STAFF ROLE

• Follow-up staff charged with overseeing that the family is connected to a diagnostic team and outcomes are obtained after an out-of-range newborn screening result
  • Contact Primary Care Provider and/or make connection to Specialists
    • May be done by phone, fax, secure email, web portals, or a combination
  • Outcome information should be discussed regularly with the laboratory in order to facilitate appropriate review of testing algorithms
    • Case definitions are particularly important in ensuring that a case is indeed a case

• Population health screening requires balance – between knowns and unknowns; false positives and false negatives
Congenital Hypothyroidism (CH) is relatively common: 1:3000 to 1:4000*

Only blood spot condition that is not typically inherited

Partial or complete loss of thyroid function due to:
  • Failure of the thyroid gland to develop or function properly

Prior to NBS, was one of the most common causes of preventable intellectual disability
  • CH screening added by states in late 60s/70s/80s

* Incidence reported to be increasing
NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM

• Screening for CH involves examining one or both of the following*:
  • Thyroid Stimulating Hormone (TSH)
    • Thought to be more specific for Primary CH
  • Thyroxine (T4)
    • Thought to be more sensitive for Secondary CH, but less specific for Primary CH (e.g., higher false positives in low birth weight/premature infants)

* General disagreement exists on which method is best for CH screening
CONGENITAL HYPOTHYROIDISM IS AN UMBRELLA TERM

• **Permanent Primary CH:**
  - True target of Newborn Screening; caused by thyroid gland development or issue with thyroid hormone biosynthesis

• **Permanent Secondary (Central) CH:**
  - Results from defect in TSH production/hypopituitarism; may be detected if using T4 as the primary analyte

• **Transient CH:**
  - Transient abnormality of thyroid function, which later reverts to normal (not well defined)
  - May or may not require treatment, usually challenged around 3 years of age

• **Subclinical CH:**
  - Increased TSH with normal free and total T4 with no overt symptoms in infancy

• **Iatrogenic Hypothyroidism:**
  - Reason for lab finding secondary to medications or interventions
NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM

• Components that make screening for CH difficult:
  • Known endocrine surge at birth – elevated TSH/dynamic T4 changes
    • Results in high false positives, especially on specimens collected early
  • Delayed TSH elevations in premature infants
    • May result in false negatives if subsequent screening is not conducted
  • Known maternal/infant intervention effects
    • Dopamine/Glucocorticoids/Iodine/Cardiac medications
  • Reported possible intervention effects
    • Head Cooling; ECMO
ADJUSTMENTS TO IMPROVE DETECTION OF CH

• Varying cut-offs by age at time of collection
  • Accounts for endocrine surge
  • Relies on integrity of data coming into the program

• Low Birth Weight/Premature Serial Screening Protocol
  • Recommends multiple specimens on low birth weight babies
  • Accounts for delayed elevations seen in premature infants

• Routine 2\textsuperscript{nd} Screen
  • Accounts for delayed elevations seen in premature infants
• **Borderline Screen Result**
  • Request repeat screen or clinical TSH/free T4 labs

• **Presumptive Positive Screen Result**
  • Request clinic TSH/free T4/endocrine consult
  • Urgency depends upon value(s)

• **Potential False Negatives**
  • Clinicians must be encouraged to report these to the NBS program
    • Some states do have mandated reporting of false negatives in statute
  • Especially difficult with CH as many cases are followed by primary care
Reference ranges for clinical TSH and T4 values vary widely

<table>
<thead>
<tr>
<th>TSH Reference Range Provided (uIU/ml)</th>
<th>T4 Reference Range Provided (ng/dL)</th>
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<tbody>
<tr>
<td>0.43 – 16.10</td>
<td>0.70 – 1.80</td>
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<tr>
<td>0.52 – 16.00</td>
<td>0.70 – 2.00</td>
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<tr>
<td>0.55 – 7.10</td>
<td>0.70 – 2.00</td>
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<tr>
<td>0.72 – 13.10</td>
<td>0.70 – 2.00</td>
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<tr>
<td>0.46 – 4.68</td>
<td>0.78 – 2.19</td>
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<tr>
<td>0.50 – 4.80</td>
<td>0.80 – 1.80</td>
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<tr>
<td>0.40 – 3.99</td>
<td>0.70 – 1.70</td>
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<td>0.30 – 4.20</td>
<td>0.80 – 1.60</td>
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<tr>
<td>0.35 – 4.94</td>
<td>0.70 – 1.48</td>
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<tr>
<td>0.30 – 5.00</td>
<td>0.70 – 1.80</td>
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<tr>
<td>0.70 – 11.00</td>
<td>0.83 – 3.09</td>
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<td>0.80 – 1.80</td>
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<td>0.64 – 12.75</td>
<td>0.78 – 1.52</td>
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<td>0.27 – 4.20</td>
<td>0.93 – 1.70</td>
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<tr>
<td>0.20 – 4.50</td>
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<td>0.36 – 3.74</td>
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<td>0.80 – 8.20</td>
<td>0.90 – 1.40</td>
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<td>1.70 – 9.10</td>
<td>0.90 – 1.50</td>
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<td>0.34 – 4.82</td>
<td>0.80 – 2.20</td>
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<tr>
<td>0.34 – 5.60</td>
<td>0.61 – 1.12</td>
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<td>0.50 – 6.00</td>
<td>0.76 – 1.46</td>
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As reported for infants 4 days to 2 months of age
FOLLOW-UP OF CLINICAL TSH/T4 RESULTS

• Determining outcome with such largely variable reference ranges is difficult
  • Program staff and local specialists must decide whether they will:
    A) Accept the value(s) within the context of the reported reference range, or
    B) Choose a value over or under which they will continue to recommend follow-up
  • Approach will likely alter reported incidence and reported outcomes

![Confirmed Primary (Perm and Trans) CH Cases in MN](chart.png)
Given that CH is an umbrella term for several disorders, agreement between lab and follow-up on categorization is critical

- Understanding that primary permanent and transient CH are likely to be lumped together until 3 years of age (and most programs do not have resources to follow cases this long)

Outcome reported back to the laboratory will be dependent upon:

- Follow-up practices
- Clinical expertise in state
  - Specialists differ on preferred screening strategy; definitions of various types of congenital hypothyroidism; treatment approach
• Population screening, especially in the context of rare diseases, is complex beyond the testing itself

• Variable reference ranges/cut-offs are not unique to Newborn Screening
  • Other Population screening programs
  • Clinical diagnostic labs

• Ongoing communication between lab and follow-up staff is vital to the success of any screening program
ACKNOWLEDGEMENTS

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Thank you

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