DEPARTMENT OF HEALTH

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**

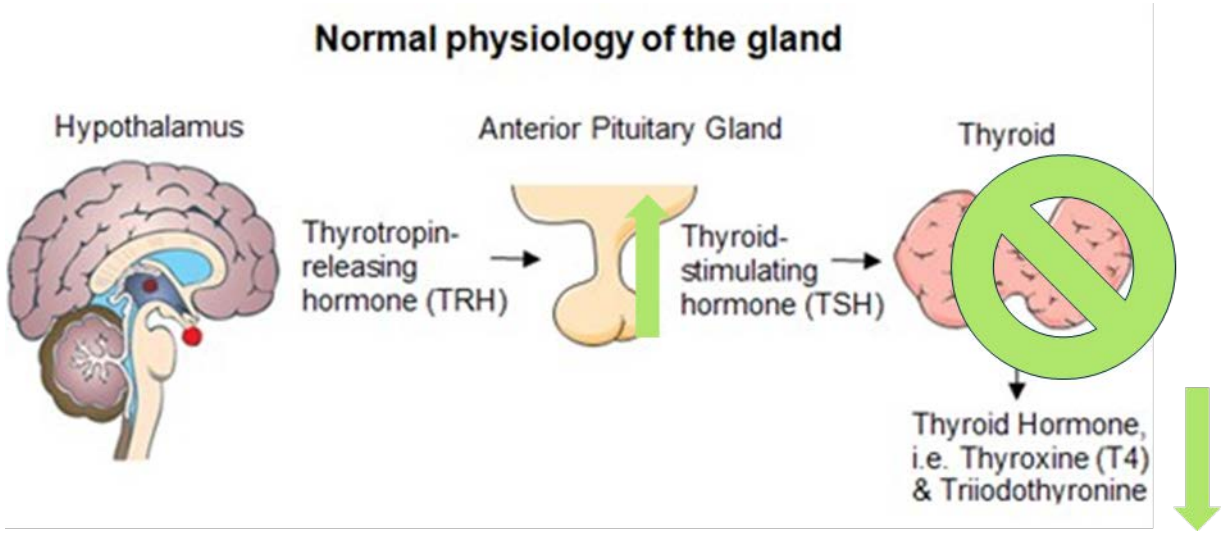
NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM

- **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 2nd Screen**
  - Accounts for delayed elevations seen in premature infants

COMMUNICATION TO AND FROM PROVIDERS

- **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

CLINICAL TSH/T4 RESULTS

- **Reference ranges for clinical TSH and T4 values vary widely**

TSH Reference Range Provided (uIU/ml)	T4 Reference Range Provided (ng/dL)
0.43 – 16.10	0.70 – 1.80
0.52 – 16.00	0.70 – 2.00
0.55 – 7.10	0.70 – 2.00
0.72 – 13.10	0.70 – 2.00
0.46 – 4.68	0.78 – 2.19
0.50 – 4.80	0.80 – 1.80
0.40 – 3.99	0.70 – 1.70
0.30 – 4.20	0.80 – 1.60
0.35 – 4.94	0.70 – 1.48
0.30 – 5.00	0.70 – 1.80
0.70 – 11.00	0.83 – 3.09

TSH Reference Range Provided (uIU/ml)	T4 Reference Range Provided (ng/dL)
3.20 – 21.00	0.80 – 1.80
0.43 – 16.10	0.70 – 1.80
0.64 – 12.75	0.78 – 1.52
0.27 – 4.20	0.93 – 1.70
0.20 – 4.50	0.70 – 1.50
0.36 – 3.74	0.76 – 1.46
0.80 – 8.20	0.90 – 1.40
1.70 - 9.10	0.90 – 1.50
0.34 – 4.82	0.80 – 2.20
0.34 – 5.60	0.61 – 1.12
0.50 – 6.00	0.76 – 1.46

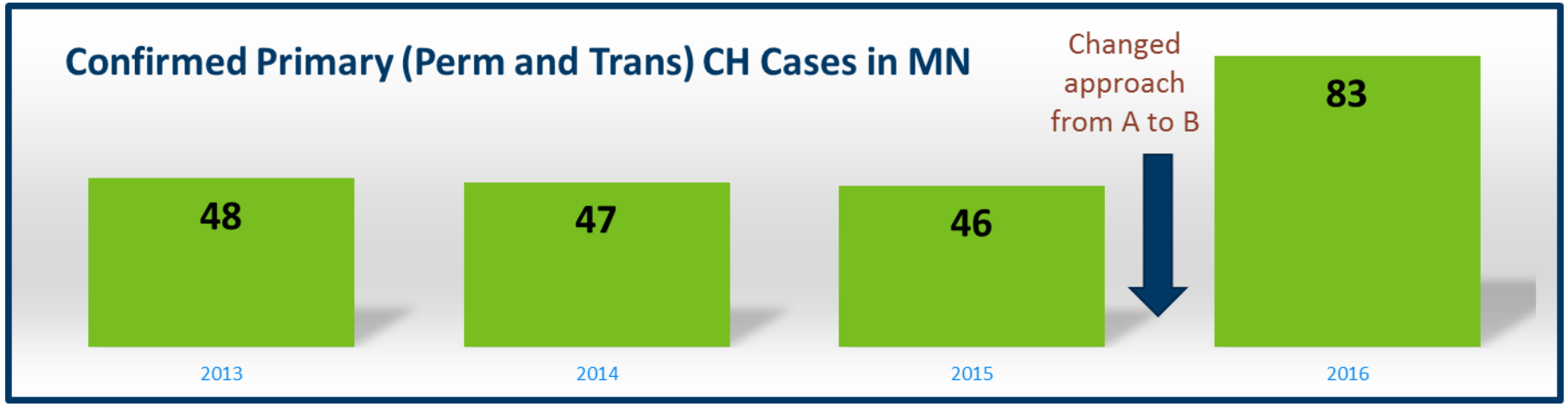
As reported for infants 4 days to 2 months of age

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



CATEGORIZATION AND FOLLOW-UP DICTATE INCIDENCE

- **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

TAKE HOME MESSAGES

- **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**

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DEPARTMENT OF HEALTH

Thank you

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