AACC | Better health through laboratory medicine.

Improving Children's Health Through Better Laboratory Testing

Wednesday, February 27, 2019

Luncheon Briefing: 11:30 am – 12:30 pm

Room HC-8, The Capitol

Improving Children's Health Through Better Laboratory Testing

Moderator:

- Dr. David Koch

Speakers:

- Dr. Dennis Dietzen
- Dr. Patrick Mason
- Dr. Hubert Vesper

Pediatric Reference Intervals – Why? How? Now?

Dennis J. Dietzen, PhD, DABCC, FAACC
Immediate Past President, AACC
Professor of Pediatrics and Pathology
Washington University School of Medicine
Medical Director, Lab Services
St. Louis Children's Hospital

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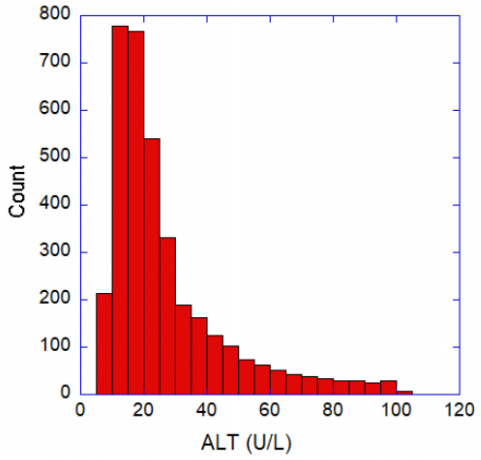
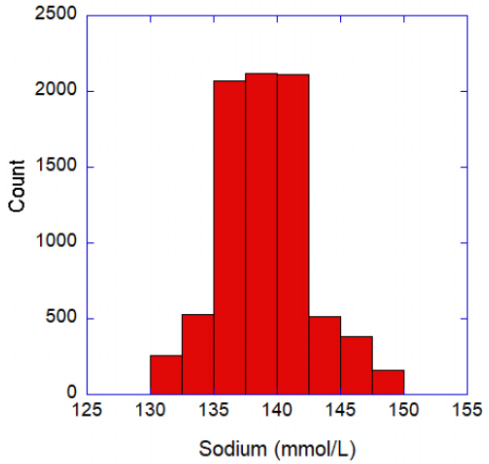
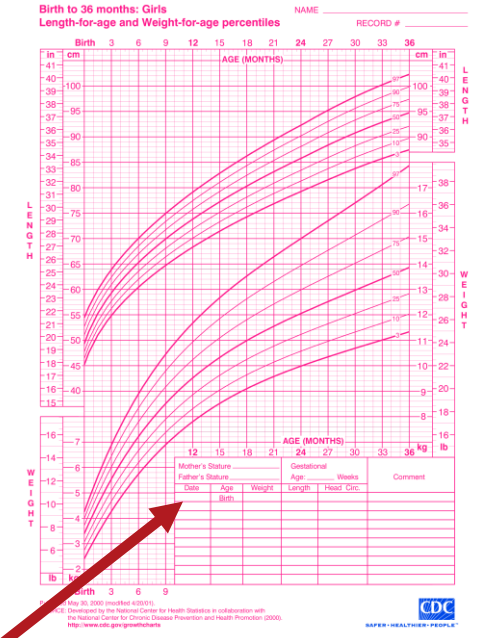
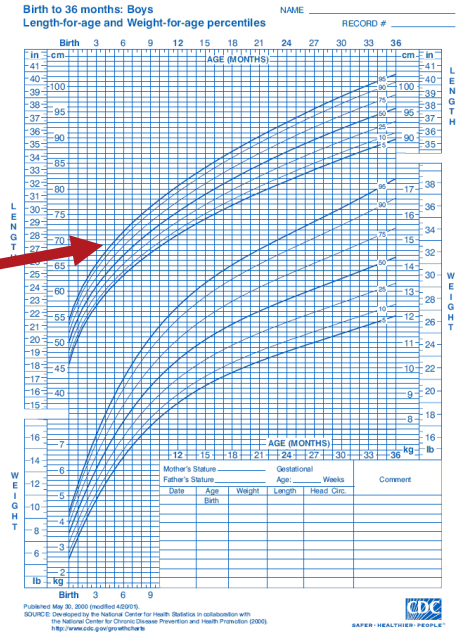
What is a Reference Interval?









- Age
- Gestational Age
- Developmental Age
- Genetics
- Weight
- Birth-weight
- Ethnicity
- Geography
- Diet
- Drugs
- Season
- Posture
- Method
- Equipment

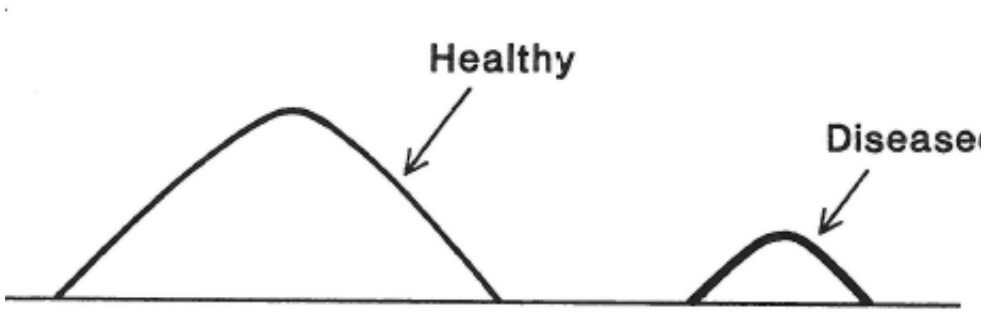
How do we use Pediatric Reference Intervals?

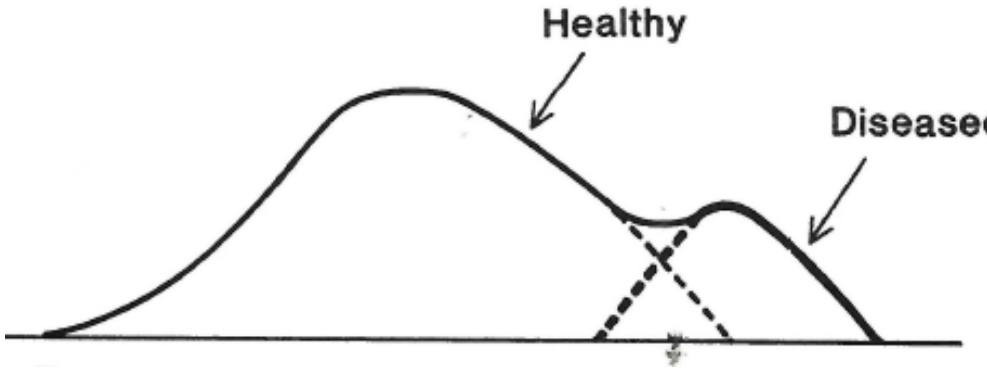
Component	Latest Ref Rng & Units	11/29/2018	11/30/2018	12/1/2018	12/3/2018	12/5/2018	12/8/2018	12/10/2018	12/12/2018	12/15/2018
										6:48 AM
Sodium	135 - 145 mmol/L	136	139	136	137	141	136	136	138	137
Potassium, pl	3.3 - 4.9 mmol/L	2.9 (L)	2.7 (L)	3.2 (L)	3.0 (L)	3.7	4.2	4.9	3.9	5.1 (H)
CO2	20 - 30 mmol/L	23	24	22	24	27	27	27	26	25
BUN	9 - 18 mg/dL	5 (L)	5 (L)	5 (L)	7 (L)	8 (L)	12	13	12	13
Glucose	70 - 199 mg/dL	120	97	108	145	131	119	98	128	94
Creatinine	0.40 - 1.00 mg/dL	0.38 (L)	0.44	0.33 (L)	0.34 (L)	0.30 (L)	0.32 (L)	0.35 (L)	0.38 (L)	0.37 (L)
Calcium	8.5 - 10.3 mg/dL	9.0	8.7	8.4 (L)	8.7	9.1	9.0	9.5	9.0	9.1
Chloride	100 - 114 mmol/L	105	108	109	108	108	105	104	104	106
Anion Gap	2 - 15 mmol/L	8	7	5	5	6	4	5	8	5

How do we use Pediatric Reference Intervals?

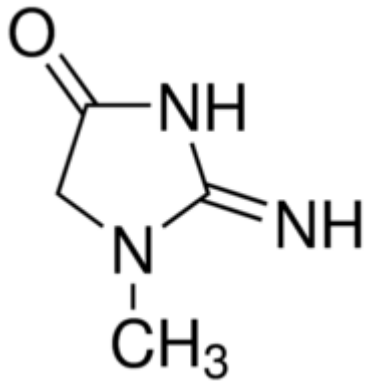
Amino Acid	Result (mcmol/L)		Reference Range (mcmol/L)
Phenylalanine	69		35-90
Tyrosine	49		25-85
Isoleucine	89	HIGH	15-75
Leucine	121		40-150
Valine	281		85-320
Allo-Isoleucine	0		0-2
Threonine	206	HIGH	40-200
Serine	191		90-200
Glycine	163		125-300
Methionine	48		10-50
Homocystine	0		0
Cystathionine	0		0
Cystine	8	LOW	10-50
Glutamine	705		475-750
Glutamic Acid	177	HIGH	60-130
Citrulline	50	HIGH	10-40
Argininosuccinic Acid	0		0
Arginine	73		70-160
Ornithine	45		30-200
Homocitrulline	2		0-2
Alanine	302		150-400
Hydroxyproline	19		0-50
Proline	317	HIGH	110-230
Lysine	215	HIGH	85-205
a-Amino Adipic Acid	1		0-5
B-Amino Isobutyric Acid	7	HIGH	0-5
B-Alanine	3		0-20
Sarcosine	3		0-5
Gamma-Amino Butyric Acid	0		0-5
Histidine	76		25-100
Carnosine	0		0-2
a-Amino Butyric Acid	20		0-50

What Happens if we don't have Accurate Pediatric Reference Intervals?

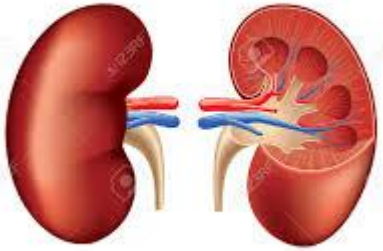


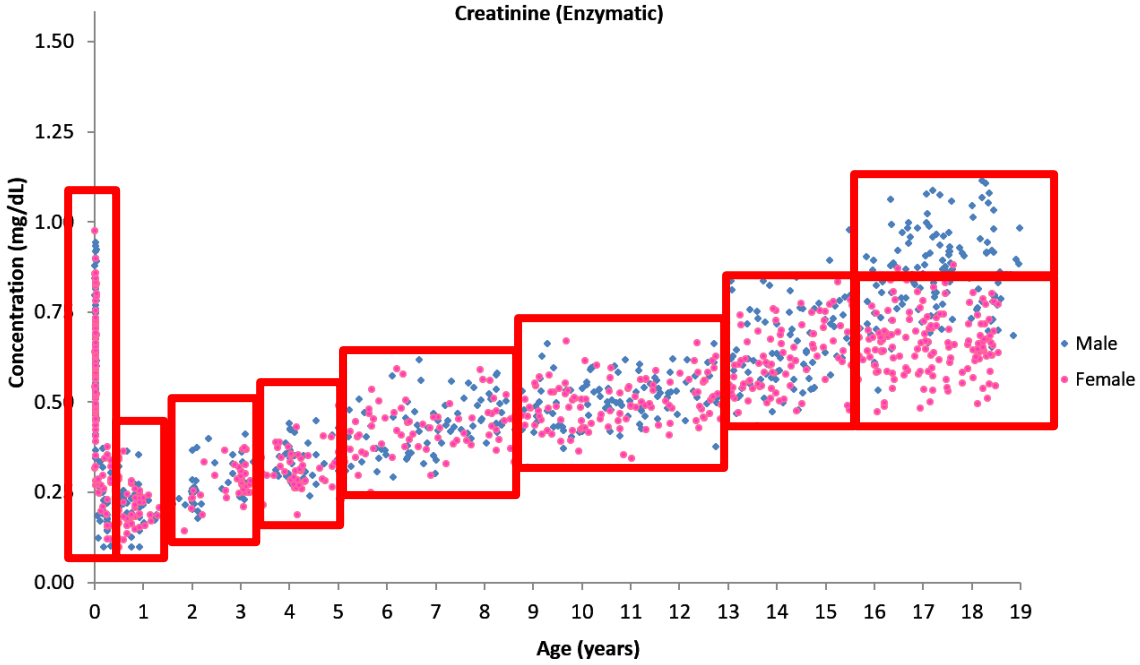


Why are Pediatric Reference Intervals so hard to build?



Creatinine





Bins: Age + Gender

9 bins x 120 individuals =

1080 “Healthy Volunteers”

What do we need to build better Pediatric Reference Intervals?

- A large cohort of “healthy” children from birth through adulthood.
- Cohort with maximal gender, geographic, and ethnic diversity
- Associated physical data (e.g., height, weight, diet, sexual development)
- Sample collection infrastructure
- Sample processing and storage infrastructure
- Sample analysis infrastructure
- Data analysis infrastructure

Parting Thoughts about Pediatric Reference Intervals

- Reference intervals are key to medical decision making.
- Reference intervals depend on geography, gender, diet, season, time of day…..
- Accurate reference intervals require large numbers of healthy participants.
- Pediatric reference intervals must account for rapid growth and development.
- There are large gaps and mistakes in current pediatric reference intervals.
- Recent progress has been promising.
- Much more to do……..

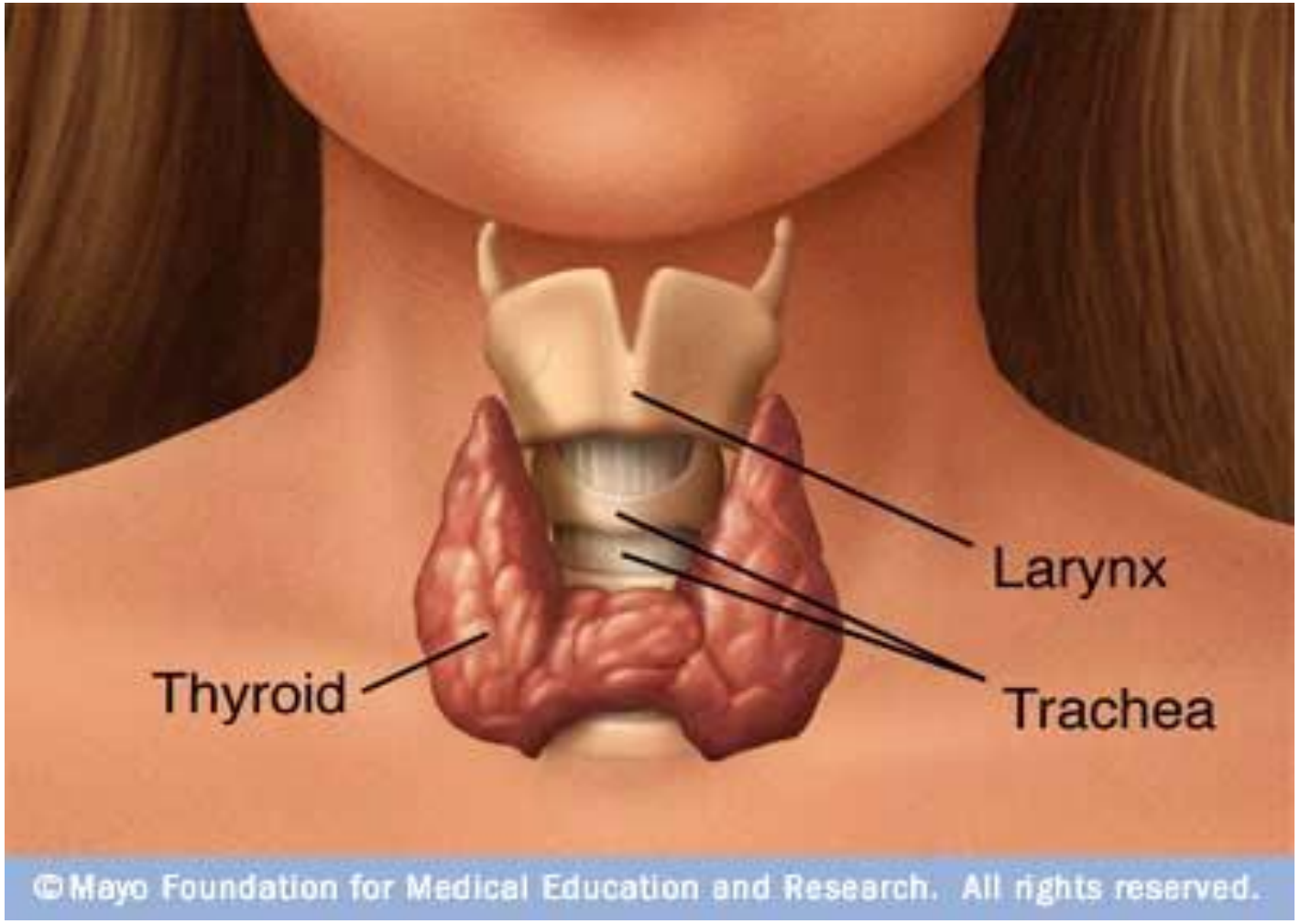
Thank you!

Importance of Pediatric Reference Intervals – Clinical Cases

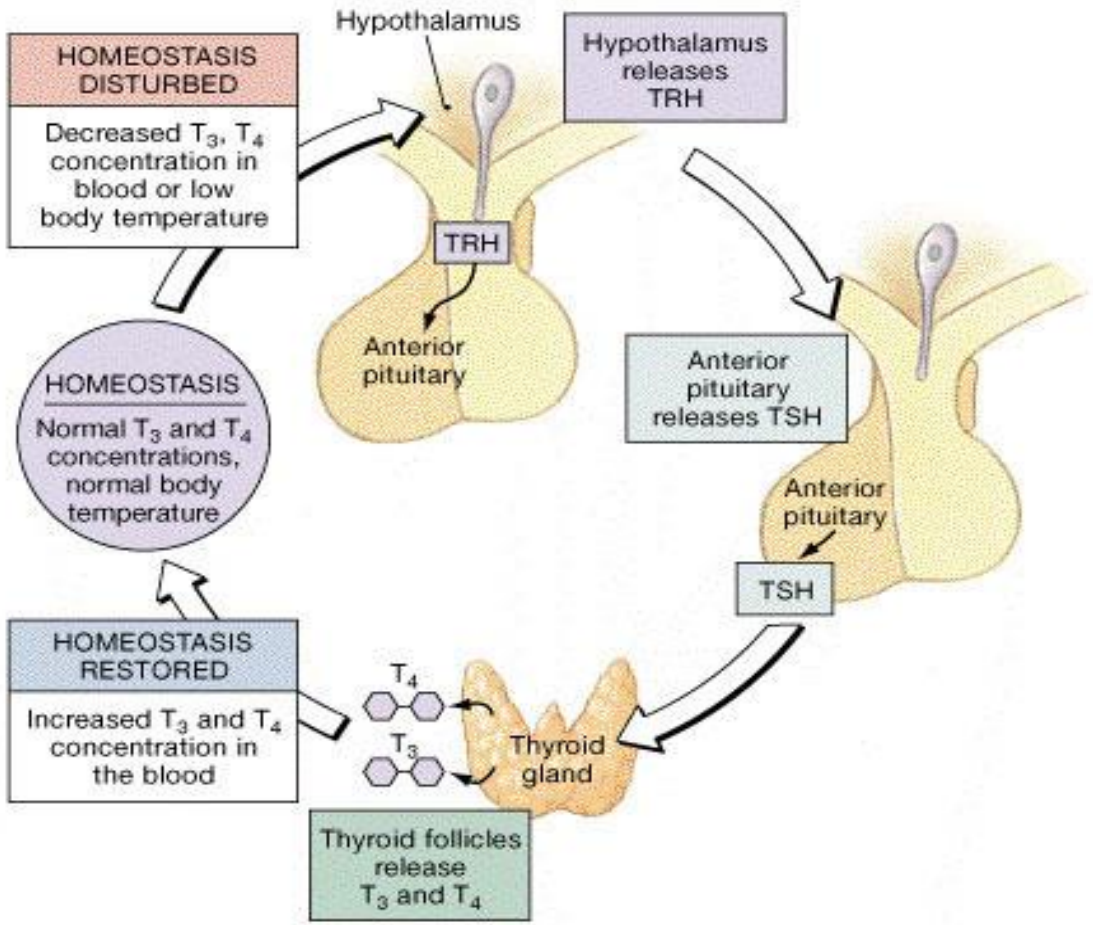
Patrick Mason, MD, PhD
Regional Medical Director
Quest Diagnostics

Children are not Little Adults

Location of the Thyroid Gland



Regulation of Thyroid Hormones



Thyroid Abnormalities – In Adults

- Hypothyroid (Low)
  - Tired
  - Weight gain
  - constipation
  - dry skin
  - brittle hair
  - cold intolerance
  - See High or normal TSH and low T4
- Hyperthyroid (High)
  - Tired but trouble sleeping
  - Weight loss
  - loose and frequent stools
  - increased sweating
  - heat intolerance
  - Often high T4 and low TSH

Thyroid in Babies

- Umbilical hernia
- Large tongue
- Poor feeding
- Coarse facial features
- Low muscle tone
- Hearing loss
- May cause Severe growth failure
- Mental retardation – many parts of the world it's the leading cause of preventable mental retardation

All symptoms can be prevented with early diagnosis and treatment

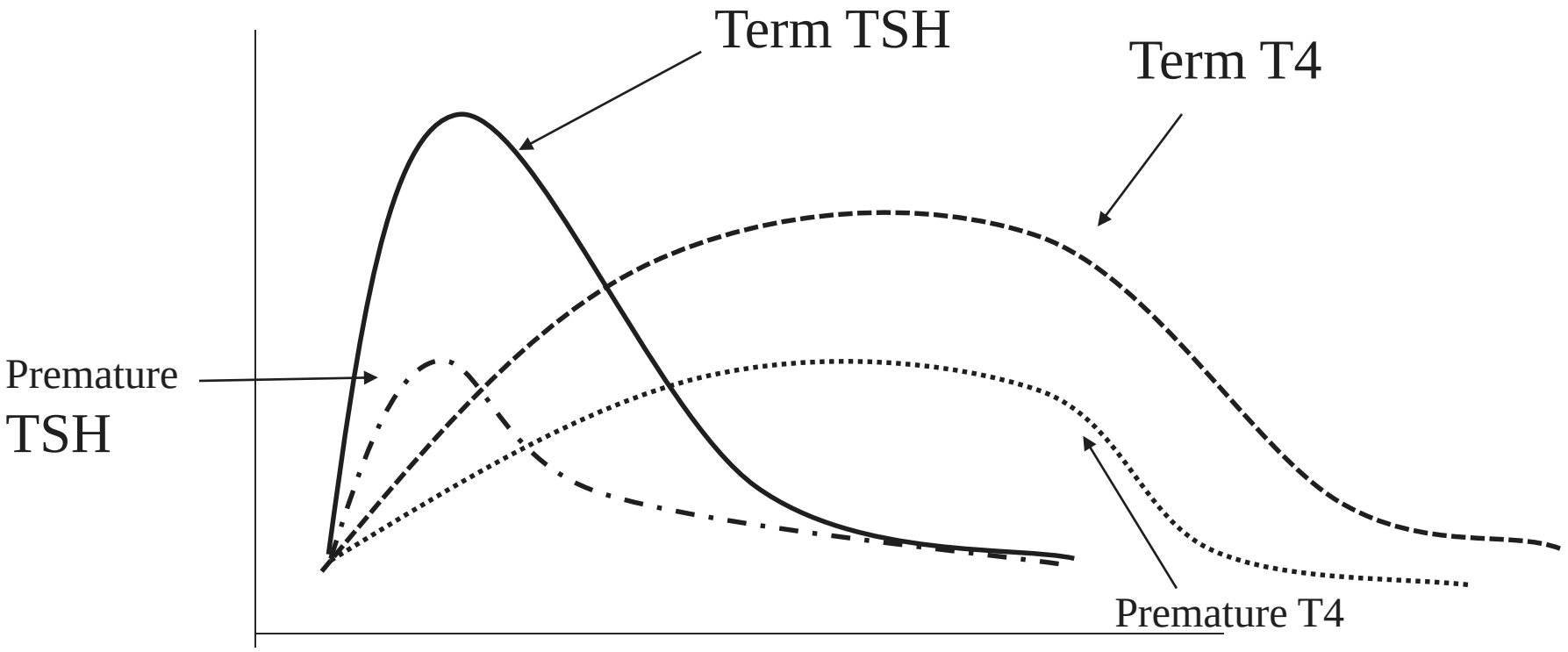
Case One

- You are called by State newborn screening about one day old full term baby's state screen
    - T4 15 mcg/dL (adult normal – 4.8-10.4 mcg/dL)
    - TSH 40 miU/L (adult normal - 0.4-4.5 mIU/L)
- Should you treat the baby?
- What should be done next?

Newborn Screening

- US programs initially screen for T4 with TSH secondary screen
- Screen by 3-5 days most reliable
- Blood spots on day 1 elevated due to physiologic neonatal TSH surge.
    - Early discharge increase false positives to 5:1

Thyroid Hormone in the Infants



Diagnosis???

Premature testing with elevation secondary to newborn surge

Case Two

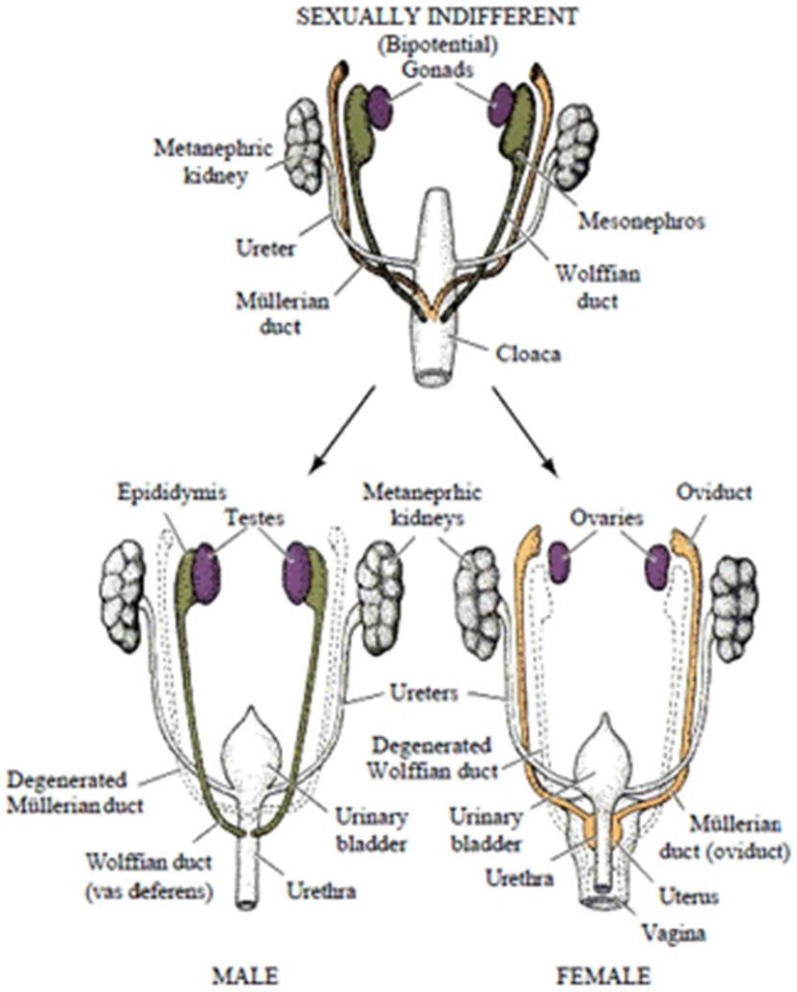
- Called to the newborn nursery to evaluate a baby
- Past history was significant for
    - 25 year old mother who just delivered her first child
    - No prenatal issues or concerns noted
    - Physical examination showed a baby with normal vital signs
    - Physical examination was unremarkable except…….
        - The child had a normal penis but no testicles were noted on examination.

Evaluation of the baby?

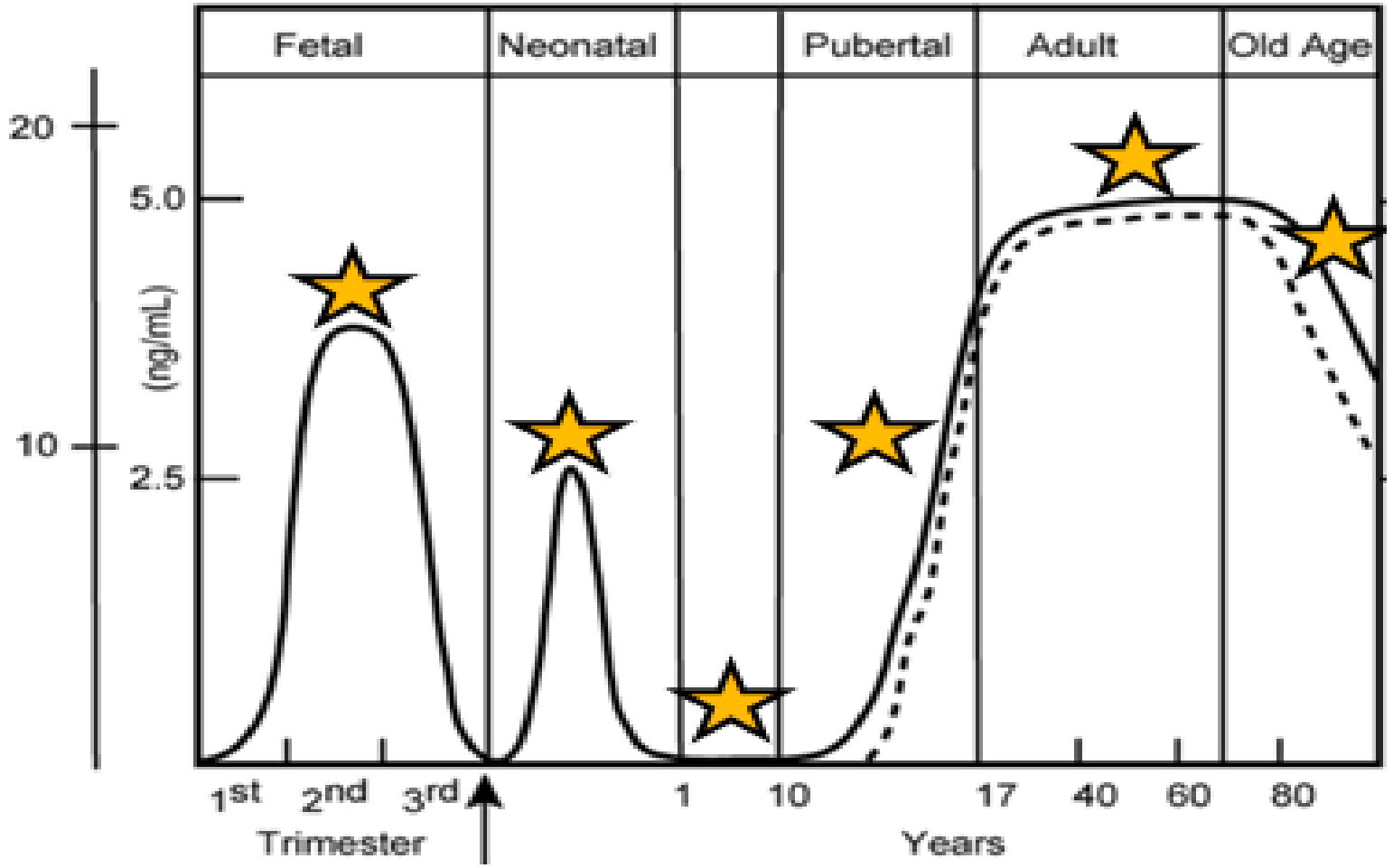
- Hormonal evaluation showed low levels of testosterone at 1 week of age.
- Parents want to know if their child was a boy or girl
- What do you tell them?

Bipotential Gonads and Ducts

- Virilization- “Becoming a boy”
  - Begins around 7 weeks done by 13 weeks
- If SRY found on Y chromosome then gonads become testicles.
- Testicles make
  - AMH which causes regression of Mullerian structions
  - Testosterone preserves Wolffian structures



Testosterone levels – throughout life



Laboratory follow up

- Baby's testosterone levels at 8 weeks were 250 ng/dL
- Ultrasound showed presence of testicles
- Surgery will bring testicles into the boys scrotum.

Thank you!

Expertise at CDC to generate better pediatric reference intervals

Hubert W. Vesper, PhD

Director, Clinical Standardization Programs

Division of Laboratory Sciences

National Center for Environmental Health

Agency for Toxic Substances and Disease Registry

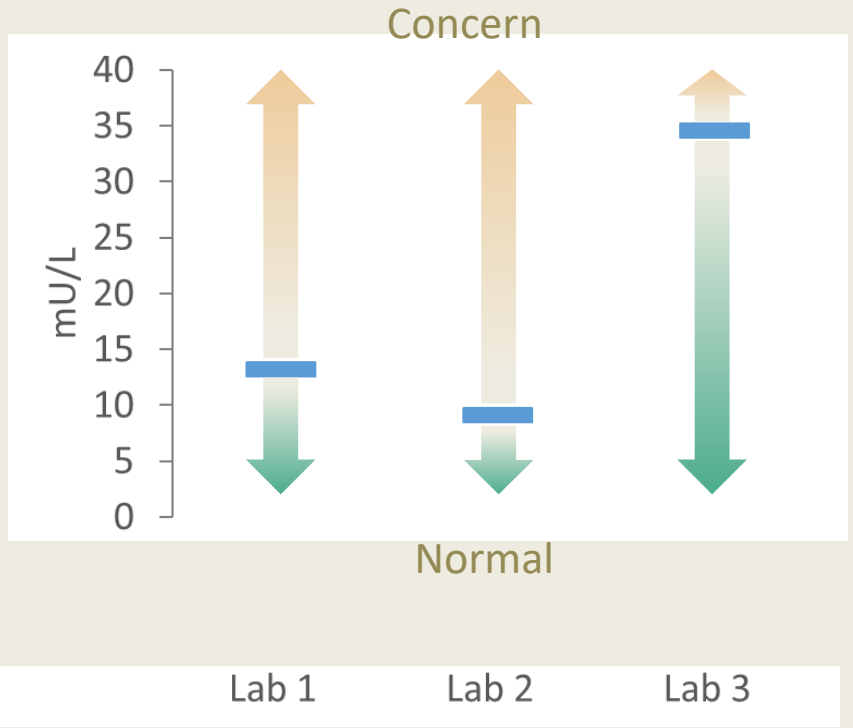
Division of Laboratory Sciences

Problem: Pediatric reference intervals used by laboratories are very inconsistent

Pediatric reference intervals describe biomarker levels in healthy children

Pediatric reference intervals are not sufficiently consistent and accurate to reliably diagnose and treat children in a cost-effective manner

Upper level of normal
for thyroid stimulating hormones
in children less than 1 week old
used in 3 labs

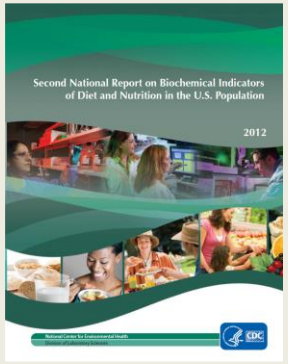


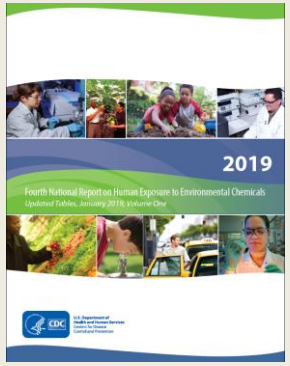
Solutions: Common pediatric reference intervals

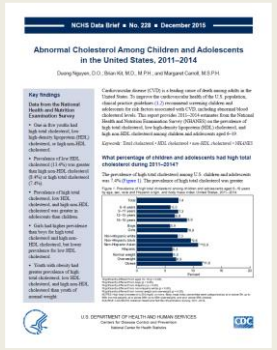
- Created using well-characterized children
- Measured with reliable and accurate laboratory tests

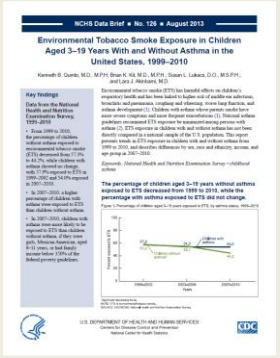
CDC Environmental Health Laboratory together with Division of Health and Nutrition Examination Surveys

has a good track record in developing and applying highly accurate and reliable laboratory tests in well-characterized pediatric populations





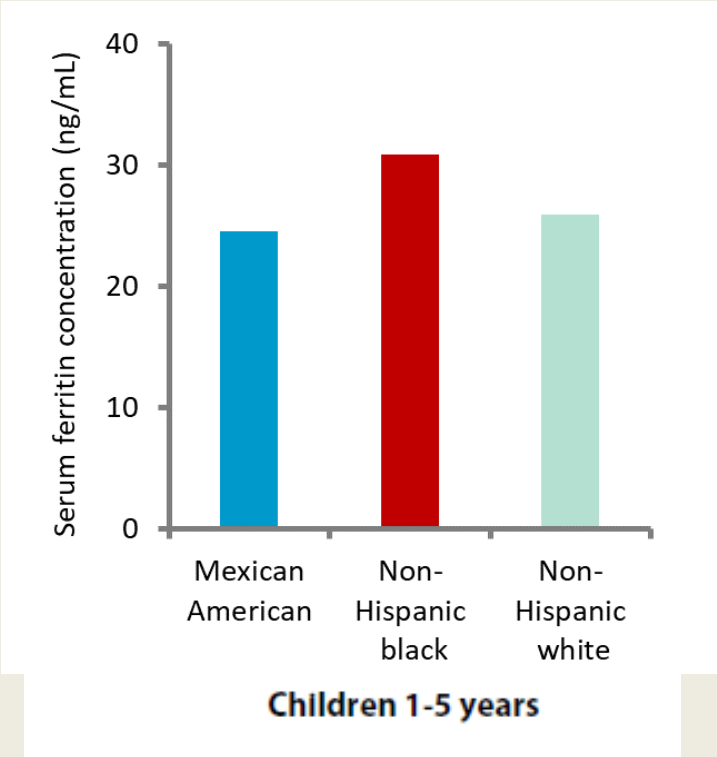




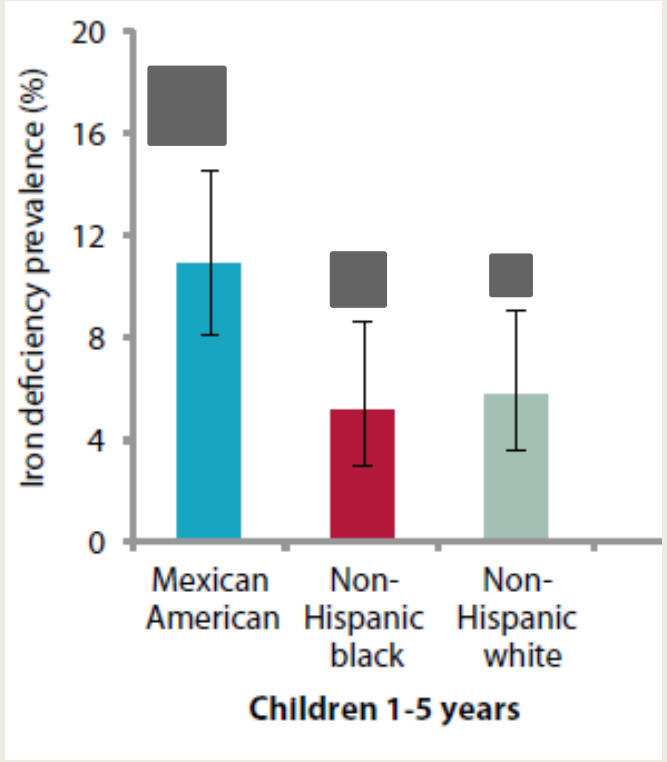
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

CDC NHANES data on iron-status indictors help health care providers identifying iron deficiency in children

Iron-status biomarker levels in children



Prevalence of iron deficiency in children

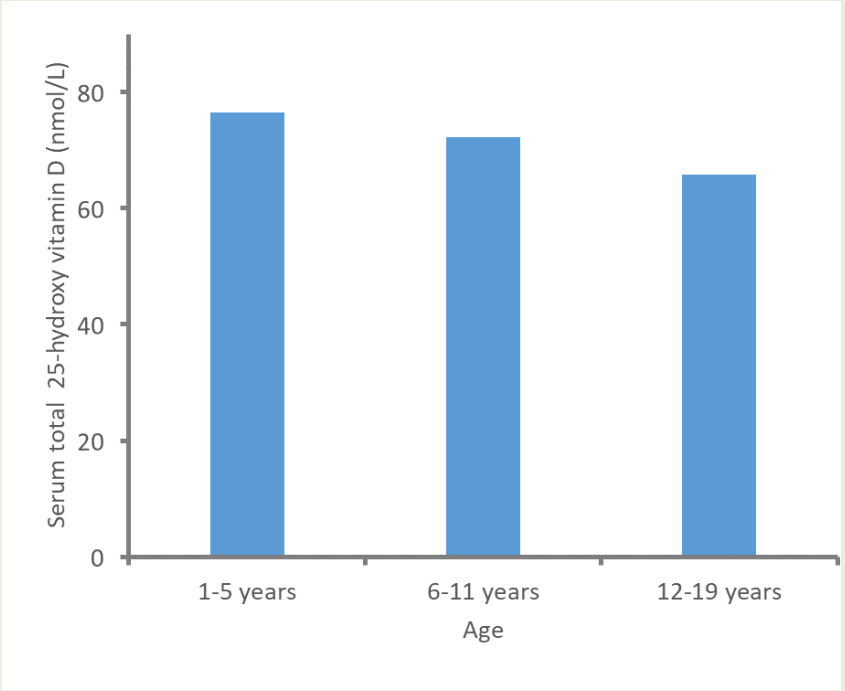


Source: 2nd National Report on Biochemical Indicators of Diet and Nutrition in the U.S. Population. https://www.cdc.gov/nutritionreport/index.html

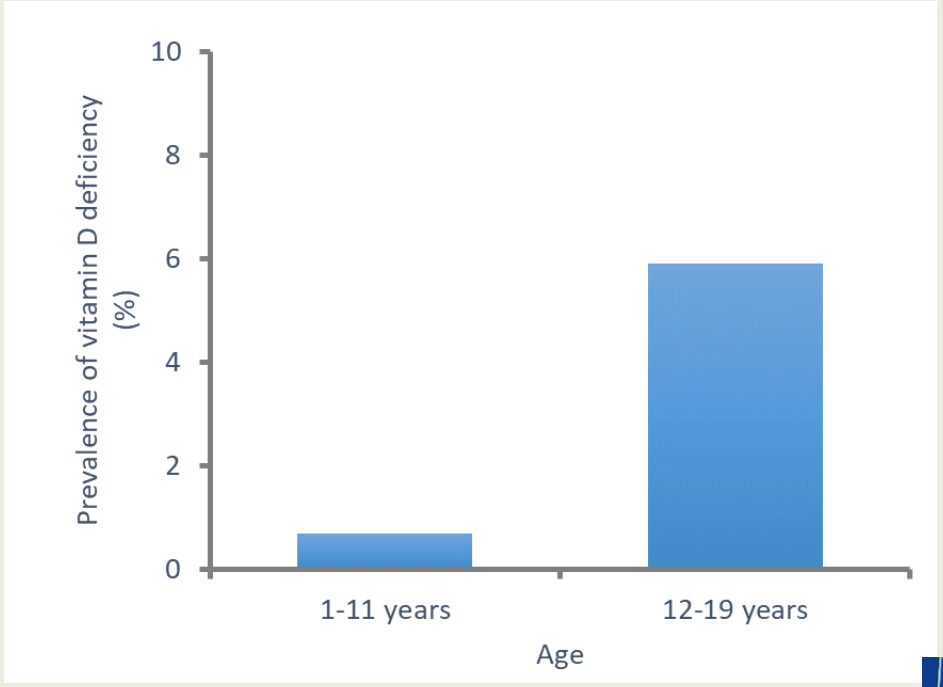
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

CDC NHANES data on vitamin D
help health care providers identifying children with vitamin D deficiency at risk for rickets

Vitamin D concentrations in children



Prevalence of vitamin D deficiency in children



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CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

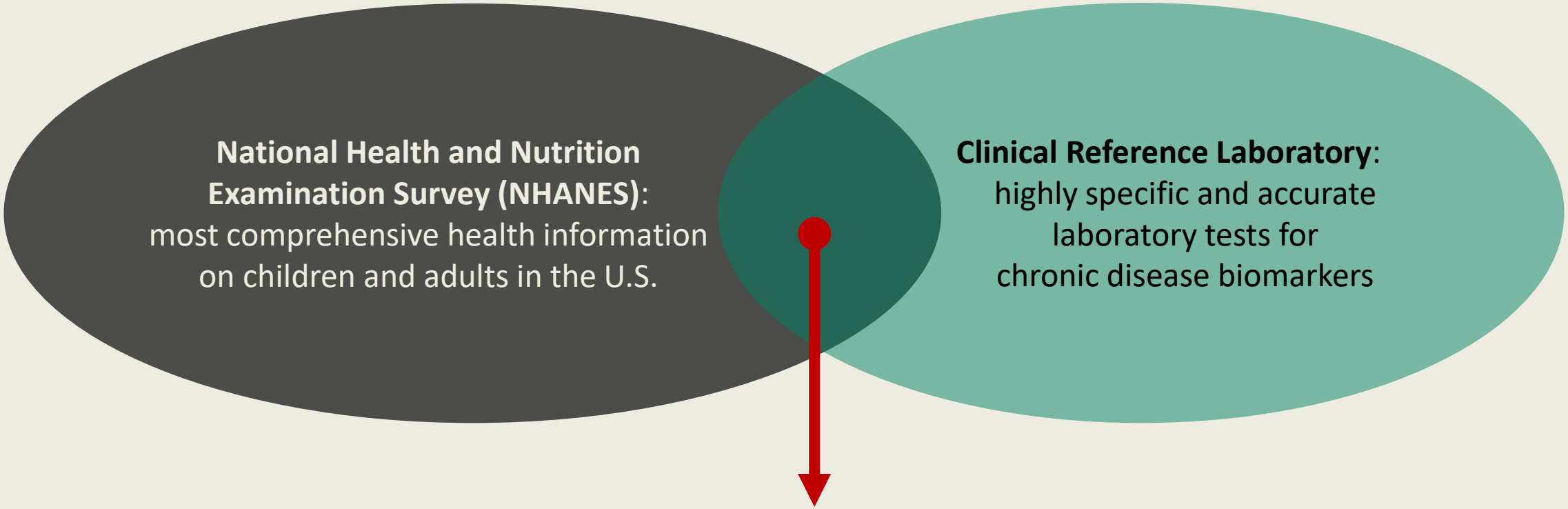
CDC creates data that are widely used by health care providers and clinical laboratories

- CDC reference intervals are broadly accepted by clinical laboratories and physicians

More reference intervals in children at all stages of development are needed

National Center for Health Statistics
Division of Health and Nutrition Examination Surveys

CDC Environmental Health Laboratory



Accurate and reliable laboratory data
suitable to establish pediatric reference intervals
for laboratories and health care providers

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

NHANES provides data on over 30 health and disease biomarkers in children and adolescents

Examples:

- Hormones
- Lipids
- Iron Status

More biomarker measurements are needed

CDC Environmental Health Laboratory together with NCHS's Division of Health and Nutrition Examination Surveys

- conduct the only survey highly suitable to collect appropriate specimens and data from children in the U.S. population
- have highly accurate and reliable laboratory tests that generate data applicable to all clinical laboratories and health care providers

THANK YOU

For more information, contact NCEH/ATSDR
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Questions?