Laboratory Testing for Pediatric Patients: Concerns, Challenges and Solutions

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Medical Director, ARUP Laboratories
Endocrinology and Core Laboratories
Outline

ARUP: Background, Resources, Research and Development

Pediatric Reference Intervals: Challenges and Concerns

CHILDx Initiative

Current Improvements and Future Developments

Conclusions and Questions
Outline

ARUP: Background, Resources, Research and Development

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CHILDx Initiative

Current Improvements and Future Developments

Conclusions and Questions
ARUP: More Than a Lab

- Formed in 1984
- Privately held
- Nonprofit enterprise of the University of Utah and its Department of Pathology

70 medical directors and consultants (board certified; MD and/or PhD)

Department of Pathology
ARUP: More Than a Lab

- Has one of the broadest test menus in the industry
  - > 3,000 tests and test combinations
- Performs 99 percent of all testing on-site
- Operates 24 hours per day, seven day a week
- Processes more than 30,000-35,000 specimens of blood, body fluid, and tissue biopsies per day
ARUP: Pediatric Hospitals Are Well Served

The Children’s Hospital of Philadelphia®
Hope lives here.

Cincinnati Children’s®

Seattle Children’s hospital • research • foundation

Nationwide Children’s
When your child needs a hospital, everything matters.

Intermountain
Primary Children’s Hospital
The Child First and Always®

Shriners Hospitals for Children®
Love to the rescue®
ARUP is the most automated laboratory in North America

Bottom line: Consistent handling of specimens, patient safety
ARUP Institute for Clinical and Experimental Pathology®

- Research arm of ARUP Laboratories
- Founded in 1996
- More than 50 technical sections, 50 medical directors, and 75 scientists
- Unique combination of investigator-initiated and goal-oriented research effectively brings new tests to market and improves existing assays, ultimately improving patient care

MAJOR FOCUS AREAS:

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Creating new lab tests</td>
</tr>
<tr>
<td>Improving current lab tests</td>
</tr>
<tr>
<td>Evaluating lab tests (including testing site protocols)</td>
</tr>
<tr>
<td>Basic and clinical research</td>
</tr>
</tbody>
</table>
ARUP Institute for Clinical and Experimental Pathology®

1600

# of peer-reviewed research publications in leading journals published by ARUP research scientists (since 2000)

600

# in-house tests developed by the institute

200

# improved and validated

400

# developed by institute scientists
Pediatric Testing

Why do so many children’s hospitals in the United States use ARUP as their reference laboratory?

R&D
• Approximately 10 percent of ARUP R&D budget is used for test development related to pediatrics

Extensive menu
• Accommodates more than 99 percent of pediatric testing requests
• Majority performed at ARUP
  • Allows children’s hospitals to be more operationally efficient

Test Interpretation
• Pediatric Pathology Consultation Services
  • Academic affiliation with University of Utah’s Division of Pediatric Pathology
• ARUP Consult
  • Physician’s Guide to Laboratory Test Selection and Interpretation
Pediatric Testing – Specialty Services

- Biochemical genetics
- Electron microscopy
- Fetal autopsy
- Kidney and liver
- Molar pregnancy
- Muscle and nerve
- Pediatric pathology (including tumors)
- Perinatal pathology
- Placental pathology
ARUP Consult®

ARUP Consult® is a laboratory test selection support tool with more than 2,000 lab tests categorized into disease-related topics. Topics include clinical background information, concise diagnostic advice, screening and monitoring recommendations, pharmacogenetics information, test ordering suggestions, and algorithms to support clinical decision-making. All information is congruent with national guidelines and includes direct links to relevant references. For more information on how we create and maintain our content, please see our editorial policy.

Related ARUP Websites

- ARUP Scientific Resource for Research and Education – offers the opportunity to earn free continuing medical education credits
- ARUP Pain Management – pain management test menu, reports, and resources

Visit the iTunes Store today and join the thousands who have already downloaded the ARUP Consult app!
Diabetes Mellitus

Diagnosis

Indications for Testing
- Known risk factors for DM type 2
  - Obesity (BMI > 25 kg/m²) – consider testing to detect pre-DM and DM type 2 in asymptomatic people
  - Family history of DM type 2 in first- or second-degree relative
  - Race/ethnicity – Native American, African American, Latino, Asian American, Pacific Islander
  - Signs of insulin resistance or conditions associated with insulin resistance (acenthosis nigricans, hypertension, dyslipidemia, PCOS, low birthweight)
  - Maternal history of DM or GDM during gestation

Criteria for Diagnosis
- Consensus criteria for the diagnosis of DM, impaired glucose, or GDM [American Diabetes Association (ADA) 2011, American Association of Clinical Endocrinologists (AACE), United States Preventive Services Task Force (USPSTF), WHO (2010)]
- Diagnosis must meet one of the following
  - Fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L)
    - Fasting is defined as no caloric intake for at least 8 hours
  - Symptoms of DM and a casual plasma glucose ≥ 200 mg/dL (11.1 mmol/L)
    - Casual is defined as any time of day without regard to time since last meal
    - Classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss
  - 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (OGTT)
    - Test should be performed as described by WHO using a glucose load containing the equivalent of 75 grams of anhydrous glucose dissolved in water
  - HbA1c ≥ 6.5%
  - Impaired glucose tolerance
    - Fasting plasma glucose 100-125 mg/dL (5.6-6.9 mmol/L)
    - 2-hour plasma glucose 140-199 mg/dL (7.8-11.0 mmol/L) during OGTT
    - HbA1c 5.7-6.4%
  - Testing to differentiate DM type 1 from type 2
    - Insulin antibodies
    - ADA (2008)
Adrenal Hyperfunction (Cushing Syndrome) Testing

INDICATIONS FOR TESTING
Suspected Cushing Syndrome
(central obesity, muscle weakness, refractory hypertension)

Rule out Metabolic Syndrome or Polycystic Ovarian Syndrome

ORDER
Cortisol Urine Free by LC-MS/MS

>60 µg/day male
>45 µg/day female

no

>60 µg/day male
>45 µg/day female

Repeat Cortisol Urine Free by LC-MS/MS test

normal

>50 µg/day male
>45 µg/day female

Cushing Syndrome unlikely; no further testing

Cushing Syndrome likely

Low dose dexamethasone suppression test (DST) protocol:
1 mg dexamethasone PO (taken between 11 pm and midnight)

Then measure at 8 am the following morning:
Cortisol, Serum or Plasma
(or Cortisol Urine Free by LC-MS/MS)

no

Urine cortisol <7.2 µg/day or serum cortisol <3 µg/dL

ORDER
Adrenocorticotrophic Hormone

<5 pg/mL
<200 pg/mL
≥200 pg/mL

Cushing Syndrome unlikely; however, if high suspicion, repeat with high dose DST (4 mg taken between 11 p.m. and midnight) over 2 days
AND ORDER
Cortisol, Serum or Plasma

Serum Cortisol <3 µg/dL
Outline

ARUP: Background, Resources, Research and Development

**Pediatric Reference Intervals: Challenges and Concerns**

CHILDX Initiative

Current Improvements and Future Developments

Conclusions and Questions
How are reference intervals determined?

1. Identify a reference population
2. Measure analyte
3. Determine the most common results
4. Establish lower and upper limits of “healthy”
Reference Intervals (RIs): Standard Approaches

- Verify
  - 20 samples per partition
- Establish
  - 120 samples per partition
Establishing RIs: Number of Healthy Adults Studied

Potassium
N = 129 labs

- 21-50 (50%)
- 51-100 (22%)
- > 100 (25%)
- 20 (3%)
Lab Values Throughout Childhood: Moving Targets
Establishing Pediatric RIs: Inherent Challenges

- Healthy volunteers
  - Define “healthy”
  - Consent
  - Research Ethics Board
- Dynamic testing
- Tanner staging
  - Subjective
- Sampling limitations
- Numerous partitions
  - Appropriate, relevant
Establishing Pediatric RIs: Statistical Approaches

Validity of establishing pediatric reference intervals based on hospital patient data: A comparison of the modified Hoffmann approach to CALIPER reference intervals obtained in healthy children

Julie L.V. Shaw\textsuperscript{a,b,1}, Ashley Cohen\textsuperscript{a}, Danijela Konforte\textsuperscript{a,b,2}, Tina Binesh-Marvasti\textsuperscript{b}, David A. Colantonio\textsuperscript{a,b}, Khosrow Adeli\textsuperscript{a,b,*}

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\textsuperscript{b} Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
Establishing Pediatric RIs: Statistical Approaches

Findings:

- Reference intervals based on hospitalized populations are commonly wider than those based on healthy populations.
- Ideally, >50% of data from healthy individuals (Soldin et al., Clin Biochem 2008;41:937).
- RI validation per CLSI guidelines may not be appropriate in pediatric populations.
- *Hoffmann statistical approach is limited in pediatrics, particularly when data originates from tertiary care center.*
Letter to the Editor

Limitations of the Hoffman approach to determine pediatric reference intervals for two steroids

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Department of Internal Medicine, University of Utah,
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16 July 2009
Evaluating Existing Pediatric RIs: Critical Questions

- Reference population?
  - Small sample number
  - Data mining or indirect-sampling
  - Sick vs. healthy
  - Test bias
  - Tanner staging

- Method?
  - Method specific
  - Outdated methods

- Historical literature?

- Rampant adoption without validation
  - Lab to lab to lab…
  - Method specific
  - Are RIs even valid anymore?
Pediatric RIs: Sources

- Pkg Insert: 44%
- Literature, Textbooks: 24%
- Internal Study: 16%
- Other Labs (Internal Validation): 11%
- Medical Staff Recommendation: 4%
- Other: 3%
- Other Labs (No Internal Validation): 5%

TSH
N = 134 labs

From: Friedberg et al., Arch Pathol Lab Med (2007) 131:348
Practical Concerns in Pediatric Testing

Sample volumes:

• Adequate volume for dilution
• Adequate volume for repeat testing
• Multiplex testing when possible
• Avoid sample splitting
Outline

ARUP: Background, Resources, Research and Development

Pediatric Reference Intervals: Challenges and Concerns

CHILDx Initiative

Current Improvements and Future Developments

Conclusions and Questions
• Formed in 1999
• Address:
  – Poor number of analytes
  – Poor sample size
• Board of Directors established, 15 institutions
• Largest U.S. study of its kind
National Advisory Board:

- Marzia Pasquali, PhD: Chair
- Edward Ashwood, MD
- Mark Astill, MS
- Phillip Bach, PhD
- Carlo Brugnara, MD
- Gregory Buffone, PhD
- Cheryl Coffin, MD
- Sharon Geaghan, MD
- Marilyn Hamilton, MD, PhD
- Harry Hill, MD
- Patricia Jones, PhD
- Michael Laposata, MD, PhD
- Nicola Longo, MD, PhD
- Naomi Luban, MD
- Wayne Meikle, MD
- Mary Murray, MD
- Jeanne Panlener, MS, MT(ASCP)
- Sherrie Perkins, MD, PhD
- Deborah Perry, MD
- Maria Proytcheva, MD
- Theodore Pysher, MD
- William Roberts, MD, PhD
- Joe Rutledge, MD
- Suresh Shelat, MD, PhD
- Paul Steele, MD
- Darrel Yamane, MBA
Goal: Establish reference intervals for pediatric patients, for a wide variety of analytes
ARUP Pediatric Reference Interval Study:

Blood specimens were collected from healthy children 6 months through 17 years of age. Demographic information and health histories were obtained from each subject.

6 mos through 6 yrs

7 yrs through 17 yrs
6 Months Through 6 Years:

- Started 2006, collection ongoing
- Goal = 3,360 children
  - 240 boys each year of life
  - 240 girls each year of life
- Screened prior to elective surgeries
- Fasting
- No prescription medications
- Blood (serum) collected through IV, after induction of anesthesia
- Height and weight (BMI)
- Chart review, no exam
7 Years Through 17 Years:

- Started 2002; completed Spring, 2011
- Goal = 2,640 children
  - 120 boys each year of life
  - 120 girls each year of life
- Recruited via community advertisement
- No prescription medications
  - Allergy, BCP, acne, antidepressants
- Serum, citrated plasma, and urine collected
- Physical exam, including Tanner stage and BMI
  - Performed by single individual

Serum, plasma, and urine were collected from children 7 years through 17 years of age, with a goal of 120 males and 120 females from each year of life, totaling 2,640 healthy children. Reference intervals for over 55 analytes established.
### Expanded Collection: Fasting Samples

- Started 2011; collection ongoing
- Serum collection, fasting individuals
- Ages 7 through 17 years
- Goal = 880 children
  - 40 boys each year of life
  - 40 girls each year of life
- Collections > 30% completed
Example: RI by Age & Gender

![Graph showing Osteocalcin Reference Limits (ng/mL) by age and gender.](image)
**Table 1.** Serum androgen reference intervals for males according to TS and age.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Androstenedione, ng/L</th>
<th>DHEA, ng/L</th>
<th>Testosterone, ng/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>278</td>
<td>35–320</td>
<td>110–2370</td>
<td>16–150</td>
</tr>
<tr>
<td>2</td>
<td>131</td>
<td>79–480</td>
<td>370–3660</td>
<td>33–3030</td>
</tr>
<tr>
<td>3</td>
<td>140</td>
<td>140–870</td>
<td>750–5240</td>
<td>100–8510</td>
</tr>
<tr>
<td>4 and 5</td>
<td>204</td>
<td>270–1070</td>
<td>1216–67030</td>
<td>1620–8470</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–24 months</td>
<td>123</td>
<td>25–150 (&lt;140)^a</td>
<td>&lt;2500 (&lt;2170)</td>
<td>&lt;370 (&lt;280)</td>
</tr>
<tr>
<td>2–3 years</td>
<td>125</td>
<td>&lt;110 (&lt;100)</td>
<td>&lt;630 (&lt;430)</td>
<td>&lt;150 (&lt;130)</td>
</tr>
<tr>
<td>4–5 years</td>
<td>125</td>
<td>23–170 (&lt;150)</td>
<td>&lt;950 (&lt;880)</td>
<td>&lt;190 (&lt;180)</td>
</tr>
<tr>
<td>6–7 years</td>
<td>125</td>
<td>10–290 (20–240)</td>
<td>60–1930 (80–1780)</td>
<td>&lt;130 (10–130)</td>
</tr>
<tr>
<td>7–9 years</td>
<td>206</td>
<td>30–300</td>
<td>100–2080</td>
<td>17–81</td>
</tr>
<tr>
<td>10–11 years</td>
<td>140</td>
<td>70–390</td>
<td>320–3080</td>
<td>23–1650</td>
</tr>
<tr>
<td>12–13 years</td>
<td>143</td>
<td>100–640</td>
<td>570–4100</td>
<td>30–6190</td>
</tr>
<tr>
<td>14–15 years</td>
<td>141</td>
<td>180–940</td>
<td>930–6040</td>
<td>310–7330</td>
</tr>
<tr>
<td>16–17 years</td>
<td>136</td>
<td>300–1130</td>
<td>1170–6520</td>
<td>1580–8260</td>
</tr>
<tr>
<td>18–40 years</td>
<td>70</td>
<td>330–1340</td>
<td>1330–7780</td>
<td>2070–6970</td>
</tr>
<tr>
<td>40–67 years</td>
<td>61</td>
<td>230–890</td>
<td>630–4700</td>
<td>1320–6930</td>
</tr>
</tbody>
</table>

^a Values in parentheses correspond to the central 90% of the distribution.
# Table 2. Serum androgen reference intervals for females according to TS, menstrual status, and age.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Androstenedione, ng/L</th>
<th>DHEA, ng/L</th>
<th>Testosterone, ng/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>296</td>
<td>45–510</td>
<td>140–2760</td>
<td>19–170</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>150–1370</td>
<td>830–4870</td>
<td>45–400</td>
</tr>
<tr>
<td>3</td>
<td>135</td>
<td>370–2240</td>
<td>1080–7560</td>
<td>100–630</td>
</tr>
<tr>
<td>4 and 5</td>
<td>205</td>
<td>350–2050</td>
<td>1240–7880</td>
<td>110–620</td>
</tr>
<tr>
<td><strong>Menstrual status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before menarche</td>
<td>413</td>
<td>48–1080</td>
<td>160–4050</td>
<td>19–350</td>
</tr>
<tr>
<td>After menarche, ≤18 years</td>
<td>323</td>
<td>330–2130</td>
<td>1110–7700</td>
<td>100–630</td>
</tr>
<tr>
<td>Premenopausal, &gt;18 years</td>
<td>104</td>
<td>260–2140</td>
<td>1120–7430</td>
<td>90–550</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>86</td>
<td>130–820</td>
<td>600–5730</td>
<td>47–320</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–24 months</td>
<td>92</td>
<td>&lt;150 (&lt;130)*</td>
<td>&lt;1990 (&lt;780)</td>
<td>&lt;90 (&lt;90)</td>
</tr>
<tr>
<td>2–3 years</td>
<td>126</td>
<td>&lt;160 (&lt;130)</td>
<td>&lt;850 (&lt;680)</td>
<td>&lt;200 (&lt;140)</td>
</tr>
<tr>
<td>4–5 years</td>
<td>127</td>
<td>20–210 (&lt;180)</td>
<td>&lt;1030 (70–770)</td>
<td>&lt;300 (10–200)</td>
</tr>
<tr>
<td>6–7 years</td>
<td>131</td>
<td>20–280 (40–300)</td>
<td>&lt;1790 (120–1520)</td>
<td>&lt;70 (10–60)</td>
</tr>
<tr>
<td>7–9 years</td>
<td>206</td>
<td>40–420</td>
<td>140–2350</td>
<td>10–110</td>
</tr>
<tr>
<td>10–11 years</td>
<td>148</td>
<td>90–1230</td>
<td>430–3780</td>
<td>29–320</td>
</tr>
<tr>
<td>12–13 years</td>
<td>142</td>
<td>240–1730</td>
<td>890–6210</td>
<td>60–500</td>
</tr>
<tr>
<td>14–15 years</td>
<td>143</td>
<td>390–2000</td>
<td>1220–7010</td>
<td>60–520</td>
</tr>
<tr>
<td>16–17 years</td>
<td>138</td>
<td>350–2120</td>
<td>1420–9000</td>
<td>90–580</td>
</tr>
<tr>
<td>18–40 years</td>
<td>74</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1330–7780</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt;40 years</td>
<td>116</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>630–4700</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Values in parentheses correspond to central 90% of the distribution.

<sup>b</sup> NA, not applicable because menstrual-status dependent.
Published Articles and Abstracts

Aldolase


Alpha-Fetoprotein (AFP)

Amylase


Androstenedione

...
Letter to the Editor

Pediatric reference intervals for four serum bone markers using two automated immunoassays

Clinica Chimica Acta 415 (2013) 169–172

Sara P. Wyness
William L. Roberts
Joely A. Straseski*

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CHILDx:
Recent Publications & Manuscripts

- Beckman DxI
- Roche Modular E170
THYROID REFERENCE INTERVALS FOR THE ACCESS 2 IMMUNOASSAY:

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age Range (years)</th>
<th>N</th>
<th>Lower Reference Limit (ug/L)</th>
<th>90% CI*</th>
<th>Upper Reference Limit (ug/L)</th>
<th>90% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>M&amp;F</td>
<td>0.5 - 3</td>
<td>279</td>
<td>7.4</td>
<td>6.2 - 8.6</td>
<td>48.7</td>
<td>44.0 - 62.1</td>
</tr>
<tr>
<td>M&amp;F</td>
<td>4 - 7</td>
<td>284</td>
<td>4.1</td>
<td>2.5 - 5.5</td>
<td>40.5</td>
<td>34.0 - 43.6</td>
</tr>
<tr>
<td>M&amp;F</td>
<td>8 - 17</td>
<td>698</td>
<td>0.8</td>
<td>0.3 - 1.3</td>
<td>29.4</td>
<td>27.2 - 33.8</td>
</tr>
</tbody>
</table>

*CI = confidence interval
CHILDx:
Recent Publications & Manuscripts

FT4 Reference Intervals Using ED-MS/MS:

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age Range (years)</th>
<th>N</th>
<th>Lower Limit (pmol/L)</th>
<th>95% CI* (Lower Limit)</th>
<th>Upper Limit (pmol/L)</th>
<th>95% CI* (Upper Limit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M&amp;F</td>
<td>0-6</td>
<td>840</td>
<td>18.0</td>
<td>16.7 – 18.0</td>
<td>34.7</td>
<td>33.0 – 37.3</td>
</tr>
<tr>
<td>M&amp;F</td>
<td>7-17</td>
<td>1373</td>
<td>14.2</td>
<td>14.2 – 14.2</td>
<td>25.7</td>
<td>25.7 – 27.0</td>
</tr>
</tbody>
</table>

*CI = confidence interval
FT3 Reference Intervals Using ED-MS/MS:

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age Range (years)</th>
<th>N</th>
<th>Lower Limit (pmol/L)</th>
<th>95% CI* (Lower Limit)</th>
<th>Upper Limit (pmol/L)</th>
<th>95% CI* (Upper Limit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>0-6</td>
<td>401</td>
<td>5.8</td>
<td>5.4 – 6.3</td>
<td>13.1</td>
<td>12.1 – 13.4</td>
</tr>
<tr>
<td>F</td>
<td>7-12</td>
<td>378</td>
<td>5.5</td>
<td>5.4 – 5.8</td>
<td>10.0</td>
<td>9.8 – 10.1</td>
</tr>
<tr>
<td>F</td>
<td>13-17</td>
<td>305</td>
<td>4.5</td>
<td>4.3 – 4.8</td>
<td>8.6</td>
<td>8.6 – 9.1</td>
</tr>
<tr>
<td>M</td>
<td>0-6</td>
<td>438</td>
<td>5.7</td>
<td>5.4 – 6.3</td>
<td>11.8</td>
<td>11.5 – 12.1</td>
</tr>
<tr>
<td>M</td>
<td>7-12</td>
<td>381</td>
<td>5.7</td>
<td>5.2 – 6.0</td>
<td>9.8</td>
<td>9.7 – 10.1</td>
</tr>
<tr>
<td>M</td>
<td>13-17</td>
<td>310</td>
<td>5.2</td>
<td>5.1 – 5.5</td>
<td>9.4</td>
<td>9.1 – 9.8</td>
</tr>
</tbody>
</table>

*CI = confidence interval
Outline

ARUP: Background, Resources, Research and Development

Pediatric Reference Intervals: Challenges and Concerns

CHILDx Initiative

Current Improvements and Future Developments

Conclusions and Questions
New Resource: 
*ARUP Pediatrics Website*

www.aruplab.com/pediatrics
Welcome to ARUP Pediatrics

Why do so many children's hospitals in the United States use ARUP as their reference laboratory?

Commitment to Pediatric Patient Care

Our commitment to children's health prompted ARUP to initiate the Children's Health Improvement through Laboratory Diagnostics (CHILDx) study more than a decade ago. The study established laboratory reference intervals for a variety of analytes for pediatric patients. Thus far, we have completed 92 percent of the 5,000 specimens needed to reach our goal and commitment to this special group of patients.

ARUP Laboratories provides quality care for pediatric patients and offers one of the most extensive reference laboratory test...
ARUP Pediatrics Test Menu

ARUP offers a test menu that accommodates more than 99 percent of pediatric testing requests for the diagnosis and management of conditions that affect the healthy growth and development of the pediatric patient. With a large percentage of testing performed at ARUP, children’s hospitals can be more operationally efficient with their referral testing.

Search our Full Laboratory Test Directory

Search our entire Laboratory Test Directory for all available pediatric testing:

Featured Pediatric Tests

- Allergens
- Cardiovascular
- Developmental Delay Evaluation
- Drugs, Toxins, and Trace Elements
- Endocrine Disorders
- Gastrointestinal Disease
- Hematology
- Inherited Hematological/Hemostasis Disorders
- Leukemia, Lymphoma, and Oncology
- Immunologic and Autoimmune Disorders
- Infectious Disease Testing
- Bacteriology/Virology
- Molecular
- Parasitology
- Serology
- Inherited Metabolic Disorders
- Maternal/Fetal
- Molecular Testing for Inherited
Pediatric Reference Intervals

ARUP is committed to establishing pediatric reference intervals. Jointly sponsored by ARUP Laboratories and the University of Utah Department of Pathology, the Children’s Health Improvement through Laboratory Diagnostics (CHILDx) program was formed in 1999 and included a National Advisory Committee.

CHILDx focused on the unique challenges of pediatric laboratory medicine. Working in partnership with pediatric healthcare professionals across the country, the program aspired to improve the healthcare of children through service, education, and research in pediatric laboratory testing.

To validate a method for use in the diagnosis of clinical disorders, the hormones or chemical substances must be measured in large normal populations of various ages and both genders. In 2002, the pediatric reference interval study was initiated at ARUP for the purpose of determining pediatric reference intervals for a number of clinical laboratory assays. Demographic and health histories were obtained on each subject, with specimens collected at ARUP and Primary Children’s Medical Center in Salt Lake City, Utah.

Children 6 months through 5 years:
- Fasting serum collected
- Collection goal: 240 males and 240 females from each year of life (85 percent complete)
- 35 reference intervals established toward the 55 proposed

Children 7 years through 17 years:
- Full physical exam
ARUP Pediatrics Experts

Consultations for anatomic and clinical pathology for pediatrics are provided by ARUP's medical directors and clinical consultants. These staff members hold faculty appointments in the Department of Pathology at the University of Utah School of Medicine and are board-certified in their areas of specialty. They conduct research and remain current on diagnostic and therapeutic issues through their involvement in academic and clinical practice.

Peter E. Jensen, MD
Chair, Department of Pathology and ARUP Board

Jerry W. Hussong, MD, MS
Vice President
Chief Medical Officer and Director of Laboratories

Division of Pediatric Pathology

Theodore J. Pysher, MD
Chief, Pediatric Pathology and Electron Microscopy

Amy Lowichik, MD, PhD
Staff Pathologist, Pediatric Pathology

Jessica Comstock, MD
Pediatric Pathologist

Mouied Alashari, MD
Pediatric Pathologist
**Neonatal Drug Screen**

Timely detection of *in utero* drug exposure is critical for effective detection and management of intoxication, withdrawal syndrome, and long-term needs (social and medical) for exposed neonates. Two modes of testing are available: umbilical cord and meconium.

**Spotlight on Testing: Drug Testing with Umbilical Cord Tissue**
Watch this video presented by Gwen McMillin, PhD.

Candidates for testing include infants born to:
- High-risk mothers—such as mothers with a history of drug use, prostitution, or sexually transmitted disease
- Mothers with little or no prenatal care
- Mothers with unexplained placental abruption or premature labor
- Infants with unexplained neurological complications, unexpected intrauterine growth retardation, or evidence of intoxication and/or drug withdrawal symptoms are also good candidates.

**Features of Umbilical Cord Testing**
- Comprehensive high-resolution drug screen:
  - Detects natural and synthetic opioids, amphetamines, barbiturates, benzodiazepines and cocaine.
  - Qualitative detection of nearly 60 drugs/drug metabolites in cord tissue.
  - Test currently does not screen for marijuana.
- Aids in the detection of prenatal exposure to drugs (drugs administered during labor and delivery may also be detected).
- **Confirmation testing is usually not required** due to high specificity and accuracy of time-of-flight (TOF) mass spectrometry.
- Generally provides faster return of results compared to meconium testing
- Analyte list and cutoffs: Example Report

**Chain-of-Custody**

Chain-of-custody may not be required:
Umbilical cord and meconium drug tests are performed to support clinical and social management decisions, and do not usually require chain-of-custody.

If chain-of-custody is required, ARUP will provide you a form or will honor an external form. Contact ARUP Client Services for more information.
Reference Intervals and Reporting:
IGF-1 (Insulin-Like Growth Factor 1) Pubertal Ranges by Tanner Stage:

<table>
<thead>
<tr>
<th>FEMALE PUBERTAL RANGES BY TANNER STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>3 years</td>
</tr>
<tr>
<td>4 years</td>
</tr>
<tr>
<td>5 years</td>
</tr>
<tr>
<td>6 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MALE PUBERTAL RANGES BY TANNER STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>3 years</td>
</tr>
<tr>
<td>4 years</td>
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<tr>
<td>5 years</td>
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<td>6 years</td>
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<td>7 years</td>
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<td>14 years</td>
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<td>15 years</td>
</tr>
<tr>
<td>16 years</td>
</tr>
<tr>
<td>17 years</td>
</tr>
<tr>
<td>18 years</td>
</tr>
</tbody>
</table>
Endocrine-Related Analytes With RIs by Tanner Stage:

Examples

- Follicle Stimulating Hormone
- Luteinizing Hormone
- Free Testosterone
- Bioavailable Testosterone
- Total Testosterone
- Sex Hormone Binding Globulin
- Androstenedione
- 17-Hydroxyprogesterone
- 17-Hydroxypregnenolone

- Fractionated Estrogens
- Pregnenolone
- Dehydroepiandrosterone
- Dehydroepiandrosterone Sulfate
- 11-Deoxycortisol
- IGF-1
- IGFBP-3
Endocrine-Related Panels: *Examples*

- Congenital Adrenal Hyperplasia Panel, 11-beta Hydroxylase Deficiency
- Congenital Adrenal Hyperplasia Panel, 21-Hydroxylase Deficiency
- Congenital Adrenal Hyperplasia Treatment Panel
- Adrenal Steroid Quantitative Panel
- Virilization Panel 1
- Virilization Panel 2
- Hirsutism Evaluation Panel
Hepatitis C Virus RNA Quantitative, Real-Time PCR

**Patient History**

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Accession</th>
<th>Result (log IU/mL)</th>
<th>Collected</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>7.1</td>
<td>2/16/2012 3:30:00 PM</td>
<td>2/18/2012 9:05:45 AM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.7</td>
<td>7/17/2012 9:00:00 AM</td>
<td>7/19/2012 7:20:17 AM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.2</td>
<td>1/16/2013 1:00:00 PM</td>
<td>1/17/2013 6:46:20 PM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.9</td>
<td>9/5/2013 1:40:00 PM</td>
<td>9/7/2013 7:54:03 PM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.7</td>
<td>1/30/2014 1:44:00 PM</td>
<td>2/1/2014 5:32:56 PM</td>
</tr>
</tbody>
</table>

**Hepatitis C RNA Viral Load Results**

- **Detected** - Quantified or above linear range.
- **Detected – Not Quantified** ( < 1.6 log IU/mL; virus cannot be accurately quantified below this level).
- **Not Detected** - Below limit of detection ( < 1.2 log IU/mL).

*Consecutive test results are displayed on this chart; however, this report set may be incomplete due to variations in the demographic information submitted for prior tests. If the information shown on this chart appears incomplete, please consult this patient’s prior charts.*
Interpretation:
M-spike in the alpha-2/beta region. The monoclonal protein peak accounts for 2.31 g/dL of the total protein in the alpha-2 and beta regions. This quantitation may include transferrin components. M-spike in the gamma region. The monoclonal protein peak accounts for 0.55 g/dL of the total 1.22 g/dL of protein in the gamma region. Suggest IFE to identify the monoclonal protein(s). Immunofixation electrophoresis (IFE) is a more sensitive technique for the identification of small M-proteins.
**Chromosome Analysis, Amniotic Fluid**

**Slide ID: 0011**

**Interpretation**

Specimen received

Specimen type: Amniotic Fluid  
Reason for referral: Abnormal U/S/Oligohydramnios, Selective Intrauterine Growth Restriction of Mono/Di Twins  
Test performed: Chromosome Analysis

**Laboratory analysis**

Number of cells counted: 15  
Number of colonies counted: 15  
Number of cells analyzed: 15  
Number of cells karyotyped: 15  
ISCN Band level: 400  
Banding Method: G-Banding

Chromosome results: 46,XX

**Diagnostic Impression:**  
Metaphase cells analyzed from multiple cultures of amnioscyes revealed a normal female chromosome complement.  
The standard cytogenetic methodology used in this analysis may not detect small rearrangements or low level mosaicism, and cannot detect submicroscopic deletions or duplications that are detectable by microarray analysis.

NOTE: FISH was performed on this sample and reported under patient ID#14-023-109730. FISH results were NORMAL.

This result has been reviewed and approved by Jia Xu, M.D., FACMG

Electronic Signature

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C
### Calculi (Stone) Analysis with Photo

#### Patient's calculi specimens submitted for testing

![Image of calculi specimens]

<table>
<thead>
<tr>
<th>Component</th>
<th>Unit</th>
<th>Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculi Mass</td>
<td>mg</td>
<td>188</td>
</tr>
<tr>
<td>Calculi Number</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Calculi Size</td>
<td>mm</td>
<td>Various</td>
</tr>
<tr>
<td>Calculi Description</td>
<td></td>
<td>Specimen consists of four, various sized, dark brown, irregular calculi fragments.</td>
</tr>
<tr>
<td>Calculi Composition</td>
<td></td>
<td>Calculi composed primarily of calcium oxalate monohydrate.</td>
</tr>
</tbody>
</table>

#### Interpretive Information

Calculi are the products of physiological processes that yield crystalline compounds in a matrix of biological compounds and blood. Matrix components are not reported. The clinically significant crystalline components identified in calculi specimens are reported. Gross description may not be consistent with the composition determined by FTIR analysis.

*For additional information please refer to Nephrolithiasis Kidney (Stone) topic at www.arupconsult.com*
Supersaturation Profile, Urine

**ARUP Accession number:**

**Patient:**

**Date of birth:**

**Age:**

**Gender:**

**Collection date:**

**Received in lab:**

**Completion date:**

**ARUP Test Code:** 2008771

**Physician:**

**Client ID:**

**Client:**

### Calculus

#### Calculated Risk

**Calcium Oxalate**

9.83

**Calcium Phosphate**

2.08

**Uric Acid**

1.88

Calculated risk is derived by a computer program that models the thermodynamics of calculi formation using measured urine components.

### Component Results

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Units</th>
<th>Reference Interval</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Volume</td>
<td>800</td>
<td>mL</td>
<td></td>
<td>Low urine volume (&lt;1L/24h) promotes calculi formation.</td>
</tr>
<tr>
<td>pH</td>
<td>5.40</td>
<td></td>
<td>5.00-7.50</td>
<td>Acidic urine (pH&lt;5.5) promotes precipitation of Ura. Alkaline urine (pH&gt;7.2) promotes formation of CaHPO4 stones.</td>
</tr>
<tr>
<td>Calcium</td>
<td>305</td>
<td>mg/d</td>
<td></td>
<td>Hypercalcemia (&gt;200 mg/d) promotes formation of CaOx and CaHPO4 stones.</td>
</tr>
<tr>
<td>Oxalate</td>
<td>12</td>
<td>mg/d</td>
<td>4-31</td>
<td>Hyperoxaluria (&gt;40 mg/d) promotes formation of CaOx stones.</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>608</td>
<td>mg/d</td>
<td>400-1300</td>
<td>Forms insoluble complexes with calcium.</td>
</tr>
<tr>
<td>Sodium</td>
<td>94</td>
<td>mmol/d</td>
<td>51-286</td>
<td>Increased sodium promotes formation of CaOx and CaHPO4 stones.</td>
</tr>
<tr>
<td>Sulfate</td>
<td>12</td>
<td>mmol/d</td>
<td>6-30</td>
<td>Normal to high sulfate promotes precipitation of CaOx and CaHPO4 stones.</td>
</tr>
<tr>
<td>Urate</td>
<td>369</td>
<td>mg/d</td>
<td>250-750</td>
<td>Hyperuricosuria (&gt;600 mg/d) promotes formation of Ura stones.</td>
</tr>
<tr>
<td>Citrate</td>
<td>546</td>
<td>mg/d</td>
<td>320-1240</td>
<td>High citrate inhibits formation of CaOx and CaHPO4 stones.</td>
</tr>
<tr>
<td>Magnesium</td>
<td>58</td>
<td>mg/d</td>
<td>12-199</td>
<td>High magnesium inhibits formation of CaOx and CaHPO4 stones.</td>
</tr>
<tr>
<td>Potassium</td>
<td>21</td>
<td>mmol/d</td>
<td>25-125</td>
<td>Forms soluble complexes and inhibits stone formation.</td>
</tr>
<tr>
<td>Chloride</td>
<td>85</td>
<td>mmol/d</td>
<td>140-250</td>
<td>Forms soluble complexes and inhibits stone formation.</td>
</tr>
<tr>
<td>Creatinine</td>
<td>704</td>
<td>mg/d</td>
<td>500-1400</td>
<td>Excretion provides a measure of completeness of 24h urine collection.</td>
</tr>
</tbody>
</table>
Future: Assay Improvement and Development

Currently On-Line:

- Latest adrenal steroid panel
  - Corticosterone
  - 11-Deoxycortisol
  - 11-Deoxycorticosterone
  - 17-Hydroxyprogesterone
  - Progesterone

- Pico AMH assay
  - Newly established reference intervals \(n = 1,324\), lower sensitivity \(0.003\) ng/mL

Currently In Development:

- 17-Hydroxypregnenolone, pregnenolone
- Ultrasensitive luteinizing hormone
- Aldosterone by LC-MS/MS

Future Development:

- Free testosterone in women and children
  - Equilibrium dialysis
- IGF-II
- IGFBP-1
Outline

ARUP: Background, Resources, Research and Development

Pediatric Reference Intervals: Challenges and Concerns

CHILDx Initiative

Current Improvements and Future Developments

Conclusions and Questions
Conclusions:

- Establishing quality reference intervals in pediatric populations can be challenging.
  - Sources
  - Sample numbers
  - Healthy definitions

- ARUP is invested in serving the needs and missions of pediatric-focused institutions.
  - R&D efforts
  - Automation
  - Publications
  - CHILDx repository
  - www.aruplab.com/pediatrics
End Goal:
Quality results for each and every patient, large or small.