Inclusivity in Laboratory Medicine: Endocrine Testing in Transgender Individuals

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inclusivity

noun [U]

US /ˈɪnkluːsɪvɪtɪ/ UK /ˈɪnkluːsɪvɪtɪ/

the fact of including all types of people, things or ideas and treating them all fairly and equally:
Laboratory Medicine & Transgender Patients: Hot Topics

Proper test utilization

Reference intervals
Presentation Outline:

- Definitions & background
- Gender-affirming hormone therapies (GAHT)
  - Testosterone
  - Estrogen(s)
- Hormone measurements
  - Testosterone
  - Estradiol
- Reference intervals (RI)
- Electronic medical record (EMR)/Laboratory information system (LIS) challenges
- Possible approaches

*Note: This presentation will focus solely on transgender adults; refer to pediatric guidelines as appropriate.*
Definitions & Background:
Basic Definitions:

- Gender, sex
- Cis-, trans-
- Trans*/Transgender terms
Gender/Sex: Defined
Cis-/Trans- Prefixes: Defined

Cisgender: sex assigned at birth aligns with gender you identify with

Transgender: sex assigned at birth does not align with gender you identify with
Trans*/Transgender Terms: Defined

**Binary**
Relating to, or consisting of 2 things, in which everything is either one thing or another.
(Also: Using a system of numbers that uses only 0 and 1.)

**Non-binary**
Not exclusively one thing or another.
Having a gender identity that is not exclusively male or female.

Adapted from: dictionary.cambridge.org
Trans*/Transgender Terms: Defined

Gender Incongruence
Discordance between gender identity and sex assigned at birth

Gender Dysphoria
Psychological effect or distress associated with gender incongruence

Not all transgender people experience dysphoria!
Trans*/Transgender Terms: Defined

**Trans man**
An individual that was assigned the female sex at birth; gender identity is male. Also: trans male, transgender male

**Trans woman**
An individual that was assigned the male sex at birth; gender identity is female. Also: trans female, transgender female


Background image credit: learn.uvm.edu
Challenges Facing Transgender Populations: Examples

- Mental health
- Substance abuse
- STIs, HIV prevalence
- Suicide
- Access to care
- Insurance coverage/access
- Medical mistrust
- Provider/lab education
- Discrimination
- Lack of research
- Access to care
- Insurance coverage/access
- Medical mistrust
- Discrimination
- Provider/lab education
- Lack of research
Gender-affirming Hormone Therapies (GAHT):

Testosterone

Estrogen(s)
Gender-affirmation and Therapies:

- All, some, none...
- Individual preference!
- Spectrum, may change
- Remember: not *all* transgender individuals experience gender dysphoria

Goal: “Align gender identity with gender expression and/or to reduce the distress caused by gender dysphoria.”¹

¹Goldstein et al., Clin Chem 2017;63(8);1342-52
Gender-affirming Hormone Therapies: Use of Testosterone and Estrogen(s)

**Cisgender males**
- Testosterone
  - Estradiol

**Trans males**
- Exogenous T
- Goal = ↑ T (and ↓ E)

**Cisgender females**
- Estradiol
  - Testosterone

**Trans females**
- Exogenous E
- Goal = ↑ E (and ↓ T)

“Testosterone hormone therapy” & “Estrogen hormone therapy” & “Testosterone-suppressing hormone therapy”

T = testosterone; E = estrogen
Gender-affirming Hormone Therapies: Associated Risks

- Cardiovascular disease, ↑ lipids
- Hypertension
- Venous thrombosis
- Polycythemia
- Osteoporosis
- Prolactinoma

Hembree et al., J Clin Endocrinol Metab 2017;102(11):3869-903;
Cheung et al., J Clin Endocrinol Metab 2021;106(3):893-901
Gender-affirming Hormone Therapies: Monitoring Recommendations

**Trans males**
- Testosterone
  - Within cisgender male reference interval (method specific)
    - 400 – 700 ng/dL
    - (~300 – 1000 ng/dL)
- Estradiol
  - Decrease concurrent with T therapy

**Trans females**
- Testosterone
  - Within cisgender female reference interval
    - Less than 50 ng/dL
- Estradiol
  - Within peak physiological range
    - 100 – 200 pg/mL

Gender-affirming Hormone Therapies:
Don’t forget the goal!

- Titrate to recommended concentration
- Titrate to clinical response
Hormone Measurements:

Testosterone

Estradiol
Measurement of Testosterone & Estradiol: The Options

- **Immunoassay (IA)**
  - High throughput
  - Moderate cost
  - Less specific
  - Less sensitive

- **Mass Spec (MS)**
  - Less automated
  - High overall cost
  - Excellent specificity
  - Excellent sensitivity
What concentrations can we expect for total testosterone measurements?
What **performance** can we expect to see for total testosterone measurements?

Similar story for estradiol...

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**Testosterone Measurements: The Performance**

Data from: Owen et al., Clin Chim Acta 2010;411:1073-9
Testosterone Immunoassays: Functional Sensitivities Vary Considerably

Data from: La'ulu, Kalp, and Straseski, Clin Biochem 2018:58,64
Estradiol Immunoassays: Functional Sensitivities Vary Considerably

Adapted from:
# Testosterone Assay Performance: Brief Literature Summary

<table>
<thead>
<tr>
<th>Imprecision:</th>
<th>Greater immunoassay imprecision at lowest T concentrations</th>
</tr>
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<tbody>
<tr>
<td><em>La’ulu, Kalp, and Straseski, Clin Biochem 2018:58;64</em></td>
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</table>

<table>
<thead>
<tr>
<th>Sample matrix:</th>
<th>Most immunoassays are optimized for better recovery in male matrix samples</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Kane et al., Ann Clin Biochem 2007:44;5</em></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunoassay vs. Mass Spectrometry</th>
<th>Bias is most apparent at the lowest concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Taieb et al., Clin Chem, 2003:49:1381</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Imprecision is a concern at the lowest concentrations for MS assays, as well</th>
</tr>
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<tbody>
<tr>
<td><em>Vesper et al., Steroids 2009;74:498</em></td>
<td></td>
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</tbody>
</table>
Testosterone: The Plot Thickens

- Free
- Bioavailable
- Total

Adapted from: Williams Textbook of Endocrinology, 11th Ed., ©2008
Methods

Immuno-assay
Mass spectrometry

T Flavors

Total + +
Bioavailable +
Free

E Flavors

Estradiol
Estrone
“Total” Estrogens +
Free

Free T Methods

Calculation
Equilibrium dialysis (ED)
Testing Recommendations for Monitoring of Gender-affirming Hormone Therapy:

**Immuoassay (IA) vs. Mass Spectrometry (MS)?**

- Guidelines do not address preferred methods\(^1,2\)

- Overall, MS likely best for trans population\(^3\)
  - Focus: low concentrations\(^4\)
  - Use to confirm any inconsistencies\(^4,5\)

- IA adequate in many scenarios
  - Routine monitoring, established therapy (esp. trans males\(^5\))

**Total Testosterone vs. Free/Bioavailable Testosterone?**

- Assays can be challenging, not standardized\(^1,6\)

- Overall, Free T not required for most clinical scenarios (esp. trans males\(^5\))

- Use to evaluate elevated T in trans females\(^4\)
  - Estrogen affects SHBG concentrations

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4. Greene et al., JALM 2021;6(1):15-26;
5. Greene et al., JALM 2021;6(1):41-50;
Reference Intervals (RI):
Reference Intervals For Individuals Using GAHT: How do we approach this?

- Assigned sex at birth?
- Transgender-specific?
- Nonbinary-specific?
- Affirmed sex?

Example: Trans male
Reference Intervals For Individuals Using GAHT: Many Variables

- Route of therapy administration
- Dosing strategy
- Length of time on therapy
- Lack of test standardization
- Inclusion/exclusion criteria to evaluate health status
Reference Intervals For Individuals Using GAHT: Many Challenges

- Small number of studies
- Small sample size (n)
- Consensus or expert opinion
- Lack of clear guidance
- Therapy changes over time
- No long-term outcome data for safety of RIs
“The pivotal question is how we can have a ‘one size fits all’ solution to cater for a heterogenous group (with biological) changes that increase or decrease at different velocities and magnitudes?”

Cheung et al., J Clin Endocrinol Metab 2021;106(3):893-901
Selecting a RI in Transgender Patients: Two Key Principles

Has GAHT been initiated? How long ago?

What organs are present or affected?

Cheung et al., J Clin Endocrinol Metab 2021;106(3):893-901
Which RIs are recommended?

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommended Reference Range for Interpretation</th>
<th>Transgender-specific?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Total Testosterone</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Estimated GFR</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Hematocrit</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Iron studies</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Liver function</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Lipid profile</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Prostate-specific antigen (PSA)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>High-sensitivity cardiac troponin</td>
<td></td>
<td>✓</td>
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</table>

Note that consideration should be made as to the duration and dose of feminizing or masculinizing hormone therapy used in interpretation of laboratory tests.

Modified from: Cheung et al., J Clin Endocrinol Metab 2021;106(3):893-901
Greene et al., JALM 2021;6(1):15-26 and 41-50
Transgender Reference Intervals:
At the end of the day...

“Due to the paucity of literature on reference intervals for transgender patients, clinicians will need to use clinical judgement in interpretation of results.”
Electronic Medical Record (EMR)/Laboratory Information System (LIS) Challenges:
Transgender Patients & The Electronic Medical Record: Challenges

- Binary input
- No designation for sex vs. gender
- Limited reference interval interpretation/guidance
- Varied use of “Sex” demographic field
- “Administrative Sex” vs. “Clinical Sex”
- Test rejection based on entered sex
Current Best Practice For Data Collection:

Two-Step Approach For Data Collection

1. Current gender identity
   ("How do you describe yourself?")

2. Assigned sex at birth
   ("What sex were you assigned at birth, on your original birth certificate?")

Important: EMR ≠ LIS
### Recommendations for Reporting RI in Transgender/Non-binary Individuals:

<table>
<thead>
<tr>
<th>GAHT Type</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No GAHT:</strong></td>
<td>Use RI for the assigned sex at birth</td>
</tr>
<tr>
<td></td>
<td>Individualized interpretation and decision-making is still critical</td>
</tr>
<tr>
<td><strong>Early or low-dose GAHT:</strong></td>
<td>Appropriate values may be between male and female RIs</td>
</tr>
<tr>
<td></td>
<td>RI for affirmed sex may be appropriate, other than tissue-specific analytes (e.g., PSA, troponin)</td>
</tr>
<tr>
<td></td>
<td>Individualized interpretation and decision-making is still critical</td>
</tr>
<tr>
<td><strong>Established GAHT (&gt; 3-6 months):</strong></td>
<td>Use RI for affirmed sex, other than tissue-specific analytes (e.g., PSA, troponin)</td>
</tr>
<tr>
<td></td>
<td>Individualized interpretation and decision-making is still critical</td>
</tr>
</tbody>
</table>

GAHT: gender-affirming hormone therapy
Recommendations for Laboratory Reporting for Transgender/Non-binary Individuals:

- Add comment(s) to inform clinicians that RI may not be appropriate for all patients; clinical judgement is required
  - For most analytes, RI have not been established in transgender individuals
  - Point to cisgender RI when appropriate
- Provide interpretation guidance for patients using GAHT or post-surgery
Recommendations for Laboratory Reporting for Transgender/Non-binary Individuals:

- Organ-based approach, or organ inventory, is recommended
- Do not cancel tests based on the provided sex
  - Do not flag these tests based on sex
  - Examples: pregnancy-associated testing, PSA
  - Site-specific examples: anatomic pathology, microbiology, cytology, histology
Possible Approaches:
Possible Approaches to RI, EMR Challenges: A Few Examples

- Include transgender-specific RI
- Include all RI on all charts (M, F)
- Provide additional information via comment
  - Website
  - Literature
  - Guideline, expert opinion
  - Transgender-specific RI
  - “RI may not apply to all patients.”
- Create separate panels or tests

- Rename relevant tests
  - Method
    - Immunoassay
    - Mass spectrometry (LC-MS/MS)
  - Population
    - Transgender
    - Gender non-conforming
  - Therapy
    - Testosterone/estrogen therap(ies)
    - Masculinizing/feminizing therap(ies)
Possible Approaches to RI, EMR Challenges: One Example

<table>
<thead>
<tr>
<th>Test names</th>
<th>Ordering rec.</th>
<th>Interpretive comments</th>
<th>Testing algorithms</th>
<th>Glossaries</th>
<th>ARUP Consult® topics</th>
<th>Interactive tables</th>
</tr>
</thead>
</table>

Inclusivity-focused Updates: (ARUP Laboratories)
Summary:

- Transgender and non-binary patients represent a diverse spectrum; no one-size-fits-all approach or solution to laboratory-based challenges.
- Hormone therapy may be titrated to recommended concentrations or desired clinical response.
- Testosterone and estradiol testing should be selected based on the individual clinical scenario.
- Reference intervals in transgender and non-binary populations are complex with little empirical data available.
- Electronic health records are historically built on binary inputs but are evolving.
- Laboratory guidance will help clinicians make the best decisions in these clinical situations.
The overall goal...
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