Inclusivity in Laboratory Medicine: Endocrine Testing in Transgender Individuals

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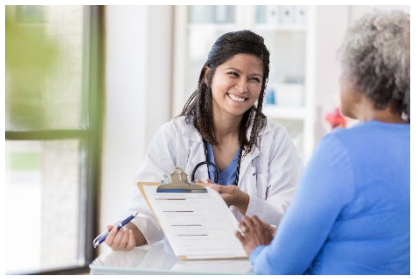
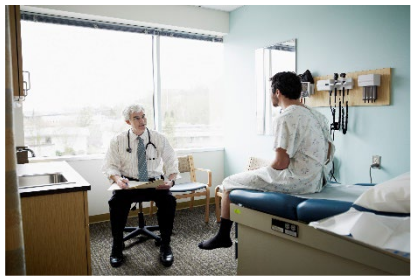
inclusivity

noun [U]

US /ˌɪn.kluːˈsɪv.ə.ţi/ UK /ˌɪn.kluːˈsɪv.ɪ.ti/

the fact of including all types of people, things or ideas and treating them all fairly and equally:

Cambridge Dictionary

Laboratory Medicine & Transgender Patients: Hot Topics

Proper test utilization

Reference intervals

Presentation Outline:

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

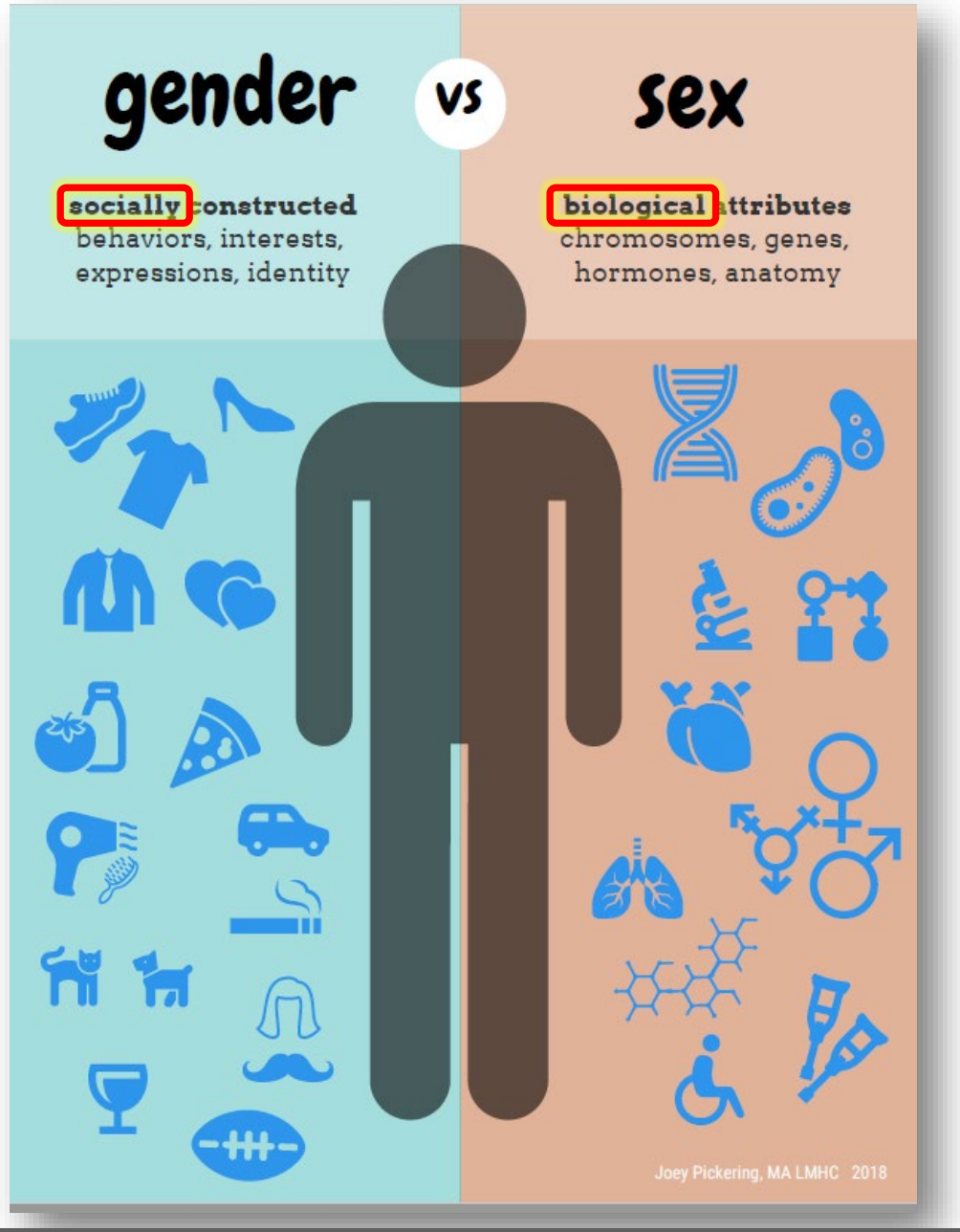
- Definitions & background
- Gender-affirming hormone therapies (GAHT)
  - Testosterone
  - Estrogen(s)
- Hormone measurements
  - Testosterone
  - Estradiol
- Reference intervals (RI)
- Electronic medical record (EMR)/Laboratory information system (LIS) challenges
- Possible approaches

Definitions & Background:

Basic Definitions:

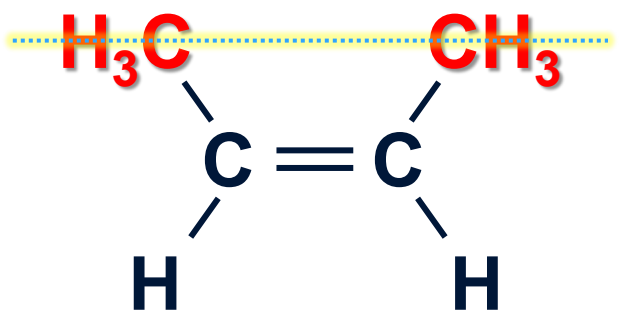
- Gender, sex
- Cis-, trans-
- Trans*/Transgender terms

Gender/Sex: Defined



Cis-/Trans- Prefixes: Defined

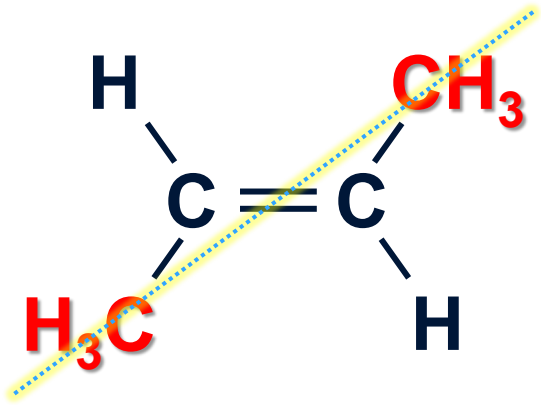
Cis-



"this side of"

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

Trans-



"the other side of"

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.

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!

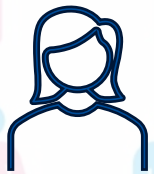
Hembree et al., J Clin Endocrinol Metab 2017;102(11):3869-903;
Coleman et al., Int J Transgend 2012;13:165-232

Background image credit: learn.uvm.edu

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

Hembree et al., J Clin Endocrinol Metab 2017;102(11):3869-903;
Coleman et al., Int J Transgend 2012;13:165-232

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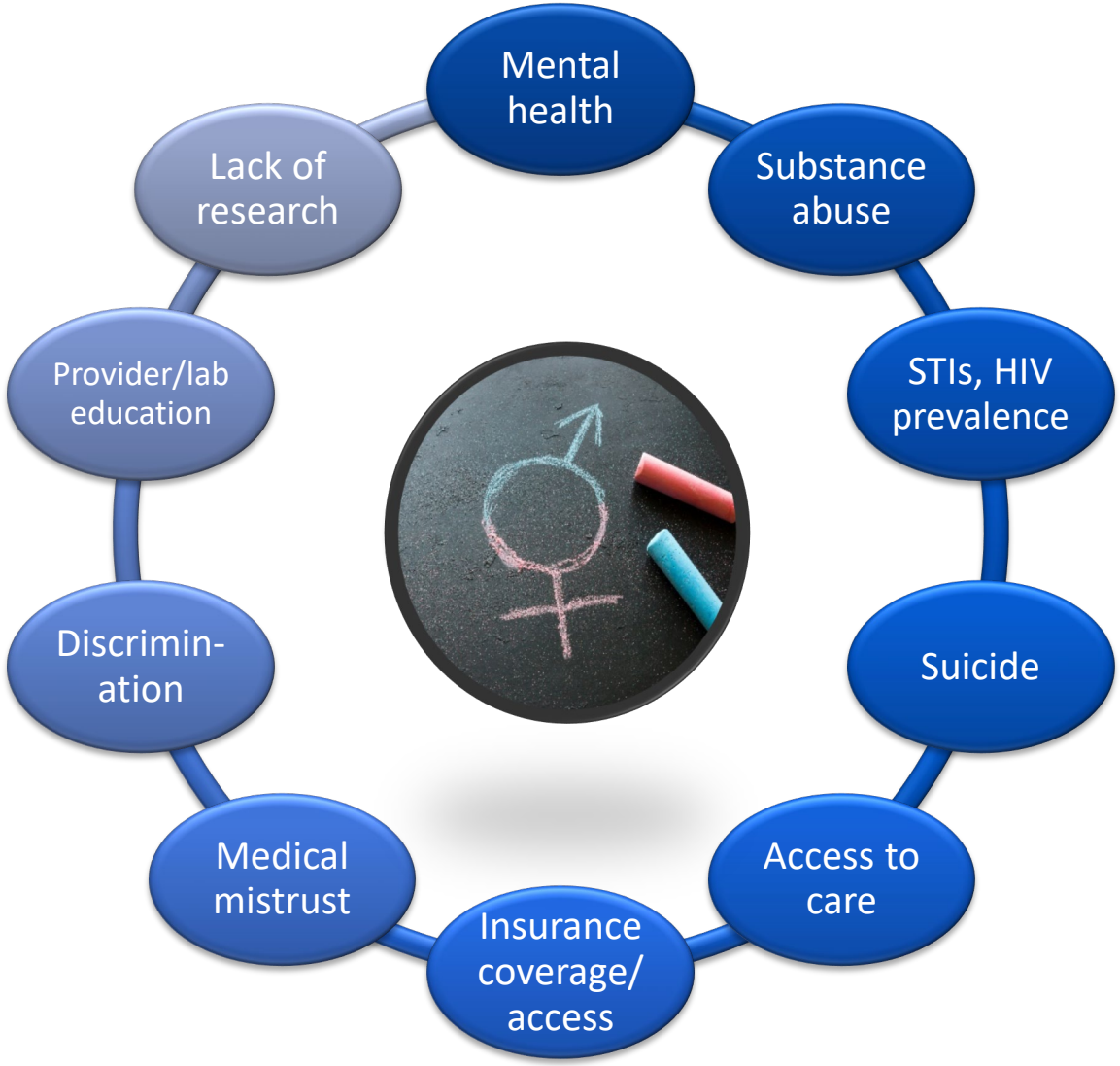
Challenges Facing Transgender Populations: Examples



Gender-affirming Hormone Therapies (GAHT):

Testosterone

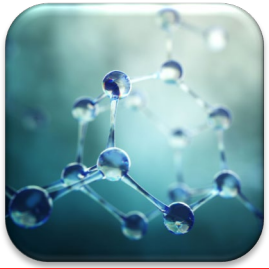
Estrogen(s)

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]

Social



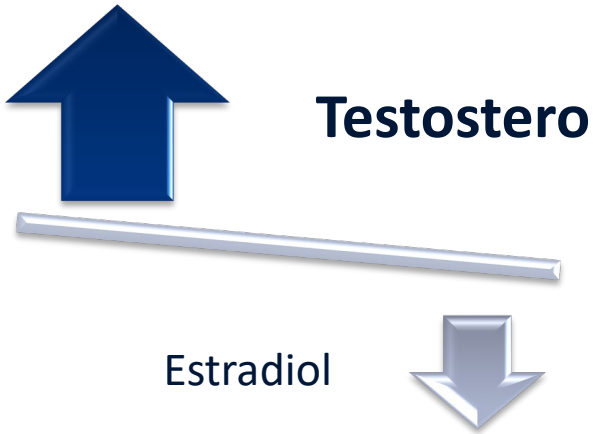
Medical

Surgical

[1]Goldstein et al., Clin Chem 2017;63(8);1342-52

Gender-affirming Hormone Therapies: Use of Testosterone and Estrogen(s)

Cisgender males



Trans males

- Exogenous T
- Goal = ↑ T (and ↓ E)

"Testosterone hormone therapy"

Cisgender females

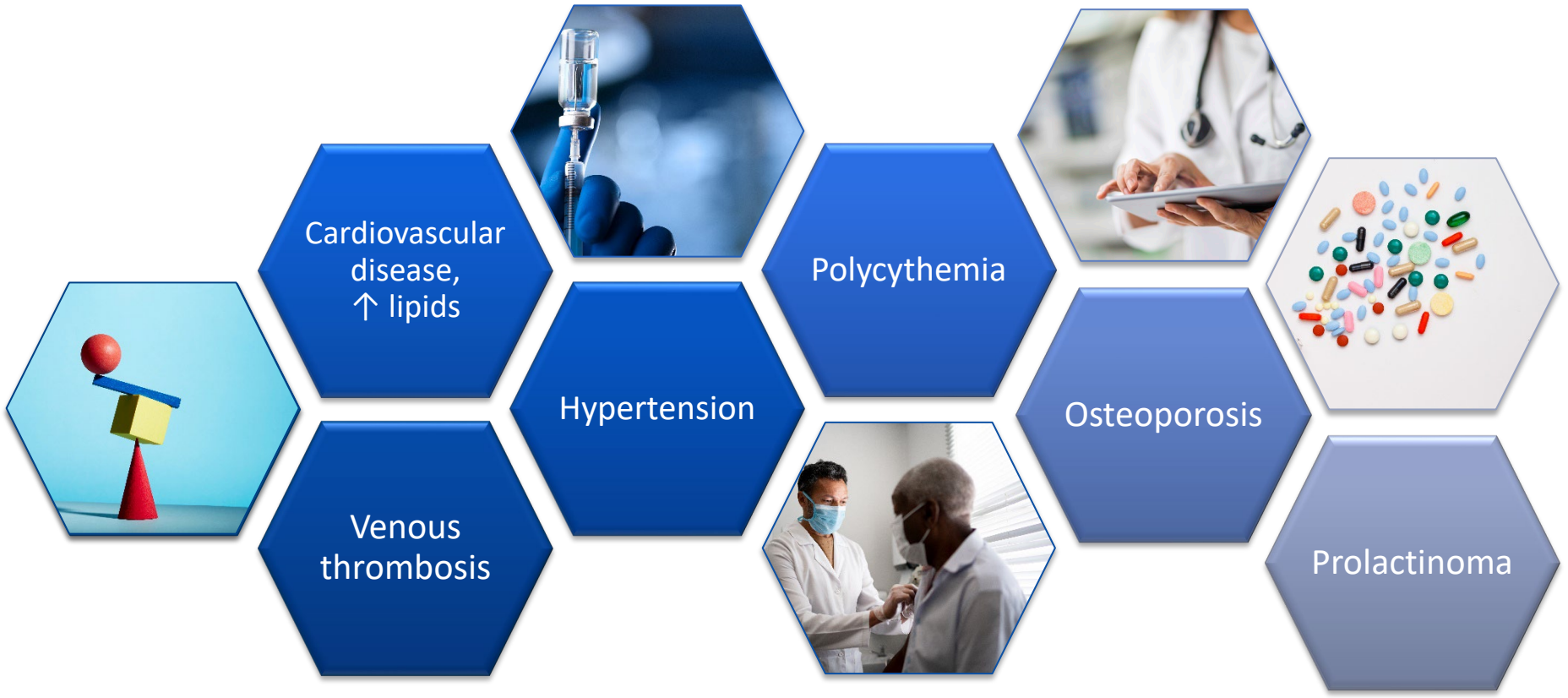
Trans females

- Exogenous E
- Goal = ↑ E (and ↓ T)

"Estrogen hormone therapy" & "Testosterone-suppressing hormone therapy"

T = testosterone; E = estrogen

Gender-affirming Hormone Therapies: Associated Risks



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

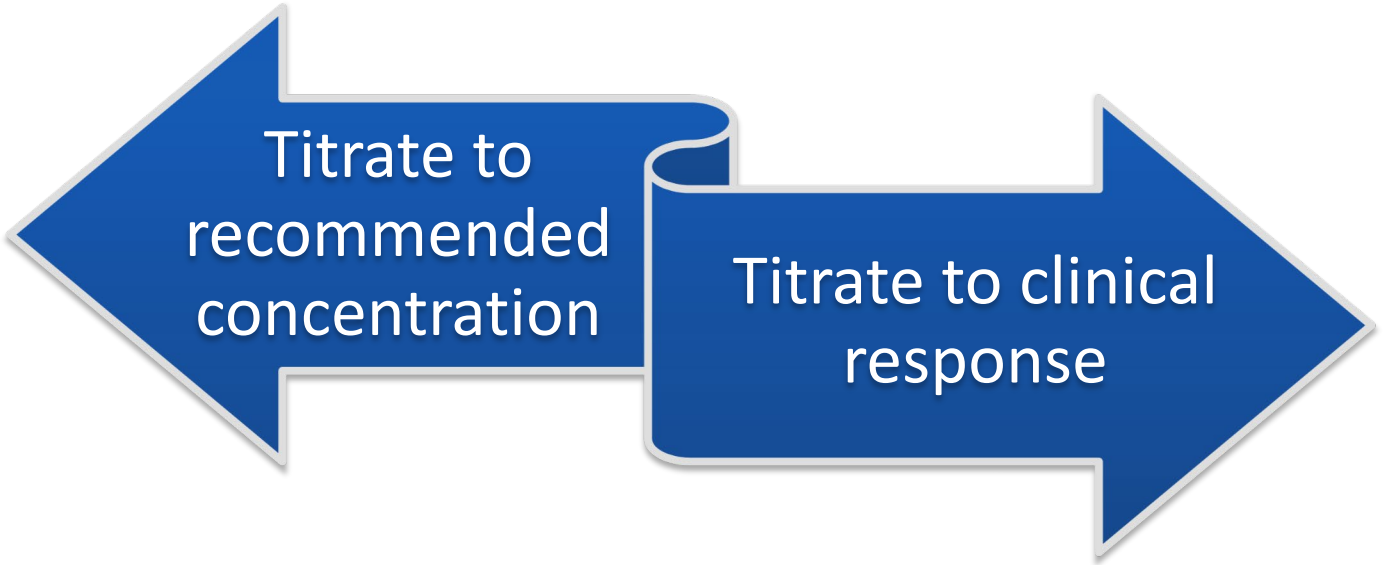
Estradiol

- Within peak physiological range
  - 100 – 200 pg/mL

ENDOCRINE SOCIETY | WPATH WORLD PROFESSIONAL ASSOCIATION FOR TRANSGENDER HEALTH | UCSF Transgender Care

Hembree et al., J Clin Endocrinol Metab 2017;102(11):3869-903; Coleman et al., Int J Transgend 2012;13:165-232; Deutsch, ed., 2nd edition, June 2016, transcare.ucsf.edu/guidelines

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



Hormone Measurements:

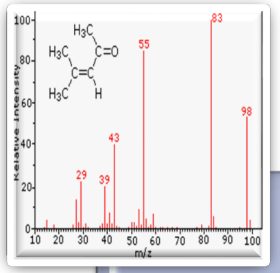
Testosterone

Estradiol

Measurement of Testosterone & Estradiol: The Options

Immunoassay (IA)

- High throughput
- Moderate cost
- Less specific
- Less sensitive

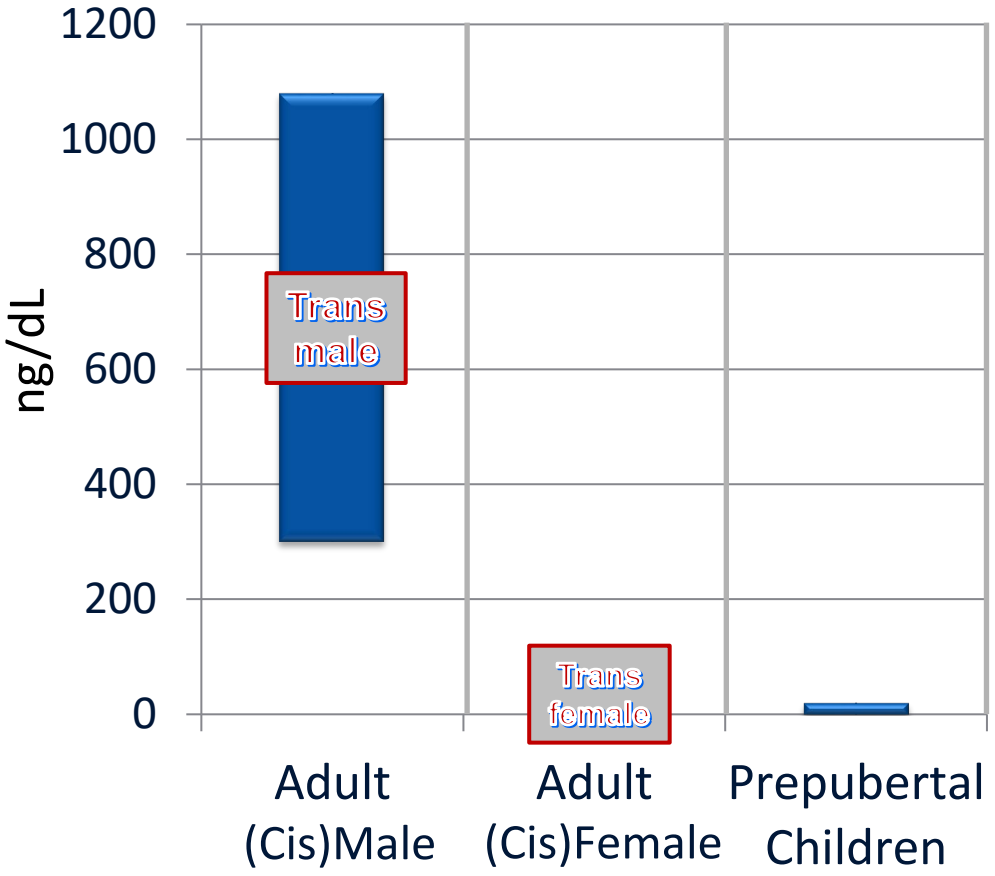


Mass Spec (MS)

- Less automated
- High overall cost
- Excellent specificity
- Excellent sensitivity

Testosterone Measurements: The Need

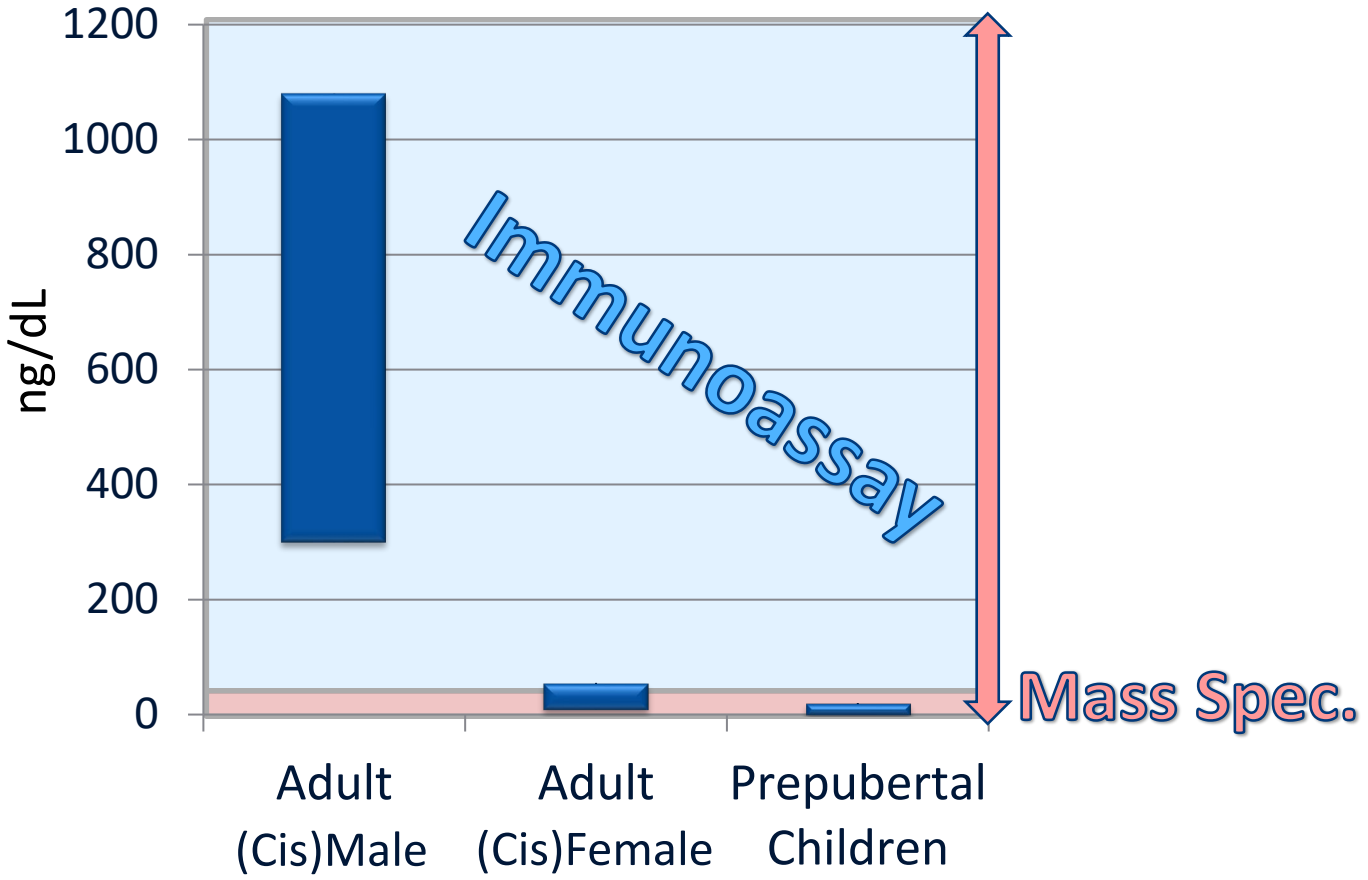
What *concentrations* can we expect for total testosterone measurements?



Testosterone Measurements: The Performance

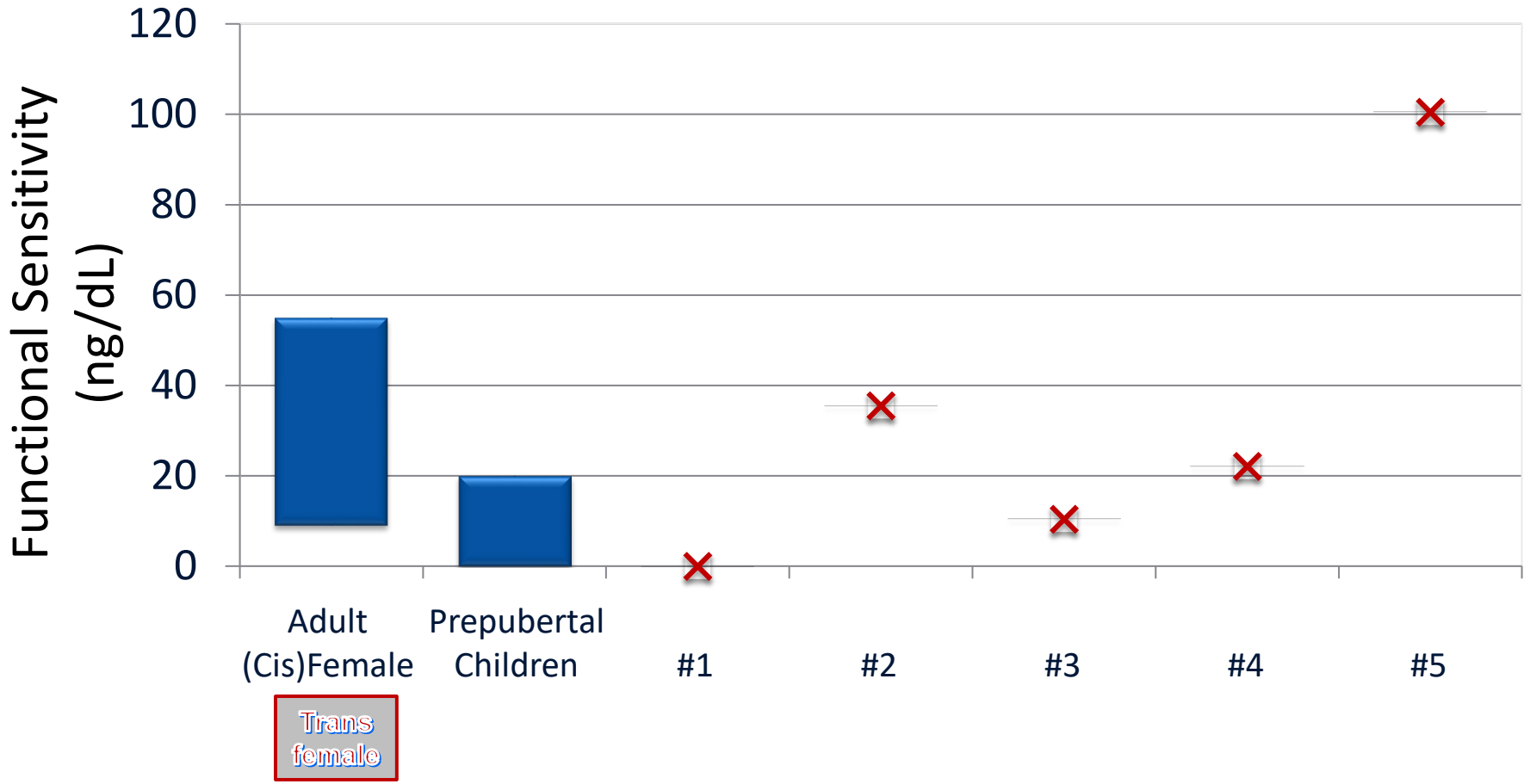
What *performance* can we expect to see for total testosterone measurements?

Similar story for estradiol…



Data from:
Owen et al., Clin Chim Acta 2010;411:1073-9

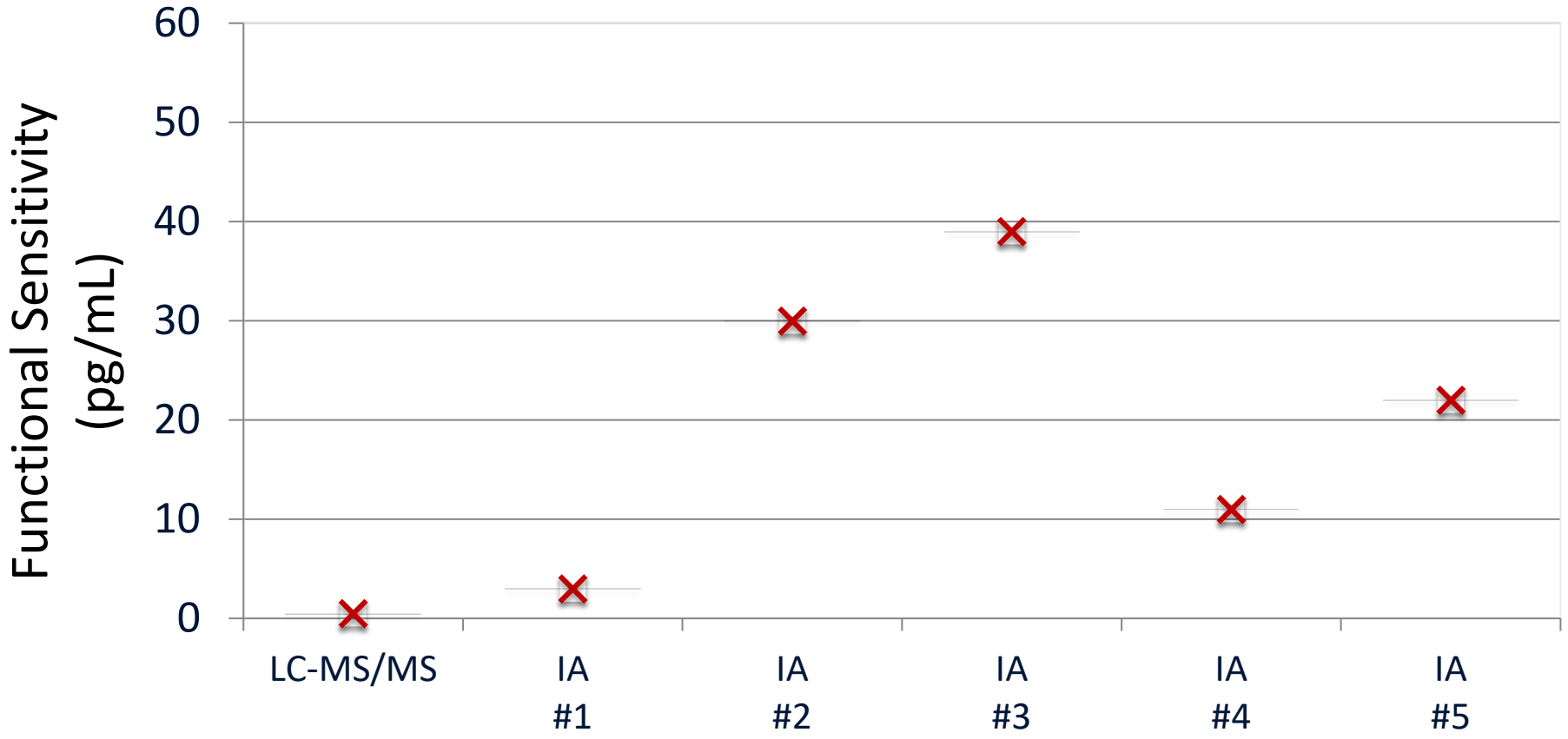
Testosterone Immunoassays: Functional Sensitivities Vary Considerably



IA = Immunoassay

Data from:
La'ulu, Kalp, and Straseski, Clin Biochem 2018:58;64

Estradiol Immunoassays: Functional Sensitivities Vary Considerably



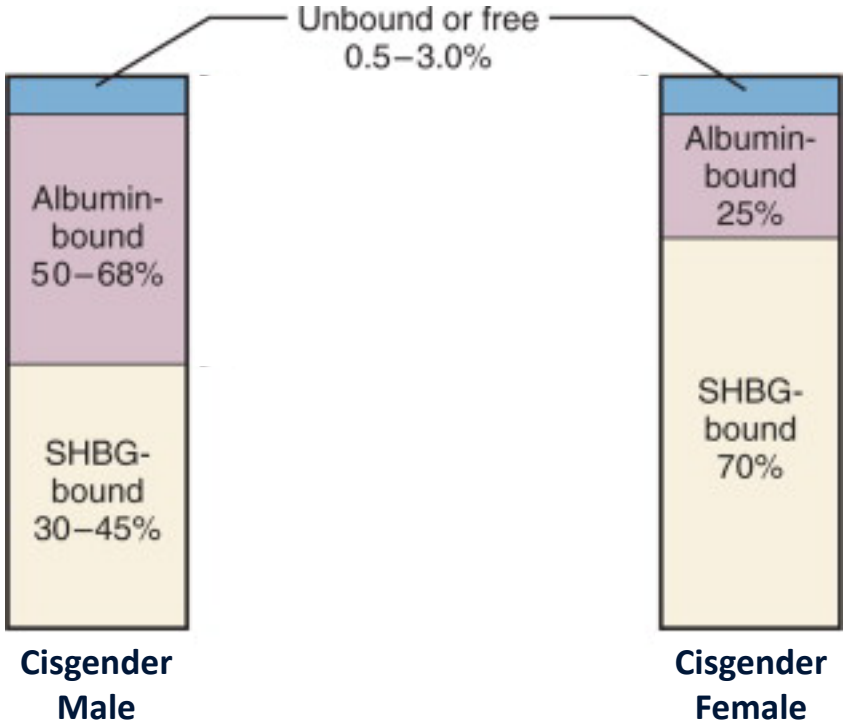
IA = Immunoassay

Adapted from:
Owen and Straseski, Clin Chem (2014) 58(10):A73

Testosterone Assay Performance: Brief Literature Summary

Imprecision:	Greater immunoassay imprecision at lowest T concentrations *La'ulu, Kalp, and Straseski, Clin Biochem 2018:58;64*
Sample matrix:	Most immunoassays are optimized for better recovery in male matrix samples *Kane et al., Ann Clin Biochem 2007:44;5*
Immunoassay vs. Mass Spectrometry	Bias is most apparent at the lowest concentrations *Taieb et al., Clin Chem, 2003;49:1381* Imprecision is a concern at the lowest concentrations for MS assays, as well *Vesper et al., Steroids 2009;74:498*

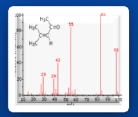
Testosterone: The Plot Thickens



- Free
- Bioavailable +
- Total + +

The Plot Thickens:

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:

Immunoassay (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])

"[High] vs. [Low]"

Total Testosterone vs. Free/Bioavailable Testosterone?

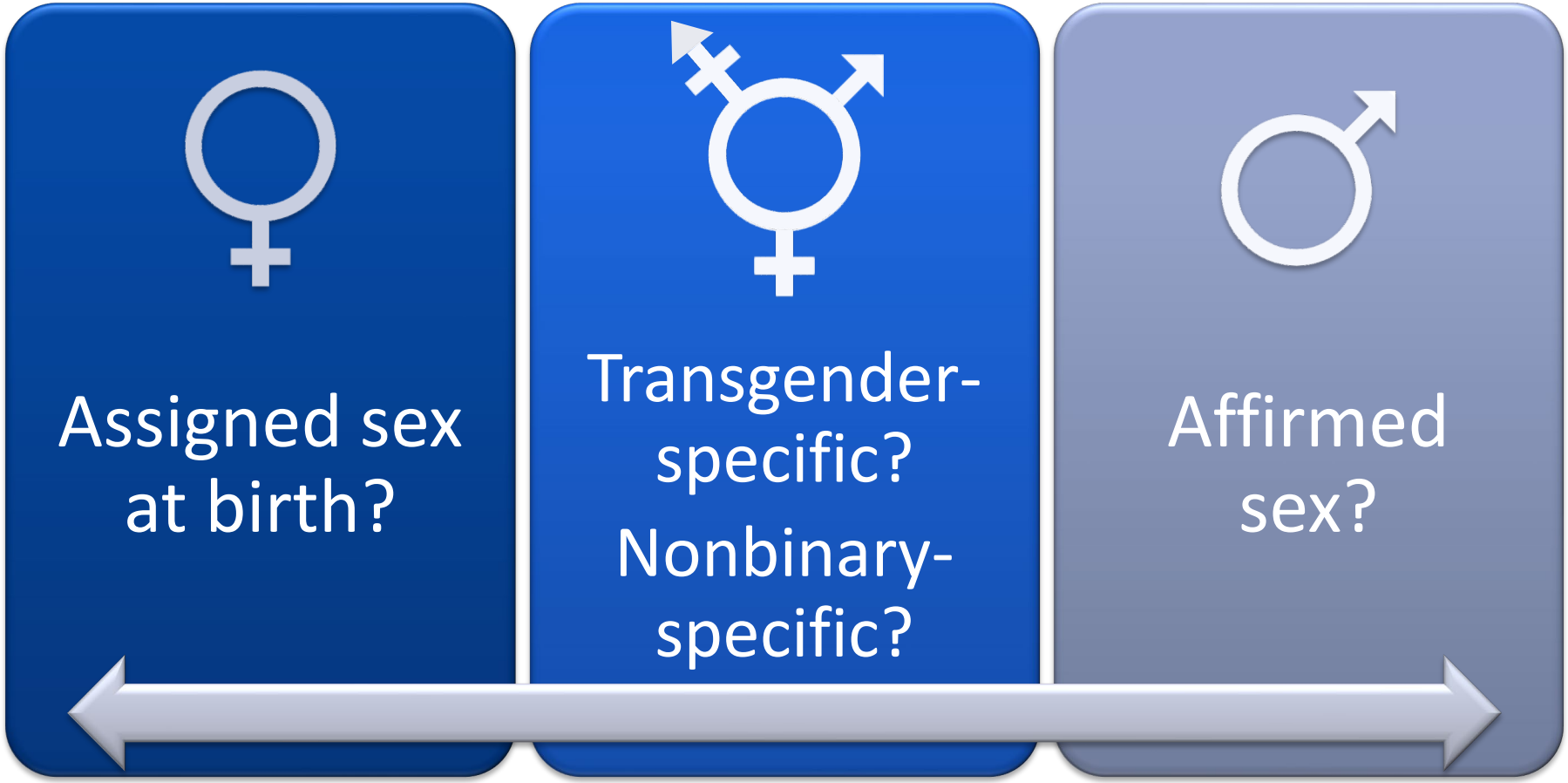
- Assays can be challenging, not standardized[1,6]
- Overall, Free T not required for most clinical scenarios (esp. trans males[5])
- Use to evaluate elevated T in trans females[4]
  - Estrogen affects SHBG concentrations

"Complex"

[1]Deutsch, ed., 2nd edition, June 2016, transcare.ucsf.edu/guidelines; [2]Hembree et al., J Clin Endocrinol Metab 2017;102(11):3869-903; [3]Goldstein et al., Clin Chem 2017;63(8);1342-52; [4]Greene et al., JALM 2021;6(1):15-26; [5]Greene et al., JALM 2021;6(1):41-50; [6]Faix, Best Pract Res Clin Endo Metab 2013;59:372-80

Reference Intervals (RI):

Reference Intervals For Individuals Using GAHT: How do we approach this?



Example:
Trans male

Reference Intervals For Individuals Using GAHT: Many Variables

Reference Intervals For Individuals Using GAHT: Many Challenges

Transgender Reference Intervals: Current Landscape

"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?

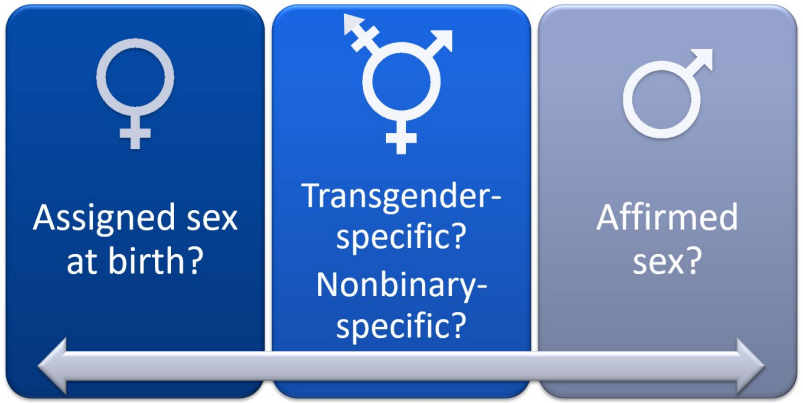


Table 1. Recommendations for Laboratory Tests With Sex-Specific Reference Ranges in Trans People Using Gender-Affirming Hormone Therapy

Test	Recommended Reference Range for Interpretation		Transgender-specific?
	Affirmed Gender	Presumed Sex at Birth	
Estradiol	✓		(✓)
Total Testosterone	✓		(✓)
Creatinine	✓		
Estimated GFR	✓		Alternatively, perform a 24-hour urine creatinine clearance.
Hemoglobin	✓		
Hematocrit	✓		
Iron studies	✓		Insufficient data. Premenopausal female reference range should be used for menstruating or pregnant individuals regardless of gender.
Electrolytes	✓		No sex-specific reference ranges. Minor changes in sodium observed in small retrospective uncontrolled studies; sodium reduced with feminizing hormone therapy and increased with masculinizing hormone therapy.
Liver function	✓		No sex-specific reference ranges. There is no clear evidence to suggest clinically significant changes occur with gender-affirming hormone therapy (16, 19, 23, 25, 48).
Lipid profile	✓		No sex-specific reference ranges. Masculinizing hormone therapy associated with decreases in HDL-c (19, 20, 23, 24, 49, 50). Feminizing hormone therapy associated with inconsistent lipid effects (19, 23-25, 51). If raised triglycerides observed, consider use of transdermal rather than oral estradiol formulations (52).
Prostate-specific antigen (PSA)		✓	Valid only for people with a prostate. The prostate remains in situ even after orchiectomy, vaginoplasty, or labioplasty surgery. PSA is expected to be low in the setting of low testosterone concentrations.
High-sensitivity cardiac troponin		✓	Cardiac troponin is based upon organ size, which is not expected to change with gender-affirming hormone therapy.

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:

No GAHT:	Use RI for the assigned sex at birth
	Individualized interpretation and decision-making is still critical
Early or low-dose GAHT:	Appropriate values may be between male and female RIs
	RI for affirmed sex may be appropriate, other than tissue-specific analytes (e.g., PSA, troponin)
	Individualized interpretation and decision-making is still critical
Established GAHT (> 3-6 months):	Use RI for affirmed sex, other than tissue-specific analytes (e.g., PSA, troponin)
	Individualized interpretation and decision-making is still critical

GAHT: gender-affirming hormone therapy

Institute for Quality Management in Healthcare, Center for Education, Version 2.0, 2019;
Cheung et al., J Clin Endocrinol Metab 2021;106(3):893-901

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

Institute for Quality Management in Healthcare, Center for Education, Version 2.0, 2019;
Goldstein et al., Clin Chem 2017;63(8);1342-52

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

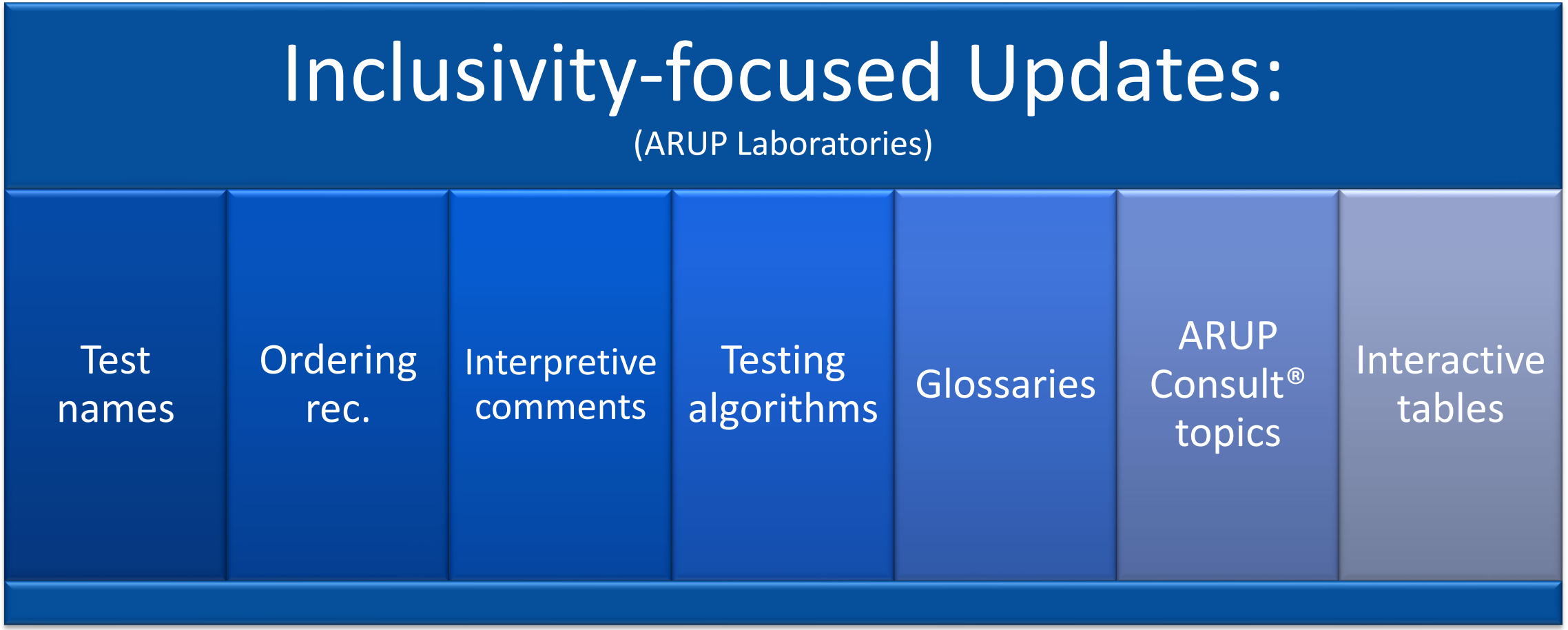
Institute for Quality Management in Healthcare, Center for Education, Version 2.0, 2019;
Goldstein et al., Clin Chem 2017;63(8);1342-52; Reisner et al., J AIDS 2016;72:S235-42

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



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…

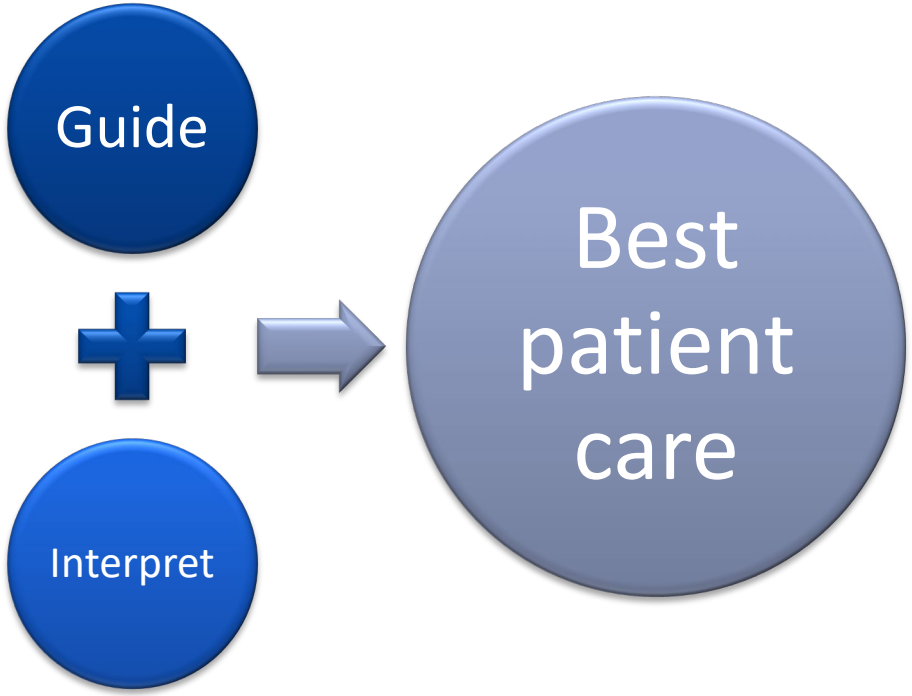
inclusivity

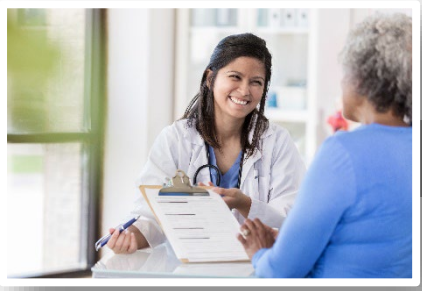
noun [U]

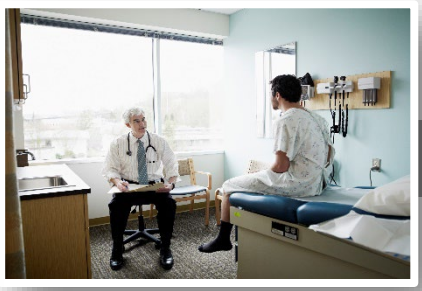
US /ˌɪn.kluːˈsɪv.ə.t̬i/ UK /ˌɪn.kluːˈsɪv.ɪ.ti/

the fact of including all types of people, things or ideas and treating them all fairly and equally:

Cambridge Dictionary







Acknowledgements:

- Kelly Doyle, PhD
- Jenna Rychert, PhD
- ARUP Support Teams
  - Becca Parker, Medical Writer (Decision Support)
  - Kelly Killian, Managing Editor (Decision Support)
  - Kellie Carrigan, Marketing and PR Specialist (Marketing, IMC)
  - Tiffany Faerber, Senior Clinical Product Manager (Market Research)
  - Janalee Renshaw, IT Clinical Systems
- Drs. Katie Kaput and Erika Sullivan, Transgender Health Physicians, University of Utah

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