AACC’s Congressional Briefing: Improving Patient Care through Harmonized Test Results

Wednesday, October 5, 2016
Lunch Briefing: 11:30 am – 12:30 pm
Room B-369, Rayburn House Office Building
Improving Patient Care through Harmonized Test Results

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Sponsored By:
- Representative Renee Ellmers (R-NC)

Moderator:
- Dr. David Koch

Speakers:
- Dr. Stephen Master
- Dr. Darius Paduch
- Dr. James Pirkle
Harmonization of Laboratory Tests

Stephen Master, MD, PhD, FCAP, FACB
Director, Central Laboratory, New York Presbyterian / WCMC
Associate Professor of Pathology and Laboratory Medicine
Weill Cornell Medical College, New York, NY
Outline

• What is Harmonization?
• Why does it matter for patients?
• Why does it matter to the healthcare system?
• Examples of important analytes
• AACC Perspective
What is Harmonization?
What is Harmonization?

Non-harmonized laboratory testing

- Lab 1
- Lab 2
- Lab 3

Non-harmonized Results

- Question mark

Valid Guideline Application

- Question mark
- Question mark
- Question mark

Patient Outcome Unclear
Why Does it Matter for Patients?

- Difficulty in comparing results from different providers
  - “I’m using a new laboratory, and my results changed; is something wrong?”
- May lead to retesting
  - Example: tumor markers require establishment of new baseline test results when the method changes
- Makes it confusing to investigate the medical implications of test results
  - Possible unnecessary visits to healthcare provider
Why Does it Matter for the Healthcare System?

- Problems for the portable medical record
- Outcomes-based reimbursement
  - If we can’t compare lab values, how can we tell who is doing a good job with their patients?
- Makes it more difficult to assess health trends
- Complicates longitudinal testing
- Inhibits the development of accurate national guidelines for treatment
  - Also, implications for federally-funded research
Benefits of Harmonization

Harmonized laboratory testing

Diagnostic Test Request

- Lab 1
- Lab 2
- Lab 3

Non-harmonized Results

Harmonized Results

Valid Guideline Application

Better Patient Outcome
Examples of tests requiring harmonization

- Human growth hormone (growth abnormalities)
- Thyroid stimulating hormone (thyroid disorders)
- Prostate-specific antigen and other “tumor markers”
- Thyroglobulin (cancer)
Example: Cancer Recurrence

- Patient diagnosed with cancer and treated by removal of their tumor
- “Tumor marker” used to detect presence of the cancer
Why is this a hard problem?

Lack of harmonization

- Different methods
- No “gold standard” assay
- Different manufacturers
- Variability in what is being measured
- No pure compound
- Material unlike patient sample
- No reference materials
Solutions: AACC Recommendations

• Coordinated action among many groups will be required to address harmonization issues:
  • Education on the scope of variability in laboratory test results
  • Base clinical practice guidelines on harmonized testing procedures
  • Streamlined/standardized regulatory processes to expedite the recalibration of medical tests
  • Funding from government and private sector sources to harmonize high-priority laboratory tests
Thank You
Improving accuracy in hormonal testing: clinical implications

Darius A Paduch, MD, PhD
Herbert Fisk Johnson Associate Professor of Reproductive Medicine and Urology
**Regulation**

- FSH - LH
- Estradiol
- Testosterone
- DHT
- Aromatase CYP19
- 5-alpha-reductase

**Amplitude**

- (-)
- (-)
- (-)
- (+)

**Frequency**

- (-)
- (-)

**Leydig cell**

**Testicles**

**Pituitary**

- Stress
  - Environmental pollution
  - Food additives and supplements
  - Medications and narcotics
  - Brain tumors
  - Trauma (concussions)

**Testosterone and estrogens**

1. Normal development
2. Cognitive function
   - (depression/memory)
3. Energy
4. Bone and muscle strength
5. Reproductive functions
6. Prostate, adrenal, testicular, breast cancer
7. Cardiovascular health
8. Diabetes
9. Obesity

**Stress**

- Environmental pollution
- Food additives and supplements
- Medications and narcotics
- Brain tumors
- Trauma (concussions)
TESTOSTERONE and ESTRADIOL EFFECTS
Testosterone: clinical implications for patient and healthcare system

• 1/3rd of men older than 45 years in primary care had undiagnosed low testosterone

Risks factors associated with low testosterone:

• hypertension (1.84x)
• hyperlipidaemia (1.47x)
• diabetes (2.09x)
• obesity (2.38x)
• prostate disease (1.29x)
• asthma or chronic obstructive pulmonary disease (1.40x)

Healthcare expenditure of conditions associated with low testosterone
When what you read is not the actual truth.
How do labs tell the “truth?”

295 ng/dL

Reference value

Accuracy

Precision

Probability density

Value
“My doctor in DC said my T is normal.”
How does it affect daily practice of physicians and patient care

1. Results make no clinical sense: someone who has no signs of low testosterone will have low testosterone
   • Need to repeat testosterone measurement to avoid overtreatment, adds cost

2. Difficulties with assessing response to treatment: patient has been on testosterone and still feels fatigue and low sex drive; decision to increase testosterone depends on accurate laboratory measurement
   • Frustration with T measurement leads many physician to abandon using it

3. Lack of portability of the basic laboratory measurement: results obtained from different laboratories during treatment are very difficult to compare, insurance companies dictate where to measure testosterone and such contracts change annually
   • Problematic monitoring of safety of treatment
True implications in care

- Lack of harmonization and standardization makes the process of establishing “normal” ranges futile task. If we can’t get same results in three different labs how we can propose universal set of normal ranges.

- Comparing results of research studies (hundreds of millions of dollars spent) is close to impossible because results and conclusions depend on using tool which is precise and reproducible only within specific laboratory where the research was performed.

- Self treatment in younger men common leading to anabolic drug abuse: norms used right now are not age adjusted.

- Overtreatment of older men common because only 20% of internists actually check testosterone before prescribing testosterone: reason: the test result is like tossing a coin.
Do men care more about their cars than about their testosterone?

Government regulated accuracy of dispensing gasoline in USA:
Max error of 6 cubic inch per 5 gallons of dispensed gas
= 0.53% of error allowed

Current accuracy of testosterone testing in USA
= 30% of error allowed

Women produce testosterone first and then covert it to estradiol

Hormone assays harmonization and standardization is critical not only for men and boys but also for girls and women; affects us all
Thank You
CDC Harmonization Programs

James L. Pirkle MD PhD
Director, Division of Laboratory Sciences
National Center for Environmental Health
Problem:

Important laboratory measurements are not sufficiently accurate and precise for:

• effective diagnosis, treatment and prevention of diseases and

• reduction of medical costs
Solution: Harmonization

- assures laboratory measurements are accurate and precise across
  - laboratories
  - analytical methods
  - time

- can correct the inadequate accuracy and precision of important laboratory measurements
Develop and maintain reference methods

Calibrate and evaluate manufacturers

Monitor accuracy of clinical laboratories

CDC Clinical Reference Laboratory

CDC Certificates Program

Accuracy based surveys including CDC Lipid Testing Monitoring Program
CDC, in collaboration with the private sector,

has a good track record of

harmonizing 8 important lab measurements,

but more are in need.
Lab measurements CDC has harmonized

<table>
<thead>
<tr>
<th>Test</th>
<th>Accuracy</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>±1.0%</td>
<td>≤1%</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>≤2%</td>
<td>≤1.5%</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>≤1.0 mg/dL</td>
<td>≤1 SD</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≤2.5%</td>
<td>≤2.5%</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D2, 25-Hydroxyvitamin D3</td>
<td>±1.7%</td>
<td>≤5.0%</td>
</tr>
<tr>
<td>Testosterone</td>
<td>±2.1%</td>
<td>≤2.7%</td>
</tr>
<tr>
<td>Estradiol</td>
<td>±2.8%</td>
<td>≤5.7%</td>
</tr>
</tbody>
</table>
Excellent accuracy of cholesterol measurements from 87 labs in CDC Harmonization Program from 2013-2016
(acceptable is ± 3%)
Unacceptable bias in testosterone measurement from different manufacturers

Mean bias (%)

Manufacturer

A  B  C  D  E

CDC harmonized
Measurement accuracy of testosterone clearly improved among participants in the CDC Hormones Harmonization Program.
Different laboratories produce markedly different estradiol measurements.

[Bar chart showing mean bias (%) across different laboratories (1 to 17), with laboratory 16 and 17 having significantly higher mean bias compared to others.]
Much better estradiol accuracy from participating in the CDC Hormones Harmonization Program

![Mean bias of labs (%) over time](chart)

- **Before**: 2012
- **After**: 2014, 2015
Improved accuracy of 25-hydroxyvitamin D from participation in CDC’s Vitamin D Harmonization Program

Before
After

Mean bias (%)

30 nmol/L (Insufficient Vitamin D)
50 nmol/L (Adequate Vitamin D)
Study by RTI International found that the CDC Lipid Harmonization Program resulted in a cost benefit of

$338 million to $7.6 billion per year

Thank you.

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333  
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348  
Visit: www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info  

The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Questions?
Thank you!