PARTNERSHIP for the ACCURATE TESTING of HORMONES

STEERING COMMITTEE NEWSLETTER September 30, 2020

PATH UPDATES

- **PATH Educational Curriculum –** Development of the PATH Core Curriculum is underway and the first module is planned to be released in November! The Working Group met in late May to discuss the outline developed by the program chair, Dr. Alvin Matsumoto, and review potential options for how to best present the course. After this kick-off call, staff circulated a survey to all meeting participants to solicit feedback on the proposed module groupings, example and case topics, and timeline. Additionally, each member was asked to indicate their preferred manner of participation in the development of this course: As content developers and presenters; as case and/or example creators; and/or as peer-reviewers. Six respondents indicated they would like to be included as core faculty for the development of the PATH curriculum course in varying ways.

  Based upon respondent feedback and in collaboration with the program chair, the course was broken into 4 distinct modules. Each module will feature voice over presentations with examples from various endocrine specialty areas, and case-based questions will be available for learners to answer after the presentations. Each module, including examples and cases, will be peer-reviewed by 2 workgroup members.

  Dr. Matsumoto is developing the first module, which will be released in November 2020 and eligible for 1.5 AMA PRA Category 1 Credits. The first presentation will focus on hormone standardization and the importance of standardized measurements, followed by case questions. The second presentation in this module will provide a very high-level overview of modules 2-4, to serve as an introduction to the overall course. An outline for this presentation has been provided and peer-reviewed, along with outlines for the cases and examples. The faculty are now working on building out their respective content based upon the peer-review feedback; once more developed, they will all be reviewed again prior to finalization. Dr. Matsumoto will then record his presentation and staff will build out the online component with recording, examples, and cases.

  Module 2 is planned to release in March 2021 and will focus on hormone types and the characteristics of an ideal hormone assay. Module 3 is planned to release in July 2021 and will focus on methods used to measure hormones and validity and judging the quality of

hormone assays. Module 4 is planned to release in November 2021 and will focus on factors affecting interpretation of hormone concentrations, specifically for use in diagnosing endocrine disorders. Each of these modules will be eligible for 1.0 AMA PRA Category 1 Credit and the overall process will be assessed after each module to ensure improvements are made as needed.

- **PATH Initiative with Payors –** PATH co-chairs Drs. Alvin Matsumoto and Hubert Vesper, along with CDC, NACDD, and ES project staff, have continued to hold phone calls with Avalon Healthcare Solutions, a laboratory benefits manager for health insurance companies including several BlueCross BlueShield affiliates. We will be working with Avalon on three topics: providing education to their physician network, updating clinical policies, and incentivizing the use of standardized tests. Avalon has also been invited to join PATH.

NEWS FROM STEERING COMMITTEE MEMBERS

CDC Clinical Standardization Programs (CSP)

- CDC CSP is preparing for a new program to standardize PTH measurements planned to be launched in 2021. The CDC reference method will measure intact PTH as well as several PTH fragments. This program complements CDC's Vitamin D Standardization Certification Program (VDSCP) and broaden CDC's standardization activities in the areas of bone and chronic kidney diseases.
- CDC CSP is finalizing preparations for its standardization program on thyroid function tests with free thyroxine (fT4) and TSH as the initial focus. It is anticipated that recalibration of fT4 assays as part of these standardization activities may change normal ranges and patient values by 50% for some assays. CDC CSP is working with stakeholders to facilitate this transition.
- CDC CSP is working with the PCOS Challenge: The National Polycystic Ovary Syndrome Association, to establish reference intervals for testosterone in women and children.
- CDC CSP is providing Accuracy-based Monitoring Program (AMP) for Total 25-hydroxyvitamin D, Total Testosterone in Males, Total Testosterone in Females to laboratories and investigators. AMP allows continuous monitoring of the accuracy of measurements in patient care and research studies over time. The program operates similarly to our long-standing CDC Lipids Standardization Program (CDC LSP). Contact CDC AMP at: Standardization@cdc.gov
- CDC CSP offers standardization programs for hormones such as Total Testosterone, Estradiol, Free Thyroxine and Total 25-hydroxyvitamin D. For a complete list of analytes covered in CDC CSP, visit: https://www.cdc.gov/labstandards/hs.html

MEMBER SPOTLIGHT: North American Menopause Society

Founded in 1989, The North American Menopause Society (NAMS) is North America's leading nonprofit organization dedicated to promoting the health and quality of life of all women during midlife and beyond through an understanding of menopause and healthy aging. Its multidisciplinary membership of 2,000 leaders in the field – including clinical and basic science experts from medicine, nursing, sociology, psychology, nutrition, anthropology, epidemiology, pharmacy, and education – allows NAMS to be uniquely qualified to provide information that is both accurate and unbiased, not for or against any point of view.

- **In what ways does your/your organization's work intersect with PATH's mission?**

Accurate measurement of estradiol (and estrone) in postmenopausal women is necessary in several clinical circumstances, for example to determine risk of breast or uterine cancer. Another primary goal is to demonstrate that estradiol levels do not exceed the reference range in women being treated with vaginal estradiol. As assay sensitivity and specificity is increased substantially with newer mass spectrometry assays, it is important to develop a globally accepted reference range for estradiol using standardized and certified assays that could be adopted by clinical and research communities. In order to translate research results to clinical care, establishment of a single harmonized reference range for estradiol concentrations in postmenopausal women should be developed.

- **What are some current or upcoming activities that your organization is working on that would be of interest to PATH members?**

NAMS continues to request FDA to enact modifications in the estrogen therapy black box warning for low-dose vaginal estrogen formulations dosed within the postmenopause estradiol reference ranges. Such modifications would include removal of the black box warning and replacement with cautions regarding the need for medical evaluation if postmenopausal bleeding or spotting occurs and for women to engage their oncologists in decision making if they have a prior estrogen-sensitive cancer.

- **What are the major challenges your organization and/or its members are facing right now related to hormone standardization?**

The key challenge at this point is to find the funding necessary to carry out a detailed plan for measurement of estradiol by the CDC and to analyze these data using state-of-the-art biostatistical methods suitable for harmonization.

- **How has being a member of PATH been beneficial to you/your organization?**

Measurement of estradiol (and estrone) is a key tool in the evaluation of certain aspects of menopause management. PATH has put together a forum which provides input from many different types of organizations, including medical societies, the CDC, biostatisticians, and companies that develop or utilize these assays, to further develop the assay sensitivity and

specificity needed for the measurement and standardization of hormones. PATH is a key resource for bringing organizations, scientists, and clinicians together ensuring that we can develop and harmonize accurate hormone testing for different types of hormones. Ideally, international harmonization will also be achieved.

- **Can you update us on your efforts to establish a reference range for estradiol? What is next?**

A workshop on the measurement of estradiol levels in postmenopausal women was held September 23-24, 2019, in Chicago, Illinois. The workshop was organized to provide a roadmap for the establishment of estradiol reference ranges in postmenopausal women. This workshop was part of NAMS' ongoing efforts to educate women, providers, and insurers about the safety of vaginal estrogen when systemic absorption and circulating levels do not exceed the postmenopause normal reference range and address the need for more appropriate and evidence-based labeling of low-dose vaginal estrogen.

Short term goals

Establish harmonized reference ranges for estradiol and estrone in postmenopausal women using appropriate assay in adequately powered studies of well-characterized populations. The plan is to obtain approximately 8,000 serum samples from four studies in which estradiol was measured by mass spectrometry assays in postmenopausal women and re-run 100 from each of the four studies with the Centers for Disease Control (CDC) state-of-the-art, ultra-sensitive assay. Harmonize the results from each of the four studies with the CDC assay. The next step is to utilize statistical methods to establish the reference range. Finally, a subset analysis will be conducted to determine the effects of BMI, age, and age of onset of menopause on estradiol levels.

Intermediate-term goals

- Conduct studies of the association between the clinical measurement of serum estradiol levels (and estrone) and prespecified clinical outcomes using previously published data bases.
- Obtain definitive evidence to examine the relationship between low and ultra-low dose vaginal estrogen formulations that induce short-term or long-term increases in plasma/serum estradiol levels.

Long-term goals

- Conduct additional clinical studies to determine the association between estradiol and estrone levels measured by using standardized LC or GC tandem mass spectrometry assays and the risk of breast cancer, endometrial cancer, CVD, cognitive dysfunction, and fractures.

- Measure estradiol and estrone levels in women taking aromatase inhibitors/estrogen receptor antagonists for breast cancer to determine the association between suppressed levels and recurrence rate in these patients.
- Encourage longer-term safety studies of vaginal estrogen preparations and the site of placement in the vagina to minimize any risk of endometrial neoplasia.

Upcoming 2020 Meeting Dates for Steering Committee Organizations

We have updated our list of dates for 2020 meetings for Steering Committee organizations taking into account changes because of the pandemic.

PATH Member	Annual Mtg Date	Location
NAM	September 30 – October 3	**Now virtual**
CAP	October 10-14, 2020	**Now virtual**
International Society of Andrology	December 9-12, 2020	Munster, Germany
AACC	December 13-17, 2020 **[new dates]**	**Now virtual**

If your organization has news to share about what it is doing related to hormone testing, please send to mbecker@endocrine.org so we can post it on the PATH website, forward to the PATH Steering Committee and/or include in our next newsletter.

VISIT THE PATH WEBSITE WWW.HORMONEASSAYS.ORG