The Monitor

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From the Mind of the Chair

Dear Colleagues,

We need to talk! In the day and age of molecular medicine you may be asking yourself quite frequently, what is the standard for existing and new biomarkers? In an environment where new platforms are emerging almost every minute, the standards are becoming exponentially more complex. Thanks to Dr. Google and other "tweet technologies", today's world is flooded by a tsunami of information that leads many to a sea of uncertainty. Thus, let me be the first to thank our existing members and welcome new world experts to our division; these individuals have the responsibility to screen this data, set the standards and advocate for mothers and their children.

On that note, our division goal is to enhance the communication among members as well as to screen and provide constant and accurate information on up to date topics that matter most. In the current issue of our newsletter, you will find some of your answers in Dr. Nakamoto's life experience report on Tanner stage-based reference ranges, Dr. Hammond's review of testosterone and Dr. Geaghan's interview with a rising star, Dr. Ann Gronowski.

Finally, we hope to discuss these and many other issues with you at the International Congress of Pediatric Clinical Laboratory in Istanbul (June 20-22) and at the annual AACC meeting in Chicago (July 27-31). Make plans to join us at the Pediatric Reference Range Committee meeting and enjoy our mixer with the Translational Medicine and Laboratory IS and Medical Informatics divisions. As we move forward, we would like to hear your thoughts on rare diseases, biobanking and other initiatives that could enhance our experiences and processes. Please feel free to contact us anytime in person or electronically with your ideas and concerns.

Sincerely,

David Carpentieri, M.D.

Reference Interval Corner

Pediatric Reference Intervals and the Puberty Factor

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Laboratory Medical Director, Quest Diagnostics Nichols Institute, San Juan Capistrano, CA
Associate Professor (Voluntary) of Pediatrics and Endocrinology, University of California, San Diego

Painfully obvious fact of the month: Hormones and many other analytes change substantially during puberty. But the age at which puberty starts can vary by up to five years in healthy children, approximately between 8 (perhaps younger in some populations) and 13 years of age in girls and between 9 and 14 years of age in boys. Therefore, a 9 year old "early blooming" boy might have similar testosterone levels to those found in an otherwise healthy "late-blooming" 13 year old adolescent. Is it therefore valuable to offer reference intervals adjusted for pubertal stage, rather than only offering age-stratified information? Absolutely, yes. Does everyone agree on how to generate these puberty-adjusted norms, and is it straightforward to obtain them? Absolutely not. Read on for a brief introduction to what, like adolescence itself is a surprisingly complex topic.

First of all, a brief review of how puberty is classified. James Tanner, a British pediatrician, was the first to standardize how clinical examination of breasts in girls, genitals in boys, and pubic hair in both sexes could be used to define specific stages of sexual maturation. Despite his protests that efforts to do this had started well before his time, the five point scale (classically using Roman numerals, but acceptable nowadays as Arabic) he defined became known as the Tanner stage scoring system and remains the de facto standard for clinical assessment of puberty. There are reasonably objective criteria for breast, genital and pubic hair development; for example, the transition from Tanner II to Tanner III pubic hair development is defined by when hairs become darker, coarser, and meet in the midline of the symphysis pubis. Summaries of Tanner staging (with pictures or diagrams) can be found in pediatric textbooks or online[1,2].

Although Tanner stages have proven their utility in clinical practice, staging is not absolutely precise, with many ambiguities and variations that must be acknowledged. Training is required, as inter-rater reliability (IRR) can be quite low among untrained individuals. Even among trained individuals, there are certain stages that are extremely difficult to distinguish (e.g., male genital stage II versus stage III) and many specialists find the male genital staging to be so subjective that they prefer to use testicular volume or length for evaluating sexual maturity in boys, even though testicular size was not part of the original Tanner staging system. Tanner staging of breast development can also be difficult; although the original Tanner staging was based solely on inspection, it is clear that in overweight girls the examiner must actually palpate the breast in search of glandular tissue (true pubertal development) to distinguish it from increased breast size due to fat accumulation (not true puberty). The transition from breast Tanner II to Tanner III development can be difficult to define, and there may even be confusion between Tanner III development in a large-breasted individual versus Tanner V in a young woman with smaller breasts, although diameter of the breast papillae (nipples) > 1 cm can help define Tanner V breast development. Some women may always retain the secondary mound of the nipple and areola that defines Tanner IV, and may therefore never officially reach Tanner V.

An additional issue to consider is that breast/genital development (driven by pituitary-gonadal activation) may not always follow the same timing as that for pubic hair (driven by both gonadal and adrenal activation). It is not uncommon for a girl to have Tanner III pubic hair development but only Tanner II breast development – so is her pubertal stage Tanner II or Tanner III? Ideally she should be defined simply as Tanner “B II, PH III”, but this introduces substantial complexity to developing reference

intervals stratified by Tanner stage. A related issue is that levels of some hormones correlate better to the stage of breast development while others are more closely related to the pubic hair Tanner stage. Thus, it may ultimately be wise for the endocrine and clinical chemistry communities to agree that Tanner stage-adjusted reference intervals for estradiol must be based specifically on girls defined by breast development, while those for DHEA-sulfate should be based on children stratified primarily by pubic hair stage. At present, few if any laboratories make this distinction.

A further difficulty with Tanner stage stratification lies in lack of complete homogeneity within a given stage, particularly within the important prepubertal (Tanner I) group. An infant, toddler, pre-schooler, and a 7-year old may all be Tanner I by breast/genital and pubic hair development, and yet have very different hormonal profiles. It is clear, for example, that adrenal activation (adrenarche) and rising DHEA-sulfate starts before age 6 years[4], at least 3-4 years before the first appearance of pubic hair. Therefore, a study that included in the Tanner I category children age 1-7 years would have much lower average DHEA-sulfate levels as compared to a study that only used Tanner I children aged 5-7 years. Currently there is no standardization in how to define the study population for Tanner I children.

Beyond these methodological issues, there are often practical barriers to generating Tanner stage adjusted reference intervals. It can be difficult to obtain sufficient numbers of accurately-staged and truly representative subjects. The laboratory must have access to the subjects or at least to the clinical information, including detailed staging information (breast/genital development versus pubic hair, or whether testicular volume was used in place of male genital development). As noted above, those doing the staging must be properly trained. Institutional review boards and parents alike are often reluctant to allow breast palpation or external genital examinations of otherwise healthy children, but Tanner staging by inspection alone has inherent limitations (particularly for assessment of breast development), and studies of children performing self-assessment of their own breast or pubic hair development demonstrate unacceptably inaccurate scoring relative to that done by trained observers[3]. Given known ethnic differences in the timing of puberty and typical hormonal levels, it is desirable but not always achievable to draw from a population with diverse demographics. All of these barriers tend to make the already relatively small sample sizes in pediatric reference interval studies even smaller for Tanner stage adjusted reference interval studies. Since there is still rather large inter-individual variability of hormonal levels within a given Tanner stage, small datasets lead to increased variability due to sampling error, and even the smallest amount of data contamination (inaccurate Tanner staging; children with cryptic endocrinologic abnormalities) can skew the data analysis significantly.

In spite of the myriad difficulties noted, having both puberty-adjusted and age-adjusted reference intervals for selected analytes is extremely useful for the specialist. During the months or years that it can take to conduct the studies to obtain reference intervals by Tanner stage, there are interim alternatives available. First of all, because variation in the timing of puberty is common, groups of children stratified by age tend to include both early- and late-bloomers, and the reference intervals generated tend to be wide enough to be inclusive of most children regardless of differences in pubertal stage, much as commonly-used cross-sectional growth charts are still useful despite differences in timing of growth spurts by age. Secondly, an approximate adjustment for early- or late-bloomers can be

made by looking at the reference intervals for older or younger age groups. This crude workaround performs surprisingly well and is preferable to using Tanner-stage adjusted data from an improperly-designed or inadequately-sized reference interval study.

In summary: it's clinically useful for certain hormones and other analytes to have reference intervals stratified by Tanner stage, but doing the studies requires a lot of careful thought and planning. And like much that is valuable in life, they're certainly not easy!

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3. Bonat S, et al. Self-assessment of pubertal stage in overweight children. Pediatrics 2002; 110:743-7.
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The ABC's of Pediatric Laboratory Medicine- T is for Testosterone

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Testosterone is the primary androgenic hormone, which is synthesized from cholesterol via the steroid pathway. The most prominent production of testosterone is by the Leydig cells in the testis. However, other sources of testosterone synthesis include the thecal cells of the ovaries, placenta, adrenal cortex (zona reticularis), adipose tissue, brain, muscle and skin. This may occur via de novo synthesis or by peripheral conversion of precursors. The quantities produced by these alternate sources are significantly smaller than that of the testis. In males, the regulation of testosterone production occurs via the hypothalamus-pituitary-testicular axis. To increase testosterone, gonadotropin-releasing hormone (GnRH) from the hypothalamus exerts effect on the pituitary to secrete lutenizing hormone (LH) and follicle stimulating hormone, which act in the testis to increase both the number of Leydig cells and the synthesis of testosterone in the Leydig cells. Rising concentrations of testosterone then provide negative feedback to the hypothalamus and pituitary to inhibit further synthesis.

Testosterone circulates in blood as free (unbound, <5%), tightly bound (~45%) to sex hormone binding globulin (SHBG) and loosely bound (~55%) to albumin and corticosteroid binding globulin. The free and loosely-bound forms are considered the 'bioavailable' fractions, as the SHBG-bound form is not available to target tissues. Free testosterone enters cells via passive diffusion and either binds to androgen receptors in the nucleus to exert its effects or may also be converted into a different hormone. Testosterone can be a precursor for a weaker androgen (androstenedione), a hormone with different activities (estradiol) or for a more potent hormone having similar activities (5α-dihydrotestosterone (DHT)).

The nuclear testosterone-receptor complex alters gene expression and related protein transcription to produce androgenic and anabolic effects in cells. It is through this mechanism that testosterone regulates the growth and development of male reproductive organs, as well as the development and establishment of secondary 'male' sex characteristics during puberty. The anabolic effects include increased muscle mass and strength and maintenance of bone mass, density and strength. The effects and concentrations of testosterone vary according to age and gender to regulate necessary androgenic and anabolic functions from gestation through adulthood. This fact creates challenges in the measurement of testosterone, as it requires assays that precisely and accurately detect a wide range of concentrations (e.g., <5 to >500 ng/dL). Lowest concentrations of testosterone are found in pre-pubertal children and women. Hypogonadal men and those with 'castrate' levels of testosterone will also have concentrations in this problematic range (e.g., <50 ng/dl). Testosterone is an important diagnostic tool in these populations but most commercially available, direct immunoassays (IAs) are not reliable in these cases.

Table 1 lists examples of clinical scenarios involving measurement of testosterone.

Table 1.	Clinical Scenarios Involving Testosterone Measurement
Males	
	Hypogonadism Puberty disorders Delayed Precocious Monitor response to therapy Testosterone replacement Anti-androgen or GnRH-analogs
Females	
	Irregular or no menses Ambiguous genitalia Hirsuitism Polycystic ovary syndrome (PCOS) Non-classical congenital adrenal hyperplasia (NCCAH) Idiopathic hirsuitism Androgen-secreting tumor Monitor response to therapy Testosterone replacement Anti-androgen or GnRH-analogs

There are a variety of methods used to measure testosterone and they have been in existence for decades. The most common are either IA- or mass spectrometry (MS)-based. The earliest of these methods utilized a radioimmunoassay (RIA) platform and incorporated labor-intensive sample pre-treatment. The sample preparation steps served to release the hormones from binding proteins and to remove potential interferents from the sample matrix and chromatography steps further enhanced the

selectivity. Due to the up-front processing, these assays are commonly referred to as 'indirect'. As the need for higher-throughput, reduced complexity and the availability of non-RIA platforms increased, automated IAs gained popularity. These so-called 'direct' IA methods eliminated the sample purification steps and relied on improved performance of reagents and antibodies to directly measure testosterone in patient serum. They were validated for use in primarily normal adult male samples and met performance specification, as such. Reports emerged demonstrating the severe limitations of direct IAs for accurate and precise measurement of testosterone in children, women and hypogonadal men (1-3). Additionally it was becoming clear that there was a lack of standardization across IA platforms. However, even decades later, presumably due to the availability, cost and turn-around-time of these methods, they are still used, despite limitations leading to misidentification and misclassification of diseases in these select populations. Alternative, mass spectrometry-based methods are increasingly available in clinical labs and although these methods have improved sensitivity and specificity over most direct IAs, they lack standardization.

Mass spectrometry-based methods for testosterone measurement have been in use since the 1960s. These early methods incorporated sample preparation steps similar to the indirect RIAs. They also included derivitization with separation by gas chromatography (GC) and detection by MS, based on an isotope-labeled internal standard. Therefore, these methods were highly sensitive and specific but due to the complexity, low throughput and high sample volume requirements they were better suited as reference or comparator methods than for routine use in clinical care. The advancement of liquid chromatography (LC) tandem mass spectrometry (MS/MS) methods for clinical use enabled testosterone measurements to become widely available in reference/specialty labs and also in many hospital labs. LC-MS/MS methods, due to their improved sensitivity and specificity over IAs were favored and deemed suitable for measurements in situations with low (e.g., <50 pg/mL) concentrations. However, due to differences in sample preparation, calibration and other methodological differences in these methods that are developed and validated by individual labs, there was variability reported between LC-MS/MS methods.(4)

The mounting evidence and concern about IA performance at low testosterone concentrations with the high degree of variability noted across all methods led to a workshop in 2010, focused on the need for standardization of testosterone methods. This included perspectives from researchers, clinical laboratorians, clinicians, professional and governmental organizations and industry. The Endocrine Society issued a consensus document outlining the limitations with testosterone assays and recommending actions for improvement. (5) The recommendations included the need for technical improvement and standardization of testosterone assays. The CDC developed an initiative for ensuring testosterone results are traceable to a single source and would, thus, be comparable across all methods and performing labs and over time.(6) The program consists of 3 steps: developing a reference system, calibrating individual assays, and verifying end-user test performance. The CDC's candidate reference method was published in 2013 and has been used to assign values to single-donor sera. These commutable samples are intended for use by assay developers and manufacturers as calibrators and/or trueness controls. (7) Labs and manufacturers participating in the Hormone Standardization (HoSt) Program perform a calibration/calibration verification with the CDC method and samples and their

performance is monitored on a quarterly basis. Laboratories with a mean bias ± 6.4% from 4 consecutive challenges are considered sufficiently accurate and standardized to CDC. To date, there are 9 methods certified as standardized to CDC (8 LC-MS/MS and 1 IA). (8) End-user performance is verified by CDC's collaborations with proficiency testing manufacturers to provide accuracy-based materials. The reference values for these materials are assigned using the CDC's reference method. The efforts to standardize testosterone are beginning to show positive impact as the inter-laboratory variability for MS-based methods decreased (mean absolute bias decreased by ~50%) in a recent comparison of measurements in 2007 and 2011.(9) The need for standardization in clinical measurements is clear and the progress made to date with the testosterone program is promising, however, smaller, lower volume clinical labs performing testosterone measurement by LC-MS/MS face challenges in participating in the HoSt program.

Measurement of testosterone is an important diagnostic tool in the evaluation of androgen inadequacy and excess. Most direct IA methods do not meet accuracy and precision requirements for use in women, children and hypogonadal men, due to the extremely low circulating testosterone concentrations in these populations. It is recommended that testosterone measurements in these populations be performed using a validated LC-MS/MS method. Although generally more sensitive and specific than direct immunoassays, LC-MS/MS methods still lack standardization. A standardization initiative to address the measurement variability for testosterone was proposed and is underway with recent reports of success among its participants. It is important to note that the limitations described herein about testosterone measurement (e.g., lack of standardization, commercially available direct IAs with inadequate accuracy and precision at low end concentrations) are also true for estradiol. Mounting evidence indicates that most commercially available direct IAs are not suitable for measurement of estradiol at concentrations typically found in children, post-menopausal women and those on aromatase inhibitors.(10) Standardization efforts, parallel to those for testosterone, are in progress for estradiol measurement, as the available methods also show high variability.

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Excerpts from the Literature

Articles of interest compiled by the editorial board.

Use of Inhaled Nitric Oxide in Preterm Infants Summarized

Praveen Kumar and COMMITTEE ON FETUS AND NEWBORN. *Pediatrics* 2014;133;164 (UG)

Due to its vasodilating effects, nitric oxide (NO) is used in the treatment of full-term and late-preterm infants with persistent pulmonary hypertension of the newborn and hypoxemic respiratory failure. Several randomized controlled trials have evaluated the role NO in the management of preterm infants with varying results. In this paper the authors summarize the existing evidence for the use of inhaled nitric oxide in preterm infants and provide guidance regarding its use in this population. The authors reviewed the literature on the use of NO in preterm infants with respiratory failure and in preterm infants to improve the rate of survival without bronchopulmonary dysplasia (BPD). Among other findings, their meta-analysis indicated that neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure (Evidence quality, A; Grade of recommendation, strong); evidence does not support treating preterm infants who have respiratory failure with iNO for the purpose of preventing/ ameliorating BPD, severe intraventricular hemorrhage, or other neonatal morbidities (Evidence quality, A; Grade of recommendation, strong); the incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated with iNO is similar to that of control infants (Evidence quality, A). They also concluded that there are limited data and inconsistent results regarding the effects of iNO treatment on pulmonary outcomes of preterm infants in early childhood.

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. (JS)

Shaw JLV, Cohen A, Konforte D, Binesh-Marvasti T, Colantonio DA, Adeli K. Clin Biochem (2013) (2014) 47(3):166-72

Establishing reference intervals in a healthy population of individuals requires an exorbitant amount of work. Two considerable challenges include the need to carefully define and verify "healthy" (often on an analyte-by-analyte basis) and the need for a minimum of 120 individual specimens per partition (e.g., age, gender, menopausal status, smoking status, etc.). These specific challenges are exponentially more difficult in a pediatric population. Biological samples are often not obtained from children unless pathology is suspected and total blood collection amounts are limited by patient size.

Methods to establish reference intervals based on data from hospitalized patients have been suggested previously, most notably the "Hoffmann approach" first published in 1963 (JAMA (1963)185:150-9, Clin Chim Acta (2009)405:43-48). The benefit of these approaches is that numerous samples are readily available, thereby circumventing the types of challenges outlined above. The Hoffmann approach assumes two important factors. First, it assumes data from hospitalized patients forms a Gaussian distribution. Second, hospitalized patients are assumed to represent normal individuals. In 2008, Soldin et al. recommended that reliable intervals may be generated using this type of statistical approach if at least 50% of individuals in the reference population are healthy (Clin Biochem (2008)41:937-42).

The goal of the Shaw et al. publication was to determine the validity of reference intervals determined using inpatients (a modified "Hoffmann approach") as compared to those determined from the healthy CALIPER (Canadian Laboratory Initiative in Pediatric Reference Intervals) repository. The CALIPER initiative is a collaborative project that aimed to recruit over 2000 healthy children from 0 to 18 years of age. They included 12 analytes measured using the Vitros 5600 in their analysis (albumin, alkaline phosphatase, ALT, AST, calcium, cholesterol, creatinine, HDL-cholesterol, iron, phosphate, triglycerides and magnesium). The number of patients used to calculate intervals varied by age, gender and analyte (range 10 to 231 after outlier removal). Hospital-based data were age- and gender-partitioned similar to previously published data using the CALIPER population. Ninety percent confidence intervals and reference change values (RCV) were calculated to compare the hospitalized and healthy intervals. Reference samples were also measured to verify the intervals determined using the Hoffmann approach (<10% outside the proposed interval, per CLSI guidelines).

The authors' predominant finding was that intervals based on hospitalized patients were much wider than those determined using healthy individuals. No reference intervals calculated using the Hoffmann approach fell within the 90% confidence intervals as calculated using the CALIPER data. One partition for creatinine and most phosphate partitions had RCV within acceptable limits. The authors surmise that the inclusion of biological variation, which can be significant for some analytes, in the RCV calculation explains why comparisons between Hoffmann and CALIPER intervals based on RCV were more favorable than those based on confidence intervals. The reference samples overall verified the Hoffmann intervals, presumably due to the wide acceptance criteria (<10%) outlined by the CLSI guidelines.

Overall, the authors concluded that the Hoffmann statistical approach is limited in pediatrics, particularly when data originates from a tertiary care center. In general, it may be surmised that hospitalized children comprise a "sicker" population than an adult inpatient population, thus

contributing to the wider intervals determined using this patient group. Due to this, use of the Hoffmann approach in pediatric populations was not endorsed by the authors. The authors suggested that outpatient clinics or community hospitals may be a better source of inpatient data if the Hoffmann approach must be used in pediatric cases. They also concluded that the CLSI guideline for verification of reference intervals may be too lenient in cases such as these.

This conclusion is similar to the findings published by Roberts et al. in a 2010 Letter to the Editor (Clin Biochem (2010)43:933-4). The comparison of intervals determined using the Hoffmann approach (Clin Biochem (2009)42:823-7) to those derived from healthy children (CHILDx sample repository) suggested limitations in using pediatric samples from inpatient or clinic settings. Comparisons of testosterone and 17-hydroxyprogesterone specifically highlighted these issues, as it is presumed that differences in intervals may be attributed to the clinical presentation of patients used for the Hoffmann approach. This is another example suggesting that use of hospitalized or clinic patients may not be appropriate to establish pediatric reference intervals and caution should be used when considering applying this statistical approach.

Trends in the Prevalence of Ketoacidosis at Diabetes Diagnosis: The SEARCH for Diabetes in Youth Study (VLP)

Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, Imperatore G, D'Agostino RB Jr, Mayer-Davis EJ, Pihoker C. Pediatrics. 2014 Apr;133(4):e938-45.

In this latest study by the SEARCH for Diabetes in Youth Study Group the goal was to report the prevalence of diabetic ketoacidosis (DKA) at diagnosis of type 1 and 2 diabetes. The study consisted of 7040 subjects aged 0 to 19 years, of which 5615 were diagnosed with type 1 and 1425 with type 2. The data collected spanned an 8 year period from 2002 to 2010. The criteria for reporting DKA were: if bicarbonate was <15 mmol/L, and/or a pH<7.25 (venous) or <7.30 (arterial/capillary), and/or DKA diagnosis was on the medical record.

After analyzing the data the authors found that the prevalence of DKA was higher in type 1 versus type 2 diagnosis. In type 1 patients, DKA had a prevalence of approximately 30%, and was stable throughout the time period analyzed. In type 2 patients, the prevalence was approximately 12% at the start of the time period and it progressively decreased by about 10% per year until the end of the period to 5.7%. In both types, younger patients had a higher prevalence of DKA when compared to older subjects. The data in type 1 patients was consistent with other similar studies, while the type 2 data was novel, according to the authors.

The authors also looked at some of the factors that were associated with DKA presentation. These data was obtained by questionnaire forms. The results showed that DKA was more prevalent in minority populations, lower family income and lack of private insurance. Limitations to the study included the relative short time period that could have prevented detection of small changes in DKA prevalence. Also, minority patient's records were more likely to have missing medical information, therefore their data

could have been underrepresented. It would be interesting to see in the future the inclusion of more laboratory data in the evaluation and follow-up of patients with DKA, including glucose, HgbA1C % and ketone values.

Interview with a Distinguished Colleague: Dr. Ann Gronowski

by Sharon Geaghan

I had a chance to catch up with Ann via a virtual interview, and she shares her insights with you as the next in a series of conversations with distinguished colleagues in our discipline

Q1. How did you come to the career decision to choose Clinical Chemistry as your profession?

I owe my career to Mitch Scott who interviewed me at a FASEB meeting in 1992. At that time, he went to FASEB and cell biology meetings to recruit doctoral students into the Clinical Chemistry Fellowship program. I had never heard of Clinical Chemistry, but I went to the interview. I was intrigued by the profession. I liked the idea of being able to combine my interest in research with a clinical application. Washington University subsequently invited me for an interview in St. Louis. The rest is history. I loved my training and was ultimately invited to stay on as a faculty member. I have been very fortunate.

Q2. Did you have a mentor and if so what did he/she teach you?

Mitch Scott and Jack Ladenson have both been mentors to me. They have taught me to think critically, to act with integrity, to give generously of my time, and to mentor our trainees like they were our own children. Both have led by example. I still look to both of them for advice and guidance. In return they continue to give me opportunities and advertise my achievements. I am very grateful for their continued

support.

Q3. For newly-minted chemists, do you have any pearls of wisdom for career development?

You have to work hard and you have to step up to the plate and take opportunities-- even if, on the surface, the opportunity doesn't seem to have an immediate return for you. It is amazing how one thing leads to another and what starts out as not much of an opportunity can turn into something great.

Q4. What is your most enjoyable part of your professional work?

I really enjoy working with trainees of all kinds. I enjoy teaching them, I enjoy seeing them mature and, ultimately, succeed on their own. Trainees have tons of energy and lots of great ideas. They tend to believe anything is possible, which can be so refreshing and great for research. I cannot imagine a job where I did not get to work with trainees.

Q5. What is the hardest part of your professional work?

I enjoy most every part of my job. I guess the hardest part is not having enough time to pursue everything I find interesting & enjoy doing.

Q6. The next generation of chemists has been characterized as looking for work-life balance; do you have advice for them, in managing that balance from your experience?

I'm not sure there is a perfect balance. Every day for me is a give and take between family and profession. Find a workplace that values family. Be organized. Be willing to work in lots of places outside the office (for me that includes: home, baseball games, the car, the orthodontist's office, and the roller skating rink!) Find community support either from family or friends. You cannot do it all. Enjoy the ride! It's great fun to have a family and a career.

Q7. What developments would you most like to see occur in the field, over the next 5 years?

Well, related to the previous question, it would be great to see more workplaces that value family and allow (male and female) workers to juggle their busy home life. It would also be nice to see more women at the top. There is still a well recognized glass ceiling for women in science. I hope that the next generation sees more women CEOs, full professors, department chairs, and college deans.

2014 Annual Meeting

Once again, it is time for the AACC Annual Meeting. Here are some sessions of interest for members of the Pediatric and Fetal Maternal Division.

Indicates a ticket is required for the session

Sunday July 27

Opening Plenary: Wallace H. Coulter lecture by Eric J. Topol, MD

"Creative Destruction of Medicine-The Digital Revolution Creates Better Health Care"

Monday July 28

Plenary: Viktor Mayer-Schönberger, "Understanding Big Data and its Impact on Your Laboratory"

Roundtables:

Anti-Mullerian Hormone (AMH): Ovarian Reserve and Beyond

Polycystic Ovary Syndrome (PCOS)-A women's Health Issue from Adolescence to Menopause and Beyond

Drug Testing in the Neonate

The CDC Hormone Standardization (HoSt) Program- Improving the Clinical Measurements of Testosterone and Estradiol

Symposia:

Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline

The Skinny on Fats: Current Recommendations and Controversies in Lipid Testing

 **Short courses/Interactive Workshops:**

Banking on the Numbers: Laboratory Assessment of Ovarian Reserve

Special Events:

Pediatric Maternal Fetal /Clinical Translational Medicine/ Laboratory Information Systems and Medical Informatics Divisions Joint Mixer and Abstract/Poster Awards

Tuesday July 29

Plenary: Piero Rinaldo, MD, PhD, and Kaitlyn bloom, PhD, "Newborn Screening for Inborn Errors of Metabolism in the 21st Century"

Morning Meet the Expert: Newborn Screening for Inborn Errors of Metabolism in the 21st Century

 **Roundtables:**

Measurement of Total Testosterone by Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

The Role of the Laboratory in the Diagnosis and Treatment of Congenital Adrenal Hyperplasia

Symposia:

A Celebration of 50 Years of Newborn Screening for Metabolic Disorders

 **Short courses/Interactive Workshops:**

Critical Values: Improving the Design, Practice, and Communication of Critical Laboratory Results

Special Events:

Pediatric Reference Range Committee Meeting

Wednesday July 30

Plenary: Jeffrey M. Friedman, MD, PhD, "Leptin and the Biological Basis of Obesity"

 **Roundtables:**

Blood Draws in Pediatrics: Physiological Effects and Recommendations

hCG Point-of-Care False Negatives: Is Your Device Affected?

Clinical Implementation of Pharmacogenetic Testing in a Pediatric Setting

Symposia:

Laboratory Testing During Pregnancy: Three Frequently Discussed Topics

Biomarkers for Chronic Kidney Disease- Limitations and Best practices

Thursday July 31

Plenary: Sharon Lewin, MD, PhD "Tackling HIV Latency: Moving Toward a Cure for HIV"

Call for nominations for the Trainee Member of the Board

We are pleased to accept nominations for our next Pediatric Maternal Fetal Division fellow / trainee Executive Board member, beginning July 1, 2014.

Eligible candidates are current fellows enrolled in PhD or MD pathology training programs in 2014-2015. The term is one year. Nominee's names and positions should be accompanied by a brief reference letter from a faculty member and sent to Nominations Chair Dr. Sharie Geaghan at sgeag@stanford.edu by May 31, 2014.

Our first fellow, Dr Joe El-Khoury, is happy to discuss his experience with interested candidates at joe.eldouss@gmail.com.

We wish Dr. El-Khoury well and thank him for his contributions as our first fellow member of the PMF Board.

Save the Date

ICPLM 2014

The ICPLM 2014 will be June 20th-22nd, 2014, prior to the IFCC-WorldLab in Istanbul, Turkey. The exciting symposium program can be accessed using the link below. Please save the dates for this exciting pediatric focused meeting which would be ideal for both the specialist and non specialist laboratory medicine professional. The names of the plenary speakers have been announced, and the deadline for abstract submission is **February 15th, 2014.** http://www.icplm2014.org/