This is the January 2014 special Women's Health issue of *Clinical Chemistry*, Volume 60, Issue 1.

On the cover this month: *Mature woman, portrait*. Although women represent half of the world's population, much of the medical literature has focused predominantly on males. We have been slow to appreciate the differences in normal physiology, as well as disease pathology, between men and women. In this special issue of *Clinical Chemistry*, which focuses on advancing women's health, we explore recent studies involving determinants and detection of health outcomes that uniquely affect women, as well as the differences in risk between males and females for shared diseases. But be sure to look beyond the original research studies because every feature, from the Preamble at the beginning to the monthly Science in the Arts at the end, presents a unique and often refreshing angle on women's health.

Prognostic Performance of a High-Sensitivity Cardiac Troponin I Assay in Patients with Non–ST-Elevation Acute Coronary Syndrome
By Erin A. Bohula May, et al.

High-sensitivity troponin assays are not commercially available in the United States, in part, due to concerns that detection of very low concentrations has eroded their prognostic implications. These assays have enabled resolution of the 99th percentile at different concentrations for men and women. The authors address these 2 important issues for a high-sensitivity troponin I assay currently under US regulatory consideration. Evaluation in a large, well-characterized cohort with non-ST elevation myocardial infarction or unstable angina revealed robust prognostic performance at the 99th percentile decision-limit and a clearly increased risk at very low concentrations. Additionally, the data from this study do not support use of gender-specific cutpoints for prognostication.

Circulating Fetuin-A and Risk of Ischemic Stroke in Women
By Monik C Jiménez, et al.

Fetuin-A levels have been associated with cardiovascular events, particularly ischemic stroke; however, the data have not been replicated. A nested case-control design was conducted among 459 female case-control pairs of the Nurses' Health Study, matched by age, race/ethnicity, menopausal status, postmenopausal hormone use, and smoking status. The highest quartile of fetuin-A was not significantly associated with increased risk of incident ischemic stroke when adjusted for matching factors. Additional adjustment for lifestyle factors, cardiovascular disease risk factors, and biomarkers did not alter results. In this sample of women, fetuin-A was not significantly associated with risk of ischemic stroke. Further research is warranted.

Age, Body Mass, Usage of Exogenous Estrogen, and Lifestyle Factors in Relation to Circulating Sex Hormone–Binding Globulin Concentrations in Postmenopausal Women
By Atsushi Goto, et al.

Emerging evidence indicates that circulating concentrations of sex hormone-binding globulin are associated with the development of various diseases, including hormone-dependent cancers, cardiovascular diseases, type 2 diabetes, and hip fracture. However, correlates of sex hormone-binding globulin concentrations are not well understood. In a pooled analysis of postmenopausal women who participated in the Women's Health Initiative, the authors of this study found that age, exogenous estrogen use, physical activity, and regular coffee intake were positively associated with sex hormone-binding globulin concentrations, whereas body mass index was inversely associated with sex hormone-binding globulin concentrations.

Circulating 25-Hydroxyvitamin D, *IRS1* Variant rs2943641, and Insulin Resistance: Replication of a Gene–Nutrient Interaction in 4 Populations of Different Ancestries
By Ju-Sheng Zheng, et al.

This study sought to determine whether circulating 25-hydroxyvitamin D modulates the association of a potential functional variant of the insulin receptor substrate 1 gene known as *IRS1* variant rs2943641 with insulin resistance. Significant interaction was observed in female participants of the Boston Puerto Rican Health Study and in the African-American, non-Hispanic white and Hispanic populations of the Multi-Ethnic Study of Atherosclerosis. Participants with different genotypes of the *IRS1* rs2943641 variant exhibit differential benefit from high circulating 25-hydroxyvitamin D for the reduction of insulin resistance and type 2 diabetes risk. This gene-nutrient interaction, likely restricted to women, has significant implications for vitamin D supplementation in the prevention of type 2 diabetes.

Prognostic Significance of Metastasis-Related MicroRNAs in Early Breast Cancer Patients with a Long Follow-up
By Athina N. Markou, et al.

This study describes a systematic evaluation of the prognostic significance of metastasis related microRNAs in early breast cancer. The authors explored the expression levels of miR-10b, miR-21, miR-205, miR-210, miR-335, and let-7a in early breast cancer patients. They also investigated the relationships between the expression of these biomarkers with clinical outcome, in all patients and in specific subgroups defined by differences in their expression of estrogen and progesterone receptors, HER-2 and lymph node status. Univariately, both miR-21 and miR-205 were found significantly associated with disease free interval, and miR-205 with overall survival, whereas multivariately, miR-205 and miR-21 were found to be independent factors associated with early disease relapse. Deregulation of metastasis-associated microRNAs in primary tumors is associated with clinical outcome in patients with early breast cancer and can differentiate patients at higher risk in well-characterized subgroups.

Circulating U2 Small Nuclear RNA Fragments as a Novel Diagnostic Tool for Patients with Epithelial Ovarian Cancer
By Jan Dominik Kuhlmann, et al.

Noncoding RNA molecules, such as microRNA or small nuclear RNA, have been suggested as promising novel biomarker candidates for noninvasive cancer diagnosis. However, their clinical utility for ovarian cancer remains to be elucidated. In this regard, this study sought to identify differentially expressed microRNAs and small nuclear RNAs in sera of ovarian cancer patients by microarray analysis and RT-qPCR. This is the first report suggesting that fragments of the noncoding U2-1 small nuclear RNA can serve as a diagnostic tool for ovarian cancer, identifying a subgroup of patients with high risk of recurrence and poor prognosis.

Prognostic Relevance of Viable Circulating Tumor Cells Detected by EPISPOT in Metastatic Breast Cancer Patients
By Jean-Marie Ramirez, et al.

The detection of circulating tumor cells is a rapidly growing field of cancer research, and the clinical utility of circulating tumor cells as a new biomarker is currently being tested in more than 250 clinical trials. Here, the authors report the first study where the detection of circulating tumor cells using the EPISPOT assay was evaluated on a large cohort of metastatic breast cancer patients, showing prognostic relevance of the presence of viable circulating tumor cells. The authors found that the majority of metastatic breast cancer patients harbor viable circulating tumor cells expressing and releasing CK19, and the presence of these tumor cells in the peripheral blood predicts an unfavorable clinical outcome, especially if combined with the CellSearch® system.

Genetic Variants in the Fibroblast Growth Factor Pathway as Potential Markers of Ovarian Cancer Risk, Therapeutic Response, and Clinical Outcome
By Qing H Meng, et al.

This study examined the associations of genetic variants within fibroblast growth factor and fibroblast growth factor receptor genes with risk, therapeutic response, and survival of ovarian cancer. One hundred eighty-three single nucleotide polymorphisms from 24 fibroblast growth factor and fibroblast growth factor receptor genes were genotyped in a total of 339 ovarian cancer cases and 349 healthy matched controls. Significant associations of multiple genetic variants in the fibroblast growth factor/fibroblast growth factor receptor axis were seen with risk of ovarian cancer, therapeutic response, and survival, including higher-order gene-gene interactions and cumulative effects of multiple variants. These associations with single nucleotide polymorphisms in the fibroblast growth factor pathway may provide a potential molecular approach for risk prediction, monitoring therapeutic response, and predicting prognosis of ovarian cancer.

Circulating Proteolytic Products of Carboxypeptidase N for Early Detection of Breast Cancer
By Yaojun Li, et al.

This manuscript investigated a potential enzymatic mechanism for the generation of circulating biomarkers for noninvasive and early diagnosis of breast cancer. The authors examined products of carboxypeptidase N activity in both a mouse model of breast cancer and clinical human samples. They used nanopore-based on-chip fractionation to isolate circulating peptides, followed by detection and quantification by mass spectrometry. These investigations revealed that proteolytic activity of carboxypeptidase N, particularly at tumor sites, caused increases in its circulating peptide products at an early stage of breast cancer. This methodology appears promising for translation to the clinic in the diagnosis of breast cancer and perhaps other pathologies.

Circulating Fetal Cell-Free DNA Fractions Differ in Autosomal Aneuploidies and Monosomy X
By Richard P. Rava, et al.

Within 1 year of becoming clinically available in the United States, massively parallel sequencing of cell free DNA in maternal plasma has become rapidly integrated into clinical practice to detect fetal chromosomal aneuploidy. In this study the authors directly determined the fetal fraction using massively parallel sequencing tag counting results and examined the relationships of fetal fraction to biological parameters such as fetal karyotype and maternal demographics. The fetal fraction distributions in euploid and aneuploid pregnancies are different, and this has potential consequences for establishing threshold cutoff values in noninvasive prenatal testing.

Maternal Mosaicism Is a Significant Contributor to Discordant Sex Chromosomal Aneuploidies Associated with Noninvasive Prenatal Testing
By Yanlin Wang, et al.

The contribution of an abnormal maternal karyotype to discordant noninvasive prenatal test results for sex chromosome aneuploidies is not known. The authors developed and validated a rapid karyotyping method using massive parallel sequencing for measuring low levels of X chromosome mosaicism in known XO and XXX mosaic white blood cell DNA samples. In a prospective study, 8.6% of the discordant sex chromosome aneuploidy results were due to either an altered or mosaic maternal karyotype. These findings indicate that the results from maternal white blood cell DNA sequencing can increase the overall sensitivity and specificity of noninvasive prenatal testing for sex chromosome aneuploidies.

Measurement of Unconjugated Estriol in Serum by Liquid Chromatography–Tandem Mass Spectrometry and Assessment of the Accuracy of Chemiluminescent Immunoassays
By Xianzhang Huang, et al.

This article addresses the accuracy of chemiluminescent immunoassays for unconjugated estriol, specifically those implemented on the Beckman-Coulter ACCESS 2 and Siemens IMMULITE 2000 analyzers. The rationale for the study was that unconjugated estriol is routinely analyzed in clinical laboratories for risk assessment for Down syndrome using immunoassay methods. However, the accuracies of immunoassays have been questioned, and there have been no independent studies investigating the accuracy of these automated chemiluminescent immunoassay analyzers. The authors approached the problem by comparison with a liquid chromatography-tandem mass spectrometry method. Results revealed concentration-dependent biases of the immunoassays. These findings indicate a need for standardization of the immunoassays for unconjugated estriol measurements.