2020 UNIVANTS Honorees:

Redefining reference ranges to improve care effectiveness

How three multidisciplinary and innovative care teams changed clinical pathways

Hospital Clínico San Carlos
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Hospital Virgen de la Luz
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Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute
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A reference range defines the thresholds for which clinicians consider a laboratory test result "normal." But a normal test result does not always verify health, and an abnormal result does not necessarily confirm a patient is ill. These ranges can vary widely due to confounding factors, such as differences in sex, age, location/environmental factors and specific conditions such as pregnancy or renal impairment. Test method variations apply as well, all of which can potentially impact what's considered normal for an individual patient's health status. Real-world data can and should be used to reevaluate and fine tune the reference ranges when appropriate.

An increasing number of healthcare leaders are revisiting the reference ranges used in their institutions for specific conditions, recognizing opportunities to improve diagnostic accuracy and clinical outcomes. A missed diagnosis could lead to an acute event or prolonged deterioration in a patient's health. But fine-tuning the reference ranges for specific patient populations can mitigate this risk for both the patient and the healthcare organization. It's also an opportunity to reduce potential overdiagnosis and avoid unnecessary procedures, medications and hospital stays, as patients may not need further evaluations. This can lead to organizations experiencing significant clinical and financial benefits when diagnostic tools have been refined to ensure that the right patients are diagnosed at the right time.

In this article, we profile three care teams—two in Spain and one in India— that received global recognition from the UNIVANTS of Healthcare Excellence™ award program. The recognition highlights their success in improving patient care after investigating and applying refined reference ranges across different laboratory tests within their organizations. Their integrated clinical care initiatives altered existing reference thresholds to better account for confounding factors. The initiatives were also implemented in a collaborative manner that positively impacted all stakeholders: patients, clinicians, payers and entire health systems.

Early detection and management of gestational diabetes mellitus

The incidence of gestational diabetes mellitus (GDM) is rising, largely due to higher rates of obesity, the increasing age of pregnant women and higher prevalence of sedentary lifestyles. It's important to diagnose and treat this glucose tolerance

disorder in a timely manner, as it is associated with short-term complications such as premature labor, pregnancy-induced hypertensive disorders, higher rates of cesarean section and abnormal birth weights. It's also associated with long-term serious complications, such as increased risk of developing cardiovascular disease, cancer and glucose disorders.

With no international consensus on screening methods and optimal reference range cut-offs for diagnosis or intervention, a multidisciplinary team at Hospital Clínico San Carlos in Madrid sought to improve GDM detection in their community, developing more concrete reference ranges and streamlining their existing screening process.

The clinical care team used a multi-factorial approach to better coordinate fasting glucose and oral glucose tolerance testing. This led to earlier detection of "low hyperglycemia," which they defined as baseline blood glucose levels between 92 and 95 mg/dL. Patients in this range would be excluded from GDM diagnosis using traditional two-step Carpenter-Coustan criteria, but would be identified as at-risk for GDM. The team introduced the one-step GDM screening recommendations from the International Association of Diabetes and Pregnancy Study Groups (IADPSG), which increased patient diagnoses of GDM from 10.6 percent of patients to 35.5 percent—a three-fold increase in patients who may otherwise have been missed.

Their integrated clinical care initiative also reduced the diagnosis timing from 24 days to 4 days. That included the first visit for GDM screening to the final diagnosis, with 96 percent of GDM screening occurring by the 28th gestational week. The clinical team accomplished these outcomes through close and cross-discipline collaboration with obstetrics, endocrinology, clinical laboratory and nursing. "Screening was overseen by the clinical laboratory, avoiding duplicity of appointments across different specialists and enabling shortened time periods between diagnosis and treatment," said Dr. María José Torrejón, a clinical biochemist and head of the hormones and metabolism laboratory at Hospital Clínico San Carlos.

Gestational diabetes mellitus diagnosis timing reduced from 24 days to 4 days

Hospital Clínico San Carlos

In addition to likely preventing GDM-related complications, resulting in safer pregnancies, the streamlined care led to significant cost savings. The team estimated that the hospital will save approximately 15,000 Euros per 100 patients, translating to 250,000 Euros annually in mitigated costs for the 1,700 pregnancies they treat each year. The approach reduces the potential for serious complications like cesarean sections (estimated increase in vaginal birth rates rose from 57.9 percent to 69.7 percent), neonatal care admissions (estimated drop from 12.4 percent to 9.6 percent), premature births (estimated 10.9 percent reduction) and gestational hypertension (estimated 14.6 percent reduction).

Optimized detection and management of thyroid dysfunction during pregnancy

Both hyper- and hypothyroidism can lead to significant complications for mothers and babies. Yet the reference ranges used to measure thyroid stimulating hormone (TSH). TSH levels in pregnant women are often disputed on both ends of the spectrum. A pregnant woman's increasing metabolic demands plays a role in this shift, as do regional factors, like the amount iodine in the patient's water supply. Using a local reference range that accounts for iodine in addition to pregnancy, can lead to a more accurate diagnosis.

An accurate TSH reference range is important for pregnant women, as those with a dysfunctional thyroid can put them at higher risk for high blood pressure, miscarriage and a baby with a low birthweight. Some studies suggest that babies born to mothers with hypothyroidism may suffer from impaired brain

development and a lower IQ. In addition to care costs, incorrect diagnosis can lead to higher patient stress levels.

An integrated clinical care team at Hospital Virgen de la Luz in Cuenca, Spain was concerned that a notable number of pregnant women in their care were being unnecessarily flagged for potential thyroid dysfunction. Prior to 2019, they used the same reference range for pregnant women in their first trimester as they did for a traditional healthy population (TSH from 0.35 to 4.94 mU/L). They also perform thyroid peroxidase-antibody (Anti-TPO AB) screening, as pregnant women with Anti-TPO antibodies and increased TSH values can experience higher rates of complications. The team performed a comprehensive medical records analysis for 910 patients including Anti-TPO status and TSH values, along with reviewing pregnancy outcomes. This resulted in a new TSH reference range (0.064 to 3.5 mIU/L).

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> **Dr. Enrique Prada de Medio, Laboratory Director Hospital Virgen de la Luz**

The clinical team used this new range with 794 pregnant women, finding that 12.8 percent (102 women) were more accurately classified, with 9.2 percent (73 women) diagnosed as euthyroid instead of hyperthyroid per the prior reference range. This eliminated unnecessary follow-up appointments for the 73 women, not only improving their care experience and potential lowering harmful anxiety levels, but also saving about 176 Euros per patient. Total annual savings the first year were 12,849 Euros. The reference range also decreased for the percentage of patients diagnosed with hypothyroidism by 3.6 percent, resulting in similar clinical and financial benefits.

Dr. Enrique Prada de Medio, the hospital's laboratory director, noted that the effort required significant collaboration with gynecology, endocrinology and laboratory medicine to agree upon the new approach and ensure adoption of the refined reference ranges.

"The project was seen by all stakeholders as an important opportunity to improve the healthcare offered to such a sensitive group as pregnant patients," Prada de Medio said. "Pregnant patients receive excellent care and great peace of mind, knowing that they are well cared for."

Increased detection of acute myocardial infarction in women using sex-specific troponin levels

Men and women can present with different symptoms when experiencing an acute myocardial infarction (AMI). This increases the importance of lab-based tests to confirm AMI occurrence. The gold standard lab test is troponin, a protein released by damaged cardiac muscle. "We know that troponin is a good measure. A high-sensitivity troponin test can detect small changes," said laboratory medicine consultant Dr. Barnali Das. However, if the high-sensitivity troponin (hsTn) reference range is not calibrated to individual circumstances, like sex, it can miss the patients it is intended to identify. Women's hearts, and specifically their lower left ventricular masses, are generally smaller than men's, resulting in lower circulating levels of troponin. The hsTn assay can capture this level, but the appropriate reference range must then indicate it's in an abnormal range, in order to contribute an AMI diagnosis.

14% more women were properly diagnosed and able to receive timely treatment for acute myocardial infarction

Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute

Studies show that the hsTn upper reference limits used to diagnose AMI in seemingly healthy individuals can differ by as much as 50 percent in men and women. Yet clinicians at Das' institution, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute in Mumbai, India typically relied on the same hsTn reference ranges for all patients. Das and her colleagues were concerned that this generic approach was excluding some women from diagnosis. Their thesis was that their reference range could lead to fewer women receiving the correct AMI diagnosis, leading to delayed diagnoses and poorer outcomes. They wanted to investigate whether a change to a sex-specific upper reference limit for hsTn would improve that situation.

Das coordinated an integrated clinical care team that included emergency medicine, cardiology and laboratorians to review current standards plus data from 2,797 female patients, to determine if there was a more accurate sex-specific range which could highlight elevated troponin levels associated with AMI. The Kokilaben Dhirubhai Ambani researchers found that when the upper reference limit for troponin (>26.2 ng/L) was replaced with sex specific reference limits (i.e., >15.6 ng/L for women), the percent of women diagnosed with an acute cardiac event increased from 68 percent to 82 percent.

The adjusted reference range meant that 14 percent more women would be properly diagnosed and able to receive timely treatment. Globally, cardiovascular disease is the leading cause of mortality for women, and studies show it's underdiagnosed and undertreated. But the new approach positively impacted men as well, reducing potential over-treatment and associated clinical risk. The research led to a 3 percent decrease in the number of men inappropriately diagnosed with a heart attack, leading to avoidance of invasive follow-up procedures and lowering associated risks by 2.9 percent.

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> Laboratory Medicine Consultant
> Kokilaben Dhirubhai Ambani Hospital
> and Medical Research Institute

Determining a more appropriate range was only part of the care dynamic. Das and her colleagues needed to build acceptance to gain adoption of the updated sex-specific reference ranges at Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute. They paired the new reference ranges with a clinical pathway protocol change for chest pain diagnosis, reducing patients' triage and wait time from 6 hours to 3 hours. Adherence to the new chest pain protocol rose from 7 percent to 93 percent.

The three cases highlighted here draw awareness to the issue of utilization of appropriate reference ranges in improving diagnosis and management of coronary artery disease, GDM and thyroid disorders. Single institution studies, followed by educational programs to implement adoption, can be manageable projects which have an outsized impact on stakeholders. "This project is highly-scaled because it doesn't have significant infrastructure requirements," Das said. "I'm proud of our achievement because it has had a major, positive effect on patient outcomes, and a major impact on society."