UNIVERSITY MEDICAL CENTER OF EL PASO

Path-O-Gram

Pathology laboratory news for you!

Department of Pathology

TTUHSC EL PASO
Texas Tech University Health Sciences Center El Paso

Dr. Jude Abadie, Editor | January 2023 | Volume 3 | No. 1

■ Pathology passed the CAP inspection! ■ Pathology residency program updates ■ New core lab instrumentation ■ TTUHSC EL PASO Pathology & the El Paso Public Health Laboratory updates ■ New core lab instrumentation ■ Laboratory testing

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I. Department Highlights

a. College of American Pathologists (CAP) inspection

- Our pathology department successfully passed our CAP inspection in August 2022.
- This success is a testament to our remarkable pathology team: administration, testing personnel, faculty, and leadership.
- We remain in fully compliance and full accreditation status.
- CAP is our department's accreditation body, and our inspection cycle occurs once every two years.
- There are essentially thousands (~~3000) of checklist questions and areas.
- While we are proud of our successes, we continuously strive for the best quality of care for patients and services for providers.

b. Residency program updates/stats

The pathology department is preparing for our flagship start of the 4-year combined Anatomic Pathology & Clinical Pathology (AP-CP) residency program. Our program starts in July 2023. We will have three starts per year and a total of 12 residents when all four PGY groups are filled.

The National Resident Matching Program (NRMP) results are scheduled to be released on Friday, 17 March 2023.

Here is a breakdown of our applications:

- Number of PGY1 slots: 3
- Number of applicants: 504
- Applicants interviewed 71
- Applicants to be ranked: 42
  - U.S. Graduates: 33
  - Foreign Medical Graduates: 9

c. Publications and Presentations

Our Department Chair, **Dr. Attilio Orazi** is presenting at the 2023 Tutorial on Neoplastic Hematology course scheduled for January 23 – 27, 2023 in San Diego, CA. Please see this link for more details. https://www.european-association-for-haematopathology.org/wp-content/uploads/2022/08/Neoplastique-Hematopathology-UCCME-Conference-Brochure-January-2023.pdf

D. Arber, **A. Orazi**…….A. Tefferi. International consensus classification of myeloid neoplasms and acute leukemia: Integrating morphological, clinical, and genomic data. Review Article. Blood. June 19, 2022. https://doi.org/10.1182/blood.2022015850.

I. Valsova and **Jude Abadie.** Prophylactic Ribonucleic acid vaccines to combat RNA viral infections in humans. Book Chapter: *RNA Therapeutics-History, Design, Manufacturing, and Applications*; DOI: http://dx.doi.org/10.5772/intechopen.108163.

Hansen, Rollo, Shapiro, Aden, **Abadie**, Mu Novel use of umbilical cord blood to obtain complete blood counts for critical neonatal assessment. (August 14, 2022) The Novel Use of Umbilical Cord Blood to Obtain Complete Blood Counts for Critical Neonatal Assessment. Cureus 14(8): e28009. doi:10.7759/cureus.28009

Rojansky…….. **Jonathan Lavezo**…….Folkins. Rapid deployment of whole slide imaging for primary diagnosis in surgical pathology at Stanford Medicine…. Responding to the challenges of the COVID-19 Pandemic. *Arch Pathol Lab Med*. Doi:10.5858. 2021-0438OA.

Singh B, **Lavezo J,** Gavito-Higueroa J, Ahmed F, Narasimhan S, Brar S, Cruz-Flores S, Kraus J. Updated Outlook of Cerebral Amyloid Angiopathy and Inflammatory Subtypes: Pathophysiology, Clinical Manifestations, Diagnosis and Management. J Alzheimers Dis Rep. 2022 Oct 18;6(1):627-639. doi: 10.3233/ADR-220055. PMID: 36447738; PMCID: PMC9661355.

Brentlinger M N, **Padilla O, Qiao J** (2022) Primary Urethral Malignant Peripheral Neural Sheath Tumor in a 58-Year-Old Female in the Absence of Neurofibromatosis Type 1. Cureus 14(12): e32634. doi:10.7759/cureus.32634

d. The El Paso Public Health Laboratories

Mission: Provide accurate and reliable test results to aid in the detection, prevention, and protection of human populations from infectious disease, food- and water-borne disease, and public health emergencies

TTUHSC EL PASO Pathology is a partner with the El Paso Public Health Laboratory (EP-PHL) through the pathology faculty member (Dr. Jude Abadie) who serves as the medical director for the EP-PHL.

The El Paso PHL operates at two locations:

- 9566 Railroad Dr. El Paso, TX 79924
- 5115 El Paso Dr. El Paso, TX 79905

Laboratory Certification/Accreditation

- Clinical Laboratory Improvement Amendments (CLIA)
- Department of State Health Services – Dairy
- National Environmental Laboratory Accreditation Program- Drinking Water

The PHL recently passed federal regulatory CLIA inspections with superb scores from the state inspector. In conjunction with leadership support, the continual strong work by the clinical, technical, and managerial personnel allowed continued PHL accomplishments to appear transparently and/or effortlessly executed.

Clinical Service Testing:

- HIV screen and confirmation
- Syphilis screen, titer, and confirmation
- Wet mounts (bacterial/parasite testing)
- Gram stains
- Hepatitis B and C molecular testing
- Urine analysis and pregnancy testing
- Chlamydia/Gonorrhea testing
- Tuberculosis testing

Environmental Testing:

- Rabies
- Milk & Dairy
- Water

Laboratory Response Network:

- Coronavirus variants
- Influenza
- Zika
- Chikungunya
- Dengue
- Foodborne pathogens
- Waste water surveillance
- Bioterrorism

Our EP-PHL Family at the Main Laboratory:

Featured areas in anatomic and clinical pathology

II. Anatomic Pathology:

Hepatoblastoma vs. Hepatocellular Carcinoma in a 7-year-old boy

Dr. Dan Bustamante

A 6-year-old male with no significant medical history presented to the ED with recent intermittent fevers, decreased appetite, and increasing abdominal pain. A distended, tender abdomen was noted on physical exam.

- Computed Tomography (CT) of the abdomen showed a large, lobulated solid mass in the liver (15.3 x 13.5 x 13.8 cm).
- Radiologic diagnostic impressions were consistent with a primary malignant hepatic tumor- PRETEXT 3 (C, E, P, & IVC/V).
- The diagnostic differential was most concerning for hepatoblastoma vs. hepatocellular carcinoma.

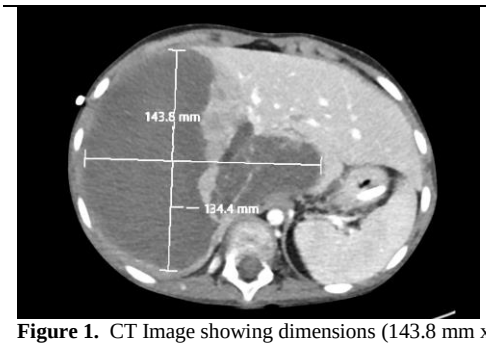


Figure 1. CT Image showing dimensions (143.8 mm x 134.4 mm) of mass occupying most of the liver parenchyma

An exact initial alpha-fetoprotein (AFP) level could not be obtained due to assay limitations.

- The main University Medical Center (UMC) pathology laboratory reported the AFP as '> 52,000 ng/mL'.
- A numerical value above this level could not be reported because the laboratory had not conducted validation studies.
- Such validation studies are required to accurately demonstrate that instrumentation is capable of reporting values greater than vendor-reported linearity.

In order to perform linearity studies that surpass vendor analytical measurement range (AMR), samples with extraordinarily high levels must be tested against results from a laboratory that has already established the accuracy at those levels.

- This is how labs can extend ranges for reporting analytes such as tumor markers (e.g., β-hCG, PSA, AFP) where changes in levels above the AMR can be used to guide clinical decisions.

In this case, an accurate and precise AFP level above 52,000 ng/mL (actual amount in the sample) was requested for both clinical management to compare baseline values and for enrollment into a Children's Oncology Group (COG) protocol study.

- The patient's serum sample was sent to another testing lab that was validated to report AFP values up to 1,000,000 ng/mL.
- The reference lab reported a markedly elevated AFP value of 925,420 ng/mL in our patient's sample.

Image-guided needle core biopsies generated 8 samples for histologic diagnostic evaluation.

- Microscopic findings showed focal areas of immature appearing hepatocytes arranged in sheets, nests, and acinar configurations.
- Extensive necrosis was present on a background normal appearing liver parenchyma. Immunohistochemical (IHC) stains demonstrated positivity for AFP and Hep-par1.
- Beta-catenin, a regulator of cell-cell adhesion and embryogenesis, was expressed as illustrated by the positive IHC stain.
- A cytoplasmic and nuclear neoplastic population with an absence of reticulin fibers in areas of neoplasia on histology.
- These IHC findings, in conjunction with histologic morphology and an AFP approaching 1,000,000 ng/mL, are indicative of hepatoblastoma.

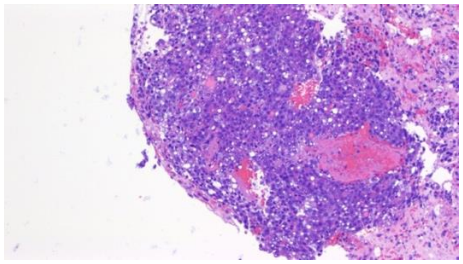


Figure 2. 40X magnification of hyperchromatic epithelial neoplastic cells.

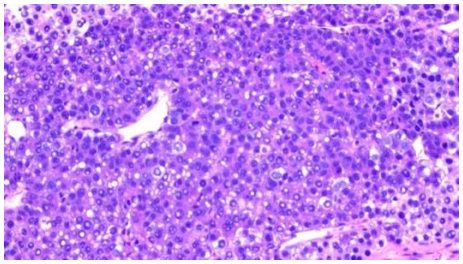


Figure 3. 100X magnification illustrating trabecular pattern with cellular pleomorphism near vacuoles/inclusions and numerous mitotic bodies.

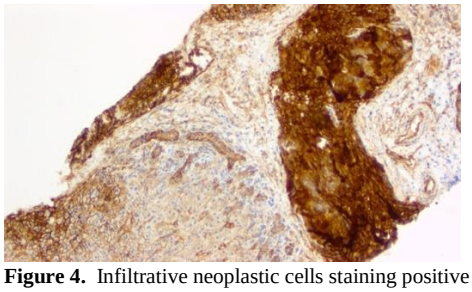


Figure 4. Infiltrative neoplastic cells staining positive for β-catenin. Activated β-catenin normally drives cell cycle progression and hepatic regeneration. However, aberrant expression is associated with hepatocellular carcinoma.

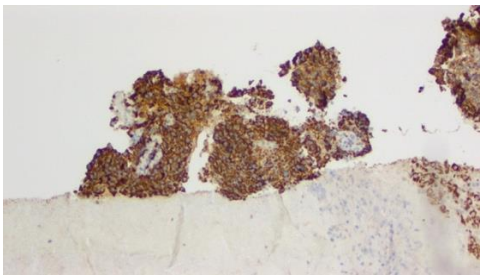


Figure 5. Neoplastic population of cells positive for Hep-Par1, which is a monoclonal antibody associated with hepatocellular carcinoma.

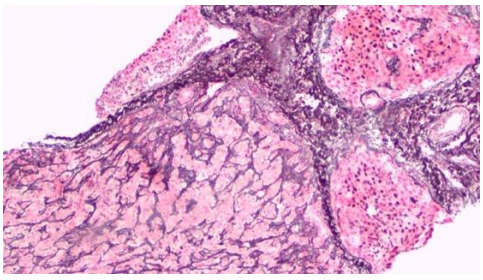


Figure 6. Reticulin stain illustrating intact reticulin fibers between normal hepatocyte plates (left) but absent in neoplastic populations (right). The loss of reticulin staining in hepatic tissue supports a diagnosis of hepatocellular carcinoma.

A hepatic stain for AFP, while not shown above, was positive. AFP, the plasma protein synthesized by the yolk sac and fetal liver, is mainly used in adults as a tumor marker for hepatocellular carcinoma.

Histology slides were sent to Texas Children's (transplant facility) for a secondary pathology review. The secondary review was consistent with the initial differential diagnosis of hepatocellular carcinoma.

- A truncating *PRS6KA3* gene variant (p.P1531L*fs12*) subsequently identified on gene analysis performed at Texas Children's Hospital.
- Fewer than 8% of hepatic cancers have mutations in *PRS6KA3*. The normal function of this gene in the brain is to in mediating cell signaling pathways required for long-term memories.
- No variants were reported in the *CTNNB1* gene, which codes for β-catenin.
- Consultation with Hematology-Oncology confirmed that continued treatment per the COG protocol was warranted in the context of hepatoblastoma clinical management.

An additional consultation sent to St. Jude's pathology department was reported as "Hepatocellular tumor, favor hepatocellular neoplasm, Not Otherwise Specified (NOS)".

- Additional comments stated that the cytologic and nuclear grade of this tumor exceeds what is usually observed in conventional hepatoblastoma.
- Furthermore, there were no areas of fetal or embryonal hepatoblastoma histology.

It is important to note that the nuclear positivity for beta-catenin is not typically seen in hepatocellular carcinoma, especially with markedly elevated AFP as was observed in this case.

- Additionally, *RPS6KA3* truncations have been extensively described in hepatocellular carcinoma but have also been reported in hepatoblastoma and hepatocellular neoplasm, NOS. The later (i.e., hepatocellular neoplasm, NOS) was the final diagnosis in this case.

Hepatocellular Neoplasm NOS is new provisional entity that represents a subset of pediatric hepatocellular tumors which have histological features of neither hepatoblastoma nor hepatocellular carcinoma.

- Hepatoblastoma rarely occurs in children older than 4 years old.
- Pediatric hepatocellular carcinoma rarely occurs in children < 5 years old.
- AFP levels are usually elevated in both cancer types; however, AFP levels are typically lower in hepatocellular carcinoma compared to hepatoblastoma, with the former having a poorer prognosis.
- Recent studies have shown that Hepatocellular Neoplasm NOS shares a high-risk clinical profile but a relatively favorable outcome following chemotherapy and complete surgical resection.

The patient was enrolled into the COG protocol, and subsequent management is now able to include accurate and precise AFP measurements.

Clinical testing laboratories should always take opportunities to extend analytical measurement ranges greater than vendor's suggestions, especially for tumor markers.

Reference:

1. Zhou et al. Hepatocellular malignant neoplasm, NOS: a clinicopathological study of 11 cases from a single institution. Histopathology. 2017 November; 71(5): 813-822.

For related questions, contact Dr. Daniel Bustamante at dan-iel.bustanante@TTUHSC El Paso.edu

III A. Clinical Pathology: Blood Bank & Transfusion Medicine

Identification and lab diagnosis of anemia in the context of appropriate blood patient management
Dr. Jesse Qiao

Why is there an urgent need for patient blood management?

- As the allogeneic blood supply remains markedly reduced since COVID-19 pandemic, the need to implement patient blood management measures has gained increasing significance [1].
    - Anemia presents as a global public health challenge that affects 1.95 to 2.36 billion people worldwide. Detection, treatment, and optimizing physiological tolerance of anemia are amongst the three pillars of patient blood management that focuses [2].
    - From a public health and patient-centered treatment perspective, the recognition and treatment of iron deficiency not only reduces the need for total blood transfusions, but it also improves patient outcomes, morbidity and mortality, and quality of life.

Why should providers treat anemia seriously?

- When anemia is simply "followed-up" rather than treated, patients that are admitted to the hospital are often treated with a blood transfusion, which may or may not be in accordance with best practices.
- While blood transfusions may "instantaneously" increase hemoglobin levels, this strategy alone could miss opportunities to work-up and adequately treat the etiology of anemia.

- Appropriate anemia management defined:
    - Appropriation patient blood management.
    - Note: Effective patient blood management measures in surgical patients can not only decrease unnecessary perioperative and postoperative transfusions, but improve patient outcomes and decrease hospital lengths of stay.

Review of red blood cell (RBC production):
- RBCs provide critical oxygen carrying capacity for the body's tissues and are produced in the bone marrow, with maturation spanning several weeks from a pluripotent stem cell.
- In the bone marrow, there is dependence on erythropoietin (10-14 days), with subsequent dependence on Iron, vitamin B12 and folate (3-4 days) for the synthesis of the heme.
- Reticulocytes are the first cells to enter the circulation which subsequently become mature red blood cells.
- Erythropoietin produced by the kidneys regulate the RBC production process through a biofeedback mechanism.
- Vitamin C is required for oral iron absorption, and the iron binding proteins responsible for transport are synthesized by the liver.

Start with the clinical history:
- Anemia and iron deficiency should always be considered on the differential diagnoses when patients present with nonspecific and vague symptoms such as weakness, fatigue, poor concentration, and difficulty with exertion.
- Anemia of the elderly is multifactorial and should not be regarded as a "normal" consequence of aging.
- In addition to iron and macronutrient deficiency (including iron deficiency), anemia of the elderly is complicated by chronic inflammation, chronic renal disease, or chronic liver disease, all of which leads to decreased production.

Proper use of laboratory tests:
- Providing clinical decision support on triaging and specifying the etiology of anemia are two critical components of the clinical laboratory's role in patient blood management.
- Providers often use the hemoglobin and hematocrit as the basis to assess for the need for a blood transfusion.
- Providers often use the mean cell corpuscular volume (MCV) to triage the etiology of anemia.
- Both indices have limitations on the ability to specify the etiology.

The following table provides a summary of caveats when using common lab tests to diagnose for anemia and iron deficiency:

Laboratory Test(s)	What is measured	Limitations
Hemoglobin (Hb)	Concentration of hemoglobin	Quantifies the hemoglobin value only, as a number
Mean corpuscular volume (MCV)	Average size of red blood cells	A "normal" MCV can miss early iron deficiency anemia and/or concurrent B12/folate deficiency
Mean cell hemoglobin concentration (MCHC)	Average hemoglobin content in red blood cells	Measures content mainly in mature cells already in circulation
Serum Iron	Concentration	Since iron is also present in myoglobin, deficiency may occur long before serum iron levels become low
Ferritin	Serum protein with bound iron in circulation	Ferritin is an acute phase protein and typically elevated in inflammatory states. High ferritin does NOT equal iron overload. Quite contrary, elevated ferritin is associated with functional iron deficiency (abnormal storage)
Vitamin B12 and folate	Serum levels	Typically send-outs, normal or high levels do not preclude additional supplementation in cases of iron deficiency

What is the Ret-He?
- Reticulocyte hemoglobin equivalent (Ret-He) is measured in pictograms per milliliter (pg/mL).
- This can be ordered as the reticulocyte panel at UMC El Paso on a lavender top sent for complete blood count.
- In contrast to the MCHC, the Ret-He measures the hemoglobin content only in reticulocytes.
    - Reticulocytes are the first cells to enter circulation from the bone marrow [4-5].

Strengths and Limitations of the assay:

Strengths:

- Rapid screen for iron deficiency
    - No additional lavender tube needed if CBC already ordered
    - Ret-He < 28 pg/mL is highly indicative of iron deficiency.
        - For inpatients: Start Anemia Power-Plan, *to include Vitamin B12, folate and C* ***daily***.
        - For outpatients: Supplement iron, optimize nutrition, ensure vitamin C intake
    - If necessary, order confirmatory tests such as an iron panel.
    - Bone marrow biopsy is not necessary unless there is also a clinical need to exclude a concurrent bone marrow abnormality.

- At UMC, Ret-He is already included with the Reticulocyte Panel order.
    - Can be added on to existing CBC order - no need for an additional lavender top tube
    - Quick turn-around time for testing

- Earliest marker to assess iron treatment response, including response to IV iron
    - Ret-He will normalize first – IV Iron: after 3-4 days after completing therapy
    - MCV and Hb will improve later after treatment.
    - Ordering an Iron panel after administration of IV Iron may yield uninterpretable results

Limitations:

- Hemoglobinopathies may affect hemoglobin synthesis – interpret with caution in individuals with known hemoglobinopathy (e.g., sickle cell disease, thalassemia).
- The use of this lab test may be increasing, but it is currently not widely adopted by hospitals nationwide.

Point of Contact: Jesse Qiao, MD, Department of Pathology, TTUHSC EL PASO El Paso; Use of the Anemia Power-Plan: Bradford Ray, LP RABT, PBMT, Patient Blood Management Services, El Paso

References:

1. Shander A, Goobie SM, Warner MA, et al; International Foundation of Patient Blood Management (IFPBM) and Society for the Advancement of Blood Management (SABM) Work Group. Essential Role of Patient Blood Management in a Pandemic: A Call for Action. Anesth Analg. 2020 Jul;131(1):74-85.

2. World Health Organization Policy Brief: The Urgent Need to Implement Patient Blood Management, 2021. Accessed online at: https://apps.who.int/iris/bitstream/handle/10665/346655/9789240035744-eng.pdf.

3. Andres E, et al. Anemia in Elderly patients: new insight into an old disorder. Geriatr Gerotol Int. 2013 Jul;13(3):519-27.

4. Brugnara C, et al. Reticulocyte Hemoglobin equivalent (Ret He) and assessment of Iron-deficient states. Clin Lab Haem. 2006;28: 303-308.

5. Ucar MA, et al. The Importance of the Ret-He in the diagnosis of iron deficiency and iron deficiency anemia and the evaluation of response to oral iron therapy. J Med Biochem 38: 496-502, 2019.

III B. Clinical Pathology: Core lab clinical chemistry

Implementing the new CKD-EPI eGFR equation to better support the diagnosis of kidney disease

MS1 Mason Bettes and Dr. Jude Abadie

On 11 JAN 2023, the Pathology Laboratory at TTUHSC El Paso-UMC and outlying clinic labs implemented the CKD-EPI 2021 equation for the calculation of creatinine-estimated glomerular filtration rate (eGFR). This new equation is recommended by the National Kidney Foundation and the American Society of Nephrology's (ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease.

- The new equation does NOT include a race coefficient.
- It has similar overall performance characteristics as the older equations and has removed potential consequences that disproportionately affect any one group of individuals.
    - For most patients, the new CKD-EPI equation will provide results similar to the previous equation; however, for some patients, values may differ > 10%.

- This difference may be especially noticeable at higher values of eGFR and for younger adult patients.

The eGFR values using the new equation will only report one value. Results will not trend with those using the older equations. The new report name is $eGFR_{cr}$ (calculated using only creatinine)

eGFR values are estimates and should be interpreted in clinical context.

- Clinical practice recommendations suggest ordering cystatin C as a confirmatory test for patients with eGFR of 45-59 mL/min/1.73m^2 with uACR <30 mg/g, and in patients for whom the creatinine may be a less reliable indicator of GFR near decision points.
- Cystatin C is a send-out test and not performed in our main pathology laboratory.

The new CKD-EPI 2021 equation is described in Exhibit 1.

- The equation was derived from the same data used in the original derivation of CKD-EPI 2009 development data set ($eGFR_{cr}$).
- The regression function that was used for the 2009 and 2012 equations was used to fit the new equation with the exclusion of race as a variable.
- The equation was validated in an analysis of 12 studies containing 4,050 participants with and without CKD (self-reported: Black or non-Black.
- Black participants accounted for 14.3-39.7% of study participants.

The CKD-EPI 2021 $eGFR_{cr}$ equation performed similarly to the CKD-EPI 2009 equation with respect to % of measured GFR values within ± 30% of the corresponding eGFR value and assignment of GFR stage.

- Whereas the CKD-EPI 2009 equation underestimated GFR in Black participants (-3.7 ml/min/1.73m^2), the CKD-EPI 2021 $eGFR_{cr}$ equation overestimated GFR (3.6 ml/min/1.73m^2).
- Based on these studies, the NKF-ASN task force recommended implementation of the CKD-EPI 2021 $eGFR_{cr}$ equation.
- The CKD-EPI 2021 $eGFR_{cr}$ equation has fewer limitations than previous estimating equations because it:
    - Was developed in a diverse cohort
    - Exhibits performance characteristics acceptable for clinical use
    - Does not disproportionately affect any one group of individuals, and
    - Achieves the goal of eliminating the use of race in estimating GFR.

- Laboratories should verify the accuracy of the equation.
    - This may be achieved by evaluating several different biomarker concentrations in the background of age, sex, and race.
    - It is critical for laboratories to confirm that the same eGFR is generated for a Black and non-Black person of the same age, sex, and blood creatinine concentration.
    - It is also recommended that laboratories test the correct flagging of abnormal results and correct triggering of testing algorithms (e.g., reflex testing), as appropriate.

Re-baselining (aka parallel testing) across the new and old equations is not necessary. Further, reporting of eGFR should be standardized and reported as a whole number in units of mL/min/1.73m^2.

- While the historic upper limit of eGFR reporting was 60 mL/min/1.73 m^2, this was attributed to poor performance of previous equations at higher GFRs.
- With improved performance of CKD-EPI equations, eGFR values above 60 mL/min/1.73 m^2 should be reported to support early detection of declining kidney function.

Sample report comments are available on the NKF website and can be modified to meet the laboratory needs, health care professionals, and patients.

- Calculations from programmed CKD-EPI 2021 equations must be verified for accuracy across different creatinine concentrations, races, ages, and sexes

- eGFR can be reported as integers > 60 mL/min/1.73 m^2 when calculated using the CKD-EPI 2021 equations.
- eGFR results will include a comment indicating that the DKD-EPI 2021 eGFR equation was used and that it should not be trended with previous equations or with point-of-care devices.

- An unintended consequence of the widespread clinical use of eGFR is that eGFR thresholds dictate care even though the value is an estimate.

    - Removal of the Black race coefficient and transition to the new CKD-EPI will predictably lead to a lower eGFR in individuals for whom the Black race coefficient was previously applied and a slightly increased eGFR in those for whom it was not.
    - Combined, changes to the calculation for eGFR will alter CKD classification in patients where eGFR was close to care thresholds.

In individuals with an eGFR close to normal, a shift to the race-neutral equation only impacts potential kidney donor candidates whose eGFR decreases to <90 ml/min/1.73 m^2.

- For these individuals, the shift to the new equation may prevent harm to a potential donor because the CKD-EPI 2009 equation (inclusive of the Black race coefficient) may have overestimated kidney function in potential Black donors, and use of a CKD-EPI 2021 equation may instead prompt appropriate evaluation for kidney disease, such as screening for albuminuria.

When the eGFR flanks a clinical decision point, providers may consult with nephrology or pharmacy for support in dosing considerations.

- In addition, confirmatory assessment of kidney function can be performed using direct measurement of glomerular filtration, measurement of creatinine clearance, repeated creatinine-based measurements, or estimation of GFR using cystatin C.

When using eGFR for medication dosing, the eGFR value should be de-indexed from BSA.

- This is particularly important in individuals at extremes of weight because drug clearance is related to total eGFR.

Creatinine-based eGFR equations utilize sex and age as proxies for creatinine variations unrelated to filtration or non-GFR determinants of creatinine.

- Thus, individuals whose sex assigned at birth does not align with their gender identity may have differences in creatinine generation due to changing muscle mass that influence estimates of kidney function.
- Age is used as a proxy for expectations regarding muscle mass over time.
- For individuals with sarcopenia because of medical conditions such as cirrhosis, heart failure, spinal cord injury and progressive neurodegenerative disorders, creatinine generation is reduced and the eGFR is likely to be an overestimate (**Table 1**).
- In contrast, the eGFR may be underestimated in individuals with considerable muscle such as body builders, individuals with high exogenous creatinine ingestion, and anabolic steroid users
- Individuals taking medications that block creatinine secretion, including older medications such as cimetidine or trimethoprim, and newer antivirals such as cobicistat or dolutegravir, will have a small increase in creatinine and consequently, a decrease in the eGFR, without an actual decline in kidney function.

Implementation of the CKD-EPI 2021 $eGFR_{cr}$ equation will lead to a lower eGFR in Black individuals and higher eGFR in non-Black individuals compared to eGFR calculated with formulas that included race.

eGFR is designed to estimate kidney function when patients are medically stable and cannot be used when the kidney function is changing, such as with acute kidney injury.

- When assessing kidney function in transgender, non-binary, or intersex people, eGFR should be evaluated using both the

male and female constants with CKD-EPI 2021 equations. Both values may be relevant at the onset of CKD and/or when approaching thresholds.

- When eGFR crosses a clinical threshold, a holistic approach should be taken to determine appropriate management anchored to the muscle mass of the individual based on their sex hormone profiles and gender.
- Early detection and awareness of kidney disease in clinically and socioeconomically high-risk populations are critical to achieving equitable care
- Laboratorians can contribute towards closing racial/ethnic disparities in CKD through:
    - Harmonization of CKD biomarker testing and reporting
    - Optimization of CKD biomarker test utilization and interpretation
    - Integration of data-driven population health initiatives
- Development of CKD screening guidelines would streamline CKD testing strategies nationally and critical in achieving health equity in kidney disease. The development of consensus critical action and delta values for eGFR and uACR represent additional opportunities for improved CKD detection.

Table 1: KDIGO recommended GFR categories of CKD

GFR Category	**GFR (mL/min/1.73m^2)**	**Terms**
G1	≥90	Normal or high*
G2	60-89	Mildly decreased (relative to young adult level)*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

*In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD. At GFR>60 mL/min/1.73m^2, markers of kidney damage must be present to fulfill the criteria for CKD.

Exhibit 1. eGFR equations & reporting recommendations

CKD-EPI 2021 eGFRcr (note: Age is in years.)
$eGFR_{cr} = 142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female], where, S_{cr} = serum creatinine in mg/dL, divide by 88.4 for creatinine in µmol/L $\kappa = 0.7$ (females) or 0.9 (males) $\alpha = -0.241$ (female) or -0.302 (male) $\min(S_{cr}/\kappa, 1)$ is the minimum of S_{cr}/κ or 1.0 $\max(S_{cr}/\kappa, 1)$ is the maximum of S_{cr}/κ or 1.0
Assay: Creatinine using methods that are traceable to IDMS reference measurement procedures. Enzymatic assays are preferable over assays based on the Jaffe reaction, which are impacted by several interferences. Report to 2 decimal points in mg/dL units and 1 decimal point in µmol/L units.
Reporting: Report eGFRcr as a whole number in units of mL/min/1.73 m^2 in adults ≥ 18 years of age. Do not allow results to trend with eGFR values calculated using older equations.
Assays: Creatinine using methods that are traceable to IDMS reference measurement procedures. Enzymatic assays are preferable over assays based on the Jaffe reaction, which are impacted by several interferences. Report to 2 decimal points in mg/dL units and 1 decimal point in µmol/L units.

Table 2: CKD-EPI eGFRcr equation; males and females

Logic for "if" statements		**CKD-EPI 2021 $eGFR_{cr}$ Equation**
Sex	**Serum Creatinine (mg/dL)**	
Female	≤0.7	$eGFR=142 \times (S_{cr}/0.7)^{-0.241} \times 0.9938^{age} \times 1.012$
	>0.7	$eGFR=142 \times (S_{cr}/0.7)^{-1.200} \times 0.9938^{age} \times 1.012$
Male	≤0.9	$eGFR=142 \times (S_{cr}/0.9)^{-0.302} \times 0.9938^{age}$
	>0.9	$eGFR=142 \times (S_{cr}/0.9)^{-1.200} \times 0.9938^{age}$

Pathology would like to thank Dr. Prakrati Acharya (TTUHSC El Paso Nephrologist) and Internal Medicine for the strong support in collaboration of this laboratory update.

A big thanks to both Mr. Alex Ramirez and Mr. Frank Hamilton!

- These are our UMC Pathology IT Team leaders who performed the 'heavy lifting' to ensure formula validations at the main pathology lab and at our outlying clinic lab locations.

References:

1. Greg Miller, et.al. National Kidney Foundation Laboratory Engagemen Working Group recommendations for implementing the CKD-EPI 2021 race-free equations for estimated glomerular filtration rate: Practical guidance for clinical laboratories. Clinical Chemistry 68:4, 511-520 (2022).
2. Delgado C, et al. A unifying approach for GFR estimation: recommendat tions of the NKF-ASN Task Force on reassessing the inclusion of race in diagnosing kidney disease. Am J Kidney Dis 2021:S0272 6386(21). doi:10.1053/.ajkd. 2021.08.003.

Please direct any questions to Dr. Jude Abadie at jude.abadie@TTUHSC.edu or to Dr. Prakrati Acharya at prakrati.acharya@TTUHSC.edu

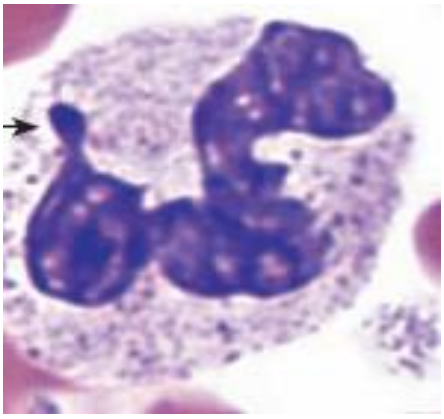
III C. Clinical Pathology: Molecular pathology puzzler…….

Question written & submitted by Dr. Jude Abadie

The following neutrophil was observed on a peripheral blood smear. Which of these individuals is the most likely source of this cell? (HINT: Arrow in figure.)

A. A male with Down syndrome
B. A female with Turner syndrome
C. A male with Klinefelter syndrome
D. A female without a chromosome aneuploidy
E. A male without a chromosome aneuploidy

The answer to this question and explanation appear at the end of this Path-O-Gram in the 'Announcements' section.



Announcements

1. As of NOV 2022, the UMC-TTUHSC El Paso pathology core lab no longer performs or supports specific gravity testing on body fluids. This decision was made in collabora-tion with Internal Medicine through review of very low testing volume, and more im-portantly, negligible clinical utility.

2. The image below shows our UMC technologists training with the vendor for our core lab's new CLINITEK Novus® Urine analytical platform. This analytical system combines urine chemistry and imaging technology that will improve the quality of our services. Assays include specific gravity, pH, protein, glucose, ketone, blood, leukocyte, nitrite, urobilinogen, bilirubin, as well as digital microscopic analysis. Our planned go-live goal is Feb 2023.

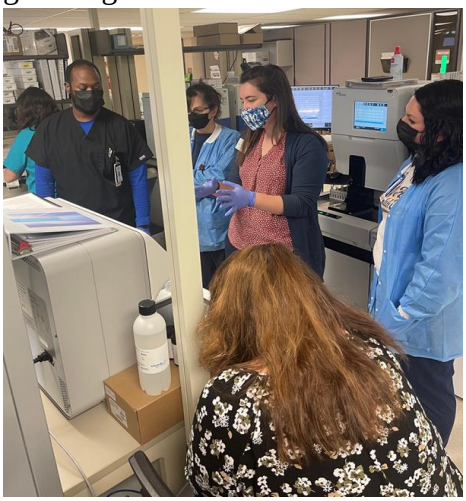


Image of the new instrumentation:

3. Our pathology department was awarded the Roche Diagnostics (vendor) contract for our main core lab as well as outlying clinics. This $12.2 million, 7-year contract will provide the mechanism for replacing all clinical chemistry and immunoassays. Fall 2023 is

the expected go-live. The summer 2023 Path-O-Gram will highlight the processes and impacts of implementation.

Correct answer to the Puzzler: Choice D

The figure shows a normal neutrophil with one Barr body. The Barr body represents the inactivation of one X chromosome. Note that Barr bodies are not present in all neutrophil; therefore, other neutrophils in the same patient may not demonstrate a Barr body.

From the choices, the most likely answer is a female whose karyotype is 46,XX. Individuals represented by Choices A (46,XY+21), B (45,X), and E (46,XY) have only one X chromosome, and therefore do not have Barr bodies in the nuclei of their cells. Choice C, a male with Klinefelter syndrome (i.e., 47,XXY) would have a Barr body because and could be the source of this cell; however, the most likely choice is D (46,XX) due to more individuals with 46,XX vs. 47,XXY genotypes.