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Kaiser Permanente Medical Center, San Francisco
Northern California Region
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Work Instruction

Title: AU 680 Creatinine		**WI Number** SFOWI-1282 **Revision:** 5
Department: Chemistry **Area:** 2425 Geary Blvd SFO Hospital Lab	***Approved & Released Work Instruction***	**Implementation Date:** 04/08/2019
Type of Document: Work Instruction		**Review Period -** 365 **Days**

Intended Use	System reagent for the quantitative determination of Creatinine in human serum, plasma or urine on Beckman Coulter AU Clinical Chemistry analyzers.
Principle	The AU Creatinine procedure is a kinetic modification of the Jaffe procedure in which creatinine reacts with picric acid at alkaline pH to form a yellow-orange complex. However, this reaction is not completely specific for creatinine since other reducing substances such as glucose, pyruvate, ascorbic acid, and acetoacetates will react with picrate to form a similar color. Fabiny and Ertingshausen found that alkaline creatinine picrate reaches maximum color development at a different rate than pseudo-creatinine material. Cook utilized different reaction rates of alkaline picrate positive substances to obtain greater specificity with the Jaffe reaction. The rate of change in absorbance at 520/800nm is proportional to the creatinine concentration in the sample. **Creatinine + Alkaline Picrate ----------> Yellow-Orange Complex**

Clinical Indication	Creatinine is synthesized in the body at a fairly constant rate, and is independent of diet. As a result, its concentration depends almost entirely upon its rate of excretion by the kidneys. Serum creatinine is used to monitor renal function, since levels increase with kidney disease. However, creatinine determinations will not indicate unilateral kidney disease, because one good kidney is sufficient to give normal concentrations. Serum creatinine is not sensitive to early renal damage and responds more slowly than blood urea nitrogen (BUN) to hemodialysis during treatment of renal failure. Both serum creatinine and BUN are used to differentiate prerenal and postrenal (obstructive) azotemia. An increase in serum BUN without concomitant increase of serum creatinine is key to identifying prerenal azotemia. With postrenal azotemia, both serum BUN and creatinine rise, but the rise is disproportionately greater for BUN. Although serum creatinine is in general, highly specific for renal disease, elevations may also be due to congestive heart failure, shock or mechanical obstructions in the urinary tract such as prostatic hypertrophy, neoplasms compressing against both ureters or congenital abnormalities such as torsion or kinking of the ureters. Surgical correction of the obstructions may bring serum creatinine to a normal level. Serum creatinine result is used to estimate glomerular filtrate rate (eGFR) for the staging of chronic kidney disease in adult patients (≥ 18 years) with stable creatinine from day to day. eGFR can also be used to follow associated stage specific treatment recommendations. Elevated urinary creatinine levels are indicative of muscle diseases such as poliomyelitis, muscular dystrophy and myasthenia gravis. Creatinine clearance is a sensitive test for early renal disease and is commonly corrected for body surface area. Early renal disease is characterized by decreasing creatinine clearance. As the disease progresses, the creatinine clearance continues to diminish and serum creatinine concentrations arise. A rapid decrease in creatinine clearance, along with hypertension, indicates a poor chance of survival. The same extrarenal factors which raise serum creatinine concentrations also tend to lower creatinine clearance.

<table>
<tr>
<td>Sample Type</td>
<td>
Type:
Lithium Heparin Plasma

Urine:
Timed [e.g., 24 hour] or random urine collected without preservatives and refrigerated. Collection date, hours of collection, and total volume should be recorded.
Sample preserved in 6N HCL is acceptable.
Mix well and centrifuge urine samples containing precipitates.
Creatinine Clearance: Serum and urine samples are collected within 48 hours of each other.
NOTE:
24 hour and timed urine will be sent to Regional Lab for testing.
Body Fluids: Request for body fluid analysis are forwarded to Regional Laboratory.

Volume:
Minimum- Serum & Urine:0.5 mL
Sample Size (dead space excluded)- Serum & Urine: 1.6 uL

Stability
<table>
<tr><th></th><th>Serum/Plasma</th><th>Urine</th></tr>
<tr><td>Refrigerated (2 - 8°C)</td><td>7 days</td><td>6 days</td></tr>
<tr><td>Room Temp. (15 -25°C)</td><td>not established</td><td>2 days</td></tr>
<tr><td>Frozen (≤-20°C)</td><td>> 7 days</td><td>> 6 days</td></tr>
</table>
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Reagent

Beckman Coulter AU System Creatinine Reagent:

Reagent	Ingredient	Concentration	Preparation
R1	Sodium Hydroxide **(Corrosive)**	120 mmol/L	Ready for use
R2	Picric acid **(Poison)**	2.9 mmol/L	Ready for use

Storage and Stability:

	Storage	Expiration Date
Unopened	2 - 8°C R1 is light sensitive and is stored in the dark before placing on the analyzer.	Stable until expiration date on label.
Opened	In refrigerated compartment of the analyzer.	7 days Record open & exp dates on vial.

Indications of Deterioration:

Discoloration of the reagent, visible signs of microbial growth, turbidity or precipitation in reagent may indicate degradation and warrant discontinuance of use.

Precautions:

- Reagents contain preservatives. Flush with plenty of water when discarding reagents.
- Dry picric acid explodes when rapidly heated or subjected to percussion. Dilute any spills with water and wipe up immediately.

<table>
<tr>
<td>Calibration</td>
<td>
Serum:
Two-point calibration (AA) using a water blank and Beckman Coulter Chemistry Calibrator (DR0070)
Urine:
One-point calibration (AB) using a water blank and Beckman Coulter Urine Chemistry Calibrator (DR0091 Lot 1708088 and Higher).

Frequency:
• every 8 hours prior to running QC (serum and urine)
• When reagent lot changes
• When QC has shifted
• After major preventive maintenance, or replacement of a critical part

Calibrators:
Serum:
Lyophilized Chemistry Calibrator DR0070 Level 1 & 2 , traceable to an isotope dilution mass spectrometry (IDMS) reference method using NIST Standard Reference Material SRM 967.
Urine:
Liquid Urine Chemistry Calibrator (DR0091), directly traceable to NIST SRM 3667, Creatinine in Frozen Human Urine.

(Warning: Potentially biohazardous material. Calibrators are manufactured from human serum)

<table>
<tr><th>Preparation for Calibrator</th><th>Storage & Stability</th></tr>
<tr>
<td><u>Serum Chemistry Calibrator (DR0070)</u>
• Let calibrator and diluent stand at room temperature (18 - 28ºC) for 5 minutes.
• Remove the cap and stopper. Using a volumetric pipette, add exactly 5.0 mL of diluent to the calibrator vial.
• Replace the cap and stopper. Allow material to remain undisturbed for 5-10 minutes
• Gently swirl the contents until completely dissolved
• Gently swirl for 30 seconds prior to each use

<u>Urine Chemistry Calibrator (DR0091)</u>
• Ready to use. No preparation is needed.
• Record reconstituted or open date, and expiration date on calibrator vials.</td>
<td>• Un-reconstituted serum calibrator, diluent and urine calibrator are stable until expiration date on the label when stored at 2-8ºC
• After reconstitution, serum calibrator is stable for 7 days at 2-8ºC.
• Once opened, urine calibrator is stable for 8 months.</td>
</tr>
</table>
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</tr>
</table>

Quality Control	**Frequency:** • Two levels of QC every **8** hours • Each new reagent bottle (even if same Lot #) • Each new reagent lot • After every calibration • After each shipment of the same Lot # • After specific maintenance or troubleshooting as detailed in the operators manual or after service/repair performed by Clinical Technology. **Control Name, Preparation, Storage and Stability:** Refer to SFOFCD-0407 AU680 Controls and Calibrators **QC Acceptable Criteria:** Refer to SFOWI-0218 Chem Quality Assurance Plan Section C. Quality Control
Maintenance	Refer to: • AU680 Daily Start Up Flow Chart (SFOFCD-0408) • AU680 Chemistry Analyzer User's Guide-Chapter (8) -Maintenance
Test Procedures	Centrifuge urine samples for 10 minutes. Refer to AU Operating procedures: SFOWI-1268 AU680 General Operating Procedures

Calculations	GFR, timed urine creatinine, creatinine clearance uncorrected and creatinine clearance corrected, Body Surface Area (BSA) and patient's height and weight in correct units are calculated automatically by RILIS using the following formulas: **GFR** (mL/min/1.73 m^2) The CKD-EPI equation uses a 2-slope "spline" to model the relationship between GFR and serum creatinine, age, sex and race. **GFR**: CKD=EPI Creatinine equation is used for estimated GFR: eGFR (mL/min/1.73 m^2) = 141 x min(S_{Cr}/ê, 1)^{á} x max(S_{Cr} /ê, 1)$^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if Black] Abbreviations / Units : eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2 S_{Cr} (standardized serum creatinine) = mg/dL ê = 0.7 (females) or 0.9 (males) á = -0.329 (females) or -0.411 (males) min = indicates the minimum of S_{Cr}/ê or 1 max = indicates the maximum of S_{Cr}/ê or 1 age = years Note: *The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.* **GFR calculation** is available at the National Kidney Disease Education Program website: https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators/ckd-epi-adults-conventional-units **24 hour timed urine creatinine** (mg/24 hr), report as mg/TV = urine creatinine random (mg/dL) x 24 hr Total Volume (mL) /100 **Creatinine clearance uncorrected** (mL/min/1.73 m^2) =urine creatinine random (mg/dL) x TV (mL) x 1.73 serum creatinine (mg/dL) (Hrs Collected x 60min) 1.73 **Creatinine clearance corrected** (mL/min/1.73 m^2) =urine creatinine random (mg/dL) x TV (mL) x 1.73 serum creatinine (mg/dL) (Hrs Collected x 60min) **BSA**

	Body Surface Area (BSA): Log BSA = 0.725 x Log[**H**x2.54 (convert inches to cm)] + 0.425 x Log **[W**/2.2 (convert lbs to kg)] - 2.144 Patient's height and weight are entered into RILIS in inches to one decimal place, and pounds in whole number respectively. Units are converted by RILIS for BSA calculation.
Analytical Measurement Range (AMR)	Serum/Plasma: 0.20 - 25.00 mg/dL Urine: 1 - 300 mg/dL
Reportable Range (Linear Limits in LIS)	**Serum/Plasma:** 0.20 - 112.50 mg/dL Results outside the linear limits are reported as "<0.20 mg/dL", or ">112.50 mg/dL". **Random Urine:** 1 - 1400 mg/dL Results outside the linear limits are reported as "< 1 mg/dL", or "> 1400 mg/dL". **Timed Urine:** When urine concentration is less than 1 mg/dL, timed urine creatinine is calculated using 1 mg/dL as the urine creatinine value. Timed urine creatinine is reported as "< ___ " result from the above calculation. When urine concentration is greater than 1400 mg/dL, timed urine creatinine is calculated using 1400 mg/dL as the urine creatinine value. Timed urine creatinine is reported as "> ___ " result from the above calculation. **Creatinine Clearance:** If calculated creatinine clearance is less than 1.0 mL/min, report < 1 mL/min **Total Protein/Creatinine Ratio:** Reportable Range for Creatinine: 21 - 1400 mg/dL Results outside the linear limits are reported as "<21 mg/dL", or ">1400 mg/dL"

<table>
<tr><td>Dilution</td><td>
<table>
<tr><td></td><td>Serum/Plasma</td><td>Urine</td></tr>
<tr><td>On-board auto dilution</td><td>x5</td><td>x5</td></tr>
<tr><td>Maximum dilution</td><td>x5</td><td>x5</td></tr>
<tr><td>Diluent</td><td>D.I. Water</td><td>D.I. Water</td></tr>
</table>
On-board dilution = Maximum dilution

Auto dilution:
• When on-board auto dilution is performed, results are automatically multiplied by the instrument.
Manual dilution: n/a
</td></tr>
<tr><td>Repeat</td><td>
• Follow laboratory repeat policy
• Review instrument printouts for result reasonableness, questionable results are repeated
• Review instrument print out for LIH indices and any flags.
• If lipemic index = ABN, airfuge the sample and repeat Creatinine assay.
• Repeat testing is required if there is any flag / LIH index associated with result obtained by manual dilution
</td></tr>
</table>

Reporting	**<u>Confirm ALL flags and indices are properly addressed before reporting any result.</u>** **Serum/plasma Creatinine**: Report results in mg/dL to two decimal places **GFR**: Report results in mL/min/1.73 m^2 and in whole number. GFR results greater than 60 are reported as ">60". GFR value is automatically reported except for patients < 18 years old, inpatients, and ambulatory surgery patients. Two GFR results (African American and Non-African American) are reported for each serum creatinine result reported on outpatients and patients from the Emergency Department. **Random Urine Creatinine** Report results in mg/dL and in whole number **24 hour Urine Creatinine:** Report results in mg/TV and in whole number **Urine Creatinine Clearance, corrected:** Report results in mL/min/1.73 m^2 and in whole number Review the instrument printout for result reasonableness, LIH indices and flags. If any index shows ABN, visually check the sample appearance to confirm the index ABN is correct. Extreme lipemia, hemolysis, or icterus can show all indices as "ABN". Refer to SFOFCD-0411 "AU680 Comment Codes for Reporting Interference due to Lipemia, Icterus, and Hemolysis" Global Interpretive comment for serum creatinine with GFR order: "Glomerular Filtration Rate estimate is expressed in mL/min/1.73 m^2 body surface area. A GFR estimate is validated only for patients greater than or equal to 18 years of age. Since this test is not useful if renal function is changing rapidly, a GFR estimate is not reported for inpatients. Many elderly patients have mildly to moderately reduced GFR."

Reference Intervals

Serum:

Age Group	Males	Females
0 - 1 month	0.30 - 1.00 mg/dL	0.30 - 1.00 mg/dL
1 mo - 2 years	0.20 - 0.40 mg/dL	0.20 - 0.40 mg/dL
2 years - 12 years	0.30 - 0.70 mg/dL	0.30 - 0.70 mg/dL
12 years - 150 years	≤ 1.34 mg/dL	≤ 1.11 mg/dL

Urine:

	Males	Females
24 hour Timed Urine	630 -2500 mg/TV	630 -2500 mg/TV
Creatinine Clearance corrected	95-135 mL/min/1.73 m^2	85-125 mL/min/1.73 m^2

GFR:

>59 mL/min/1.73 m^2 body surface area.

Reference Table for Population Mean GFR from NHANES III

Age (years)	Average GFR (mL/min/1.73 m^2)
20-29	116
30-39	107
40-49	99
50-59	93
60-69	85
70+	75

K/DOQI Clinical Practice Guidelines on Chronic Kidney Disease stage (CKD) as follows:

GFR	CKD Stage
>90	Stage 1 (with evidence of renal damage - e.g. proteinuria)
60 - 89	Stage 2 (with evidence of renal damage - e.g. proteinuria)
30 - 59	Stage 3
15 - 29	Stage 4
<15	Stage 5

Critical Values

0 - 12 years: ≥ 3.90 mg/dL
12 - 150 years: None

Early Notification Values

12 - 150 years: ≥ 7.1 mg/dL

Interference	Bilirubin : Interference less than 5% up to 40 mg/dL Bilirubin Hemolysis : Interference less than 3% up to 500 mg/dL Hemolysate Lipemia : Interference less than 10% up to 1000 mg/dL Intralipid*. Protein: Interference less than 10% up to 9 g/dL Protein * Intralipid, manufactured by KabiVitrium inc., is a 20% IV fat emulsion used to emulate extremely turbid samples. The Lipemia, Icterus, and Hemolysis (LIH) indices are graded 7 levels as follows: N, +, ++, +++, ++++, +++++, and ABN. N=Normal, ABN = > 5+ **Limitations:** Accurate estimation of GFR from creatinine requires a stable creatinine from day to day. In-patients and ambulatory surgery patients are not reported due to possible rapidly changing kidney function and /or changes in fluid infusion. Patients less than 18 years old are not reported because low creatinine values in this age group make eGFR from MDRD equation inaccurate.
Test Availability	24 hours, routine and stat
Back Up Testing	The second AU 680 analyzer
References	RWLQCWI-2069 rev.6 AU 680 Creatinine RLWI-2170 rev.5 Serum and Urine Creatinine on AU Analyzer RLWI-1209 rev.15 MWS Creatinine Beckman Coulter Instructions for Use: Creatinine, CLSIOSR6x78.02 March 2012, BAOSR6x78.06 , 2013-077

Associated Documents:

External Documents

Beckman Product Announcement.pdf

Associated Quality System Documents - None

Document Revision History:

Revision: 5	**Date Created:** 08/09/2016 **Date of Last Revision:** 04/08/2019	**Last Approval Date:** 04/08/2019

Document Author: Kevin W LUI/CA/KAIPERM	**Document Manager:** Vaiju Ruikar/CA/KAIPERM

Reason for Change:

Revision:	Sec/Para Changed	Change Made:	Date
1	N/A	Initial Issue of Document. This document was a modification of Regional Lab's AU procedures RLWI-1209 rev.15, and RLWI-2170 rev.6.	08/09/2016
2	Calibration	Calibration frequency changed.	06/28/17
3	Calculations	Changed eGFR calculation link from MDRD to CKD-EPI equation.	06/12/17
4	Product insert	Attached Product Announcement: New Creatinine Calibrator	09/11/18
5.	References Reportable Range Approver	RWLQCWI-2069 rev.6 AU 680 Creatinine RLWI-2170 rev.5 Serum and Urine Creatinine on AU Analyzer RLWI-1209 rev.15 MWS Creatinine Beckman Coulter Instructions for Use: Creatinine, CLSIOSR6x78.02 March 2012, BAOSR6x78.06 , 2013-077 **Total Protein/Creatinine Ratio:** Reportable Range for Creatinine: 21 - 1400 mg/dL Results outside the linear limits are reported as "<21 mg/dL", or ">1400 mg/dL" Changed CLIA Director	4/8/2019 4/8/19

Approvals:

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