Educational Discussion: Cystatin C

2015-B Cystatin C Survey (CYS)

The data from CYS-B 2015 mailing reflects cystatin C results being reported by clinical laboratories in September 2015. It is interesting to compare this new data to that submitted by laboratories in April 2014 with the CYS-A 2014 Survey sample set. In this previous set, we included not only two typical processed human plasma materials, but also two fresh frozen, off-the-clot serum pools which had no processing or additives and were therefore likely to be commutable. In the CYS-B 2015 mailing there were several new method-specific groups added. Furthermore, several of the groups had less than 10 participants, so only median, high, and low values and no method-specific means are reported in the Summary Report table. In addition, the two CYS-B 2015 samples were processed human plasma, so their commutability is uncertain making conclusions about any given method's traceability to ERM-DA471/IFCC international reference material for cystatin C questionable. Nevertheless, since the same basic processing and additives were used for the two CYS-B 2015 samples and the two CYS-A 2014 CYS-01 and CYS-02 samples, one can most likely infer whether there have been any major changes in the various methods' calibration traceability. Table 1 below summarizes the percent deviation of each method's median from the all-method median for each sample. The uncertainty of the median may be reasonably large for some methods with a low number of responses. For some of the samples the relatively low cystatin C concentrations (e.g., CYS-B 2014's CYS -01 and CYS-A 2015's CYS-02 samples) make the percentage biases look quite large when the actual bias in mg/L is fairly small.

With the above considerations and limitations in mind, a few observations can be made. Diazyme Laboratories results seem to be consistently high in both April 2014 processed and fresh frozen samples and September 2015 processed samples, in the range of 20 to 40% above the other methods and by inference above ERM-DA471/IFCC traceable value. Siemens results are still approximately 7 to 18% low compared to the other methods and by inference comparably below the ERM-DA471/IFCC traceable value. Note that Siemens

results reflect a mixture of US and non-US users which have different calibration traceabilities.[1] Siemens has indicated they are in the process of converting the calibration of their US kits to make their results ERM-DA471/IFCC traceable.[2]

Most clinicians simply use cystatin C measurements that their laboratory provides in various eGFR equations, such as the CKD-EPI cystatin-C eGFR equations,[3] without regard for or knowledge of their standardization status to ERM-DA417/IFCC international reference material traceability. It is very difficult for a clinician to know what calibration and calibration corrections a clinical laboratory have or have not employed for reporting cystatin C concentration. Consequently, it is important that clinical laboratories ensure they provide cystatin C results using methods with calibration traceable to the ERM DA471/IFCC international reference material. Lack of uniform calibration traceability of many routinely used clinical cystatin C measurement procedures has seriously impeded cystatin C's acceptance as a biomarker used for estimating GFR. All laboratories should carefully check their instruments' and/or reagents' and calibration systems' to be sure they are traceable to ERM-DA471/IFCC international reference material to prevent erroneous eGFR values being reported to clinicians.

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References:

1. Eckfeldt JH, Karger AB, Miller WG, Rynders GP, Inker LA. Performance in measurement of serum cystatin C by laboratories participating in the College of American Pathology 2014 CYS Survey. *Arch Pathol Lab Med.* 2015;139:888-893.
2. Mueller L, Prumper C. Performance in measurement of serum cystatin C by laboratories participating in the College of American Pathologists 2014 CYS Survey. *Arch Pathol Lab Med* in press, Letter to the Editor.
3. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. *N Engl J Med* 2012;367:20-9.

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Table 1. Method-specific Medians (mg/L) and Percentage Deviation from the All-Method Median by Method-specific Group

	CYS-B 2015 (mailed to labs in September 2015)			
Method	**Processed Human Plasma CYS-03 median cystatin C concentration (mg/L) and Bias (%)**		**Processed Human Plasma CYS-04 median cystatin C concentration (mg/L) and Bias (%)**	
Binding Site SPAplus	1.71	3.6%	0.50	16.3%
Diazyme Laboratories	2.32	40.6%	0.58	34.9%
Gentian	1.71	3.6%	0.38	-11.6%
Roche cobas c series	1.70	3.0%	0.44	2.3%
Original Reagent	1.70	3.0%	0.45	4.7%
New Reagent	1.71	3.6%	0.44	2.3%
Roche Modular	1.64	-0.6%	0.44	2.3%
Roche COBAS Integra	1.72	4.2%	0.40	-7.0%
Siemens Nephelometer Systems	1.44	-12.7%	0.40	-7.0%
Siemens Dimension Vista	1.44	-12.7%	0.41	-4.7%
All Method Median	1.65		0.43	

	CYS-A 2014 (mailed to labs in April 2014)			
Method	**Processed Human Plasma CYS-01 median cystatin C concentration (mg/L) and Bias (%)**		**Processed Human Plasma CYS-02 median cystatin C concentration (mg/L) and Bias (%)**	
Diazyme Laboratories	2.24	40.9%	0.35	20.7%
Gentian	1.54	-3.1%	0.23	-20.7%
Roche Hitachi/ cobas c	1.67	5.0%	0.39	34.5%
Siemens Diag Nephelometer Systems	1.34	-15.7%	0.27	-6.9%
Siemens Dimension Vista	1.30	-18.2%	0.27	-6.9%
All Method Median	1.59		0.29	

Method	**Fresh Frozen Serum CYS-WC1 median cystatin C concentration (mg/L) and Bias (%)**		**Fresh Frozen Serum CYS-WC2 median cystatin C concentration (mg/L) and Bias (%)**	
Diazyme Laboratories	1.12	25.8%	2.91	31.7%
Gentian	0.88	-1.1%	2.29	3.6%
Roche Hitachi/cobas c	0.96	7.9%	2.25	1.8%
Siemens Diag Nephelometer Systems	0.77	-13.5%	2.01	-9.0%
Siemens Dimension Vista	0.78	-12.4%	2.02	-8.6%
All Instruments Median	0.89		2.21	