To: arosendorff@gmail.com[arosendorff@gmail.com]
From: Adam Rosendorff
Sent: Wed 10/29/2014 2:11:09 AM
Importance: Normal
Subject: FW: fingerstick vs venous
Received: Wed 10/29/2014 2:11:09 AM

From: Daniel Young
Sent: Thursday, September 05, 2013 11:00 AM
To: Adam Rosendorff; Paul Patel; Chinmay Pangarkar; Surekha Gangakhedkar; Erez Galil; Clarissa Lui; Michael Chen
Subject: RE: fingerstick vs venous

Adam,

Are you suggesting that that we should (nice to have?) establish reference ranges for both venous and capillary samples on all our LDTs?

Thanks,
Daniel

From: Adam Rosendorff
Sent: Wednesday, September 04, 2013 5:56 PM
To: Daniel Young; Paul Patel; Chinmay Pangarkar; Surekha Gangakhedkar; Erez Galil; Clarissa Lui; Michael Chen
Subject: RE: fingerstick vs venous

Daniel

I favor establishing de-novo reference ranges on capillary blood (EDTA and LiHep), based on already collected and Walgreens normals, with locked down preanalytic (BCD) and analytic (anticoag, chemistries, dilutions etc) which we will collect very rapidly. We may *already* have collected enough data to establish preliminary reference ranges for the launch on Monday, as described in CLSI C28-A3C Section 11 (c) "An evaluation of a larger number of reference individuals but fewer than N=120, the number needed to perform a standard reference interval study." PLEASE CAN WE LOOK AT THESE RANGES ASAP??? Erez did a great job implementing C28 for a few analytes where I was able to compare T assays with S assays.

The main reason I favor jumping to RR studies is that it is not critical that we understand the reasons for bias when we compare fingerstick versus venous, many of which you outlined in your last email. These include pre-analytic (gel separators, specimen type, anticoagulant) and analytic (method chemistry, dilutions.) The reference range Validation (CLSI C28-A3C Section 11 (b)): ie. the protocol of doing 20 samples and ensuring no more than one is outside the reference range might be good enough for an FDA approved test for a hospital lab, where all that is changing is the patient population, but I don't think it works well when so many parameters are changing, as is our case.

ALL of our changed parameters could be controlled for with carefully planned reference range studies on capillary blood- EDTA and LiHep. As I mentioned, we probably *already* have this data (eg 60-70 normals for each analyte on fingerstick LiHep and EDTA), but Nick, Rose, Erez and Doug would need to advise whether this is the case.

That being said, there are certain hard numbers that have become standard of care eg. A fasting glucose of 126 mg/dL which is diagnostic of diabetes, electrolyte panic values, and the NCEP cholesterol target values- if we change our reference ranges, then we have to make a disclaimer that our absolute values are not useable for adhering to guidelines, and I think this is problematic. I would rather adjust QC, calibrators or (least desireable at this point) chemistries to make sure our values line up.

There are certain analytes where each lab is expected to fine tune their reference ranges because of large method dependant variation. These include fT4, TSH, cortisol, estradiol, testosterone etc... Then there are other analytes where changing the reference range is not recommended: these include electrolytes, blood gasses, glucose.

I have a question about the gel: are we going to have gel on both sides of the BCD (EDTA and LiHep) or just the LiHep side? Gel in SST is known to interfere with a large number of immunoassays. In fact, Becton-Dickinson were ordered by the FDA to recall glass and plastic SST tubes in 2004 due to higher than expected values for Total T3, Total T4, HBsAg, Folate, Vitamin B12, FSH and Cortisol. There is an excellent powerpoint on this topic here:

http://www.aacc.org/members/loc_sections/ncalifornia/LSNCMtgAnnouncements/Documents/tube_study_AACC_2012_for_members.pdf

For approach #2in your email below, we would have to use heparinized glass silicate tubes like those used for "spun" crits or microhematocrits as they are known. However, how are we going to recover plasma from glass capillary tubes- seems like it might be quite hard to do this. Some have plungers, but it's still going to be impractical.

If there is bias between capillary blood results and venous blood results (with matched anticoagulant and chemistries), then the assumption is that it is the BCD that is doing it? I think there might be reasons why capillary blood would give lower, but accurate, results for things like bicarbonate and glucose. One could argue that capillary blood and venous blood are two entirely different fluid types. I am sure you have seen the BD website link on this issue:

http://www.bd.com/vacutainer/labnotes/Volume17Number1/composition_differences.asp

Innovation is our great strength, but it becomes a weakness when we try to peg our values to old standards of care.
Adam

From: Daniel Young
Sent: Wednesday, September 04, 2013 1:55 PM
To: Adam Rosendorff; Paul Patel; Chinmay Pangarkar; Surekha Gangakhedkar; Erez Galil; Clarissa Lui; Michael Chen
Subject: fingerstick vs venous

I wanted to follow up on a conversation from yesterday and make sure that we are all on the same page, as there are multiple factors/issues to consider regarding fingerstick vs venous comparisons.

I do not think the "method comparison" is the ideal way to think about fingerstick vs venous comparisons for our assays. But rather we should perform a verification of the reference interval between fingerstick and venous collection (after the venous reference interval is verified using Theranos chemistry in our patient population). The reason for this approach is that the method is not being changed (ie, same chemistry and same matrix). If there is a difference between fingerstick/venous, it is not presumed to be due to a method problem. Rather, if such a difference is material, we would look to establish a new reference interval for fingerstick samples.

However, the additional complication is a potential impact of the BCD and gel on the assay performance. There could be an effect or interference from the BCD device itself on the assay that is not related to the sample type. To account for this, I suggest that if we find a difference in fingerstick vs venous reference interval, that we evaluate it in two ways:

1) perform a targeted study to evaluate BCD performance compared to vacutainer with venous samples only, looking only at the assay(s) that showed a capillary/venous difference, and
2) use a predicate capillary blood collection device and compare these results to our BCD assay results for the assays in question

I think it may be wise to perform both #1 and #2 above to fully evaluate the root cause. If these two tests show no BCD affect, then we proceed to establish a capillary reference range for that assay. If either of the above show a difference, we would need to consider a larger method comparison study to assess the impact.

Please let me know if there are questions about this. And then we can update our validation protocols accordingly.

Thanks,

Daniel Young, PhD
Vice President, Theranos Systems
Theranos, Inc
1601 S. California Ave
Palo Alto, CA 94304
650-470-6119 (office)
650-804-8185 (mobile)

Theranos, Inc., 3200 Hillview Avenue, Palo Alto, CA, 94304
650-838-9292 www.theranos.com