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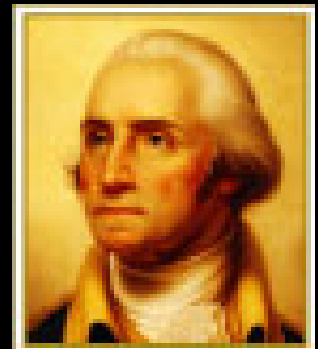
DOWN WITH THE TOWER OF BABEL!

WHY ALT VALUES DIFFER BETWEEN LABS AND WHAT CAN BE DONE

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DISCLOSURE

- I have no relevant conflicts to disclose.



WHY DO ALT RESULTS DIFFER BETWEEN LABS?

- Several factors contribute to different test results between laboratories:
 - Differences in methods used
 - Differences between manufacturers
 - Different approaches to establishing reference values




HOW IS ALT MEASURED?

- All laboratories use a form of the assay developed by Karmen, which measures enzymatic activity
- Assays may differ in a variety of parameters that can affect this activity, such as pH, buffer, concentration of reagents
- A necessary co-factor for activity is pyridoxal-5'-phosphate (P-5'-P), which is not added by many manufacturers



HOW COMPARABLE ARE ALT METHODS?

- In US, laboratories are required to measure unknowns, and report results, termed proficiency testing (PT).
- US law sets degree of agreement needed to pass PT, which labs generally consider acceptable performance
- Acceptable results for ALT are $\pm 20\%$ of the average of all labs using the same method



HOW COMPARABLE ARE ALT METHODS?

- In the US, College of American Pathologists (CAP) is the major provider of PT material; same material is tested by all labs
- In most recent data, ALT was performed on assays by 5 main manufacturers in about 5200 laboratories
- In samples with mildly elevated ALT, average values by method ranged from 59-81 U/L in one sample, and 76-99 on another sample



HOW COMPARABLE ARE ALT METHODS?

- Results from same manufacturer generally more comparable, but were slightly higher (average 2-3 U/L in range 70-90) if P-5'-P was in reagents
- Differences were similar even at much higher ALT results (for example, averages ranged from 173-213 for highest sample tested)



REFERENCE INTERVALS

- Minimum requirement for laboratories is to validate that the range they use is appropriate for their population (often use what is suggested by manufacturer)
- Establishing reference interval requires many apparently healthy volunteers (for tests such as ALT, minimum of 400); validation only requires 20, and reference interval accepted if 2 or less results outside interval



REFERENCE INTERVALS

- If manufacturer has not considered the factors discussed by Dr. Prati, then proposed reference interval may be wider than what would be reasonable for “healthy” values
- Some laboratories select their own sample, which can lead to different results as well
- The combination of different methods and different labs making reference intervals makes for lack of uniformity



WHAT CAN BE DONE?

- There are informative lessons from other tests that could be applied to ALT to make both actual results and their interpretation more uniform
- Will require cooperation between clinical and laboratory organizations to make this happen



CHOLESTEROL

- In 1980's, the situation with cholesterol was similar to that with ALT currently
- The NHLBI established the National Cholesterol Education Program to define cholesterol levels associated with increased risk of cardiac events
- As part of this, there was a laboratory effort to make cholesterol results agree in all labs



CHOLESTEROL

- Risk levels were defined for cholesterol and LDL-cholesterol based on likelihood of adverse outcomes, replacing reference intervals defined for population
- In most recent CAP PT surveys, at cholesterol values around 190 mg/dL, averages ranged from 183-196 for the 5 major manufacturers, with most between 190 and 194.



HEMOGLOBIN A1c

- In 1990's, Diabetes Control and Complications Trial showed good correlation between A1c levels and risk of diabetic microvascular complications
- Major issue identified was difference in A1c results between different assays
- This prevented use of A1c results interchangeably for monitoring or diagnosis



HEMOGLOBIN A1c

- The National Glycohemoglobin Standardization Program was developed to work with manufacturers to improve agreement of A1c results
- Currently, manufacturers must show that their A1c results are within $\pm 6\%$ of the actual result (for example, at an A1c of 7%, between 6.6-7.4%)



HEMOGLOBIN A1c

- Based on improved agreement, the American Diabetes Association allowed use of A1c to diagnose diabetes starting in 2010
- The diagnostic level for A1c (6.5%) was not based on the central 95% of values, but by the level at which risk of significant retinopathy began to increase



PATH

- Hormone results are often markedly different between laboratories due to similar factors to ALT results
- The Endocrine Society developed partnership with several government agencies (CDC, NIH, NIST) and laboratory groups (CAP, AACC among others), termed the Partnership for Accurate Testing of Hormones (PATH)



PATH

- To date, manufacturers and large laboratories have worked to develop a program to make results agree more closely for a number of hormones (testosterone, estradiol, vitamin D)
- The plan is to expand the effort to other hormones over time



SUMMARY

- ALT results can differ significantly from one assay to another, and their interpretation can differ based on criteria used to establish reference intervals
- Alternative approaches exist, however, to make results more comparable and improve interpretation of results run in different laboratories



SUMMARY

- This approach requires support of professional societies of clinicians AND laboratorians
- Together can address both health implications and laboratory procedures needed to assure comparable results between labs