D. Robert Dufour, MD, FCAP, FACB
Consultant, Pathology and Hepatology
VA Medical Center

Click to view Biosketch and Presentation Abstract
or page down to review presentation

DOWN WITH THE TOWER OF BABEL!

WHY ALT VALUES DIFFER BETWEEN LABS AND WHAT CAN BE DONE

D. Robert Dufour, MD, FACB, FCAP

Consultant Pathologist
Attending, Liver Clinic
VAMC, Washington DC
Emeritus Professor
of Pathology

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’-phoshpate (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 ± 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 interchangably 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 ± 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