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State of the art: Proficiency testing

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Proficiency testing (PT, also known as External Quality Assurance or EQA), is an essential tool to assess the performance of clinical laboratories. Under U.S. federal clinical laboratory regulations (CLIA), clinical laboratories must regularly demonstrate their ability to achieve a satisfactory performance for samples sent from an authorized PT program. PT is regarded as an important, objective, external system of monitoring laboratory performance, and failure to achieve satisfactory results in a PT program can lead to various sanctions including mandatory cessation of testing for an analyte, and up to revocation of the laboratory's certificate to operate.

U.S. regulations mandate enrollment in a formal PT program for 87 analytes (the so-called "regulated analytes"), a list that has not changed since 1992. For analytes not on that list, alternative assessment of test method performance must be conducted at least twice a year, although many laboratories do elect to enroll in formal PT, which is available for many more analytes than just the 87 regulated analytes. For many analytes that are reported with quantitative measurements, grading criteria are established by federal regulation. These are generally based on comparison with other laboratories that use the same instrumentation or methodologic principles for analysis (peer-group grading). The passing scores are set as a difference from the peer group mean result. The acceptable difference from the peer group means varies by analyte and can include percentage difference, number of standard deviations, or absolute concentration (or activity) of analyte difference. The passing score is generally set as success rate of 80%, but is 100% for some tests in blood banking (such as identification of the correct ABO and Rh types).

Peer group grading allows laboratories to compare their performance to others in the same peer group, but does not provide direct comparison with truth because for most PT surveys, reference method assignment of the true concentration or activity of the analyte is not performed. Even comparison of the results among different peer groups is problematic because of the nature of many PT materials, especially in clinical chemistry, which are often non-commutable with native human serum samples. The non-commutability arises because of differences in the matrix of the PT material, which can influence the measurement of the analyte of interest in different ways among different instruments. The use of native human samples is impractical for PT surveys with large numbers of participants, other than the provision of samples collected from normal donors, which are expected to produce results within the reference interval. This somewhat limits their usefulness for PT surveys, where an important consideration is provision of a wide range of analyte concentrations, both below and above the reference interval.

Nevertheless, as a way of offering commutable samples in PT programs, the College of American Pathologists (the organizer of the largest PT programs in the U.S.) has developed a number of PT programs that include native human serum samples as follows:

Apolipoprotein A1	25-OH Vitamin D (D2, D3)	Sex hormone-binding globulin
Apolipoprotein B	Albumin	(SHGB)
Cholesterol	Calcium	Testosterone
HDL cholesterol	Cortisol	Testosterone, bioavailable
Non-HDL cholesterol	Estradiol	Testosterone, free
LDL cholesterol	Sex hormone-binding globulin	Urine calcium, creatinine, albumin
Hemoglobin A_1c		

Some of these analytes have reference values assigned to them by national or international reference labs, enabling participating laboratories to compare their results to truth. For other analytes, comparison between different instruments and methods is possible without concern for non-commutability of the material. Analysis of the results of these surveys has revealed occasional significant biases among different methods that would impact the interpretation of patient results. These data will be presented.

The use of PT survey materials that are commutable has proven to be important for monitoring the status of standardization and harmonization for clinical laboratory testing for a number of analytes. Creatinine is an example of an analyte that has undergone significant improvement across manufacturers in the last decade because of adoption of consistent calibration schemes traceable to a higher order reference method (isotope dilution mass spectrometry). In a 2003 survey across U.S. laboratories, observed biases ranged from -7% to +34%. Today, after adoption of more reliable calibration, the observed biases range from approximately -5% to +10% relative to the reference value. Another example of an analyte that has undergone significant improvement in assay performance is hemoglobin A_1c. By gradually decreasing the acceptable range for passing PT, manufacturers have had to standardize their method performance so that the users of their equipment can pass PT.

The improvements offer examples for standardization of more assays, but there remain many significant problems, especially for analytes that are incompletely defined (e.g., many proteins of medical interest). The approach forward will involve the collaboration of many groups, including clinical laboratory groups, medical professional societies, instrument manufacturers, and regulatory agencies. Initial work usually involves the establishment and acceptance of higher order reference materials and reference method procedures, often with definition and agreement on the measurand. Clinical laboratory and medical societies can set goals and priorities for standardization and harmonization of assays. This is likely to be a multi-decade project to drive changes and improvements in this field.

In conclusion, PT serves both an important regulatory function to assess the performance of clinical laboratories, and, with the use of commutable materials, is a means to assess the overall state of measurement of various analytes across different instruments and methodologies. Much work is yet to be done on harmonization and standardization of clinical laboratory assays.