2010 Proficiency Testing Workgroup Report

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Workgroup Report Overview

- Issues Raised by Workgroup Members
- Analyte Inclusion and Prioritization
- Determination of Criteria for Acceptable Performance and PT Sample Grading
- Microbiology PT Requirements
- PT Referral

Issues Raised by Workgroup Members

- PT is one component of a laboratory's quality system and helps assure quality between inspections
- Concerns regarding PT (cost of materials, staffing turnover) vary with laboratory size
- Physician offices or other small laboratories may not understand PT requirements or the value of PT
- Surveyors and PT programs educate laboratories and provide assistance with PT enrollment
- The list of regulated analytes and grading criteria needs to be updated and should have the capacity to be flexible over time, to the extent permitted by law
- PT should be required for all analytes and instruments, including waived testing and back-up analyzers
- When possible, PT should cover the entire testing process, to include pre- and post-analytical phases of testing

Issues Raised by Workgroup Members (cont'd)

- Method-based PT should be considered
- Determination of required PT for immunohematology and histocompatibility testing presents challenges
- Reaching consensus is sometimes challenging and perhaps lowering consensus could help laboratories
- When grading PT, reaching consensus doesn't necessarily indicate achieving the correct result
- Inadvertent vs. intentional PT referral can be difficult to distinguish, and education of personnel would be helpful in preventing inappropriate referral
- Inadvertent PT referral tends to occur more frequently in larger organizations with multiple laboratories, where there is increased staff turnover, or when one individual performs testing at multiple sites

Factors for Adding Regulated Analytes

What factors should be considered for adding regulated analytes to subpart I of the CLIA PT regulations?

WORKGROUP AGREEMENT:

Consider as criteria for analyte inclusion:

- PT exists and material is available
- Volume of testing for an analyte
- Clinical relevance
- Cost

PT Exists and Material is Available

- Consider the number of PT programs offering the analyte and availability of data for evaluation
  - Sufficient participation is important for adequate data
  - Suggest data be available from at least 100 laboratories
  - Suggest PT performance data from at least 2 years be available
- For some analytes, especially genetic tests, test frequency is low, there are limited sources of material, and samples may be extremely expensive
- Some analytes not currently offered by PT programs should be considered

Volume of Testing for an Analyte

Include both:

- Number of laboratories that perform testing for an analyte
- Total nationwide volume of tests performed for that analyte

Clinical Relevance Components

- To objectively assess clinical relevance consider:
  - Clinical practice guidelines, professional consensus guidelines, and testing requirements from professional organizations
  - Workgroup consensus
  - PT programs' scientific committees
  - Input from physician stakeholders, Institute of Medicine, Agency for Healthcare Research and Quality
  - Literature searches
  - Number of reimbursements
  - How test results affect patient treatment or if critical values exist
- High risk tests, though difficult to characterize, should be a priority
- Institutions may check their diagnostic pathways to determine what tests are relevant

Cost

- Consider burden on laboratories
  - Affordability to smaller laboratories and physicians office laboratories
- Assess cost to PT programs for materials, shipping, computer programming, staffing, and literature
- Perform cost/benefit analysis before adding analyte

Additional Considerations

- Criteria need to be well-defined, specific, and consistent
- Regulations need to be flexible to allow for evolution of testing and changes in medical practice
  - List of regulated analytes should be reviewed and updated periodically
  - Consider if there is a way to have an analyte list other than in regulation, but consider enforceability and legal ramifications
  - Create a process to include new analytes, with criteria defined in the regulations
- For flexibility, consider specifying groups of tests, such as drugs-of-abuse or cardiac markers, rather than individual analytes

Assessing Factors or Criteria

How should the factors or criteria for analyte inclusion be objectively assessed?

- Inclusion criteria need to be weighted or scored
- Clinical relevance is difficult to score
- Consider:
  - Volume of testing in conjunction with practice guidelines
  - Existence of standardized or reference methods
  - Availability of tests with years of experience in field and with PT and grading

Assessing Factors or Criteria (cont'd)

- While the process may not be specified in the regulations, suggest considering a model similar to CLIA test categorization
- Score each criterion separately and determine a total
- Each criterion must meet some minimal threshold to be considered for inclusion
- Example scoring scheme for consideration:
  - 0 = does not meet the criterion
  - 1 = minimally meets the criterion
  - 2, 3, or higher = higher rank for priority

Assessing Factors or Criteria (cont'd)

- Examples of scoring:
  - Testing volume

    0 = Not enough laboratories for peer grouping

    1 = Meets minimum for peer grouping

    >1 = Many laboratories performing testing for that analyte
  - Cost

    0 = Cost to include is prohibitive

    1 = Minimal cost

    2 = Little or no cost

Assessing Factors or Criteria (cont'd)

- Additional scoring considerations
  - 1 point difference in scoring does not distinguish well
  - Not all tests are independent
  - Need to apply scoring to new analytes and for deletion of some currently regulated analytes

Number of Analytes to Add

Should there be a reasonable limit on the number of analytes added to each new regulation published for proficiency testing?

- No agreement was expressed on the number of analytes to include
- Consider requiring new analytes in phases
  - Analytes for which PT is already available and testing is frequently performed should be a priority
  - Three year phase-in after FDA approval was suggested
  - Consider the costs when adding new analytes for PT programs and laboratories
  - Consider the length of time required for making changes to required PT

Required PT for Other Specialities

Should PT be required for other specialties, such as histocompatibility or cytogenetics? If so, should factors similar to those listed in the first question be considered?

- Differing opinions were expressed as to whether PT for histocompatibility testing should be required
- Histocompatibility may already be suitably monitored under CLIA and therefore requires no further regulatory action
- No comments were shared regarding cytogenetics PT

Data for Analyte Inclusion

What data are needed to make decisions for inclusion of new analytes? What are sources for the data and how should CDC and CMS obtain and assess this data?

Data for Analyte Inclusion (cont'd)

- Collect data from PT programs:
  - Number of subscribers for unregulated analytes
  - Data may only include accredited laboratories or those with other mandates
- Look at frequency of testing as shown by representative laboratories or CMS Medicare information, with caveat that the later is not representative of all patients
- Private payers, accrediting organizations, states, instrument and reagent vendors, and CDC have data that could be used
- The number of national and institutional clinical practice guidelines for a given analyte may be used as quantitative data to assess clinical relevance

Analytes for Consideration

Based on your experience, what analytes should have required PT?

Workgroup Comments:

- Individual workgroup members suggested:
  - LDL direct measurement
  - PSA
  - D-dimer
  - INR
  - Myoglobin
  - Vitamin D
  - Vitamin B12
  - Free T3
  - FSH
  - Hepatitis viral testing other than B
  - HbA1c
  - Markers measured by flow cytometry
  - Urine drugs
  - Clinical toxicology
  - Illicit drugs
  - Drugs for pain management

Analytes for Consideration (cont'd)

- Strongly consider adding new analytes used to screen blood for emerging infectious diseases
- Consider tests done once in a lifetime or for life threatening conditions:
  - Genetic tests, such as Her-2/neu
  - Tests for life threatening conditions, such as troponin, BNP, tumor markers
- Default to all analytes regulated unless there are valid reasons against it

Impact of Additional Required PT

How would an expansion in the number of required analytes impact your laboratory or PT program?

- Some laboratories already receive unregulated chemistry analytes in panels, so added cost for those analytes would be minimal
- Cost is more than cost of the PT, labor costs for additional PT should be considered
- The costs of adding certain analytes at the number and frequency required by regulations may be excessive

Impact of Additional Required PT (cont'd)

- Addition of analytes may not affect some PT programs that already offer analytes not required by current regulations
- Costs could be adjusted for an increase in number or frequency of challenges

Process for Adding PT Analytes

Should there be a staging process for identifying analytes for which PT should be required but may not now be available?

- There should be a phased-in approach to making PT analyte changes
  - Limit the number of analytes added/removed from the list
  - Need time to see if PT for an analyte can be manufactured and distributed
  - Prior to requiring PT, there should be a period of offering it as ungraded or for educational purposes
- List of required PT analytes should be reviewed periodically as determined by CMS

Deletion of Required PT Analytes

Should required PT for any of the analytes currently specified in subpart I be discontinued?

- Suggest criteria be developed for deleting analytes, perhaps the same criteria as for including them
- For some analytes, eliminating required PT may result in increased errors

Deletion of Required PT Analytes (cont'd)

- Analytes should be removed from the list if laboratories no longer perform testing for those analytes
- Analytes proposed for possible deletion from required PT:
  - Ethosuximide
  - LDH isoenzymes
  - NAPA and procainamide
  - Quinidine
  - T3 uptake

PT of the Total Testing Process

Could PT be improved to assess more steps in the total testing process?

- There are the limitations of PT in pre- and post-analytical phases
  - PT does not evaluate how laboratories handle specimens in real life
  - Lyophilized PT samples cannot be handled like patient specimens
- Samples could be improved to include pre-analytical processes such as extraction steps in molecular testing

PT of the Total Testing Process (cont'd)

- Clerical errors, resulting in failed challenges, suggest problems in the total testing process
- PT tests a laboratory's ability to adapt and follow processes and directions

Method-based PT

Would method-based PT be more appropriate for certain tests or analytes? What are the barriers to this approach?

- Method-based PT would be feasible in certain instances such as genetic testing where individual PT for every variant would be too costly
- If an indicator of performance for a method is consistent over time, it would not be beneficial to require additional of PT
- Lack of method-based PT specifications in the current regulations has allowed flexible adaptation to new testing methodologies
- Method-based PT could add costs for materials, and cross-reactivity of samples could also be an issue

Committee Discussion

Criteria for Acceptable Performance for Currently Regulated Analytes

Are the criteria for acceptable performance for the currently regulated analytes appropriate and which of the current criteria should be revised?

- Use of standard deviation (SD) for setting limits is only appropriate with normal distributions

Criteria for Acceptable Performance for Currently Regulated Analytes (cont'd)

- Three SD limit may be too broad
  - Suggestion for change from three SD to two SD
  - Consider range between two and three SD and a system that includes fractional credit rather than just pass/fail
  - A change from acceptance limits of three SD to two SD would theoretically make the fraction that is outside the limits increase from about 1% to 5%
- SD limits are not necessarily clinically relevant
- Some analytes, such as those in toxicology, need fixed limits

Criteria for Acceptable Performance for Currently Regulated Analytes (cont'd)

- In some cases, a combination of fixed and proportional limits should be used
  - If using proportional limits, may need to also have fixed limit for lower values
  - Glucose is a good example of an analyte where a combination of limits is optimal (+/- 6 mg/dL or 10%, whichever is greater)
- Concept of SD and peer group should be specific to method

Criteria for Acceptable Performance for New Quantitative Analytes

How should criteria for acceptable performance be determined for quantitative tests or analytes that are added to the list of regulated tests?

- Criteria considered may include clinical relevance, method performance, biological variability of the analyte, and the existence of a gold standard
- Need to cover clinically relevant ranges in a scientifically defensible manner
- Conduct a review of the performance data for an analyte over time, and then determine the grading

Criteria for Acceptable Performance for New Quantitative Analytes (cont'd)

- Include "state of the art" limits along with clinically acceptable limits
- Look at failure rates to determine if there is a need to update the current criteria
- Consider multiple criteria depending on the analyte, for example +/- SD, fixed concentration, proportional limits and failure rates

Determination of Criteria for Acceptable Performance for Qualitative Tests

For qualitative tests, should the criteria for acceptable performance be revised?

- In cases where positive and negative results are determined by cutoff values, there is a grey zone. In some instances, "indeterminate" may be reported, such as in measuring β-hCG, troponin
- Consider including criteria that recognize different degrees of severity for misidentification of cells in hematology

Grading Criteria

Should the criterion for determining the correct response by comparing the laboratory's response for each analyte with an established percentage of referee or participating laboratories be changed? Aside from blood banking, are the two options to determine the target value either by agreement with 80% of referee laboratories or by agreement with 80% of participants equally valid? Should one approach be preferred? If so, what would you suggest, and should it be required for scoring in <u>all</u> specialties and subspecialties?

Grading Criteria (cont'd)

- Grading by peer group consensus was implemented to increase the possibility of grading more laboratories
- The majority of analytes, particularly in chemistry, would achieve 80% consensus at the all method level, but certain instrument/reagent combinations may fail. Peer grouping is fairer in these cases
- PT programs agree that 80% consensus seems to be working
- Laboratories would object if there was a drop to below 80% consensus for grading

Standardized PT Scoring

Are the current grading criteria sufficiently detailed and specific to assure standardized scoring by all programs?

- Suggest using a fixed SD together with some variability that allows for grading a wide range of analytes
- Suggest setting criteria based on analytic value
  - For example, glucose values <100 mg/dl might have certain criteria and values >100 mg/dl have another set of criteria
- As more analytes are regulated, may have a wider range of target concentrations with appropriate criteria so they are not deemed ungradable

Matrix Effects

To what extent does matrix effect limit the impact of PT by allowing peer-grouping? Does this occur often enough to warrant the addition of requirements for PT programs that would minimize the matrix effects within samples? What should these requirements be?

WORKGROUP AGREEMENT:

- There is no need for requirements to minimize matrix effects since true matrix problems affect very few samples
- PT requirements mandate that PT samples mimic a patient's specimen as much as possible
- Peer grouping was designed to minimize matrix effects and must continue to be monitored
- PT programs are working with sample manufacturers to minimize matrix effects

Ungradable Challenges

What are the major reasons for ungradable challenges?

Workgroup Comments:

- Lack of consensus
- Small peer groups sometimes do not fit into an all methods category
- Challenges with less than 10 participants

Ungradable Challenges (cont'd)

Are there ways to minimize the number of ungradable results?

- Reasons for ungraded results should be clarified to and provided to laboratories for educational purposes
- Programs may elect to send out samples that are not graded, in an effort to provide additional educational challenges

Ungradable Challenges (cont'd)

Should PT programs be expected to validate the stability and homogeneity of the samples they provide?

WORKGROUP AGREEMENT:

- Stability and homogeneity of PT samples are not issues that need to be addressed by any changes to the CLIA PT requirements

Peer Group Definition

Should "peer group" be defined in the regulations? Are there additional terms that need to be defined?

- Suggested definition of a Peer Group: A group of laboratories whose testing process utilizes similar instruments, methodologies, and/or reagent systems
- Comments on definition
  - May not be applicable for microbiology which includes all participants in grading
  - Suggest establishing peer groups by size or type of testing facility
  - Need to know the reason for peer groups

Committee Discussion

PT Referral

How can the current regulatory language be changed to allow CMS flexibility and discretion, yet still conform to the statutory requirement for PT referral?

Background

- When the CLIA law was established and regulations implemented, stringent penalties were included for intentional PT referral

<u>The "CLIA" Law (42 USC 263a)</u>

(i)(4) Improper referrals

Any laboratory that the Secretary determines intentionally refers its proficiency testing samples to another laboratory for analysis shall have its certificate revoked for at least one year and shall be subject to appropriate fines and penalties as provided for in subsection (h) of this section.

Background (cont'd)

- 14 PT referral cases have been reviewed by CMS
  - Seven cases resulted in a revocation of the laboratory's CLIA certificate for one year and the director unable to direct for two years
  - Five cases resulted in less stringent sanctions, and two are currently being reviewed
- CMS requested assistance with the definition of "intentional PT referral"
- Confusion arises in laboratories because regulations state PT samples must be tested as patient samples and also states PT samples must not be sent to another laboratory
- Laboratories in a single organization with multiple CLIA certificates are considered multiple laboratories
- Viewing results from another laboratory Is considered PT referral even if those results are not reported

Background (cont'd)

- Some PT referral cases are likely not intentional, but due to lack of understanding
- Examples of PT referral cases investigated by CMS:
  - PT challenges were delivered to the incorrect laboratory and the receiving laboratory performed testing
  - One laboratory received PT samples referred from another laboratory with a completed requisition form noted "PT sample"
  - Single rogue employee within a medical group resulted in 19 physician office laboratories involved in a single PT referral incident

PT Referral

- Staff working in multiple laboratories at the same time can lead to inadvertent PT referral
- High personnel turnover in small laboratories may be a cause of inadvertent PT referral
- Consider what the laboratory policy is for referring a test or portion of a test such as reflex, confirmatory, or distributive testing
  - Sometimes multiple tests from multiple laboratories are required to get a result
  - Example given of a quad pregnancy screen test where the triple screen is performed in-house and the remaining test is referred

PT Referral (cont'd)

- Allow laboratories to treat PT exactly as patient samples and do reflex or referral testing when it is included in their standard procedure
- Possible criterion for determining PT referral could be whether the laboratory has the test on its test menu

PT Referral (cont'd)

- The laboratory could provide verification that the test is not on their menu to allow for PT referral in certain cases
  - Suggest including a place on the PT result form for laboratories to state they do not perform this test
  - Suggest saying on PT form that part of this result is dependent on another laboratory and including that laboratory's CLIA number
  - One PT program already allows laboratories to declare that they would send out a patient specimen

PT Referral (cont'd)

- Each laboratory could order PT material from different programs to avoid a single individual running the same PT at multiple sites
- Recommend educating employees and implementing robust policies and procedures to prevent PT referral
- Need to have regulatory language to give laboratories the latitude to refer pieces needed to report complete result or report PT only for the parts completed in their laboratory
- Recommend separating referral and intent in regulations at §493.801(b)(4) allowing CMS more flexibility in imposing sanctions on laboratories