Laboratory Regulations and Quality Management

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Overview

- Performance review
- Quality control materials & use
- Proficiency testing surveys
- Laboratory regulation
- Proficiency testing components
- Total quality management
Laboratory regulation

• The Clinical Laboratory Improvement Act of 1967 (CLIA ‘67):
  – The first attempt by the federal government to regulate laboratories

• CLIA ’88 expanded federal oversight to virtually all clinical laboratories in the country

• Laboratories are classified based on testing complexity, “test-site neutral”
CLIA ’88

• Standards included requirements for:
  – Laboratory testing personnel
  – Patient management
  – Quality assurance
  – Proficiency testing (PT)
  – Quality control

• Quality is overseen by:
  – Federal and State agencies
  – FDA
  – Professional organizations
Agencies

• CMS in conjunction with CDC were originally charged with developing and enforcing CLIA regulations

• CMS continues to oversee much of these regulatory activities:
  – Laboratory registration
  – On-site inspections
  – Training
  – Accreditation
TRUE OR FALSE?

ALL LABORATORIES IN THE U.S. ARE REGULATED UNDER CLIA
FALSE — Who is exempt?

- Law enforcement agencies determining legal status of individuals
- Laboratories licensed by an approved state
- Forensics testing laboratories
- In-vivo and externally attached patient-dedicated monitoring
- Testing for research purposes with no patient-specific use
- Self administration of tests at home
- VA laboratories subject only to VA rules published and enforced
- Department of Defense (DOD) laboratories subject only to rules published and enforced by the DOD
FDA

• Regulates vendors and medical devices

• FDA regulations include in vitro diagnostic tests

• FDA: the regulation of laboratory services is in its “jurisdiction”

• Enforcement discretion:
  – Regulating the practice of medicine
  – Laboratories are regulated under CLIA
  – Legality
Professional guidelines

- AMP:
  - Laboratory guidelines and position statements
- ACMG:
  - Practice guidelines
- CAP:
  - Checklist for molecular pathology laboratories
- CLSI:
  - Guidelines
- Other:
  - CDC
  - Genetic testing under CLIA
  - NY State Dept of Health Laboratory Standards
Laboratory regulatory oversight

- Centers for Medicare and Medicaid services
- Laboratory accreditation agencies
- Food and Drug Administration
- Individual U.S. States
- Professional Specialty Certification organizations
Total quality management

• Pre-analytic => Analytic => Post-analytic
• Quality control : Quality assurance

QUALITY ASSESSMENT

• Documentation
• Monitoring
• Statistics
• Competency
• Systems approach
• Proficiency testing
• Inspections
Assay verification

• FDA approved or FDA cleared assays

  » Precision
  » Accuracy
  » Reference range
  » Reportable range
TRUE OR FALSE?

MOST MOLECULAR TESTS ARE FDA APPROVED BY REGULATION
FALSE – Most tests are LDTs

- Most molecular tests are Laboratory Developed Tests (LDT)
- “This test was developed and its performance characteristics determined by Stanford Clinical Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (‘CLIA’) as qualified to perform high complexity clinical laboratory testing.”
Assay validation

- Laboratory developed assays

  - Precision
  - Accuracy
  - Analytic sensitivity
  - Analytic specificity
  - Reference range
  - Reportable range
  - Other characteristics
Laboratory inspections

• CAP accredited labs are inspected by qualified inspectors using the checklist

• CAP committees reviewing PT are blinded to the laboratory name, inspectors are provided with a history of PT performance

• Inspectors can investigate persistent problems during an inspection
Laboratory inspections

- Inspection of the laboratory, its testing in practice, its documentation
- Compare the testing with the procedures and relate this back to the CAP checklist
- Inspectors may follow a sample
- Inspectors may ask technologists how they do an assay
- Summation:
  - Summary report
  - Recommendations
  - Deficiencies
TRUE OR FALSE?

THERE ARE TWO TYPES OF LABORATORY DEFICIENCIES POSSIBLE AT A CAP INSPECTION
TRUE – Deficiencies

• Phase I:
  – It is sufficient to submit a statement regarding the corrective action taken. At future inspections, any deficiencies will be reviewed carefully.

• Phase II:
  – Must provide satisfactory documentation for accreditation: submit corrective action with all supporting records such as procedure changes, work sheets, meeting minutes, (etc.) to prove full compliance.
Proficiency testing

• Moderate / high complexity labs and provider performed microscopy (PPM)

• An important part of laboratory QA

• CLIA requires participation in a system that validates accuracy at least 2x / year

• Approved programs

• Alternative programs
PT components

• **Pre-analytical:**
  
  – This is a check for clerical errors which lead to the reporting of incorrect results
  
  – Appropriate receipt
  
  – Labeling
  
  – Processing of the sample: often does not reflect real patient samples and bypasses one of the testing challenges
PT components

• **Analytical result:**
  – Analytical performance is typically very good
  – Most platforms are robust
  – Points out platform limitations
  – Assays may be affected by sequence variants
PT components

• Post-analytical interpretations:
  – Interpretation of the analytical result
  – Clinical implications of a test result
  – Examples:
    • Fragile X interpretations
    • CF interpretations of different mutations
    • MTHFR 677C>T heterozygous
TRUE OR FALSE?

PROFICIENCY TESTING ERRORS ARE MOST COMMON IN THE PRE-ANALYTICAL PHASE
TRUE – Proficiency testing errors

• Most often clerical or labeling errors
The CAP provides the most extensive PT program available

Worldwide

- Labs can be CAP accredited
- Labs can order and use CAP PT surveys
Resources required for CAP PT

- Laboratories to QC exchange materials

- Committees to:
  - select samples
  - review data
  - assess problems
  - write summaries and publications

- CAP staff support

- Well characterized samples and control materials
Molecular Pathology proficiency testing

• Molecular Pathology and Genetics cluster:
  – CAP/ACMG Biochemical and Molecular Genetics Resource Committee
  – CAP/ACMG Cytogenetics Resource Committee
  – Histocompatibility/Identity Testing Committee
  – Microbiology Resource Committee
  – Molecular Pathology Resource Committee
PT by CAP/ACMG

- **Molecular Genetics:** CAP MGL survey
- Managed by the BMG Resource Committee
- Members from CAP and ACMG
- Proficiency testing, products and services, education, checklist, responses to inquiries
- Participant summaries
- Publications
MGL surveys

- **Molecular Genetics (MGL) surveys:**
  - MGL1: FVL, FrX, HChr, MTHFR, PW/AS, PT
  - MGL2: CF, DMD/BMD, FA, Hb S/C, Hunt, MD, RhD, SMA, SA
  - MGL3: BRCA1/2, MEN2, CX26
  - MGL4: Canavan, FD, Tay Sachs (etc.)
  - MGL5: CF
  - Pharmacogenetics survey
  - SEC: DNA sequencing challenge
Survey limitations

- 1995: CF, SC, FrX, DMD
- Current: 21 conditions offered
- New: sequencing based challenges

But: there is an inability to keep up with the growth of the field:
- Develop programs, obtain mutant samples, pilot test each new disease analyte
Survey limitations

- Number of conditions testable
- Heterogeneous mutations
- Complex variations
- Recent discoveries
- Genotype-phenotype interpretations
- Rare diseases
- Rare mutations
- Method variability
Alternative testing

• Sample Exchange Registry for Alternative Assessment:
  – Internet-based
  – CAP facilitated genetic testing
  – To connect laboratories doing low volume genetic tests
  – Minimum of three labs required
  – No cost
Methods based PT?

- CLIA guidelines for regulated analytes:
  - Participate in organized/informal PT
  - For every analyte tested in the lab
  - NOT for every method in the lab
- No longer realistic for all testing
- Cytogenetics has methods-based testing
- Molecular pathology:
  - SEC survey
  - Next generation sequencing PT?
How is methods-based PT used?

- For rare disorders
- Identify the sequence change
- Heterozygosity versus homozygosity
- Correctly name the nucleotide change
- Correctly name the predicted protein change
- Interpret:
  - Likely benign
  - Likely pathogenic
  - Variant of uncertain significance
- Pros and cons
Other PT: CF newborn testing (example)

- CDC’s Newborn Screening Quality Assurance Program (NSQAP)
- Targets DNA testing for multiple CFTR mutations
- Participation is voluntary and free
- Five dried blood spots from adult CF patients per quarter
QC material resources

- DNA or cell line controls (Coriell Cell Repository)
- Genetic Testing QC Materials Program (GTQC)
- DSMZ (German Resource Center for Biological Material)
- American Type Culture Collection (ATCC)
- Previously tested laboratory samples:
  - Blinded sample exchange between laboratories
  - Blinded sample testing within a laboratory
TRUE OR FALSE?

ALL MUTATIONS TO BE TESTED MUST BE RUN AS CONTROLS IN EVERY ASSAY RUN
FALSE – Running controls

• Rotating controls is acceptable practice
• Limitations of genomic controls for multiplex / complex / microarray assay testing

• Testing a genomic control for each mutation on a spot is difficult (stock) and cost-prohibitive

• Rotating controls is acceptable

• Ideally each new lot is tested with all controls
Synthetic controls

- An alternative to genomic, with limitations
- Advantage: all controls can be run every time
- Example: CF carrier screening panels
- Genomic DNA-like control: Plasmid in a synthetic blood-like matrix
- Synthetic oligonucleotides
Performance review

- External quality assessment and performance trending:
- Biochemical and Molecular Genetics Resource Committee
- ACMG QA / Laboratory Practice Committee
- European Molecular Genetics Quality Network (EMQN)
Performance review

• Performance assessment in an inter-laboratory exchange:
  • Discrepancies to be repeated in both labs
  • Continued discrepancies can be resolved by independent laboratories
  • Essential to compare methods used:
    – Sensitivity?
    – Primers used?
    – Method claims?
    – Mutation panel?
Summary

• Laboratory regulation in the U.S.
• Total quality management
• Proficiency testing components
• Proficiency testing surveys
• Quality control materials and use
• Performance review