Mass Spectrometry in the Clinical Laboratory

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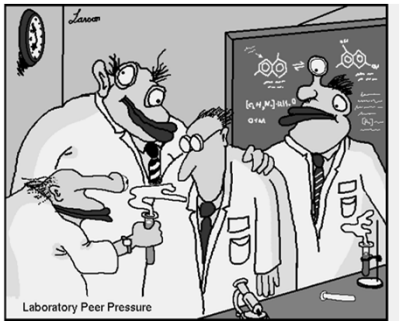
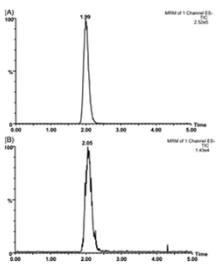
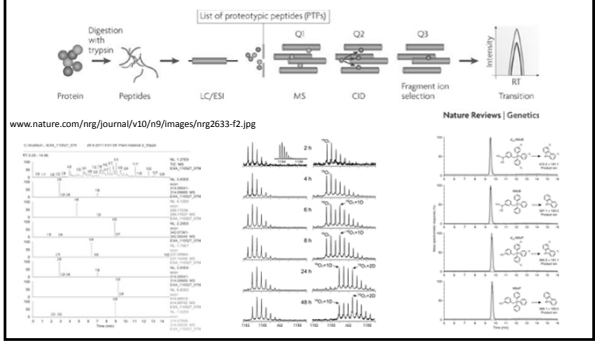
What's so great about Mass Spec?



Analytical Sensitivity



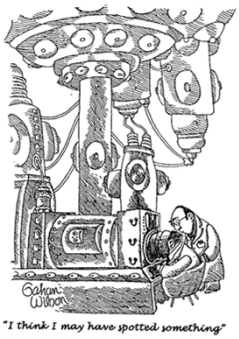
Analytical Specificity (Selectivity)



www.nature.com/nrg/journal/v10/n9/images/nrg2633-f2.jpg

Cost and Flexibility

What's the downside?



"I think I may have spotted something"

Throughput and Automation

Typical Systems

- LC-MS/MS system
  - Throughput of 10-20 specimens/hour
  - Not “one size fits all” for analytes
  - Samples preparation performed in batches
- Automated Clinical Chemistry Analyzer (Tox)
  - Throughput of 50-100 tests/hour (theoretical up to 600)
  - Multiple methods are available linked to test order
  - Random access testing – no batches needed
  - Parallel analysis

Lab Developed Tests

- FDA has determined that LDTs must be regulated at some level
- 2-day public hearing in 2010 for comment
- Risk-based review of LDTs
- Guidance has not been released yet

What does the FDA have to do with this?

What does the FDA have to do with this?

Enforcement Discretion

FDA Concerns

- Increasing number of LDTs
- Lack of clinician/pathologist/patient relationship
- Used as 'market entry' for newly developed tests
- Higher risk applications; less clinical validity

Concerns from Lab Industry

- Uneven playing field for IVD
- FDA review is slow
- Limit uptake of testing by 'local' labs
- Quality of tests

Concerns from Clinical Labs

- Limits availability of tests for patient care
- Limited resources to deal with FDA process
  - Most LDTs could be classified as high-risk
- Inconsistent evaluation of analytical and clinical validity
- Minimized role of laboratory director
  - Clinician-FDA-patient alternative

Proposed Guidance for LDTs

- CAP: joint system combining lab accreditation and regulatory review (risk-based)

Classification	Determining Factors	Oversight
Low Risk: the consequence of an incorrect result or incorrect interpretation is unlikely to lead to serious morbidity/mortality.	The test result is typically used in conjunction with other clinical findings to establish or confirm diagnosis. No claim that the test result alone determines prognosis or direction of therapy.	The laboratory internally performs analytical validation and determines adequacy of clinical validation prior to offering for clinical testing. The accreditor during the normally scheduled inspections will verify that the laboratory performed appropriate validation studies.
Moderate Risk: the consequence of an incorrect result or incorrect interpretation may lead to serious morbidity/mortality AND the test methodology is well understood and independently verifiable.	The test result is often used for predicting disease progression or identifying whether a patient is eligible for a specific therapy. The laboratory may make claims about clinical accuracy.	The laboratory must submit validation studies to the CMS-deemed accreditor for review and the accreditor must make a determination that there is adequate evidence of analytical and clinical validity before the laboratory may offer the test clinically.
High Risk: the consequence of an incorrect result or incorrect interpretation could lead to serious morbidity/mortality AND the test methodology is not well understood or is not independently verifiable.	The test is used to predict risk of, progression of, or patient eligibility for a specific therapy to treat a disease associated with significant morbidity or mortality, AND; The test methodology uses proprietary algorithms or computations such that the test result cannot be tied to the methods used or inter-laboratory comparisons cannot be performed.	The laboratory must submit test to FDA for review prior to offering the test clinically. CMS and accreditor determine compliance.

Proposed Guidance for LDTs

- CAP: lab accreditation + regulatory review
- FDA: framework to encompass ALL LDTs and close regulatory gap
  - Some exemptions for 'rare disease' tests

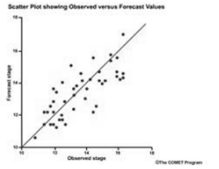
Proposed Guidance for LDTs

- CAP: lab accreditation + regulatory review
- FDA: regulate ALL tests; provide exemptions for rare diseases
- Burgess Legislation: introduced this year; removes FDA from the LDT loop

Burgess Legislation

- Oversight of LDTs by HHS rather than FDA
- Creates LDT test registry
- Data on analytical and clinical validity must be submitted for new LDT
- Lab must investigate adverse events linked to LDT results
- HHS can use accreditation organizations
- New program supported by fees assessed to labs performing LDTs

Harmonization of Methods

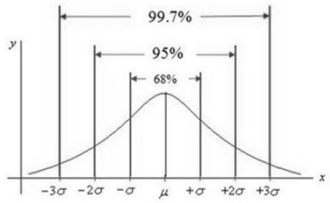


NIST

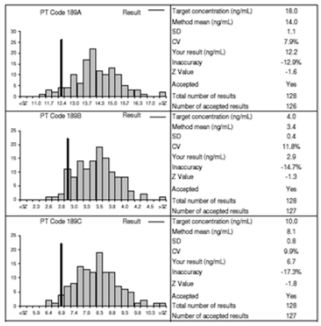
CAP Acceptability Criteria for TDM

Analyte	Target Value	Evaluation Criteria
Acetaminophen	Peer Group	± 3 SD or 10% (whichever is greater)
Amikacin	Peer Group	± 3 SD or 10% (whichever is greater)
Caffeine	Peer Group	± 3 SD or 10% (whichever is greater)
Carbamazepine	Peer Group	± 25%
Carbamazepine, free	Peer Group	± 3 SD or 10% (whichever is greater)
Digoxin	Peer Group	± 20% or ± 0.2 ng/mL (whichever is greater)
Digoxin, Free	Peer Group	± 3 SD or 10% (whichever is greater)
Disopyramide	Peer Group	± 3 SD or 10% (whichever is greater)
Ethosuximide	Peer Group	± 20%
Gentamicin	Peer Group	± 25%
Lidocaine	Peer Group	± 3 SD or 10% (whichever is greater)
Lithium	Peer Group	± 20% or ± 0.3 mmol/L (whichever is greater)
Methotrexate	Peer Group	± 3 SD or 10% (whichever is greater)
N-acetylprocainamide	Peer Group	± 25%
Phenoberbitol	Peer Group	± 20%
Phenytoin	Peer Group	± 25%
Phenytoin, free	Peer Group	± 3 SD or 10% (whichever is greater)
Primidone	Peer Group	± 25%
Procainamide	Peer Group	± 25%
Quinidine	Peer Group	± 25%
Salicylate	Peer Group	± 3 SD or 10% (whichever is greater)
Theophylline	Peer Group	± 25%
Tobramycin	Peer Group	± 25%
Valproic Acid	Peer Group	± 25%
Valproic Acid, free	Peer Group	± 3 SD or 10% (whichever is greater)
Vancomycin	Peer Group	± 3 SD or 10% (whichever is greater)

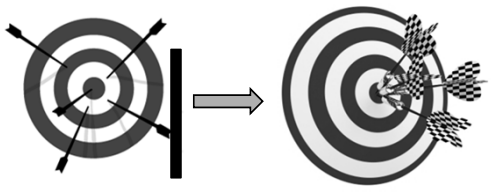
3 Standard Deviations



Immunosuppressant Proficiency Testing



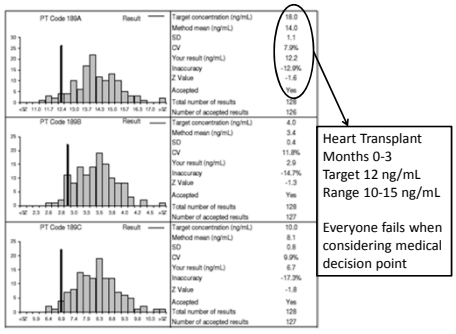
Medical Decisions



Medical Decisions

- Tacrolimus
  - Therapeutic target published at 5-15 ng/mL (sometimes even 20)
  - Peer mean is not always 'truth'
  - Actual targets are narrower and dependent on time relative to transplantation

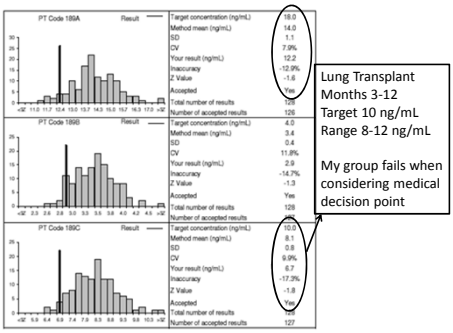
Immunosuppressant Proficiency Testing



Heart Transplant
Months 0-3
Target 12 ng/mL
Range 10-15 ng/mL

Everyone fails when considering medical decision point

Immunosuppressant Proficiency Testing



Lung Transplant
Months 3-12
Target 10 ng/mL
Range 8-12 ng/mL

My group fails when considering medical decision point

How are these challenges being met?

Vendors

Guidance Documents

- Food and Drug Administration (FDA)
  - Guidance for Industry – Bioanalytical Method Validation
- Clinical Laboratory Standards Institute (CLSI)
  - C50, C57 (in development), C60 (in development)
- Scientific Working Group for Forensic Toxicology (SWGTOX)
  - http://www.swgtox.org/documents/Validation_public_comment.pdf
- European Medicines Agency (EMA)
  - Guideline on Bioanalytical Method Validation

QUESTIONS??

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What's in store for the next day or so?

- Discussion of CLSI C60 guideline in development
- Interactive session on LC-MS troubleshooting
- Discussion of tools available for method development and testing
- Updates on existing LC-MS applications
- Discussion of emerging applications for LC-MS