Committee on Policy Issues in the Clinical Development and Use of Biomarkers for Molecularly Targeted Therapies

Panel Three: Evolving Regulatory Environment

Curtis A. Hanson, M.D.
Professor of Laboratory Medicine and Pathology
Department of Laboratory Medicine and Pathology (DLMP)
Mayo Clinic
and
Chief Medical Officer
Mayo Medical Laboratories (MML)

April 1, 2015
Our Principles

• The needs of the patient are always at the center of our practice with a deep commitment to patient safety

• Use modern principles to provide the highest quality laboratory results

• Only offering testing to our physician colleagues and patient care givers that is clinically validated

• Ensure that all patients have access to the highest quality laboratory testing
Background: Mayo DLMP and MML

- Over 3200 employees in the DLMP in Rochester, MN
- ~160 faculty – pathologists, scientists, and other physicians
- Support Mayo Clinic - a large and complex tertiary care practice in Rochester, MN
- Mayo has community-based hospitals/clinics - but doing very complex medical care - in Florida and Arizona
- We have over 65 clinics and hospitals in rural MN, IA, and WI
Background: Mayo DLMP and MML

- Mayo Medical Laboratories (MML) – third largest diagnostic laboratory in the country
- Serve over 4000 hospitals and clinics around the world
- A test menu of over 3500 tests
- ~1600 LDTs
- At the forefront of innovating and bringing scientific discoveries to patient care
- We bring a very unique perspective to this discussion!
A system for defining, documenting and implementing standardized processes and documentation. The system was developed through careful evaluation and consideration of CLIA, CAP and NYS requirements, along with study of medical device design requirements in anticipation of increased oversight from FDA. (began in 2010)
• Why are the current regulatory standards effective or ineffective for oversight of tests (including single biomarker tests and NGS tests) for molecularly targeted therapies from your perspective?
Current standards are ineffective for oversight

- It is too easy to get a CLIA-only certificate; CAP accreditation is not required
- Incomplete standards for LDTs – especially if accreditation is outside of CAP
- Niche laboratories that are not associated with a clinical practice cannot demonstrate the same level of clinical competence or validation
- Variation amongst labs on understanding the requirements on how to do test development
- Even CAP criteria varies between specialties – molecular and genetics is more advanced
Current standards are ineffective for oversight (con’t.)

• Adverse event reporting is inconsistent
• Quality systems vary between institutions
• No consistent standard for the design validation stage for LDTs
• May end up with inappropriate controls for validation studies – using “normals” that are not based on the intended use
• Variable understanding of positive and negative predictive values when establishing a LDT and how results should be reported
So are all labs a problem? NO!!!

- Mayo Clinic reports and collects all sentinel events related to patient safety and adverse, unexpected outcomes.
  - Submitted by patients, employees, or physicians
  - Evaluated by an institutional sentinel event office
  - We use this same process with our MML clients.
- Over the last 6 years:
  - 2.5 million LDTs for Mayo Clinic patients
  - 0 sentinel events related to the design or validation of LDTs
  - 19 million LDTs for MML clients
  - 0 sentinel events related to the design or validation of LDTs
- Mayo and our experience is not unique!
• If ineffective, what changes do you propose?
What changes could happen?

- Structural/Over-arching
  - FDA guidances implemented – with or without changes
  - FDA guidances are withdrawn – and we continue down our current path with CLIA
    - Not a solution
  - New statutory approach that covers diagnostic laboratories
FDA Guidances

• The intent of the guidances is admirable and they identify problems that need to be fixed.

• However, the unintended consequences of the guidances – as currently written – will have a significant and deleterious impact on the practice of medicine and on our ability to provide patient care.

• Remember: estimated ~100,000 LDTs in US
FDA Guidances

- Labs/LDTs are different than manufacturers/IVDs – you cannot regulate them the same way without a negative impact.

- Allow reference and academic laboratories to offer LDTs outside of their own facility.

- Recognize and accept that the regulatory system cannot separate the laboratory performing the test from the test being performed.

- Replace definition for Rare Disease, Unmet Needs, and Traditional LDTs and eliminate the requirement to stop testing once a FDA-approved test becomes available.

- Replace the proposed LDT risk classification system with a risk classification system that contains more granular and specific criteria.

- Do not require notification or submission for an LDT if it is a modified FDA cleared/approved test and the modification does not have a clinically significant impact.
• How would such changes affect relevant stakeholders?
Impact on Stakeholders

- Impact academics, pathologists & laboratories, clinicians, and patients
  - Slow innovation. Submission requirements are substantial. Also, if you have to stop offering an LDT when an alternative is on the market, then limited incentives to bring discovery to the bedside.
  - FDA-approved kits are frequently not better – especially when there are few in the market.
    - Tacrolimus, ALK, BRAF, KRAS
  - Financial costs are not trivial; submission costs and additional internal administrative costs will limit the number of LDTs that can get done
  - Access for patients – You can send “Mrs. Johnson” to the hospital across town, but you can’t send her tube of blood???
  - If LDTs can only be used in a local practice, will we be required to repeat those LDTs done on the outside when a patient comes to us?
  - Submissions for FDA kit modifications will inhibit bringing new discovery to fruition as modifications can:
    - Improve process; Add different specimen types; Offer across tumor types; etc.
Companion Diagnostics – What can we learn?

• Concept is appealing, but it is not new

• We have had companion diagnostics for decades
  • Antimicrobials, immunosuppressives, drug monitoring, BCR-ABL, PML-RARA, PDGFR α /β, KIT 816V, 5q-, p53, etc.

• Learning points:
  • Inability to bring new findings quickly to patients
  • Specimen type limitations, e.g., FNAs not included
  • Procedural snafus – e.g., use of xylene; manual vs. automated; storage temps; etc.
  • Not always better assay
  • Multiple drugs, targets, kits, etc.: Payer confusion or hesitation
  • ALK FISH – Validation studies could be considered minimal
    • Kit: 15% failure rate; Mayo LDT: 2% failure rate
Many pathologists argue that the CLIA/CMS oversight of LDTs is sufficient. What additional regulatory standards could be implemented (and by which agency) to address the concerns of lack of evidence for clinical validity and clinical utility, as well as adverse event reporting?
CLIA/CMS

• CLIA is insufficient
• Regardless of jurisdictional issues, CLIA needs to be updated
• Needs to include molecular, genetics, etc. certifications
• Should issue a separate Certificate of Accreditation for those labs doing LDTs with the expectation of obtaining CAP or other higher standards
• What specific recommendations would you like to see the committee make in our report?
Recommendations

• Develop principles that are key to your organization and stakeholders: e.g., clinical validation, patients safety, high quality testing, and patient access to all.

• Acknowledge that there is a problem, but insist that the solution cannot be worse than the current problem

• Acknowledge that the FDA should be part of the solution

• Insist that we draw careful but solid lines of jurisdiction between test development (FDA), laboratory operations (CLIA), and practice of medicine (States). Overlapping jurisdictional responsibilities cannot occur.

• Demand a thoughtful yet precise definition of an LDT and insist that LDTs cannot be simply lumped into the rest of the IVDs and regulated as such – there is a difference!

• Provide input into precisely defining the risk classification process as this will impact how we practice medicine. Vague classifications benefit nobody.

• Insist on as much clarity as possible up front to allow clinical laboratories the time to plan, the financial realities, etc.
Thank you!
Risk Classification – FDA Guidance

“In determining the risk an LDT poses to the patient and/or the user, FDA will consider several factors including whether the device is intended for use in high risk disease/conditions or patient populations, whether the device is used for screening or diagnosis, the nature of the clinical decision that will be made based on the test result, whether a physician/pathologist would have other information about the patient to assist in making a clinical decision (in addition to the LDT result), alternative diagnostic and treatment options available to the patient, the potential consequences/impact of erroneous results, number and type of adverse events associated with the device, etc. To provide additional clarity, FDA intends to issue draft guidance to describe what the Agency considers generally to be Class I, II or III within 18 months of finalization of this guidance.”