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IOM Workshop:

Refining Processes for the Co-Development of Genome-Based Therapeutics and Companion Diagnostic Tests

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Response to Solutions Proposed

- ***Solutions Proposed:***
  - Include test cost in drug price
  - CAP: Define relevant analyte for drug efficacy rather than specific test
  - ASCO: Need regulatory certainty regarding FDA oversight of LDT CoDx's
  - ACLA: Strengthen CLIA for LDT oversight (HR 3207)
  - AdvaMed: Ensure risk-based approach be applied to LDT+IVD
- Would these proposed solutions address the problems identified?
- Are there other solutions to propose?
- What steps could be taken to implement solutions that would be effective?

IVD as Companion Diagnostic: Key High-Level Assumptions

- **Singular critical aim is to accurately identify those patients who can most benefit from therapy**
- Limit either false positive or false negative (depending on whether positive or negative selection biomarker)
- IVD Test robustness is critical
- Test must be available in all markets the therapy is to be commercialized
- Tests are not viewed as a means of restricting access to therapeutics
- Efficient testing of multiple biomarkers (BMs) early is desired

Patient Eligibility by Analyte Only

- All tests for a biomarker may not be equal, so:
  - If no IVD, rigorous analytical concordance equivalent to appropriate elements of PMA validation would be required
  - If no IVD, commutable standards to validate biomarker measurements in individual labs are an ***absolute*** requirement
  - IVD or not, ongoing *challenging* Proficiency Testing (PT)/ External Quality Assurance (EQA) programs critical to ensure standards are maintained (even for approved IVDs)
    - Test ability to discriminate at clinical decision point (cut-off)
- Biological plausibility for biomarker *AND* the cut-off essential to address multiple therapies using same BM
  - Cross-referencing of multiple IVDs may be enabled

Analyte-only approach supported if rigorous concordance is established with IVD that has associated clinical utility

Test-Specific Considerations

- Binary test results, *e.g.,* somatic mutation tests:
  - Data suggests that greater sensitivity is better, as biology is likely Yes/No, but the assay has a cut-off (defined sensitivity)
  - Variation in a lab's ability to identify mutations, due to different levels of sensitivity, will pose risk to patients
- Continuous variable test results, *e.g.,* mRNA, FISH, etc:
  - Variability can occur in at least two variables:
    1. % of cells expressing BM
    2. particular level of BM expression (+ a third, tumor heterogeneity?)
  - Distribution of complex assays across labs often not undertaken
  - Biological plausibility is key to supporting cut-off established from clinical trial outcome data (studies need to be undertaken)

Even binary tests unlikely to always identify the same patients, continuous variable tests often face additional issues

Test Reimbursement with Drug

- In principle this is not a barrier – but will it stop LDT offerings/development once a companion diagnostic test is approved?
- Lower barrier when sample testing is conducted by a single or limited number of labs
- Lower barrier if limited patient population served
- Significant barrier when testing is distributed across multiple labs and a large population served
- Solution needs to account for reimbursement logistics associated with distributed testing and whether lab-associated costs over and above test costs, present another barrier to LDT-PMA transition

Summary: Key Responses to Solutions

- Singular aim is accurate identification of patients' eligibility for a specific therapy
- FDA approval of an IVD provides the desired level of confidence in the specific assay – this must be achieved independent of the proposed solution
- It is essential that robust and challenging EQA is established for approved IVDs (and LDTs)
- Smaller patient populations may be addressed with LDTs characterized in a single (or few) lab(s) with appropriate risk-based approach (PMA equivalent)

Suggested Solutions

- Educate physicians and patients of need to understand the quality/status of patient selection test offered
- Investigate utility of earlier testing of multiple biomarkers (from both sample conservation and payer perspective)
- Ensure risk-based approach employed such that LDT testing meets same standards as IVD at highest risk (plus consider patient population size)
- Implement more robust EQA programs for consistent patient selection (+ transparency of labs EQA results)

Key: Accurate determination of patient eligibility