Importance of Methodology Certification and Accreditations to Perform Assays

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Disclosures

No disclosures relevant to this presentation
A bad predictive marker for a drug is as bad as a bad drug.
Molecular Pathology Assay Issues

• Discordant results in same tumor:
  Intra-tumoral heterogeneity (biology, methodologies)

• Discordant sequencing results with same starting material (methodologies, informatics of alignment and variants)

• Post-analytic decision support (databases for actionability, algorithms)

• Level of risk for patients
Parties Interested in the Issues

- Clinical laboratorians
- Clinicians
- Professional organizations
- Patients
- Payers
- Regulatory agencies
Molecular Pathology Assay Issues

• Criteria for evaluating assays (Centers for Disease Control and Prevention’s Office of Public Health Genomics):
  – Analytic validity: Lab parameters
  – Clinical validity: Health condition
  – Clinical utility: Patient management
  – Ethical, legal, and social implications
Molecular Pathology Assay Issues

• Components for consideration in regulations, certifications and accreditation:
  – Pre-analytics
  – Analytics
  – Post-analytics
Molecular Pathology Assay Issues

- Pre-analytics: Specimen collection and processing
  - Fit-for-purpose tissue type
  - Timing and type of specimen
  - Caveats
  - "Liquid biopsies"
Molecular Pathology Assay Issues

• Pre-analytics: Fit-for-purpose, clinical question(s) to be answered:
  – Risk analysis
  – Screening
  – Surveillance
  – Diagnosis
  – Classification
  – Prognosis
  – Prediction
  – Monitoring
Molecular Pathology Assay Issues

- Pre-analytics: Fit-for-purpose
- Most commonly advanced disease
  - Progression
  - Selective effects of therapy
  - Tumor microenvironment
- Recommendation: Proximate tumor that threatens the patient
• Pre-analytics: Specimens
  – Primary tumor or metastasis
  – Sampling and heterogeneity
    • Intra-tumoral
    • Inter-tumoral, intra-patient
  – Amount of material for analysis
  – Tumor enrichment
  – “Liquid biopsies”
Fine Needle Aspiration and Core Needle Biopsy Specimens

- FNA smear
- FNA cell block
- Core Biopsy
20% tumor (don’t use)

90+% tumor

8000 tumor cells, tumor fraction >60%

90+% tumor

1000 cells

1000 cells
Molecular Pathology Assay Issues

• Pre-analytics: Caveats
  – Relatively little attention so far
  – Quality of analytes: DNA, RNAs, proteins
  – Effects vary with sensitivity
    • Mutations
    • Copy number variations (ratios)
    • Re-arrangements
Molecular Pathology Assay Issues

• Pre-analytics: “Liquid biopsies”
  – Phlebotomy or body fluid instead of tumor tissue acquisition
  – Analytes
    • Circulating tumor cells
    • Cell-free DNA (cfDNA) and microRNA
    • Exosomes
    • Vesicles
  – Theoretical advantage of addressing heterogeneity
  – At least 27 companies
Molecular Pathology Assay Issues

• Analytics
  – Focus area for most of the interested parties
  – Methodologies have different advantages and disadvantages.
  • Content actionability
  • Number of genes covered
  • Formalin-fixed, paraffin-embedded tissue: Quality of analytes
  • Quantity of analytes (FNA, liquid biopsy)
  • Turnaround time (batch size)
Molecular Pathology Assay Issues

• Analytics
  – Single genes and alterations or panels
  – Definition of actionable: “Able to be done or acted upon; having practical value”.
  – Standards, quality control materials, and proficiency testing
  – Assays beyond nucleic acid sequencing: Transcriptomics, proteomics
  – Reimbursement issues
Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

This document provides the anticipated details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) that FDA intends to issue in 60 days, and is being provided to Congress pursuant to section 1143 of the Food and Drug Administration Safety and Innovation Act of 2012.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Biologics Evaluation and Research
Molecular Pathology Assay Issues

• Post-analytics
  – Variants of unknown significance
  – Germline findings
  – Co-alterations and pathway analyses
  – Alignment and variant-calling software
  – Report understandability by physicians and by patients (required by CLIA)

• FDA Regulatory-grade Database initiative:
  • Curation of actionability, treatment, trials
Examples of Interested Parties

• For regulations with enforcement powers:
Regulatory agencies:
- FDA
- Center for Medicare and Medicaid Services (CMS) for federal Clinical Laboratory Improvement Amendments (CLIA)
- College of American Pathologists (CAP) for CLIA
- New York State Board of Health
Examples of Interested Parties

• For guidelines with recommendations (format of Institute of Medicine of the National Academy of Sciences of the USA):

Professional organizations:
- College of American Pathologists (CAP)
- American College of Genetics and Genomics
- American Society of Clinical Oncologists (ASCO)
Examples of Interested Parties

Professional organizations (continued):

- Association of Molecular Pathologists (AMP)
- Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG) of Center for Disease Control and Prevention’s Office of Public Health Genomics
- Et cetera
Examples of Interested Parties

Professional organizations (continued):

- Partnerships:
  - CAP, IASLC, AMP for lung cancer biomarker guidelines
  - CAP, ASCO, AMP, American Society of Clinical Pathologists/ASCP for colorectal cancer biomarkers
  - ASCO, CAP for HER2 in breast cancer
Examples of Interested Parties

• Payers power of the purse:
  - Blue Cross Blue Shield Association
  - Palmetto Molecular Diagnostics Services (MolDX) Program

• Patient advocates: Green Park Collaborative

• Vendors: Actionable Genome Consortium
Examples of Interested Parties

• Others:
  - MED-C (academic institutions, payers, commercial laboratories, vendors, medical data analysis companies, etc.)
  - National Institute of Standards and Technology Genome in a Bottle Consortium with academic institution
  - National Comprehensive Cancer Network (NCCN)
• Et cetera
Summary

• Numerous organizations are addressing improvements in the quality of molecular testing: No shortage of efforts, but parallelism and lack of coordination.

• Those organizations with regulatory authority (CMS, FDA) have the most impact on the use of molecular testing for patient care and clinical trials.

• Methodologies are evolving rapidly, making efforts rapidly obsolete.
Summary

• Communication among clinicians and molecular diagnostics labs is essential to meeting the needs for high-quality patient care and clinical research.

• The impact of regulations and requirements for accreditation and certification are especially great in international clinical trials due to the differing requirements in different countries.