Genetic Testing

IVD Roundtable
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Genetic Tests – 510(k) or PMA

- Tests for
  - Genotyping for
    - Carrier screening (e.g., CFTR, etc.)
    - Aid in diagnosis (e.g., FVL/FII/MTHFR, CFTR, etc.)
  - Likelihood of adverse event/appropriate dosing (e.g., 2C9, VKORC1, etc.)
  - Identification of one or more markers for
    - Disease risk, prognosis, response to therapy
    - Therapeutic decisions
  - Identification of chromosomal variation linked to developmental syndromes (e.g., developmental delay, mental retardation, etc.)
  - Infectious diseases
- Genetic signatures for prognosis/prediction
  - Common complex diseases
  - Subclassification of disease
  - Therapeutic decisions

Topics

- Performance Information
  - Preanalytical/Analytical Validation
  - Clinical Validation
  - Recurring issues

- Cytogenetic arrays
- RUO/Reagents/Instruments
- Personalized Medicine

Validation of Genetic Tests:

- Well-known association between gene(s) and disease
- Allele status:
  - wild type = benign
  - mutations correlated with specific disease or carrier status
- For each claimed allele:
  - Peer-reviewed articles
  - Genotype and phenotype
- Analytical validation such as accuracy and reproducibility evaluated for every claimed allele/result
- Expect nearly 100% correct results across multiple operators
- Multiple clinical samples per allele
- Test provides results, limited interpretation required

Preanalytical

- Nucleic acid isolation:
  - 3 commonly used methods
  - Multiple samples
  - Generally method(s) are not mentioned or recommended in package insert/labeling
    - If listed or recommended in labeling – <u>must</u> be
      - cGMP
      - Registered & Listed (21 CFR 862.2310 Clinical Sample concentrator (Class I, Exempt, JJH Product Code)
      - Labeled appropriately (21 CFR 809.10)
- Bio-specimen stability:
  - Stability of the marker/target in the patient specimen (e.g., peripheral blood, excised tumor, etc.)
  - Include ship-stress studies.

Analytical Performance

- Precision / Reproducibility
  - 3 sites
  - Adequate coverage of all genotypes/tumor types
  - Use clinical samples
  - Include pre-analytical steps (e.g., extraction/purification)
- Accuracy
  - Real clinical samples
  - Cover all possible genotypes, subtypes/classes
  - Compare genotyping to Bi-directional sequencing
  - Expression tests compare to clinical diagnosis
- Limit(s) of Detection
  - Serial dilutions (highest to lowest conc. of input specimen)
  - Lowest concentration of target in normal background (cancers)
- Potential Interferences
  - Co-administered drugs
  - Pre-analytical test components (e.g., extraction buffer)
  - Common endogenous and exogenous substances – differ with specimen

Challenges for Clinical Validation

- Specimen availability
- Clinical study design and data don't support intended use,
- Clinical studies to validate molecular diagnostic test often have unique statistical challenges
- Pre-specified clinical/statistical analysis plan is crucial
- Expression Patterns, Proteomic patterns, or Genetic Algorithms should be pre-specified, developed in one data set, "locked," and confirmed in an independent data set (training set and validation set, respectively)
- Sensitivity of assay vs. comparator method
- Appropriate determination of clinical cut-offs

The pivotal validation study must investigate test use in the claimed clinical population in intended setting using the final test configuration!

Array-based Cytogenetic Assays:

- Used to detect chromosomal abnormalities [copy number changes (CNV) (gains/losses)] in the DNA of a patient
- Aid to diagnose genetic cause of mental retardation, developmental delay, and multiple congenital abnormalities
- Survey of the whole genome at a higher resolution than “conventional cytogenetics”
- Unlimited results, open to interpretation

Regulatory development for cytogenetic arrays

- Don't fit easily into current regulatory paradigm
- Rapid move from research to clinical use and rapid changes in technology
- Clinical significance of results not well understood
- Different considerations given to type of CNV, size of CNV, location and gene content, etc.
- Variable phenotypes
- CNVs (both inherited and de novo) are detected in the healthy population
- Difficult to determine clinical truth
- Impossible to demonstrate analytical reliability of all possible outputs
- Cannot expect clinical samples that span the whole genome for studies
- Accuracy –reference method?
- Difficult to capture all sources of variation
- Unknown significance of results, complexity of devices
- Lack of established controls

Reagent Considerations

- Be sure that reagents for use with your platform are for IVD use (not labeled RUO)
- General Purpose Reagents (GPRs - 21 CFR 864.4010) – meant to be reagents that do not require instructions for use, except storage, mixing, etc. (e.g., Tris buffer, MgCl, etc.) Note: collection kits and extraction kits are not GPRs
- Nucleic Acid Extraction kits:
  - Validated with the assay(s)
  - Should be listed under 21 CFR 862.2310 [Clinical Sample concentrator (Class I, exempt, GMPs required)]
- Nucleic acid sample collection kits:

  Are regulated by type-
  - With preservation/stabilization functions under 21 CFR 862.1675 [Blood specimen collection device (Class II)]
  - Passive collection under 21 CFR 864.3250 [Specimen transport and storage container (Class I, exempt)]

RUO-labeled materials create challenges for clearance/approval

Instrument Considerations

- Be sure that instruments for use with your test are for IVD use (not labeled RUO)
- General Purpose Equipment (21 CFR 862.2050)
  - Meant to be basic equipment (e.g., balances, pipettes, pipette tips, etc.) <u>but not instruments</u>
  - Users with general laboratory training can operate
  - Do not contain interpretive software
- Instruments have separate regulations by type
  - Many/most platforms for genetic testing may be classified under 21 CFR 862.2570 [Instrumentation for clinical multiplex test systems (Class II)]
    - Real-time nucleic acid amplification system, Product code: OOI)
  - Software validation and documentation based on Level of Concern not classification of instrument (Instruments used with IVDs are typically a Moderate Level of Concern)
- Instruments with dual functionality:
  - Incorporate FDA cleared/approved functionalities and allow users to define test parameters for use with non-FDA cleared/approved tests
  - New software and labeling policy requirements (e.g., protecting IVD software features, labeling requirements, etc.)

RUO-labeled instruments create challenges for clearance/approval

Continuing Challenges

- Genetic tests:
  - Samples of rare alleles difficult to find
  - Tests that evaluate a panel of alleles using complex algorithms often require complex validation
  - Comparator method:
    - Bi-directional sequencing – standard for most genetic assays but can be difficult for somatic mutations, deletions, translocations
    - Appropriate comparator – when the proposed assay and its technology is analytically more sensitive than the comparator (e.g., qRT-PCR vs. bi-directional sequencing or karyotyping)
  - Incorporation of RUO reagents and instruments
  - Modification of assay midstream
- Genomic/Proteomic tests:
  - Analytical variability is an issue (Sometimes pre-analytical)
  - No analytical gold standard for comparison
  - QC and standards may not exist

Most frequent issues…

- Lack of samples covering all genotypes
- Lack of literature to support validity
  - One or two references may not be sufficient
  - Genotype and Phenotype not indicated
- Pre-analytical issues
  - Extraction
  - Interference
  - Lack of specimens from start to end (e.g., whole blood → assay result)
- Continued reliance on contrived specimens (cell line and/or plasmid) even for common/very common mutations/polymorphisms
- Sample matrix issues
- Lack of clinical specimens for assay validation

What is the utility for rare mutations or polymorphisms considering their low frequency in the population and the sparse literature available?

Recent clearances (’09-’10)

- k093737 HemosIL FII & FV DNA Controls for use with Xpert™ HemosIL FII & FV genotyping assay
- k081754 Vermillion Ova1 Test
- k083845 Luminex X-Tag CF60 kit v2
- k083846 Luminex X-Tag CF39 kit v2
- k093128 Illumina BeadXPress instrument (for use with k093129)
- k093129 Illumina Veracode Genotyping test for FV and FII
- k093974 Osmetech eSensor FII-FV-MTHFR Genotyping test
- k082118 Cepheid Xpert Hemosil Factor II & Factor V assay
- k092967 Pathwork Dx Tumor of Origin – FFPE
- k101879 Cepheid Xpert MRSA/SA Blood culture assay
- k091409 Roche Molecular LightCycler (2.0) MRSA Advanced test
- k093346 BD Diag. BD Geneohm MRSA ACP assay
- k093383 bioMérieux’s NucliSENS EasyQ System
- k092705 Abbott Molecular m2000sp AND m2000rt (for use with k092704)
- k092704 Abbott Molecular RealTime CT/NG assay

Companion Diagnostics

- A companion diagnostic (CDx) is a biomarker test that is *required* for correct use of a therapeutic (part of drug labeling)
  - In US requires FDA approval
  - Approval of both must occur on the same day
- Biomarker may be “recommended” in the drug labeling
  - To provide extra information
- **But….. if the test doesn’t work, how can you use drug correctly?**

CDx Advantages

- Identify patient populations in which a drug is most effective
- Avoid serious adverse events
- Rescue a failed trial / new drug
- Mechanistically link a treatment to the disease

Companion Diagnostics

- Open discussions with both CDRH and CDER early
  - preIDE submissions allow for informal communication between CDRH and sponsors
    - Feedback on analytical studies for test validation and information required for clinical validation
    - Test-specific challenges can be discussed prior to the start of validation studies
- CDx assays are typically considered high risk/Class III devices requiring submission of a PMA
- Standardize your assay platform as early as possible
  - Hardware and software
  - If you cannot, bridging studies will be needed
    - Retain and bank specimens from Phase 2 and 3 studies (marker positive and negative) for use in any bridging studies that might be necessary
- BEFORE Pivotal Trials (Phase III) begin the assay should be fully verified, including
  - all reagents, instrument, software, assay outputs, algorithm, etc.

CDx Challenges

- CDx Genetic tests:
  - Lack of communication between pharma and device companies
  - Need to appropriately validate assays not always considered prior to beginning studies
  - Use of LDT assays for clinical trial
    - Lack of appropriate validation and/or design controls
    - Not the assay to be marketed (single site or distributed) – requires bridging
    - Discordances between LDT/CTA and test to be marketed
  - Use of existing FDA cleared/approved assays not cleared/approved for trial's intended use/indications for use
  - Marker negative specimens not retained for marker positive studies (or vice versa)
  - Availability of clinical trial specimens for analytical validation
  - Complex statistical issues
  - Timing/coordination between different review Centers

Recent Relevant FDA Meetings

- Array-Based Cytogenetic Tests: Questions on Performance Evaluation, Result Reporting and Interpretation (6/30/10)
- FDA/CDRH Public Meeting: Oversight of Laboratory Developed Tests (LDTs) (7/19-20/10)
- Oncologic Drugs Advisory Committee Meeting - ChemGenex Pharmaceuticals, OMAPRO (omacetaxine mepesuccinate) for Bcr-Abl T315I positive CML (3/22/10)
- Public Meeting: Strengthening the CDRH's 510(k) Review Process (2/18/10)
- Public Meeting: Incorporation of New Science Into Regulatory Decision making Within the CDRH (2/9/10)
- FDA-IDSA Public Workshop: Advancing Clinical Development of Molecular and Other Diagnostic Tests for Respiratory Tract Infections (11/12-13/09)

Questions?

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