The Importance of Biospecimen Quality in FDA Submissions

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Biospecimen Quality Matters

- Test development
  - Discovery
  - Validation
  - Instructions for use
- Test use
  - Adequate collection, preparation (pt, specimen, etc)
  - Correct measurement
  - Correct interpretation

Specimens

- For validation
  - Must be able to show that test works on specimen type (patient) to be used
    - Access to appropriate specimen types, e.g. biopsy
    - Evidence that specimen source (patient) meets intended use population, e.g., age, sex, disease state
    - Specimens handled/stored in controlled manner?
    - Often need treatment history, e.g. prior therapy

Matrices

- For validation
  - Must account for all claimed matrices
    - How uniform is “matrix”?
      - FFPE processing
        - » Fixative
        - » Quality
        - » Duration
    - How long is analyte stable in matrix?
    - What storage conditions are required?
    - Is purification, concentration required?
    - Does matrix interfere with measurement?

Stored Specimens

- Annotated?
  - Demographics, diagnosis, treatment history, etc.
- Match Intended Use population?
  - Geography, age, disease stage, etc?
- Consented?
- Bias?
  - Collection setting, specimen age, size, etc.
- Storage history?
- Does storage reflect future use?

Testing

- Instructions for use
  - List of variables to be controlled
    - Patient preparation and concurrent exposures
  - Procedures needed prior to testing
  - Control materials

Societal Costs

- Failed development
  - Inadequate
    - Specification of Intended Use population
    - Specification of specimen parameters
    - Control materials
    - *Availability of useful specimens*

Patient Costs

- Inconsistent test results
  - No/poor mechanisms to control/manage specimen collection variables
  - Lack of recognition that variables matter
  - Lack of standards (material or method) to trace collection/handling/storage history

FDA Issues

- Test demonstrates performance that supports clinical diagnostic use in intended population (intended use)
- Studies to validate test are controlled—analytically, and for patient safety
  - *Informed consent*, IRB oversight, investigational use
- Test instructions for use actually correspond to reality

Key Elements in In Vitro Diagnostic (IVD) Submissions

- Intended Use (IU)
  What is device supposed to do?

- Indications for Use (IFU)
  When should it be used?

- Both analytical and clinical data are supporting evidence for Intended Use and Indication For Use

Intended Use Statement (how/by whom device is used)

- What is the device measuring, identifying or detecting? (analyte, organism, ..)
- Specimen types, sources (whole blood, serum,..)
- Conditions for use (hospital lab, home use,..)
- What type of data output? (quantitative, qualitative, semi-quantitative)

Indication for Use Statement (for what/on whom device is used)

- Target condition
  - a particular disease, a disease stage, health status, or any other identifiable condition of event within a patient

- Target population (intended use population)
  -those subjects for whom the test is intended to be used

- Medical Testing Contexts
  - as, for screening, diagnosis, monitoring, prognosis and so on.

Examples of IVD Medical Testing Contexts

- **Diagnosis** (target condition is present or not during the time of testing)
- **Screening** (maybe in a general population [asymptomatic subjects at average risk] or a subpopulation [subjects at high risk])
- **Risk assessment** (assessment of predisposition to disease in future)
- **Prognosis** (stratifying already diagnosed cancer patients into poor or good prognosis)
- **Monitoring** (is therapy working for a patient?)
- **Companion Diagnostics/Co-development paradigm** (Therapeutic response prediction)

* This is not a comprehensive list

Intended Use/Indication For Use drives:

- Study design
- Kinds of patients (Asymptomatic,..)
- Clinical sites (e.g. doctor's office, ER, hospital)
- Sample size justification

…..

N subjects in the clinical study
(N subjects from target population)

Every subject

Test under investigation:	Clinical Reference Standard (Gold Standard):
Positive, Negative	D+ = Target condition present, D- =Target condition absent

We considered an ideal scenario when N randomly selected subjects are from the intended use population and each subject has result of the test and verification of disease (D+, D-).

Potential Biases

1) Selection bias (when the study population does not represent the IU population) – spectrum bias
2) Verification bias

Banked (retrospective) samples (potential selection biases)

- How representative are banked samples (inclusion/exclusion criteria)
- Only leftovers from big tumors (sample volumes)?
- Storage does not impact analyte of interest

Provide unbiased estimates of performance

Spectrum Bias

Example

Diseased subjects in the Intended Use population =
50% of Stage II and 50% of Stage I
Test ABC has sensitivity for Stage II = 90%; Stage I = 50%

Sensitivity of test ABC in the IU population =
0.5 * 90%+ 0.5 * 50% = **70%**

Retrospective samples in the clinical study
80% of Stage II and 20% of Stage I:
Sensitivity in the clinical study =0.8 * 90% + 0.2 * 50* = **84%**

Sensitivity is biased (overestimated)

Verification Bias

Example

Clinical study with 100 subjects: each subject has verification of disease and test result

		Gold Standard		Total
		D+	D-	
Test	Pos	20	5	25
	Neg	30	45	75
Total		50	50	100

Se = 40% (20/50)

Sp = 90% (45/50)

Example (cont.)

Subjects were referred to the GS based on the "Current clinical practice".

In the study, all 25 subjects with pos. test results -> GS; only 1/3 of 75 subjects with neg. test results -> GS.

Analysis of the data with verified disease status

		Gold Standard		Total
		D+	D-	
Test	Pos	20	5	25
	Neg	10	15	25
Total		30	20	50

Se = 67% (20/30) Sensitivity is biased (overestimated)

Sp = 75% (15/20) ⇐ Specificity is biased (underestimated)

Verification Bias

occurs when a non-random group of subjects in the clinical study selectively receive clinical reference standard.

Prostate cancer

T_{New} – new biomarker as an aid to make a decision who needs a prostate biopsy

Complex pattern describes how subjects are referred to prostate biopsy (current practice uses age, race, digital rectal exam, PSA, family history...)

How to evaluate T_{New} in unbiased way?
Very challenging problem!

Possibilities

- In an ideal discovery and product development world
  - Well-curated specimen collections with:
    - Complete demographic cross-section
    - Complete handling/storage history from moment of collection
    - Complete patient history and follow-up
    - Matched specimens from same patients
    - Longitudinal specimens
    - Broad informed consent

Biospecimen Benefits

- Better discovery
- Better tests
- Patient benefit
- Good Science

- Address variability and bias

Thank You

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