An Introduction to Pre-IDEs

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The Basics -

- What, why, when, how, where,
- Who

What is a pre-IDE?

- “Pre-submission” process [510(k) and PMA]
- Lets you ask complicated questions in a non-review forum
  - Protocol review
  - Regulatory pathway
- Free, confidential advice on regulatory process and feedback on proposed studies
- Not necessarily a prelude to an IDE
- Non-binding - not an agreement meeting

Why would I need a pre-IDE?

- Allows FDA opportunity to become familiar with new technology or intended uses
- Interactive and flexible process (can send in supplements)
- Especially useful for
  - New Intended Uses
  - Novel devices
  - Companion diagnostics
- May prevent costly delays or errors
- Goal - improve the quality of future submission

When to submit a pre-IDE

- Intended use defined
- Patient population defined
- Ready to discuss protocols regulatory pathway

Types of submissions where pre-IDE recommended:

- Waiver studies (January 2008 guidance)
  Waivers are not 510(k)s
- PMA or deNovo 510(k) anticipated
- Multiplex panels (e.g. genotyping; pathogens)
- Multivariate assays with composite score
- Drug-device companion diagnostics
- Submissions where an IDE may be required

Is this your first submission? Maybe a pre-IDE is useful.

How do I get the process started?

- Submit written request and materials to the Document Mail Center*
- Format of interaction can be:
  - Written comments
  - Meetings:
    - teleconference, videoconference, in-person

* **Where =** U.S. Food and Drug Administration
Center for Devices and Radiological Heath
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

What do I include in my pre-IDE?

- Content depends on the questions you're asking:
  - Clinical ?s = clinical protocol review
  - Analytical ?s = validation protocol review
  - Regulatory ?s = regulatory pathway review
- Specific questions are helpful!
- Cover letter with:
  - Contact information
  - Cover letter briefly describing device, intended use, proposed outcome, predicate if known

Making the most of Pre-IDE discussions – written or meeting[1]

- Know your:
  - Intended use !!!
  - Study population
  - Protocol
  - Plans for pre-clinical testing
  - Statistical analysis Plan
    - Sample size justification
    - Statistical methodology
  - Suggest a regulatory pathway, justify

[1]adapted from Gen Engineering & Biotechnology News March 1, 2009 (J. Gibbs)

Making the most of pre-IDE meetings

- To make the most efficient use of time and resources, submit :
  - A brief statement of the purpose of the meeting
  - Specific questions to be addressed by FDA
  - A preliminary proposed agenda
  - A list of all individuals who will participate from your company
  - A list of FDA personnel who you believe should participate (a medical officer, statisticians, etc.)
  - An information package, the content of which is dependent upon the objectives of the discussion or meeting

What outcome should I expect from the pre-IDE process?

- FDA's most current thinking and advice on your proposal

Advanced Topics

- Intended use
- Training and Validation
- Protocols
    1. Clinical studies
    2. Analytical studies
- Multiplex assays
- IVDMIAs
- Conclusions

Most Common 510(k): “Me, too”

- Use a preIDE when you want to change it up –
  - New intended use population
  - New and different technology

- Intended use population
- Method comparison study - Split sample design
- ***Predicate selection (are we choosing an appropriate predicate wisely?)*** *is there a predicate?*

Recommended readings

- Predicate decision summaries
- CLSI document EP-9 Quantitative
- CLSI document EP-12 Qualitative
- Statistical Guidance for Reporting diagnostic tests (www.fda.gov/cdrh/osb/guidance/1620.html)
- CLSI Guidances for analytical studies
  (e.g. EP5, EP6,EP17)

Intended Use

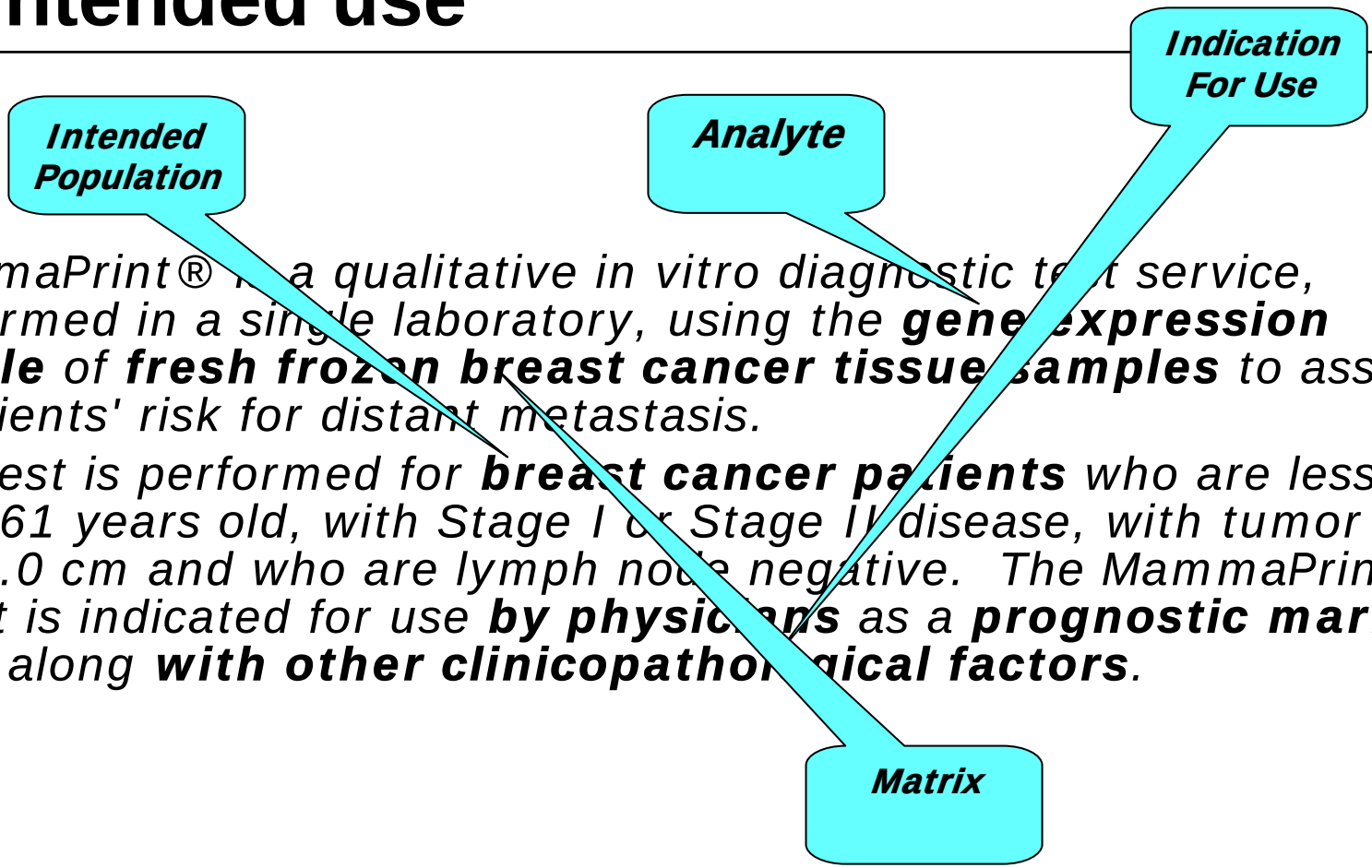
- Who, what, and when
  - Intended population, analyte, clinical usefulness
- Same device can have more than one use
- Study should match intended use.
- Study should be consistent with US practice or if not, justification for why not

- Devices are regulated by their intended use:

  PSA: screening PMA

  PSA: monitoring already diagnosed patients 510(k)

Intended use



MammaPrint® is a qualitative in vitro diagnostic test service, performed in a single laboratory, using the ***gene expression profile*** *of* ***fresh frozen breast cancer tissue samples*** *to assess a patients' risk for distant metastasis.*

The test is performed for ***breast cancer patients*** *who are less than 61 years old, with Stage I or Stage II disease, with tumor size <= 5.0 cm and who are lymph node negative. The MammaPrint® result is indicated for use* ***by physicians*** *as a* ***prognostic marker*** *only, along* ***with other clinicopathological factors****.*

Types of Biomarkers† Oncology

- **Early detection (diagnosis),** enabling intervention at an earlier and potentially more curable stage than under usual clinical diagnostic conditions
- **Prognosis**, allowing for more aggressive therapy for patients with poorer prognosis
- **Prediction** of response to a therapy, thereby providing guidance in choice of therapy
- **Monitoring of disease** response during therapy, with potential for adjusting level of intervention (e.g. dose) on a dynamic and personal basis
- **Early detection of recurrence**
- **Risk assessment** leading to preventive interventions for those at sufficient risk

†*Adapted From AACR-FDA-NCI Cancer Biomarkers Collaborative, Biomarker Assay Validation Subcommittee*

Development versus Validation

Development: Training

- Pilot studies and studies to determine cutoffs
- With more complex assays, development may involve building a classifier
- Assay interpretation understood (you know what the result means)
- In house analytical studies well underway (you know how the assay behaves)

Validation

- Validation study provides confirmatory evidence for the intended use of device
- Performance in validation study goes into label
- Reproducibility

Assay interpretation development

- Finalize Assay Steps before final validation phase! Includes:
- Defined interpretations of all outputs (including equivocals)

- Interpretation, for example:

  Ct>37 Negative

  Ct≤37 Positive
- Equivocals (??): e.g. 36.5 to 37.5
- Invalid (control failed) ≠ equivocal
- All results are reported!

Clinical Protocols for Validation

- Consistent with intended use
- Site types (e.g. Point of Care)
- Inclusion/exclusion criteria
- Case report forms
- Stated objectives: performance goals
- Statistical methodology defined
- Sample size justified (tied to claim)

Retrospective studies

- A good reason for a preIDE!
- May be allowed:
  Storage doesn't impact the assay[1]
  Clinical context on specimens
- Not just left-over big tumors
- Need adequate clinical follow-up:
  May depend on disease
- Provide unbiased estimates of performance
- Some analytical studies may be needed

Performance Goals Drive Sample Size

- Sample size

  How good is your device?

  Appropriateness of banked specimens

  Clinical performance needed

- Not one size fits all:

  Genotyping, Basic Clinical Chemistry, Hematology, Flu

Protocols for Analytical studies

- CLSI guidelines:
  - EP5-A2 Establishing precision
  - EP6-A Establishing linearity
  - EP7-A Interference studies
  - EP9 Method comparison studies
  - EP12 Qualitative tests
  - EP17 Limits of Detection and Limits of Quantitation
  - EP21 Total error
  - C28-A2 Reference ranges
- Statistical Guidance for Reporting diagnostic tests (www.fda.gov/cdrh/osb/guidance/1620.html)

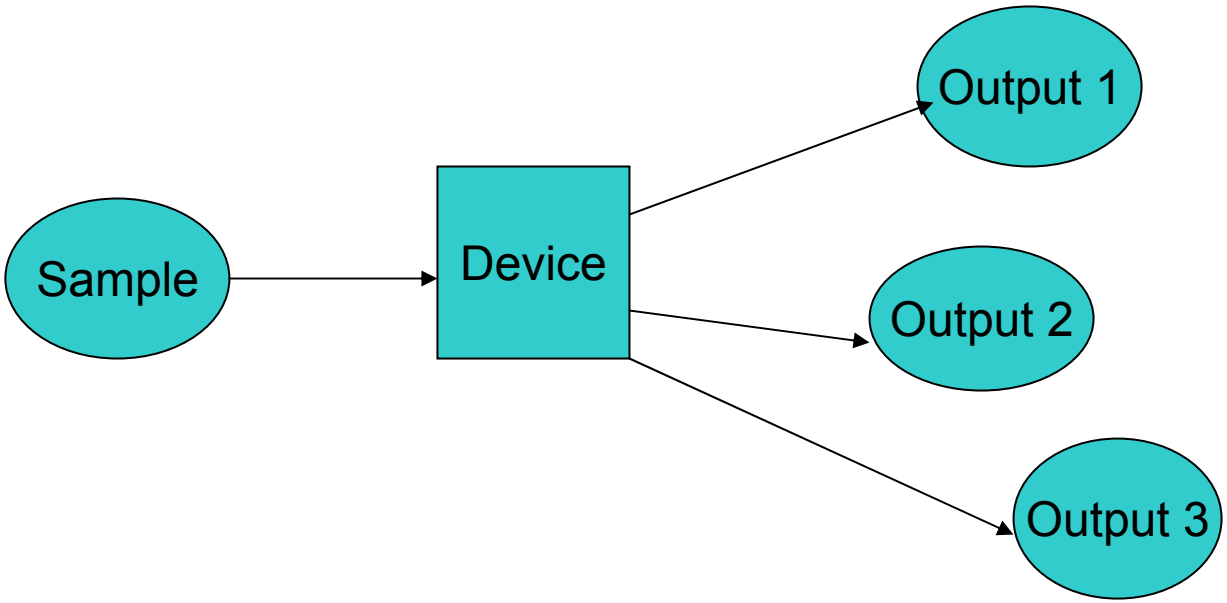
Multiplex Assays – all outputs tied to intended use

"Two or more targets simultaneously detected via common process of sample preparation, target or signal amplification, allele discrimination, and collective interpretation."

Clinical Lab Standards Institute Guidance:

MM17-A Verification and Validation of Multiplex Nucleic Acid Assays

Multiplex paradigm with no composite score



Examples

- Genotyping assays

  Roche CYP450 Amplichip (K042279)

  CF panel (K043011)

- Pathogen assays

  Respiratory Viruses Panel (K081483)

"Sensitivity" - challenge of meeting performance for all analytes in multiplex

Number specimens	Observed Performance	95% Lower Conf. Bound
5	5/5=100%	55.6%
25	25/25=100%	86.7%
30	30/30=100%	88.6%
35	35/35=100%	90.1%
30	24/30=80%	62.7%
50	40/50=80%	67.0%

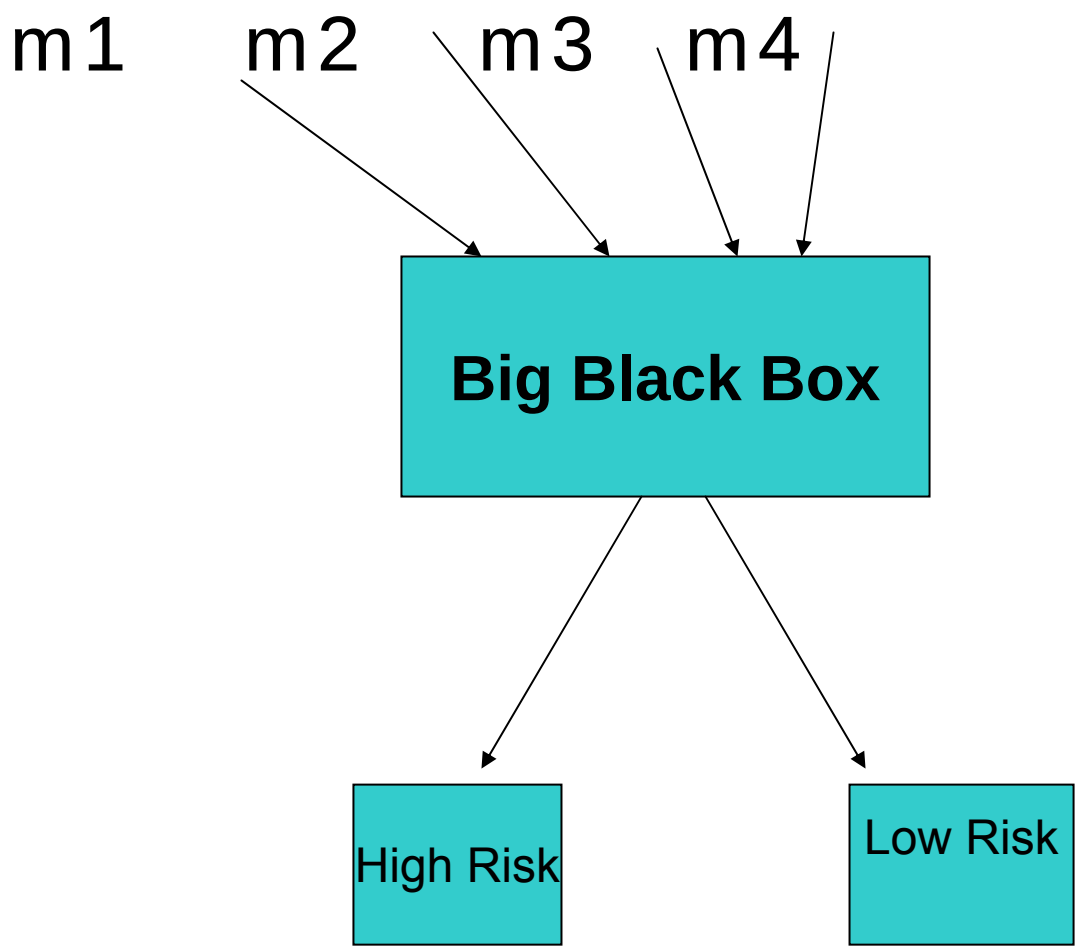
Establishing Clinical utility of multiplex assays

- Use of the device: when, where and how
- All outputs tied to the same intended use
- For example,
  - Subjects with a family history of CF
  - A newborn suspected of having CF
- Implications
  - Device works for disease carriers
  - Device works in disease positive subjects
- Limitations: not for pre-implantation testing

IVDMIA: In Vitro Diagnostic Multivariate Index Assay

- A device that:
- 1) Combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., a “classification,” “score,” “index,” etc.), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and
- 2) Provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user.

IVDMIA Paradigm



Training and Validation Steps

- Training Set(s)
- Develop classifier (sponsor approach)
- Cross Validation
- Lock down classifier

- Independent Validation

  Confirmatory studies w/Protocols

Internal Validations: Sponsor responsibility

- **Internal checks are useful**:
  Cross Validation, Jackknife, Bootstrap
- **10-fold Cross Validation:**
  Partition training set into 10 parts
  Use 9 parts to build classifier: 1 to test
  Repeat this 10X..take average
  Less biased than using 100% to fit & assess
  If this looks poor….go back to drawing board

Independent Validation

- **Cross Validation does not consider the R&D process of manufacturer…**
- **FDA asks for an independent validation**
- **Study represents intended use population**

- **Performance on label:**
  From Validation trial

- **Some IVDMIAs are “Prognostic”**

Endpoints for Prognostic and Predictive Markers

- Defined in advance of confirmatory trial
  e.g. Recurrence free survival, time to metastases, Overall survival
- Can be measured in time to event or survival times
- Ask: why patients disappeared
- Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics March 2007

Pitfalls of Retrospective Samples: Especially for time to event data

- **Only looking at cases with a minimum follow up….biased estimates of survival**
- **Avoiding any censored cases**
  - **… patients lost to followup**
  - **… biased estimates of survival**
- **Looking from current samples backward**
  - **…May be biased compared to prospective look**
- **Samples may not survive 10 years in freezer**
- **How representative are banked specimens?**

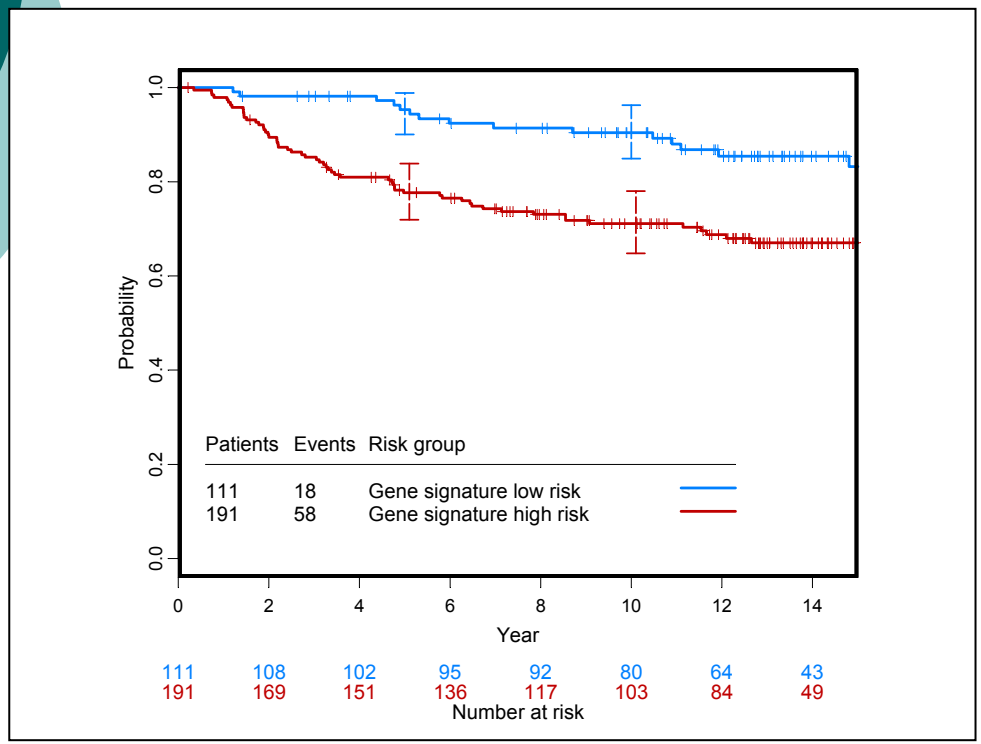
Clinical performance metrics

- **Mammaprint** (Low risk vs high risk):
  Relative hazard (Cox PH model),
  5 year rate of metastases
  10 year rate of metastases

Prognostic claim:

1) **Report absolute risk estimate :**
   5 year or 10 year rate (pre-specified) or
   Median survival
2) **Demonstrate value added over common clinical covariates**

Mammaprint TRANSBIG study (N=302)



5-year:
Low risk group: 0.95 (0.91-0.99)
High risk group: 0.78 (0.72-0.84)

10-year:
Low risk group: 0.90 (0.85-0.96)
High risk group:0.71 (0.65-0.78)

Conclusions

- Pre-IDEs are good for:
  - Sponsors & FDA
- Effective pre-IDEs require preparation
- Statisticians should be involved early