



# **NCI-FDA-NIST Workshop on Standards in Molecular Diagnostics**

Friday December 7, 2012

## **Regulatory Aspects when reviewing a device – PCA3, a case study**

Nisar Pampori, Ph.D., FDA

# In this presentation

## Agenda:

- Introductory slides – what we do
- What we learnt from PCA3 assay review process
  - Intended Use elements
  - Clinical studies performance: interpretations and **lessons learnt**
  - Analytical studies performance: **lessons learnt**
- Some references will be given to issues in other devices

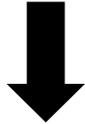
## Disclaimer

- Thoughts presented here do not represent finalized FDA policy
- We recommend pre-submission for outstanding questions

# Biomarker assays (Device)

Translating Discovery into Clinical Practice

Biomarker Discovery



Assay Development



FDA Requirement  
Reasonable Assurance of Safety and Effectiveness  
Valid Scientific Evidence



Device in Clinical Practice

# Issues

- Lack of knowledge of FDA requirements in research community
- Different Goals:
  - NIH: research/exploratory goals– relationship of biomarker(s) to disease
  - FDA: clinical/regulatory goals– safety/effectiveness of device for patients
- FDA Challenges:
  - Growth in new technologies
  - Increasing public expectation

# Examples of technologies used in IVDs

- Nucleic Acid Tests
  - RT-PCR, microarrays
  
- Immunoassays (Singleplex/Multianalyte/Multiplex)
  - Lateral flow, EIA, ELISA, bead assays, IHC, IFA, Flow cytometry
  
- Chemical tests
  - HPLC, mass spec, electrochemical



# Pre-Market Submission Types

What types of submissions we review:

- Investigational Device Exemptions (IDE)
- Premarket Approval Applications (PMA)
- Premarket notifications [510(k)]
- Device classifications requests [513(g)]
- Humanitarian Device Exemptions (HDE)
- Pre-Submissions



# Three regulatory classes of Devices

Based on the level of control necessary to provide assurance of safety and effectiveness

| Class                      | I or II Exempt   | II                                       | III  |
|----------------------------|------------------|--|--|
| Risk level                 | Low              | Medium                                   | High                                       |
| Pre-market submission type | Exempt           | 510(k) (pre-market notification)         | PMA  |
| Controls                   | General controls | General controls<br>And special controls | General controls<br>and Premarket Approval |
| Pre-market review standard | None             | Substantial equivalence to predicate     | Safety and effectiveness                   |

## Risk Dependent on Intended Use (Same Test , Different Use)

A molecular assay may be used

- ✓ for screening, diagnosis in asymptomatic patients (high risk)
- ✓ for prognosis in already diagnosed patients (moderate risk)

# Intended Use

- Analyte(s)
- Technology
- Result outcome: Quantitative / Semi-quantitative / Qualitative (two outcomes - neg., pos.; or with three outcomes - neg., equiv., pos.)
- Intended patient population? (e.g., gender, age)
- Clinical indications? Clinical use? (Diagnostic, Prognostic, Screening, Monitoring, Predictive)
- Intended users (clinical laboratory , home use, POC, OTC, etc.)

# Intended Use

## Indication For Use

## Analyte

## Technology

## Intended Population

The PROGENSA PCA3 Assay is an in vitro **nucleic acid amplification** test. The assay measures the concentration of prostate cancer gene 3 (**PCA3**) and prostate-specific antigen (**PSA**) RNA molecules and calculates the ratio of PCA3 RNA molecules to PSA RNA molecules (**PCA3 Score**) in post-digital rectal exam (DRE) first catch male urine specimens. The PROGENSA PCA3 Assay is indicated for use in conjunction with other patient information to **aid in the decision for repeat biopsy** in **men 50 years of age or older who have had one or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended** by a urologist based on current standard of care, before consideration of PROGENSA PCA3 Assay results.

A PCA3 Score <25 is associated with a decreased likelihood of a positive biopsy. Prostatic biopsy is required for diagnosis of cancer.

# Did the Clinical Studies design achieve its goals?

- Intended Use Population:
  - Men over age 50
  - who have had one or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended
  
- Aid in:
  - the decision for repeat biopsy

## did the studies show that?

- Restrictions
  - Black box warning
  - Warning
  - Limitations

## why?

# Clinical Performance Studies

## Target Population:

- Demographic distribution
- Age/Sex - Men over age 50
- Clinical condition: Previous negative biopsy must have been performed at least 42 days

## Trial Design:

- Size: 507 subjects
- Prospective, multicenter
- Inclusion and exclusion criteria

## Safety and effectiveness results (example in PCA3):

- 466 subjects - valid PCA3 Scores and disease status (determined by Prostatic biopsy)
- Median total serum PSA was 5.80 ng/mL
- Results compared to pathological findings

# Clinical validity of the test

Does my test result correlate with the expected clinical presentation? How reliably?

Clinical sensitivity: How often does the test pick up patients with disease? (frequency of false negatives)

PCA3 assay: IU states “A PCA3 Score <25 is associated with a decreased likelihood of a positive biopsy”.

Potential for false negative result is that patient will not get biopsy

Clinical specificity: How well does the test pick up patients without the disease? (frequency of false positives)

PCA3 assay: False positive result is that patient is getting biopsy (as recommended under standard-of-care)



# Performance Characteristics of the PCA3 Assay

|                              | Biopsy Result   |                 | Total | Performance Characteristic | Estimate       |
|------------------------------|-----------------|-----------------|-------|----------------------------|----------------|
|                              | Biopsy Positive | Biopsy Negative |       |                            |                |
| PCA3 Score $\geq$ 25         | 79              | 156             | 235   | Sensitivity %              | 77.5 (79/102)  |
| PCA3 Score <25               | 23              | 208             | 231   | Specificity %              | 57.1 (208/364) |
| Total                        | 102             | 364             | 466   | PPV %                      | 33.6 (79/235)  |
|                              |                 |                 |       | NPV %                      | 90.0 (208/231) |
| Positive Biopsy Prevalence % | 21.9 (102/466)  |                 |       | PLR                        | 1.81           |
|                              |                 |                 |       | NLR                        | 0.40           |
|                              |                 |                 |       | Odds Ratio                 | 4.58           |



# Improvement in Performance Characteristics

When PCA3 Score is Added to a Multivariable Logistic Regression Model

| Test Description                             | Se           | Sp%<br>(95% CI)      | PPV%<br>(95% CI)     | NPV%<br>(95% CI)     | Improvement by Adding<br>PCA3 Score |                   |                    |
|--|--------------|----------------------|----------------------|----------------------|-------------------------------------|-------------------|--------------------|
|  |              |                      |                      |                      | Sp<br>(90% CI)                      | PPV<br>(90% CI)   | NPV<br>(90% CI)    |
| Current standard of care model <sup>1</sup>  | 90%<br>Fixed | 18.9<br>(10.3, 36.9) | 23.8<br>(21.9, 28.7) | 86.9<br>(79.2, 93.5) | N/A                                 | N/A               | N/A                |
| PCA3(25) +<br>Current standard of care model | 90%<br>Fixed | 41.5<br>(32.5, 49.9) | 30.2<br>(27.1, 33.5) | 94.0<br>(92.3, 95.4) | 22.6<br>(9.0, 33.1)                 | 6.4<br>(2.8, 9.6) | 7.1<br>(1.7, 13.4) |

# Contribution of Assay Information Beyond Existing standard of care Factors

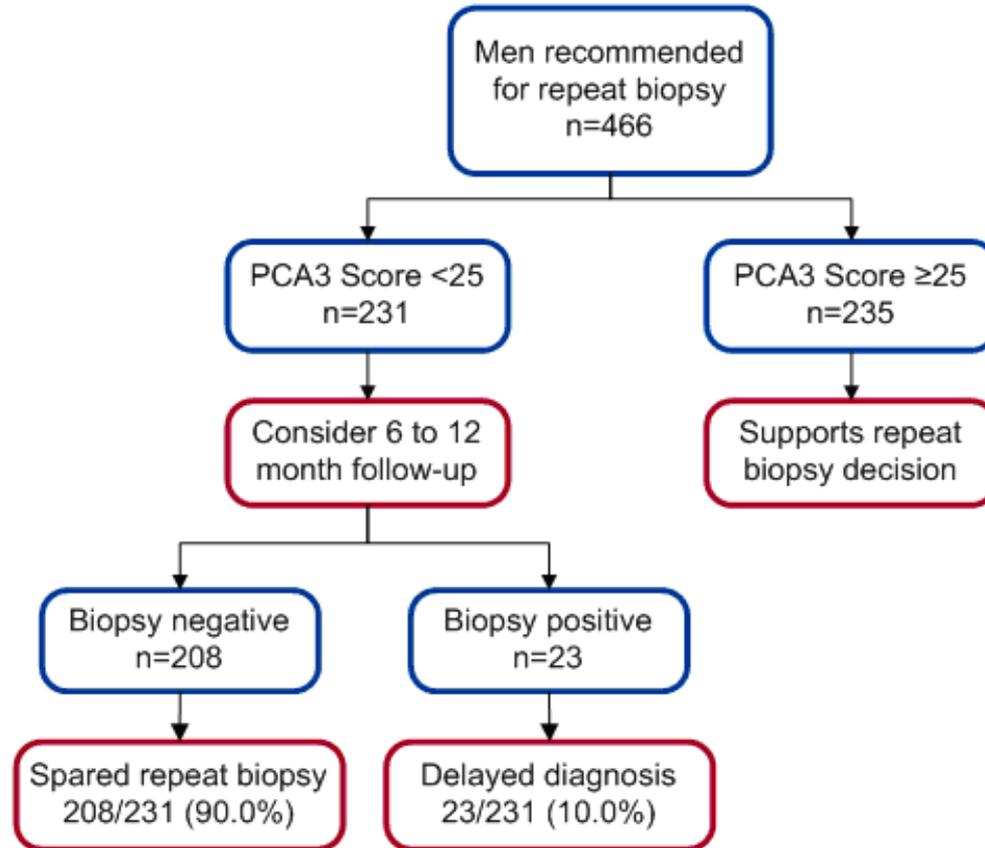
Multivariable logistic regression analysis was conducted to determine whether the addition of the PCA3 Assay information improved diagnostic accuracy over the standard of care (age, DRE result, family history, race, serum PSA test result, and number of previous negative biopsies) information that is currently used for repeat biopsy decisions.

In this analysis, the odds ratio (OR) for PCA3 Score (expressed as a binary categorical variable [positive or negative using a cutoff of 25]) was statistically significant.

OR = 4.56 (95% CI - 2.65, 7.83)

# Impact of PCA3 Assay Use

Clinical study should demonstrate benefit beyond the Urologists biopsy assessment



**Warning:**

The Clinical Study only included men who were recommended by urologists for repeat biopsy. Therefore, the performance of the PROGENSA PCA3 Assay has not been established in men for whom a repeat biopsy was not already recommended.



# Performance Characteristics of the PCA3 Assay in Men with ASAP on their Most Recent Negative Biopsy

(Poor performance in ASAP is addressed through the boxed warning)

|                      | Biopsy Result   |                 |       | Performance Characteristic | Estimate     | 95% CI    |
|----------------------|-----------------|-----------------|-------|----------------------------|--------------|-----------|
|                      | Biopsy Positive | Biopsy Negative | Total |                            |              |           |
| PCA3 Score $\geq$ 25 | 10              | 24              | 34    | Sensitivity %              | 66.7 (10/15) | 41.7-84.8 |
| PCA3 Score $<$ 25    | 5               | 10              | 15    | Specificity %              | 29.4 (10/34) | 16.8-46.2 |
| Total                | 15              | 34              | 49    | PPV %                      | 29.4 (10/34) | 19.1-38.2 |
|                      |                 |                 |       | NPV %                      | 66.7 (10/15) | 44.7-87.0 |
| Positive Biopsy      |                 |                 |       | PLR                        | 0.94         | 0.54-1.40 |
| Prevalence %         | 30.6% (15/49)   |                 |       | NLR                        | 1.13         | 0.34-2.80 |
|                      |                 |                 |       | Odds Ratio                 | 0.83         | 0.23-3.07 |

## **Black box warning:**

The PROGENSA PCA3 Assay should not be used for men with atypical small acinar proliferation (ASAP) on their most recent biopsy. Men with ASAP on their most recent biopsy should be treated in accordance with current medical guidelines.

# Analytical validation (Pre-clinical)

- Precision - CLSI document EP5-A2 concentrations “close to the cutoff” clinical decision point is important
  - Repeatability: Total imprecision from Within-Run, Between-Run and Between-Day
  - Reproducibility: Total imprecision from Within-Run, Between-Run, Between-Operators, Between-Lots (critical reagents calibrators, antibodies) and Between-Sites

| Parameter Panel Member | PCA3 copies/mL |        |        | PSA copies/mL |           |         | PCA3 Score |    |      |
|------------------------|----------------|--------|--------|---------------|-----------|---------|------------|----|------|
|                        | 1              | 2      | 3      | 1             | 2         | 3       | 1          | 2  | 3    |
| Mean Value             | 678            | 18,969 | 97,006 | 16,747        | 1,638,117 | 994,851 | 41         | 11 | 98   |
| Total CV%              | 17.2           | 6.8    | 8      | 19.3          | 11.7      | 10.5    | 25         | 15 | 12.3 |

## Analytical validation (Pre-clinical)

The additional statistical modeling showed that 94% of subjects in the clinical study with PCA3 Score close to the cutoff=25 had total imprecision of 14%-18% (6% of subjects had total imprecision of 18%-25%). (and additional simulation on the score will be discussed in detail by Dr. Marina Kondratovich in the afternoon session)

Due to normal assay variability, specimens with PCA3 Scores near the cutoff of 25 (i.e., 18 to 31) could yield a different overall interpretation of POSITIVE or NEGATIVE upon repeat testing. **PCA3 Scores in the range from 18 to 31 should therefore be interpreted with caution.**

# Analytical validation (Pre-clinical)

- Analyte specificity

What do we need to know to say the test specifically identifies and measures the analyte?

- Molecular details to identify specific target for detection (protein characterization, nucleic acid sequence specificity, oligonucleotide info)
- Analyte in Singleplex / Multiplex assays – Cross-reactivity
- Interfering Substances - CLSI EP7-A2, Endogenous and Exogenous at its highest medically-relevant concentration (“the worst case”) in a simulated matrix with a target concentration close to the assay cutoff
- Matrix effect
- Assay Carry-over/Cross-contamination (multi-sample assays )



## How to learn more

- FDA/CDRH “device advice” and transparency
  - <http://www.fda.gov/cdrh>
- FDA guidance documents
- Annual AMDM workshops
- Pre-Submission meetings
- When a new analyte is identified
  - ✓ Guidance Document
  - ✓ Reflects FDA guidance to industry



# Resources

## MDUFA III Guidance Documents

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MDUFAIII/ucm313674.htm>

## OIVD Guidance Documents

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070274.htm>

## FDA Recognized Consensus Standards:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>

## Pre-submission Draft Guidance:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm310375.htm>

## PCA3 assay: Summary of Safety and Effectiveness Data at:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P100033>



Thank you.....



**U.S. Food and Drug Administration**  
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# Discovery to FDA Approval - Time Line (e.g., PCA3 assay)

- April 1997 Original PCA3 patent filed
- May 1998 DD3/PCA3 first mentioned in a European Urology supp
- Dec 1999 First description of DD3/PCA3 gene
- Feb 2004 First report on Canadian multicenter study
- Dec 2005 PCA3 reagents available in the US for LDT
- April 2006 First face-to-face discussion with FDA**
- Aug 2009 Pivotal clinical trial starts
- May 2010 Pivotal clinical trial ends
- Aug 2010 Premarket approval application submitted to FDA**
- Feb 2012 FDA approval**

Extracted from "*The Long and Winding Road to FDA Approval of a Novel Prostate Cancer Test: Our Story*"; Rittenhouse et. al., Clinical Chemistry 59:1; Published November 28, 2012



# Multivariable Logistic Regression Results

for the Occurrence of Prostate Cancer Associated with PCA3 Score Using a Binary Cutoff of 25 and Other Clinical Factors.

| Factor*   | Regression Coefficient (SE) | Odds Ratio (95% CI)        | p- value |
|---|-----------------------------|----------------------------|----------|
| PCA3 Score ( $\geq 25$ vs. $<25$ )              | 1.5175<br>(0.2762)          | 4.5610<br>(2.6542, 7.8376) | <.0001   |
| Age in years (continuous)                       | 0.0073<br>(0.0158)          | 1.0073<br>(0.9766, 1.0389) | .6458    |
| Suspicious DRE (yes vs. no)                     | 0.0251<br>(0.2801)          | 1.0254<br>(0.5923, 1.7753) | .9287    |
| Family History (any vs. none)                   | -0.0795<br>(0.3162)         | 0.9235<br>(0.4970, 1.7163) | .8014    |
| Family History (unknown/refused vs. none)       | 0.3756<br>(0.5054)          | 1.4558<br>(0.5406, 3.9203) | .4574    |
| Race (black vs. non-black)                      | -0.5506<br>(0.4700)         | 0.5766<br>(0.2295, 1.4485) | .2414    |
| Serum PSA in ng/mL (continuous)                 | 0.0669<br>(0.0215)          | 1.0691<br>(1.0250, 1.1152) | .0019    |
| Number of Previous Negative Biopsies (2 vs. 1)  | -0.7955<br>(0.3259)         | 0.4513<br>(0.2383, 0.8549) | .0146    |
| Number of Previous Negative Biopsies (3+ vs. 1) | -0.8028<br>(0.4545)         | 0.4481<br>(0.1839, 1.0921) | .0774    |