Decentralized Multiplexed Companion Diagnostics on the NanoString nCounter® Analysis System

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Sean Ferree, Ph.D.
Vice President of Diagnostic Development
NanoString Technologies, Inc.

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nCounter®: The only direct, digital, nucleic-acid counting technology

**Molecular Barcoding**

- Novel chemistry invented in Leroy Hood’s lab at Institute of Systems Biology
- Probes up to 800 genes simultaneously
- Digital gene expression applied to biological pathways

Single molecule fluorescent barcodes, each attached to an individual nucleic acid molecule
Prosigna®
3407 FFPE samples, two clinical, two analytic studies, FDA submission, FDA review, FDA clearance…in 1008 business days

2000

2008
nCounter RUO Early Access Program

December 2011
First clinical validation study presented

September 2013
FDA 510(k) Clearance

July 2010
World wide license of PAM50 gene signature

February 2013
CE Marked EU and Israel

Researchers first describe the patterns of gene expression or intrinsic subtypes in ESBC

3,407 total FFPE samples examined to develop the assay
514 for initial signature training
256 for testing of training process
1017 for 2011 clinical study #1
1620 for 2012 clinical study #2

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# Prosigna: Proven technology being adopted worldwide

<table>
<thead>
<tr>
<th>US Testing Labs</th>
<th>ex-US Testing Labs*</th>
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</thead>
<tbody>
<tr>
<td>[Logos and names of laboratories and clinics]</td>
<td>[Logos and names of laboratories and clinics]</td>
</tr>
</tbody>
</table>

* Logos for ARCO (Italy), Viersen Pathology Lab (Germany), University of Halle (Germany), and EuroDNAPath (France) are not shown.
Prosigna: Building a track record in oncology diagnostics

- March '15
  - Inclusion in German AGO Guidelines
  - Recognition in NCCN Guidelines

- May '16
  - Cigna Coverage
  - Aetna Coverage
  - ASCO Guidelines
  - First Coast Medicare Coverage
  - Noridian Medicare Coverage
  - CGS Medicare Coverage
  - ESMO Guidelines
  - Palmetto Medicare Coverage
  - Decision Tree Revised, 2A listing
  - ASCO Guidelines
  - Aetna Coverage
  - First Coast Medicare Coverage
  - Noridian Medicare Coverage
  - CGS Medicare Coverage
  - ESMO Guidelines
  - Palmetto Medicare Coverage

Prosigna Breast Cancer Prognostic Gene Signature for use on the nCounter Dx Analysis System is 510(k) cleared and CE-marked for in vitro diagnostic use in the United States and EU, respectively. See Package Insert in www.prosigna.com for details.

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Companion Dx
NanoString Capabilities Span Entire CDx Development Path

**Translational Research**

- Complete Biomarker Discovery Platform

**Pre-IDE Activities**

- Biomarker Validation to CDx Development

**CDx Development (IDE/PMA)**

- Full IDE/PMA Work Plan

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- **Biomarker Discovery**
- **Biomarker Feasibility and Optimization**
- **Biomarker Validation**

- **Retrospective Analysis of early phase studies**
- **Early phase IUO Studies Development:**
  - Algorithm
  - Reagents
  - Assay
  - Software

- **Regulatory interactions (IDE & Pre-Subs)**
- CTA/IVD deployment
- Pivotal study clinical trials
- PMA Submissions
- Commercialization
Partnering Rationale
NanoString: Best in Class Clinical Dx Platform

- Install Base
- Pipeline of tests
- Enables commercial labs:
  - Fast turnaround
  - Sample control
  - Economic participation

- Sample flexibility
- Reproducible and robust
- Ease of use
- No enzymes or amplification
- Seamless migration from research to Dx

- Team: BioPharma, Dx and Tools
- Multiple Major Pharma global CDx Collabs
- Rapid Development time
- Regulatory clearance in 30 countries
- Commercial / Market Access Leadership
Companion Dx
Leveraging the RUO install base to discover new DX assays

- Invented by a consortium of 11 academic institutions
- Invented by a consortium of 4 academic institutions
- Discovered by MDVN
- Developed by MRK
Lymphoma Subtyping Test
CELG Collaboration was Catalyst for Future CDx Opportunities

DLBCL – Two Primary Subtypes\(^1\)

- Collaboration initiated March 2014
  - NSTG develops IVD test to subtype DLBCL
  - IVD test being used to randomize DLBCL patients in global Revlimid pivotal study
  - NSTG flexibility to use IVD to collaborate with other DLBCL drug developers
- Patients currently enrolling in global pivotal study
  - Study expanded to include Russia and China

- DLBCL no longer considered to be a single disease
- Prognosis (OS) substantially worse for ABC subtype
- Lymphoma Subtyping Test (LST) establishing as standard
- Better concordance vs IHC algorithms\(^2\)

1. Wallden et al. ASCO 2015; Poster 8536
“The nCounter system appears to fulfill all needed criteria due to its demonstrated utility in FFPET, documented inter-laboratory reproducibility, and FDA-clearance of the platform of the Prosigna breast cancer assay.”

26 Pilot studies with 13 companies
Leveraging Breast Cancer Franchise for CDx Success Collaboration with Medivation/Astellas

Progression free survival according to novel genomic assay in patients with mTNBC who received enzalutamide in 1st or 2nd line

Objective:
Translate novel Dx gene expression algorithm into potential companion Dx for patients with advanced Triple Negative Breast Cancer

Approach:
Adapt PAM50-based Prosigna® assay with novel algorithm

“Diagnostic positive status was correlated with improved clinical outcomes with enzalutamide”

Parker et al. J Clin Oncol 33, 2015 (suppl; abstr 1083)
Merck IFN-γ signature provided good NPV in multiple tumor types

- **Gastric**
  - PPV = 45%
  - NPV = 92%

- **HNSCC**
  - PPV = 40%
  - NPV = 95%

- **Melanoma**
  - PPV = 59%
  - NPV = 90%

**Merck:** Developed signatures to predict response to Keytruda

- **May ’15:** Collaboration to explore feasibility
- **June ’15:** Keytruda studies presented at ASCO
- **Feb ’16:** CDx collaboration in multiple tumor types

Shankaran V et al. J Clin Oncol 33, 2015 (suppl; abstr 3026); Siewert T et al. J Clin Oncol 33, 2015 (suppl; abstr 6017); Ribas A et al. J Clin Oncol 33, 2015 (suppl; abstr 3001)
Tumor Inflammation Signature Profiles Four Areas of Immune Biology

- TIS has been clinically verified in HNSCC, gastric, TNBC, urothelial, anal, biliary, colorectal, esophageal, and ovarian cancer.

<table>
<thead>
<tr>
<th>IFNγ Biology</th>
<th>T Cell Exhaustion</th>
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<tr>
<td>CCL5</td>
<td>TIGIT</td>
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<tr>
<td>CXCL9</td>
<td>CD8A</td>
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<td>CD27</td>
<td>LAG3</td>
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<td>IDO1</td>
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<tr>
<td>STAT1</td>
<td>CD276</td>
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<table>
<thead>
<tr>
<th>T Cell/NK Signature</th>
<th>Antigen Presenting Cell Signature</th>
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<tbody>
<tr>
<td>HLA-E</td>
<td>PSMB10</td>
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<tr>
<td>NKG7</td>
<td>HLA-DQA1</td>
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<td>CMKLR1</td>
<td>HLA-DRB1</td>
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</table>

Piha-Paul SA et al. J Clin Oncol 34, 2016 (suppl; abstr 1536).
Tumor Inflammation Signature
Tumor Immunology, Not Tumor Intrinsic Biology

Wallden B et al. J Clin Oncol 34, 2016 (suppl; abstr 3034)

Anti-PD1 Assay is for investigational use only. Limited by United States law to investigational use.
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Tumor Inflammation Signature
Using nCounter in Translational Research Leads to a Robust Clinical Assay

- Maintaining the same platform makes transitioning from translational research through clinical application simple and robust

Wallden B et al. J Clin Oncol 34, 2016 (suppl; abstr 3034)
Tumor Inflammation Signature
Tissue input doesn’t impact estimation of tumor inflammation

Does the amount of adjacent non-tumor tissue impact the test result?

Patient biopsies may be surgical resections, core needle biopsies, or small biopsies. Does it matter?

Wallden B et al. J Clin Oncol 34, 2016 (suppl; abstr 3034)

Anti-PD1 Assay is for investigational use only. Limited by United States law to investigational use.
Tumor Inflammation Signature
Robust Performance with Clinical Samples

Reproducibility in 11 different tumor types shows variance <5% of the score range

Variance of assay at 50 ng relative to 250ng estimated to be 2% of the score range

Wallden B et al. J Clin Oncol 34, 2016 (suppl; abstr 3034)

Anti-PD1 Assay is for investigational use only. Limited by United States law to investigational use.
Host, cancer cells, and environmental factors shape tumor-immune system interactions

IO biomarkers need to integrate the multi-dimensionality of tumor-immune-environment interactions AND of type of informative analytes (DNA, RNA and proteins)
Immuno-Oncology Strategy
Cancer-Immune Cycle and individual germline immune “make-up”

Effects of Germline SNPs in the Cancer-Immunity Cycle Stimulatory/Inhibitory factors

Reprinted from Immunity, Chen DS, Mellman I. Immunity 2013; 39: 1-10., Copyright ©2013, with permission from Elsevier.

nCounter Immune Profiling Panel and Vantage Assays are for Research Use Only. Not for use in diagnostic procedures.

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Immuno-Oncology Strategy
Vision for Universal IO Clinical Assay

Tumor Inflammation Signature

- T cell inflamed signature “Hot”
- Non-T cell inflamed signature “Cold”

Defects in T cell trafficking to tumor
- Oncogenic pathway activation
  - Epigenetic TME reprogramming
  - Tumor vasculature/stroma
  - Poor tumor Ag presentation in LN
  - Low neoepitope burden

PD-1/PD-L1 pathway activation only
- Other inhibitory receptors
- Additional TME suppression
- MDSC, Treg

PD-1/PD-L1 blockade
- Lag 3, TIM3, CD137 IDO blockade
- MDSC Targeting agents: Carbo/Taxol
- Treg targeting agents: Ipilimumab CFM

Integrated IO profile

- Wnt inhibitors
- PI3K inhibitors
- HDAC inhibitors
- HMA
- Anti-angiogenics
- CTLA-4 inhibition
- TLRs/probiotics
- Vaccines

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Building a Deep Funnel of CDx Opportunities
Extend Leadership in Molecular Diagnostics

<table>
<thead>
<tr>
<th>Pilot</th>
<th>Feasibility</th>
<th>Pivotal</th>
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<tbody>
<tr>
<td>prosigna</td>
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<tr>
<td>DLBCL CDx</td>
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<td>Immuno-Oncology CDx</td>
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Pilot studies
- 7 studies
- 4 companies
- 26 studies
- 13 companies
NanoString product line spans research and diagnostics

<table>
<thead>
<tr>
<th>Instruments</th>
<th>Research*</th>
<th>Diagnostics†</th>
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<tbody>
<tr>
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<th>Consumables</th>
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<th>miRNA Expression</th>
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<td>Copy Number Variation</td>
<td>Gene Fusions</td>
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<tr>
<td></td>
<td>Single Cell Expression</td>
<td>Proteins</td>
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* SPRINT and MAX nCounter Analysis Systems as well as Consumables for the listed applications are For Research Use Only. Not for use in diagnostic procedures.
† nCounter Dx Analysis System with FLEX configuration is 510(k)-cleared for use with the Prosigna Assay. nCounter Elements reagents are For Laboratory Use.