Molecular Profiling & Circulating Tumor Cells: Challenges as Declining Reimbursement & Clinical Policies Collide

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Board Certified Medical Oncologist
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Clinic Incubates Biotech
Accelerates Translational Research Towards Personalized Medicine

Carolina BioOncology Institute
CANCER THERAPY & RESEARCH CENTER

BioCytics
HUMAN APPLICATIONS LABORATORY
Financial Disclosure: Sponsors

BioPharma Trial Sponsors
- Abbott Labs
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- Amplimmune
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- Progenics
- Regeneron
- Sanofi-aventis
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- PRA International
- Premier Research International
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- Novella

BioCytics Translational Lab Sponsors
- Genentech
- Progenics (PSMA Development Company, LLC)
- Millennium
- Fluxion
- Peregrine

Academic Collaborations & Grants
- UNCC BioInformatics, Raad Gharaibeh PhD
- UNCC Cancer Immunology Pinku Mukherjee, PhD
- NC Research Campus, BioInformatics, Cory Brouwer PhD
- Cornell BioMedical Engineering, Mike King PhD
- Duke, Cancer Immunology, Mike Morse PhD
Pharmaceutical Industry
Product

Biotechnology Industry
Product

Personalized Medicine
Cellular and Gene Therapy
Process
Service
Complimentary Missions

- Carolina BioOncology Institute, PLLC
  - Provide oncology care & clinical trial access to patients
  - Only independent phase I cancer research center on East Coast
  - >3,000 patients since opening 2005
  - Developed >40 cancer drugs

- BioCytics, Inc
  - Develop Circulating Tumor Cell (CTCs) Companion Diagnostics
  - CTC Molecular Profiling and Trial Matching
  - Develop autologous cellular immunotherapy

Founded 2005
Robust Clinical Trial Accrual

- >40 early phase trials opened since 2005
  - Average Accrual: 10-15 patients per trial
  - Enrollment Average: 50 patients per year (1 accrual per week)
  - > 300 patients enrolled onto early phase clinical trials
  - > 30 publications in cancer research, focus on immunotherapy

Examples of early phase trials:
- ipilimumab
- panitumumab
- nivolumab PD1 mAb
- BHCG vaccine MDX-1307
- aflibercept VEGF trap
- PDGFR mAb
- NY-ESO-1 vaccine CDX-1401
- MPDL3280A PDL1 mAb
- AMP-224 PD1 blockade
- PSMA antibody drug conjugate
- Vemurafenib BRAF inhibitor
Quick Activation Leads to Efficient Accrual

- Small site with no administrative delays
  - On-site pharmacy
  - Efficiency of a central IRB
  - No ancillary committee approvals required
  - Limited overhead costs

- Quick turnaround times
  - Contract and Budget negotiations: 2 weeks
  - Regulatory Documents: 2-3 weeks
  - IRB approval: 1-2 weeks
Efficient Accrual and Study Management

- Patient waiting list for Phase I solid tumor trials, > 50 regional referring oncologists
- Searchable electronic medical records
- Experienced staff
  - Investigational drug
  - PK, PD sample prep
  - Shipping
- Large infusion area, 10 chairs
- NIH Inspected & Approved Institutional BioSafety Site for gene transfer trials
North Carolina
- #3rd largest biotech Industry
- #1 fastest growing biotech industry
- Tobacco state, high cancer mortality

Charlotte: Largest major city without a medical school

International Airport Hub
- 6th busiest airport in world
- 90 minute flight from 100 million Eastern US population

Proximity to Novant Medical Center at Huntersville
MEDICINES IN DEVELOPMENT FOR CANCER*

- Bladder Cancer: 17
- Brain Cancer: 60
- Breast Cancer: 90
- Cervical Cancer: 16
- Colorectal Cancer: 64
- Head/Neck Cancer: 28
- Kidney Cancer: 39
- Leukemia: 122
- Liver Cancer: 24
- Lung Cancer: 110
- Lymphoma: 86
- Multiple Myeloma: 44
- Ovarian Cancer: 47
- Pancreatic Cancer: 49
- Prostate Cancer: 88
- Sarcoma: 23
- Skin Cancer: 64
- Solid Tumors: 204
- Stomach Cancer: 14
- Cancer-Related Conditions: 46
- Other Cancers: 51
- Unspecified Cancers: 77
Impact of Companion Diagnostics

- Patient selection into clinical trials
  - matches drug to patients most likely to benefit
  - Better clinical response
  - Improvement in attrition rates
  - FDA requests biomarkers
  - More likely FDA approved
- Extends drug lifecycle
  - Higher revenue
Financial Impact of Companion Diagnostic Co-development

Cancer Companion Diagnostics

15 already FDA approved

20 more in development
Clinical Laboratory
Carolina BioOncology

- CLIA & CAP Accredited
- Veridex CellSearch®
  - Isolation and enumeration of CTC
  - Downstream molecular profiling
CTCs = Substrate of Personalized Medicine

Frequency of CTCs in Blood
Magnetic Mounting Holds Cells in Place
Scanning Makes Their Position Known
CTC BEFORE INITIATION OF THERAPY
METASTATIC CARCINOMAS

Breast  
n=177

Colorectal  
n=451

Prostate  
n=219

Logrank p < 0.0001
< 5CTCs  
n = 89 (50%)  
10.9 Months

Favorable

≥ 5CTCs  
n = 88 (50%)  
21.9 Months

Unfavorable

Logrank p < 0.0001
< 3CTCs  
n = 334 (74%)  
8.5 Months

Time from Baseline (Months)

Logrank p < 0.0001
< 5CTCs  
n = 94 (43%)  
11.5 Months

Time from Baseline (Months)

Logrank p < 0.0001
≥ 5CTCs  
n = 125 (57%)  
21.7 Months

Time from Baseline (Months)

Summary of CTC Data from Patients seen at CBI

Total 160 pts with 1,299 samples
Predominately Stage IV pts

Prostate: 14 pts and 197 samples
Breast: 31 pts and 429 samples
Lung: 39 pts and 308 samples
Colorectal: 30 pts and 157 samples
Ovarian: 13 pts and 88 samples
Pancreatic: 10 pts and 44 samples
Other: 23 pts and 76 samples
Cell Search Extra Channel
Realtime Biomarker Analysis

- Fluorophore Markers:
  - Her2, EGFR, Ki67, M30, AR, IGF1R, cMET, MUC1, PDL1, PSMA
BioCytics Clinical CTC Her2+ example
Cellular Imaging

[Image of a centrifuge and a fluorescent microscopy image showing cellular structures labeled with Cytokeatin (green) and CD45 (red).]
Laser Capture Microdissection

60x magnification
TMPRSS2-ERG Intrachromosomal Fusion FISH (3 color)  
BioCytics Optimization

A. Normal

B. Fusion = yellow

C. centromere → ERG → TMPRSS2 → telomere

LCaP cl FGC p3  

RP11-164E1 FITC  
RP11-367P1 Pacific Blue  
RP11-814F13 TRITC  

VCaP p3
Prostate Specific Membrane Antigen (PSMA) Antibody Drug Conjugate (ADC) Progenics Inc.
BioCytics Development of Companion Diagnostic: Prostate Specific Membrane Antigen on CTCs
CTC PSMA Expression: Correlated with reduction in CTC percentage, p = 0.0191

(Presentation + Discussion of the Interim Results of 2 Phase 2 Trials in Prostate Cancer; Progenics Webcast, January 2014)
FDA NEWS RELEASE

For Immediate Release: Nov. 19, 2013
Media Inquiries: Susan Laine, 301-796-5349, susan.laine@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA allows marketing of four “next generation” gene sequencing devices
Two devices aid in screening and diagnosis of cystic fibrosis

Today the U.S. Food and Drug Administration allowed marketing of four diagnostic devices that can be used for high throughput gene sequencing, often referred to as “next generation sequencing” (NGS). These instruments, reagents, and test systems allow labs to sequence a patient’s DNA (deoxyribonucleic acid).

The new technology also gives physicians the ability to take a broader look at their patients’ genetic makeup and can help in diagnosing disease or identifying the cause of symptoms.
Genomic Sequencers <$100,000

- Ion Torrent
- Illumina MiSeq
CTCs as Liquid Biopsy: BRCA1&2 Gene Sequencing
G. Linchangco, R Gharaibeh, J White, B Greene, E Keller, J Powderly, C Brouwer,
UNCC Life Sciences Symposium 2012
PDL1 Expression on Tumor Correlates with anti-PD1 mAb Response (Nivolumab, Phase I, BMS) Topalian, et al, NEJM 2012

Association between Pretreatment Tumor PD-L1 Expression and Clinical Response

<table>
<thead>
<tr>
<th>Response Status</th>
<th>PD-L1–Positive</th>
<th>PD-L1–Negative</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective response</td>
<td>9 (36)</td>
<td>0</td>
<td>9 (21)</td>
</tr>
<tr>
<td>No objective response</td>
<td>16 (64)</td>
<td>17 (100)</td>
<td>33 (79)</td>
</tr>
<tr>
<td>All</td>
<td>25</td>
<td>17</td>
<td>42</td>
</tr>
</tbody>
</table>

P=0.006 for association by Fisher's exact test
51-year-old male with RCC s/p L nephrectomy, sunitinib, XRT T9, temsirolimus, PD-L1 positive

Carolina BioOncology Institute (Powderly)
Biomarkers at baseline:
PD-L1 positive
CD8+ T cells present

Biomarkers at week 4 post C1D1:
PD-L1 positive
Increased CD8+ T-cell infiltrate

On-treatment H&E:
dense lymphocytic infiltrate and no viable tumor cells seen

Carolina BioOncology Institute (Powderly).
PDL1 Profiling of Circulating Tumor Cells
Carolina BioOncology Institute and BioCytics Inc.
### Circulating tumor cell test, reimbursement 2007-08

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Technical Component Payment</th>
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<tbody>
<tr>
<td>88346-TC</td>
<td>Immunohistochemistry, each antibody (EpCAM antibody)</td>
<td>$51.63</td>
</tr>
<tr>
<td>88346-TC-59</td>
<td>Immunohistochemistry, each antibody (CK-PE antibody)</td>
<td>$51.63</td>
</tr>
<tr>
<td>88346-TC-59</td>
<td>Immunohistochemistry, each antibody (CD-45 antibody)</td>
<td>$51.63</td>
</tr>
<tr>
<td>88313-TC</td>
<td>Special stains, Group II, all other except immunocytochemistry and immunoperoxidase stains (DAPI nuclear stain)</td>
<td>$55.64</td>
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<tr>
<td>88361-TC</td>
<td>Morphometric analysis, tumor immunohistochemistry, quantitative or semiquantitative, each antibody, using computer assisted technology (CK-PE antibody)</td>
<td>$81.67</td>
</tr>
<tr>
<td>88361-TC-59</td>
<td>Morphometric analysis, tumor immunohistochemistry, quantitative or semiquantitative, each antibody, using computer assisted technology (CD-45 antibody)</td>
<td>$81.67</td>
</tr>
</tbody>
</table>

**Total Laboratory Reimbursement $373.87**
Decline of Clinical Diagnostic CTCs for Billable Standard of Care

- 2006 FDA Approved Veridex Cell Search IVD platform for CTC enumeration (Breast, Colon, Prostate)

- 2007 Clinic bought Veridex device, $200,000 device, PhD to operate. Reagents $250/test (with controls). 16 tests/kit (must use from 30 days after opening kit, or entire kit expires). Flow cytometry CPT codes reimburse $370/test.

- 2008 Medicare contractors declared Local Coverage Determination (LCD) that CTCs are “investigational, noncovered” (despite FDA approval). Oncologists who bought device panicked, Veridex offered to take back the leased machines.

- 2009 CMC Medicare declared National Coverage Decision (NCD) that CTCs are “covered” and that new CPT code would be developed. Use Immunology Unlisted code 86849 pays $284/test (but required every progress note to be faxed, to determine clinical necessity).

- 2010 Private Insurers declare CTCs as “investigational, noncovered”

- 2011 Veridex reagents continue to increase reagents/maintenance cost 15%/year

- 2012 New CPT code: 86152 pays $284 (clinic stops performing diagnostic CTCs, focuses only on CTC biomarker research contracts)
Community Oncology Practice Impact Report

1,338 Cancer Clinics
Community Oncology Alliance (COA)
www.communityoncology.org
U.S. Health Care Dollar
$1.3 Trillion/yr

Sources:
- Public: 12%
- Private: 6%
- Medicaid: 15%
- Medicare: 17%
- Out of Pocket: 15%
- Other Public: 12%
- Other Private: 6%

Spent:
- Hospital: 32%
- Physician/Clinical Services: 22%
- Prescription Drugs: 9%
- Nursing Home: 7%
- Administration: 6%
- Other Spending: 24%

U.S. Cancer Dollar
$74 Billion/yr

Research
$23 Billion/yr (31%)

Physician & Clinical Services $18 Billion/yr (24%)
(3.6% of CMS Physician Fees)
Chemo $33 Billion/yr (45%)
(1.9% of CMS)
Direct Cancer Costs = $51 Billion
Cancer = Largest % spent/person

US Cancer Population
1.3 Million U.S. Cancer Patients Diagnosed Yearly
(Half will die)
3% Cancer Patients Participate in Clinical Trials
(39,000 Patients)

U.S. Oncologists
8,404

Average # Principal Investigators per site
- 150 Academic Medical Centers x 6 = 900
- 200 Community Cancer Centers x 1 = 200
- 1200 Oncology Practices x 0.2 = 240
Total 1,340 Principal Investigators 16%

$23 Billion/yr
1,340 Principal Investigators
= $17,000,000 research dollars spent per Principal Investigator/yr

$23 Billion/yr
39,000 Patients/yr
= $590,000 research dollars spent per patient/yr

$23 Billion/yr
365 Days
= $63,000,000 research dollars spent per day

= Millions of research dollars lost per day on idle research trials

Source:
- CMS, Office of Actuary, National Health Statistics Group
- CMS, Office of Research, Office of Information Services
- American Board Internal Medicine (ABIM)
- National Cancer Institute (NCI)
- Pharmaceutical Research and Manufacturers of America (PhRMA)
Access to Personalized Medicine Research Trials

- Critical shortage of oncology principal investigators
  - Insurance denial of investigators on network
    - Need “any willing provider law”
  - Insurance denial of diagnostic labs on network
    - Need “any willing lab law”

- Critical shortage of community based cancer clinics
  - Decline reimbursement of oncology care
    - AWP + 4.3%, prompt pay, sequestration, 340B, SGR
  - Decline in reimbursement of cancer diagnostics
    - Unable to perform any clinical diagnostic CTC samples since 2012
    - FDA approved devices, tests, and drugs are not covered by insurances

- Lack of personalized medicine infrastructure
  - Translational highway, biobank, EMR-EDC, molecular profiling and matching into adaptive clinical trials, no standardized systems

- Fixing regulations can promote innovation, increase access to clinical trials and molecular profiling, & level playing field