“Companion Diagnostics – A Unique Outcome and Opportunity - from Two Awkward Healthcare Industry Parents!”

Andrew J Beard. PhD.
Head of Siemens Companion Diagnostics & Strategic Biomarkers Group.
Todays Out-of the Box Agenda
Todays Out-of-the-Box Agenda

What do we know about Companion Diagnostics and Personalized Medicine?

Good Parenting and Partnering?

What is Siemens doing in this space?
“A companion diagnostic device can be an in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product.”

– U.S. Food and Drug Administration
Companion Diagnostics (Personalized Medicine) is a Major Trend in Healthcare Today and in Future

What is Driving Personalized Medicine?

- Safer, More Effective Drugs
- Faster Time to a Cure
- Cost-Effective Healthcare
HIV Co-receptor Tropism Example of a Companion Diagnostic Test

A CCR5 antagonist, like maraviroc, can help block R5 virus.

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Evolution of Molecular Characterization of Lung Cancer

48-yr old Female Non-smoker with NSCLC ALK Fusion

After 2 cycles of Therapy

Kwak EL, et al. ESMO/ECCO 2009 (Abstract G6 and oral presentation)
Marketed Therapeutics Reliant on a CDx Generated ~$19B in Therapeutic Revenues in 2013

- **Gleevec** (Novartis)
- **Tarceva (Roche)**
- **Sprycel (BMS)**
- **Herceptin (Roche)**
- **Tasigna (Novartis)**
- **Iressa (AZ)**
- **Leritux (BMS)**

### Biopharma WW marketed CDx drug revenue segmentation (2013)*

#### Percent of revenues

**Drug (Company)***

- ~$19B
  - Other***
  - Gleevec (Novartis)
  - Herceptin (Roche)
  - Iressa (AZ)
  - Tasigna (Novartis)
  - Sprycel (BMS)
  - Tarceva (Roche)**

**Therapeutic area**

- ~$19B
  - Oncology
  - Infectious disease

**Test purpose**

- ~$19B
  - Therapy selection / monitoring
  - Therapy selection

*2013 revenues are actual or analyst estimates; PHC products include those with labels that require / recommend PharmDx tests for candidacy.
**Includes all Tarceva revenues, not just those from first-line treatment for EGFR+ NSCLC patients.
***Other includes Mekinist, Bosulif, Tafinlar, Vectibix, Selzentry, Kadcyla, Xalkori, Tykerb/Tyverb, Perjeta, Zelboraf, and Victrelis.

Source: Company websites and press releases, Annual reports, EvaluatePharma®, L.E.K. analysis of therapeutic sales.

A New Landscape for the Pharmaceutical Industry

42% of all drugs in development are personalized medicines\(^1\)  
73% of oncology drugs in development are personalized medicines\(^1\)

Biopharmaceutical firms expect investment in the field to increase by a third in the next five years\(^1\)

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Policy Issues In Personalized Medicine
Parents and Partnering for a Companion Diagnostic Test!
Parents and Partnering for a Companion Diagnostic Test!

In US...

- 40-50% if marriages end up with divorce
- Average marriage is 8 years

Common reasons…

“Lack of commitment”

“Lack of equality”

“Un-realistic expectations”
Parents and Partnering for a Companion Diagnostic Test!

### Observations and Behaviours

<table>
<thead>
<tr>
<th></th>
<th>RX</th>
<th>DX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>20x</td>
<td>1x</td>
</tr>
<tr>
<td><strong>Business Risk</strong></td>
<td>Therapy development high risk!</td>
<td>Test development low risk!</td>
</tr>
<tr>
<td><strong>Timeline expectations</strong></td>
<td>Long development programs (typically 10yrs)</td>
<td>Short development programs (typically &lt;5yr)</td>
</tr>
<tr>
<td><strong>Commitment</strong></td>
<td>A part of therapy strategy?</td>
<td>Opportunistic or strategic?</td>
</tr>
<tr>
<td><strong>Partnering</strong></td>
<td>Low DX knowledge</td>
<td>Low RX knowledge</td>
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Not unlike a marriage, these CDx partnerships need much work
Clinical trial tests needed along therapy development process - with varying degree of regulations

<table>
<thead>
<tr>
<th>Phase</th>
<th>Therapy Status</th>
<th>Test Status</th>
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</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Small size; 40-60 patients</td>
<td>No application defined</td>
</tr>
<tr>
<td></td>
<td>Safety/tolerability</td>
<td>May be run in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>research lab</td>
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<tr>
<td>Phase II</td>
<td>Medium size; 100-400 patients</td>
<td>Proven analytical performance</td>
</tr>
<tr>
<td></td>
<td>Dose determination</td>
<td>Testing application hypothesis</td>
</tr>
<tr>
<td>Phase III</td>
<td>Large size; &gt;1000 patients</td>
<td>Proven analytical performance</td>
</tr>
<tr>
<td></td>
<td>Efficacy-seeking</td>
<td>Clinically validated decision points</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prospective clinical validation</td>
</tr>
</tbody>
</table>

- Preclinical Development / Proof of Concept
- Phase I Trials
- Phase II Trials
- Phase III Trials
- FDA approval
- Product Launch
Siemens Clinical Laboratory
A Center of Clinical Excellence and Innovation

Siemens Clinical Laboratory (SCL), Berkeley, CA.
A CAP accredited CLIA clinical laboratory in a global diagnostics company since 1994

CLIA Testing Services
Customer & Product Support
Dx / Pharma Development Support
Clinical Trials
Education / Professional

Technical Expertise
- RNA & DNA Qualitative and Quantitative Analyses
- RNA Expression Analysis
- RNA/DNA sequencing
- Immunoassays
- HPLC and MS
- RNA & DNA Qualitative and Quantitative Analyses
- Genotyping

Disease Focus
- Infectious disease
- Oncology
- Cardiovascular
CDx&SB acts as the conduit between pharmaceutical companies and Siemens

Pharmaceutical Company Partners

Companion Diagnostics Group (inc. Siemens Clinical Laboratory Operation)

Siemens Healthcare
Example: Siemens Zika Reference Laboratory Services Concept

- Leverage the CLIA lab capabilities to offer Zika test LDTs ** to support pharmaceutical vaccine development and Siemens product health group

2016

**Molecular Test**
- **Zika kPCR test** LDT **
  - Detect presence of zika virus
  - Using Siemens RUO zika kit* test components & protocol

**Serology Tests**
- **Zika antibody (IgM) LDT** **
  - Detect acute zika virus infection
  - Using Siemens Novagnost zika IgM kit*** components

- **Zika antibody (IgG) LDT** **
  - Detect previous exposure to zika virus infection
  - Using Siemens Novagnost zika IgG kit** components

* Research use only  
** Under development  
*** CE-IVD; Not currently available for sale in the U.S.
CD&SB Business Model

Companion Diagnostics Solutions
Publicly Disclosed Companion Diagnostics Partnerships

**Pfizer**
Master Services Agreement (MSA) for Companion Diagnostics collaboration

**Janssen Pharmaceuticals**
Companion Diagnostics immunoassay test for novel heart-failure drug

**ViiV Healthcare**
Companion Diagnostics next-generation sequencing (NGS) tropism test for HIV-1 treatment

**Tocagen Inc.**
Novel clinical-trial tests for cancer-selective gene therapy for patients with brain cancer
Current treatment for the most common—and the most deadly—form of primary brain cancer (glioblastoma, GBM) is limited:

One-third of GBM patients remain alive **1 year** after diagnosis.¹

10 months median survival after diagnosis for all patients.²

16 months Median survival with current maximal therapy:³ Surgery, radiation, and alkylating. Clinical trials recommended upon recurrence.

**Tocagen Inc. of San Diego, California,** has developed a cancer-selective retroviral replicating gene therapy (Toca 511™) to combat brain cancers including GBM—and they needed a collaboration partner to support their clinical-trials testing and commercialization.

**Siemens Clinical Laboratory** – Supporting Tocagen clinical trials with viral load, DNA, therapy and antibody tests.
Toca 511 & Toca FC Selectively Turns Tumor into 5-FU Factory

Dual Actions: 5-FU Kills Tumor and Activates Immune System Against Cancer

Brain and tumor samples from Tocagen clinical trial patients

CD = cytosine deaminase

Modified from M.K. Aghi, MD, SNO-SCIDOT, Nov. 18th, 2015.

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Partial Response in Subject with GBM
PR at 6 months; continuing at 21 months

Patients tested and monitored with Siemens Clinical Laboratory clinical trials tests:

- Viral load (RNA)
- Viral DNA
- Viral antibody
- Therapy concentrations (5FC)

Lesion 2 complete disappearance
Lesion 1 ongoing PR, 81% shrinkage
Lesion 1 PR, 68% shrinkage
Lesion 1 measurable
Lesion 2 evaluable

Pre Toca FC Baseline
Post 5 cycles Toca FC
Post 13 cycles Toca FC

FC cycle is every 6 weeks
Summary

- Companion diagnostic tests are here to stay.
- It is anticipated most future new biomarker tests will be companion diagnostic tests.
- Bringing these new tests to laboratories requires good partnering and parenting!
- Siemens is actively participating by leveraging the Siemens Clinical Laboratory group for CDx development with strategic pharmaceutical partnerships.
Companion Diagnostics Today