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Innovation Levers in Diagnostic Patents

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“Innovation Levers in Precision Medicine”
Colleen Chien
Professor, Santa Clara University Law School

November 5, 2015
White & Case Digital Health: Rethinking Healthcare in a Digital World Conference
Why Precision Medicine?

Source: Schork (2015), *Nature*
The potential rewards of personalized medicine are great

“Right medicine at the right time for the right patient population”

Paradigm Shift, from traditional to personalized medicine...

- Blockbuster “one size fits all” drug → market for one
- 50%+ do not have favorable outcomes → smart prescribing
- Adverse events, regardless of outcomes → minimize side effects

Types of Dx Innovation

- **Prognostic Dx**: Myriad BRACAnalysis® test assesses hereditary breast cancer risk; Ariosa DNA-based blood test that screens for trisomy 21, 18 and 13
- **Monitoring Dx**: CareDx’s Allomap test, Google Smart Contact lens
- **Companion Dx**: Genentech-Roche: Herceptin – for HER2- positive breast cancer
- **Dx Tech/Services**: Nanostring’s nCounter life science tool, Illumina sequencers, 10X
- **Services**: Invitae aggregates many tests into a single catalog
The challenges associated with building a Dx business are also great.

<table>
<thead>
<tr>
<th>Cost Drivers</th>
<th>Revenue Drivers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology</td>
<td>Adoption</td>
</tr>
<tr>
<td>Science (trials, validation)</td>
<td>Reimbursement</td>
</tr>
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<td>FDA Regulation</td>
<td>Inefficiency of current Rx/Dx (companion, monitoring diagnostics)</td>
</tr>
<tr>
<td>Partnerships, data sharing</td>
<td>Enforceability of IP (competition)</td>
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Some challenges are greater for **Dx** than *Rx*

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<td>Adoption <em>need to educate patients and clinicians</em></td>
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<tr>
<td>Science (trials, validation)</td>
<td><em>Reimbursement challenging, one-time use of many diagnostics</em></td>
</tr>
<tr>
<td>FDA Regulation <strong>untested/charted pathways</strong></td>
<td>Inefficiency of current Rx/Dx (companion, monitoring diagnostics)</td>
</tr>
<tr>
<td>Partnerships, data sharing</td>
<td>Enforceability of IP (competition) <strong>IP uncertainty</strong></td>
</tr>
</tbody>
</table>

*Rx profit margins of ~20% vs. Dx single digit margins*
Innovation incentives have been depressed recently among several dimensions (with some improvement)

**Cost Drivers**
- Technology
- Science (trials, validation)
- FDA Regulation: July 2014: FDA begins process of developing LDT regulations
- Partnerships, data sharing: Jan 2015: President’s Precision Medicine initiative

**Revenue Drivers**
- Adoption
- CMS Reimbursement: introduction of clinical utility requirements ~2012, October 2015: CLFS price cuts
- Inefficiency of current Rx/Dx (companion, monitoring diagnostics)
- Enforceability of IP (competition): SCOTUS Prometheus, Myriad, Akamai, Bilski, Alice, Sequenom v. Ariosa,
Patents play a different role in Rx than in Dx, where the market is underdeveloped and multiplex tests combine innovations

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Traditional Rx</th>
<th>Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innovation</td>
<td>Chemical, biologic</td>
<td>Algorithmic, Multi-Actor, Genetic</td>
</tr>
<tr>
<td>Product Profile</td>
<td>Single molecule (blockbuster)</td>
<td>Trend towards multi-gene or expression test panel</td>
</tr>
<tr>
<td>Validation Model</td>
<td>FDA Clinical Trials</td>
<td>Variable based on class</td>
</tr>
<tr>
<td>Distribution</td>
<td>Pharmacy, OTC (small molecules)</td>
<td>CLIA-Qualified Laboratory (LDTs)</td>
</tr>
<tr>
<td>Revenue</td>
<td>“Drugs sell themselves.” Largely monopoly pricing.</td>
<td>Need to prove “better outcome,” develop demand, payment scheme.</td>
</tr>
</tbody>
</table>
These factors impact different business models differently

DX Startup X
Myriad has successfully leveraged their data, relationships, and increasingly diversified product line despite patent challenges...
Non-invasive prenatal testing (NIPT) innovation is “one of the bright spots” – more accurate + less invasive = rapid adoption
Companion diagnostics economics are compelling for drug companies at the clinical test phase

<table>
<thead>
<tr>
<th>Drug name and developer</th>
<th>Date of US approval</th>
<th>Relative development cost (% based on standard cost/patient)</th>
<th>Number of patients in clinical trials</th>
<th>Time from Phase I to New Drug Application filing (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xalkori® (crizotinib) – Pfizer</td>
<td>August 2011</td>
<td>100</td>
<td>960</td>
<td>1.8</td>
</tr>
<tr>
<td>Iressa® (gefitinib) – Astra Zeneca</td>
<td>May 2003</td>
<td>146</td>
<td>2,850</td>
<td>7.0</td>
</tr>
<tr>
<td>Tarceva® (erlotinib) – OSI and Genentech</td>
<td>November 2004</td>
<td>154</td>
<td>3,110</td>
<td>5.3</td>
</tr>
</tbody>
</table>

*Note: ‘Xalkori® approved based on a Phase II trial.*

Agarwal, Ressler, Snyder, 2015 (Pharmacogenomics and Personalized Medicine)
Reimbursement and adoption hurdles are chilling investment in VC investment in prognostic diagnostics

Heart transplant test maker to gov't agency: You're killing us

Oct 8, 2015, 2:44pm PDT
INDUSTRIES & TAGS: Health Care, Insurance, Biotech, Pharmaceuticals

Unless the federal agency that sets reimbursement rates for Medicare has a change of heart, a Peninsula company with a test that helps predict heart transplant rejection could have three months to live.

That's no exaggeration, says Peter Maag, the president and CEO of CareDx Inc. (NASDAQ: CDNA): A proposed 77 percent drop in the rate that Medicare would reimburse the Brisbane company for its AlloMap test is less than CareDx's costs.

Ron Leuty
Reporter, San Francisco Business Times

RELATED CONTENT
Feds to diagnostics companies: We're here to help (you lose money)
Thus, while there is VC investment in some sectors, e.g. in diagnostic imaging...
...the incentives for certain forms of Dx innovation are depressed. Innovation areas mentioned by interviewees:
- Venture-backed prognostic Dx. Costs and risks are too high, returns are too uncertain.
- Companion Dx for generic Rx. Poor business case.
- Dx for conditions without molecular/genetic bases: immunology, transplants, infections, cancer immunotherapy, autoimmune diseases. Science isn’t there.
Denying broad patentability on upstream correlations and methods impacts different sorts of diagnostic companies differently

- Easier for technology companies to offer multiplex tests in the absence of patent thickets
- Competition in tests reduce prices, increases access to tests, and barriers to technological innovation
- Limited incentive to invest in new uses of existing drugs
- Harder to build a standalone prognostic diagnostic business based on IP. Who will fund the next generation of Dx innovation and development?
Policy interventions beyond patents to close the gaps?

#1: Reimbursement – improve, rationalize, stabilize the reimbursement regimes

#2: Provide a cheaper faster path to validation and clinical utility
- Fund creation of big data sets, discovery and validation of correlations, development, incentivize dataset sharing/collaboration (Price, Sachs)

#3: Carrots and sticks
- FDA priority review vouchers for certain neglected diagnostics (Sachs)
- Regulatory exclusivity (Sachs), coupled with disclosure of algorithms (Price)
- FDA licensing requirements to facilitate sharing (Laakman), validation bounty to encourage vetting of black-box medicine (Price)
- Orphan diagnostics?