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Innovation Levers in Diagnostic Patents

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“Innovation Levers in Precision Medicine”

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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

<u>Types of Dx Innovation</u>

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 Invitae aggregates many tests into a single catalog

The challenges associated with building a Dx business are also great

Cost Drivers

Technology

Science (trials, validation)

FDA Regulation

Partnerships, data sharing

Revenue Drivers

Adoption

Reimbursement

Inefficiency of current Rx/Dx (companion, monitoring diagnostics)

Enforceability of IP (competition)

Some challenges are greater for Dx than Rx

Cost Drivers

Technology

Science (trials, validation)

FDA Regulation untested/charted pathways

Partnerships, data sharing

Revenue Drivers

Adoption need to educate patients and clinicians

Reimbursement challenging, one-time use of many diagnostics

Inefficiency of current Rx/Dx (companion, monitoring diagnostics)

Enforceability of IP (competition) IP uncertainty

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,

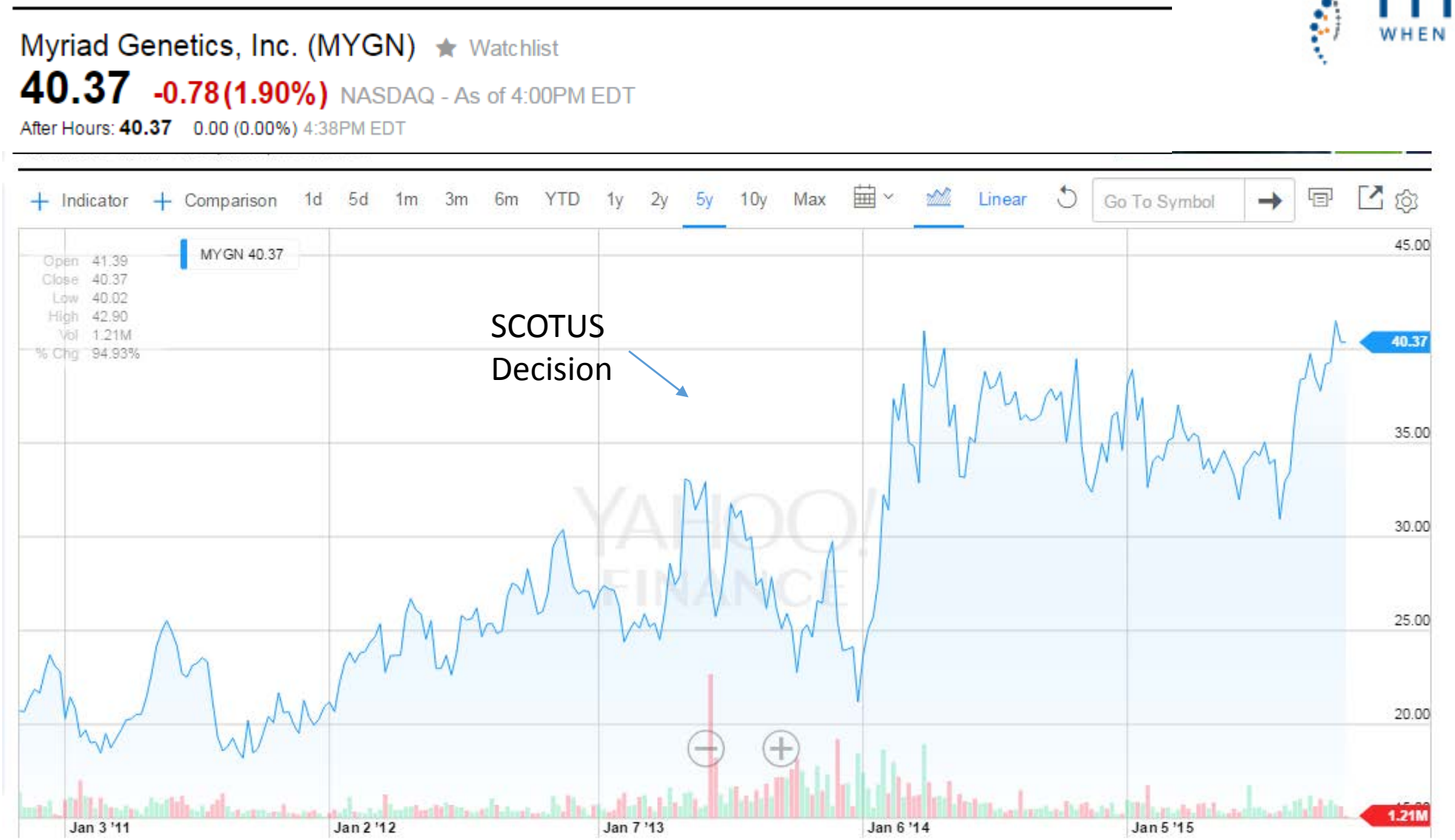
Patents play a different role in Rx than in Dx, where the market is underdeveloped and multiplex tests combine innovations

Dimension	Traditional Rx	Dx
Innovation	Chemical, biologic	Algorithmic, Multi-Actor, Genetic
Product Profile	Single molecule (blockbuster)	Trend towards multi-gene or expression test panel
Validation Model	FDA Clinical Trials	Variable based on class
Distribution	Pharmacy, OTC (small molecules)	CLIA-Qualified Laboratory (LDTs)
Revenue	"Drugs sell themselves." Largely monopoly pricing.	Need to prove "better outcome," develop demand, payment scheme.

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 2 Comparison of development costs, patient enrollment, and time for non-small-cell lung cancer drugs

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

Note: [a]Xalkori® approved based on a Phase II trial.

Roche

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

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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.

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Thus, while there is VC investment in some sectors, e.g. in diagnostic imaging…

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Diagnostic imaging equipment startups will be all but certain to set a new fundraising record for the sector for 2015, Timothy Hay reports for Dow Jones VentureWire. The third quarter of 2015 saw $145 million invested in U.S.-based privately held diagnostic imaging equipment companies, the largest single-quarter total that the sector has seen since industry tracker Dow Jones VentureSource began tracking totals in 1992.

DX Startup X

…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.

DX Startup X

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?

References: Price*, Cardozo L. Rev. (2015),* Sachs*, UC Davis L. Rev.(2015),* Laakman, *UCI L. Rev. (2015)*