Economics of Linked Diagnostics and Drugs: Policy and Business Implications

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Acknowledgments and Disclaimers

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- I work for Roche and Roche gives me monetary compensation for that work.

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Agenda

- **Background—Economic Rationale for Personalized Medicine**
- Pricing and Reimbursement Environments
- A Simple Economic Model of Value Creation and Capture
- Regulatory and Policy Environments: Implications & Discussion

Commercial/Economic Rationale

Personalized Medicine—and a linked PGx/Biomarker Dx-Tx--could create additional economic value in at least four ways:

1. As the non-responders or poor responders are removed from the pool of users, their costs (monetary and negative utility) for **adverse events** are avoided.
2. Better targeting can lead to a **greater volume of adoption** by good responders (some of whom would not have used the drug previously).
3. Good responders may have **improved compliance**—and therefore additional net benefits— especially for long-term chronic therapies.
4. The improvement of predictability of outcome creates additional value for patients as they face **less uncertainty**.

The Dx-Tx Incentive Barrier for Existing Products

- Given current pricing and reimbursement structures, it is widely recognized that for pharmaceutical products already on the market, a Rx manufacturer has limited financial incentive to invest in developing a diagnostic that would restrict the size of the market.
- The outlook for Dx manufacturers and Clinical Service Laboratories is also mixed.
- Biomarker discovery and validation is not a slam dunk. Considerable research investment may be required with no guarantee of success.

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Current Business Models

- Prescription Pharmaceuticals
  - » Intellectual property protection
  - » High risk/high margins
  - » Blockbuster financing (3 drugs fund 10)
  - » Detailing
- Diagnostics
  - » Manufacturers and Clinical Service Labs
  - » Low margin/High volume
  - » Compete on platform not content IP
  - » Customer and Competitor (Home brew)

Pricing and Reimbursement of Pharmaceuticals

- Patents confer some degree of monopolistic power.
- There is the countervailing monopsonistic power of buyers,
  - » Governments exert via mandating price controls on new drugs.
  - » Major types of price controls are: (1) therapeutic group reference prices, (2) international price referencing.
- The major exceptions ("free pricing" environments) have been U.S., Germany, and the UK (sort of).
- Outside U.S., drug companies have little latitude to increase price after a drug is on the market.
  - » Initial price negotiations are critical—outside the U.S.--for capturing any additional value created by innovation.

Pricing and Reimbursement of Diagnostics

- Compared to pharmaceuticals: competitive entry for given product is easier, and pricing and reimbursement are more controlled in most markets.
- Reference pricing is common, especially in EU.
- In the US, if a test is similar to others on the market (either by analyte or methodology), Medicare will set the payment rate by linking it to the payment rate of a currently marketed test – cross-walking.
- For de novo tests, Medicare will rely upon its local carriers to collect pricing data by a method known as gapfill. The data is used to establish the payment rate.
- CMS can set the "tone" for private payers, but not always a factor.
- Little consideration is given to the extra value provided by a new test, though health outcomes measures are increasingly requested. Recent CMS pay for performance initiatives may require cost effectiveness data.
- 1 – 3% of healthcare dollar; low volume low overall cost tests fly under private payer radar.

Summary: Current Pricing and Reimbursement Environments

- Pharmaceuticals:
  - » Somewhat value-based in the US.
  - » In EU, more price controls and limited flexibility.

- Diagnostic tests:
  - » Cost-based in both US and EU.

- Role of intellectual property: can only capture value above short-run marginal cost with patent protection and accompanying monopoly power.

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A Simple Framework and Example: Defining Economic Value

- What is "economic value"?

- "Value"= what fully informed patients would be willing to pay (WTP) for a new Dx or Tx based on:

  1) any cost savings,

  2) life years gained,

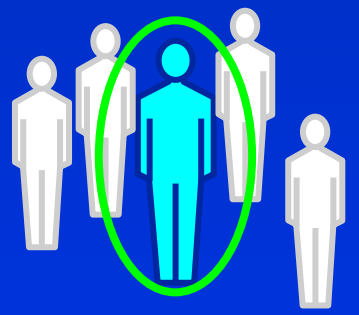
  3) improvements in quality of life or morbidity, and

  4) reduction in uncertainty.

Example: New Therapeutic (Tx) with and without Diagnostic Test (Dx)

A new response-prediction test (Dx)

- Accurately predicts response to the Tx
- Based on readily-detectable biomarker
- Screen all patients, only treat those likely to respond



Total Value Created by Tx with and without Dx

Base Case: Tx with no Dx

- 100 patients receive Tx
- 20% respond
- Willingness to pay (WTP): $1000 per patient
- Total value generated:
  - (100 x $1000) =$100,000

Tx with perfect Dx

- 100 patients are tested
- 20 receive Tx
- Willingness to pay (WTP): $6000 per patient
- Total value generated:
  - (100 x .2 x $6000) =$120,000

Therefore, a perfect Dx test has the potential to generate an additional $20,000.

Who captures the value created?

With Uncertainty

About Who Responds

(Value of Tx Alone)

$100,000

With Certainty

About Who Responds

(Value of Tx+Dx)

$120,000:

Who Captures This?

Scenario Analysis: Who Captures the Value?

Vary in terms of:

1. Whether Tx and Dx pricing reimbursement are value-based or cost-based, and how flexible they are over time.
2. Timing--whether Tx is already on the market. *(Ex post vs. Ex ante).*
3. Whether Dx has intellectual property protection—to prevent copycats– and is a barrier to entry for competitors.
4. Competitiveness of insurance market over short versus long term.

→**Examined five hypothetical scenarios.**

Other Assumptions--Costs

Costs (not charges) for Tx and Dx:

- Short-term marginal cost of Tx = **$5** per patient. (No sunk cost included).
- Long-term marginal cost of Dx = **$100.** (Sunk costs plus fair rate of return).

BASE CASE: Only Tx is available; 100 Patient population

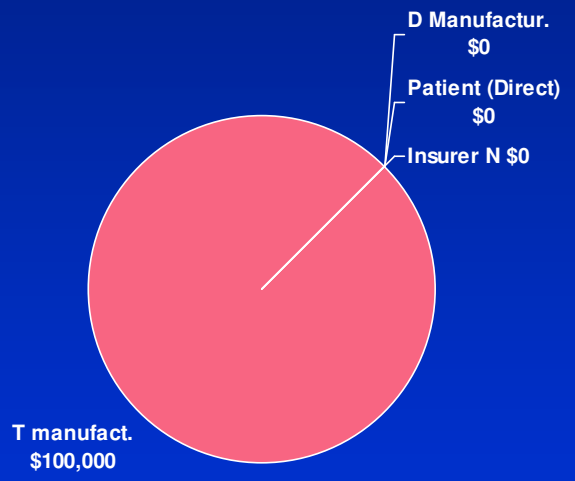
Key Assumptions:

- Tx already on market
- No Dx available for targeting.

Implications:

•Total value created is $20,000 lower than could be achieved with targeting

Value Distribution (Total=$100,000)



VALUE DISTRIBUTION:	
•T manufacturer:	$100K
•D manufacturer:	$ 0K
•Insurer N:	$ 0K
•Patient (Direct):	$ 0K
TOTAL	$100K

Scenario I: *Ex post* situation; new diagnostic; no Tx price flexibility; Dx with administered pricing

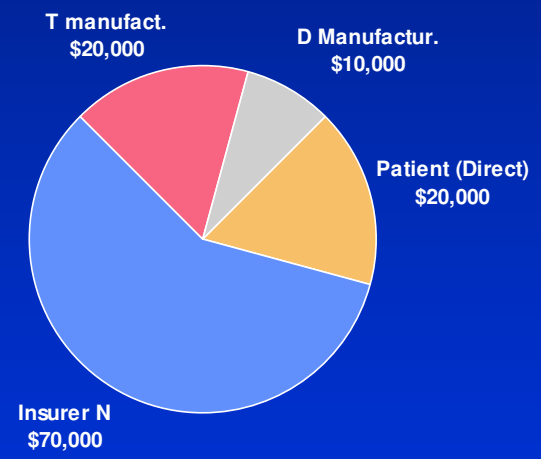
Key Assumptions:

- Tx already on market
- T can't raise price
- D set at cost=charge
- Insurer premiums unchanged

Implications:

- Tx price $1000→ -$80K revenues; 80% reduction profit; low incentive
- Dx price $100→Low profit; normal incentive
- Premium collected $100,000→Claims paid out $30,000; high incentive.
- Patient gets better value for money spent

Value Distribution (Total=$120,000)



VALUE DISTRIBUTION:	
•T manufacturer:	$20K
•D manufacturer:	$10K
•Insurer N:	$70K
•Patient (Direct):	$20K
TOTAL	$120K

Scenario II: *Ex post* situation with some Tx price flexibility; insurer budget constrained; Dx with administered pricing

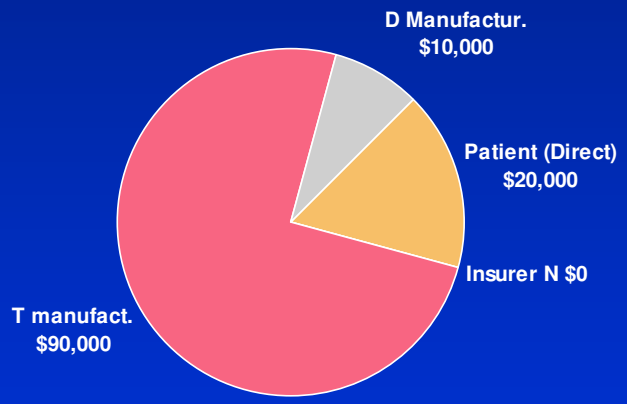
Key Assumptions:

- Tx on market already
- T can raise price to equal total current spending
- D set at cost=charge
- Insurer premiums unchanged

Implications:

- Manufacturer can set price at $4500 for the 20 responders; slightly worse off
- Dx price $100 Low profit; normal incentive
- Premium collected $100,000, Claims paid out $100,000.
- Patient gets better value for money spent

Value Distribution (Total=$120,000)



VALUE DISTRIBUTION:	
•T manufacturer:	$90K
•D manufacturer:	$10K
•Insurer N:	$ 0K
•Patient (Direct):	$20K
TOTAL	$120K

Scenario III: *Ex post* situation with no Tx price flexibility; Dx with price flexibility and IP protection

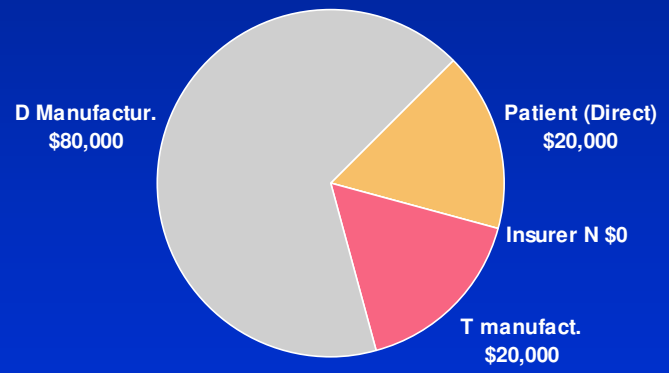
Key Assumptions:

- Tx on market already
- T can't raise price
- D can charge up to maximum value added
- Insurer premiums unchanged

Implications:

•D manufacturer captures majority of the value at $80,000; High incentive

Value Distribution (Total=$120,000)



VALUE DISTRIBUTION:	
•T manufacturer:	$20K
•D manufacturer:	$80K
•Insurer N:	$ 0K
•Patient (Direct):	$20K
TOTAL	$120K

Scenario IV: *Ex ante*, linked situation with Tx price flexibility and Dx cost-based reimbursement

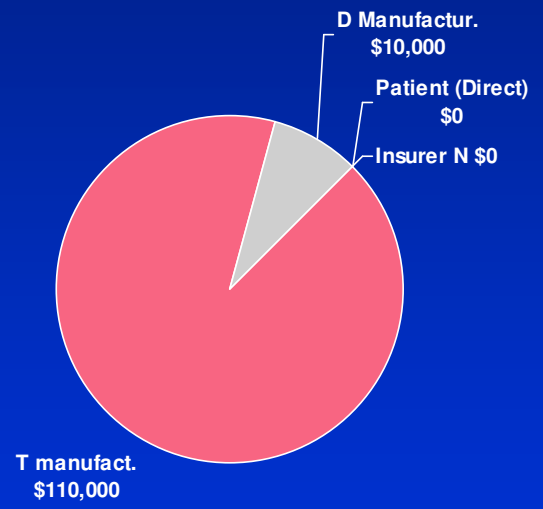
Key Assumptions:

- Linked Dx-Tx launched at same time
- T value-based pricing
- D set at cost=charge
- Insurer raises premiums in competitive market

Implications:

- **T manufacturer captures value created by targeting, including value of reduced uncertainty.**
- **Patients pay $120,000 in premiums, and they receive this value in services.**

Value Distribution (Total=$120,000)



VALUE DISTRIBUTION:	
•T manufacturer:	$110K
•D manufacturer:	$ 10K
•Insurer N:	$ 0K
•Patient (Direct):	$ 0K
TOTAL	$120K

Scenario V: *Ex ante* linked situation; Tx and Dx price flexibility; IP protection on both.

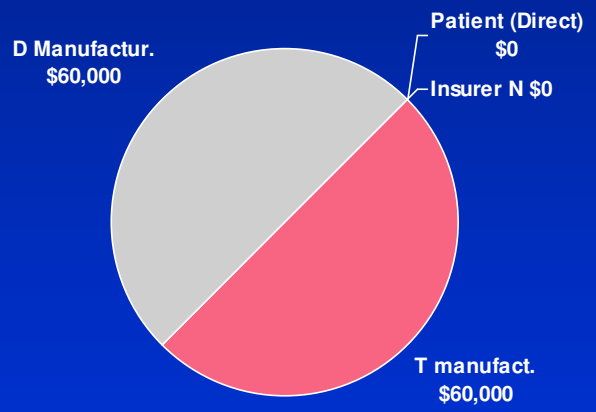
Key Assumptions:

- Linked Dx-Tx launched at same time
- Tx pricing is flexible and value-based.
- Dx pricing is flexible and value-based.
- Insurer raises premiums in competitive market

Implications:

- How the value capture is split between Dx and Tx is "arbitrary"—but competitive market conditions could be key determinant.

Value Distribution (Total=$120,000)



VALUE DISTRIBUTION:	
•T manufacturer:	$ 60K
•D manufacturer:	$ 60K
•Insurer N:	$ 0K
•Patient (Direct):	$ 0K
TOTAL	$120K

Limitations and Caveats

- Size of the uncertainty premium is assumed.
- This example assumes no adverse events in the non-responder group.
- This is theoretical model: empirically—in terms of explaining the small number of linked Dx-Tx PGx technologies available thus far--it's not known how much weight to put on these incentives versus the substantial scientific challenges.

Economic Implications of Scenarios

- Who will capture the value of a linked diagnostic-therapeutic depends on many factors:
  - » pricing and reimbursement constraints
  - » intellectual property protection
  - » competitive market conditions
  - » regulatory environment
  - » timing of entry
  - » insurance market competitiveness
  - » the characteristics of the diagnostic and therapeutic products.

Public Policy Implications from a Value Creation Perspective

- Flexible and value-based pricing and reimbursement for drugs and diagnostics could provide drug and diagnostic manufacturers a stronger incentive to evaluate the business case for linked diagnostics and therapeutics during drug development.
- Incentive-oriented reforms--linking pricing and reimbursement for drugs and diagnostics to value creation--may encourage personalized medicine.
- Strong, consistent, predictable IP environment remains key to pharmaceuticals. How content vs. platform protection is resolved in diagnostics will affect long-term business prospects and models.
- Regulatory requirements and allowances into market affect the Dx business case.

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Push and Pull Incentive Mechanisms vs. Regulatory Constraints

- **Pull:** Demand side/pricing & reimbursement; patents; market exclusivity.
- **Push:** Subsidies to the cost side (information as a public good):
  - » Public investment in basic research: NIH, CDC, public-private consortia, inter-agency collaborations.
  - » Little risk for academic/government researchers to seek markers.
- **Regulatory constraints**:
  - » "Market failure" rationale.
  - » Genomic data submission guidance (GDS) tries to strike a balance: voluntary information sharing or requirement?
  - » Concern is increasing Dx-Rx development costs without providing additional benefits in the form of new, targeted products. Or increasing costs above efficiencies gained by new products.
  - » Interaction with product liability: including tests in drug label could create costs without benefits.
  - » Not all tests regulated the same.

Diagnostics: Value Driver or Poor Step-child

- Some push but little pull
  - » CMS reimbursement for diagnostics - $1.00 in 1984 is 75 cents in 2005
- Little incentive to
  - » Undertake large prospective trials to determine clinical utility and economic outcome studies
  - » Go to FDA first (or even at all)
- Attitude towards diagnostics: should be better, faster and cheaper!
  - » From The Business Case for Pharmacogenomics - 2nd Edition:

  "Adoption of pharmacogenomics will require the participation of many players in the health care arena. One such player is the central reference laboratory, whose most important role is the standardization of diagnostic assays into tests that can be adopted for high-throughput and **low-cost** formats."

Regulatory Environment for Drugs and Diagnostics

- Historically, different pathways and units in the FDA (CDER/CDRH).
  - » Drugs:
    - Longer development and review times.
    - High evidence requirement for clinical utility to demonstrate favorable risk-benefit profile.
  - » Diagnostics:

    FDA approved IVDs
    - Many approved as “substantially equivalent” under 510(k).
    - For novel tests requiring PMA manufacturer must produce clinical utility data.

    Home Brews
    - Only regulated under CLIA and therefore do not share the same regulatory environment as IVDs.
    - Can be put on market without clinical utility data.

Current Landscape

- **Public and political awareness has grown over the implications of the home brew market**
  - » Differences cited in press
  - » Safety concerns by patient advocates
- **FDA/CDER drug labeling**
  - » Thiopurines, Camptosar, Tamoxifen, Warfarin - ?
  - » Recent flip flop on label change strategy
- **2004 – 2006 FDA/CDRH Enforcement Letters to labs**
- **CDER/CDRH Co-development concept paper**
  - » Draft guidance coming
- **July Senate hearing** "At Home DNA Tests: Marketing Scam or Medical Breakthrough?"
  - » GAO report and FDA Consumer Alert
- **FDA/CDRH issued two draft guidance**
  - » (1) Draft Guidance for Industry and FDA Staff - Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions OIVD
  - » (2) Draft Guidance for Industry, Clinical Laboratories, and FDA Staff - In Vitro Diagnostic Multivariate Index Assays (IVD MIAs)

Current Landscape

- **Kennedy's office** circulated draft bill "Laboratory Test Improvement Act"
  - » Requires registration and FDA approval in certain circumstances.
- **CMS** abandoned creation of genetics specialty under CLIA
  - » "CLIA regulation would not resolve the problem that these tests are not currently FDA-approved, and, therefore, not clinically validated".
- **Payer coverage/reimbursement response mixed**
  - » Negative tech assessments.
  - » Mixed coverage decisions.
  - » Medco Mayo Wafarin study.
  - » FDA Wafarin economic analysis – Billion $ savings!

Implications

- In short run, prospects for flexible and value-based pricing and reimbursement doesn't look promising.
  - » Pricing for drug is somewhat value-based, but limited flexibility.
  - » Under current reimbursement, there are limited incentives for Dx companies to do fundamental biomarker work.
  - » Dx product life cycle is typically shorter than Rx; particular test version ~3 years.
- Commercially, the more co-development of biomarkers and products that companies can do upfront, the better. This requires sufficient basic knowledge to support development of informed hypotheses. Can the NIH funded individual investigator model produce this type of knowledge?
- Companies need to explore biomarkers earlier in development.
  - » As with all things, those who assume the majority of the risk are in the best position to capture the majority of the reward.
  - » Test quality and utility will drive value creation and sustained market trust.

Concluding Comments

- There remains a fundamental uncertainty about how fast the progress of the science of biomarkers can be translated in useful applications in drug development and clinical use.
- When can/will Rx do it alone v. seek a Dx partner, and vice versa?
  - » Marriage made in heaven or shotgun wedding?
- At this stage, it is important to have appropriate flexibility in the regulatory system to be able to respond to the science (not force it), and to encourage the basic science and information sharing for hypothesis generation. This must be balanced against appropriate patient safety considerations.
- New Dx business models are emerging based on current regulatory environment. Efforts underway to change that environment to enhance patient safety.
- It is important to remember how significant the US health insurance "system" is not only in encouraging innovation, but also in influencing the form that innovation takes.
- Market ignite and guide, government enable.

Reducing Uncertainty Brings Value to Healthcare – Who Will Capture the Reward?

"Sure the medicine cured him .... but I'm the one who guessed it!"

Thank you!

Questions & Discussion?