

NEW YORK UNIVERSITY
JOURNAL OF INTELLECTUAL PROPERTY
AND ENTERTAINMENT LAW

VOLUME 6

FALL 2016

NUMBER 1

THE CHALLENGING ECONOMICS OF THE COMPANION
DIAGNOSTICS INDUSTRY: A COMPELLING CASE FOR
INVIGORATED PATENT PROTECTION

DORAN SATANOVE*

Diagnostic tests are a core component of modern health care practice: they determine a patient's susceptibility to developing cancer and other disorders; they diagnose biological conditions; they monitor the progress of disease; and they can assess the risk of disease recurrence. Ensuring their innovative growth is therefore an important issue in innovation policy. While legal scholarship addresses much about the relevance of patents and other forms of intellectual property protection for diagnostic methods as a general matter, far less attention has been paid to a distinct class of diagnostic tests that deserves its own innovation policy debate: companion diagnostic tests. This note seeks to draw more attention to the economic challenges facing the companion diagnostics industry. It begins by providing the necessary background to understand what companion diagnostic tests are, and why they are vital to the future of modern healthcare. It then explores the unique underlying incentive structure amongst the key industry stakeholders, revealing how the incentives of these stakeholders are misaligned in ways that impede the industry's growth. Relying on empirical data from case studies collected in pharmacology and biotechnology business literature, this note ultimately argues that the microeconomics of the companion diagnostics industry present a compelling case for invigorated patent protection of companion diagnostic tests.

* J.D. Candidate, New York University School of Law, 2017; B.Sc. Pharmacology, First Class Honors, McGill University. I thank Professors Rochelle Dreyfuss, Scott Hemphill, and Christopher Sprigman for their helpful comments on this note. I also thank the 2016-2017 Editorial Board of the NYU Journal of Intellectual Property & Entertainment Law for their assistance in the editing process. Any errors are my own.

INTRODUCTION.....	144
I. BACKGROUND.....	145
A. <i>Personalized Medicine Is the Future of Health Care</i>	145
B. <i>Companion Diagnostics Are An Essential Component of Personalized Medicine</i>	146
C. <i>Scientific Progress of Companion Diagnostic Development Outpaces Economic Progress</i>	149
II. COMPANION DIAGNOSTIC DEVELOPMENT FACES CHALLENGING ECONOMICS.....	150
A. <i>The Interests of the Stakeholders Are Diverse</i>	151
1. <i>The Payers</i>	151
2. <i>The Diagnostic Developers</i>	153
3. <i>The Pharmaceutical Companies</i>	155
4. <i>The Regulators</i>	157
5. <i>The Medical Providers</i>	158
B. <i>Co-Developed Companion Diagnostics Are More Conducive to Companion Diagnostic Microeconomic Growth</i>	159
1. <i>Companion Diagnostic Co-Development Leads to Better Evidence of Clinical Utility</i>	159
2. <i>Co-Development Uses Resources More Efficiently</i>	162
C. <i>A Misalignment of Stakeholder Incentives Impedes Necessary Companion Diagnostic Co-Development</i>	163
1. <i>Disparate Diagnostic and Pharmaceutical Business Models Hinders Co-Development</i>	163
2. <i>For Drug Companies, Co-Development Is Economically Preferable Over Post-Approval Companion Diagnostic Development</i>	164
3. <i>For Diagnostic Developers, Post-Approval Companion Diagnostic Development Is Economically Preferable to Co-Development</i>	167
D. <i>The FDA's Proposed Guidelines For Diagnostic Tests Could Exacerbate The Economic Challenges</i>	170
III. RE-INVIGORATING PATENT PROTECTION FOR COMPANION DIAGNOSTICS IS THE MOST EFFICIENT WAY TO STIMULATE COMPANION DIAGNOSTIC MICROECONOMIC GROWTH	172
A. <i>Strengthening a Weak Business Case</i>	172
B. <i>Patents Can Facilitate Co-Development</i>	173
C. <i>The Case Against Patents Does Not Apply to the Companion Diagnostic Niche</i>	174
D. <i>Patent Law's Subject Matter Eligibility Doctrine Has Undermined the Prospects of Patenting Companion Diagnostic Tests</i>	176
CONCLUSION	178

INTRODUCTION

Diagnostic tests are a core component of modern health care practice: they determine a patient's susceptibility to developing cancer and other disorders; they diagnose biological conditions; they monitor the progress of disease; and they can assess the risk of disease recurrence.¹ Ensuring their innovative growth is therefore an important issue in innovation policy. While legal scholarship addresses much about the relevance of patents and other forms of intellectual property protection for diagnostic methods as a general matter,² far less attention has been paid to a distinct class of diagnostic tests that deserves its own innovation policy debate: companion diagnostic tests.

This note seeks to draw more attention to the unique economic challenges facing the companion diagnostics industry.³ Part I provides the necessary background to understand what a companion diagnostic test is, and why it is vital to the future of modern health care. It presents the fundamental problem this note addresses, which is the sub-optimal growth that the companion diagnostics industry is currently experiencing. Part II focuses on why the industry faces challenging economics, relying on discussion and empirical case studies from pharmacology and biotechnology business literature. Part II.A introduces the key stakeholders in companion diagnostic test development. Part II.B argues that the empirical results of case studies suggest that one specific development pathway for companion diagnostics, referred to as the "co-development pathway," is most conducive to economic growth for the industry as a whole. Part II.C explains how the incentives of the stakeholders in the companion diagnostics industry are misaligned in ways that impede pursuit of the preferable co-development pathway.

¹ See *infra* Part I.B (defining diagnostic tests more specifically and elaborating on their importance to clinical health care practice).

² See, e.g., Christopher M. Holman, *The Critical Role of Patents in the Development, Commercialization and Utilization of Innovative Genetic Diagnostic Tests and Personalized Medicine*, 21 B.U. J. SCI. & TECH. L. 297 (2015); Eldora L. Ellison & David W. Roadcap, *Diagnostic Method Patents – Not All Hope Is Lost*, 22 NO. 15 WESTLAW J. INTELL. PROP. 1 (2015); Rebecca Eisenberg, *Diagnostics Need Not Apply*, 21 B.U. J. SCI. & TECH. L. 256 (2015); Note, *Diagnostic Method Patents and Harms to Follow-On Innovation*, 126 HARV. L. REV. 1370 (2013); Daniel K. Yarbrough, *After Myriad: Reconsidering the Incentives for Innovation in the Biotech Industry*, 21 MICH. TELECOMM. & TECH. L. REV. 141 (2014).

³ The authors who have addressed companion diagnostics specifically in the legal literature have yet to analyze the complicated underlying economic structure of industry. See, e.g., Alison Hill, Comment, *Ambiguous Regulation and Question Patentability: A Toxic Future for In vitro Companion Diagnostic Devices and Personalized Medicine?*, 2013 WIS. L. REV. 1463 (2013) (addressing the application of FDA regulations and patentability standards to companion diagnostic tests).

Part II.D addresses how recently-proposed FDA guidance on diagnostics tests might affect the economics of the companion diagnostics industry. Finally, Part III argues that the microeconomics of the companion diagnostics industry present a compelling case for invigorated patent protection of companion diagnostic tests.

I BACKGROUND

A. Personalized Medicine Is the Future of Healthcare

Imagine you have been diagnosed with early onset of a disease. Your doctor prescribes an expensive drug therapy that your insurance only partly covers, but you decide to pursue the treatment anyway because to you, health comes first. Weeks pass, but the disease shows no decline in progress. You wonder whether the drug is even working, and whether it ever will. The sad truth is that it probably isn't working, and it probably ever won't.

This predicament is common because a given drug, on average, is only effective in 30% to 40% of the prescribed patient population.⁴ One esteemed academic geneticist has suggested that over 90% of drugs work for less than half of those prescribed them.⁵ This problem is largely attributable to immense genetic variation across individuals.⁶ Genetic variation affects how drugs are absorbed and distributed; how they act on their targets; how they are metabolized; and how they are eventually excreted, all of which influence the efficacy and toxicity of drugs administered to patients.⁷ This forms the basis of the study of pharmacogenetics and pharmacogenomics, both of which, at the risk of oversimplification, assess

⁴ Jakka Sairamesh & Michael Rossbach, *An Economic Perspective on Personalized Medicine*, 7 THE HUGO JOURNAL 1, 2 (2013) (defining an "ineffective drug" as one where the costs from adverse events outweigh the benefits); see also Culbertson et al., *Personalized Medicine: Technological Innovation and Patient Empowerment or Exuberant Hyperbole?*, 8(3) DRUG DISCOVERY WORLD 18 (2007) (finding that the efficacy of a drug can vary from 30% to 75% depending on the drug class and therapeutic use).

⁵ Steve Connor, *Glaxo Chief – "Our Drugs Do Not Work On Most Patients"*, THE INDEPENDENT (London), Dec. 13, 2011, available at <http://www.rense.com/general69/glax.htm> (interviewing Allen Roses, an academic geneticist from Duke University and worldwide vice-president of genetics at GlaxoSmithKline).

⁶ See generally Ashraf G. Madian et al., *Relating Human Genetic Variation to Variation in Drug Responses*, 28(10) TRENDS GENETICS 487 (2012) (summarizing the evidence accumulated over the last three decades of how genetic variation plays a major role in drug response variability).

⁷ *Id.*

genetic characteristics of individuals and sub-populations to determine whether a drug will trigger a great response, bad response, or no response in a particular person.⁸ This is accomplished not only by analyzing an individual's genes, but also by analyzing the downstream biochemical and molecular processes that are influenced by genetic variation and that play important roles in managing the body's response to drugs.⁹ These distinct genetic, biochemical, and molecular characteristics of individuals are broadly referred to as "biomarkers," and studying them informs how clinical care management can be maximized and tailored to subpopulations of patients.¹⁰

The efforts of scientists to understand and develop innovative applications from the presence, absence, or level of expression of specific biomarkers, to improve health outcomes for patients, is the foundation of "personalized medicine." Personalized medicine represents the modern aspiration of a health care system that is predictive, preventive, personalized and participatory,¹¹ where every patient receives the right drug, at the right dose, at the right time.¹²

B. Companion Diagnostics Are An Essential Component of Personalized Medicine

The tools that scientists use to ascertain differences in biomarkers across patient populations are known as *in vitro* diagnostic devices. These are medical devices used to test human samples *outside* the living body, in test tubes (hence the name *in vitro*).¹³ For example, many women undergo testing of the *BRCA1* and

⁸ More specifically, pharmacogenetics is a field that explains how different people respond to a given drug in different ways. Pharmacogenomics explains the role of differences in the level of *expression* of given genes (i.e., how 'active' genes are), which also influences drug responses. DEVARAJAN THANGADURAI & JEYABALAN SANGEETHA, BIOTECHNOLOGY AND BIOINFORMATICS 37 (2015).

⁹ Madian, *supra* note 6, at 487.

¹⁰ Elizabeth Drucker & Kurt Krapfenbauer, *Pitfalls and Limitations in Translation from Biomarker Discovery to Clinical Utility and Personalised Medicine*, 4 THE EPMA JOURNAL 1, 2 (2013).

¹¹ Sairamesh & Rossbach, *supra* note 4, at 1.

¹² U.S. Food and Drug Administration, *Paving the Way for Personalized Medicine: FDA's Role in New Era of Medical Product Development*, <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf>. A more rigorous definition of personalized medicine would be "the use of genetic or other biomarker information to improve the safety, effectiveness, and health outcomes of patients via more efficiently targeted risk stratification, prevention, and tailored medication and treatment-management approaches." THANGADURAI & SANGEETHA, *supra* note 8, at 37.

¹³ *In vitro* is Latin for "in glass" and is a term of art for conducting tests on components of an organism isolated from or outside of their biological surroundings, such as in a test tube. OXFORD DICTIONARIES, http://www.oxforddictionaries.com/us/definition/american_english/

BRCA2 genes to inform them of their risk of developing breast and ovarian cancers; these tests are completed by *in vitro* diagnostic devices.¹⁴ *In vitro* diagnostic devices can also be used to diagnose disease, to inform the selection of treatment plans, to monitor the progress of disease, and to assess the risk of disease recurrence.¹⁵

This note is about one category of *in vitro* diagnostic devices in particular: companion diagnostics. Companion diagnostics are the class of *in vitro* diagnostic devices that assess the likely safety and efficacy of a particular drug in a particular patient.¹⁶ They accomplish this by assessing *pharmacodynamic* biomarkers – genetic, biochemical, and molecular characteristics that help predict the outcome of a drug’s interaction with its target.¹⁷ This enables scientists and physicians to identify segments of a patient population in which a drug will be most effective, ineffective, or even harmful. Companion diagnostic tests, through their analysis of biomarkers, can also inform the optimal dosages of drugs for different sub-segments of the relevant population.¹⁸ Companion diagnostics (“CDx’s”) are thus an essential component of personalized medicine because they are the vehicle for

in vitro. In contrast, “in vivo” testing is carried out in a living organism such as electrocardiography or diagnostic imaging (for example, X-rays). For a denser definition of *in vitro* diagnostic devices, see 21 C.F.R. § 803.3.

¹⁴ National Institute of Health, *BRCA1 & BRCA2: Cancer Risk and Genetic Testing*, NATIONAL CANCER INSTITUTE, <http://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet#q1> (last visited Apr. 22, 2016).

¹⁵ *In Vitro Diagnostics*, U.S. FOOD AND DRUG ADMINISTRATION, <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm> (last updated Oct. 24, 2016).

¹⁶ *Companion Diagnostics*, U.S. FOOD AND DRUG ADMINISTRATION, <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407297.htm> (last updated Oct. 5, 2016).

¹⁷ Drucker & Krapfenbauer, *supra* note 10, at 2. Pharmacodynamic biomarkers aren’t limited to genetic information. The other “biochemical and molecular characteristics” referred to include proteins, metabolites, essential elements, and tracers since all these molecules can affect drug action. Amit Agarwal et al., *The Current and Future State of Companion Diagnostics*, 8 PHARMACOGENOMICS AND PERSONALIZED MED. 99 (2015).

¹⁸ Zivana Tezak et al., *FDA and Personalized Medicine: In Vitro Diagnostic Regulatory Perspective*, 7 PERSONALIZED MED. 517, 522 (2010). For example, the drug Warfarin, which is used to treat blood pressure, is metabolized at different rates depending on what version of the *CYP2C9* gene a patient possesses. A CDx for Warfarin enables physicians to identify the 30% of European and Caucasian populations that metabolize Warfarin at a slower rate, and therefore require a lower dose, to avoid internal bleeding. Simon Sanderson et al., *CYP2C9 Gene Variants, Drug Dose, and Bleeding Risk in Warfarin-Treated Patients: A HuGenetTM Systematic Review and Meta-Analysis*, 7 GENETICS IN MEDICINE 97 (2005).

ascertaining the selection of the right drug, at the right dose, at the right time, for the right person.¹⁹

The benefits of more sophisticated methods of drug treatment selection attributable to CDx testing are plenty. Companion diagnostic testing can enhance the lifespan of patients, preventing them from undergoing therapies that are ineffective or cause harmful side effects.²⁰ “HerceptTest,” the first broadly-marketed companion diagnostic whose companion is the breast cancer drug trastuzumab (sold as “Herceptin”), identifies the 25-30% subpopulation with overexpression of the *HER-2* gene for which Herceptin is uniquely effective.²¹ The CDx “HLA-B*5701,” used alongside HIV treatment with the drug Abacavir, singles out the 10% of patients that will experience adverse reactions, saving the health care system costs from hospitalizations caused by these adverse side effects.²²

The more recently developed “Cobas 4800 BRAF V600E mutation test” illustrates how CDx’s ensure that drugs that are effective in smaller segments of the population still make their way to market. The actual benefit of this test’s companion drug, Zelboraf, in an unselected clinical population would have been around 50%, and therefore insufficient to obtain FDA approval.²³ Armed with the knowledge from the Cobas 4800 CDx that Zelboraf appeared to be more effective in patients with a certain mutation, *only* those patients with the mutation were

¹⁹ Stephen Naylor & Toby Cole, *Overview of Companion Diagnostics in the Pharmaceutical Industry*, DRUG DISCOVERY WORLD, <http://www.ddw-online.com/personalised-medicine/p92845-overview-of-companion-diagnostics-in-the-pharmaceutical-industry-spring-10.html> (last visited Feb. 22, 2016) (acknowledging widespread agreement that a companion diagnostic provides biological and/or clinical information that enables better decision making about the use of a potential drug therapy).

²⁰ E.g., Christopher P. Leamon & Mike A. Sherman, *The Rise of Companion Diagnostics: A Step Towards Truly Personalized Medicine*, ONCOLOGY BUSINESS REVIEW (OBR) GREEN, <https://obroncology.com/obrgreen/article/The-Rise-of-Companion-Diagnostics-A%20Step-Towards-Truly-Personalized-Medicine> (last visited Mar. 1, 2016).

²¹ Remarkably, the HerceptTest is now also used to identify those in the 22% subpopulation of patients with *stomach* cancer that are eligible for treatment with Herceptin. *Dako: FDA approval of Diagnostic Tests Provides Hope for Patients with Stomach Cancer*, THOMSON-REUTERS, <http://www.reuters.com/article/idUS47201+21-Oct-2010+MW20101021> (last visited Apr. 22, 2016).

²² A.R. Hughes, *Pharmacogenetics of Hypersensitivity to Abacavir*, 8 THE PHARMACOGENOMICS JOURNAL 365 (2008). See also Leamon & Sherman, *supra* note 20 (acknowledging the benefit of CDx’s at reducing health care costs by minimizing incidences of adverse reactions); Sairamesh & Rossbach, *supra* note 4 (same).

²³ Edward Blair et al., *Aligning the Economic Value of Companion Diagnostics and Stratified Medicines*, 2 J. PERS. MED. 257, 261 (2012).

selected for the Phase III trial. The results demonstrated a tremendous clinical benefit over chemotherapy.²⁴ In 2015, Zelboraf was the 391st-biggest drug in the world, with sales of \$219 million, an unobtainable achievement were it not for the CDx.²⁵ Evidently, the economic gains that can be realized from CDx's are substantial.²⁶

C. Scientific Progress of Companion Diagnostic Development Outpaces Economic Progress

The science and business literature expresses disappointment and dissatisfaction with CDx economic growth,²⁷ even though the science underlying CDx's has transformed dramatically since the launch of the HercepTest in 1998, and especially after the completion of the human genome project in 2003.²⁸ Acknowledgment of the potential of CDx's and personalized medicine is juxtaposed with statements that the use of CDx's "is currently constrained;"²⁹ that their progress has been "slower than expected;"³⁰ that their potential has "yet to be

²⁴ *Id.*

²⁵ Drug Analyst, Equity Research, *Zelboraf*, DRUGANALYST CONSENSUS DATABASE, <http://consensus.druganalyst.com/Roche/Zelboraf> (last visited Apr. 22, 2016).

²⁶ *But see* Gregory Zaric, *Cost Implications of Value-Based Pricing for Companion Diagnostic Tests in Precision Medicine*, PHARMACOECONOMICS, <http://link.springer.com/article/10.1007%2Fs40273-016-0388-x> (2016) (finding in some scenarios analyzed that companion diagnostic tests will lead to an increase in healthcare costs).

²⁷ *E.g.* Lisa M. Meckley & Peter J. Neumann, *Personalized Medicine: Factors Influencing Reimbursement*, 94 HEALTH POL. 91, 97 (2010) (concluding from six case studies that "the hype of personalized medicine technologies has outpaced its evidentiary support to date"); Mark D. Hughes, *Molecular Diagnostics Market Trends and Outlook*, ENTERPRISE ANALYSIS CORPORATION, <http://www.eacorp.com/images/PDFS/Molecular%20Diagnostics%20IVD%20Article%20v21%20MEK%20-%20Reprint%20FINAL.pdf> (last visited Mar. 3, 2016) (describing pharmacogenetics as a "disappointment" from the perspective of molecular diagnostic vendors despite initial enthusiasm about sales).

²⁸ *See e.g.*, Drucker & Krapfenbauer, *supra* note 10 (noting that thousands of putative biomarkers have been identified and published, dramatically increasing the opportunities for developing more effective therapeutics); James Buchanan et al., *Issues Surrounding the Health Economic Evaluation of Genomic Technologies*, 14 PHARMACOGENOMICS 1833 (2013) (acknowledging the promise of new genetic diagnostic technologies).

²⁹ Dee Luo et al., *A Quantitative Assessment of Factors Affecting the Technological Development and Adoption of Companion Diagnostics*, 6 FRONTIERS IN GENETICS 1 (2016).

³⁰ Adrian Towse et al., *Understanding the Economic Value of Molecular Diagnostic Tests: Case Studies and Lessons Learned*, 3 J. PERSONALIZED MEDICINE 288 (2013).

fully realized;”³¹ that “significant opportunity remains untapped;”³² and that there exist “several operational challenges.”³³ In fact, as of 2014, CDx’s made up only 3% of the worldwide market for *in vitro* diagnostics.³⁴ They account for a small percentage of today’s health insurance expenditures.³⁵ Many have yet to gain widespread adoption,³⁶ and few CDx-drug pairs have been approved since Herceptin’s breakthrough.³⁷ Forecasts show this trend will continue.³⁸ In the meantime, society is left with a plethora of commonly used and costly therapeutic agents that are ineffective in a high percentage of patients prescribed them, even though the science says the health care industry could know better.³⁹ Scientific challenges do undoubtedly remain,⁴⁰ but the consensus is loud and clear that the growth rate of CDx’s is sub-optimal and disappointing in light of how far the science has progressed. The obstacles responsible for this less-than-optimistic view of CDx-driven personalized medicine are *not* scientific; they are economic.

II

COMPANION DIAGNOSTIC DEVELOPMENT FACES CHALLENGING ECONOMICS

This Part explores the economic challenges of the CDx industry, drawing from the results of several case studies from the pharmacologic literature that examine the most successful CDx’s on the market. Part A introduces the key stakeholders in CDx development, and begins to reveal how the stakeholders’

³¹ Mark R. Trusheim et al., *Quantifying Factors for the Success of Stratified Medicine*, 10 NATURE REVIEWS: DRUG DISCOVERY 817 (2011).

³² Robert McCormack et al., *Co-development of Genome-Based Therapeutics and Companion Diagnostics*, 311 J. AMER. MEDICAL ASSOC. 1395 (2014).

³³ Sairamesh & Rossbach, *supra* note 4, at 2; Jerel Davis et al., *The Microeconomics of Personalized Medicine*, MCKINSEY & COMPANY, <http://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/the-microeconomics-of-personalized-medicine>. (last visited Feb. 22, 2016).

³⁴ Agarwal et al., *supra* note 17, at 106 (2015).

³⁵ *E.g.*, Joshua Cohen et al., *Clinical and Economic Challenges Facing Pharmacogenomics*, 13 PHARMACOGENOMICS J. 367 (2013) (purporting to explain why there is a lack of comprehensive reimbursement of CDx’s).

³⁶ Hughes, *supra* note 22; Naylor & Cole, *supra* note 19 (companion diagnostics have been “cautiously adopted”); Sairamesh & Rossbach, *supra* note 4, at 2 (“[O]nly a few personalized medicine based diagnostic tests have achieved high levels of clinical adoption.”).

³⁷ Drucker & Krapfenbauer, *supra* note 10, at 44; Luo et al., *supra* note 29, at 2-3.

³⁸ Cohen et al., *supra* note 35.

³⁹ *E.g.* McCormack et al., *supra* note 32 (calling attention to the fact that many commonly-used and costly agents don’t have validated CDx tests and are ineffective in large number of patients).

⁴⁰ *E.g.* Drucker & Krapfenbauer, *supra* note 10, at 3 (identifying challenges in developing biomarkers for CDx tests that are of high sensitivity and specificity).

incentives are misaligned. Part B examines the important distinction between *co-developed* CDx's (CDx's that are developed in tandem with their companion drug), and *post-approval* CDx's (CDx's that are developed after their companion drug has been put on the market). It argues that co-developed CDx's are economically and socially preferable to post-approval ones, and that stimulating CDx-drug co-development is a necessary step to move the CDx industry forward as a whole. Part C presents the challenges in incentivizing diagnostic companies and drug companies to engage in the requisite collaboration for CDx-drug co-development.

A. *The Interests of the Stakeholders Are Diverse*

The key stakeholders in the CDx industry are the payers, diagnostic developers, drug companies, the regulators, and healthcare providers.

1. *The Payers*

The payers possess power in the CDx industry because, ultimately, their reimbursement policies allow or restrict access to the market.⁴¹ Payers include governmental and private organizations that manage reimbursement of healthcare costs. They vary in their size, scope, and management of patient care.⁴²

Companion diagnostics may pose large potential cost savings to payers by eliminating payments for ineffective drugs and reducing the costs associated with adverse events.⁴³ But this is no guarantee.⁴⁴ Consider the overall cost savings to payers as a function of: (1) the cost of the treatment decision in the absence of the CDx; (2) the cost of the treatment decision made in light of the CDx; (3) the probability that the CDx will change the treatment decision; and (4) the cost of administering the CDx.⁴⁵ Permutations of these variables reflect some interesting results. Most obviously, if the CDx has a low probability of changing a patient's

⁴¹ See generally P.M. Danzon, *Pricing and Reimbursement of Biopharmaceuticals and Medical Devices in the USA*, 3 ENCYCLOPEDIA OF HEALTH ECONOMICS 127 (2014) (providing an overview of payer reimbursement for drugs and medical devices in the USA); see also P. Deverka, *Pharmacogenomics, Evidence, and the Role of Payers*, 12 PUB. HEALTH GEN. 49 (2009).

⁴² Eric Faulkner et al., *Challenges and Development and Reimbursement of Personalized Medicine-Payer and Manufacturer Perspectives and Implications for Health Economics and Outcomes Research*, 15 VALUE HEALTH 1162, 1163 (2012).

⁴³ E.g., Davis et al., *supra* note 33 (estimating that CDx's save \$600 to \$28,000 per patient).

⁴⁴ See Faulkner et al., *supra* note 42 (qualifying the fact that payers recognize the potential advantages of personalized medicine with the notion that they are cautious regarding the potential downsides of the CDx approach).

⁴⁵ See Davis et al., *supra* note 33.

treatment decision (for example, the CDx reveals that only 10% of a patient subpopulation should avoid an expensive drug therapy), the cost savings to the payer will be less than if the CDx revealed that 50% of the patient population should avoid the drug therapy. Whether either of these scenarios presents a net savings to the payer, however, will depend on the cost of the new treatment decision. If a CDx reveals that either 10% or 50% of a patient subpopulation should avoid a particular drug therapy because it will be ineffective or cause adverse side effects, the cost of the alternative treatment could still be significantly higher. And while the cost of the tests themselves are not prohibitive (some are priced as low as \$40 per test; many cost under \$300 per test, and few cost over \$1000 per test),⁴⁶ the consequences of reimbursing every eligible member of the patient population, compared to the savings when only a few patients benefit, are uncertain.⁴⁷ The savings to payers presented by CDx's are therefore variable.

The quality of clinical utility evidence available is also a key factor in payer decision-making.⁴⁸ Clinical utility evidence is the body of evidence that showcases the added value of a CDx to treatment management, as compared with treatment management without a CDx. The more the CDx has been clinically tested, the more evidence is available to assure a payer that the variations in biomarkers revealed by the CDx actually lead to overall health care savings in the patient population.⁴⁹

Analyzing cost savings to payers is also complicated by the high rate of customer turnover for commercial payers in the United States.⁵⁰ This factor is most relevant to patients diagnosed with a long-term disease: a payer might cover the cost of an initial screening and CDx that reveals which drug therapy will be most optimal if and when the disease begins to progress. If that patient leaves the payer before the disease begins to progress, the payer will not see the benefit in the reduction of cost of the patient's future treatments.⁵¹

⁴⁶ Cohen et al., *supra* note 35, at 387.

⁴⁷ *Id.*

⁴⁸ See *infra* Part II.B.1 for further discussion on the importance of the quality of clinical utility evidence to payer decision-making, and the consequences arising from the difficulties in assessing clinical utility.

⁴⁹ Paul Engstrom et al., *NCCN Molecular Testing White Paper: Effectiveness, Efficiency and Reimbursement*, 9 J. NAT'L COMPREHENSIVE CANCER NETWORK (Supl. 6) S1 (2011)

⁵⁰ Sairamesh & Rossbach, *supra* note 4, at 3.

⁵¹ *Id.* (turnover also makes it less attractive to reimburse *prophylactic* tests that minimize likelihood of disease occurring later in life).

All of these factors lead payers to behave variably and unpredictably.⁵² Payers will differ in terms of which CDx's and drugs they choose to cover and when, with some enforcing strict coverage rules, and others extending more room for medical providers to determine what they deem to be the appropriate care for their patients.⁵³

2. *The Diagnostic Developers*

Diagnostic test developers range from modest research labs to large companies. Across the entire range, significant obstacles exist in the way of profitability.⁵⁴

Generally, the potential revenues to be generated from a CDx are not substantial. Diagnostics are valued and paid for at far lower levels compared to their companion drugs. While common drug treatments cost between \$15,000 and \$149,000 per patient in the United States, the CDx's range from \$40 to \$2,000 per test.⁵⁵ One economic simulation of a co-developed CDx using favorable assumptions for the diagnostic developer⁵⁶ found the expected net present value (eNPV) of CDx tests to be 2-4% of the eNPV of their corresponding drugs.⁵⁷ The difficulty in reaping large revenues from CDx's is augmented by the fact that few diagnostic developers have a large enough sales force to educate healthcare providers about ordering the appropriate CDx.⁵⁸

⁵² See *infra* Part II.D for further discussion of the variability of payer decision making.

⁵³ For example, the payer company Aetna, does not cover *CYP2C9* testing for Warfarin, citing the lack of clinical and cost-effectiveness evidence in their "Policy on Pharmacogenomic Testing" as a reason for not covering the test, while the payer Cigna does cover the test. Meckley & Neumann, *supra* note 27, at 94.

⁵⁴ E.g. Davis et al., *supra* note 43; McCormack et al., *supra* note 32 (describing the financial position of diagnostic companies as "fragile").

⁵⁵ Joshua P. Cohen & Abigail E. Felix, *Personalized Medicine's Bottleneck: Diagnostic Test Evidence and Reimbursement*, 4(2) J. PERSONALIZED MED. 163 (2014); Agarwal et al., *supra* note 17 (emphasizing that the potential revenue from a "blockbuster" CDx is rarely over \$100 million while annual sales of the companion drug can reach up to ten times that amount).

⁵⁶ These were that the drug company would absorb most of the diagnostic development costs and that the diagnostic company would receive net \$200 payer reimbursement per test. Trusheim et al., *supra* note 31, at 829.

⁵⁷ *Id.*

⁵⁸ Agarwal et al., *supra* note 17; see also McCormack et al., *supra* note 32 (noting that the financial position of diagnostic companies for developing a CDx is often fragile); Leland Ekstrom et al., *Well Begun Is Half Done: Success Factors for Companion Diagnostic Launch*, in PERSONALIZED MEDICINE, THE PATH FORWARD, 28 (McKinsey & Company, eds. 2013).

Beyond the difficulties in obtaining a revenue stream, the development costs of a CDx are substantial, varying widely based on which of two possible classes of CDx's the developer chooses to pursue. The first class of CDx a developer may pursue includes commercial CDx testing kits ("commercial CDx's"). As the name implies, these CDx's are developed with the intention of being commercialized and broadly marketed to other labs, to physicians, and to the public through direct-to-consumer marketing.⁵⁹ Companion diagnostics can be co-developed alongside a particular drug and used in the drug's clinical trials, or they can be developed "post-approval;" that is, after their corresponding drug has been FDA approved for market. The CDx's in the second class are "laboratory developed CDx's" ("LDT-CDx's"). These are CDx's that are manufactured and offered within a single laboratory and are *not* sold as commercial products in the marketplace. Instead, they are sold as services, with the diagnostic developing lab being the sole performer of the CDx (unlike commercial CDx's, which can be performed by all entities to which the CDx is marketed).⁶⁰ LDT-CDx's are most often not co-developed with drugs, since co-developed CDx's are typically commercially marketed with their companion drug.

The development costs for a commercial CDx are far greater than for an LDT-CDx, primarily because the FDA imposes costlier regulatory hurdles for commercial CDx's.⁶¹ The FDA has actually exercised its enforcement discretion with regard to LDT-CDx's, which are only subject to minimal regulation by the Center for Medicaid and Medicare Services (CMS).⁶² Developers pursuing commercial CDx's thus face greater upfront expenses. It is perhaps not surprising that the value of commercial CDx's in the market is far less than that of LDT-

⁵⁹ For example, a diagnostic company that owns several clinical laboratories may develop a CDx in one of its labs and then transfer the CDx to several clinical labs within its network. This would be a considered a commercial CDx. U.S. Food & Drug Admin., Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) (Oct. 3, 2014), <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm416685.pdf> [hereinafter, FDA Guidance for LDTs].

⁶⁰ For example, a laboratory will use peer-reviewed articles and its own instruments to develop a testing protocol that will be verified and validated within the lab. Once validated, the CDx can be used by the lab to provide clinical diagnostic results for health care providers. *Id.* LDT-CDx's are sometimes developed as novel CDx's for post-approval drugs on the market, but more often, they are developed as copies of co-developed CDx's.

⁶¹ The additional cost of obtaining FDA approval for a CDx as compared to an LDT-CDx can range from \$24–\$75 million. Frost & Sullivan, *Opportunities and Growth Strategies for the APAC IVD Industry*, SLIDESHARE, <http://www.slideshare.net/FrostandSullivan/diagnostic-world-asia-apac-ivd-outlook-2010> (last visited Feb. 29, 2016).

⁶² Agarwal et al., *supra* note 17.

CDx's: in 2012, the value of commercial CDx's was \$405 million and the value of LDT-CDx's was \$1.17 billion.⁶³

Difficulties in obtaining payer reimbursement further complicate the business model of a diagnostic developer. Payer reimbursement is essential to assist in covering the extensive upfront costs just described, but the amount of time to payer coverage is unpredictable as previously alluded to in Part II.A.1 and further discussed in Part II.B. The same is true for the time until physicians adopt the tests. The diagnostic developer must consider *ex ante* what minimum economic data and evidence of clinical utility will be necessary to obtain payer reimbursement, and how to get past potential barriers in the adoption of the tests by medical providers.⁶⁴

In summary, CDx development is more capital-intensive compared to other diagnostic tests, and the diagnostic developer faces a high degree of uncertainty in securing returns which depend heavily on the regulatory requirements at play and payer reimbursement practices.

3. *The Pharmaceutical Companies*

Pharmaceutical companies are wholly distinct from diagnostic developers. The latter employ completely different technology in their development platforms compared to the former. The business models and economics of the pharmaceutical industry are equally distinct from diagnostics, as each industry develops products with different life cycles and timelines, customers, and regulatory requirements.⁶⁵ The top priorities for a pharmaceutical company are to obtain as much value as possible after market launch of their drugs, and, to a lesser extent, reduce development costs.⁶⁶

Decisions to pursue CDx development versus conventional "treat-all" approaches are complex, and depend on many factors including the size of the patient population, the class of disease the drug targets, the degree of payer management of the target indication, and the potential for value differentiation.⁶⁷

⁶³ *Id.*

⁶⁴ Faulkner et al., *supra* note 42, at 1166.

⁶⁵ Maham Ansari, *The Regulation of Companion Diagnostics: A Global Perspective*, 47 THERAPEUTIC INNOVATION & REGULATORY SCIENCE 405, 406 (2013).

⁶⁶ See Davis et al., *supra* note 33 (claiming that the potential to generate greater value after marketing is more important for the economics of pharmaceutical companies than making development more productive).

⁶⁷ Faulkner et al., *supra* note 42, at 1165.

Each of the above factors is further influenced by whether the CDx is co-developed with its companion drug, or developed post-approval. Co-development of a CDx with its companion drug has several benefits for a pharmaceutical company.⁶⁸ The CDx can significantly reduce the costs of clinical trials because if the drug company knows in advance which patient subpopulation is most likely to benefit from it, it can tailor the trial to that specific subpopulation. This increases the chance of demonstrating drug efficacy and of obtaining approval, and can decrease the amount of time it takes to get the drug to market.⁶⁹ At the same time, however, there is a risk that a suitable diagnostic will not be approved for use in clinical trials with the drug or be discovered at all.⁷⁰ Other studies have explored additional factors suggesting that savings in CDx co-development for drug companies may be offset by other costs associated with using a CDx in clinical trials.⁷¹

Post-approval CDx's have the potential to take a well-known drug therapy on the market that is a second-line or third-line treatment option for the general population, and turn it into a first-line treatment for a select group of patients.⁷² The drug Tarceva is a good example. Since its CDx was approved in 2013, Tarceva's forecast changed to projections of increased growth over the next five years.⁷³ Post-approval CDx's, on the other hand, have the potential to divide the treatable population of patients into sub-segments, thereby decreasing the number

⁶⁸ See *infra* Part II.B.1 for further dissection of the incentives of drug companies to engage in CDx co-development.

⁶⁹ Davis et al., *supra* note 33; Drucker & Krapfenbauer, *supra* note 10, at 3; Sairamesh & Rossbach, *supra* note 4, at 3; Leamon & Sherman, *supra* note 20. For example, Pfizer's drug Zalkori was able to obtain FDA approval in a lightning-fast 1.8 years with the assistance of its co-developed CDx, the ALK Break Apart FISH Probe Kit. Agarwal et al., *supra* note 17. The drugs Tarceva and Iressa, which were *not* initially approved with a CDx, took 5.3 and 7.0 years respectively. *Id.*

⁷⁰ *E.g.* Davis et al., *supra* note 33. For further discussion on the risks associated with CDx co-development to a diagnostic developer see *infra* Part II.B.2.

⁷¹ Sairamesh & Rossbach, *supra* note 4, at 4 (noting that co-development might increase costs and delay drug developments since clinical trials must frequently be larger when CDx's are employed and that this is more likely to occur when the drug's mechanism of action is less well-understood); Mark R. Trusheim, *Economic Challenges and Possible Policy Actions to Advance Stratified Medicine*, 9 PERSONALIZED MEDICINE 413, 414 (2013) (listing other factors that offset the potential gains of co-development).

⁷² Agarwal et al., *supra* note 17.

⁷³ *Id.* The increase in sales growth is modest, but it is so rare for a drug to experience faster growth eight years after its initial launch, that the example is worth nothing.

of patient customers.⁷⁴ A post-approval CDx also has the potential to direct segments of the patient population to a competitor's product, a drug company's worst nightmare. Ultimately, the potential costs and benefits of post-approval CDx's for drug companies are also difficult to ascertain.

The incentives of drug companies to engage in CDx co-development with diagnostic developers, and the advantages and disadvantages posed by the development of post-approval CDx's, are discussed in greater detail in Part III. For now, it is simply worth noting that the incentive structures are complicated and that there is clear potential for the incentives of drug companies and diagnostic developers to point in opposite directions.

4. *The Regulators*

As noted earlier, the FDA regulates commercial CDx's, and has exercised its enforcement discretion for LTD-CDx's, leaving their regulation in the hands of the CMS.⁷⁵ The CMS and the FDA have different regulatory goals. The FDA addresses "the safety and effectiveness of the diagnostic tests themselves and the quality of the design and manufacture of the diagnostic tests."⁷⁶ The CLIA regulates "the quality of the clinical testing process itself, mostly by assessing the quality of the clinical laboratory."⁷⁷

The FDA's regulatory oversight of commercial CDx's is more substantial than the CMS's regulatory oversight of LDT-CDx's. The CMS only evaluates LDT-CDx's for their analytical validity, which is the ability of a CDx to measure the biomarker it is intended to measure.⁷⁸ The FDA evaluates the analytical validity of commercial CDx's, but it also evaluates the tests' *clinical* validity – the ability of the test to predict the likelihood of a clinical outcome from its measurement of a biomarker.⁷⁹ In addition, commercial CDx's are subject to pre-market review, systematic adverse event reporting, and a process for corrections or

⁷⁴ Davis et al., *supra* note 33; Sairamesh & Rossbach, *supra* note 4, at 4 (noting that CDx's divide the market of treatable patients into groups and clusters thereby reducing market share of the patient population).

⁷⁵ Amanda Sarata & Judith Johnson, *Regulation of Clinical Tests: In Vitro Diagnostic (IVD) Devices, Laboratory Developed Tests (LDTs), and Genetic Tests*, Congressional Research Service Report 11 (2014). The Clinical Laboratory Improvement Amendments Act (CLIA) of 1988 provides the CMS with authority to regulate clinical labs that carry out diagnostic testing. 42 U.S.C. § 263(a).

⁷⁶ Sarata & Johnson, *supra* note 75, at ii.

⁷⁷ *Id.* at 11.

⁷⁸ *Id.*

⁷⁹ *Id.*

recalls.⁸⁰ This discrepancy in the level of regulatory overseeing between LDT-CDx's and commercial CDx's, and between *all* laboratory-developed tests (LDTs) and commercial diagnostic tests for that matter, has attracted significant attention in light of the increasing complexity of LDTs and their expansion from academic institutions to commercial ones.⁸¹ The FDA has developed "serious concerns" regarding the lack of independent review of the evidence of clinical validity of LDTs generally, including LDT-CDx's.⁸² Consequently, it issued a draft guidance in the Federal Register in October 2014 to begin regulating LDTs on a risk-based approach.⁸³ If the guidance were to become final, LDT-CDx's would be classified under the highest-risk category and in effect would be subject to the same regulatory standards as commercial CDx's.⁸⁴ The economic implications of the current regulatory overseeing regime as well as the FDA's recent proposal are discussed in Part III.

5. *The Medical Providers*

Economically, CDx's can have a positive or negative impact on medical providers depending on what the results of the test suggest for further treatment. Under the current procedure-based reimbursement for providers, physicians are incentivized to use CDx's that will increase, rather than decrease, the number of subsequent procedures a patient requires.⁸⁵ Where diagnostic tests make existing procedures unnecessary, doctors might be disinclined to perform them. Providers are likely to wait some time to ascertain the effects of a CDx on treatment procedures before deciding whether it is in their economic interest to use the test. Providers might not pay much attention to companion diagnostics at all if they aren't committed to molecularly-guided therapeutic decisions.⁸⁶ Educating

⁸⁰ *Id.*

⁸¹ See, e.g., Report of the Secretary's Advisory Committee on Genetics, Health and Society, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*, http://oba.od.nih.gov/oba/sacghs/reports/sacghs_oversight_report.pdf (April 2008).

⁸² See, e.g., Office of Public Health Strategy and Analysis, FDA, *The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies* (Nov. 16, 2015) (examining events involving 20 LDTs with inaccurate results that placed patients at risk).

⁸³ U.S. Dep't of Health and Human Services, FDA, Center for Devices and Radiological Health, *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*, Draft Guidance, Oct. 2014 [hereinafter FDA Draft Guidance].

⁸⁴ *Id.* at 23-27.

⁸⁵ Sairamesh & Rossbach, *supra* note 4, at 6; Davis et al., *supra* note 33.

⁸⁶ Ildar Akhmetov et al., *Market Access Advancements and Challenges in "Drug-Companion Diagnostic Test" Co-Development in Europe*, 5 J. PERSONALIZED MED. 213, 224 (2015).

providers on newly-developed CDx's is therefore critical to clinical adoption of CDx's and their commercial success.

The subsequent sections take on the more complicated task of analyzing how the stakeholders' incentives interact in the context of developing CDx's along the various pathways, and the economic consequences for the CDx industry that flow therefrom.

*B. Co-Developed Companion Diagnostics Are More Conducive to CDx
Microeconomic Growth*

This Part argues that CDx's that are co-developed with their companion drugs provide greater economic and social benefit over post-approval CDx's, drawing on the empirical findings of case studies of CDx-drug pairs on the market for support.

1. CDx Co-Development Leads to Better Evidence of Clinical Utility & Greater Patient Access

Clinical utility refers to the body of evidence that showcases the added value of a CDx to treatment management.⁸⁷ A CDx may accurately measure a biomarker (i.e., be analytically valid), and from that measurement, a CDx may accurately predict how a particular subpopulation will respond to a drug (i.e., be clinically valid). But that doesn't necessarily mean that the benefit of this knowledge outweighs the costs of developing the CDx; that is, that the CDx has strong clinical utility. To ascertain the latter, controlled studies must be conducted.

Case studies find that the quality of clinical utility and cost-effectiveness evidence for CDx's is highly variable, and often very weak.⁸⁸ For instance, the 2013 Cohen et al. study analyzed data from the Cost Effective Analyses ("CEA") Registry, a publically-available database of over 2,000 different cost-utility analyses published in peer-reviewed journals, for eight CDx-drug pairs.⁸⁹ It found that the quality and quantity of both the clinical and cost-effectiveness studies in the registry varied significantly, with "surprisingly few CEAs show[ing] conclusive evidence as to whether [the companion diagnostic] represents 'good value' to society."⁹⁰ Likewise, in 2014, Cohen et. al. and Towse et al. found a

⁸⁷ Engstrom et al., *supra* note 49, at S-3.

⁸⁸ Cohen & Felix, *supra* note 55; Cohen et al., *supra* note 35; Meckley et al., *supra* note 27; Towse et al., *supra* note 30.

⁸⁹ Cohen et al., *supra* note 35.

⁹⁰ Cohen & Felix, *supra* note 55, at 386.

dearth of evidence concerning the comparative clinical effectiveness of CDx-drug combinations.⁹¹

Nevertheless, the CDx's from the case studies demonstrate that the greatest clinical utility evidence base is typically found for CDx's that were co-developed rather than developed post-approval.⁹² Because the FDA doesn't actually assess a CDx's clinical utility (the FDA only assesses analytical and clinical validity),⁹³ the fact that co-developed CDx's have a better clinical utility evidence base is not due to the fact that they are FDA regulated and commercially marketed.⁹⁴ In fact, seven of the eight post-approval CDx's in the Cohen, 2014 study, for example, were indeed FDA approved and sold as commercial CDx's.⁹⁵

Co-developed CDx's are supported by greater evidence of clinical utility because they are a core component of their companion drugs' clinical trials. For *drugs* to be FDA-approved, clinical utility must be established in Phase III,⁹⁶ and when a CDx is co-developed with its companion drug, the CDx-drug pair are tested together in Phase III.⁹⁷ Therefore, co-developed CDx tests generate evidence of their clinical utility automatically from their use in clinical trials (that is, the clinical utility of the CDx is self-evident when it is used to select the patients in the study and the drug is proven effective in those patients).⁹⁸

Since post-approval CDx's stand alone in their development, they do not partake in the clinical trial process that drugs do. So demonstrating clinical utility for a post-approval test requires generating evidence distinct from the drug itself. The case studies illustrate that randomized control trials are the best route to demonstrate clinical utility for the sake of obtaining payer reimbursement.⁹⁹ Diagnostic companies are often not in the financial position to be able to accommodate these studies,¹⁰⁰ which would explain why the evidence base of post-approval tests is weak. But when a diagnostic developer collaborates with a drug company, the drug company will typically sponsor the costs of the clinical trials,

⁹¹ *Id.*; Towse et al., *supra* note 30, at 169 (finding only four studies in the CEA registry that included a CDx in analyzing the cost-effectiveness of the corresponding drug).

⁹² Cohen & Felix, *supra* note 55, at 171; Cohen et al., *supra* note 35, at 380; Towse et al., *supra* note 30, at 297-99.

⁹³ Sarata & Johnson, *supra* note 75.

⁹⁴ Meckley & Neumann, *supra* note 27, at 96.

⁹⁵ Cohen & Felix, *supra* note 55, at 167.

⁹⁶ McCormack et al., *supra* note 32, at 1396.

⁹⁷ *Id.*

⁹⁸ Meckley & Neumann, *supra* note 27, at 94.

⁹⁹ *Id.* at 97.

¹⁰⁰ Towse et al., *supra* note 30; Davis et al., *supra* note 33.

since the clinical utility of the test might be necessary for the drug to obtain approval and achieve its full value.¹⁰¹ Therefore, co-development in effect subsidizes the costs of generating clinical utility evidence of a CDx for a diagnostic developer, and enhances the value of the clinical trial process.

Ultimately, the impact of a stronger clinical utility evidence base on the payers and medical providers opens the door for greater market access to CDx's. Case studies that examine payer reimbursement practices, and that survey payers to ascertain the influence of different kinds of evidence on reimbursement decisions, find that evidence of clinical utility and cost-effectiveness are the top priorities in deciding whether to reimburse a CDx.¹⁰²

The lack of evidence on clinical utility would understandably make payers insecure and hesitant to immediately cover CDx's. This is supported by the survey data from payers across multiple studies which has found that a large majority question the clinical utility of CDx tests, often viewing the conclusiveness of test evidence to be inadequate.¹⁰³ Reimbursement, while variable, is generally limited and slow, with payers sometimes refusing to reimburse diagnostics that the FDA explicitly requires.¹⁰⁴ Even for co-developed CDx's that include better evidence of clinical utility, however, the variability in payer response suggests that methods for incorporating this evidence into economic evaluations are inconsistent. Consequently, critics have called for health technology assessment agencies and payers to implement more explicit decision criteria, guidelines, and policies over the economic evaluation of CDx's.¹⁰⁵ Despite the overwhelming consensus that the

¹⁰¹ Blair et al., *supra* note 23, at 258–59; Meckley & Neumann, *supra* note 27, at 97.

¹⁰² Meckley & Neumann, *supra* note 27, at 91-92 (conducting six case studies of CDx tests and examining the practices of five different payers and finding the strength of the evidence of the test to be the strongest predictor of reimbursement); Cohen et al., *supra* note 35, at 383 (surveying payers and finding that among the 12 that responded, clinical utility was unanimously ranked as the most strongly considered criteria in making coverage decisions).

¹⁰³ For example, the commercial payer Aetna does not cover *CYP2C9* testing for Warfarin, citing the lack of clinical and cost-effectiveness evidence in their “Policy on Pharmacogenomic Testing” as a reason for not covering the test, while the payer Cigna does. Meckley & Neumann, *supra* note 27, at 94. *See also* Cohen & Felix, *supra* note 55, at 169 (surveying payers and finding that among the eleven that responded, the largest majority questioned the clinical utility of the CDx tests in the study over any other criteria); Faulkner et al., *supra* note 42, at 1164-66 (noting skepticism of the efficacy of CDx's to predict responses to therapy and uncertainty of the necessity of a CDx slows reimbursement).

¹⁰⁴ *E.g.*, Cohen et al., *supra* note 35, at 382-84 (finding that three out of the twelve payers who completed the survey do not provide reimbursement for the *KRAS* CDx explicitly required by the FDA for use with the colon cancer drug cetuximab).

¹⁰⁵ Faulkner et al., *supra* note 42.

evidence base establishing linkage between diagnostic testing and positive health outcomes must be strengthened,¹⁰⁶ it is clear that pursuing co-development will lead to better evidence of clinical utility and payer reimbursement, thereby increasing patient and provider access to CDx's.

2. Co-Development Uses Resources More Efficiently

CDx-drug co-development provides significant opportunity to use the resources of both companies more effectively by reducing the development costs of the CDx and corresponding drug, and increasing the likelihood of therapeutic success and improved cost-effectiveness.¹⁰⁷ Co-development allows both companies to streamline their research¹⁰⁸: as the pharmaceutical company narrows in on the selection of a lead compound, and the diagnostic company narrows in on corresponding biomarkers, each side will learn from each other's research developments.¹⁰⁹ Both will then make better-informed decisions that they would not have otherwise made in isolation. The compound and diagnostic method ultimately selected will jointly run through Phase III (and potentially earlier phases as well),¹¹⁰ increasing the chances that the drug will have a significant enough benefit in the clinical trial population to be approved, and generating evidence of clinical utility for the diagnostic developer. This illustrates the "regulatory efficiency" of tying the drug and CDx together at the outset.¹¹¹ If the CDx and drug both pass FDA approval, patients for whom the drug is effective will have received a cure they might not have were it not for the presence of the CDx, and at a faster speed, with a faster turnaround of payer coverage.¹¹²

¹⁰⁶ E.g. Meckley & Neumann, *supra* note 27 (arguing that evidence on the impact of CDx testing on actual patient outcomes is lacking).

¹⁰⁷ E.g. Cohen & Felix, *supra* note 55, at 171; Luo et al., *supra* note 29, at 2. The FDA's 2014 guidance document regarding CDx's also recommends that the CDx be co-developed especially where it is essential for the safe and effective use of the product. U.S. Food and Drug Administration, *In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff*, <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf> (Aug. 6, 2014).

¹⁰⁸ Leamon & Sherman, *supra* note 20.

¹⁰⁹ *Id.*

¹¹⁰ See Cohen et al., *supra* note 35, at 379 (claiming that a CDx intended to inform uses of a drug in development should be studied in parallel in Phases I or II).

¹¹¹ Dorothea K. Thompson, *From Research to Clinical Application: Challenges in Regulating Companion Biomarker Tests for "Personalized" Drugs*, 1 J. PHARMACEUTICAL ANALYTICS & INSIGHTS 1 (2016).

¹¹² This embodies the example of the Cobas 4800 Mutation CDx, used with the drug Zelboraf, discussed in Part I.

Comparatively, post-approval CDx's can inform patients that a drug they might have been prescribed will be ineffective, cause adverse side effects, or should be taken at a different dose. Co-developed CDx's do the same for their corresponding drug, in addition to helping ensure that the most effective drugs for certain populations that would not necessarily have ever made it to market, do. Further, as more drugs are co-developed with a CDx, the number of drugs in need of a post-approval CDx only goes down. Therefore, co-developed CDx's ultimately capture more value than post-approval ones, and are the key to driving personalized medicine forward.

C. A Misalignment of Stakeholder Incentives Impedes Necessary CDx Co-Development

Despite the economic benefits of co-development just described, the number of post-approval CDx's is larger than the number of co-developed CDx's.¹¹³ Ultimately, this reflects a lack of willingness on the part of drug and diagnostic companies to collaborate. This Part presents the obstacles and deterrents of co-development for each stakeholder, which reveals how their underlying incentives are misaligned.¹¹⁴ It argues that based on the empirical evidence from the case studies, the drug companies have a greater incentive to engage in CDx co-development, while diagnostic companies have a greater incentive to focus on post-approval CDx's, primarily LDT-CDx copies of co-developed CDx's already on the market.

1. Disparate Business Models Hinder Co-Development

A popular assertion in the pharmacologic and biotech business literature is that economic collaboration between drug and diagnostic developers is undermined by their different business models.¹¹⁵ As noted above, each stakeholder employs

¹¹³ Joshua Cohen, *Overcoming Regulatory and Economic Challenges Facing Pharmacogenomics*, 29 NEW BIOTECHNOLOGY 751-56 (2012); Drucker & Krapfenbauer, *supra* note 10; Thompson, *supra* note 111.

¹¹⁴ That the incentives of drug companies and diagnostic companies are misaligned when it comes to CDx development is a frequently-held position in the pharmacologic and biotech business literature. *See generally* Thompson, *supra* note 111.

¹¹⁵ This difference in business models has led many authors in the pharmacologic and biotech business literature to claim that the incentives of the stakeholders in the CDx industry are misaligned. *See e.g.*, Agarwal et al., *supra* note 17; Davis et al., *supra* note 33; Sairamesh & Rossbach, *supra* note 4, at 2-4; Faulkner et al., *supra* note 42, at 1163-67. Scientific factors can and do still slow co-development as well, mostly in situations where the drug's mechanism of action is poorly understood. Leamon & Sherman, *supra* note 20. However, that does not change the fact that economic growth still lags behind the science.

completely different technology in its development platforms, produces a different class of products, and has different development timelines, costs, rates of return, customers, and regulations.¹¹⁶ Few have endeavored to empirically test how these differences in drug and diagnostic business models impact their collaboration, but at least two studies shed light on the question.¹¹⁷

Luo et al. selected nine successful CDx-drug pairs, and quantitatively assessed the impact of factors pertinent to drug and diagnostic companies that influence their calculus in deciding whether to collaborate.¹¹⁸ The priority factors selected for drug companies were drug prices, drug efficacy, patient responses, and patient subpopulation; CDx price and CDx sensitivity were the priority factors selected for the diagnostics.¹¹⁹ The study found no significant relationship between the economic factors for the two industries.¹²⁰ For example, the CDx price did not significantly correlate with any of the factors that impact drug development; high-risk, high-benefit drugs that are priced high to reflect their greater development costs may only require cheap and simple CDx's to accurately stratify the patient population. And moderate-risk or low-risk drugs might require CDx's that are more complex and expensive to develop to accurately segment the patient population. These findings thus support the view that the disparate business models of the CDx and pharmaceutical industries are a legitimate obstacle to CDx-drug co-development.¹²¹

2. *For Drug Companies, Co-Development Is Economically Preferable Over Post-Approval CDx Development*

Despite the potential ability of CDx co-development to reduce development costs for drug companies discussed in Part II.B, research has suggested that CDx's may sometimes do little to improve drug development productivity and might actually increase overall costs.¹²² Some of these scenarios are now considered.

As a general matter, additional complexities associated with running clinical trials with a CDx include "recruiting special patients at additional sites, executing

¹¹⁶ Peter Collins, *Personalized Medicine: From Biomarkers to Companion Diagnostics*, GEN: GENETIC ENGINEERING & BIOTECHNOLOGY NEWS (March 27, 2013), <http://www.genengnews.com/gen-articles/personalized-medicine-from-biomarkers-to-companion-diagnostics/4820/>.

¹¹⁷ See Luo et al., *supra* note 29. The second case study was completed at MIT by Trusheim et al., *supra* note 31, and is discussed *infra* Part II.C.1.

¹¹⁸ Luo et al., *supra* note 29.

¹¹⁹ *Id.* at 3.

¹²⁰ *Id.* at 6.

¹²¹ See *supra* note 109 and accompanying text.

¹²² Davis et al., *supra* note 33.

the clinical protocols, demonstrating effects in biomarker-negative patients, and analyzing biomarker data.”¹²³ These can reduce the savings associated with smaller clinical trials.¹²⁴ There is also the risk that a suitable CDx will not be adequately developed.¹²⁵ If so, the associated costs will not be offset by any savings in clinical trials. Similarly, if a CDx is used in clinical trials but the drug still fails to be approved, the CDx will not have conferred a benefit to the drug company. It is also possible that a drug will be co-developed with a CDx in its early phases, but that later trials reveal that the drug performs well enough in the broader population to obtain FDA approval without the CDx.¹²⁶ The CDx, then, will have been unnecessary to achieve FDA approval, and the development costs of the CDx will not be offset. This is what happened with the drug ponatinib,¹²⁷ though it is not a common occurrence given the reduced odds of a drug being effective enough in the broader patient population. Nevertheless, these factors conceivably influence a drug company’s calculus in deciding whether to collaborate with a diagnostic company for CDx co-development.

The economic risks associated with co-development for a drug company pale in comparison with the risks of the development of post-approval CDx’s. In co-development, the risks previously described are offset by the potential gains achieved by obtaining FDA approval for a drug for segments of the patient population, when the drug would be incapable of obtaining FDA approval for the broader population.¹²⁸ But novel post-approval CDx’s are developed by diagnostic companies for drugs that have *already* obtained FDA approval.¹²⁹ What a new post-approval CDx ultimately accomplishes, then, is the stratification of the patient population that reveals those who are *not* ideal responders, patients that would have been prescribed the drug prior to the arrival of the post-approval CDx. This

¹²³ Trusheim, *supra* note 71; *see also* Trusheim et al., *supra* note 31, at 827 (explaining that the need to screen more patients with a CDx increases the complexity of clinical trials and may lengthen the duration of the study).

¹²⁴ Trusheim, *supra* note 71.

¹²⁵ Trusheim et al., *supra* note 31, at 827.

¹²⁶ Heather Thompson, *Companion Diagnostics from a Business Perspective*, MDDI: MED. DEVICE & DIAGNOSTIC INDUSTRY (MARCH 8, 2013), <http://www.mddionline.com/article/companion-diagnostics-business-perspective>.

¹²⁷ *See id.* Phase I results of the ponatinib trial suggested the drug may be more effective in patients with a particular mutation. Phase II showed better results in the subpopulation with the mutation, but on the whole, stratifying would not be required for the clinical trial results to meet the primary end point for all patients. The FDA submission for pre-market approval of the CDx was therefore withdrawn by the drug company. *Id.*

¹²⁸ Thompson, *supra* note 126.

¹²⁹ *See supra* Part II.A.2.

undeniably benefits the public. For the drug company, however, the post-approval CDx in effect divides the treatable population into smaller segments, reducing the drug's sales and the market share of the relevant patient population.¹³⁰ Economic theory would predict that the drug company would increase its price in response, to make up for this decrease in revenues, and that payers would correspondingly pay the higher price, reflecting the greater drug's greater efficacy with the CDx and the resulting savings from fewer patients taking the drug.

This does not appear to occur in practice, however. A study from the Massachusetts Institute of Technology that quantitatively analyzed economic value to drug and diagnostic companies in case studies of co-developed and post-approval CDx's illustrates the point.¹³¹ In 2006, the drug panitumumab was FDA approved with a co-developed CDx for patients with metastatic colorectal cancer and *EGFR* overexpression (the biomarker measured by the CDx).¹³² A year later, an additional CDx developed by an independent diagnostic company, showed that the drug was actually ineffective in a subset of this *EGFR* over-expressing subpopulation, and thus the patient population to which the drug could subsequently be marketed decreased.¹³³ Reimbursement levels did *not* rise to reflect the higher efficacy in the smaller selected subpopulation, causing the drug developer to suffer a loss in revenues¹³⁴ – perhaps a disappointing outcome to those who despise market inefficiencies, and a pleasing outcome for those hostile towards corporate America. Either way, this pricing inflexibility on the part of payers might reflect the externality of renegotiating drug prices, or might also reflect payer skepticism regarding the cost savings attributable to CDx's, as discussed in Part II.¹³⁵

The increased risk in revenue reduction attributable to the development of post-approval CDx's by third parties would seem to provide an incentive for drug companies to engage in CDx co-development. By doing so, they increase the accuracy of their business projections, and increase the likelihood of capturing potential losses in revenues from CDx stratification in the drug price, by negotiating *ex ante* with payers as opposed to *ex post*.¹³⁶

¹³⁰ See *supra* note 70 and accompanying text.

¹³¹ Trusheim et al., *supra* note 31.

¹³² *Id.* at 822.

¹³³ *Id.*

¹³⁴ *Id.* at 823.

¹³⁵ See *supra* Part II.A.1.

¹³⁶ The quantitative study by Trusheim suggested that price negotiations with drug companies prior to when a drug is FDA-approved have greater flexibility for the drug company. See Trusheim et al., *supra* note 31.

3. *For Diagnostic Developers, Post-Approval CDx Development Is Economically Preferable to Co-Development*

Diagnostic developers face many disincentives in collaborating with drug companies for CDx-drug co-development. Despite CDx companies conducting business on vastly smaller scales than drug companies, CDx deals are still very capital-intensive for the diagnostic partner.¹³⁷ The co-development process will require the diagnostic developer to submit a pre-market approval application to the FDA, increasing upfront costs dramatically, and adding risk associated with obtaining approval. While the diagnostic partner always has to account for the risk associated with being unable to develop a suitable CDx,¹³⁸ in the co-development world it must also account for the risk associated with the *drug* not being approved. The latter risk is magnitudes greater than the former.¹³⁹ For instance, Trusheim's statistical model found that delaying a drug launch by one year, for the purposes of developing a CDx, nearly doubles the diagnostic eNPV due to the decreased risk of cancellation of the drug development program.¹⁴⁰

The diagnostic companies also face limited ability to gain a return on the more expensive R&D spent in co-development.¹⁴¹ They often desire royalties from the pharmaceutical company on the sales of the drug or sales-based milestones to compensate for the risk that the drug won't be approved or will have lackluster sales.¹⁴² But generally drug development partners have structured payments to test developers as a "fee for service."¹⁴³ This typically doesn't cover the full investment cost of the diagnostic developer,¹⁴⁴ so some degree of payer reimbursement to the diagnostic developer is necessary for them to recoup their full investment.¹⁴⁵

¹³⁷ Agarwal et al., *supra* note 17; Towse et al., *supra* note 30; Blair et al., *supra* note 23, at 259-60.

¹³⁸ Trusheim et al., *supra* note 31, at 827.

¹³⁹ Nicholas A. Meadows et al., *An Evaluation of Regulatory and Commercial Barriers to Stratified Medicine Development and Adoption*, 15 PHARMACOGENOMICS J. 6, 10 (2015).

¹⁴⁰ Trusheim et al., *supra* note 31, at 829.

¹⁴¹ McCormack et al., *supra* note 32.

¹⁴² Agarwal et al., *supra* note 17, at 105.

¹⁴³ *Id.*

¹⁴⁴ McCormack et al., *supra* note 32 (noting that some diagnostic companies sell tests at costs that reflect running the test and not overall investment of co-development or value CDx delivers to patient).

¹⁴⁵ Payer reimbursement for diagnostics has its own complications, however. Up until 2013, all payers billed *in-vitro* diagnostic devices using the method of "non-specific coding/code stacking". Meckley & Neumann, *supra* note 27, at 97. This method describes the process associated with testing and therefore reimburses the cost of carrying out the individual

The costlier and higher-risk nature of co-development for a diagnostic company incentivizes those companies to gravitate towards CDx development for drugs already on the market.¹⁴⁶ These post-approval CDx's can be novel and commercial, like their co-developed counterparts. More often, however, they are LDT-CDx copies of previously co-developed commercial CDx's. This is largely achievable because of the weak intellectual property protection afforded to CDx test methods.¹⁴⁷ By generating LDT-CDx's, a diagnostic firm avoids the increased costs of applying for FDA pre-market approval. It can then amass more revenue in the short term to satisfy the investment community, at the expense of encouraging collaboration with drug companies, which only *might* lead to returns in the future for the diagnostic company. The large upfront investment and decreased certainty involved in developing a novel CDx through co-development consequently discourages competition between CDx developers until the first CDx reaches the market. The result is a dominance of late-stage over early-stage competition, facilitated by free-riding on first movers.¹⁴⁸ For example, after the FDA approved Roche's CDx, "Cobas 4800 BRAF Mutation Test" for the drug vemurafenib, at least nine laboratories began to offer their own LDT version of the test.¹⁴⁹ It has been estimated that as of 2013, at least 45% of BRAF testing is performed via LDT-CDx's.¹⁵⁰

components of a CDx test, *not* the value provided by the CDx. *Id.* Fortunately, some payers such as Medicare payers, have begun to move towards "value-based pricing" for diagnostics (the method always applied for drugs), which should help diagnostic companies to capture more value from their CDx's. *See* Meadows et al., *supra* note 139, at 9. But many authors still emphasize that there remains a lack of uniform standards for applying criteria across payers that makes coverage decisions unpredictable, and continues to make it difficult for diagnostic developers to obtain full reimbursement. *E.g.*, Real World Health Care, *Personalized Medicine & Companion Diagnostics: What You Need to Know*, HEALTH WELL FOUND. (Oct. 28, 2015), <http://healthwellfoundation.org/news/2015/10/28/personalized-medicine-companion-diagnostics-speaking-with-dr-joshua-cohen-tufts-cent>; Faulkner et al., *supra* note 42, at 1169.

¹⁴⁶ Luo et al., *supra* note 29, at 9; Agarwal et al., *supra* note 17, at 106-08.

¹⁴⁷ McCormack et al., *supra* note 32; Leeland Ekstrom et al., *Capturing Value for Dx in Personalized Medicines—Is There a Path?*, in *Personalized Medicine, The Path Forward*, 28 (McKinsey & Company, eds. 2013) (noting that lab services companies can provide substitutes for commercial CDx's without fear of patent challenges).

¹⁴⁸ *See infra* Part II.A.2.

¹⁴⁹ U.S. Food and Drug Administration, *The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies*, 29-30 (2015), <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777pdf>.

¹⁵⁰ Ekstrom et al., *supra* note 147, at 36 (stressing that first mover advantage is limited because of significant competition from LDTs).

The success of other diagnostic developers in developing LDT-CDx's is attributable to the fact that many payer billing practices still don't allow the payer to discriminate between a commercial CDx and an LDT-CDx.¹⁵¹ This allows labs who have spent less money on creating an LDT-CDx to be reimbursed the same amount as the more costly commercial, co-developed CDx. Fortunately, in November of last year, Medicare and Medicaid payers adopted a new reimbursement program known as "MoIDx," which requires labs to use separate codes for commercial CDx's and LDT-CDx's.¹⁵² The program will need to gain more momentum against payers before this issue is resolved.¹⁵³

In theory, one might suspect that diagnostic companies are still better off pursuing co-development because co-development will lead to better evidence of clinical utility and a faster rate of payer reimbursement. But the reality is that the disparity in regulatory oversight between LDT-CDx's and commercial CDx's, coupled with remarkably weak IP protection for CDx biomarkers and methods, pulls diagnostic developers away from the world of co-development and pushes them towards late-stage, post-approval competition.¹⁵⁴ This is illustrated in the disparity in the number of co-developed versus post-approval CDx's, and the greater value of LDT-CDx's versus commercial CDx's in the market.¹⁵⁵

Despite the misaligned incentives to engage in co-development detailed in this section, the number of deals between pharma and diagnostic companies has increased over recent years.¹⁵⁶ The deals are typically concentrated in a small number of companies with the appropriate financial stability, regulatory knowledge, technical expertise, and global reach for commercialization.¹⁵⁷ Deals are structured in four ways. The drug developer will develop companion diagnostics internally ("in house"), partner with a diagnostic company to develop the test, acquire the diagnostic company, or engage in a hybrid of those three

¹⁵¹ McCormack et al., *supra* note 32, at 1396.

¹⁵² MoIDx, CLINICAL TEST EVALUATION PROCESS (CTEP) M00096, VERSION 5.0 (2015), [http://www.palmettogba.com/Palmetto/Moldx.Nsf/files/MoIDx_Clinical_Test_Evaluation_Process_\(CTEP\)_M00096.pdf/\\$File/MoIDx_Clinical_Test_Evaluation_Process_\(CTEP\)_M00096.pdf](http://www.palmettogba.com/Palmetto/Moldx.Nsf/files/MoIDx_Clinical_Test_Evaluation_Process_(CTEP)_M00096.pdf/$File/MoIDx_Clinical_Test_Evaluation_Process_(CTEP)_M00096.pdf).

¹⁵³ MoIDx also adopts a set of standards and best practices for assessing clinical utility and cost-effectiveness but many have disavowed the clinical utility assessment criteria. Cohen & Felix, *supra* note 55, at 172.

¹⁵⁴ McCormack et al., *supra* note 32; Faulkner et al., *supra* note 42, at 1169.

¹⁵⁵ See Frost & Sullivan, *supra* note 61; see also *supra* note 113 and accompanying text.

¹⁵⁶ Agarwal et al., *supra* note 17, at 104-05.

¹⁵⁷ *Id.*

methods.¹⁵⁸ What these deals ultimately reflect are examples of successful risk-sharing between drug and diagnostic companies, underscoring the need for innovative risk-sharing models between the two types of companies, to drive co-development.¹⁵⁹

Expediting CDx growth by incentivizing diagnostic companies to engage in co-development requires far more than innovative risk-sharing models, however. Before addressing the unique capabilities of stronger patent protection to solve many of the problems in this field, this part considers the possible ramifications of the FDA's recently proposed guidelines for increased regulatory oversight over all LDT-CDx's.

D. The FDA's Proposed Guidelines For Diagnostic Tests Could Exacerbate The Economic Challenges

In October 2014, the FDA formally issued draft guidance in the Federal Register to start regulating *all* LDTs in the future under a risk-based approach, rather than continuing to exercise its enforcement discretion.¹⁶⁰ The comment period ended in February of last year, but a final guidance document has yet to issue.¹⁶¹ The guidelines describe the FDA's plan to take a "risk based approach" to oversight, by dividing all LDTs into three risk categories and subjecting each to different levels of increased regulation.¹⁶² The FDA has made clear that CDx's will fall into the highest risk category and must therefore meet new registration, listing, adverse event reporting, and pre-market review requirements.¹⁶³

¹⁵⁸ *Id.* See also Leamon & Sherman, *supra* note 20 (illustrating the four deal types in a table and providing examples of companies that engage in each of the deal methods).

¹⁵⁹ Cohen et al., *supra* note 35, at 387 (noting a specific example of successful risk-sharing, the agreement between United Healthcare and Genomic Health for the Oncotype Dx test used in breast cancer treatment).

¹⁶⁰ See FDA Guidance for LDTs, *supra* note 59; Kenneth D. Levy et al., *FDA's Draft Guidance on Laboratory-Developed Tests Increases Clinical and Economic Risk of Adoption of Pharmacogenetic Testing*, 55 J. CLINICAL PHARMACOLOGY 725, 725–26 (2015).

¹⁶¹ See Levy et al., *supra* note 160, at 726.

¹⁶² FDA Guidance for LDTs, *supra* note 59, at 8, 11-15.

¹⁶³ The FDA will focus its enforcement efforts on the highest risk category, giving diagnostic labs twelve months from the date of final issuance to comply with the new regulations. *Id.* at 13–14. Pre-market review can be accomplished in one of two ways. The first route is for the diagnostic developer to conduct clinical studies and subsequently submit a pre-market approval application. If there is evidence providing a reasonable assurance that the test is safe and effective, the FDA will grant pre-market approval. The second and less expensive route is for the diagnostic developer to submit a 510(k) application proving that the test is substantially

From a public health and safety perspective, the proposal appears to be beneficial. A study conducted by the FDA of 20 LDTs, which included two LDT-CDx's, found that often manufacturer claims were unsupported, as evidenced by an overly large number of false positive and false negative results for some tests, risking harm to patients. This was attributed to the fact that LDTs are not subject to adverse event reporting, and that their safety and efficacy is undermined by a lack of agency review of performance data. LDT performance data is "informally" reviewed via the peer-review publication process, but the FDA maintains that this is insufficient to protect against patients and healthcare providers being misled.¹⁶⁴

The chief concern for diagnostic developers is the prospect of bearing the burden of the costs of obtaining approval or clearance. The burden will fall most heavily on more modest diagnostic developers: academic research centers, labs based in hospitals, and other CLIA-certified labs that are typically not accustomed to complying with the regulatory requirements associated with conducting clinical studies, and that lack the expertise to do so.¹⁶⁵ In light of these increased hurdles, it is reasonable to suspect that these smaller diagnostic developers will be unable to continue to provide LDTs in general, absent federal funding agencies relieving this financial burden.¹⁶⁶

But perhaps that would be a good thing. Consistent regulatory requirements across LDT-CDx's and commercial CDx's would level the playing field between commercial kit manufacturers and laboratories.¹⁶⁷ This could potentially mitigate the issue of LDT-CDx's proliferating after a commercial co-developed one reaches the market; the costs of obtaining FDA approval for LDT-CDx's would reduce the benefit associated with free-riding.¹⁶⁸ This could incentivize diagnostic companies to engage in earlier CDx co-development instead. Diagnostic developers with the resources to handle an additional pre-market approval, however, might still

equivalent to one already FDA approved and on the market. If so the FDA will "clear" the test. *Id.* at 20, 23-24.

¹⁶⁴ See U.S. Food & Drug Administration, *supra* note 149, at 2, 4, 27.

¹⁶⁵ *Laboratory Developed Tests*, AM. CLINICAL LABORATORY ASS'N, <http://www.acla.com/issues/laboratory-developed-tests/> (last visited Feb. 28, 2016).

¹⁶⁶ *Id.*

¹⁶⁷ The FDA has emphasized leveling this "uneven playing field" in supporting its recommendation. See *e.g.*, FDA, *supra* note 82, at 4.

¹⁶⁸ FDA pre-market approval for a commercial CDx can cost up to \$75 million more to develop than a corresponding LDT-CDx. Doug Dolginow et al., *Mystery Solved! What is the Cost to Develop and Launch a Diagnostic?*, DIACEUTICS, INC., <http://www.diaceutics.com/wp-content/uploads/2016/03/mystery-solved-what-is-the-cost-to-develop-and-launch-a-diagnostic.pdf> (last visited Mar. 3, 2016).

develop LDT-CDx versions of co-developed CDx's because they would still save on the upfront R&D expenses. The potential impact of the regulations is therefore questionable.

III

RE-INVIGORATING PATENT PROTECTION FOR COMPANION DIAGNOSTICS IS THE MOST EFFICIENT WAY TO STIMULATE COMPANION DIAGNOSTIC MICROECONOMIC GROWTH

This Part addresses how patent protection for CDx tests can help resolve the misaligned incentive structure amongst the key stakeholders that continues to hamper CDx microeconomic growth.

A. *Strengthening a Weak Business Case*

Part II explained the difficulties diagnostic companies face in securing solid returns on R&D investment (what some have called the “weak business case” supporting CDx development).¹⁶⁹ On the one hand, partnering with drug companies helps diagnostic developers establish better evidence of clinical utility which can increase rates of payer reimbursement. On the other hand, however, the diagnostic company is burdened by the heightened risk associated with approval of the drug, and can spend less on upfront R&D expenses by developing an LDT-CDx version of a co-developed CDx already on the market. So even though avoiding the co-development process in favor of developing post-approval CDx's can increase the time it takes for payers to approve the test, the market is clear that diagnostic companies still prefer to develop LDT-CDx's. Stronger patent protection for CDx's can transform this “weak business case” supporting CDx development into a stronger one.

The function of patents as “signals” to investors that an invention possesses commercial potential is well-documented by scholars.¹⁷⁰ Particularly in the life sciences, patents increase prospects of obtaining earlier venture capital funding

¹⁶⁹ McCormack et al., *supra* note 32, at 1395-96.

¹⁷⁰ See, e.g., Robert P. Merges, *A Transactional View of Property Rights*, 20 BERKELEY TECH. L.J. 1477, 1489–90 (2005); Clarisa Long, *Patent Signals*, 69 U. CHI. L. REV. 625, 653 (2002) (arguing that patents can be used to signal the quality of a startup to investors); Stuart J.H. Graham et al., *High Technology Entrepreneurs and the Patent System: Results of the 2008 Berkeley Patent Survey*, 24 BERKELEY TECH. L.J. 1255, 1280–83 (2009); Ted Sichelman & Stuart J.H. Graham, *Patenting by Entrepreneurs: An Empirical Study*, 17 MICH. TELECOMM. & TECH. L. REV. 111, 159 (2010).

which facilitates commercialization.¹⁷¹ This financial boost goes far for CDx developers. It can allow for greater expenditures on demonstrating clinical utility, thereby increasing rates of payer adoption and promoting greater patient access. It can help cover the cost of obtaining FDA approval. If the FDA's guidance becomes final, this will be particularly beneficial to smaller companies and research labs at universities and hospitals. These latter actors may not normally be as incentivized by the prospect of a patent as larger commercial ventures, but faced with the costs associated with obtaining FDA approval, the necessity of a patent is more compelling. Further, an increase in funding attracted by the patent can help in educating medical providers about the availability of the tests to encourage their adoption.

Then comes the most fundamental benefit of a patent: the right to exclude free-riders, or for our purposes, diagnostic developers who wait to develop LDT-CDx copies of commercial CDx's on the market, reducing the ability of the innovative CDx developers to recoup their investment.¹⁷² Patents can therefore shift the abundance of late-stage competition between CDx developers into earlier-stage competition since the threat of liability for infringement will deter CDx developers from competing in LDT-CDx's that mimic the earlier, commercial one. This will force CDx developers to focus on the creation of *novel* CDx's. The FDA's proposed guidance might help to shift competition towards co-development, by increasing the costs of copying a commercial CDx with an LDT-CDx. But without the patent to attract investment upfront, and to spur collaboration with drug companies, as the next section argues, the costs to develop innovative, commercial CDx's will be prohibitive for all but the best-funded developers.

B. Patents Can Facilitate Co-Development

Greater patent protection eliminates many of the obstacles that stand in the way of CDx-drug development, and adds to the already existing benefits of co-development for diagnostic companies. For diagnostic companies, it reduces the risk that the increased costs associated with co-development will cause them to see a loss by increasing the diagnostic company's bargaining power against the drug company; the patent puts the diagnostic company on a less uneven playing field.¹⁷³ With patents in hand, diagnostic companies are in a stronger position to negotiate more favorable risk-sharing agreements: no longer can drug companies argue that

¹⁷¹ DAN L. BURK & MARK LEMLEY, *THE PATENT CRISIS AND HOW THE COURTS CAN SOLVE IT* 4 (2009).

¹⁷² See *infra* Part II.C.3.

¹⁷³ See *supra* note 166 and accompanying text.

the lack of IP protection on the CDx reduces its value such that royalty payments on sales of the drug are not feasible. And if the drug company doesn't budge, the diagnostic developer is now in a position to shop around for better co-development deals, without concern over potential appropriation of its data. This illustrates how when two parties bargaining at arm's length *each* have patents, Arrow's paradox disappears¹⁷⁴ – the security of the patent enables a sharing of information that might not otherwise occur when one party is concerned about keeping its proprietary information secret. Greater CDx patent protection for the diagnostic company would also provide a stronger incentive for drug companies to engage in CDx co-development: the exclusivity of a commercial CDx would reduce the amount pharmaceutical companies have to pay diagnostic developers to cover the costs associated with the reduction in the value of the CDx due to LDT-CDx competition.

Both drug and diagnostic companies could also stand to gain from considering joint or integrated patent strategies throughout the co-development process.¹⁷⁵ Coordinating patent filings and tailoring them to the specific CDx-drug pair could increase the commercial value of both products, and provide greater security of patent validity.¹⁷⁶ Patenting combinations of methods that apply both the drug and the CDx and vary the subject matter would increase the chances that at least some claims would withstand invalidity attacks.¹⁷⁷ If the relationship between the CDx and drug companies is a partnership, filing patents that overlap both company's products could create control problems. The drug company may want exclusive control so that competitors don't have access to the CDx, while the CDx may want exclusive control so it can do business with other drug companies. On balance, however, it is apparent that more secure patent protection for CDx developers would catalyze collaboration between stakeholders and drive CDx growth forward.

C. The Case Against Patents Does Not Apply To the CDx Niche

This Part briefly addresses some of the common counterarguments to extending patent protection in genetics-related research, and asserts that they don't

¹⁷⁴ See, e.g., Shyamkrishna Balganesh, "Hot News": *The Enduring Myth of Property in News*, 111 COLUM. L. REV. 419, 433 (2011) (describing "Arrow's information paradox" wherein "[a] potential licensee has no way of evaluating the information/intangible until it is disclosed to him; yet, upon such disclosure he has little reason to want to pay for it").

¹⁷⁵ See Ekstrom et al., *supra* note 58, at 22.

¹⁷⁶ Cynthia H. Zhang & Y. Philip Zhang, *Maximizing the Commercial Value of Personalized Therapeutics and Companion Diagnostics*, 31 NATURE BIOTECHNOLOGY 803, 803–04 (2013).

¹⁷⁷ *Id.*

apply in the unique context of the CDx industry. Critics of patent protection in the life sciences frequently point to the 2010 report written by the Secretary of Health and Human Services' Advisory Committee on Genetics, Health, and Society (the "SACGHS report").¹⁷⁸ The report found that patent rights were neither necessary nor sufficient conditions for the development of commercial diagnostic testing kits and LDTs.¹⁷⁹ This was because it determined that private funding was "supplemental to the significant federal government funding in this arena," and that most genetic research is conducted by academic researchers.¹⁸⁰

These conclusions fail to differentiate between basic genetic research and the research involved in developing a CDx. Genetic research simply refers to the identification of genes associated with different conditions, and the case studies cited in the SACGHS report are circumscribed in this arena.¹⁸¹ Developing a CDx, however, requires a more complicated understanding of how different variations in given genes correlate with the actions of a given drug.¹⁸² CDx targets extend beyond genes themselves to other proteins, metabolites, and tracers that are all influenced by genetic variation and its downstream molecular processes.¹⁸³ Developing this research from scratch requires expensive, large-scale validation and replication studies, and is therefore more often funded by the private sector.¹⁸⁴

Another concern is that greater patent protection in genetics-related research will interfere with research by academics and impede upstream experimental research.¹⁸⁵ Again, this may well be a valid concern for standard genetic research, but in the context of CDx development, it is not. The CDx industry is made up of many private firms because of the substantial costs associated with development and commercialization.¹⁸⁶ Empirical studies have also found that basic researchers follow a practice of ignoring patent infringement, while patent owners ignore

¹⁷⁸ SEC'Y'S ADVISORY COMM. ON GENETICS, HEALTH, & SOC'Y, DEP'T OF HEALTH & HUMAN SERVS., GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS (2010), *available at* http://osp.od.nih.gov/sites/default/files/SACGHS_patents_report_2010.pdf [<http://perma.cc/RT2Y-7TYT>].

¹⁷⁹ *Id.* at 20-36.

¹⁸⁰ *Id.* at 1, 9.

¹⁸¹ *Id.*

¹⁸² Drucker & Krapfenbauer, *supra* note 10, at 2-4.

¹⁸³ *See supra* note 118 and accompanying text.

¹⁸⁴ Frost & Sullivan, *supra* note 61.

¹⁸⁵ *See, e.g.*, Brief for American Medical Association et al. as Amici Curiae Supporting Petitioners at 13-16, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.* 133 S. Ct. 2107 (2013) (No.12-398).

¹⁸⁶ *See* Cohen et al., *supra* note 35, at 387 (providing price ranges for various CDx's).

enforcement against basic researchers so long as no one is engaged in commercial endeavors associated with the patent.¹⁸⁷

Fear that increased patent protection will promote monopoly pricing over CDx tests is another valid concern, especially where payer reimbursement is not increased to match the savings of the CDx, and costs are shifted onto the consumer. Given that the costs of CDx development pale in comparison to therapeutics, however, the concern is arguably less warranted. And while no one wants to have to pay more for diagnostic testing, the CDx tests, as explained in Part I, can save consumers far greater costs in the long-run by preventing them from using up their insurance policies on treatments that prove to be ineffective.

Of course, it would be myopic to assert that re-invigorating patent rights for CDx's is the *only* way to achieve an increase in CDx growth. There are other policy tools that could also be effective in different ways: non-patent exclusivities, government subsidies, prizes, and tax credits to name a few.¹⁸⁸ Evaluating the comparative merits of those proposals is beyond the scope of this note. But from a broad perspective, it is clear that the unique challenges facing the CDx industry embody all the most fundamental justifications for patent protection: significant upfront R&D expenses; significant risks associated with regulatory hurdles; uncertainty in the ability to recoup investments; cutting-edge, important science and technology; flagrant free-riding; and a need to share proprietary information with parties at arm's length.

D. Patent Law's Subject Matter Eligibility Doctrine Has Undermined the Prospects of Patenting Companion Diagnostic Tests

Patentability of diagnostic methods faced its first attack in the Supreme Court's decision in *Mayo Collaborative v. Prometheus Labs*.¹⁸⁹ There, the Court articulated a new two-part test for assessing the subject matter eligibility of inventions,¹⁹⁰ which was reiterated in the software case *Alice v. CLS Bank*.¹⁹¹ It is now commonly referred to by the U.S. Patent & Trademark Office and the Federal Circuit as the *Mayo* or *Alice* "two-step."¹⁹² Step one requires a court to determine

¹⁸⁷ See Holman, *supra* note 2, at 305.

¹⁸⁸ See Trusheim, *supra* note 71, at 418 (discussing some of these policy proposals).

¹⁸⁹ *Mayo Collaborative Servs. v. Prometheus Labs*, 132 S. Ct. 1289, 1294 (2011).

¹⁹⁰ *Id.* at 1294, 1302.

¹⁹¹ *Alice Corp. Pty. Ltd. v. CLS Bank Int'l et al.*, 134 S. Ct. 2347, 2355 (2014).

¹⁹² See, e.g., 2014 Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. 74618, 74619, 74622 (Dec. 16, 2014) (to be codified at 37 C.F.R. pt. 1); *Content Extraction & Transmission LLC v. Wells Fargo Bank, N.A.*, 776 F.3d 1343, 1346 (Fed. Cir. 2014) (noting that

whether the claims at issue are directed to a patent-ineligible concept (*i.e.*, an abstract idea, natural phenomenon or product of nature).¹⁹³ Step two asks the court to consider the elements of each claim individually, and as an ordered combination, to determine whether any additional elements transform the nature of the claim into a patent-eligible application (also known as the search for the “inventive concept”).¹⁹⁴

On its face, *Mayo* appears to be a flexible test: individual elements of all claims can be routine, conventional, and ordinary, but so long as the claims when considered *as an ordered combination* “transform” the naturally occurring phenomenon into a patent-eligible application, they are patent-eligible.¹⁹⁵ One might suspect that the debatable meaning of “as an ordered combination” and “patent-eligible application” would leave good room to distinguish the most innovative and meritorious applications of diagnostic methods from those that contain little more than the underlying unpatentable principles on which they rely. In practice, however, the Federal Circuit seems to have applied *Mayo* as a rule that diagnostic method patents are categorically unpatentable.¹⁹⁶ Only three cases involving diagnostic method claims have been decided since *Alice* so the sample size to evaluate how *Mayo* has affected the patentability of diagnostic methods is admittedly small.¹⁹⁷ But the fact that several diagnostic method claims have been invalidated across these cases, especially those in *Ariosa*¹⁹⁸ – included diagnostic method claims arising out of what scientists have lauded as one of the most remarkable discoveries of the century – suggests a bleak future for their survival.

Consequently, practitioners are undoubtedly reconsidering how to write diagnostic method claims to survive under the recent doctrine.¹⁹⁹ But while the patentability of diagnostic methods as a general matter has become dubious, the patentability of co-developed CDx’s could be more promising if strategically

“the two-step framework described in *Mayo* and *Alice* guides [the subject matter eligibility] analysis”).

¹⁹³ *Alice*, 134 S. Ct. at 2355.

¹⁹⁴ *Id.*

¹⁹⁵ *Mayo*, 132 S. Ct. at 1298.

¹⁹⁶ Eisenberg, *supra* note 2, at 257.

¹⁹⁷ See *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1373 (Fed. Cir. 2015) (reh’g *en banc* denied); *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 999 F.Supp. 2d 1377 (J.P.M.L. 2014); *Genetic Techs. Ltd. v. Lab. Corp. of Am. Holdings*, No. CV 12-1736-LPS-CJB, 2014 WL 4379587, at *13-14 (D. Del. Sept. 3, 2014).

¹⁹⁸ *Ariosa Diagnostics*, 778 F.3d at 1373 (laying out the key patent claims at issue).

¹⁹⁹ Rachel E. Sachs, *Innovation Law and Policy: Preserving the Future of Personalized Medicine*, 49 U.C. DAVIS L. REV. 1881, 1912 (2016).

tailored to the companion drug as well.²⁰⁰ Even so, the heightened difficulties in obtaining patent protection for CDx's as a result of the doctrinal developments in subject-matter eligibility suggests that legislative or regulatory changes are necessary to enable economic growth in CDx development to catch up with its scientific growth – two unpredictable alternatives to a centuries-old system that was built to solve the very problems that plague this industry.

CONCLUSION

Furthering innovation in the development of all kinds of diagnostic tests is important to modern healthcare. But not all diagnostic tests should be viewed in the same light when debating innovation policy. As this note has illustrated, companion diagnostic tests possess unique economic challenges that stem from a complicated and misaligned incentive structure amongst the key industry stakeholders. Accordingly, CDx tests deserve their own innovation policy debate. Yet while literature in economics and pharmacology has addressed the unique circumstances surrounding the CDx industry and conducted insightful case studies, legal scholarship addressing innovation policy has yet to engage with these critical diagnostic tests as vigorously. In an effort to begin doing so, this note has imported many valuable insights from empirical case studies in other fields to argue that co-developing CDx tests with their companion drugs is the optimal pursuit for furthering economic growth in the CDx industry. It has further argued that increased patent protection in the narrow niche of CDx tests is the optimal policy choice for catalyzing the economic growth of CDx tests to enable them to one day match their rate of scientific growth. Unfortunately, strengthening patent protection in this niche seems a doubtful possibility in practice in light of the constraints that current subject-matter eligibility doctrine has created. Coupled with the potential for increased FDA regulation of companion diagnostic tests, the incentives to innovate in the CDx sector might become further eroded. In the meantime, the healthcare system that is predictive, preventive, personalized and participatory, where every patient receives the right drug, at the right dose, at the right time, will remain a fantasy. The science will have to remain patient.

²⁰⁰ Zhang & Zhang, *supra* note 176, at 804.