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## PHARMACOGENOMICS, GENETIC TESTS, AND PATENT-BASED INCENTIVES

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# Pharmacogenomics, Genetic Tests, and Patent-Based Incentives

Michael J. Meurer\*

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## INTRODUCTION

The patent system, university medical systems, and federal research funding, come together to provide a complicated set of incentives to promote medical R&D. Pharmaceutical and medical device innovations are provided mostly by the private sector and depend heavily on patent protection. Medical and surgical procedure innovations are provided mostly by the public sector and largely outside the domain of the patent system. This division of labor is not rigid. Private sector R&D often builds on basic research funded by the government and conducted in universities. Universities obtain patents, use private sector funds, and enter ventures with private companies for medical R&D. Not much is known about the optimal mix of public and private incentives for encouraging medical R&D. This Article takes a step in that direction by analyzing the effect of these incentives on medical R&D in the new field of pharmacogenomics.

Pharmacogenomics is the application of genomics to drug therapy.<sup>1</sup> Medical researchers hail the progress of genomics research and proclaim its potential for revolutionizing drug therapy. With luck, we will soon enjoy the benefits of customized drugs prescribed in optimal dosage with minimized side effects. This revolution is grounded in the belief that much of the variation in patient response to drugs is determined by measurable genetic variation in patients. New genetic tests and knowledge of the links between genes and drug response will make better drug therapy possible.

Thus far, public sector funding and R&D have been critical to the creation and deployment of pharmacogenomic innovations.<sup>2</sup> As the field matures, much innovative activity will probably shift to the private sector. In particular, drug patent owners are likely to generate most future innovation in this field. One reason is that pharmacogenomic research is likely to become a routine part of the drug discovery process, and the development of genetic tests will be ancillary to drug development. Another reason is that genetic tests may be able to resuscitate patented drugs that were

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<sup>1</sup> Pharmacogenomics also plays a role in drug research and development. This Article focuses mainly on the drug therapy application of pharmacogenomics. Some authors distinguish between pharmacogenetic and pharmacogenomic approaches to drug therapy, the distinction is not important for my purposes. See Allen Buchanan, Andrea Califano, Jeffrey Kahn, Elizabeth McPherson, John Robertson, & Baruch Brody, *Pharmacogenetics: Ethical Issues and Policy Options*, 12 KENNEDY INST. OF ETHICS J. 1, 1-2 (2002).

<sup>2</sup> Cf. Antonio Regalado, *Mining the Genome*, 102 TECHNOLOGY REV. 56, 63 (1999) (the NIH recommends significantly increased support for computational biology in American universities).

abandoned because of problems with adverse reactions. Nevertheless, it may be desirable to continue public sector support of pharmacogenomics.

Patents do not always provide adequate private incentives to develop genetic tests. Genetic tests designed to improve therapy with existing drugs might be underprovided by the private sector. Private incentives may be too low because private returns are low relative to social returns, and because private costs are high relative to social costs. The main contribution of this Article is an analysis of the private and social returns to pharmacogenomic innovation in markets for existing patented drugs. Introducing genetic tests could increase or decrease the profit from patented drugs that are used in conjunction with the tests. Similarly, social value could rise or fall after tests are introduced. I will try to identify factors that cause private returns to fall below social returns.

Social value generated in the market for a patented drug tends to rise with the introduction of a genetic test because of the social benefit from better matching between patients and drugs. Social value is also influenced by the change in sales of the patented drug caused by testing. The introduction of testing can decrease sales because of a price increase that pushes untested patients out of the market. But testing can also increase sales, for example when the test avoids harmful side effects and makes a drug newly available.

The introduction of a genetic test unambiguously increases profit from the sale of an associated patented drug in cases in which the drug cannot be marketed absent the test. This might occur because the drug has severe side effects for a subset of patients that cannot be identified without the test. This might also occur if the drug is efficacious for only a small subset of patients. Testing also increases profit in a market in which duopolists offer drugs that are imperfect substitutes. Testing raises profit to each firm through two different effects. First, testing allows doctors to better match patients with one of the two drugs; this leads to higher demand for each of the drugs.<sup>3</sup> Second, testing differentiates the two drugs and gives more market power to each of the two firms.

The introduction of a genetic test might decrease monopoly profit from the sale of a patented drug that is marketed even without the test. Profit might fall because certain patients learn they are not well matched with the drug and so they drop out of the market. This effect may be offset if the drug maker is able to increase price enough. Genetic tests can also hurt profits from the sale of drugs because the tests give private information to patients about their valuation for the drugs. Private information can increase consumer bargaining power and reduce seller profit.

In addition to direct threats to drug profit, the private sector incentive to invent genetic tests might be too weak for two other reasons. First, the use of more than one patented drug might be influenced by a single genetic test. In this case, a test that has a favorable effect on the profitability of each drug is a kind of a public good that is apt to be underprovided.<sup>4</sup> Second, the private costs of genetic test innovation are likely to be

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<sup>3</sup> This statement is true if the two drugs serve a roughly equal market share after testing. It is possible that the profits from one drug will fall if the genetic tests reveal that most patients are better matched with the other drug.

<sup>4</sup> This is true even though the test and the affected drugs are all patented. Some tests will inherently reveal information relevant to more than one drug, and the test patent owner will not be able to selectively disclose that information.

higher than the social costs, because the private costs of licensing database access and rights to patented research tools are mere transfers that do not count as social costs.

The existence of independent diagnostic firms who compete with drug patent owners to develop genetic tests is a factor weighing against public sector R&D. Competition to get a patent is a potent stimulant of innovation that can more than offset problems appropriating the full social value of a genetic test. Independent inventors have an incentive to invent genetic tests based on the prospective profit from the sale or licensing of the tests, or from the assignment of the patent on the test to a drug patent owner.<sup>5</sup> Drug patent owners are likely to acquire such patents because drugs and genetic tests are complements that are marketed most efficiently by a single firm. Normally, drug patent owners have a strong and socially optimal incentive to push for broad adoption of genetic tests. But there are cases in which profit maximization requires suppression of a genetic test — surprisingly, such suppression can be socially desirable.<sup>6</sup>

## I. PHARMACOGENOMICS AND THE PROMISE OF CUSTOMIZED DRUG THERAPY

Genomics is the study of the function and structure of genes and gene products.<sup>7</sup> It has become a vital new research tool of life science industries; one that promises more efficient drug research and development. This efficiency arises because genomics improves the understanding of the disease process;<sup>8</sup> helps identify drug targets;<sup>9</sup> guides drug design;<sup>10</sup> and ultimately reduces the cost and increase the success rate of R&D.<sup>11</sup>

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<sup>5</sup> Independent inventors are likely to face obstacles when competing with drug patent owners when they control access to drugs and clinical data in a way that discourages independent inventors from developing a genetic test.

<sup>6</sup> Part III discusses the diffusion of genetic tests. There are a variety of factors outside the scope of my model that will affect the profit and social value from use of genetic tests.

<sup>7</sup> See U.S. Dept. of Energy Human Genome Program, *Genomics and Its Impact on Science and Society: The Human Genome Project and Beyond*, March 2003, available at: [http://www.ornl.gov/TechResources/Human\\_Genome/glossary/glossary\\_p.html](http://www.ornl.gov/TechResources/Human_Genome/glossary/glossary_p.html), (last visited April 18, 2003).

<sup>8</sup> See *id.* at: [http://www.ornl.gov/TechResources/Human\\_Genome/publicat/primer2001/6.html](http://www.ornl.gov/TechResources/Human_Genome/publicat/primer2001/6.html).

<sup>9</sup> See Allen D. Roses, *Pharmacogenetics and the Practice of Medicine*, 405 NATURE 857 (2000); Comment: *Panning For Biotechnology Gold: Reach-Through Royalty Damage Awards For Infringing Uses Of Patented Molecular Sieves*, 39 IDEA: J. L. & TECH. 553, 554 (1999) (describing high-throughput screening of drug candidates); Regalado, *supra* note 2, at 63 (gene expression profiles help predict toxic effects from a drug candidate which allows researchers to exclude losers at an early stage).

<sup>10</sup> See U.S. Dept. of Energy Human Genome Program, *supra* note 7, at [http://www.ornl.gov/TechResources/Human\\_Genome/publicat/primer2001/6.html](http://www.ornl.gov/TechResources/Human_Genome/publicat/primer2001/6.html).

<sup>11</sup> See e.g., Gary A. Pulsinelli, *The Orphan Drug Act: What's Right With It*, 15 SANTA CLARA COMPUTER & HIGH TECH. L.J. 299, 304, 339 (1999) (Pharmacogenomics will reduce the cost of research and development of the drugs because of the ability to pinpoint the population which would be effected by the drug.); James Kling, *Opportunities Abound in Pharmacogenomics*, THE SCIENTIST, (May 10, 1999) available at: [http://www.the-scientist.com/yr1999/may/prof\\_990510.html](http://www.the-scientist.com/yr1999/may/prof_990510.html) (last visited Mar. 27, 2002) (New hardware devices will cut drug development costs by providing genetic information at a lower cost and in less time.); Andrew Pollack, *DNA Chip May Help Usher in a New Era of Product Testing*, N.Y.TIMES, Nov. 28, 2000, [www.nytimes.com/2000/11/28/science/28TOXI.html](http://www.nytimes.com/2000/11/28/science/28TOXI.html) (Toxicogenomics aims to judge the toxicity of food additives, drugs, and cosmetics by using gene chips to measure the pattern of gene activity in response to exposure to a chemical. If this method is successful it should reduce the cost of testing.); Arti Kaur Rai, *The Information Revolution Reaches Pharmaceuticals: Balancing Innovation Incentives, Cost, and Access in*

Genomics also has great potential as applied to drug therapy. This branch of genomics, called pharmacogenomics, is less developed than the application to drug discovery, but it may be just as significant.

### A. Genomics and the Practice of Medicine

Pharmacogenomics promises tailored medicine. Future doctors are likely to routinely collect genetic information from patients who need medication so they can avoid adverse drug reactions, and select the optimal medication and dosage.<sup>12</sup> Genetic differences between patients apparently explain why some patients but not others suffer from harmful drug side effects.<sup>13</sup> Research is under way to devise genetic tests that will help doctors avoid fatal side effects from an AIDS drug,<sup>14</sup> severe diarrhea from a chemotherapy drug,<sup>15</sup> and allergic reactions to penicillin.<sup>16</sup> Genetic testing could also soon be used to exclude certain patients from receiving a drug because the patients' metabolism renders the drug ineffective.<sup>17</sup> Someday, doctors are likely to test the genetic make-up of tumors, viruses, bacteria, and other pathogens<sup>18</sup> and use the results to select

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*the Post-Genomics Era*, 2001 U. ILL. L. REV. 173, 189-90 (2001) (Genomics promises faster and cheaper pre-clinical drug research).

<sup>12</sup> See Roses, *supra* note 9; U.S. Dept. of Energy Human Genome Program, *supra* note 7, at: [www.ornl.gov/hgmis/medicine/pharma.html](http://www.ornl.gov/hgmis/medicine/pharma.html) ("Pharmacogenomics is the study of how an individual's genetic heritage affects the body's response to drugs. Pharmacogenomics holds the promise that drugs might one day be tailor-made for individuals and adapted to each person's own genetic makeup. Environment, diet, age, lifestyle, and state of health all can influence a person's response to medicines, but understanding an individual's genetic makeup is thought to be the key to creating personalized drugs with greater efficacy and safety."). *But see* John Robertson, Baruch Brody, Allen Buchanan, Jeffrey Kahn, & Elizabeth McPherson, *Pharmacogenetic Challenges for the Health Care System*, 21 HEALTH AFFAIRS 155, 157 (2002) (not yet clear that genetic effects are significant and predictable enough to significantly change drug therapy).

<sup>13</sup> See Laviero Mancinelli, Maureen Cronin, & Wolfgang Sadee, *Pharmacogenomics: The Promise of Personalized Medicine*, AAPS PHARMACUETICA, (March 7, 2000) available at: [www.pharmsci.org/scientificjournals/pharmsci/journal/4.html](http://www.pharmsci.org/scientificjournals/pharmsci/journal/4.html) (last visited Mar. 27, 2002); *but see* Lars Noah, *The Coming Pharmacogenomics Revolution: Tailoring Drugs to Fit Patients' Genetic Profiles*, 43 JURIMETRICS J. 1, 10 (2002) (cautioning that not all adverse drug reactions will be prevented by pharmacogenomics).

<sup>14</sup> See Mark Schoofs, *AIDS-Drug Side Effect Linked to Genes*, WALL ST. J., Feb. 28, 2002, B2. (Scientists have shown that people with certain genetic patterns are vulnerable to potentially fatal side effects from a leading AIDS drug.)

<sup>15</sup> See *id.* (A company is developing a genetic test that will screen out patients who suffer severe diarrhea from a chemotherapy drug called irinotecan.)

<sup>16</sup> See Pollack, *supra* note 11 (Scientists have found 260 genes that are differentially activated in people allergic to penicillin compared to people who are not.)

<sup>17</sup> See John Weinstein, *Pharmacogenomics--Teaching Old Drugs New Tricks*, 343 NEW ENGL. J. MED. 1408 (2000) (SNPs affecting drug metabolism explain why certain drugs are not effective in treating a subset of patients); David Stipp, *Blessing From the Book of Life*, 141 FORTUNE F-21, 24, Mar. 6, 2000 (a SNP chip will be able to determine that a medication will not work on a particular patient whose liver enzymes break down the medication too quickly).

<sup>18</sup> See Regalado, *supra* note 2, at 62 (scientists have distinguished two types of leukemia solely by comparing the gene expression profiles for cells affected by the two types of leukemia); Stipp, *supra* note 16, at F-21, 24 (gene chips will be able to distinguish different types of T-cell cancers); Andrew Pollack, *Telling the Threatening Tumors from the Harmless Ones*, N. Y. Times, Apr. 9, 2002, available at: <http://www.nytimes.com/2002/04/09/science/09GENE.html> (last visited Apr. 9, 2002) (the National Cancer

appropriate medications.<sup>19</sup> Finally, future doctors are likely to use genetic information about patients' metabolism to tailor the appropriate dosage and schedule for administering drugs.<sup>20</sup>

### B. Genetic Testing Technology

Genetic testing is likely to be deployed in three different ways to facilitate the practice of pharmacogenomics. First, preventive screening will identify genes that cause or have an association with a disease.<sup>21</sup> Ideally, preventive screening will be coupled with preventive treatment of patients facing elevated risk of disease.<sup>22</sup> Second, general purpose testing will produce information relating to drug metabolism and potential adverse drug reactions.<sup>23</sup> Third, specific genetic testing of diseased cells and pathogens will improve the precision of tailored drug therapy.<sup>24</sup>

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Institute and Merck are developing a test based on a genetic fingerprint that distinguishes breast cancer that requires chemotherapy from breast cancer that does not). "Children with acute lymphoblastic leukemia, for instance, already undergo several separate tests costing about \$1,000 to help subclassify the cancer to help determine therapy, he said. But in a newly published study involving 327 patient samples, one of the largest DNA chip studies to date, Dr. Downing and colleagues showed that the genetic patterns could classify the cancers as accurately as all the other tests combined, if not more so." *Id.* "Millennium Pharmaceuticals ... has found that if a particular gene in a melanoma skin tumor is inactive, the tumor is more likely to spread throughout the body." *Id.*

<sup>19</sup> See Andrew Pollack, *When Gene Sequencing Becomes a Fact of Life*, N.Y. TIMES, Jan. 17, 2001, available at: [www.nytimes.com/2001/01/17/business/17AIDS.html](http://www.nytimes.com/2001/01/17/business/17AIDS.html) (sequencing HIV can help a doctor choose from among 15 drugs available to fight AIDS).

<sup>20</sup> See U.S. Dept. of Energy Human Genome Program, *supra* note 7.

<sup>21</sup> Patients can be screened for particular mutations like BRCA1 and BRCA2, and for markers, called SNPs, that are linked with genes that are implicated in some disease. See Allen C. Nunnally, *Commercialized Genetic Testing: The Role of Corporate Biotechnology in the New Genetic Age*, 8 J. SCI. & TECH. L. 1, 12 (2001); U.S. Dept. of Energy Human Genome Program, *supra* note 7, at [http://www.ornl.gov/TechResources/Human\\_Genome/publicat/primer2001/6.html](http://www.ornl.gov/TechResources/Human_Genome/publicat/primer2001/6.html) (several hundred genetic tests are currently in use mainly to detect rare genetic disorders).

<sup>22</sup> But see Gina Kolata, *Test Proves Fruitless, Fueling New Debate on Cancer Screening*, N.Y. TIMES, April 9, 2002, available at: <http://www.nytimes.com/2002/04/09/science/09CANC.html> (last visited Apr. 9, 2002) (describing the debate among oncologists about the value of cancer screening tests and the problem of false positives).

<sup>23</sup> See LORI B. ANDREWS, MAXWELL J. MEHLMAN, & MARK A. ROTHSTEIN, *GENETICS: ETHICS, LAW AND POLICY* 423 (2002) (genetic test that helps determine how patients metabolize a variety of drugs); National Institute of General Medical Sciences, *Your Genes and Your Medicines*, <http://www.nigms.nih.gov/funding/htm/yrgenes2.html> (last visited Mar. 26, 2002). ("In most cases, research to find normal variations in the genes for the proteins that handle medicines in the body will involve a simple test. In many cases, researchers will rub the inside of a volunteer's cheek with a cotton swab and then examine the DNA in those cheek cells."); Arti K. Rai, *Fostering Cumulative Innovation in the Biopharmaceutical Industry: The Role of Patents and Antitrust*, 16 Berkeley Tech. L. J. 813, 842 (2001) (SNP gene chips will be used to predict adverse drug reactions). Kathleen Giacomini, PhD, professor and chair of biopharmaceutical sciences in UCSF's School of Pharmacy predicts: "[I]n the future, you may go in for a doctor's visit and have your blood drawn for a genotype to be done which would indicate what genes you have for drug transporters, drug targets, or drug elimination enzymes. Then after you are diagnosed, a pharmacist could interpret the panels of genetic results and advise on which drugs would be 'best' for your particular genes." *What Is Pharmacogenomics?* IMPACT: THE UCSF FOUNDATION'S ONLINE MAGAZINE, available at: [http://www.ucsf.edu/foundation/impact/archives/1999/17\\_pharmacog.html](http://www.ucsf.edu/foundation/impact/archives/1999/17_pharmacog.html) (last visited Mar. 26, 2002).

<sup>24</sup> See *supra* note 18.

Genetic testing technology captures two different kinds of data: gene sequence data, and gene expression data. Gene sequence testing reveals selective information about the DNA of a tested patient or the DNA of a pathogen. For example, Myriad Genetics makes a test of human DNA that detects the presence of mutated genes that cause a form of inherited breast cancer.<sup>25</sup> Visible Genetics developed a sequencing test of the HIV virus that helps tailor prescription of AIDS drugs.<sup>26</sup> Companies are working to develop a low-cost method capable of sequencing a patient's entire genome.<sup>27</sup> Such tests are necessary before pharmacogenomics can achieve its full potential.

Besides gene sequence data, doctors also need to know which genes are active in particular cells. This information is obtained by observing the messenger RNA (mRNA) produced in a cell. The mRNA is an essential intermediary in the production of protein in a cell. Biologists say that a gene is expressed when the cell produces the protein that the gene encodes. A newly developed device that marries microchip technology with molecular biology produces gene chips that monitor gene expression. These gene chips work by detecting all of the mRNA present in a cell; this information gives a snapshot of what genes are being expressed and in what quantity.<sup>28</sup> The data from the gene chip is called a gene expression profile. This profile has therapeutic value when it is correlated with optimum drug therapy.<sup>29</sup>

Before routine pharmacogenomic therapy becomes a reality many factors must fall into place.<sup>30</sup> Doctors and patients must have access to kits and equipment to sequence genes or produce gene expression profiles.<sup>31</sup> Several companies have shown an interest in producing kits and equipment,<sup>32</sup> but it is not yet clear how willing health care providers are to pay for these items.<sup>33</sup> Equally important, doctors and diagnostics manufacturers

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<sup>25</sup> See Rita Rubin, *To Test, or Not to Test, for Breast Cancer Genes*, USA TODAY.COM (Jan. 10, 2002) available at: <http://www.usatoday.com/news/health/cancer/2002-01-09-usat-breastcancer-gene.htm> (last visited Apr. 17, 2003).

<sup>26</sup> See Chael Needle, *Gene Genie: Visible Genetics Makes Good on the Wish for Better Resistance Testing Technology*, A&U America's AIDS Magazine (Apr. 17, 2003) available at: [http://www.aumag.org/www\\_aumag\\_org/archives/archives\\_contents.cfm?a\\_id=3730&c\\_id=86](http://www.aumag.org/www_aumag_org/archives/archives_contents.cfm?a_id=3730&c_id=86) (last visited April 17, 2003).

<sup>27</sup> See David Orenstein, *A Genetic Hole in One: David Deamer's "Nanopore" Device Might Eventually Allow Doctors to Decode Your DNA — While You Wait*, Business2.0 (October 2001) available at: <http://www.business2.com/articles/mag/0,1640,16900,FF.html> (last visited April 17, 2003).

<sup>28</sup> See Regalado, *supra* note 2, at 59-62 (DNA chips identify a gene expression profile for a cell, the gene chips recognize the type and quantity of mRNA in a cell to get a snapshot of what proteins are being expressed in a cell).

<sup>29</sup> Predicting that in the future "each drug [will] be bundled with a specific set of diagnostic tests for those positions in the human genome which alter drug response." Charles R. Cantor, 1 GENELETTER 3 April 2000 available at <http://www.geneletter.org/04-01-00/features/pharmacogenomics.html> (last visited Mar. 26, 2002).

<sup>30</sup> See *Personal Pills: Genetic Differences May Dictate How Drugs Are Prescribed*, SCIENTIFIC AMERICAN, available at: <http://www.sciam.com/1998/1098issue/1098infocus.html> (last visited Mar. 26, 2002) (William Haseltine the CEO of Human Genome Sciences warns that diagnostic tests can be unreliable in part because environmental factors have a significant influence on drug behavior).

<sup>31</sup> See Andrew Pollack, *When Gene Sequencing Becomes a Fact of Life*, N.Y. TIMES, Jan. 17, 2001, [www.nytimes.com/2001/01/17/business/17AIDS.html](http://www.nytimes.com/2001/01/17/business/17AIDS.html) (the company Visible Genetics plans to give away small sequencing machines to clinical laboratories, hospitals, and doctors' offices, and make a profit from the sale of kits required to do a test).

<sup>32</sup> See ANDREWS, ET AL., *supra* note 23, at 423 (listing three gene tests that will soon be available).

<sup>33</sup> See *infra* notes 41 and x.



must have access to theories and data that yield improved drug therapies.<sup>34</sup> The public and private sectors have both started producing the data and compiling the databases that are required for genomic research.<sup>35</sup> As genomics plays a bigger role in drug research, theories about disease mechanisms and the links between genes and diseases will frequently emerge during drug R&D.<sup>36</sup> Theories linking genetic data to drug therapy will also be produced by academic researchers and diagnostic companies interested in making and selling genetic tests.<sup>37</sup>

## II. THE IMPACT OF GENETIC TESTS ON PROFIT AND SOCIAL WELFARE IN THE MARKET FOR EXISTING DRUGS

### A. *The Basic Model*

The market for prescription drugs is difficult to model because of the complicated relationship between the patient who demands the drug and the pharmaceutical company that sells the drug. Typical patients have relatively little to say about the variety or quantity of drug they will purchase. Instead that choice is made by a doctor acting on behalf of the patient facing possible constraints imposed by the party who pays for the drug, the pharmacist, and government regulations.<sup>38</sup> Despite these complications, economists have had some success analyzing this market in a traditional framework.<sup>39</sup> To keep my model simple, I assume that a doctor will prescribe drugs in a way that maximizes the utility of the patient.

In the basic model, a patented drug is given to a patient population; it is effective for half of the population and has no effect on the other half. Suppose that a genetic test is

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<sup>34</sup> Some observers are skeptical about rapid progress in the application of genomics to medicine. *See e.g.*, Leslie Roberts, *SNP Mappers Confront Reality and Find It Daunting*, 287 *SCI.* 1898 (2000); Neil A. Holtzman & Theresa M. Marteau, *Will Genetics Revolutionize Medicine?* 343 *NEW ENG. J. MED.* 141 (2000).

<sup>35</sup> *See* Arti Kaur Rai, *Regulating Scientific Research: Intellectual Property Rights and the Norms of Science*, 94 *NW. UNIV. L. REV.* 77, 146 (1999) (American universities have reached a consensus that SNPs data should be dedicated to the public domain through a public database.); *Scientific American*, *supra* note 30 (The firm Genset has created a private database of 60,000 SNPs that mark genes that cause disease or differing drug reactions).

<sup>36</sup> The drug company Abbot will use the Genset SNP database during clinical trials to identify patients who do not respond to tested drugs. They will then turn these results into a diagnostic test to screen out patients who do not respond. *See* *Scientific American*, *supra* note 30. Drug companies monitor the effect of approved drugs on patients; in the future this monitoring will produce information that aids tailored drug therapy. *See* *Roses supra* note 9.

<sup>37</sup> *See* Rob James, *Differentiating Genomics Companies*, 18 *NATURE BIOTECHNOLOGY* 153, 155 (2000) (The company Gene Logic has developed a database of gene expression profiles for normal cells that can be compared to the gene expression profiles for diseased cells, and cells exposed to toxic substances.); Associated Press, *Miami Herald*, Mar. 25, 2002, available at: <http://www.miami.com/mld/miami/business/2932460.htm> (last visited Mar. 27, 2002) (IBM and the Mayo Clinic plan to create a medical database including 4 million patient records and genetic data from the patients.)

<sup>38</sup> *See* Sarah Ellison, Iain Cockburn, Zvi Griliches, and Jerry Hausman, *Characteristics of Demand for Pharmaceutical Products: An Examination of Four Cephalosporins*, 28 *RAND J. ECON.* 426 (1997).

<sup>39</sup> *See e.g., id.* (showing the demand for drugs is sensitive to price by presenting evidence of high cross-price elasticity in demand for brand-name drugs with generic substitutes, and significant elasticities for therapeutic substitutes).

available that can identify whether a particular patient will gain a benefit from use of the drug. Suppose that a fraction  $\alpha$  of the population is given the test. One-half of those tested will be a “good match” and gain a benefit  $V$  from use of the drug. The other half will be a “bad match” and gain no benefit from the drug.<sup>40</sup> The remaining fraction  $1 - \alpha$  of the population will be uninformed about how well they match with the drug and gain an expected benefit of  $V/2$  from use of the drug. The following table summarizes the information about patient types, probabilities, and valuations.

	Uninformed	Good Match	Bad Match
Probability	$1 - \alpha$	$\alpha/2$	$\alpha/2$
Valuation	$V/2$	$V$	$0$

**Table One**

Suppose that the drug maker sets a uniform price for the drug. The seller knows the information in the Table One, but does not know whether a particular patient is uninformed, a good match, or a bad match. The seller incurs a constant marginal cost of  $C$  from the production and distribution of the drug where  $C < V/2$ . The profit maximizing price depends on the value of  $\alpha$ . If no patients are informed, then all patients have a valuation of  $V/2$  and the monopoly price is  $V/2$ . If all the patients are informed, then only good matches will purchase, and the monopoly price is  $V$ .<sup>41</sup> If there is a mix of informed and uninformed patients, then the monopoly price is  $V/2$  if the fraction informed is sufficiently small, and the monopoly price rises to  $V$  when the fraction informed is sufficiently large.

The profit to the seller from setting a price of  $V/2$  is

$$\pi = (1 - \alpha/2) (V/2 - C),$$

and the profit to the seller from setting a price of  $V$  is

$$\pi = \alpha/2 (V - C).$$

The optimal price is  $V/2$  when  $\alpha \leq \alpha_0$ , and  $V$  otherwise, where

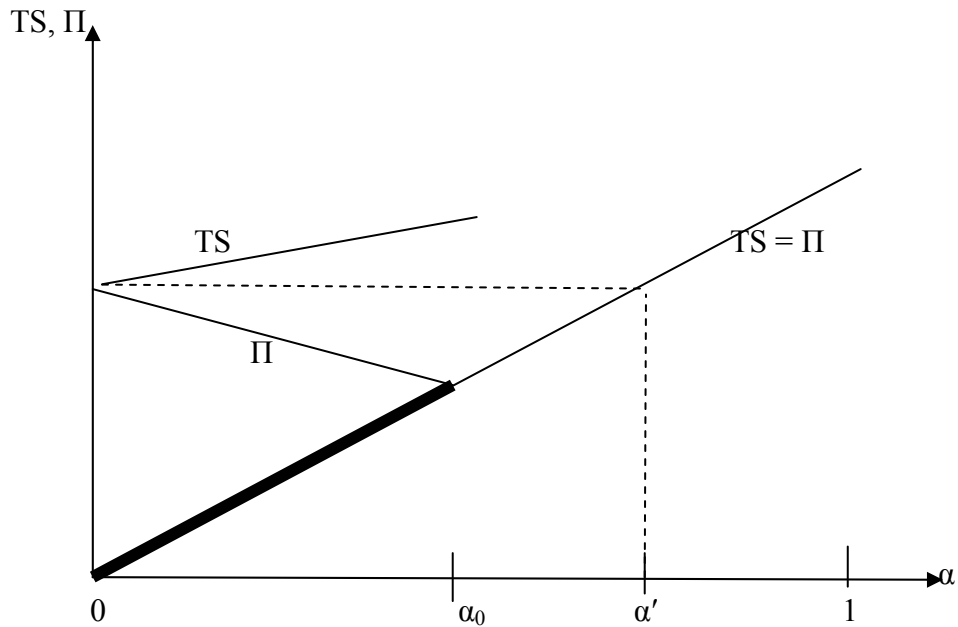
$$\alpha_0 = \frac{2V - 4C}{3V - 4C}.$$

Figure 1 displays profit and total surplus using solid lines (the bold line is relevant to the version of the model analyzed in the next section). The figure shows that the profit to the seller falls as the fraction of informed grows as long as the fraction informed,  $\alpha$ , is less

<sup>40</sup> After the introduction pharmacogenomics, drugs which are currently prescribed to almost all patients will be prescribed only to those patients with a genetic profile indicating drug effectiveness. See Pulsinelli, *supra* note 11, at 339.

<sup>41</sup> See Noah, *supra* note 13, at 18 (making similar observation). But see Patricia Danzon & Adrian Towse, *The Economics of Gene Therapy and of Pharmacogenetics*, 5 VALUE IN HEALTH 5, 9 (2002) (payers are likely to bargain hard to contain drug price increases linked to genetic tests).

than  $\alpha_0$ . Profit grows with the fraction that is informed when  $\alpha$  is sufficiently large (i.e., greater than  $\alpha_0$ ).



**Figure 1**

The effect of the information from genetic testing on profits is easy to understand. Better information has a negative effect on profit because the bad matches drop out of the market.<sup>42</sup> Better information also has a positive effect on profit; the good matches have a higher valuation than the uninformed patients do, and when there are enough good matches the seller raises the price. Figure 1 shows that profit falls for  $\alpha \leq \alpha_0$  because the price is fixed at  $V/2$ , and the only effect of genetic testing is that sales are lost to bad matches. For  $\alpha \geq \alpha_0$ , profit rises with  $\alpha$  because only good matches buy the drug at the price of  $V$ , and increasing genetic testing increases the fraction of patients who know they are good matches. The fraction  $\alpha' \equiv (V - 2C)/(V - C)$  shown in Figure 1 indicates the positive fraction of informed patients that yields the same level of profit achieved when no patients are informed. When  $\alpha > \alpha'$ , genetic testing increases profit because the positive influence of the price increase is greater than the negative influence of lost sales.

Economists measure the social value derived from the drug market by adding consumer surplus to profit; this sum is called total surplus. Figure 1 displays the total surplus as a function of the fraction of patients who get genetic testing. The total surplus in the drug market is easy to calculate. Consumer surplus is zero when the price equals  $V$ , because only good matches buy the drug, and the price equals their valuations. Therefore, total surplus equals profit when  $\alpha \geq \alpha_0$ . For smaller values of  $\alpha$  there is positive consumer surplus. Uninformed patients do not get any consumer surplus at a price of  $V/2$

<sup>42</sup> The negative effect of lost sales on profit is mitigated because the seller avoids the cost of making the drug for bad matches.

because that price equals their valuation. Bad matches do not get any surplus because they do not buy the drug. But good matches get consumer surplus equal to  $V - V/2$ . Thus the expected consumer surplus when  $\alpha \leq \alpha_0$  is  $\alpha/2 (V/2) = \alpha V/4$ . Total surplus when  $\alpha \leq \alpha_0$  is:

$$TS = V/2 - (1 - \alpha/2) C.$$

Total surplus increases with the fraction of informed patients except for a discontinuous drop at  $\alpha = \alpha_0$ . Total surplus drops at the point where the seller switches from a relatively low price of  $V/2$  to the higher price of  $V$ . The drop is large enough that total surplus in the interval  $(\alpha_0, \alpha')$  is lower than total surplus when  $\alpha = 0$ . The availability of genetic testing has an obvious positive effect on total surplus; testing leads to better matching of patients with drug treatment. The social gain from testing is offset by the seller's response to testing — a price increase. The price increase excludes the uninformed patients from the market and causes a social loss. Either the positive or negative effect may predominate so total surplus may either rise or fall after genetic testing is introduced.

The surprising results from the previous analysis are summarized in the following proposition.

*Proposition 1.* The introduction of genetic testing reduces profit on the interval  $(0, \alpha')$ , and it reduces total surplus on the interval  $(\alpha_0, \alpha')$ .

Proposition 1 is helpful in thinking about the incentive effects of pharmacogenomics. A drug maker in a market similar to the one in the model would oppose the introduction of genetic testing unless the testing reaches a relatively large fraction of the market. Intuitively, genetic testing causes profit to fall because of lost sales. Profit only recovers to the level without testing when there are enough patients who have been informed that they are a good match and so have a high valuation that leads to a price increase. A social planner might also oppose the introduction of genetic testing when the fraction of informed patients falls in the interval  $(\alpha_0, \alpha')$ . Total surplus in this interval is low because the output restriction caused by monopoly pricing is substantial and more than offsets the benefit from better matching.<sup>43</sup>

### B. The Information Content of the Test

The basic model assumed that the drug worked in exactly half of the patient population. This subsection generalizes the basic model by assuming that some fraction  $\theta$  benefits from the drug and the remaining  $1 - \theta$  get no benefit. Table Two displays the probabilities and valuations associated with the three types of patients. Informed patients who are a good match get a benefit of  $V$ , uninformed patients get an expected benefit of

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<sup>43</sup> The socially optimal policy is difficult to evaluate when  $\alpha$  takes on other values. When  $\alpha \leq \alpha_0$ , introducing the genetic test raises ex post total surplus, but reduces drug profit and might inefficiently diminish the incentive to invent the patented drug. When  $\alpha > \alpha'$ , the social planner might oppose the genetic test even though it raises total surplus because consumer surplus falls to zero, or because the incentive to innovate is excessive.

$\theta V$ , and bad matches get a benefit of  $\theta$ . The fraction of uninformed patients is  $1-\alpha$ , the fraction of good matches is  $\alpha\theta$ , and the fraction of bad matches is  $\alpha(1-\theta)$ .

	Uninformed	Good Match	Bad Match
Probability	$1 - \alpha$	$\alpha\theta$	$\alpha(1-\theta)$
Valuation	$\theta V$	$V$	$0$

**Table Two**

If  $\theta V \geq C$ , then the basic model of the previous section applies, and the solid lines in Figure 1 shows profit and total surplus.<sup>44</sup> Profit initially falls in  $\alpha$ , and grows when  $\alpha \geq \alpha_0$ . Total surplus equals profit when  $\alpha \geq \alpha_0$ , but diverges from profit when the fraction informed is relatively small, i.e.,  $\alpha \leq \alpha_0$ . Now suppose that a relatively small fraction of patients gain a benefit from the drug, specifically,  $\theta V < C < V$ . In this case the drug maker will not sell the drug if there is no genetic testing, because the expected value of the drug to an uninformed patient is less than the marginal cost of the drug.<sup>45</sup> Thus testing is crucial to the sale of the drug. Given testing, the drug maker will set the price at  $V$  and sell to the good matches. The seller captures all consumer surplus so profit and total surplus are equal. The expression for profit is

$$\pi = \alpha\theta (V - C).$$

The bold line in Figure 1 and the solid continuation of that line represents both profit and total surplus in this case.

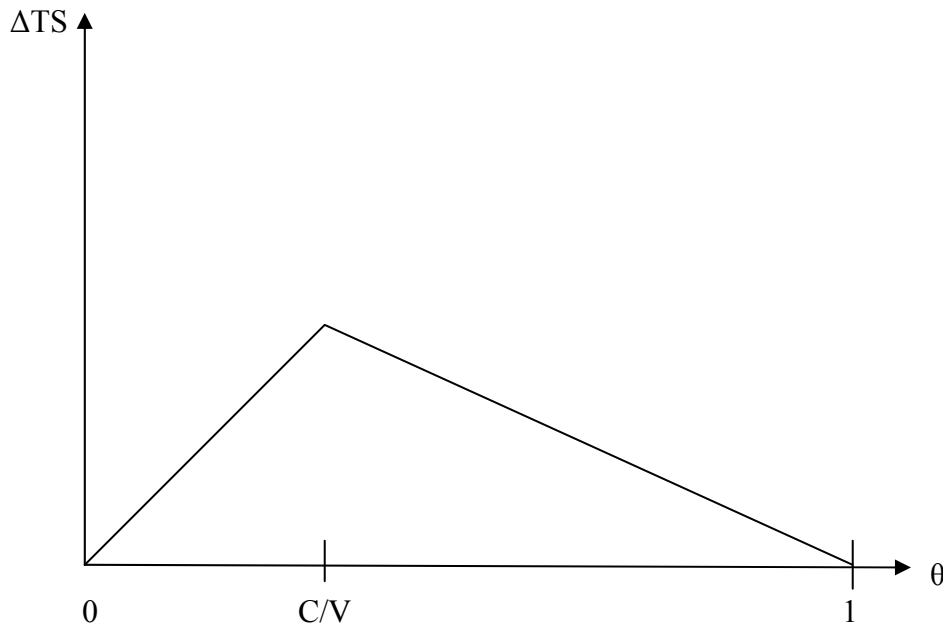
An interesting policy issue arises from the relationship between the informational value of a test and the magnitude of  $\theta$ , the fraction of patients benefiting from the test. The policy issue is captured by the question: How should the magnitude of  $\theta$  affect public sector support for genetic test R&D? One plausible response is that public support should target drugs that can be used with a genetic test and cannot be used without a test, i.e., drugs such that  $\theta V < C < V$ . I think that response is mistaken. A better response considers

<sup>44</sup> Price equals  $\theta V$  and profit equals  $(1 - \alpha + \alpha\theta) (\theta V - C)$  if  $\alpha \leq \alpha_0$ , and price equals  $V$  and profit equals  $\alpha\theta(V - C)$  if  $\alpha \geq \alpha_0$ , where  $\alpha_0$  is defined to be  $[\theta V - C]/[(2 - \theta) \theta V - C]$ .

<sup>45</sup> A similar problem arises when side effects rather than efficacy are the issue. Some drugs are effective but cause severe side effects in a small subset of the population. Such drugs cannot be used unless doctors have a way to screen out patients who might suffer the side effects. Work is under way on a genetic test that can screen out patients that could suffer fatal side effects from an AIDS drug. See Schoofs, *supra* note 14; Jochen Duelli and Ashish Singh, *Tailoring Drugs to Patient Gains Ground*, BOSTON GLOBE, G5, June 30, 2002 (the drug Lotronex was linked to severe intestinal problems and some deaths, but the FDA has allowed Glaxo-SmithKline to reintroduce the drug with patient restrictions based on pharmacogenomic information) (the cancer drug Herceptin is designed exclusively for patients with multiple copies of the HER-2/neu gene) (Glaxo is developing a genetic test that will identify the five percent of patients who could suffer potentially fatal side effects from its AIDS drug Ziagen); Melody Petersen, *Whistle-Blower Says Marketers Broke the Rules to Push a Drug*, N.Y. Times, March 14, 2002, available at: <http://www.nytimes.com/2002/03/14/business/14DRUG.html> (last visited March 14, 2002) (a whistle-blower claims that Warner-Lambert marketed the drug Neurontin to doctors for more than a dozen unapproved conditions) (doctors are allowed to prescribe medicines for uses not approved by the FDA, but drug makers are not allowed to promote unapproved uses) (in 2000 seventy-eight percent of the prescriptions for Neurontin were for off-label uses).

two factors: whether the private sector has adequate incentive to develop the test; and the informational value of the test. Intuitively, a genetic test has little informational value if  $\theta$  is close to zero, or if  $\theta$  is close to one. If a drug is almost never effective for anyone, then there is not much information revealed when a test is performed that indicates the drug will not work for a specific patient. Similarly, not much information is revealed when the drug is almost always effective, and a test shows that it is effective for a specific patient. Rough intuition might suggest that the test is most informative when  $\theta = 1/2$ . Actually, it turns out the social value of a test is highest when  $\theta = C/V$ , a fraction that is likely to be much smaller than  $1/2$ .

One measure of the social value of the test is the difference between total surplus when every patient is tested and the total surplus when no patient is tested.<sup>46</sup> That difference is graphed in Figure 2 as a function of  $\theta$ . The expression for the social value is  $\theta (V-C)$  when  $\theta < C/V$ . This is simply the expected value of the drug when it is administered to every patient who can benefit from it. The expression for social value is  $(1-\theta) C$  when  $\theta \geq C/V$ . This is simply the expected cost saving gained when the drug is not given to patients who cannot benefit from it.<sup>47</sup> The two expressions differ because in the first case when there is no testing the drug is not marketed, but in the second case when there is no testing the drug is sold to everyone. The social value grows with the probability that the drug is effective for small values of  $\theta$ , and it falls in relation to that probability for large values of  $\theta$ .



**Figure 2**

The result displayed in Figure 2 supports a policy that targets genetic tests designed for drugs that work for a fraction of the patient population  $\theta \approx C/V$ , not a policy

<sup>46</sup> A more complicated measure is required when I relax the assumptions that the genetic test is costless and will be used by the entire patient population.

<sup>47</sup> Generally, a social benefit occurs if the marginal cost of drug therapy is greater than the marginal cost of the genetic test.

that targets tests with  $\theta < C/V$ .<sup>48</sup> Thus, policymakers should not target drugs simply because they can only be used with a test. Instead, they should target drugs such that the genetic test yields the greatest social value. Figure 2 is helpful in identifying such tests, but it does not capture all the relevant factors. Obviously, the size of the patient population matters as much as the fraction of the population that can be helped. Further, the analysis should incorporate distributional concerns about providing treatment for small patient groups. The distributional concerns are well articulated in the analogous context of orphan drug policy.<sup>49</sup> Finally, government intervention is not warranted within the framework of this model unless the private incentive to develop genetic tests falls short of the socially optimal incentive. I will defer discussion of that issue until Section III.B.

### C. Tests with No Medical Value

In my second refinement of the basic model, I suppose that every patient gains a benefit from the use of the patented drug, but some patients are a good match and they get a large benefit  $V$ , and other patients are a bad match and they get a smaller benefit  $W > C$ . The valuations and probabilities of each type of patient are displayed in Table 3.

	Uninformed	Good Match	Bad Match
Probability	$1 - \alpha$	$\alpha/2$	$\alpha/2$
Valuation	$(V+W)/2$	$V$	$W$

**Table Three**

A test that informs patients whether they are a good or bad match has no “medical value” in this case in the sense that it is socially desirable for every patient to take the drug.<sup>50</sup> But a test has economic value to certain patients because it gives them private information that allows them to extract surplus from the seller. The drug patent owner has an incentive to block the development of this sort of test.<sup>51</sup>

There are three different profit maximizing prices in this case depending on what fraction of patients are informed. If the fraction of informed patients is relatively small,

<sup>48</sup> Implementing this policy depends on the government’s ability to measure  $\theta$  and the other relevant variables. I suspect a good estimate of  $\theta$  is possible given data on the fraction of patients that respond to a drug.

<sup>49</sup> Commentators have raised the related question of whether the orphan drug statute should be used to promote drug discovery to serve “orphan genotypes.” See Mark A. Rothstein & Phyllis Griffin Epps, *Ethical and Legal Implications of Pharmacogenomics*, 2 NATURE REVIEWS GENETICS 228 (2001) (questioning whether orphan drug statutes should cover drugs intended to treat uncommon genotypes); Arti K. Rai, *Pharmacogenetic Interventions, Distributive Justice, and Orphan Drugs: The Role of Cost-Benefit Analysis*, 19 SOCIAL PHILOSOPHY & POLICY (2002) (discussing the role of genomic data in segregating patient populations in smaller disease categories thereby increasing the problem of sustaining research directed toward diseases affecting rare genotypes); Noah, *supra* note 13, at 17 (discussing orphan genotypes).

<sup>50</sup> Andrew Pollack, *supra*, note 18 (“In some cases, there are no treatments available. So genetic fingerprinting may merely tell patients how quickly they can expect to die, without allowing doctors to do anything about it.”)

<sup>51</sup> Cf. Robertson et al., *supra* note 12, at 75 (drug patent owner may block development of genetic test).

i.e.,  $\alpha \leq \alpha_1$ , then the seller maximizes profit by choosing a price of  $(V+W)/2$  and selling to good matches and uninformed patients. Profit is

$$\pi = (1 - \alpha/2) [(V+W)/2 - C].$$

If the fraction of informed patients is in an intermediate range so that  $\alpha_1 \leq \alpha \leq \alpha_2$ , then the seller maximizes profit by choosing a price of  $W$  and selling to all patients. Profit is

$$\pi = W - C.$$

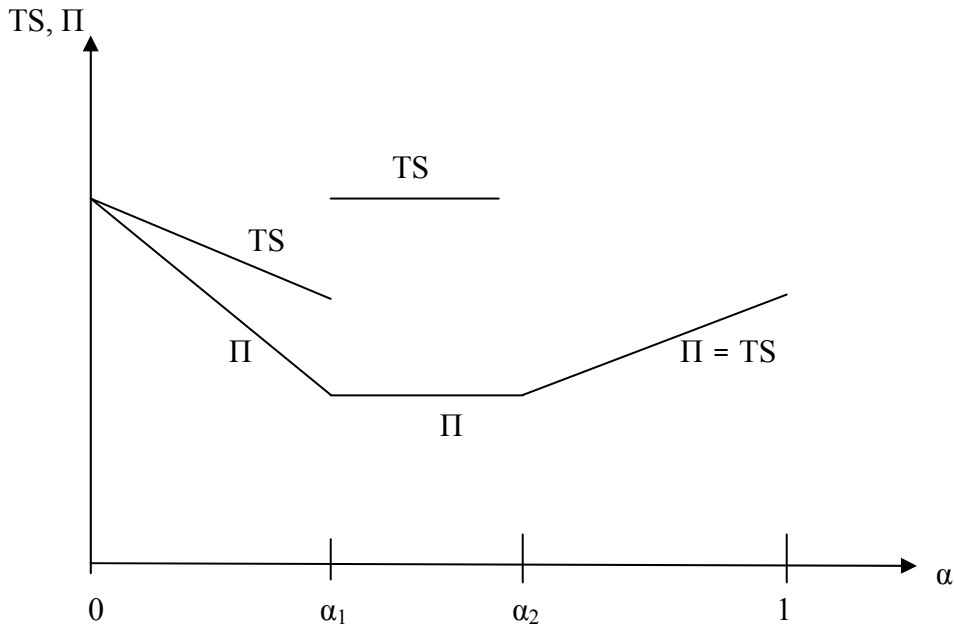
If the fraction of informed patients is relatively large, i.e.,  $\alpha_2 \leq \alpha \leq 1$ , then seller maximizes profit by choosing a price of  $V$  and selling only to good matches. Profit is

$$\pi = \alpha/2 (V - C).$$

The critical values of  $\alpha$  are given by the following expressions.

$$\alpha_1 = \frac{2(V - W)}{V + W - 2C} \qquad \alpha_2 = \frac{2(W - C)}{V - C}$$

I assume that  $\alpha_2 < 1$ , i.e.,  $V - W < W - C$ , otherwise setting a price of  $V$  is never optimal.



**Figure 3**

Figure 3 displays profit and total surplus as a function of the fraction of patients who are informed. Notice that profit is maximized when none of the patients is informed. Profit falls for small values of  $\alpha$  because bad matches drop out of the market and the price is fixed at  $(V + W)/2$ . For intermediate values of  $\alpha$ , profit is not sensitive to the



fraction of patients who are informed because every patient purchases regardless of test results when the price is  $W$ . For large values of  $\alpha$ , profit rises as more patients are informed because only good matches purchase at the price of  $V$ .

Total surplus maximization in this case simply requires that all patients buy and use the drug. Total surplus is maximized when no patients are informed and the price is set at a level such that they all purchase.<sup>52</sup> Total surplus is also maximized when an intermediate fraction of the patients are informed,  $\alpha_1 \leq \alpha \leq \alpha_2$ , and the seller chooses a price of  $W$  and sells to all patients. Consumer surplus is maximized for intermediate values of  $\alpha$ , because all patients buy the drug and the price is lower than for other values of  $\alpha$ . In contrast, consumer surplus is zero, when no patients are informed. These observations reveal the antagonistic interests of patients and the drug patent owner in this case. The drug patent owner wants to maximize the size of the pie and take all of that pie by suppressing the genetic test. Patients might prefer to absorb the cost of developing and deploying the therapeutically unnecessary test to increasing their bargaining power against the drug seller.

#### D. Differentiated Drugs in a Duopoly Market

The model in this section features two drugs available to treat a certain population of patients. One drug, labeled A, is more effective or safer for half of the population, and the other drug B is better for the other half of the population. A test is available that will inform patients whether they are better matched with drug A or B.<sup>53</sup> Suppose that a good match bestows a benefit  $V$ , and a bad match gives no benefit. The valuations and probabilities of each type of patient are displayed in Table Four.

	Uninformed	Good Match A	Good Match B
Probability	$1 - \alpha$	$\alpha/2$	$\alpha/2$
Valuation of A	$V/2$	$V$	$0$
Valuation of B	$V/2$	$0$	$V$

**Table Four**

I will analyze the effect of a genetic test on prices, profits, and total surplus in a duopoly market for drugs A and B. Suppose that one firm has a patent on drug A and another firm has a patent on drug B. Suppose the firms simultaneously set the price for the two drugs given that some fraction  $\alpha$  of the patients will take the genetic test.

<sup>52</sup> When price  $P = (V + W)/2$ , consumer surplus is derived by good matches. Each good match gets utility of  $V - P = (V - W)/2$ , so the expected consumer surplus is  $(\alpha/2)(V - W)/2$ , and total surplus is just the sum of consumer surplus and profit. When  $P = W$ , consumer surplus is derived by good matches and uninformed patients. Each good match gets utility of  $V - P = V - W$ . Each uninformed patient gets utility of  $(V + W)/2 - P = (V - W)/2$ . Expected consumer surplus is  $(\alpha/2)(V - W) + (1 - \alpha)(V - W)/2 = (V - W)/2$ . Since profit  $\pi = W - C$ , total surplus equals  $(V + W)/2 - C$ .

<sup>53</sup> For a possible example see Alison Davis, *News Release, First Awards Made in NIH Effort to Understand How Genes Affect People's Responses to Medicines*, April 4, 2000, available at: <http://www.nigms.nih.gov/news/releases/pharmacogenetics.html> (last visited Mar. 26, 2002) (an NIH grant is funding research to discover which genes affect widely variable responses to the three main types of asthma drugs).

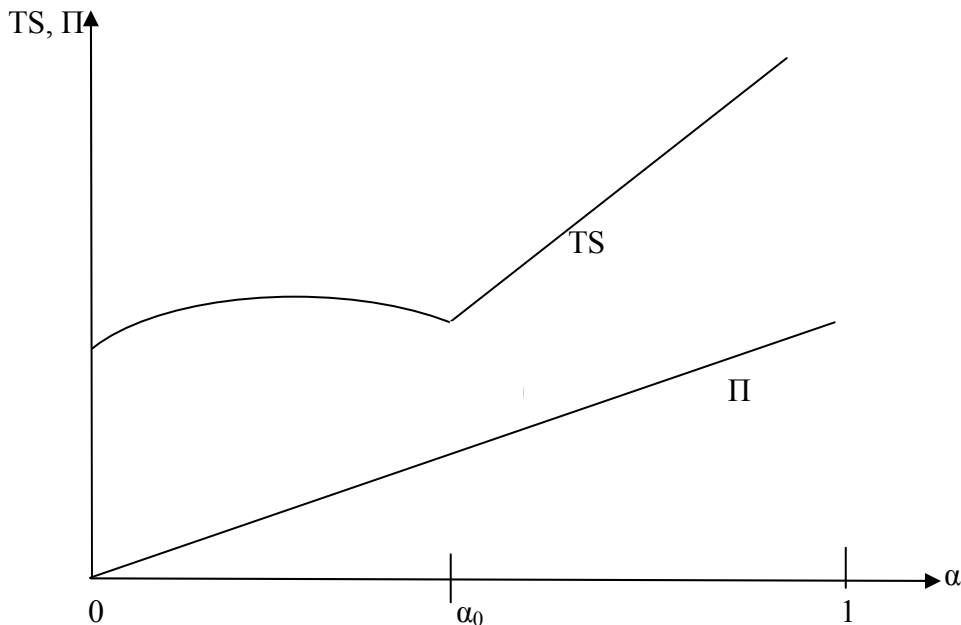
Uninformed patients get equal expected value from drugs A and B. Informed patients strongly prefer the drug that is a good match for them. An article by Meurer and Stahl characterizes the Nash equilibrium for this problem.<sup>54</sup>

*Proposition 2.* If the fraction of informed patients is large enough, i.e.,  $\alpha \geq \alpha_0$ , then both sellers choose a price  $P_A = P_B = V$ , and profit for each firm is

$$\pi = (\alpha/2) (V - C).$$

If the fraction of informed patients is lower,  $\alpha \leq \alpha_0$ , then the sellers choose prices from a symmetric mixed strategy equilibrium, and the same expression represents expected profit.<sup>55</sup>

Intuitively, when a large fraction of patients are informed each of the firms sell only to patients who are a good match at the price of  $V$ . Neither firm is interested in cutting its price to  $V/2$  to sell to the uninformed patients. Such a price cut would increase sales, but not enough to offset the lost revenue from the good matches. In contrast, when the fraction of informed patients is lower the two firms waver between targeting just good matches, and trying to capture the uninformed patients. The mixed strategy equilibrium requires that each firm sets the price at  $V$  with the same positive probability, and otherwise sets a price somewhere in an interval less than or equal to  $V/2$ . Each firm introduces a random element into its pricing decision to avoid being easily undercut by its rival.



**Figure 4**

<sup>54</sup> See Michael Meurer & Dale O. Stahl, *Informative Advertising and Product Match*, 12 INT'L J. INDUSTRIAL ORG. 1 (1994).

<sup>55</sup> Proof of results stated in this section and Figure 3 are contained in Meurer & Stahl. See *id.*

Figure 4 displays the profit of a duopolist and the total surplus as a function of the fraction of patients tested. Figures 1 and 3 both show that total surplus declines over an intermediate range of values of  $\alpha$ . The same explanation applies to the monopoly and duopoly markets. As the fraction of untested patients declines, prices rise and the untested patients are forced out of the market. For other values of  $\alpha$ , total surplus grows because increased testing leads to better matching of patients and drugs.

The private incentive to develop genetic tests is probably weaker in the duopoly market depicted in this section than the monopoly market in section A.<sup>56</sup> Testing has two favorable effects on the profit of the duopolists. First, it increases sales by increasing the number of good matches when the fraction tested is high. Second, it decreases competition for untested patients when the fraction tested is low. But the private incentive to develop tests is diminished by a classic free-riding problem. The value of the test flows equally to the two firms in this model, and either firm would be tempted to delay test development in hopes that its rival will provide the public good. A patent on the genetic test is not likely to solve the free-riding problem. To see why, suppose firm A develops and patents a test. Firm A cannot credibly commit to a policy that prohibits the use of the test in conjunction with drug B, and at the same time, authorize use of the test in conjunction with drug A. A physician that performs the test and finds out that a patient is a good match with B and a bad match with A cannot deliberately forget the information, and cannot ethically ignore it. Thus, the free-riding problem is likely to cause underinvestment in genetic tests used to choose among substitute patented drugs.<sup>57</sup>

### III. INCENTIVES TO CONDUCT AND DEVELOP GENETIC TESTS

#### A. *The Incentive to Conduct Genetic Testing*

Section II reveals that the rate of adoption of genetic tests has subtle and significant effects on profit in complementary drug markets. In some markets, the rate of adoption will be one hundred percent,<sup>58</sup> but in other markets adoption will be slowed many factors. Tort law, cost containment concerns of health care purchasers, and norms of good medical practice will encourage testing.<sup>59</sup> Optimists expect that physicians will rapidly embrace pharmacogenomics and it will soon be incorporated into the standard diagnostic repertoire. Laggards would be encouraged to embrace genetic testing for fear

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<sup>56</sup> An interesting topic for future research is the incentive to develop genetic tests for use in markets with unpatented drugs. I conjecture that the test developer could capture a larger share of the surplus generated by the test when the drug market is relatively competitive.

<sup>57</sup> The firms might overcome the free riding problem by jointly developing the test, or if allowed by antitrust law, by jointly marketing the test and their drugs.

<sup>58</sup> Certainly, testing will always be done when it screens out patients who would suffer lethal side effects.

<sup>59</sup> See Buchanan, et al., *supra* note 1, at 4 (payers are likely to embrace genetic tests that reduce expenditures on drugs); Danzon & Towse, *supra* note 41, at 8-9 (willingness to pay for testing depends on health benefit from treatment and avoiding adverse reactions and the cost of testing); See Rothstein & Epps, *supra* note 49 (“[E]thical concerns, economic considerations and the threat of malpractice liability are likely to encourage physicians to begin testing for and prescribing medications designed for use by specific, smaller groups of individuals...[but] budgetary constraints imposed by insurers could slow acceptance of drugs developed through pharmacogenomics...”).

of a malpractice claim.<sup>60</sup> In a promising example, Danzon and Towse document significant savings to health care payers from adoption of a genetic test used in conjunction with drug treatment of a particular form of breast cancer.<sup>61</sup> But skeptics warn that the pharmacogenomic revolution will be slowed by limited insurance coverage,<sup>62</sup> privacy concerns,<sup>63</sup> and physician resistance or inertia.<sup>64</sup> Further impediments will be created by the high cost of developing and implementing the new tests, and by the proliferation of costly new tailored drugs.<sup>65</sup> Optimists respond that the cost of testing is likely to fall as the industry gains experience in making and performing tests, and there are likely to be economies of scale and scope in testing.<sup>66</sup>

Industry participants will surely influence the rate of adoption to advance their goals. Generally, health care payers and drug companies have divergent interests in promoting genetic tests. In some markets, both groups will favor tests, in some markets drug companies will resist tests, and in other markets health care payers will resist tests. In existing markets with a single patented drug, drug companies will push for complete adoption of tests that accomplish useful sorting at a marginal cost less than the marginal cost of the drug. Looking back to Figure 1, we see that drug company profit is maximized when all patients are tested.<sup>67</sup> Drug companies are apt to promote the test by marketing to physicians and perhaps bundling tests with drugs.<sup>68</sup> Figure 1 also shows that consumer surplus is maximized when the fraction of patients tested is  $\alpha_0 < 1$ .<sup>69</sup> Thus, a managed care organization or other party acting to maximize consumer surplus might prefer

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<sup>60</sup> Possible tort liability for failure to warn about drug risks will push pharmacists and drug companies to encourage pharmacogenomic medicine. See Rothstein & Epps, *supra* note 49.

<sup>61</sup> See Danzon & Towse, *supra* note 41, at 11 (The FDA has approved three diagnostic tests that indicate whether a patient will benefit from the chemotherapy drug trastuzumab. The cost is less than \$100 per test.).

<sup>62</sup> See Rothstein & Epps, *supra* note 49 (questioning the extent of insurance coverage related to pharmacogenomic drug therapy); Rai, *supra* note 11, at 202 (many Medicare beneficiaries do not have prescription drug coverage).

<sup>63</sup> See ANDREWS, ET AL., *supra* note 23, at 430-31 (discussing privacy risks of genetic testing associated with pharmacogenetics and pharmacogenomics).

<sup>64</sup> See Buchanan, *supra* note 1, at 16; Noah, *supra* note 13, at 22-23 (physicians may be slow to accept pharmacogenomics).

<sup>65</sup> One factor that might contribute to high testing cost is the need to obtain upstream gene patent licenses to perform tests. High cost of license to perform test for breast cancer related genes, and gene related to Canavan's disease. The analysis in Section II.A shows that the price of currently available drugs might also rise. Noah, *supra* note 13, at 27 (payers may not be enthusiastic about pharmacogenomics).

<sup>66</sup> See Scientific American, *supra* note 30 ("Affymetrix expects to be able to mill through 100,000 SNPs dispersed through a patient's genome in several hours, for as little as a few hundred dollars."); Pollack, *supra* note 18 ("Some scientists say the gene chips may be too expensive and difficult to use in the average clinic. But others say the tests will come down to a few hundred dollars apiece. While powerful computers may be needed to find the patterns initially, once they are found a sample can be analyzed on a laptop. And the number of genes that need to be tested may also shrink. Merck started out analyzing 25,000 genes but found that only 70 were needed to predict breast cancer outcome.")

<sup>67</sup> Similarly, drug companies will promote widespread adoption of tests that bring a drug to the market that has been shelved because of adverse reactions or low rates of efficacy.

<sup>68</sup> See Robertson et al., *supra* note 12, at 159. Cf. Iain Cockburn, *Comments on: The Proper Scope of IP Rights in the Post-Genomics Era* (by Arti K. Rai), B. U. J. SCI. & TECH. L. (2001) (genomics may disrupt current drug marketing practices).

<sup>69</sup> That value of  $\alpha$  maximizes the difference between total surplus and profit. Notice that  $\alpha_0$  also minimizes profit. The interest of the drug company and consumers are strongly opposed.

limited adoption of genetic testing.<sup>70</sup> In contrast, when the genetic test is not medically necessary because all patients will take the drug regardless of the test outcome then drug companies will oppose tests because the tests give health care payers information that augments their bargaining power against drug companies in the market for drugs. Genetic tests might not diffuse as widely in markets with patented substitutes or markets with unpatented drugs because the test seller does not (fully) internalize the increased profit from drug sales. If the test seller cannot bundle the test with the complementary drugs, then it will set a price above marginal cost that will slow test adoption.

### B. *The Incentive to Develop Genetic Tests*

The genetic tests required for customized drug therapy will be costly to develop, thus it is important to consider whether the private sector has an adequate development incentive. Drug innovators have a strong incentive to develop genetic tests because the tests are likely to reduce the cost of clinical trials for *new drugs*.<sup>71</sup> If pharmacogenomics becomes an essential step in drug discovery, then drug patent owners will routinely develop complementary genetic tests.<sup>72</sup> It is less clear whether incentives are adequate for tests that are designed for use with *existing drugs*. Typically, patents on tests provide adequate incentives, but patents fail to provide adequate incentives under certain market conditions and public support should supplement private sector R&D. I evaluate the adequacy of private incentives by comparing the private costs and benefits to the social costs and benefits of test development. Private costs diverge from social costs mostly because of licensing fees. Private benefits diverge from social benefits for reasons related to the structure of the market for drugs, the structure of the market for genetic tests, and the rate of adoption of tests.

The private cost of developing a genetic test includes both the transfer payments required to license relevant patents and gain access to genomic databases, and the real costs associated with research personnel, instruments and material.<sup>73</sup> The social cost of developing a test excludes transfer payments related to patent licenses and database access. The firm views a wealth transfer as a cost but it is not a social cost because it does not consume resources. Thus, private and social costs are equal only when transfer payments are zero. Patents on research tools could add significantly to the cost of

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<sup>70</sup> Managed care organizations are likely to weigh the costs and benefits of using any diagnostic test. Cf. Muin J. Khoury & Jill Morris, *Pharmacogenomics and Public Health: The Promise of Targeted Disease Prevention*, available at: <http://www.cdc.gov/genomics/info/factshts/pharmacofs.htm> (last visited Mar. 26, 2002) (discussing a cost-benefit analysis of testing for the factor V Leiden allele, which is associated with an elevated risk of venous thrombosis among women who take oral contraceptives).

<sup>71</sup> See Danzon & Towse, *supra* note 41, at 10.

<sup>72</sup> But Sections II.A and II.C show that the innovator may suppress the tests if they are not medically useful or if they will not be widely adopted.

<sup>73</sup> A likely regulatory cost arises from FDA oversight of genetic tests. See Michael J. Malinowski & Robin J.R. Blatt, *Commercialization of Genetic Testing Services: The FDA, Market Forces, and Biological Tarot Cards*, 71 TUL. L. REV. 1211, 1229-32 (1997) (describing FDA regulation of predictive genetic test kits and services); Buchanan, *supra* note 1, at 6. In the future, the economically relevant cost to develop a genetic test may be quite low, because the information required for the genetic test will be produced during the normal course of drug development. In other words, since pharmacogenomic information will be gathered as part of an efficient drug development project, then that same information can be used at no cost during the development of genetic testing. See Rai, *supra* note 10, at 191.

pharmacogenomic research.<sup>74</sup> For example, gene patents owners are likely to collect royalty payments from companies who make gene chips used to predict adverse drug reactions.<sup>75</sup> The research exemption in patent law is very limited and will not diminish these costs,<sup>76</sup> and pharmacogenomics is outside the reach of the limitations imposed on enforcement of medical process patents.<sup>77</sup> It is possible, though, that these patent licensing costs are overstated.<sup>78</sup> Many existing gene patents may not survive validity challenges.<sup>79</sup> And many genes are unpatentable because of gene sequence data placed in the public domain.<sup>80</sup> License fees required for access to genomic databases could also add significantly to development cost.<sup>81</sup> The high fixed cost of producing a database means that the market is not competitive,<sup>82</sup> but prices are constrained by the existence of non-profit databases,<sup>83</sup> relatively weak intellectual property protection,<sup>84</sup> and the possibility of entry.

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<sup>74</sup> See Janice M. Mueller, *No "Dilettante Affair": Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools*, 76 WASH. L. REV. 1, 8 (2001) (commenting on high transaction costs associated with obtaining patent rights for gene chip); Rebecca S. Eisenberg, *Re-Examining the Role Of Patents in Appropriating the Value of DNA Sequences*, 49 EMORY L. J. 783, 6-9 (2000) (genomics companies aim to protect information rather than molecules with their gene patents); Andrew Pollack, *3-D RNA Folds and Molds Like a Key for a Specialized Work*, N. Y. Times (Jan. 21, 2002) available at: <http://www.nytimes.com/2003/01/21/science/21SHAP.html> (discover of aptamers (short strands of RNA that interact with proteins) believes basic research on aptamers has been slowed because of his reluctance to license his patent); Philippe Ducor, *New Drug Discovery Technologies and Patents*, 22 RUTGERS COMPUTER & TECH. L.J. 369, 388 (1996) ("A cursory search of U.S. patent titles pertaining to such screening methods identified over forty-two issued patents in the past three years alone, a tally that does not account for patents which may claim such methods without stating so in their titles."); Rebecca Eisenberg, *The Shifting Balance of Patents and Drug Regulation*, 19 Health Affairs 119, 127 (2001) (Merck supports the SNPs consortium to reduce the number of upstream patents and avoid licensing costs); Rebecca Eisenberg, *Reaching Through the Genome*, [This book] (2003) (reach through licenses and claims are used by upstream gene patent owners to gain downstream revenue); See Rai, *supra* note 23, at 816-17 (drug developers need to get licenses to SNP patents to develop certain targeted drugs).

<sup>75</sup> See *id.* at 842.

<sup>76</sup> See *Roche Prods., Inc. v. Bolar Pharmaceuticals, Inc.*, 733 F.2d 858 (Fed. Cir.), cert. denied, 469 U.S. 856 (1984). The 271(e) research exemption is limited to research designed to gather data related to FDA regulation. See Mueller, *supra* note 74, at 25-27. For a full discussion of the research exemption, see Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017 (1989).

<sup>77</sup> See Nunnally, *supra* note 21, at 20 (2001).

<sup>78</sup> See F. Scott Kieff, *Facilitating Scientific Research: Intellectual Property Rights and the Norms of Science – A Response to Rai and Eisenberg*, 95 NW. U. L. REV. 691, 701-03 (2001).

<sup>79</sup> The utility requirement is likely to be a problem for many gene patents. See *Brenner v. Manson*, 383 U.S. 519 (1966). Gene patent claims that are valid may be read narrowly so that downstream genetic test developers are not infringers. See Kieff, *supra* note 78, at 700 (EST patents could be read narrowly).

<sup>80</sup> See Rai, *supra* note 23, at 832-33 (pharmaceutical companies are building public domain genomic databases to ward off potential patents); Nunnally, *supra* note 21, at 12-13 (the SNP consortium will not patent its discoveries and hopes to thwart SNP patents by others).

<sup>81</sup> See *supra* notes 35-37.

<sup>82</sup> See J.H. Reichman & Pamela Samuelson, *Intellectual Property Rights in Data?* 50 VAND. L. REV. 51 (1997) (database markets tend toward natural monopoly).

<sup>83</sup> See Nunnally, *supra* note 21, at 12-13 (the SNP consortium hopes to achieve economies of scale by avoiding redundant research).

<sup>84</sup> Trade secret law is the main source of intellectual property protection of genomic databases. Databases get fairly little protection under copyright law. See *Feist Publications v. Rural Telephone Service*, 499 U.S. 340 (1991). Jane C. Ginsburg, *No Sweat? Copyright and Other Protection of Works of Information After*

The private benefit from developing a genetic test depends on the structure of the market for the drug or drugs that are used in conjunction with the test. In many markets, only a drug patent owner would pursue development of a genetic test designed for use with a patented drug.<sup>85</sup> The patent owner could deter competing innovators by threatening a patent infringement suit, if developing the genetic test requires use of the patented drug. Furthermore, the patent owner enjoys cost advantages in developing a genetic test because of access to the drug and patients' genetic information acquired during clinical testing.<sup>86</sup>

The benefit to a drug patent owner from developing a genetic test is the sum of the profit from selling the test plus the increase in profit from sale of the drug that is used in conjunction with the test. If the drug is not currently marketed, then the patent owner has a strong incentive to develop a genetic test that would get the drug on the market.<sup>87</sup> For example, a drug might be kept off the market because of adverse reactions. A test might allow doctors to screen out patients who are likely to suffer an adverse reaction, making the drug marketable. If the drug is already marketed, then the drug patent owner may gain or lose from the introduction of the genetic test. Section II shows that the profit from drug sales depends on the fraction of the patient population that is tested. For example, if the test is not medically useful, then testing always hurts profit. If testing is medically useful, then testing every patient maximizes monopoly profit.<sup>88</sup> In contrast, if the fraction tested is less than  $\alpha'$  as displayed in Figure 1, then even medically useful genetic testing cuts profit for drugs that are already marketed. To achieve a high rate of testing the firm should set a low price on the genetic test, and capture its profit through the price of the drug.<sup>89</sup> In fact, the firm should offer the test free of charge to promote widespread adoption. The test and the drug are complements and patients care about the total expected price of drug therapy not the separate prices of testing and drugs. Essentially, genetic testing plays a role similar to advertising. Just as a firm offers advertising information at no charge, it should offer the testing information at no charge in order to gain a favorable change in the demand for the drug.<sup>90</sup>

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*Feist v. Rural Telephone*, 92 COLUM. L. REV. 338 (1992). But Congress has considered establishing new intellectual property rights that apply to databases. Reichman & Samuelson, *supra* note 58, at 95-112 (1997) (explaining forces that push the United States toward adoption of a database statute).

<sup>85</sup> Drug patent owners may develop a test directly or indirectly. Big pharmaceutical firms have started to collaborate with universities and bio-tech start-ups to make genetic tests used for drug therapy. *Id.*

<sup>86</sup> See Allen C. Nunnally, Scott A. Brown, & Gary A. Cohen, *Intellectual Property and Commercial Aspects of Pharmacogenomics*, in PHARMACOGENOMICS: SOCIAL, ETHICAL, AND CLINICAL DIMENSIONS, ed. MARK A. ROTHSTEIN (2003).

<sup>87</sup> The model in Section II.B exaggerates the strength of the private incentive to develop a test for a drug that is not currently marketed. The model assumes that all patients who should use the drug derive the same benefit of  $V$ . In a more realistic model with heterogeneous valuations, the drug company would not capture all the consumer surplus from introducing the drug, and therefore, profit would be less than total surplus.

<sup>88</sup> If the genetic test is used by all potential patients then in the basic model the profit from sale of the drug is  $\pi = 1/2 (V - C)$ . In contrast, the profit if the genetic test is not developed and all patients are uninformed is  $\pi = V/2 - C$ . The difference between these two profit levels is  $C/2$ . Thus, the change in profit to the firm from developing the genetic test is  $C/2$ . Intuitively, testing increases profit because it allows the firm to avoid the cost of making and selling drugs to patients who will not benefit from the drugs.

<sup>89</sup> Assuming the marginal cost of testing is low compared to the marginal cost of drug therapy.

<sup>90</sup> Drug companies might be constrained by antitrust concerns. See Noah, *supra* note 13, at 21-22 (discussing antitrust issues presented by bundling drugs and genetic tests).

The private benefit from test development equals the social benefit when the test developer captures the increase in total surplus caused by adoption of the test. Sections II.A and B suggest drug patent owners will effectively capture the social benefit from test development when medically useful tests are widely adopted. In contrast, when the fraction of patients tested is relatively low there can be wide divergence between the private and social benefit. For example, Figure 1 shows profit declines while total surplus grows from test introduction when the fraction of patients tested is less than  $\alpha_0$ . Section II.C shows that there is no social benefit from development and introduction of tests that are not medically necessary. For such tests, private and social benefits are equal and maximized when no patients are tested and no test is developed. Section II.D shows that the private benefit from test introduction falls short of the social benefit in duopoly markets. The free rider problem discourages firms from developing a test used in conjunction with substitute patented drugs owned by different firms.

Finally, consider test development incentives when multiple firms race to get a patent on a test.<sup>91</sup> This problem is outside the scope of the model in Section II, but two points deserve comment. First, the expected profit from the test is lower because the profit is discounted by the probability of winning the patent race, and because a genetic test inventor who does not own the patent on the associated drug gets a smaller profit than the drug patent owner could.<sup>92</sup> Second, the expected profit from a patent on a genetic test is more potent in stimulating R&D by firms in a patent race. It is possible the private incentive to develop the genetic test exceeds the social incentive. This can be true even though the expected profit from patenting a test is lower. The difference from the single inventor case arises because firms are driven to win the winner-take-all patent race. A social planner does not care which firm wins the race, but of course the firms care. Therefore, even if the winner earns far less than the expected social value from competing in the race, firms might invest more than the social optimum.

## CONCLUSION

Federal subsidies and public sector research currently play significant roles stimulating the development of the first generation of genetic tests designed to customize drug therapy. If pharmacogenomics fulfills its promise, then we should expect that as this sector of the pharmaceutical industry matures, most of the R&D on genetic tests will shift to the private sector. Drug manufacturers have a strong incentive to develop tests during the drug development process. They also have a strong incentive to develop tests that allow them to market drugs that have been shelved because of adverse reactions or low efficacy rates. Drug manufacturers and independent diagnostic manufacturers are apt to

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<sup>91</sup> Biotech firms are starting to enter this market. See Scientific American, *supra* note 30.

<sup>92</sup> The test inventor can profit either by selling the test to patients or by assigning the patent to the drug patent owner. Because the test and the drug used in conjunction with the test are complementary products, assigning the genetic test patent to the drug patent owner is likely to be more profitable. The maximum profit that the drug patent owner can derive from introducing a genetic test is  $C/2$ . That amount is the upper bound on the profit available to an outside inventor who patents the genetic test. It is likely that the drug patent owner and the inventor of the genetic test would share that amount, thus the private gain to the inventor is lower than in the case when the drug patent owner is also the inventor of the genetic test. The drug patent owner would market the test when profitable, but would still be willing to acquire the patent and suppress the test if usage was unprofitable.



play the leading role in developing genetic tests used in conjunction with drugs that are currently marketed, but the presence of certain factors may dampen private incentives to develop tests for existing drugs and require continued public sector participation in genetic test R&D. The case for public subsidy is strongest when genetic tests are not widely adopted, when tests are designed for use with substitute drugs manufactured by different companies, or when the private cost of test development is high because of licensing costs.

Public sector support for development of genetic tests can take many different forms. Presently, federal grants directly support public sector pharmacogenomic research,<sup>93</sup> and indirectly support pharmacogenomics through subsidies encouraging the production of research inputs (like gene data) that are used in the development of genetic tests.<sup>94</sup> The government can encourage adoption of genetic tests through drug law and health insurance regulation.<sup>95</sup> Finally, the drug laws may be used to subsidize the development of drugs designed to treat “orphan genotypes.”<sup>96</sup> An interesting question for future research is the optimal mix of these subsidies.

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<sup>93</sup> See Davis, *supra* note 53 (the NIH made nine grants in the year 2000 totaling \$12.8 million for research in pharmacogenetics).

<sup>94</sup> See Pollack, *supra* note 18 (“[The] International Genomics Consortium [is] a group of companies and academic institutions that wants to analyze at least 10,000 tumors to develop standard methods [of genetic analysis] and to generate genetic signatures that would be public, not patented.”)

<sup>95</sup> See Rai, *supra* note 11, at 203-05 (Pharmacogenomics will put pressure on the federal government to subsidize drug purchases by people lacking prescription drug insurance.)

<sup>96</sup> Pharmacogenomics will identify genotypes that should not be treated with existing drugs. See Roses, *supra* note 9 (pharmacogenetics will encourage parallel drug development to treat the heterogeneous forms of some diseases). Drug companies may not be willing to develop new drugs to treat small patient groups who have a rare genotype. See Danzon & Towse, *supra* note 41, at 12 (socially valuable genetic tests may impair incentives to develop new drugs to serve small niches). The Orphan Drug Act spurs development of orphan drugs by providing marketing exclusivity, tax credits, and grants. The Act may apply to drugs that treat rare genotypes. See Pulsinelli, *supra* note 11, at 310; Buchanan, *supra* note 1, at 12 (suggesting federal subsidies for research to develop drugs for orphan genotypes).