

# Saint Louis University Journal of Health Law & Policy

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Volume 3  
Issue 1 *Living in the Genetic Age: New Issues,  
New Challenges*

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Article 6

2009

## Beyond Bidil: The Expanding Embrace of Race in Biomedical Research and Product Development

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### Recommended Citation

Jonathan Kahn, *Beyond Bidil: The Expanding Embrace of Race in Biomedical Research and Product Development*, 3 St. Louis U. J. Health L. & Pol'y (2009).

Available at: <https://scholarship.law.slu.edu/jhlp/vol3/iss1/6>

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## BEYOND BIDIL: THE EXPANDING EMBRACE OF RACE IN BIOMEDICAL RESEARCH AND PRODUCT DEVELOPMENT

JONATHAN KAHN\*

### I. INTRODUCTION

In 2005, the U.S. Food and Drug Administration (FDA) approved the drug, BiDil®, for treatment of heart failure in “black” patients.<sup>1</sup> The approval of this first, and currently only, race-specific drug provoked an energetic and sustained discussion of the propriety of using racial categories in drug development in a wide array of media and professional journals.<sup>2</sup> BiDil is the prototype of using race as a placeholder during the “meantime” of pharmacogenomic development. As one article in the journal *Science* stated at the time, “By backing BiDil, the FDA panel gave another push to pharmacogenomics, an approach that promises to revolutionize both drug discovery and patient care.”<sup>3</sup>

The 2005 FDA approval was based on results from the African-American Heart Failure Trial (A-HeFT)<sup>4</sup> that were published the previous November in the *New England Journal of Medicine*.<sup>5</sup> The trial design itself was groundbreaking because it included *only* self-identified African

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1. News Release, U.S. Food & Drug Admin., FDA Approves BiDil Heart Failure Drug for Black Patients (June 23, 2005) [hereinafter FDA News Release], <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108445.htm>.

2. See, e.g., Jonathan Kahn, *How a Drug Becomes “Ethnic”: Law, Commerce, and the Production of Racial Categories in Medicine*, YALE J. HEALTH POL’Y L. & ETHICS, Winter 2004, at 3, 33 (discussing the use of race in the development of BiDil). See also Timothy Caulfield & Simrat Harry, *Popular Representations of Race: The News Coverage of BiDil*, 36 J.L. MED. & ETHICS 485, 485-86 (2008) (reporting that when the term “BiDil” was searched in the Lexis-Nexis database it yielded a total of 167 U.S. newspaper articles).

3. Robert F. Service, *Going from Genome to Pill*, 308 SCIENCE 1858, 1858 (2005).

4. FDA News Release, *supra* note 1.

5. See Anne L. Taylor et al., *Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure*, 351 NEW ENG. J. MED. 2049, 2050 (2004).

Americans.<sup>6</sup> The results therefore give the impression that BiDil works *only* in African Americans. This is clearly not the case. The trial investigators themselves concede that BiDil will work in people regardless of race.<sup>7</sup> Without a comparison population, the investigators cannot even claim that the drug works differently in African Americans than in any other group.<sup>8</sup> Nonetheless, NitroMed, the corporate sponsor of BiDil, applied for and received FDA approval for the drug with a race-specific indication to treat heart failure only in African Americans. Pervasive media coverage of the announcement of the results and the FDA approval also focused on the racial-specificity of the drug, often explicitly claiming that it shows race is genetic.<sup>9</sup>

Underlying the trial design, however, is a race-specific patent issued by the United States Patent and Trademark Office (PTO) on October 15, 2002, that is premised on a biological or genetic conception of race.<sup>10</sup> It confers intellectual property protection for the method of using the drug to treat heart failure in African Americans until 2020.<sup>11</sup> A previous patent issued in 1987 to the same inventor for the same method of using the same drug in the general population without regard to race expired in 2007.<sup>12</sup> Therefore, in this case, bringing race into the patent system allowed the inventor to gain a substantial extension of his intellectual property monopoly.

Both the patent and the drug trial for BiDil relate their race-specific design to a search for genetic markers underlying heart disease. On the

6. *Id.*

7. See Denise Gellene, *Heart Pill Intended Only for Blacks Sparks Debate*, L.A. TIMES, June 16, 2005 at C1 (reporting that trial investigator and cardiologist Jay N. Cohn prescribes the generic drugs that make up BiDil to white patients as well, saying "I actually think everybody should be using it.").

8. *Id.*

9. See Jonathan Kahn, *Misreading Race and Genomics after BiDil*, 37 NATURE GENETICS 655, 655 (2005) [hereinafter Kahn, *Misreading Race*].

10. Methods of Treating & Preventing Congestive Heart Failure with Hydralazine Compounds & Isosorbide Dinitrate or Isosorbide Mononitrate, U.S. Patent No. 6,465,463 (filed Sept. 8, 2000) (issued Oct. 15, 2002).

11. *Id.*; U.S. Patent & Trademark Office, General Information Concerning Patents (Jan. 2005), <http://www.uspto.gov/web/offices/pac/doc/general/index.html> (explaining that the term of a new patent in the United States is 20 years from the date on which the patent application was filed). See also Kahn, *Misreading Race*, *supra* note 9, at 655 (noting that NitroMed, Inc. also "holds a patent for a non-race-specific use of BiDil" that expires in 2007).

12. Method of Reducing Mortality Associated with Congestive Heart Failure Using Hydralazine & Isosorbide Dinitrate, U.S. Patent No. 4,868,179 (filed Apr. 22, 1987) (issued Sept. 19, 1989). See also Jonathan Kahn, *From Disparity to Difference: How Race-Specific Medicines May Undermine Policies to Address Inequalities in Health Care*, 15 S. CAL. INTERDISC. L.J. 105, 112 (2005) (noting that through receiving a new, race-based patent, NitroMed extended their monopoly on BiDil).

one hand, this reflects an approach, largely sanctioned by many in the emerging field of pharmacogenomics,<sup>13</sup> of using race instrumentally as a surrogate to get at underlying genetic variation that could be ultimately identified without reference to race. On the other hand, for the foreseeable future, it presents the immediate reality of race being used as a quasi-genetic category to obtain patents and drug approvals and to increase market share.

The question then becomes, is BiDil an anomaly or a harbinger of things to come? The answer, it turns out, is a little of both. This article will consider two prominent and recent examples of the continued use of race in biomedical research and product development. The first is the beta-blocker Bystolic® (nebivolol), a drug used to treat cardiovascular conditions such as hypertension.<sup>14</sup> It treats similar conditions as BiDil, but is a different class of drug.<sup>15</sup> Unlike BiDil, Bystolic is not a combination of two generic drugs but rather has its own independent patent on the actual composition of matter that comprises the drug itself.<sup>16</sup> The marketers of Bystolic, however, have taken a page from the BiDil playbook, as it were, in using race to differentiate their product in a crowded marketplace by mentioning the drug's effect with respect to race in its package insert.<sup>17</sup> At this point, there are no race-specific patents issued for Bystolic, but several are pending before the PTO.<sup>18</sup>

The second example of the use of race in biomedical research and product development involves the drug warfarin, a widely prescribed blood-thinning agent. Warfarin itself is a generic drug and not directly the subject

13. Wolfgang Sadée, *Drug Therapy and Personalized Health Care: Pharmacogenomics in Perspective*, 25 PHARMACEUTICAL RES. 2713, 2714 (2008) (noting that pharmacogenomics incorporates pharmacogenetics—the “study of genetic causes of variability in drug response”—in order to fulfill pharmacogenomics’ broader goal of using genetics to aid “drug discovery, development, and therapy”). See also Francis S. Collins, *What We Do and Don’t Know About ‘Race’, ‘Ethnicity’, Genetics and Health at the Dawn of the Genome Era*, 36 NAT. GENETICS S13 (2004).

14. FOREST PHARMACEUTICALS, INC., BYSTOLIC® (2008) (package insert), available at [http://www.frx.com/pi/Bystolic\\_pi.pdf](http://www.frx.com/pi/Bystolic_pi.pdf).

15. See NITROMED, INC., BIDIL® PACKAGE INSERT (2005), available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2005/0207271bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/0207271bl.pdf).

16. Compositions Containing Micronized Nebivolol, U.S. Patent No. 5,759,580 (filed Feb. 10, 1995) (issued June 2, 1998).

17. See FOREST PHARMACEUTICALS, INC., *supra* note 14 at 6 (noting that “[e]ffectiveness was established in Blacks”).

18. See, e.g., Hyroxylated Nebivolol Metabolites, U.S. Patent Application No. 20070014733 (filed Jan. 18, 2007) (claiming “[a] method of reducing mortality associated with cardiovascular disease in a black patient comprising administering to the black patient a therapeutically effective amount of . . . nebivolol”). See also Glucuronidated Nebivolol Metabolites, U.S. Patent Application No. 20070014734 (filed Jan. 18, 2007).

of race-specific marketing. In recent years, however, biomedical researchers have discovered several specific genetic variations that have a significant impact on patient response to warfarin.<sup>19</sup> Race becomes a factor for warfarin through the field of pharmacodiagnosics—the development of tests which identify whether individuals have certain genetic variants that may affect drug response.<sup>20</sup> In the past several years many companies have come forward offering such tests.<sup>21</sup> Some studies have shown that these genetic variations appear at different frequencies in different racial groups.<sup>22</sup> One company, AutoGenomics, has explicitly embraced such racial variation as a basis for distinguishing its product from other genetic tests on the market.<sup>23</sup> In addition, PharmiGene, a company in Taiwan, reportedly has a race-specific patent pending concerning its particular method of testing for genetic variations in warfarin response.<sup>24</sup> Again, like BiDil, race is being used to create market opportunity and gain patent protection; but unlike BiDil, we do not specifically see race being used to extend or resurrect patent protection for existing products.

## II. BYSTOLIC: MAKING THE EIGHTEENTH BETA-BLOCKER STAND OUT

Ethnic niche marketing is well-established in American product development and advertising. Commercial biotechnology seems to have discovered the potential of such marketing in the case of BiDil. It is here that the model of BiDil, for all its distinctiveness, has most clearly taken hold. Big Pharma is plagued with a plethora of “me-too” products. Once one company develops a particular blockbuster drug, whether in pain relief (e.g. Cox-2 inhibitors) or cardiovascular health (e.g. statins), others clamber to join the bandwagon by producing biologically similar, yet legally distinct (i.e. non-patent-infringing) pharmaceutical products. With numerous similar products on the market, it becomes essential for each producer to try to

19. See Warfarin, Race, and the Business of Pharmacodiagnosics, *infra* Part III. See also Ann K. Daly, *Pharmacogenomics of Anticoagulants: Steps toward Personal Dosage*, 1 GENOME MED. 10.1, 10.1 (2009).

20. See H. Ngow et al., *Role of Pharmacodiagnostic of CYP2C9 Variants in the Optimization of Warfarin Therapy in Malaysia: A 6-Month Follow-Up Study*, 38 XENOBIOTICA 641, 642-43 (2008).

21. See Turna Ray, *Competition Heats Up in Warfarin Dx Market as New Tests Seek FDA OK*, PHARMACOGENOMICS REP., Oct. 10, 2007, <http://www.genomeweb.com/dxpgx/competition-heats-warfarin-dx-market-new-tests-seek-fda-ok>.

22. See *infra* notes 71-75 and accompanying text.

23. See Ray, *supra* note 21.

24. Press Release, Pharmigene Obtains European Patent for Genetic Discovery Predicting Warfarin Sensitivity (Mar. 24, 2009), [http://pharmalicensing.com/public/press/view/1237856381\\_49c8307dbb1e6/pharmigene-obtains-european-patent-for-genetic-discovery-predicting-warfarin-sensitivity](http://pharmalicensing.com/public/press/view/1237856381_49c8307dbb1e6/pharmigene-obtains-european-patent-for-genetic-discovery-predicting-warfarin-sensitivity).

distinguish its drug from the competition. Traditionally, this was done through claims of improved efficacy or lesser side effects. More recently, pharmaceutical and medical device companies have discovered race as a means to distinguish their products (and patents) as well. In the realm of pharmaceuticals, particularly striking is the beta-blocker, nebivolol, marketed as Bystolic by Forest Laboratories.

Beta-blockers comprise a class of drugs that have been used for decades to treat hypertension and other cardiovascular conditions such as heart failure.<sup>25</sup> There are currently at least eighteen beta-blockers on the market, several available as low-cost generics.<sup>26</sup> In such a market, it seems striking, therefore, that Forest Laboratories would take the time and incur the expense to bring yet another beta-blocker to the FDA for approval in 2007. Yet this is exactly what it did with nebivolol, a beta-blocker that had been used in Europe for over a decade but whose original inventor, Janssen Pharmaceutical NV, had never sought to bring it to the American market.<sup>27</sup> Forest received approval for nebivolol in December, 2007 and began marketing it as Bystolic shortly thereafter.<sup>28</sup> In numerous press releases and discussions of funded clinical research, Forest and its surrogates (including the doctors conducting Forest-sponsored clinical trials) emphasized two key aspects of Bystolic's profile in order to differentiate it from the other seventeen beta-blockers on the market: First, it has fewer side effects—in particular, fewer incidences of erectile dysfunction;<sup>29</sup> and second, it worked well in African Americans in a drug trial.<sup>30</sup> This latter claim is particularly significant because there has been ongoing debate in the medical literature about the relative efficacy of beta-blockers in self-identified African-

25. See generally Michael B. Fowler, *Hypertension, Heart Failure, and Beta-Adrenergic Blocking Drugs*, 52 J. AM. C. CARDIOLOGY 1073, 1073 (2008) (commenting on the use of beta-blockers for hypertension and heart failure).

26. Brian Orelli, *New Beta Blocker on the Crowded Street*, MOTLEY FOOL, Dec. 17, 2007, <http://www.fool.com/investing/dividends-income/2007/12/19/new-beta-blocker-in-a-crowded-forest.aspx>.

27. See Press Release, Forest Laboratories, Inc., Bystolic™, a Novel Beta Blocker, Is Now Approved by the FDA for the Treatment of Hypertension (Dec. 18, 2007), <http://www.frx.com/news/PressRelease.aspx?ID=1088188>.

28. See *id.*

29. Press Release, Forest Laboratories, Inc., Nebivolol Lowers Blood Pressure in Mild-to-Moderate Hypertensive Patients as Demonstrated in a Study Published in the Journal of Clinical Hypertension (Sept. 4, 2007), <http://www.frx.com/news/PressRelease.aspx?ID=1047743>.

30. Press Release, Forest Laboratories, Inc., UPDATE: Nebivolol Lowers Blood Pressure in African Americans With Stage I-II Hypertension as Demonstrated in a Study Published in the Journal of Clinical Hypertension (Nov. 1, 2007), <http://www.frx.com/news/PressRelease.aspx?ID=1071168>.

American patient populations.<sup>31</sup> Being able to make affirmative claims about the efficacy of Bystolic in African Americans thus immediately distinguished it from the pack of other beta-blockers. Forest Laboratories made this claim based on a race-specific drug trial, mimicking in many respects the A-HeFT trial for BiDil that tested Bystolic exclusively in self-identified African Americans.<sup>32</sup>

As Doctor Elijah Saunders stated in reporting the results of this race-specific study, "There is a perception that beta blockers are not effective in blacks. But this study refutes that idea."<sup>33</sup> Dr. Paul Underwood, a Phoenix cardiologist and President of the Association of Black Cardiologists (which co-sponsored the A-HeFT trial with NitroMed) praised the nebivolol study, stating, "We're excited to add another therapeutic tool to the armamentarium in the treatment of high blood pressure in African-Americans."<sup>34</sup> An article on the study in the web-based journal *MedScape Today*, quoted Saunders as stating that

The findings of this study are important considering the excessive burden of high blood pressure in African Americans and the need for new treatment options . . . Advances like this in the beta blocker class are *particularly important because African Americans have a historically poor response to beta blocker therapy for hypertension*.<sup>35</sup>

The article went on to note that "[d]ata suggesting that beta-blockers as a class are less effective than other agents in black patients, as well as the association with poor tolerability and adverse metabolic effects, have *led to underuse of traditional beta-blockers in black patients*."<sup>36</sup> What is striking here is the juxtaposition of the concepts of efficacy and underuse. "Underuse" implies that more blacks should be using beta-blockers but do not. The tension here is that if blacks "have a historically poor response to beta blockers," then lesser use is not "underuse," but rather simply reflects

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31. See, e.g., Sidney Goldstein, *Beta Blocker Therapy in African American Patients with Heart Failure*, 9 HEART FAILURE REVIEWS 161, 161 (2004). See also Paul G. Shekelle et al., *Efficacy of Angiotensin-Converting Enzyme Inhibitors and Beta-Blockers in the Management of Left Ventricular Systolic Dysfunction According to Race, Gender, and Diabetic Status: A Meta-Analysis of Major Clinical Trials*, 41 J. AM. C. CARDIOLOGY 1529, 1529 (2003); Clyde W. Yancy, *Race-Based Therapeutics*, 10 CURRENT HYPERTENSION REP. 276, 276 (2008).

32. See Elijah Saunders et al., *The Efficacy and Tolerability of Nebivolol in Hypertensive African American Patients*, 9 J. CLINICAL HYPERTENSION 866, 867 (2007).

33. Daily News Central, *Beta Blocker Controls High Blood Pressure in Blacks* (July 18, 2005), <http://health.dailynewscentral.com/content/view/1308/63>.

34. *Id.*

35. Linda Brookes, *New Drug Algorithms, New Drug Approvals, New Drugs: New Data Reported as Nebivolol Moves Toward Launch in the United States*, MedScape.com (Jan. 17, 2008), [http://www.medscape.com/viewarticle/568786\\_4](http://www.medscape.com/viewarticle/568786_4) (emphasis added).

36. *Id.* (emphasis added).

an appropriate level of use due to differential response. As framed here, the advance seems to be as much about opening up the beta-blocker market to greater use by blacks as to finding a distinctive new therapy—or rather, the distinctiveness of the therapy opens up the market. In this regard, the purportedly poor response of blacks to beta-blockers becomes a market opportunity.

In February of 2008, Dr. Saunders gave a presentation on Bystolic to pharmacists in Pennsylvania titled, “The Treatment of Hypertension in the Very Tough to Treat Patient (obese, diabetic, African-American).”<sup>37</sup> The promotional material emphasizes that “Bystolic is a *totally unique and novel* Beta-Blocker that is cardio selective and is a vasodilator.”<sup>38</sup> Here the promoters of Bystolic have linked novelty, difficulty, and race. The typical “tough” patient is African American. On one hand, the presentation clearly aims at helping a racially identified population that might need better therapy. Dr. Saunders, himself African American, is a distinguished professor of Medicine at the University of Maryland and has demonstrated over his long career a commitment to helping improve the health of minority communities.<sup>39</sup> On the other hand, the presentation frames African Americans as a problem, akin to such undesirable physical states as obesity and diabetes. The presentation does not simply link Bystolic to race, it implies it will make a “tough” racial group, African Americans, not only more treatable but more tractable—i.e. less “tough.” All this as a means not simply to promote Bystolic, but to differentiate it from what other beta-blockers on the market can (or cannot) do.

The positive results from the African-American nebivolol trial have provided the basis for its marketing claims and also for two race-specific patent applications currently pending before the U.S. Patent and Trademark Office.<sup>40</sup> These patent applications, however, are not quite the same as the patents related to BiDil. They are rather hybrids, containing claims regarding the efficacy of nebivolol in a general population early on, and then later adding race-specific claims pertaining to a particular type of efficacy in “black patient[s].”<sup>41</sup> Thus, they are both affirmatively used to claim specific racialized territory of intellectual property, but also used defensively, by adding a concentric ring of protection to the battlements of

37. PA Pharmacists Ass’n, Invitation to Program on Bystolic (Feb. 14, 2008), *available at* [www.papharmacists.com/2-14-08\\_%20a%20program%20on%20Bystolic.doc](http://www.papharmacists.com/2-14-08_%20a%20program%20on%20Bystolic.doc).

38. *Id.* (emphasis added).

39. See Maryland Heart Center, Heart Center Physician Biographies, <http://www.umm.edu/heart/biographies.htm#Saunders> (last visited Jan. 06, 2010).

40. See U.S. Patent Application 20070014733 and U.S. Patent Application 20070014734, *supra* note 18.

41. See *id.*



the larger patent. (The idea being that if a broader claim is challenged—e.g. the use of nebivolol in a “human”—a narrower claim may survive—e.g. the use of nebivolol in a person of “African descent”). If granted, the patents also will provide a legally sanctioned basis for using race to distinguish Bystolic in the marketplace. Thus, in 2008, on a list of the top pharmaceutical advertisers in the country, Forest Laboratories moved up from number seven to number two.<sup>42</sup> The trade journal, *Medical Marketing and Media* noted, Bystolic, at \$8.4 million, was the most heavily advertised drug in the country during the first half of 2008.<sup>43</sup> As Forest Laboratories rolls out Bystolic, reports of its race-specific efficacy serve as a critical adjunct to its general advertising efforts as it seeks to gain a foothold in the crowded beta-blocker market.

In the latest stage of nebivolol’s journey into race-specific marketing, Dr. R. Preston Mason, a consultant to Forest Laboratories,<sup>44</sup> led a study comparing the effect of nebivolol in “Mexican Americans” to “non-Hispanic Whites.”<sup>45</sup> Comparing nebivolol against the beta-blocker, atenolol, the study concluded that, “[t]reatment with nebivolol, but not atenolol, enhanced both the expression and coupling efficiency of eNOS in Mexican American endothelium.”<sup>46</sup> That is, race (or here, perhaps more accurately, Mexican American/Hispanic ethnicity) is claimed to make a difference in nebivolol efficacy, further distinguishing it from other beta-blockers on the market.

Mason was also involved in the earlier African American study of nebivolol.<sup>47</sup> He is on the faculty of the Harvard Medical School-affiliated Brigham and Women’s Hospital in Boston, Massachusetts, and also President and Founder of Elucida Research LLC, a private biotechnology firm, in Beverly, Massachusetts.<sup>48</sup> He now also has a race-specific patent application pending before the PTO titled, “Treatment of Cardiovascular

42. Eugene M. May, *The Hits Keep on Coming*, MED. MARKETING & MEDIA, Oct. 2008, at 57, 58 (listing the top spending pharmaceutical companies by advertising dollars).

43. *Id.* at 60.

44. theheart.org, *Emerging Options for Hypertensive Patients with Osteoarthritis* (Aug. 25, 2009), <http://www.theheart.org/article/974377.do>.

45. R.P. Mason et al., *Nitric Oxide Bioavailability Is Lower in Endothelium of Healthy Mexican American Donors as Compared to Non-Hispanic White Donors: Effect of Nebivolol*, Abstracts from Scientific Sessions 2007, 116 SUPPLEMENT TO *CIRCULATION* 11-295, 11-295 (2007).

46. *Id.*

47. See R. Preston Mason et al., *Nebivolol Reduces Nitroxidative Stress and Restores Nitric Oxide Bioavailability in Endothelium of Black Americans*, 112 *CIRCULATION* 3795, 3795 (2005), available at <http://circ.ahajournals.org/cgi/content/full/112/24/3795>.

48. 2009 Cardiometabolic Health Congress, Distinguished Faculty, Biography: R. Preston Mason, MBA, PhD, <http://www.cardiometabolichealth.org/2009/bios/MasonRPreston.asp> (last visited Jan. 06, 2010).

Disease in Mexican Americans Using Nebivolol.”<sup>49</sup> Race and ethnicity are thus evolving from categories of biomedical research into ways of organizing the strategic development of patent portfolios. The potential value of race and ethnicity for generating patents, in turn, provides incentives for designing and implementing race-specific clinical trials.

### III. WARFARIN, RACE, AND THE BUSINESS OF PHARMACODIAGNOSTICS

Closely related to, but distinct from pharmacogenomic drug development is the field of pharmacodiagnosics—the use of genetic testing to identify specific genetic variations that affect individual drug response.<sup>50</sup> Pharmacodiagnosics is thus a critical component of the drive toward genetically informed personalized medicine. Being focused on specific genes, one might think that race would be even less relevant in this field than in drug development. Yet, here also, race has persisted, and even thrived. Similar to the case of Bystolic, some manufacturers of genetic tests have found race to be a useful tool for differentiating their products in a crowded marketplace. A prominent example involves tests developed to identify specific genetic variations recently discovered to have a significant effect on individual response to the widely prescribed blood-thinning drug warfarin (marketed by Bristol-Meyers Squibb under the trade name Coumadin®).<sup>51</sup>

Warfarin, an anticoagulant, is among the most widely prescribed drugs in modern medicine.<sup>52</sup> In 2004, more than thirty million prescriptions were written for the drug in the United States alone.<sup>53</sup> Sales of warfarin in the U.S. were approximately \$500 million in 2002.<sup>54</sup> “There was a 1.5-fold increase in warfarin prescriptions between 1999 and 2005,”<sup>55</sup> perhaps reflecting the demographic shift toward an aging population, which is typically a primary target of warfarin therapy. It is commonly prescribed to patients who are at risk of developing blood clots, such as persons with

49. Treatment of Cardiovascular Disease in Mexican Americans Using Nebivolol, U.S. Patent Application No. 20090030071 (filed July 15, 2008).

50. See H. Ngow, *supra* note 20, at 642-43.

51. See, e.g., PGXL Laboratories, Warfarin, (describing PGXL Laboratories’ Pharmacogenetic warfarin test) <http://www.pgxl.com/clinician/warfarin.php> (last visited Jan. 06, 2010).

52. Nanogen, *Pharmacogenetics and Warfarin Therapy*, NEXT GENERATION PHARMACEUTICALS, Jan. 2007, <http://www.ngpharma.com/article/Pharmacogenetics-and-warfarin-therapy/>.

53. Int’l Warfarin Pharmacogenetics Consortium, *Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data*, 360 NEW ENG. J. MED. 753, 754 (2009).

54. Nanogen, *supra* note 52.

55. Myong-Jin Kim et al., *A Regulatory Science Perspective on Warfarin Therapy: A Pharmacogenetic Opportunity*, 49 J. CLINICAL PHARMACOLOGY 138, 139 (2009).

atrial fibrillation (a type of abnormal heart beat), recurrent strokes, deep venous thrombosis, pulmonary embolism, or those who have received heart valve replacements.<sup>56</sup> It is difficult to calibrate the correct dose for an individual patient because it has a narrow therapeutic window of efficacy and a wide-range of inter-individual variability in response.<sup>57</sup> Finding a correct dosage can be a delicate matter, involving the gradual upward titration of an initially low dose with regular monitoring of the coagulation rate using the “international normalized ratio” or INR (INR compares the blood’s clotting ability at a given moment to a standardized measure) and adjusting the dosage until the appropriate rate of coagulation is obtained.<sup>58</sup> Too much warfarin places a patient at risk of developing a potentially fatal hemorrhage, while too little may increase the risk of blood clots and stroke.<sup>59</sup> The complexity of warfarin dosing is indicated by the fact that warfarin is the second most common drug (after insulin) implicated in emergency room visits, having caused 1,234 emergency room cases in 2004.<sup>60</sup> Further, it is estimated that there are actually over 43,000 adverse drug events related to warfarin each year.<sup>61</sup>

In the past decade, great strides have been made toward identifying specific genetic variations that have significant impacts on individual response to warfarin. Researchers have identified genes responsible for producing the enzymes that metabolize warfarin (enzymes that break warfarin down and destroy its anticoagulant activity).<sup>62</sup> In particular, specific polymorphisms in the CYP2C9 gene and VKORC1 gene have been identified as accounting for thirty to fifty percent of variation in individual warfarin response.<sup>63</sup> CYP2C9 affects pharmacokinetics—or what a body does to a drug.<sup>64</sup> People with certain CYP2C9 alleles that metabolize

56. *See id.* at 138.

57. *Id.*

58. *See* Daly, *supra* note 19, at 10.1.

59. U.S. Food & Drug Admin., Critical Path Initiative - Warfarin Dosing (interviewing FDA staff involved in pharmacogenetics of warfarin therapy), <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/FacesBehindCriticalPath/ucm077473.htm> (last visited Dec. 28, 2009). *See* Daly, *supra* note 19, at 10.1-10.4.

60. Daniel S. Budnitz et al., *National Surveillance of Emergency Department Visits for Outpatient Adverse Drug Events*, 296 JAMA 1858, 1864 (2006).

61. *Id.*

62. *See* Anna Wilde Mathews, *In Milestone, FDA Pushes Genetic Tests Tied to Drug*, WALL ST. J., Aug. 16, 2007, at A1, available at <http://mednews.wustl.edu/clip/page/normal/15608.html>.

63. M. Teichert et al., *Genotypes Associated with Reduced Activity of VKORC1 and CYP2C9 and Their Modification of Acenocoumarol Anticoagulation During the Initial Treatment Period*, 85 CLINICAL PHARMACOLOGY & THERAPEUTICS 379, 379 (2009).

64. *See* Alan HB Wu et al., *Dosing Algorithm for Warfarin Using CYP2C9 and VKORC1 Genotyping from a Multi-Ethnic Population: Comparison with Other Equations*, 9

warfarin more slowly than average would need a lower dose of warfarin.<sup>65</sup> VKORC1, in contrast, involves pharmacodynamics,<sup>66</sup> or “what a drug does to a body . . . .”<sup>67</sup> Warfarin works, in part, by suppressing the production of vitamin K, which is vital to blood clotting.<sup>68</sup> Individuals with certain VKORC1 alleles might also need a lower dose of warfarin.<sup>69</sup> Carriers of two CYP2C9 alleles commonly referred to as \*1, also known as the “wild type” or standard type, “are extensive metabolizers of warfarin.”<sup>70</sup> The two common relevant CYP2C9 variants are referred to as CYP2C9\*2 and \*3.<sup>71</sup> The most common relevant VKORC1 variant is referred to as VKORC1 3673 G>A (or -1639 G>A).<sup>72</sup> These variants have become particular targets for genetic testing.

With the proliferation of genetic data one might think that race would cease to play a significant role in studies of warfarin response. Yet, as genetic studies have proliferated, so has the use of race and related categories to assess variable frequencies of particular polymorphisms in specific population groups. Thus, numerous studies have observed that some relevant CYP2C9 and VKORC1 alleles vary in frequency across certain ethnic or racial groups.<sup>73</sup> Usually these studies use such broad categories as “Asian,” “Caucasian,” “Hispanic” or “African-American,”<sup>74</sup> but some studies are more nation-specific, identifying allele frequencies and response, for example, in Swedes, Koreans, Iranians, Japanese, and Israelis.<sup>75</sup> Ironically, there seems to have been an increase in such racial,

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PHARMACOGENOMICS 169, 176 (2008). See generally Milo Gibaldi & Gerhard Levy, *Pharmacokinetics in Clinical Practice: I. Concepts*, 235 JAMA 1864, 1864 (1976) (defining pharmacokinetics as being “concerned with the study and characterization of the time course of drug absorption, distribution, metabolism, and excretion, and with the relationship of these processes to the intensity and time course of therapeutic and adverse effects of drugs”).

65. See Kim, *supra* note 55, at 140.

66. See Wu, *supra* note 64, at 176.

67. See Merck, The Merck Manuals Online Medical Library, Introduction: Pharmacodynamics (2007) (defining pharmacodynamics), <http://www.merck.com/mmpe/sec20/ch304/ch304a.html>.

68. See Mathews, *supra* note 62. See also Wu, *supra* note 64, at 169.

69. Wu, *supra* note 64, at 169.

70. Kim, *supra* note 55, at 140.

71. Julie A. Johnson, *Ethnic Differences in Cardiovascular Drug Response: Potential Contribution of Pharmacogenetics*, 118 CIRCULATION 1383, 1384 (2008).

72. *Id.*

73. See, e.g., *id.* at 1384-85; Wu, *supra* note 64, at 169.

74. See, e.g., Wu, *supra* note 64, at 169.

75. See, e.g., Hyun-Jung Cho et al., *Factors Affecting the Interindividual Variability of Warfarin Dose Requirement in Adult Korean Patients*, 8 PHARMACOGENOMICS 329, 329 (2007); P. Ghadam et al., *VKORC1 Gene Analysis in an Iranian Warfarin Resistant Patient*, 8 J. BIOLOGICAL SCI. 691, 691 (2008); Kenji Nakai et al., *Ethnic Differences in the VKORC1 Gene Polymorphism and an Association with Warfarin Dosage Requirements in*

ethnic, or nation-specific studies of allele frequencies in recent years as the significance of specific genetic variations has been more fully elaborated and characterized.

#### IV. LABELS, TESTS, AND "ETHNIC" PRODUCT DIFFERENTIATION

By August 2007, enough data on the genetics of warfarin response had been published to convince the FDA to authorize a labeling change to Coumadin to explain how users' genetics may affect their responses to the drug.<sup>76</sup> In a conference call announcing the change, the FDA's Lawrence Lesko noted that, "this marks the first time that such pharmacogenomic information has been included in a widely used drug . . . . This means that personalized medicine is no longer an abstract concept, but has moved into the mainstream, where it is recognized as a factor in a product used by millions of Americans."<sup>77</sup> Or, as an article in the journal *Medical Marketing & Media* enthused, "The FDA rang in the era of personalized medicine with a labeling change on blood thinner warfarin cautioning that patients with either of two genetic variations might respond differently to the drug."<sup>78</sup>

Significantly, news reports of the FDA-mandated label change also noted some of its regulatory, legal, and commercial implications. First, Jane Woodcock, deputy commissioner and chief medical officer of the FDA, emphasized that the labeling update was "not a directive to doctors to use genetic tests for warfarin therapy" since current clinical studies do not definitively support such a recommendation.<sup>79</sup> This caution was warranted given the fact that no prospective clinical trials had yet been conducted comparing the outcomes of using genetic tests to guide warfarin dosing as compared to existing practices.<sup>80</sup> It reflects well-established understandings of the FDA's role of regulating drugs and not the practice of medicine.

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*Cardiovascular Surgery Patients*, 8 PHARMACOGENOMICS 713, 713 (2007) (assessing allele frequencies of Japanese and Israeli populations); Fumihiko Takeuchi et al., *A Genome-Wide Association Study Confirms VKORC1, CYP2C9, and CYP4F2 as Principal Genetic Determinants of Warfarin Dose*, PLOS GENETICS, Mar. 2009, at 1 (study identifying allele frequencies in Swedish patients), available at <http://www.plosgenetics.org/article/info:doi/10.1371/journal.pgen.1000433>.

76. Turna Ray, *FDA Updates Warfarin to Explain Genetic Links to Response; Says Change Not Meant As 'Directive' for Doctors*, GENOMEWEB DAILY NEWS, Aug. 16, 2007, <http://www.genomeweb.com/fda-updates-warfarin-label-explain-genetic-links-response-says-change-not-meant->.

77. *Id.*

78. Matthew Arnold, *Warfarin Label Change Advises on Genetic Factors*, MED. MARKETING & MEDIA, Aug. 16, 2007, <http://www.mmm-online.com/Warfarin-label-change-advises-on-genetic-factors/article/30045/>.

79. Ray, *supra* note 76.

80. See Mathews, *supra* note 62.

Second, it also reflects a concern involving potential legal claims of malpractice liability. A report in the *Wall Street Journal* noted that prior to the labeling change, a medical group called the Anticoagulation Forum wrote a letter to Dr. Lesko warning that doctors might place too much reliance on the genetic tests, and subsequently fail to monitor their patients effectively.<sup>81</sup> The Anticoagulation Forum worries that some doctors might even hold off in starting a patient on warfarin until the doctors have the results of the test in hand.<sup>82</sup> "The group asked that any new label 'reflect the uncertainty' so doctors wouldn't be held liable in court for failing to do the tests."<sup>83</sup> Third, even without a directive to test, large insurers like Aetna consider such labeling changes when deciding whether to reimburse for a genetic test.<sup>84</sup> The labeling change, thus, had significant implications for the growing industry of pharmacodiagnosics. Indeed, since the labeling change, a number of companies have petitioned the FDA for approval of diagnostic kits that test for a variety of CYP2C9 and VKORC1 polymorphisms related to warfarin response.<sup>85</sup>

Numerous companies offer one form of genetic testing or another related to warfarin response.<sup>86</sup> These range from smaller dedicated diagnostic companies such as Autogenomics, Nanosphere, and Osmetech,<sup>87</sup> to new, large, full-service direct-to-consumer genomics companies such as 23andMe, DNA Direct, and deCODE genetics.<sup>88</sup> These latter direct-to-consumer companies offer so-called "home brew" tests that do not require specific FDA approval to be offered to the public.<sup>89</sup> Additional companies offering such tests include ARUP Laboratories, Laboratory Corporation of America, Mayo Medical Laboratories, Kimball Genetics, PGXL Laboratories, Clinical Data, and Genelex.<sup>90</sup>

81. Mathews, *supra* note 62.

82. *Id.*

83. *Id.*

84. Ray, *supra* note 76.

85. *See* Ray, *supra* note 21.

86. *Id.*

87. *Id.*

88. Turna Ray, *23andMe Begins Reporting Three SNPs for Warfarin Sensitivity; Plans to Study Others*, PHARMACOGENOMICS REP., Apr. 1, 2009, <http://www.genomeweb.com/dxpgx/23andme-begins-reporting-three-snps-warfarin-sensitivity-plans-study-others>.

89. GenomeWeb News, *CombiMatrix Forms Molecular Dx Unit to Perform Home-Brew Tests; Eyes Eventual FDA Clearance*, GENOMEWEB DAILY NEWS, May 10, 2005, <http://www.genomeweb.com/combimatrix-forms-molecular-dx-unit-perform-home-brew-tests-eyes-eventual-fda-cl>. *See also* Genetics & Public Policy Center, *Who Regulates Genetic Tests?* (Feb. 27, 2006) (discussing federal regulation of genetic testing), [http://www.dnapolicy.org/policy.issue.php?action=detail&issuebrief\\_id=10](http://www.dnapolicy.org/policy.issue.php?action=detail&issuebrief_id=10).

90. Ray, *supra* note 21.

In this crowded market, one basic way for a company to differentiate its product is to obtain FDA approval for its particular test, thereby certifying its clinical validity.<sup>91</sup> A number of companies have obtained such approval, including Autogenomics, Nanosphere, Paragon Dx, and Osmetech.<sup>92</sup> Beyond this, companies are also highlighting their ability to provide distinctive services such as fast turnaround time, additional consultation, or even help with processing claims.<sup>93</sup> Finally, because there are numerous alleles, both of CYP2C9 and VKORC1, for which it is possible to test, some companies distinguish their tests by allele.<sup>94</sup> The most commonly tested alleles are CYP2C9\*2 and \*3, and VKORC1 mutations at the -1639G>A positions.<sup>95</sup> Nanosphere, for example, distinguishes its test in part by noting that it also tests at the VKORC1 1173C>T positions.<sup>96</sup>

In the realm of allelic product differentiation, AutoGenomics has come up with race, or as it says “ethnicity,” as a means to make its product stand out in the crowd.<sup>97</sup> It does this by looking at some of the less common CYP2C9 and VKORC1 alleles and evaluates how their frequencies vary across ethnic groups.<sup>98</sup> As one news article on competition in the warfarin gene-testing market put it:

AutoGenomics boasts that its INFINITI assay detects 15 2C9 and VKORC1 variants, more than any other company in the market. Most other warfarin sensitivity assays look for the 2C9 \*2 and \*3, and the 3673 (-1639G>A) VKORC polymorphisms.

Among the 15 variants the INFINITI assay detects, several polymorphisms will be specific to particular ethnicities – such as the \*4 variant identified exclusively among Japanese people and the 8773 SNPs in VKORC1 found in 21 percent of African Americans.

91. *See id.*

92. CENTERS FOR MEDICARE & MEDICAID SERV., PROPOSED DECISION MEMO FOR PHARMACOGENOMIC TESTING FOR WARFARIN RESPONSE (CAG-00400N) (2009), <https://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?from2=viewdraftdecisionmemo.asp&id=224&>.

93. Ray, *supra* note 21.

94. *See* Turna Ray, *AutoGenomics’ Warfarin Test Wins FDA OK; Gauges Variants Competitors Don’t*, PHARMACOGENOMICS REP., Jan. 30, 2008, <http://www.genomeweb.com/dxpgx/autogenomics%E2%80%99-warfarin-test-wins-fda-ok-gauges-variants-competitors-don%E2%80%99t>.

95. *Id.*

96. Ray, *supra* note 21.

97. *See id.*

98. *Id.*

Therefore, in marketing its test, *AutoGenomics will likely specifically target certain ethnic groups*, in addition to widely promoting it for the 200,000 to 500,000 patients who get initiated on warfarin each year.<sup>99</sup>

AutoGenomics is a privately held company, based in Carlsbad, California.<sup>100</sup> Its mission is “to empower clinical laboratories with an automated cost effective solution to perform molecular testing that will significantly enhance work flow, cost efficiency, quicker turn-around time and result with enhanced patient care.”<sup>101</sup> AutoGenomics offers an array of genetic tests on its website. Many are currently for research use only (RUO), meaning they have not obtained FDA approval.<sup>102</sup> It currently markets four FDA-approved tests, including a Warfarin Assay product.<sup>103</sup> This particular assay, however, only covers the common CYP2C9\*2 and \*3 variations, and the VKORC1 3673 (-1639G>A) variant.<sup>104</sup> The assay is not marketed with explicit reference to ethnicity.<sup>105</sup>

AutoGenomics also has an extended “Warfarin XP” assay which tests for six different CYP2C9 variants and eight VKORC1 variants, but it is not yet FDA approved, so it is still only marketed for research use.<sup>106</sup> Nonetheless, while its application for FDA approval of its basic warfarin gene test was still pending, the AutoGenomics website was rife with information on differing allele frequencies across ethnic groups and highlighted the Warfarin XP assay’s distinctive abilities to test broadly across an array of ethnic groups.<sup>107</sup>

One AutoGenomics webpage, for example, ran with the title caption, “Warfarin XP: Enhanced Ethnic Characterization.”<sup>108</sup> The expanded panel

99. *Id.* (emphasis added).

100. AutoGenomics, About Us, <http://www.autogenomics.com/1/aboutUs.php> (last visited Jan. 06, 2010).

101. *Id.*

102. AutoGenomics, INFINITI® Test Menu (RUO), [http://www.autogenomics.com/1/RUO\\_main.php](http://www.autogenomics.com/1/RUO_main.php) (last visited Dec. 28, 2009).

103. *Id.*

104. AutoGenomics, INFINITI® Warfarin Assay (IVD), [http://www.autogenomics.com/1/pharma\\_warfarinassay.php](http://www.autogenomics.com/1/pharma_warfarinassay.php) (last visited Jan. 06, 2010).

105. *See id.*

106. AutoGenomics, INFINITI™ CYP450 2C9-VKORC1, [http://www.autogenomics.com/1/pharma\\_2C9.php](http://www.autogenomics.com/1/pharma_2C9.php) (last visited Jan. 06, 2010).

107. AutoGenomics, Home Page, <http://www.autogenomics.com/1/> (last visited Jan. 06, 2010). After FDA approval was obtained AutoGenomics has updated its website and no longer contains pre-approval information. *See Ray, supra* note 21 (explaining that before FDA approval, AutoGenomics claimed INFINITI assay detected several polymorphisms across ethnicities and would likely market the assay towards specific ethnic groups).

108. AutoGenomics, Warfarin XP: Enhanced Ethnic Characterization, <http://www.autogenomics.com> (last visited July 14, 2008) (no longer available); *see also* AutoGenomics, Data



test explicitly linked genetics to ethnicity. In a section discussing the “clinical relevance” of the test, AutoGenomics discusses the frequency of certain less common variants directly in terms of frequency in “Japanese,” “African-Americans,” and “Caucasians.”<sup>109</sup> Here is a clear example of when specific alleles are identified and testable yet a company still uses race to characterize the product. Yet, why would AutoGenomics continue to use race if the gene has already been identified? Certainly it is the gene variants, not race, which make the difference in clinical response. It becomes evident that AutoGenomics is layering ethnicity onto its more basic Warfarin Assay product in order to differentiate its test and expand its market share. Most companies, including AutoGenomics, will test for the three most common genetic variants affecting warfarin response.<sup>110</sup> Ethnicity here provides AutoGenomics the basis for offering a second test that covers those three common variants plus an additional eleven variants.<sup>111</sup> The ethnicities identified also conveniently correspond to major racial groups—Asian (assuming Japanese comes to be taken as a stand-in for “Asian”), African (or African American), European (Caucasian). Who might want this test then? Apparently everyone in Japan, the United States (with the exception of Native Americans), and Europe—i.e. the world’s major medical markets—comprise the targeted population. It might seem at first blush that developing a test for less common alleles might narrow one’s market, but when bundled with the test for common alleles and layered with racial identities, it becomes a potential means to capture greater market share.

The salience of race in AutoGenomics’ marketing strategy is most evident in a 2008 PowerPoint presentation from its website, titled “Infiniti™ Warfarin XP: Because Ethnic Diversity Matters When Dosing With Warfarin.”<sup>112</sup> The presentation begins with a slide noting the importance of the recent FDA re-labeling of warfarin for genetic data.<sup>113</sup> It then discusses the variation across race of the particular CYP2C9 and VKORC1 alleles for which it tests, noting that its product is “THE ONLY TEST AVAILABLE THAT INCLUDES ALL RELEVANT VARIANTS!”<sup>114</sup> The inevitable conclusion is that “[d]etecting 2C9 variants in addition to [the common] \*2, \*3 is essential for

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Sheet, <http://www.autogenomics.com/1/DataSheets/warfarinxp/dosingAlgorithms.pdf> (last visited Jan. 06, 2010).

109. AutoGenomics, 2C9-VKORC1 Pharmacogenetics, [http://www.buhlmannlabs.ch/files/documents/molecular/autogenomics/flyer\\_2c9-vkorc1.pdf](http://www.buhlmannlabs.ch/files/documents/molecular/autogenomics/flyer_2c9-vkorc1.pdf) (last visited Jan. 06, 2010).

110. Ray, *supra* note 94.

111. *Id.*

112. AutoGenomics, Infiniti™ Warfarin XP: Because Ethnic Diversity Matters When Dosing with Warfarin 1 (on file with author).

113. *Id.* at 2.

114. *Id.* at 23.

a broader identification of high risk warfarin metabolizers in several ethnic groups.”<sup>115</sup> The emphasis here is on the need for an expanded panel testing for more variants. Ethnicity provides a rationale for offering an expanded test panel that differentiates the AutoGenomics test from others on the market.

One of AutoGenomics’ most explicit uses of race to differentiate its product occurs in the following slide:<sup>116</sup>

**Expanded Panel**

- **Platforms other than INFINITI™ 2C9-VKORC1:**
  - Panel of variants limited; \*2, \*3, 1173
  - *virtually ALL* non-caucasian patients; Asian, African American, Chinese, Japanese, Hispanic, etc. would be missed using a panel limited to these variants.
- **Variants specific to African American Population/Significance:**
  - *Washington University publication*- significance of \*5, \*6, \*11 in African American *and* Caucasian population
- **Variants specific to Asian Population/Significance:**
  - *San Francisco General – Alan Vu* \*381

**SPOT ON**  
INFINITI

According to this slide, tests other than AutoGenomics Infiniti platform would miss relevant genetic variants in “*virtually ALL* non-caucasian [sic] patients; Asian, African American, Chinese, Japanese, Hispanic, etc., would be missed using a panel limited to these variants.”<sup>117</sup> The slant here is quite striking; it makes racial and ethnic identification appear to be essential to finding relevant genetic variants. In fact, the common \*2, \*3, and 1173 variants mentioned in this slide occur in *all* of these groups at differing frequencies.<sup>118</sup> The only possible way to make sense of its claim about “missing” “non-Caucasians” is to assume it is referring to the patients with the rarer alleles who would be missed by products that do not test for them.

115. *Id.* at 24.

116. *Id.* at 28.

117. *Id.*

118. See Johnson, *supra* note 71, at 1384.

In developing its test, therefore, AutoGenomics is not just looking for genes; it is looking for racial and ethnic groups to whom it can market its product. This is also evident in the slide's reference to variations "specific" to Asians and African Americans. (Ironically, the reference to African American-specific variants also are said to be of significance to "Caucasians"). AutoGenomics is attempting to translate racially identified gene frequencies into racially identified market share. In this case, finding specific genes has not led researchers to leave race behind. To the contrary, it has led to the rise of new ways to exploit race in the biomedical marketplace.

Marketing based upon race also provides rationale for its commercial viability. If AutoGenomics simply tested for rare alleles, e.g. CYP2C9 \*5, \*6 or \*11, it might have difficulty gaining acceptance in the market against products that tested for the most common significant variants. Simply adding an array of rare alleles that only marginally increases the odds of finding a significant genetic variation could easily make AutoGenomics' test appear needlessly complex. Yet, by tying rare alleles to specific ethnic or racial groups, AutoGenomics provides a hook to draw in potential consumers. You might not know whether you have a rare allele but you do know if you are black, white or Asian. A product that says it tests for a rare allele that is found primarily in the individual's racial or ethnic group is one he or she may choose despite its rarity. AutoGenomics thus uses race not to identify alleles but rather to induce consumers to identify their own race or ethnicity (and hence themselves) with certain alleles. AutoGenomics frames the test so that African, Asian, or European race becomes identified in the consumer's mind with allele frequency. Beyond this, for the product actually to succeed in the market place, biomedical professionals and insurance companies must similarly identify race with genetics in warfarin response. Through its product development and marketing strategies, AutoGenomics is not only selling a pharmacogenomics assay, it is producing a conception of race as genetic.

Ironically, following its 2008 approval of AutoGenomics' basic warfarin assay that tested only for the three most common CYP2C9 and VKORC1 variants, the FDA required AutoGenomics to remove all material of "clinical relevance" associated with its various RUO assays from its website.<sup>119</sup> The Warfarin XP expanded panel is not yet FDA approved, i.e. it is for "Research Use Only."<sup>120</sup> All of AutoGenomics' references to race appeared under "Clinical Relevance" headings for Warfarin XP and have since been removed from the website. Similarly, the "Because Ethnic Diversity Matters . . ." presentation has also been removed from the website.

119. Email from Anand Vairavan, Marketing Manager and personalized Medicine Specialist for AutoGenomics, (May 20, 2009) (on file with author).

120. AutoGenomics, *supra* note 106.

Nonetheless, Anand Viaravan, Marketing Manager and Personalized Medicine Specialist for AutoGenomics, insists that “we still absolutely believe that Ethnic Diversity Matters when developing genetic tests to help with Warfarin dosing.”<sup>121</sup> Indeed, he notes that “we still do offer this assay and sell more of the Expanded Panel assay as opposed to the [FDA approved] IVD assay.”<sup>122</sup>

Here, regulatory approval extracted a trade-off among tactics for product differentiation. On the one hand, AutoGenomics gained the legitimacy and distinction conferred by the FDA approval. On the other hand, it has since been forced to downplay the racial aspect of the Expanded Assay at least until it gets FDA approval for that test as well. Nonetheless, AutoGenomics’ commitment to racialized marketing of its product remains clear and the expanded assay continues to be a more profitable test. Indeed, AutoGenomics has licensed the technology to several companies in Europe, one of which, the Swiss Company Buhlmann Laboratories, AG, continues to post AutoGenomics’ slides on its website describing the expanded assay with race-specific information.<sup>123</sup> AutoGenomics thus is working to minimize the impact of this trade-off and maintain its commitment to producing and capturing a racialized market.

There is an additional and deeper irony embedded in AutoGenomics’ marketing strategy. At first glance, the use of race to help target therapies, whether for warfarin or for BiDil, may appear to be a means to redress historically race-based inequities in the delivery of health care in the United States. Certainly, taking account of the distinct needs and concerns of historically disadvantaged minority communities is a laudable and worthy goal. The Civil Rights Act of 1964, the Voting Rights Act of 1965, and the Fair Housing Act of 1965 all took race into account in fashioning remedies for historical race based inequities.<sup>124</sup> In the realm of biology, however, the use of race becomes far more problematic than in other areas of past discrimination such as employment, voting, or housing. As biologist Anne Fausto-Sterling notes, “Only rather slowly has the medical community realized that what appears at first to be an inclusive move—mandating participation by racially and sexually distinguishable groups in drug and other trials—might have a scorpion’s sting, diverting attention from socioeconomic explanations of (and remedies for) health disparities.”<sup>125</sup>

121. Email from Anand Vairavan, *supra* note 119.

122. *Id.*

123. AutoGenomics, *supra* note 109.

124. See Eric K. Yamamoto et al., *Dismantling Civil Rights: Multiracial Resistance and Reconstruction*, 31 CUMB. L. REV. 523, 530-31 (2001).

125. Anne Fausto-Sterling, *Refashioning Race: DNA and the Politics of Health Care*, DIFFERENCES, Fall 2004, at 1, 3.

How much more powerful might this dynamic prove when driven by commercial considerations of developing a market niche for a biomedical product?

#### V. RACE, COMMERCE, AND REGULATORY CLASH

Market differentiation is one type of commercial imperative driving the use of race in biomedical research and product development. More straightforward concerns for economy and efficiency may also be providing further impetus for continuing to use race in the face of genetic discovery. Such concerns are alluded to in a study by Yen-Revollo et al., which notes that using race as a surrogate is also appealing “because personal genotyping is cost prohibitive.”<sup>126</sup> Simply stated, it is cheaper to identify a patient by race than by genotype. Beyond this, it turns out race can be economically relevant not only as an alternative to genotyping but also as a complement to it. Thus, for example, a 2008 policy statement on gene testing for warfarin response issued by the American College of Medical Genetics (ACMG) states:

CYP2C9\*2 and \*3 are found in the major racial groups, but with different allelic frequencies. *These alleles should be tested in all individuals.* There are also several *rare alleles* of CYP2C9 alleles that have different frequencies in different *ethnic populations*, and some alleles are preferentially found in only certain racial groups. Some CYP2C9 alleles, such as CYP2C9 \*5, \*6, and \*11, are preferentially found in African-descendant populations at low allele frequencies, but are not found in Asian-descendant populations. On the other hand, the rare CYP2C9 \*4 polymorphism has only been reported in individuals from Asia. The decision to test for polymorphisms other than CYP2C9 \*2 and \*3 *should be based on the populations being tested* by a laboratory and the capability to make patient management decisions informed by these less-frequently encountered alleles.<sup>127</sup>

Race is front and center here right alongside specific genetic variation. Given the nature of genetic variation, however, it will always be possible to find certain genetic variations that occur at differing frequencies across racial groups.<sup>128</sup> For example, studies of a particular VKORC1 variant have

126. Jane L. Yen-Revollo et al., *Race Does Not Explain Genetic Heterogeneity in Pharmacogenomic Pathways*, 9 PHARMACOGENOMICS 1639, 1643 (2008).

127. David A. Flockhart et al., *Pharmacogenetic Testing of CYP2C9 and VKORC1 Alleles for Warfarin*, 10 GENETICS MED. 139, 144 (2008) (emphasis added).

128. As sociologist Troy Duster has noted: “It is possible to make arbitrary groupings of populations (geographic, linguistic, self-identified by faith, identified by others by physiognomy, etc.) and still find statistically significant allelic variations between those groupings. For example, we could examine all the people in Chicago, and all those in Los Angeles, and find statistically significant differences in allele frequency at *some* loci. Of

found a range of frequencies in European populations from 39% in "Swedish" to 52% in "Spanish."<sup>129</sup> One comprehensive review article found frequency variation for having at least one CYP2C\*2 allele in different "Caucasian" populations ranging from 0.9% to 20.4%, and a range for "Africans" from 0.0% to 8.7%.<sup>130</sup> On one hand, there certainly is a difference in frequency between Africans and Caucasians. On the other hand, there is also significant overlap, and the overall variation within the Caucasian group seems to dwarf that between Africans and Caucasians. The question is which differences the researchers and product developers *choose* to make matter and how.

A sense of how these choices are made is provided by an examination of the studies cited by the ACMG report to support its recommendation to take race into account. Thus, to support its assertion that "[s]ome CYP2C9 alleles, such as CYP2C9 \*5, \*6, and \*11, are preferentially found in African-descendant populations at low allele frequencies, but are not found in Asian-descendant populations,"<sup>131</sup> the report cites an article by Guyong Tai et al., "In-Vitro and In-Vivo Effects of the CYP2C9\*11 Polymorphism on Warfarin Metabolism and Dose."<sup>132</sup> As is evident from the title, this study discusses only the CYP2C9\*11 polymorphism and says nothing about frequencies for the \*5 and \*6 alleles.<sup>133</sup> Moreover, this was a study of 303 "Caucasians" and 101 "African-Americans;" it says nothing about allele frequencies in Asian populations.<sup>134</sup> Additionally, to support its assertion that "the rare CYP2C9 \*4 polymorphism has been found only in individuals from Asia,"<sup>135</sup> the ACMG report cites an article titled, "A Case Report of a Patient Carrying CYP2C9\*3/4 Genotype with Extremely Low Warfarin Dose Requirement."<sup>136</sup> As is evident again from the title, this study was a case

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course, at many loci, even most loci, we would not find statistically significant differences." Troy Duster, *Buried Alive: The Concept of Race in Science*, in *GENETIC NATURE/CULTURE: ANTHROPOLOGY AND SCIENCE BEYOND THE TWO-CULTURE DIVIDE* 258, 265 (Alan H. Goodman et al. eds., 2003).

129. Pharmacogenomics Knowledge Base, Important Variant Information for VKORC1 (Oct. 30, 2008), <http://www.pharmgkb.org/search/annotatedGene/vkorc1/variant.jsp>.

130. Craig R. Lee, Joyce A. Goldstein & John A. Pieper, *Cytochrome P450 2C9 Polymorphisms: A Comprehensive Review of the In-Vitro and Human Data*, 12 *PHARMACOGENETICS* 251, 252 (2002).

131. Flockhart et al., *supra* note 127, at 144.

132. Guoying Tai et al., *In-Vitro and In-Vivo Effects of the CYP2C9\*11 Polymorphism on Warfarin Metabolism and Dose*, 15 *PHARMACOGENETICS & GENOMICS* 475, 475 (2005).

133. *See id.*

134. *See id.* at 476.

135. Flockhart et al., *supra* note 127, at 144.

136. Soo-Youn Lee et al., *A Case Report of a Patient Carrying CYP2C9\*3/4 Genotype with Extremely Low Warfarin Dose Requirement*, 22 *J. KOREAN MED. SCI.* 557, 557 (2007).

report of a single Korean patient.<sup>137</sup> The report itself notes, “This is the first report of a Korean patient with the CYP2C9\*3/\*4 showing warfarin intolerance. The CYP2C9\*4 allele including 1076T>C (Ile359Thr) has been reported in only one Japanese subject.”<sup>138</sup> Thus, the ACMG has taken a report of one Korean individual that also cites one additional Japanese subject and expanded into a technically accurate, but highly misleading, assertion that this allele is only found in “individuals from Asia.” There may well be studies that provide better support for the ACMG’s assertions, but the studies ACMG cites certainly are not sufficient. They only casually add to an accumulating sort of folk wisdom or common sense in the medical community that promotes the continued relevance of race alongside the development of specific genetic information.

The basis for making the choice to frame allele frequency data in terms of race takes on a distinctly economic feel when considered in light of the statement’s overall purpose of identifying which groups should get which tests. In the ACMG report, race becomes relevant here at the margins, where allele frequencies are low and variable across racially defined population groups.<sup>139</sup> The ACMG, in effect, suggests using race as a screening mechanism to determine which individuals should get which genetic tests; yet, multiplex assays such as those offered by AutoGenomics (not to mention those now being offered by such genetic testing behemoths as 23andMe) are currently able to test efficiently for a range of alleles at once.<sup>140</sup> The only apparent reason remaining for preferentially assigning tests by race therefore appears to be economic, rather than scientific, efficiency. If testing for more alleles costs more, then race may be used to perform a sort of economic triage to focus on those for whom the test is most likely to produce a useful result.

Lawrence Lesko and other senior FDA officials have echoed the logic of the ACMG’s report, stating, for example, that:

The type of genomic data (e.g., which alleles, what genotypes) that needs to be evaluated, and when, is one of the critical issues in drug development and regulatory review. In some cases, consideration of racial/ethnic differences in the distribution of various alleles with no or reduced metabolic activity in the evaluation of dose-response relationships is important.<sup>141</sup>

137. *See id.*

138. *Id.* at 558 (italics in original).

139. *See* Flockhart et al., *supra* note 127, at 144.

140. *See, e.g.*, AUTOGENOMICS, INFINITI™ WARFARIN ASSAY (2C9 & VKORC1 MULTIPLEX ASSAY), 3 (2008), available at [http://www.autogenomics.com/1/pdf/warfarinAssayPackage\\_Insert.pdf](http://www.autogenomics.com/1/pdf/warfarinAssayPackage_Insert.pdf).

141. Shiew-Mei Huang et al., *Application of Pharmacogenomics in Clinical Pharmacology*, 16 TOXICOLOGY MECHANISMS & METHODS 89, 93 (2006) (internal citations omitted).

The article goes on to specify CYP2C9 as one of the “recommended polymorphic alleles to measure in specific population groups.”<sup>142</sup> These groups, not surprisingly, are racialized as “Caucasians,” “African Americans,” and “Asian Americans.”<sup>143</sup> For the FDA, then, race remains not only a legitimate but a “critical factor” in evaluating drug dose response—again, even as specific genes are being identified.<sup>144</sup> In this conceptualization of the promise of pharmacogenomics, genes are not replacing race, they are complementing race.

All of this brings us back to AutoGenomics and its marketing campaign for its Warfarin XP assay built around the proposition that “Ethnic Diversity Matters.”<sup>145</sup> The commercial value of this product is intimately tied to the statements of biomedical professionals, such as the ACMG, and federal regulators, such as Lesko at the FDA. Research, regulation, and commerce are thus mutually implicated in producing an understanding of race as relevant to pharmacogenomics and in constructing consumers and clinicians who identify race with genetics when making medical decisions.

Research, regulation, and commerce, however, are not monolithic phenomena. As already discussed above, there is ongoing debate among researchers concerning the utility of race in pharmacogenomics. There is also something of a regulatory clash between the FDA and the Centers for Medicaid and Medicare Services (CMS) concerning warfarin testing. The clash grows out of the 2007 FDA labeling change for warfarin that specified the significance of specific alleles.<sup>146</sup> The labeling change gave urgency to efforts to develop viable genetic dosing algorithms and also provided a great impetus to companies to develop and market genetic tests.<sup>147</sup> A recent market report from MarketResearch.com titled, “Pharmacodiagnosics and Personalized Medicine 2009 (Markets, Challenges, Forecasts and Key Players)” discusses warfarin and the economic significance of the FDA label change at length.<sup>148</sup>

142. *Id.*

143. *Id.* at 94.

144. *See id.* at 96.

145. AutoGenomics, Infiniti™ Warfarin XP: Because Ethnic Diversity Matters When Dosing with Warfarin, *supra* note 112.

146. Press Release, U.S. Food & Drug Admin., FDA Approves Updated Warfarin (Coumadin) Prescribing Information (Aug. 16, 2007), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108967.htm>.

147. *See Ray, supra* note 21.

148. KALORAMA INFO., PHARMACODIAGNOSTICS AND PERSONALIZED MEDICINE 2009 (MARKETS, CHALLENGES, FORECASTS AND KEY PLAYERS) (2009), *available at* <http://www.marketresearch.com/product/display.asp?productid=2128157&xs=r&SID=95957877-452044944-524917733&curr=USD&kw=warfarin&view=abs>.



Gene tests for warfarin response average between \$300 and \$500 per test.<sup>149</sup> Paying for such tests obviously is central to the test's commercial success, and central to payment is the issue of insurance coverage. The problem for companies that offer genetic tests is that the FDA recommendation is based on the clinical *validity* of the tests while insurance coverage tends to be based on considerations of clinical *utility* and related concerns for cost-effectiveness.<sup>150</sup>

The clinical utility of genetic testing for warfarin dosing has not yet been established to the satisfaction of numerous insurers. One article in the *Wall Street Journal* noted that "major insurers such as Aetna Inc., WellPoint Inc. and Cigna Corp." do not cover the costs of such tests, possibly because "[s]ome specialists say testing hasn't been proved to reduce the risks of the drug."<sup>151</sup> Indeed, even such influential studies as that conducted by the IWPC were retrospective and did not measure whether incorporating genetic data into dosing algorithms materially reduced adverse drug events (ADEs).<sup>152</sup> As University of Washington professor, Ann Wittkowsky, said of the FDA labeling decision, "It is fascinating science, but it is not yet ready for prime time [sic]."<sup>153</sup>

Similarly, a 2008 report of the Secretary of Health and Human Services' Advisory Committee on Genetics, Health and Society (SACGHS) titled "Realizing the Potential of Pharmacogenomics: Opportunities and Challenges" while referring to the use of CYP2C9 and VKORC1 testing to guide warfarin dosage as an early application of pharmacogenomics, nonetheless indicated that "much of the valuable information about PGx [pharmacogenomics] is in the form of early scientific discoveries. Although this information has the potential to be useful, its clinical utility is not yet well understood."<sup>154</sup> Francis Collins, shortly after he stepped down as Director of the National Human Genome Research Institute, stated his belief that researchers still did not "have the right type of evidence 'to enable a clear statement to providers about whether this kind of genetic testing ought to be done prospectively before trying to prescribe this drug with all of its

149. Ray, *supra* note 21.

150. Turna Ray, *Personalized Rx Advocates Call on FDA, CMS to Align Standards After CMS' Restricted Coverage of PGx Warfarin Dosing*, PHARMACOGENOMICS REP., May 20, 2009, <http://www.genomeweb.com/dxpgx/personalized-rx-advocates-call-evidence-guidelines-wake-cms-decision-restrict-co>.

151. Mathews, *supra* note 62.

152. See Int'l Warfarin Pharmacogenetics Consortium, *supra* note 53, at 754.

153. Mathews, *supra* note 62.

154. DEPT. OF HEALTH & HUM. SERV., SECRETARY'S ADVISORY COMM. ON GENETICS, HEALTH & SOCIETY, REALIZING THE POTENTIAL OF PHARMACOGENOMICS: OPPORTUNITIES AND CHALLENGES 1 (2008), available at [http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS\\_PGx\\_report.pdf](http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_PGx_report.pdf).

complications.”<sup>155</sup> Even the FDA’s own deputy commissioner and chief medical officer, Janet Woodcock, noted that they would “have to wait for outcomes data” before actually changing the label to mandate genetic testing.<sup>156</sup>

So it was that in May 2009 that CMS announced its intention to deny Medicare coverage for pharmacogenomic testing that aims to predict warfarin responsiveness, stating that it “believes that the available evidence does not demonstrate that [such testing] improves health outcomes in Medicare beneficiaries.”<sup>157</sup> CMS held out the possibility that coverage might be granted in the future, but only for a prospective, randomized clinical trial.<sup>158</sup>

In the January 2009 issue of the *Annals of Internal Medicine*, a timely study was published questioning the cost-effectiveness of using pharmacogenomics information in warfarin-dosing.<sup>159</sup> Dr. Mark Eckman, the lead author on the study, pointedly criticized a 2006 study conducted jointly by the American Enterprise Institute and the Brookings Institution that estimated an annual savings of \$100 million to \$2 billion from integrating genetic testing into warfarin therapy,<sup>160</sup> as “optimistic” in its assumptions.<sup>161</sup> The AEI-Brookings report was actually conducted by FDA staff<sup>162</sup> and had been posted by the FDA to support the drive toward incorporating pharmacogenomic data in drug submissions.<sup>163</sup> It was also cited by

155. Matt Jones, *Francis Collins Addresses State of Personalized Medicine*, GENOMEWEB DAILY NEWS, Jan. 30, 2009, <http://www.genomeweb.com/dxpgx/francis-collins-addresses-state-personalized-medicine>.

156. Ray, *supra* note 76.

157. CENTERS FOR MEDICARE & MEDICAID SERV., *supra* note 92.

158. *Id.*

159. Mark H. Eckman et al., *Cost-Effectiveness of Using Pharmacogenetic Information in Warfarin Dosing for Patients With Nonvalvular Atrial Fibrillation*, 150 ANNALS INTERNAL MED. 73, 80 (2009).

160. Andrew McWilliam et al., *Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin 3* (AEI-Brookings Joint Center for Reg. Stud., Working Paper No. 06-23, 2006), available at [http://aei-brookings.org/admin/authorpdfs/redirect-safely.php?fname=.../pdffiles/WP06-23\\_topost.pdf](http://aei-brookings.org/admin/authorpdfs/redirect-safely.php?fname=.../pdffiles/WP06-23_topost.pdf).

161. Eckman et al., *supra* note 159, at 81. See also Monica R. McClain et al., *A Rapid-ACCE Review of CYP2C9 and VKORC1 Alleles Testing to Inform Warfarin Dosing in Adults at Elevated Risk for Thrombotic Events to Avoid Serious Bleeding*, 10 GENETICS MED. 89, 96 (2008) (criticizing the Brookings-AEI study, the author argues that “close examination of this study reveals that the authors made several assumptions that may not be valid”).

162. McWilliam et al., *supra* note 160, at title page.

163. U.S. Food & Drug Admin., *supra* note 59.

diagnostic companies, such as Iverson Genetic Diagnostics, Inc.,<sup>164</sup> and Osmetech,<sup>165</sup> to support the marketing of their products.

As one might expect, the CMS announcement was not well received by companies offering genetic tests, especially given the fact that many private payors follow CMS's lead when determining whether to cover new technologies.<sup>166</sup> Ramanath Vairavan, senior VP of sales and marketing for AutoGenomics, opined:

This illogical decision perhaps has been influenced by the lobbying of big pharma, that in spite of numerous prospective studies and publications that have clearly shown the benefit for genetic testing and the FDA relabeling of the drug, CMS has succumbed into making a contradictory decision that will certainly impact patient well being and the cost of healthcare. As a manufacturer of the test we appeal to CMS to revisit this controversial decision at the earliest.<sup>167</sup>

Vairavan's concern regarding "big pharma" is notable and highlights the fact that the pharmacogenomics industry is not monolithic. He is apparently alluding to one of the great tensions at the heart of pharmacogenomics: on one hand, it is understood as the wave of the future, saving money and improving therapies. On the other hand, it involves narrowing the market for a drug down to smaller and smaller subgroups that show the best response.

One of the little known facts about blockbuster drugs is that they are "typically effective in only forty to sixty percent of the patient population."<sup>168</sup> "By identifying true responders, pharmacogenomics also threatens to reduce substantially (often by more than 50%) the potential consumer base for any given drug."<sup>169</sup> One study of data from the Physician's Desk Reference found "[t]he percent of responders range from a low of 25% (oncology products) to a high of 80% (Cox2 inhibitors), with the majority of drugs

164. Iverson Genetic Diagnostics, Inc., Warfarin Dosing Panel, [http://www.iversongenetics.com/ig\\_warfarin.html](http://www.iversongenetics.com/ig_warfarin.html) (last visited Jan. 06, 2010).

165. Press Release, Osmetech Molecular Diagnostics, Osmetech Licenses VKOR Pharmacogenetic Marker for Warfarin Dosage Management from University of Washington (Mar. 9, 2007), available at [http://www.osmetech.com/pdf/University\\_%20of\\_Washington.pdf](http://www.osmetech.com/pdf/University_%20of_Washington.pdf).

166. Turna Ray, *CMS Denies Medicare Payment for Warfarin PGx Testing; Proposes Limiting Coverage to Evidence Studies*, PHARMACOGENOMICS REP., May 6, 2009, <http://www.genomeweb.com/dxpgx/cms-denies-medicare-payment-warfarin-pgx-testing-proposes-limiting-coverage-evid>.

167. *Id.*

168. DrugResearcher.com, Pharmacogenomics to Replace Pharma's Business Model (Feb. 28, 2005), <http://www.drugresearcher.com/content/view/print/76486>.

169. Jonathan Kahn, *Exploiting Race in Drug Development: BiDil's Interim Model of Pharmacogenomics*, 38 SOC. STUD. SCI. 737, 742 (2008).

having a responder rate of 50-60%.”<sup>170</sup> The marketing model for genetic tests ultimately depends on the ability to use genomics to identify which subjects should get which drugs—i.e. to narrow the market for specific drugs. The more pharmacodiagnosics companies are able to identify genes that correspond with drug response, the greater will be the market for their products. Each success for a company like AutoGenomics represents a potential threat to big pharmaceutical companies marketing blockbuster drugs to large, undifferentiated populations. Yet, one review of the comments submitted to CMS before it announced its intentions found that most of those opposing coverage (about eighteen percent of the total) were “professional organizations, payors, and some healthcare providers . . . .”<sup>171</sup> Those with the most immediate interest in the CMS decisions appear to have been those with an immediate stake in the payment for diagnostic tests.<sup>172</sup>

In the aftermath of the CMS decision, the Center for Medicine in the Public Interest (CMPI) announced plans to develop a proposal outlining areas where the FDA and CMS “can harmonize the way they evaluate outcomes and guide treatment . . . .”<sup>173</sup> The CMPI is a conservative, free-market oriented group associated with the Pacific Research Institute, a think tank founded in 1979 whose stated vision is the promotion of “the principles of individual freedom and personal responsibility [which], [t]he Institute believes . . . are best encouraged through policies that emphasize a free economy, private initiative, and limited government.”<sup>174</sup> Since the plans were announced, in part, as a response to the CMS decision, it seems evident that the CMPI is casting the CMS as an impediment to product development and hence the “harmonization” sought by the CMPI primarily involves getting CMS to follow the more industry-friendly FDA in its attitude toward genetic testing for warfarin.<sup>175</sup>

Hope is on the horizon for pharmacodiagnostic companies, however, as prospective studies of the clinical utility of pharmagenomic dosing algorithms are being designed and carried out. Prominent among these is a trial known as COAG (Clarification of Optimal Anticoagulation through

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170. Penelope K. Manasco & Teresa E. Arledge, *Drug Development Strategies*, in PHARMACOGENOMICS: SOCIAL, ETHICAL, AND CLINICAL DIMENSIONS 83, 85-86 (Mark A. Rothstein ed., 2003).

171. Ray, *supra* note 166.

172. *See id.*

173. Ray, *supra* note 150.

174. Pacific Research Institute, About PRI, <http://liberty.pacificresearch.org/about/default.asp> (last visited Jan. 06, 2010); Pacific Research Institute, Our Vision, <http://liberty.pacificresearch.org/about/our-vision> (last visited Jan. 06, 2010).

175. *See* Ray, *supra* note 150.

Genetics) directed by the National Heart, Lung, and Blood Institute.<sup>176</sup> The study will enroll 1,200 patients and cost nearly ten million dollars.<sup>177</sup> In February 2009, Raynard Kington, then acting Director of the NIH asserted, "These efforts showcase NIH's firm commitment to building a future of personalized medicine—a future in which doctors will be able to prescribe the optimal dosage of medicine for each patient right from the start."<sup>178</sup>

Race does not seem to have played much of a role in the CMS decision or subsequent debates about the merits of insurance coverage for genetic tests. In the minutes of the February 2009 CMS meeting discussing genetic testing, there is barely a mention of race or ethnicity.<sup>179</sup> Race seems to be much more important to FDA officials, such as Lawrence Lesko or Robert Temple, who see it as a means to drive their agenda of pursuing pharmacogenomic drug development, than it is to CMS officials (and private insurers) who are focusing on the more contained, and less easily racialized issues of clinical utility and cost-effectiveness. Indeed, warfarin is front and center as a poster child for the FDA's "Critical Path Initiative," a major effort begun in 2004 to "stimulate and facilitate a national effort to modernize the sciences through which FDA-regulated products are developed, evaluated, and manufactured."<sup>180</sup> The first of a series of interviews posted on the FDA website to explore Critical Path projects focused on warfarin.<sup>181</sup> Race is useful to the FDA to the extent that it furthers the progress of drugs such as warfarin towards the promise of "personalized medicine," and thus validates efforts such as the Critical Path Initiative.<sup>182</sup> CMS, in contrast, does not have any particular institutional imperative to use race in making coverage determinations.

## VI. THE CONTINUING VALUE OF RACE IN BIOTECHNOLOGY PATENTS

Race has re-entered the regulatory scene, however, in proceedings before the PTO. Interestingly, it is not the genetic-testing companies, such

176. Turna Ray, *NIH Launches Large Randomized Trial to Determine Utility of PGx-Based Warfarin Dosing*, PHARMACOGENOMICS REP., Feb. 18, 2009, <http://www.genomeweb.com/dxpgx/nih-launches-large-randomized-trial-determine-utility-pgx-based-warfarin-dosing>.

177. *Id.*

178. *Id.*

179. See CENTERS FOR MEDICARE & MEDICAID SERV., MEDICARE EVIDENCE DEVELOPMENT & COVERAGE ADVISORY COMM., MEETING MINUTES OF THE CENTERS FOR MEDICARE AND MEDICAID SERVICES (2009).

180. Andrew C. Von Eschenbach, Comm'r of Food & Drugs, Critical Path Initiative: Statement Before the Subcomm. on Agriculture, Rural Development, Food & Drug Admin., & Related Agencies, S. Comm. on Appropriations (June 1, 2007) [hereinafter Critical Path Initiative].

181. U.S. Food & Drug Admin., *supra* note 59.

182. Critical Path Initiative, *supra* note 180.

as AutoGenomics, who are using race in their patents—their patents tend to cover the technical specifications of their assay platforms (the actual apparatus conducting the tests) with race being reserved for certain marketing efforts. Rather, it is certain warfarin researchers themselves who have introduced race into the realm of intellectual property. On December 21, 2005, Yuan-Tsong Chen, Hsiang-Yu Yuan, and Jin-Jer Chen filed a patent application titled “Genetic Variants Predicting Warfarin Sensitivity.”<sup>183</sup> The lead inventor, Yuan-Tsong Chen, is a Distinguished Research Fellow at the Genomics Research Center and Director of the Institute of Biomedical Sciences at the Academia Sinica in Taipei, Taiwan.<sup>184</sup> He is also a Professor in the Department of Genetics at Duke University in Durham, North Carolina.<sup>185</sup> The other inventors were also associated with the Academia Sinica at the time of the application, and the patent rights have been assigned to that institution.<sup>186</sup> The Academia Sinica is a member of the IWPC and is credited with supplying data to the dosing algorithm study published so prominently in the *New England Journal of Medicine* in February, 2009.<sup>187</sup>

The Abstract of the patent application states, “We discovered that a polymorphism in the promoter of the VKORC1 gene is associated with warfarin sensitivity. This polymorphism can explain both the inter-individual and *inter-ethnic* differences in warfarin dose requirements.”<sup>188</sup> The Claims section includes the following:

1. A method of determining the dose range of a warfarin for a subject, comprising investigating the sequence of the promoter of the VKORC1 gene of the subject.”

\* \* \*

9. The method of claim 1 wherein the subject is an *Asian*.

10. The method of claim 1 wherein the subject is a *Caucasian*.

11. The method of claim 1 wherein the subject is an *African, African American, or Hispanic*.<sup>189</sup>

183. Genetic Variants Predicting Warfarin Sensitivity, U.S. Patent Application No. 20060166239 (filed Dec. 21, 2005).

184. Genomics Research Center, Academia Sinica, Yuan-Tsong Chen, [http://www.genomics.sinica.edu.tw/index.php?option=com\\_content&view=article&id=96&Itemid=211&lang=en](http://www.genomics.sinica.edu.tw/index.php?option=com_content&view=article&id=96&Itemid=211&lang=en) (last visited Jan. 06, 2010).

185. *Id.*

186. Genetic Variants Predicting Warfarin Sensitivity, *supra* note 183.

187. Int’l Warfarin Pharmacogenetics Consortium, *supra* note 53, at 753-54, 763.

188. Genetic Variants Predicting Warfarin Sensitivity, *supra* note 183 (emphasis added).

189. *Id.* (emphasis added).

The mention of race in the Claims section is particularly significant because the claims specify the legally operative scope of the patent, defining the formal legal “metes and bounds” of the territory covered by an invention.<sup>190</sup> The force and authority of the United States government is thus conscripted into legitimating the use of race in relation to genetics in a manner that implies that race itself is genetic. The basis for making such race-specific claims is found in studies of allele frequencies that vary across population groups. Such variation is here reductively solidified into rigid racial differences that are then given the imprimatur of the state through the potential grant of patent protection.

A news report on Academia Sinica and its role in the IWPC noted that there is a follow-up study of 600 patients in Taiwan in order to verify the predictive accuracy of the model.<sup>191</sup> One of the Academia Sinica researchers asserted, “The result of the study on the island is significant in that it will serve as the dosing guideline for people of *ethnic Chinese origin*. This is the largest community in the world.”<sup>192</sup> The report goes on to note:

The research efforts may turn out to be profitable as well. In 2005 Academia Sinica created a spin-off business called PharmiGene Inc., which focuses on the creation of personalized medicine products. The company has already used the scientific knowledge gained by Academia Sinica to manufacture several gene-detection kits, including a warfarin dosing prediction model developed in 2005.<sup>193</sup>

With PharmiGene and its race-specific patent, Academia Sinica is positioning itself to sell its warfarin tests to “people of ethnic Chinese origin,” not only the largest “community” in the world, but also the largest potential market. Race, in short, persists as a viable basis for framing and capturing a pharmacogenomic market.

Importantly, an average patent application takes at least two years to process.<sup>194</sup> As Academia Sinica’s race-specific patent is working its way through the PTO (known as the “patent prosecution” process) it has encountered some problems. To obtain patent protection for inventions, all patent applications must meet several statutory requirements. The most prominent of these are known as “useful[ness]” (or utility),<sup>195</sup> “novelty,”<sup>196</sup>

190. ROGER E. SCHECHTER & JOHN R. THOMAS, *INTELLECTUAL PROPERTY: THE LAW OF COPYRIGHTS, PATENTS AND TRADEMARKS* 404 (2003).

191. Meg Chang, *Genetics May Hold the Key to Warfarin Dosing*, TAIWAN TODAY, Mar. 13, 2009, <http://taiwantoday.tw/fp.asp?xItem=49357&CtNode=427>.

192. *Id.* (emphasis added).

193. *Id.*

194. U.S. Patent & Trademark Office, *Frequently Asked Questions*, <http://www.uspto.gov/main/faq/> (last visited Dec. 30, 2009).

195. 35 U.S.C. § 101 (2006).

196. 35 U.S.C. § 102 (2006).

“non-obvious[ness],”<sup>197</sup> and “specification.”<sup>198</sup> In January 2009, the patent examiner rejected certain claims in the application as obvious and anticipated (i.e. not “novel”) by two patent applications filed by University of Washington researcher Mark Rieder (also a member of the IWPC)—particularly the second application, #20080057500 (referred to as “Rieder II”).<sup>199</sup> The Rieder application (a continuation of an earlier patent filed on October 18, 2004) was titled “Methods and Compositions for Predicting Drug Responses.”<sup>200</sup> The application directly referenced the VKORC1 gene and warfarin response, stating in the abstract, “the present invention provides methods and compositions for determining individualized Warfarin dosages based on genotype of DNA polymorphisms and haplotypes derived from them in the VKORC1 gene.”<sup>201</sup> Given Academia Sinica’s patent application’s explicit focus on VKORC1, this presented something of a problem.

In response, Yuan-Tsong Chen filed an “Inventor’s Declaration” setting forth his reasons why the Rieder application did not negate his submission.<sup>202</sup> He placed race at the center of his argument as he asserted,

although only 4% [of] Caucasians carry the haplotypes [a group of linked genes] unrelated to warfarin response, i.e., H3-H6, these haplotypes constitute as high as 39% of the African-American population and as high as 19% in Hispanic Americans. As another example, the total frequency of H3-H6 is 20% in ethnic groups other than Caucasians, African-Americans, Asians, and Hispanic-Americans. These teachings clearly indicate that haplotypes H3-H6, which, according to Rieder II, are unrelated to warfarin response, CANNOT be ignored in the whole human population.<sup>203</sup>

Chen is here explicitly using race to show the relevance of haplotypes H3-H6 and thus differentiating his patent application from Rieder’s. He adds race to make his claims appear novel and non-obvious. The motivation here is not scientific, but legal and commercial. The connection between

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197. 35 U.S.C. § 103 (2006).

198. 35 U.S.C. § 112 (2006).

199. See U.S. Patent & Trademark Office, Patent Application Information Retrieval Portal, <http://portal.uspto.gov/external/portal/pair> (from this website: enter 11/316406 for Application Number; select the “Image File Wrapper” tab; then select the link for “Non-Final Rejection”) (last visited Jan. 06, 2010).

200. Methods and Compositions for Predicting Drug Responses, U.S. Patent Application No. 20080057500 (filed Mar. 16, 2007).

201. *Id.*

202. YUAN-TSONG CHEN ET AL., INVENTOR DECL. UNDER 37 C.F.R. §1.132 1 (2005), available at <http://portal.uspto.gov/external/portal/pair> (from this website: enter 11/316406 for Application Number; select the “Image File Wrapper” tab; then select the link for “Rule 130, 131 or 132 Affidavits”).

203. *Id.* at 3 (internal citations omitted).



genes and race primarily serves the purpose of obtaining patent protection, not of furthering science.

## VII. CONCLUSION

Hearkening back to the role of patents in the case of BiDil, we can see how the cases of Bystolic (nebivolol) and warfarin response testing are both similar and different. The story of BiDil involved the use of race to re-capitalize the value of existing generic drugs. The need to create a patentable product in order to convince corporate backers of the drug's viability as a commercial product led to using race as a frame for interpreting existing science, developing clinical trial protocols, compiling regulatory filings, and designing marketing campaigns. Patenting and marketing strategies mutually incentivized the use of race independent of any specific scientific or medical utility. The new nebivolol patent application indicates a BiDil-like strategy to use race to extend patent life. In contrast, the Academia Sinica patent application process has not directly involved the reconfiguration of an existing product as racial in order to extend patent life, but it does show how race can be used to differentiate one product or process from another as a potential means to obtain initial patent protection. Both models involve the exploitation of race in order to enhance the commercial value of scientific research by creating race-specific market-niches for products. The story of warfarin testing further demonstrates that even after specific genes for drug response are identified, race continues to be commercially useful as a means to gain patent protection and carve out niches in a crowded marketplace. Biotechnology firms and biomedical professionals thus continue to embrace race as a central component of patenting and marketing strategies, even after it has ceased to serve any scientific purpose.