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THE OPTIMAL SCOPE OF FDA REGULATION OF GENETIC TESTS: MEETING CHALLENGES AND KEEPING PROMISES

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I. INTRODUCTION

With the completion of the Human Genome Project and the advent of increasingly sophisticated genetic technologies, the promise that genetic advances will revolutionize medicine appears closer than ever. Soon, tests will function as medical crystal balls, forecasting risks of disease years into the future based on genetic variations. Medical care might soon benefit from tests that accurately predict the risk of common diseases with complex etiologies, such as cancers, Parkinson's disease, or Alzheimer's disease.[1]

Despite these hopes, fears have risen about the potential dangers of genetic testing. For instance, misleading and inaccurate tests can generate false diagnoses and lead to unnecessary treatment such as mastectomies for breast cancer patients.[2] Furthermore, without guar-

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1. *See* Alan E. Guttmacher & Francis S. Collins, *Genomic Medicine — A Primer*, 347 NEW ENG. J. MED. 1512, 1512 (2002) (noting that these common disorders are "all due to the interactions of multiple genes and environmental factors" and that "[g]enetic variations in these disorders may have a protective or a pathologic role in the expression of diseases").

2. *See* SEC'Y'S ADVISORY COMM. ON GENETIC TESTING, NIH, ENHANCING THE OVERSIGHT OF GENETIC TESTS: RECOMMENDATIONS OF THE SACGT 7 (2000) [hereinafter

antees of privacy and confidentiality, both accurate and inaccurate genetic information might be used by employers[3] or insurers[4] to discriminate against patients. In response to some of these fears, many states have enacted legislation specifically to safeguard genetic information privacy[5] and to regulate the use of genetic information by health insurers.[6]

Given the risks associated with genetic testing, both the general public and the federal government have focused on perceived gaps in the regulatory oversight of genetic tests.[7] Most new genetic tests are developed and conducted in-house at a single clinical laboratory; these laboratory-developed tests are also known as "home brew" tests.[8] Tests may also be packaged as complete testing systems ("kits") and sold to multiple laboratories.[9] Although the Food and Drug Administration ("FDA") regulates kits, it does not regulate lab-developed tests.[10] This discrepancy drew the attention of federal oversight committees.[11] In recent months, the FDA has taken the first concrete step toward regulating lab-developed tests by issuing

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SACGT RECOMMENDATIONS], *available at* http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf.

3. *See* Anita Silvers & Michael Ashley Stein, *Human Rights and Genetic Discrimination: Protecting Genomics' Promise for Public Health*, 31 J.L. MED. & ETHICS 377, 377 (2003) ("For example, to mitigate responsibility for an employee's injury or disease, an employer might argue that the individual was genetically disposed to such an outcome . . . .").

4. *See* Henry T. Greely, *Banning Genetic Discrimination*, 353 NEW ENG. J. MED 865, 865 (2005) ("In general, the fear [of genetic discrimination] has focused on health insurance, since insurers have an incentive to identify and avoid clients who will cost them more money than the average client.").

5. National Conference of State Legislatures, State Genetic Summary Table on Privacy Laws, http://www.ncsl.org/programs/health/genetics/prt.htm (last visited Mar. 11, 2007).

6. National Conference of State Legislatures, State Genetic Nondiscrimination in Health Insurance Laws, http://www.ncsl.org/programs/health/genetics/ndishlth.htm (last visited Mar. 11, 2007).

7. *See* SACGT RECOMMENDATIONS, *supra* note 2, at 13 ("In light of public concerns as well as the potential revolutionary and widespread impact of genetic tests . . . society should be assured that genetic tests meet the highest standards available and that information obtained through genetic testing is protected from abuse."). In 1998, the Department of Health and Human Services ("HHS") created The Secretary's Advisory Committee on Genetic Testing ("SACGT") to study "the medical, scientific, ethical, legal and social issues raised by the development and use of genetic tests." *Id.* at vi. Heightened regulation of lab-developed tests, whether by the FDA or other agencies, was a key issue addressed by the SACGT. *See id.* at 8–32.

8. *Id.* at 10. This Note uses the term "lab-developed tests" to denote the "in-house" or "home-brew" category of tests. Such tests may also be developed by a third party and exclusively licensed to the conducting laboratory. *See* Jonathan F. Tait, Exclusive Licenses for Home-Brew Genetic Tests: Some Questions and Answers (Dec. 23, 1998), http://depts.washington.edu/labweb/docs/tait101.html.

9. *See* SACGT RECOMMENDATIONS, *supra* note 2, at 10.

10. *See* Steven Gutman, *The Role of Food and Drug Administration Regulation of In Vitro Diagnostic Devices — Applications to Genetics Testing*, 45 CLINICAL CHEMISTRY 746, 746 (1999).

11. *See, e.g.*, SACGT RECOMMENDATIONS, *supra* note 2, at 10.

preliminary guidance for a subset of such tests known as In Vitro Diagnostic Multivariate Index Assays ("IVDMIAs").[12]

Despite the FDA's initial efforts toward more sweeping regulation, questions remain about its legal authority and the proper boundaries of increased oversight.[13] This Note investigates the sources of the FDA's jurisdiction over lab-developed genetic tests and provides a guiding principle to ensure that expanded regulation does not nullify the benefits of genetic testing. Part II describes the trends in genetic tests and the current regulatory framework for such tests. Part III explores the constitutional and statutory sources of authority for FDA oversight of lab-developed genetic tests. Part IV argues that the FDA's long-standing policy against interfering with the "practice of medicine" should act as a limiting principle in the regulation of these tests. Part V suggests that such a principled approach will allow the FDA to ensure genetic test quality while avoiding the damaging effects of unbounded regulation on developing technologies.

II. THE STATE OF THE ART

A. Trends in Technology

Before exploring the proper scope of increased regulation, some understanding of the present state of genetic testing and the current regulatory framework may be helpful. Each person's DNA sequence is composed of billions of nucleotides, comprising a genetic code that programs the person's biological makeup.[14] Variations or mutations in the code affecting just a single nucleotide can correlate to a clinical outcome such as disease risk or drug response.[15] In their most basic form, genetic tests consist of two major steps: first, they identify key variations in a patient's DNA, and second, they correlate those variations to a clinical outcome to aid in medical care.[16] Thus, genetic tests

12. *See* CTR. FOR DEVICES & RADIOLOGICAL HEALTH, FDA, DRAFT GUIDANCE FOR INDUSTRY, CLINICAL LABORATORIES, AND FDA STAFF: IN VITRO DIAGNOSTIC MULTIVARIATE INDEX ASSAYS (2006) [hereinafter IVDMIA DRAFT GUIDANCE], *available at* http://www.fda.gov/cdrh/oivd/guidance/1610.pdf.

13. *See, e.g.*, Denise Caruso, *Genetic Tests Offer Promise, but Raise Questions, Too*, N.Y. TIMES, Feb. 18, 2007, § 3, at 5.

14. JAMES D. WATSON WITH ANDREW BERRY, DNA: THE SECRET OF LIFE 165–66 (2003).

15. See Allen D. Roses, *Pharmacogenetics and the Practice of Medicine*, 405 NATURE 857, 861–62 (2000), for an introduction to how single-nucleotide differences, known as single nucleotide polymorphisms, can be used to identify and understand disease risk and drug response.

16. The definition of genetic testing from the SACGT reflects this process: "A genetic test is an analysis performed on human DNA, RNA, genes, and/or chromosomes to detect heritable or acquired genotypes, mutations, phenotypes, or karyotypes that cause or are likely to cause a specific disease or condition." SACGT RECOMMENDATIONS, *supra* note 2, at 1.

can be used to diagnose a condition, predict risk, or aid in the selection of therapeutics or dosages of drugs.[17] This Note will focus on predictive testing, considered by some to require the most regulation due to its inherent uncertainty.[18]

The latest generation of tests is the product of ongoing advances in both steps. First, the technology available to determine a person's genetic code is gaining speed and accuracy. Whereas the sequencing of a single composite human genome took the Human Genome Project thirteen years and billions of dollars,[19] scientists are developing sequencing technology that is far more efficient.[20]

Second, manufacturers are looking beyond single-gene variations with high penetrance to the impact of multiple genes in complex diseases. Penetrance measures the causal link between the genetic variation and the health outcome, so a gene variant of high penetrance is one that correlates well with a disease outcome.[21] Traditionally, tests were developed to detect variants of a single gene with a well-established correlation to a disease.[22] Recent tests, however, start with a disease and identify multiple, often novel, genes of interest.[23] Such tests employ complex analytical methods to determine the impact of multiple genes.[24] This new approach is predicated on the idea that although any one gene may be weakly penetrant, considering combinations of multiple genes can boost predictive power.[25] Private companies are embracing this approach by creating their own data banks

17. Notice of Meeting and Request for Public Comments on Preliminary Final Recommendations on Oversight of Genetic Testing, 65 Fed. Reg. 21,094, 21,096–97 (Apr. 19, 2000).

18. *See* SACGT RECOMMENDATIONS, *supra* note 2, at 6, 21.

19. Press Release, Nat'l Human Genome Research Inst., International Consortium Completes Human Genome Project (Apr. 14, 2003), http://www.genome.gov/11006929.

20. *See, e.g.*, Margulies et al., *Genome Sequencing in Microfabricated High-Density Picolitre Reactors*, 437 NATURE 376, 376–80 (2005) (describing an apparatus able to sequence twenty-five million bases in one four-hour run, claimed to be an approximately hundredfold increase in throughput over traditional sequencing technology); Press Release, Perlegen Scis., Perlegen Sciences Develops Massively Parallel Genotyping Platform (Sept. 12, 2002), http://www.perlegen.com/index.htm?newsroom/pr/2002/2002_09_12_Phase_1_Press_Release.html (claiming the capacity to sequence "nearly one genome every ten days").

21. Guttmacher & Collins, *supra* note 1, at 1513.

22. For example, tests for cystic fibrosis, Huntington's disease, and common late-onset Alzheimer's disease are based on the well-established risk profiles of specific mutations in single genes. *See* Roses, *supra* note 15, at 857 box 1; *see also* Michael S. Watson, *The Regulation of Genetic Testing*, *in* GENETIC TESTING AND THE USE OF INFORMATION 89, 94 (Clarissa Long ed., 1999) (describing the development of a genetic test for cystic fibrosis).

23. Monya Baker, *New-Wave Diagnostics*, 24 NATURE BIOTECHNOLOGY 931, 931–32 (2006); *see also, e.g.*, Shiffman et al., *Identification of Four Gene Variants Associated with Myocardial Infarction*, 77 AM. J. HUM. GENETICS 596 (2005).

24. *See, e.g.*, Soonmyung Paik et al., *A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer*, 351 NEW ENG. J. MED 2817 (2004).

25. Andrew Pollack, *F.D.A. Seeks to Regulate New Types of Diagnostic Tests*, N.Y. TIMES, Sept. 6, 2006, at C4, *available at* http://www.nytimes.com/2006/09/06/business/06drug.html.

of gene-disease correlations.[26] The results of these efforts are genetic tests that can provide predictive data for complex and common diseases based on multi-gene analysis.

B. Current Oversight

The regulatory requirements for genetic tests differ considerably based on whether they are marketed as kits or lab-developed tests. Kits are complete test systems with all of the reagents, components, and instructions needed to conduct the test and are intended for sale to multiple laboratories.[27] Lab-developed tests are generally assembled and conducted in-house at a single lab.[28] Unlike kits, they are sold as services to individual health care providers and patients who request them.[29]

Kits are regulated as medical devices by the FDA.[30] Medical devices are categorized from class I (lowest risk) to class III (highest risk) and regulated depending on the level of control necessary to assure safety and effectiveness.[31] The latest genetic tests are likely to be class III devices due to their complexity and use.[32] Class III device manufacturers must submit an application for premarket approval,[33] which requires that manufacturers submit data supporting any claims of analytical and clinical validity,[34] unless they can demonstrate that the device is "substantially equivalent" to a previously marketed device.[35] Of the hundreds of available genetic tests, only a few have been approved as kits because of the substantial cost and delay these requirements impose.[36]

By contrast, lab-developed tests are largely unregulated and consequently constitute the majority of genetic tests marketed today. Unlike kits, lab-developed tests are not subject to any premarket requirements or external validation.[37] Although the FDA has asserted

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26. *See* Baker, *supra* note 23, at 931.

27. Gail H. Javitt & Kathy Hudson, *Federal Regulation of Genetic Testing Neglect*, ISSUES SCI. & TECH., Spring 2006, at 59, 61.

28. *See id.* at 61.

29. *See id*.

30. *See* 21 C.F.R. pt. 809 (2006).

31. IVDMIA DRAFT GUIDANCE, *supra* note 12, at 4; *see also* 21 U.S.C. § 360c (2000 & Supp. 2006).

32. Michael J. Malinowski & Maureen A. O'Rourke, *A False Start? The Impact of Federal Policy on the Genotechnology Industry*, 13 YALE J. ON REG. 163, 206 (1996).

33. 21 U.S.C. § 360e(c).

34. Barbara J. Evans, *What Will It Take to Reap the Clinical Benefits of Pharmacogenomics?*, 61 FOOD & DRUG L.J. 753, 768 (2006); *see also* 21 U.S.C. § 360e.

35. Class III devices are exempted from the premarket approval process if they are "substantially equivalent" to a device marketed prior to May 28, 1976. 21 C.F.R. § 814.1(c) (2006). Instead, the manufacturer must submit a premarket notification (510(k)) submission. *Id.* § 807.81.

36. *See* Javitt & Hudson, *supra* note 27, at 61.

37. *See* Evans, *supra* note 34, at 768.

the authority to impose such regulations on lab-developed tests, it has historically exercised its "enforcement discretion" by declining to do so.[38] Therefore, laboratories have the freedom to decide whether a test is medically meaningful and whether it is supported by valid data.[39] In 1997, the FDA considered revoking the exception for lab-developed tests.[40] Ultimately, however, it decided to simply limit the exception by regulating the chemical components of lab-developed tests. These components, called analyte specific reagents ("ASRs"),[41] are regulated by the FDA if they move in commerce.[42] Current regulation of ASRs imposes only general quality controls, however, and does not address their eventual use in genetic tests.[43]

In September 2006, the FDA issued preliminary guidance for a subset of lab-developed tests denoted as In Vitro Diagnostic Multivariate Index Assays.[44] IVDMIAs are defined as test systems that use data from in vitro assays and an algorithm to provide a medically useful, patient-specific test result.[45] The preliminary guidelines suggest that most IVDMIAs are likely to be class II or class III devices subject to premarket and postmarket safety and effectiveness requirements.[46] The FDA recently sent letters to certain manufacturers stating that their new tests may be subject to FDA approval requirements.[47] At least with regard to these new tests, the FDA has suggested that the technology warrants regulation because of its complexity and its potential role in diagnosing diseases or affecting treatment.[48]

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38. *Id.*; *see also* Gutman, *supra* note 10, at 748; Analyte Specific Reagents, 62 Fed. Reg. 62,243, 62,250 (Nov. 21, 1997); IVDMIA DRAFT GUIDANCE, *supra* note 12, at 2.

39. *See* Javitt & Hudson, *supra* note 27, at 61.

40. *See* Analyte Specific Reagents, 62 Fed. Reg. at 62,252.

41. The regulations define ASRs to include antibodies, receptor proteins, ligands, nucleic acid sequences, and similar reagents that "are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens." 21 C.F.R. § 864.4020(a) (2006).

42. *See id.* §§ 864.4020, 809.30, 809.10(e); IVDMIA DRAFT GUIDANCE, *supra* note 12, at 2 (noting that the FDA does not regulate lab-developed ASRs that do not move in commerce). Resource limitations and confidence in the laboratories certified under the Clinical Laboratory Improvement Amendments influenced the decision to limit oversight over the lab-developed tests. *See* IVDMIA DRAFT GUIDANCE, *supra* note 12, at 2; Gutman, *supra* note 10, at 748.

43. *See* Analyte Specific Reagents, 62 Fed. Reg. at 62,244–46 (stating that the majority of ASRs used in genetic tests will be regulated as class I devices, which are subject only to general controls).

44. IVDMIA DRAFT GUIDANCE, *supra* note 12, at 1.

45. *Id.* at 1, 3.

46. *Id.* at 3–4.

47. Such letters have been sent to Correlogic, Roche, Agendia, and Genomic Health. *See* Baker, *supra* note 23, at 935. Letters have also been sent to CombiMatrix and InterGenetics. *See* Steve Usdin, *Stumbling Down the Path*, BIOCENTURY, Feb. 12, 2007, at A2.

48. *See* IVDMIA DRAFT GUIDANCE, *supra* note 12, at 4. The FDA suggests that IVDMIAs may require more oversight because they may provide more than just genetic information. *See id.* ("For example, a device intended as an indicator of a patient's risk of cancer recurrence may be a class II device, while the same device intended to predict which patients should receive chemotherapy might require Premarket Approval.").

In light of the recent preliminary guidelines, it is important to determine the proper scope of FDA regulation of lab-developed tests. Any regulatory oversight must consider at least two key parameters: analytical validity and clinical validity.[49] Analytical validity indicates "how well a test measures the property or characteristic it is intended to measure. In a DNA-based test, an analytically valid test would be positive when the particular gene mutation is present (*analytical sensitivity*) and negative when the gene mutation is absent (*analytical specificity*)."[50] A test's clinical validity is the accuracy of the test in diagnosing or predicting risk for a health condition.[51] Clinical validity is measured by a test's predictive value for a given health condition.[52] For newer genetic tests, a test's clinical validity will depend on the quality of the clinical data on which it is based and the algorithms used to compute the test result.[53]

While no uniform, comprehensive regulatory system exists, the federal government has already implemented some regulations to ensure a test's analytical validity.[54] All genetic test laboratories are subject to basic laboratory proficiency requirements under the Clinical Laboratory Improvement Amendments ("CLIA") of 1988,[55] which promote analytical validity through general and specialty-specific quality control measures.[56] CLIA has no specialty guidelines for molecular or biochemical genetics labs; the proposal to create such guidelines was abandoned in 2006.[57] Some analysts continue to argue

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49. *See* Sec'y's Advisory Comm. on Genetic Testing, 65 Fed. Reg. 21,094, 21,094–95 (Apr. 19, 2000). These criteria were identified by the SACGT as relevant to assessing the benefits and risks of genetic tests. *See id.* Two additional factors were also proposed: clinical utility and social issues. Clinical utility involves identifying the outcomes associated with positive and negative test results. This is sufficiently related to clinical validity that it will be considered concurrently with clinical validity throughout this Note. The social issues factor, however, is beyond the scope of this Note. Explicit consideration of social policy in device approval procedures is likely beyond the FDA's institutional expertise, however HHS has recommended that the FDA develop a mechanism to address the issue. *See id.* at 21,108.

50. *Id.* at 21,102.

51. *Id*.

52. *See id.* There are two types of predictive value. The positive predictive value is the proportion of patients with positive results who are correctly diagnosed; negative predictive value is the proportion of patients with negative test results who are correctly diagnosed. Douglas G. Altman & J. Martin Bland, *Statistics Notes: Diagnostic Tests 2: Predictive Values*, 309 BRIT. MED. J. 102, 102 (1994).

53. *See* Sec'y's Advisory Comm. on Genetic Testing, 65 Fed. Reg. at 21,102–03.

54. Audrey Huang, Who Regulates Genetic Tests? (Feb. 2006), http://www.dnapolicy.org/images/issuebriefpdfs/Who_Regulates_Genetic_Tests_Issue_Brief.pdf.

55. Clinical Laboratory Improvement Amendments of 1988, Pub. L. No. 100-578, 102 Stat. 2903 (1988) (codified as amended at 42 U.S.C. § 263a (2000)).

56. *See* 42 U.S.C. § 263a; Genetic Testing Under CLIA, 65 Fed. Reg. 25,928, 25,929–30 (May 4, 2000); Huang, *supra* note 54.

57. *See* Richard Park, *CMS Abandons Genetic Testing Specialty Plans*, IVD TECH., Jan. 2007, at 12, *available at* http://www.devicelink.com/ivdt/archive/07/01/002.html. This decision was based on the determination that there was no evidence of increased problems

that existing CLIA regulations are inadequate,[58] but the lack of response by the Department of Health and Human Services ("HHS") suggests that new regulations are unlikely to be enacted any time soon.

The regulation of clinical validity is also subject to debate. Analysts and industry leaders generally agree that the FDA is the appropriate federal agency to oversee any further regulation of clinical validity.[59] To regulate lab-developed tests, however, the FDA must have a legal basis for asserting authority over such tests. While the FDA claims to have such authority, it has yet to formally substantiate this claim.[60] The next Part examines possible sources of the FDA's authority to regulate lab-developed tests.

III. SOURCES OF FDA JURISDICTION

The Federal Food, Drug, and Cosmetic Act ("FDCA") of 1938[61] is the primary source of the FDA's regulatory authority. It mandates that the FDA regulate certain prohibited activities, including "[t]he introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded."[62] The FDA's jurisdiction over lab-developed tests is therefore premised on the presence of both a device and some element of interstate commerce.[63] As the following Sections will argue, courts will likely conclude that both of these elements are satisfied for lab-developed tests.[64]

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in genetic testing labs compared to labs performing other types of tests, and that a CLIA regulation would not resolve concerns about the clinical validity of genetic tests. *See id.* HHS had previously indicated its intent to revise the CLIA regulations to specifically address human genetic testing. Genetic Testing Under CLIA, 65 Fed. Reg. at 25,928–29.

58. *See* Park, *supra* note 57. Some who are critical of HHS's decision argue that creation of the specialty regulations would have increased public confidence in genetic testing. *See id*.

59. SACGT RECOMMENDATIONS, *supra* note 2, at 27.

60. *See* Anna Wilde Mathews, *FDA Asserts Its Authority to Regulate Novel Type of Test; Rules Cover Products Used to Decide on Treatments for Breast, Ovarian Cancer*, WALL ST. J., Sept. 6, 2006, at A15.

61. Pub. L. No. 75-717, 52 Stat. 654 (codified as amended at 21 U.S.C. §§ 301–399 (2000 & Supp. 2006)).

62. 21 U.S.C. § 331(a) (2000).

63. Anny Huang, *FDA Regulation of Genetic Testing: Institutional Reluctance and Public Guardianship*, 53 FOOD & DRUG L.J. 555, 576–77 (1998).

64. *See id.* at 576–79 (arguing that the FDCA delegates sufficient regulatory authority to the FDA and analyzing the interstate commerce element of the FDA's asserted jurisdiction).

A. Devices

The FDA may only regulate lab-developed tests if they qualify as devices under the FDCA. The Medical Device Amendments of 1976[65] amended the FDCA and imposed more stringent standards for devices.[66] As amended, the FDCA defines a device as:

> an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part or accessory, which is . . . intended for use in the diagnosis . . . or in the cure, mitigation, treatment, or prevention of disease . . . and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals . . . .[67]

Under a straightforward application of the statute, genetic tests appear to be devices since they can certainly be used "in the diagnosis, treatment, or prevention of disease." Furthermore, the FDA already regulates test kits as devices.[68] Given the definition of a device, it seems difficult to rationalize different regulatory treatment for test systems marketed together as kits and test systems that are instead used in a single lab.

Opponents of FDA regulation may counter that lab-developed tests are clinical laboratory services.[69] Unlike products, such services have not been regulated by the FDA in the past, suggesting that they do not qualify as devices.[70] The service-product divide, however, may increasingly be a distinction without a difference. Today, genetic tests for common, complex diseases are conducted predominantly by commercial laboratories marketing nationally, rather than by aca-

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65. Pub. L. No. 94-295, 90 Stat. 539 (codified as amended in scattered sections of 21 U.S.C.).

66. *See* 21 U.S.C.A. § 360 (West 1999 & Supp. 2006).

67. 21 U.S.C. § 321(h) (2000).

68. Javitt & Hudson, *supra* note 27, at 61.

69. *See, e.g.*, Petition from Washington Legal Foundation to FDA, Citizen Petition Regarding FDA Regulation of Laboratory Developed Tests (Sept. 28, 2006) (No. 2006P-0402), at 8–10, *available at* http://www.fdalawblog.net/fda_law_blog_hyman_phelps/files/wlf_citizen_petition.pdf.

70. The Centers for Medicare and Medicaid Services have assumed responsibility for regulating clinical laboratory services. *See id.* at 8.

demic research centers serving affiliated providers.[71] With such a profile, these tests indeed seem more like products than services.[72]

Furthermore, courts have historically shown broad deference to the FDA's own interpretation of the FDCA. For example, the Supreme Court has accepted the FDA's broad interpretation of certain regulatory categories. In 1969, before the enactment of the Medical Device Amendments, the FDA determined that antibiotic sensitivity discs, used as screening tools to help select the proper antibiotic to administer, were drugs rather than devices.[73] This determination subjected the discs to the more stringent drug regulations.[74] Despite Justice Douglas' argument that this definition ran contrary to the FDCA's plain language,[75] the Court upheld the construction in *United States v. An Article of Drug . . . Bacto-Unidisk . . . .*[76]

The Court's justification in *Bacto-Unidisk* has become a maxim of food and drug law: "we must give effect to congressional intent in view of the well-accepted principle that remedial legislation such as the Food, Drug, and Cosmetic Act is to be given a liberal construction consistent with the Act's overriding purpose to protect the public health."[77] Since the enactment of the Medical Device Amendments, the device category has only grown; it now encompasses such disparate items as toothbrushes and human heart valves.[78] The broadening of the device category makes it likely that a court would accept the FDA's assertion that lab-developed tests are devices.

B. Interstate Commerce

A more involved inquiry than whether lab-developed tests satisfy the device requirement is whether lab-developed tests contain a sufficient element of interstate commerce. Kits are physical objects that clearly cross state lines and easily fit under FDA authority. In con-

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71. *See* Neil A. Holtzman*, FDA and the Regulation of Genetic Tests*, 41 JURIMETRICS J. 53, 56 (2000).

72. *See* Huang, *supra* note 63, at 578 (arguing that "[a] nationally advertised single-test 'service' . . . bears a rather suspicious resemblance to a nationally distributed product, the very object of historical FDA regulation").

73. United States v. An Article of Drug . . . Bacto-Unidisk . . . ., 394 U.S. 784, 784 (1969).

74. *Id.*

75. *Id.* at 801 n.* (arguing that it would "be difficult to write a clearer description of an antibiotic sensitivity disc" than the statutory definition of "device").

76. *Id.* at 800.

77. *Id.* at 798.

78. *See, e.g.*, Ala. Tissue Ctr. of Univ. of Ala. Health Serv. Found. v. Sullivan, 975 F.2d 373, 378 (7th Cir. 1992) (finding heart valves to be "devices"); United States v. 2000 Plastic Tubular Cases, 231 F. Supp. 236, 238 (M.D. Pa. 1964) (finding toothbrush kits to be "devices"); *see also* Jay M. Zitter, Annotation, *What Is "Device" Within Meaning of § 201(h) of Federal Food, Drug, and Cosmetic Act (21 U.S.C.S. § 321(h))*, 129 A.L.R. FED. 343 (1996).

trast, lab-developed tests are conducted entirely within a single lab. Certainly, components of the test such as the patient sample, the ASRs, and the test result may travel across state lines. Arguably, however, the most important substantive activity to be regulated occurs entirely intrastate: genetic analysis of the sample and construction of a test result report. Nevertheless, under both constitutional and statutory delegations of power, the FDA likely has the authority to regulate lab-developed tests.

First, the Constitution permits federal regulation of lab-developed tests under the Commerce Clause.[79] The Supreme Court has held that the Commerce Clause enables Congress to regulate "activities that substantially affect interstate commerce."[80] The "substantially affects" test has a very broad reach under Supreme Court jurisprudence.[81] In applying this test, the Supreme Court has used an aggregation principle to find that many instances of a purely local activity can impact interstate commerce if the activity is part of an "economic class of activities."[82] Genetic testing services are undoubtedly an economic class of activity and thus may be readily aggregated.[83] Under this principle, even a nonprofit laboratory with entirely intrastate activities — for instance, only serving local hospitals — can affect a national market. Thus, FDA regulation of lab-developed tests is likely to withstand a Commerce Clause challenge because such tests substantially affect interstate commerce.

Second, the FDA also has statutory authority to regulate lab-developed tests. Under the FDCA, the FDA can regulate devices found to be "in interstate commerce."[84] For all lab-developed tests, whether used nationally or locally, a theory for finding the tests "in interstate commerce" can be premised on the statutory language. Specifically, under 21 U.S.C. § 331(k),[85] jurisdiction may be based on

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79. U.S. CONST. art. I, § 8, cl. 3 (empowering Congress "to regulate Commerce with foreign Nations, and among the several States, and with the Indian Tribes").

80. United States v. Lopez, 514 U.S. 549, 558–59 (1995).

81. *See* 1 LAURENCE H. TRIBE, AMERICAN CONSTITUTIONAL LAW § 5-4, at 823 (3d ed. 2000).

82. Gonzales v. Raich, 545 U.S. 1, 17 (2005); *see also* Wickard v. Filburn, 317 U.S. 111, 127–28 (1942) (holding that intrastate production and consumption of homegrown wheat impacted the national market).

83. In the few recent cases striking down legislation as failing to have a substantial effect, the link between the regulated activities and some sort of economic activity was considered too attenuated. *See* United States v. Morrison, 529 U.S. 598, 611 n.4 (2000) (stating that all intrastate activities the Court has held to be within Congress's power to regulate have been "of an apparent commercial character"); *Lopez*, 514 U.S. at 561 (distinguishing the Gun-Free School Zones Act of 1990 from "activities that arise out of or are connected with a commercial transaction"). *See generally* TRIBE, *supra* note 81, at 819–21.

84. *See* 21 U.S.C. § 331(a)–(c), (k) (2000).

85. This section of the FDCA gives the FDA jurisdiction to regulate

> [t]he alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, or cosmetic, if such act is done while

devices that do move interstate, such as the ASRs[86] or test results.[87] According to this theory, ingredients shipped in interstate commerce confer jurisdiction over the final product,[88] and then "[a] logical and persuasive argument can be made that the components previously shipped in interstate commerce can be 'adulterated' within the meaning of section 331(k) by assembling them into a genetic test that does not conform to regulations."[89] FDA jurisdiction over lab-developed tests could therefore be predicated on the shipment of ASRs or test results in interstate commerce,[90] and thus likely withstand a statutory challenge.

The foregoing jurisdictional analysis merely addresses a threshold issue. The existence of legal authority does not answer the much harder question of the optimal scope of such jurisdiction. The next Part suggests that existing limitations on regulating the practice of medicine should define the outer reach of the FDA's authority.

IV. THE PRACTICE OF MEDICINE LIMITATION

One potentially significant limitation on the FDA's regulatory power is the long-standing policy against direct regulation of the practice of medicine,[91] a matter historically left to the states.[92] The legislative history of the FDCA evidences that Congress did not intend the FDA to interfere with medical practice or to regulate the practice of

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> such article is held for sale (whether or not the first sale) after shipment in interstate commerce . . . .

Id. § 331(k).

86. ASRs are already regulated as devices. *See* 21 C.F.R. §§ 864.4020, 809.30, 809.10(e) (2006).

87. The test result can likely be considered a device because it is a "part . . . intended for use in the diagnosis of disease." 21 U.S.C. § 321(h).

88. *See* Baker v. United States, 932 F.2d 813, 814 (9th Cir. 1991) ("Thus, the 'shipment in interstate commerce' requirement is satisfied even when only an ingredient is transported interstate."); United States v. Dianovin Pharms., Inc., 475 F.2d 100, 103 (1st Cir. 1973) ("The appellants' use of components shipped in interstate commerce to make vitamin K for injection brought their activities within § 331(k) . . . ."); United States v. 40 Cases of Pinocchio Oil, 289 F.2d 343, 346 (2d Cir. 1961) ("Congress surely intended the provisions of the Food, Drug, and Cosmetic Act to apply to foods processed within a state, after shipment in interstate commerce . . . .").

89. Huang, *supra* note 63, at 577.

90. Although patient sample containers are considered devices, they are unlikely to be a good premise for jurisdiction given their generic function. *See, e.g.*, United States v. An Undetermined No. of Unlabeled Cases, 21 F.3d 1026, 1029 (10th Cir. 1994) ("Common sense suggests the function of generic urine and saliva specimen containers does not vary with the protocols later executed upon the samples they hold.").

91. *See* Richard A. Merrill*, Genetic Testing: A Role for FDA?*, 41 JURIMETRICS J. 63, 64 (2000) ("[The] FDA has long embraced the proposition that it is not empowered to regulate 'the practice of medicine.'").

92. *See* Linder v. United States, 268 U.S. 5, 18 (1925) ("Obviously, direct control of medical practice in the states is beyond the power of the federal government."); *see also* Huang, *supra* note 63, at 579–80 (arguing that courts have continued to support this principle).

medicine as between the physician and the patient.[93] This doctrine has been reiterated in laws throughout the years, for example in device and Medicare legislation,[94] and supported in judicial decisions involving drugs and devices.[95]

It is difficult if not impossible to provide a precise definition of the "practice of medicine." Although the statutory definition varies tremendously from state to state, most versions include diagnosis, prescription or treatment, and surgical operation as the key activities of medical practice.[96] These terms provide little guidance. Courts have struggled in defining the contours of the practice of medicine standard when determining whether physicians engage in medical practice when reviewing insurance coverage decisions, and whether non-physicians such as nurses practice medicine without authorization when exercising physicians' functions.[97]

The *use* of genetic testing clearly constitutes medical practice. The argument that testing asymptomatic persons for disease risk is neither "diagnosis" nor "treatment" because no disease or pathology is involved[98] assumes a limited view of medicine and the role of genetic tests. Multivariate genetic tests are valuable precisely because they provide additional information as to a patient's disease risk. When a test identifies a patient whose risk is not accurately quantified or detected with traditional risk factors, the patient's care suddenly takes on a real component of disease diagnosis or treatment.

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93. *See* Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the FDA, 37 Fed. Reg. 16,503 (proposed Aug. 15, 1972) (to be codified at 21 C.F.R. pt. 130).

94. *See* 21 U.S.C. § 396 (2000) ("Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."); 42 U.S.C. § 1395 (2000) ("Nothing in this subchapter shall be construed to authorize any Federal officer or employee to exercise any supervision or control over the practice of medicine or the manner in which medical services are provided . . . .").

95. *See* John J. Smith, *Physician Modification of Legally Marketed Medical Devices: Regulatory Implications Under the Federal Food, Drug, and Cosmetic Act*, 55 FOOD & DRUG L.J. 245, 251 (2000); *see also* Schlessing v. United States, 239 F.2d 885, 886 (9th Cir. 1956) ("The agency has no jurisdiction or authority to attempt to regulate the practice of medicine . . . ."); United States v. Evers, 453 F. Supp. 1141, 1149–50 (M.D. Ala. 1978) ("Congress did not intend the Food and Drug Administration to interfere with medical practice as between the physician and the patient."), *aff'd on other grounds*, 643 F.2d 1043 (5th Cir. 1981).

96. Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 KAN. L. REV. 149, 162 (2004).

97. *See id*. at 162–64.

98. *See, e.g.*, Allen C. Nunnally, *Commercialized Genetic Testing: The Role of Corporate Biotechnology in the New Genetic Age,* 8 B.U. J. SCI. & TECH. L. 306, 326–27 (2002); Alexander van Voorhees, Note, *Truth in Testing Laws: A Shot in the Arm for Designer Gene Tests*, 16 HEALTH MATRIX 797, 815–16 (2006).

It is harder to determine at what point regulation of test development and use becomes improper interference with medical practice.[99] On the one hand, physicians need some level of regulation to ensure that drugs and devices are safe and effective. On the other hand, limiting access to helpful tools hinders physicians' ability to exercise their best judgment in diagnosing and treating patients.[100]

A. The Example of Off-Label Prescribing

In applying the practice of medicine limitation to genetic test regulation, it is instructive to consider the example of off-label prescribing, an area in which FDA regulation has been restricted to avoid direct interference with medical practice.[101] The FDA allows a physician to use approved drugs and devices for unapproved uses when the physician feels it is medically appropriate.[102] Courts have protected such activity,[103] and off-label use has become an entrenched aspect of medical practice.[104]

The case of off-label prescribing demonstrates that some FDA regulation of a medical tool's safety and efficacy claims is not an un-

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99. *See* Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001) ("[T]he FDA is charged with the difficult task of regulating the marketing and distribution of medical devices without intruding upon decisions statutorily committed to the discretion of health care professionals.").

100. *See, e.g.*, Analyte Specific Reagents, *supra* note 38, at 62,248 (stating that minimal regulation of ASRs was proper because "in-house modification of materials and methods falls within the scope of the practice of medicine, and a more stringent classification would hamper the ability to provide quality medical services and care to patients"); Comments of the American Clinical Laboratory Association on the Draft Guidance for Industry Premarket Notifications for In Vitro Drug Resistance Genotype Assays: Special Controls (Nov. 8, 2001), http://www.fda.gov/ohrms/dockets/dailys/01/Nov01/110801/01D-0286_emc-000003-01.doc ("The resulting elimination of the most current technology interferes with the practice of medicine, may endanger the health of currently diagnosed HIV patients, and may prevent physicians from choosing the correct treatment regimen for newly diagnosed HIV patients.").

101. *See, e.g.*, *Buckman*, 531 U.S. at 350 ("'[O]ff-label' usage of medical devices . . . is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine.").

102. *See* FDA, Information Sheets: "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices, http://www.fda.gov/oc/ohrt/irbs/offlabel.html (last modified Apr. 17, 2001); *see also* CTR. FOR DRUG EVALUATION AND RESEARCH & CTR. FOR BIOLOGICS EVALUATION AND RESEARCH, FDA, GUIDANCE FOR INDUSTRY: IND EXEMPTIONS FOR STUDIES OF LAWFULLY MARKETED DRUG OR BIOLOGICAL PRODUCTS FOR THE TREATMENT OF CANCER 4 (2004), *available at* http://www.fda.gov/cder/guidance/6036fnl.pdf (noting that oncologists often use approved drugs off-label after evaluating the published data and past clinical experience and that this use is permitted under 21 C.F.R. § 312.2(d)).

103. *See, e.g.*, Ortho Pharm. Corp. v. Cosprophar, Inc., 32 F.3d 690, 692 (2d Cir. 1994) (off-label drug); Weaver v. Reagen, 886 F.2d 194, 198 (8th Cir. 1989) (off-label drug); Femrite v. Abbott Nw. Hosp., 568 N.W.2d 535, 540 (Minn. Ct. App. 1997) (off-label device).

104. *See* David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1021 (2006).

warranted interference with medical practice. Only FDA-approved drugs with proven safety and efficacy for their labeled use can be used off-label.[105] This requirement shows that the practice of medicine limitation does not completely insulate medical tools from agency oversight.

Once basic safety and efficacy of a drug is determined, however, the practice of medicine limitation restrains further regulation to insure that physicians can use the approved drug in varying ways to both benefit their patients and advance medical knowledge. The central medical practice concerns served by this restraint are variation and delay:

> For a product to have the most effective potential benefits, law and regulation should and must follow, not precede, science. There are too many variations in clinical circumstances and too much time delay in regulations to allow the government to impede the physician's ability to practice in these regards, when it is medically appropriate.[106]

Physicians therefore maintain that the off-label exception is critical.[107] Off-label use helps close the gap between regulatory approval and useful science,[108] particularly if clinical data for the off-label use is not easily obtainable.[109] It also attends to variations in clinical circumstances: physicians often use drugs off-label to help patients who cannot benefit from other available therapies.[110]

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105. Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the FDA, 37 Fed. Reg. 16,503, 16,503 (proposed Aug. 15, 1972) (to be codified at 21 C.F.R. pt. 130).

106. *Promotion of Drugs and Devices for Unapproved Uses: Hearing Before the Subcomm. on Human Res. and Intergovernmental Relations and the Gov't Operations Comm.*, 102d Cong. 103 (1991) (statement of George D. Lundberg, M.D., Editor-in-Chief for Scientific Publications of the American Medical Association).

107. *See id.*

108. *See* Richardson v. Miller, 44 S.W.3d 1, 13 n.11 (Tenn. Ct. App. 2000) ("Because the pace of medical discovery runs ahead of the FDA's regulatory machinery, the off-label use of some drugs is frequently considered to be 'state-of-the-art' treatment.").

109. *See* Evans, *supra* note 34, at 783–84 (arguing that conducting clinical trials for every potential use of a drug is neither feasible nor cost-effective and that certain subpopulations are more difficult to include in clinical trials).

110. *See* Jane E. Henney, *Safeguarding Patient Welfare: Who's in Charge?*, 145 ANNALS INTERNAL MED. 305, 305 (2006) ("The physician rationale for prescribing off-label is often based on the lack of FDA-approved effective treatments . . . ."). *See generally Prescription Drugs: Implications of Drug Labeling and Off-label Use: Hearing Before the Subcomm. on Human Res. and Intergovernmental Relations and the Comm. on Gov't Reform and Oversight*, 104th Cong. 5 (1996) (statement of Sarah F. Jagger, Director of Health Services Quality and Public Health Issues, Health, Education, and Human Services Division, GAO) (citing high rates of off-label prescription in the treatment of cancer, AIDS, and rare diseases).

Congress has also acknowledged that the compelling needs of addressing patient variation and avoiding excessive delay can help delineate the scope of proper regulation. The Food and Drug Administration Modernization Act of 1997[111] demonstrates respect for physician flexibility by explicitly permitting off-label device prescribing.[112] The Act's legislative history also evidences Congress's concern that burdensome regulatory standards could choke the incremental development of devices.[113]

B. A Guiding Principle for Genetic Test Regulation

The justifications for off-label use weigh equally in favor of restrained oversight of genetic tests. This argument can be summarized by the guiding principle that the FDA should regulate the analytical validity of a genetic test's information but not its *predictive value*, the measure of clinical validity.[114]

As a threshold matter, physicians may desire assurance of the analytical validity of a genetic test just as they welcome assurance of a drug's safety and efficacy for its approved use. Factual accuracy of a drug's or device's information furthers, not hinders, the physician's ability to tailor use of these tools. The FDA should fulfill its statutory role by ensuring that an approved drug has the safety and efficacy characteristics it claims,[115] and that a test accurately conducts the genetic analysis it claims.[116] Regulation of a test's analytical validity is thus appropriate because it promotes the accurate detection of mutations of interest.

By contrast, the FDA should be restricted in its regulation of predictive value, which is the probability that a test result yields the correct prediction or diagnosis.[117] This principle applies equally to regulation of kits and lab-developed tests. Although kits are already regulated for analytical and clinical validity, predictive value likely has not been a determinative factor in the regulation of genetic test kits to date.[118] As tests utilizing complex analysis to address multifac-

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111. Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended in scattered sections of 21 U.S.C.).

112. *See* 21 U.S.C. § 396 (2000).

113. *See* COMM. ON LABOR & HUMAN RES., ERRATA TO FOOD AND DRUG ADMINISTRATION MODERNIZATION AND ACCOUNTABILITY ACT OF 1997, S. Rep. No. 105-043, at 3 (1997) (noting that "medical devices tend to evolve incrementally" and citing the need for approval standards to enable "new and innovative technologies to reach consumers in a more timely manner").

114 For further information on analytical and clinical validity, see *supra* text accompanying notes 49–53.

115. *See* 21 U.S.C. § 355(d).

116. *See id.* § 360e(e)(1)(A)–(C).

117. *See* Altman & Bland, *supra* note 52, at 102.

118. Most genetic test kits today are based on single genes with well-established medical significance and thus do not require rigorous oversight for clinical validity. *Cf.* Javitt &

torial diseases raise more complicated issues of clinical validity, pressure may be mounting to increase scrutiny. For example, cut-off levels for predictive value have been proposed in discussions regarding increased regulation of predictive genetic tests.[119] Nevertheless, the FDA should refrain from imposing standards for predictive value of genetic tests under any regulatory regime.

Regulating use of a genetic test based on predictive value would mar the proper relationship between regulation and medical practice by excessively delaying development and use of the test and ignoring an important source of patient variation. First, regulation of predictive value would precede and possibly impede further scientific development. Part of the FDA's mission is "advancing the public health by helping to speed innovations."[120] Regulating based on predictive value could greatly frustrate this mission by hindering the development of certain genetic tests. Particularly for tests targeting rare conditions or weakly penetrant diseases for which it is difficult to build a statistically sufficient sample,[121] blocking use forecloses further data collection and may stifle all progress in that field. Furthermore, regulating predictive value can unnecessarily delay valid and useful tests from reaching the market.[122] Not regulating predictive value gives test developers the flexibility to integrate the most recent clinical data into their tests and provide increasingly predictive tools for patient care without constantly reapplying for FDA approval. This flexibility has been a historical benefit of the lab-developed test exception to FDA device regulation.[123]

Second, regulation of predictive value would ignore a critical source of variation in the clinical setting: the diversity of individuals' responses to uncertain information. To illustrate, imagine that the FDA requires that a new test for a complex disease obtain premarket approval. If the test can only determine with sixty percentcertainty

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Hudson, *supra* note 27, at 61 (noting that the FDA has only approved test kits detecting genetic variations in genes for CYP450, factor II and factor V Leiden, and cystic fibrosis).

119. *See* SACGT RECOMMENDATIONS, *supra* note 2, at 17 ("The acceptable level of the predictive value of a genetic test may vary depending upon the purpose for which the test is used . . . . [A] higher predictive value may be required of a test for which no other confirmatory test or clinical measure is available.").

120. FDA, FDA's Mission Statement, http://www.fda.gov/opacom/morechoices/mission.html (last visited Mar. 13, 2007).

121. *See* SACGT RECOMMENDATIONS, *supra* note 2, at 17 (acknowledging the difficulty of gathering clinical validity data for rare diseases); Joel N. Hirschhorn & Mark J. Daly, *Genome-Wide Association Studies for Common Diseases and Complex Traits*, 6 NATURE REVIEWS GENETICS 95, 100 (2005) ("[B]ecause variants that contribute to complex traits are likely to have modest effects, large sample sizes are crucial.").

122. A more permissive regulatory threshold can bring medically useful technology to the market sooner. For example, the ThinPrep test for cervical cancer and imaging techniques such as the positron emission topography were available on the market without regulatory delays because lab services do not require premarket approval. *See* Kris Novak, *Where the Chips Fall*, 12 NATURE MED. 158, 159 (2006).

123. *See* Usdin, *supra* note 47.

that a patient with a positive result will actually become symptomatic, the FDA might deem the predictive value inadequate. However, people vary widely in their willingness to use a test that predicts a future status with uncertainty[124] or receive information about circumstances they cannot fully control.[125] Due to this variation, only the individual patient and his physician, not the FDA, can determine what level of certainty will be more beneficial than harmful. In such individualized situations, the FDA should not intervene.

One might argue, however, that failing to regulate predictive value poses a kind of safety threat to patients. Predictive information can cause emotional and psychological harm if administered without proper informed consent or without counseling to help patients understand the information.[126] This is a safety threat, however, that the FDA is not equipped to regulate. Clinical safeguards such as informed consent, physician education, genetic counseling, or information privacy are generally considered outside the FDA's area of expertise.[127]

Application of this guiding principle does not eviscerate the FDA's ability to ensure a quality genetic test. The practice of medicine limitation does not bar FDA review of the quality of the clinical data or algorithm used by a test, and such quality underlies the accuracy of a test's predictive value.[128] For example, data from poor tissue samples or software algorithms based on faulty assumptions would corrupt the predictive value of a test. Certainly, so long as reasonable minds differ regarding the proper standards for the clinical data[129] and

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124. *See, e.g.*, Ellen S. Tambor et al., *Offering Cystic Fibrosis Carrier Screening to an HMO Population: Factors Associated with Utilization*, 55 AM. J. HUMAN GENETICS 626 (1994); Caryn Lerman et al., *Genetic Testing in Families with Hereditary Nonpolyposis Colon Cancer*, 281 JAMA 1618 (1999).

125. If treatment is not effective, as in Huntington's disease, the rate of information avoidance can be more than ninety percent. *See* Kimberly A. Quaid & Michael Morris, *Reluctance to Undergo Predictive Testing: The Case of Huntington Disease*, 45 AM. J. MED. GENETICS 41, 43 (1993).

126. *See, e.g.*, Henry T. Lynch et al., *A Descriptive Study of BRCA1 Testing and Reactions to Disclosure of Test Results*, 79 CANCER 2219 (1997); Barbara A. Koenig et al., *Genetic Testing for* BRCA1 *and* BRCA2*: Recommendations of the Stanford Program in Genomics, Ethics, and Society*, 7 J. WOMEN'S HEALTH 531, 538 (1998).

127. *See* Merrill*, supra* note 91, at 63–64 (questioning the FDA's institutional competence to regulate areas of great need in genetic testing, such as "autonomy, consent, and privacy that lie outside FDA's statutory mandate and recognized expertise"); *see also* Gutman, *supra* note 10, at 749 ("[T]hese tests raise several unique issues, many of which are outside of the purview of FDA review."); Secretary's Advisory Committee on Genetic Testing: Twelfth Meeting 29 (Feb. 14, 2002) (statement of Steven Gutman, M.D., M.B.A., Dir., Div. of Clinical Lab. Devices, Ctr. for Devices and Radiological Health), *available at* http://www4.od.nih.gov/oba/sacgt/transcripts/2-14-02transcript.pdf ("We do have precedent for pushing the envelope when we get worried about tests . . . but we certainly haven't visited this particular enterprise before and you're correct, we don't have any particular expertise.").

128. *See* IVDMIA DRAFT GUIDANCE, *supra* note 12, at 3.

129. The proper study design for the clinical data supporting genetic tests is still an open question for many recent tests. There is a debate between those demanding prospective

statistical methods[130] supporting analytical validity, the FDA could insist on standards that most in the medical community would consider too stringent in an attempt to regulate tests with inadequate predictive value. Transparency in the approval process is therefore critical to prevent back-door FDA regulation of predictive value and to make the FDA accountable for its regulatory process.[131]

V. CONCLUSION

The FDA has recently extended its reach without proper consideration of the practice of medicine limitation and the pressing need for a clear, principled approach to the regulation of genetic tests. The IVDMIA preliminary guidance fails to define, among other details, what levels of review will be applied to which test types or what kinds of supporting data will be required.[132] Furthermore, instead of issuing a proposed rule for comment along with the preliminary guidance, the FDA chose the more tentative strategy of issuing letters to industry.[133] Preliminary guidance, letters to manufacturers, and informal statements made by FDA officials do not constitute official FDA policy and are not binding.[134] Despite this lack of formal procedures, on February 7, 2007, the FDA cleared the first IVDMIA test, Agendia's MammaPrint.[135]

In light of the guiding principle proposed in this Note, the FDA should focus on setting forth clear standards for clinical trial design and analysis, both areas within the agency's expertise. As the FDA's experience in the genetic testing field grows and regulations become more comprehensive, attentiveness to the practice of medicine limitation will become more important to avoid stifling the benefits of promising technologies.

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studies and those arguing that retrospective studies, which are cheaper and easier to do, are adequate in some cases. *See, e.g.*, Novak, *supra* note 122, at 158.

130. Within the genetic testing industry, these issues are still the focus of cutting edge research and debate. *See, e.g.*, Paola Sebastiani et al., *Genetic Dissection and Prognostic Modeling of Overt Stroke in Sickle Cell Anemia*, 37 NATURE GENETICS 435, 435–36 (2005) (describing statistical challenges of analyzing complex interactions between genetic and non-genetic factors and suggesting analysis using Bayesian networks).

131. See Evans, *supra* note 34, at 773–76, for a proposal that clinical validity should be treated as an issue of medical practice and its oversight left to either agencies regulating medical practice or the medical profession itself. The author suggests that FDA labeling could simply reference guidelines made by external bodies within the scientific and medical communities. *Id.*

132. Usdin, *supra* note 47.

133. *See supra* note 47 and accompanying text.

134. *See* 21 C.F.R. § 10.85(k) (2006).

135. *See* Press Release, FDA, FDA Clears Breast Cancer Specific Molecular Prognostic Test (Feb. 6, 2007), *available at* http://www.fda.gov/bbs/topics/NEWS/2007/NEW01555.html. MammaPrint is a gene expression test, rather than a genetic test. The IVDMIA category encompasses many new technologies with complex clinical validity issues, so the distinction is not important here.