THE LIMITS OF FDA'S AUTHORITY TO REGULATE CLINICAL RESEARCH INVOLVING HIGH-THROUGHPUT DNA SEQUENCING

Barbara J. Evans, Ph.D., J.D., LL.M.[1]

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ABSTRACT

The U.S. Food and Drug Administration (FDA) recently signaled its interest in subjecting clinical investigations that employ high-throughput gene sequencing, also called next-generation sequencing, to the agency's Part 812 investigational device exemption (IDE) regulation. Genome sequencing—for reasons explained in this article—blurs the line between categories of IVD research that FDA traditionally has regulated and categories of research that FDA traditionally has not regulated. This blurring creates a risk that FDA may overstep its proper authority to regulate fundamental genomic and medical research.

This article surveys the legal limits of FDA's authority to subject research to its IDE requirements. Section 1 explains that FDA has authority to regulate clinical investigations *of* devices, but is not authorized to regulate investigations that merely *use* devices to expand medical knowledge or to conduct fundamental research, unless special circumstances apply. Section 2 discusses five special circumstances that can expand or limit FDA's authority to regulate a specific clinical investigation, and Section 3 offers a practical example. Section 4 explores concerns that arose in recent years about risks to human subjects in a certain type of investigation known as sponsor-investigator studies. In response to these concerns, FDA has suggested that it can regulate such studies in ways that threaten to expand FDA's regulation of research at academic medical centers beyond its proper scope. These concerns, while valid in some academic research contexts, seem inapposite in the setting of genomic research programs funded by responsible entities such as the National Institutes of Health (NIH). Moreover, FDA's regulations do not appear to support the proposition that FDA can regulate sponsor-investigator studies more expansively than it regulates other studies. Section 5 explores specific ways that NIH, clinical investigators, and FDA might work together to rationalize FDA's regulation of NIH-funded genomic research.

[1] Professor of Law and George Butler Research Professor; Director, Center for Biotechnology & Law, University of Houston Law Center, bjevans@central.uh.edu. This research received support from the NIH, NHGRI/NCI U01 HG006507, U01 HG007307, the Greenwall Foundation, and the University of Houston Law Foundation.

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Introduction

For almost 20 years, advisory bodies have called on the U.S. Food and Drug Administration (FDA) to play a greater role in regulating genetic and genomic testing,[2] and the agency recently responded with several initiatives. It published two draft guidances outlining a general framework[3] and some specific details[4] of a proposed scheme for FDA regulation of laboratory developed tests (LDTs), a category that includes many but not all genomic tests, and convened a Workshop on February 20, 2015 to discuss FDA oversight of high-throughput genome sequencing technologies, also known as next-generation sequencing (NGS).[5] These actions sparked heated debates about whether FDA has authority to regulate genomic testing and the potential impact such regulation may have on genomic discovery and innovation.[6] Related initiatives include President Obama's Precision Medicine Initiative, which charges FDA with modernizing its approach to NGS and calls for $10 million of funding for FDA to help develop high-quality, curated databases to support the effort.[7] The Senate and House also have efforts under way to address regulatory issues related to genomic and other diagnostic technologies.[8]

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2 *See, e.g.*, Joint Nat'l Insts. of Health-Dep't of Energy Working Group on Ethical, Legal, & Social Implications of Human Genome Research, *Promoting Safe and Effective Genetic Testing in the United States* (Neil A. Holtzman & Michael S. Watson eds., 1997); Secretary's Advisory Comm. on Genetic Testing, *Enhancing the Oversight of Genetic Tests* (2000), *available at* http://osp.od.nih.gov/sites/default/files/oversight_report.pdf.

3 U.S. Dep't of Health & Human Servs., Food & Drug Admin., *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) – Draft Guidance* (Oct. 3, 2014).

4 U.S. Dep't of Health & Human Servs., Food & Drug Admin., *FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs) – Draft Guidance* (Oct. 3, 2014).

5 U.S. Dep't of Health & Human Servs., Food & Drug Admin., *Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests—Preliminary Discussion Paper*, Federal Register 79(248):78,092-78,093 (Dec. 29, 2014).

6 *See, e.g.*, Paul D. Clement & Lawrence H. Tribe, *Laboratory Testing Services, As the Practice of Medicine, Cannot Be Regulated as Medical Devices* (American Clinical Laboratory Association White Paper, 2015), at http://www.acla.com/wp-content/uploads/2015/01/Tribe-Clement-White-Paper-1-6-15.pdf; James P. Evans, Michael S. Watson, *Genetic Testing and FDA Regulation – Overregulation Threatens the Emergence of Genomic Medicine*, JAMA published online Jan. 5, 2015; Gail Javitt, *FDA's Legally-Suspect Shift of Clinical Lab Test Regulations Through Guidance Documents*, THE LEGAL PULSE (Aug. 20, 2014), at http://wlflegalpulse.com/2014/08/20/fdas-legally-suspect-shift-of-clinical-lab-test-regulation-through-guidance-documents/; Joshua Sharfstein, *FDA Regulation of Laboratory-Developed Diagnostic Tests*, JAMA published online Jan. 5, 2015.

7 *See, e.g.*, The White House, Office of the Press Secretary. Fact Sheet: President Obama's Precision Medicine Initiative (Jan. 30, 2015); Francis S. Collins, A New Initiative on Precision Medicine, 372 N. Eng. J. Med. 793-795 (2015).

8 *See, e.g.*, Energy and Commerce Committee, U.S. House of Representatives, 21st Century Cures Legislative Phase Now Underway - Continued Feedback Sought as #Cures2015 Begins in Earnest (Jan. 27, 2015) at http://energycommerce.house.gov/press-release/21st-century-cures-legislative-phase-now-underway-continued-feedback-sought-cures2015-begins-in-earnest; SEN. LAMAR ALEXANDER AND SEN. RICHARD BURR, INNOVATION FOR HEALTHIER AMERICANS: IDENTIFYING OPPORTUNITIES FOR MEANINGFUL REFORM TO OUR NATION'S MEDICAL PRODUCT DISCOVERY AND

Even before FDA published its LDT draft guidances[9] and NGS discussion paper,[10] the agency already had stepped up its oversight of genomic research.[11] When the National Institutes of Health (NIH) funded several newborn sequencing research projects in September 2013, FDA asserted its authority to regulate the studies,[12] marking the first time the agency has subjected studies funded by the NIH's National Human Genome Research Institute to its investigational device exemption (IDE) regulation.[13] FDA contacted academic investigators, some who had no previous experience with FDA regulation, to express interest in their activities and, later, took the position that all of the projects needed to go through the IDE process.[14] Fifteen months after NIH funded the projects, only one had cleared the regulatory hurdles and launched its research activities.[15]

This is not a new policy. FDA's device regulations have always been relevant to some categories of biomedical research. FDA's LDT draft guidance[16] notes that "regulatory requirements for investigational devices are the same for academic medical center investigators as for other investigators. Investigational IVDs, including LDTs, are … subject to the Investigational Device Exemption (IDE) regulation (21 CFR Part 812), which is intended to protect the safety of study subjects."[17] Two things are new, however: (1) FDA's regulations may soon be more vigorously enforced than in the past, and (2) genome sequencing—for reasons discussed below--blurs the line between categories of IVD research that FDA traditionally has regulated and categories of research that FDA traditionally has not regulated. This blurring creates a risk that FDA may overstep its proper authority to regulate fundamental genomic and medical research. This article is motivated by concern that intrusive FDA regulation of genomic research has the potential to: (1) slow the progress of genomic discovery; (2) interfere with scientific inquiry and suppress investigators' and clinicians' speech in ways incompatible with the First Amendment to the U.S. Constitution; and (3) upset longstanding Congressional and FDA policies on federalism that respect the primacy of States to regulate the practice of medicine.

These concerns are relevant to all genome sequencing research, but they are especially intense in the context of publicly funded academic medical research that already is subject to

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DEVELOPMENT (Jan. 29, 2015), at http://www.help.senate.gov/imo/media/Innovation_for_Healthier_Americans.pdf.

9 *See supra* notes 3-4.

10 *See supra* note 5.

11 *See, e.g.,* Julia Karow, *First Newborn Sequencing Study Gets FDA Green Light While Others Still Await Approval*, GENOMEWEB (Dec. 17, 2014) at https://www.genomeweb.com/sequencing-technology/first-newborn-sequencing-study-gets-fda-green-light-while-others-still-await?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A%20genomeweb/inseq uence%20%28In%20Sequence%29&utm_content=Google%20Feedfetcher (discussing impacts of FDA research oversight on several genomic research projects); Turna Ray, *NIH Language in RFAs Tells Researchers to Prepare to Discuss Study Protocols with FDA*, GENOMEWEB (Dec. 8, 2014), at https://www.genomeweb.com/sequencing-technology/nih-language-rfas-tells-researchers-prepare-discuss-study-protocols-fda (same).

12 Karow, *supra* note 11.

13 *Id.; see* IDE regulation at 21 C.F.R. pt. 812.

14 Karow, *supra* note 11.

15 *Id*.

16 *See supra* note 3.

17 *Id*. at 36.

oversight by the Department of Health and Human Services' (HHS) Office for Human Research Protections (OHRP), which oversees regulation of human-subject research under the Common Rule.[18] FDA's additional human-subject protections may offer little additional benefit in terms of human-subject protection, while introducing a potential for significant delay.

This article offers a quick tour of factors that affect whether a particular clinical investigation is subject to FDA's IDE requirements. Section 1 describes the general limitation on FDA's authority to regulate research: FDA has authority to regulate clinical investigations *of* devices, but is not authorized to regulate investigations that merely *use* devices to expand medical knowledge or to conduct fundamental research, unless special circumstances apply. Section 2 discusses five special circumstances that can expand or limit FDA's authority to regulate a specific clinical investigation, and Section 3 offers an example. Section 4 explores concerns that arose in recent years about risks to human subjects in a certain type of investigation known as sponsor-investigator studies. In response to these concerns, FDA has suggested that it can regulate such studies in ways that threaten to expand FDA's regulation of research at academic medical centers beyond its proper scope. These concerns, while valid in some academic research contexts, do not seem valid in the case of genomic research programs funded by responsible entities such as the NIH. Moreover, FDA's regulations do not appear to support the proposition that FDA can regulate sponsor-investigator studies more expansively than it regulates other studies. Section 5 explores specific ways that NIH, clinical investigators, and FDA might work together to rationalize FDA's regulation of NIH-funded genomic research.

The goal of this article is simply to help genomics researchers understand how FDA's research regulations may apply to research that uses high-throughput DNA sequencing. The information provided here is not, however, sufficient to equip researchers to represent themselves before FDA. Researchers should give the general counsel's office at their institution a heads-up whenever FDA unexpectedly writes or comes calling. FDA is not merely a public health agency but also is a law enforcement agency. It is beneficial to have legal representation when FDA investigates one's activities, just as if one were under a police investigation. If the general counsel's office at one's institution lacks staff experienced in FDA regulatory matters—as often is the case at academic medical centers—researchers should ask their general counsel to help arrange access to suitably qualified outside counsel or regulatory affairs consultants.

1. General limitation of FDA's authority to regulate research

FDA implements research regulations that require informed consent,[19] review by an institutional review board (IRB),[20] disclosure of investigators' financial conflicts of interest,[21] appropriate labeling, manufacturing, and distribution of investigational devices,[22] and compliance with FDA's Part 812 IDE regulation.[23] Part 812 provides a pathway that makes it lawful to ship an otherwise-unlawful experimental device for use in a specific research protocol that FDA has approved, and it clarifies various responsibilities of sponsors and investigators in FDA-regulated research.

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[18] 45 C.F.R. pt. 46, subpt. A.
[19] 21 C.F.R. pt. 50.
[20] *Id*. pt. 56.
[21] *Id*. pt. 54.
[22] *Id*. pt. 809.
[23] *Id*. pt. 812.

With a few exceptions, FDA's informed consent and IRB regulations at 21 C.F.R. Parts 50 and 56 are worded almost identically to the Common Rule. The Common Rule has no counterpart to FDA's Part 812 IDE regulation, however, and this introduces major conceptual differences between the FDA and Common Rule human-subject protections. For example, the Common Rule has no counterpart to Part 812's implicit requirement that a federal regulator—FDA—approve the proposed research protocol. The Common Rule does not require such review, perhaps because it was designed primarily to regulate federally funded research where it can be presumed that the agency funding the research has reviewed and approved the research plan. FDA, on the other hand, typically regulates research funded by private entities like drug and device manufacturers, so its regulations provide an opportunity for the regulator to review the research protocol itself. This FDA review is potentially duplicative, however, when FDA asserts jurisdiction to regulate research funded by other federal agencies, such as the NIH. If the research incorporates a specific test article, FDA may be well-positioned to assess the safety of that article; however, is it warranted for FDA to second-guess whether the research itself is ethical to conduct, when a sister federal agency already has made that determination?

Another important difference is that OHRP, which administers the Common Rule, has a broad mandate to regulate many different kinds of biomedical research, ranging from basic, upstream scientific inquiries to very practical studies of specific products and methods of healthcare delivery. In contrast, FDA's legal authority as a research regulator is narrowly circumscribed, because FDA's authority to regulate research is merely an incident of its authority to regulate medical products such as drugs and devices. This limitation is evident in Part 812.

As a general rule, Part 812 allows FDA to regulate investigations *of* devices, as opposed to regulating investigations that merely *use* devices as tools to study other things. Part 812 states that it applies "to all clinical investigations of devices to determine safety and effectiveness"[24]—in other words, it regulates research in which the device itself is the thing being studied. Part 812 defines the word "investigation" very narrowly to mean "a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device."[25]

Many of the studies that medical geneticists ordinarily think of as clinical investigations may not even be "investigations" under Part 812's narrow definition of the term.Merely using an experimental device as a means to study a medical or physiological phenomenon does not, by itself, cause the research to fall under Part 812. The agency's own training materials state that no IDE is required for "basic physiological research" that is "investigating a physiological principle" with "no intent to develop the device for marketing," if the investigation is "only using the device to address the research question."[26] FDA enunciated this principle in the preamble to the final rule when Part 812 first was published on January 18, 1980:

> Several comments argued that an IDE should not be required for an investigation to expand medical knowledge or conduct fundamental research. FDA agrees with these comments insofar as they concern clinical investigations conducted for purposes other than determination of safety and effectiveness. Accordingly … the

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[24] *Id.* § 812.2(a)).

[25] *Id.* § 812.3(h).

[26] Lynn Henley, IDE and HDE Programs, Office of Device Evaluation, Center for Devices and Radiological Health, Food & Drug Admin., How to Put Together an IDE Application, *in* 2013 Clinical Investigator Training Course (November 14, 2013), at sl. 17, *available at* http://www.fda.gov/downloads/Training/ClinicalInvestigatorTrainingCourse/UCM378680.pdf.

regulation applies only to clinical investigations of medical devices to determine safety and effectiveness."[27]

Statements, like this one, that FDA makes in rulemaking preambles have the legal status of agency advisory opinions[28] and are admissible in administrative and court proceedings as evidence of how the agency's regulatory standards should be interpreted.[29] To amend or revoke one of its advisory opinions, FDA must do so using the same method of communication that it used when issuing the original advisory opinion[30]—in this case, FDA would need to publish a revocation in the *Federal Register*. FDA has not done so, so this 1980 advisory opinion is still an accurate statement of how Part 812's standards should be construed by courts and in the agency's own decision-making.

In deciding whether FDA can regulate research, there is a crucial legal distinction between sequencing people's genes for general genetic and biomedical research purposes (for example, to study which variants appear in the human genome, or to study the medical significance of specific gene variants, or to study optimal procedures for communicating and utilizing genetic information in clinical settings, or to study the psychological impact of genetic disclosures on patients) *versus* sequencing people's genes in order to study the analytical and clinical performance characteristics of the sequencing technology itself. As FDA explores whether to require IDEs for clinical studies that involve NGS, the agency must not blur this crucial distinction, which has deep legal roots in the regulatory history of Part 812.[31]

2. Legal nuances that affect FDA's authority to regulate research

Several fine points affect whether a particular study will be subject to regulation by FDA. These are summarized below and then discussed in more detail, followed by an example in Section 3.

A. Summary. Part 812 generally does not regulate "investigations to expand medical knowledge or conduct fundamental research,"[32] but two nuances may allow FDA to regulate these types of studies in specific circumstances:

- **Broad scientific studies that incorporate a device study.** The preamble to FDA's 1980 IDE final rule added a *proviso*: "If the expansion of medical knowledge or the conduct of fundamental research involves an investigation to determine the safety or effectiveness of a device, an IDE will be required."[33] The examples below will unpack what this means.
- **Uses that present significant risks.** FDA can regulate uses of experimental devices in studies of broad scientific and medical questions, if the use of the device presents "significant risk" for the research subjects.[34] This would be the case, for example, if a high-radiation experimental imaging device were used to measure tumor growth in a

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27 U.S. Dep't of Health, Educ. & Welfare, Food & Drug Admin., Medical Devices; Procedures for Investigational Device Exemptions, 45 Fed. Reg. 3732, 3735 (January 18, 1980).
28 21 C.F.R. § 10.85(d)(1).
29 *Id*. § 10.85(j).
30 *Id*. § 10.85(g).
31 *See supra* notes 27-30 and accompanying text.
32 45 Fed. Reg. at 3735.
33 *Id*. at 3735.
34 *Id*. at 3738.

study of the biological processes of cancer progression. Here, the device is not itself the focus of the research, but its use to answer other research questions entails significant risk for the human subjects, so an IDE would be required.

Other legal nuances set boundaries on the activities that FDA can regulate. These boundaries may provide a basis to contend that a particular study does not fall under Part 812. Understanding the boundaries also may help investigators proactively structure their investigations in ways that avoid triggering regulation by FDA.

- **FDA's flexible concept of studies that "determine the safety or effectiveness of a device."**[35] FDA's regulations provide no fixed definition of what types of investigation constitute a study to determine the safety or effectiveness of a device. FDA notes that "approval of a drug or medical device for one intended use does not assure its safety and effectiveness for other uses."[36] Thus the types of evidence needed to prove safety and effectiveness will vary, depending on the device's intended use and the claims that the developer plans to make about the device. When FDA takes the position that a study amounts to an investigation "to determine the safety or effectiveness of a device" and falls under Part 812, the agency is not applying a bright-line regulatory definition. Rather, the agency is making a judgment that incorporates assumptions about researchers' planned uses of the device and the claims they implicitly will be making about its performance for purposes of the research. "FDA is not bound by the manufacturer's or distributor's subjective claims of intent"[37] and the agency is free to make its own determination of what the intended use actually is. However, there may be room for reasoned debate about whether the agency's assumptions are correct and whether the study does or does not fall under Part 812.
- **Medical practice exception**. Section 1006 (formerly 906) of the Federal Food, Drug, and Cosmetic Act (FFDCA) prevents FDA from regulating the practice of medicine. It states that FDA is not authorized 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."[38] The practice of medicine, even when it departs from the standard of care, is not research that FDA can regulate. In the course of medical practice, physicians can use devices off-label and in novel ways without obtaining an IDE. FDA advises that physicians should base such decisions on "firm scientific rationale and sound medical evidence"[39] although physicians failing to do so would not be answerable to FDA but rather to their state medical practice licensing boards and to plaintiffs in state medical malpractice suits.
- **Unlawful promotion: the exception to the medical practice exception.** Section 1006's medical practice exception does not alter the fact that it is unlawful to promote unapproved uses of legally marketed devices.[40] A key unresolved issue is where FDA plans to draw the line between use and promotion in the context of genomic testing and scientific communication of emerging information about genotype-phenotype

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35 21 C.F.R. § 812.3(h).

36 U.S. Food & Drug Admin., Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices (Revised Draft Guidance) 3 (Feb. 2014).

37 *Id.*

38 21 U.S.C. § 396.

39 Henley, *supra* note 26, at sl. 16.

40 21 U.S.C. § 396.

relationships. Part 812's prevents sponsors, investigators, and persons acting on their behalf from communications that promote an investigational device that has not been cleared or approved[41] or that represent the device as safe and effective for the purposes for which it is being studied.[42] Application of these provisions in genomic research has the potential to chill scientific speech unless the boundaries of promotion are carefully drawn. This problem is beyond the scope of this article but requires careful attention as FDA expands its regulation of genomic research. Inappropriate line-drawing by the agency could open the door to intrusive FDA regulation of scientific communication about the clinical significance of gene variants. For example, will FDA regulate the distribution of clinical practice guidelines, such as the American College of Medical Genetics and Genomics' recommendations for reporting of incidental findings in clinical exome and genome sequencing,[43] based on the assertion that such guidelines discuss (and potentially promote) non-FDA-approved uses of genomic testing? This potential exists[44] and the line between use and promotion needs to be clarified.

B. Discussion. In genomic research, these legal nuances give rise to four important principles. These principles help delimit FDA's authority to regulate clinical investigations involving the use of high-throughput sequencing technology.

Principle #1 — Studying a gene is not the same as studying a test that detects the gene.

If research aims to evaluate the safety or effectiveness of a device, it is subject to regulation under Part 812. With many types of devices, it is obvious whether a study is or is not evaluating the device's safety or effectiveness. In genomic research, this matter is potentially confusing. The confusion stems from the long history, dating at least as far back as the 1997 NIH-DOE[45] and 2000 SACGT[46] studies, of framing the safety and effectiveness of genetic testing in terms of the so-called A-C-C-E parameters: safety and effectiveness depend on the Analytical validity of the test; the Clinical validity and Clinical utility of the gene variant(s) that the test detects, and the Ethical and social implications of testing.

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41 21 C.F.R. § 812.7(a).

42 *Id*. at § 812.7(d).

43 Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, McGuire AL, Nussbaum RL, O'Daniel JM, Ormond KE, Rehm HL, Watson MS, Williams MS, Biesecker LG; American College of Medical Genetics and Genomics. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. 15 GENET MED. 565-74 (2013).

44 The more likely interpretation may be that FDA would regulate this activity only if manufacturers of genome sequencing devices were using the guidelines in promoting sales of their devices, yet this interpretation could be debated.

45 TASK FORCE OF GENETIC TESTING, NAT'L INSTS. OF HEALTH-DEP'T OF ENERGY WORKING GRP. ON ETHICAL, LEGAL & SOCIAL IMPLICATIONS OF HUMAN GENOME RESEARCH, PROMOTING SAFE AND EFFECTIVE GENETIC TESTING IN THE UNITED STATES ch. 2 (Neil A. Holtzman & Michael S. Watson eds., 1997), *available at* http://www.genome.gov/10002404.

46 SEC'Y'S ADVISORY COMM. ON GENETIC TESTING, ENHANCING THE OVERSIGHT OF GENETIC TESTS: RECOMMENDATIONS OF THE SACGT 15 (2000), *available at* http://osp.od.nih.gov/sites/default/files/oversight_report.pdf .

Research that aims to assess the clinical validity or utility of a gene variant has an ambiguous status under this framework: On one hand, studying the phenotypic significance of a gene variant is in the nature of basic physiological or fundamental scientific research. As noted in the famous Katskee[47] case, a person's genes are a physiological feature of the person's body, albeit at a very microscopic level of physiology. On the other hand, the A-C-C-E framework treats evidence of the clinical validity or utility of specific gene variants as evidence bearing on the safety and effectiveness of tests that detect those variants. This latter view potentially categorizes any study of the clinical significance of a gene variant as a study of the test that detects the variant. It creates a risk that FDA may deem basic scientific studies of *genes* to be studies of *devices*, even when the gene is studied with no intent to commercialize a device.

To guard against such blurring, the sponsor's intent in performing a study is a relevant factor FDA considers when assessing whether an IDE is required. The need for an IDE may turn on whether there is "intent to develop the device for marketing".[48] FDA's training materials indicate that an IDE is required if the study sponsor intends to use data from the study "to support a marketing application" such as a premarket approval, humanitarian device exemption, or 510(k) clearance of a device, or if the study is for "collection of safety and effectiveness information (e.g., for a new intended use for legally marketed device)."[49] Under these principles, the need for an IDE is triggered when there are plans to submit data from the study to FDA to support a marketing application or a labeling change for a specific device. Basic scientific research, where there is no intent to submit the results to FDA to support a marketing application, would not trigger the need for an IDE.

In recent years, however, FDA officials have suggested that certain studies require an IDE irrespective of whether a marketing application is planned[50]—in other words, regardless of whether the study is fundamental scientific research or instead aims to generate data to commercialize a specific device. The studies in question are known as sponsor-investigator studies—clinical investigations in which the investigator and the sponsor are the same person.[51] As discussed later in this article, the text of FDA's regulations does not clearly support imposing heightened IDE requirements on such studies,[52] yet the possibility has been raised in agency training materials.[53] An investigator may qualify as a sponsor, under FDA's definitions, if the investigator initiated the study or is significantly involved (for example, by being a major shareholder) in the company or research organization that initiated it.[54] Such studies are thought to pose special risks for human research subjects, because they lack the inherent layer of monitoring and oversight that is present when a separate sponsor and investigator keep an eye on each other's activities. In 2005, noting a high incidence of human-subject protection problems in

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47 *See* Katskee v. Blue Cross/Blue Shield of Nebraska, 245 Neb. 808, 817-818 (1994) (holding that genetic predisposition to a disease, even in an asymptomatic patient, constituted a "bodily disorder" within the meaning of the patient's health insurance contract, because the patient's "genetic make-up" contained a "deviation from what is considered a normal, healthy physical state or structure").

48 Henley, *supra* note 26, at sl. 12.

49 *Id*.

50 *Id*.

51 *Id*.

52 *See infra* notes 127-130 and accompanying text.

53 *See supra* note 50.

54 *See* discussion and definitions *infra* at Section 4.

studies where investigators are also sponsors, an FDA official questioned: "How do you monitor yourself as sponsor-investigator?"[55]

In response to this concern, FDA's training materials advise that IDEs are required for any "sponsor-investigator study of an unapproved device or a new intended use of an approved device (even if no marketing application is planned)."[56] Requiring an IDE in this situation ensures that the research protocol and human subject protections will receive external oversight by FDA, in case the conflicted sponsor-investigator fails to ensure adequate protections. However, it ominously transforms FDA into a broad, general regulator of scientific research and creates a risk that the agency may stray far beyond its traditional role as a regulator of studies to evaluate the safety and effectiveness of devices.

When FDA asserts broad authority to regulate fundamental scientific or medical research at academic medical centers, the agency may be assuming that the study is a sponsor-investigator study. Section 4 will explain why this may not be a valid characterization of NIH-funded genomic research programs at academic medical centers. Investigators and the NIH may need to probe FDA's assumptions and push back against inappropriate FDA intrusions on NIH-funded genomic research. To borrow a phrase a federal judge wrote in a famous case[57] that challenged FDA's overreaching in an unrelated regulatory context, if FDA insists that every study of a gene is a study of an FDA-regulated genetic test, then "FDA exaggerates its overall place in the universe."[58]

Principle #2 — Genomic research may be exempt from FDA's IDE requirements if the findings produced using investigational sequencing technologies can be—and are—confirmed using an established testing technology.

FDA has determined that research involving investigational IVD devices *does not* pose significant risks to research subjects—and should be exempt from FDA's IDE requirements—if certain conditions are met. These conditions are stated in 21 C.F.R. § 812.2(c)(3), which provides an IDE exemption for certain investigations of diagnostic devices—that is, for investigations of genetic and other *in vitro* diagnostic (IVD) tests as well as *in vivo* diagnostics such as imaging equipment. This exemption states flatly that Part 812 "does not apply"[59] to investigations of diagnostic devices that meet all of the following criteria:

- The sponsor must comply with applicable requirements of 21 C.F.R. § 809.10(c), which requires special labeling of investigational devices.

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55 *Lepay: FDA to take closer look at investigator-initiated trial*, 12 No. 4 Guide to Good Clinical Practice Newsletter 1 (Thomson Publishing Group, Inc., January, 2005).

56 Henley, *supra* note 26, at sl. 12.

57 Wash. Legal Found. v. Friedman, 13 F.Supp.2d 51 (D.D.C. 1998].

58 *Id*. at 67.

59 21 C.F.R. § 812.2(c). Note, however, that even an exempted investigation is still required to comply with § 812.119, which allows investigators to be disqualified from participating in FDA-regulated research if they engage in certain forms of research misconduct such as reporting false data to FDA or failing to obtain informed consent and IRB review.

- The testing to be done during the investigation is "noninvasive"[60] and "does not require an invasive sampling procedure that presents significant risk."[61] Part 812 considers testing to be noninvasive if it only requires simple venipuncture or uses leftover specimens that were collected for a non-investigational purpose.[62]
- The testing does not "by design or intention introduce energy into a subject."[63]
- The testing is "not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure."[64]

When FDA first published Part 812 in 1980, the agency determined that research that meets these conditions does not pose significant risk to human subjects:

> Investigations of diagnostic devices meeting the conditions set forth in § 812.2(c)(3) of the final regulations are not required to be subject to the IDE regulation. Such investigations either do not truly involve human subjects or present risks so small as to be negligible, or present no risk at all. Consequently, the policy set forth in section 520(g)(1) of the [Food, Drug, and Cosmetic] act does not require regulation of investigations of such devices. Even investigational diagnostic products for life-threatening conditions would, if they meet the conditions of § 812.2(c)(3), not present significant risk. Investigations of diagnostic products for life-threatening conditions would, however, present risk and be subject to the regulation if the conditions of § 812.2(c)(3) are not satisfied: for example, if a diagnostic product were used as the basis for diagnosis without confirmation.[65]

In June 2010 guidance, FDA clarified how this applies to novel diagnostics that have no established counterparts that can be used for confirmation purposes:

> If an investigational test uses a new technology or represents a significant technological advance, established diagnostic products may not be adequate to confirm the diagnosis provided by the investigational IVD. … Under these conditions, the study would not meet the criteria for exemption under 812.2(c) with a medically established diagnostic procedure.[66]

This June 2010 guidance gave the example of an investigational test that identifies viral infection at an earlier stage than any established diagnostic product is able to detect the infection.

Whether research that uses an investigational gene sequencing technology can qualify for the IDE exemption at 21 C.F.R. § 812.2(c)(3) depends on how the sequencing results will be used. The planned uses determine whether there is "another, medically established diagnostic

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60 *Id*. § 812.2(c)(3)(i).
61 *Id*. § 812.2(c)(3)(ii).
62 *Id*. § 812.3(k).
63 *Id*. § 812.2(c)(3)(iii).
64 *Id*. § 812.2(c)(3)(iv).
65 45 Fed. Reg. at 3738.
66 U.S. Dep't of Health & Human Servs., Food & Drug Admin., Center for Devices and Radiological Health, Center for Biologics Evaluation and Research, Draft Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions 7 (June 25, 2010), 2010 WL 2765940 (FDA).

product or procedure"[67] available to confirm the results. Before discussing this further, two additional principles require discussion.

Principle #3 — It is crucial to distinguish whether a study is using gene sequencing to make analytical claims or to make clinical claims.

When communicating with FDA, researchers need to be very clear how their study intends to use an investigational device. Whether the research is or is not a study "to determine the safety or effectiveness of a device" in the intended use depends, obviously, on what the use is. A key consideration is whether the investigational gene sequencing technology (such as a newly developed sequencing analyzer and/or new software) will be used only to support analytical claims or also will support clinical claims.

Analytical claims. FDA imposes no legal requirement for developers of IVD devices to make clinical claims about them, and devices can be marketed and used in research for analytical purposes only.

- **Marketing a device for analytical use only**. An IVD device can be cleared or approved for analytical use only (for example, to detect a specific analyte, such as the presence of a gene variant) without making any claims about the clinical significance or utility of that information. At the point when FDA clears or approves such devices for marketing, evidence of analytical validity alone may be sufficient to demonstrate safety and effectiveness. An example is that in November 2013, FDA granted *de novo* petitions to classify Illumina's MiSeqDx™ instrument platform and its Universal Kit reagents as Class II (moderate risk) and Class I (low risk) medical devices, respectively, making them "the first FDA-regulated test system that allows laboratories to develop and validate sequencing of any part of a patient's genome."[68] The intended use of the MiSeqDx Platform is "for targeted sequencing of human genomic DNA from peripheral whole blood samples"[69]—in other words, the manufacturer only makes analytical claims. To support that the device is safe and effective in this intended use, the company provided analytical performance data showing that the device accurately and consistently identified variants known to exist in well-characterized genomes sequenced by other methods.[70]

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67 21 C.F.R. § 812.2(c)(3)(iv).

68 U.S. Food & Drug Admin., FDA allows marketing of four "next generation" gene sequencing devices (Nov. 19, 2013), ***at*** http://www.FDA.gov/newsevents/newsroom/pressannouncements/ucm375742.htm ; *see also* Letter of Courtney H. Lias, Food & Drug Administration to Leanne Kiviharju, Illumina, Inc. (Nov. 19, 2013) regarding Illumina MiSeqDx Universal Kit 1.0 Evaluation of Automatic Class III Designation—Request (classifying the device as Class I subject to regulation 21 CFR § 862.3800), *at* http://www.accessdata.FDA.gov/cdrh_docs/pdf13/k133136.pdf ; *and see* Letter of Courtney H. Lias, Food & Drug. Admin. To Leanne Kiviharju, Illumina, Inc. (Nov. 19, 2013) regarding Order Granting the Request for De Novo Classification – Illumina MiSeqDx Platform, *at* http://www.accessdata.FDA.gov/cdrh_docs/pdf12/k123989.pdf (classifying the device as Class II subject to regulation 21 C.F.R. § 862.2265).

69 *See* Lias, Letter regarding MiSeqDx Platform, *supra* note 68, at 1.

70 U.S. Food & Drug Admin., Evaluation of Automatic Class III Designation for MiSeqDX Platform: Decision Summary—Instrument Only Template (summarizing data submitted to support submission), *at* http://www.accessdata.fda.gov/cdrh_docs/reviews/K123989.pdf.

- **Using a device in research for analytical purposes only**. Research sometimes uses an investigational device for analytical purposes, without basing any diagnostic or clinical claims on findings made with the device. For example, suppose a study uses an investigational genome sequencing technology simply to screen whether research subjects possess any of 30 gene variants known to be of clinical interest, but then confirms these variant calls, and any associated diagnoses, using established diagnostic products and procedures. In this example, the investigational genome sequencing technology is merely being used for analytical purposes, to assess the suspected presence or absence of specific gene variants, subject to confirmation. No clinical claims are being made about its usefulness in diagnosing health conditions associated with the variants detected, because all diagnoses are confirmed using established products and procedures. This research is, at most, making analytical claims about the investigational genome sequencing technology.

Clinical claims. Some uses of a device involve both analytical and clinical claims (such as claiming the device can be used to diagnose a particular medical condition in a particular population or can be used to guide selection of therapies for individual patients).

- **Marketing a device for specific clinical uses**. If a test developer intends to market a device for clinical uses, FDA generally requires evidence of clinical validity before concluding that the device is safe and effective for those claimed uses. Even in this situation, however, there is considerable flexibility about the specific types of evidence FDA requires before determining that the device is safe and effective. Consequently, there is no fixed concept of what constitutes a study "to determine the safety or effectiveness of a device."
  - Even for novel or higher-risk tests that must pass through FDA's premarket approval or *de novo* submission processes, FDA may allow the use of peer-reviewed literature to support the clinical validity of well-established genetic markers, although proving that a new genetic marker has clinical validity often will require at least one clinical investigation.[71]
  - Tests that are similar to an older test FDA already has cleared or approved may be able to enter the market through FDA's 510(k) clearance process. The 510(k) process does not actually require any evidence that the new device is safe and effective; instead, FDA infers safety and effectiveness if the new device is shown to be substantially equivalent to the predicate device (which may itself never have been shown to be safe or effective).[72]
  - Various other factors affect the level of evidence of clinical validity that FDA requires for devices intended for specific clinical uses. For example, if a test is labeled for prescription use or states that its "results are intended to be interpreted by

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[71] U.S. Dep't of Health and Human Servs., Food & Drug Admin., Guidance for Industry and FDA Staff: Pharmacogenetic Tests and Genetic Tests for Heritable Markers (June 19, 2007).

[72] COMM. ON THE PUBLIC HEALTH EFFECTIVENESS OF THE FDA 510(K) CLEARANCE PROCESS, INST. OF MED., MEDICAL DEVICES AND THE PUBLIC'S HEALTH: THE 510(K) CLEARANCE PROCESS AT 35 YEARS 5 (2011) (concluding that "[t]he 510(k) clearance process is not intended to evaluate the safety and effectiveness of medical devices" and "connot be transformed into a pre-market evaluation of safety and effectiveness as long as the standard for clearance is substantial equivalence to any previously cleared device.").

a board-certified molecular geneticist or equivalent and should be used in conjunction with other available laboratory and clinical information,"[73] FDA may be convinced that it is safe and effective at a lower threshold of evidence than the agency would require for a direct-to-consumer test.

- **Research uses that implicitly make clinical claims about an investigational device**. Research implicitly makes clinical claims about an investigational device if the research uses findings from that device as inclusion criteria in a clinical trial, or to guide selection of treatments participants will receive, or for diagnostic purposes. The implicit claim is that the device has clinical validity for those purposes. Unless these clinical claims can be confirmed using established technologies, an IDE will be required.
  - **Example where an IDE is not required**. Assume an investigational sequencing technology will be used to screen research subjects for variants associated with cystic fibrosis to diagnose their condition, as an inclusion criterion for an investigation of a treatment for cystic fibrosis. As long as this diagnosis is confirmed using a medically established product or procedure, the study would qualify for the IDE exemption.
  - **Example where an IDE is required**. Assume an investigational sequencing technology will be used to screen research subjects to identify whether they possess specific gene variants. Then, based on these findings, researchers will assign them to receive one or another therapy to test the hypothesis that therapeutic response is related to those gene variants. Because the hypothesis has not yet been tested, it is unlikely that there is an established medical product or procedure that can be used to confirm the validity of these treatment selections. The research, in effect, is making both analytical and clinical claims about the investigational sequencing technology—that is, researchers are asserting that the sequencing technology can detect certain variants and that these variants have clinical validity for use in making treatment selections. The analytical claims (the variant calls) can be confirmed using established medical products or procedures, such as Sanger sequencing or a sequencing platform that has been cleared by FDA for analytical use. The clinical claims, on the other hand, cannot be confirmed. This study would not qualify for an IDE exception under FDA's June 2010 guidance discussed earlier,[74] because the researchers are implicitly making novel clinical claims that cannot be confirmed using established technologies. Another way of viewing this example is that this study falls into the *proviso* stated in the preamble to FDA's 1980 IDE final rule: an IDE is required when "the expansion of medical knowledge or the conduct of fundamental research involves an investigation to determine the safety or effectiveness of a device."[75] The hypothesis being tested in this study is whether the use of these variants to direct treatment selection is safe and effective. This may be a study to expand medical knowledge, but it incorporates a study to determine whether a specific device is safe and effective in a specific clinical use.

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[73] *See, e.g.,* U.S. Food & Drug Admin, 510(k) Substantial Equivalence Determination Decision Summary, Illumina MiSeqDx Cystic Fibrosis 139-Variant Assay 2 (describing the device's intended uses), *at* http://www.accessdata.fda.gov/cdrh_docs/reviews/k124006.pdf.

[74] *See supra* note 66 and accompanying text.

[75] 45 Fed. Reg. at 3735.

Various claims may be implicit in a proposed research use of an investigational device. Researchers should probe FDA's assumptions, to make sure there is a meeting of the minds about how the investigational device is being used and about the claims implicit in that use. Whether an IDE will be required depends on the nature of those claims (analytical only, or analytical plus clinical claims); whether established medical products and procedures exist that can be used to confirm those claims; whether the research plan actually provides such confirmation; and on an additional factor: who, specifically, will be making clinical claims.

Principle #4 — FDA can regulate claims that laboratories and device manufacturers make about the clinical significance of gene variants, but it cannot regulate clinical claims that physicians make in the course of medical practice.

FDA is authorized to regulate medical products but not medical practice. Courts have never found a constitutional constraint on the federal government's power to regulate medical practice,[76] but Congress made clear as it was enacting the FFDCA in 1938 that it did not intend for FDA to regulate the practice of medicine.[77] Medical practice traditionally has been regulated at the state level[78]—for example, through medical licensing statutes and through common-law malpractice lawsuits. As a matter of policy, FDA takes care to avoid intruding on the practice of medicine.[79] The agency has stated, for example, that product labeling "is not intended either to preclude the physician from using his best judgment in the interest of his patient, or to impose liability if he does not follow the package insert." [80] Thus, FDA regulates statements *device manufacturers* can make about the clinical significance of IVD test results and, as FDA steps up its oversight of LDTs, the agency may increase its oversight of claims by *laboratories*. Physicians, on the other hand, remain free (at least as far as FDA is concerned) to make claims about the clinical significance of gene variants, even not-fully-validated ones, if they do so in the context of medical practice.[81]

FDA has made the following statement about physicians' off-label claims about legally marketed products (those that have been cleared or approved):

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[76] David G. Adams, *The Food and Drug Administration's Regulation of Health Care Professionals*, in 2 FUNDAMENTALS OF LAW AND REGULATION: AN IN-DEPTH LOOK AT THERAPEUTIC PRODUCTS 423 (David G. Adams, Richard M. Cooper & Jonathan S. Kahan, eds., 1999).

[77] *See, e.g.*, William B. Schultz, Deputy Comm'r for Pol'y, Food & Drug Admin., Promotion of Unapproved Drugs and Medical Devices (testimony before the the Senate Committee on Labor and Human Resources (February 22, 1996), available at http://www.fda.gov/newsevents/testimony/ucm115098.htm; Barbara J. Evans, *Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 Notre Dame L. Rev. 500-503 (discussing Congressional debate about the FFDCA).

[78] Joel E. Hoffman, *Administrative Procedures of the Food and Drug Administration*, in 2 FUNDAMENTALS OF LAW AND REGULATION, *supra* note 76, at 17-24.

[79] Adams, *supra* note 76, at 425-426.

[80] Dep't of Health, Education & Welfare, Food & Drug Admin., *Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration (Notice of Proposed Rulemaking)*, 37 Fed. Reg. 16504 (July 30, 1972); William L. Christopher, *Off-label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247 n.6 (1993).

[81] *See infra* note 82 and accompanying text (discussing state regulation of medical practice).

> Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics, and devices according to their best knowledge and judgement [sic]. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner *when the intent is the 'practice of medicine'* does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB).[82]

FDA notes that investigational use differs from medical practice: Investigational use suggests the use of a clinical study protocol, and an IDE or IND may be required when "the principal intent of the investigational use … is to develop information about the product's safety or efficacy."[83] For other types of investigations–such as those that aim to expand medical knowledge or conduct fundamental scientific research– the implication is that an IDE or IND would not be required. The example in Section 3 explores this nuance.

The fact that FDA does not regulate physicians' speech does not mean that physicians' claims about the clinical significance of gene variants are unregulated. State medical practice boards can take disciplinary action against a physician's license if the physician's statements to patients are so unfounded that they violate the standard of care.[84] State tort lawsuits can sanction the physician if a patient is injured as a result of irresponsible statements that lie outside the standard of care. But FDA cannot regulate statements physicians make about IVD test results during the course of medical practice.

This raises a natural question: Do physician claims that fall beneath the standard of care still qualify as "medical practice" for purposes of the medical practice exception at § 1006 of the FFDCA? The simple answer is, "Yes, they qualify." The concept of "medical practice" refers to physicians' activities in the course of rendering clinical care in the context of a physician-patient relationship. As such, medical practice includes medical malpractice, which, sadly, is a regularly occurring part of medical practice. FDA does not set or enforce the medical standard of care regarding physicians' use of devices that FDA clears and approves. For example, many men have suffered unnecessary and debilitating iatrogenic injuries as a result of their physicians' off-label use of the prostate-specific antigen test for screening asymptomatic patients, even though

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82 Food & Drug Admin, "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices – Information Sheet, *at* http://www.fda.gov/regulatoryinformation/guidances/ucm126486.htm [emphasis in original].

83 *Id*.

84 *See, e.g.*, Breiner v. State, 23 Conn. L. Rptr. 110, No. CV 98061275, 1998 WL 738066, *6 (Oct. 7, 1998 Super. Ct. 1998) (unpublished opinion) (finding that it did not violate the First Amendment for a state dental licensing board to discipline a dentist for advising his patients that amalgam fillings were poisonous--advice that, in the board's view, was against the weight of scientific evidence); *see also*, Robert Post, *Informed Consent to Abortion: A First Amendment Analysis of Compelled Physician Speech*, 2007 U. ILL. L. REV. 939, 947-948 (2007) (discussing the ability of states to regulate "professional speech," or communications professionals such as physicians, accountants, and attorneys make in the course of their professional practice through mechanisms such as disciplinary license proceedings or malpractice tort suits).

FDA has never approved the test as safe and effective for this use.[85] FDA does not interfere with physicians' prerogative to order this use. Similarly, it is estimated that 70% of off-label drug uses lack significant scientific support,[86] but FDA does not prohibit such uses except in rare instances where an off-label use poses such known and serious dangers that FDA can restrict the drug's use under a Risk Evaluation and Mitigation Strategy.[87] FDA has stated:

> Once a drug or medical device has been approved or cleared by FDA, generally, healthcare professionals may lawfully use or prescribe that product for uses or treatment regimens that are not included in the product's approved labeling (or, in the case of a medical device cleared under the 510(k) process, in the product's statement of intended uses). These off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care.[88]

The wording of that last phrase ("*may even* constitute…") suggests that FDA is well aware that such uses *often do not* constitute a medically recognized standard of care. Yet such uses are still "medical practice" for purposes of § 1006 of the FFDCA.

Section 1006 prevents FDA from interfering with physicians' authority to "administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship." This raises another question: Is a physician "administering a legally marketed device" if the physician, in the course of medical practice, answers a patient's questions about the patient's gene variants that were detected using a non-FDA cleared sequencing technology? This question has the potential to become a battleground in future years. It is a battleground on which FDA seems likely to lose—on a variety of First Amendment and federalism grounds—if the agency asserts that it can restrict physician-patient discussion of variants that have been detected, without the physician's prior involvement, using a non-FDA-cleared sequencing technology. At present, many non-FDA-cleared sequencing services are lawfully marketed as LDTs by laboratories that comply with the Clinical Laboratory Improvement Amendments of 1988 (CLIA)[89] regulations.[90] The recent LDT draft guidances[91]

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85 NAT'L CANCER POLICY FORUM, INST. OF MED., DEVELOPING BIOMARKER-BASED TOOLS FOR CANCER SCREENING, DIAGNOSIS, AND TREATMENT: WORKSHOP SUMMARY 70 (Margie Patlak & Sharyl Nass rapporteurs, 2006) [hereinafter IOM, BIOMARKER-BASED TOOLS], *available at* http://books.nap.edu/openbook.php?record_id=11768 (reporting presentation of Dr. Scott Ramsey). *See also*, intended use in patient labeling of an FDA-approved PSA test at http://www.accessdata.fda.gov/cdrh_docs/pdf/P930027S004c.pdf.

86 Marc Rodwin, *Managing Off-Label Drug Use*, HEALTH AFFAIRS BLOG (Dec. 17, 2013), at http://healthaffairs.org/blog/2013/12/17/managing-off-label-drug-use/.

87 *See* Evans, *supra* note 77, at 508-515 (discussing FDA's authority to restrict distribution and use of drugs subject to a REMS).

88 Off. of Comm'r., Off. of Pol'y, Food & Drug Admin., Guidance for Industry - Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (Jan. 2009), *available at* http://www.fda.gov/regulatoryinformation/guidances/ucm125126.htm [emphasis added].

89 Pub. L. No. 100-578, 102 Stat. 2903 (codified as amended at 42 U.S.C. § 263a.

90 42 C.F.R. pt. 493.

91 *See supra* notes 3-4.

envision a phased introduction of FDA oversight of LDTs,[92] but indicate no immediate plan for FDA to declare them unlawful. Even if FDA eventually were to declare LDTs unlawful, there already are vast stores of genomic information that were generated in the past using non-FDA-cleared sequencing technologies (which were lawful at the time the information was generated). Recent changes to the CLIA regulations and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule[93] grant individuals a right of access upon request to variant call format (VCF) files and other uninterpreted information about gene variants detected during NGS, if those files are stored at a CLIA-compliant, HIPAA-covered laboratory.[94] Patients thus will have direct access to uninterpreted data about their gene variants, and many are likely to turn to their physicians for interpretive assistance. FDA cannot forbid those conversations without gravely intruding on the practice of medicine, violating the First Amendment, and potentially infuriating tens of thousands and eventually millions of ordinary Americans who want to be able to speak to their doctors about their own genomes.

More broadly, there is a trend toward unbundling DNA sequencing from genomic interpretation services,[95] and this trend further complicates FDA's oversight of genomic interpretation. Some laboratories already offer data-only sequencing services that identify a person's gene variants without interpreting them, leaving the interpretation to be performed by others.[96] As genomic interpretation is unbundled from device-mediated services such as specimen collection and test administration, FDA's authority to regulate grows dim. It seems clear that FDA can deem data-only sequencing services to be medical devices and can require them to provide analytically valid results. However, the agency faces jurisdictional hurdles if it attempts to regulate unbundled genomic interpretation services that are completely divorced from any underlying medical device.[97]

Unbundled services also intensify the First Amendment issues, because interpreting the clinical significance of the genome amounts to speech.[98] Genomic interpretation is, in essence, an informational service that formulates and communicates opinions about the clinical impact of a person's gene variants. It is true that information has the potential to cause harm if people take ill-advised actions in response to the information, which they may do even if its uncertainty and

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92 *See supra* note 3.

93 U.S. Department of Health and Human Services, CLIA program and HIPAA privacy rule; patients' access to test reports, Federal Register Feb. 6, 2014;79(25):7290 – 7316.

94 Barbara J. Evans, Michael O. Dorschner, Wylie Burke, Gail P. Jarvik, *Regulatory Changes Raise Troubling Questions for Genomic Testing*, GENET. MED. (forthcoming 2014).

95 Curnutte MA, Frumovitz KL, Bollinger JM, McGuire AL, Kaufman DJ, *Development of the Clinical Next-Generation Sequencing Industry in a Shifting Policy Climate*, 32 NATURE BIOTECHNOLOGY 980-2 (2014).

96 *See, e.g.*, D. Vorhaus, "DNA DTC: The Return of Direct to Consumer Whole Genome Sequencing," Genomics Law Report (Nov. 29, 2012), at http://www.genomicslawreport.com/index.php/2012/11/29/dna-dtc-the-return-of-direct-to-consumer-whole-genome-sequencing/; Barbara J. Evans, *Economic Regulation of Next-Generation Sequencing*, *in* SPECIAL ISSUE: POLICY ISSUES IN NEXT-GENERATION SEQUENCING (Amy L. McGuire, David J. Kaufman & Margaret A. Curnutte, *eds.*), 42 JOURNAL OF LAW, MEDICINE, AND ETHICS (*forthcoming* 2014).

97 Gail H. Javitt & Katherine Strong Carner, Regulation of Next Generation Sequencing. 42(Supp1) J. Law, Med. & Ethics 9, 16-17 (2014).

98 Barbara J. Evans, *The First Amendment Right to Speak About the Human Genome*, 16 U. PENN. JOURNAL OF CONSTITUTIONAL LAW 549 - 636 (2014).

limitations have been properly disclosed. FDA's November 2013 warning letter to direct-to-consumer genetic testing service 23andMe underscored that FDA is concerned about genomic interpretation, because the agency believes erroneous interpretation may lead to harmful medical interventions such as prophylactic surgery.[99] Nevertheless, the mere fact that a communication may cause patients to make bad medical decisions does not by itself imply that FDA can regulate that communication.[100] FDA has some ability, within First Amendment constraints, to regulate the speech of persons who are manufacturers, investigators, sponsors, or promoters of a medical product. A stand-alone genomic interpretation service that is none of the above seemingly lies beyond the reach of FDA speech regulation. This is especially true when genomic interpretation is performed by a physician in the course of medical practice.

3. An example application of the principles

Suppose that a planned study will use an investigational sequencing technology to scan research subjects' genomes to identify whether they possess a group of 10 specific gene variants. The subjects' biospecimens will consist of blood draws taken by simple venipuncture. Assume, also:

- These variants are known, from previously published literature, to be associated with specific health conditions, and clinicians regularly use those gene variants to help diagnose those health conditions in symptomatic patients. It is not presently standard medical practice to use the variants to screen asymptomatic patients, however.
- FDA has never yet cleared or approved a diagnostic test that uses those gene variants for diagnostic purposes in any population—symptomatic or asymptomatic.
- The research subjects include some individuals with symptoms of the health conditions, and other asymptomatic healthy patients.
- The analytical validity of the new sequencing technology has not been established, so each subject's identified gene variants will be confirmed using a well-established laboratory procedure, such as Sanger sequencing or an FDA-cleared sequencing technology that has been shown to produce analytically valid results.
- Analytical results of this testing (that is, the variant calls) will be conveyed to each subjects' clinician, and the clinicians will discuss the possible clinical significance of the detected gene variants with their patients.
- The clinicians will have access to a library, prepared by the researchers, that compiles information from peer-reviewed literature about the clinical significance of the gene variants.
- The aims of this study are to assess: (1) whether clinicians make good use of library resources when counseling symptomatic and asymptomatic patients, and (2) to assess whether research subjects are pleased or upset by the information their clinicians share with them.

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[99] A Gutierrez, Director, Office of In vitro Diagnostics and Radiological Health, Food & Drug Administration, Letter to Ann Wojcicki, C.E.O. 23andMe, Inc. (Document No. GEN1300666, Nov. 11, 2013), at http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm376296.htm .

[100] *See* Evans, *supra* note 98, at 618-23 (summarizing and discussing First Amendment commercial speech cases that held that suppressing speech as a means of preventing harmful consequences that flow from the speech is not the least restrictive means of addressing the consequential harms).

According to one view of this research, the investigational sequencing technology is being used to diagnose symptomatic patients and to counsel asymptomatic patients. Because there is presently no established diagnostic product that harnesses the 10 gene variants for those purposes, FDA might take the position that an IDE is required, citing its June 2010 guidance concerning advanced products for which no confirming technology exists.

The researchers can offer an alternative account of the research that carefully delineates the implicit claims that it will make about the investigational device. This research is only using the investigational sequencing technology to "diagnose" which gene variants the research subjects possess. In other words, the new technology is only being used to support analytical claims. These analytical claims will be confirmed using well established products or procedures for identifying those same gene variants, so this part of the research fits into the IDE exemption at 21 C.F.R. § 812.2(c)(3).

The researchers and the laboratory that performs the sequencing are not actually making any clinical claims about the validity of the new technology for diagnosing specific diseases. The only clinical claims being made in this study will be made by licensed physicians in the context of their physician-patient relationships with the research subjects, and these claims will be based on the physicians' perusal of a library that summarizes published, peer-reviewed literature. The medical practice exception seemingly applies: FDA cannot regulate the remarks physicians make to their patients in the course of medical practice.

An important point is that any clinical claims actually will be based on analytical results from the confirming technology (Sanger sequencing or an FDA-cleared sequencing platform), rather than from the investigational technology. If FDA takes the position that an IDE is required whenever clinical claims are made about a person's gene variants, then the agency seemingly would need to require an IDE for the confirming technology, rather than for the investigational technology, because the confirming technology is the one ultimately used to determine the patients' gene variants in this example.

May FDA attempt to regulate the researchers' creation of the library that compiles information about the clinical significance of gene variants? It raises First Amendment concerns for FDA or another federal agency to limit the information that researchers may hold in a library. Still, FDA could attempt to regulate the library if FDA regards the investigators as manufacturers of the investigational sequencing technology (or as representatives of the manufacturer) and takes the position that their creation of the library amounts to promotion of the technology for unapproved uses. Because this library is based on peer-reviewed scientific and medical literature, however, the most that FDA seemingly can require is that researchers must follow practices recommended in FDA's various guidances on distribution of scientific and medical publications that discuss unapproved uses of medical products.[101] Moreover, if the researchers involve medical geneticists in curating the library, the library is in the nature of physician-to-physician communication and seems more suitable for regulation by state medical boards than by FDA.

Another question is whether FDA can restrict the clinicians' access to the available, analytically valid, and confirmed information about their patients' gene variants. To do so would mark a clear interference with medical practice, akin to restricting clinicians' ability to receive known information about their patients' blood pressure. Were FDA to interfere with medical practice in this manner, it is debatable whether the Federal Tort Claims Act[102] would shield the

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[101] *See supra* notes 88 (2009 guidance) and 36 (2014 revised draft guidance).

[102] 28 USCA §§ 1291, 1346, 1402, 2401, 2402, 2411, 2412, 2671 - 2680.

agency from tort liability for any harms patients suffer as a result of their physicians' forced ignorance.

Physicians who choose to discuss the clinical significance of the gene variants with asymptomatic patients apparently will be violating the current medical standard of care. However, these physician-patient communications still fit within the medical practice exception at § 1006 of the FFDCA. State medical licensing boards and state courts hearing tort actions could sanction physicians if these conversations are, in fact, found to breach the medical standard of care, but FDA cannot do so.

Based on its aims, this is a study to advance medical knowledge. It is testing hypotheses about: (1) physician's use of library resources in the medical practice setting, and (2) patients' reactions to genetic counseling that their physicians provide. Neither of these hypotheses tests the safety and effectiveness of using these gene variants for the purpose of diagnosing (or predicting patients' future risk of) the associated diseases. In other words, the study is not testing the hypothesis that the identified gene variants have clinical validity for these purposes, and it thus cannot be viewed as incorporating a study of the safety and effectiveness of a device. Therefore, it does not fit within the *proviso* in the preamble to the 1980 IDE final rule that allows FDA to require IDEs for certain basic scientific studies if they incorporate a device study.

Here, it may be useful to explain why the Aim 2 study (looking at the emotional impact genetic disclosures on patients) is not a "study to determine the safety and effectiveness of a device" that is subject to Part 812. Despite calls to consider ethical and social implications when assessing the safety of genetic testing[103] and calls for FDA to be the entity responsible for premarket evaluation of genetic tests,[104] SACGT recognized that FDA's "review will focus on assuring the analytical and clinical validity of a test" and that FDA's capacity to assess ethical and social implications is limited.[105] When FDA evaluates the safety and effectiveness of a device during its review of marketing applications, the agency does not weigh the broader ethical and social impacts of making the device commercially available.[106] Thus, for example, an application to market a silicon breast implant device for cosmetic use raises many ethical and social issues: for example, is it ethical to commercialize products that may psychologically harm women through unhealthy fixation on body image and is it socially useful to devote scarce healthcare resources to installation of products that have a documented but as-yet-poorly-explained association with subsequent suicidality of the recipients, as breast implants seem to do?[107] The ethical issues posed by FDA-regulated devices are real, yet FDA has neither a legal mandate nor the appropriate staffing to examine those issues when assessing the safety and effectiveness of a device. A clinical study of the emotional impact of physicians' communication of genetic information to symptomatic and asymptomatic patients is not a study to "determine the safety and effectiveness of a device," because it is not designed to generate analytical and

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103 *See, e.g.*, SACGT, *supra* note 1.

104 *Id*. at ix.

105 *Id*. at xi.

106 *See* Gary Marchant, Ann Meyer & Megan Scanlon, *Integrating Social and Ethical Concerns Into Regulatory Decision-Making for Emerging Technologies*, 11 MINN. J. J. SCI. & TECH. 345, 346 (2010) (noting that legal and practical concerns frequently prevent agencies from considering ethical and social issues when making regulatory decisions that raise such concerns).

107 *See* American Association of Suicidology, Suicide and Breast Augmentation (summarizing and providing a bibliography of 17 peer-reviewed articles examining the association between breast augmentation and subsequent increased rates of suicide among patients) (copy on file with author).

clinical validity data, on which FDA bases its determinations that IVDs are safe and effective. Such a study is better characterized as a study to advance medical knowledge.

Based on these considerations, the researchers would have grounds to engage in a dialogue with FDA, if the agency asserts authority to regulate the research under Part 812.

4. NIH-funded genomic research is not the type of sponsor-investigator study that requires heightened FDA scrutiny

It has been suggested that, in sponsor-investigator studies, FDA can regulate a broader range of studies than it ordinarily regulates.[108] Specifically, FDA's training materials suggest that the agency can require IDEs for sponsor-investigator studies that pursue broad scientific aims, "even if no marketing application is planned."[109] FDA has displayed a concerning tendency to assume that studies at academic medical centers are sponsor-investigator studies.[110] This potentially places academic researchers under expansive regulation by FDA. This section explores issues motivating FDA's expanded regulation of sponsor-investigator studies and questions whether these concerns are valid in the case of NIH-funded genomic research.

The roles of sponsors, investigators, and sponsor-investigators in FDA regulation. Part 812 defines "sponsors" and "investigators" and assigns specific legal duties to each. A "sponsor-investigator" has the attributes of both and must carry out both sets of duties. In these definitions, the word "person" refers means a legal person and could include corporations or institutions as well as individuals[111]:

> *Sponsor* means a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual [i.e., a company or institution] that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.[112]

Sponsors have a long list of legal responsibilities set out in Subparts C and G of Part 812. These include such things as selecting qualified investigators and ensuring that IRB review and approval are obtained,[113] labeling the device to reflect its investigational status,[114] controlling shipments and disposition of the device to make sure it only is used for the specific research purposes FDA has authorized; and monitoring the research, keeping records, and making reports to FDA.[115] In the world of FDA-regulated research, the typical sponsor would be a commercial

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[108] *See supra* notes 50-53 and accompanying text..

[109] Henley, *supra* note 26, at sl. 12.

[110] *See, e.g., Lepay: FDA to take closer look at investigator-initiated trial*, *supra* note 55 (reporting that "Part of the problem, he said, is that many academic investigators, who use FDA-regulated products in their studies, "don't understand that they can become sponsors of those studies and what that means in terms of responsibility.")

[111] 21 C.F.R. § 812.3(l).

[112] 21 CFR § 812.3(n).

[113] *Id*. §§ 812.40-.43.

[114] *Id*. § 809.10(c) and § 812.2(c)(3) (requiring sponsors to ensure appropriate labeling as a condition of the exemption for diagnostic devices).

[115] *Id.* §§ 812.140(b), 812.150(b).

device manufacturer or a device inventor that wishes to apply for an FDA clearance or approval to market its device and, toward that end, is funding or arranging clinical investigations to generate data to support its marketing application.

> *Investigator* means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.[116]

Investigators' duties are outlined in Subparts E and G of Part 812 and include such things as conducting the research and protecting the rights, safety, and welfare of subjects under the investigator's care,[117] maintaining control of the investigational device and using it only as FDA has authorized,[118] making financial disclosures,[119] and keeping records and making various reports to the sponsor.[120] Typical investigators in FDA-regulated research include researchers employed by device companies as well as academic investigators with whom such companies enter research contracts.

> *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor.[121]

The prototype of a sponsor-investigator might be a college professor or other individual who has invented a promising device concept and wishes to commercialize it, but who remains closely involved in the actual conduct of the clinical investigations. FDA's guidances on INDs (for drugs) and IDEs (for devices) tend to portray the sponsor-investigator as an academic[122] who works alone on an "*individual* investigator-initiated study"[123] at "a single site."[124] This individual inventor may, for example, have formed a start-up company that will sponsor the research and

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116 *Id*. § 812.3(i).
117 *Id*. § 812.100.
118 *Id*. § 812.100-.110.
119 *Id*. § 812.110(d).
120 Id. §§ 812.140(a), 812.150(a).
121 *Id*. § 812.3(o).
122 See, e.g., Food & Drug Admin., Center for Drug Eval. & Research, Center for Biologics Eval. & Research, Draft Guidance for Industry: Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can be Conducted Without an IND 1 note 2 (Oct. 2010), 2010 WL 4568473 (F.D.A.) ("The term sponsor-investigator typically refers to an individual at an academic institution.").
123 Food & Drug Admin., Off. of Good Clinical Practice, Center for Drug Eval. & Research, Center for Biologics Eval. & Research, Center for Devices and Radiological Health, Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed 5 (Aug. 2013), 2012 WL 6561315 (F.D.A.) [emphasis added].
124 Food & Drug Admin, *supra* note 123.

the subsequent FDA marketing application, but the individual holds significant shares in that company and thus is wearing the hat of sponsor as well as investigator. In such settings, it is easy to appreciate FDA's concern that the sponsor-investigator's conflicting roles and commercial interests may erode human-subject protections.

How applicable are these concepts to NIH-funded genomic research? Part 812 is not well-tailored to the realities of modern academic genomic research. This is perhaps understandable, because it was not designed for broad regulation of "investigations to expand medical knowledge or conduct fundamental research"[125]—which describes a sizeable portion of academic research in the field of genomics. Instead, it was designed primarily to regulate commercially motivated investigations of the safety and effectiveness of specific devices.

Part 812 presumes a commercial medical device industry environment—and a 1980s-era one at that—where there is a unified entity (the sponsor) that performs an entire group of functions that Part 812 frames as responsibilities of the sponsor. In contrast, modern genomic research tends to involve multiple parties that play roles that imbue them with various attributes of a "sponsor," as this term is defined in FDA's regulations. Because these roles are partitioned among a cast of several entities, there may be no one of them that fulfills the entire set of responsibilities that Part 812 associates with "the sponsor."

This problem is is especially apparent in the context of large, carefully coordinated, multi-site genomic research programs that academic medical centers carry out with extramural funding from the NIH. It is debatable who the sponsor is in an NIH-funded study that uses an NGS platform that is commercially available either as an LDT or as an FDA-cleared 510(k) device.

- The NIH carries out some of the duties that Part 812 associates with the role of sponsor, such as initiating the research program by calling for proposals, ensuring the selection of qualified investigators, approving the specific research protocols, and ensuring compliance with informed consent and IRB review requirements (albeit under the Common Rule rather than under FDA's corresponding regulations at 21 C.F.R. Parts 50 and 56).
- Other sponsor-like roles, such as labeling the device and shipping it to the investigators, seemingly belong to the manufacturers and suppliers of any commercially available NGS analyzers, software, or analytical services that investigators purchase for use in their research. These commercial suppliers own intellectual property in the products they supply and seemingly would be the legally correct entities to sponsor an FDA marketing application, such as a 510(k) submission, if one were needed. These commercial suppliers—rather than the investigators—arguably bear responsibility under Part 812 to obtain an IDE if one is needed for an investigational use of the products and services they ship and supply. It is they, rather than the investigators, who may be motivated to engage in promotion of their device and who would be the proper focus of FDA's efforts to curtail inappropriate promotion of unapproved devices.
- On the other hand, a study protocol may call for investigators to develop their own devices and/or algorithms to use either alone or in conjunction with commercially available products and services. If this is the case, then investigators may well be in the role of sponsor-investigator with respect to any devices or algorithms that they themselves develop—but only with respect to those specific items.

[125] 45 Fed. Reg. at 3735.

FDA, for its own convenience, may prefer to treat academic investigators as "sponsor-investigators" because this gives the agency a single point of contact for addressing all the issues that Part 812 treats as responsibilities of the sponsor and of the investigator. Yet academic investigators may be poorly positioned to discharge some of the responsibilities that sponsors are assigned under Part 812—for example, can they control the labeling of a commercially-supplied analyzer shipped to them by another party?

FDA's concern about weak human-subject protections in sponsor-investigator studies is understandable in the prototypical sponsor-investigator academic study where a commercially motivated professor/inventor aspires to become a commercial device entrepreneur. This concern seems less valid, however, in academic medical investigations funded by the NIH. It is worth remembering that FDA's own Part 50 and 56 regulations were largely modeled on the framework of human-subject protections NIH pioneered for its own use starting in the early 1960s. It would violate comity among the various HHS sub-agencies for FDA's Bioresearch Monitoring Program (BIMO), which oversees human-subject protections in FDA-regulated research, to second-guess determinations by NIH that the research NIH is funding is sufficiently ethical—as determined by an IRB acting under the Common Rule—to move forward. NIH and OHRP have a long history with ethical oversight of human-subjects research in general and of genomics research in particular. It seems unsound for FDA to equate NIH-sponsored genomic research programs with the fly-by-night sponsor-investigator studies that originally gave rise to FDA's concerns about sponsor-investigator studies.[126]

The notion that FDA has an expanded authority to regulate sponsor-investigator studies appears to have no clear legal basis. FDA's regulations state that a sponsor-investigator has the duties of *both* the sponsor and investigator.[127] That means that a sponsor-investigator is required to obtain an IDE in situations where a sponsor would be required to obtain one. Yet FDA officials at times have suggested that sponsor-investigators must obtain IDEs for studies that would not require an IDE if carried out with a separate sponsor and investigator—in other words, studies where "no marketing application is planned."[128] If true, that would amount to imposing a duty on sponsor-investigators that is *incremental* to the duties of a sponsor—a notion directly at odds with the text of Part 812.[129] Imposing an incremental duty of this sort would, in effect, amend Part 812 without notice-and-comment rulemaking procedures, violating FDA's own administrative procedures[130] as well as the Administrative Procedure Act.[131] If FDA wishes to impose an incremental duty for sponsor-investigators to obtain IDEs in situations where sponsors are not required to do so, this will require rulemaking and cannot be accomplished through guidance or informal statements by agency officials. Alternatively, FDA should explain where, in its regulations, it is basing its putative authority to subject sponsor-investigators to incremental IDE requirements.

A 2010 FDA guidance on INDs for drugs portrays the law in a way that seems more accurate, and the concepts it expresses also seem relevant to IDEs. The 2010 guidance stops short of asserting that FDA can *require* INDs for sponsor-investigator studies that are not

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126 *See supra* notes 53-55 and accompanying text.
127 21 C.F.R. § 812.3(o).
128 Henley, *supra* note 26, at sl. 12.
129 21 C.F.R. § 812.3(o).
130 21 C.F.R. pt. 10.
131 5 USCA §§ 551 - 559, 701 - 706, 1305, 3105, 3344, 4301, 5335, 5372, 7521.

intended to support a drug marketing application or labeling change. Instead, the guidance merely states that "FDA *strongly encourages*" INDs in this situation.[132] The guidance points out that it is not always clear at the outset whether study results will be used to support a marketing application or labeling change, but notes that when the study is sponsored by a drug manufacturer, it seems reasonable for FDA to infer such intent.[133] Thus, an IND would be required in that situation. The guidance then admits that "the sponsor-investigator of an investigator-initiated study in an academic setting (a study designed and initiated by the investigator independent of the manufacturer) probably does not intend that his or her study of a marketed drug influence labeling or promotion, even if the sponsor-investigator is receiving some limited support from the drug's manufacturer."[134] The agency bases its recommendation to obtain an IND on the fact that "certain investigator-initiated research *has the potential*"[135] to influence FDA's decisions about product safety and effectiveness, even if the study was not intended to do so. It concludes:

> "Similarly, certain studies of effectiveness conducted by government agencies (e.g., National Institutes of Health, Veterans Administration) have the potential to influence labeling. FDA strongly encourages IND submissions for these types of studies so that the Agency can have an opportunity to provide advice on study design."[136]

The use of the phrase "strongly encourages" suggests that the submissions may be desirable but not mandatory. FDA presumably would benefit if all scientific studies—even those not intended for submission to FDA—were done in a way that makes it possible for FDA to utilize the findings as part of the agency's evidence base for regulatory decision-making. For this to happen, however, the studies would need to obtain INDs or IDEs and be designed so that their results will satisfy FDA's rigorous evidentiary standards.

Congress has not granted FDA the power to require all scientific research in the nation to be done according to the agency's own specifications.[137] Congress once again made this clear in in July 2012 when enacting Section 601 of the Food and Drug Administration Safety and Innovation Act (FDASIA).[138] Section 601 amended the IDE provisions at § 520(g)(4)(C)[139] of the FFDCA to make it clear that FDA cannot disapprove an IDE application merely because the study in question will not produce evidence that would be of use to FDA.[140] The power to disapprove an IDE amounts to a power to prevent certain types of research with devices from going forward. The amendment to § 520(g)(4)(C) negates the potential for FDA to hold

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132 Food & Drug Admin., *supra* note 123, at 6 [emphasis added].
133 *Id.*
134 *Id*.
135 *Id.*
136 *Id.*
137 *See supra* notes 24-25 and accompanying text.
138 Public Law 112-144, 126 Stat 993 (July 9, 2012).
139 21 U.S.C. § 360j(g)(4)(C),
140 *See id*. (stating that the Secretary shall not disapprove an IDE application based on a determination that "(i) the investigation may not support a substantial equivalence or de novo classification determination or approval of the device; (ii) the investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device; or (iii) an additional or different investigation may be necessary to support clearance or approval of the device.").

researchers hostage by preventing them from using a needed device in their research unless they agree to design their studies to FDA's specifications. Section 601 displays Congress's determination to avoid abuses of FDA's power to regulate scientific research.

5. Rationalizing the regulatory framework for NIH-funded genomic research

FDA's concept of a sponsor-investigator study is not well-tailored to large, multisite genomic research programs funded by responsible entities like the NIH. NIH, its funded investigators, and FDA should work together to devise a better solution that is tailored to the realities of modern genomic research.

NIH-funded investigators are not well-positioned to fulfill all of the responsibilities that Part 812 assigns to sponsors. Some of these responsibilities correspond to functions that NIH is already fulfilling—such as initiating studies, selecting investigators, ensuring IRB review. There are, however, some important differences in the functions that IRBs perform under the Common Rule and under FDA's human-subject protection framework. NIH could easily adopt a policy to ensure that the ethical oversight of genomic research it funds meets both the Common Rule and FDA human-subject protection requirements. In return, FDA could use its enforcement discretion to defer to NIH's ethical oversight of NIH-funded research.

Some of a sponsor's responsibilities differ from roles NIH currently performs. A few of these, such as labeling investigational devices, may best be placed on device manufacturers that supply gene sequencing products and services to researchers. Other responsibilities, such as fulfilling the sponsor's reporting obligations to FDA, may exhibit economies of scale that would recommend centralizing them at NIH rather than decentralizing them to individual research sites. FDA's regulations are designed for a commercial research environment where it is assumed that scientists are well supported by a staff of attorneys and regulatory affairs personnel experienced in FDA regulatory matters. Academic investigators generally lack these same resources. NIH may be in the best position to arrange the needed administrative and legal support structures. For example, one of the functions sponsors must perform is to make the initial determination of whether an IDE is required, which in turn requires an assessment of whether the research meets FDA's definitions of "significant risk," "non-significant risk," or "exempt" research.[141] The sponsor presents its initial determination to the IRB, which must itself review the determination if the sponsor has concluded that the research poses non-significant risk.[142] Individual academic institutions may not have FDA-savvy legal staff to guide their IRBs in these decisions, and they may not have a sufficient volume of FDA-regulated research to justify hiring such staff. Centralizing support for these determinations at NIH may make sense, insofar as NIH would have a sufficient volume of IDE-related questions on a program-wide basis to justify staffing a small office to help guide local IRBs through IDE-related decisions. Alternatively, NIH could fund a regulatory support component in its genome research programs as it did in its Clinical and Translational Science Awards.

NIH also may be in a better position than investigators to communicate emerging information about the clinical significance of gene variants. As noted earlier, characterizing investigators as sponsors subjects them to FDA's restrictions on promotion, which can have very serious legal consequences if violated. NIH, on the other hand, has traditionally enjoyed a relationship of trust with FDA, as once noted in an FDA official's testimony before a Senate committee:

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[141] U.S. Food & Drug Admin., *supra* note 123, at 6.

[142] *Id.*

> Generally, FDA does not prohibit the dissemination of information to health care professionals. Physicians access information about off label uses through compendia, journal articles, continuing medical education programs, symposia, and professional meetings. Physicians also have access to a number of databases that provide information about off label uses. For example, the National Cancer Institute's Physician Data Query (PDQ) system is an excellent source for oncologists to obtain information about current oncologic therapies. The National Library of Medicine (NLM) offers a Medical Literature Analysis and Retrieval System (MEDLARS), which is a computerized system of databases and databanks pertinent to biomedical research and patient care. NLM currently offers free access to three databases relating to AIDS. FDA does not regulate a physician's access to any of these types of independent off label use information -- no matter how preliminary it may be. [143]

FDA's LDT draft guidances and NGS discussion paper are still works in progress, and many details remain unclear. It is conceivable that FDA may take the position that investigators' communications about suspected, but non-FDA-approved, associations between genotype and phenotype amount to promotion of an unapproved use of sequencing technology. If FDA should move in that unfortunate direction, NIH is better positioned to communicate emerging understandings about the clinical significance of gene variants to clinicians, without risking action by FDA for unlawful promotion. Flows of information between NIH-funded investigators and clinicians could be channeled as needed to mitigate these concerns.

The specifics of such arrangements are beyond the scope of this article. They would need to be worked out among NIH, its funded investigators and their institutions, and FDA. The process is straightforward, however. A logical place to begin would be to consult FDA's regulations and guidances to identify all the various responsibilities of sponsors and investigators that need to be performed and, for each, identify the parties best suited to perform the function (NIH, the funded institution, or another entity such as a device manufacturer or CLIA laboratory whose technology is being used in the research). After comparing the relative costs and efficiencies of performing these functions centrally vs. in a decentralized manner, NIH could enunciate policies to govern how they should be carried out in its genomic research programs. FDA could then issue guidance indicating that the agency will exercise its enforcement discretion with regard to NIH-funded genomic research, provided those policies are followed.

Conclusion

FDA, as a science-based regulatory agency, values good science and, in its role as a public health agency, is motivated to protect the public from bad or nonexistent science. FDA is rightly concerned that there is a potential for genomic researchers to make unfounded or irresponsible clinical claims about the human genome during the course of studying it. FDA's good motivations may, nonetheless, impede scientific progress in ways that ultimately harm the public, unless FDA carefully heeds the limitations of its power to regulate genomic research.

[143] Schultz, *supra* note 77.

FDA's dilemma evokes the contradictions of Diego de Landa, Bishop of Yucatan, a respected scholar whose 1566 treatise is still seen as "the source book on Maya culture."[144] On July 12, 1562,[145] Bishop de Landa ordered a pyre on the main square of the town of Maní that destroyed thousands of artifacts and scrolls constituting the Mayan Codex,[146] thus denying future generations the benefit of any knowledge that may have been contained therein and virtually eradicating the Maya written language. Bishop de Landa reportedly defended this action by testifying, "because they contained nothing that was free from superstition and the devil's trickery, we burnt them."[147] Apparently he believed speakers have the burden to prove the truth of their statements before they utter them. A short 200 years later, the framers of the U.S. Constitution placed the burden of proof elsewhere, requiring governmental authorities to prove that statements are untruthful or misleading before they can burn or otherwise suppress speech.

If FDA begins a quest to stamp out any clinical claims about the human genome that the agency has not previously found to be "free of superstition," the agency goes the way of Bishop de Landa and steers itself to an eventual collision with the First Amendment and with well-settled principles of federalism. Evolving knowledge is never free of superstition until after it evolves, and inquisitions to stamp out superstition can easily stamp out the process of research that moves knowledge beyond superstition. If FDA emulates Bishop de Landa, it is the duty of scientists to use all legal tools—including litigation in U.S. federal courts—to ensure that the agency's involvement with their activities is kept in its proper bounds.

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144 Eric Thompson, American Anthropologist, 40: 309b–310. doi: 10.1525/aa.1938.40.2. (reviewing Thompson, E. (1938), Yucatan Before and After the Conquest by Friar Diego de Landa: with Other Related Documents, Maps, and Illustrations. William Gates (tr.) (Baltimore: MayaSociety, 1937)), available at ttp://onlinelibrary.wiley.com/doi/10.1525/aa.1938.40.2.02a00180/pdf.

145 Anthony Padgen, Diego de Landa in Mexico, 25 History Today 480, 482, 485 (Jul. 1975).

146 *Id*. at 486. Nicoletta Maestri, Diego de Landa (1524-1579), Bishop and Inquisitor of Early Colonial Yucatan, at http://archaeology.about.com/od/mayaresearchers/ss/Diego-de-Landa_3.htm.

147 *Id*. *See also* Nicoletta Maestri, Diego de Landa (1524-1579), Bishop and Inquisitor of Early Colonial Yucatan, at http://archaeology.about.com/od/mayaresearchers/ss/Diego-de-Landa_3.htm.

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