Understanding FDA Regulation of DTC Genetic Tests within the Context of Administrative Law

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How the FDA should regulate direct-to-consumer genetic tests is fiercely contested. Passing a rule or issuing an order is only one down in the series. There is more to the regulatory game.

Introduction

The direct-to-consumer (DTC) genetic testing industry is under considerable scrutiny by federal agencies and by Congress[1–3] and has been the subject of scholars' calls for new or increased federal regulations.[4–9] In March of this year the National Institutes of Health, NIH, launched a new voluntary registry of genetic tests to help mitigate the industry's transparency problems.[10] In April the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) made recommendations to close gaps in regulatory oversight of DTC genetic tests.[11] In July the Food and Drug Administration (FDA) held public hearings to discuss its proposed broad regulation of all laboratory-developed tests (LDTs),[1] congressional subcommittees considered the topic,[3] and the Government Accountability Office (GAO) announced the results from its latest undercover investigation of the DTC genetic-testing industry.[12]

The decisions made in Washington, D.C. are bound to have tremendous repercussions on the personal-genomics industry's practices and viability and may have considerable impacts on academic genetics and genomics research as well. Geneticists in the industry and in academia might be unaware of how this regulatory game will play out—specifically, they might be unaware of what happens *after* a rule or order is issued by an agency such as the FDA. The purpose of this commentary is to provide a brief introduction to the "rules of the game" for those unfamiliar with the relevant legalese. Understanding the implications of expanding federal oversight of DTC genetic tests and debating the appropriate scope and means to ensure consumer (and human research participant) protection requires everyone—legislators, bioethicists, geneticists, and others—to be on a level playing field. Here, I provide a primer on administrative law, first by explaining the source of federal agencies' authority and then by discussing the procedure under which agency decisions are challenged and scrutinized. Subsequently, I explore the FDA and its proposed regulation of genetic tests within the context of administrative law.

Administrative Agencies and Their Sources of Power

The U.S. Constitution separates powers into three governmental branches: Article I gives rulemaking powers to the legislative branch, Article II gives enforcement powers to the executive branch, and Article III gives adjudicatory powers to the judicial branch. The U.S. Constitution specifically delegates all rulemaking power to Congress[13] and authorizes Congress to do all that is "necessary and proper"[14] to carry out that rulemaking power. Drawing from these constitutional powers, Congress creates federal administrative agencies (which typically are part of the executive branch) to handle particular statutory schemes. Administrative agencies cannot act without authorization from Congress; when an agency exceeds its authorization, it is said to be acting "ultra vires." In addition to rulemaking powers, Congress also has the limited ability to delegate adjudicatory powers to agencies;[15] these forums are referred to as "non-Article III courts" because they are not within the judicial branch. To ensure Congress is respecting the separation of powers established by the Constitution and not usurping the role of the judicial branch, courts require Congress to pass a four-prong test when it delegates adjudicatory powers (the test considers Congress's motivations for giving the agency adjudicatory powers, the origin and significance of the rights to be decided by the agency, whether the agency is given specific, limited directions as to the scope of its authority, and whether judicial review is available such that the agency's "adjudication" can be seen as a temporary decision upon which courts can later rely).[16]

When an agency acts to fulfill the substantive duties delegated to it by Congress, it must comply not only with procedural requirements set forth by the Constitution's due process clause but also with the Administrative Procedure Act (APA), the outside statute that specifically applies to the situation, and the established requirements of the particular agency. If the agency is making a prospective decision based on generalized or statistical facts and the decision affects a large number of people, the agency is engaged in rulemaking.[17] On the other hand, if the agency is making a retrospective

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DOI 10.1016/j.ajhg.2010.09.003.

decision based on particular, individualized facts and the decision affects one person, the agency is engaged in adjudication.[18] Under the APA this distinction essentially hinges on whether the agency is issuing a "rule" or an "order."[19] Whether the agency is setting public policy through rulemaking or adjudicatory decisions is significant because it determines the procedural requirements that are applicable. From a practical standpoint, setting policy through rulemaking might be preferable when the agency is prepared to establish a comprehensive strategy, whereas setting policy through adjudications might be preferable when the agency needs to take a more incremental approach to a rapidly changing or nuanced problem.[20]

Generally, when an agency is engaged in rulemaking, there are no procedural requirements under the due process clause of the U.S. Constitution.[17] Although the APA requires only a notice and comment period for informal rulemaking ,[21] more stringent measures are imposed for formal rulemaking.[22] On the other hand, when an agency is engaged in adjudications, the due process clause requires notice and an opportunity to be heard.[18] When the agency's adjudication is formal, the applicable APA requirements are even more demanding.[23] The requirements of the APA are the default for agency action and will apply unless Congress, in an outside statute, specifically expresses a deviation from these procedures.[24]

Challenging Agency Decisions

Agency actions may be challenged on a number of fronts, beginning with a challenge to the actual delegation of power by Congress. The nondelegation doctrine is the concept that although Congress can delegate certain tasks to administrative agencies with specialties required to handle particular problems, Congress cannot constitutionally usurp the adjudicatory powers of the judicial branch by giving those powers to agencies and, moreover, cannot shirk its rulemaking duties by transferring them to agencies. Accordingly, when Congress delegates its authority to an agency, it must provide "intelligible principles" that guide an agency in the agency's exercise of discretion.[25] "[T]he degree of agency discretion that is acceptable varies according to the scope of the power congressionally conferred."[26] Although the nondelegation doctrine serves important purposes (for example, ensuring that important policy decisions are made by the legislature, which has broad expertise and the ability to balance and prioritize diverse, competing policy interests and whose members are elected by and therefore directly accountable to the people), challenges to Congressional delegation of powers have generally been unsuccessful (although there are exceptions[27,28]) so long as Congress limits the agency's discretion in a sufficient manner. However, if Congress has unconstitutionally delegated too much authority, the agency's actions—regardless of the agency's efforts or rationale—will not withstand judicial scrutiny.

Section 702 of the APA provides an individual disagreeing with an agency's action with a right to judicial review,[29] as long as the individual has exhausted all available remedies within the agency. In other words, the agency's action must be final or the matter is not ripe for judicial review.[26] When a court reviews an agency's decision, the court cannot substitute its own opinion as to what action should have been taken. Rather, a court reviewing an agency's actions will set aside the agency's determination if the court finds the agency's decision to have been "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law."[30–32] These are legal terms of art and provide distinct grounds for challenging an agency's decision. When the court reviews the agency's decision, the court "must consider whether the [agency's] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment. At a minimum, the agency must have considered relevant data and articulated an explanation establishing a 'rational connection between the facts found and the choice made.'"[33]

To determine whether an agency's action was "not in accordance with law," the court will first investigate whether Congress has directly addressed the precise question at issue. If Congress has spoken on the issue, the agency must follow that congressional intent. If, however, Congress has not spoken on the issue (i.e., if the statute is ambiguous or silent), the agency has the first opportunity to interpret the statute's meaning, and courts will generally defer to the agency's interpretation so long as it is reasonable.[32,34,35]

To determine whether an agency's action was "arbitrary, capricious, or an abuse of discretion," the court will take a "hard look" at the agency's actions and investigate whether the agency relied on factors Congress had not intended, failed to consider an "important aspect" of the problem, provided an explanation that is contrary to the evidence, or provided an explanation that is so implausible that it cannot be given deference as agency-specific expertise.[31]

Case Study: FDA's Regulation of DTC Genetic Tests

Within the context of this administrative law, we can now consider the FDA's regulation of DTC genetic tests. Anticipating how the FDA's decisions will probably be challenged will assist us in the promulgation of effective, well-reasoned regulations and in minimizing unintended and costly consequences. Legal advocates for geneticists will be more effective if their clients understand the context within which regulatory actions are challenged.

The Food and Drug Administration (FDA) traces its roots to the passage of the Food, Drug, and Cosmetic Act of 1938 (FDCA).[36–39] The FDCA has been amended on countless occasions,[40] including—perhaps most notably for present purposes of regulating genetic tests—the Medical Device Amendments of 1976 (MDA).[41] The

Table 1. Targets of FDA Letters Concerning Genetic Tests

June 10, 2010 Letters	July 19, 2010 Letters
23andMe, Inc.; Personal Genome Service	Graceful Earth Inc.; Graceful Earth Alzheimer's Test
Pathway Genomics Corporation; Genetic Health Report	SeqWright DNA Technology Services, Inc.; Genomic Profiling Service
deCODE Genetics; deCODEme Complete Scan	Interleukin Genetics, Inc.; Inerent Health
Navigenics; Navigenics Health Compass	DNATraits; Ashkenazi Jews Genetic Disease Panel
Illumina, Inc.; Illumina Infinium HumanHap550 Array	CyGene Direct; Metabolic Health Assessment DNA Analysis Test
Knowme, Inc.; KnowmeCOMPLETE	Consumer Genetics, LLC; AsthmaGEN DNA Test
	Matrix Genomics, Inc.; Matrix Genomics Breast Cancer Panel
	The Genetic Testing Laboratories, Inc.; The Genetic Testing Laboratories DNA Predisposition Test
	Sequenom, Inc.; SEQureDx
	EnteroLab Reference Laboratory; Gene Test for Gluten Sensitivity/Celiac Sprue
	BioMarker Pharmaceuticals, Inc.; Gene Essence
	DNA Dimensions; Predisposition DNA Test
	HealthCheckUSA; HealthCheckUSA Celiac Disease DNA Test
	easyDNA; Genetic Predisposition Health Test

FDCA and the MDA together "are intended to regulate medical devices to allow the public to receive the benefits that medical research and experimentation provide while at the same time protecting the public from increasingly complex devices which pose serious risks if inadequately tested or improperly designed or used."[42] When the FDA engages in policymaking—whether through rulemaking or adjudications—it must act within its constitutional scope, pursuant to the statutory scheme Congress used to establish the agency's delegated authority (notably that of the FDCA and MDA) and pursuant to the procedural requirements of the APA.[43] On previous occasions when FDA actions have been reviewed by courts, the courts have noted that an "agency's reading of its own rule is entitled to substantial deference"[44] and have found the broad deference (often referred to by attorneys as "Chevron deference") to be appropriate.[45] It is clear that the MDA preempts state consumer-protection laws that are "different from, or in addition to, any requirement" of the federal law.[44,46] Moreover, when the FDA deviates from its own "settled course of behavior," it must "supply a reasoned analysis for the change."[47]

Congress has charged the FDA with the important task of ensuring that products marketed to the public are both safe and effective, giving the FDA considerable authority to regulate genetic tests. However, the FDA has not comprehensively exercised its authority to do so. In the past, distinctions have been made between test kits, laboratory developed tests (LDTs), and a subset of complex LDTs known as multivariate index assays (IVDMIAs).[48] A comprehensive historical review of the FDA's past approaches to regulating genetic tests is outside the scope of this commentary but is available elsewhere.[49,50] In 2006 the FDA sought to exercise its authority to regulate IVDMIAs,[51] but the FDA did not issue a final rule articulating its policy.[52–54] More recently, the FDA decided to broaden is regulatory strategy to include all LDTs and requested comments on this plan; these administrative actions can be characterized as rulemaking.[55–57] In June 2010, the FDA issued letters to a handful of recipients and thus undertook administrative actions that can be characterized as informal adjudications (Table 1). In those letters, the FDA indicated it interpreted the genomic tests as falling under the statutory definition of "medical devices" pursuant to FDCA §201(h). The FDA explained during public hearings held in July[58] that a "genetic test is only subject to FDA oversight if it is a medical device; that is, if it is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease."[59] That the FDA takes this position is no surprise, given the constitutional limits to the FDA's authority under the MDA. But what about the genetic and genomic tests not intended for such health-related purposes (e.g., what about DNA ancestry, paternity, or identification tests)? What about tests with multiple intended uses? Who defines the intended use—the consumer, manufacturer, retailer, or FDA officials? The §510k review process for premarket approval (PMA) has been described as a "rigorous" one that has been known to involve 1200 hr of review per application,[44] although it is unclear whether this description is a fair representation. It will be challenging, indeed, for the FDA to achieve its stated goals of ensuring public safety without simultaneously stifling scientific and medical innovation,[57] and there seems to be no consensus as to how the FDA should proceed.[60–63]

Table 2. Risk-Based Approach to FDA Regulation of Medical Devices[70,71]

Classes of "Medical Devices"	Definition	Risk Category	General Requirements
Class I	"Devices for which the general controls of the Act are sufficient to provide reasonable assurance of their safety and effectiveness. They typically present minimal potential for harm to the user and the person being tested…."	Low	General controls, e.g., registration and listing, labeling, adverse reporting, and good manufacturing practices
Class II	"Devices for which general controls alone are insufficient to provide reasonable assurance of their safety and effectiveness and for which establishment of special controls can provide such assurances…"	Moderate	General and special controls, e.g., registration and listing, labeling, adverse reporting, and good manufacturing practices as well as premarket notification, special labeling, mandatory performance standards, risk-mitigation measures, and postmarket monitoring
Class III	"Devices for which insufficient information exists to provide reasonable assurance of safety and effectiveness through general or special controls. Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury…"	High	General controls and premarket approval

Device classification depends on "intended use" and "indications for use."

Some scholars have called the FDA's medical-device PMA program ineffective and have identified at least eight serious flaws.[64] The FDA regulates medical devices by using a risk-based approach and three-tiered classification scheme, as summarized in Table 2. The risk-based classification of medical devices has been described as having the potential to be "somewhat arbitrary."[65] Determining just how to categorize tests and their associated risks has been problematic, even when experts consider the issue.[66] Although the criterion for categorizing genetic tests within this framework has not yet been fully articulated, the FDA has hinted that direct-to-consumer marketing and sales "can increase the risk of a test."[59] Is this suggestion in accordance with the evidence presently available? Perhaps for some tests it is, although it is both naive and misleading to conceptualize all genetic tests as being "medical" or health related, regardless of their potential psychosocial effects. DTC genetic tests are diverse and include raw sequencing or genotyping services with no interpretation; limited "recreational" information on biogeographical ancestry; normal trait prediction; and disease-risk estimation. A nuanced approach to risk-based classifications will be necessary because no two genetic tests—even if they are the same type—are exactly alike. When the FDA classifies each genetic test, that adjudicatory action is subject to challenge as being "arbitrary and capricious." The FDA must devise a deliberate, well-reasoned basis for its risk classifications. The FDA recently hinted at revising this three-tiered scheme by splitting Class II medical devices into two subcategories[67]—in essence, creating a four-tiered system with a new category situated between Class II and Class III. If the FDA sets a new scheme of Class II(a) and Class II(b) medical devices, the rulemaking action is open to challenge as being "not in accordance with law." Because Congress is neither silent nor ambiguous on the issue, the proposed subclassification might reasonably be interpreted as being outside the FDA's constitutionally delegated authority (that is, ultra vires and unconstitutional) and contrary to statutory requirements. Moreover, although reliance on recent recommendations made by SACGHS[11] and provision of multiple public hearings for comments may help the FDA overcome any challenges that it has made arbitrary and capricious decisions, such reliance would not overcome challenges that the FDA has acted outside the constitutional boundaries of its authority.

Although the FDA has contemplated broad regulation of genetic tests since as early as 2001,[49] the agency is obligated to justify its proposed deviation from its long-standing policies disregarding (or, to some, neglecting) genetic tests. This justification should not be difficult in light of the rapid advances since the completion of the Human Genome Project and the growing numbers of genetic tests available. But how will all of the existing rules applied to medical devices be applied to genetic tests? This is far from clear and is a laborious task that will require flexibility to accommodate future genetic and genomic innovations. Many questions, including how the grandfathering provision might be applied (i.e., will some genetic tests, such as pre- and neo-natal screening tests,[61] be exempt or excluded from the pre-marketing approval process and, if so, how or why?) and how the regulatory framework might accommodate modifications of the genetic tests after pre-marketing approval, must be addressed. Both industry and academic geneticists could be affected by these decisions. The FDA and interested parties must make certain that policies are

Table 3. Critical Questions for Agencies Contemplating Federal Regulation of DTC Genetic Tests

1.	Has Congress addressed the specific issue? If so, is the agency acting in accordance with that congressional intent? If not, is the agency interpreting the statute reasonably?
2.	Has Congress provided sufficient "intelligible principles" by which the agency can discharge its regulatory duties? In other words, is the statutory scheme under which the agency is acting a lawful delegation of congressional power?
3.	Is the agency considering only those factors that were intended by Congress when Congress enacted the statutes delegating regulatory authority to the agency? In other words, is the agency acting squarely within the mission with which it has been charged by Congress?
4.	Is the agency omitting or neglecting an important aspect of the problem during its deliberations and policymaking?
5.	Are the agency's explanations of its policies in line with the evidence or is some aspect of the explanation contrary to the evidence?

articulated and implemented only after careful consideration of the diversity of genetic tests available already, acknowledgment of the rapidly evolving genomic technologies, and recognition of existing legal protections available to the public through the oversight of other federal agencies, state-specific statutory and common-law contract, and tort remedies, as well as after recognition that FDA action to regulate all genetic tests as medical devices will probably destroy these remedies through federal preemption (Table 3).

Conclusion

It is important for all of us to be engaged in the debate over the appropriate means to regulate genetic tests, but we must recognize that passing a rule, regulation, or bill is merely one down in the series. There is more to the regulatory game. Once the final rules are announced and/or individual orders are issued, the agency's actions will be scrutinized and challenged, blogged and tweeted. The federal regulatory oversight of DTC genetic testing[68]—whether by the FDA in its authority to enforce the FDCA and MDA;, the Center for Medicaid and Medicare Services (CMS) in its authority to enforce the Clinical Laboratories Improvement Amendments of 1988, the Federal Trade Commission (FTC) in its authority to protect consumers from unfair and deceptive trade practices, or perhaps a new agency if Congress deems it appropriate[69]—will be challenged and reviewed within the context of administrative law. As such, the policies articulated through rulemaking and adjudications will be handled distinctly, and the game will be played according to the basic rules outlined here. All interested players (whether called stakeholders or lobbyists, patients or consumers, academic or industrial scientists, etc.) should be aware of the rules of the game before taking the field. Only then can teams be chosen, playbooks written, fans generated, and history made.

Acknowledgments

I would like to thank three anonymous reviewers and Anne Buchanan, Ken Weiss, Mark Shriver, and Charmaine Royal for providing thorough and thoughtful feedback on an earlier draft of this commentary. I owe gratitude to Law Professor Donald Hornstein for providing me with exceptional instruction in administrative law at the University of North Carolina.

Web Resources

The URLs for data presented herein are as follows:

NIH Genetic Testing Registry, http://www.ncbi.nlm.nih.gov/gtr/.

Copies of the FDA letters sent to recipients listed in Table 1, http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm111104.htm and http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm219582.htm.

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