Regulating Direct-to-Consumer Polygenic Risk Scores

Recently, polygenic risk scores (PGSs)—genome-wide measures of individuals’ genetic propensities—have come to consumers. PGSs are now directly available to individuals to assess type 2 diabetes risk, measure elite athletic endurance, and determine the likelihood of depression, among other traits, without a health care clinician serving as an intermediary. These PGSs are available to consumers both through typical direct-to-consumer (DTC) genetic tests, where the consumer provides a genetic sample to be sequenced and analyzed by a company or as pure software, where consumers upload their previously sequenced genetic data to be analyzed. Although the US Food and Drug Administration (FDA) actively regulates DTCs, many DTC-PGSs evade regulatory scrutiny as general wellness products or unregulated software over which the FDA declines to exercise enforcement. This is problematic because the potential harms from these tests are much the same harms as those posed by traditional DTCs (ie, DTC without PGS): harms to consumer health stemming from misunderstandings of the tests’ accuracy or utility. This new paradigm of software-based, wellness DTC-PGSs and their attendant regulatory difficulties counsels for better regulatory scrutiny of these products.

Although the FDA has authority to regulate medical devices, including in vitro devices such as genetic testing kits, the agency generally does not have the authority to directly regulate medical practice—sometimes a difficult line to draw. Since 1992, the FDA has drawn that boundary as nonetheless covering laboratory-developed genetic tests (LDTs)—tests conducted within a single laboratory—while it has historically declined to police it. This policy of enforcement discretion, however, has been in flux. In 2013, the FDA issued a warning letter to 23andMe, a DTC company, concerning its reporting of disease propensities to customers based on single-nucleotide variants (SNVs).1 Then, during the COVID-19 pandemic, Health and Human Services (HHS) Secretary Alex Azar nixed the FDA’s oversight of LDTs, a policy that was reversed shortly into the Biden administration by incoming HHS Secretary Xavier Becerra.2

As outlined in its 2013 warning letter to 23andMe and a follow-up Federal Register notice, the FDA’s concerns with SNV DTC were 3-fold: effectiveness, patient safety, and public health. In its warning letter, the FDA expressed concerns about the SNV tests’ analytic validity—specifically, how well the tests accurately reported sequencing data—and its clinical validity—the accuracy of the tests’ clinical conclusions based on that data. This, in turn, implicated consumer safety. Consumers were at risk of taking interventions—like adjusting drug dosages or refusing preventive screening—based on their test results. The easy availability of the tests also elicited the agency’s larger concern that health care clinicians would use such tests for diagnosis even though they were not validated for such purposes.

Today, PGSs are marketed to consumers and health care clinicians as improvements on traditional, single-gene SNV analyses. PGSs generally consist of the summation of risk scores of multiple, genome-wide, SNV risk variants for a particular condition. These can consist of a small handful of variants to hundreds of them. This summation is then calculated into a unitless risk score, often a measure of the total contribution of the variants to the observed phenotype. This includes, for example, using PGSs to assess consumers’ pharmacogenetic profiles for certain drugs, risk of developing certain types of cancer, and likelihood of some cardiac events.

Some of these clearly come within the FDA’s authority to regulate LDTs; it’s hard to legally distinguish a PGS for developing a form of cancer from a monogenic test used to measure the same. But two developments in the DTC-PGS space provide challenges to the FDA’s role in regulating them. First, some DTC-PGS marketers, sponsors, or retailers combine PGSs with other features of disease risk (diet, exercise, lifestyle factors) to market the scores along general wellness lines rather than for the purpose of diagnosing or preventing disease. For example, ADNTRo4 offers a personality report that includes a PGS that assesses among other behaviors a “genetic predisposition to alcohol consumption,” based on a 2019 study5 that measured alcohol dependence syndrome, a recognized medical condition. Such a claim—despite the risk score’s provenance—would likely evade the FDA’s scrutiny as a general wellness product, a low-risk device about “a general state of health that do[es] not make any reference to diseases or [medical] conditions.”6 Much as it did with typical DTCs prior to 2013, the FDA has declined to police PGSs both as a matter of enforcement policy and the agency’s interpretation of the statute governing purely software-based wellness products, which places these outside “devices” under FDA’s purview.

Second, some DTC-PGSs are now entirely software-based: consumers can upload their previously obtained genomic sequences—whether from a clinical laboratory or otherwise—to third-party services, which then provide several PGS reports. This includes not only ADNTRo but also Genome Link, Allelica, and Nucleus,

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among others. Although software can constitute a regulable medical device, the FDA generally limits its oversight of such products to software intended for a “medical purpose,” namely, the “diagnosis, prevention, monitoring, treatment or alleviation of disease.” In addition, in a separate guidance issued by the FDA, the agency has suggested that software that merely “matches patient-specific medical information to peer-reviewed literature publications on related topics” to a disease, is not a “device” that it will police. It is unclear—but likely—that this includes third-party DTC-PGS services.

As of this writing, the FDA has not asserted its regulatory authority over DTC-PGS, nor has it proposed new guidance for the agency or industry on DTC-PGSs. This state of affairs leaves DTC-PGSs largely unregulated in the US; there are few other agencies, if any, with the legal authority and competence to police DTC-PGSs. The lack of oversight poses harms to consumers because they are likely to misinterpret or mistrust PGSs in ways that are different—and potentially more harmful—from traditional DTC tests. The first harm is that a complex and, in some cases, middling correlational risk output from PGSs may be equated by consumers to a clinical diagnosis. This is, in many instances, not true because few PGSs have been validated for diagnostic purposes. Consumers are also unlikely to appreciate the nuance between PGS’ accuracy and their predictive value—that is, the PGS’ ability to predict future risk rather than merely describe the characteristics of the underlying population from which the PGSs were derived. Consumers are unlikely to understand that the PGSs may not be translatable from subpopulation to subpopulation; for example, a PGS based on individuals of British ancestry may not be informative for individuals with Japanese ancestry.

These acts of misinterpretation risk affecting consumers’ health care decision-making by, for example, using PGS as a substitute for consultation with a licensed health care professional. This is especially problematic in the US where insurance status is often a barrier to preventive care. One can easily imagine a scenario in which consumers may substitute a free, online PGS—if they already have their raw DNA—for better validated, more traditional diagnostics. This may include, for example, relying on 23andMe’s type 2 diabetes PGS risk report over a traditional hemoglobin A1C test from a physician.

In light of these potential harms, it may be useful to return to the FDA’s initial justifications in policing 23andMe a decade ago. As DTCs exploded in the 2010s, the FDA became increasingly concerned that consumers may make health decisions based on unvalidated genetic reports. The harms sought to be guarded against were, at their core, health harms to consumers based on misinterpretation or misuse. The potential harms from DTC-PGSs—despite their differences from traditional DTCs—are health harms just the same.

Accordingly, the FDA should police DTC-PGSs, including, possibly, considering new guidance on the issue. Rather than shoehorning DTC-PGSs into current guidance by, for example, narrowly focusing on whether a marketed PGS falls under a general wellness claim, the FDA can exercise its authority over the harms stemming from PGS misinterpretation and misuse. Where the harms associated with PGSs are similar to the harms a consumer would have experienced through misuse of a traditional DTC—over which FDA has sporadically exercised its authority—the FDA should police PGSs similarly. This requires no major revamping of the agency’s statutory authority or shift in policy. At the same time, the FDA must recognize that the HHS’ ever-shifting policy on LDTs could upend its efforts. As a better alternative, then, Congress should consider using the rise in DTC-PGSs as an opportunity to clarify, by statute, the FDA’s LDT authority over noninvasive, software-based products that pose health risks resulting from consumer misinterpretation or misuse. This would have the benefit of escaping the cycle of HHS statutory authority or shift in policy. The first time that a novel technology has challenged the FDA’s authority, and it will not likely be the last. But as genomic sequencing and interpretation complexities, improves, and becomes more akin to software than true laboratory-based tests, a nimble regulatory approach will be key to safeguarding the public health.

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REFERENCES