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Expanding Applications of Clinical Genetic Testing — Ethical Challenges

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You are the primary care provider (PCP) for a 30-year-old self-identified Black woman with a strong family history of coronary heart disease (CHD). She wants to better understand her own risks, and she saw an advertisement for a new Food and Drug Administration (FDA)–approved test that provides an individualized polygenic risk estimate for CHD. The test also provides pharmacogenomic results to guide the use of medications for hypertension and hyperlipidemia. The genetics professionals in your region have months-long waiting lists, and you're intrigued by the idea of a genetic test that could guide your use of medication to reduce CHD risk. Insurance does not cover this test, so your patient agrees to pay for it out of pocket. You order the test and several weeks later receive a report. Results indicate that your patient is at moderate genetic risk for CHD and that some of the medications you have prescribed for her might not be optimal for her, even though her insurance covers them. As you prepare for your appointment with this patient, you must decide how to explain the findings and what steps to take next.

Thanks to advances in human genomics, both technological and discovery-based, genetic and genomic testing (which we will refer to collectively as "genetic testing") are playing an increasingly important role in clinical care. Although genetic testing has long been recognized as raising thorny ethical dilemmas, the widening scope and scale of genetic tests are reshaping old concerns and posing new challenges. Moreover, the need to address these ethical challenges is no longer restricted to clinicians in particular niches, instead becoming immediately relevant for all clinicians.

Genetic tests now routinely inform time-sensitive treatment decisions. Simultaneously, testing is becoming more complex, with exome and genome testing being the norm and newer, aggregate risk estimators such as polygenic risk scores beginning to enter clinical use. Though no FDA-approved polygenic tests like the one in the hypothetical case above are yet available, they will be soon. Insurance coverage, on the other hand, will probably take much longer. The trained medical geneticists and genetic counselors who might help patients and clinicians navigate this confusing new landscape remain scarce. The burden of re-

sponsibly ordering, interpreting, and acting on genetic information will therefore increasingly fall to generalist practitioners.

In recent years, numerous specialties including oncology, endocrinology, and neurology have seen growth in the use of genetic testing, both to identify risks for inherited diseases and to inform the selection of relevant treatment methods or disease-surveillance strategies. Other fields are not far behind, with genetic testing increasingly being used in the prescribing of psychotropic, anticoagulant, and antiplatelet agents. Nearly 200,000 genetic tests, 90% of which are available for clinical use, have already been catalogued in the Genetic Testing Registry.[1] Newer genomic tests, resulting in polygenic risk scores, provide aggregate estimates of genetic risk based on the simultaneous evaluation of thousands of common susceptibility variants. These tests, just now coming into clinical use, can indicate where a person's degree of genetic risk falls within the population risk distribution and may help identify at-risk patients for diagnostic follow-up or surveillance; as with other genomic tests, a single blood sample can be used to estimate risks for numerous diseases. Exactly which risks are reported out is a function of both the specific order placed by the clinician (which determines which disease-linked variants and genes will be explicitly examined) and the policies and practices of the laboratory involved.

Whether such a test is ordered by a specialist who is not a geneticist to inform a patient's diagnosis or treatment (and generates other findings not related to their specialty) or is explicitly requested by an interested patient (as in the above case), a PCP will often have to help the patient understand its implications and findings. In some instances, this task may involve helping to weigh the pros and cons of undergoing testing when referral to genetic services is not an option. Though regulatory approval (e.g., from the FDA) and insurance authorization generally signal that a test is reliable and has demonstrated clinical utility, other potential sequelae should be addressed to ensure informed decision making.[2] For example, is the patient aware of the additional procedures or recommended medications that could follow from a positive finding? In the case of CHD-related risks, some combination of additional imaging, cardiac stress testing, and biomarker tests will probably be required for diagnosing specific conditions and informing prescribing and possible referral. What will be the implications for patients' out-of-pocket expenses, especially if they are asymptomatic?

Similarly, are patients comfortable with having information about a genetic predisposition in their health record? Although the Genetic Information Nondiscrimination Act protects against gene-based discrimination in employment or health insurance, it provides no equivalent protections for life or long-term care insurance (though evidence is scant that discrimination is occurring in these areas). Finally, do patients appreciate what their results might mean for biologic family members? Though a genetic test result is, in many respects, similar to a suggestive family health history, the identification of a specific pathogenic variant for monogenic disease (or, as in the case above, a pharmacogenomic drug response) makes all the patient's first-degree relatives candidates for related genetic testing. Because the Health Insurance Portability and Accountability Act imposes strict limitations on the sharing of patient data, informing family members of the need for such testing will usually fall to patients themselves. PCPs can, however, help patients understand the potential benefits of sharing these results with family. The significance for family members of a risk estimate based on a polygenic risk score is still being investigated, but it's likely to raise ethical and regulatory challenges similar to those raised by results of other genetic tests. Given the breadth of potential results that could be received, genetic-counseling research increasingly shows that pretest counseling need not address every possible downstream outcome, but it's important to alert the patient to the types of challenges that could arise. In primary care settings, doing so would still probably require an additional visit.

In addition to ordering and managing genetic tests without support from a genetic professional, PCPs will also increasingly find themselves responsible for managing results ordered by other non-genetics specialists. Tests required for time-sensitive specialty care, such as tumor sequencing to inform chemotherapy selection, are often ordered without traditional pretest genetic counseling. Yet many genetic tests used by specialists can uncover disease risks unrelated to the original reason for testing and outside the purview of the ordering spe-

cialist. The American College of Medical Genetics and Genomics currently recommends that laboratories performing genomic testing also screen for pathogenic or likely pathogenic variants in a minimum of 81 gene–phenotype pairs, with results considered to be "secondary findings."[3] Testing for CHD-related risks could thus reveal that a patient also harbors a disease-linked variant in a breast cancer–associated gene such as *BRCA1* and therefore requires a different form of clinical care than the ordering cardiologist anticipated. PCPs, who coordinate specialists' care and take initial steps while awaiting specialty appointments, will increasingly have to manage secondary findings for such patients.

Rapid technological advances have reduced the cost of genetic testing, though wide variability remains in health care funders' coverage for tests in various clinical circumstances. More insidious sources of inequity in genomic testing are the interpretational challenges posed by the longstanding underrepresentation of people of non-European ancestry in genomics research, which means that patients from underrepresented ancestral backgrounds are more likely to be found on clinical genetic tests to have variants of unknown significance in disease-linked genes.[4] Similarly, polygenic risk scores developed and validated in populations with European ancestry underestimate risk in patients from other genetic backgrounds. Although racial identity and genetic ancestry do not correspond in predictable ways, the patient in the above case may have some non-European ancestry that could explain the discrepancy between the estimated risk based on her family history and that based on her polygenic risk score.

An audio interview with Stephanie Fullerton is available at NEJM.org

These issues are well known in the genomics research community (for additional readings, see the Supplementary Appendix, available at NEJM.org), and efforts are under way to address the resulting clinical complications. Unfortunately, the patients most likely to be affected in the near term are also those likely to experience other disparities created by systemic racism; health inequity will thus be compounded. Discussing such complex issues with patients is challenging, but acknowledging these limitations is an important responsibility for clinicians ordering genetic tests.

Whereas genetic testing and its ethical complexities were once largely the domain of medical geneticists and genetic counselors, the growing number of genetic-testing applications makes the issues raised here of concern to nearly all clinicians. In addition to requiring adequate provider training to support patient counseling and test interpretation, health care institutions will need to devote resources to reducing inappropriate test ordering, for instance by funding genetics specialists to spend part of their clinical time curating educational resources for patients and clinicians and providing peer-to-peer genetic consultation services for ordering clinicians. Much work is also needed to ensure that genetic test results are searchable and readily available to clinicians in the electronic health record, ideally paired with explanatory materials for patients and clinicians. The current state of non–machine-readable genetic test reports (e.g., scanned PDF documents) is a recipe for patient harm.[5] Finally, the potential for the benefits of genetic testing to be unevenly distributed must be recognized and transparently discussed at the time of test ordering. Equity-oriented training will be required to prepare PCPs for discussing potential disparities with patients and mitigating them, to the extent possible, with their test-ordering practices, so that these powerful precision-medicine approaches can alleviate, not exacerbate, existing health disparities.

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