

## CASE AND COMMENTARY

### How Should Primary Care Physicians Respond to Direct-to-Consumer Genetic Test Results?

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#### Abstract

In this case, a primary care physician is presented with direct-to-consumer genetic test results and asked to provide counseling and order follow-up diagnostics. In order to deal effectively with this situation, we suggest physicians need look no further than the practice principles that guide more routine clinical encounters. We examine the rationale behind 2 major clinical ethical considerations: (1) physicians have obligations to help their patients achieve reasonable health goals but are not obligated to perform procedures that are not medically indicated; and (2) primary care physicians do not need to know everything; they just need to know how to get their patients appropriate care.

#### Case

A 34-year-old woman, Sarah, schedules a routine visit with her family physician, Dr S, to discuss results of a direct-to-consumer genetic test she ordered from an online vendor. After sending a saliva sample, Sarah received several reports that she accessed online and printed for her visit with Dr S.

The first report shows information about Sarah's likely ancestry. The second report contains genetic information and states that Sarah's genetic make-up includes heterozygosity for the e4 variant of the *APOE* gene, which confers an increased risk for late-onset Alzheimer disease. The second report also states that Sarah is a carrier of a pathogenic variant in the *PKHD1* gene, which is associated with autosomal recessive polycystic kidney disease (ARPKD).

Sarah has many questions for Dr S about this information. First, she wants to know what she can do about her increased risk for Alzheimer disease. Should she change her approach to retirement planning, for example? Second, Sarah is concerned about being a carrier for a *PKHD1* pathogenic variant. Although her first child was born without evidence of ARPKD and is now 2 years old, Sarah wonders about the risk of passing on this disease if she tries to have another child.

Dr S listens carefully to Sarah's questions. Although the 2 reports are written in a straightforward, consumer friendly manner, the information in the second report, in particular, contains technical and specific genetic information that is outside of her expertise.

### **Commentary**

Nearly every primary care clinician has experienced a complicated patient request that demands significant time. Until recently, however, requests to interpret and follow up on direct-to-consumer (DTC) genetic testing were not particularly common. A turning point might have been 2017, when the number of people who sought genetic results through DTC testing companies increased dramatically.<sup>1</sup> Given that interest in pursuing DTC testing remains robust,<sup>2,3</sup> it is likely that the use of this type of consumer service will continue to grow and that primary care physicians will increasingly be asked to help their patients interpret these results. In recent years, primary care physicians have faced increasing demands from patients for this kind of assistance, so there is precedent for thinking about how they can respond and assume new, time-intensive responsibilities. In this discussion of the case of Sarah and Dr S, we will first examine challenges that could be raised by the widespread use of DTC testing and then explore how traditional practice guidelines can be drawn upon by primary care clinicians seeking to help patients interpret and respond to DTC genetic testing results.

### **Potential Problems with DTC Genetic Testing**

A number of technical and practical concerns have been raised about DTC genetic testing. First, DTC genetic testing companies vary widely in their laboratory practices, including which genotyping technologies they use and the techniques used to validate results. A recent study showed that 40% of genetic variants identified in DTC laboratories (using various genotyping technologies) were not confirmed when Sanger sequencing (a rigorous testing method) was employed for confirmation.<sup>4</sup> In the same study, several variants that were successfully confirmed by Sanger sequencing had been misclassified as conferring risk for a condition. These types of errors can be reduced by using laboratory practices that adhere to requirements of the Clinical Laboratory Improvement Amendments of 1988, which emphasizes the importance of ensuring that only valid and technically rigorous results are returned to patients.<sup>5</sup> DTC genetic testing companies can also address these concerns by using high-quality criteria for pathogenicity. Criteria proposed by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, for example, specify types of direct and indirect evidence needed to classify a genetic variant as pathogenic. A finding that a variant occurs at a higher frequency in persons affected by a certain condition compared with unaffected persons is, for example, one piece of evidence that could legitimately be used to conclude that a variant is pathogenic.<sup>5</sup>

Another major challenge for the widespread use of DTC genetic tests is the [lack of skilled physicians](#) and other professionals who can properly interpret these results. DTC genetic testing companies sometimes offer access to genetic counselors by phone, but these conversations are inherently limited. In order to contextualize a genetic finding within the overall health of an individual, it is typically necessary for a patient's own clinician to assess her medical and family history and perform a physical examination. With the proper clinical skill and knowledge related to genetics, such information can be synthesized to guide a shared decision-making process. While primary care clinicians typically possess the necessary history and physical exam skills, physicians typically do not have sufficient expertise to interpret and assess risk conferred by individual genetic variants and to develop either a diagnostic or a surveillance program tailored to a patient's particular needs. In one systematic review, two-thirds of studies highlighted insufficient knowledge as a significant barrier to provision of genetic services.<sup>6</sup> Even subspecialty-trained physicians can feel reluctant to interpret such test results. For example, a recent study conducted at a large comprehensive pediatric cancer center demonstrated low confidence among pediatric oncologists in interpreting results of germline genetic sequencing.<sup>7</sup> A majority of physicians (93%) in the study wished to speak to a genetic counselor before disclosing germline test results.<sup>7</sup>

Given both primary care and subspecialist physicians' limited comfort with interpreting and responding to genetic test results, it seems that a dramatic increase in DTC genetic testing is likely to create significant challenges for clinicians. The current workforce of geneticists and genetic counselors is already insufficient to meet estimated needs,<sup>8</sup> so primary care clinicians will be obligated to fill the gap. This scenario is problematic not only because primary care clinicians rarely possess skill for interpreting and assessing genetic information, but also because most primary care practices are generally not designed to accommodate the time-intensive visits that counseling on DTC genetic testing results typically require.

### **Counseling on DTC Genetic Testing: There Are No Stupid Questions**

If there is a first rule of medicine, it is that physicians should never order a test unless there is a foreseeable benefit from ordering that test. No test is completely risk free. Invasive tests, like phlebotomy, confer obvious risks such as infection. But even noninvasive tests, like cheek swabs and ultrasounds, have risks of a false positive result that could lead to something more invasive or a false negative result that could provide false reassurance or forestall future testing. While most of these risks are unavoidable, diagnostic tests can be justified if there is an anticipated benefit that obtaining the test results will likely provide. When diagnostic tests offer no significant benefit, even small risks can provide compelling reasons not to order a test.

Because so many physicians strive to prevent harms to their patients by following this rule, DTC genetic testing results can seem out-of-place in clinical contexts. If physicians

feel that it was a bad idea to purchase DTC testing in the first place, they might want to either disavow an obligation to discuss these results with patients or at least try to convince patients to ignore the results. This latter response is particularly tempting, given the risk concerns discussed above. These types of negative clinician responses are similar to how some clinicians respond when they are asked to provide guidance on other diagnostic tests or treatments that they would not typically recommend. Examples include radiography performed in chiropractic clinics, DTC Lyme disease testing, topical cosmetic treatments, over-the-counter medications, and complementary and alternative treatments.

Primary care clinicians have learned through experience—sometimes tragic experience—that ignoring patients' use of alternative diagnostic and treatment options—or worse, deriding patients for them—can be harmful. These responses make patients feel even more distanced from their biomedical practitioners and less willing to disclose alternative treatments they are using. It is far better for clinicians to educate themselves about the types of products that patients are using. Physicians also have duties to respond to questions about these products in respectful ways that encourage patients to ask questions and enable meaningful opportunities for clinicians and patients to engage in conversation, build trust, and consider professional advice.

### **Referring for Management of DTC Genetic Testing Results: Know What You Know, and Know What You Don't Know**

If primary care clinicians are going to field questions about DTC genetic testing, they need to be ready to help patients think about responding to those results. In the short term, however, it will likely be extremely difficult for most primary care physicians to develop an adequate understanding of genetics and genomics to counsel their patients appropriately. This is not only because requests of this sort are still relatively uncommon, but also because the science behind genetic testing results develops and changes rapidly. Numerous nuances deserve consideration prior to responding to a genetic test result that might indicate a patient's risk for developing a condition. Which evidence supports the claim that a particular genetic variant confers risk for this condition? Which preventative or surveillance measures are available to potentially mitigate risk, and what are their potential risks and benefits? These questions are not just difficult to answer; the potential answers change rapidly as new scientific knowledge is gained. Of particular importance is recent evidence that many of the genetic variants formerly thought to be pathogenic (even by more traditional laboratories) might confer less risk than thought or might confer no risk at all.<sup>9</sup> This evidence, combined with variations in testing quality,<sup>4</sup> significantly increases the likelihood that a DTC genetic test result will be a false positive.

For the present, then, primary care clinicians will need to be aware of what they do not (indeed, cannot) know about genetic testing. They can initially respond to patients' requests for counseling by explaining possible quality problems with DTC genetic testing

and welcoming their questions. For now, most primary care clinicians should refer their patients to appropriate experts to interpret and further evaluate DTC test results to ensure their patients receive the best care possible.

In general, primary care clinicians have significant leeway in deciding which types of care fall within their scope of practice and which they will [refer to specialists](#). There are relatively narrow ethical obligations to provide care for certain problems in primary care settings. For example, clinicians might be obligated to assume dimensions of specialty care when specialists are not readily available or when referring a patient would create a harmful delay. Since it is not reasonable at this point to expect primary care physicians to have extensive knowledge of DTC genetic testing performed by private companies, primary care clinicians should have the option to refer patients to specialists for both interpretation and treatment of a DTC genetic testing result as long as genetic specialists are willing to accept them. Given current shortages of these specialists, however, it might not take long for medical geneticists and genetic counselors to become overwhelmed with these types of referrals.<sup>10</sup> The day will soon come, then, when practical constraints will force many primary care clinicians to learn more and begin counseling patients about DTC genetic results without involving genetics specialists.

#### **Follow-Up Testing from DTC Genetic Results: Look before You Leap**

One implication of DTC genetic testing is that persons who use this service will likely seek follow-up testing to clarify their risk for developing conditions identified through these tests. In this case, Sarah might request that Dr S order a renal ultrasound, a test that is often perceived to be harmless. However, diagnostic tests of this sort carry significant risks precisely because they are intended to guide future medical care. A renal ultrasound in a child might incidentally reveal a renal mass, which might then prompt a needle biopsy or even a surgery. While this kind of follow-up might be appropriate, the Japanese experience with population screening for neuroblastoma suggests that renal masses discovered in infants and toddlers often do not require surgery, a finding made after many infants were exposed to unnecessary surgeries.<sup>11</sup> While unnecessary surgeries as a result of DTC genetic test results will be exceedingly rare, what happened in Japan highlights that clinicians have an important obligation to help patients carefully weigh the potential benefit of peace of mind with the potential risks of unneeded follow-up tests.

When responding to DTC genetic testing results, physicians should advise against [unnecessary follow-up tests or interventions](#) and instead propose a surveillance plan informed by clinical parsimony. Deciding upon a course of action will fall to individual patients and physicians, like Sarah and Dr S, working together. Shared decision making does not, however, mean that primary care physicians should order any test a patient wants. Shared decision making is about seriously engaging in conversation together so that physicians understand their patients' unique circumstances and concerns and so

patients have opportunities to benefit from their clinicians' expertise, including learning about the first rule of medicine: a test should never be ordered in the absence of a foreseeable benefit.

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#### **Editor's Note**

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