# Potential pitfalls of reproductive direct-to-consumer testing

Frank Z. Stanczyk, Ph.D.,[a,b] Rachel S. Mandelbaum, M.D.,[a] and Rogerio A. Lobo, M.D.[c]

[a] Department of Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles, California; [b] Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, California; and [c] Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, New York

The availability of direct-to-consumer (DTC) testing has dramatically increased over the past 2 decades, particularly those targeted at reproduction and fertility. Several ethical concerns exist with regard to DTC tests, including the lack of governmental regulation and consumer protection, standardized laboratory methodology, and clinical validity and actionability. Physicians must familiarize themselves with the pitfalls of DTC tests to best aid patients in interpreting DTC test results and guide them toward evidence-based treatment plans. (Fertil Steril Rep® 2022;3:3–7. ©2022 by American Society for Reproductive Medicine.)

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Direct-to-consumer (DTC) testing emerged in the mid-2000s with the launch of 23andme, a private company that sought to offer consumers insight into their genetic makeup from a simple saliva sample. Consumers were offered access to an enticing comprehensive genetic report that included information pertaining to not only relatively insignificant traits such as the ear lobe shape but also those as significant as cancer risk. A decade-long battle then ensued between 23andme and governmental organizations that sought to curtail DTC testing on the grounds of public protection from "abusive marketing" and "exaggerated claims" regarding genetic health risk and lack of clinical validity (1). This culminated in the US Food and Drug Administration's authorization of 23andme's DTC test in April 2017, which approved genotyping for a limited set of genetic diseases and liberal inclusion of testing for genetic health risks (2). This landmark decision paved the way for the rapid expansion of DTC testing that has occurred over the past 5 years.

A wide range of DTC tests are now available without an order or consultation from a physician or health care provider, including those to evaluate genetics, ancestry, disease or cancer risk, pharmacogenetics, and hormones. Instead, the consumer collects a specimen either at home or at a local laboratory, usually blood, urine, or saliva, and sends it to a DTC testing laboratory for analysis. Results are then reported directly to the consumer.

Direct-to-consumer testing offers several advantages for consumers. These tests are convenient and can provide useful information to consumers for whom clinical testing may be inaccessible, unindicated from insurance coverage or clinical standpoint, or cost-prohibitive (3, 4). Amid the global COVID-19 pandemic, DTC testing is also increasingly relevant to minimize face-to-face contact while increasing access to care. Another concept that is central to the attractiveness of DTC testing is the principle of autonomy. One has access and control over their own genetic or health information to act independently and confidentially on that knowledge. Finally, DTC tests often represent an evolution toward more individualized medicine and the opportunity for disease prevention.

There are, however, several general concerns regarding DTC testing. First, many DTC tests are of limited diagnostic or clinical value. These tests are often only intended to identify risk for a particular condition or subset of conditions and are not typically for diagnostic purposes, which is often difficult for the average consumer to understand without appropriate counseling (4). Results may not be actionable; for example, a person may be identified to be at-risk for a disease, but there is no strategy available for them to mitigate or reduce that risk. Moreover, even when the results are actionable, there is little integration with the traditional health care system for follow-up or further intervention or treatment. Direct-to-consumer laboratories typically recommend that consumers consult with health care

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Reprint requests: Frank Z. Stanczyk, Ph.D., Reproductive Endocrine Research Laboratory, 333 S. Arroyo Parkway, Rm 2, Pasadena, CA 91105 (E-mail: fstanczyk@att.net).

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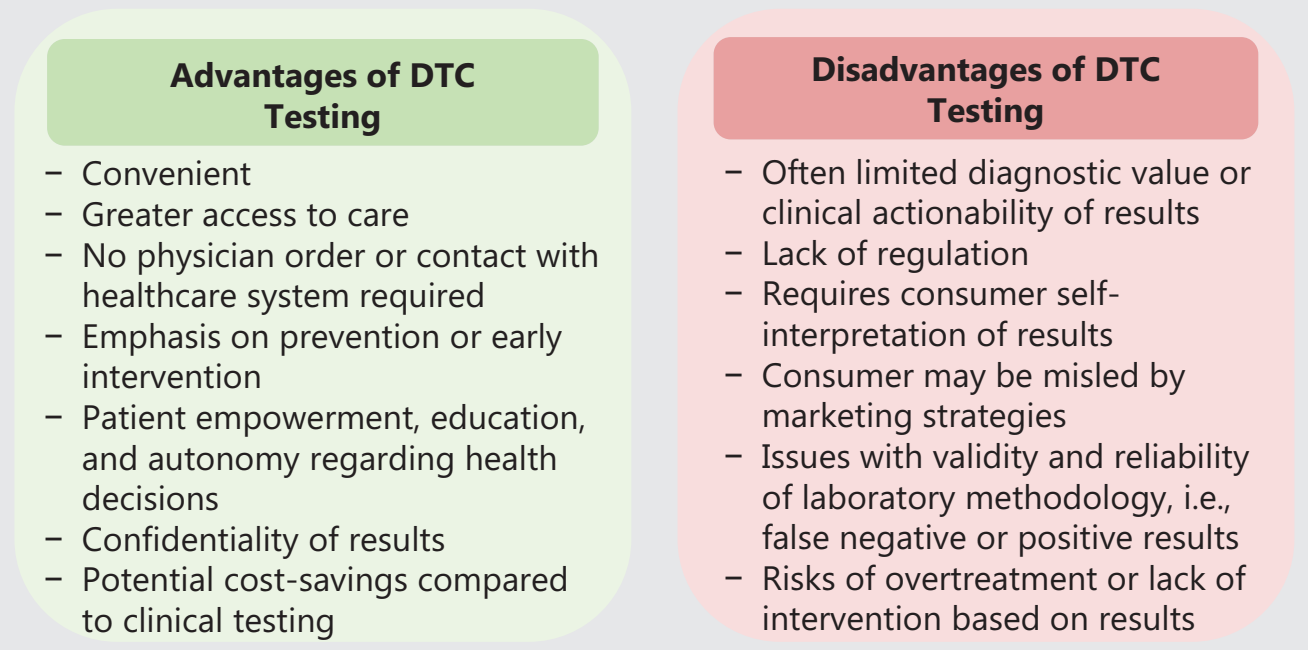
**FIGURE 1**




Advantages and disadvantages of reproductive direct-to-consumer testing are depicted in the *green* and *red* boxes, respectively.

*Stanczyk. Pitfalls of reproductive DTC testing. Fertil Steril Rep 2022.*

providers before and after testing, but this is often not done; consumers typically select tests and interpret the results on their own.

The regulation is also still lacking to protect the consumer. Not all DTC tests are reviewed by the US Food and Drug Administration before marketing, and there may be poor oversight regarding laboratory techniques, ensuring the clinical application of results, monitoring consumer response or comprehension of results, and surveillance for unintended downstream consequences (5, 6). Direct-to-consumer tests that are not reviewed by the US Food and Drug Administration are those considered to be for low-risk conditions, whereas those that have greater implications are reviewed to determine analytical and clinical validity (6).

Additionally, the accuracy or reliability of the results may be poor, which may have significant implications for the consumer. For example, 2 laboratories using different methodologies to measure the same analyte could get significantly different results using the same sample from the same individual. Results that are either erroneous, such as false negatives or positives, or those that are misinterpreted by the consumer, may lead to exposure to risks involved in further invasive diagnostic testing, excessive anxiety or false reassurance, delay in seeking treatment, and/or emotional and financial burden (4). See Figure 1 for a summary of the advantages and disadvantages of reproductive DTC testing.

Direct-to-consumer testing platforms focused on ovarian reserve and fertility testing have garnered tremendous public support over the past few years for the aforementioned reasons. These tests may expand access to empowering reproductive- and biology-related knowledge, allowing individuals to make more informed family-building decisions, such as pursuing elective oocyte or embryo cryopreservation or altering their timeline regarding childbearing in some capacity. Their timely arrival on the market parallels increasing social pressures on women to complete education and career goals and achieve financial stability before reproduction. They are also convenient, negating the need to wait at a physician's office, relatively noninvasive, and low-cost compared with a formal evaluation at a fertility or gynecology clinic. Confidentiality is another benefit because the patient can choose whether the test results are reported to their insurance company, doctor, or partner.

On the other hand, DTC ovarian reserve testing platforms may fall short of delivering on their promise. Direct-to-consumer ovarian reserve testing is currently limited to hormonal evaluation without an ultrasound, which is typically also recommended in the clinical setting to estimate antral follicle count and to detect any anatomic abnormalities. Direct-to-consumer hormonal analysis often includes the measurement of steroid hormones, including estradiol and sometimes progesterone or testosterone, and protein hormones such as follicle-stimulating hormone and antimüllerian hormone (AMH).

Of particular concern with ovarian reserve testing is the accuracy in measuring these hormones and the limitations of several of the assays used. Many diagnostic laboratories use a direct immunoassay on an automated platform to quantify steroid hormones. However, it is now well-recognized that direct immunoassay methods, that is, without one or

more preceding purification steps, lack the specificity and sensitivity to measure estradiol accurately. Estradiol is converted rapidly to estrone, and these 2 estrogens are then metabolized via sulfation and glucuronidation reactions to produce approximately 100 circulating conjugated and unconjugated metabolites. One or more of these metabolites are likely to cross-react with the estradiol antibody in the immunoassay and falsely elevate the levels (7). In addition to poor specificity, direct immunoassays generally lack the sensitivity to quantify accurate estradiol levels below 30 pg/mL (8). Similarly, it is well known that direct immunoassays should not be used to measure serum testosterone levels in female samples (8).

Additionally, the interference of protein hormones such as follicle-stimulating hormone, luteinizing hormone, prolactin, and human chorionic gonadotropin in sandwich-type immunoassays can also have a significant effect on their measurements (9). These interferences include the effects of biotin, heterophilic antibodies, autoimmune antibodies, and the hook effect (10, 11). The average consumer of DTC testing is highly unlikely to be aware of the limitations of assay methodology, as many clinicians are not even aware of these limitations. The Endocrine Society has recently taken steps to attempt to correct this through their 4-module course for fellows and endocrinologists on accurately testing and reading hormone assays.

The measurement of the AMH, which is a key component of nearly all DTC tests currently marketed to evaluate fertility or ovarian reserve, also has significant limitations both in terms of the reliability and validity of currently available AMH assays and its clinical utility in a low-risk population. From a laboratory standpoint, there are currently more than 20 different AMH immunoassay platforms available, with others also in development (12). Values from different assays are highly correlated but vary with regard to the numeric value, depending on the test used. In 1 study, the median AMH levels measured using 5 different commercial immunoassay kits in healthy women without polycystic ovary syndrome ranged from 2.3 to 3.4 ng/mL, with wide confidence intervals (13). Wide variation in results between laboratories not only may lead to consumer misinterpretation of results and downstream effects such as overtreatment or undertreatment but also confusion may arise if consumers were to send their samples to different testing laboratories.

Variability in AMH quantification is a result of multiple factors. First, AMH is initially produced as a larger precursor protein that undergoes posttranslational cleavages to its active form. The AMH precursor protein has no binding ability to the AMH receptor in vivo but is detectable in the serum, and reported values are typically a composite of the different circulating forms of the AMH. Different immunoassays also may use different antibodies, which may have variable binding affinities or specificity for the isoforms of the AMH. There may also be additional proteolytic cleavages of AMH that may lead to unknown isoforms of AMH that may affect results (14). Second, interference by the complement system in blood, particularly C1q, has also been shown to interfere in the measurement of AMH in some assays, and premixture with a buffer to reduce the interference may be required (12, 15). Finally, AMH tests may also vary in terms of protocol, sample preparation and stability, assay time, and detection system. Laboratories seldom determine their own reference range, and there is also no international reference material to calibrate or compare different assays, despite recent attempts by the World Health Organization to generate a reference reagent for AMH (12, 16, 17).

In addition to the issues encountered with the reproducibility and reliability of quantifying AMH, consensus opinions from the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine do not advise the use of AMH as a screening tool in a low-risk population. In the infertile population considering in vitro fertilization (IVF), AMH is an important tool for predicting response to ovarian stimulation and informing clinical decision-making regarding IVF protocol and risk of ovarian hyperstimulation. However, in the general population and those without infertility, AMH does not predict future fertility potential, the likelihood of unassisted pregnancy, the time to pregnancy, or the timing of menopause (18–21).

Consumer self-interpretation of AMH results without a physician or medical professional's insight into the limitations of AMH measurement may lead to inappropriate intervention. This may involve unnecessary procedures, therapies, medications, and/or lifestyle changes. Most commonly, those identified to have results indicating low ovarian reserve on DTC testing may be urged to seek elective oocyte cryopreservation or modify life choices regarding childbearing (22). Elective oocyte cryopreservation may offer patients the ability to defy the ovarian "biologic clock" and have greater autonomy regarding the timing of reproductive decisions. Yet, oocyte cryopreservation is costly and invasive, and evidence shows that few women actually use their cryopreserved oocytes for pregnancy (23). Additionally, elective oocyte preservation does not guarantee a live birth, as oocyte survivability and viability after thaw and embryo culture is unknown. Although small studies report optimistic results with pregnancy rates similar to conventional IVF without oocyte cryopreservation, data regarding pregnancy outcomes after elective oocyte cryopreservation are lacking (23). Hence, if not counseled appropriately regarding the chances of a live birth on the basis of the number of oocytes frozen, there is the potential that women may over rely on cryopreserved oocytes as an "insurance policy" for future childbearing.

Lastly, it is possible that those identified as having a normal or high result may be falsely reassured to delay fertility goals. Among markers used to estimate ovarian reserve, age alone remains the most important factor in predicting oocyte quality and reproductive success (24, 25). Ovarian reserve is also only one of several factors that may impact fertility. Even if the hormonal analysis is reassuring, counseling regarding the other components of a typical infertility evaluation that could be abnormal or affect a woman's ability to conceive should be performed in those women actively trying to conceive. These include factors such as semen quality, tubal disease, and the presence of other pelvic pathology such as endometriosis.

Although reproductive age women have been the overwhelming targets of marketing for at-home "fertility"

diagnostic testing, DTC semen analyses have also recently become available (26). At-home collection offers men the opportunity to produce semen samples in the privacy and comfort of their own home, which offers significant benefit for those who are uncomfortable with or have difficulty producing a sample in the office. Depending on the test, patients can then either mail in the sample for analysis or platforms have even been developed to allow an at-home analysis of sperm concentration. Previously, the World Health Organization recommended that semen be analyzed within 1 hour of collection due to decreases in motility and morphology (27). Recent studies, however, suggest that sperm motility and morphology appear to be largely stable, and results are highly correlated over a 1- to 2-day delay from the time of collection to allow for expedited shipping of a sample (26).

Despite the clear advantages of improved access to testing and reduced patient anxiety or stress, there are several unique concerns with the at-home semen collection kits in particular. First, consumers need to be aware that the technique with which the sample is collected may have a significant impact on the results. For example, the presence of saliva or certain lubricants or failure to collect the entire ejaculate may falsely lower the parameters. Second, consumers may be responsible for key processing steps before mailing the sample, and failure to perform these correctly may also deleteriously impact results. Subtle decreases in parameters because of these factors may be very significant for men with low-normal values and may cause alarm in men who may indeed have normal results in a clinical setting. Third, routine semen analysis is subject to considerable interobserver variability and has been difficult to standardize, particularly with regard to the quantification of concentration and morphology. Thus, results may be highly dependent on the quality of the laboratory, andrologist, or the automated testing platform that analyzes the sample (27). Finally, the results of semen analysis are also often nuanced, making self-interpretation of results difficult without the guidance of a reproductive physician. Individual semen analysis parameters, even if abnormal, may be weak indicators of a man's fertility potential. Therefore, tests that market analysis of only 1 or a couple parameters, such as only sperm concentration, may be misleading. Rather, a composite of the parameters together has the greatest clinical significance (28).

It is time for a call-to-action regarding DTC testing in the field of reproduction. Direct-to-consumer tests are here to stay, particularly with the current COVID-19 pandemic, when many patients may think twice about entering a physician's office and prefer an at-home option to initiate an evaluation. We are now increasingly seeing patients in the clinical setting who already bear results or diagnoses from DTC testing. Some patients may even have already decided to pursue particular treatments such as oocyte or embryo cryopreservation or IVF on the basis of self-interpretation of results. It is remarkable to see more and more patients empowered to make reproductive decisions and seek care to try to ensure their family-building goals as a result of DTC testing. But, as the demand for reproductive medicine increases and we continue to battle a sea of misinformation from media and internet outlets regarding fertility and reproductive health, we need to ensure that assisted reproductive technologies are practiced both ethically and judiciously. It is, therefore, imperative that we are educated regarding the pitfalls of DTC testing so that we can best counsel and serve our patients along their reproductive paths.

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