In a study of 320 patients with different hereditary cancer syndromes , most were unaware of PGT; however, the majority expressed interest in learning more about the availability of PGT.[14] Patients also preferred having a discussion about PGT with their genetic counselor or primary physician. Disease-specific factors (e.g., severity of the hereditary condition, quality of life, and medical interventions) and individual factors (e.g., gender, childbearing status, and religious beliefs) affected patient attitudes about PGT.

In some cases (e.g., carriers of germline pathogenic variants in ATM, BLM), assessing an individualâ€™s partner's risk for carrying a pathogenic variant associated with a dominant or recessive syndrome (i.e., his or her personal and family history and ethnicity) is indicated. In the unlikely event that both parents are heterozygous for specific pathogenic variants, there is a 25% risk that a child will be homozygous and could have a severe phenotype . In light of this information, couples may consider PGT or prenatal testing.

Assisted reproductive technology can be used for preimplantation genetic testing (PGT) and for prenatal cancer predisposition genetic testing using chorionic villus sampling and amniocentesis.[9 - 11] For individuals with autosomal dominant cancer syndromes (e.g., those associated with APC, BRCA1/BRCA2, PTEN, or TP53 pathogenic variants), reproductive options exist for prenatal testing and PGT to detect offspring with one copy of the pathogenic variant (heterozygotes).

There is a risk of carriers passing on cancer-associated pathogenic variants to offspring. When an individual tests positive for one pathogenic variant in a cancer susceptibility gene, counseling about reproductive implications addresses not only the risks associated with autosomal dominant inheritance but also the potential risks of having a child with two pathogenic variants in the same gene (biallelic) that could result in a severe condition.

The Affordable Care Act (ACA) requires that private insurers coverâ€”with no out-of-pocket costs to the insuredâ€”genetic counseling and BRCA1/BRCA2 testing for unaffected women meeting United States Preventive Services Task Force guidelines.[6 , 7] Importantly, under ACA guidelines, women with a prior cancer diagnosis are not covered. The ACA does not stipulate that follow-up care based on genetic test results be covered (e.g., risk-reducing surgeries). However, some insurance companies require that pretest genetic counseling be performed by a credentialed genetics provider before testing is authorized. Before testing is ordered, it is important to verify costs and insurance coverage, including for Medicaid and Medicare patients. Medicare does not cover genetic testing if the patient has not had a cancer diagnosis associated with the pathogenic variants for which testing is ordered. In addition, unaffected individuals with Medicare are not covered for testing, even if they are tested for only a known familial pathogenic variant. Further, Medicare does not cover genetic counseling as a separately billable service.[8] For individuals without insurance coverage and the underinsured, some laboratories offer low-cost options or have financial assistance programs.

Insurance coverage varies for cancer susceptibility testing, including multigene (panel) testing. In general, most individuals who meet specific criteria (e.g., National Comprehensive Cancer Network [NCCN] guidelines for BRCA1/BRCA2 or Lynch syndrome testing) are able to obtain insurance coverage for multigene testing.[5] Of note, some insurance companies have contracts with specific laboratories through which testing must be ordered.

In summary, genetic education and counseling includes identifying the most informative person in the family to test, which may be an affected family member rather than the individual seeking genetic services. In addition, counseling includes a discussion of the limitations of the test, all possible test outcomes, and the consequences of identifying a VUS.[4]

If the familial pathogenic variant is detected in a family member, their cancer risks are based on penetrance data for pathogenic variants in that specific gene. If the documented pathogenic variant is not found in a family member, the risk of cancer in that individual is equivalent to cancer risk in the general population. However, other risk factors and family history from the side of the family not associated with the documented pathogenic variant may increase the cancer risk above the general population levels.

If there is no close, living, affected relative to undergo testing, or the living affected relative declines testing, other options may be discussed with the patient and the testing laboratory. In rare instances, if proper authorization is secured from the family, testing the stored tissue of a deceased relative may be considered. However, genetic tests done on stored tissue are technically difficult and may not yield a definitive result. Therefore, testing an unaffected person without prior testing of an affected family member may be performed. In these instances, counseling includes discussing that a negative test result does not rule out the presence of a cancer susceptibility gene in the family or in the patient and may be uninformative.

Lastly, testing may reveal a VUS. This result means that a genetic variant has been found; however, the extent that this variant increases cancer risk, or whether it is associated with the history of cancer in the family, is uncertain. In this circumstance, some clues as to the significance of the variant can be derived from the following:

If a documented pathogenic variant (associated with cancer risk) is identified, risks are based on penetrance data for pathogenic variants of that specific gene. In addition, other family members may be tested for the presence or absence

of this specific pathogenic variant. If no variant is found in an affected family member, testing is considered uninformative and thus there is no basis for testing unaffected relatives. Failure of the laboratory to detect a pathogenic variant in an affected family member does not rule out an inherited basis for the cancer in that family. Reasons why testing could be uninformative include the following:

Genetic susceptibility testing generally yields the most useful information when a living family member with the cancer of concern is tested before other family members; this can help determine if his/her cancer has a genetic origin. If testing is deferred while follow-up with an affected relative is pending, consider providing interim cancer risk management guidelines to the unaffected proband .[3] Possible genetic testing outcomes include the following (for more information, see Figure 2):

Genetic education and counseling approaches (including the interpretation of genetic test results) will vary if genetic testing has already been attempted (for more information, see Figure 2). In general, there are two primary circumstances in which genetic testing is performed:

ASCOâ€™s position is that when a test, regardless of clinical utility, is ordered by a health care professional, the provider is responsible for organizing follow-up care based on the findings. For tests that are ordered by the consumer without health care professional involvement, management decisions are based on the evidence for clinical utility. For tests with accepted clinical utility, follow-up care can be guided by the evidence for cancer risk associated with the genetic test finding. However, in tests ordered by the consumer that have uncertain clinical utility, ASCO recommends that follow-up care consist of education regarding the lack of evidence regarding the test's clinical utility and that cancer risk management decisions be guided by established cancer risk factors.[1 , 2]

Characteristics used in making this determination are discussed in the PDQ summaries on the genetics of specific cancers. Even when individual and family history characteristics indicate a possible inherited cancer syndrome, individuals may elect not to proceed with testing after discussion of potential risks, benefits, and limitations, as discussed below. Conversely, individuals whose pedigrees are incomplete or uninformative due to very small family size, early deaths, or incomplete data on key family members may elect to pursue genetic testing in an attempt to better define their risk status. In these situations, it is particularly important that the pretest counseling fully explore the limitations of the testing process.

In October 2014, the FDA posted the notification regarding its plans to develop draft guidance on the regulation of laboratory-developed tests.[53] Draft guidance documents outlining the framework for regulatory oversight for the industry and clinical laboratories were published later in 2014 for public review and comment. Given the potential of such regulatory action to affect the wide spectrum of genetic tests in clinical practice, proposed draft guidelines have been discussed and reviewed by a number of professional associations, eliciting policy statements and analyses from various professional associations, including the American Society of Human Genetics (ASHG) and the Association for Molecular Pathology . The issue of FDA oversight of laboratory-developed tests remains under consideration.

The U.S. Department of Health and Human Services Secretaryâ€™s Advisory Committee on Genetics, Health, and Society has published a detailed report regarding the adequacy and transparency of the current oversight system for genetic testing in the United States.[52] The Committee identified gaps in the following areas:

The most frequent reason cited for lack of proficiency testing participation was lack of available proficiency testing programs. Laboratory directors estimated that in the past 2 years 37% issued three or fewer incorrect reports, and 35% issued at least four incorrect reports. Analytic errors such as faulty reagent, equipment failure, or human error, increased 40% with each decrease in level of proficiency training completed.[47] An international genetic testing laboratory director survey involving 18 countries found that 64% of the 827 laboratories that responded accepted samples from outside their country.[51] Similar to the U.S. study, 74% reported participation in some form of proficiency testing. Fifty-three percent of the laboratories required a copy of the consent to perform the test, and 72% of laboratories retained specimens indefinitely that were submitted for testing.[51]

Evidence regarding the implications of this narrow regulatory oversight of genetic tests is limited and consists predominantly of laboratory director responses to quality assurance surveys. A survey of 133 laboratory directors performing genetic tests found that 88% of laboratories employed one or more American Board of Medical Genetics (ABMG)-certified or ABMG-eligible professional geneticists, and 23% had an affiliation with at least one doctoral-prepared geneticist. Eight percent of laboratories did not employ and were not affiliated with doctoral-level genetics professionals. Laboratory-developed tests were performed in 70% of laboratories. Sixty-three percent of laboratories provided an interpretation of the test result as part of the test report.[50] Another survey of 190 laboratory directors found that 97% were CLIA-certified for high complexity testing. Sixteen percent of laboratories reported no specialty area certification; those without specialty certification represented laboratories with the most volume of tests performed and offered the most extensive test selection.[47] Of laboratories with specialty

certification, not all had certification relevant to genetic tests, with 48% reporting pathology certification, 46% chemistry certification, and 41% clinical cytogenetics certification. Sixteen percent of directors reported participation in no formal external proficiency testing program, although 77% performed some informal proficiency testing when a formal external proficiency testing program was not available.

In addition to the regulation of classical clinical genetic tests is the regulatory oversight of research genetic testing. Laboratories performing genetic testing on a research basis are exempt from CLIA oversight if the laboratory does not report patient-specific results for the diagnosis, prevention, or treatment of any disease or impairment or the assessment of the health of individual patients.[47] However, there are anecdotal reports of research laboratories providing test results for clinical purposes with the caveat that the laboratory recommends that testing be repeated in a clinical CLIA-approved laboratory. In addition, there is no established mechanism that determines when a test has sufficient analytic and clinical validity to be offered clinically.[49] Currently, the decision to offer a genetic test clinically is at the discretion of the laboratory director.

In regard to analytic validity, genetic tests fall into two primary categories; test kits and laboratory-developed tests (previously called home brews). Test kits are manufactured for use in laboratories performing the test and include all the reagents necessary to complete the analysis, instructions, performance outcomes, and details about which genetic variants can be detected. The U.S. Food and Drug Administration (FDA) regulates test kits as medical devices; however, despite more than 1,000 available genetic tests, there are fewer than ten FDA-approved test kits.[49] Laboratory-developed tests are performed in a laboratory that assembles its own testing materials in-house;[49] this category represents the most common form of genetic testing. Laboratory-developed tests are subject to the least amount of oversight, as neither CLIA nor the FDA evaluate the laboratories' proficiency in performing the test or clinical validity relative to the accuracy of the test to predict a clinical outcome.[47 , 49] The FDA does regulate manufactured analyte-specific reagents (ASRs) as medical devices. These small molecules are used to conduct laboratory-developed tests but can also be made by the laboratory. ASRs made in the laboratory are not subject to FDA oversight. For laboratory-developed tests utilizing manufactured commercially available ASRs, the FDA requires that the test be ordered by a health professional or other individual authorized to order the test by state law. However, this regulation does not distinguish between health providers caring for the patient or health providers who work for the laboratory offering the test.[49]

Government regulation of genetic tests to date remains extremely limited in terms of both analytic and clinical

validity with little interagency coordination.[47] The Centers for Medicare & Medicaid Services, using the Clinical Laboratory Improvement Act (CLIA), regulates all clinical human laboratory testing performed in the United States for the purposes of generating diagnostic or other health information. CLIA regulations address personnel qualifications, laboratory quality assurance standards, and documentation and validation of tests and procedures.[48] For laboratory tests themselves, CLIA categorizes tests based on the level of complexity into waived tests, moderate complexity, or high complexity. Genetic tests are considered high complexity, which indicates that a high degree of knowledge and skill is required to perform or interpret the test. Laboratories conducting high complexity tests must undergo proficiency testing at specified intervals, which consists of an external review of the laboratory's ability to accurately perform and interpret the test.[47 , 49] However, a specialty area specific for molecular and biologic genetic tests has yet to be established; therefore, specific proficiency testing of genetic testing laboratories is not required by CLIA.[47]

Another important consideration is that multigene tests may include genes in which pathogenic variants are associated with moderate or uncertain penetrance. Management of individuals with pathogenic variants in such genes can present additional challenges, particularly when expert consensus or evidence-based recommendations are not available. For more information on moderate- and low-penetrance, see Figure 1 in Cancer Genetics Overview. Moreover, there may be limited or no evidence to support changes to medical management based on the level of risk or uncertain risk; however, management may still be affected by family history.[1 , 2] A framework for clinical management incorporates emerging data on age-specific, lifetime, and absolute cancer risks conferred by pathogenic variants in several moderate-risk genes.[46] For more information about frameworks for clinical management, see the Penetrance of Inherited Susceptibility to Hereditary Breast and/or Gynecologic Cancers section in Genetics of Breast and Gynecologic Cancers.

Practice guidelines for optimal clinical use of multigene tests continue to evolve.[2 , 45] The NCCN and ASCO guidelines suggest that multigene panel testing may be more efficient when there are multiple cancer syndromes or genes on the differential diagnosis list.[2 , 45] Additionally, NCCN states that there may be a role for multigene panel testing when a patient has a personal or family history of cancer that is consistent with an inherited susceptibility, but single-gene testing has not identified a pathogenic variant.[45]

Providers who determine a patient's genetic testing strategy may also consider these additional challenges: the patient's out-of-pocket and overall expenses, insurance reimbursement for the genetic test, the genetic test's turn-around-time, ease of ordering the genetic test from a laboratory, the probability of identifying a VUS and

managing this finding (via VUS reclassification and access to additional variant data), technical differences between genetic tests (such as the presence of a deletion /duplication assay), patient preference, and a patient's clinical history.[2 , 40 , 41 , 44]

However, there can be challenges when employing this testing approach. Clinical laboratories now offer a varying array of clinical cancer susceptibility gene panels.[41 , 42] Multigene panels continue to evolve, and the genes included on the panels can change. Other challenges of interpreting multigene test results include higher rates of VUS than those seen in single-gene testing (the rate of VUS increases with the number of genes tested),[24] higher rates of VUS in some racial and ethnic minority populations,[32 , 43] and the detection of variants in genes associated with uncertain cancer risks.

Using multigene panels can be complex. However, this approach may offer advantages over sequential testing strategies. For example, in some types of cancer, several genes can be associated with specific phenotypes; therefore, testing for all genes associated with a given phenotype can save both time and money.[40] Additionally, multigene panel testing may identify the genetic basis of cancer in families with the following: a differential diagnosis list that includes multiple syndromes, or a family history that does not meet genetic testing criteria for a hereditary cancer syndrome.[21 , 40] For more information on factors that make family history difficult to interpret, see the Analysis of the family history section.

Results can also reveal more than one finding given that multiple genes are being tested simultaneously and the elevated rate of VUS.[21] There has been no assessment of outcomes of multigene tests such as comprehension, psychosocial outcomes, and uptake of cancer risk management options.

A large study published by a commercial laboratory included more than 252,000 individuals who were tested with a 25-gene panel between 2013 and 2016.[39] The study population did not have prior cancer genetic testing, 97% were female, and 93% met NCCN criteria for hereditary breast and ovarian cancer (HBOC) or Lynch syndrome testing. Half of the pathogenic variants found for HBOC or Lynch syndrome were not in the expected genes associated with these syndromes (BRCA1, BRCA2, MLH1, MSH2, MSH6, and PMS2).

Selected reports from 2014 to 2018, which included 1,000 to 10,000 tested individuals, showed variation in pathogenic variant and VUS rates.[23 , 24 , 26 , 30 , 35 - 38] Pathogenic variant rates ranged from 7% to 14%; VUS rates ranged

from 19% to 41% and increased with the number of genes included on the panel, but decreased in the later studies, likely because of larger data pools and refinements in variant interpretation. Additionally, VUS rates were higher in non-White individuals, likely because of the limited availability of test result data needed for accurate determination of risk.[38]

In high-risk individuals who meet criteria for hereditary cancer genetic testing but in whom no pathogenic variant was identified from single-gene testing, panel testing may identify other clinically actionable variants.[27 , 28] For example, the additional yield of multigene testing in individuals in whom a BRCA1/BRCA2 pathogenic variant was not detected currently seems to be approximately 4%.[26 , 29 , 30] The most common non-BRCA pathogenic variants found are in CHEK2, ATM, and PALB2.[26 , 29 - 31] In some cases, the identification of pathogenic variants from panel testing resulted in additional recommendations for screening and risk reduction beyond what would have been indicated based on family history alone.[30 , 32 - 34]

The range of results from NGS multigene panels is emerging in both data from clinical and laboratory series. Several of the studies are collaborations between the two. There are several important caveats about the research that has been conducted so far with regard to multigene testing:

ASCO has stressed the importance of genetic counseling to ensure patients are adequately informed about the implications of this type of testing and recommends that tests be ordered by cancer genetic professionals.[2 , 19] Yet, the use of multigene testing requires modification of traditional approaches to genetic counseling.[20 , 21] Optimal evidence-based counseling strategies have not yet been established. Unlike in-person, single-gene pretest genetic counseling models, these approaches have not been examined for outcomes of counseling such as comprehension, satisfaction, psychosocial outcomes, and testing uptake. Table 2 summarizes recommendations from ASCO on elements of pretest genetic counseling and informed consent for germline cancer genetic testing.[2]

Next-generation sequencing (NGS) and the removal of most patent barriers to diagnostic DNA sequencing [18] have resulted in the availability of multigene testing, which can simultaneously test more than 50 genes for pathogenic variants, often at costs comparable to single-gene testing. These multigene panels can include genes with pathogenic variants that are associated with high risks of cancer and genes that confer moderate and uncertain risks. The multigene panels can be limited to specific cancer types (e.g., breast, ovarian, colon) or can include many cancer types. This type of testing has both advantages and disadvantages, and much of the information presented in this

section is not based on empirical data but rather on commentaries.

Allelic heterogeneity (i.e., different variants within the same gene) can confer different risks or be associated with a different phenotype. For example, though the general rule is that adenomatous polyposis coli (APC) pathogenic variants are associated with hundreds or thousands of colonic polyps and colon cancer of the classical FAP syndrome, some APC pathogenic variants cause a milder clinical picture, with fewer polyps and lower colorectal cancer risk.[16 , 17] In addition, other disorders may be part of the FAP spectrum. Pathogenic variants in a certain portion of the APC gene also predispose to retinal changes, for example, when pathogenic variants in a different region of APC predispose to desmoid tumors.

In some genes, the same pathogenic variant has been found in multiple, apparently unrelated families. This observation is consistent with a founder effect, wherein a pathogenic variant identified in a contemporary population can be traced back to a small group of founders isolated by geographic, cultural, or other factors. For example, two specific BRCA1 pathogenic variants (68_69delAG and 5266dup, also known in the literature as 185delAG and 5382insC) and one BRCA2 pathogenic variant (5946delT, also known as 6174delT) have been reported to be common in Ashkenazi Jews. Other genes also have reported founder pathogenic variants . The presence of founder pathogenic variants has practical implications for genetic testing. Many laboratories offer directed testing specifically for ethnic-specific alleles . This greatly simplifies the technical aspects of the test but is not without limitations. For example, approximately 15% of BRCA1 and BRCA2 pathogenic variants that occur among Ashkenazim are nonfounder pathogenic variants.[15] Also, for genes in which large genome rearrangements are common in the founder population, ordering additional testing using different techniques may be needed.

Genetic testing is highly specialized. There are also multiple molecular testing methods available, each with its own indications, costs, strengths, and weaknesses. Depending on the method employed and the extent of the analysis, different tests for the same gene will have varying levels of sensitivity and specificity . Even assuming high analytic validity, genetic heterogeneity makes test selection challenging. A number of different genetic syndromes may underlie the development of a particular cancer type. For example, hereditary colorectal cancer may be due to familial adenomatous polyposis (FAP), Lynch syndrome, Peutz-Jeghers syndrome, juvenile polyposis syndrome, or other syndromes. Each of these has a different genetic basis. In addition, different genes may be responsible for the same condition (e.g., Lynch syndrome can be caused by pathogenic variants in one of several mismatch repair [MMR] genes).

In 2016, a statement by the American College of Medical Genetics and Genomics about DTC genetic testing similarly endorsed the involvement of qualified genetics professionals in the processes of test ordering and interpretation.[80] The statement also emphasized the need to incorporate established methods of risk assessment into disease risk prediction (such as personal and family medical history information) and stressed that consumers need to be informed about the potential limitations and risks associated with DTC testing.

Given the complexity of genomic testing, several professional organizations have released position statements about DTC genetic testing. For example, in 2010, ASCO published a position statement outlining several considerations related to DTC cancer genomic tests, including those mentioned above.[1] They endorsed pre- and posttest genetic counseling and informed consent by qualified health care professionals. ASCOâ€™s 2015 position statement on genetic and genomic testing for cancer susceptibility reinforces the importance of provider education given the complexity of genomic testing and interpretation and discusses their recommendations for regulatory review of genomic tests, including those offered by DTC companies.[2]

There may be potential benefits associated with DTC testing. DTC marketing and provision of genetic tests may promote patient autonomy.[59] Individuals may develop an increased awareness of the importance of family history, the relationship between risk and family history, the role of genetics in disease, and a better understanding of the value of genetic counseling.[73] Although results of SNV-based DTC testing appear to motivate some individuals to seek the advice of their doctor, make lifestyle changes, and pursue screening tests,[74 - 77] short-term modest effects on risk perception after notification of an elevated risk (e.g., for cancer) may not significantly alter lifestyle or cancer screening behaviors.[78 , 79] Further, psychological distress has not been widely reported among consumers who have undergone DTC testing for a variety of conditions.[76] However, little is known about how individuals respond after learning that they carry pathogenic variants in high-risk genes such as BRCA1/BRCA2 when testing is performed within a DTC context and without traditional forms of pre- and posttest genetic education and counseling.

Some factors to consider when determining the accuracy and utility of sequence data for cancer (or other disease) risk assessment include the sequencing depth of the genes of interest, whether large rearrangements or gene deletions would be detected, and whether or how positive results are confirmed (e.g., through Sanger sequencing). For example, if sequencing depth is low or rare variants cannot be detected, then there is a concern about false-negative results. There is also a risk that sequence changes will be erroneously labeled as pathogenic when confirmatory testing or different interpretative approaches would determine that the variant identified is benign (false positive). When WES

or WGS is performed, VUS are also likely to be identified,[71] and DTC companies have varying protocols for classification, which may or may not be consistent with national guidelines.[72] In addition, as evidence evolves and variants are reclassified, consumers need to be aware of the process the DTC lab has, if any, for updating information and re-contacting consumers with revised interpretations.

Increasingly, DTC testing companies offer whole-genome sequencing (WGS) or whole-exome sequencing (WES), including SNV data. For more information on WGS and WES, see the Clinical Sequencing section in Cancer Genetics Overview. In addition, consumers who submit their DNA to a DTC lab may have access to their raw sequence data and may consult with other companies, websites, and open-access databases for interpretation.[68 , 69] However, these data must be interpreted with caution. A clinical lab found that 40% of variants reported in DTC raw data were false positives (i.e., low analytic validity because the identified variant was not present).[70] In addition, several variants that were designated as â€œincreased riskâ€• in the raw data were classified as benign by clinical laboratories and public databases.[70] Given the potential for misinterpretation, which may lead to unnecessary medical procedures or testing, these findings underscore the importance of clinical confirmation of all potentially medically actionable gene variants identified by DTC testing.

Studies have begun to examine whether SNV testing could be used together with other established risk factors to assess the likelihood of developing cancer. For example, adding SNV data to validated breast cancer prediction tools such as those included in the National Cancer Institute's Breast Cancer Risk Assessment Tool (based on the Gail model) [65] may improve the accuracy of risk assessment.[66 , 67] However, this approach is not currently FDA-approved.

Another area of investigation is whether predicted disease risks from SNV testing are consistent with family historyâ€“based assessments. Studies using data from one commercial personal genomic testing company revealed that there was generally poor concordance between the SNV and family history risk assessment for common cancers such as breast, prostate, and colon.[62 - 64] Importantly, one of these studies highlighted that the majority of individuals with family histories suggestive of hereditary breast/ovarian cancer or Lynch syndrome received SNV results yielding lifetime cancer risks that were average or below average.[62]

In the past, several DTC companies offered only SNV -based testing to generate information about health risks, including risks of cancer. Selection of SNVs may be based on data from genome-wide association studies (GWAS); however, there is no validated algorithm outlining how to generate cancer risk estimates from different SNVs, which

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individually are generally associated with modestly increased disease risks (usually conferring odds ratios

Reference

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