HHS Public Access

Author manuscript

Am Soc Clin Oncol Educ Book. Author manuscript; available in PMC 2018 July 20.

Published in final edited form as:

Am Soc Clin Oncol Educ Book. 2016 ; 35: e72–e78. doi:10.14694/EDBK_160391.

How Far Do We Go With Genetic Evaluation? Gene, Panel, and Tumor Testing

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OVERVIEW

The traditional model by which an individual was identified as harboring a hereditary susceptibility to cancer was to test for a mutation in a single gene or a finite number of genes associated with a particular syndrome (e.g., *BRCA1* and *BRCA2* for hereditary breast and ovarian cancer or mismatch repair genes for Lynch syndrome). The decision regarding which gene or genes to test for was based on a review of the patient's personal medical history and their family history. With advances in next-generation DNA sequencing technology, offering simultaneous testing for multiple genes associated with a hereditary susceptibility to cancer is now possible. These panels typically include high-penetrance genes, but they also often include moderate- and low-penetrance genes. A number of the genes included in these panels have not been fully characterized either in terms of their cancer risks or their management options. Another way some patients are unexpectedly identified as carrying a germline mutation in a cancer susceptibility gene is at the time they undergo molecular profiling of their tumor, which typically has been carried out to guide treatment choices for their cancer. This article first focuses on the issues that need to be considered when deciding between recommending more targeted testing of a single or a small number of genes associated with a particular syndrome (single/limited gene testing) versus performing a multigene panel. This article also reviews the issues regarding germline risk that occur within the setting of ordering molecular profiling of tumors.

Throughout the past several decades, we have witnessed tremendous advances in our knowledge of evaluating and treating patients with germline mutations in hereditary cancer syndromes, with studies clearly demonstrating the feasibility and clinical utility of genetic testing. Perhaps most importantly, studies have provided convincing evidence that implementing prevention strategies in some instances prolongs the survival of mutation carriers. For example, for unaffected women who carry a *BRCA1* or *BRCA2* mutation, risk-reducing salpingo-oophorectomy results in a significant reduction in all-cause mortality (3% vs. 10%; hazard ratio [HR] 0.40; 95% CI, 0.26–0.6), breast cancer-specific mortality (2% vs. 6%; HR 0.44; 95% CI, 0.26–0.76) and ovarian cancer–specific mortality (0.4 vs. 3%; HR 0.21; 95% CI, 0.06–0.8) when compared with carriers who chose not to undergo this procedure.[1] Additionally, Markov modeling suggests that a 30-year old healthy *BRCA1*

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Disclosures of potential conflicts of interest provided by the authors are available with the online article at asco.org/edbook.

mutation carrier would gain 0.2 to 1.8 years in life expectancy with risk-reducing salpingo-oophorectomy and 0.6 to 2.1 years from risk-reducing mastectomies.[2,3] Given these findings, genetic testing for hereditary cancer syndromes has now become part of standard practice.

As set forth in the Evaluation of Genomic Applications in Practice and Prevention (known as EGAPP) initiative[4] and further supported by the recent American Society of Clinical Oncology (ASCO) policy statement on testing for genetic and genomic cancer susceptibility, [5] a number of criteria must be considered when evaluating existing or emerging genetic tests. These criteria include analytical and clinical validity, clinical utility, and the associated ethical, legal, and social issues. In the context of genetic testing, analytic validity refers to the accuracy and reproducibility by which the assay detects the presence or absence of a mutation. Clinical validity focuses on whether the test accurately and reproducibly predicts the clinically defined disorder. Clinical utility can be defined as the evidence that a genetic test results in improved health outcomes typically based on early detection or prevention strategies, and the test's usefulness and added value to patient management decision making. For genetic testing, particularly for moderate-penetrance genes, clinical utility remains the fundamental issue.[5] The EGAPP framework is key when evaluating the utility of genetic testing for hereditary cancer syndromes. Failure to meet some of these criteria forms the basis for many concerns regarding the current clinical actionability of multigene panel testing.

SINGLE/LIMITED GENE TESTING

For well over a century, it has been recognized that some families harbor a hereditary predisposition to a variety of malignancies. In 1913, Warthin described a kindred known as Family G, in which he noted an aggregation of endometrial carcinoma along with gastric and colorectal cancer.[6] This family, among others, formed the basis of the initial descriptions of hereditary nonpolyposis colorectal cancer syndrome, now more commonly known as Lynch syndrome. Similarly, astute clinicians recognized other hereditary cancer syndromes such as Li-Fraumeni and Cowden syndromes and hereditary breast and ovarian cancer based on the cancer phenotype of the family.[7–12] By the mid-1990s, linkage analyses and other studies resulted in the ability to pinpoint individual genes associated with some of these hereditary cancer syndromes.[13,14] These included the identification of *BRCA1* and *BRCA2* associated with hereditary breast and ovarian cancer; *MLH1, MSH2, MSH6, PMS2*, and more recently *EPCAM* associated with Lynch syndrome; *FAP* with familial adenomatous polyposis; and *TP53* with Li-Fraumeni syndrome.

However, it became apparent that many families with striking histories consistent with either a hereditary colorectal or breast/ovarian cancer syndrome are not found to carry a mutation in one of the mismatch repair genes associated with Lynch syndrome or in *BRCA1/2*. For example, studies indicate that a mutation in a mismatch repair gene is found in approximately 40% to 80% of families that meet the Amsterdam I criteria and only about 5% to 50% of families meeting the Amsterdam II criteria.[15] Similarly, only about 5% to 10%of unselected patients with breast cancer[16] and 20% to 25% of patients with hereditary breast cancer[17] are found to carry a deleterious *BRCA1* or *BRCA2* mutation. Additionally, a

number of other genes associated either with rare high-penetrance syndromes or a more moderate penetrance were identified.

Based on these findings, the general paradigm of testing evolved whereby the more common genes such as *BRCA1* and *BRCA2* were tested first, and, if negative, sequential testing for additional gene(s) was performed if the patient met criteria for testing for other syndromes. This process had both advantages and disadvantages. In terms of advantages, the genes tested in this setting typically have well-described cancer risks and often have established management guidelines. Additionally, through the pretest counseling process, patients undergoing this testing have had the opportunity to fully consider the benefits, risks, and limitations of testing in their particular situation. In terms of disadvantages, such testing is less comprehensive than multigene testing, and, if performed, sequential testing is quite time-consuming and costly.

MULTIGENE PANELS

There has been a dramatic shift in the genetic testing landscape over the past several years in large part because of two major factors. The first is the development of next-generation sequencing, a high-throughput approach to DNA sequencing that allows for massively parallel sequencing of multiple genes more efficiently and at a lower cost than the traditional Sanger sequencing methods. The second is the Supreme Court decision in 2013 for *Association for Molecular Pathology v. Myriad Genetics*, which invalidated many patents restricting *BRCA1/2* testing. Very shortly after the ruling, many companies and some academic institutions announced they would offer BRCA testing in addition to the existing genes on their multigene panels.[18,19] As a result of these two factors, offering relatively rapid turnaround times for multigene testing in a reasonably affordable manner became feasible.

The panels differ from company to company. They may be comprehensive, tumor-specific, and focus only on highly penetrant genes, or be customizable (Table 1). The price of testing also has dropped significantly. It now can range from $249 to $6,040, with most costing $1,500 to $6,040. The cost varies among laboratories and differs based on the number of genes included. In most cases, the cost of multigene panel testing does not significantly differ from the cost of more single/limited gene testing. Furthermore, the cost of testing likely will continue to diminish over time. Adding to the complexity of testing choices is that insurance companies have different policies and may cover some but not all choices.

A number of studies have evaluated the utility and impact of multigene testing in a variety of settings. The key questions that must be addressed revolve around the clinical utility or actionability of the findings from such testing, namely (1) the numbers of patients who are found to have a deleterious mutation in a gene for which cancer risks are known and management strategies exist, (2) patients who are found to have a mutation with uncertain cancer risks and/or no evidence-based recommendations for management, and (3) the rate detection of variants of uncertain significance (VUS). As summarized in Tables 2 and 3, the rate of VUS varies between 3.3% and 42%, and many patients were reported to have two or

more VUS. The VUS rate is still high in some reports, but it is expected to fall in the near future because of the rapid accumulation of data from multigene panel testing.

Given the high rate of VUS and the detection of genes for which the cancer risks are not well-defined, several registries have been created to catalog and curate these variants with the goal of advancing our knowledge about their clinical utility. The Prospective Registry of Multiplex Testing (PROMPT)[34] is a multi-institutional online registry that encourages patients to self-enter information about their genetic testing results and to complete questionnaires about their personal medical and family histories. Others involved in reclassifying variants include ENIGMA (Evidence-based Network for the Interpretation of Germline Mutant Alleles) Consortium[35] and ClinVar, a peer-reviewed database funded by the National Institutes of Health, which is a freely available archive of reports of relationships among medically important variants and phenotypes.[36] Professional societies such as the American Medical Association also have adopted positions in favor of data sharing.[37]

SINGLE/LIMITED GENE VERSUS MULTIGENE PANEL TESTING

Several factors guide the decision to pursue testing of a single gene or a finite set of genes associated with a particular syndrome versus multigene panel testing. These include (1) the characteristics of the proband's personal and family history, (2) an individual's preferences and tolerance regarding the possibility of ambiguous results, (3) insurance-related issues, and (4) the rapidity with which results are needed. A publication in the *New England Journal of Medicine* in 2015, authored by experts from the United States, United Kingdom, the Netherlands, Germany, Australia, and Canada, thoughtfully reviewed the issues that must be addressed when considering multigene panels.[45] Additionally, ASCO released a policy statement on genetic and genomic testing for cancer susceptibility to reflect the impact of advances in this field.[5]

Single/limited gene testing remains an excellent option when the clinical features, such as the patient's personal and family history, are strongly indicative of a particular syndrome associated with a single or finite set of genes. This approach allows for a focused and comprehensive pretest evaluation in which individuals have an opportunity to more fully consider the impact of testing for a particular gene or set of genes. Additionally, such testing minimizes the likelihood of detecting a VUS or a deleterious mutation in a gene with limited clinical information.

Multigene panel testing is an appropriate option when the family phenotype is not suggestive of a single specific mutation and one or more hereditary cancer syndromes are in the differential. Additionally, panel testing is often considered if more focused initial testing is negative (e.g., *BRCA1/2* testing followed by multigene breast/ovarian panel). Multigene panel testing has a number of advantages and potential disadvantages (Table 4). The advantages include gains in efficiency both in terms of cost and time. Such testing also would result in a more comprehensive assessment of the genes that could account for the cancer phenotype in the family. Finally, pragmatically, in this era of multigene panel testing, it is unclear if an individual could obtain insurance coverage for repeat testing if the initial,

more limited testing results were negative. In terms of disadvantages, as described previously, multigene panel testing has a higher rate of detection of VUS. Individuals undergoing testing must be fully informed of this possibility before testing and counseled on the interpretation of such a result. Furthermore, it is important that an individual undergoing panel testing understands it is possible that a high-penetrance mutation in an uncommon or rare gene may be identified, even in the absence of a classic presentation of the associated syndrome. Consequently, aggressive interventions may be recommended, such as consideration of prophylactic gastrectomy if a *CDH1* mutation was found, even in the absence of gastric cancer in the family. At this moment, it is unclear if the cancer risks for patients identified through panel testing without features of the associated syndrome are the same as quoted in the literature because of ascertainment bias. Moreover, laboratories have varying methods by which they assure the analytic and clinical validity and the clinical utility of the variants they report. Expertise in this area is required to ensure accurate interpretation of the clinical significance of the findings reported. Given the panoply of testing options, this expertise is also critical to guide the choice of which test to order and from which laboratory. These issues further underscore the importance of ensuring that patients undergo pre- and post-test genetic counseling by well-trained professionals, as endorsed by ASCO and the National Comprehensive Cancer Network.[46]

GERMLINE FINDINGS ON MOLECULAR PROFILING OF TUMORS

An important challenge when performing vast-scale sequencing is the potential for detecting incidental findings. Incidental findings are defined as unexpected positive findings. In this context, they refer to the detection of deleterious or likely deleterious alterations in genes that have clinical significance and are unrelated to the indication for obtaining the sequencing test. Typically, these are germline mutations. As such, the only way to truly determine if an identified sequence variant is somatic or inherited is to simultaneously analyze tumor and normal DNA. This analysis allows for a determination on which variants are unique to the cancer (i.e., somatic) and which are germline. Determining whether, which, and how incidental findings are returned to the patient is becoming increasingly important and controversial. The American College of Medical Genetics and Genomics published a policy statement on clinical sequencing that included exome and genome sequencing.[47] The policy statement recommended that constitutional mutations from a panel of 56 disease-associated genes be reported to the ordering clinician, regardless of the indication for which the clinical sequencing was ordered (Table 5). These genes were chosen because they result in disorders for which preventive strategies and/or treatments are available. About half are associated with syndromes that increase the risk of cancer; the others are primarily associated with various cardiac diseases. The American College of Medical Genetics and Genomics also states that the ordering clinician/team is responsible for providing the patient with comprehensive pre- and post-test counseling.

Several challenges are inherent in this process. They range from analytic issues (e.g., determining if the variant is germline and, if so, if it is deleterious/likely deleterious, a VUS, or a benign polymorphism) to practical issues related to obtaining informed consent and delivering traditional pre- and post-testing genetic counseling. ASCO recently published a policy statement on genetic and genomic testing for cancer susceptibility that includes

germline implications of somatic mutation profiling.[5] The policy statement recognizes that standard pre- and post-test counseling may not be feasible in this setting for all patients. It recommends that the possibility of identifying secondary incidental germline information as well as the clinical relevance, benefits, risks, and limitations of such incidental findings be discussed with all patients before they undergo tumor sequencing. ASCO also endorses that providers should honor patients' decisions if they elect not to receive information about such incidental findings.

CONCLUSION

Next-generation sequencing has introduced substantial complexity and promise in the field of cancer risk assessment. Although multigene panel testing provides a more comprehensive and efficient approach to testing an individual for a hereditary susceptibility to cancer, the information obtained can be challenging to interpret. Furthermore, many of the genes included in multigene panels have not been fully characterized either in terms of their cancer risks or management strategies. In many cases, single/limited gene testing remains a very appropriate testing option. Presently, we live in an era in which our technical capabilities have outstripped our medical knowledge. A strong and continuous partnership among clinicians, individuals with genetics expertise, and laboratory geneticists is critical to bridge this gap.

As to the detection of incidental findings on tumor sequencing, more research is clearly necessary to better clarify how to approach this complex area. Until such time, as stated by ASCO, it is critical that individuals undergoing tumor sequencing be fully apprised of the possibility, benefits, risks, and limitations that such testing could uncover unanticipated mutations in cancer susceptibility genes.

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KEY POINTS

- Advances in technology have resulted in the ability to test for multiple genes associated with a hereditary predisposition to cancer.
- Multigene panel testing can allow for a more comprehensive and efficient approach to testing, but many of the genes included in multigene panels have not been fully characterized either in terms of their cancer risks or management strategies. In many cases, single/limited gene testing remains a very appropriate testing option.
- The decision to pursue single or limited gene testing is complex and referral to clinicians with expertise in cancer genetics is critical. Testing must be carried out with pre- and post-test genetic counseling.
- In the tumor molecular profiling setting, secondary incidental germline mutations may be detected. ASCO recommends that the possibility of identifying secondary incidental germline information and the clinical relevance, benefits, risks, and limitations of such findings be discussed with all patients before they undergo tumor sequencing.

TABLE 1

Examples of Genes Included on Some Next-Generation Sequencing Cancer Panels *

	Company	Test	Number of Genes	Genes Included
Comprehensive Panels	Ambry Genetics	CancerNext[20]	32	*APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, BMPR1A, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GREM1, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, POLD1, POLE, PTEN, RAD50, RAD51C, RAD51D, SMAD4, SMARCA4, STK11, TP53*
	GeneDx	OncoGene Dx Comprehensive Cancer Panel[21]	32	*APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SCG5/GREM1, SMAD4, STK11, TP53, VHL, XRCC2*
	Myriad Genetics	MyRisk[22]	25	*BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, EPCAM, APC, MUTYH, CDKN2A, CDK4, TP53, PTEN, STK11, CDH1, BMPR1A, SMAD4, PALB2, CHEK2, ATM, NBM, BARD1, BRIP1, RAD51C, RAD51D*
	Invitae	Invitae Multi-CancerPanel[23]	79	*ALK, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CASR,CDC73, CDH1, CDK4, CDKN1B, CDKN1C, CDKN2A, CEBPA, CHEK2, DICER1, DIS3L2, EGFR, EPCAM, FH, FLCN, GATA2, GPC3, GREM1, HOXB13, HRAS, KIT, MAX, MEN1, MET, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NF2, PALB2,PDGFRA, PHOX2B, PMS2, POLD1, POLE, PRKAR1A, PTCH1, PTEN, RAD50,RAD51C, RAD51D, RB1, RECQL4, RET, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TERC, TERT, TMEM127, TP53, TSC1, TSC2, VHL, WRN, WT1*
Breast/Ovarian Panels	Ambry Genetics	BRCAplus[24]	6	*BRCA1, BRCA2, CDH1, PALB2, PTEN, TP53*
		BreastNext[25]	17	A*TM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, TP53*
		OvaNext[26]	23	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMARCA4, STK11, TP53*
	Invitae	Breast and Gynecologic Cancers Guidelines Based Panel[27]	14	*ATM, BRCA1, BRCA2, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2,PTEN, STK11, TP53*
		Breast Cancer Guidelines Based Panel[28]	9	*ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53*
	Color Genomics[29]	Color	19	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MHL1, MSH2, MSH6, NBM, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53*

	Company	Test	Number of Genes	Genes Included
	GeneDx	Breast Cancer High/Moderate Risk Panel[21]	9	*ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53*
		Breast/Ovarian Cancer Panel[21]	21	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53, XRCC2*
Gastrointestinal Panels	Ambry Genetics	ColoNext[30]	17	*APC, BMPR1A, CDH1, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH6, MUTYH, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TP53*
	Invitae	Colorectal Cancer Guidelines Based Panel[31]	12	*APC, BMPR1A, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11, TP53*
	Myriad Genetics	COLARIS[32]	6	*MLH1, MSH2, EPCAM, MSH6, PMS2, MUTYH*
		COLARIS AP[33]		*APC, MUTYH*
	GeneDx	Colorectal Cancer Panel[21]	19	*APC, ATM, AXIN2, BMPR1A, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, POLD1, POLE, PTEN, SCG5/GREM1, SMAD4, STK11, TP53*
		Lynch/Colorectal High Risk Panel[21]	7	*APC, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2*

Abbreviation: VUS, variants of uncertain significance.

*Current as of February 2, 2016.

TABLE 2

Rate of Deleterious Mutations and VUS Reported in Multigene Testing Associated with Hereditary Breast Cancer

Publication	No. of Participants	Panel Tested	BRCA Mutations Detected (%)	Non-BRCA Mutations Detected (%)	VUS Rate (%)
apoor et al[38]	337	Ambry Genetics; different panel types and genes tested	3.6%	3.9%; gene mutations more often detected: *PALB2, CHEK2, ATM*	3.3% *BRCA1/2* and 13.4% non-*BRCA1/2*
Slavin et al[39]	348	Not provided	3.4%	16.4%	42%
Tung et al[40]	2,158	Cohort 1: Referred for commercial *BRCA1/2* gene testing and	9.3%	4.2%	41.7%
		Cohort 2: Previously tested negative for *BRCA1/2* mutations		3.7%	41.6%
Chong et al[41]	3,000	BRCAPlus: 6-gene panel (*BRCA1, BRCA2, TP53, CDH1, PTEN, SKT11*)	4.6%	1%	7.6%
Kurian et al[42]	198 (57 BRCA1/2, 141 BRCA1/2 neg)	Invitae		11.4%	2.1% VUS/average per participant
LaDuca et al[43]	2,079 (874 had breast panel)	Ambry Genetics	All previously underwent *BRCA* sequencing and BART testing and were negative	7.4% gene mutations detected: *CHEK2* (19), *ATM* (18), *PALB2* (15), *TP53* (4), *PTEN* (3), *RAD50* (3), *RAD51C* (2), *BRIP1* (1), *MRE11A* (1), *NBN* (1)	19.8%

Abbreviation: VUS, variants of uncertain significance.

TABLE 3

Rate of Deleterious Mutations and VUS Reported in Multigene Testing Associated with Colorectal Cancer

Publication	No. Patients	Panel Tested	LS Genes (MLH1, MSH2, MSH6, PMS2, EPCAM) Mutations Detected (%)	Non-LS Genes Mutations Detected (%)	VUS Rate (%)
LaDuca et al[43]	557	Ambry Genetics	4.5%: *MSH* (7), *MLH1* (7), *PMS2* (6), *MSH* (5)	4.7% (26): *APC* (6), *CHEK2* (6), *MUTYH* biallelic (6), *SMAD4* (4), *PTEN* (3), *CDH1* (1), *STK11* (1), *TP53* (1)	15.1% (84)
Yurgelun et al[44]	1,260	Myriad MyRisk Hereditary Cancer	9.5%	3.8% (48): *BRCA1/2 (15), APC* biallelic *MUTYH, PTEN, STK11, ATM, BARD1, BRIP1, CHEK2, NBN, PALB2,* and *RAD51C*	44%

Abbreviations: LS, Lynch syndrome; VUS, variants of uncertain significance.

TABLE 4

Pros and Cons of Single/Limited Gene Testing and Multigene Panels

	Single/Limited Gene Testing	Multigene Panels
Advantages	Phenotype-directed testing	More cost effective (less expensive per gene cost)
	Cancer risks and management options often more established	More time efficient
		Decrease in testing fatigue for patients and providers
	Lower likelihood of detecting VUS	Efficient use of single specimen
	More rapid turnaround time	Higher mutation detection rate, genes individually rare but collectively significant
Disadvantages	Higher risk of loss to follow-up during sequential testing multiple single genes (test fatigue)	Increased prevalence of VUS
	Less comprehensive	Cancer risks and management options often not well-defined, particularly for some moderate- and low-penetrance genes
		Unexpected findings such as “off-phenotypic-target” gene mutation
		Longer turnaround time
		Panels may include genes that patients don’t wish to test for

Abbreviation: VUS, variants of uncertain significance.

TABLE 5

Conditions and Genes Recommended by the American College of Medical Genetics and Genomics for Return of Incidental Findings in Clinical Sequencing[47]

Phenotype	Gene
Hereditary breast and ovarian cancer	*BRCA1, BRCA2*
Li-Fraumeni syndrome	*TP53*
Peutz-Jeghers syndrome	*STK11*
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*
Familial adenomatous polyposis	*APC*
MYH-**associated polyposis; adenomas; multiple colorectal cancers; familial amyloid polyneuropathy type 2; colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas**	*MUTYH*
Von Hippel-Lindau syndrome	*VHL*
Multiple endocrine neoplasia type 1	*MEN1*
Multiple endocrine neoplasia type 2	*RET*
Familial medullary thyroid cancer	*RET*
PTEN **hamartoma tumor syndrome**	*PTEN*
Retinoblastoma	*RB1*
Hereditary paraganglioma-pheochromocytoma syndrome	*SDHD, SDHAF2, SDHC, SDHB*
Tuberous sclerosis complex	*TSC1, TSC2*
WT1-**related Wilm syndrome**	*WT1*
Neurofibromatosis type 2	*NF2*
Ehlers-Danlos syndrome (vascular type)	*COL3A1*
Marfan syndrome, Loeys-Dietz syndrome, familial thoracic aortic aneurysms and dissections	*FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYLK, MYH11*
Hypertrophic cardiomyopathy, dilated cardiomyopathy	*MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA*
Catecholaminergic polymorphic ventricular tachycardia	*RYR2*
Arrhythmogenic right-ventricular cardiomyopathy	*PKP2, DSP, DSC2, TMEM43, DSG2*
Romano-Ward Long QT syndrome types 1, 2, and 3; Brugada syndrome	*KCNQ1, KCNH2, SCN5A*
Familial hypercholesterolemia	*LDLR, APOB, PCSK9*
Malignant hyperthermia susceptibility	*RYR1, CACNA1S*