Clinical Actionability of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer Risk Assessment

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IMPORTANCE The practice of genetic testing for hereditary breast and/or ovarian cancer (HBOC) is rapidly evolving owing to the recent introduction of multigene panels. While these tests may identify 40% to 50% more individuals with hereditary cancer gene mutations than does testing for BRCA1/2 alone, whether finding such mutations will alter clinical management is unknown.

OBJECTIVE To define the potential clinical effect of multigene panel testing for HBOC in a clinically representative cohort.

DESIGN, SETTING, AND PARTICIPANTS Observational study of patients seen between 2001 and 2014 in 3 large academic medical centers. We prospectively enrolled 1046 individuals who were appropriate candidates for HBOC evaluation and who lacked BRCA1/2 mutations.

INTERVENTIONS We carried out multigene panel testing on all participants, then determined the clinical actionability, if any, of finding non-BRCA1/2 mutations in these and additional comparable individuals.

MAIN OUTCOMES AND MEASURES We evaluated the likelihood of (1) a posttest management change and (2) an indication for additional familial testing, considering gene-specific consensus management guidelines, gene-associated cancer risks, and personal and family history.

RESULTS Among 1046 study participants, 40 BRCA1/2-negative patients (3.8%; 95% CI, 2.8%-5.2%) harbored deleterious mutations, most commonly in moderate-risk breast and ovarian cancer genes (CHEK2, ATM, and PALB2) and Lynch syndrome genes. Among these and an additional 23 mutation-positive individuals enrolled from our clinics, most of the mutations (92%) were consistent with the spectrum of cancer(s) observed in the patient or family, suggesting that these results are clinically significant. Among all 63 mutation-positive patients, additional disease-specific screening and/or prevention measures beyond those based on personal and family history alone would be considered for most (33 [52%] of 63; 95% CI, 40.3%-64.2%). Furthermore, additional familial testing would be considered for those with first-degree relatives (42 [72%] of 58; 95% CI, 59.8%-82.2%) based on potential management changes for mutation-positive relatives. This clinical effect was not restricted to a few of the tested genes because most identified genes could change clinical management for some patients.

CONCLUSIONS AND RELEVANCE In a clinically representative cohort, multigene panel testing for HBOC risk assessment yielded findings likely to change clinical management for substantially more patients than does BRCA1/2 testing alone. Multigene testing in this setting is likely to alter near-term cancer risk assessment and management recommendations for mutation-affected individuals across a broad spectrum of cancer predisposition genes.
Genetic testing for hereditary cancer predisposition genes represents an important advance in cancer medicine. In particular, the identification of individuals at elevated risk for hereditary breast and/or ovarian cancers (HBOCs) has allowed the development of consensus recommendations for cancer screening and prevention. Implementing mutation-based cancer screening and prevention guidelines, such as prophylactic salpingo-oophorectomy for carriers of germline BRCA1 and BRCA2 (hereafter BRCA1/2) mutations, is associated with an increase in both cancer-specific and overall survival. While the clinical implementation of genetic testing for BRCA1/2 preceded the development of firm mutation-based management guidelines, the wide availability of a validated platform for this testing contributed to our understanding of genetic cancer risk and ultimately to more effective management of these patients.

Advances in technology and the overturning of patents on genetic testing have now made practical the simultaneous assessment of virtually an unlimited number of genes. Consequently, a number of clinical laboratories now offer clinical genetic testing incorporating multigene cancer panels. In theory, such panels offer the potential for more comprehensive genetic cancer risk assessment and may provide a more rational approach for genetic assessment of those individuals whose personal and family cancer histories do not fit neatly into a single syndrome. Indeed, it is now established that many individuals harboring important cancer risk genes, including BRCA1/2, are overlooked because they would not meet current criteria for testing under the traditional single gene- and syndrome-focused approach.

The rapid clinical introduction of multigene panel testing has, however, raised several concerns. In particular, many of the tested genes are low- to moderate-risk genes for which consensus management guidelines have not been established or have been introduced only very recently. In the absence of an identified mutation, recommendations for cancer-specific screening and prevention approaches for patients and family members are typically based on personal and/or family cancer history. Thus, it is uncertain whether identifying such low- to moderate-risk gene mutations would change individual clinical management recommendations in patients referred for genetic testing, most or all of whom are already established to have a clinically significant personal or family history. While prior studies have reported the prevalence of various cancer risk mutations in appropriately selected cohorts, whether these findings would change clinical management for the affected individuals has not been systematically addressed. Given this uncertainty and the very recent introduction of expanded gene-based practice guidelines for HBOC risk assessment, there is a substantial and pressing unmet need to understand how and whether multigene testing will affect near-term screening and prevention recommendations.

We sought to understand the clinical actionability of multigene cancer predisposition panel testing based on current practice standards in a typical academic cancer genetics practice. We enrolled patients referred for genetic counseling for HBOC predisposition at 3 large academic medical centers. We restricted enrollment to those who were appropriate candidates for HBOC genetic evaluation based on established criteria. These include age at cancer onset, history of multiple primary cancers (eg, breast cancer), and number of close relatives diagnosed with HBOC-associated cancers. We then assessed on a research basis the prevalence of deleterious mutations in cancer risk genes using representative multigene panel tests conducted in commercial diagnostic laboratories. Through detailed analysis of personal and family history and the application of established gene- and risk-based clinical practice guidelines, we demonstrate that finding a non-BRCA1/2 mutation is likely to change clinical management recommendations for the majority of affected individuals and to warrant testing of additional family members. Collectively, these findings define the potential near-term clinical effect of multigene panel testing for patients with suspected HBOC predisposition.

### Methods

#### Participant Accrual

Eligible participants included those referred for genetic counseling and/or testing for HBOC risk assessment at 3 academic medical centers (Massachusetts General Hospital [MGH] Center for Cancer Risk Assessment, Stanford University Clinical Cancer Genetics Program, and Beth Israel Deaconess Medical Center [BIDMC] Breast/Ovarian Cancer Genetics Clinic) and their community affiliates between 2001 and May 2014 (eFigure in the Supplement). All personal and family history data were ascertained by licensed genetic counselors. All participants met current National Comprehensive Cancer Network (NCCN) criteria for further genetic risk evaluation for HBOC. Patients were excluded if they were found to have a deleterious BRCA1/2 mutation or if the only referral indication was

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### At a Glance

- Multigene panel genetic tests are increasingly recommended for patients presenting for hereditary breast and/or ovarian cancer (HBOC) evaluation, but it is unknown how often the results will change patient management.
- We sought to determine how often multigene panel testing would identify clinically actionable mutations among patients appropriately tested for but lacking BRCA1/2 mutations.
- Uniform multigene testing of BRCA1/2-negative patients revealed that 3.8% (40 of 1046; 95% CI, 2.8%-5.2%) harbored other deleterious mutations, most commonly in moderate-risk HBOC genes and Lynch syndrome genes.
- Among 63 non-BRCA1/2 mutation-positive patients, additional cancer screening and/or prevention measures beyond those based on personal or family history would be considered for the majority (33 [52%] of 63, 95% CI, 40.3%-64.2%), as would testing of first-degree relatives.
- Multigene testing in this setting is likely to alter cancer risk assessment, clinical management, and familial testing recommendations for substantially more patients than does BRCA1/2 testing alone.
for single-site testing for a mutation already known to be present within the family. In addition, accrual at BIDMC was restricted to patients with a personal history of breast cancer. Race and ethnicity, including Ashkenazi Jewish ancestry, were self-reported. In total, 1046 participants were prospectively accrued solely based on these criteria and were not otherwise selected for personal or family history (Table 1 and eTable 1 in the Supplement).

An additional 23 participants harboring non-BRCA1/2 mutations were included in the clinical management analysis. These participants were referred to our centers under the same criteria and had family histories and mutation spectra comparable to the rest of the cohort (eTable 2 in the Supplement). However, these individuals were enrolled outside of the prospective enrollment period at the respective sites and/or underwent testing other than the multigene panels described herein.

All participants signed informed consent statements approved by the institutional review boards of either Stanford University or the Dana-Farber Harvard Cancer Center. Participants were asked to donate 10 to 15 mL of blood at the time of their initial clinic visit and consented to the possibility of recontact for future studies. Prior studies including these individuals are detailed herein.10,16,20

**Gene Selection, Sequencing Analysis**

Patients were tested with the 29-gene Hereditary Cancer Syndromes test (In vitea), used at Stanford and MGH, or the 25-gene MyRisk test (Myriad Genetics), used at BIDMC. These germline genetic tests are substantially similar and include genes with established hereditary cancer risks (eTable 3 in the Supplement). The testing was performed for research purposes, and results were not returned directly to participants except as stipulated in the study consent. Return of results is ongoing for participants who consented to this option. The presence of non-BRCA1/2 mutations in a subset of this cohort (14 of 63) was reported in our group’s recent studies,10,16 as detailed in eTable 4 in the Supplement. A complementary technical manuscript scheduled for publication July 21, 2015,20 provides detailed specifications of sequencing, variant classification, and validation in the MGH and Stanford participants.

**Clinical Management Determination**

For those participants identified to harbor non-BRCA1/2 mutations (ie, pathogenic and likely pathogenic variants, n = 63), we established whether the positive test result would change management from that based on personal and family history alone. This involved applying the established gene-specific NCCN management guidelines and mutation-associated cancer risks in the context of the individual personal and/or family history, and comparing the resulting recommended management to risk-driven management in the absence of genetic data.1,21-28 as detailed in Table 2. In separate analyses, we assessed (1) altered management for the participant and (2) altered testing recommendations for first-degree relatives based on a management change for them resulting from a positive test result. This conservative analysis did not consider all potential management changes resulting from genetic testing but rather focused on clear differences between gene-specific consensus guidelines vs practice standards based on personal and family history alone. Potential implications of negative results of mutation testing by family members were not considered in this analysis.

**Data Submission**

Deidentified panel test results for the variants in this study have been submitted to the ClinVar database.29 All non-BRCA1/2 mutations identified in this study are also provided in eTable 4 in the Supplement.

**Statistical Analysis**

Binomial proportion confidence intervals (CIs) were calculated with the Wilson method using numpy/scipy in Python software, version 2.7. For the 63 non-BRCA1/2 positive cases, the half width of the 95% CI on management changes would be at most 12%.

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**Table 1. Testing Results by Gene Category and Personal History**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Any Deleterious Mutation by Test Result, No. (%) of Individuals</th>
<th>Result by Gene Category, No. (%) of Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-Risk BR and/or OV‡</td>
<td>Mod- and/or Low-Risk BR and/or OV‡</td>
</tr>
<tr>
<td>At any age</td>
<td>32 (4.0)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>BR (n=832)</td>
<td>5 (11)</td>
<td>0</td>
</tr>
<tr>
<td>OV (n=47)</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Ashkenazi Jewish (n=143)</td>
<td>4 (2.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Cancer unaffected (n=150)</td>
<td>40 (3.9)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Total (n=1046)</td>
<td></td>
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</tbody>
</table>

Abbreviations: BR, breast cancer; Mod, moderate; OV, ovarian cancer.

* TP53, PTEN, STK11, CDH1.

† BARD1, CHEK2, PALB2, ATM, BRIP1, RAD51C, RAD51D, NBN.

‡ MLH1, MSH2, MSH6, PMS2, EPCAM.

§ APC, BMPRIA, SMAD4, CDK4, CDKN2A, PALLD, MET, MEN1, RET, PTCH1, VHL, MUTIL1 biallelic.

‡ Among 40 patients there were 41 mutations; 1 patient had concurrent ATM and BARD1 mutations. Numbers in this column do not total 40 because 1 patient had BR/OV, and one Ashkenazi Jewish patient had OV.
Results

We first assessed the overall prevalence of potentially relevant cancer risk gene mutations in 1046 individuals who were referred to our centers for HBOC predisposition evaluation and who lacked BRCA1/2 mutations (eFigure in the Supplement). The vast majority were women, and 83% had a personal history of breast and/or ovarian carcinoma, while only 14% were cancer unaffected (eTable 1 in the Supplement). Of those affected with cancer, more than 70% were younger than 50 years at the time of cancer diagnosis. By self-reported ethnicity, most were white (82%), and nearly 14% reported Ashkenazi Jewish descent (Table 2).

All of these individuals underwent multigene testing using either a 29-gene (n = 669) or a 25-gene (n = 377) panel, which included established high-risk and low- or moderate-risk HBOC predisposition genes (eTable 3 in the Supplement). Consistent with recently reported findings from other similar cohorts, and our group’s published work, we found that 3.8% of BRCA1/2 mutation-negative individuals (95% CI, 2.8%-5.2%) harbored deleterious mutations in other hereditary cancer predisposition genes. In the majority of these individuals (26 of 40, 63%), the mutant gene identified was associated with low to moderate HBOC risk (Table 1). In a minority of individuals (8 of 40, 20%) mutations were found in genes associated with Lynch syndrome, which confers increased ovarian cancer risk (Table 1).

Notably, only 3 mutations were found in established high-risk breast cancer genes other than BRCA1/2 (all 3 in CDH1). Only 4 mutations were found in genes without a well-established link to HBOC (2 in CDKN2A, 1 biallelic in MUTYH, and 1 in APC).

An additional 23 patients referred to our centers and harboring non-BRCA1/2 mutations were enrolled and included in subsequent analyses. These patients demonstrated demographic characteristics, family history, and mutation profiles comparable to the rest of the cohort (eTable 2 in the Supplement).

In the large majority of mutation-positive cases (58 of 63, 92.3%; 95% CI, 83.9%-95.4%), the personal and/or family history included cancers associated with the respective mutant genes, suggesting that these mutations are clinically significant for these individuals (eTable 5 in the Supplement). Analysis of mutation prevalence in patient subsets defined by personal cancer history showed that those with a history of ovarian cancer, although they were relatively few in number (n = 47), had a rate of mutations higher than the cohort as a whole (5 of 47, 11%) (Table 1). In contrast, subsets of the cohort with low rates of mutations were those with triple-negative breast cancer (n = 59, 1 NBN mutation) (Figure 1) and those reporting Ashkenazi descent (1 of 143 participants had a Lynch gene mutation) (Table 1). Notably, among patients with breast cancer, we did not observe an effect of age at diagnosis on the prevalence of breast cancer–associated genes (Figure 1). This situation is quite different from BRCA1/2, the prevalence of which is strongly age dependent, and suggests that diagnosis age is not a reliable indicator of mutation probability when testing for these other genes. Collectively, these data suggest that ours is a representative population and underscore that a substantial proportion of patients who present for HBOC testing harbor deleterious mutations in relevant cancer predisposition genes other than BRCA1/2.

To address the central clinical question of how often a positive mutation finding is likely to change management recommendations otherwise based on personal and family history alone, we undertook a detailed review of the 63 patients in whom a non-BRCA1/2 mutation was identified. For each mutation-positive individual, we noted the consensus NCCN guideline recommendations for cancer screening and prevention corresponding to that mutation, and we noted published gene-specific cancer risk data, in both cases incorporating the individual’s personal and family history. We then asked whether management based on these factors was different from that recommended on the basis of personal and family history alone (Table 2). In addition, using the same analysis, we determined whether first-degree family members would...
Nearly one-third of mutation-positive patients (20 of 63) were found to harbor mutations in high-risk genes associated with detailed NCCN management guidelines (Table 2), and in each case finding the mutation would change the pretest recommendations for screening and/or preventive surgery (Table 2 and Table 3). For example, 9 participants were found to have deleterious mutations in genes associated with Lynch syndrome, and in most of these cases the personal and/or family history included Lynch syndrome cancers (eTable 5 in the Supplement). In every case this finding would prompt heightened colorectal cancer screening for the participant as well as additional familial testing. Potential additional interventions for family members harboring deleterious mutations in the context of a proband with ovarian cancer and this mutation might include, in particular, prophylactic hysterectomy and salpingooophorectomy (Figure 2A).22

As anticipated, the most common mutations found were those in genes associated with low or moderately increased breast cancer risk (40 of 63) (Table 1). A management change would be recommended for these patients in a minority of cases (10 of 40), involving either increased screening or preventive surgery (Table 2 and Table 3). For example, among 5 (unre-
rated) participants identified with deleterious \textit{PALB2} mutations, 4 had been treated for breast cancer, while 1 was unaffected but had a clinically significant family history of breast cancer (Figure 2B). Recent work suggests that breast cancer risk for \textit{PALB2} carriers may overlap with that of \textit{BRCA2} carriers, particularly in the context of a significant family history.\textsuperscript{24} Accordingly, recently introduced NCCN practice guidelines suggest that \textit{PALB2} carriers should undergo enhanced breast screening.\textsuperscript{1} In the context of the significant family histories observed in our patients, prophylactic breast surgery would also be a consideration.\textsuperscript{1}

We found that the potential effect of identifying these low- and moderate-risk HBOC genes was greater for family members than for the patients themselves. Close female family members of those found to harbor deleterious \textit{ATM} and \textit{CHEK2} mutations, for example, would in many cases be deemed to have a low pretest cumulative risk of breast cancer (<20%) by current prediction models (Table 2).\textsuperscript{26} The most recent NCCN gene-based guidelines predict a greater than 20% cumulative risk for \textit{ATM} and \textit{CHEK2} mutations-positive individuals and consequently recommend magnetic resonance imaging screening.\textsuperscript{1,21} Similarly, \textit{RAD51c} mutations have been identified in families with HBOC and could trigger a recommendation for enhanced breast screening in individuals with appropriate family histories.\textsuperscript{25,26} In total, 36 of 40 patients with low- to moderate-risk HBOC genes had first-degree female relatives, and in 20 of these 36 families, 1 or more such relatives would be recommended for enhanced screening were they to test positive (Table 2 and eTable 5 in the Supplement).

In total, among 63 patients identified with these cancer-risk mutations, 52% (33 of 63; 95% CI, 40.3%-64.2%) would receive a posttest management recommendation for additional screening and/or prevention based on current consensus practice guidelines. Importantly, these recommendations are above and beyond those based on personal and family history alone. Furthermore, for those individuals with first-degree family members, the mutation would prompt a recommendation for familial testing in 72% of cases (42 of 58; 95% CI, 59.8%-82.2%) (Table 2).
Discussion

We sought to determine the near-term clinical effect of deleterious germline mutations beyond BRCA1/2 identified through multigene panel testing in patients presenting for HBOC cancer risk assessment. Previous studies have reported on the prevalence of deleterious mutations with particular multigene panels.10,15-20 Our study is distinguished from previously published work by the size of our cohort together with the availability of detailed personal and family history data collected directly from involved participants. In addition, our study avoids biases inherent in studies conducted exclusively on samples available to genetic testing laboratories because our participants were all enrolled directly at the site of referral under uniform criteria. Nevertheless, the prevalence of non-BRCA1/2 mutations of 3.8% in our cohort is consistent with this prior work.10,15-20 Notably, among a subset of patients initially enrolled at 2 of our centers without respect to BRCA1/2 status (n = 735), deleterious mutations in BRCA1/2 were observed in 9.0% (95% CI, 7.1%-11.3%), which is also in keeping with prior studies and further suggests that our cohort is a representative one.10,15 Thus, a 3.8% prevalence of additional mutations represents a substantial (>40%) increase in diagnostic yield of risk-associated mutations compared with BRCA1/2 testing alone. Importantly, the vast majority of the non-BRCA1/2 mutations were found in genes conferring HBOC risk and not in genes lacking association with these cancers (Table 1), suggesting that these findings are relevant to the clinical history.

There is currently considerable uncertainty as to how and whether results from multigene testing will be applied in clinical practice.12,14,31 Furthermore, the practical clinical effect of the recently introduced practice guidelines pertaining to low- and moderate-risk HBOC genes is unknown.1 We asked whether, under current consensus practice guidelines, finding a non-BRCA1/2 mutation would alter the management recommendations that would otherwise be made based on personal and family history alone. We determined that 33 of 63 such patients (52%) would receive additional recommendations for cancer screening and/or preventive measures, based on current gene-based and risk-based NCCN guidelines.1,21,22 This proportion may be an underestimate of the potential clinical consequences of these mutations because we did not consider all potential management changes that might result from these findings but only those that are most strongly supported by consensus practice guidelines.1,21,22 For example, our analysis did not consider whether increased breast screening would be recommended for breast cancer–affected patients based on finding such mutations, since these individuals could already be undergoing such screening, and applicable risk models to guide screening decisions are lacking. In support of the multigene testing approach, we found that virtually every gene identified as mutated in this study changed management for some individuals and families (except for NBN and BRIP1, mutated in a total of 3 cases) (Table 3 and eTable 5 in the Supplement).

A substantial subset of individuals (20 of 63) were found to have mutations in high-risk genes associated with detailed NCCN consensus management guidelines, and in these instances finding the mutation would always change management (Table 2). Notably, although these individuals had personal and/or family histories consistent with the mutation, many would not have met established gene and/or syndrome-specific testing criteria. Thus, these clinically significant mutations may have been missed by the traditional, focused testing approach. The potential clinical effect of finding these mutations was equally important for patients' family members: testing of additional family members would be recommended in all cases (Table 1).1,22

The most prevalent deleterious mutations in our cohort were found in genes associated with moderate to low increased risk for HBOC (Table 1). We determined clinical effect in these cases by applying mutation-associated cancer risk estimates, risk-based and new gene-based consensus practice guidelines.1,25,26 Considering personal and family histories, we found that many patients and family members had relatively low pretest predicted cancer risk (Table 2). Consequently, these mutations would alter risk estimates and management recommendations for a minority of individuals (10 of 40) and would prompt a recommendation for testing in the majority of families (20 of 36), since a positive result would result in a management change (Table 2). Importantly, those family members testing negative for the familial mutation would not necessarily be absolved of risk but would in some cases be managed based on personal and family history alone. We anticipate that as increasing data from multigene panel testing become available, higher confidence in risk estimates will be achieved and will drive development of explicit management guidelines.

While this study provides key new information regarding the utility of multigene genetic testing in this clinical setting, some limitations should be noted. The clinical effect that we demonstrate for this testing is likely to apply only to an appropriately ascertained cohort. Both cancer risk estimates and the probability that an identified mutation would change clinical management are affected by ascertainment and would not apply, for example, to population screening for such mutations.32 In addition, the clinical utility we define is based on current consensus management recommendations and is therefore likely to evolve in the future. Nonetheless, increased use of multigene panel testing coupled with centralized data collection and reporting are likely to enhance the clinical value of these tests over time.13

Finally, we recognize that our data regarding clinical actionability are based on consensus practice guidelines rather than actual clinical practice. Indeed, many factors will ultimately influence the clinical effect of multigene testing. These could include which patients choose to be tested (potentially driven in part by testing costs), which clinicians choose to follow gene-based management guidelines, and which patients follow those clinician recommendations. Future studies of these questions are warranted.15 Our data provide a baseline and reference point for these future studies, showing how often finding a mutation would change management according to national practice standards.
Conclusions

Multigene panel testing for patients with suspected HBOC risk identifies substantially more individuals with relevant cancer risk gene mutations than does BRCA1/2 testing alone. Identifying such mutations is likely to change management for the majority these individuals and their families in the near term, and in the long term should lead to development of effective management guidelines and improved outcomes for at-risk individuals.

REFERENCES


Usefulness of Multigene Testing
Catching the Train That’s Left the Station

Elizabeth M. Swisher, MD

In the mid-1990s, clinical testing for \textit{BRCA1} and \textit{BRCA2} mutations rapidly followed gene cloning. Given the lack of clinical experience with \textit{BRCA1} and \textit{BRCA2} testing, many cancer genetics experts spoke against clinical testing, advocating that testing be done in the research setting only. Increasingly, women and their physicians ignored those recommendations, and testing expanded beyond very high-risk families to include patients with only a moderate likelihood of testing positive. In this way, millions of women worldwide were tested for \textit{BRCA1} and \textit{BRCA2} mutations, leading to the accumulation of large amounts of clinical data, which have in turn confirmed the utility of \textit{BRCA1} and \textit{BRCA2} testing and, most importantly, our ability to decrease the mortality of mutation carriers through guided cancer prevention.

The advent of next-generation sequencing has opened the door to broader evaluation of cancer risk genes without additional cost. For women with breast or ovarian cancer or at-risk relatives, multiplex testing for many cancer-risk genes provides a more comprehensive risk assessment. Many cancer genetics experts have again urged caution, characterizing the use of multigene testing in the clinical setting as premature. Yet thousands of women and their physicians are ignoring this advice, ordering a wide selection of multiplex tests daily. The train has left the station and is unlikely to return. It is therefore critical that we assess the clinical utility of such testing.

Desmond et al\cite{Desmond2018} have provided an important addition to the literature with their assessment of the clinical actionability of hereditary breast and ovarian cancer assessment using multigene testing in a multi-institutional collaborative effort. Most previous studies have been limited to reporting the fraction of additional cases with mutations identified with multigene testing. And some studies that attempted to assess the clinical significance of multiplex testing included genes of uncertain significance (ie, \textit{SLX4}) as well as variants of uncertain significance.\cite{Jaboin2015} In contrast, Desmond and colleagues focus on genes with proven hereditary cancer significance and apply stringent criteria for “actionability” using National Comprehensive Cancer Network (NCCN) guidelines for hereditary breast and ovarian cancer.

In line with previous studies, the authors identified 3.8% of \textit{BRCA1}/2-negative cases to have deleterious mutations in other cancer-risk genes. Reassuringly, more than 90% of these mutations occurred in genes consistent with the personal or family history, demonstrating the clinical relevance of these results and the relative rarity of incidental mutations. Importantly, the majority of mutations resulted in changes in recommendations for cancer screening or prevention. It is important to realize that participants in this study had predominantly breast cancer that was not of the triple-negative subtype or were unaffected by cancer. Choosing a cohort with triple-negative breast cancer or with ovarian cancer would be expected to result in a similar mutation rate but a different gene distribution.\cite{Desmond2018, Jaboin2015}

Actionability is a critical reason to order genetic testing, but defining actionability is not trivial. The authors use NCCN guidelines as a standardized measure, but the NCCN recommendations are incomplete for many genes. For example, the greatest clinical value in identifying a mutation in \textit{RAD51C}, \textit{RAD51D}, or \textit{BRIP1} is probably in defining the level of ovarian cancer risk in the patient and family. However, the NCCN does not yet have guidelines for managing ovarian cancer risk for these genes, and thus identifying the mutation would not result in any actionable change in ovarian cancer screening or prevention. The authors have chosen NCCN guidelines as a conservative measure of actionability, but, as in this example, the utility of testing may be undervalued by current guidelines.

Actionability may also be undervalued by only assessing the effect of identifying damaging mutations. This approach assigns no utility to negative findings, which can also lead to changes in clinical care and improved risk assessment. Take, for example, an individual with early-onset breast cancer and a sibling with breast cancer, a history that, without genetic testing information, increases that individual’s risk of ovarian cancer. However, if she tests negative for all known ovarian cancer-associated genes, she can be reassured that she is not at elevated risk of ovarian cancer. Furthermore, that reassurance is more complete than would have been provided by negative \textit{BRCA1} and \textit{BRCA2} testing alone. For this patient, a negative test result does not eliminate an increased breast cancer risk for family members, but it still provides useful clinical in-