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eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.
eMETHODS

eResults 1. Variant Classification and Reclassification

Variant classification by the testing laboratory was based on ACMG/AMP guidelines as described in eFigure 1. Variants were classified at the time of identification based on available functional, statistical, segregation, and literature evidence. All available data were reviewed by a panel of multi-disciplinary experts. Following this review, variants were classified using a 5-tier classification system (eFigure 1). A small number of variants did not fit one of these five categories and were classified as Special Interpretation. This indicated to providers that there may be complex or specialized information regarding variant pathogenicity. For example, this classification was given when there was conflicting evidence regarding pathogenicity for variants that would otherwise have been classified as likely Pathogenic (LP) or Pathogenic (P) on ACMG guidelines. In addition, variants given this classification may have interesting features, such as evidence of reduced penetrance or association with the recessive rather than dominant disease state.

*BRCA2* c.9699_9702del (p.Cys3233Trpfs*15) is an example of a variant classified as Special Interpretation.¹ This variant results in a frameshift and premature stop codon and is near the 3’ end of the gene; however, there are known pathogenic variants downstream of this variant. Based on this information, this variant could be considered pathogenic according to ACMG/AMP guidelines.² This variant has also been observed *in trans* (on opposite alleles) with known pathogenic *BRCA2* variants in individuals with features of Fanconi anemia, the expected phenotype for individuals with two pathogenic *BRCA2* variants on opposite alleles. However, it has also been observed *in trans* with known pathogenic *BRCA2* variants in individuals without features of Fanconi anemia. In addition, analysis with the laboratory-developed clinical history weighting algorithm³⁴ shows that the personal and family cancer histories of individuals with this variant are not consistent with those of individuals with known pathogenic *BRCA2* variants. Despite the presence of some evidence that the variant may be benign, the
mechanism of action for this mutation should result in increased cancer risk and the in trans presence of the variant does cause Fanconi anemia in some patients. Therefore, this variant does not fit into one of the five classification categories so Special Interpretation is used to alert providers and patients to the uniqueness of this variant.
Reclassification from LP/P to VUS in UTSW Medical Center Subset

Within the subset of patients tested from UTSW Medical Center, three variants were reclassified from P/LP to VUS within this time period. The details of the initial and updated classifications are provided below.

**BRCA1** dup exons 1-22: At the time that this variant was initially classified as LP, large duplications were generally thought by the medical genetics community to disrupt gene expression and/or function. However, it was later determined that most duplications are oriented in a tandem head-to-tail configuration, which if true for this variant, could result in an intact and functional copy of the gene. With this new evidence, the variant was reclassified to VUS.

**TP53** c.542G>A (p.Arg181His): This variant was initially classified as LP based on significant published evidence that this variant disrupts apoptosis. This variant was reclassified to VUS after re-review of the published functional literature showed that although this variant disrupts one critical tumor suppressor function (apoptosis) of the TP53 protein, other functions may not be significantly impacted leaving question about the pathogenicity.

**BRIP1** c.2992_2993del (p.Lys998Glu*3): This variant was initially classified as P because it results in a frameshift and introduction of a premature stop codon. Based on ACMG/AMP guidelines, such variants are typically pathogenic. However, this variant occurs near the 3’ end of the **BRIP1** gene. As noted in the ACMG/AMP guidelines, truncating variants in this region may not actually be pathogenic. Additional review of this end of the **BRIP1** gene left some uncertainty about this area/variant resulting in a reclassification to VUS.

e Results 2. Comparison of Ancestry and Personal Cancer History in Full Cohort versus UTSW Subset

In order to assess demographics information of clinical significance (ancestry, personal cancer history), analyses were performed for exclusive cohorts (full cohort excluding the UTSW subset versus
the UTSW subset). This resulted in slightly different results for the full cohort (excluding the UTSW cohort) compared to the full cohort (including the UTSW cohort) reported in Table 1.

All comparisons were significant. For all hereditary cancer testing, the differences between the full testing cohort versus the UTSW cohort were significant (p<0.001): European, 51.9% versus 43.5%; Latin American or Caribbean, 6.5% versus 21.0%; African, 5.6% versus 15.1%; Asian, 2.6% versus 2.8%; Native American, 1.3% versus 0.1%; Near or Middle Eastern, 0.8% versus 1.6%; Multiple, 9.1% versus 9.5%; None Specified, 22.4% versus 6.3%. For single-syndrome testing, the differences between the full testing cohort versus the UTSW subset were significant (p<0.001): European, 52.9% versus 48.0%; Latin American or Caribbean, 6.3% versus 17.7%; African, 5.5% versus 14.3%; Asian, 2.7% versus 2.9%; Native American, 1.2% versus 0.2%; Near or Middle Eastern, 0.8% versus 1.6%; Multiple, 8.7% versus 8.4%; None Specified, 22.0% versus 7.0%. For panel testing, the differences between the full testing cohort versus the UTSW cohort were significant (p<0.001): European, 48.3% versus 34.6%; Latin American or Caribbean, 7.4% versus 27.5%; African, 6.1% versus 16.8%; Asian, 2.4% versus 2.8%; Native American, 1.3% versus 0.1%; Near or Middle Eastern, 0.7% versus 1.5%; Multiple, 10.5% versus 11.8%; None Specified, 23.2% versus 4.8%.

Similar to ancestry, the statistical significance of personal cancer history differences was assessed by evaluating the data for the exclusive full testing cohort versus the UTSW subset using Fisher’s exact test, as above. For all hereditary cancer testing, the differences between the full testing cohort versus the UTSW cohort were significant (p<0.001): Affected, 56.6% versus 71.5%; Unaffected, 35.3% versus 25.6%; Polyps Only, 1.3% versus 1.5%; Not Specified, 6.8% versus 1.4%. For single-syndrome testing, the differences between the full testing cohort versus the UTSW cohort were significant (p<0.001): Affected, 60.6% versus 77.7%; Unaffected, 29.6% versus 18.5%; Polyps Only, 1.3% versus 1.7%; Not Specified, 8.5% versus 2.1%. For panel testing, the differences between the full testing
cohort versus the UTSW cohort were significant (p<0.001): Affected, 42.7% versus 59.3%; Unaffected, 56.0% versus 39.6%; Polyps Only, 1.2% versus 0.9%; Not Specified, 0.1% versus 0.1.
Table 1. Genes included in genetic testing from the single commercial laboratory included in this study

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Genes Included (NCBI Accession)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Breast and Ovarian Cancer syndrome</td>
<td>BRCA1 (672), BRCA2 (675)</td>
</tr>
<tr>
<td>(HBOC) Testing</td>
<td></td>
</tr>
<tr>
<td>Lynch Syndrome Testing</td>
<td>MLH1 (4292), MSH2 (4436), MSH6 (2956), PMS2 (5395), EPCAM (4072)</td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis (FAP) Testing</td>
<td>APC (324)</td>
</tr>
<tr>
<td>MUTYH-Associated Polyposis (MAP) Testing</td>
<td>MUTYH (4595)</td>
</tr>
<tr>
<td>Hereditary Pancreatic Cancer Testing</td>
<td>PALB2 (79728), BRCA2 (675)</td>
</tr>
<tr>
<td>Hereditary Melanoma Testing</td>
<td>CDKN2A (1029)</td>
</tr>
<tr>
<td>Pan-Cancer Panel Testing*</td>
<td>APC (324), ATM (472), BARD1 (580), BMPR1A (657), BRCA1 (672), BRCA2 (675), BRIP1 (83990), CDH1 (999), CDK4 (1019), CDKN2A (p16INK4a and p14ARF) (1029), CHEK2 (11200), EPCAM (4072), GREM1** (26585), MLH1 (4292), MSH2 (4436), MSH6 (2956), MUTYH (4595), NBN (4683), PALB2 (79728), PMS2 (5395), POLD1** (5424), POLE** (5426), PTEN (5728), RAD51C (5889), RAD51D (5892), STK11 (6794), SMAD4 (4089), TP53 (7157)</td>
</tr>
</tbody>
</table>

*Initially offered in September 2013

**Added to multi-gene panel test in July 2016.

Abbreviation: NCBI, National Center for Biotechnology Information gene data base
eFigure 1. Summary of the testing laboratory process for variant classification and reporting.

<table>
<thead>
<tr>
<th>Variant identified during testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All relevant variant information is compiled</td>
</tr>
<tr>
<td>- <strong>Functional Data</strong>: mRNA splice-site analysis, functional assays, structural biology</td>
</tr>
<tr>
<td>- <strong>Statistical Data</strong>: clinical history weighting algorithm,(^3,4) In trans co-occurrence/homozygosity, mutation co-occurrence</td>
</tr>
<tr>
<td>- <strong>Additional Testing</strong>: Family testing of affected relatives, chromosome breakage analysis</td>
</tr>
<tr>
<td>- <strong>Peer-Review Literature</strong>: Literature reports regarding variant pathogenicity, including publications from scientific organizations such as the ENIGMA consortium(^14) and InSiGHT consortium.(^15)</td>
</tr>
<tr>
<td>• All available evidence is reviewed by a multi-disciplinary panel of experts.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variant classified based on panel review of available evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Benign (B), Likely Benign (LB), Variant of Uncertain Significance (VUS), Likely Pathogenic (LP), Pathogenic (P); Special Interpretation (SI)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initial report sent to provider</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Positive</strong>: ≥1 variant classified as P/LP variant; may include variants classified as B, LB, and/or VUS</td>
</tr>
<tr>
<td>• <strong>Negative</strong>: No P/LP variants; ≥1 variant classified as B, LB, and/or VUS</td>
</tr>
<tr>
<td>• Variants classified as B (single-syndrome &amp; panel testing) or LB (panel testing) were not specified on the report, which only included the “Negative” test result</td>
</tr>
<tr>
<td>• <strong>Special Interpretation</strong>: ≥1 variant classified as SI; no P/LP variants</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New information available regarding variant pathogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Automated systems to monitor evidence daily</td>
</tr>
<tr>
<td>• Classification re-evaluated immediately upon identification of new information</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variant reclassified if supported by new evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Amended report sent to notify provider of reclassification</td>
</tr>
<tr>
<td>• Includes all classification changes except downgrades from LB to B for pan-cancer panel testing (variant not on original report)</td>
</tr>
</tbody>
</table>

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Table 2. Distribution of variants initially classified as variant of uncertain significance by gene for the full clinical testing cohort.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Initially Reported VUSs</th>
<th>Reclassified VUSs</th>
<th>Amended Reports*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>APC</td>
<td>13,302</td>
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<td>ATM</td>
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<td>6,539</td>
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<td>BMPR1A</td>
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<td>CDH1</td>
<td>6,150</td>
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<td>CDK4</td>
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<tr>
<td>CDKN2A (p14ARF)</td>
<td>1,427</td>
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<td>CDKN2A (p16INK4a)</td>
<td>4,606</td>
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<td>TP53</td>
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<tr>
<td>TOTAL</td>
<td>184,327</td>
<td>100</td>
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Abbreviations: VUS, variant of uncertain significance
*Amended reports may contain multiple variants. The values in this column include any amended report that included a variant in the listed gene.
eTable 3. Distribution of variants initially classified as variant of uncertain significance by gene for the subset of patients tested through the University of Texas Southwestern Medical Center.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Initially Reported VUSs</th>
<th>Reclassified VUSs</th>
<th>Amended Reports*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>APC</td>
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<td>7.97</td>
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<td>ATM</td>
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Abbreviations: VUS, variant of uncertain significance  
*Amended reports may contain multiple variants. The values in this column include any amended report that included a variant in the listed gene.
**eFigure 2. Year-specific Time to Reclassification for BRCA1/2 variants.**

For amended reports sent due to the reclassification of variants in *BRCA1* and/or *BRCA2*, the time to amended report is shown according to the year of the initial report. Pan-cancer panel testing was introduced in 2013. Prior to 2013, all amended reports were for single-syndrome testing. The median time for each year is indicated by the thick horizontal line and the interquartile range is indicated by the box. The error bars represent 1.5 times the interquartile range. Data points beyond error bars represent outlying points.
eFigure 3. Year-specific Time to Reclassification for MMR gene variants.
For amended reports sent due to the reclassification of variants in genes associated with Lynch syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM), the time to amended report is shown according to the year of the initial report. Pan-cancer panel testing was introduced in 2013. Prior to 2013, all amended reports were for single-syndrome testing. The median time for each year is indicated by the thick horizontal line and the interquartile range is indicated by the box. The error bars represent 1.5 times the interquartile range. Data points beyond error bars represent outlying points.
eTable 4. Initial classification and reclassification details for variants of uncertain significance that were reclassified as part of single-syndrome testing for full cohort.

<table>
<thead>
<tr>
<th>Original Classification</th>
<th></th>
<th>Upgrades</th>
<th></th>
<th>Downgrades</th>
<th></th>
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<th>Total</th>
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<td>B/LB</td>
<td>VUS</td>
<td>VUS</td>
<td>LP</td>
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<td>41</td>
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Abbreviations: B, Benign; LB, Likely Benign; P, Pathogenic; LP, Likely Pathogenic; VUS, Variant of Uncertain Significance
## Table 5. Initial classification and reclassification details for variants of uncertain significance that were reclassified as part of pan-cancer panel testing for full cohort.

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Abbreviations: B, Benign; LB, Likely Benign; P, Pathogenic; LP, Likely Pathogenic; VUS, Variant of Uncertain Significance
**Table 6.** Classification and reclassification details for variants of uncertain significance that were reclassified as part of single-syndrome testing for the University of Texas Southwestern Medical Center cohort.

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Abbreviations: B, Benign; LB, Likely Benign; P, Pathogenic; LP, Likely Pathogenic; VUS, Variant of Uncertain Significance
**eTable 7. Classification and reclassification details for VUS that were reclassified as part of pan-cancer panel testing for the University of Texas Southwestern Medical Center cohort.**

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</table>

Abbreviations: B, Benign; LB, Likely Benign; P, Pathogenic; LP, Likely Pathogenic; VUS, Variant of Uncertain Significance
**Table 8.** Details of variant reclassification and clinical history for cases from the University of Texas Southwestern Medical Center where VUSs were reclassified to or from pathogenic or likely pathogenic.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant Information</th>
<th>Initial</th>
<th>New</th>
<th>Time to Amended Report, mos</th>
<th>Reason for Reclassification</th>
<th>Personal Cancer History*</th>
<th>Family Cancer History*</th>
<th>Surgical History*</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>BRCA1</em></td>
<td>Dup exons 1-22</td>
<td>LP</td>
<td>VUS</td>
<td>65</td>
<td>Re-evaluation with updated knowledge and peer reviewed literature</td>
<td>Unilateral BC at 58</td>
<td>BC, LC, skin, throat, leukemia</td>
<td>BM, TAH-BSO**</td>
<td>None</td>
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<tr>
<td><em>TP53</em></td>
<td>c.542G&gt;A, (p.Arg181His)</td>
<td>LP</td>
<td>VUS</td>
<td>8</td>
<td>Re-evaluation of peer reviewed literature</td>
<td>Unilateral BC at 39</td>
<td>None</td>
<td>BM</td>
<td>Managed as LFS with possible risks still conferred</td>
</tr>
<tr>
<td><em>BRIP1</em></td>
<td>c.2992_2993del (p.Lys998Glu*3)</td>
<td>P</td>
<td>VUS</td>
<td>9</td>
<td>Re-evaluation of evidence for truncating variants at the 3’ end of <em>BRIP1</em></td>
<td>None</td>
<td>BC, CRC, PC, liver, melanoma</td>
<td>None</td>
<td>GI screening based on APC AJ variant, c.3920T&gt;A (p.Ile1307Lys) family history</td>
</tr>
<tr>
<td><em>BRCA1</em></td>
<td>c.5453A&gt;G (p.Asp1818Gly)</td>
<td>VUS</td>
<td>P</td>
<td>26</td>
<td>Clinical history weighting algorithm, segregation</td>
<td>None</td>
<td>BC</td>
<td>BSO**</td>
<td>Declined high risk screening; diagnosed with breast cancer</td>
</tr>
<tr>
<td><em>BRCA1</em></td>
<td>c.5165C&gt;T (p.Ser1722Phe)</td>
<td>VUS</td>
<td>P</td>
<td>22</td>
<td>Clinical history weighting algorithm, segregation, published functional studies</td>
<td>Unilateral BC at 39</td>
<td>EC</td>
<td>Lumpectomy</td>
<td>Relative diagnosed with OC prior to reclassification; Proband had BSO after reclassification</td>
</tr>
<tr>
<td><em>BRCA1</em></td>
<td>c.4484G&gt;A (p.Arg1495Lys)</td>
<td>VUS</td>
<td>P</td>
<td>6</td>
<td>Internal mRNA splice site analysis, clinical history weighting algorithm</td>
<td>Unilateral BC at 59, OC at 61</td>
<td>None</td>
<td>Lumpectomy, TAH-BSO**</td>
<td>None</td>
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<tr>
<td>Gene</td>
<td>Variant</td>
<td>Type</td>
<td>Int.</td>
<td>Sig.</td>
<td>Study Details</td>
<td>Age at Diagnosis</td>
<td>Family History</td>
<td>Standard Surgical Intervention</td>
<td>Surgical Intervention Prior to Reclassification</td>
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<td>VUS</td>
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<td>13</td>
<td>Published functional studies, structural biology analysis</td>
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<td>BRCA1</td>
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<td>VUS</td>
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<td>4</td>
<td>Published functional studies, clinical history weighting algorithm</td>
<td>None</td>
<td>None</td>
<td>Breast</td>
<td>Prophylactic bilateral mastectomies after reclassification</td>
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<td>LP</td>
<td>28</td>
<td>Structural biology analysis, segregation</td>
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<td>PC, BC, CRC, abdominal</td>
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<td>BRCA2</td>
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<td>VUS</td>
<td>LP</td>
<td>10</td>
<td>Published functional studies, segregation</td>
<td>Unilateral BC at 28</td>
<td>EC</td>
<td>BM</td>
<td>TAH-BSO after reclassification</td>
</tr>
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<td>CDH1</td>
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<td>LP</td>
<td>15</td>
<td>Peer reviewed literature (functional and clinical evidence)</td>
<td>None</td>
<td>OC</td>
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<td>CHEK2</td>
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<td>VUS</td>
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<td>BC, LC, PC, thyroid, GB</td>
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<td>VUS</td>
<td>LP</td>
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<td>Segregation, structural biology analysis, published functional studies</td>
<td>CRC at 43</td>
<td>Leukemia, melanoma, PC</td>
<td>Partial colon resection, TAH-BSO**</td>
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<td>LP</td>
<td>86</td>
<td>Internal mRNA splice site analysis</td>
<td>CRC at 46</td>
<td>BC, CRC</td>
<td>Partial colon resection</td>
<td>Managed as Lynch syndrome based on Amsterdam II criteria prior to reclassification</td>
</tr>
</tbody>
</table>

Abbreviations: AJ, Ashkenazi Jewish; BC, Breast Cancer; BM, Bilateral mastectomy; BSO, bilateral salpingo-oophorectomy; CRC, Colorectal Cancer; EC, Endometrial cancer; FHx, Family cancer history; GB, glioblastoma; LC; Lung cancer; LFS, Li Fraumeni syndrome; OC, Ovarian cancer; PHx, Personal cancer history; PC, Prostate cancer; TAH, total abdominal hysterectomy; P/LP, Pathogenic/Likely Pathogenic; UM, Unilateral mastectomy; VUS, variant of uncertain significance. *At time of initial test report. **Surgical intervention performed prior to receipt of the initial genetic test report.
eReferences