Since the discovery of the \textit{BRCA1} and \textit{BRCA2} genes, multiple predisposition genes have been identified and included on genetic testing panels for breast cancer (1,2). In fact, breast cancer is now recognized as a heterogeneous disease with a complex genetic architecture (3,4). However, the full spectrum of genetic variation contributing to triple-negative breast cancer (TNBC), an aggressive breast cancer subtype, has not yet been fully elucidated. TNBC, which accounts for 10–25\% of breast tumors, is characterized by absence of expression of the estrogen receptor (ER), progesterone receptor (PR) and lack of amplification of the human epidermal growth factor receptor 2 (HER2) (3,4). Patients with TNBC do not benefit from hormonal or anti-HER2 therapy, and exhibit high recurrence risk and poor survival rate in the first 5 years following diagnosis (5). TNBC patients usually have an early onset of disease and positive family history of breast and/or ovarian cancer, suggesting a strong association with genetic factors (3). Emerging studies also suggest TNBC may have a genetic risk profile different from other subtypes of breast cancer (6,7). Establishing the genetic landscape of TNBC and identifying actionable mutations may lead to better clinical management and therapy response prediction for this aggressive and difficult-to-treat subtype.

Limited studies have investigated genetic predisposition to TNBC beyond the \textit{BRCA1} and \textit{BRCA2} genes (3,6). Mutations in multiple non-\textit{BRCA} genes have been observed in women with TNBC, and subsequent studies reported higher mutation prevalences of \textit{BARD1}, \textit{BRIP1}, \textit{FANCM}, \textit{PALB2} and \textit{RAD51C} in TNBC compared to other breast cancer subtypes (3,7-15) (Table 1). In a recent article published in \textit{Journal of the National Cancer Institute}, Shimelis and colleagues examined germline pathogenic/likely pathogenic variants in 21 and 17 cancer susceptibility genes across 8,753 patients from a clinical cohort referred for genetic testing and 2,148 individuals from a research cohort, respectively (5). With this design, authors were able to estimate both the relative risks and absolute lifetime risks associated with TNBC, as compared to >26,000 non-Finnish European (NFE) reference controls represented by the ExAC (Exome Aggregation Consortium) and women with other pathologic subtypes of breast cancer, for each gene.

Shimelis \textit{et al.} observed high TNBC risks in five cancer genes (\textit{BARD1}, \textit{BRCA1}, \textit{BRCA2}, \textit{PALB2}, and \textit{RAD51D}) and moderate risks in three genes (\textit{BRIP1}, \textit{RAD51C} and \textit{TP53}) among Caucasians. Furthermore, they found pathogenic/likely pathogenic mutations were enriched in \textit{BRCA1}, \textit{BRCA2}, \textit{BARD1}, \textit{PALB2}, \textit{RAD51C} and \textit{RAD51D} genes in TNBC patients compared to non-TNBC breast cancer patients. Similar genetic associations were observed in African Americans, who are known to have high prevalence of TNBC compared to Caucasians (3). The authors concluded that their findings may be used to promote comprehensive genetic testing and improve risk management for TNBC.

Among the non-\textit{BRCA} genes, \textit{BARD1} and \textit{PALB2} are well-established breast cancer susceptibility genes (16,17), and mutations \textit{TP53} cause Li-Fraumeni and Cowden syndrome and are associated with elevated risks of breast cancer (1,10). However, while \textit{BRIP1}, \textit{RAD51C} and \textit{RAD51D} are widely accepted as ovarian cancer
Table 1: Estimated risks of TNBC for cancer susceptibility genes

<table>
<thead>
<tr>
<th>Genes</th>
<th>Mutation detected (reference)</th>
<th>TNBC vs. controls [OR (95% CI) (reference)]</th>
<th>TNBC vs. non-TNBC breast cancer [OR (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARD1</td>
<td>n=9 (11); n=53 (12); n=4 (10)</td>
<td>5.92 (3.36–10.27) (5)*</td>
<td>3.73 (2.30–5.95) (5)<em>; higher prevalence (8)</em></td>
</tr>
<tr>
<td>BRCA1</td>
<td>n=155 (11); n=82 (12)</td>
<td>16.27 (12.65–20.95) (5)*</td>
<td>5.77 (4.96–6.71) (5)<em>; higher prevalence (3,8)</em></td>
</tr>
<tr>
<td>BRCA2</td>
<td>n=49 (11); n=42 (12)</td>
<td>5.42 (4.13–7.05) (5)*</td>
<td>1.43 (1.17–1.75) (5)*; higher prevalence (3)</td>
</tr>
<tr>
<td>BRIP1</td>
<td>n=8 (11); n=53 (12); n=2 (10)</td>
<td>2.28 (1.30–4.00) (5)#</td>
<td>1.41 (0.84–2.35) (5); higher prevalence (8)#</td>
</tr>
<tr>
<td>FANCM</td>
<td>n=8 (13)</td>
<td>3.56 (1.81–6.98) for c.S101C&gt;T (14)</td>
<td>Higher prevalence (3)</td>
</tr>
<tr>
<td>PALB2</td>
<td>n=8 (15); n=1 (7); n=21 (11); n=53 (12); n=11 (10)</td>
<td>14.41 (9.27–22.60) (5)*; 8.27 (2.65–30.37) (10)#</td>
<td>2.12 (1.63–2.74) (5)*; higher prevalence (8,9)#</td>
</tr>
<tr>
<td>RAD51C</td>
<td>n=6 (11); n=3 (10)</td>
<td>2.64 (1.44–4.80) (5)#</td>
<td>3.82 (2.23–6.39) (5)*; higher prevalence (8)#</td>
</tr>
<tr>
<td>RAD51D</td>
<td>n=1 (7); n=7 (11); n=53 (12)</td>
<td>6.97 (2.60–18.66) (5)#</td>
<td>3.13 (1.42–6.43) (5)#</td>
</tr>
<tr>
<td>TP53</td>
<td>n=1 (11); n=53 (12); n=4 (10)</td>
<td>2.75 (1.18–6.16) (5)#</td>
<td>0.90 (0.46–1.71) (5)</td>
</tr>
</tbody>
</table>

* Sun et al. reported 53 mutations in non-BRCA genes combined; #, statistically significant findings.

predisposition genes (18,19), conflicting evidence exists for their associations with overall breast cancer risk (2,10,20). It is possible that inconsistencies in these previously reported associations are due in part to their differential effects on risk for specific breast cancer subtypes, such as TNBC (5). In 2015, Ollier et al. screened 36 DNA repair-related genes in 50 TNBC patients with family history of breast cancer but not carrying BRCA1/2 mutations; researchers identified seven pathogenic variants in six genes, including PALB2 and RAD51D (Table 1) (7). The same year, Couch et al. examined non-BRCA genes in 1,824 TNBC patients unselected for family history, and reported 67 pathogenic variants primarily residing in seven genes, five of which were identified by Shimelis and colleagues (BARD1, BRIP1, PALB2, RAD51C, RAD51D; Table 1) (11). In 2017, Sun et al. detected 53 mutations in non-BRCA genes among 1,104 TNBC cases, mainly in PALB2, RAD51D, and TP53 (12). Recently, Lu et al. identified 24 mutations in BARD1, BRIP1, PALB2, RAD51C and TP53, from 1,154 TNBC patients referred for genetic testing. Taken together, these studies generally support the presence of BRIP1, RAD51C and RAD51D mutations in women with TNBC. However, larger case-control or family-based studies are still needed to replicate the TNBC-specific associations with these genes, as reported by Shimelis et al.

According to the National Comprehensive Cancer Network (NCCN) guidelines, BRCA1/2 testing is generally recommended for patients fulfilling high-risk criteria or with TNBC diagnosed at or under age 60 (5). Couch et al. investigation of 17 breast cancer genes found 11.2% TNBC patients carried pathogenic variants in BRCA1/2 and 3.7% had mutations in 15 other predisposition genes (11). Shimelis et al. observed similar mutation prevalences in BRCA and non-BRCA genes, and suggested that BRCA1 mutations are the major contributors to early-onset TNBC while other genes associated with TNBC accounted for a larger proportion of TNBCs diagnosed over age 50, irrespective of family history (5). Earlier studies similarly observed that the association between TNBC and BRCA1 mutations was primarily limited to early-onset TNBC and that older TNBC patients had much lower prevalence of BRCA1 mutations compared to all TNBC cases (6). It is therefore possible that current guidelines for genetic testing are insufficient for carrier screening and should be expanded to include other predisposition genes.

In US female population (https://www.seer.cancer.gov/), the average lifetime risk for breast cancer and TNBC is approximately 12.4% and 1.2%, respectively. Shimelis et al. found that patients with pathogenic mutations in BARD1, BRCA1/2, PALB2 and RAD51D have greater than 20% lifetime risks for breast cancer and greater than 5% lifetime risks for TNBC. In addition to rare pathogenic mutations in high- and moderate-risk genes, genotype profiles assessed from common variation may also cumulatively increase cancer risk or contribute to prognosis (21,22). Several TNBC-associated single nucleotide polymorphisms (SNPs) have been identified, some of which are associated with overall breast cancer, while some are specific to the
TNBC phenotype. Such SNPs may be useful in refining risk models for identification of individuals at higher risk for TNBC (22,23).

While chemotherapy remains the primary treatment option for TNBC patients, new targeted therapies including androgen receptor inhibitors, PARP inhibitors and immunotherapy targeting the PD-1/PD-L1 pathway are currently being explored (3,24,25). A newly published study identified and validated tumor dependencies on 37 genes, based on the integration of somatic alterations of copy number and gene expression data in TNBC tumors as potential drug targets (26). In addition, gene expression profiles revealed distinct molecular subtypes of TNBC, with differences in survival and response to therapy (27). Thus, while the findings of Shimelis et al. provide a foundation for the expansion of genetic testing guidelines and clinical risk assessment, germline testing in concert with somatic and expression analysis of both established and putative TNBC-related genes may help identify patients who can benefit from targeted therapeutic strategies.

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Footnote

Conflicts of Interest: the authors are employed by Ambry Genetics Inc.

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