Supplementary Materials and Methods

BRCA2 alternate splicing event nomenclature:

The naming of *BRCA2* alternate splicing events in this study follows the convention used by Colombo *et al.* [6]. Briefly, the exon number preceded by the letter delta (Δ) indicate alternate splicing events resulting from single exon skipping. Commas or dashes indicate events resulting in skipping of two or more contiguous exons, respectively. Events involving a shifted splice donor (distal) or splice acceptor (proximal) are indicated with p or q, respectively. The alternate splice acceptor within intron 4 that adds 23 bases to the 5' end of exon 5 is indicated by the event designation ▼5p. Exonization of a region of intron 20 is indicated by the designation ▼20A. Corresponding HGVS nomenclature for the alternate splicing events is according to the Human Genome Variation Society nomenclature guidelines (http://www.hgvs.org/rechtml).

Identification of alternate BRCA2 splicing events in the literature:

We define naturally occurring alternative splicing events as those resulting from alternate splice site choices during regular mRNA processing and are not caused by RNA sequence variants.

To determine which alternate *BRCA2* mRNA splicing events have been described previously, a PubMed search was performed (http://www.ncbi.nlm.nih.gov/pubmed)

using search terms *BRCA2*, alternate splicing, and mRNA. For the purpose of this study, the results were reviewed to determine whether the cDNA fragment representing the alternate splicing event had been sequenced and whether the event occurred independently of a variation in the gene sequence.

Patient samples and cell lines:

In phase II, lymphoblastoid cell lines were taken from archival stocks of samples from eleven breast cancer patients who were consented under a protocol approved by the University of Chicago Institutional Review Board. All patients were referred for *BRCA1/BRCA2* genetic testing by the University of Chicago Cancer Risk Clinic for reasons of personal or family history of cancer. Nine subjects were diagnosed with breast cancer, one with fallopian tube cancer, and one with no cancer diagnosis. Of the eleven subjects used for all alternate splicing events, four had no detected gene sequence variants, one had a pathogenic variant in *BRCA1*, and one had a pathogenic variant in *PALB2*. The remaining five carried *BRCA2* truncating variants: three were in exon 11 at positions not predicted to affect exon 11 splicing (c.5864C>A (p.Ser1955*), c.2808_2811del , c.5350_5351del;), one was in exon 4 (c.391delT), and another in exon 18 (c.8297delC). We note that exon skipping events involving exon 4, either alone or in combination with other exons, were detected in the majority of cell lines tested, not just the cell line with the exon 4 pathogenic variant. Likewise, the exon skipping events involving exon 18 were seen in the majority of cell lines tested. We therefore suggest that these mutations did not affect the identification of naturally occurring exon-

skipping events described below. Breast cancer cell lines were MCF7 (from an ER+ invasive ductal carcinoma with a luminal epithelial phenotype), HCC1937 (from a ductal carcinoma carrying a homozygous pathogenic variant in *BRCA1*), and BT20 (from a triple-negative invasive ductal carcinoma). None of these cell lines has any known mutation in *BRCA2*. Non-cancer breast cell lines were MCF10A (derived from mammary epithelial cells associated with fibrocystic disease), 184A1 (from chemically transformed breast epithelial cells), and 184B5 (a different isolate from the procedure that generated 184A1) [50]. Breast cell lines were obtained from the American Tissue Type Collection (ATTC). Cell lines were grown with conventional media and conditions. Multiple LCLs and breast cell lines (see above) were used to test the detectability of alternate splicing events identified in phases Ia and Ib. No attempt was made to provide definitive characterization of any single cell type with respect to specific alternate splicing events in Phase II. Thus, in most cases, each cell line was tested once per alternate splicing event (Table 2).