Supplementary Tables

Supplementary Table S1

ID	gap nt	gap a.a.	deletion span	5-prime bound	3-prime bound	Found in
D1	177	59	chr13:32,913,993-32,914,169	AATTGTCCATATCTAATA	GTTACGAGGCATTGGATGA	solid 13x liquid 7x paraffin 2x
D2	66	22	chr13:32,914,104-32,914,169	AAAGACATATTTACAGACAGTTTCA	GTTACGAGGCATTGGATGATTC	solid 1x liquid 33x
D3	27	9	chr13:32,914,096-32,914,122	AAAAAGTGAAAGACATATTTACAG	ACAACGAGAATAAATCAAAAA	liquid 1x
D4	189	63	chr13:32,914,007-32,914,195	TAATAGTAATAATTTTGAGG	ATATTCTTCATAACTCTCTAG	liquid 37x
D5	240	80	chr13:32,913,935-32,914,174	AAGATATTTGCGTTGAGGAACTTGTG	GAGGCATTGGATGATTCAGA	liquid 2x
D6	132	44	chr13:32,914,031-32,914,162	GGCCACCTGCATTTAGGATA	GCAGGTTGTTACGAGGCA	liquid 2x
D7	618	206	chr13:32,913,861-32,914,479	AAAAAACACTAGTTTTTCCAAAGT	AAGACAAGTGTTTTCTGAAAT	liquid 2x

Supplementary Table S1: Patient 1 reversion alleles. NOTE: The D5 deletion reads in the liquid biopsy contain the sequence CTTGTTGAGGC. The highlighted T nucleotide must be either a G or a C to match the reference, as the consensus sequence does not indicate this patient has a SNP in the coding region that would diverge from the reference.

Supplementary Table S2

source	ID	read ID
liquid	D1	@M02686:80:000000000-AM84R:1:1108:7654:3653 1:N:0:3
liquid	D1	@M02686:80:000000000-AM84R:1:1119:7522:18241 1:N:0:3
liquid	D1	@M02686:80:000000000-AM84R:1:2104:23846:11333 1:N:0:3
liquid	D1	@M02686:80:000000000-AM84R:1:2106:8204:18124 1:N:0:3
liquid	D1	@M02686:80:000000000-AM84R:1:2111:12616:15187 1:N:0:3
liquid	D1	@M02686:80:000000000-AM84R:1:2112:17854:16007 1:N:0:3
liquid	D1	@M02686:80:000000000-AM84R:1:2112:6626:11061 1:N:0:3
solid	D1	@NS500257:40:HWFNCBGXX:1:11106:14905:12260/2
solid	D1	@NS500257:40:HWFNCBGXX:1:12302:15336:19788/2
solid	D1	@NS500257:40:HWFNCBGXX:1:13207:7388:13381/2
solid	D1	@NS500257:40:HWFNCBGXX:1:21108:14113:17753
solid	D1	@NS500257:40:HWFNCBGXX:1:21201:2306:17648
solid	D1	@NS500257:40:HWFNCBGXX:2:12310:9465:4145/2
solid	D1	@NS500257:40:HWFNCBGXX:2:21103:13016:2745/2
solid	D1	@NS500257:40:HWFNCBGXX:2:21203:4589:8875/2
solid	D1	@NS500257:40:HWFNCBGXX:2:21307:7503:19229/2
solid	D1	@NS500257:40:HWFNCBGXX:2:22102:3548:15092/2
solid	D1	@NS500257:40:HWFNCBGXX:3:11601:18802:1086/2
solid	D1	@NS500257:40:HWFNCBGXX:3:13508:14730:6160/2
solid	D1	@NS500257:40:HWFNCBGXX:4:13406:17704:10910/2
solid	D2	@NS500257:40:HWFNCBGXX:3:12403:15743:6920/2
paraffin	D1	@U6PPT:05770:05550
paraffin	D1	@U6PPT:09522:09843
liquid	D2	@M02686:80:000000000-AM84R:1:1101:22933:21197 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1103:18039:20433 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1103:20441:10714 2:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1105:21902:2073 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1106:11153:6887 2:N:0:3

liquid	D2	@M02686:80:000000000-AM84R:1:1106:13570:13503 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1107:10488:13372 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1111:20942:22000 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1111:21409:5163 2:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1112:22754:17863 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1113:3650:17283 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1115:21856:12571 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1115:5584:13201 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1117:24232:15991 2:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1118:16133:5284 2:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1119:1897:15016 2:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1119:20661:21062 2:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:1119:27426:7956 2:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2101:11686:17718 2:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2102:21663:11343 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2104:23131:15258 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2104:25277:14510 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2105:12585:11762 2:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2107:10748:16252 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2107:12484:16480 2:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2107:18061:13142 2:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2110:18776:18531 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2114:16287:6002 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2115:20435:21345 2:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2115:22703:9506 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2116:23100:7668 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2117:25249:18479 1:N:0:3
liquid	D2	@M02686:80:000000000-AM84R:1:2118:13822:24589 1:N:0:3
liquid	D3	M02686:80:000000000-AM84R:1:2115:4925:21573
liquid	D4	@M02686:80:000000000-AM84R:1:1101:9729:12511 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1103:15286:15301 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1104:16487:21269 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1105:20672:2299 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1105:24499:18040 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1107:21266:16376 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1108:16153:16552 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1110:2830:10510 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1111:12984:23682 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1111:13776:22186 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1111:26013:17798 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1112:4865:13911 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1114:23171:9528 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1115:15221:24977 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1116:21160:3075 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1117:21990:16743 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1119:7227:15176 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2101:17182:20816 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2101:17896:23804 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2104:16040:5196 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2104:20168:14427 2:N:0:3

liquid	D4	@M02686:80:000000000-AM84R:1:2105:10830:12567 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2105:2400:14970 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2105:8293:12361 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2106:8309:6546 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2107:14839:15220 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2107:22940:21528 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2108:18638:19099 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2110:5304:19578 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2113:27147:16598 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2113:4579:16758 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2113:6729:13187 2:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2115:21006:11819 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2117:5703:16909 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2118:11255:18905 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2119:23454:4875 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:2119:3803:11850 1:N:0:3
liquid	D4	@M02686:80:000000000-AM84R:1:1101:9729:12511
liquid	D4	@M02686:80:000000000-AM84R:1:1111:12984:23682
liquid	D4	@M02686:80:000000000-AM84R:1:1114:23171:9528
liquid	D4	@M02686:80:000000000-AM84R:1:2119:3803:11850
liquid	D5	@M02686:80:000000000-AM84R:1:1116:18650:13685 1:N:0:3
liquid	D5	@M02686:80:000000000-AM84R:1:2105:27012:10760 1:N:0:3
liquid	D6	@M02686:80:000000000-AM84R:1:2103:19831:15228 1:N:0:3
liquid	D6	@M02686:80:000000000-AM84R:1:2119:24234:20317 1:N:0:3
liquid	D7	@M02686:80:000000000-AM84R:1:1101:23718:2852 1:N:0:3
liquid	D7	@M02686:80:000000000-AM84R:1:2104:3080:14024 1:N:0:3

Supplementary Table 2: DNA read identifiers supporting reversion alleles. This table lists the individual reads that support deletions in *BRCA2* in Patient 1's post-talazoparib DNA. Sources are liquid (cfDNA), solid (solid tumor biopsy) or paraffin (Ion Torrent analysis of solid tumor embedded in paraffin). Deletions D1 through D7 are as shown in **Figure 1C**.

Supplementary Table S3

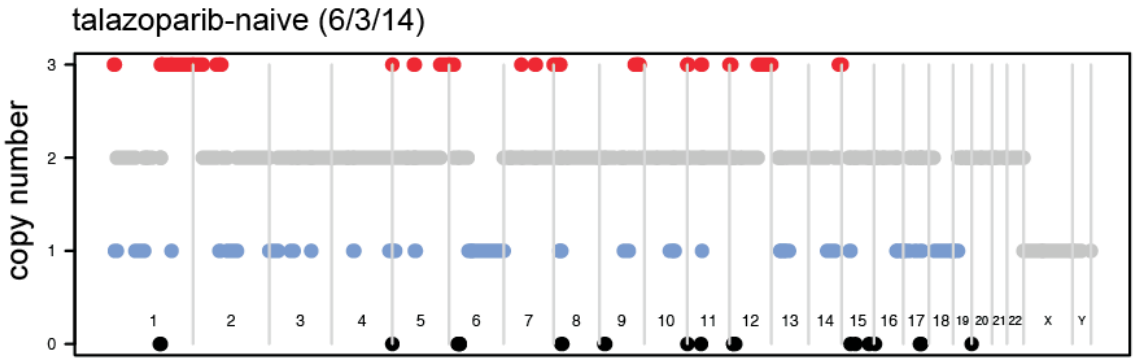
AKT1
AKT2
AKT3
APC
AR
ARID1A
ASXL1
ATM
ATR
BRAF
BRCA1
BRCA2
CCND1
CDK12
CDK4
CDK6
CDKN1B
CDKN2A
CHD1
CLU
CTNNB1

CUL1
ERCC1
ERCC2
ERCC3
ERCC4
ERCC5
ERG
FANCA
FANCC
FANCD2
FANCE
FANCF
FANCG
FBXW7
FOXA1
FOXP1
GNAS
HSD3B1
IDH1
IDH2
KDM6A
KMT2C
KMT2D
KRAS
MDM2
MDM4
MED12
MET
MLH1
MSH2
MSH6
MYC
NCOA2
NFE2L2
NKX3-1
PALB2
PIK3CA
PIK3CB
PIK3R1
PTEN
RAD51B
RAD51C
RB1
RNF43
RUNX1
RYBP
SMARCA1
SPOP
TMPRSS2
TP53
ZBTB16
ZFHX3

Supplementary Table S3: Gene targets of the SeqCap library used for cfDNA sequencing.

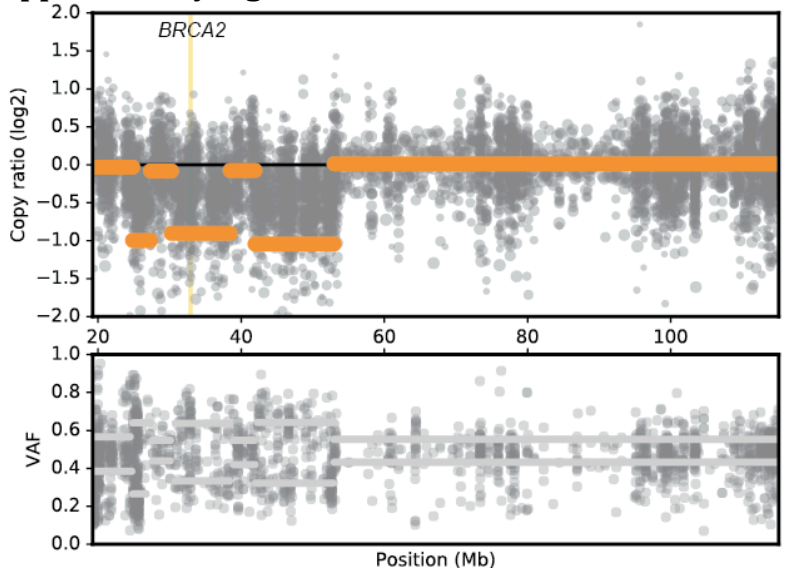
Supplementary Figures

Supplementary Figure S1



Supplementary Figure S1: Frequent loss of heterozygosity in Patient 1's tumor DNA. DNA copy number for Patient 1's pre-talazoparib solid tumor biopsy in comparison to Patient 1's germline DNA, drawn as two-copy loss (black), one-copy loss (blue), no alteration (grey), or single copy gain (red). Numbers at bottom indicate chromosomal location.

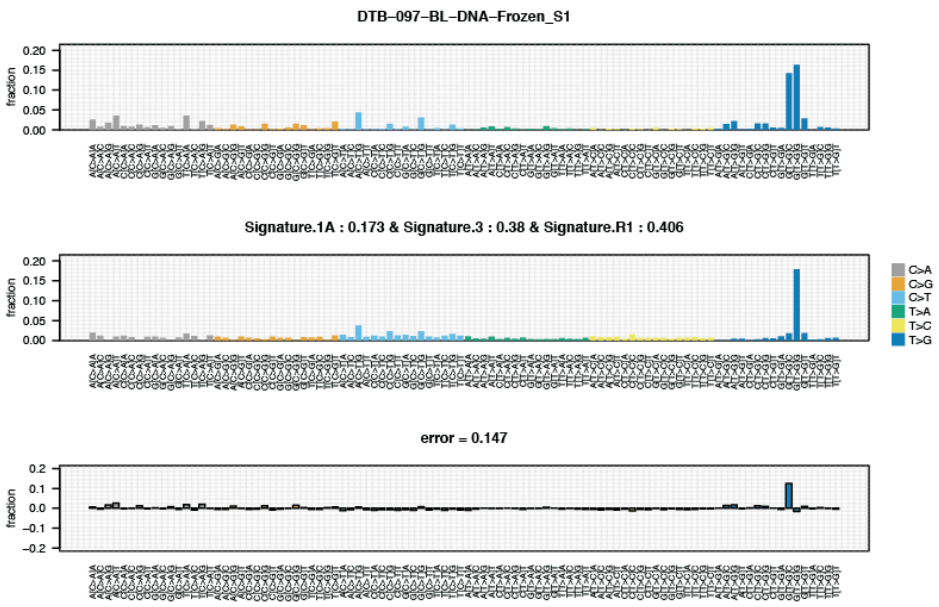
Supplementary Figure S2



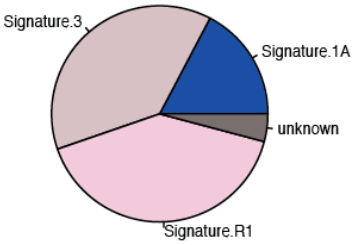
Supplementary Figure S2: A single copy of chromosome 13 at the *BRCA2* locus is present in Patient 1's tumor DNA. DNA copy number for chromosome 13 of Patient 1's pre-talazoparib solid tumor biopsy in comparison to Patient 1's germline DNA. Upper panel shows individual copy ratio values (grey dots), with the DNA copy number call after segmentation highlighted in orange. Position of *BRCA2* is noted with a vertical yellow line. Lower panel shows the Variant Allele Frequency (VAF) for each call; the increased distance from a VAF of 0.5 in regions with lower copy number is compatible with loss of heterozygosity.

Supplementary Figure S3

a

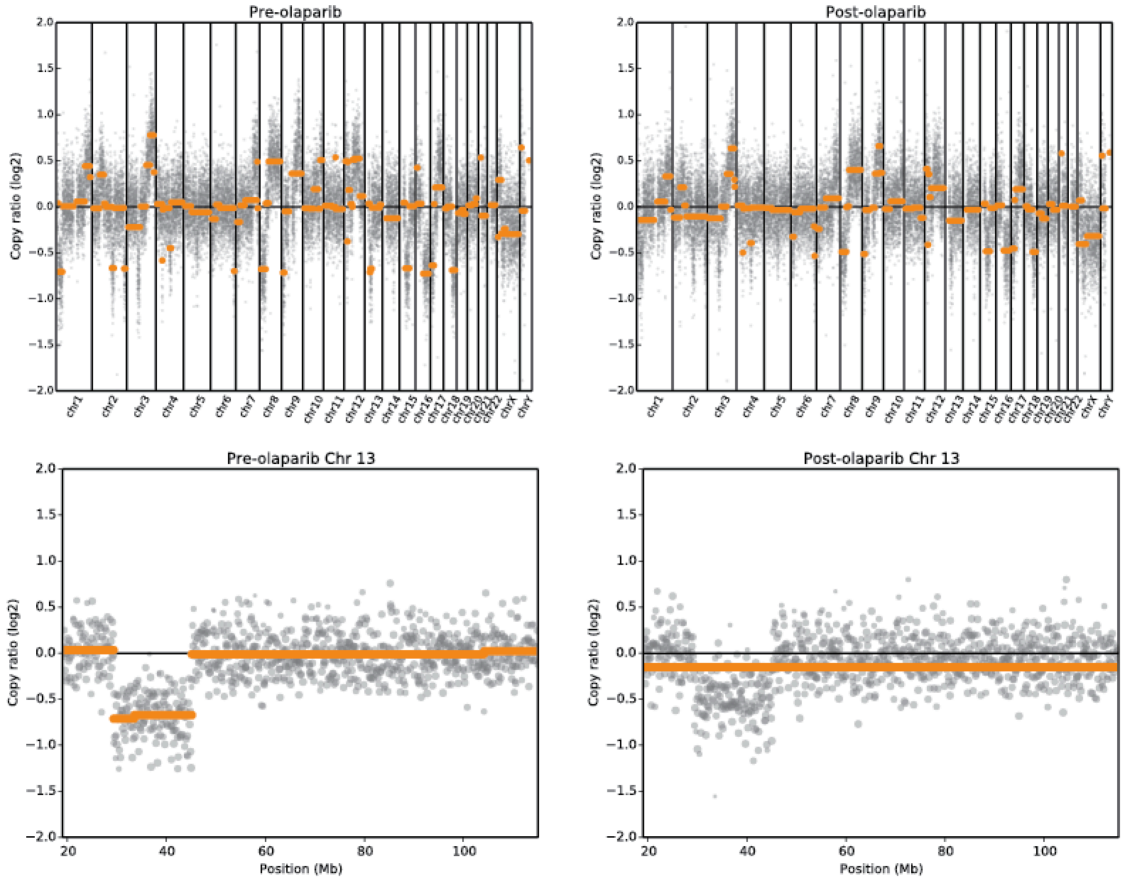


b



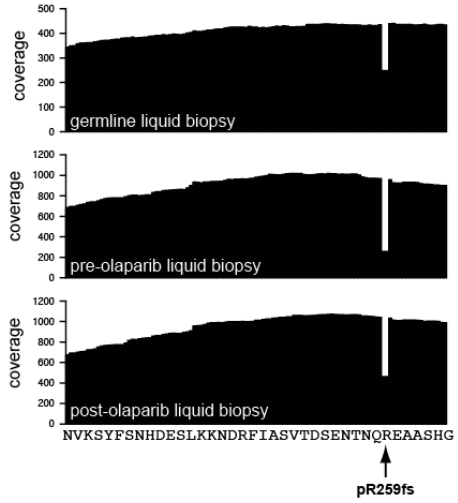
Supplementary Figure S3: Mutation signature three is present in patient 1's solid tumor. Patient 1's solid tumor DNA single nucleotide variations showed evidence for three signatures: signature 1A, signature 3, and signature R1. Signature 3 is the BRCA-associated signature; signature 1A is found in all tumors and is predicted to be the product of spontaneous 5-methylcytosine deamination; signature R1 failed validation in Alexandrov *et al.* Nature 2013 and is likely a sequencing artifact.

Supplementary Figure S4



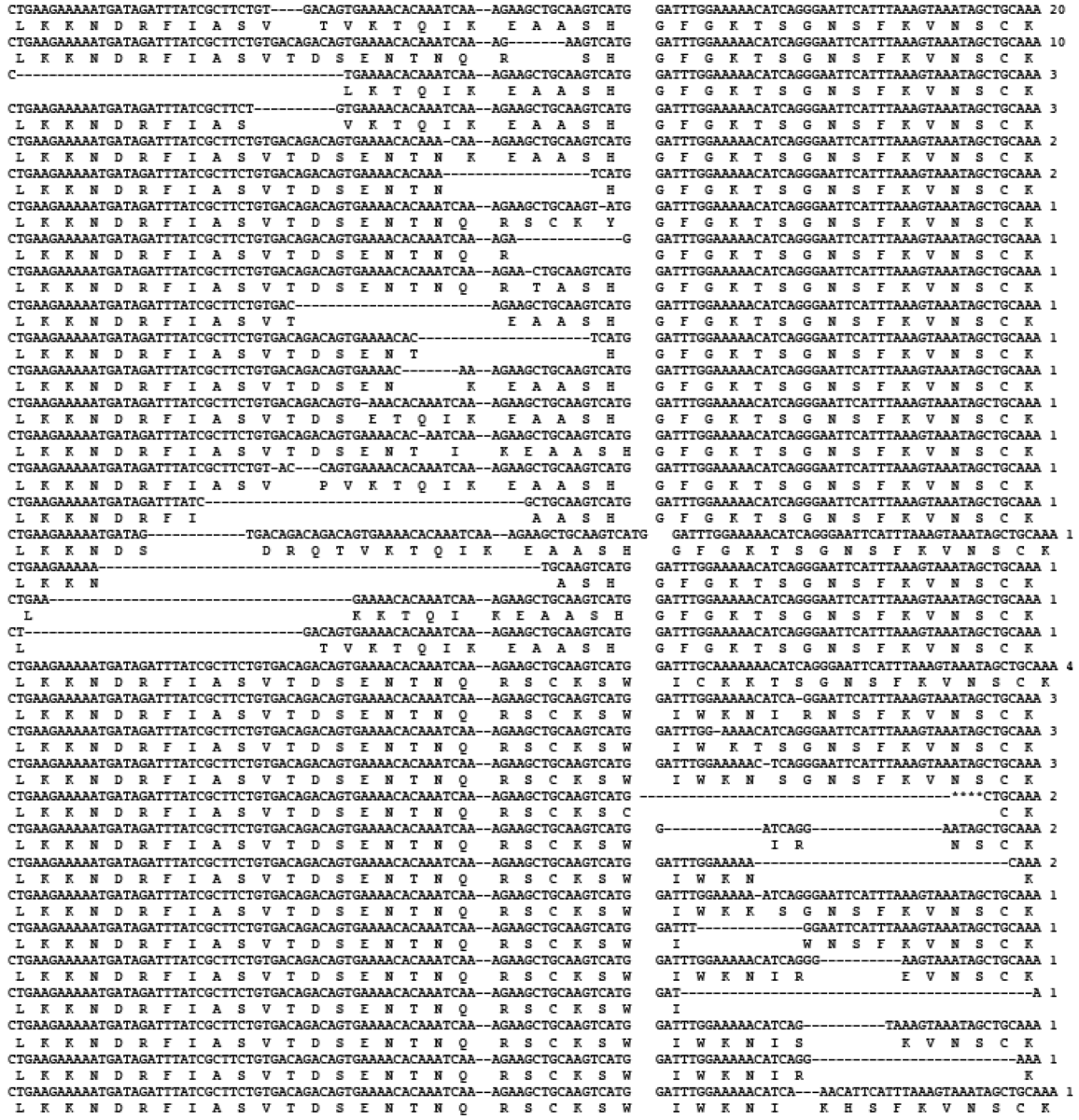
Supplementary Figure S4: A single copy of chromosome 13 at the *BRCA2* locus is present in Patient 2's tumor DNA. DNA copy number for chromosome 13 of Patient 2's pre-olaparib cfDNA biopsy in comparison to patient 2's germline DNA. Individual copy ratio values plotted as grey dots, with the DNA copy number call after segmentation highlighted in orange. Note that due to stringent thresholding DNAcopy does not call a deletion in the post-olaparib chromosome 13 sample, it is clearly present at the same locus as the pre-olaparib sample.

Supplementary Figure S5



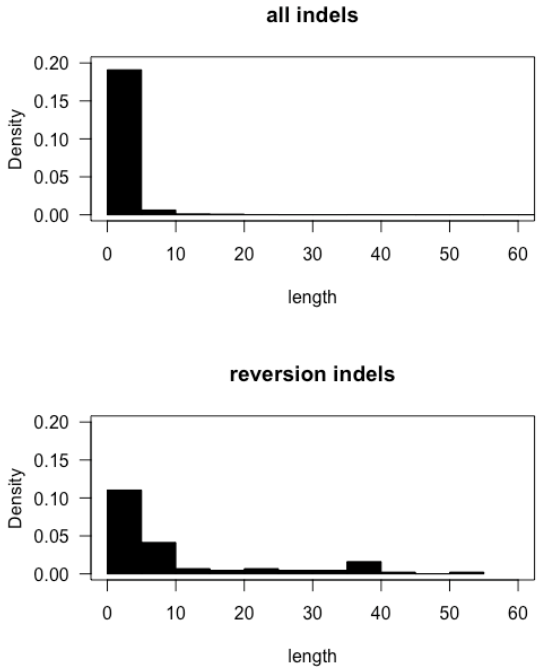
Supplementary Figure S5: Patient 2's DNA coverage depth at residue 259. The depth of DNA read coverage is shown in the region near p.R259fs (extracted from chromosome 13, 32,904,800-32,905,500). Letters at the bottom of the plot indicate the amino acid coded at that locus. The frequency of wild type DNA at the nucleotides coding for *BRCA2* residue 259 decreased in the pre-olaparib liquid biopsy in comparison with the germline biopsy.

Supplementary Figure S6



Supplementary Figure S6: Nucleotide and inferred protein sequences for patient 2's reversion alleles. Sequences are listed in order matching **Fig. 2E**. Dashes in nucleotide sequence indicate deleted nucleotides; spaces separate exons 9 and 10. Asterisks represent nucleotides that are presumed skipped in the reversion mutation that lacks the splice acceptor for exon 10. The number at the right of each nucleotide sequence represents the number of distinct read pairs that were observed with this mutation.

Supplementary Figure S7



Supplementary Figure S7: Reversion indels were significantly longer than the background distribution of indels.

Supplementary Methods

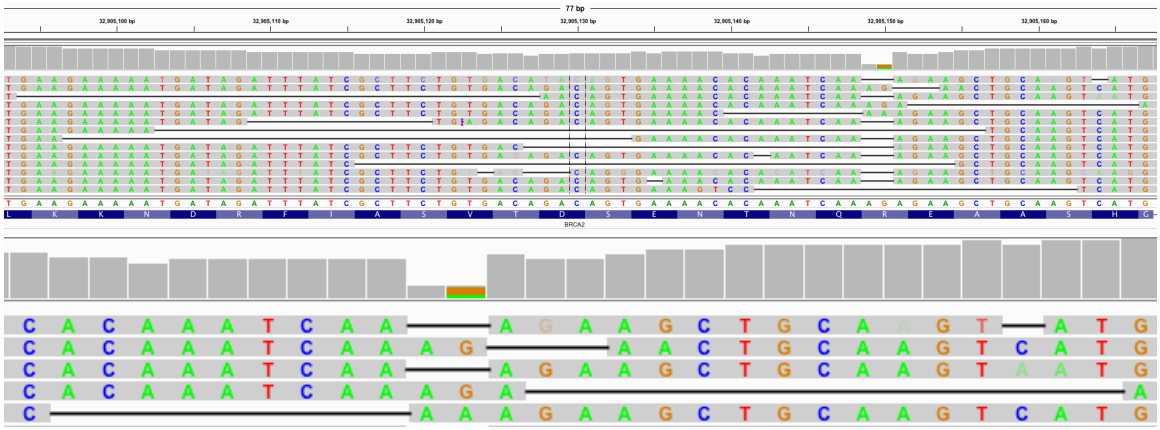
Assessing Patient Two's frameshift mutations

After alignment, reads were manually inspected using the Integrated Genome Viewer. The HG19 reference sequence near the germline pR259fs frameshift includes repeated nucleotide motifs (AAAGAGAA, with underlined sequence deleted in pR259fs). Reads adjacent to this gap were generally of high quality (Phred quality score > 30). However, this repetition prompted the BWA aligner to ocasionally offer three forms of alternate alignment, illustrated below:

```
REFERENCE   TCAAAGAGAAGC
pR259fs     TCAA__AGAAGC
alt 1       T__AAAAAAAGC
alt 2       TC__ACAGAAGC
alt 3       TC_AAGA_AAGC
alt 4       TCAAAGAG__GC
```

These alternate alignments were corrected to the germline pR259fs due to the following reasoning: Nucleotides highlighted in yellow always had low Phred scores (below 20, in some cases below 10) and therefore were less likely to be correct. For example, given the low qualtity of the highlighted A in alternate one shown above, it is reasonable to assert that the leftmost highlighted A should be a C, and the read would then be aligned as pR259fs. Given the overall high quality length of these reads outside of this region, we believed the most parsimonious interpretation for reads with alternate deletion patterns 1, 2, or 3 was that they represented incorrect alignments of the pR259fs sequence.

The BWA aligner choses an alignment by optimizing a cost value, and alignments that have a single indel are of lower cost than those with two indels. However, BWA lacks prior knowledge that the AG dinucleotide deletion is present in the germline, even when a solution with two indels rather than one is far more plausible given this knowledge. When a reversion indel was adjacent to the repeated AG dinucleotide sequence at nucleotides 32,905,149 and 32,905,152, As a detailed supporting example, below we show an IGV browser view of the 14 indels in exon 9 that were supported by a single read and a close-up view of the first five reads. Nucleotide calls are shaded to reflect quality, with lighter shades indicating lower quality individual calls.



Read 1: The indel is 13 bp distant from germline deletion, creating no ambiguity and no need for adjustment.

Read 2: BWA indicates a three bp deletion that creates a mismatched A base, as this mismatch has lower cost than two deletions. Given knowledge of the germline deletion, the read is more simply and correctly assigned as:

```
REFERENCE: AAAGAGAAGC
BWA:       AAAG---AAC (mismatch in bold italic)
CORRECTED: AA--AGAA-C
```

Read 4: The most likely solution is AA--AGA---------- given that the AGA can be assigned in either of two places.
Read 5: BWA assigns the AA motif to create a mismatch overlapping the germline deletion because this produces one indel rather than two, giving this solution a lower alignment penalty. However, the most likely solution (given the germline) is C-------AA--AG.

Counting Patient 2's indel locations
To create Figure 2d, aligned reads were extracted from the pre-treatment and post-treatment cfDNA BAM files using the Samtools filter parameter 1024. The bedtools *intersect* command was used to exclude reads that did not intersect the HG19 exon bounds, using bounds established by the UCSC refFlat file. The physical location of each individual indel was established by a script written in Python that used the read's aligned location and CIGAR string to determine the location of the one or more indels present in that read. Indels were then binned into 50 nucleotide-wide bins using code in R, with bin occupancy plotted in R.