

1 **Homologous recombination deficiency in newly diagnosed**  
2 **FIGO stage III/IV high-grade epithelial ovarian cancer: a multi-**  
3 **national observational study**

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58 **Abstract**

59

60 *Objective*

61 Olaparib plus bevacizumab maintenance therapy improves survival outcomes in  
62 women with newly diagnosed, advanced, high-grade ovarian cancers with a deficiency  
63 in homologous recombination. We report data from the first year of routine  
64 homologous recombination deficiency testing in the National Health Service (NHS) in  
65 England, Wales and Northern Ireland between April 2021 and April 2022.

66

67 *Methods*

68 The Myriad myChoice® companion diagnostic was used to test DNA extracted from  
69 formalin-fixed, paraffin-embedded tumour tissue in women with newly diagnosed  
70 FIGO (The International Federation of Gynecology and Obstetrics) stage III/IV high-  
71 grade epithelial ovarian, fallopian tube or primary peritoneal cancer. Tumours with  
72 homologous recombination deficiency were those with a *BRCA1/2* mutation and/or a  
73 Genomic Instability Score (GIS) of  $\geq 42$ . Testing was coordinated by the NHS Genomic  
74 Laboratory Hub network.

75

76 *Results*

77 The myChoice® assay was performed on 2,829 tumours. Of these, 2,474 (87%) and  
78 2,178 (77%) successfully underwent *BRCA1/2* and GIS testing, respectively. All  
79 complete and partial assay failures occurred due to low tumour cellularity and/or low  
80 tumour DNA yield. Three-hundred-and-eighty-five tumours (16%) contained a  
81 *BRCA1/2* mutation and 814 (37%) had a GIS  $\geq 42$ . Tumours with a GIS  $\geq 42$  were more  
82 likely to be *BRCA1/2* wild-type (n=510) than *BRCA1/2* mutant (n=304). The distribution

83 of GIS was bimodal, with *BRCA1/2* mutant tumours having a higher mean score than  
84 *BRCA1/2* wild-type tumours (61 versus 33, respectively, chi-squared test  $P < 0.0001$ ).

85

#### 86 *Conclusion*

87 This is the largest real-world evaluation of homologous recombination deficiency  
88 testing in newly diagnosed FIGO stage III/IV high-grade epithelial ovarian, fallopian  
89 tube or primary peritoneal cancer. It is important to select tumour tissue with adequate  
90 tumour content and quality to reduce the risk of assay failures. The rapid uptake of  
91 testing across England, Wales and Northern Ireland demonstrates the power of  
92 centralised NHS funding, centre specialisation and the NHS Genomic Laboratory Hub  
93 network.

94

95 **Key messages**

96

97 *What is already known on this topic?*

98 Olaparib plus bevacizumab maintenance therapy improves survival outcomes in  
99 women with newly diagnosed, advanced, high-grade ovarian cancers with a deficiency  
100 in homologous recombination. There is a scarcity of real world evidence describing  
101 the prevalence of homologous recombination deficiency.

102

103 *What this study adds?*

104 This is the largest real world evaluation of homologous recombination deficient tumour  
105 testing in newly diagnosed FIGO (The International Federation of Gynecology and  
106 Obstetrics) stage III/IV high-grade epithelial ovarian, fallopian tube or primary  
107 peritoneal cancer. We report the prevalence of homologous recombination deficient  
108 tumours in England, Wales and Northern Ireland as 37% using Myriad's myChoice®  
109 companion diagnostic. The complete and partial failure rate of the assay was 13% and  
110 23%, respectively. Tests failed due to low tumour cellularity and/or low tumour DNA  
111 yield.

112

113 *How might this study affect research, practice or policy?*

114 This study highlights the importance of testing tumour DNA for a deficiency in  
115 homologous recombination to optimise outcomes for women with newly diagnosed  
116 FIGO stage III/IV high-grade epithelial ovarian, fallopian tube or primary peritoneal  
117 cancer. Tumour tissue must be carefully selected prior to testing to reduce the chance  
118 of assay failure. The rapid uptake of homologous recombination deficient tumour

119 testing demonstrates the power of centralised NHS funding, centre specialisation and  
120 the NHS Genomic Laboratory Hub network.

121 **Introduction**

122 Ovarian cancer is the most common cause of gynaecological cancer-related death in  
123 Europe (1). Epithelial ovarian cancer accounts for approximately 85 to 90% of all  
124 ovarian cancers. The majority of women diagnosed with high-grade epithelial ovarian  
125 cancer present with advanced disease (The International Federation of Gynaecology  
126 and Obstetrics [FIGO] stage III and IV), meaning despite good response to first-line  
127 multi-modality therapy, at least 80% develop relapsed disease, at which point cure is  
128 unlikely (2). Consequently, the five-year overall survival for advanced ovarian cancer  
129 is approximately 35% (3).

130 Maintenance therapy aims to extend relapse-free survival in patients at high  
131 risk of recurrence, without impacting on quality of life (4). Randomised, phase III trials  
132 have demonstrated that maintenance therapy with a poly(ADP-ribose) polymerase-  
133 1/2 inhibitor (PARPi) improves progression-free survival in women with newly  
134 diagnosed FIGO stage III/IV or platinum-sensitive, relapsed high-grade serous and/or  
135 endometrioid ovarian cancer (5, 6, 7, 8, 9, 10, 11, 12, 13, 14). These small molecule  
136 inhibitors of PARP-1/2 are synthetically lethal to cells deficient in homologous  
137 recombination, a high-fidelity DNA double-strand break repair pathway that maintains  
138 genomic stability (15, 16). The best-studied causes of homologous recombination  
139 deficiency are loss-of-function mutations in *BRCA1* and *BRCA2*, which occur in 20 to  
140 25% of high-grade serous ovarian cancers (17).

141 The myChoice® companion diagnostic (Myriad Genetics, Inc.) is a next-  
142 generation sequencing assay used to detect a deficiency in homologous  
143 recombination in genomic DNA derived from formalin-fixed, paraffin-embedded  
144 tumour tissue (18). The assay reports homologous recombination deficient tumours



145 as those that harbour a *BRCA1/2* mutation and/or have a Genomic Instability Score  
146 (GIS) of  $\geq 42$ . The phase III trial, PAOLA-1, showed an improved hazard ratio (HR) for  
147 disease progression or death in women with newly diagnosed, advanced, high-grade  
148 ovarian cancer who were randomised to maintenance olaparib plus bevacizumab  
149 versus placebo plus bevacizumab, following a response to first-line platinum-taxane  
150 chemotherapy (HR 0.59; 95% confidence interval [CI] 0.49-0.72) (11, 19). The  
151 greatest reduction in HR was reported in women with tumours positive for homologous  
152 recombination deficiency (HR 0.33; 95%CI 0.25-0.45). By contrast, those women with  
153 homologous recombination proficient tumours gained no benefit from the addition of  
154 olaparib to bevacizumab (HR 1.00, 95%CI 0.75-1.35). More recently, data presented  
155 from PAOLA-1 also showed that olaparib plus bevacizumab improved the overall  
156 survival of women with homologous recombination deficient tumours (HR 0.62, 95%CI  
157 0.45-0.85), but not in women with homologous recombination proficient tumour (HR  
158 1.19, 95%CI 0.88-1.63) (20).

159 The results from PAOLA-1 led to European licensing of maintenance olaparib  
160 plus bevacizumab for women with newly diagnosed FIGO stage III/IV high-grade  
161 ovarian, fallopian tube or primary peritoneal cancers that responded to platinum-based  
162 chemotherapy and were homologous recombination deficient. Consequently, access  
163 to Myriad's myChoice® companion diagnostic became available in the United  
164 Kingdom (UK) from April 2021 onwards. We report data from the first year of routine  
165 tumour testing for homologous recombination deficiency in the National Health Service  
166 (NHS) in England, Wales and Northern Ireland between April 2021 and April 2022.

167 **Methods**

168 *Eligibility criteria*

169 Eligibility criteria for myChoice® testing included women with newly diagnosed FIGO  
170 stage III/IV high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer.  
171 Tumour testing was requested during first-line treatment. No patient who underwent  
172 tumour testing as part of a clinical trial was included.

173

174 *Tumour testing*

175 Tumour testing was co-ordinated by the NHS Genomic Laboratory Hub network. The  
176 hubs co-ordinating testing for England were North West, South West, Central and  
177 South, and North Thames. All Wales Genomics Laboratory co-ordinated testing for  
178 Wales. The North West Genomic Laboratory Hub co-ordinated testing for cancer  
179 centres in Northern Ireland.

180 Myriad's myChoice® companion diagnostic became available in England,  
181 Wales and Northern Ireland from April 2021, October 2021 and September 2021,  
182 respectively. The UK includes Scotland, although myChoice® testing did not become  
183 available in Scotland until after April 2022, therefore no cases from Scottish cancer  
184 centres were included in this study. Local medical teams obtained informed consent  
185 from the patient prior to tumour testing. All cancer centres were asked to provide 10 x  
186 slide mounted formalin-fixed, paraffin-embedded tumour sections at a thickness of 5  
187 µm.

188

189 *Myriad's myChoice® companion diagnostic*

190 The myChoice® test was performed by Myriad Genetics, Inc. (Salt Lake City, Utah)  
191 (18). The GIS was calculated as a composite score (range 0 to 100) based on three  
192 bioinformatic algorithms that assessed genome-wide putative biomarkers of  
193 homologous recombination deficiency including Loss of Heterozygosity, Telomeric  
194 Allelic Imbalance and Large-scale State Transitions. The Loss of Heterozygosity  
195 score was defined by the number of loss of heterozygosity regions longer than 15  
196 megabases but shorter than the whole chromosome. The Telomeric Allelic Imbalance  
197 score was defined by the number of regions with allelic imbalance that extend to one  
198 of the sub telomeres, did not cross the centromere, and were longer than 11  
199 megabases. The Large-scale State Transitions score was defined by the number of  
200 chromosomal breaks between two adjacent regions of at least 10 megabases, after  
201 filtering out regions less than 3 megabases and adjusting for ploidy. To quantify Loss  
202 of Heterozygosity, Telomeric Allelic Imbalance and Large-scale State Transitions the  
203 myChoice® test interrogated >27,000 genome-wide single nucleotide polymorphisms.

204 Tumours with a GIS of  $\geq 42$  were reported as 'GIS-positive', while those with a  
205 GIS of  $< 42$  were reported as 'GIS-negative'. Tumours with a *BRCA1/2* mutation and/or  
206 a GIS of  $\geq 42$  were reported as homologous recombination deficient, while those with  
207 *BRCA1/2* wild-type and a GIS of  $< 42$  were reported as homologous recombination  
208 proficient. Only tumour *BRCA1/2* pathogenic or likely pathogenic variants were  
209 reported (21).

210

211 *Statistical analysis*

212 Categorical data were reported as number (percentage). Continuous data were  
213 reported as median (range and interquartile range) and mean (standard deviation).  
214 The chi-squared test was used to determine if there were statistically significant  
215 differences between categorical variables, with a p-value of <0.05 defined as  
216 significant. The t-test was used to determine if there were statistically significant  
217 differences between the mean averages of two groups, with a p-value of <0.05 defined  
218 as significant.

219 In accordance with the journal's guidelines, we will provide our data for  
220 independent analysis by a selected team by the Editorial Team for the purposes of  
221 additional data analysis or for the reproducibility of this study in other centres if such  
222 is requested.

223

## 224 **Results**

225 The myChoice® assay was performed on 2,829 tumours. The tumour content was  
226  $\geq 30\%$  in 83% (n=2,362) of formalin-fixed, paraffin-embedded tissue sections tested.  
227 Of the 2,829 tumours tested, 2,474 (87%) and 2,178 (77%) were successfully tested  
228 for *BRCA1/2* and GIS, respectively. Testing failed due to low tumour cellularity and/or  
229 low tumour DNA yield. In the UK, early testing (April to July 2021) showed a very high  
230 rate of quantity insufficient cancellations as higher DNA inputs were required for  
231 version 1 (legacy version) of the myChoice® test. The myChoice® test version 2  
232 (improved version, due to higher yield DNA extraction and lower DNA input minimum)  
233 was implemented from August 2021 onwards and the rate of sample failures  
234 dramatically dropped (21.7% between April to July 2021, down to 5.3% between  
235 August 2021 to April 2022).

236

### 237 *Tumour BRCA1/2 mutations*

238 Of the 2,474 tumours successfully tested, 385 (16%) *BRCA1/2* mutations were  
239 detected (**Supplementary Table 1**). These included 220 (9%) *BRCA1* and 165 (7%)  
240 *BRCA2* mutations. There were 308 (80%) distinct tumour *BRCA1/2* mutations (178  
241 *BRCA1* and 130 *BRCA2*). There were no mutational hotspots in *BRCA1* or *BRCA2*,  
242 with mutations detected across the length of each gene (**Figure 1**).

243 The majority of tumour *BRCA1/2* mutations were small deletions (172/385) or  
244 single nucleotide variants (143/385) leading to premature protein terminations  
245 (201/385 frameshift-deletions and 103/385 nonsense mutations) (**Table 1**). Small  
246 deletions, duplications and insertions ranged from 1 to 116 base pairs in length. Of the  
247 385 tumour *BRCA1/2* mutations, 360 (94%) were  $\leq 40$  base pairs in length and would  
248 have been detected using local tumour *BRCA1/2* next-generation sequencing assays  
249 used in the UK (22, 23). Twenty-one (5%) pathogenic large genomic rearrangements  
250 were detected. All pathogenic large genomic rearrangements were large deletions  
251 (21/21), with no pathogenic large duplications (0/21) detected. One whole gene  
252 deletion was detected, in *BRCA2*.

253 We were unable to confirm which tumour *BRCA1/2* mutations were germline or  
254 somatic. No genetic assay has been validated to distinguish between germline and  
255 somatic *BRCA1/2* mutations from tumour DNA alone. However, multiple European  
256 *BRCA1/2* founder mutations have been described, thereby allowing us to predict those  
257 tumour *BRCA1/2* mutations that were most likely to be germline. Of the 385 tumour  
258 *BRCA1/2* mutations, 79 (21%) were European *BRCA1/2* founder mutations, including  
259 51 *BRCA1* and 28 *BRCA2*. There were 34 individual *BRCA1/2* founder mutations, of

260 which 16 (47%) were detected in 2 or more tumours. By contrast, of the remaining 306  
261 tumour *BRCA1/2* mutations, there were 274 individual mutations, of which only 25  
262 (25/274; 9%) were detected in 2 or more tumours (chi-squared test  $P < 0.0001$ ). The  
263 commonest European *BRCA1/2* founder mutations were *BRCA2:c.6275\_6276delTT*  
264 (n=9), *BRCA1:c.68\_69delIAG* (n=6), *BRCA1:c.5266dupC* (n=6) and  
265 *BRCA2:c.5946delT* (n=6;). *BRCA2:c.6275\_6276delTT* is a founder mutation from the  
266 UK and the other three *BRCA1/2* mutations are Ashkenazi Jewish founder mutations  
267 (24, 25).

268

### 269 *Genomic Instability Score*

270 Of the 2,178 tumours successfully tested, 814 (37%) had a GIS of  $\geq 42$ . Of these, 304  
271 (37%) had a *BRCA1/2* mutation, while 510 (63%) were *BRCA1/2* wild-type.

272 The GIS had a bimodal distribution (**Figure 2**). Tumours with a *BRCA1/2*  
273 mutation had higher GIS than those with *BRCA1/2* wild-type. The mean GIS for  
274 tumours with a *BRCA1/2* mutation was 61 (median 62; range 3-90; interquartile range  
275 54-70; standard deviation 13) compared to 33 for *BRCA1/2* wild-type tumours (median  
276 28; range 0-100; interquartile range 18-45; standard deviation 20; t-test  $P < 0.0001$ )  
277 (**Figure 3**).

278 Of the 337 tumours with a *BRCA1/2* mutation that were successfully tested for  
279 GIS, 33 (10%) were GIS-negative. Although these tumours did not meet the GIS  
280 threshold for homologous recombination deficiency, they were classified as  
281 homologous recombination deficient due to the presence of a tumour *BRCA1/2*  
282 mutation.

283

284 *Prevalence of tumours positive for homologous recombination deficiency*

285 By including the number of tumours successfully tested for *BRCA1/2* mutation or a  
286 GIS, the prevalence of homologous recombination deficiency was 36% (895/2,474)  
287 and 37% (814/2,178), respectively.

288

## 289 **Discussion**

### 290 *Summary of Main Results*

291 This observational study reports the largest real world evaluation of routine tumour  
292 testing for homologous recombination deficiency in women diagnosed with ovarian  
293 cancer (26). Over 12 months of testing, 895 women with newly diagnosed FIGO stage  
294 III/IV high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in  
295 England, Wales and Northern Ireland were found to have a homologous  
296 recombination deficient tumour. In the UK, around 7,500 women are diagnosed with  
297 ovarian cancer each year. Of these, approximately 5,000 will be diagnosed with FIGO  
298 stage III/IV high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer.  
299 The number of cases tested for homologous recombination deficiency in this study  
300 represents almost half of these women. Moreover, it is notable that tumour testing was  
301 not available in Wales and Northern Ireland until Autumn 2021, meaning fewer than  
302 12 months of eligible women were included from these countries. No cases from  
303 Scotland were included in this study either. The rapid uptake of homologous  
304 recombination deficiency testing across the NHS demonstrates a concerted effort  
305 amongst multi-disciplinary teams to identify women most likely to respond to first-line

306 maintenance PARPi. The substantially higher number of GIS-positive tumours with  
307 *BRCA1/2* wild-type compared to *BRCA1/2* mutations demonstrates the value of using  
308 mutational scar assays to identify potentially PARPi sensitive tumours, above and  
309 beyond standard germline and somatic *BRCA1/2* testing (18, 27, 28).

310

### 311 *Results in the Context of Published Literature*

312 The prevalence of homologous recombination deficient tumours in this study was  
313 lower than anticipated. It has been suggested that approximately 50% of high-grade  
314 serous ovarian cancers harbour a genetic or epigenetic mutation that brings about  
315 homologous recombination deficiency (17). The relative lower prevalence in this study  
316 may have occurred because of a number of reasons. Firstly, eligibility criteria specified  
317 FIGO stage III/IV high-grade epithelial ovarian, fallopian tube or primary peritoneal  
318 cancer. As a result, non-high-grade serous carcinomas such as endometrioid (grade  
319 2 or grade 3) and clear cell will have been tested. These subtypes account for  
320 approximately 10 to 15% of high-grade ovarian cancers and are rarely deficient in  
321 homologous recombination (26, 29, 30, 31, 32, 33). Secondly, eligibility criteria did not  
322 mandate a response to first-line platinum-based chemotherapy prior to tumour testing.  
323 Thus, tumours that did not respond to first-line platinum would have been tested, and  
324 these are highly unlikely to be homologous recombination deficient (18). Thirdly, fewer  
325 germline *BRCA1/2* mutations may have been included in this study. Women with  
326 newly diagnosed FIGO stage III/IV high-grade ovarian cancer who are known germline  
327 *BRCA1/2* heterozygotes can access maintenance olaparib plus bevacizumab without  
328 requiring tumour testing (11). Fourthly, observational data suggests that tumour  
329 samples with higher chemotherapy response scores (2/3 versus 1) following



330 neoadjuvant chemotherapy are more likely to be deficient in homologous  
331 recombination, but also more likely to fail testing (33). Therefore, homologous  
332 recombination proficient tumours are often disproportionately reported in cases  
333 treated with neoadjuvant chemotherapy plus delayed primary surgery. Fifthly, this  
334 study shows a relatively higher rate of complete and partial assay failure compared to  
335 clinical trials, meaning a significant number of patients with a tumour *BRCA1/2*  
336 mutation may have been missed (10, 11). Finally, our real world data is likely to include  
337 more elderly patients compared to clinical trials. Observational data from the  
338 BriTROC-1 study has demonstrated that the presence of homologous recombination  
339 deficient-related single nucleotide variant-signature 3 inversely correlates with age  
340 (34).

341

#### 342 *Strengths and Weaknesses*

343 There are three main limitations with this study. Firstly, no clinical data have been  
344 provided. This information was not mandated on the test request form. Thus, we are  
345 unable to determine the distribution of homologous recombination deficiency across  
346 demographic groups. Secondly, no follow-up data have been provided. Therefore, we  
347 cannot determine whether testing influenced clinical decision making. The UK testing  
348 scheme did not mandate treatment with first-line maintenance olaparib plus  
349 bevacizumab for *BRCA1/2* mutant or GIS-positive tumours. In fact, because the  
350 optimal first-line maintenance therapy for FIGO stage III/IV high-grade epithelial  
351 ovarian, fallopian tube or primary peritoneal cancer has not been precisely defined,  
352 several alternative options are available including olaparib, niraparib or bevacizumab  
353 (8, 10, 36). Thirdly, the germline and somatic status of each tumour *BRCA1/2* mutation

354 is unknown. No tumour DNA sequencing assay is able to distinguish between germline  
355 and somatic *BRCA1/2* variants. Thus, we are unable to report whether GIS was  
356 affected by germline or somatic status. Interestingly, 10% of tumours with a *BRCA1/2*  
357 mutation had a GIS of <42. The reason for this unusual genotype is unclear but may  
358 suggest certain *BRCA1/2* mutations having a passenger role in carcinogenesis. Those  
359 patients found to have a *BRCA1/2* mutant/GIS-negative tumour should be more  
360 closely observed for poorer response to PARPi therapy.

361

### 362 *Implications for Practice and Future Research*

363 We report data from the largest observational study evaluating homologous  
364 recombination deficiency in newly diagnosed FIGO stage III/IV high-grade epithelial  
365 ovarian, fallopian tube or primary peritoneal cancer. These data show the value of  
366 tumour testing to identify women most likely to respond to first-line maintenance  
367 PARPi. These data demonstrate the importance of homologous recombination  
368 deficiency testing to optimise outcomes for eligible women. The relatively high failure  
369 rate of testing, resulting from formalin-fixed, paraffin-embedded tissue with low tumour  
370 cellularity and/or low tumour DNA yield, also highlights the need for local multi-  
371 disciplinary teams to carefully select tumour tissue to be tested. Finally, the rapid  
372 uptake of homologous recombination deficiency testing in England, Wales and  
373 Northern Ireland demonstrates the power of centralised NHS funding, centre  
374 specialisation and the NHS Genomic Laboratory Hub network.

375

### 376 **Conclusions**

377 The real world prevalence of homologous recombination deficient tumours in women  
378 with newly diagnosed, FIGO stage III/IV high-grade epithelial ovarian, fallopian tube  
379 or primary peritoneal cancer in England, Wales and Northern Ireland was 37%. Most  
380 of tumours positive for homologous recombination deficiency were *BRCA1/2* wild-type

381 **Funding**

382 The Myriad myChoice® companion diagnostic was funded by AstraZeneca PLC  
383 (Address: 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge CB2  
384 0AA, United Kingdom; Tel: +44 (0)20 3749 5000).

385

386 **Acknowledgement**

387 The data reported in this manuscript has been presented at the European Society of  
388 Medical Oncology 2022 Congress (*Annals of Oncology* 2022;33(suppl\_7):S235-  
389 S282).

390

391 **Conflicts of interest**

392 RDM, BMB, SN, HS, LY-S, YW, MV-P, RW, SM, SMc, EH, AG, SS, SN, SST and  
393 DGRE declare no conflicts of interest.

394 KT is an employee and stockholder of Myriad Genetics.

395 ARC declares research funding from AstraZeneca.

396 SMac declares travel funding and speaker fees from AstraZeneca, Merck and Eli Lilly.

397 LT declares honoraria from AstraZeneca, Clovis Oncology, GSK and Tesaro.

398 RM declares honoraria from AstraZeneca, Merck Sharp & Dohme and GSK and  
399 research funding from Barts & The London Charity, Rosetrees Trust, GSK and  
400 Yorkshire Cancer Research.

401 JB declares honoraria from AstraZeneca and GSK and consulting and advisory roles  
402 in Clovis Oncology and GSK.

403 SB declares institutional grants from AstraZeneca and GSK, personal fees for  
404 speaker, consulting/advisory roles from Amgen, AstraZeneca, Clovis Oncology,  
405 EpsilonGen, GSK, Immunogen, Mersana, Merck Sharp & Dohme, Merck Serono,  
406 Novartis, OncXerna, Pfizer, Roche, Shattuck Labs & Takeda.

407 RSK declares honoraria from AstraZeneca, Clovis Oncology, GSK and Incyte and  
408 travel support from AstraZeneca, GSK and Sierra Oncology and trial grants from  
409 Merck Sharp & Dohme and consulting fees from Basilea Pharmaceutica and Shattuck  
410 Pharma.

411 IMcN declares honoraria from AstraZeneca, Clovis Oncology, Epsila Bio, GSK, Roche  
412 and Scancell and institutional funding from AstraZeneca.

413 JAL declares honoraria from AstraZeneca, Clovis Oncology, GSK, Eisai, Neopharm,  
414 Artios Pharma, Merck/Merck Sharp & Dohme, Mersana, Regeneron, VBL  
415 Therapeutics, Nuvation and Bristol Myers Squibb.

416 GCJ declares research funding from AstraZeneca.

417

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539

	<b><i>BRCA1</i></b> <b>(N=220)</b>	<b><i>BRCA2</i></b> <b>(N=165)</b>	<b>Total</b> <b>(N=385)</b>
<b><i>Nucleotide level</i></b>			
Small deletions	82 (37)	90 (55)	172 (45)
Single nucleotide variants	95 (43)	48 (29)	143 (37)
Small duplications	19 (9)	19 (12)	38 (10)
Large genomic rearrangements	18 (8)	3 (2)	21 (5)
Small insertion-deletions	6 (3)	3 (2)	9 (2)
Small insertions	0	2 (1)	2 (1)
<b><i>Protein level</i></b>			
Frameshift-deletions	96 (44)	105 (64)	201 (52)
Nonsense	59 (27)	44 (27)	103 (27)
Splice	22 (10)	8 (5)	30 (8)
Large genomic rearrangements	18 (8)	3 (2)	21 (5)
Missense	16 (7)	4 (2)	20 (5)
Intron	9 (4)	1 (1)	10 (3)

**Table 1. Types of tumour *BRCA1/2* pathogenic and likely pathogenic variants.**  
Data is presented as number (percentage).

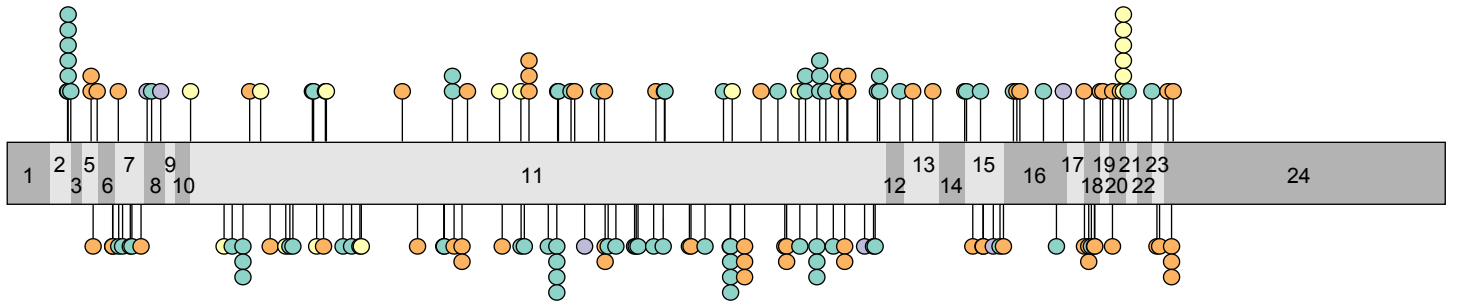
## Figure Legends

**Figure 1. Lollipop diagram showing the loci of each pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2*.** Key: (A) *BRCA1* and (B) *BRCA2*; splice site, intronic variants and large genomic rearrangements are not included; the number of circles on each lollipop stick indicates the number tumours containing that variant; the exons of *BRCA1* and *BRCA2* proteins are numbered; reference sequences are LRG\_292(*BRCA1*) and LRG\_293(*BRCA2*).

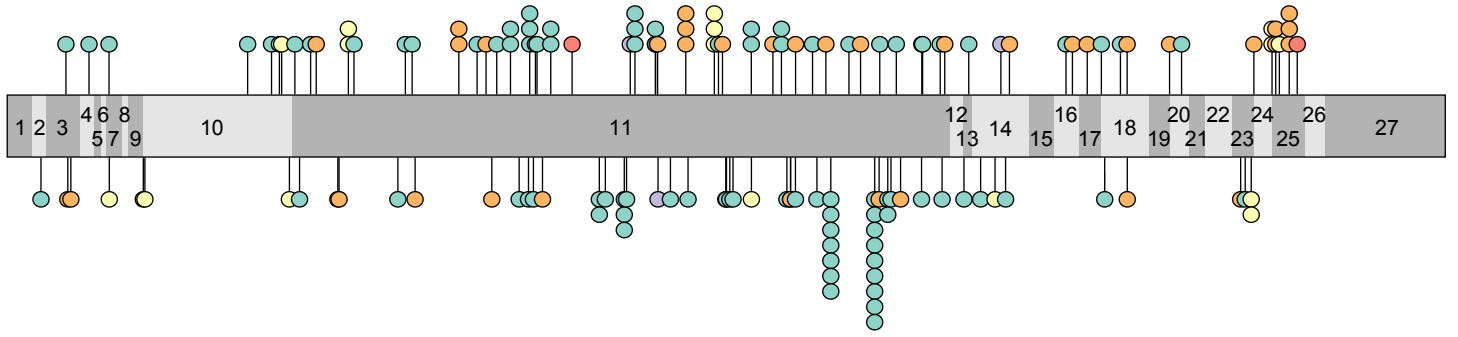
**Figure 2. Bar graph showing the distribution of Genomic Instability Scores in tumours with a *BRCA1/2* mutation or wild-type.** Two-thousand-one-hundred-and-seventy-eight tumours were successfully tested for Genomic Instability Score.

**Figure 3. Dot plot diagram showing the Genomic Instability Score of tumours with a *BRCA1/2* mutation or wild-type.** Key: each dot represents the Genomic Instability Score (GIS) for a single tumour; the dotted line at GIS = 42 represents the threshold at which a tumour is classified as deficient in homologous recombination.

A

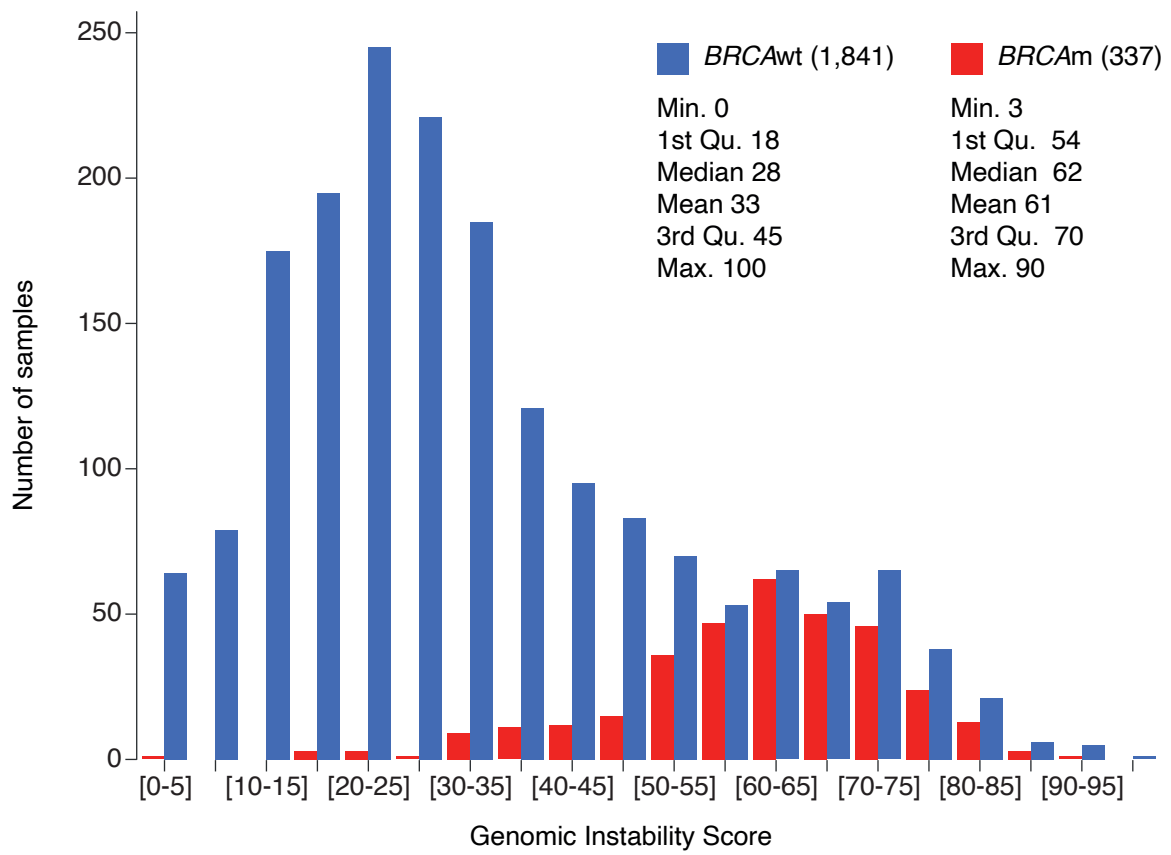


B

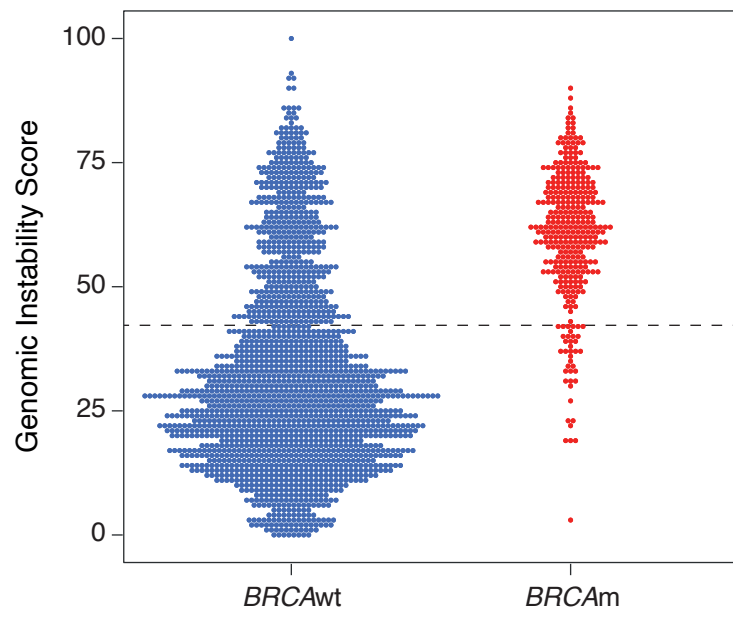


● Deletion ● Duplication ● Indel ● Insertion ● SNV

Figure 1



**Figure 2**



**Figure 3**