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Germline mutations and the presence of clonal hematopoiesis of indeterminate potential (CHIP) in 20,963 patients with *BRCA*-associated cancers

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Introduction

- The contribution of germline genetics on the emergence of CHIP in patients with solid tumor malignancies is not well understood.
- We hypothesized that those with germline (g) alterations in homologous recombination repair genes (gHRR) and *BRCA*-associated cancers (breast, ovarian, prostate and pancreas) would have different rates of CHIP than those without.

Methodology

20,963 patients profiled with tumor normal matched Tempus xT testing*

*Tempus xT assay - a targeted panel that detects single nucleotide variants, insertions and/or deletions, and copy number variants in 598-648 genes, as well as chromosomal rearrangements in 22 genes with high sensitivity and specificity.

Cohort selection:

- Presence or Absence of pathogenic/likely pathogenic alteration in select CHIP-associated genes
- VAF minimum of 2%

List of CHIP-Associated Genes			
ASXL1	*BCOR*	*BCORL1*	*CBL*
CREBBP	*CUX1*	*DNMT3A*	*GNB1*
JAK2	*PPM1D*	*PRPF8*	*SETDB1*
SF3B1	*SRSF2*	*TET2*	*U2AF1*

Retrospective Analysis

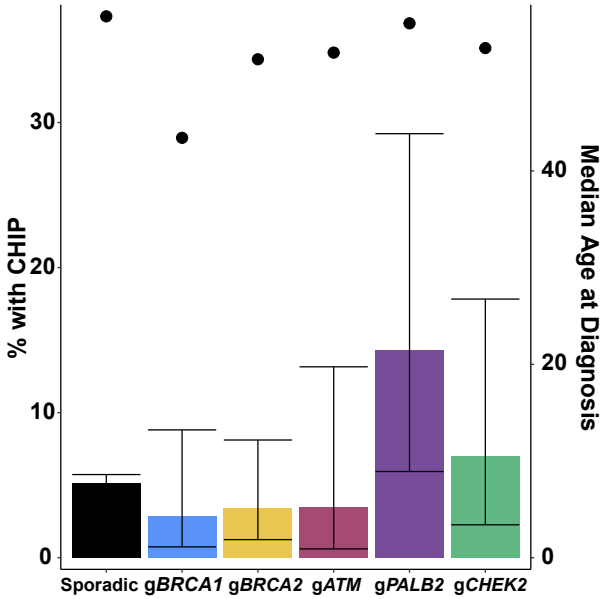
Patients with germline alterations in *BRCA1, BRCA2, ATM, CHEK2*, and *PALB2* were compared to those without gHRR alterations (sporadic).

Breast cancer cohort demographics

	Sporadic N = 6,546	**g*BRCA1*** N = 104	**g*BRCA2*** N = 148	**g*ATM*** N = 57	**g*PALB2*** N = 42	**g*CHEK2*** N = 57
Age at Diagnosis	56 (46, 65)	43 (35, 52)	52 (40, 60)	52 (42, 62)	55 (47, 69)	53 (42, 59)
Gender, n (%) Female	6,470 (99%)	104 (100%)	138 (93%)	56 (98%)	42 (100%)	56 (98%)
Race & Ethnicity, n (%)						
White	3,274 (75%)	42 (68%)	65 (71%)	27 (82%)	19 (68%)	33 (89%)
Black or African American	635 (15%)	10 (16%)	13 (14%)	4 (12%)	3 (11%)	1 (2.7%)
Asian	193 (4.4%)	5 (8.1%)	4 (4.3%)	2 (6.1%)	3 (11%)	0 (0%)
Other race	267 (6.1%)	5 (8.1%)	10 (11%)	0 (0%)	3 (11%)	3 (8.1%)
Hispanic or Latino	399 (16%)	8 (24%)	11 (17%)	2 (10%)	2 (17%)	5 (23%)
Stage of Disease, n(%)						
Stage 1	109 (2.7%)	0 (0%)	3 (3.4%)	0 (0%)	1 (3.6%)	1 (2.4%)
Stage 2	263 (6.5%)	5 (9.1%)	7 (7.9%)	3 (7.5%)	3 (11%)	1 (2.4%)
Stage 3	280 (6.9%)	3 (5.5%)	5 (5.6%)	5 (12%)	0 (0%)	1 (2.4%)
Stage 4	3,392 (84%)	47 (85%)	74 (83%)	32 (80%)	24 (86%)	39 (93%)
Any CHIP mutation	**338 (5.2%)**	**3 (2.9%)**	**5 (3.4%)**	**2 (3.5%)**	**6 (14%)**	**4 (7.0%)**

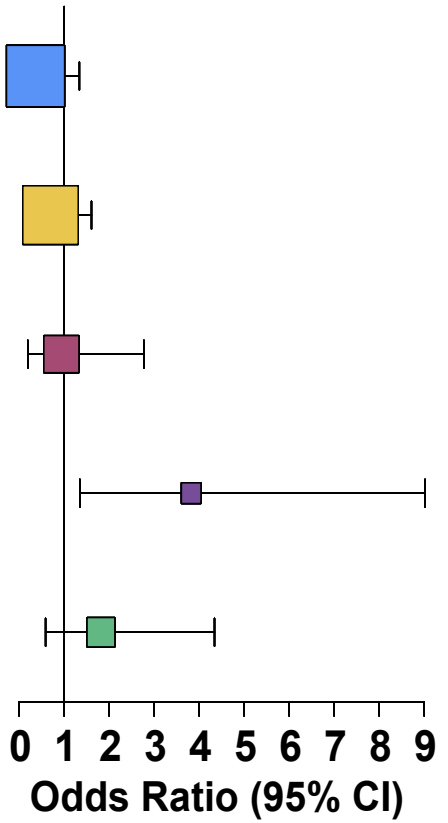
Breast cancer

CHIP altered patients



Age-adjusted CHIP risk

Germline Mutation	Total (N)	Chip (N)	OR	95% CI	p-value
g*BRCA1*	86	1	0.37	0.041-1.3	0.15
g*BRCA2*	126	1	0.7	0.23 -1.6	0.43
g*ATM*	51	1	0.94	0.19 -2.8	0.92
g*PALB2*	30	5	3.8	1.3 - 1.9	0.014
g*CHEK2*	50	4	1.8	0.59 - 4.3	0.27



Age-adjusted germline effect on CHIP status

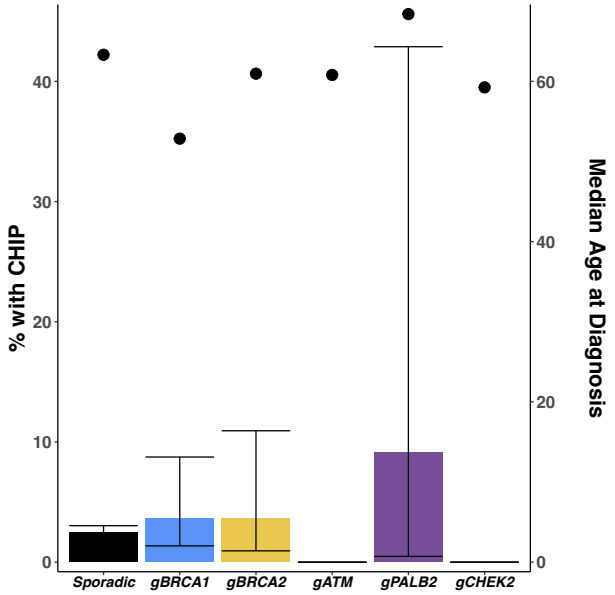
	Total (N=6,954)	CHIP (N=358)	OR	95% CI	p-value
Age Diagnosis	**5,987**	**315**	**1.01**	**1.01, 1.02**	**0.002**
Sporadic	5,644	299	Ref	Ref	Ref
g*BRCA1*	86	1	0.37	0.04, 1.34	0.15
g*BRCA2*	126	4	0.70	0.23, 1.61	0.4
g*ATM*	51	2	0.94	0.19, 2.77	>0.9
g*PALB2*	**30**	**5**	**3.82**	**1.35, 9.02**	**0.014**
g*CHEK2*	50	4	1.82	0.59, 4.34	0.3

Ovarian cancer cohort demographics

	Sporadic N = 3,979	g*BRCA1* N = 137	g*BRCA2* N = 83	g*ATM* N = 23	g*PALB2* N = 11	g*CHEK2* N = 9
Age at Diagnosis	63 (54, 71)	53 (48, 60)	61 (55, 68)	61 (54, 71)	68 (61, 72)	59 (42, 71)
Race & Ethnicity, n (%)						
White	2,186 (82%)	76 (78%)	39 (78%)	12 (71%)	9 (100%)	4 (100%)
Black or African American	225 (8.4%)	9 (9.3%)	6 (12%)	2 (12%)	0 (0%)	0 (0%)
Asian	106 (4.0%)	7 (7.2%)	3 (6.0%)	2 (12%)	0 (0%)	0 (0%)
Other race	151 (5.7%)	5 (5.2%)	2 (4.0%)	1 (5.9%)	0 (0%)	0 (0%)
Hispanic or Latino	220 (14%)	10 (19%)	2 (7.7%)	0 (0%)	0 (0%)	1 (20%)
Stage of disease, n (%)						
Stage 1	72 (5.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stage 2	85 (6.0%)	3 (7.3%)	1 (4.8%)	0 (0%)	1 (25%)	0 (0%)
Stage 3	547 (39%)	14 (34%)	9 (43%)	0 (0%)	1 (25%)	1 (33%)
Stage 4	716 (50%)	24 (59%)	11 (52%)	3 (100%)	2 (50%)	2 (67%)
Any CHIP mutation	**99 (2.5%)**	**5 (3.6%)**	**3 (3.6%)**	**0 (0%)**	**1 (9.1%)**	**0 (0%)**

Ovarian cancer

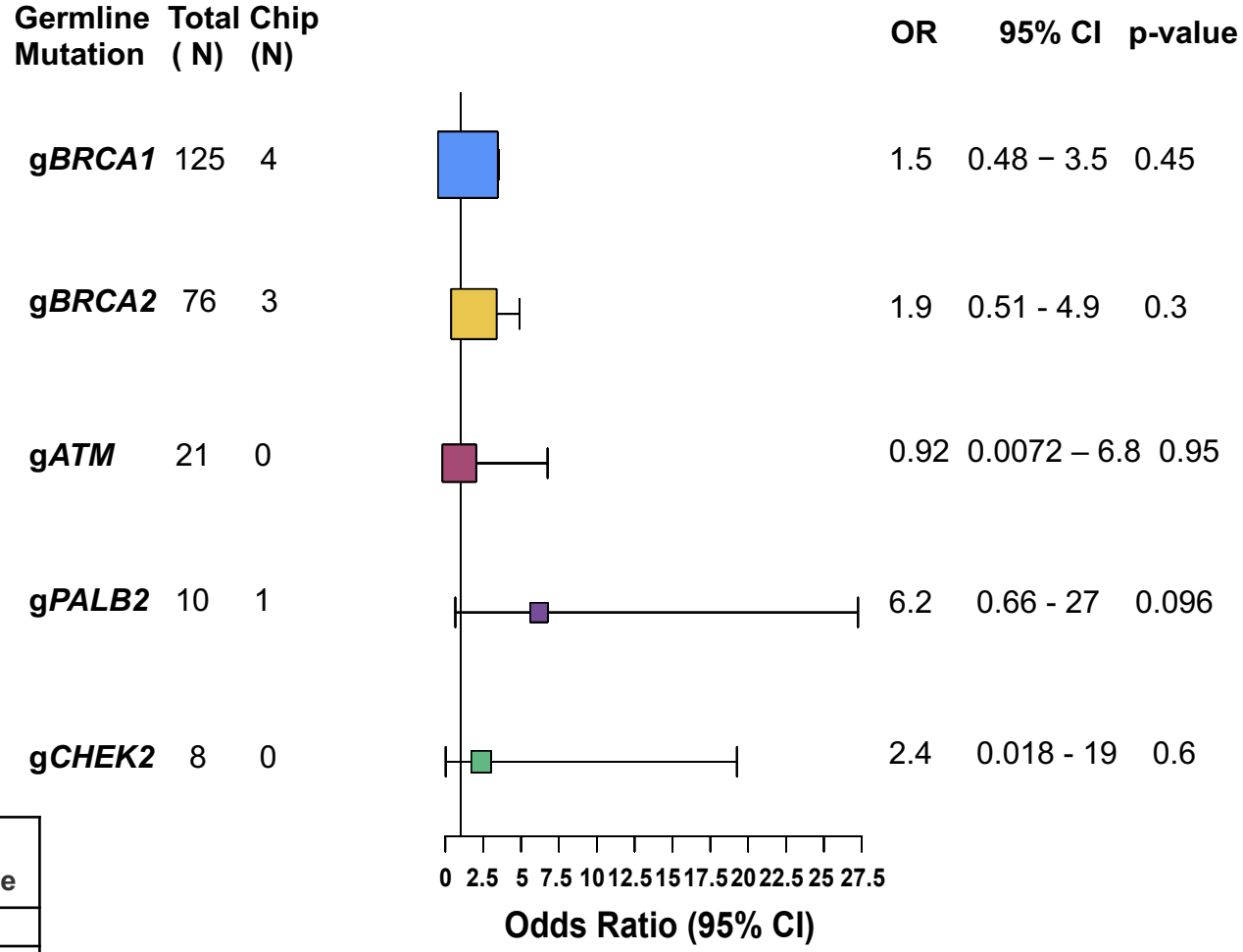
CHIP altered patients



Age-adjusted germline effect on CHIP status

Germline Group	Total (N=3,870)	CHIP (N=97)	OR	95% CI	p-value
Age at Diagnosis	3,870	97	1.00	0.99, 1.02	0.8
Sporadic	3,630	89	Ref	Ref	Ref
g*BRCA1*	125	4	1.49	0.48, 3.53	0.4
g*BRCA2*	76	3	1.88	0.51, 4.89	0.3
g*ATM*	21	0	0.92	0.01, 6.75	>0.9
g*PALB2*	10	1	6.18	0.66, 27.3	0.10
g*CHEK2*	8	0	2.37	0.02, 19.3	0.6

Age-adjusted CHIP risk

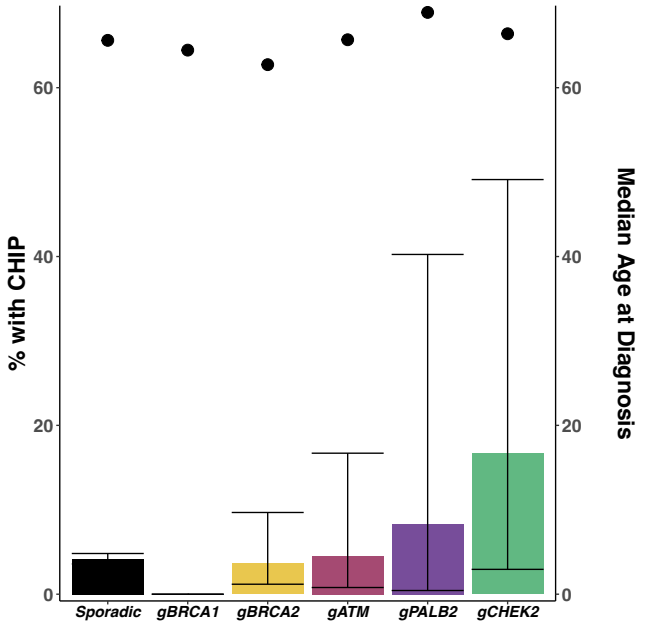


Prostate cancer cohort demographics

	Sporadic N = 4,183	**g*BRCA1*** N = 16	**g*BRCA2*** N = 109	**g*ATM*** N = 44	**g*PALB2*** N = 12	**g*CHEK2*** N = 12
Age at Diagnosis	66 (60, 72)	64 (56, 74)	63 (56, 67)	66 (62, 72)	69 (59, 72)	66 (62, 74)
Race & Ethnicity, n (%)						
White	1,944 (75%)	7 (78%)	54 (77%)	21 (78%)	9 (90%)	7 (100%)
Black or African American	456 (18%)	0 (0%)	12 (17%)	4 (15%)	0 (0%)	0 (0%)
Asian	80 (3.1%)	2 (22%)	0 (0%)	1 (3.7%)	0 (0%)	0 (0%)
Other race	113 (4.4%)	0 (0%)	4 (5.7%)	1 (3.7%)	1 (10%)	0 (0%)
Hispanic or Latino	187 (13%)	1 (20%)	6 (15%)	3 (17%)	0 (0%)	0 (0%)
Stage of disease, n (%)						
Stage 1	8 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stage 2	54 (2.4%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stage 3	165 (7.3%)	1 (25%)	3 (5.0%)	1 (4.0%)	0 (0%)	0 (0%)
Stage 4	2,048 (90%)	2 (50%)	57 (95%)	24 (96%)	8 (100%)	8 (100%)
Any CHIP mutation	**174 (4.2%)**	**0 (0%)**	**4 (3.7%)**	**2 (4.5%)**	**1 (8.3%)**	**2 (17%)**

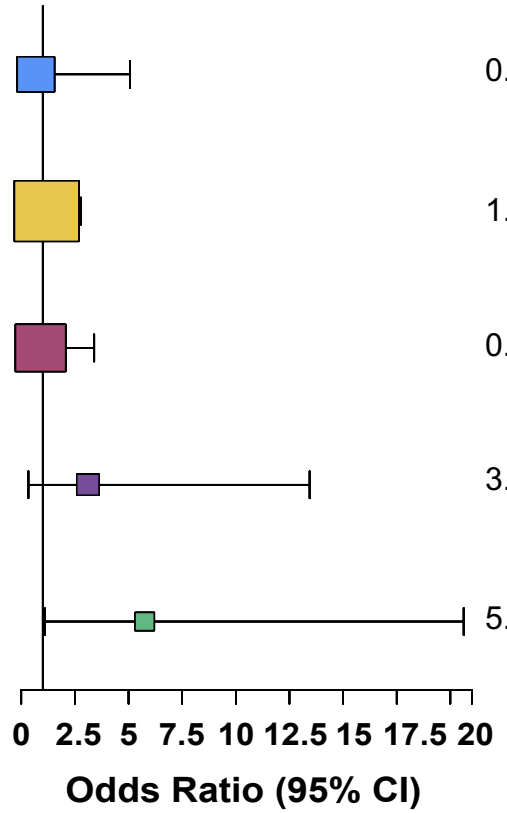
Prostate cancer

CHIP altered patients



Age-adjusted CHIP risk

Germline Mutation	Total (N)	Chip (N)	OR	95% CI	p-value
g*BRCA1*	16	0	0.68	0.0053 – 5.1	0.77
g*BRCA2*	98	4	1.2	0.39 - 2.8	0.74
g*ATM*	38	1	0.9	0.1 – 3.4	0.9
g*PALB2*	11	1	3.1	0.33 - 13	0.26
g*CHEK2*	11	2	5.8	1.1 - 21	0.041



Age-adjusted germline effect on CHIP status

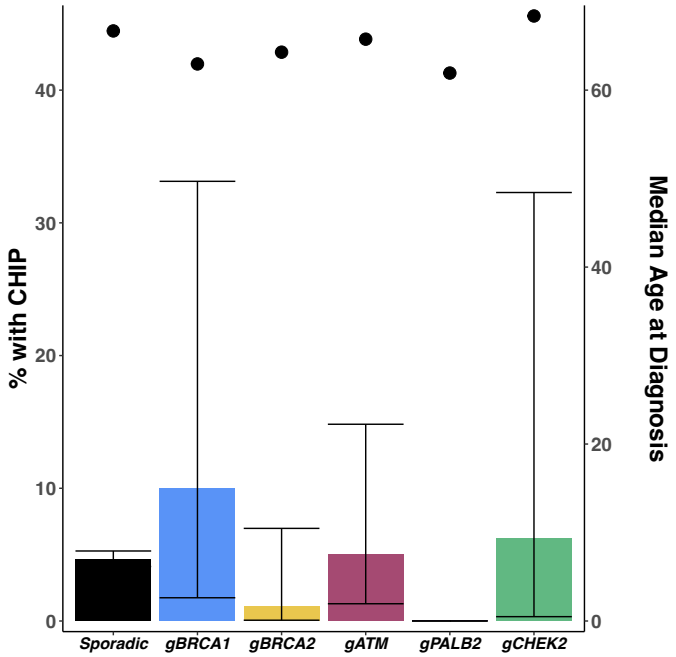
	Total (N=3,773)	CHIP (N=158)	OR	95% CI	p-value
Age at Diagnosis	**3,773**	**158**	**1.02**	**1.01, 1.04**	**0.011**
Sporadic	3,599	150	Ref	Ref	Ref
g*BRCA1*	16	0	0.68	0.01, 5.07	0.8
g*BRCA2*	98	4	1.18	0.39, 2.78	0.7
g*ATM*	38	1	0.90	0.10, 3.40	0.9
g*PALB2*	11	1	3.11	0.33, 13.4	0.3
g*CHEK2*	**11**	**2**	**5.75**	**1.09, 20.6**	**0.041**

Pancreatic cancer cohort demographics

	Sporadic N = 5,176	g*BRCA1* N = 20	g*BRCA2* N = 89	g*ATM* N = 60	g*PALB2* N = 20	g*CHEK2* N = 16
Age at Diagnosis	67 (59, 73)	63 (56, 68)	64 (57, 71)	66 (61, 71)	62 (56, 67)	68 (64, 73)
Gender, n(%) Female	2,419 (47%)	8 (40%)	39 (44%)	29 (48%)	11 (55%)	8 (50%)
Race & Ethnicity, n (%)						
White	2,546 (82%)	9 (69%)	40 (77%)	26 (79%)	18 (100%)	12 (100%)
Black or African American	319 (10%)	2 (15%)	3 (5.8%)	5 (15%)	0 (0%)	0 (0%)
Asian	113 (3.6%)	0 (0%)	5 (9.6%)	1 (3.0%)	0 (0%)	0 (0%)
Other race	129 (4.2%)	2 (15%)	4 (7.7%)	1 (3.0%)	0 (0%)	0 (0%)
Hispanic or Latino	205 (14%)	1 (11%)	6 (17%)	5 (23%)	0 (0%)	0 (0%)
Stage of disease, n (%)						
Stage 1	174 (4.8%)	1 (6.7%)	3 (4.3%)	1 (2.6%)	0 (0%)	1 (6.2%)
Stage 2	367 (10%)	2 (13%)	5 (7.1%)	7 (18%)	1 (6.7%)	1 (6.2%)
Stage 3	272 (7.5%)	0 (0%)	3 (4.3%)	6 (16%)	1 (6.7%)	2 (12%)
Stage 4	2,807 (78%)	12 (80%)	59 (84%)	24 (63%)	13 (87%)	12 (75%)
Any CHIP mutation	**241 (4.7%)**	**2 (10%)**	**1 (1.1%)**	**3 (5.0%)**	**0 (0%)**	**1 (6.2%)**

Pancreatic cancer

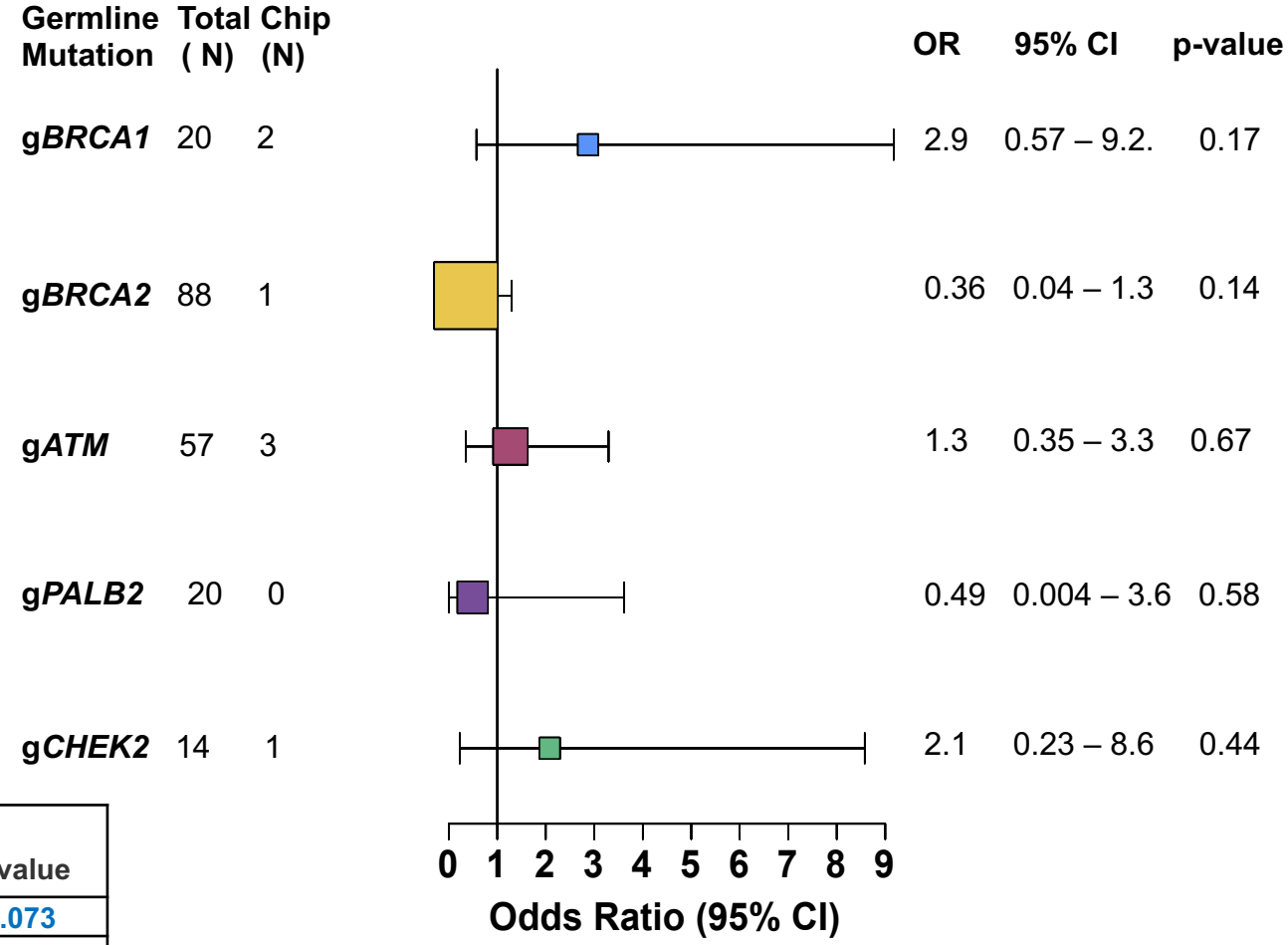
CHIP altered patients



Age- and sex-adjusted germline effect on CHIP status

Germline Group	Total (N=5,024)	CHIP (N=238)	OR	95% CI	p-value
Age at Diagnosis	**5,024**	**238**	**1.01**	**1.00, 1.02**	**0.073**
Female	**2,349**	**130**	**1.39**	**1.07, 1.80**	**0.014**
Sporadic	4,825	231	Ref	Ref	Ref
g*BRCA1*	20	2	2.87	0.57, 9.17	0.2
g*BRCA2*	88	1	0.36	0.04, 1.30	0.14
g*ATM*	57	3	1.27	0.35, 3.30	0.7
g*PALB2*	20	0	0.49	0.00, 3.62	0.6
g*CHEK2*	14	1	2.08	0.23, 8.58	0.4

Age- and sex-adjusted CHIP risk



Conclusions/Take-Away

- Women with g***PALB2*** **alterations and breast cancer**, as well as **men with g*CHEK2* mutations and prostate cancer**, had higher rates of CHIP.
- These data suggest that gHRR mutations may **influence the prevalence of CHIP** among patients with BRCA-associated cancers.
- The clinical implications of these data, especially in terms of complications from therapies like PARP inhibitors and platinum chemotherapy, deserves further study.