2023 ASCO® ANNUAL MEETING

Germline mutations shape somatic alteration landscapes in *BRCA*-associated cancers

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TEMPUS

Masonic Cancer Center
University of Minnesota

Background

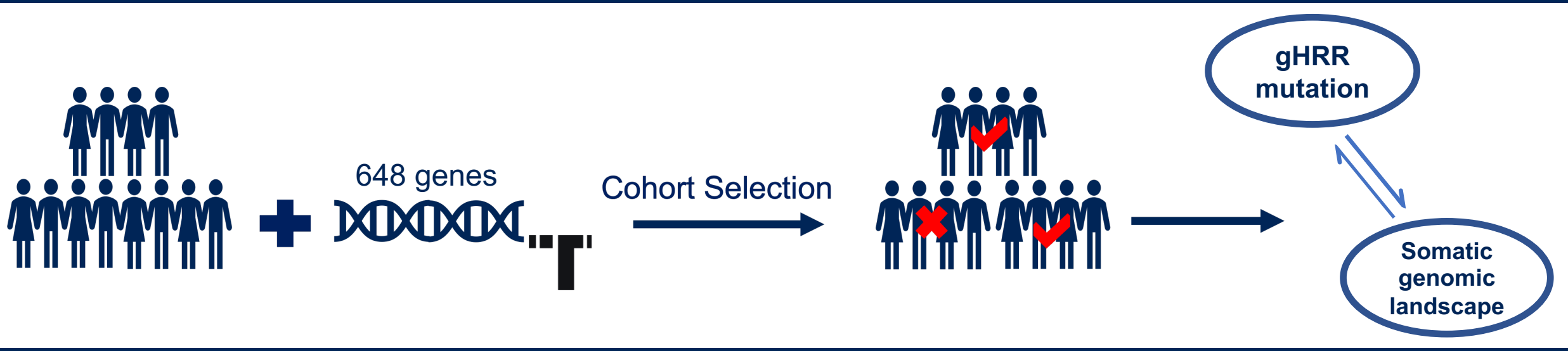
- Genomics plays a critical role in precision oncology, serving as a valuable tool for drug development and as a biomarker for predicting treatment response in clinical settings.
- Both germline and somatic genomics may influence prognosis and therapeutic considerations across multiple cancers, but paired analysis of tumor/normal samples is not routinely performed.
- As a result, the *interaction* between germline and somatic genomics (*i.e.* how one influences the other) is largely unknown.

Background

- Homologous recombination repair (HRR) genes are involved in repairing dsDNA breaks, and increase the risk of cancers of the breast, ovaries, pancreas, and prostate: often described as *BRCA*-associated cancers.

- By studying these 4 *BRCA*-associated cancers, we sought to understand *for the first time* how germline HRR gene mutations influence the somatic genomic landscape of tumors arising in these individuals.

Methods



Retrospective study of 21,263 patients:

- 7,008 Breast cancers
- 4,310 Ovarian cancers
- 5,426 Pancreatic cancers
- 4,526 Prostate cancers

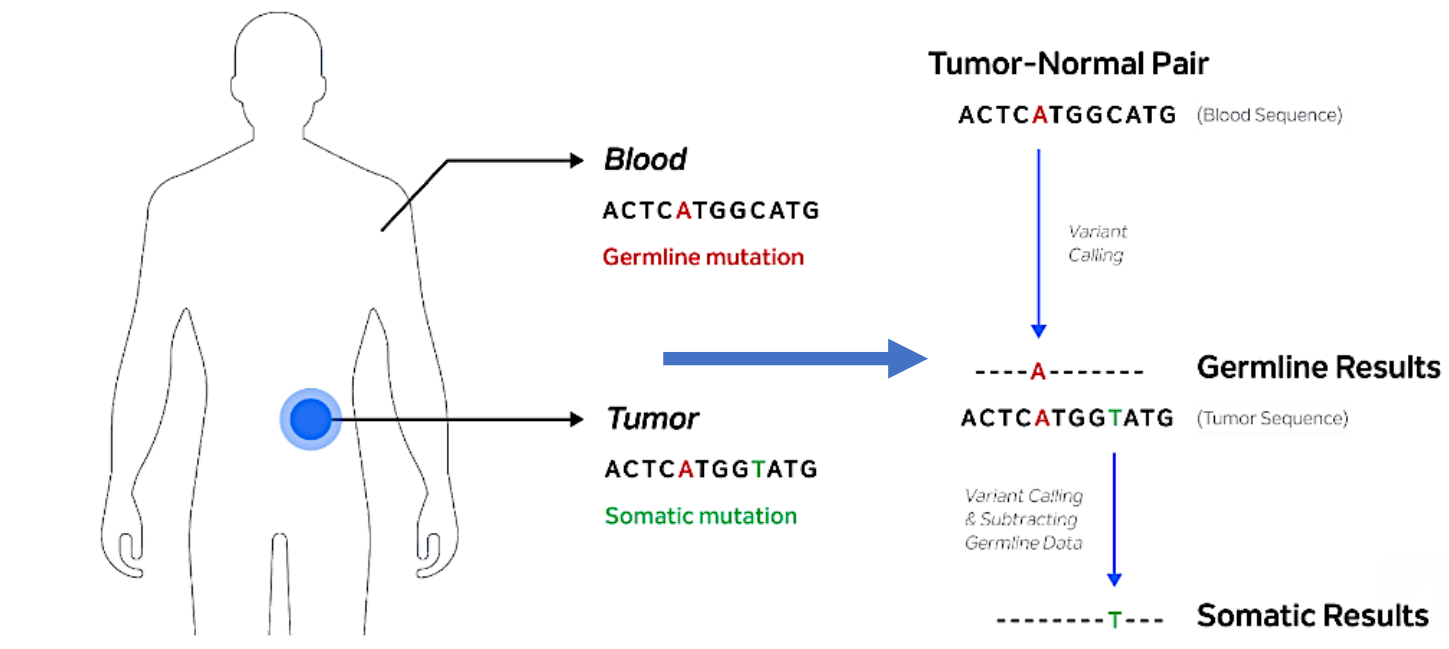
Presence of germline HRR mutations:

- g*BRCA1*
- g*BRCA2*
- g*PALB2*
- g*ATM*
- g*CHEK2*

TEMPUS Tumor-Normal DNA Analysis

Tumor-Normal Matching

- DNA sequencing of tumor tissue and a normal sample in parallel
- Normal match sequencing enables identification of incidental germline variants filtered from somatic variants



Mandelker & Ceyhan-Birsoy, Trends Cancer. 2020; 6: 31-39.

Methods

- Particular genes of interest in our somatic analysis included *:

  AR, ATM, APC, AKT1, ARID1A, BRAF, BRCA1, BRCA2, CDK12, CDKN2A, CDH1, CHD1, CHEK2, CCND1, CTNNB1, EGFR, ERBB2, ESR1, FAT3, FGFR1, FOXA1, GATA3, GNAS, HRAS, KDM6A, KMT2C, KMT2D, KMT2A, KRAS, MAP2K4, MLH1, MSH2, MSH6, MUTYH, MYC, NF1, NRAS, NOTCH1, PALB2, PMS2, PIK3CA, PIK3R1, PTEN, RB1, SPOP, SETD2, SMAD4, STK11, TMPRSS2-ERG, TP53.

** Due to the high prevalence of alterations in these 50 genes in the four cancers studied.*

Methods

- We also compared the tumor mutational burden (TMB)* of germline HRR-mutated tumors versus sporadic tumors across all 4 cancer types.

- Finally, we performed survival analysis to compare the outcomes for each germline-mutated group relative to sporadic cases, to identify common trends seen with HRR-altered patients across all 4 cancers.

**The number of nonsynonymous somatic mutations per megabase of DNA.*

1. Breast Cancer - Demographics

Characteristic	Sporadic (n=6,599)	g*BRCA1* (n=104)	g*BRCA2* (n=148)	g*PALB2* (n=42)	g*ATM* (n=57)	g*CHEK2* (n=57)
Age at diagnosis(yrs)						
Median, Range	56 (17–90)	43 (24–86)	52 (24–81)	55 (27–82)	52 (24–83)	53 (29–79)
Race						
White	3,298 (75%)	42 (68%)	65 (71%)	19 (68%)	27 (82%)	33 (89%)
Black	643 (15%)	10 (16%)	13 (14%)	3 (11%)	4 (12%)	1 (2%)
Other	268 (6%)	10 (16%)	14 (15%)	6 (22%)	2 (6%)	3 (8%)
Ethnicity						
Hispanic	409 (16%)	8 (24%)	11 (17%)	2 (17%)	2 (10%)	5 (23%)
Site of tumor sequenced						
Primary (Breast)	2,435 (39%)	36 (35%)	50 (36%)	13 (48%)	17 (31%)	15 (29%)
Metastatic	3,822 (61%)	68 (65%)	88 (64%)	24 (52%)	38 (69%)	36 (71%)

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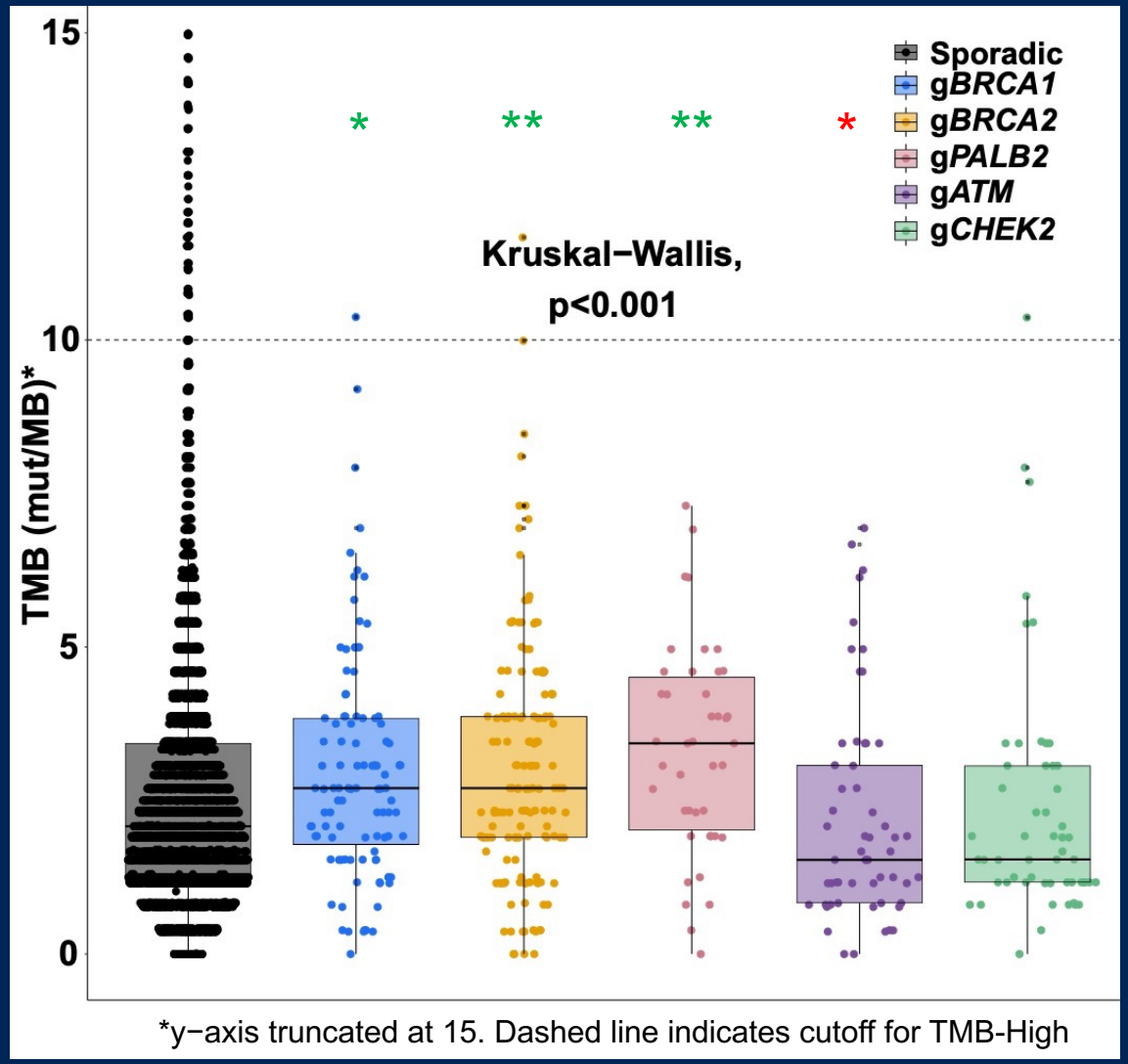

*y−axis truncated at 15. Dashed line indicates cutoff for TMB-High

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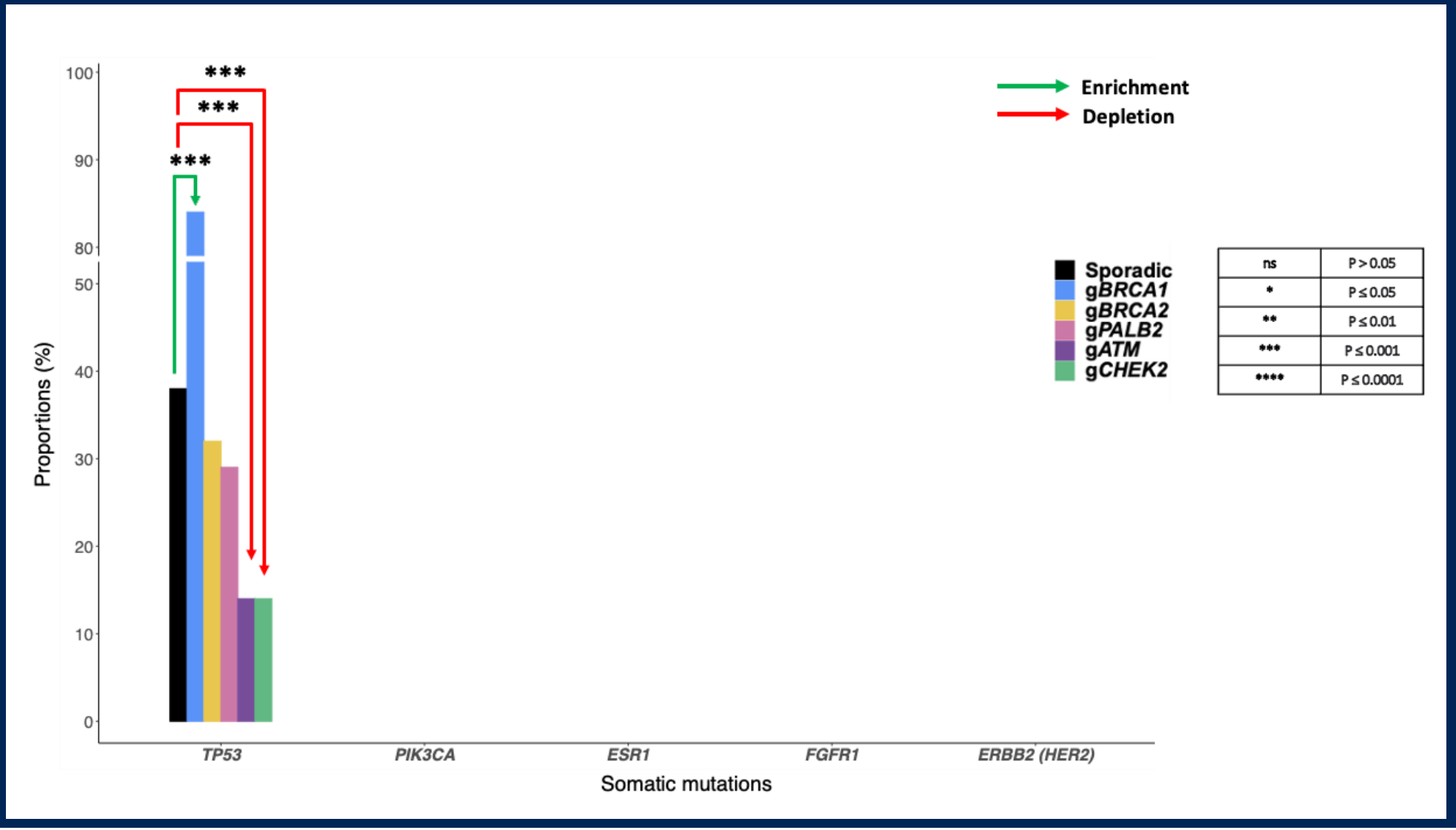

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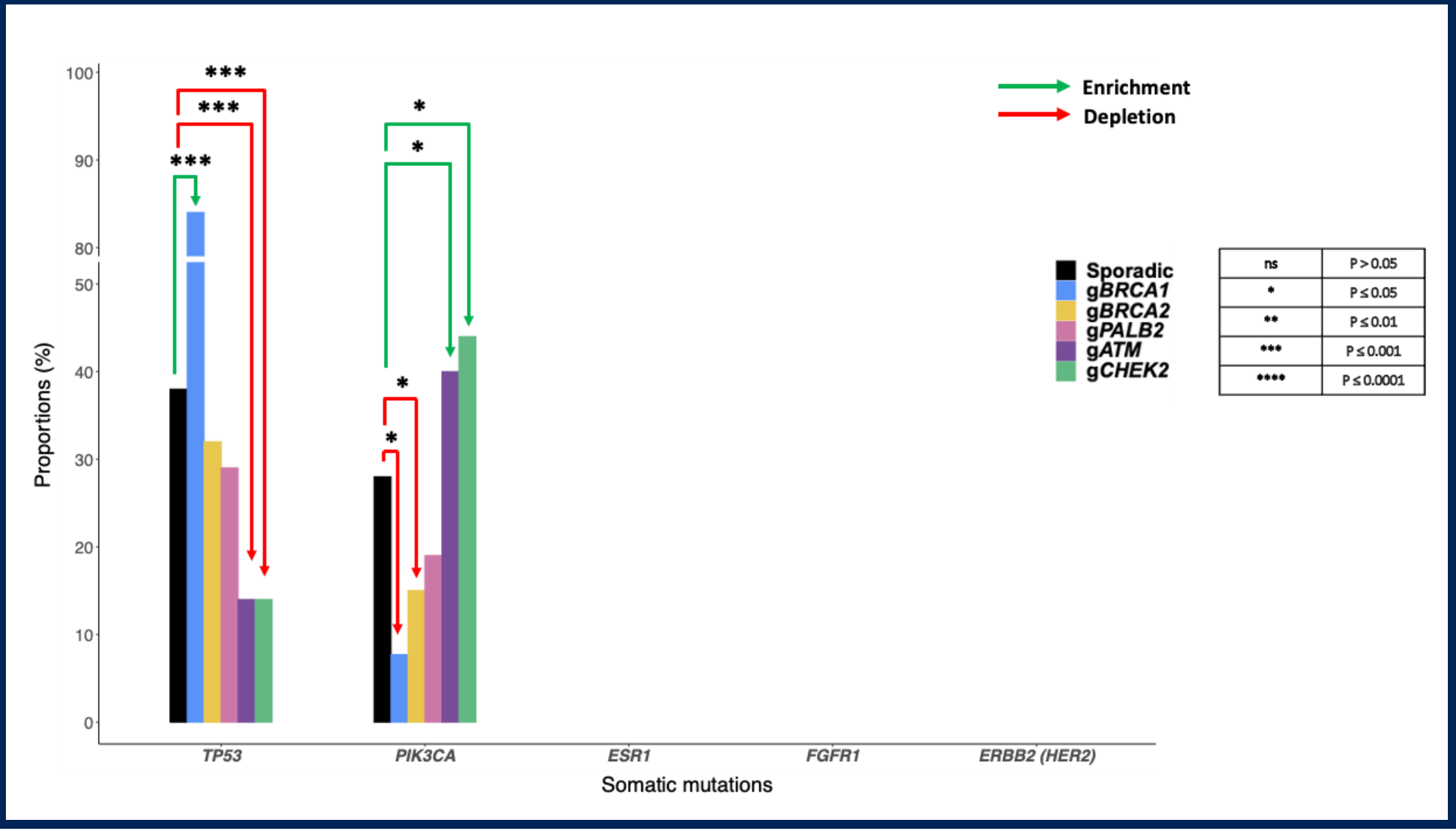

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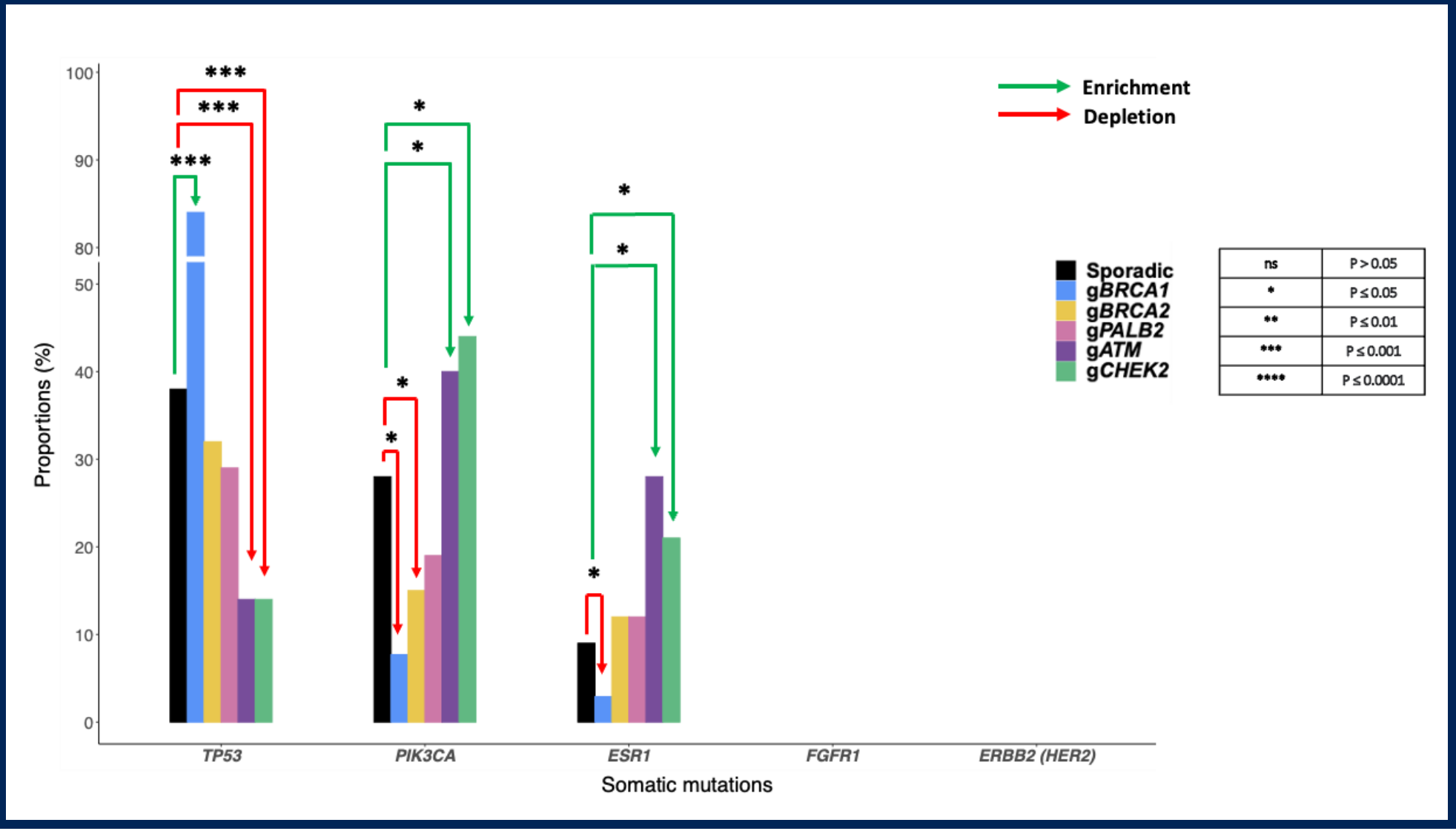

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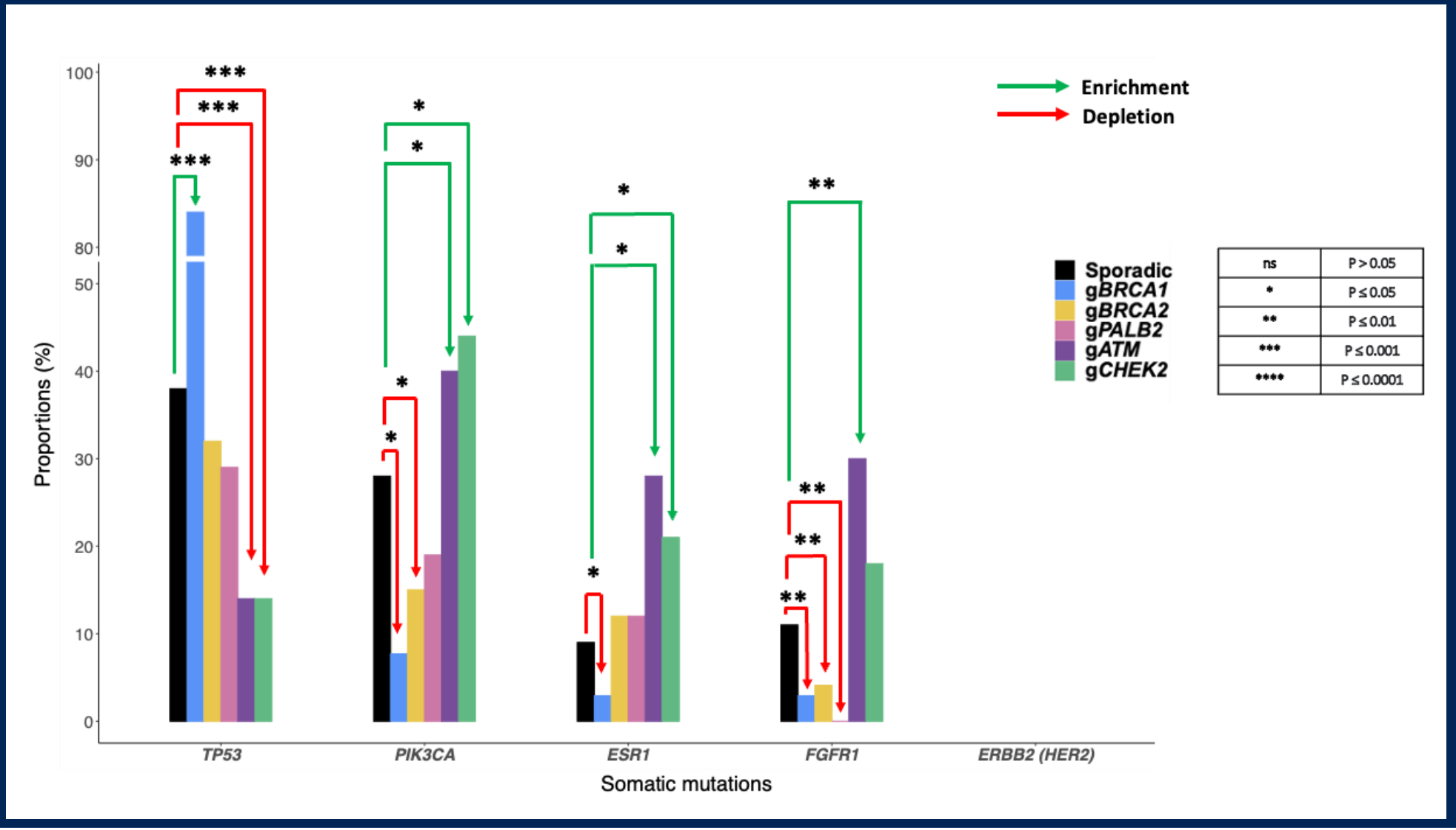

PRESENTED BY: Dr. Ali T. Arafa

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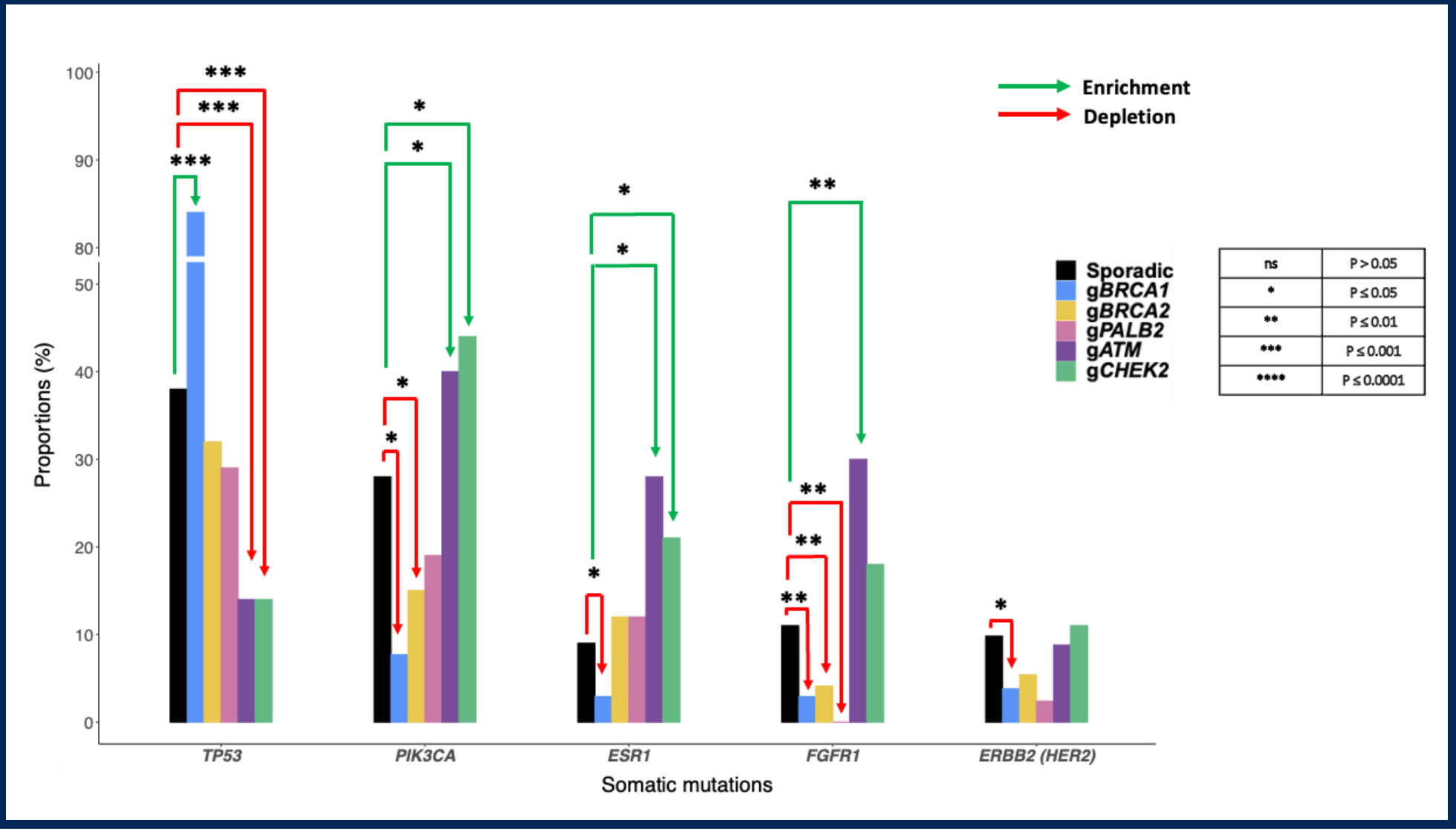

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2. Ovarian Cancer - Demographics

Characteristic	Sporadic (n=4,041)	g*BRCA1* (n=138)	g*BRCA2* (n=84)	g*PALB2* (n=11)	g*ATM* (n=24)	g*CHEK2* (n=10)
Age at diagnosis (yrs)						
Median, Range	63 (17–90)	53 (32–79)	61 (43–81)	68 (46–74)	60 (34–83)	64 (25–77)
Race						
White	2,221 (82%)	77 (79%)	39 (78%)	9 (100%)	12 (71%)	5 (100%)
Black	226 (8%)	9 (9%)	6 (12%)	0 (0%)	2 (12%)	0 (0%)
Other	262 (10%)	12 (12%)	5 (10%)	0 (0%)	3 (17%)	0 (0%)
Ethnicity						
Hispanic	229 (14%)	10 (19%)	2 (8%)	0 (0%)	1 (12%)	1 (17%)
Site of tumor sequenced						
Primary (Ovary)	1,260 (31%)	31 (24%)	27 (34%)	4 (36%)	9 (38%)	2 (22%)
Metastatic	2,752 (69%)	98 (76%)	52 (66%)	7 (64%)	15 (62%)	7 (78%)

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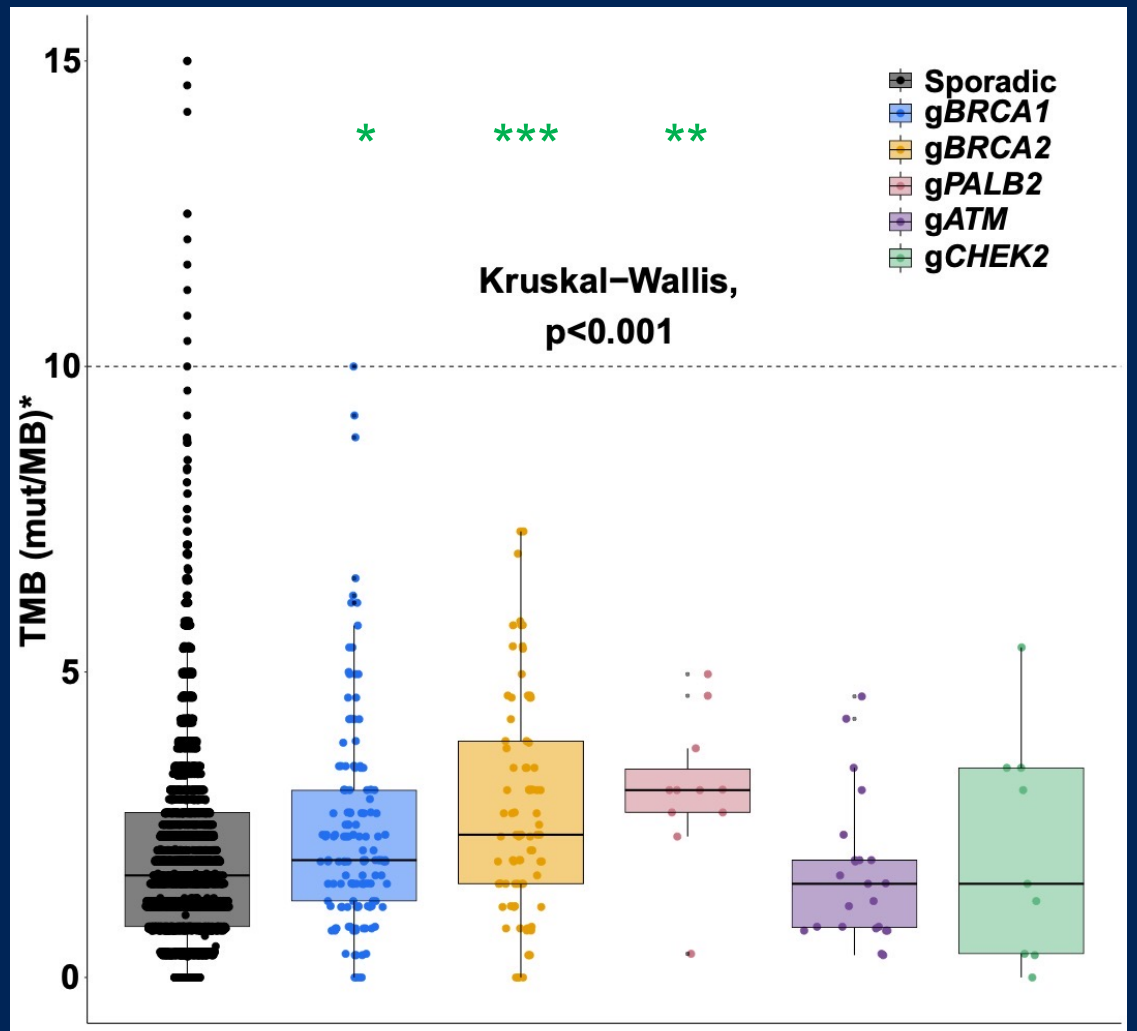

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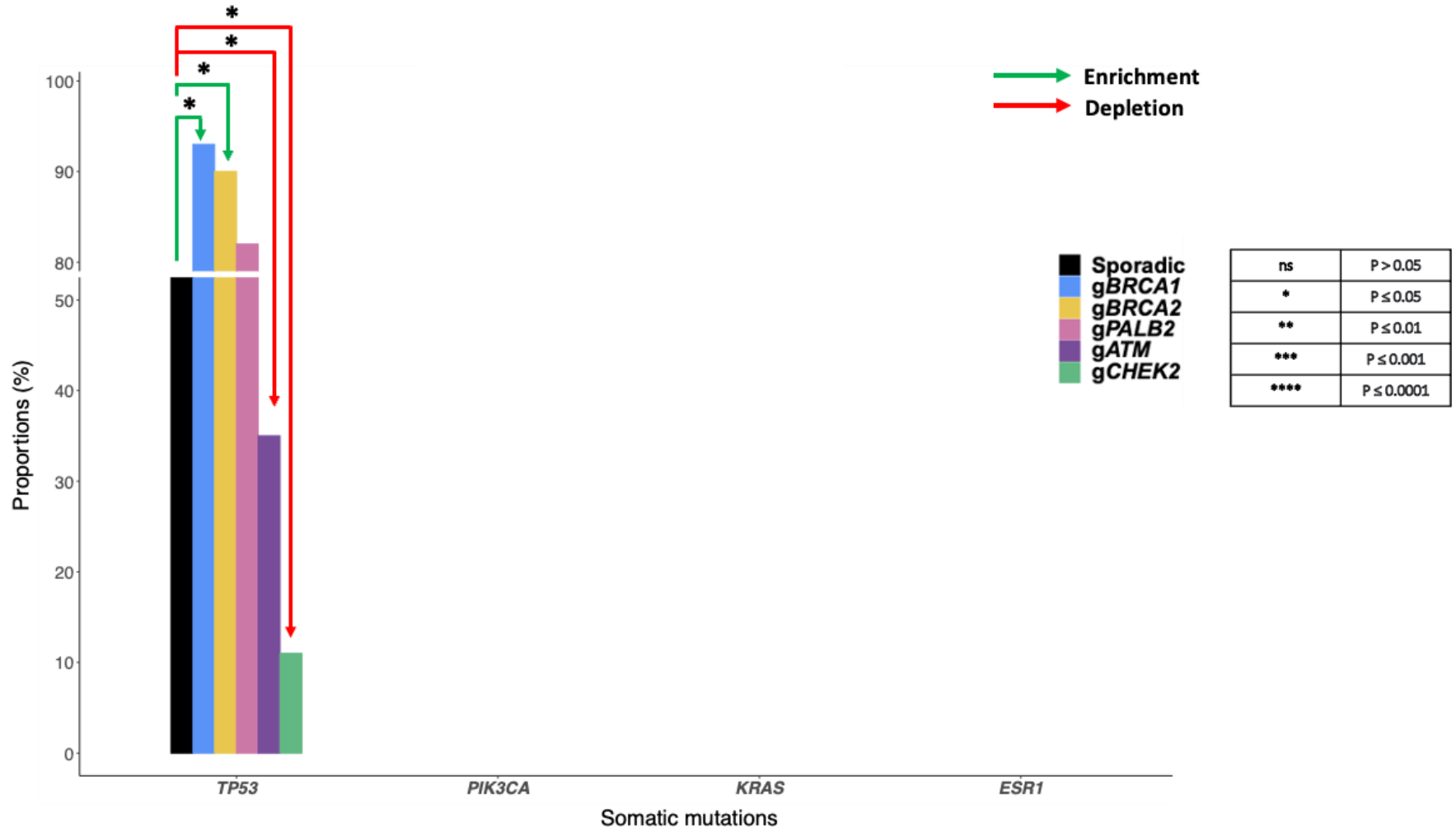

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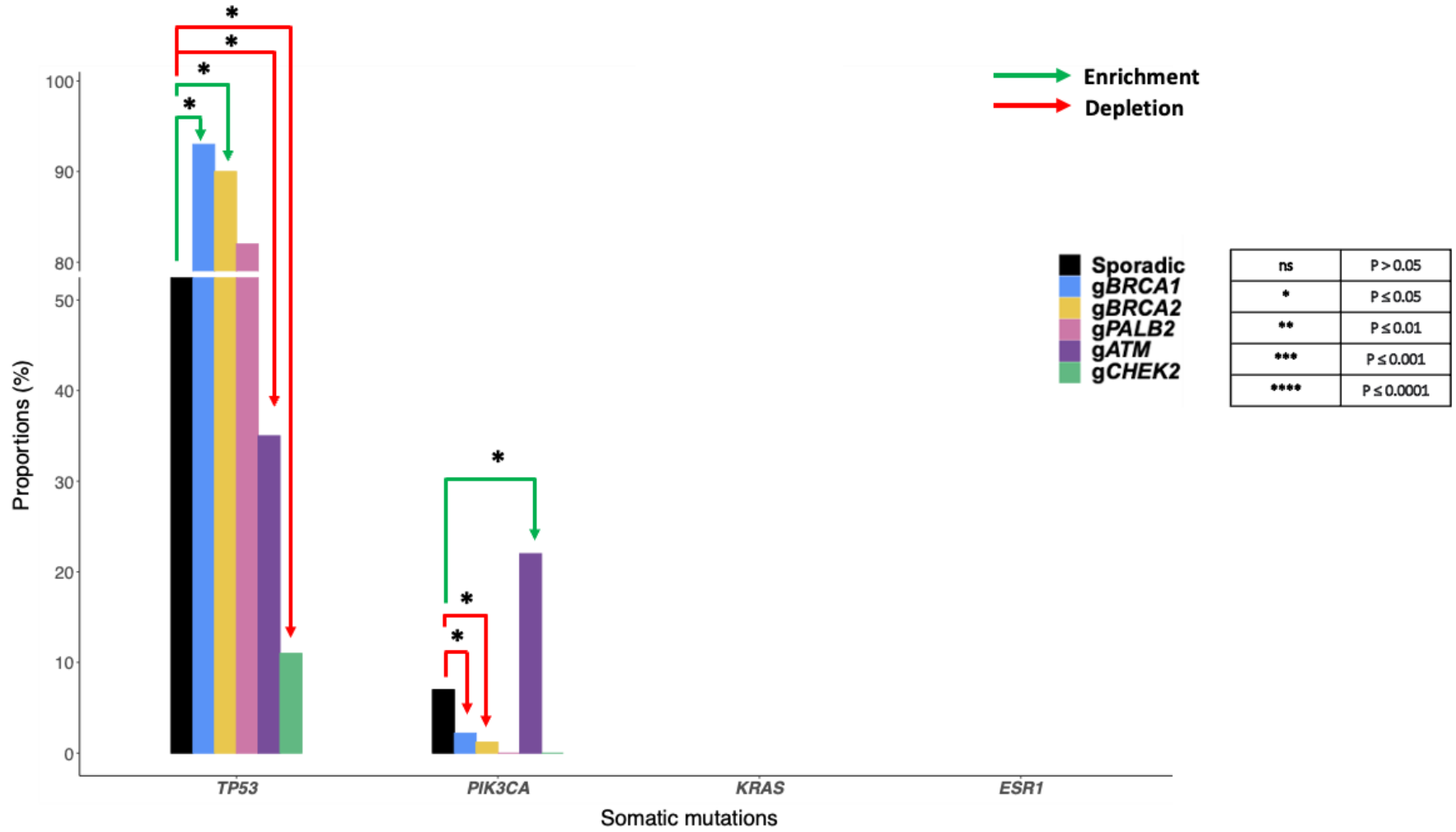

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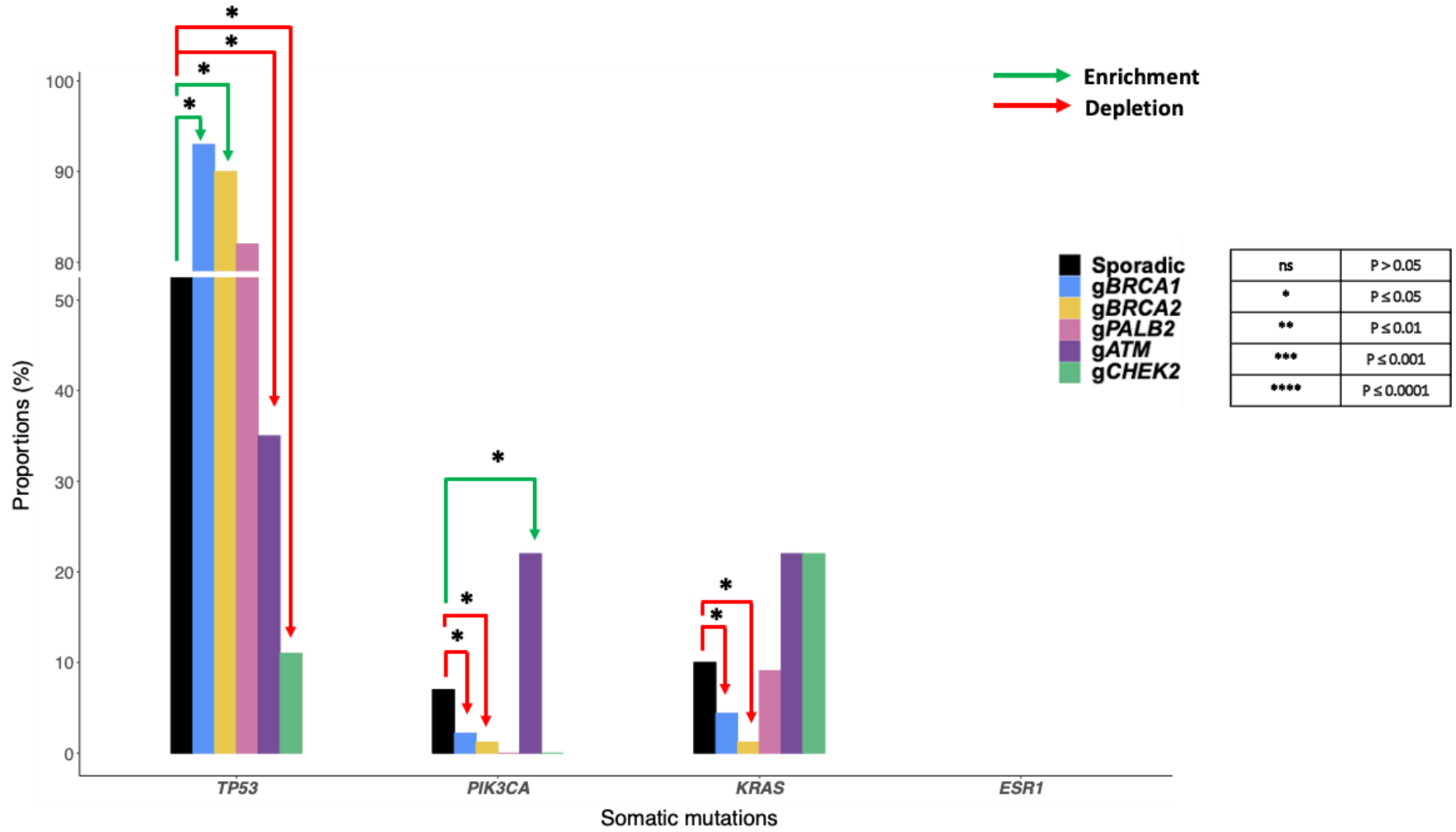

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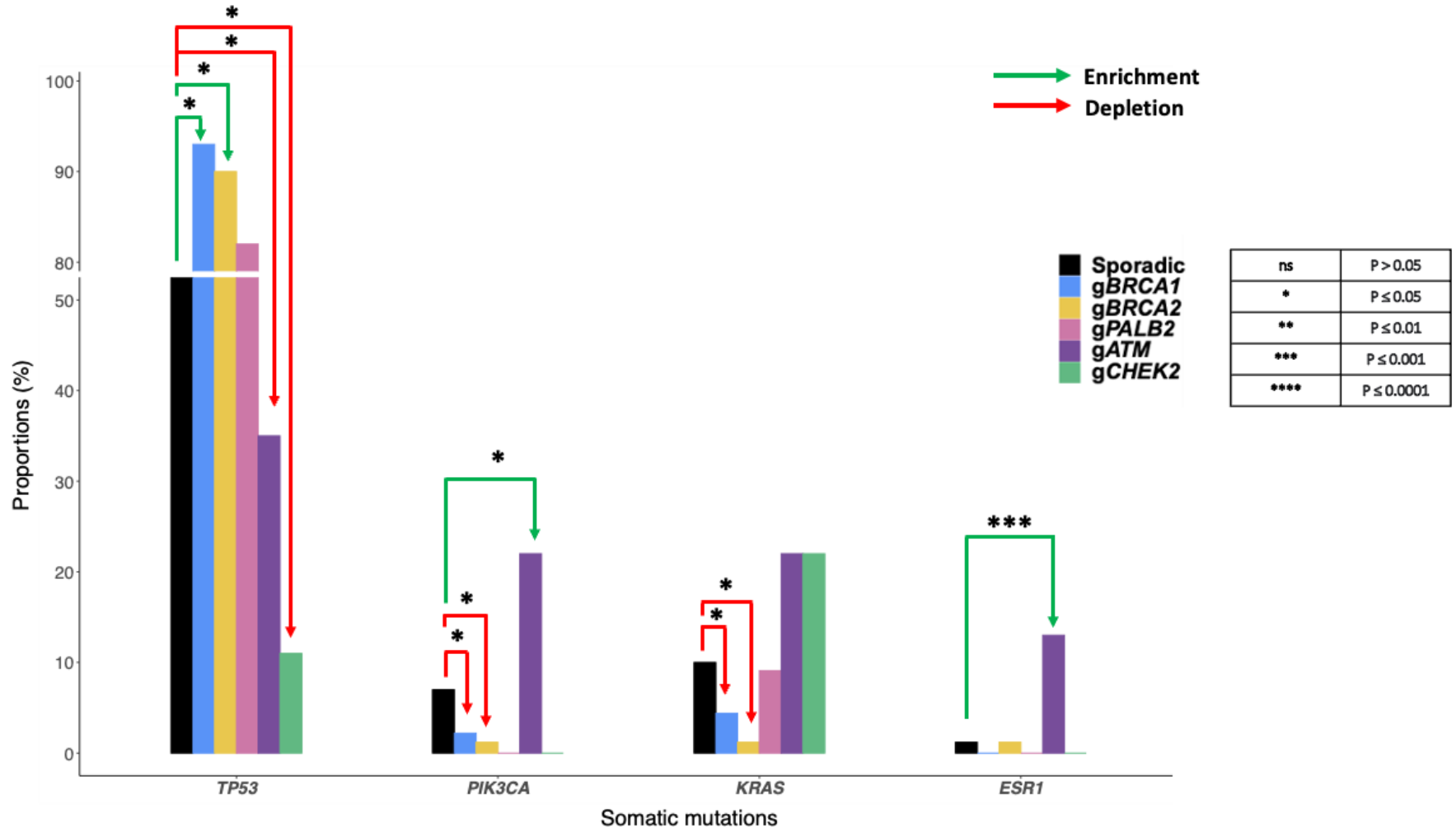

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3. Pancreatic Cancer - Demographics

Characteristics	Sporadic (n=5,213)	g*BRCA1* (n=20)	g*BRCA2* (n=89)	g*PALB2* (n=21)	g*ATM* (n=61)	g*CHEK2* (n=17)
Age at diagnosis (yrs)						
Median, Range	67 (21–90)	63 (41–88)	64 (37–85)	60 (41–78)	66 (43–84)	70 (56–81)
Gender						
Male	2,776 (53%)	12 (60%)	50 (56%)	10 (48%)	32 (52%)	8 (47%)
Female	2,437 (47%)	8 (40%)	39 (44%)	11 (52%)	29 (48%)	9 (53%)
Race						
White	2,572 (82%)	9 (70%)	40 (77%)	18 (100%)	26 (79%)	12 (100%)
Black	321 (10%)	2 (15%)	3 (6%)	0 (0%)	5 (15%)	0 (0%)
Other	243 (8%)	2 (15%)	9 (17%)	0 (0%)	2 (6%)	0 (0%)
Ethnicity						
Hispanic	205 (14%)	1 (11%)	6 (17%)	0 (0%)	5 (22%)	0 (0%)
Site of tumor sequenced						
Primary (Pancreas)	2,392 (46%)	4 (20%)	35 (40%)	8 (38%)	27 (44%)	8 (47%)
Metastatic	2,804 (54%)	16 (80%)	53 (60%)	13 (62%)	34 (56%)	9 (53%)

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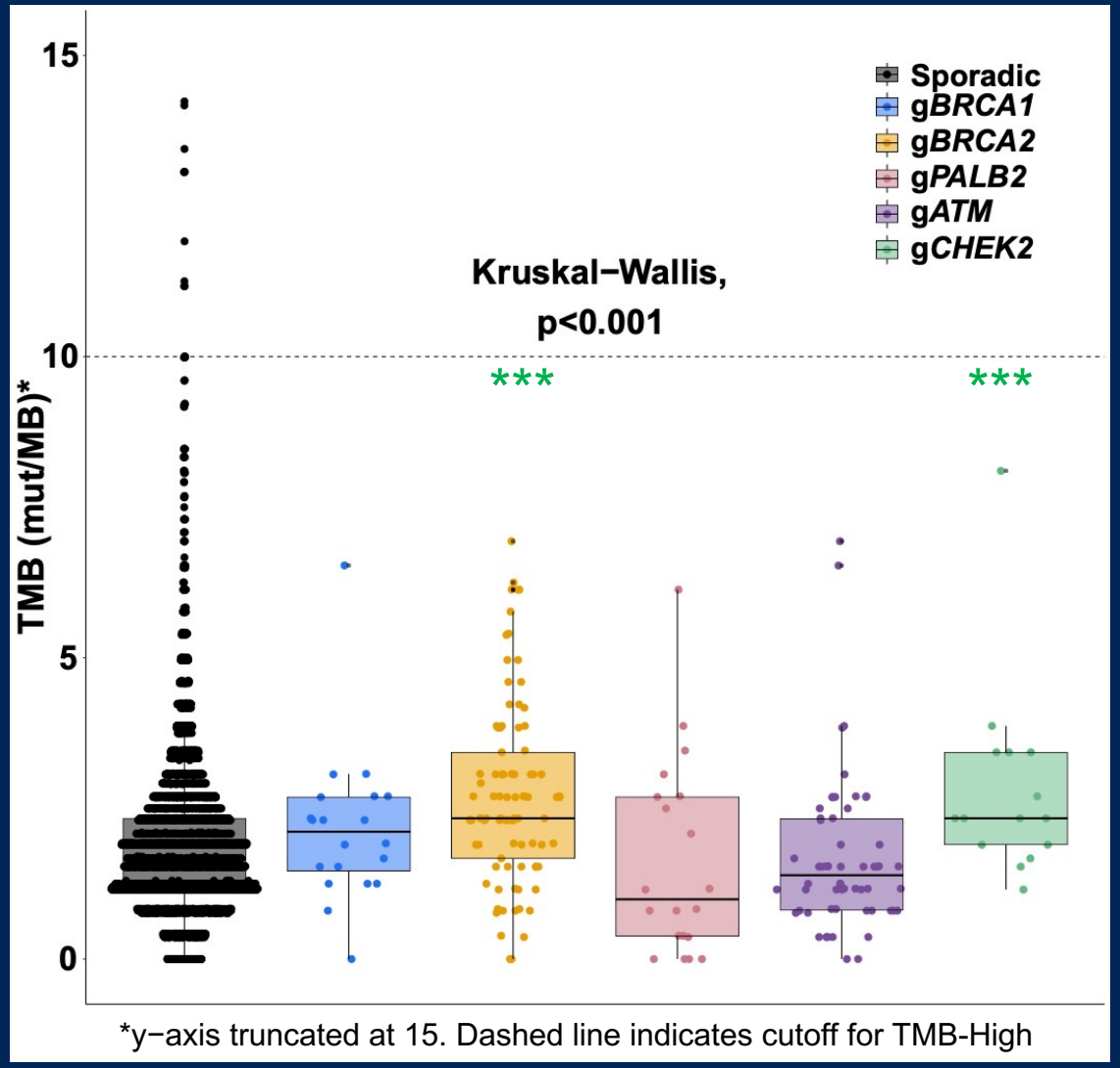

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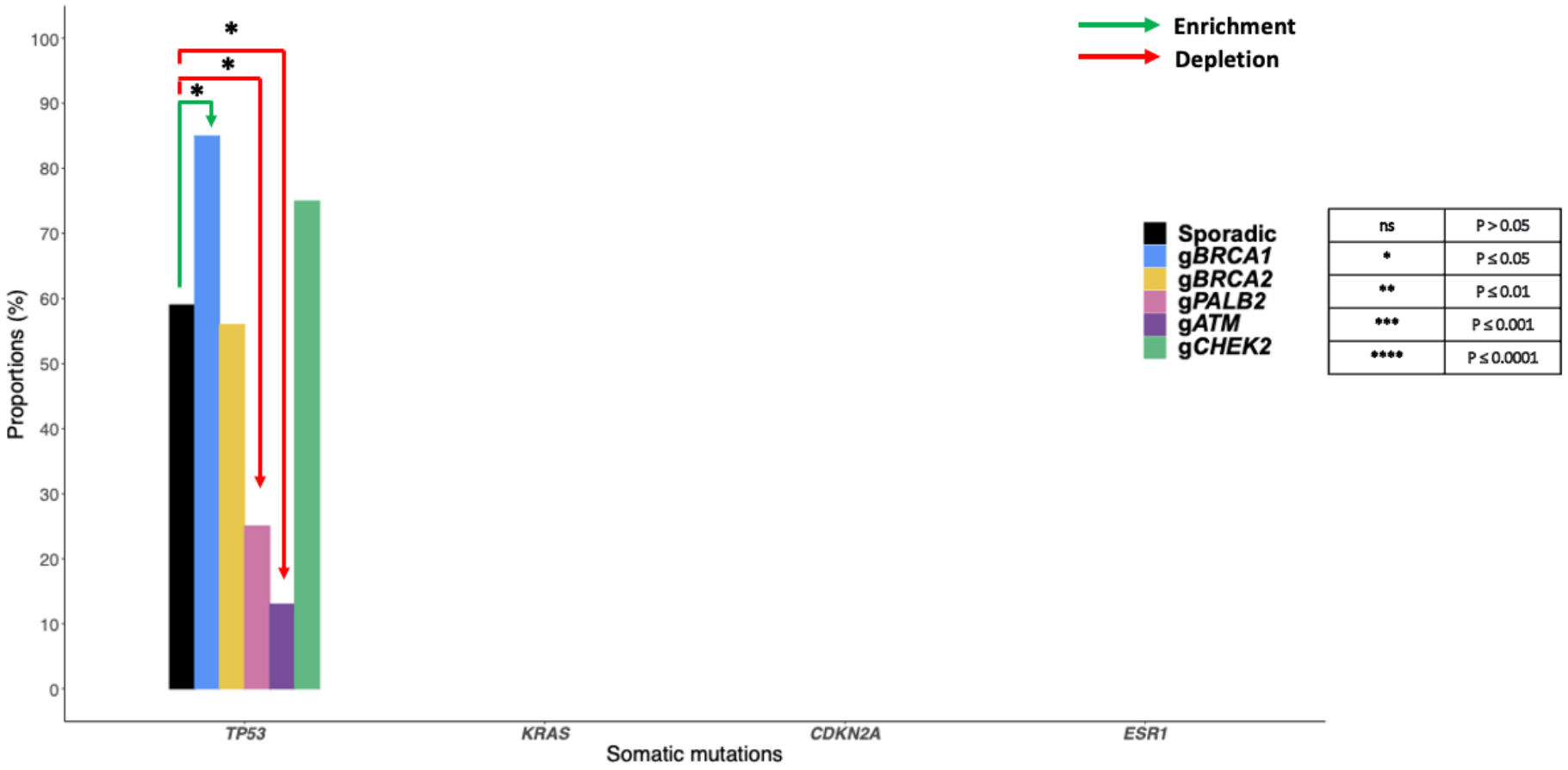

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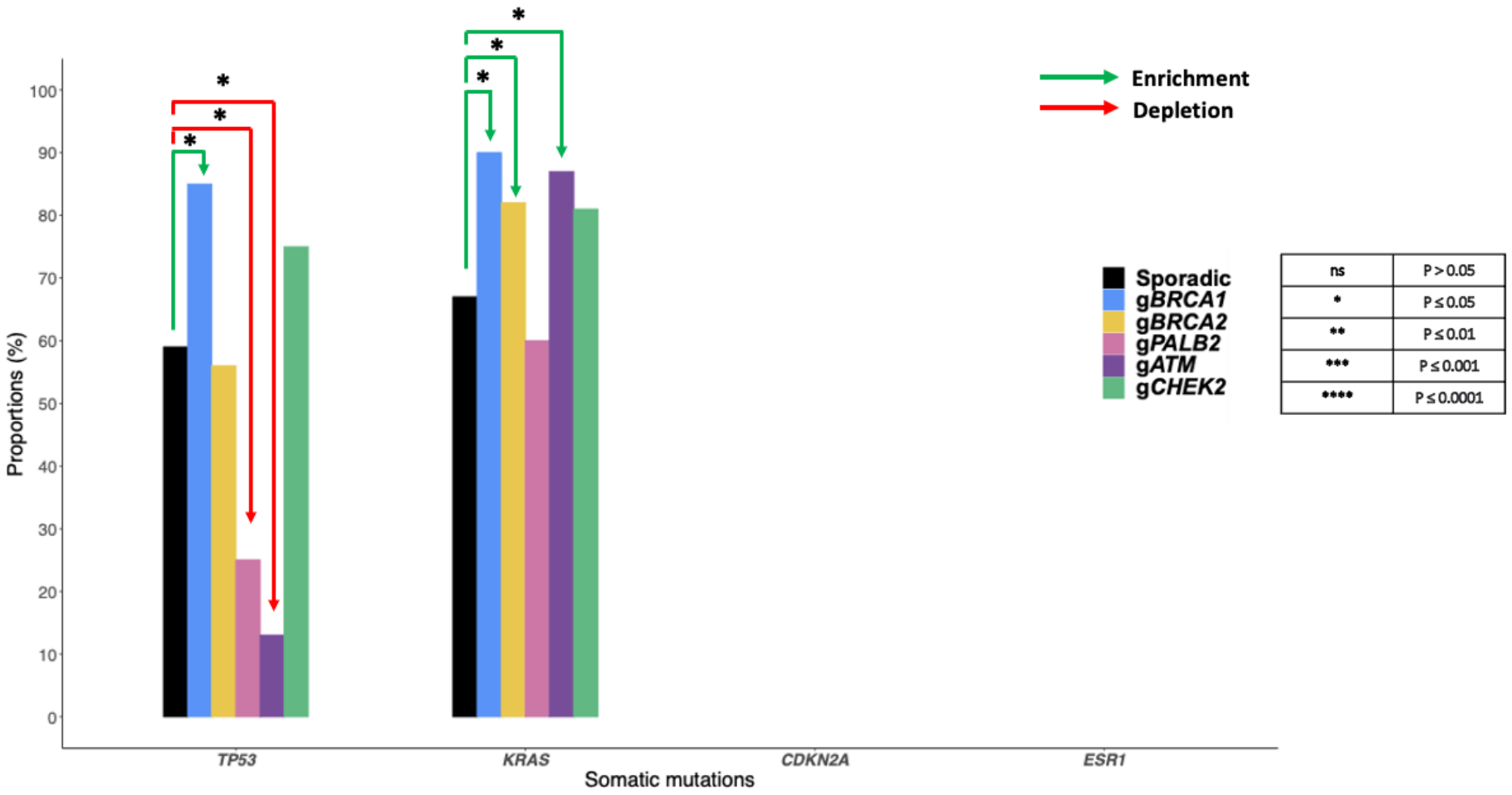

ns	P > 0.05
*	P ≤ 0.05
**	P ≤ 0.01
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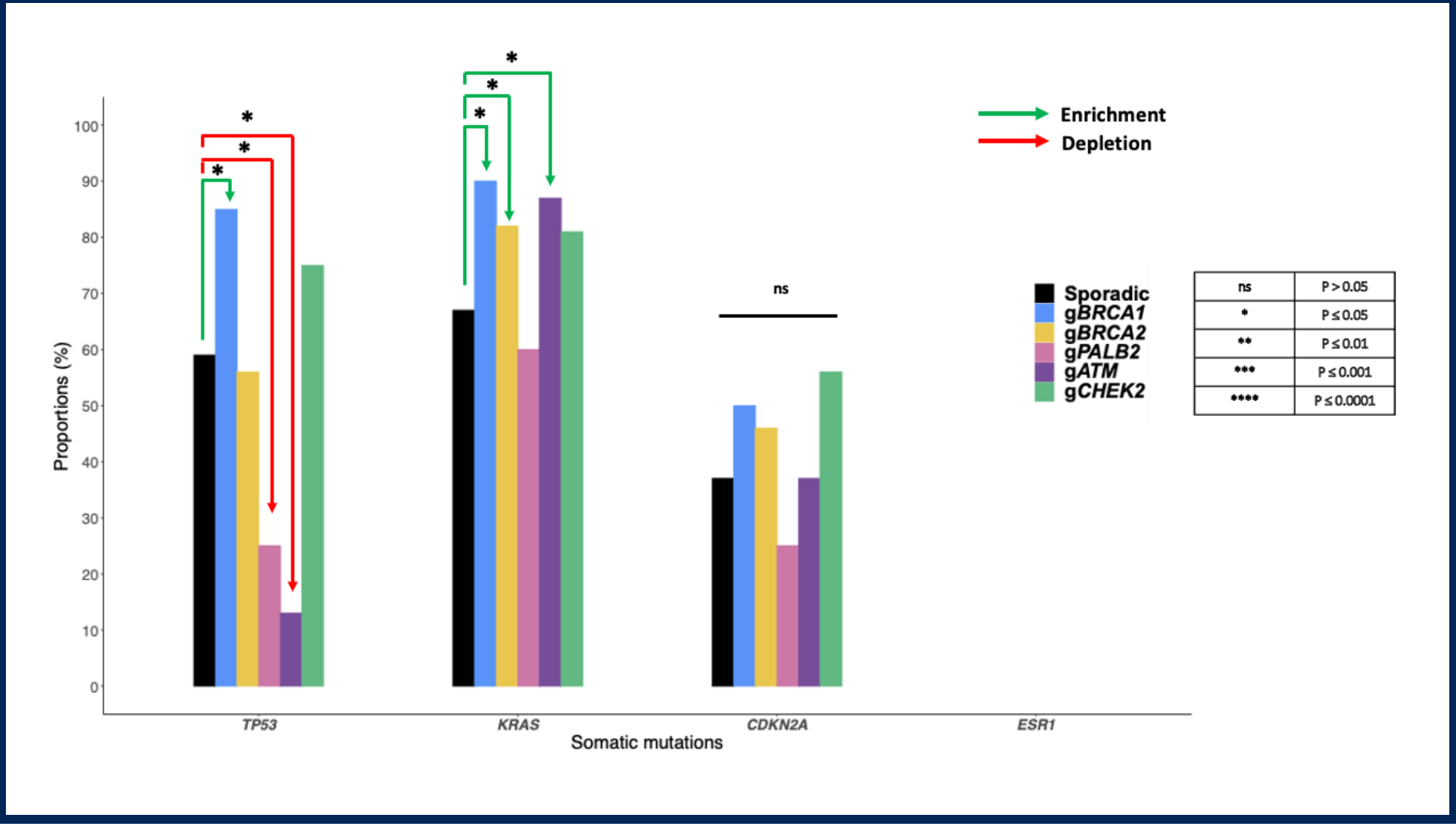

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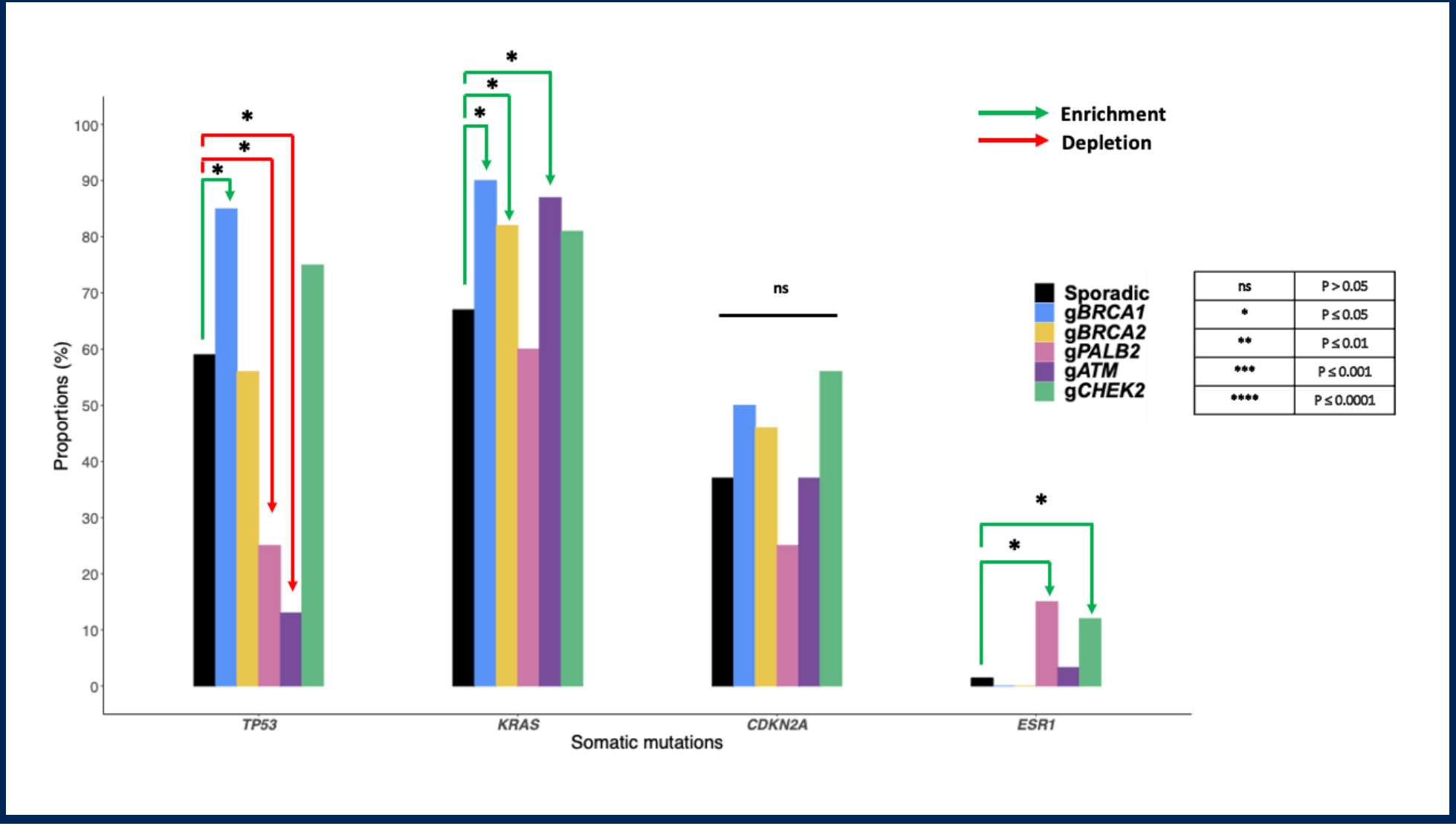

ns	P > 0.05
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4. Prostate Cancer - Demographics

Characteristics	Sporadic (n=4,329)	g*BRCA1* (n=16)	g*BRCA2* (n=110)	g*PALB2* (n=12)	g*ATM* (n=44)	g*CHEK2* (n=13)
Age at diagnosis (yrs)						
Median, Range	66 (46–89)	64 (54–83)	63 (46–84)	69 (58–89)	66 (52–82)	68 (55–83)
Race						
White	2,006 (75%)	7 (78%)	54 (76%)	9 (90%)	21 (78%)	8 (100%)
Black	479 (18%)	0 (0%)	13 (18%)	0 (0%)	4 (15%)	0 (0%)
Other	200 (7%)	2 (22%)	4 (6%)	1 (10%)	2 (7%)	0 (0%)
Ethnicity						
Hispanic	195 (13%)	1 (20%)	6 (15%)	0 (0%)	3 (17%)	0 (0%)
Site of tumor sequenced						
Primary (Prostate)	2,845 (66%)	7 (47%)	70 (69%)	7 (64%)	30 (70%)	9 (75%)
Metastatic	1,457 (34%)	8 (53%)	32 (31%)	4 (36%)	13 (30%)	3 (25%)

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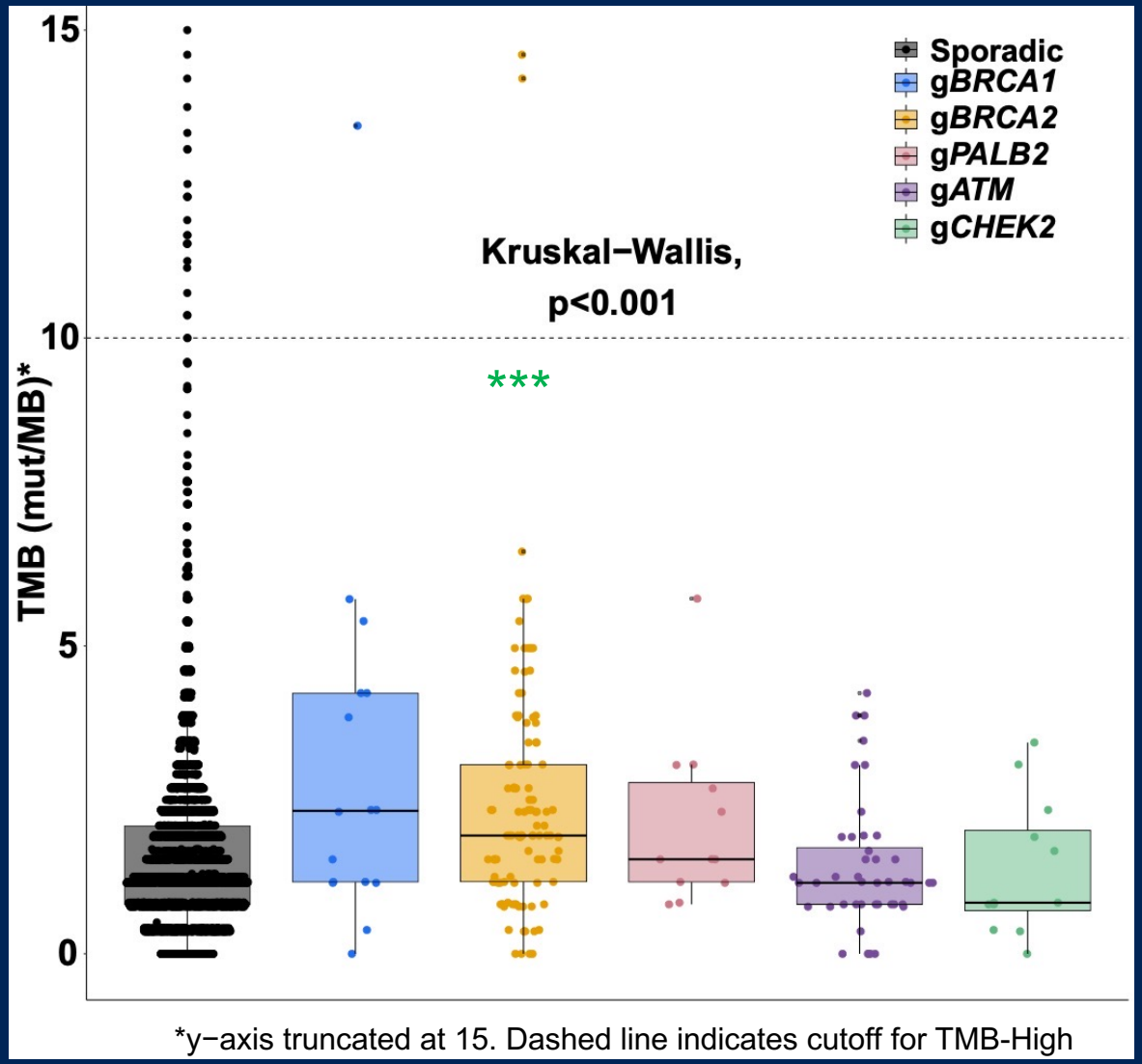
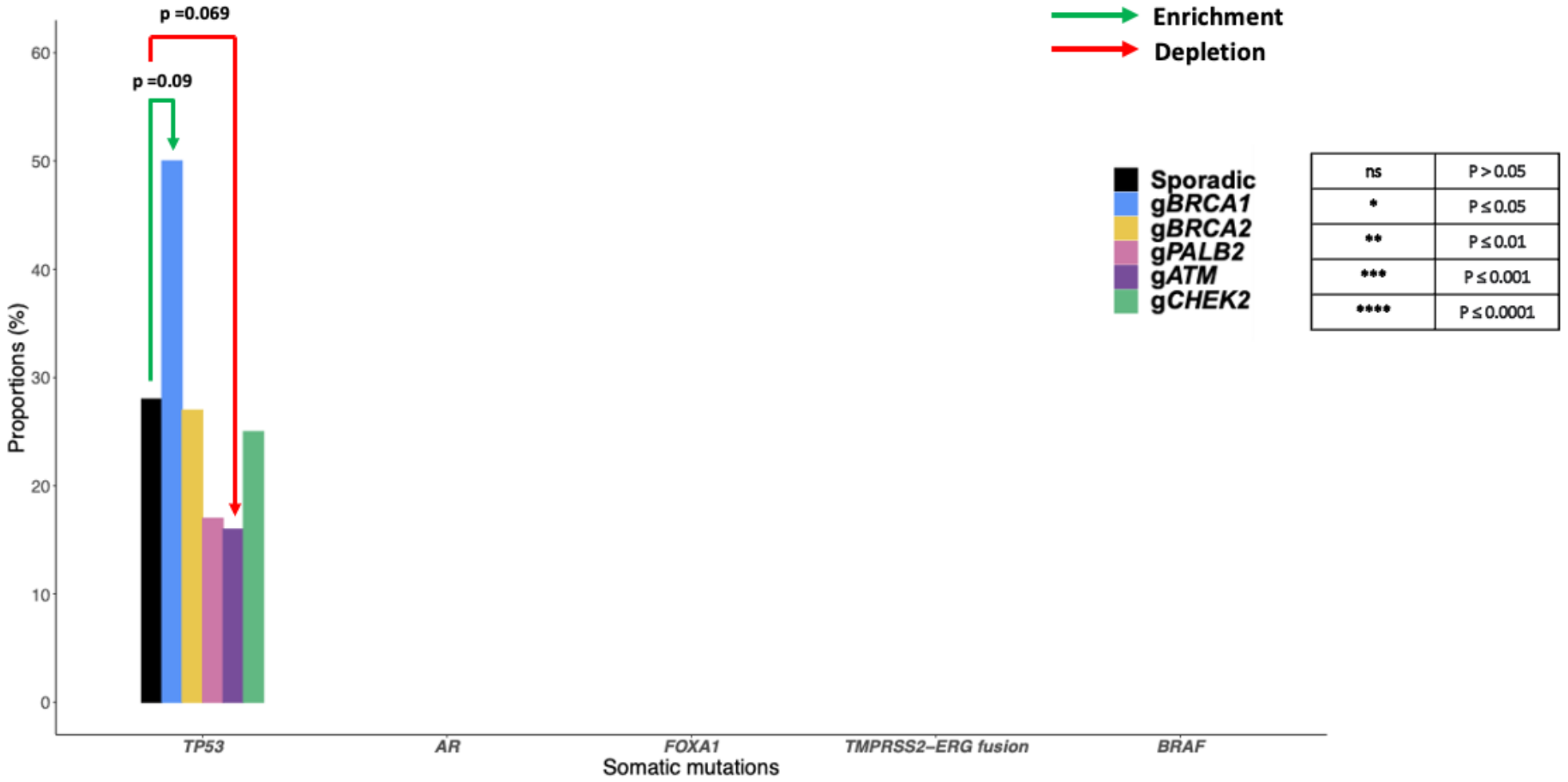
4. Prostate Cancer - Associations with TMB



*y−axis truncated at 15. Dashed line indicates cutoff for TMB-High

4. Prostate Cancer - Association with somatic mutations



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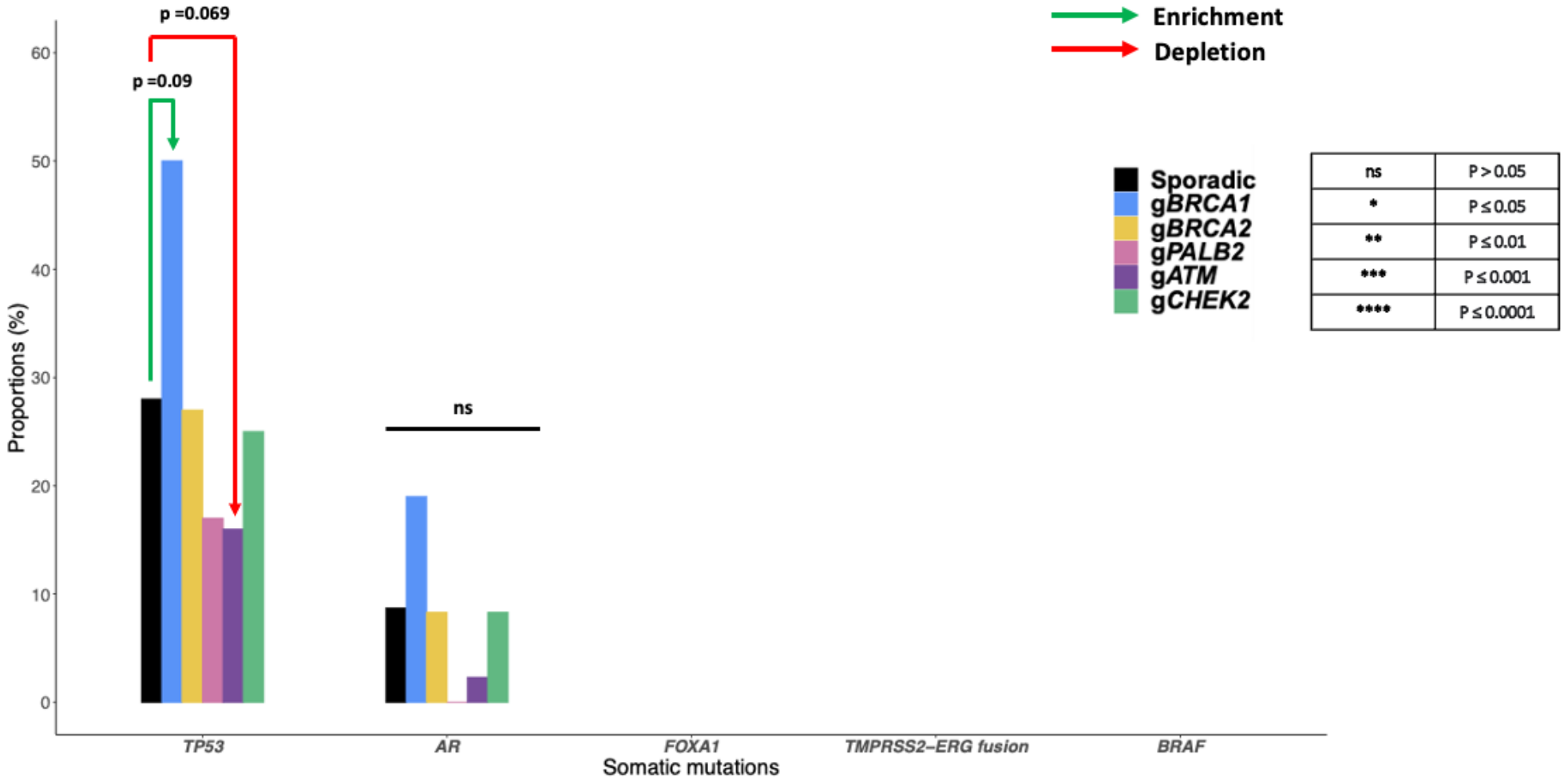

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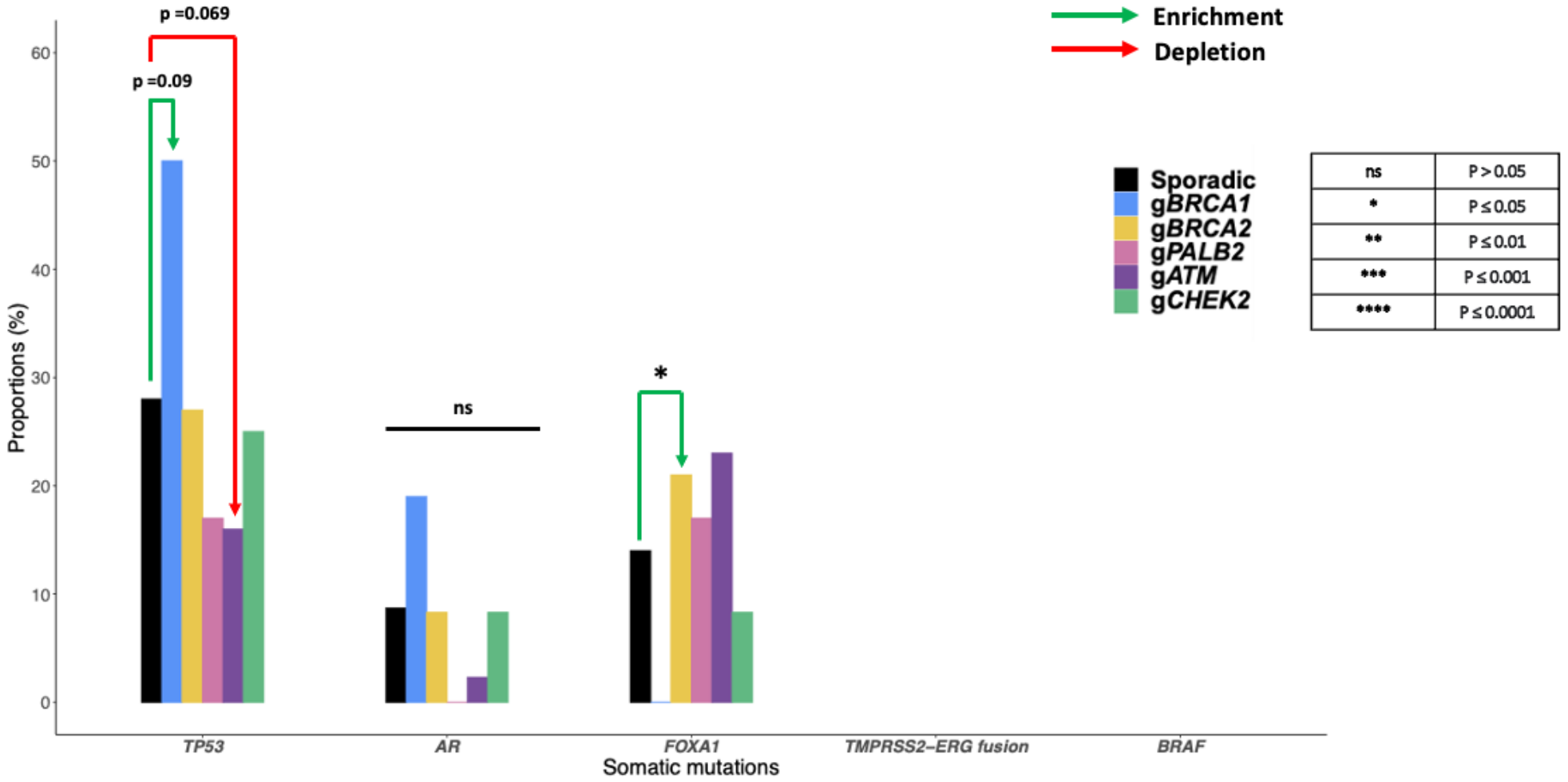

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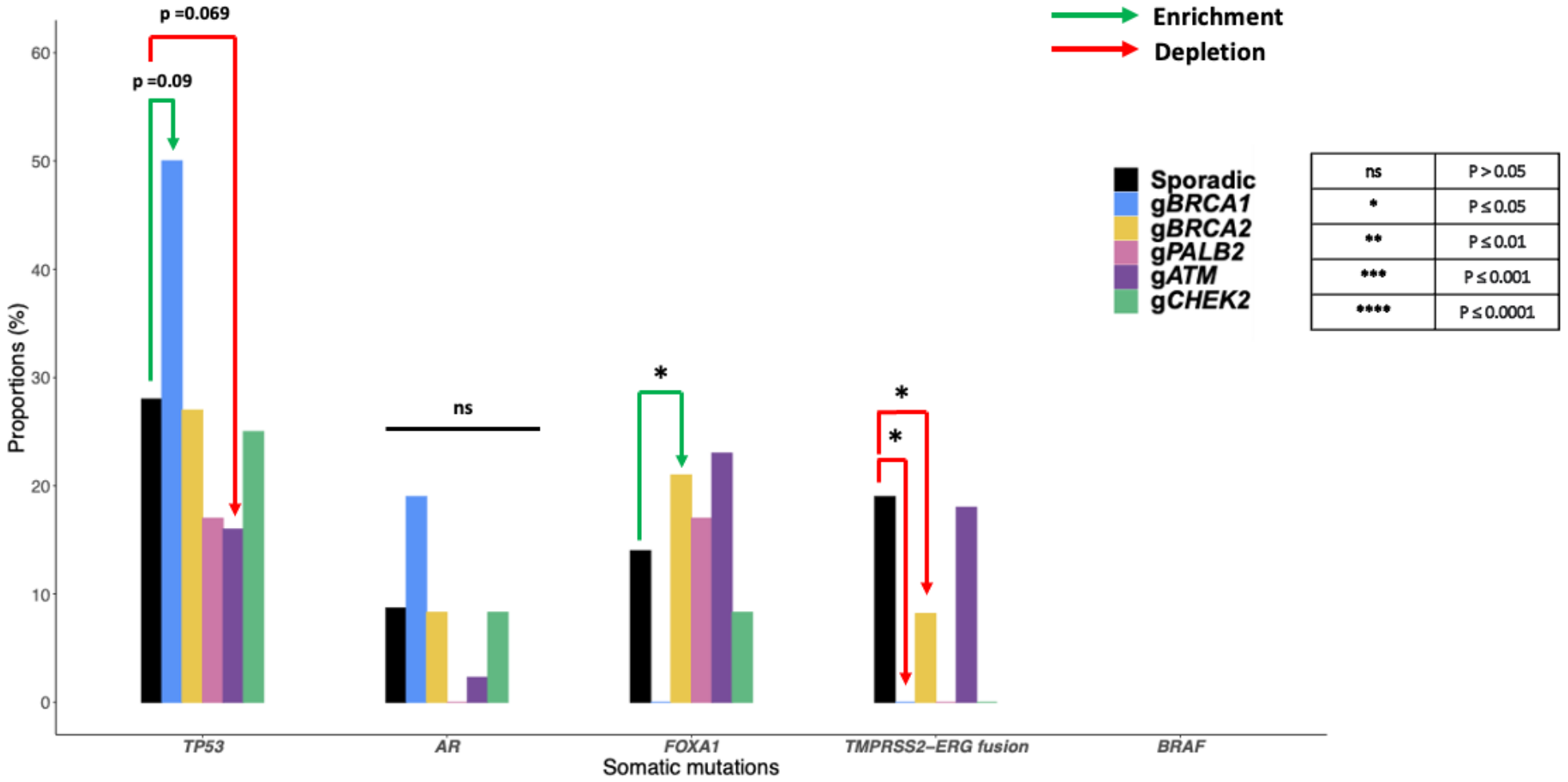

ns	P > 0.05
*	P ≤ 0.05
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***	P ≤ 0.001
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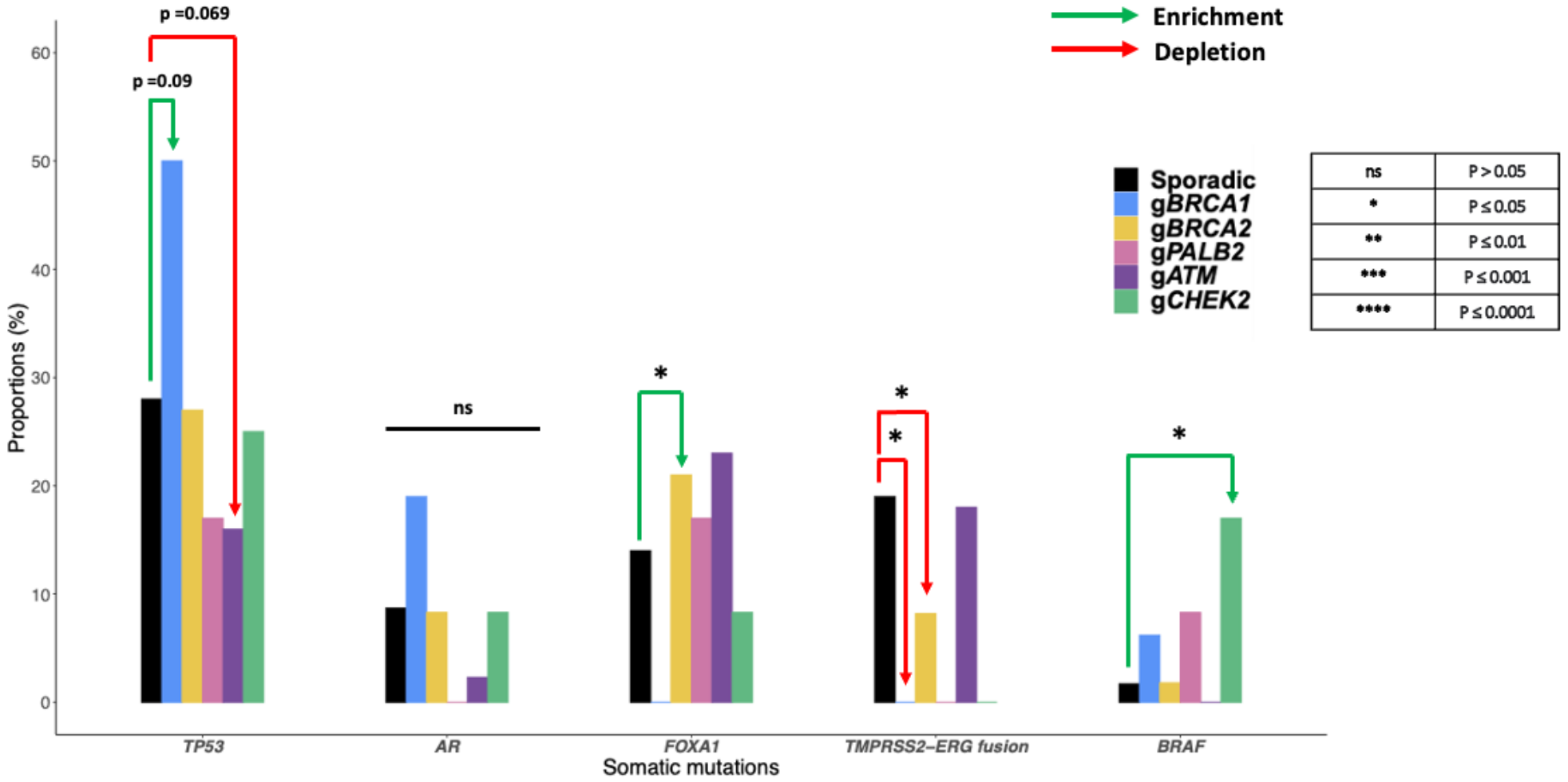
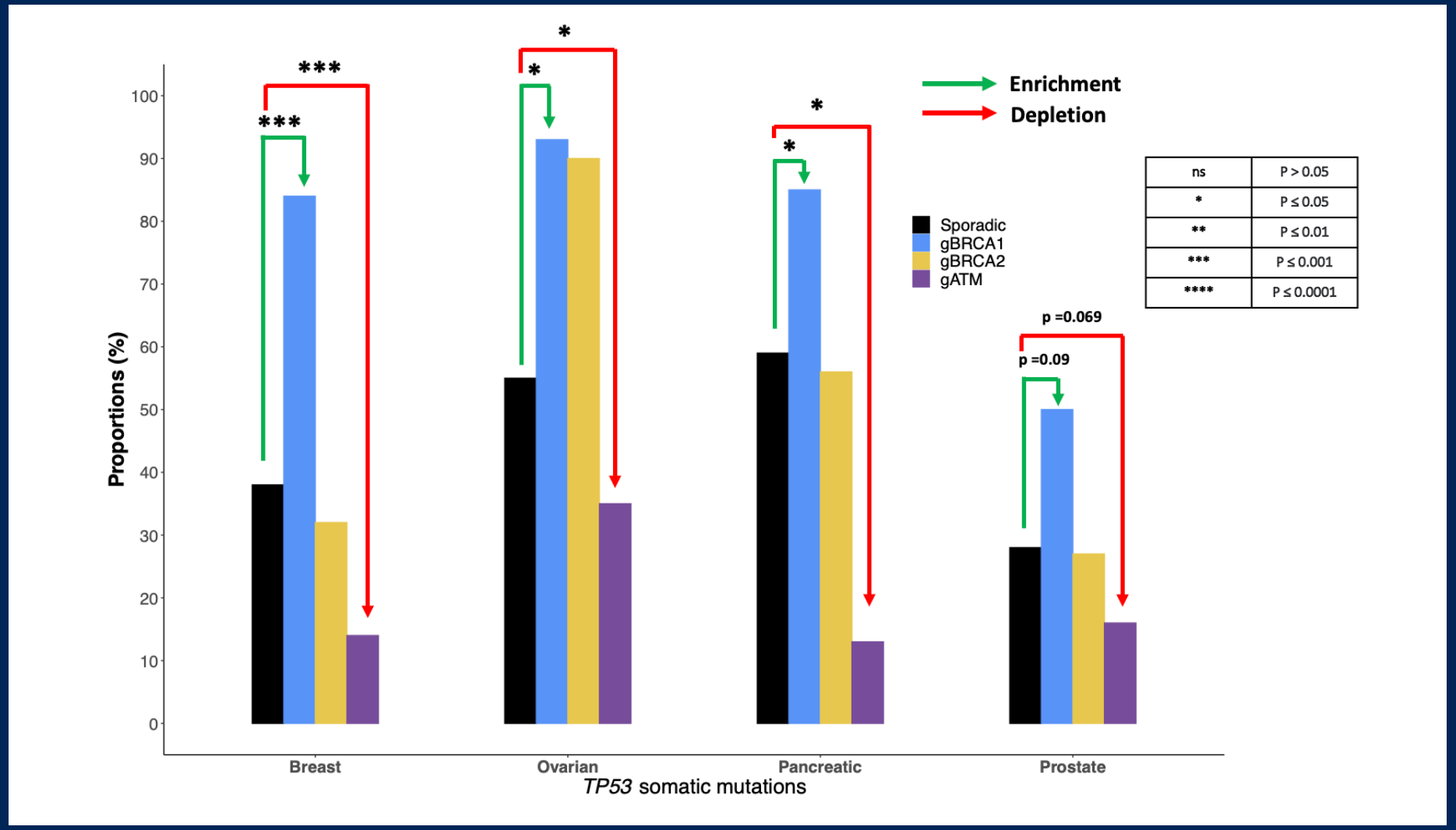
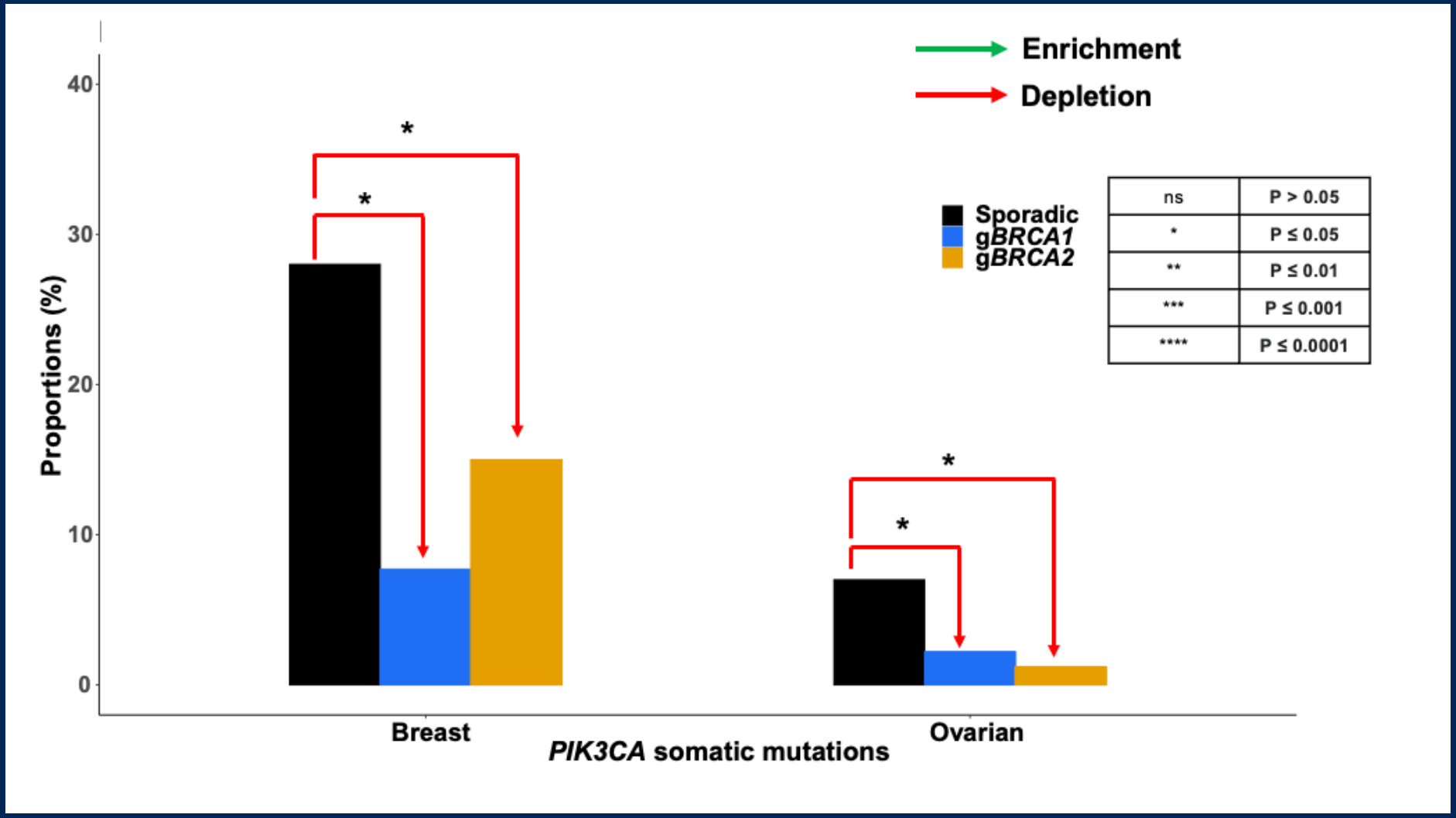


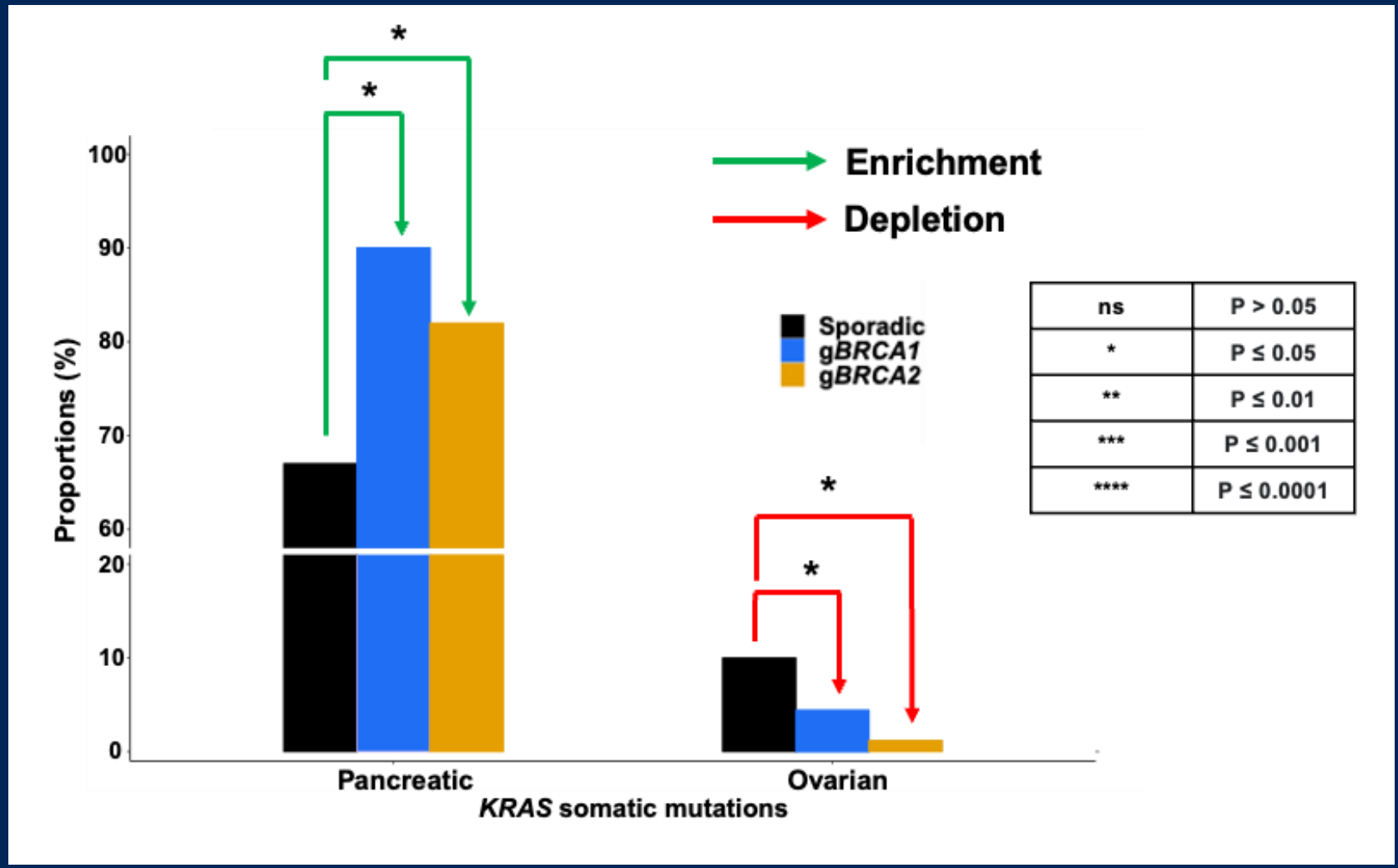
Trends across all 4 cancers – *TP53*



PIK3CA



KRAS



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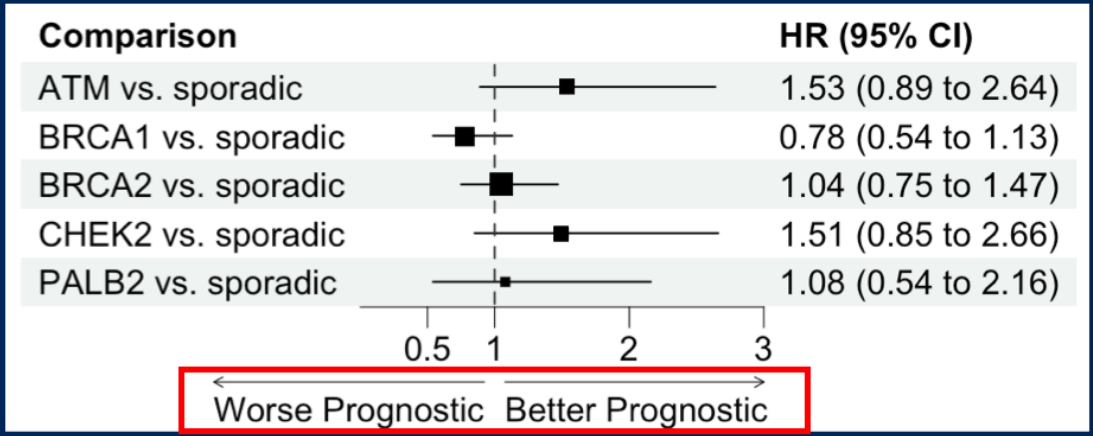
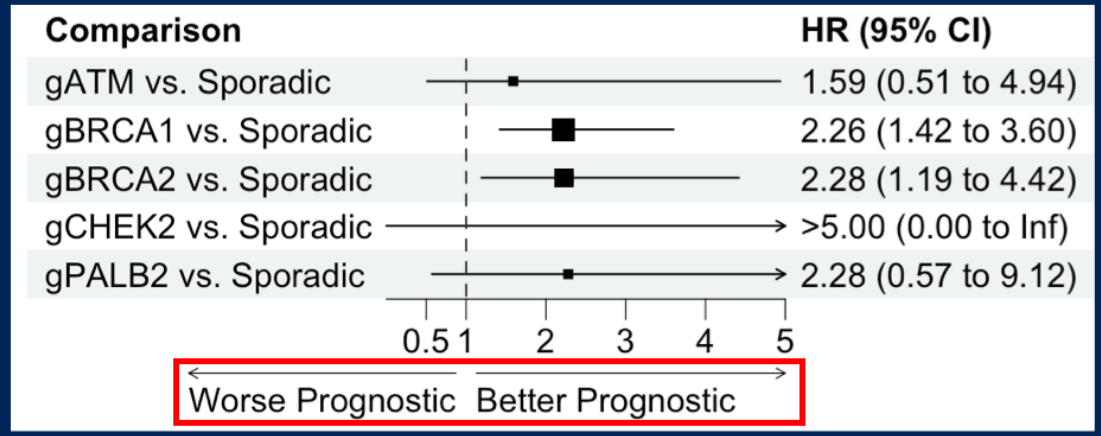
Survival Analysis

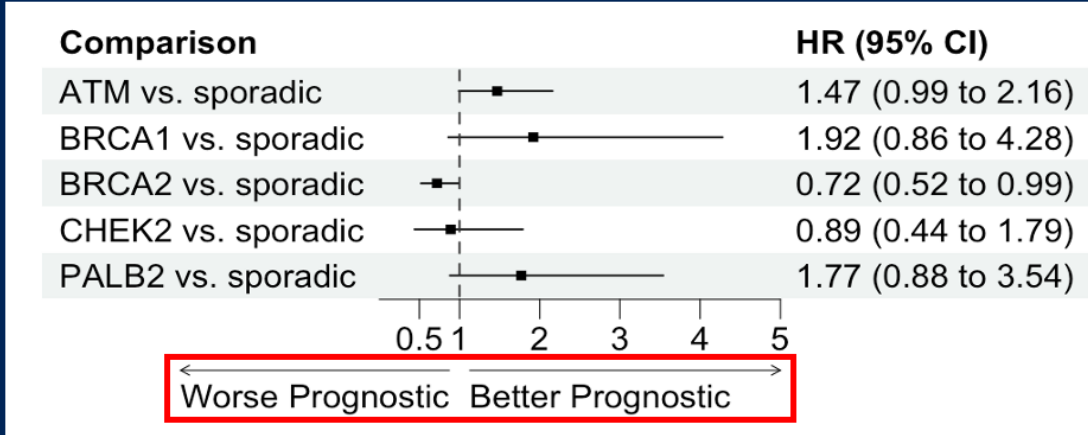
Breast cancer



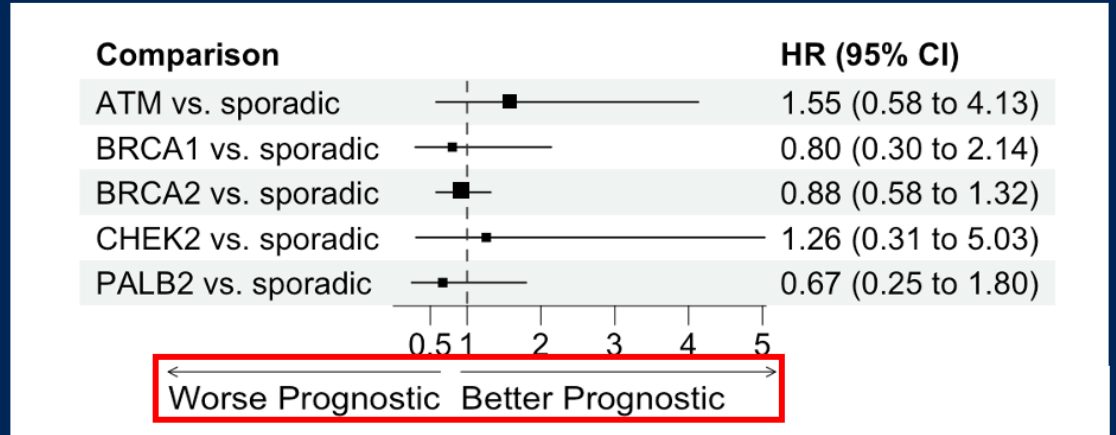
Ovarian cancer



Pancreatic cancer



Prostate cancer



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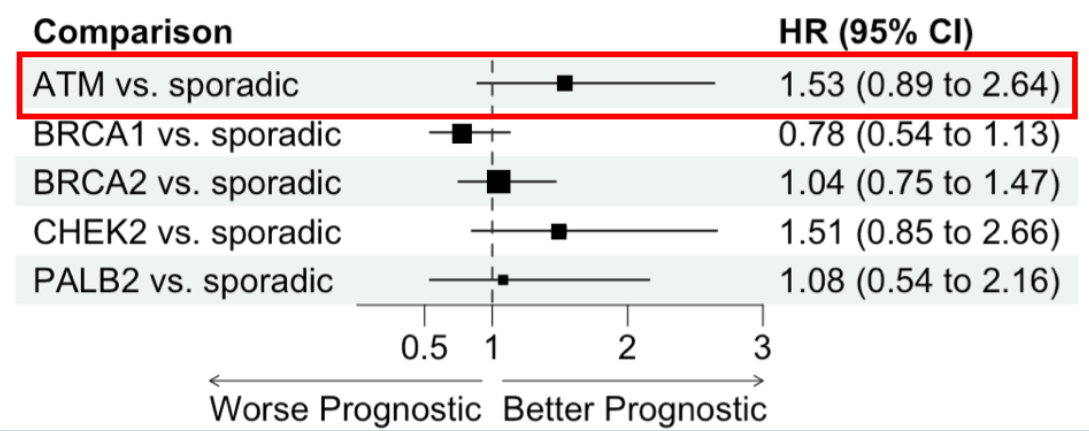

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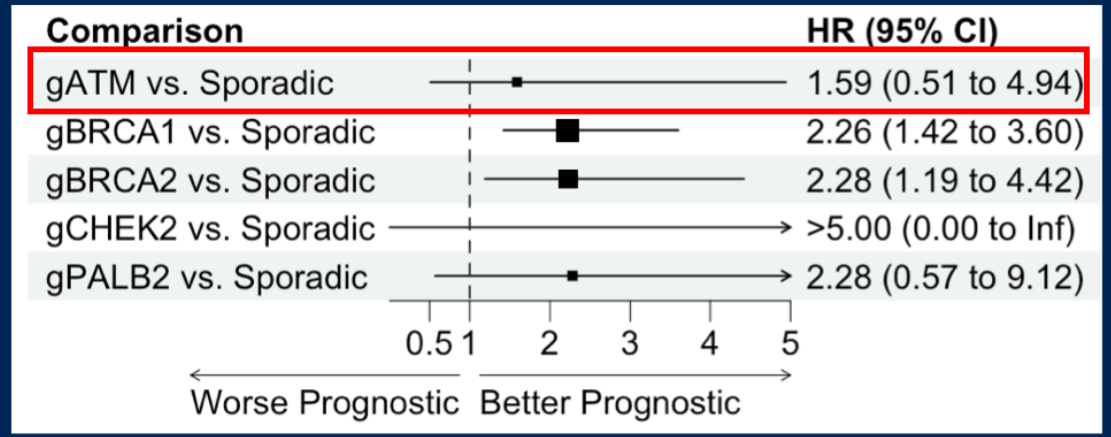

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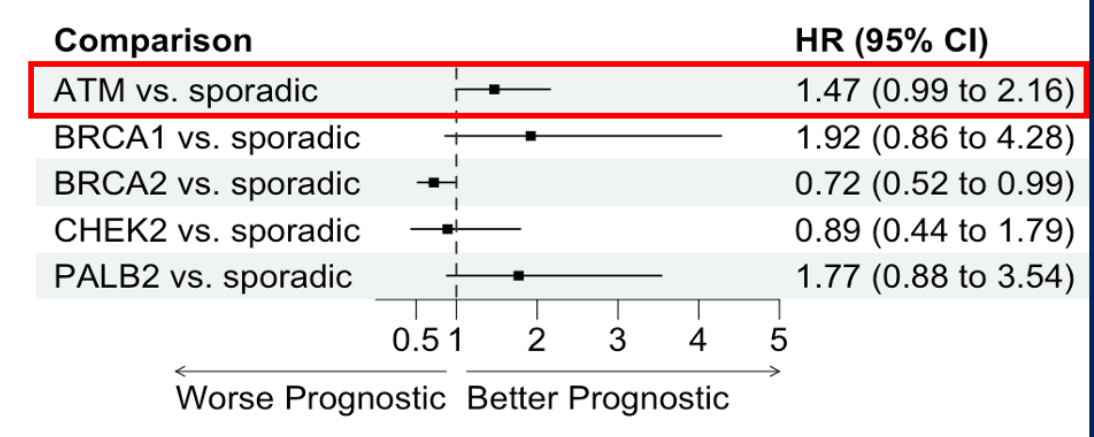

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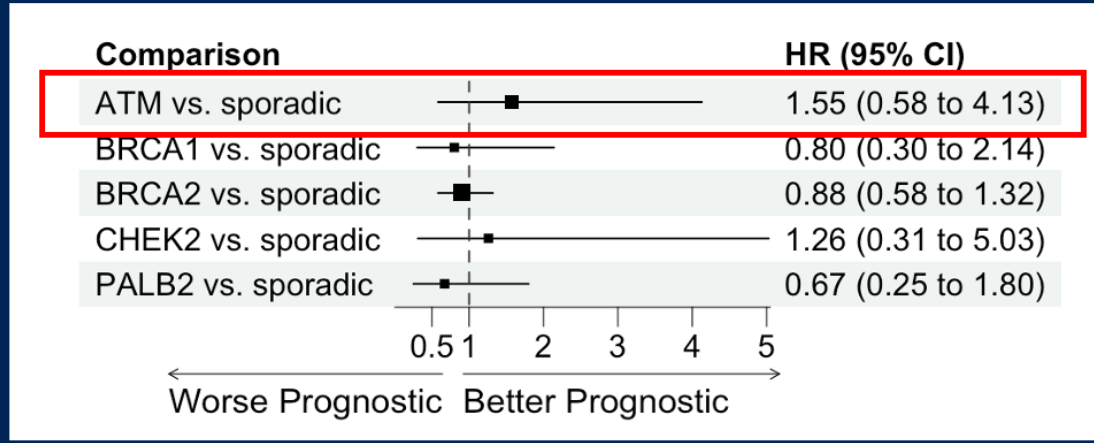

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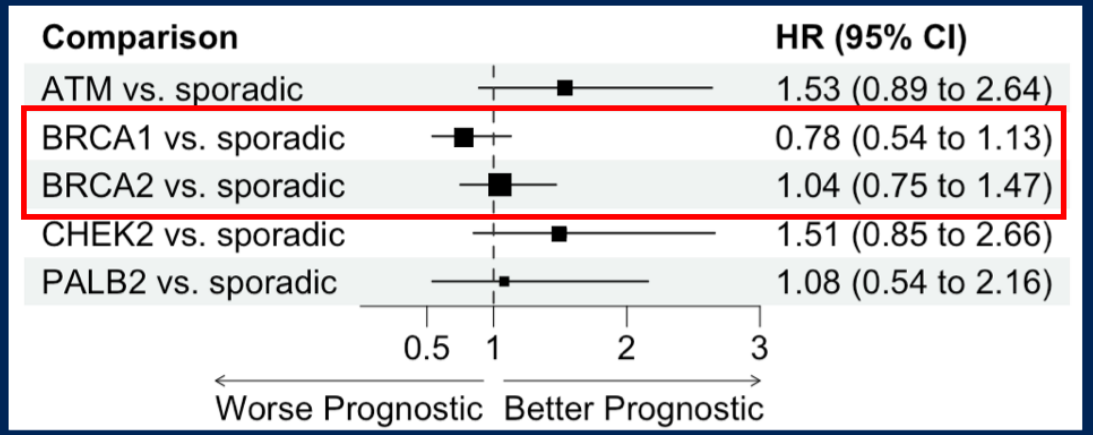

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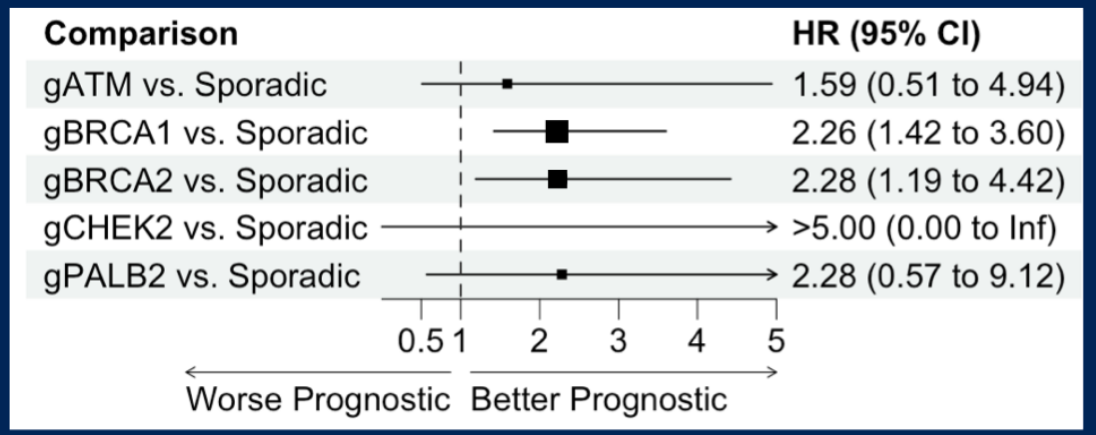

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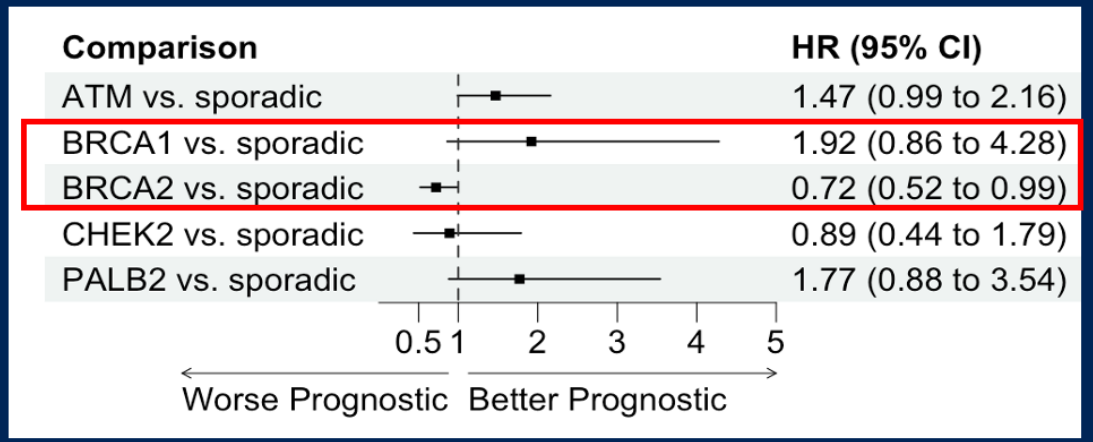

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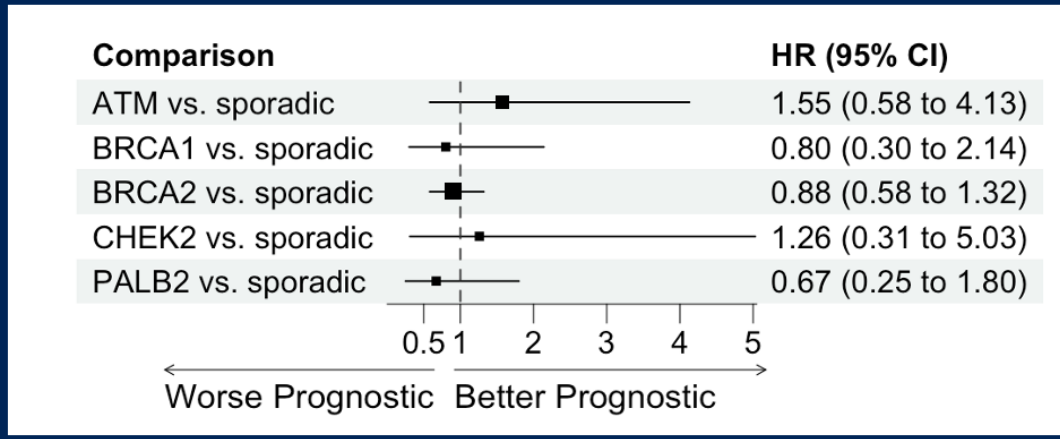

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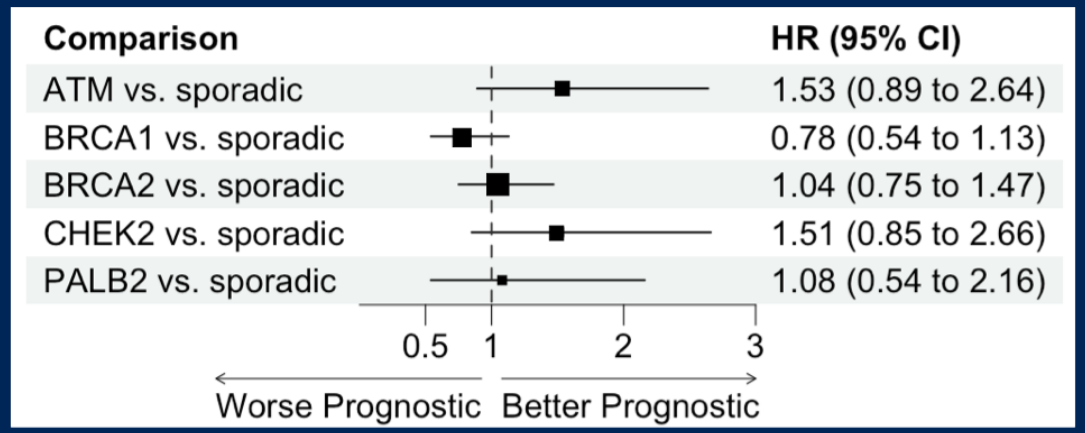

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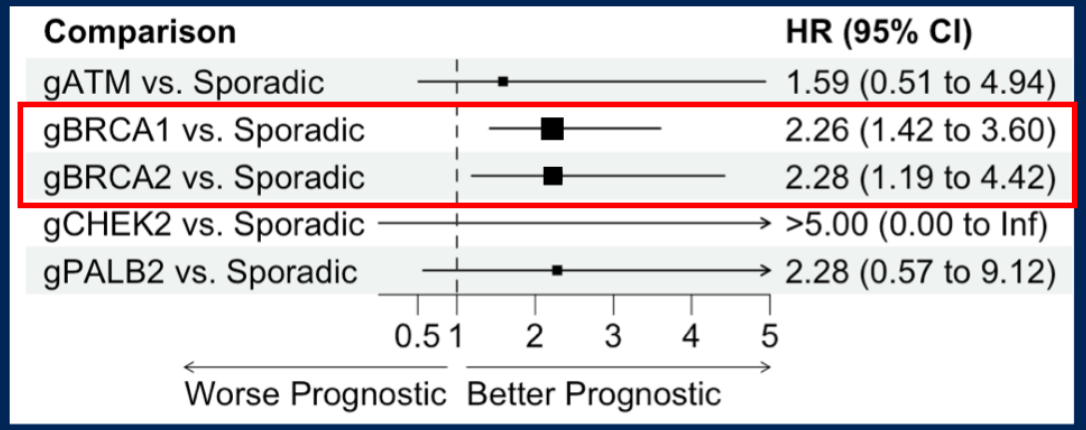

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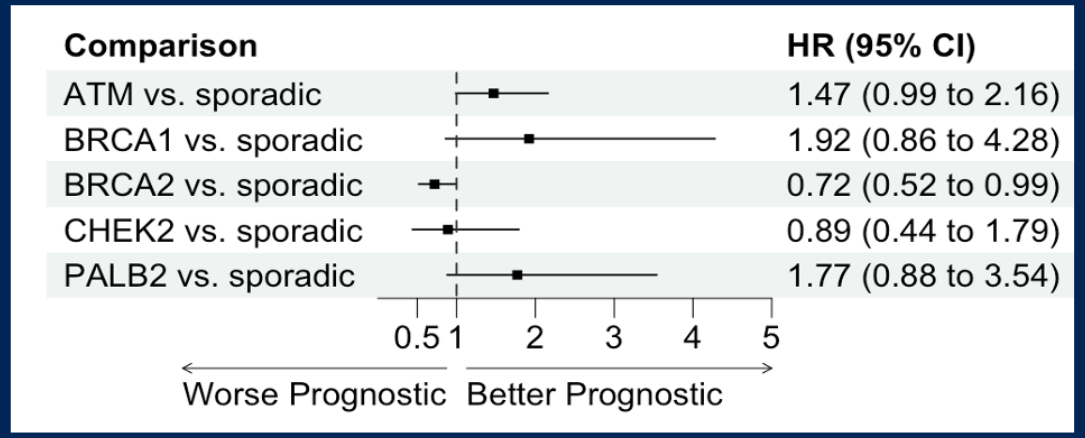

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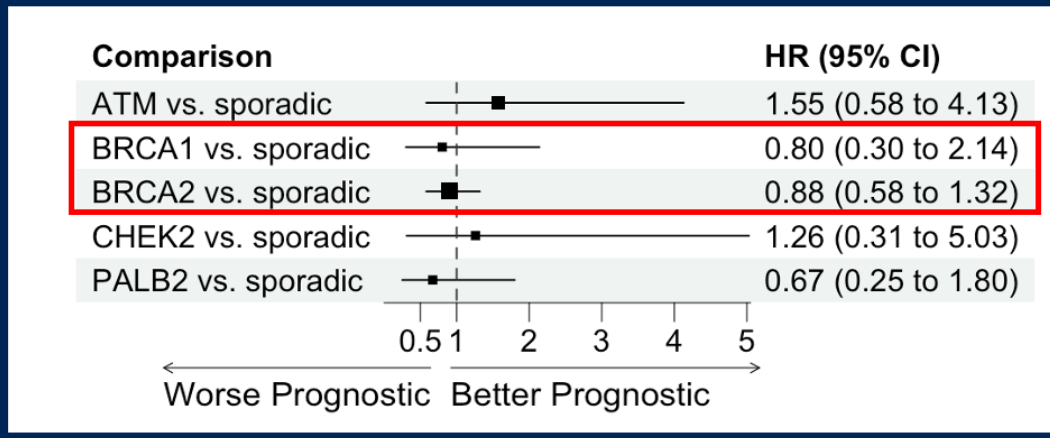

Conclusions

- gHRR-mutated cancers have divergent genomic landscapes relative to their sporadic counterparts, and this may influence therapeutic considerations.
- *TP53* mutations are enriched in g*BRCA1* patients and depleted in g*ATM* pts across all 4 cancers.
- *PIK3CA* mutations are depleted in g*BRCA1/2* patients in breast and ovarian cancers.
- *gATM*-altered patients across all 4 cancers had improved survival outcomes compared to their sporadic counterparts.
- g*BRCA1* and g*BRCA2* genes behave discordantly in some cancers, and may have opposing prognostic effects.

Clinical Implications

- g*ATM* mutations across all 4 cancers were associated with improved survival (HR 1.23, 95%CI 0.92–1.65), suggesting that tumors harboring *ATM* mutations may be synthetic-lethal with several standard therapies.
- g*BRCA1* mutations were associated with improved survival in pancreatic cancer while g*BRCA1/2* were both associated with improved survival in ovarian cancer. One hypothesis could be that coexisting *TP53* mutations may increase platinum sensitivity.
- Tumors harboring g*ATM* mutations showed a depletion of somatic *TP53* mutations. We hypothesize concurrent *ATM* and *TP53* mutations may unfavorably impact cancer-cell survival.

Acknowledgments

- The author would like to thank:
  - Patients for their contributions to science
  - TEMPUS for providing clinical and genomic data
  - My clinical and lab mentors, Drs. Emmanuel Antonarakis and Justin Drake
  - The University of Minnesota Translational Working Group for their comments on this presentation.