GEORGETOWN UNIVERSITY | Lombardi Comprehensive Cancer Center

Glutamate metabolic enzymes associate with increased tumor size in Black women with ILC: a single-institution study

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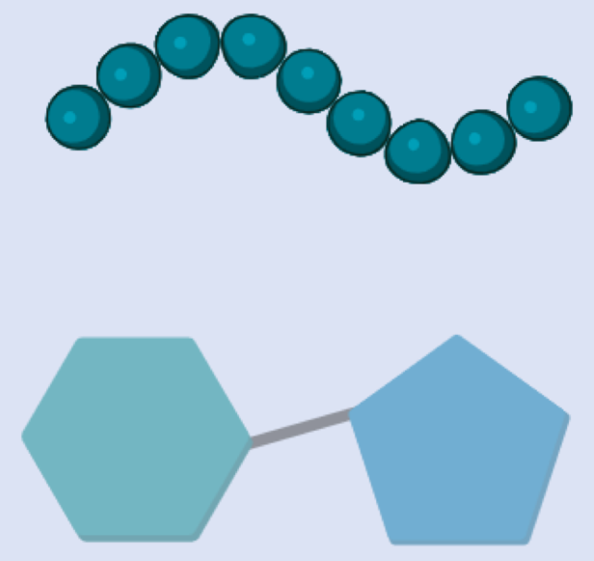
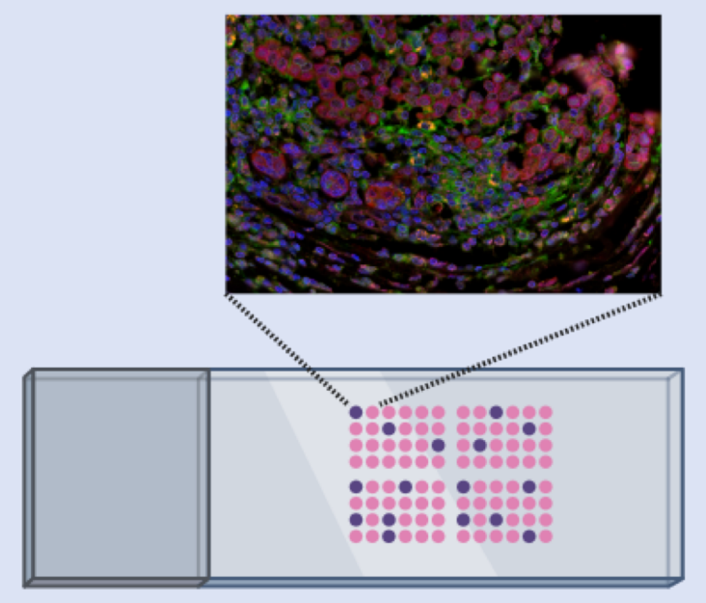
Background

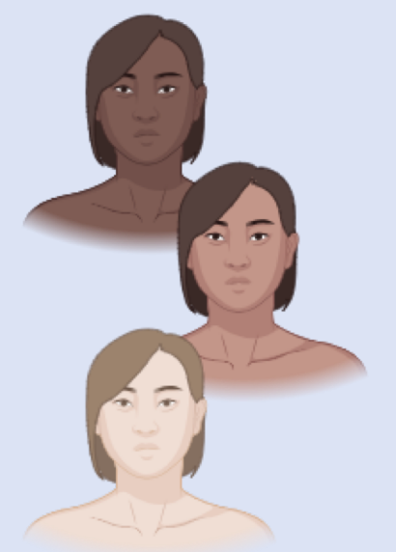
Published clinical[1] and laboratory[2] studies have suggested that invasive lobular breast cancer (ILC) may be more dependent on proteins than sugars to obtain the energy they need to grow and spread.

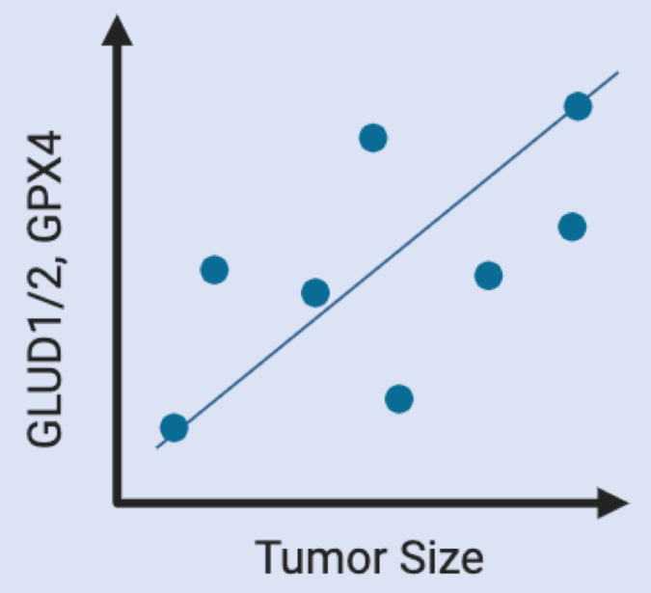


Methods

We measured the expression of four markers that contribute to how tumor cells take up and metabolize one particular amino acid (the building block of proteins) called glutamate.







Results

In a racially diverse cohort from our medical center, we found that two of these markers that regulate glutamate were highly abundant in large tumors in women with ILC, but not IDC. The link between tumor size and marker expression was strongest in Black women.

Impact

Black women are significantly underrepresented in studies of ILC, and it is our goal to actively increase representation and identify social and genetic ancestry-associated factors associated with ILC outcomes.

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[1]Ulaner et al, *J Nuclear Medicine* 2016;57:1350. [2]Du et al, *Sci Rep* 2018;8:7205.

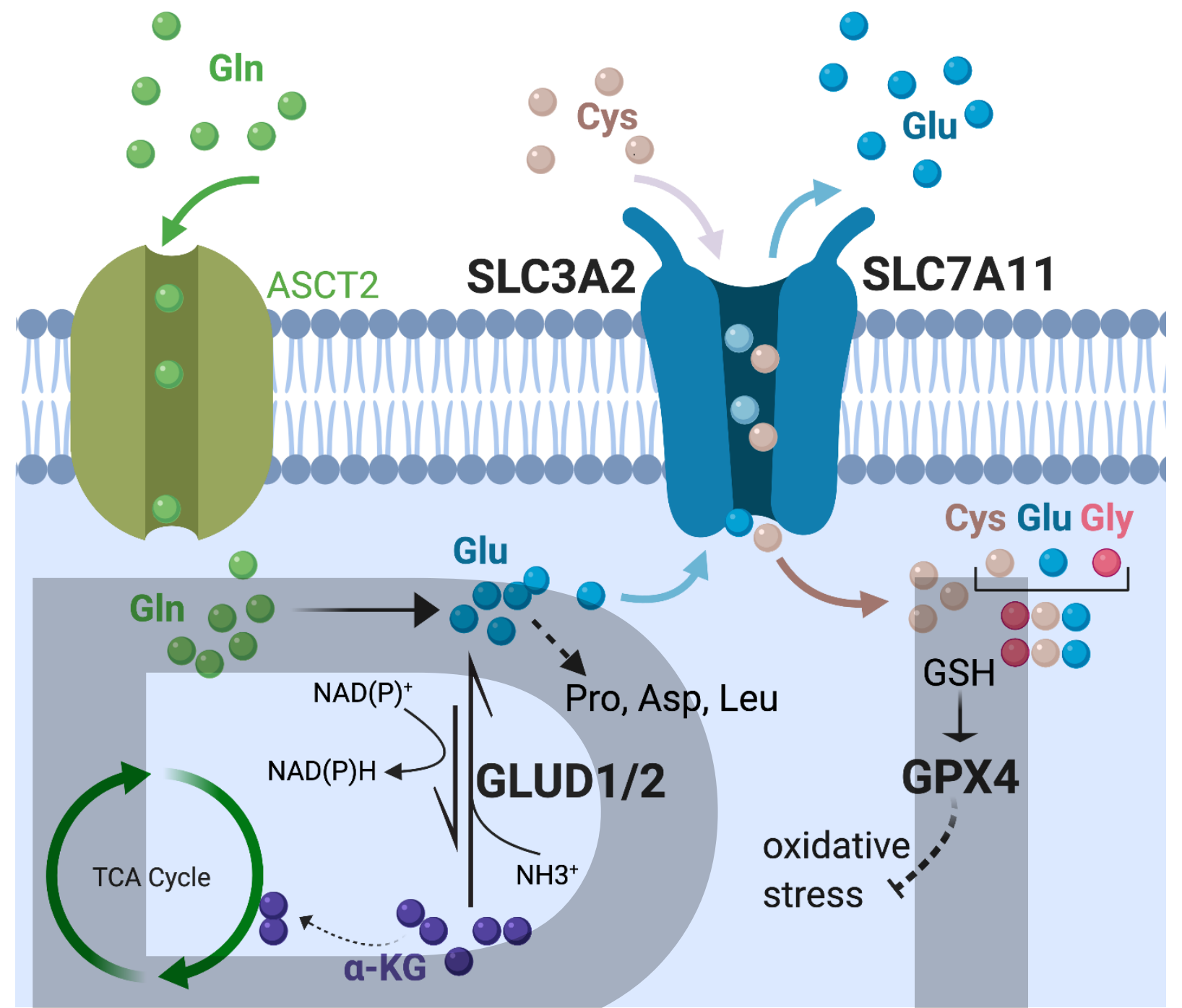

Figure 1. Schematic of Glud1/2, GPX4, SLC3A2, and SLC7A11. SLC3A2+SLC7A11 exports glutamate and imports cystine to the cell. GLUD1/2 converts glutamate into α-ketoglutarate to replenish the TCA cycle, or recycles ammonia to support amino acid synthesis. GPX4 is an enzyme that protects cells from lipid peroxidation-induced death.

Table 1. Clinical and pathological characteristics of TMA cohorts

ns, not significant for ILC vs IDC	ILC		IDC	
	Count	Percent	Count	Percent
Number of people	72	-	50	-
Number of surgical events	78	-	50	-
Cohort period	2003-2014	-	2004-2011	-
Sex				
Female	72	100%	50	100%
Male	0	0%	0	0%
Age^{ns}				
Under 40	0	0%	3	6%
40-55	37	51%	17	34%
Over 55	35	49%	30	60%
Age range, initial diagnosis (years)	40.23 - 88.05	-	30.7-90.14	-
Median age, initial diagnosis (years)	54.05	-	59	-
Race^{ns}				
Black	16	22%	15	30%
Other+Unknown	6	8%	4	8%
White	50	70%	31	62%
Lymph Node Status^{ns}				
Positive	23	32%	18	36%
Negative	49	68%	32	64%
Vital Status (as of 7/2021)^{ns}				
Alive	61	85%	32	64%
Deceased	11	15%	18	36%
Duration of follow-up (as of 7/2021)^{ns}				
Range (years)	1.49 - 17.23	-	1.06-17.24	-
Median (years)	8.42	-	10.36	-

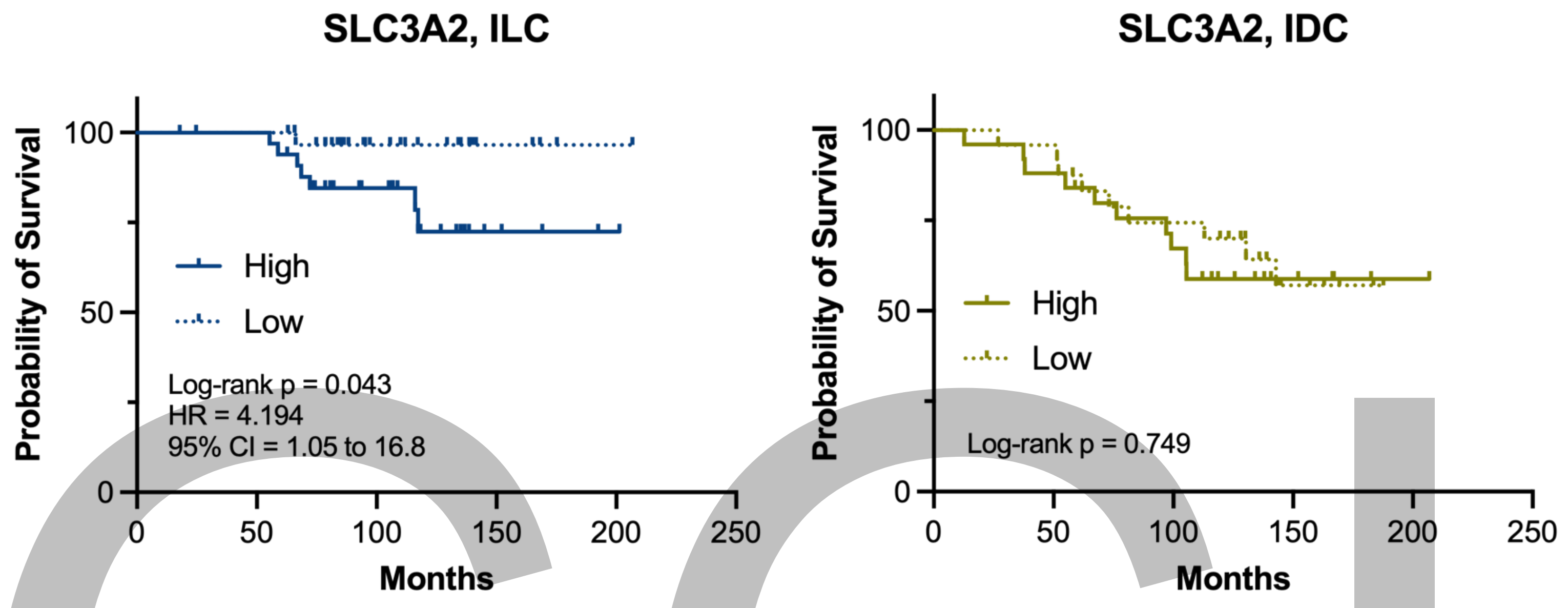

Figure 2. High SLC3A2 expression associates with poor overall survival (OS) in ILC. High/low (above/below median) expression of SLC3A2 was analyzed by log-rank test and plotted as Kaplan-Meier survival curves for the ILC (left panel) and IDC (right panel) cohorts. HR, hazard ratio. CI, confidence interval. None of the other markers showed significant association with OS in either cohort.

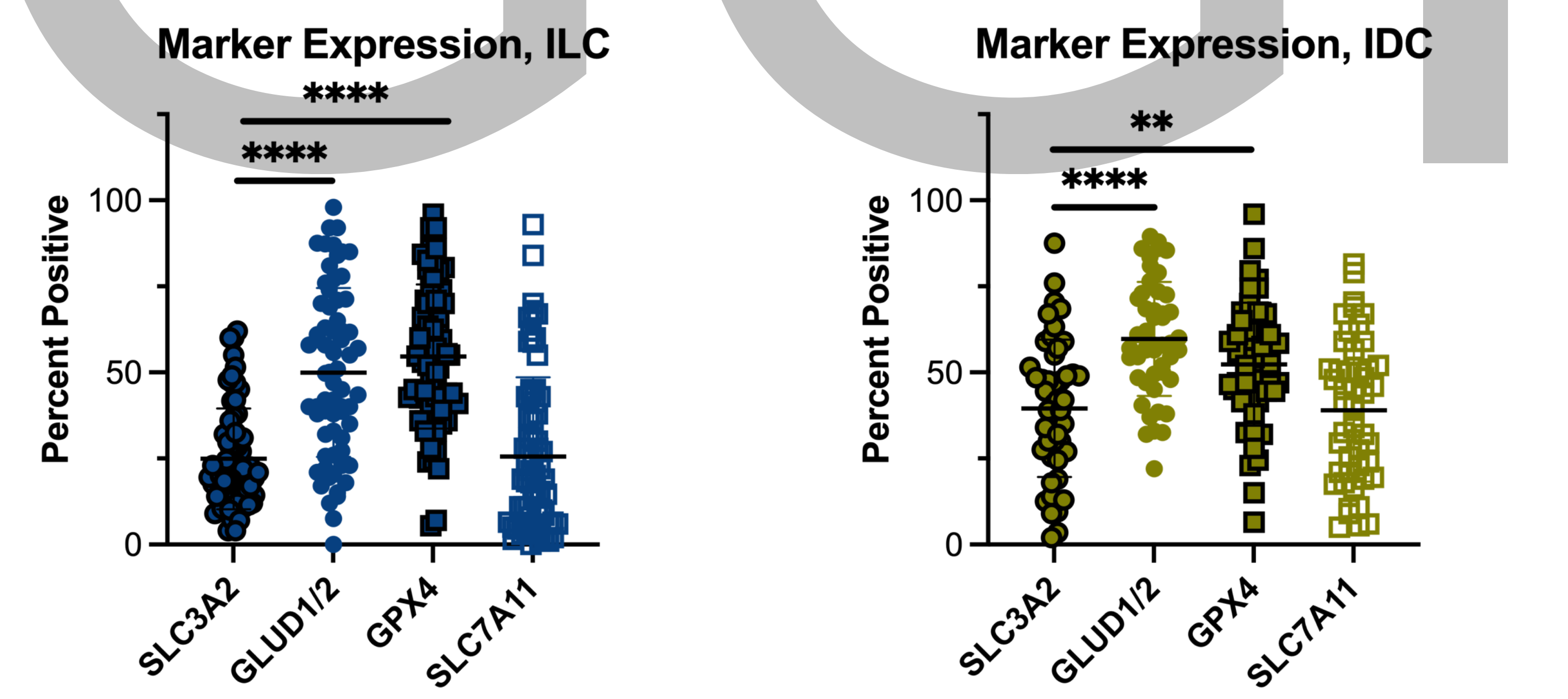

Figure 3. Greater proportion of ILC and IDC tumor cells express GLUD1/2 and GPX4. Percent cells stained positive for each marker was analyzed by one-way analysis of variance (ANOVA) followed by *post hoc* Tukey test for the ILC (left panel) and IDC (right panel) cohorts. ****, p≤0.0001. **, p≤0.01. Not shown are similar relationships for GLUD1/2 or GPX4 vs. SLC7A11.

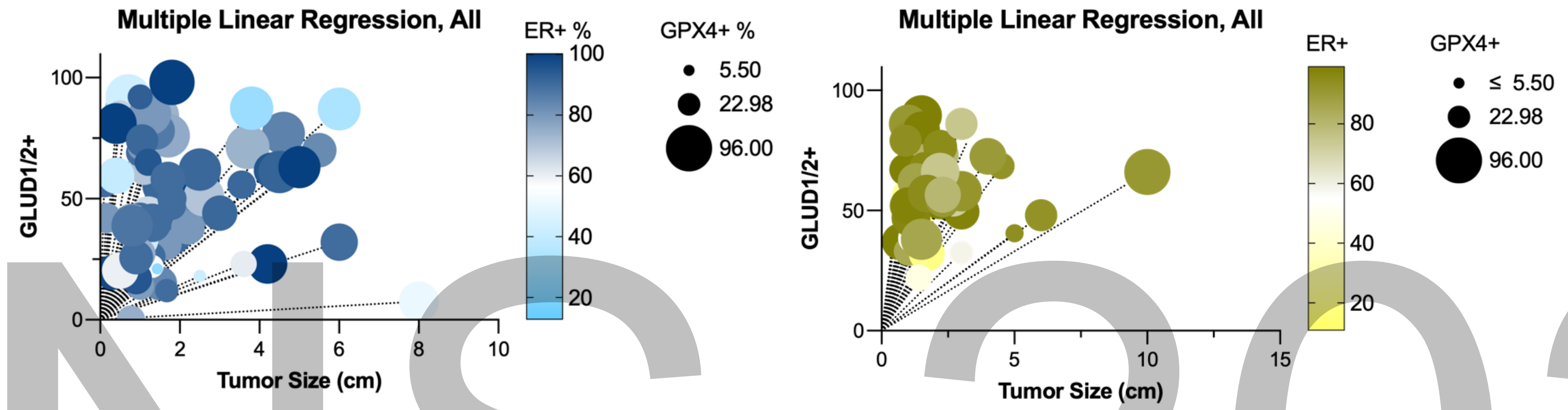

Figure 4. Multiple linear regression shows weak or no association of GLUD1/2, GPX4, and ER with tumor size in the full cohorts. Tumor size as dependent variable, and GLUD1/2, GPX4, and ER percent positive as independent variables, were analyzed by unweighted multiple least-squares regression in the ILC (left panel) and IDC (right panel) cohorts. ILC: F = 2.911, p = 0.04; β1 for GPX4 = 0.03, p= 0.005; R² = 0.125. IDC: F = 0.516, p = 0.67; R² = 0.034. Color temperature = percent cells stained positive for ER, and bubble size = percent cells stained positive for GPX4.

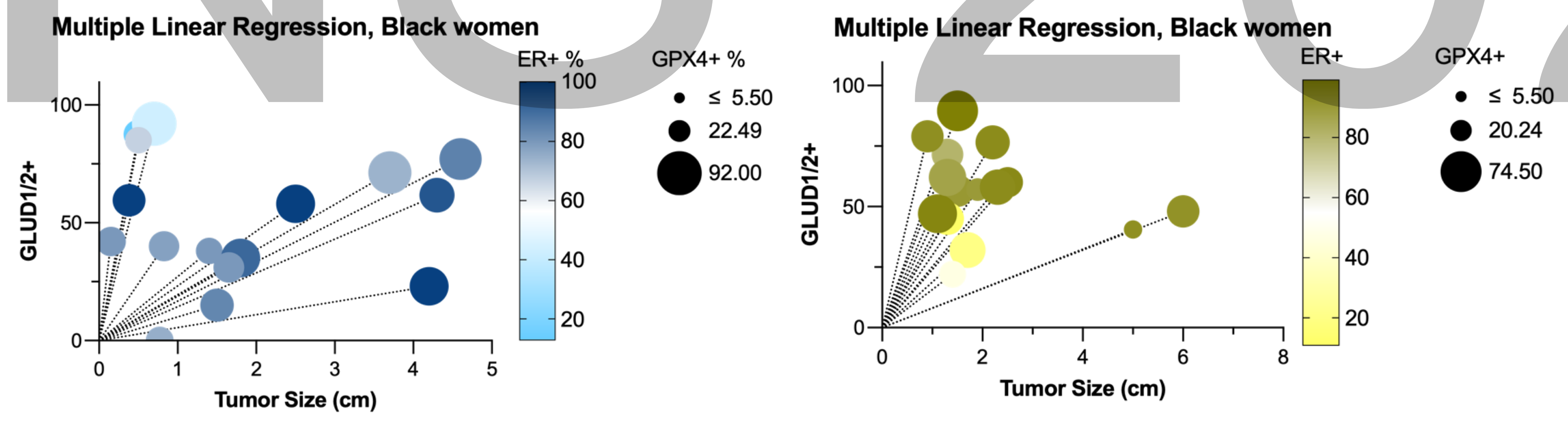

Figure 5. Multiple linear regression shows modest association of GLUD1/2, GPX4, and ER with tumor size in Black women with ILC. Tumor size as dependent variable, and GLUD1/2, GPX4, and ER percent positive as independent variables, were analyzed by unweighted multiple least-squares regression in Black women from the ILC (left panel) and IDC (right panel) cohorts. ILC: F = 3.791, p = 0.04; β1 for GPX4 = 0.02, p= 0.05; R² = 0.49. IDC: F = 1.774, p = 0.21; R² = 0.33. Color temperature = percent cells stained positive for ER, and bubble size denotes = cells stained positive for GPX4.

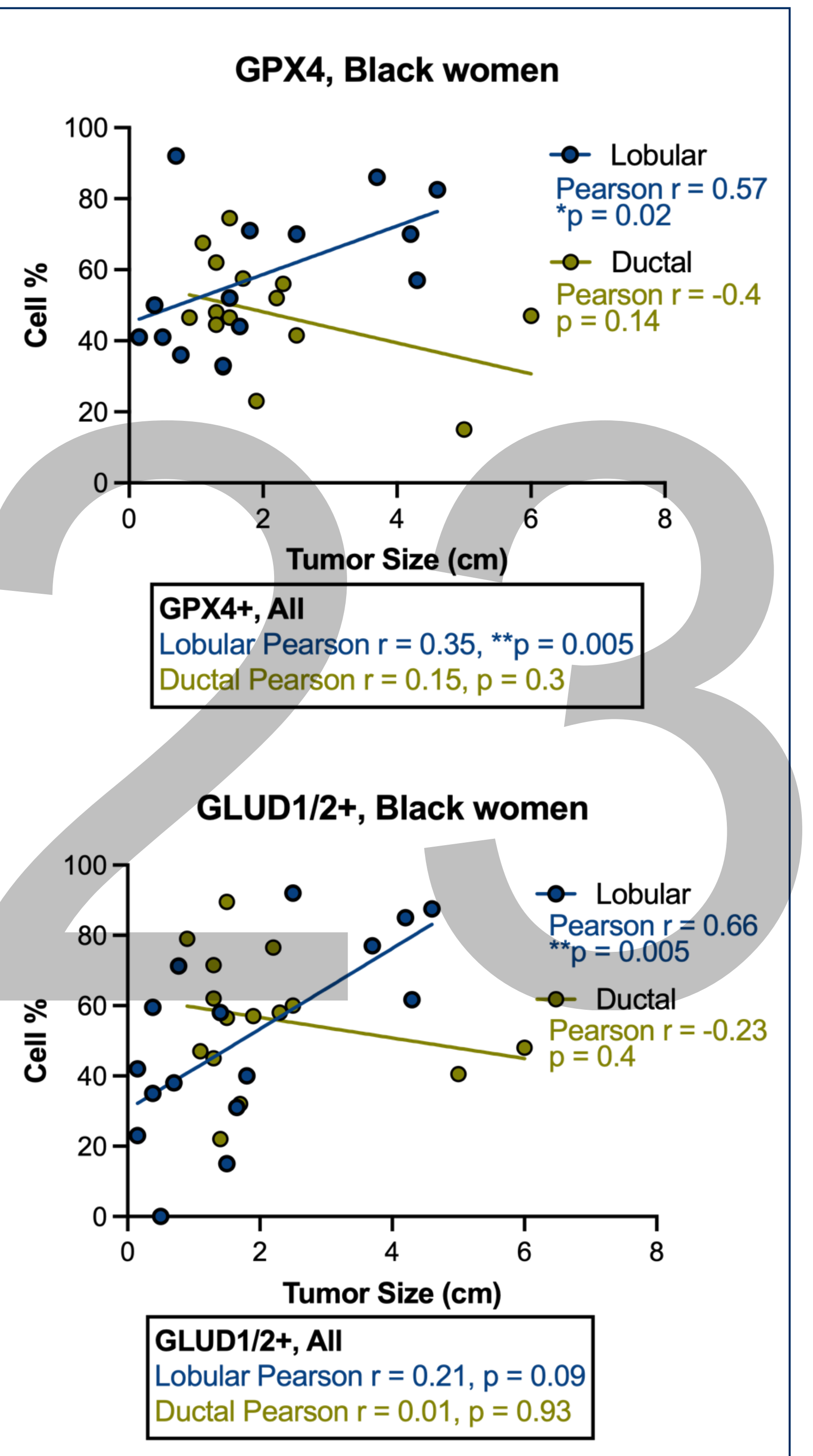

Figure 6. GLUD1/2 and GPX4 more strongly associate with tumor size in Black women with ILC. Percent cells stained positive vs tumor size was analyzed by simple linear regression and Pearson correlation. **, p≤0.01. *, p≤0.05.

Acknowledgements

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