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Supplemental material

Use of predictive spatial modeling to reveal that primary cancers have distinct central nervous system topography patterns of brain metastasis

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Supplemental Method

Model Sensitivity Analyses

To assess sensitivity of the multinomial and individual logistic GAMs to sample size, we conducted two bootstrap re-sampling experiments. Robustness of the adjusted GAM with melanoma as the reference was assessed with 500 bootstrap re-samplings, re-fitting the model to each of the datasets **(Supplemental Fig. 3A)**. All 500 bootstraps for breast had a p-value less than 0.05, 95.7% were less than 0.05 for lung, 94.7% for renal, and 64% for colon. For the logistic GAM we assessed its sensitivity by taking 100 independent random spatial samples of sizes n=100 to 1000, re-fitting the models and recording the p-values for the spatial tensor product for each sample (**Supplemental Fig. 3B**). As expected, when the sample size taken from the random sphere increased, the p-values decreased; however, even at the smallest n = 100, all p-values were less than 0.05, suggesting that the magnitude of the random sample taken does not nominally change the significance of the estimated spatial component of the logistic GAMs.

Supplemental Table 1. Brain metastases association by patient age and sex-type

	Breast	Colon	Lung	Renal
Age	0.98 (0.97, 0.99)*	1.05 (1.02,1.07)*	1.02 (1.01,1.03)*	1.01 (1.00,1.03)*
Male	--	0.84 (0.74,1.52)	0.70 (0.53,0.87)*	4.17 (2.69,6.44)*

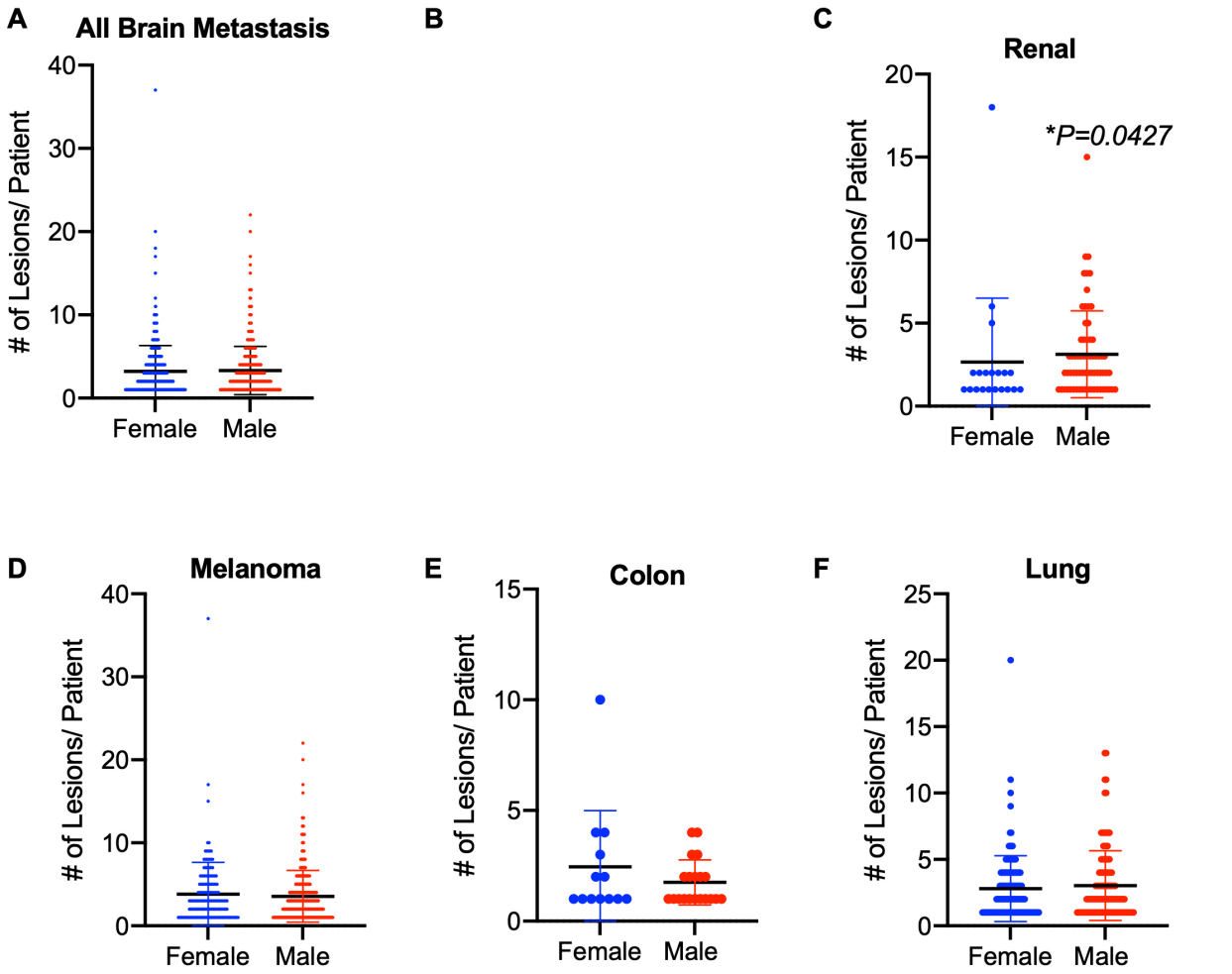
* Parameter estimates are with respect to melanoma, the reference group, and are represented as odds; $p<0.01$

Supplemental Table 2. Brain metastases association by tumor volume

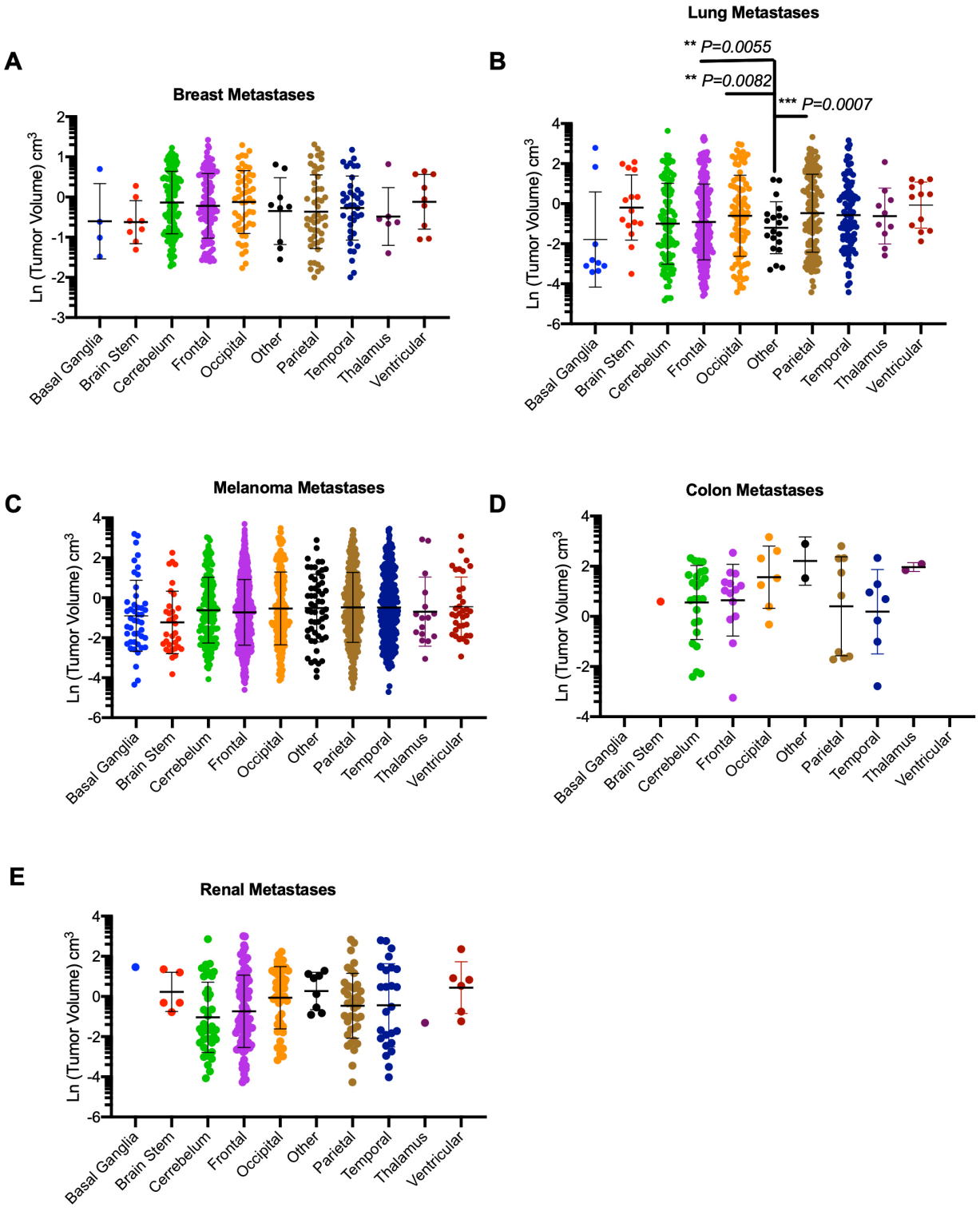
	Breast	Colon	Lung	Renal
Tumor Volume	1.04 (1.01,1.07)*	1.10 (1.05,1.15)*	1.02 (0.99,1.04)	1.01 (0.97,1.06)
Spatial (e.d.f)**	20.5 *	11.1	10.0 *	17.6

* Parameter estimates are with respect to melanoma, the reference group, and are represented as odds; $p<0.01$

** Spatial terms are represented as estimated degrees of freedom (e.d.f.) and relate to the shape and pattern of the surface estimated from the tumor locations

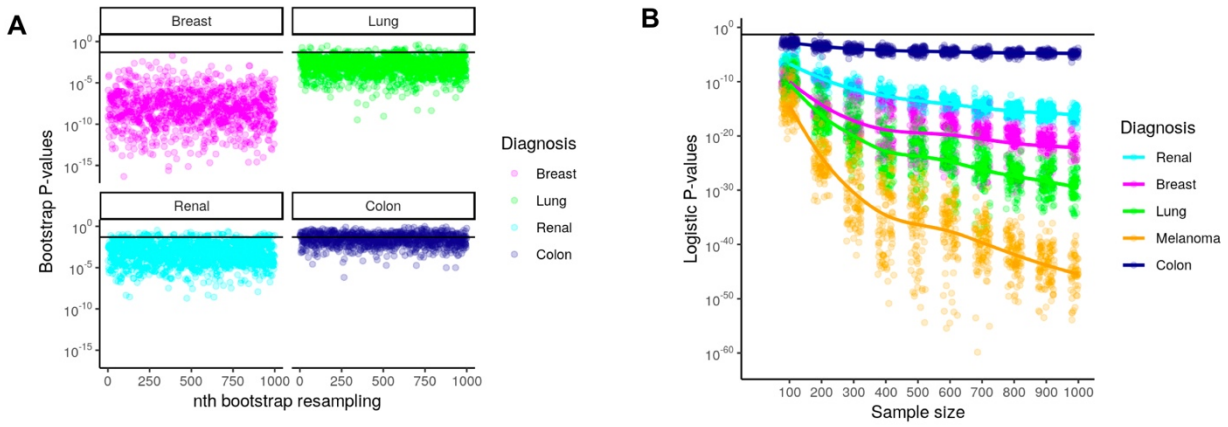


Supplemental Fig 1. Patients with Renal cell carcinoma have sex differences in number of brain metastases lesions. Stratification of the top the top 5 brain metastases lesions did not show significant difference in number of lesions/patient (**A**; mean =2.0, *P=0.458*). Furthermore, exclusion of breast cancer patients because of sex-bias, also led to no significant differences in number of lesions between men and women (**B**; mean number of lesions/patient=2.0, *P=0.651*). When tumors were analyzed according to disease site, only renal cell carcinoma metastases resulted in a differential number of lesions per patient. Specifically, males patients had significant increase in lesions (mean number of lesions/patient 2.0, *P=0.0427*) versus females (mean number of lesions/patient = 1.5; **C-F**).



Supplemental Fig. 2. Brain metastases volumetric analysis over 10 CNS anatomical locations shows distinct size distribution and representation. Tumor volume over 9 brain anatomical regions (basal ganglia, brain stem, cerebellum, frontal lobe, occipital lobe, parietal lobe, temporal lobe, thalamus, ventricular regions, subdural mater) was mapped out. Results show melanoma,

colon, renal, and breast metastases have no significant difference in tumor volumetric size across the 9 anatomical landmarks; **(A)** Breast metastases do not have significant volume difference across 9 anatomical landmarks.. **(B)** Lung metastases have significant smaller volume in the subdural mater (other) relative to frontal (*P=0.0055)*, occipital (*P=0.0082)*, parietal lobes (*P=0.0007)*. **(C)** No significant volume differences across the brain were observed in patients with melanoma to brain metastases **(D)** Colon cancer patients did not present with brain metastasis in basal ganglia, brainstem, and ventricular regional. Additionally, they did not have significant volume differences across 7 anatomical regions. **(E)** Renal cell carcinoma did not have brain metastases in the basal ganglia or thalamic regions; while they did not have significant volume differences across 8 other anatomical regions.



Supplemental Fig. 3. Sensitivity Analyses validation. (A) Robustness of the adjusted GAM with melanoma as the reference was assessed with 500 bootstrap re-samplings, re-fitting the model to each of the datasets. **(B)** For the logistic GAM we assessed its sensitivity by taking 100 independent random spatial samples of sizes n=100 to 1000, re-fitting the models and recording the p-values for the spatial tensor product for each sample.