PNAS LETTER

# Contextualizing racial associations in gene expression in patients with uterine serous carcinoma

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We read with interest the article by Foley et al. (August 12, 2024) (1) which describes uterine serous carcinoma (USC) tumor transcriptomes and immune responses in different patient groups. As the authors note, addressing racial inequities in endometrial cancer must be a priority. However, we are concerned that the framing of the research question and results could inadvertently imply that observed differences in molecular pathways and gene expression could be due to inherent categorical genomic differences between racial groups.

We believe that the paper would be strengthened by clearly stating that race is a sociopolitical construct and acknowledging that residual confounding and embodiment of inequalities can explain observed racial differences in gene expression. This would better align with the March 2023 National Academy of Sciences report on the appropriate use of population descriptors in genomic research, which states that "researchers should not use race as a proxy for human genetic variation" (2). It is important to acknowledge that residual confounding can explain the persistence of an association between racial category and gene expression after simple adjustment, as well as the fact that racial disparities in survival persist in "equal care settings" (1). An observed association does not imply inherent differences between racial groups. The authors should explain what else the "racial category" variable could be capturing other than genetic differences between patients of different self-identified racial categories. For example, many studies have linked endometrial cancer incidence, and that of more aggressive subtypes such as USC, to hypertension (3), diabetes (4), obesity (5), estrogen, and environmental toxin exposure (6, 7). The paper does briefly note the limitations that diabetes and hypertension have a potential impact (1). However, it is important to state explicitly that structural inequities and differential exposures manifest as health outcomes by affecting biological systems and that racial differences in gene expression are likely due to structural racism (8, 9).

The paper's conclusions of observed racial differences could be better contextualized with the possible causal pathways including stress, poverty, estrogen receptor expression, and more (8). The PAX8 signaling pathway could become an important therapeutic target and in turn could help reduce racial health inequities in outcomes, but acknowledging and investigating the structural social inequities that lead to differences in gene expression will be necessary to reach equity in incidence and outcomes (10).

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The authors declare no competing interest.



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