

## **Genomic insights into Mrs. Carter's UV-induced tumors and potential treatment strategies**

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Mrs. Carter, a 9-year-old mixed breed rescue, has spent much of her life outdoors in New Mexico with high UV exposure. She developed two rapidly growing skin tumors on the glabrous skin of her ventral abdomen. Pathology confirmed these as cutaneous hemangiosarcoma (HSA) with high mitotic index, 32 and 12 per 10 HPF. Both tumors were surgically removed with clean margins, and no evidence of metastasis was found.

Genomic profiling with Canine CGP revealed that, despite differences in mutations, both tumors shared key mutation patterns: low copy number alterations and structural variations, and exceptionally high tumor mutation burden (TMB), characterized by high number of single nucleotide mutations, including four TP53 mutations.

The TMB counts were 160 and 80 per mega bases for the two tumors, ranking as the highest and fourth highest among the 60+ Canine CGP tested cases. This high TMB profile is consistent with UV-induced tumors, which are characterized by high mutation rates.

Interestingly, the TMB appears to correlate with the mitotic index of the two tumors (160:32 and 80:12), suggesting a potential trend that indicates tumor aggressiveness, warranting further investigation.

Additionally, both tumors show a high prevalence of C>T transitions (cytosine to thymine) at CC, TC, CT, and TT dinucleotides, a mutational hallmark of UV-induced DNA damage, further confirming the UV-driven nature of Mrs. Carter's tumors.

Importantly, tumors with high TMB often exhibit increased neoantigen expression, making them more immunogenic and responsive to immune checkpoint inhibitors (ICIs), and neoantigen-based immunotherapies. (PMID: 32919526)

While surgical margins are clear for Mrs. Carter, the presence of 4 different TP53 mutations raises concern, as they are often associated with increased tumor aggressiveness and a higher risk of metastasis. To achieve long-term tumor-free survival, maintenance therapy with immunotherapy may still be considered.

Mrs. Carter's case is one of many that showcase the power of Canine CGP in revealing critical insights into the tumor's biological behavior, potential vulnerabilities and treatment opportunities, such as immunotherapy for high-TMB tumors, advancing genomics-precision medicine in veterinary oncology.