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**Poster Presentation**

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**Neutralizing Antibody Prevalence Toward a Hematopoietic Stem Cell-Derived AAV and Immunoassays for Clinical Trial Enrollment**

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Screening patients for pre-existing neutralizing antibodies (NAbs) against AAV capsids prior to enrollment in gene therapy clinical trials is standard practice to mitigate potential efficacy and safety risks. The typical screening approach identifies neutralizing seropositive samples as those exhibiting greater than 50% transduction inhibition (TI) relative to a seronegative control. The TI threshold is often derived from the analytical system used, and not statistically from the biological variation of the population under study, as recommended by regulatory guidance. In a study population using the TI method, there was relatively low prevalence of NAbs to AAVHSC15, one of Homology Medicines' adeno-associated viruses derived from human hematopoietic stem cells. Here, we show correlation between the TI method and a validated three-tier NAb assay for identifying anti-AAVHSC15 NAb positive serum samples. The prevalence of confirmed positive samples in commercial sera was 16% in the three-tier assay versus 24% using the TI method. All of the NAb-positive samples identified in the three-tier assay had previously been identified as positive using the TI approach. Of interest, two samples were positive for exhibiting neutralization in the absence of detectable total antibodies. Determining an anti-capsid NAb screening strategy for patient exclusion is method and vector dependent; however, there was close agreement in reported results between the two approaches used in this instance. A standardized validation of anti-capsid NAb assays, per regulatory guidance and statistical considerations for seropositivity thresholds, is recommended for enrollment in gene therapy clinical trials.