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Case Report

Systemic Human hTERT AAV Gene Transfer Therapy and the Effect on Telomere Length and Biological Age, A Case Report

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Abstract

A single adult female human was treated with AAV hTERT gene transfer therapy on two separate occasions 5 years apart. Follow-up is 5.8 years. The first dose administered on 9.16.2015 consisted of a total intravenous dose of 3e15 AAV hTERT. The second dose administered on 9.24.2020 consisted of a total intravenous dose of 3e15 AAV hTERT. Before and after each therapy and periodically in between the doses, Human Leucocyte telomere analysis was performed. The initial telomere length measurements collected on 9.15.2015 at the initiation of the AAV hTERT gene transfer therapy demonstrated a baseline average telomere length of 6.71kb which corresponded to a telomere percentage relative to age and population at the 30th percentile. The most recent telomere length measurements collected on 7.13.2021 demonstrated an average telomere length of 8.94kb which corresponded to a telomere percentage relative to age and population at the 89th percentile. The results demonstrate the progressive lengthening of the recipient's telomeres from 6.71kb to 8.94kb despite advancing 5.8 years in chronological age. Associated age as related to telomere length (also known as biological age) was calculated and compared to chronological age. Initially on 9.15.2015, and prior to the first AAV hTERT gene transfer therapy, the associated age was calculated to be 62 years. The latest telomere analysis dated 7.13.2021 demonstrated a calculated associated age of 25 years. This decrease in associated, or biological age, decreased at a rate of 5.3 years per year of chronological age advancement.

Keywords: Gene transfer therapy; Telomere length; Biological age.

Introduction

Cellular replicative ability and its lifespan is dependent on the integrity of the cells chromosomes which carries the genetic information of the cell and thus protection from damage is paramount to proper and complete genetic and cell replication. Chromosomal integrity is directly related to chromosomal telomere length. Telomeres are specialized nucleoprotein sequences on the ends of linear chromosomes composed of repetitive 5"-TTAGGG-3" sequences. With

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each cell division, 50-200 base pairs of telomeric data is lost with the result being a measurable shortening of the telomere. This progressive shortening of the telomere creates a limited replication potential in somatic cells. Ultimately the telomere length reaches a loss of such significant length that the telomere is too short to protect the chromosome from end-to-end chromosomal fusion, telomeric fusion, or direct chromosomal degradation. The cell enters replicative senescence or apoptosis. Telomere length is at the core of and explains the limited replicative potential of somatic cells [1-5].

Naturally, telomere shortening can be addressed and reversed in embryonic and pluripotent stem cells. This is accomplished by the enzyme Telomerase. Telomeres can be synthesized by the RNA-dependent DNA polymerase telomerase. Telomerase is composed of the protein subunit named "human telomerase reverse transcriptase" and the RNA subunit named "human telomerase RNA. The rate limiting subunit hTERT is repressed in normal somatic cells [6-13].

Increasing the hTERT subunit function in normal somatic cells by artificial means is presumed to lengthen telomeres in somatic cells and confer a longer cell lifespan, and potentially cellular immortality. In this case report, we demonstrate the results of systemic human hTERT AAV gene therapy and the effect on telomere length and biological age over a span of 5.8 years.

Methodology

An adult Caucasian female underwent voluntary systemic human hTERT AAV gene transfer therapy on two separate occasions to lengthen her telomeres and reduce her biological age. The patient gave her express and witnessed informed consent for the experimental therapy, and released all parties involved from legal jeopardy regarding the treatment and all associated events. Clinical laboratory analysis evaluating the serum chemistry, endocrine, and hematological, and immunological systems was performed before and after each therapy as well as periodically during the patients 5.8 years of follow-up. Physical exam with review of systems was performed before treatment and yearly thereafter. For telomere analysis, serum Human Leucocyte analysis was performed before the initial therapy, and periodically throughout the treatment follow-up period of 5.8 years. The Human Leucocyte analysis was performed by the same third-party laboratory, SpectraCell Laboratories, on all occasions. A total of 5 SpectraCell Laboratories analysis were done as listed in Table 1 of the results section.

Result

Laboratory results

Serology testing showed no statistically significant changes in the serum hematology, chemistry, endocrine, or immunological testing results over the 5.8 years of follow-up. Physical Exam and review of systems was performed before treatment and yearly thereafter. No side effects, complications, or untoward effects from the gene transfer therapy were evident.

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Testing Date	09.17.2015	03.18.2016	06.16.2018	01.28.2020	07.13.2021
Chronological age	44y, 7mo, 17d	45y, 1mo, 18d	47y, 4mo, 16d	48y, 11mo, 28d	50y, 5mo, 13 d
Telomere length	6.71Kb	7.33Kb	8.12Kb	8.58Kb	8.94Kb
Avg length for age	7.6Kb	7.3Kb	7.4Kb	7.4Kb	7.2Kb
% relative to age	30th	51st	72nd	82nd	89th

Table 1: SpectraCell Telomere Analysis Results.

Statistical Analysis of Telomere Testing

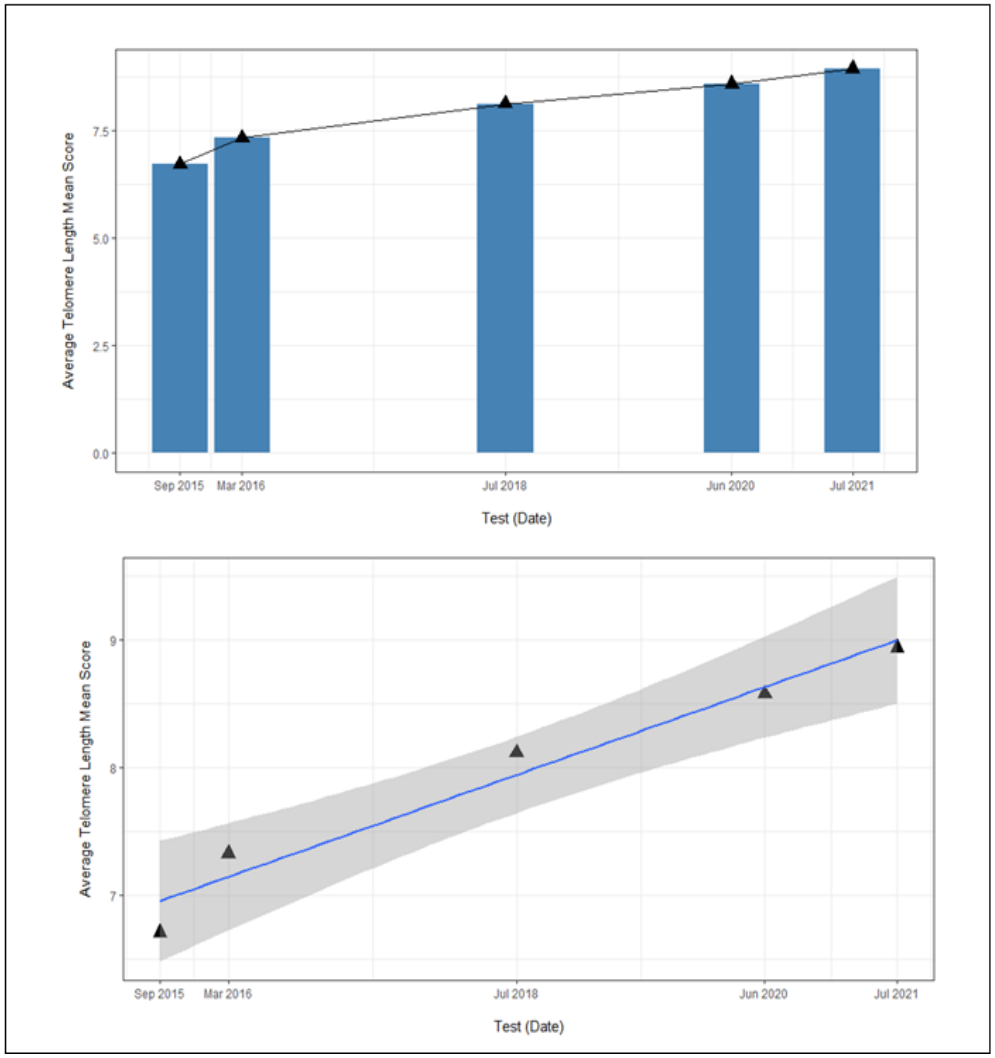

Figure 1 and 2: Average Telomere length over 5.8 years.
Statistical regression analysis: Estimate Intercept 6.958; Time 0.350.
Interpretation: Std. Err. 0.148 0.041; T Value 46.942 8.524; P Value<0.001 0.003.

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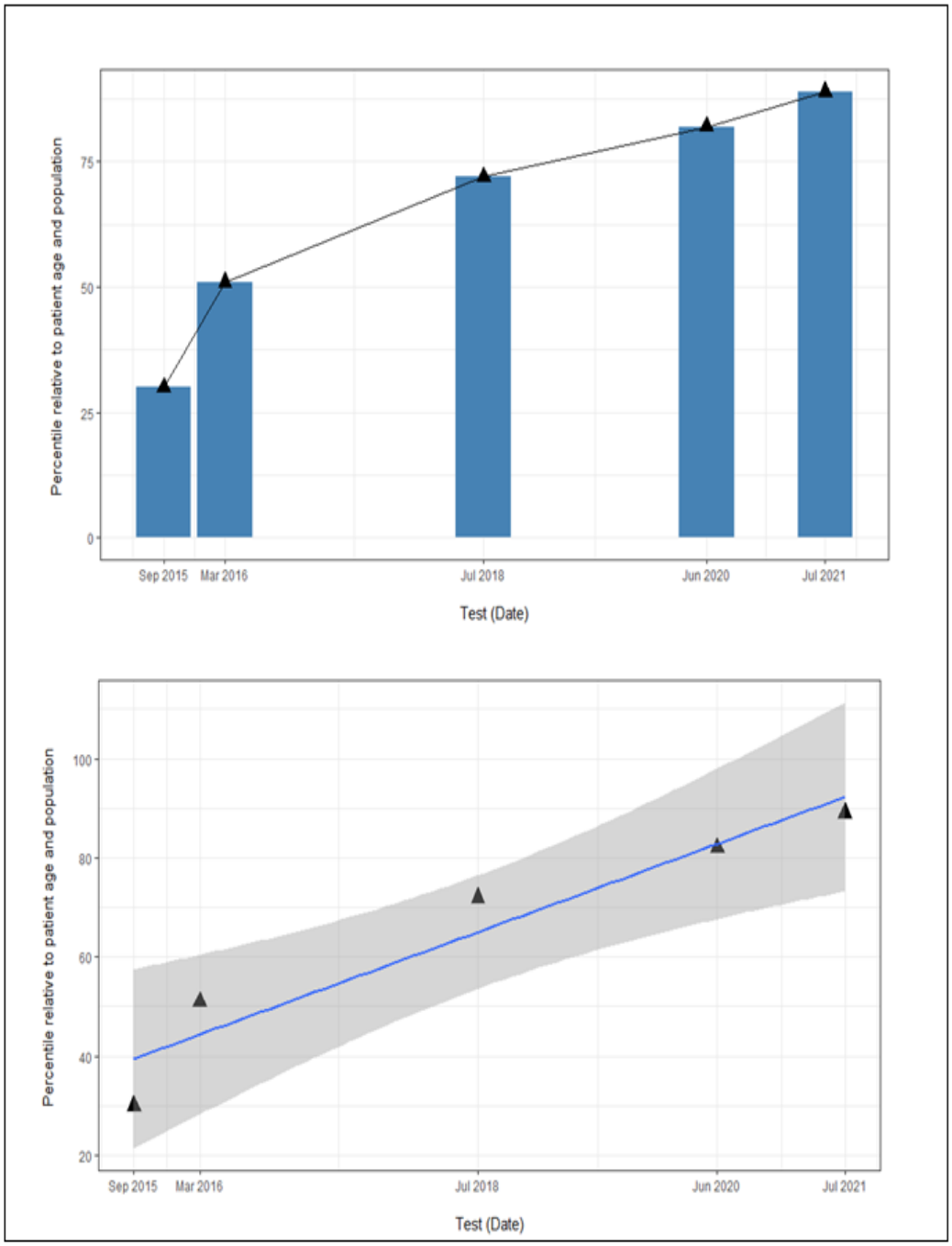

Figure 3 and 4: Percentile telomere length relative to patient age and population over 5.8 years.
Statistical regression analysis: Estimate Intercept 39.475; Time 9.069.
Interpretation: Std. Err. 5.685 1.577; T Value 6.943 5.752; P Value <0.006 0.010.

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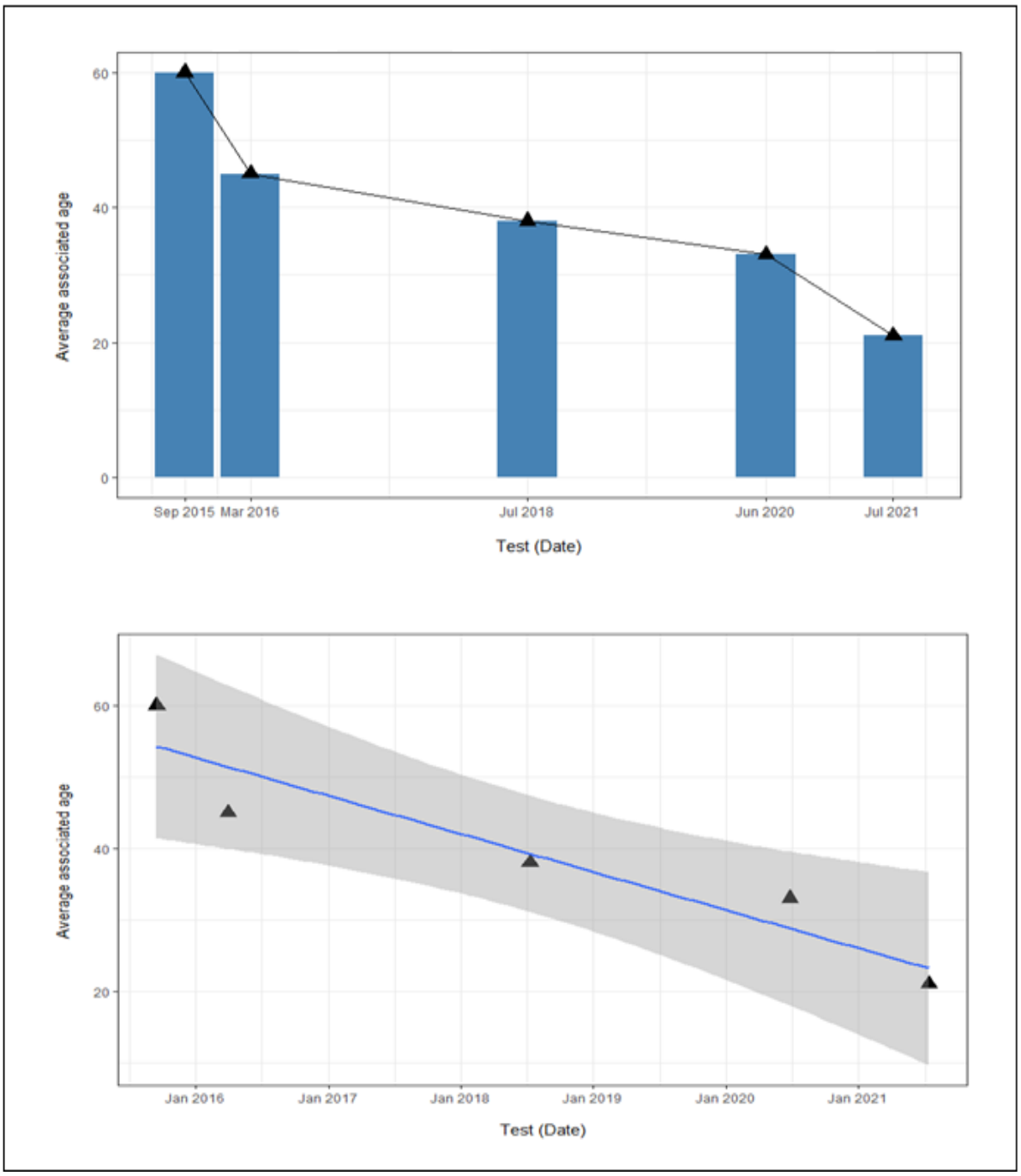

Figure 5 and 6: Associated (biological) age over 5.8 years.
Statistical regression analysis: Estimate Intercept 54.283; Time-5.329.
Interpretation: Std. Err. 4.038 1.120; T Value 13.441 _4.759; P Value <0.001 0.018.

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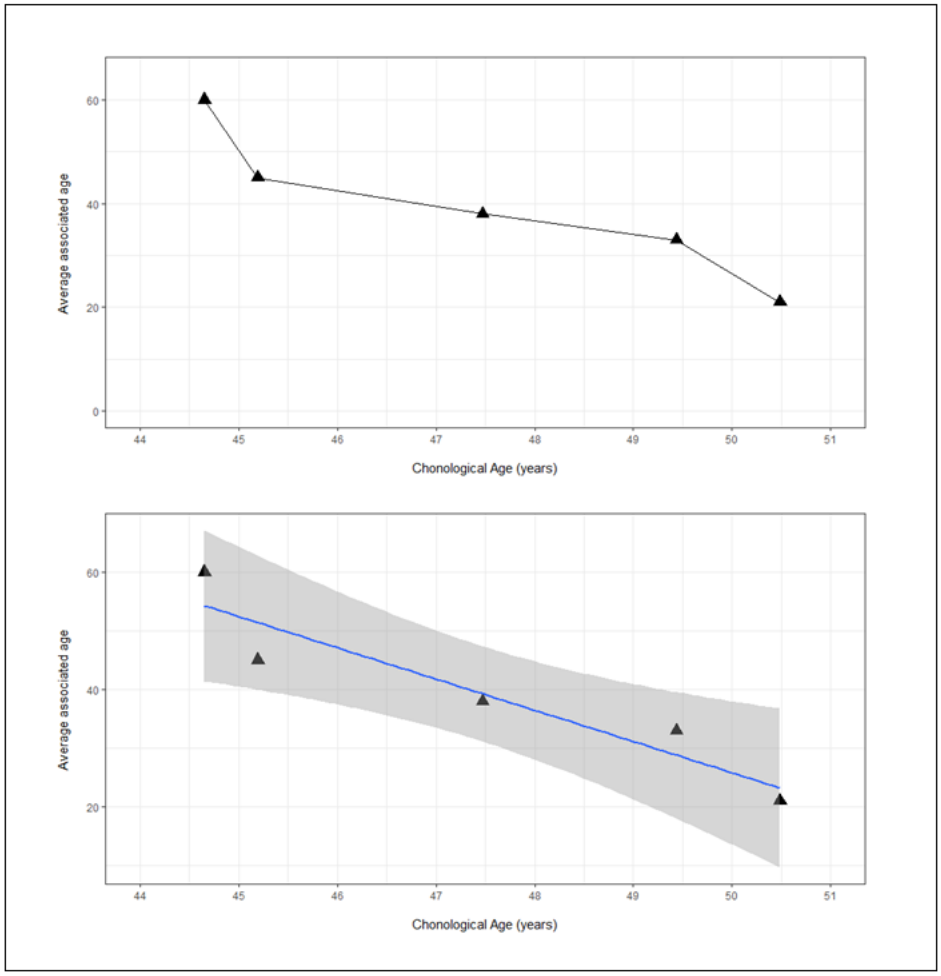

Figure 7 and 8: Associated age vs chronological age over 5.8 years.
Statistical regression analysis: Estimate Intercept 292.097; Time-5.326.
Interpretation: Std. Err. 53.162 1.119; T Value 5.494-4.759; P Value <0.012 0.018.

Telomere analysis testing summary

- Average telomere length has significantly increased during the follow up period (P=0.003).
- Average telomere length increasing rate is 0.35 Kb per year.
- Percentile relative to patient age and population has significantly increased during the follow up period (P=0.010).
- Percentile relative to patient age and population increasing rate is 9.1 percent per year.
- Average associated age has significantly decreased versus chronological age (P=0.018).
- Average associated age decreasing rate is 5.3 years per year.

Discussion

For all of time man has searched for a fountain of youth and many in the scientific world have thought that manipulation of hTERT may be one end to that search. Given the role hTERT plays in the mortality/immortality of cells, it's

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understandable how hTERT is viewed in this regard. Increasing hTERT function in cells leads to increased cellular lifespan. Increasing enough cell populations lifespans of an organism holds the potential of organism increased lifespan.

The observation that hTERT upregulation is a means by which malignant cells facilitate propagation of that malignancy has raised fears that any upregulation of hTERT will result in malignant transformation of cells. Laboratory studies have shown this fear to not be a significant concern. A laboratory study of the ectopic expression of telomerase in normal human cells demonstrated extended lifespan and the study addressed the concern of malignant transformation of the cells. The study investigated the long-term effects of forced expression of human telomerase catalytic component (hTERT) in normal human fibroblasts. By comparing the telomerase expressing cells with controls, karyotypic stability was demonstrated in both cell populations. It was noted that the ectopic expression of telomerase in human fibroblasts is sufficient for immortalization but did not result in changes typically associated with malignant transformation [14].

In this case report, we document the systemic administration of AAV hTERT gene transfer therapy and its effect on telomere length and biological age referenced to population norms and chronological age. Evaluation and surveillance with systemic multisystem laboratory analysis demonstrated an absence of treatment related abnormalities. Periodic physical exam and review of systems demonstrated no detectable abnormalities over the follow-up period of 5.8 years. Telomere analysis demonstrated a significant and progressive elongation of cellular telomeres and a remarkable reduction in biological age from 60 to 25 over the 5.8-year follow-up timeframe. The average reduction of biological age was 5.3 years for every year of chronological age advancement.

Conclusion

This case report describes the successful implementation of human systemic AAV9 hTERT gene transfer therapy with resultant elongation of cellular telomeres, biological age reduction from 60 to 25 years with an average reaction of biological age of 5.3 years per calendar year advancement, and an absence of complications or side effects.

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