Determining the Long-term Natural History of Atrophy in Patients with Choroideremia: An Meta-analysis of Individual-level Data

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Introduction

- Choroideremia (CHM) is an X-linked recessive disease of the retina and choroid, affecting ~1 in 50,000 individuals.
- Although there are currently no approved treatment options for CHM, results from phase I/II human trials of gene therapy are encouraging.[1-6]
- Visual acuity is the most common primary endpoint in the current gene therapy trials for CHM, but young patients usually have unaffected visual acuity.[1-6]
- The residual retinal pigment epithelium (RPE) area measured by fundus autofluorescence (FAF) may be an anatomic endpoint to assess disease progression in young patients.[1-5]
- We aimed to (1) determine the long-term natural history of atrophy in CHM and (2) find a reliable anatomic endpoint to monitor CHM progression.

Methods

Literature Search

- We searched: MEDLINE, Embase, Web of Science Core Collection, PubMed, BIOSIS Citations, Scopus, and clinicaltrials.gov through July 17, 2019.

Selection Criteria for Published Studies

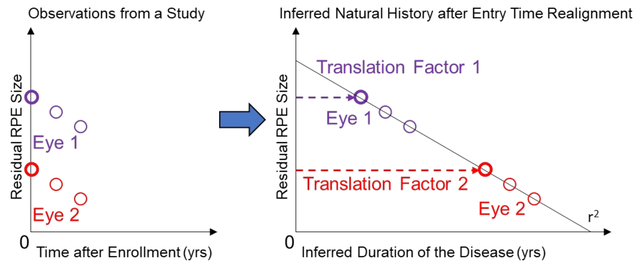
- Recruited a group of patients (≥5) diagnosed of CHM in 1 or both eyes without any treatment.
- Assessed residual RPE area of the affected eye by FAF on at least 1 occasion.
- Reported data of individual patients' ages and residual RPE area.

Three Progression Models of RPE Atrophy:

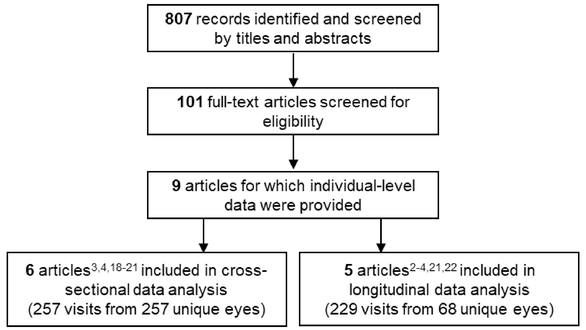
- Area linear model (ALM): residual RPE area decreases linearly with time.
- Radius linear model (RLM): residual RPE radius decreases linearly with time.
- Area exponential model (AEM): log RPE area decreases linearly with time.

Data Synthesis and Statistical Analysis

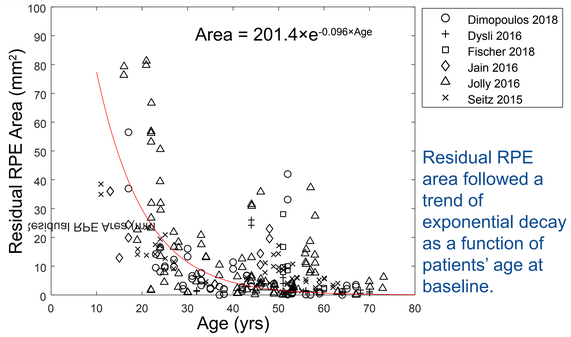
- We determined the natural decline rate of residual RPE size using a 2-stage approach.[7]
- Entry time realignment: We added horizontal translation factors to correct for different patients' entry times into the study (below image). We estimated the translation factors by adjusting 1 translation factor by 1 month at a time until the r^2 was maximized for the cumulative trendline.[8-17]



Literature Search and Screening

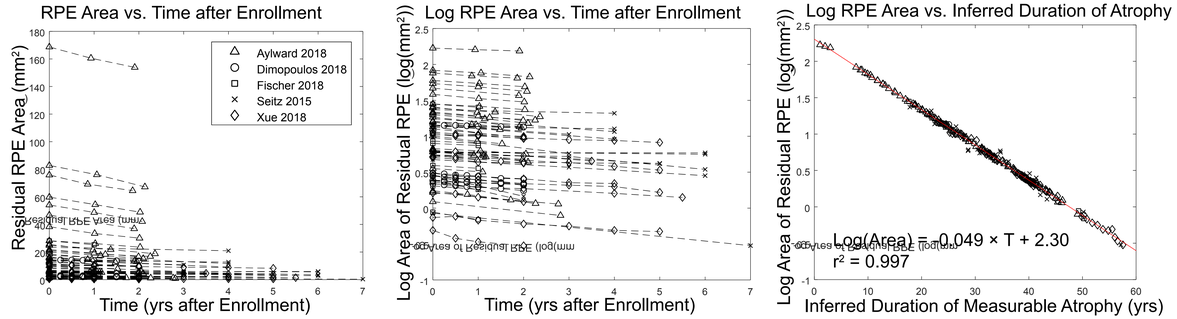


Residual RPE Area vs. Age at Baseline

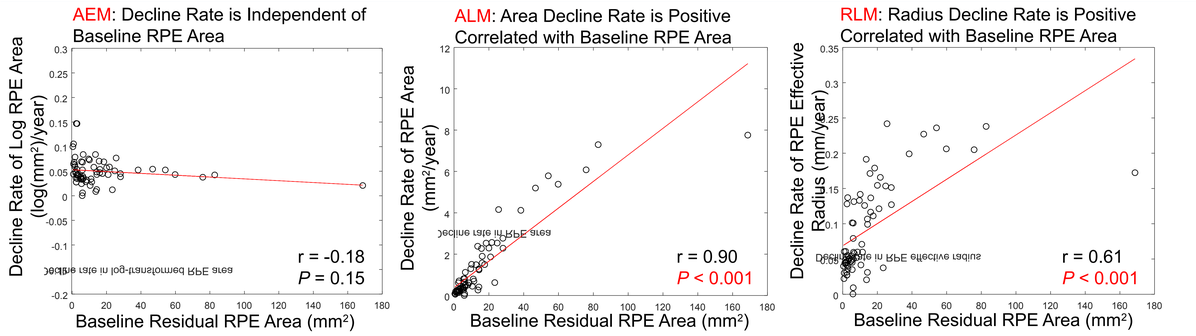


Residual RPE area followed a trend of exponential decay as a function of patients' age at baseline.

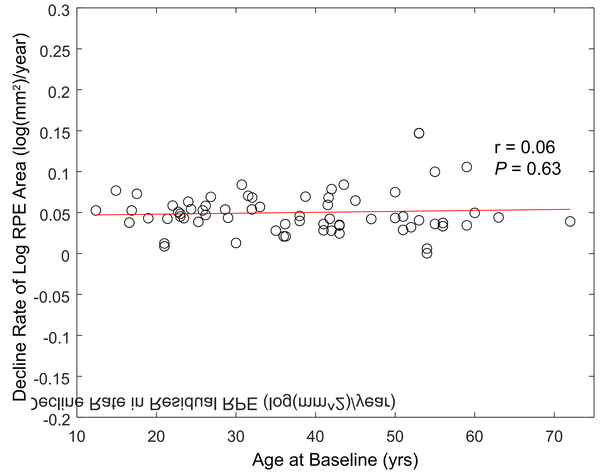
Log RPE Area Declines Linearly over ~60 Years after Entry Time Realignment



Decline Rate of Log RPE Area is Constant across Different Baseline RPE Areas



Decline Rate of Log RPE Area is Constant across Age 12 to 72 Years



Conclusion

- The loss of residual RPE area in untreated eyes with CHM follows a 1-stage exponential decay over approximately 60 years.
- The decline rate of log RPE area is 0.050 (95% CI, 0.046-0.055) log(mm²)/year, equivalent to 10.88% (95% CI, 10.05-11.90%) per year.
- The decline rate of log RPE area is consistent across different baseline RPE sizes (r = -0.18) and patients' ages (r = 0.06).
- The log-transformed RPE area measured by FAF can serve as an anatomic endpoint to monitor CHM progression in trials.

References and Acknowledgements

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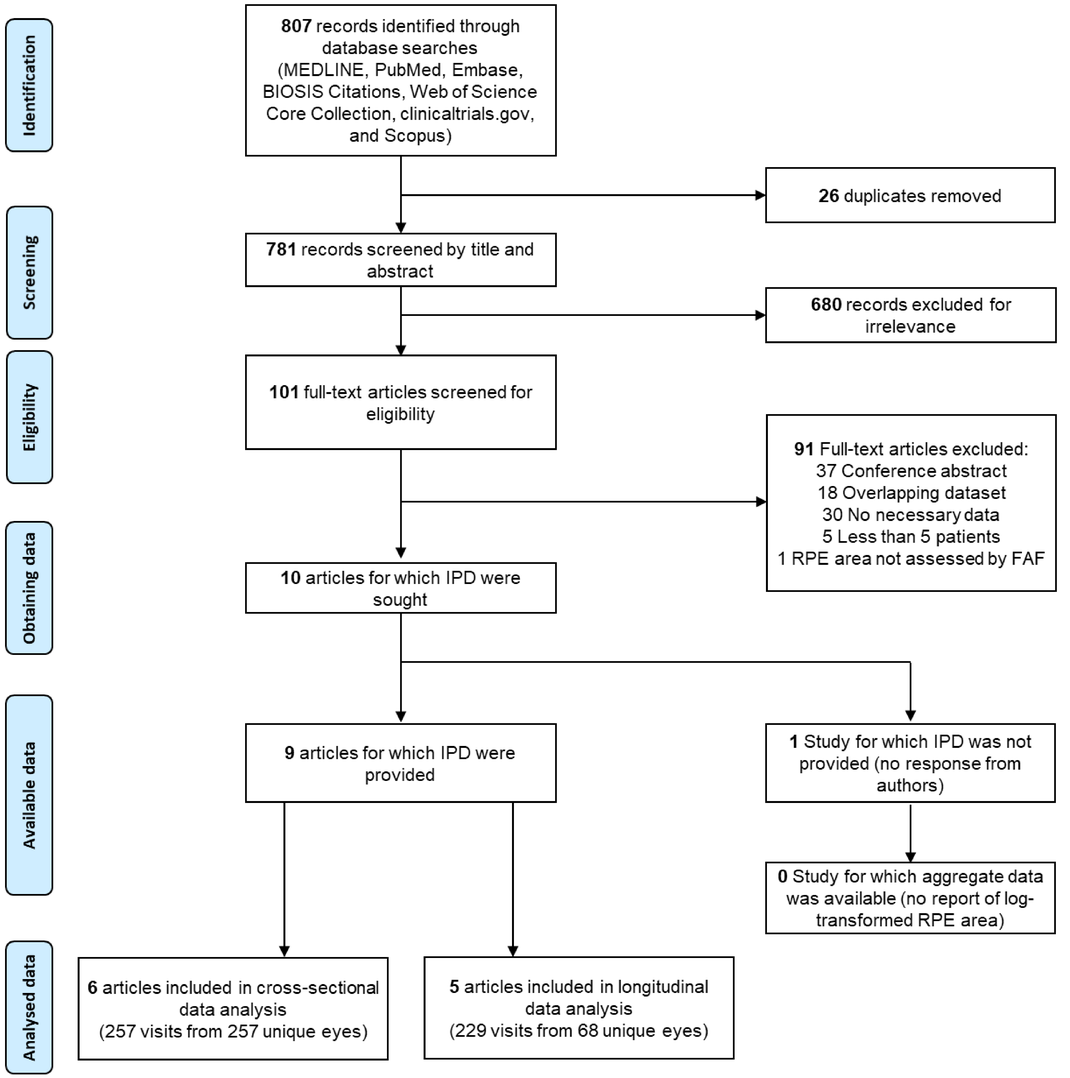
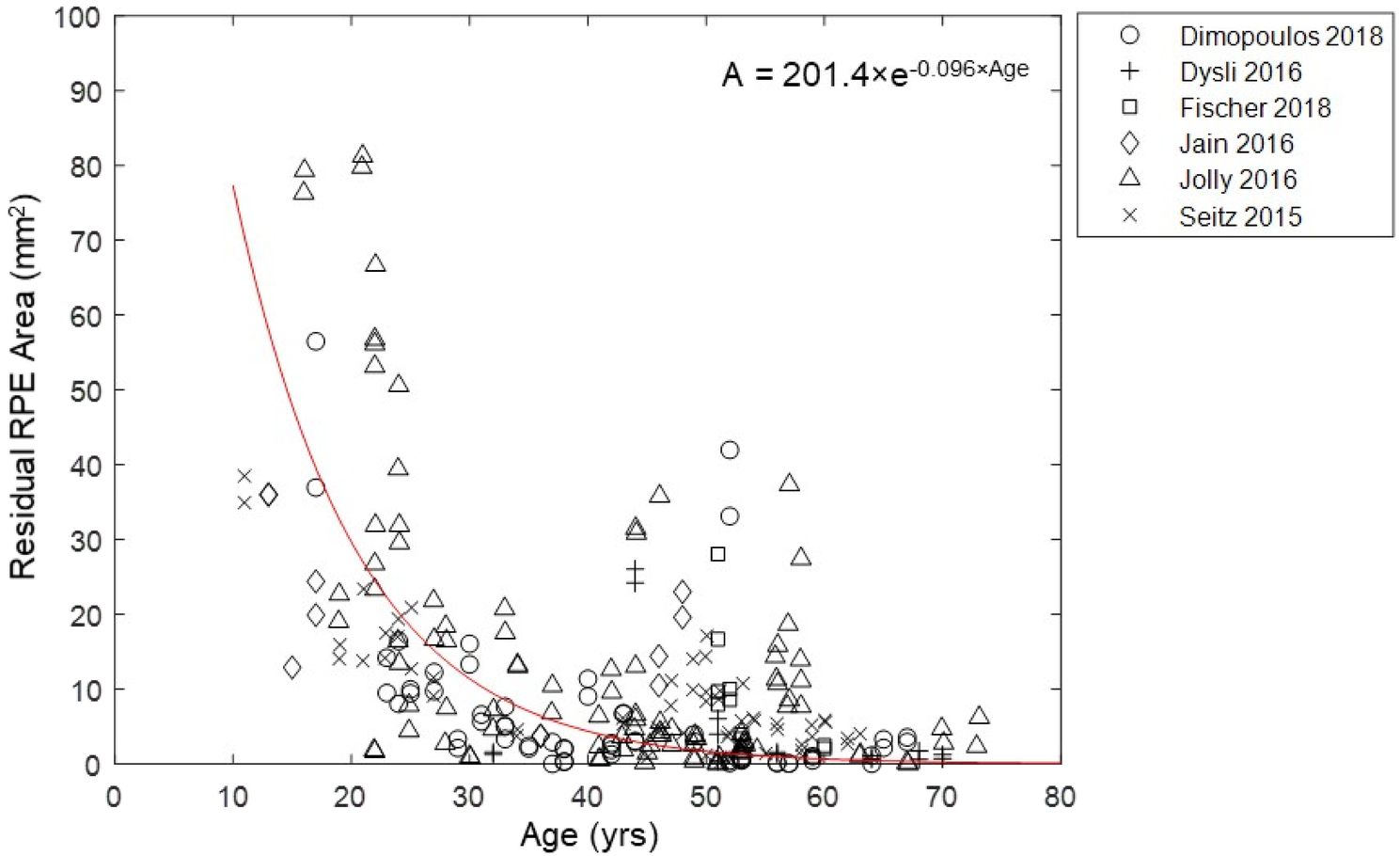
Data Synthesis and Statistical Analysis:

- Entry time realignment: We added horizontal translation factors to correct for different patients' entry times into the study (slide 4). We estimated the translation factors by adjusting 1 translation factor by 1 month at a time until the r^2 was maximized for a cumulative trendline.
- We determined the natural decline rate of residual RPE size using a 2-stage approach.

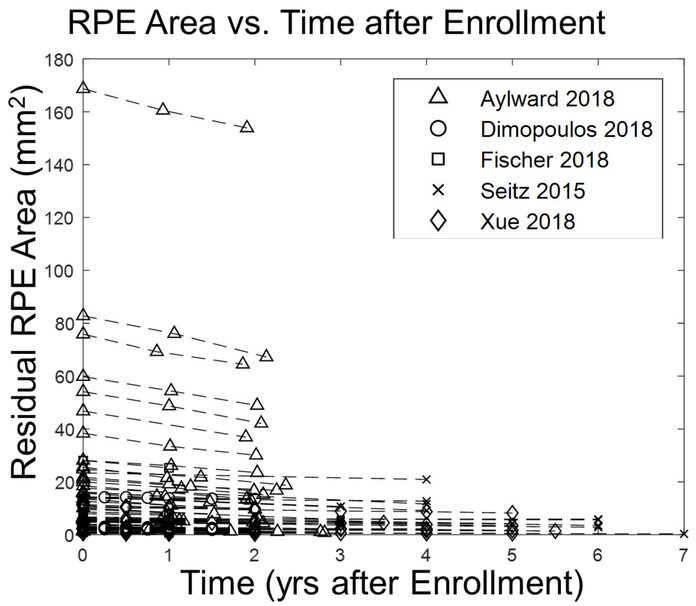


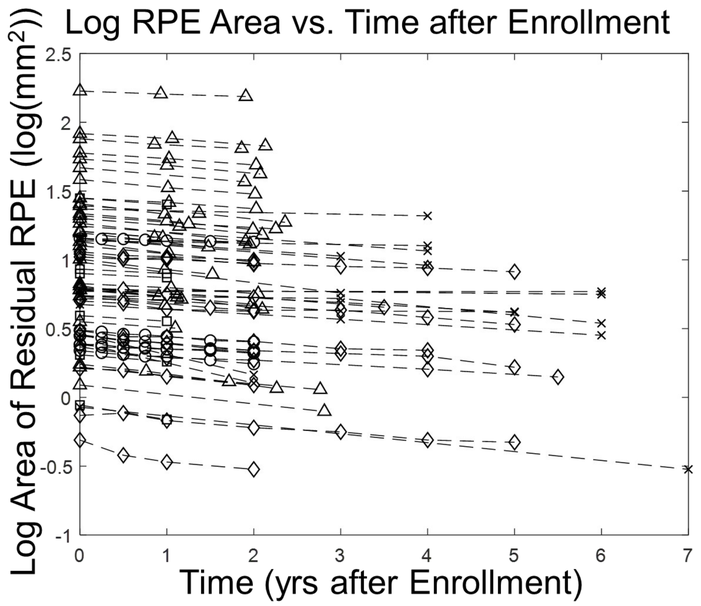
Results: Residual RPE Area as a Function of Age at Baseline

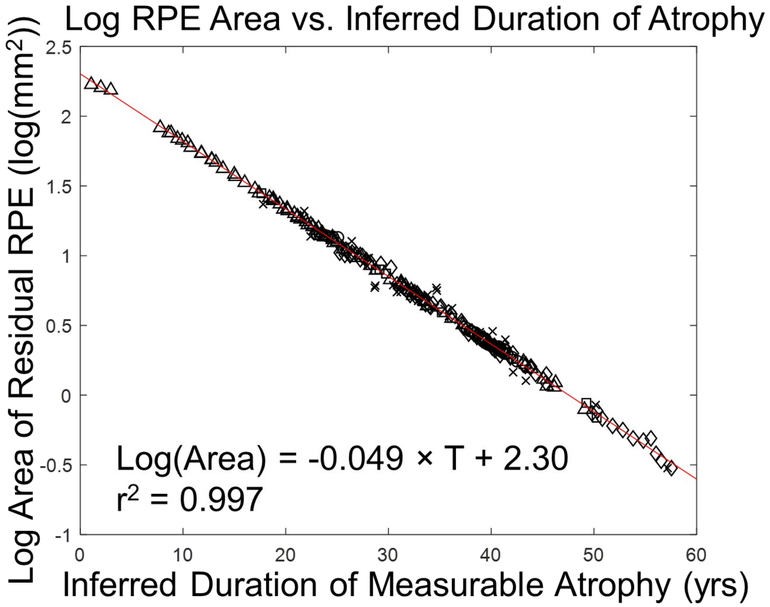


Residual RPE area followed a trend of exponential decay as a function of patients' age at baseline.

Results: Log RPE Area Declines Linearly over ~60 Years after Entry Time Realignment

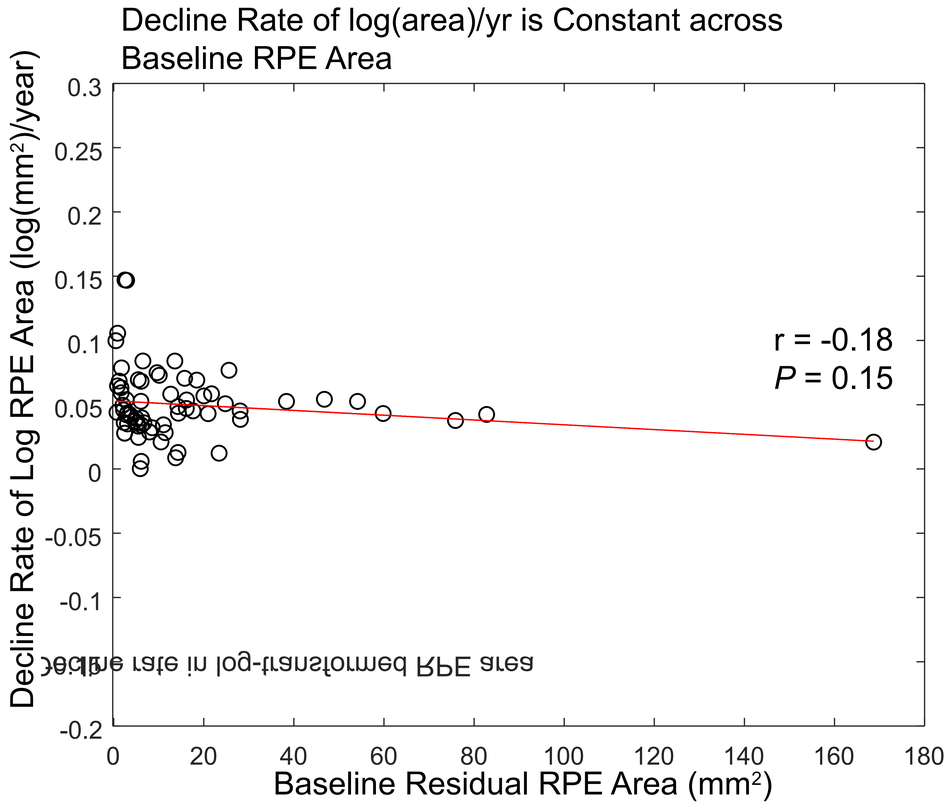


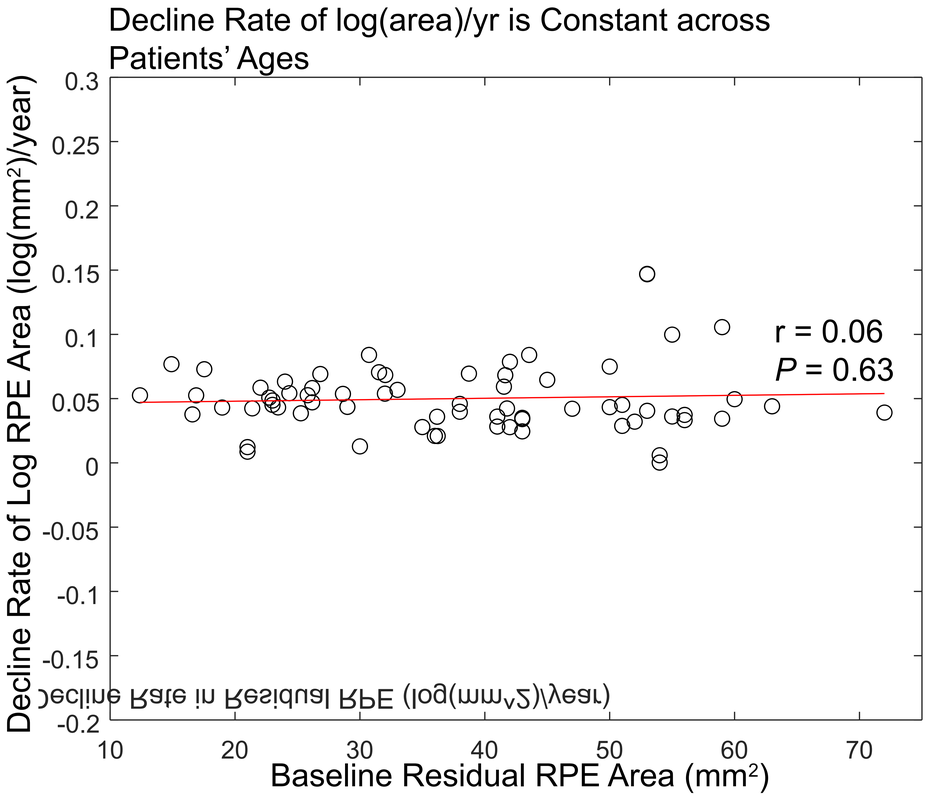




- Log-transformed residual RPE area declines at a constant rate over 60 years ($r^2 = 0.997$).
- The loss rate of residual RPE area is 10.88% (95% CI, 10.05-11.90%) per year.

Results: Decline Rate of Log RPE Area is Constant across Different Baseline RPE Areas and Patients' Ages





The decline rate of log RPE area is consistent across different baseline RPE sizes (r = -0.18; left figure) and patients' ages (r = 0.06 from age 12-72 years; right figures).

Conclusions

- The loss of residual RPE area in untreated eyes with CHM follows a 1-stage exponential decay over approximately 60 years.
- The decline rate of log RPE area is 0.050 (95% CI, 0.046-0.055) log(mm^2)/year, equivalent to 10.88% (95% CI, 10.05-11.90%) per year.
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