The Telomere Research Network

http://trn.tulane.edu/

telomerenetwork@gmail.com

Introduction to the virtual series

August 30, 2020

Stacy S Drury, MD PhD

sdrury@tulane.edu

1988 Southern Blot analysis (TRF)[1]

1995 primed in situ (PRINS) Q-FISH[2]

1996 metaphase Q-FISH[3]

1997 dot blot[4]

1998 interphase Q-FISH[5] flow-FISH[6]

1999 hybridization protection assay (HPA)[7]

2001 Q-Flow-FISH[8]

2002 TEL-FISH/TELI-FISH[10] qPCR[9]

2003 T/C-FISH[11] Single Telomere Length Analysis (STELA)[12]

2007 HT Q-FISH/Telomere Analysis Technology[13]

2009 MMqPCR[14]

2010 Universal-STELA[15]

2011 aTL qPCR[16] T/Dx dot blot[17]

2014 TelSeq[19] Luminex[18]

2015 telomere dysfunctional induced foci (TIF)[20] CompuTel[21]

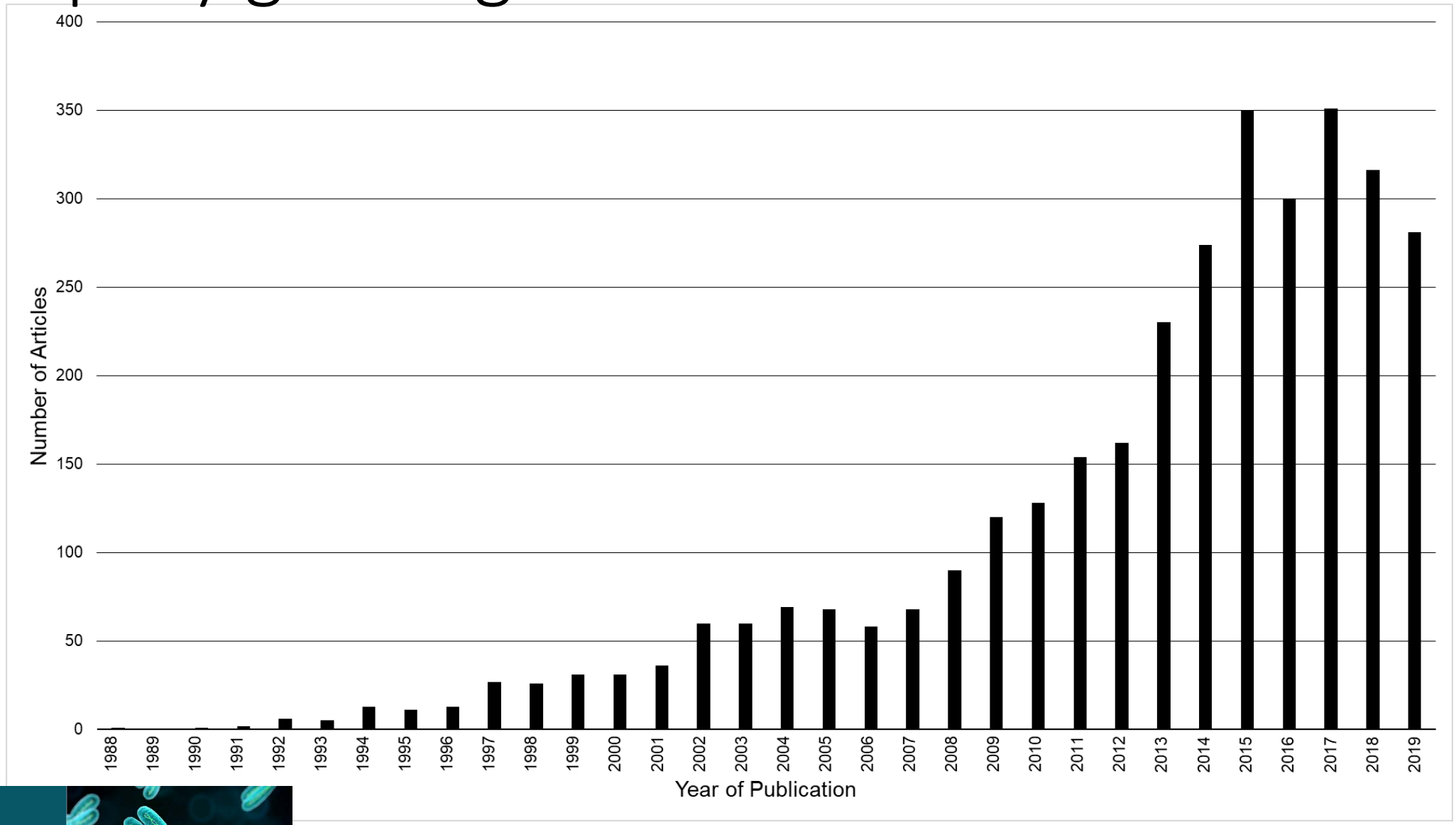
2017 HT Single Molecule Telomere Length[23] Telomere Shortest Length Assay (TeSLA)[22]

2018 Multiple Luminex[24] Telomerecat[25]

2019 TelomereHunter[27] DNAmTL[26]

2020 Telomere Analysis Technology[28]

A rapidly growing research field



TELOMERE RESEARCH NETWORK

What is the TRN? Two parts- One goal

- METHODS COMPARISONS
  - Methods comparison studies
  - Specific AIMS of each U01- impact of preanalytic factors, cross tissue correlation of different tissues used for TL measurement, development of new rapid throughput assay based on qFISH, cancer/transplant outcome prediction
- TRN
  - Develop an interactive network
  - Enhanced the understanding and applicability of telomere measurement for fields seeking to understand telomeres as a marker of psychosocial and environmental stress and a predictor of disease
  - Support innovative research efforts focused on key questions
  - Disseminate best practices

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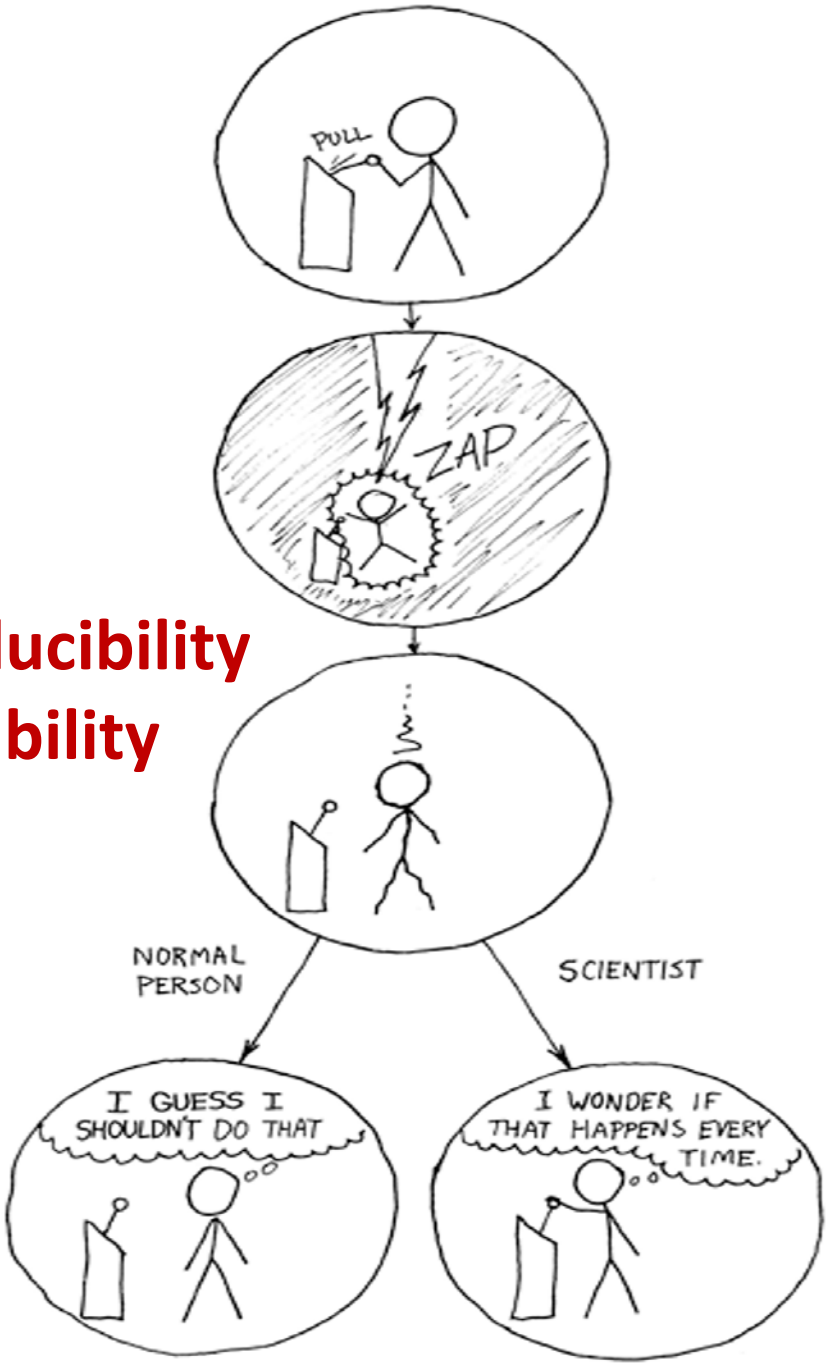
One goal- IMPACT

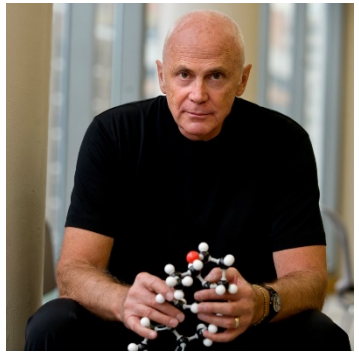
Reproducibility
Replicability



U24


Drury


Epel


McLachlan


Verhulst


Nielsen


Guo


Heacock

U01s


Aviv


Lin

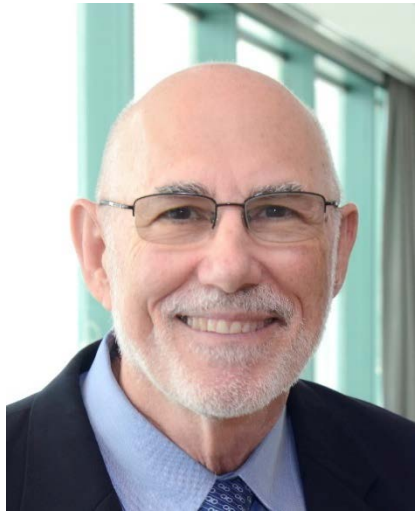
Shalev

Zheng

External Advisory Committee

Crimmins

Entringer



Shay

Eisenberg

Nettle

Belsky

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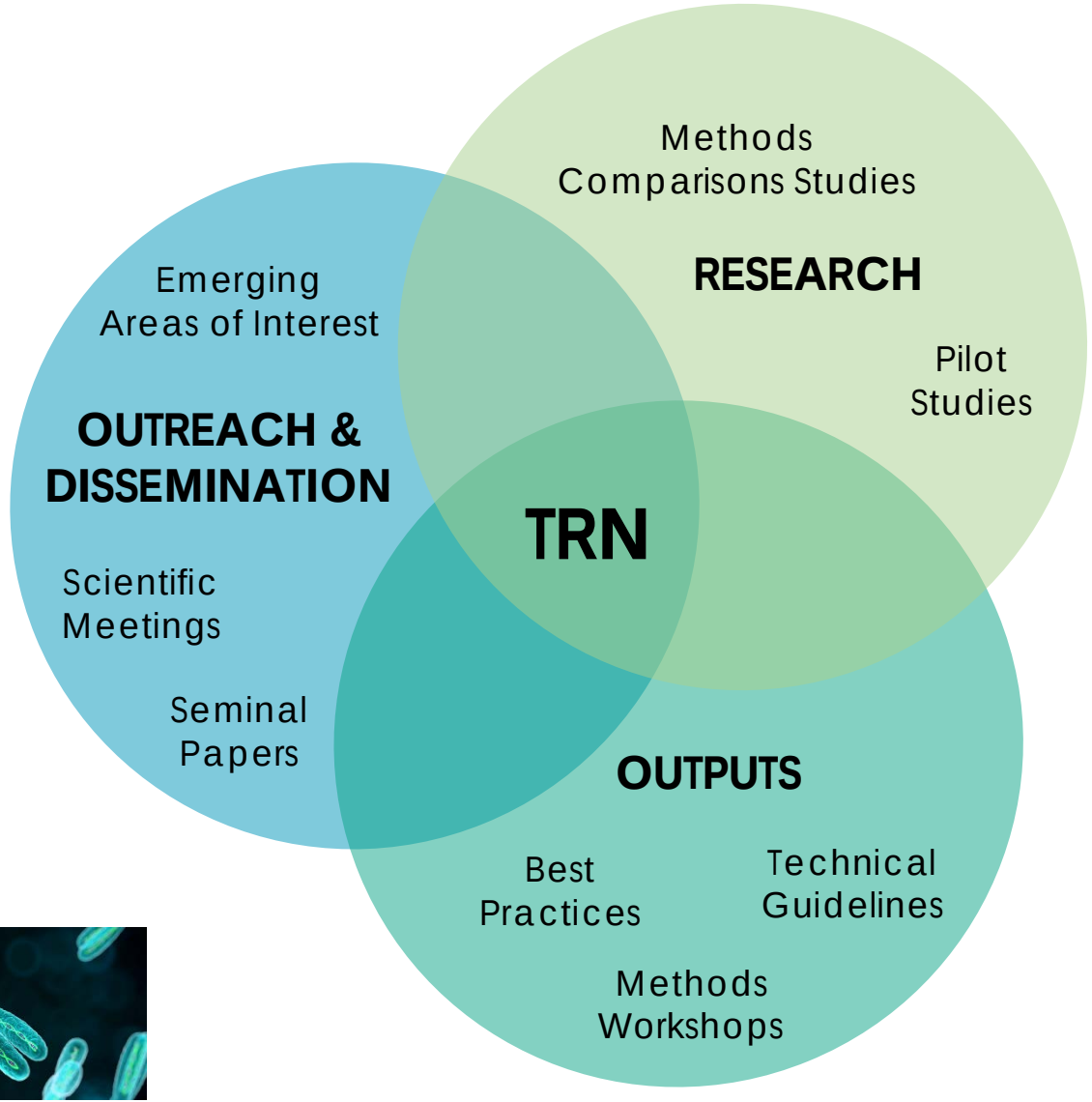
The practical pieces



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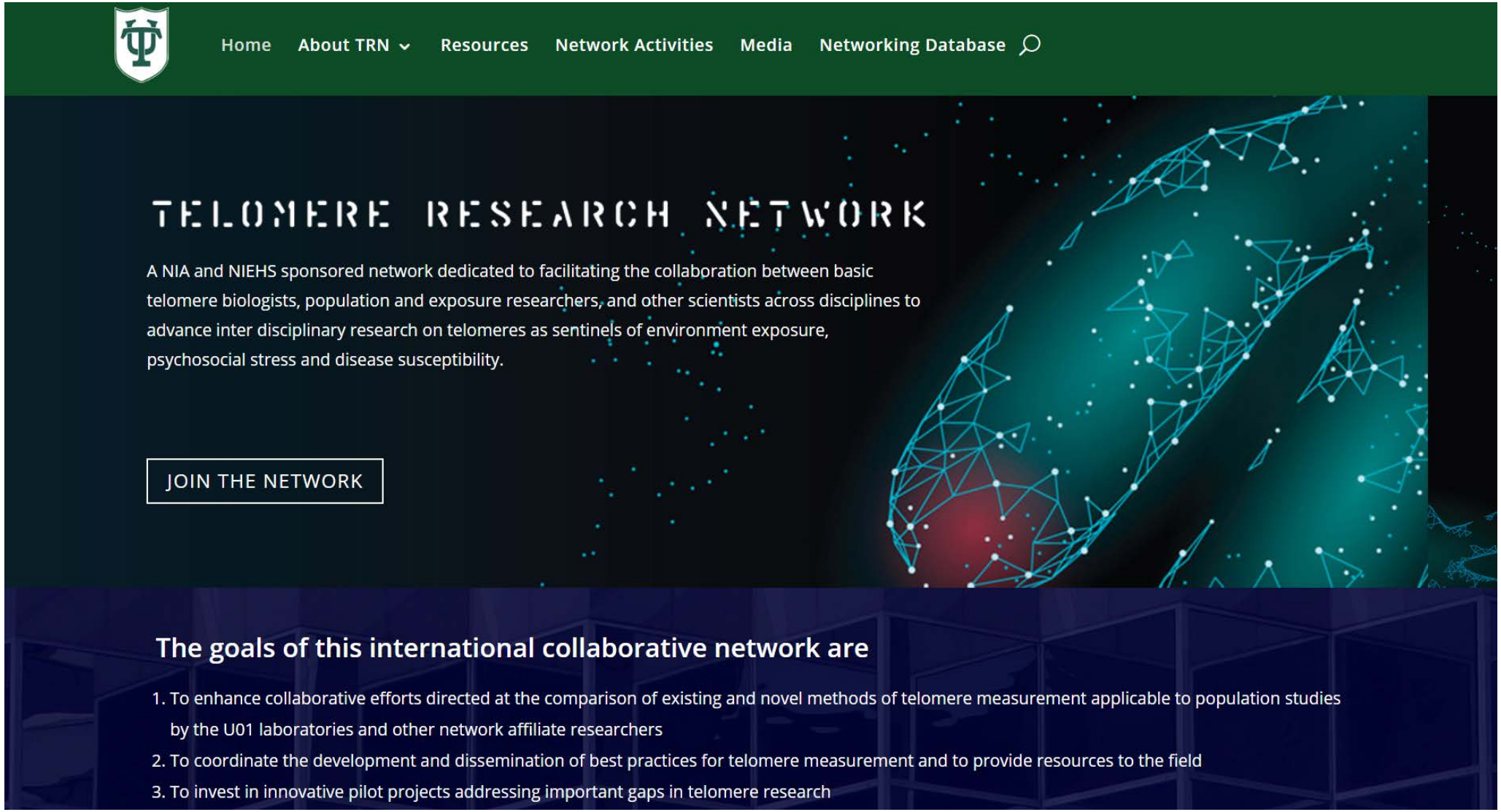
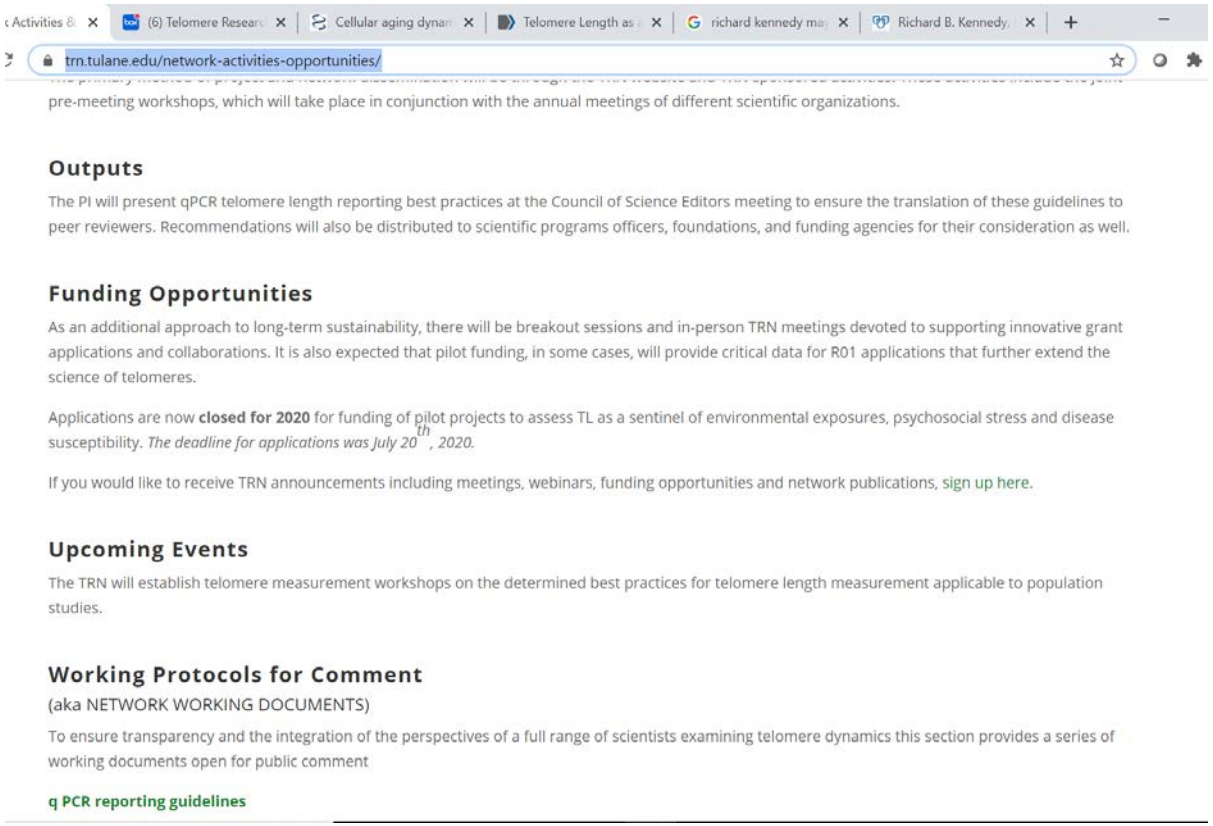
TRN website: trn.tulane.edu



TRN qPCR-based reporting recommendations



trn.tulane.edu/network-activities-opportunities/

pre-meeting workshops, which will take place in conjunction with the annual meetings of different scientific organizations.

Outputs

The PI will present qPCR telomere length reporting best practices at the Council of Science Editors meeting to ensure the translation of these guidelines to peer reviewers. Recommendations will also be distributed to scientific programs officers, foundations, and funding agencies for their consideration as well.

Funding Opportunities

As an additional approach to long-term sustainability, there will be breakout sessions and in-person TRN meetings devoted to supporting innovative grant applications and collaborations. It is also expected that pilot funding, in some cases, will provide critical data for R01 applications that further extend the science of telomeres.

Applications are now **closed for 2020** for funding of pilot projects to assess TL as a sentinel of environmental exposures, psychosocial stress and disease susceptibility. *The deadline for applications was July 20th, 2020.*

If you would like to receive TRN announcements including meetings, webinars, funding opportunities and network publications, sign up here.

Upcoming Events

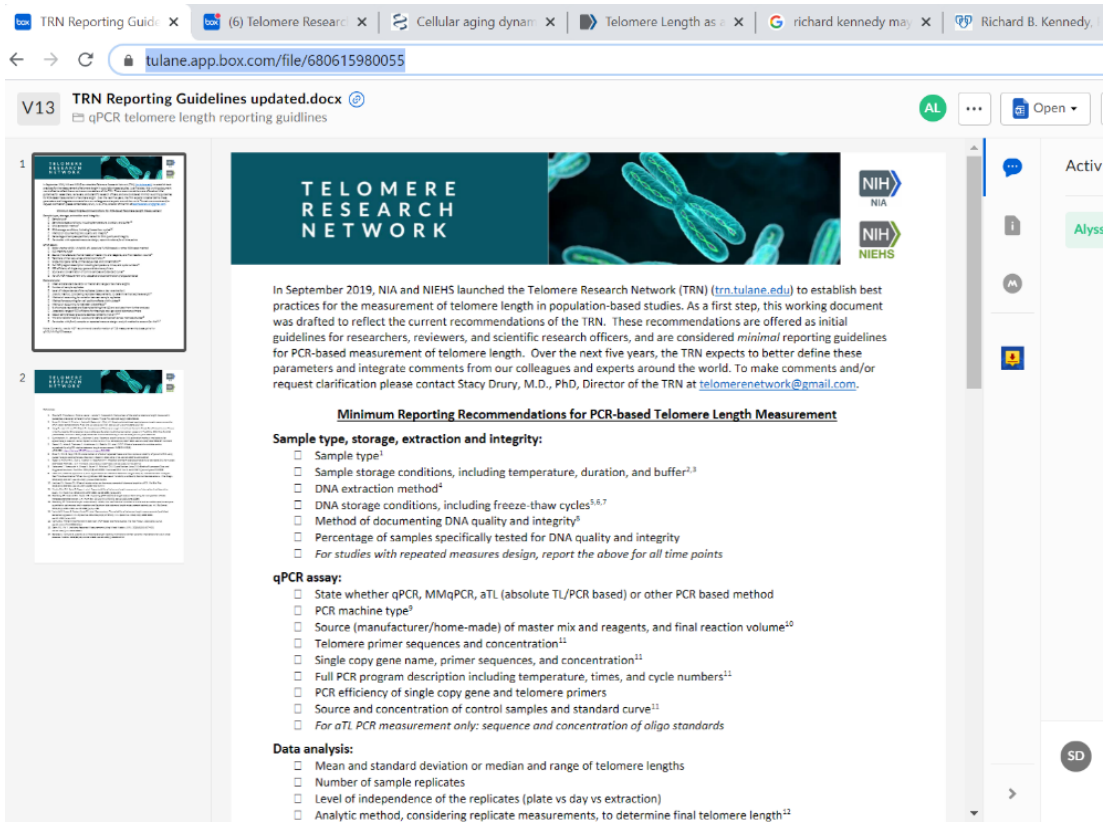
The TRN will establish telomere measurement workshops on the determined best practices for telomere length measurement applicable to population studies.

Working Protocols for Comment

(aka NETWORK WORKING DOCUMENTS)

To ensure transparency and the integration of the perspectives of a full range of scientists examining telomere dynamics this section provides a series of working documents open for public comment

q PCR reporting guidelines



tulane.app.box.com/file/680615980055

V13 **TRN Reporting Guidelines updated.docx**

qPCR telomere length reporting guidlines

TELOMERE RESEARCH NETWORK

In September 2019, NIA and NIEHS launched the Telomere Research Network (TRN) (trn.tulane.edu) to establish best practices for the measurement of telomere length in population-based studies. As a first step, this working document was drafted to reflect the current recommendations of the TRN. These recommendations are offered as initial guidelines for researchers, reviewers, and scientific research officers, and are considered *minimal* reporting guidelines for PCR-based measurement of telomere length. Over the next five years, the TRN expects to better define these parameters and integrate comments from our colleagues and experts around the world. To make comments and/or request clarification please contact Stacy Drury, M.D., PhD, Director of the TRN at telomerenetwork@gmail.com.

Minimum Reporting Recommendations for PCR-based Telomere Length Measurement

Sample type, storage, extraction and integrity:

- ☐ Sample type[1]
- ☐ Sample storage conditions, including temperature, duration, and buffer[2,3]
- ☐ DNA extraction method[4]
- ☐ DNA storage conditions, including freeze-thaw cycles[5,6,7]
- ☐ Method of documenting DNA quality and integrity[8]
- ☐ Percentage of samples specifically tested for DNA quality and integrity
- ☐ *For studies with repeated measures design, report the above for all time points*

qPCR assay:

- ☐ State whether qPCR, MMqPCR, aTL (absolute TL/PCR based) or other PCR based method
- ☐ PCR machine type[9]
- ☐ Source (manufacturer/home-made) of master mix and reagents, and final reaction volume[10]
- ☐ Telomere primer sequences and concentration[11]
- ☐ Single copy gene name, primer sequences, and concentration[11]
- ☐ Full PCR program description including temperature, times, and cycle numbers[11]
- ☐ PCR efficiency of single copy gene and telomere primers
- ☐ Source and concentration of control samples and standard curve[11]
- ☐ *For aTL PCR measurement only: sequence and concentration of oligo standards*

Data analysis:

- ☐ Mean and standard deviation or median and range of telomere lengths
- ☐ Number of sample replicates
- ☐ Level of independence of the replicates (plate vs day vs extraction)
- ☐ Analytic method, considering replicate measurements, to determine final telomere length[12]

NIH NIA

NIH NIEHS

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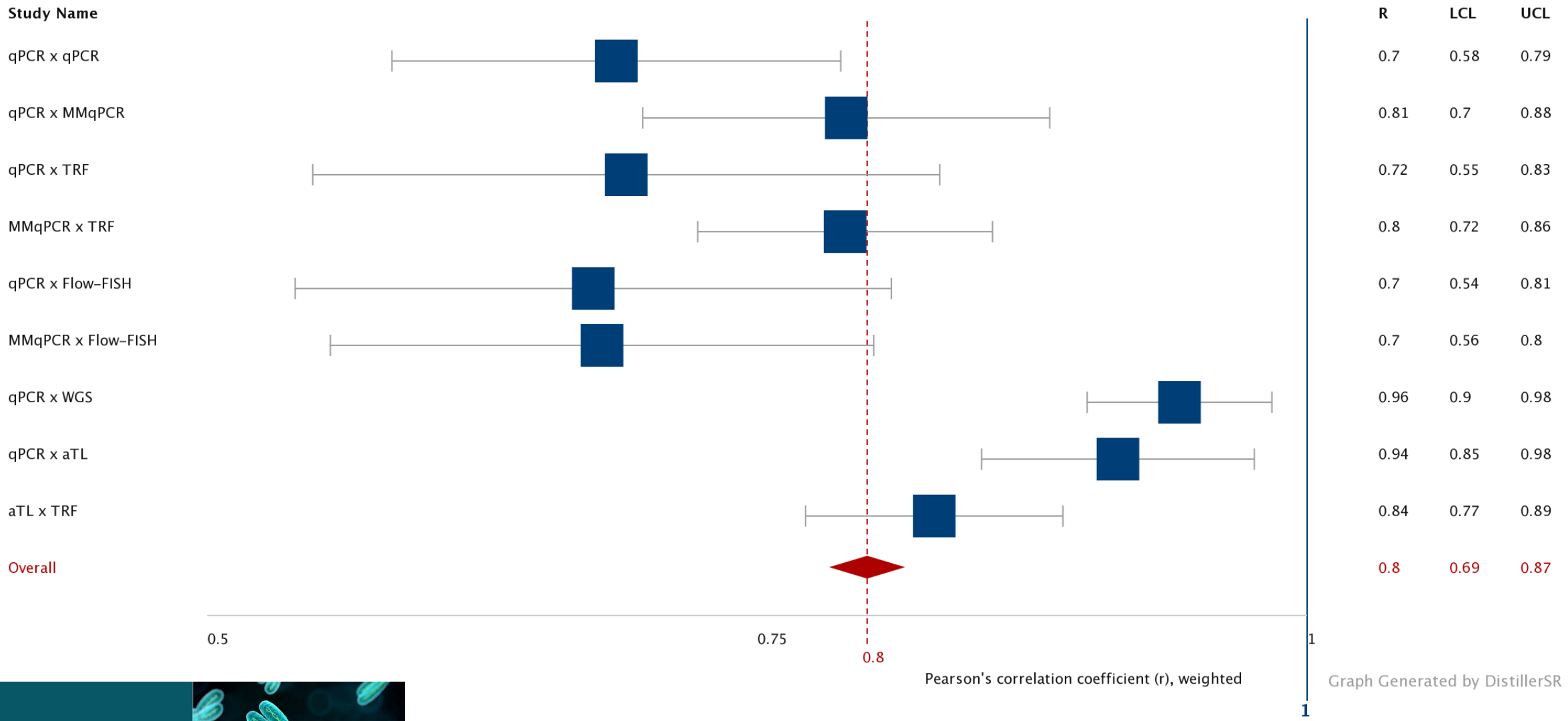
- ☐ Mean and standard deviation or median and range of telomere lengths
- ☐ Number of sample replicates
- ☐ Level of independence of the replicates (plate vs day vs extraction)
- ☐ Analytic method, considering replicate measurements, to determine final telomere length[12]
- ☐ Method of accounting for variation between sample replicates
- ☐ Method for accounting for well position effects within plates[12]
- ☐ Method of accounting for between plate effects[12]
- ☐ % of samples repeated and % samples failing final QC and excluded from further analyses
- ☐ Acceptable range of PCR efficiency for the single copy gene and telomere primers
- ☐ ICCs of sample/study groups to address variability (not CV)[13,14]
- ☐ T/S ratio transformed to a z score prior before comparison across methods/studies[15]
- ☐ *For studies with family samples or repeated measure design: analytic method to account for this*[16,17]

Note: Currently, we do NOT recommend transformation of T/S measurement to base pairs for qPCR/MMPqPCR assays.

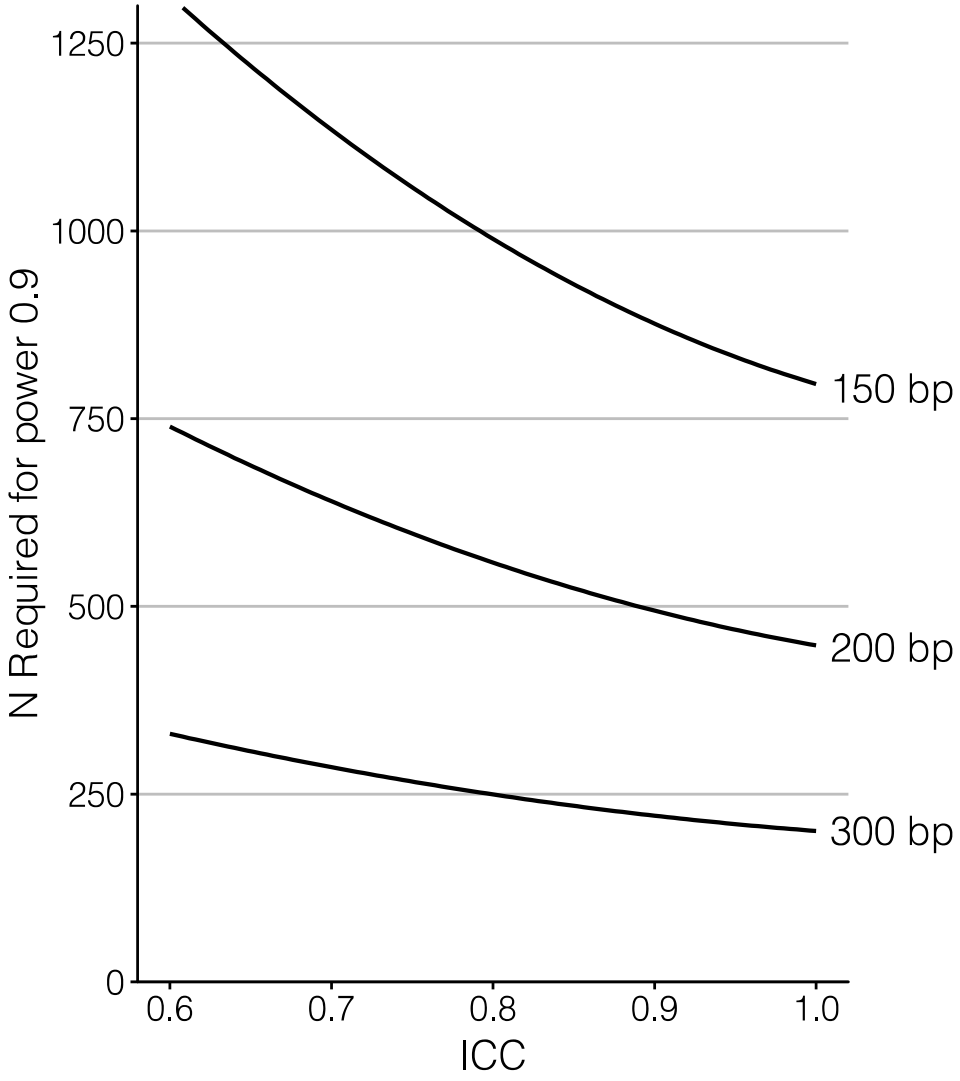
qPCR-based telomere length measurement
Reporting guidelines:
https://tulane.app.box.com/file/680615980055

Correlations of qPCR-based Comparisons



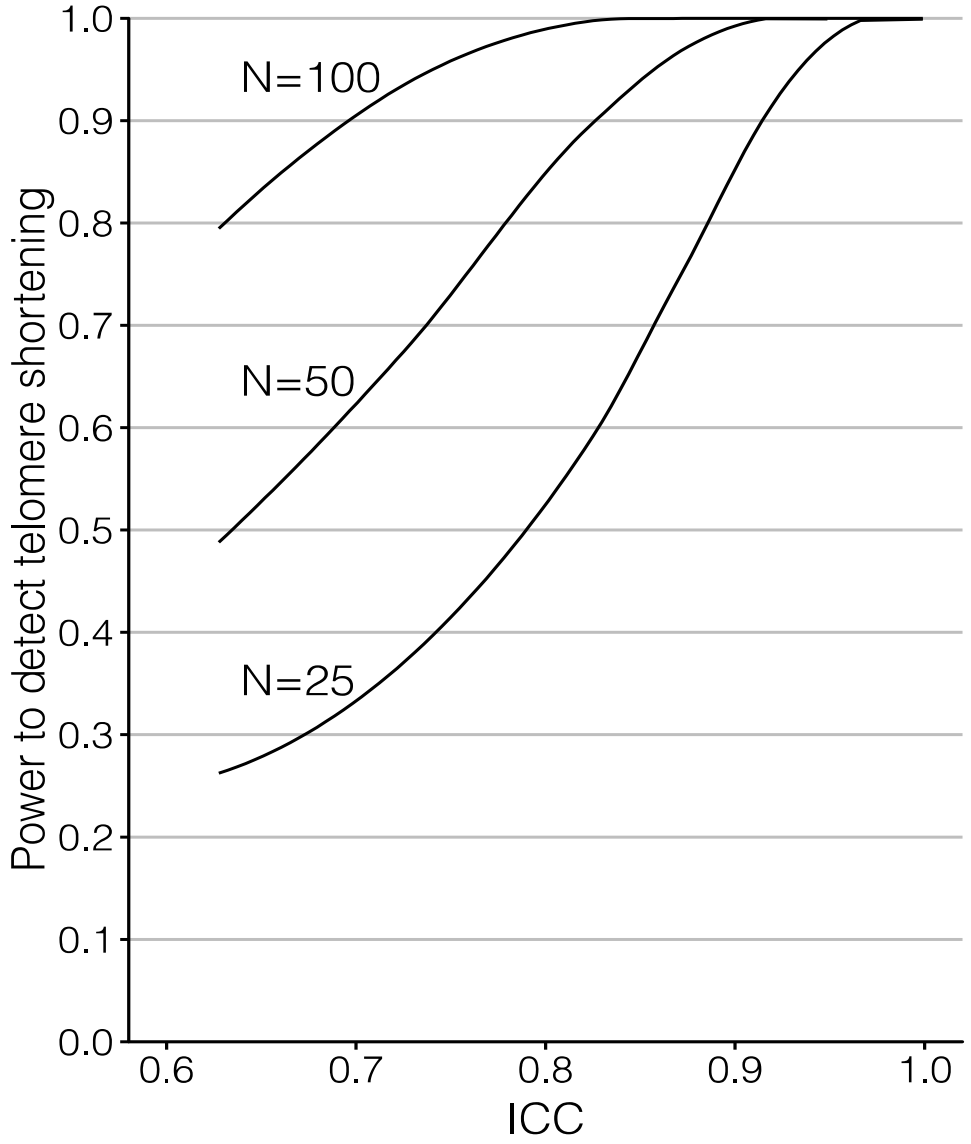
TELOMERE RESEARCH NETWORK

Lindrose et al *in preparation*



*The sample size required to test effect sizes of 150, 200 and 300 bp with a t-test with a power of 0.9, as a function of measurement error as expressed in the ICC (Intraclass Correlation Coefficient). To contextualize the differences: 150 bp is the approximate difference found between the sexes, and 300 bp is the approximate difference observed between individuals with and without atherosclerotic cardiovascular disease (e.g. Benetos et al 2018). Calculations assumed a realistic (true) standard deviation of 650 bp and power analysis was done using G*Power (Faul et al 2009). N is the combined n of the two groups to be compared and was assumed to be equally distributed among the two groups.*

Lindrose et al *in preparation*



Statistical power to detect a significant change (paired-t-test) in telomere length of 25 bp/year for sample sizes of 25, 50 and 100 individuals, and with an interval of 8 years between baseline and follow-up (i.e. on average 200 bp in total), as a function of measurement reliability expressed as the Intraclass Correlation Coefficient. Population SD of telomere length was assumed to be 0.65 kb at both time points and telomere shortening was simulated assuming a Poisson distribution with mean / variance of 25.

TELOMERE RESEARCH NETWORK

Lindrose et al *in preparation*

Methods comparison studies

- Determine the relationship between existing different TL assays, inter-assay variability, and the factors that influence results
- Development of best practice recommendations for assay protocols for TL measurement
- To provide data driven recommendations to enhance methodologic measurement precision for existing methods
- To support the development of new methods to enhance the use of TL measure

FOR POPULATION BASED HEALTH RESEARCH

TELOMERE RESEARCH NETWORK

Pilot awards

- Honorarium to support projects focused on important scientific questions in the telomere field as they apply to population-based studies
- Mentorship focused
- Travel support to attend TRN Annual Meeting in person (not required)
- Annual opportunity: 5 awards in 2020, 2021, and 2022
  - Deadline for 2021 applications will be January 11, 2021
- 2020 submissions
  - 27 applications
  - Funding 5 awards
  - Award recipients announced August 10, 2020

** All applicants invited to present August 27, 2020 or at future TRN webinars**

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Looking for epidemiologic cohorts

- TRN developing a common data model to support integration of data across large epidemiologic cohorts
- Accessible for combined data analyses
- Potential data analyses for pilot awards
- COVID telomere studies

- If you have a cohort or know of one to include:
  - Email telomerenetwork@gmail.com or
  - Belinda Needham at needhamb@umich.edu

Join the TRN email listserv or a committee

Home > Join the Network

Join a Committee

Interested in participating in a TRN subcommittee? CLICK HERE TO APPLY

TRN_stationery_art

Sign up for the TRN Listserv

Sign up below to receive TRN announcements including meetings, webinars, funding opportunities and network publications.

Get involved: participate in a subcommittee

- Identify important research gaps, establish best practices, and prioritize novel next steps in research in relation to each committee's specific topic
- Opportunities to network and collaborative with leaders in the field and shape future directions of telomere science
- Network funding may be requested for subcommittee pilot projects

TRN subcommittee areas

- Aging
- Early Life Development
- Cohorts/Epidemiology
- Cancer
- Population Study Design
- Biomarkers
- Environmental Exposures
- Animal Models

Other ways to get involved

- Comment on qPCR recommendations
  - Email telomerenetwork@gmail.com
- Become involved with the development of reporting recommendations for other methods
  - TRF
  - qFISH
  - Whole genome sequencing

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Other ways to get involved

- Become a partner laboratory to participate in method comparisons studies and pilot studies
  - Email telomerenetwork@gmail.com for more information

- Participate in upcoming **TRN public webinar**
  - **August 27, 2020 at 1pm EST**
  - Registration link on TRN webpage under “Network Activities”

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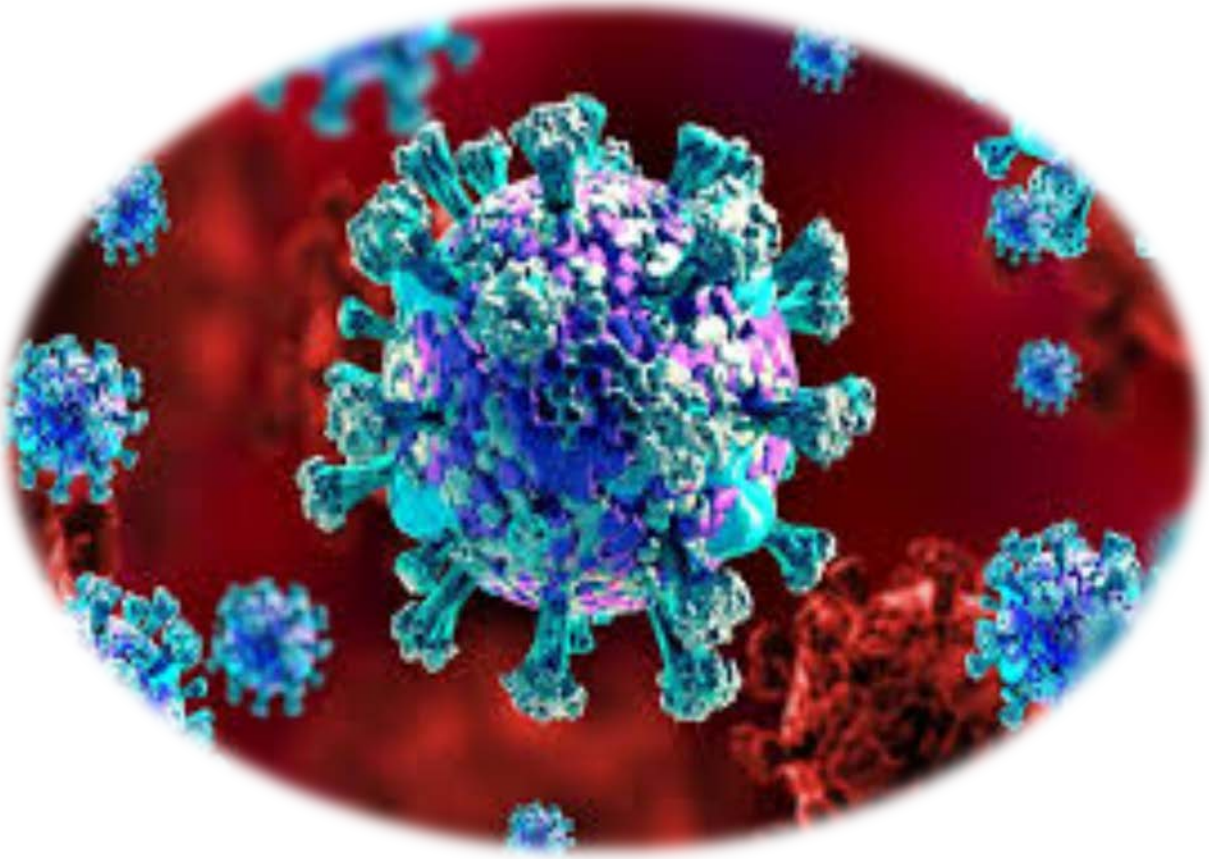
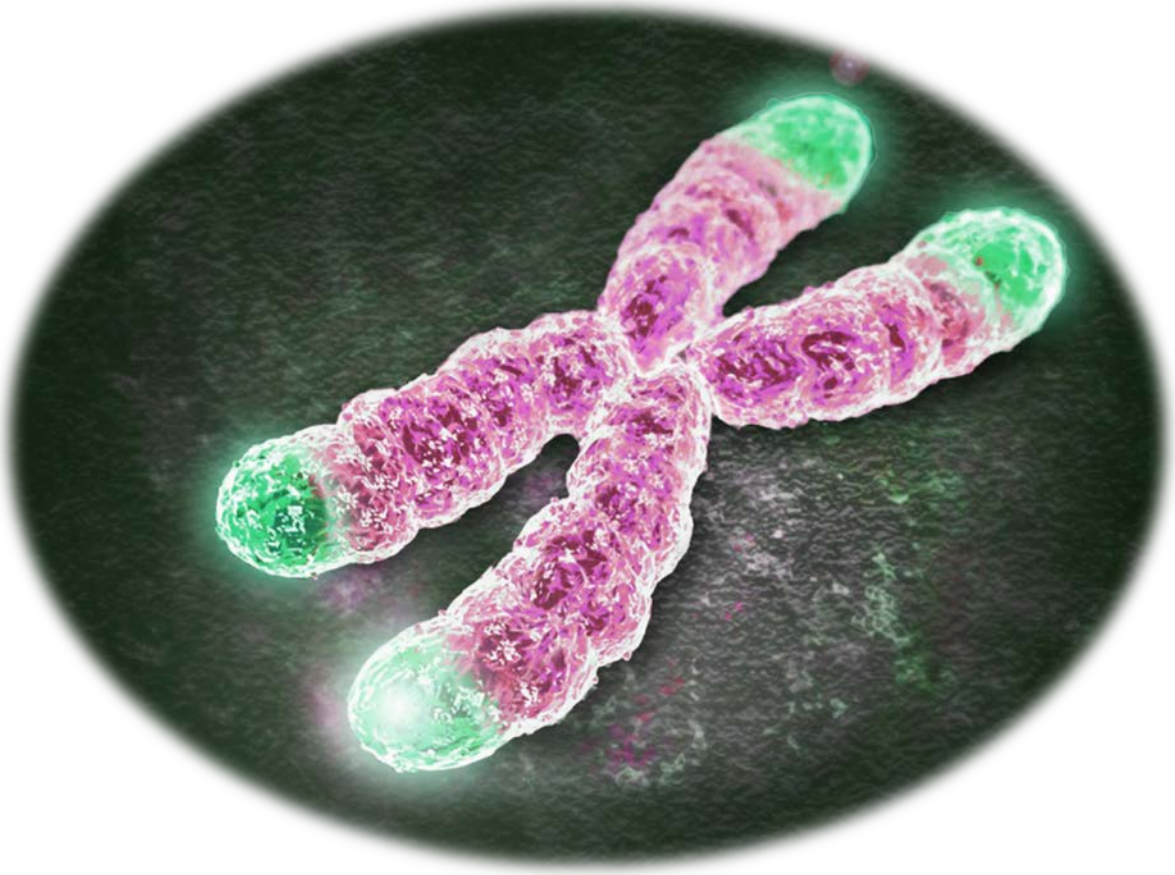
COVID-19 and telomeres





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Evidence of links between COVID and Telomeres

Health conditions linked to Telomeres

- Aging
- Diabetes
- Cardiovascular Disease
- Obesity
- Smoking

Health conditions linked to COVID

- Aging
- Diabetes
- Cardiovascular Disease
- Obesity
- Smoking

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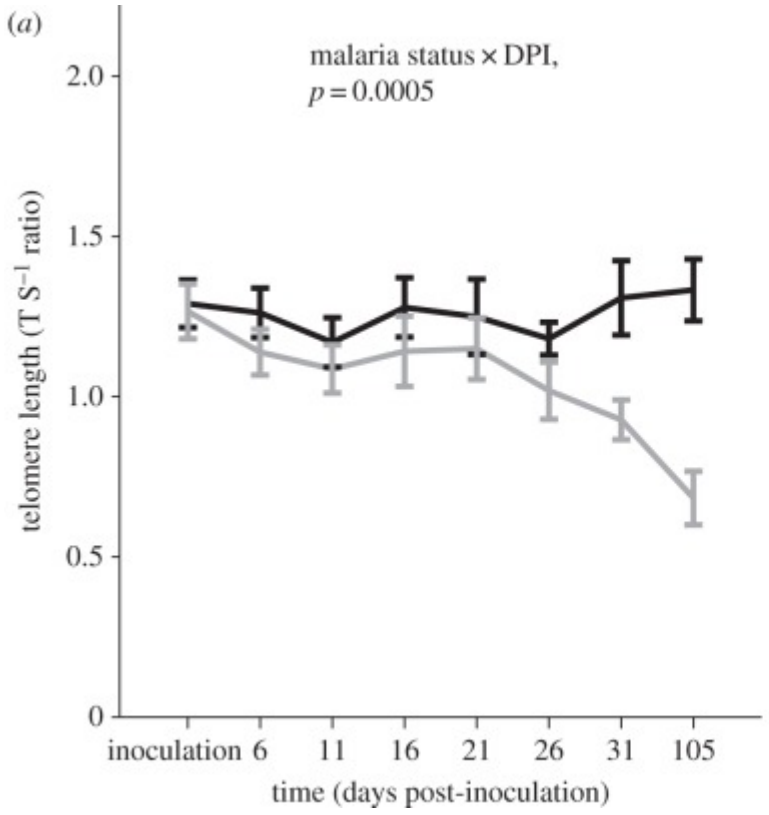
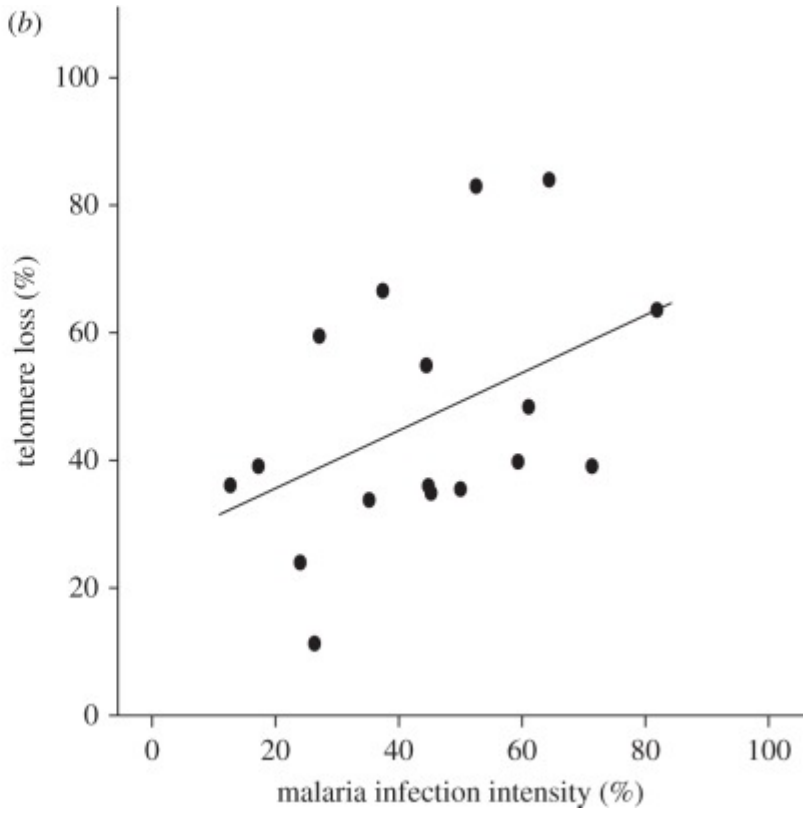
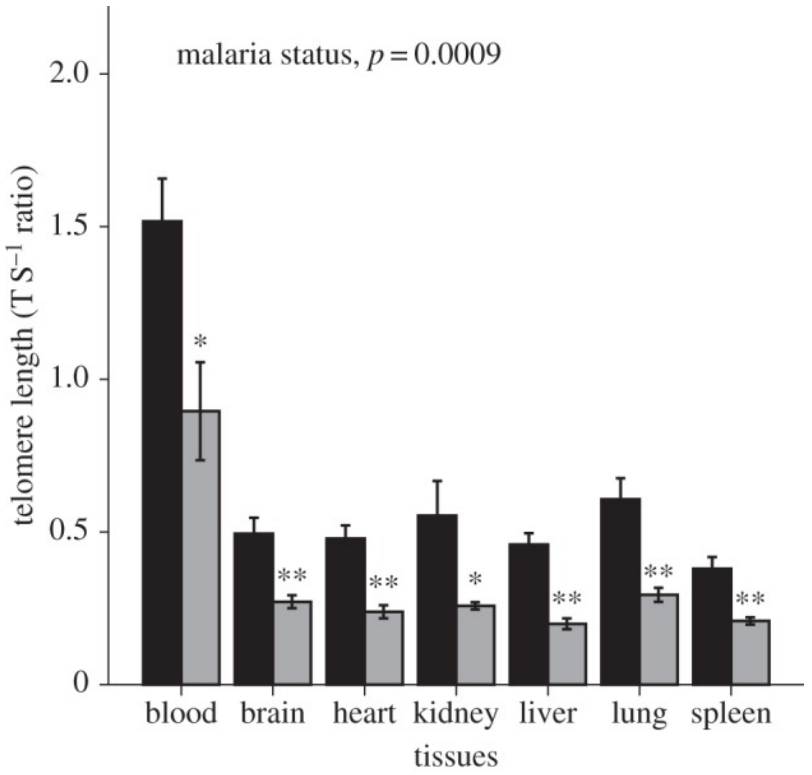
Chronic malaria infection and telomeres



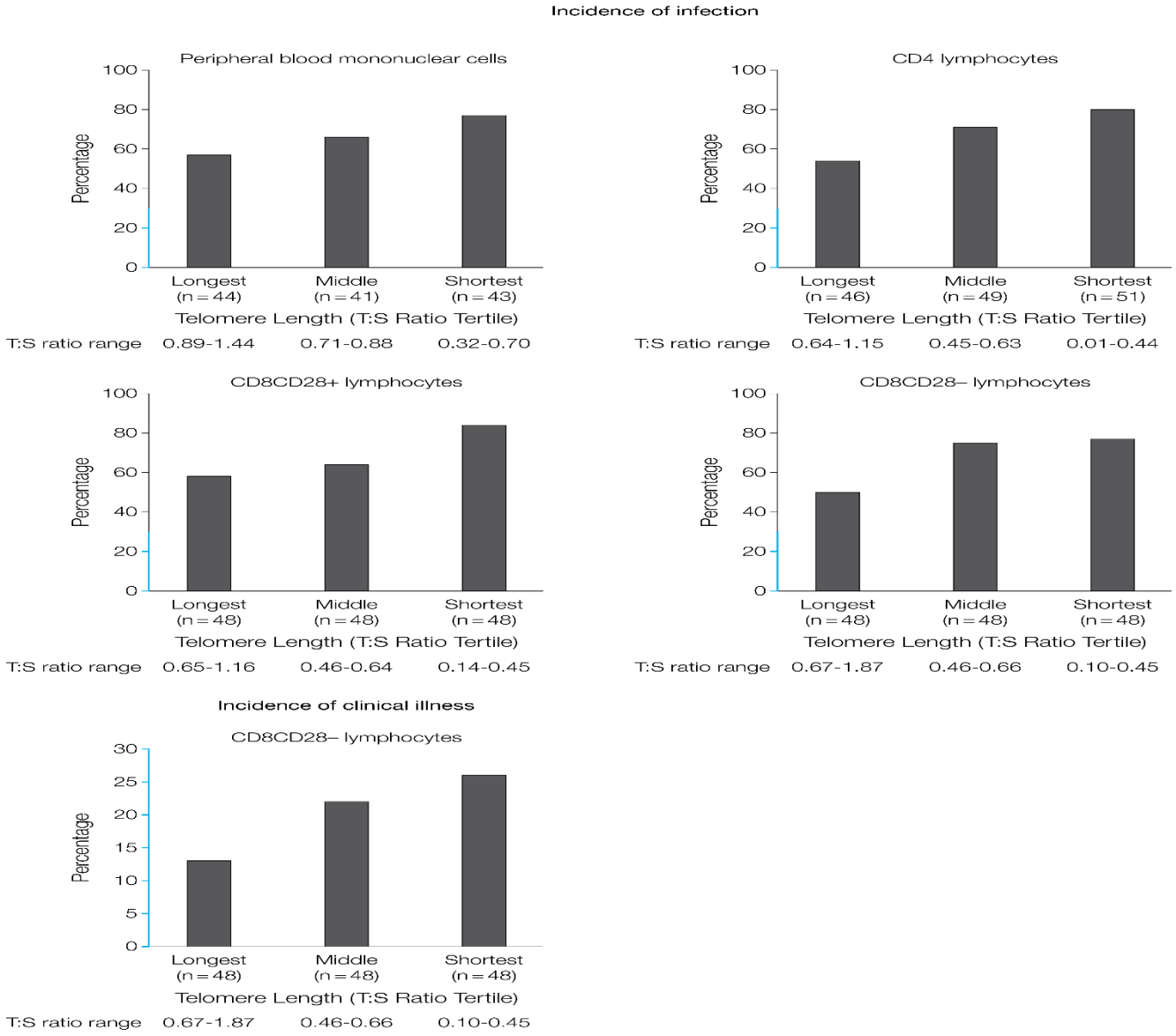




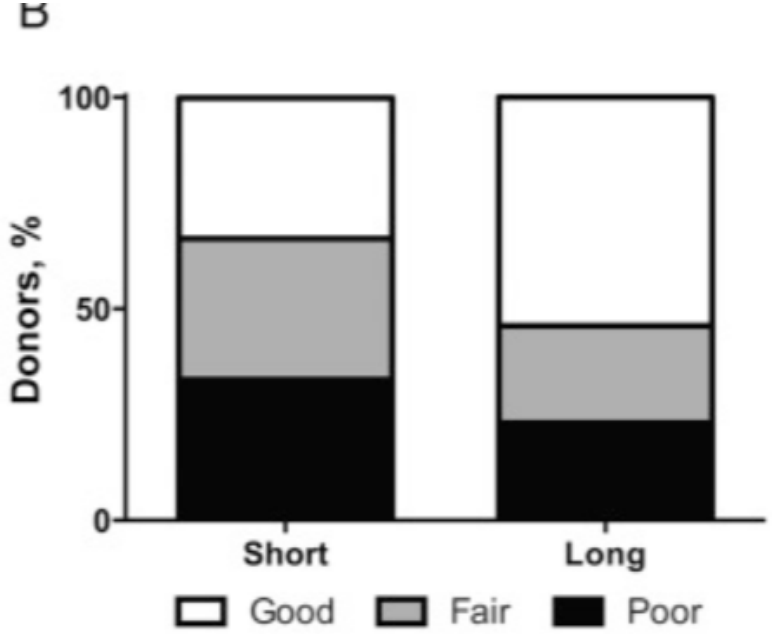
Ashgar et al 2016
https://royalsocietypublishing.org/doi/10.1098/rspb.2016.1184

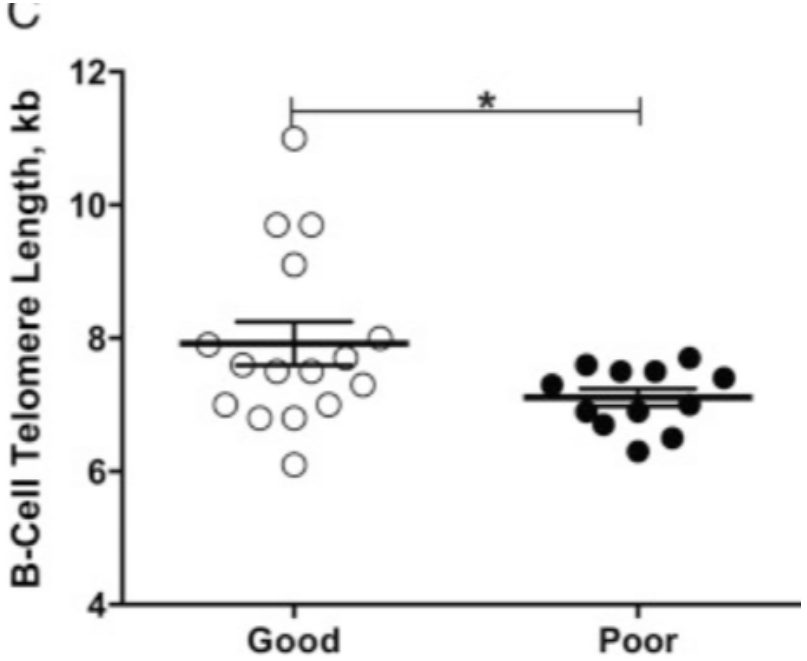
From: **Association Between Telomere Length and Experimentally Induced Upper Respiratory Viral Infection in Healthy Adults**

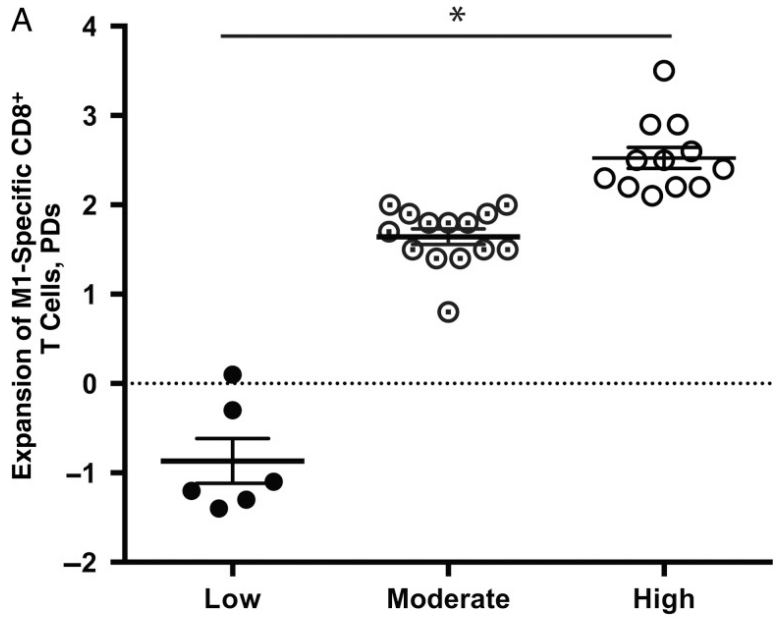
JAMA. 2013;309(7):699-705. doi:10.1001/jama.2013.613

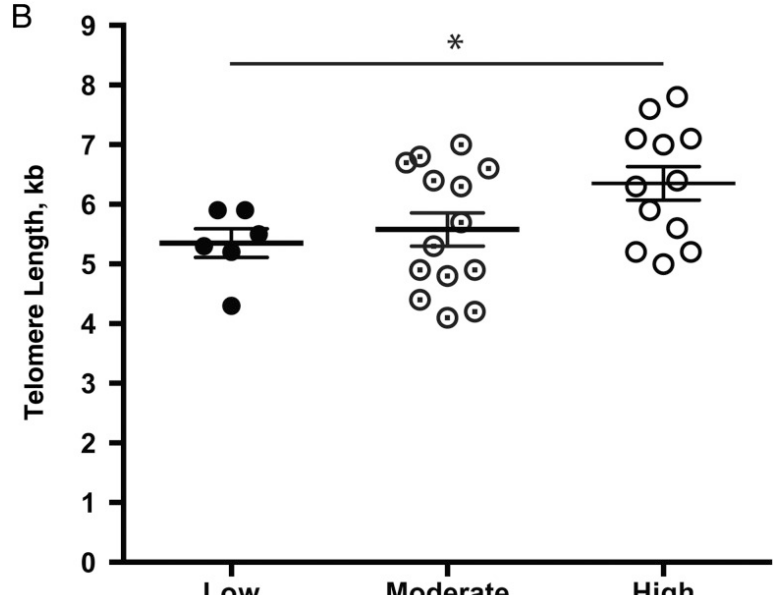


Influenza vaccine response and telomeres









Najaro et al 2015
https://academic.oup.com/jid/article/212/8/1261/2193104

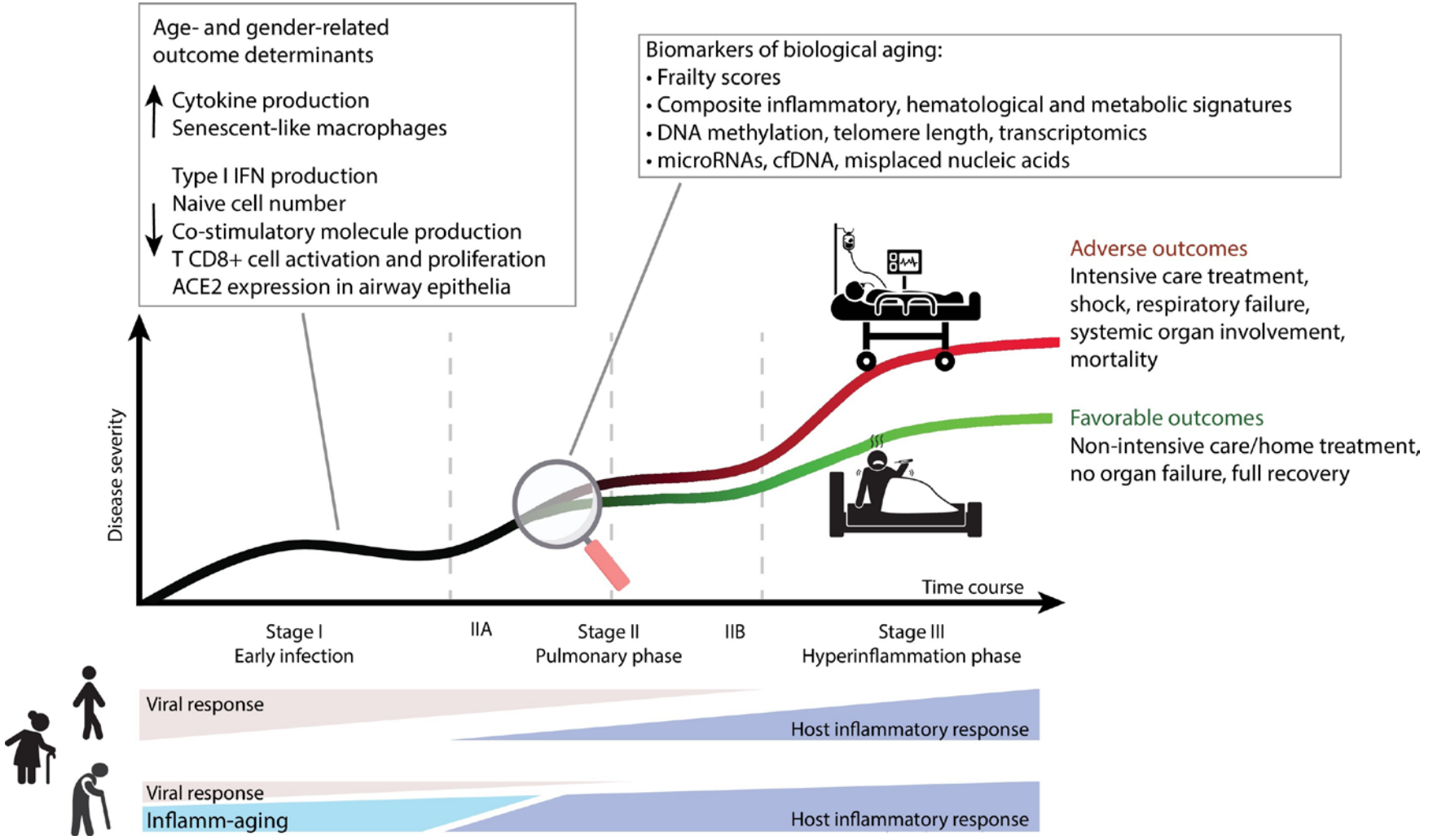
Additional ties between infection and TL

- Shorter TL and higher risk of infection in general population: http://www.haematologica.org/content/haematol/102/8/1457.full.pdf\
- Persistent Herpes infection and telomere attrition:https://academic.oup.com/jid/article/216/5/565/4004706

Telomere models to consider

- Inflammaging and lymphocyte depletion
- Specific disease models- autoimmune
  - Idiopathic Pulmonary Fibrosis
  - Lupus
- Sepsis risk
- Mitchondrial dysfunction/oxidative stress
- Some evidence of overlap in genetic risk factors

Inflammaging-attenuated T cell priming and interferon production
particularly in the alveolar macrophages and dendritic cells



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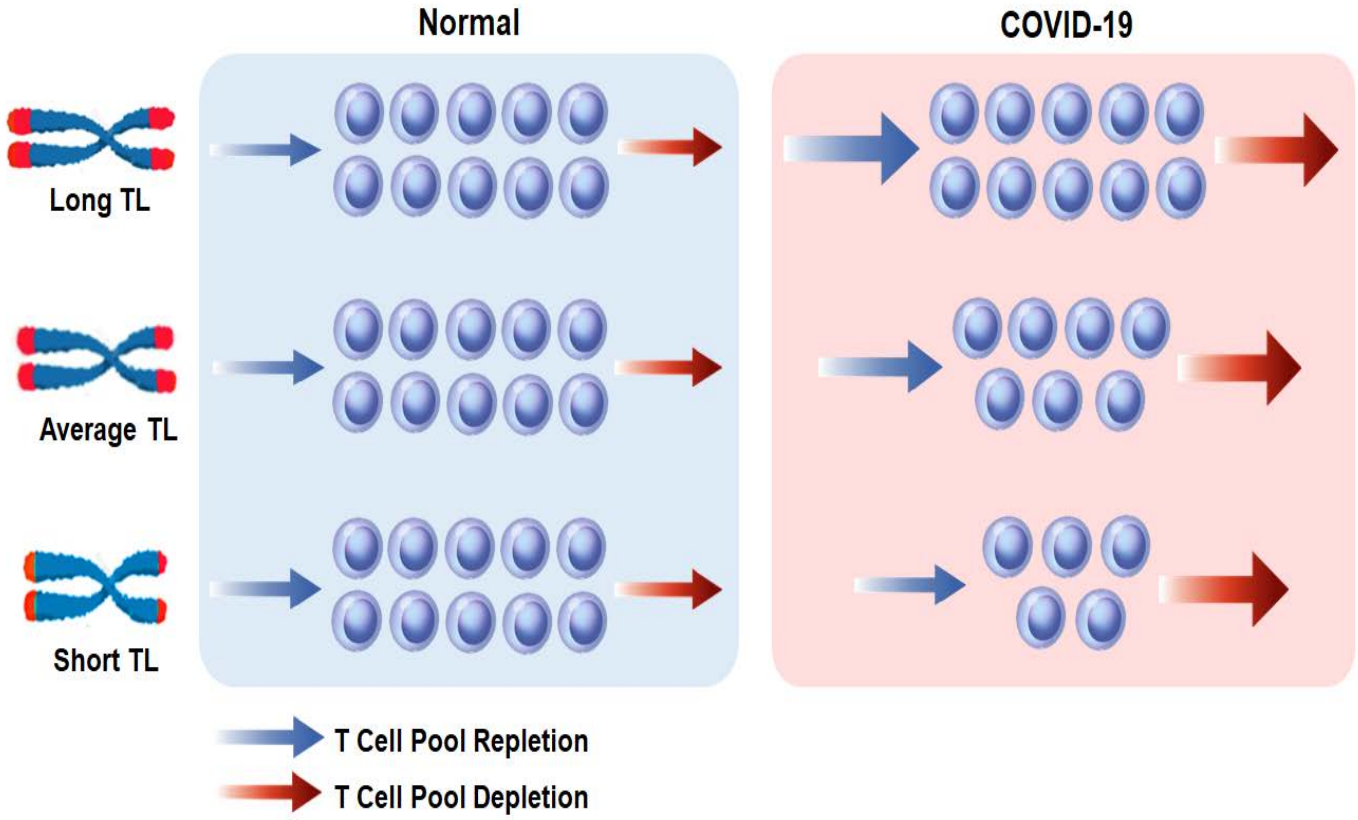

Repletion and depletion of the T cell blood pool under normal condition and COVID-19. Telomeres are displayed as red caps at the ends of the chromosomes.

Next steps

- COVID 19 and Telomeres: a scientific discussion of the different pathways by which telomere dynamics may be linked to COVID infection risk, disease outcome and vaccine response

- August 27, 2020- registration link on TRN webpage or email telomerenetwork@gmail.com

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Speakers

- **David Chae (Tulane)** TL predicting mortality in African American women with Lupus. Models linking Lupus and elevated COVID 19 risk, connecting these pathways

- **Paul Wolters (UCSF)** Telomeres and ties with sepsis and idiopathic pulmonary fibrosis, understanding pathways to severe COVID pathology in the lungs by links to IPF

- **Richard Kennedy (Mayo Clinic)** The role of inflammaging and vaccine response- consideration of multiple markers of inflammaging and understanding the mechanistic effects of these markers on vaccine response and relation to telomere length specifically.

Webinar and interactive discussion goals

- To identify high impact and important areas of research linking COVID to telomeres
- To foster interactive cross disciplinary discussion of the different models
- To develop research collaborations that can be supported by the TRN to assist in understanding the mechanisms and pathways to ending the COVID-19 pandemic
- To identify on-going projects where telomere data can be integrated into biologic sample collections either currently or sample collected for later analyses

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Thank you!

Contact:
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