Resident Research Proposal

Age is Just a Number: Biologic Age Versus Chronologic Age in Adult Spinal Deformity Surgery: A Prospective Cohort Study

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Significance

The prevalence of symptomatic adult spinal deformity (ASD) is increasing with the aging population. As one ages, physiological reserves are reduced, and the comorbidity burden increases.[6] The prevalence of complications related to ASD surgeries is as high as 60%.[1] Frailty is an measure of age-related physiological decline and is related to morbidity, mortality, and post-operative complications. The measure of biological age using DNA methylation may be superior to chronological age when interested in the physiologic effect of the passage of time. [7] Previous studies of biological age and chronological age have proposed that the disproportionate burden of age-related disease and risk of mortality of individuals of the same chronological are due to differences in biological age. [8] No studies investigating the relationship between chronological age and biological age exist in ASD. Furthermore, no studies exist investigating the relationship between biological age and complications and patient reported outcome measures (PROMS) after ASD surgeries. The data obtained from this study will inform future studies investigating patient-level factors associated with outcomes in the pursuit of personalized care pathways in ASD care.

Goals

Our long-term goal is to create personalized care pathways and risk stratification in the surgical management of ASD. The objective here, which is our next step in the pursuit of this goal, is to examine the correlation between biological age and chronological age. A second objective is to examine the relationship between biological age and perioperative complications and recovery from ASD surgery. Our central hypothesis is that biological age will show moderate correlation with chronological age and will have better predictive values for poor outcomes and slow recovery after ASD surgery. The rationale for the proposed research is that biological age more accurately reflects decline in function rather than the passage of time. Understanding the relationship between biological age and surgical outcomes will allow for the development of patient-specific protocols and pharmacologic targets to optimize results. We plan to test our central hypothesis with an observational cohort study of adults over 65 years of age undergoing surgical treatment of ASD with the following specific aims:

Hypothesis

Biological age will show moderate correlation with chronological age and will have stronger associations with poor outcomes and slow recovery when compared with chronological age after ASD surgery.

Specific aims

1. To determine the correlation between biological age and chronological age.

We hypothesize that biological age and chronological age will have a moderate correlation(r=0.6). To test this hypothesis, biological age will be calculated by two methods: (1) DNA methylation and (2) laboratory method of Cramer. Pearson correlations between these estimates and chronological age will be performed.

1. To examine the relationship between biological age and outcomes from ASD surgery. We hypothesize that biological age will have stronger associations with complications and PROMs than chronological age. To test this hypothesis we will track complications from intraoperative to 12 months postoperative. PROMS (PROMIS-CAT Physical Function, -Pain Interference, SRS-22r, Surgery Recovery Scale) will be collected at enrollment, 6 weeks, 12 weeks, 6 months and 12 months after surgery. Regression models will estimate the relationship between age measures and complication/PROMS after surgery.

The proposed study will establish the utility and importance of biological age measures in ASD care. These data will serve to support further grant support to develop personalized, preoperative protocols and risk stratification in ASD surgery.

Methods

DNA-Based Biological Age

Patients with adult spinal deformity over the age of 65 who will undergo spinal fusion will have single peripheral blood samples collected preoperatively. The Genome Technology Access Center McDonnell Genome Institute will isolate 1ug of high-quality genomic DNA form the whole blood samples. Genomic DNA is isolated using QIAamp DNA Blood Mini Kit (Qiagen), cat# 51104, per manufacturer protocol. DNA integrity is deter isolate 1ug of high-quality genomic DNA form the whole blood samples, mined using Agilent 4200 Tapestation.  500ng of high integrity genomic DNA is bisulfite-converted per manufacturer’s instructions using the EZ DNA Methylation kit (Zymo Research).  The full Methylation EPIC microarray assay is completed per manufacturer’s instructions utilizing the Illumina Inifinium HD system (Illumina). The Genome studio software will provide methylation b-values and raw data which includes chromosomal coordinates, percent GC, and locations in a CpG Islands. The division of statistical genetics will analyze the genomic data and calculate biological age using standard biological clock algorithm. Further end stream analysis will be performed to correlate CPG methyl sites to phenotypes and disease status.

Laboratory-Based Biological Age

Albumin, creatinine, glucose, c-reactive protein, lymphocyte, mean cell volume, red cell distribution width, alkaline phosphatase, and white blood cells will be measured from a single, preoperative peripheral blood sample. The biological age will be computed according to the method of Cramer.[9]

Clinical Followup

The patient will be followed in the standard intervals postoperatively at (6 weeks, 3 months, 6 months, and 1 year observing for postoperative complications. We will collect patient reported outcomes using the PROMIS-CAT Physical Function, -Pain Interference, SRS-22, and Surgery Recovery Scale. The postoperative outcomes and genomic data will be further analyzed to determine if there is a positive correlation with adverse postoperative outcomes and an increased biological age.

Sample Size Estimation

To determine moderate correlation, we use an r= 0.6, two-tailed alpha of 0.05, beta of 0.05 to derive a sample size of 30. Our second Aim is exploratory, though 30 should provide 8-12 complications for analysis versus 18-22 without

Experimental Design and Methods

Study Design: Prospective, observational cohort as a pilot study

Sample Size: 30 patients

Inclusion Criteria:

* Ages 65 and older
* Fluent English
* Undergoing spinal fusion for a diagnosis of adult spinal deformity of 8 level or more OR
* Any patient undergoing a three-column osteotomy (3CO, e.g., vertebral column resection, pedicle subtraction osteotomy) in the thoracolumbar spine

Exclusion criteria are:

* Patients with a history of or suspicion for tumor, infection, inflammatory arthropathy, or prior spinal cord injury
* Patients undergoing surgery for a diagnosis related to acute trauma
* Diagnosis of cancer within the last 5 years
* Psychiatric, immunological, and neurological conditions that would interfere with the collection and interpretation of study data
* Infectious disease within 30 days
* Renal, hepatic, cardiovascular and respiratory disease resulting functional impairment
* Arterial hypertension, diabetes mellitus, hypothyroidism, asthma

Description of the Recruitment Process

a. Subject selection will be equitable. No patient will be included or excluded on the basis of gender, race, religion, or sexual orientation. Refusal to participate in the study will not affect a patient’s access to care or surgical priority.

b. Description of where and how the study subjects will be recruited. Clinic for the PI will be prescreened to identify eligible patients prior to arrival. Upon presentation to the clinic eligible patients will be offered inclusion by a PI, collaborator, study coordinator, or IRB approved resident. Informed consent provided and obtained.

Description of the Informed Consent Process:

The PI, collaborator, or coordinator will inform all patients about the study during a preoperative clinic visit. There will be a detailed discussion with the patient regarding the aims of the study, as well as the potential risks and benefits of participation in the study. Aside for risks observed with standard of care, patients participating in this study are at no risk for complications related to the study. As a standard of care, we place central lines before surgery, which allows for easy access to blood in the postoperative period.

The procedures involved in maintaining privacy and confidentiality will be reviewed with them as outlined in the consent document to inform them that we will be collecting personal contact information from them. All personal information will be stored on a secure, password protected computer in the spine research center that will not be connected to a main network, so the Protected Health Information is not compromised. Either the principal or associate investigators will be responsible for obtaining informed consent.

Institutional Review Board Approval: Institutional Review Board approval from the Washington University School of Medicine is pending at this time. We anticipate no barriers to approval, as no interventions outside the standard of care are introduced.

**Projected cost**

1. Arrays/kits at $77/sample- $2310
2. Per-sample processing costs per batch size $20.15- $605
3. DNA extraction $15.5/sample- $ 465
4. DNA integrity QC on Tapestation- $4.00 per sample- $ 120
5. Genomic analysis- $50/sample- $1500
6. Estimated Total budget- $5000

Justification

The methyl array kits are needed to provide methylation b-values and raw data which includes chromosomal coordinates, percent GC, and locations in CpG Islands. Dr. Heinz at the Genome Technology Access Center McDonnell Genome Institute will isolate the DNA and run the methyl arrays to provide the needed data. Dr. Province at the Division of Statistical Genetics will analyze the genomic data and calculate biological age using standard biological clock algorithm. Further end stream analysis will be performed to correlate CPG methyl sites to phenotypes and disease status. The patients will be followed in the standard intervals postoperatively at 6 weeks, 3 months, 6 months, and 1 year observing for postoperative complications. The postoperative outcomes and genomic data will be further analyzed to determine if there is a positive correlation with adverse postoperative outcomes and an increased biological age. Dr. Kelly will cover the additional costs in excess of 10k.

Principle Investigator- Michael Kelly, MD

Purpose of the project/research question

Our long-term goal is to create personalized care pathways and risk stratification in the surgical management of adult spinal deformity (ASD). The objective here, which is our next step in the pursuit of this goal, is to examine the correlation between biological age and chronological age. A second objective is to examine the relationship between biological age and perioperative complications and recovery from ASD surgery. Our central hypothesis is that biological age will show moderate correlation with chronological age and will have better predictive values for poor outcomes and slow recovery after ASD surgery.

Impact that your project will have on the SRS mission, your career, or your specialty

This project embodies the mission of SRS in helping to improve optimal care provided to patients with spinal deformity. The rationale for the proposed research is that biological age more accurately reflects decline in function rather than the passage of time. Understanding the relationship between biological age and surgical outcomes will allow for the development of patient-specific protocols and pharmacologic targets to optimize results. Data, experience gained, and relationships fostered by this project are fundamental building blocks for my academic career. This project will help to improve patient outcomes in patients with adult spinal deformity and help to start my career as a physician scientist in orthopedics. The study also has implications that will improve spine deformity care but also could be used to improve care across other subspecialties.

Primary outcome measure of success

Biological age will show moderate correlation with chronological age and will have stronger associations with poor outcomes and slow recovery when compared with chronological age after adult spinal deformity (ASD) surgery. The proposed study will establish the utility and importance of biological age measures in ASD care. This data will serve to aid in further grant support to develop personalized, preoperative protocols and risk stratification in ASD surgery.

Abstract

The prevalence of symptomatic adult spinal deformity (ASD) is increasing with the aging population. As one ages, physiological reserves are reduced, and the comorbidity burden increases. The prevalence of complications related to ASD surgeries is as high as 60%. The measure of biological age using DNA methylation may be superior to chronological age when interested in the physiologic effect of the passage of time. No studies investigating the relationship between chronological age and biological age exist in ASD. Furthermore, no studies exist investigating the relationship between biological age and complications and patient reported outcome measures (PROMS) after ASD surgeries. DNA-based biological age and laboratory based biological age will be calculated using the method of Cramer and a standard biological clock algorithm. The postoperative outcomes and genomic data will be analyzed to determine if there is a positive correlation with adverse postoperative outcomes and an increased biological age. The data obtained from this study will inform future studies investigating patient-level factors associated with outcomes in the pursuit of personalized care pathways in ASD care.

Lay Summary- The presence of adult spinal deformity (ASD) is increasing as the as the general population ages. As one ages, the disease burden increases and the body’s ability to response to large changes in normal function decreases. The known complication rate related to ASD is as high as 60%. The measure of biological age may be superior to chronological age when interested in the change of normal functioning at a cellular level with the passage of time. No studies investigating the relationship between chronological age and biological age exist in ASD. Furthermore, no studies exist investigating the relationship between biological age and complications and patient reported outcome measures (PROMS) after ASD surgeries. DNA-based biological age and laboratory based biological age will be calculated using previously described techniques. The postoperative outcomes and cellular data will be analyzed to determine if there is a correlation with adverse postoperative outcomes and an increased biological age. The data obtained from this study will provide the groundwork in the pursuit of personalized care pathways in ASD care.

ROLE OF THE ORTHOPAEDIC SURGEON: Provide a statement, clarifying the role of the orthopaedic surgeon, stating significant part taken in the planning and/or execution of the design and analysis of data and time to be allocated to the project each week during the grant period, including percent of time and use of time. Simple technical roles such as obtaining tissue samples at surgery or providing patients for analysis are not generally considered to be substantial roles.

I will be involved in every aspect of this research project, from experimental design, patient enrollment, analysis, and manuscript preparation. Specifically, I will determine if patients are eligible based on the inclusion and exclusion criteria set forth in the experimental design. I will enroll the patient in the study and collect preoperative blood samples. I have developed and prepared this specific grant with counsel from my mentor Dr. Kelly. During the grant period, I have a dedicated 3 months of protected research time. One hundred percent of my time will be allocated to the project during that time. Prior to starting my research rotation, I plan to begin enrolling patients and collecting samples. This will allow maximum use of my dedicated research time for performing experiments and analyzing data. After my 3-month rotation, the percent of time allocated to the project will be significantly less and will mainly consist of data analysis and manuscript preparation. However, any remaining laboratory work can be completed on weekends and evenings as indicated, and my residency program is fully dedicated to allowing time for completion of this research project.

CAREER GOALS: Provide a statement describing your career goals, including a summary of past accomplishments in research, citing future research goals and how successful completion of this Research Grant will enhance your potential for future NIH or other large-scale funding.

My career goal is to establish myself as a true physician scientist, with active surgical and research practices. I have always been intrigued by the art of discovery —answers to the why, answers to the how, answers to the unanswerable. The desire to definitively improve someone’s life led me to orthopedic surgery. The skills needed to carry out the proposed study were developed during medical school while working in a basic science lab at Institute of Regenerative and Reparative Medicine in Augusta, GA. I have spent the last 5 years focusing my research on changes at the molecular level, specifically osteoarthritis. During this time, I learned that these vast changes occur at the molecular level due to various external elements. These various changes over time in our genome sparked my interest in biological age, and if there is any role in disease burden and postoperative outcomes. The idea that is we can look at changes on a genomic level to better understand the overall patient. Understanding the overall patient will help to risk stratify patients preoperatively, better optimize them for surgery, and develop personalized medicine to improves patient outcomes. The leadership and experience gained from my previous projects was invaluable and began to prepare me for the next step in my career.

I believe successfully securing research funding in the early stage of my career will be a key step to continuing the pursuit of my career goals. I envision building on this early research project by applying for a new investigator award during my chief year of residency and then for large-scale funding thereafter. I believe completion of this research grant will show my continued dedication to a career in research and has the potential to be a building block for future projects including studies investigating personalized medicine and improving patient outcomes.

I strive to be an orthopedic surgeon physician scientist. I am participating in research, clinical, and leadership opportunities to obtain this goal. I believe that completing this research grant will be an important step on the path to not only reaching my personal goals, but to improving patient care.

RELEVANCE OF THE PROJECT TO THE MISSION OF OREF: Provide a statement describing the relevance of the project to OREF’s mission.

This project is the embodiment of the Orthopedic Research and Education Foundation's mission to improve lives through orthopedic research. Establishing a patient specific marker to provide personalized medicine that improves patient’s outcomes has a significant chance to lead to future studies and possibly clinical trials. This project will also establish a new mentor/mentee relationship with Dr. Kelly and myself and has the possibility to foster further collaboration between our basic science, spine, sports medicine, trauma, and arthroplasty departments. Furthermore, this project will provide a strong foundation for my research career. Data and experienced gained from this study could prove to be crucial in securing my next level faculty position and funding. In summary, this project will provide the framework for improving patient lives, encourage scientific collaboration, and help start my career as a physician scientist in orthopedic surgery, the very goal of the Orthopedic Research and Education Foundation.

SPECIALTY SOCIETY RELEVANCE: Please describe how your research applies to and ultimately benefits any orthopaedic societies. Does your research apply particularly to any orthopaedic society/ies? If yes, please specify. In what way would this work ultimately benefit those specialties?

I believe that this research could apply to multiple orthopedic societies and could potentially benefit several specialties. This project most specifically benefits the Scoliosis Research Society in helping to improve optimal care provided to patients with spinal deformity. The rationale for the proposed research is that biological age more accurately reflects decline in function rather than the passage of time. Understanding the relationship between biological age and surgical outcomes will allow for the development of patient-specific protocols and pharmacologic targets to optimize results. This project will help to improve patient outcomes in patients with adult spinal deformity. The study also has implications that will improve spine deformity care but also could be used to improve care across other subspecialties. The data collected, patient-specific protocols and pharmacologic targets during this study are far reaching. Postoperative outcomes are an important measure of a successful surgery across all subspecialties. The patient-specific protocols and pharmacologic targets designed to optimize postoperative outcomes from this study will be the framework to improve outcomes in Recon, Foot and Ankle, Hand surgery, and Sports Medicine. The patient populations may differ between subspecialties, but the overall goal is to improve patient lives. Reduction of adverse postoperative outcomes in arthroplasty secondary to patient specific optimization can have a drastic impact on the financial burden associated with reoperation and hospitalization. This is one small example, but we can look at the vast majority of non-emergent orthopedic procedures and determine how we can better optimize our patients to improve outcomes.

STATEMENT ON DIVERSITY: OREF recognizes a unique and compelling need to promote diversity in the biomedical, behavioral, clinical, and social sciences research community. We encourage efforts to diversify the workforce to lead to the recruitment of the most talented researchers from all groups; to improve the quality of the educational and training environment; to balance and broaden the perspective in setting research priorities; to improve the ability to recruit subjects from diverse backgrounds into clinical research protocols; and to improve the capacity to address and eliminate health disparities. Address diversity issues to include racial and ethnic groups, gender and age, disabilities, and disadvantaged backgrounds, if applicable.

Healthcare disparities remain a major concern in orthopedics and all of medicine. Studies have shown that many health disparities seen in orthopedics are multi-factorial. Socioeconomic factors and healthcare access are important factors. Some studies have shown that nonwhite patients are less likely to undergo orthopedic procedures and when they do there is a higher associated complication rate. This project provides the framework to investigate if there is a biological difference that is associated with this disparity in outcomes. Which could provide evidence how to further optimize this patient population to reduce adverse outcomes.

Resources

The methyl array kits are needed to provide methylation b-values and raw data which includes chromosomal coordinates, percent GC, and locations in CpG Islands. These are easily purchased and there is no barrier to obtaining the methyl arrays. Dr. Heinz at the Genome Technology Access Center McDonnell Genome Institute, which is on the Washington University campus, will isolate the DNA and run the methyl arrays to provide the needed data. The lab specializes in use of methyl arrays to obtain the data that we will need in the study. He has set forth the fees associated with purchasing the arrays and running the experiments to collect the data. The lab has all the necessary equipment to run the studies without any need of outside resources. Dr. Province, at the Division of Statistical Genetics on the Washington University campus will analyze the genomic data and calculate biological age using standard biological clock algorithm. Further end stream analysis will be performed to correlate CPG methyl sites to phenotypes and disease status. The patients will be followed in the standard intervals postoperatively at 6 weeks, 3 months, 6 months, and 1 year observing for postoperative complications. The postoperative outcomes and genomic data will be further analyzed to determine if there is a positive correlation with adverse postoperative outcomes and an increased biological age. The lab has all the necessary equipment to run the genomic analysis without any need of outside resources. The spine facility at Washington University have agreed to assist in enrolling patients into the study.

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Reference

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