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Protocol for the San Diego Nathan Shock Center Clinical Cohort: a new resource for studies of human aging

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ABSTRACT

Introduction While it is well recognised that aging is a heterogeneous process, our understanding of the determinants of biological aging and its heterogeneity remains unclear. The San Diego Nathan Shock Center (SD-NSC) Clinical Cohort aims to establish a resource of biospecimens and extensive donor clinical data such as physical, cognitive and sensory function to support other studies that aim to explore the heterogeneity of normal human aging and its biological underpinnings.

Methods and analysis The SD-NSC Clinical Cohort is composed of 80 individuals across the adult human lifespan. Strict inclusion and exclusion criteria are implemented to minimise extrinsic factors that may impede the study of normal aging. Across three visits, participants undergo extensive phenotyping for collection of physical performance, body composition, cognitive function, sensory ability, mental health and haematological data. During these visits, we also collected biospecimens including plasma, platelets, peripheral blood mononuclear cells and fibroblasts for banking and future studies on aging.

Ethics and dissemination Ethics approval from the UC San Diego School of Medicine Institutional Review Board (IRB #201 141 SHOCK Center Clinical Cohort, PI: Molina) was obtained on 11 November 2020. Written informed consent is obtained from all participants after objectives and procedures of the study have been fully explained. Congruent with the goal of establishing a core resource, biological samples and clinical data are made available to the research community through the SD-NSC.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The San Diego Nathan Shock Center Clinical Cohort will provide a novel resource to support studies focused on biological aging and its heterogeneity.
⇒ Our deep phenotyping approach covers multiple domains of human aging, ranging from cellular and molecular markers to clinical and physiological outcomes.
⇒ Strict inclusion and exclusion criteria to support the focus normal human aging.
⇒ Sample size is reflective of an approach that involves intensive deep phenotyping of each participant.

INTRODUCTION

The belief that chronological age can adequately serve as a measure of aging and health status has been broadly rejected due to the well-recognised fact that the aging process is highly heterogeneous. It is clear that individuals age at different rates, and that people who share the same chronological age can have vastly different burdens of various age-related diseases and conditions.[1 2] Even at the tissue and cellular level, the impacts of advancing age can be vastly different, indicating that cellular and molecular phenotypes associated with aging likely underlie differences in biological age between individuals of the same or similar chronological age.[3 4] Epigenetic clocks, for example, are one of the best indicators of biological age among individuals of the same chronological age.[5–7] Further, epigenetic differences can be observed between different cell types of the same individual.[8] Thus, there is a need to better understand the drivers of 'biological age' and to develop a range of biomarkers that can better reflect health status beyond the number of years lived. Although no universal methodology for calculating or identifying biological age exists, most models encompass a multifaceted approach, incorporating some combination of physical, physiological or biochemical measures of functional capacity.[9–11] Since age remains a major risk factor for multiple conditions, it is imperative to tease apart and understand these multidimensional determinants of biological aging.

Previous large-scale lifespan cohorts have been designed with the goal of understanding human aging heterogeneity. For instance, the Baltimore Longitudinal Study of Aging (BLSA), conducted by the Intramural Research Program of the National Institute on Aging, enrolled over 3000 individuals and continues to collect a multitude

of clinical and functional measurements to characterise normal aging. In fact, much of the data gathered from this cohort has contributed to the understanding of aging as a heterogeneous process.[12] The Rancho Bernardo Study (RBS) of Healthy Aging began in 1972 as a heart disease risk factor screening survey of over 80% of residents in the Rancho Bernardo suburb of San Diego, California, USA. Measurements of the cohort expanded over the years to include other physical, cognitive and sensory measures, with the focus shifting towards better understanding various diseases associated with older age including cardiovascular disease, diabetes and reduced cognitive function.[13 14] While these longitudinal cohorts excel at tracking and identifying changes that occur over the aging process, they were not specifically designed to support further studies examining the basic biology of human aging.

The objective of the San Diego Nathan Shock Center (SD-NSC) Clinical Cohort is to support and facilitate studies that seek to provide deeper, mechanistic insights into the physiological and biochemical domains of aging. We designed the SD-NSC Clinical Cohort to be a resource that supports other studies of the heterogeneity of biological aging; we have neither an a priori research question nor a data analysis plan. Our primary goal is to generate and provide primary cell models of aging obtained from the 80 SD-NSC Clinical Cohort participants representing a span of adult chronological ages, starting at 20 years of age, with no predetermined upper bound. These 80 cell lines, coupled with extensive donor phenotyping focused across multiple domains—including physical, cognitive and sensory function and mental health—will comprise the bulk of our resource which also includes other biospecimens such as blood cells, plasma, serum and inducible-ready cells. The generation of human cell models of aging that are matched with multidomain indicators of healthspan will provide a rich resource for future studies aimed to advance our collective understanding of the biological drivers underlying the heterogeneity of human aging.

METHODS AND ANALYSIS

The San Diego Nathan Shock Center

The SD-NSC involves three San Diego research institutions, the Salk Institute for Biological Studies (Salk), Sanford Burnham Prebys Medical Discovery Institute (SBP) and the University of California, San Diego (UCSD). Each institution comes equipped with long histories of research into the basic biology of aging and exemplary expertise and resources. The SD-NSC comprises three innovative research resource cores: the Human Cell Models of Aging Core (Human Cell Core), the Heterogeneity of Human Aging Core (Heterogeneity Core) and the Integrative Models of Aging (Modelling Core).[15] The SD-NSC Clinical Cohort is a key component of the Human Cell Core and provides the clinical data and biospecimens collected from individuals spanning the human adult lifespan. Recruitment began in July 2021, and we expect recruitment and assessment to continue until May 2025.

Cohort design

The ongoing SD-NSC Clinical Cohort consists of 80 adults with data collected across three in-person visits and one virtual appointment via phone call as summarised in table 1. Because we have neither an a priori research question nor data analysis plan, there is no power calculation to support this sample size. We decided to enrol 80 participants to fulfil an even distribution of our target age brackets—20 individuals aged 20–40 years, 20 individuals 41–60 years, 20 individuals 61–80 years and 20 individuals 80+.

All visits take place on the campus of UCSD at the Exercise and Physical Activity Resource Centre (EPARC), a state-of-the-art equipped facility specifically designed to conduct deep phenotyping of physical activity (PA) and

Table 1 Summary and timeline of the SD-NSC Cohort recruitment and assessment visits

	Timeline				
Activity/assessment	**Pre**	**0 week**	**1 week**	**3 weeks**	**2 years**
Phone eligibility screening	X				
Informed consent, review inclusion/exclusion criteria, medications, vitals, anthropometrics, blood draw (complete blood count and bioenergetics), resting metabolic rate, dual-energy X-ray absorptiometry scan, BioDex		X			
Six min walk test, 2.5 min indoor free-living walk, cardiopulmonary exercise testing, Peak VO_2, grip strength, expanded short physical performance battery, skin punch biopsy, wireless accelerometer distribution, spirometry, medical history, activity and sleep questionnaires			X		
Skin biopsy follow-up and removal, return wireless accelerometer, cognitive and sensory assessments, muscle ultrasound				X	
Follow-up—phone call and medical history questionnaire					X

SD-NSC, San Diego Nathan Shock Center.

body composition in vivo. The three visits are completed within approximately 3 weeks from the provision of informed consent, with a final short phone-based assessment as well as electronically delivered questionnaires at 2 years to provide a subset of longitudinal data related to aging. We divide our assessments across three separate visits to minimise participant burden since the number of assessments we perform would take too long to complete in one single visit. So far there has been no loss to follow-up since our data collection is primarily cross-sectional. If a participant does not complete all assessments and biospecimen collections, we will exclude that participant from the final cohort and aim to replace them with a final cohort size of 80. Research materials obtained from participants include participant-provided demographics, a blood specimen, a skin biopsy, in vivo measures of anthropometrics, body composition, bone density, cognitive ability, sensory function, mental well-being, and physical function within the laboratory, and measures of PA, sedentary behaviour and sleep during at-home real-world activity.

We recognise that our limited cohort size (n=80) results in limited cohort diversity. Currently, our cohort consists of 88% white/Caucasian individuals. We hope to address this with continued funding and study expansion. Other demographic factors such as gender distribution are adequately addressed during recruitment. Our limited cohort size also results in lower statistical power for future analyses or comparisons of aging phenotypes. However, our primary objective is to generate 80 cell models of aging, derived from highly characterised individuals across the adult human life course.

Study population

The SD-NSC Clinical Cohort comprises healthy, community-dwelling, men and women ranging in age from 20 to over 70 years, with an emphasis on the older population age ≥60 and no designated upper age limit. The central goal of the SD-NSC Clinical Cohort is to recruit participants representative of 'normal' human aging. While it is difficult to define 'normal' or 'healthy' aging, robust inclusion and exclusion criteria have been designed to minimise extrinsic factors that may confound the assessment of normal biological aging. Inclusion and exclusion criteria are summarised in table 2. Participants with an exceptionally high physical fitness level (eg, competitive athletes) may also be excluded to prevent data skew.

Table 2 Inclusion and exclusion criteria for recruitment

Inclusion criteria	Over 20 years of age
	Able to consent and participate in the study using English or Spanish
	BMI≥18.5 and ≤30 kg/m^2
	Weight stable for the prior 6 weeks
	Normal cognitive function
	Willing and able to attend two in-person study visits that include vigorous exercise testing, blood draw and skin biopsy
	Willing to wear a wireless accelerometer for 14 days
	Has a primary care physician
Exclusion criteria	Is pregnant
	Diabetes (fasting plasma glucose >180 mg/dL or A1c>8)
	Uncontrolled hypertension (blood pressure >140/90 mm Hg)
	Heart or cardiovascular condition, including coronary artery disease, congestive heart failure, diagnosed abnormality of heart rhythm, atrial fibrillation and/or a history of myocardial infarction
	Cancer or history of cancer within the past 5 years
	Dementia or other conditions that may affect cognitive ability
	Sensory or physical impairment that would prevent participation
	Parkinson's disease, multiple sclerosis or other neurological condition, including a previous stroke, that may be causing impaired muscle function or mobility
	Supplements that may interfere with measurements or biological outcomes including but are not limited to: NAD+ supplements, MitoQ and medications that may alter cardiac and haemodynamic responses to exercise
	Active respiratory disease compromising ability to exercise
	Answers 'yes' to one or more questions in the American College of Sports Medicine's Physical Activity Readiness Questionnaire and/or report two or more risk factors for exercise testing

BMI, body mass index.

Recruitment

The SD-NSC Clinical Cohort is being recruited through printed and digital advertisements on the campuses of UCSD, SBP and Salk, as well as in the local San Diego community. We also use electronic and mailed announcements in the Stein Institute for Aging Research newsletter, university listservs and websites. We use ResearchMatch, a national electronic recruitment database to recruit individuals who have expressed interest in participating in research studies (www.researchmatch.org). Finally, we leverage EPARC's list of participants who have been part of other studies conducted at their facility and who had indicated a willingness to participate further in research.

We have the opportunity to co-enrol with other cohorts from studies led by UCSD colleagues. We are recruiting participants from the RBS of Healthy Aging, which was established in 1972 and is one of the longest observational cohorts funded by the NIH. We are actively

recruiting participants from this study using personalised mailers and community outreach events in addition to the methods described above.

Patient and public involvement

Participants are not involved in the design, conduct, reporting or dissemination of research.

Clinical phenotypes of aging

Participants in the SD-NSC Clinical Cohort are assessed across multiple domains to characterise the heterogeneity of aging. Physiological adaptability and reserve capacity decrease with age, which is reflected in clinically gathered phenotypic data such as maximal cardiovascular capacity, muscular strength and endurance, physical performance during activities of daily living, body composition, cognitive function and sensory ability. This deep phenotyping approach and comprehensive clinical analysis enhance the potential for using SD-NSC-derived cell models to identify the molecular underpinnings linked to or related to aging. We selected assessments and exams that capture a broad range of age-related phenotypes to provide insights into multiple dimensions of aging as outlined in table 3. All assessments are performed by a few highly trained staff to reduce variability between participant outcomes.

Physical performance

Physical performance and capacity are known to decline with age, alongside muscular atrophy and neuromotor impairment.[16 17] We employ multidimensional assessments of physical function ranging from simple tests of walking speed and balance to more complex assessments of muscle strength and endurance to ensure comparability among individuals across the human adult lifespan. For example, maximal cardiovascular/aerobic capacity (Peak VO_2) is well documented to identify physical function and capacity. However, it can be difficult to complete for individuals who have limited familiarity with treadmills or experience claustrophobia. Similarly, the 6-Minute Walk Test (6MWT) has been shown to be a reliable indicator of physical performance in multiple populations across the lifespan and multiple health statuses[18–20] but may not capture the true maximal capacity of individuals who are more fit and/or active. The combination of these multidimensional assessments provides a comprehensive evaluation of physical performance that is valid for participants of any age group. While this example only encompasses cardiovascular capacity, the measures were chosen to provide a combination of assessments that will be more likely to accurately capture the metrics of interest across a wide variety of functional categories and familiarity with laboratory testing.

The Expanded Short Physical Performance Battery (eSPPB) is a widely used set of short assessments to evaluate lower extremity function. During this assessment, we ask participants to complete five repeated chair stands as fast as possible, 4 m walk at normal speed and 10 s of side-by-side, semitandem and tandem standing postures while staying as still as possible.[21] We expand on the traditional SPPB by including a BTrackS balance board during the balance assessments and including the BTracks Balance Test, which measures postural sway with the eyes closed to remove the visual component of balance control. There are strong normative data across the lifespan for these assessments and they are independently predictive of both morbidity and mortality.[22]

Table 3 Summary of clinical phenotypes and specific assessments

Category	Test/exam/procedure
Physical performance	Expanded Short Physical Performance Battery
	Gait Speed test
	Chair Stand test
	Balance test
	2.5 min indoor free-living walk
	6 min Walk Test
	Indoor free-living walk
	Isometric Muscle Strength
	Grip Strength
	Resting Metabolic Rate
	Spirometry/Respiratory Evaluation
	Cardiopulmonary Exercise Testing
	Wireless Accelerometry
	International Physical Activity Questionnaire
Body composition	Hip and Waist Circumference
	Dual-energy X-ray Absorptiometry Scan
	Muscle Ultrasound Imaging
Cognitive function	Hopkins Verbal Learning Test
	Trail-Making Test
	Category Fluency Test
	Modified Mini Mental State
	NIH Cognitive Assessment Battery
	Flanker Inhibitory and Control and Attention Test
	List Sorting Working Memory Test
	Dimensional Change Card Sort
	Pattern Comparison Processing Speed Test
	Picture Sequence Memory test
Sensory ability	Audiometry Evaluation
	Visual Acuity Test
	Odour Identification Test
Haematology	Comprehensive Metabolic Panel
	Complete blood count
Mental health	The Pittsburgh Sleep Quality Index
	UCLA Version 3 Loneliness Scale
	San Diego Wisdom Scale

A 2.5 min indoor free-living walk is conducted to compare mobility and smoothness of walking compared with those observed during faster walking in the 6MWT (described below). Although our protocol uses a 50 m hallway, instead of the shorter 20 m course, the methods are otherwise very similar to those used by the BLSA.[23] Participants are asked to complete a 2.5 min walk at a 'usual pace' down a 50 m hallway. The distance travelled during the 2.5 min walk is measured and recorded. We also instrument this test with the portable indirect calorimeter (K4b2, Cosmed) to assess individualised metabolic expenditure during normal speed walking, and with a waist-worn accelerometer similar to the 6MWT, outlined below.

The 6MWT is a test originally developed to complement Peak VO_2 and evaluate the activity limitation domain in adults.[24 25] Participants are measured in a 90 m long hallway and are instructed to walk as quickly as possible for the entire 6 min. Total distance covered is measured at 2 min, 4 min and 6 min to estimate both maximal capacity and identify markers of fatigue over time. In addition to traditional distance-based measures, participants are asked to wear a waist-worn ActiGraph GT3X+accelerometer (ActiGraph; Pensacola, Florida, USA) that estimates step counts and metabolic equivalent of task (MET) levels based on amount of movement using previously validated cut-points.[26]

Isometric muscle strength is assessed using the Biodex System 4 PRO dynamometer (Biodex Medical, Shirley, New York, USA). Individual knee joint range of motion (ROM) is determined using manufacturer specifications and isometric measurements are completed for both knee flexion and extension at 45°, 75° and 90° of measured ROM. During the assessment, participants perform three repetitions of 5 s maximal isometric contraction and extension with 5 s of rest between each effort at each joint angle for each leg. There are approximately 5 min of rest between efforts at each joint angle. This method reduces the risk of injury and potential learning effects because the hamstring and quadriceps muscles remain isolated during the test.

Grip strength is measured in both hands using an adjustable grip strength dynamometer (BL5001 Hydraulic Hand Dynamometer). The dynamometer is set to zero and participants are first given a chance to familiarise themselves with the instrument and measurement. For the assessment, participants stand and hold the dynamometer in their hand with their arms down at their side; they are then instructed to take a deep breath in and squeeze as hard as possible during exhalation. After an unrecorded familiarisation attempt at ~75% of capability, the measurement is repeated twice on each hand, alternating between each side and the highest score for each hand is recorded to the nearest kilogram.

Resting metabolic rate is measured via indirect calorimetry (COSMED cardiopulmonary exercise testing (CPET), Italy) to determine caloric expenditure, and fuel sources at rest, as well as individualised normal volume per breath (tidal volume) and breaths per minute (breath rate). Participants are asked to report to the lab fasted and are instructed to refrain from high-intensity exercise for 24 hours prior to their measurement visit. Participants are fitted with a breath mask that covers the nose and mouth to capture/measure all expired air for measurement and instrumented with a chest-worn heart monitor (Polar, Finland) for real-time monitoring and to ensure ongoing resting state. During the measurement, participants lie quietly on a table for up to 30 min while remaining as still as possible without falling asleep and with no outside stimulation (eg, bright lights, noise, cell phone use). Data are collected continuously for 16 min.

Spirometry/respiratory evaluations are conducted using a nose clip and a single-use filter attached to a turbine specifically designed to measure human respiration. During the assessment, the participant is asked to first perform four cycles of normal breathing (ie, four tidal breaths), followed by as deep an inhalation as possible that is then exhaled as forcefully and quickly as possible (forced vital capacity). The total volume inhaled, total volume exhaled, and the force expiratory volume (FEV) exhaled at 0.5, 1.0, 3.0, and 6.0 s are recorded in absolute volume (liters) and percentage of total capacity. The process is first demonstrated, and the participant is asked to practice a minimum of one time (maximum of three); the assessment is repeated three times with data collection.

A second assessment is conducted during which the participant first performs four tidal breaths, then inhales as deeply as possible, and then fully exhales at a slow constant rate (slow vital capacity). At the end of their exhale, they are then instructed to perform one more tidal breath, and the test is concluded. The total volume inhaled, total volume exhaled, inspiratory capacity, and expiratory reserve volume were gathered in absolute volume.

CPET and indirect calorimetry yield important measures relating to cardiovascular, pulmonary and skeletal muscle health.[27 28] Indirect calorimetry remains the gold-standard method for assessing Peak VO_2. Participants are monitored based on pre-existing risk factors as determined by trained staff and a licensed physician, as illustrated in figure 1.

We employ a commonly used treadmill protocol including appropriate safeguards, emergency procedures and training to comply with recommendations from the American College of Sports Medicine (ACSM).[29]

Wireless accelerometry provides insight into the participant's daily activity levels and energy expenditure. Specifically, objective assessments of physical activty (PA) are measured using the ActiGraph GT3X+accelerometer (ActiGraph). The ActiGraph device has been validated and calibrated for use in both controlled and field conditions for PA and sedentary behaviours.[30] We use the seven-step algorithm identified as best practice for the collection, processing and summarising of PA accelerometer data collected with wearable systems.[31] Participants are asked

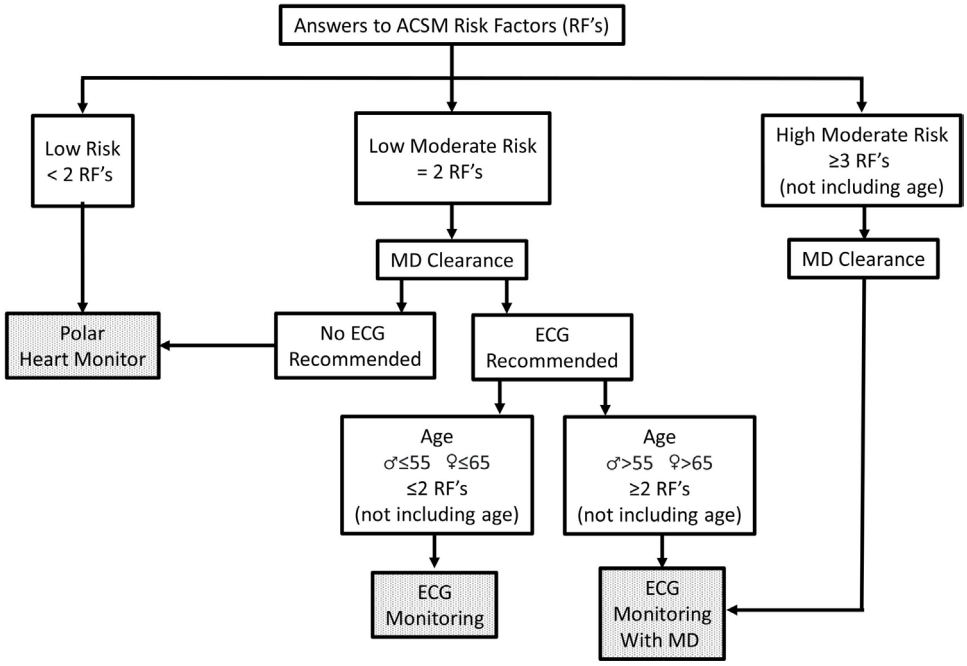

Figure 1 Flow chart of cardiovascular risk determination for cardiopulmonary exercise testing. ACSM, American College of Sports Medicine. MD, Doctor of Medicine.

to wear the ActiGraph for 7 days and are prompted twice via telephone during the monitoring period (wear days 2 and 5) to assist with compliance. On return, the ActiGraph is immediately downloaded and screened by hour for completeness and possible irregularities/malfunction according to the best-practice recommendations.[32]

The International Physical Activity Questionnaire is a self-report questionnaire that asks questions about the time an individual spent being physically active in the last 7 days, including activities completed at work, around the house/yard, as means of transportation, recreationally and for exercise or sport. This information also provides insight into daily PA and expenditure. Given that there is some indication that self-report and objectively measured markers of PA capture different domains of behaviour, a metric of self-reported activity was thought to be a useful addition to the measurement battery that added minimal participant burden.

Body composition

Parallel to age-related physical performance changes are alterations to body composition. Changes in body composition such as weight, body mass index, fat mass (and associated body fat percentage), lean mass and bone mineral density/bone mineral content (BMD/BMC), among others, are well documented to occur during the aging process.[33–35] Further, alone and in combination, these metrics have been shown to be predictive of all-cause mortality in adults.[33 36] Although historically BMI has been the major anthropometric measurement used to assess the relationship between body composition and mortality, attention has shifted towards other measures that convey more detailed insight on fat versus lean mass distribution. Waist-hip ratio and volume/mass of visceral adiposity in particular have garnered attention as strong predictors for adverse health events and mortality in older adults.[36–39]

Hip and waist circumference measurements are taken based on well-established protocols from the Centers for Disease Control and Prevention and The ACSM that have been amended for safety and precision in our population.[40 41] Each circumference measurement is taken twice from the right side of the participant and recorded to the nearest 0.1 cm. If the difference between the two measurements is >1%, a third measurement is taken and the average of the two closest measures is recorded.

Dual-energy X-ray absorptiometry whole body scans are gathered to determine whole body BMC and BMD as well as whole-body and regional fat and lean mass measurements. Additional scans are conducted of clinically relevant regions of interest (proximal femur and lumbar scan) to gather clinically meaningful assessments of bone density and allow comparisons with relevant reference populations. Scans are assessed using a Hologic Discovery W densitometer using V.14.10.022 software. All scans are gathered and analysed by one of three state-licensed technologists, one of whom is also further certified by the International Society of Clinical Densitometry. All scans are reviewed for accuracy and consistency by that technician. Additionally, markers of bone quality are gathered in the form of the Trabecular Bone Score are generated following analysis of the lumbar spine images using TBS iNsight software.

Muscle ultrasound imaging of the vastus lateralis muscle is performed using a Philips Lumify (Philips USA) portable ultrasound system. Aging is associated with declines in endurance, muscle strength, balance control

and resulting mobility, which are related to changes in muscle composition. Key readouts include vastus lateralis size and the quantification of intramuscular adipose tissue using MuscleSound software (MuscleSound, Denver, Colorado, USA). Participants are asked to change into shorts, and a short ultrasound scan is performed by a trained technician using a small hand-held ultrasound wand. Measurements are taken from both left and right vastus lateralis muscles.

Cognitive function

Aging is associated with cognitive decline and the onset of pathological memory changes. Our battery of assessments is formulated to capture multiple facets of cognitive function: verbal learning, working memory, retention, attention, executive function and task switching, among others. These neuropsychological assessments were originally designed to be simple to execute and well tolerated by a wide range of individuals. For example, the NIH Toolbox Cognition Battery (NIH-TB-CB) is widely validated in detecting cognitive decline in a variety of populations.[42–44] The Trail Making test is similarly sensitive enough to show performance differences between younger and older participants.[45 46]

The Hopkins Verbal Learning Test is a brief exam to assess verbal learning and memory, particularly for older adults.[47 48] During this assessment, participants are seated across from a trained proctor who lists 12 nouns, at a rate of one word every two seconds. The participant is then asked to repeat as many of the words as they can remember. This test is repeated twice. After approximately 20 min from the last repeat, the participant is asked to recall as many words from the list as they can remember. Finally, a list containing words from the list and not from the list is read and the participant is asked whether each word belonged in the original list.

The Trail Making Test is a neuropsychological test widely used in clinical practice to assess psychomotor speed, visual scanning and executive functioning. Participants are shown a standardised trails sheet and are asked to draw a line to connect the dots in numerical and alphabetical order as quickly as possible. They are given a practice sample sheet prior to the test.

The Category Fluency Test is a brief exam to measure executive function, memory and language among individuals of different educational levels.[49] Participants are given 1 min to list as many animals as they can.

The Modified Mini Mental State Exam is a well-used exam to assess global cognitive function as well as orientation to time and place, registration, recall, simple language and construction. Participants are seated and a 34-item battery of short questions, tasks and objectives is presented.

The NIH-TB-CB is a short battery of cognitive assessments designed to measure specific domains of cognition, including but not limited to executive function, episodic memory, language, processing speed and attention.[50] From the battery, we are employing the following assessments: Flanker inhibitory control and attention test, List Sorting working memory test, Dimensional change card sort test, Pattern comparison processing speed test and Picture Sequence memory test. Although the entire battery is computerised and administered on a secure iPad, it is necessary for an examiner to present task instructions orally, monitor compliance and ensure valid results. The iPad assessments are administered to the seated participant at a distance that is comfortable for their execution.

Sensory ability

Sensory decline is observed in human aging, resulting from physiological changes that affect multiple sensory systems. Adequate threshold measurement of sensory function is imperative because age-related sensory loss is usually difficult to recognise and accept in healthy individuals, making self-report assessments subjective and unreliable.[51 52] With this in mind, we sought to perform objective, standardised assessments of sensory function rather than rely on self-reports that may reduce data reliability.

The audiometry evaluation is performed with a Welch Allyn manual or conventional audiometer in a quiet room. Pure-tone auditory thresholds are measured at frequencies of 500, 1000, 2000 and 4000 Hz in each ear. If a participant is unable to hear the tone at 40 dB, measurement is stopped at that frequency and a value of 50 dB is assigned. The pure-tone average threshold is calculated as the average threshold across the four frequencies for each ear.

A visual acuity test is performed using an NIH Toolbox assessment on the iPad. Participants are seated 3 m from an iPad screen while letters are displayed one at a time. The participant is asked to identify the pictured letter and, if correct, a smaller one will appear. The programme will determine the smallest size letter the participant can identify.

An odour identification test is also performed using an NIH Toolbox assessment. Participants are asked to identify odours, the sources of odours and discriminate odour quality, by scratch-and-sniff cards. They identify the source of the odour by choosing pictures of that particular odour or its source on the iPad screen.

Mental health

Concerns about mental health become increasingly important for older adults who are experiencing lifestyle changes at a physiological, mental and social level. Aspects of mental health such as wisdom and loneliness are found to be intricately linked, particularly in the older adult population.[53] We incorporated multiple surveys to capture the mental health status of our participants.

The Pittsburgh Sleep Quality Index is a self-reported questionnaire assessing sleep quality over the past month. This 19-question measure has been found to be both valid and reliable and has been used as a clinical tool

across multiple populations to evaluate a broad range of elements related to sleep quality.[54 55]

The UCLA V.3 Loneliness Scale is a widely used and highly validated scale to measure a participant's loneliness on a scale from 1 to 20, with a higher score indicating greater loneliness. This scale may provide early detection of mental health-related symptoms, including depression.[56–58]

The San Diego Wisdom Scale is a self-reporting test that assesses domains of wisdom including emotional regulation, self-reflection, acceptance of divergent values, prosocial behaviours, decisiveness and social advising.[59] Higher scores indicate a greater affinity to that domain.

Haematology

There is an active effort to identify blood-based biomarkers to measure biological aging based on observed changes in blood composition and chemistry with age.[60] We collect 4 mL of fasted venous blood in one serum separator tube and 3 mL in one EDTA tube for a complete blood count and a complete metabolic panel. These provide measures of blood cell composition (eg, platelet count, white cell count) and blood chemistries (eg, glucose, anions and cations, liver enzymes) to evaluate overall health status. Many of these values are used as critical biomarkers of health and disease risk.

Biobank

Biological materials and cells from the blood draws and skin biopsies are banked to support studies of human aging. Dermal fibroblasts derived from the skin-punch biopsies provide new cellular models of aging for the aging research community. Blood cells and plasma are also banked to support future research but provide a more limited resource based on the amount of material available.

As outlined above, the blood draw is conducted by a licensed phlebotomist during the week 0 visit, and the skin biopsy is performed by the study physician during the week 1 visit. All samples are labelled with deidentifying identification numbers prior to banking, and samples used in future studies will remain deidentified. Any researcher who wishes to access biological samples from the bank, including blood components or skin fibroblasts, can contact the SD-NSC Executive Committee, which oversees the distribution of these resources.

Cell models

With the emergence of human cell-based modelling approaches (eg, cellular reprogramming, direct conversion and spheroid/organoid technologies), researchers now have access to approaches that enable a deeper level of investigation into the heterogeneity of human aging and cell-specific age-related differences. Subject-specific cell models from the SD-NSC have the power to resolve the underpinnings of aging by addressing the links between cellular aging and a wide array of clinical phenotypes. Human cell-based models of aging provided by the SD-NSC can be used to study otherwise inaccessible organs and tissues, such as cells of the central nervous system through reprogramming and differentiation. Participant fibroblast lines are derived from dermal skin-punch biopsies and induced pluripotent stem cell (iPSC) lines can be reprogrammed from dermal fibroblasts. In addition, it is possible to directly convert ('transdifferentiate') a variety of induced cell types from dermal fibroblasts without passing through an iPSC intermediate. Methods now exist to generate a variety of induced cell types directly from fibroblasts, including neurons, blood lineages, pancreatic lineages, hepatocytes, adipocytes, osteoblasts, melanocytes, cholangiocytes, as well as cardiac, skeletal and smooth muscle cells.[61–70] There are merits to each of these methods that employ different techniques and provide different types of data.

ETHICS AND DISSEMINATION

Institutional review board approval

Ethics approval from the UC San Diego School of Medicine Institutional Review Board (IRB #201 141 SHOCK Center Clinical Cohort, PI: Molina) was obtained on 11 November 2020. Written informed consent is obtained from all participants after the objectives and procedures of the study have been fully explained by a designated member of the research team. Authorisation to obtain further private health information (PHI) and to share PHI gathered as part of this project is gathered from participants in compliance with HIPAA laws. Participants may withdraw from the research at any time without giving a reason.

Resource availability

Our goal is to establish a new core resource, comprised biospecimens and phenotypic data, to support discoveries about the basic biology of aging. As this resource will be available to researchers, there are no regulations on predetermined analyses to be conducted, as these will stem from researchers who will propose to use the samples and data to be collected. Biological samples (blood cells, serum, fibroblasts, any induced and/or reprogrammed cell types) are made available through the SD-NSC Biobank, as described above. Clinical data are available through RedCap. Protocols for biological sample processing/banking, experimentation and downstream analyses are made available through the Human Cell Core, and workshops/training sessions will be made available through the Research Development Core.

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Contributors HJP, SRH, LMS and DW wrote the first draft of the manuscript, which was edited and revised by HJP, SRH, LMS and AJAM. DW, DM, RM and JFN developed and designed the physical performance protocols and assessments. DW and DM executed physical performance protocols and assessments. RM provided medical oversight. HJP and LMS developed and executed the cognitive function, sensory ability, and mental health protocols and assessments. HJP developed

biobanking protocols. LMS developed haematology protocols. SRH and HJP expanded and banked cell models. FHG provided oversight on maintenance of cell models. LMS and DW served as study coordinators. DW managed the recruitment, screening and consent of study participants. AJAM, FHG and GSS conceptualised the SD-NSC and the SD-NSC Clinical Cohort design.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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