DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

National Health and Nutrition Examination Survey (NHANES) Stored DNA Specimens; Proposed Cost Schedule and Guidelines for Proposal To Use DNA Specimens

AGENCY: Centers for Disease Control and Prevention (CDC), Department of Health and Human Services (HHS).

ACTION: Notice.

SUMMARY: The Centers for Disease Control and Prevention (CDC), located within the Department of Health and Human Services (HHS), announces the availability of stored DNA specimens obtained from participants in the National Health and Nutrition Examination Survey (NHANES) and the proposal parameters and fee schedule for use. NHANES is one of a series of health-related surveys conducted by CDC's National Center for Health Statistics (NCHS).

DATES: The stored NHANES DNA specimens are available July 11, 2022. The fee structure for these specimens is effective July 11, 2022.

FOR FURTHER INFORMATION CONTACT: Jody McLean, Division of Health and Nutrition Examination Surveys, National Center for Health Statistics, Centers for Disease Control and Prevention, 3311 Toledo Road, Hyattsville, MD 20782, Telephone: (301) 458–4683; Email: *NHANESgenetics@cdc.gov.*

Authority: Sections 301,306 and 308 of the Public Health Service Act (42 U.S.C. 241, 242k, and 242m).

SUPPLEMENTARY INFORMATION:

Background: NHANES is a program of periodic surveys conducted by NCHS. NHANES has provided national estimates of the health and nutritional status of the U.S. civilian non-institutionalized population since the 1960s. The goals of NHANES are: (1) to estimate the number and percentage of people in the U.S. population and designated subgroups with selected diseases and risk factors for those diseases; (2) to monitor trends in the prevalence, awareness, treatment, and control of selected diseases; (3) to monitor trends in risk behaviors and environmental exposures; (4) to analyze risk factors for selected diseases; (5) to study the relation among diet, nutrition and health; (6) to explore emerging public health issues and new technologies; and (7) to establish and maintain a national probability sample of baseline information on health and nutritional status.

DNA Specimens, Availability, and Resulting Data

The availability of the NHANES III Phase 2 DNA specimens was first announced in 2002. NHANES III Phase 2 DNA specimens (1991–1994) are from participants ages 12 or older (see: *https://wwwn.cdc.gov/nchs/nhanes/nhanes3/default.aspx* for more information on NHANES III).

NHANES III Phase 2 DNA specimens are crude DNA lysates extracted from cell lines; therefore, DNA concentrations vary and are estimated to range from 7.5–65.0 ng/μL with an average of approximately four micrograms in 100 μL. DNA specimens are available from 7,159 NHANES III Phase 2 participants. Forty microliters of each DNA specimen will be distributed in 82 plates, including four plates of quality control specimens. NHANES III DNA specimens are in limited supply and thus are not available as a partial set (which is a request for less than the total number of participants available). Due to the extraction method, NHANES III DNA specimens are not appropriate for all projects and assays. For background information on all DNA specimens, see the NHANES Biospecimen Program report at *https://www.cdc.gov/nchs/data/series/sr_02/sr02_170.pdf.*

In 1999, NHANES became a continuous survey, with data released every two years (see *https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx* for more information on continuous NHANES). The availability of DNA specimens from the continuous NHANES was first announced in 2007.

Continuous NHANES DNA specimens are available as collections from NHANES 1999–2002 (NHANES 1999–2000 and 2001–2002 specimens are available as one collection) and NHANES two-year cycles 2007–08, 2009–10, and 2011–12. In continuous NHANES, DNA was purified from whole blood; aliquots of DNA were normalized to concentrations of approximately 50 ng/μl, and 40 μl of each DNA specimen will be distributed. There are purified DNA specimens from 7,830 NHANES 1999–2002 participants. These specimens will be distributed into 90 plates, including four plates of quality control specimens. There are purified DNA specimens available from 4,612 NHANES 2007–2008 participants. These will be distributed into approximately 54 plates, including three plates of quality control specimens. There are purified DNA specimens available from 4,893 NHANES 2009–2010 participants. These will be distributed into 58 plates, including three additional plates of quality control specimens. There are purified DNA specimens available from 4,147 NHANES 2011–12 participants. These will be distributed into 49 plates, including three additional plates of quality control specimens.

DNA specimens will be available for testing only from participants who consented to future research.

The resulting data from DNA specimen testing will be linkable to variables (public use and restricted) and available for analyses through the NCHS Research Data Center (RDC; *https://www.cdc.gov/rdc/index.htm*) for approved proposals unless otherwise determined by the NHANES Project Officer. Access to these data at the NCHS RDC is only through an approved proposal process mechanism to assure confidentiality (see ''APPROVED PROPOSALS: Post-Testing Procedures'' section).

Parameters for DNA Specimen Use and Resulting Data

1. Investigators must justify why they need a specimen from a national probability sample of the U.S. population for their study.

2. Investigators must specify which NHANES cycles they are requesting DNA specimens from and the specific laboratory tests to be conducted on those specified DNA specimens.

3. Only those proposals for which the laboratory testing will result in findings determined not to have clinical significance for participants will be approved. The consent document for DNA storage and future research use of DNA specimens states that individual results will not be provided to participants. Therefore, no proposals involving tests with clinical significance will be approved. DHANES/NCHS will use the most recent American College of Medical Genetics and Genomics (ACMG) recommendations for reporting secondary findings [1] to assess the proposed tests and their potential for yielding clinically significant findings. Investigators must verify that the proposed tests do not produce variants (*e.g.,* single-nucleotide polymorphisms,

[1] See ''*Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens*'' (*https://nap.nationalacademies.org/catalog/18829/issues-in-returning-individual-results-from-genome-research-using-population-based-banked-specimens-with-a-focus-on-the-national-health-and-nutrition-examination-survey),* convened by the National Academies of Science Committee on National Statistics in 2014 at the request of NCHS's Board of Scientific Counselors.

translocation and inversions, copy number variations) on specific genes listed by the most recent ACMG recommendations as reportable secondary findings and describe how potential secondary findings results will be handled.

4. Upon receipt of the specimen and after conducting the approved testing, investigators must provide a copy of the resulting data obtained from DNA testing to the Division of Health and Nutrition Examination Survey (DHANES)/NCHS for quality control assessment.

5. After DHANES/NCHS has completed the initial quality control assessment of submitted data, investigators will be given up to six months to conduct a comprehensive quality assurance review. At this review's completion, the resulting data's availability will be publicly announced on the NHANES website Genetic Variant Search: *http://www.nhgeneticvariant.com/*. The resulting data can be linked to other NCHS variables (public use and restricted) for secondary data analysis. Analysis and linkage of the resulting data are conducted in the NCHS RDC via a separate proposal unless otherwise determined by the NHANES Project Officer (see ''APPROVED PROPOSALS: Post-Testing Procedures'' section).

Proposals Testing DNA Specimens Already Obtained From Previous Solicitations

Investigators who have obtained NHANES DNA specimens from previous solicitations and have sufficient DNA left may request to do additional tests on the remaining DNA. These proposals must be submitted and approved as further provided herein. The investigator must pay an additional cost (see ''COST SCHEDULE'' section) per each additional proposal).

Proposal Evaluation

All proposals for the use of NHANES DNA specimens will be evaluated by the NHANES Project Officer, a Technical Panel, the NCHS Confidentiality Officer, the NCHS Human Subjects Contact, and the NCHS Ethics Review Board (ERB). Applications will have a Scientific Review by the NHANES Project Officer and the Technical Panel. The Technical Panel comprises two members with subject matter expertise: one from CDC staff and one external to CDC, *i.e.,* from other federal agencies, academia, or industry. Only technical panel members with no conflict of interest and no previous knowledge of the research project will be asked to review the proposal. The members review each proposal for scientific and technical merit and ensure that the proposed project does not go beyond the general purpose of collecting the blood specimens for DNA in NHANES (see ''PROCEDURES FOR PROPOSALS'' section).

After the proposal is approved by the NHANES Project Officer and the Technical Panel, it will be submitted for Institutional Review. All proposals will undergo Institutional Review by the NCHS Human Subjects Contact and the NCHS ERB for any potential human subjects concerns to ensure appropriate human subjects protections are provided in compliance with 45 CFR 46 and by the NCHS Confidentiality Officer for disclosure risk. The NCHS ERB will review the proposal even if the investigators have received approval from their institutional review panel. The proposal, if approved, will become an amendment to the current NHANES ERB Protocol (*i.e.,* the NHANES ERB Protocol that is in effect at the time of the investigator's proposal approval).

If a proposal is approved, the author's title, specific aims, name, and phone number will be maintained by NCHS and released if requested by the public. NCHS will not maintain unapproved proposals.

Procedures for Proposals

All investigators (including CDC investigators) must submit a proposal for the use of NHANES DNA specimens and follow the instructions as set forth herein, including following the outline set out below. Proposals should be a maximum of 20 1.5-spaced typed pages, excluding figures and tables, using at least size 10 font. The cover of the proposal (which is not included in the 20-page limit) should include the title of the proposal, the name, address, phone number, and email address of the principal investigator (PI), and the name of the institution where the laboratory analysis will be done. The name, address, phone number, and email address of all additional investigators should also be included on the cover. Office of Human Research Protections assurance numbers for the institutions in the proposed project should be included. CDC investigators must include the expiration date of their Collaborative Institutional Training Initiative (CITI) training. All proposals should be submitted via email to *NHANESgenetics@cdc.gov*. Note: If the investigator would like to propose a subsample of the complete set, please contact the NHANES Project Officer to discuss feasibility.

The following criteria will be used for technical evaluation of proposals:

(1) *Abstract:* Please limit the abstract to 300 words.

(2) *Specific Aims:* List the broad objectives; describe concisely and realistically what the proposed project is intended to accomplish and state the specific hypotheses to be tested.

(3) *Background and Public Health Significance:*

(A) Describe the public health significance of the proposed study.

(B) Discuss how the results will be used. Analyses should be consistent with the NHANES mission to assess the health of the nation. The Scientific Review will ensure that the proposed project does not go beyond the general purpose of collecting the blood specimens for DNA in the survey or the specific stated goals of the proposal.

(4) *Design, Method, and Analytic Plan:* The appropriateness and adequacy of the methodology proposed to reach the specific aims and the appropriateness of using the NHANES (a complex, multistage probability sample of the national population) to address the goals of the proposal will be assessed.

(A) *Study Design and Methods:* Include a detailed description of the laboratory methods. The characteristics of the laboratory assay, such as reliability, and validity, should be included with appropriate references. The laboratory must demonstrate expertise in the proposed test, including the capability to handle the workload requested in the proposal. The potential difficulties and limitations of the proposed procedures should also be discussed. Address methods to ensure adequate handling and storage of DNA specimens. Proposals *must* specify variants or the commercial assay(s) used to test the proposed research hypotheses and include a statement of why the specific standard assay(s) is/are necessary to test the proposed hypotheses. Note: A standard assay is a commercially available assay for a curated set of variants or biological markers. Investigators who submit successful proposals will be provided with quality control specimens at no additional cost. Approved projects must run these quality control specimens and submit these results along with the results from the NHANES DNA specimens unless the NHANES Project Officer has approved an alternative quality control review plan. The proposal should address any additional quality control procedures the laboratory will use to assure the validity of the test results and address methods to ensure adequate handling and storage of specimens.

(B) *Analytic Plan:* Describe the data analysis and statistical methods to be employed. Include power calculations. Resulting data from DNA specimens are restricted access data and must be analyzed in the NCHS RDC. The proposal should state that the data analysis will be conducted in the RDC unless DHANES/NCHS determines otherwise.

(5) *Additional information for NHANES:*

(A) *Clinical Significance of Results:* The consent document for DNA specimen storage and future studies states that individual results will not be provided to participants; therefore, no tests that need to be reported back to the participant can be proposed. DHANES/NCHS will use the most recent American College of Medical Genetics and Genomics (ACMG) recommendations for reporting secondary findings to review the proposed tests and the potential secondary findings. Investigators must verify that the proposed tests do not produce variants on specific genes listed by the most recent ACMG recommendations as reportable secondary findings and describe how potential secondary test results will be handled. The 2021 statement, ''ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG),'' lists 73 genes where specific variants on these genes are pathogenic for 34 conditions.

(B) *Data Transfer:* Specify the secure method to transfer the resulting data to NCHS. Investigators must use a device that meets federal information processing standards (FIPS 140–2 and FIPS 197).

(C) *Period of Performance:* Specify the proposed project period. Substantial progress must be made in the first year that specimens have been obtained, and the project should be completed within a reasonable period of time. Please discuss the approximate time the investigator expects this project will take to complete. The NHANES Project Officer must be consulted about the disposition of the specimens. At the end of the project period, any unused specimens must be returned to the NHANES DNA Specimen Repository or destroyed by the investigator.

(D) *Funding:* Include the source and status of the funding to perform the requested laboratory analysis. Investigators will be responsible for the cost of processing and shipping the specimens (see COST SCHEDULE FOR PROVIDING NHANES DNA SPECIMENS and *Cost Schedule for NHANES DNA Specimens* for details).

(6) *Resumes/CV:* Please include a two-page CV for each member of the study team in the proposal (not as attachments; CVs do not count towards page maximum).

Submission of Proposals

Proposals must be submitted in MS Word format by email to *NHANESgenetics@cdc.gov.*

Proposal Timeframes

- Submission of Proposals: Can be submitted on an ongoing basis
- Scientific Review: Completed approximately two months after proposal submission
- Institutional Review: Completed approximately six weeks after completion of scientific review
- Notification of Approval: Approximately 30 days after completion of Institutional Review
- Anticipated Distribution of Specimens: Approximately 60 days after the following is completed: notification of proposal approval, agreements signed (as described below), and payments received (as described below)

Note: Timeframes may vary depending on the nature of the proposal and the results of each level of review. Unforeseen circumstances could result in a change to this schedule.

Approved Proposals

Investigators must transfer payment to DHANES/NCHS and sign terms and conditions agreements for the use of the DNA specimens with CDC/NCHS before releasing the NHANES DNA specimens. Investigator(s) must agree to: (a) use the specimens only for the approved tests; (b) use the test results only for purposes as stated in the approved proposal; (c) not link the results of the proposed project to any other data; (d) not use the DNA specimens for commercial purposes, as set forth in a legally binding Materials Transfer Agreement (MTA; if non-government investigators) or Interagency Agreement (IAA; if government investigators); and (e) sign and abide by a Designated Agent Agreement (DAA) with CDC/NCHS in accordance with NCHS' confidentiality legislation.

Agency Agreements

A formal signed agreement, embodied in the form of an MTA or an IAA, and a DAA with investigators who have projects approved, must be completed before the release of the specimens to the investigator. For the MTA or IAA, this agreement will contain the conditions for use of the specimens as stated in this **Federal Register** notice and as agreed upon by the investigators and CDC. The DAA is the mechanism by which CDC/NCHS may authorize the designation of agents to exclusively perform activities needed to produce approved data using the Confidential Information Protection and Statistical Efficiency Act (CIPSEA; Title V of the E-Government Act of 2002 [Pub. L. 107–347])-protected NHANES DNA specimens. The DAA must be signed by the investigator taking custody of DNA specimens and producing resulting data.

Continuations

A brief progress report must be submitted annually to NHANES. This report should describe the work completed and the timeline to project completion. When five years have elapsed since the initial approval of the proposal by the NCHS ERB, the investigator must provide an updated project timeline to complete the study for approval by NHANES. If a new investigator(s) is added at any time during the project, or the Principal Investigator has changed, the NHANES Project Officer must be notified.

Approved Proposals: Post-Testing Procedures

After DNA specimens are received and testing is complete, the investigators must send the resulting data back for DHANES/NCHS quality control assessment. While DHANES/NCHS quality control assessment is underway, the investigator can submit an NCHS RDC proposal (*http://www.cdc.gov/rdc*) to conduct an additional quality assurance review. The vast majority of resulting data from DNA specimens is restricted; therefore, the data are available only in the NCHS RDC. Once the investigators' quality assurance review is complete and the results are returned to DHANES/NCHS, investigators will be given up to six months to conduct a comprehensive quality assurance review in the NCHS RDC. The quality assurance review timeframe will be negotiated between the investigators and the NHANES Project Officer and will depend on the type, number, and characteristics of the tests submitted. The results of the quality assurance review will be provided to DHANES/NCHS, and appropriate aspects will become part of the data set documentation. The public announcement, informing that test results are available for secondary data analyses after submission and acceptance of proposals, will occur once the quality assurance review timeframe has ended. For a list of currently

available variant data, see: *http://www.nhgeneticvariant.com/.*

A minority of resulting data from DNA specimens are not restricted. In these cases, the resulting data will undergo disclosure review by the NCHS Confidentiality Officer and NCHS Disclosure Review Board or designee before the linked data are sent to the investigators for quality control review. Once approved by disclosure review and after the investigators have signed the Data Sharing Agreement, the linked data file will be sent to the investigators for use pursuant to the terms of the relevant agreement. The quality control review must take place within 60 days or a negotiated length of time, and the return of the data to NCHS within the next 30 days so these data may be released to the public.

Disposition of Specimens

The provided DNA specimens cannot be used for any purpose other than the specifically requested purpose outlined in the proposal and approved through the Scientific and Institutional Review. No DNA specimens can be shared with others, including other investigators, unless specified in the proposal and so approved. Specimens must be returned upon completion of the approved project or destroyed. Both options require written approval from the NHANES Project Officer.

Cost Schedule for Providing NHANES DNA Specimens

There is a nominal processing fee of $17.17 for each DNA specimen received from an NHANES DNA Repository. The costs include collecting, processing, storing, and retrieving the DNA specimens, reviewing proposals, and preparing the data files. The costs listed are for the recurring laboratory materials to dispense and prepare the DNA specimens during collection and shipping. The NHANES DNA Specimen repository costs include long-term storage (including inventory management and materials and equipment) and accessioning of specimens and specimen retrieval for shipment to the investigator. Labor costs are based on a proposal administrator to manage the proposal process and computer programmers at NCHS who prepare the data files for the release of the data along with documentation on the NHANES web page. If the investigators request to use the DNA specimens for another proposed project after the completion of the initial project, the additional cost will be 5 percent of the specimen set cost to handle the processing of the data and management of the subsequent proposal process. A new proposal must be submitted and go through the approval process before any additional use of the DNA specimens.

COST SCHEDULE FOR NHANES DNA SPECIMENS

Total costs	1999–2002, 2007–2008, 2009–2010, 2011–2012 complete sets	1999–2002, 2007–2008, 2009–2010, 2011–2012 partial set	NHANES III complete set
Materials and equipment—contractor: plates, reagents, assays, aliquoting and packaging specimens; use of equipment	$1.72	$5.15	$0.85
Labor—contractor: processing, handling, and shipping; NCHS: data quality control	5.66	28.31	2.83
Proposal review and administrative expenses—contractor: inventory management and reporting; NCHS: management of proposal process non-NCHS: technical panel fees	3.43	6.87	1.72
Space—contractor: freezer use and maintenance	6.36	6.36	3.17
Cost per specimen	17.17	46.69	8.58
Cost per new proposal:			
1999–2002	134,430.92	*	
2007–2008	79,181.82	*	
2009–2010	84,006.11	*	
2011–2012	71,181.89	*	
III	.....	.....	61,454.85
Cost per additional proposal: **			
1999–2002	6,721.94	***	
2007–2008	4,130.72	***	
2009–2010	4,200.08	***	
2011–2012	3,559.95	***	
III	.....	.....	3,072.17

* Cost calculated upon request.
** Additional research using DNA specimens already obtained from previous solicitations.
*** This charge will be 5 percent of the original cost.
Note: Applicable CDC overhead and NCHS management and oversight charges will be added to these rates for proposals coming from federal agencies.

Angela K. Oliver,

Executive Secretary, Centers for Disease Control and Prevention.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

Solicitation of Nominations for Appointment to the Board of Scientific Counselors, National Center for Injury Prevention and Control (BSC, NCIPC)

ACTION: Notice.

SUMMARY: The Centers for Disease Control and Prevention (CDC) is seeking nominations for membership on the BSC, NCIPC. The BSC, NCIPC consists of 18 experts in fields associated with surveillance; basic epidemiologic research; intervention research; and implementation, dissemination, and evaluation of promising and evidence-based strategies for the prevention of injury, violence, and drug abuse. Nominations are being sought for