DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

National Health and Nutrition Examination Survey (NHANES) DNA Samples: Guidelines for Proposals To Use Samples and Cost Schedule

AGENCY: Centers for Disease Control and Prevention, Department of Health and Human Services.

ACTION: Notice.

SUMMARY: The National Health and Nutrition Examination Survey (NHANES) is a program of periodic surveys conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). Examination surveys conducted since 1960 by NCHS have provided national estimates of the health and nutritional status of the U.S. civilian non-institutionalized population. To add to the extensive amount of information collected for the purpose of describing the health of the population, DNA specimens were collected during three NHANES surveys. DNA is available in the form of crude lysates of cell lines derived from 7,159 participants enrolled in Phase II of NHANES III (1991–1994). In addition, DNA purified from whole blood is also available from 7,839 participants enrolled in the NHANES 1999–2002 and 2007–2008 surveys. Participants are assured that data collected in the NHANES is kept in strictest confidence. During the informed consent process, survey participants are assured that data collected will be used only for stated purposes and will not be disclosed or released to others without the consent of the individual in accordance with section 308(d) of the Public Health Service Act (42 U.S.C. 242m). In NHANES 1999–2002 and 2007–2008, a separate consent form was signed by eligible participants who agreed to the storing of specimens for future genetic research. Only participants that consented specifically to future genetic research in 1999–2002 or 2007–2008 will be available for analyses. Genetic variation results will be linked to the requested information from the NHANES public use data file by the Division of Health and Nutrition Examination Surveys (DHANES) staff. All analyses must be done through an NCHS Research Data Center (RDC) approved mechanism to assure confidentiality.

Research Proposals Categories

Note that the following proposal categories differ from those used in participants. DNA concentrations are unknown and vary between samples (see NHANES III DNA Samples section for a description).

Beginning in 1999, NHANES became a continuous, annual survey rather than a periodic survey. For a variety of reasons, including disclosure and reliability issues, the survey data are released on public use data files every two years. In addition to the analysis of data from any two year cycle, it is possible to combine two cycles to increase sample size and analytic options. Blood samples for DNA purification were collected from participants age 20 or more years in survey years 1999–2002 and 2007–2008. Purified DNA samples are available from these survey years in a single set from each survey cycle. DNA samples can be obtained and analyzed with survey data from the NHANES 1999–2000 or 2001–2002 or all four years combined (NHANES 1999–2002) and NHANES 2007–2008. The data release cycle for the NHANES during the period in which DNA specimens were collected is described as NHANES 1999–2000, NHANES 2001–2002 and NHANES 2007–2008.


A more complete description of this program follows.

DATES:
• Submission of Proposals: On January 1 and July 1 of each year.
• Scientific Review: 30 days after proposal submission date.
• Secondary Review: Approximately 30 days after Scientific review is complete.
• Ethics Review Board: Approximately 30 days after Secondary review is complete.
• Notification of approval: Approximately 30 days after ERB approval.

Anticipated distribution of samples:
Announcement and to CDC. Projects and other criteria germane to this program priorities, program relevance, programmatic considerations such as the nature of the proposal and the results of each level of review. Unforeseen circumstances could result in a change to this schedule.

ADDRESSES: To send comments and for information, contact: Geraldine McQuillan, PhD, Division of Health and Nutrition Examination Surveys, National Center for Health Statistics, Centers for Disease Control and Prevention, 3311 Toledo Road, Room 4204, Hyattsville, MD 20782, Phone: 301–458–4371, Fax: 301–458–4028, E-Mail: NHANESgenetics@cdc.gov.

Authority: Sections 301, 306 and 308 of the Public Health Service Act (42 U.S.C. 241, 2421 and 242m).

SUPPLEMENTARY INFORMATION: 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; (7) to establish and maintain a national probability sample of baseline information on health and nutritional status.

The availability of the NHANES III DNA samples has been previously announced [Thursday, August 8, 2002 [67 FR 51585], Friday, January 13, 2006 [71 FR 22248]], Thursday, October 18, 2007 [72 FR 59094] and Thursday, September 3, 2009 [74 FR 45644]]. NHANES III DNA samples are in the form of crude cell lysates available from the cell lines derived from samples obtained from Phase II (1991–1994)
previous announcements for use of NHANES III DNA samples (Thursday, August 8, 2002 [67 FR 51585] and Friday, January 13, 2006 [71 FR 22248]).

**Category (A): Studies involving the typing of the complete set of NHANES DNA samples (NHANES III, 7,159 samples; NHANES 1999–2002, 7,839 samples; NHANES 2007–2008, 4,615 samples) for proposals that investigate specific research hypotheses that relate tests of selected genes and demographic or demographic and phenotypic data available from NHANES. This category is open for proposals for use of NHANES III, NHANES 1999–2002 and NHANES 2007–2008 samples. A total of ten full sets of samples for each survey will be available for any review cycle. The investigator will specify which DNA bank, NHANES III, NHANES 1999–2002 or 2007–2008, they are requesting as well as the genetic analyses to be conducted on the samples. The investigator will also include in the research protocol an analytic plan that includes a list of NHANES demographic and clinical variables that would be used for the data analyses. The researcher will conduct the genetic analyses of the approved variations on the samples that are labeled with a unique identification number that is not directly linkable to the public use file and therefore, anonymous to the researcher. To analyze these data with the NHANES public use data, the researcher will provide the genetic variation results with the identification numbers to the Division of Health Promotion and Disease Control and Prevention. These data will be available for secondary data analysis. The list of currently available SNPs is available at: http://www.cdc.gov/nchs/nhanes/genetics/genetic_types.htm.

All samples will be distributed in complete sets of samples of 96 well plates. NHANES III DNA is in the form of crude cell lysates. There will be a total of 7,159 NHANES III samples distributed in a total of 75 plates with an additional four plates of quality control samples. There are 7,839 NHANES 1999–2002 purified DNA samples. These will be distributed into 82 plates with approximately five plates of quality control samples. There are 4,615 purified DNA samples available from NHANES 2007–2008. These will be distributed into 49 plates with approximately three plates of quality control samples.

**Note:** If the investigator would like to propose a subsample of the full set please contact the Program to discuss feasibility.

**Category (B): Additional research using samples already obtained from previous solicitations:** Researchers that have obtained NHANES DNA samples from previous solicitations and have sufficient DNA left may request to do additional tests on the remaining DNA. Proposals under this Category must be submitted and approved before the DNA samples were scheduled to be destroyed or returned. The investigator will specify the genetic analyses to be conducted on the samples. The investigator will also include in the research protocol an analytic plan that includes a list of demographic and clinical variables that would be used for the data analyses.

**Category (C) Proposals involving whole-genome genotyping of DNA samples:** All proposals for whole-genome genotyping of more than 1,000 genetic variations must provide funding for the testing to the NHANES program so that the testing can be done under an NHANES contract. If funding is available, CDC intends to provide whole genome-genotyping data from NHANES III and NHANES 1999–2002 samples. These data will be available for secondary data analysis.

**NHANES III DNA Samples**

The laboratory will distribute aliquots of crude cell lysates. DNA concentrations vary and are estimated to range from 7.5–65 ng/μL with an average of approximately four micrograms in 100 μL. Each 96 well plate will be bar-coded and labeled with a readable identifier. Quality control samples (approximately 384 samples) will be sent at no charge, either inserted with the NHANES samples or in separate plates, as blind replicates and/or blanks. Description of these samples and cost has been previously published see: [Friday, January 13, 2006 [71 FR 22248]].

**NHANES 1999–2002 and 2007–2008 DNA Samples**

The laboratory will distribute aliquots of purified DNA of normalized concentrations of 50 ng/μL whenever possible. Some samples may fall below this threshold. Forty microliters of each specimen will be supplied. The amount of DNA in each aliquot may vary but will be on average approximately two micrograms. Each 96 well plate will be bar-coded and labeled with a readable identifier. Quality control samples (NHANES 1999–2002, approximately 480 samples; NHANES 2007–2008, approximately 288 samples) will be sent at no charge, either inserted with the NHANES samples or in separate plates, as blind replicates and/or blanks.

**Proposed Cost Schedule for Providing NHANES DNA Samples**

Costs are determined both for NCEH and NCHS and include the physical materials needed to process the samples at the NCEH laboratory, as well as the materials to process the requests for samples at NCHS. These costs include salaries of the staff needed to conduct these activities at each Center. The fee is estimated to cover the costs of processing, handling, and preparing the samples. Technical panel travel and expenses are based on the panel meeting twice a year. The space estimate is based on acquiring storage and sample aliquoting space in the laboratory. The cost per samples for NHANES III samples is the same as published in 2006 (Friday, January 13, 2006 [71 FR 22248]) and the cost for NHANES 1999–2002 and NHANES 2007–2008 are the same as published in 2007 (Thursday, October 18, 2007 [72 FR 5904]).
Procedures for Proposals

The investigator should follow these instructions for preparation of proposals. Once testing is complete the IRB protocol is closed and the project is transferred to the Research Data Center (RDC). The content of the IRB protocol becomes the RDC project description and the project is covered by the umbrella RDC IRB Protocol. Protocols must be written using the outline below. All proposal categories need a full research proposal for review. In addition to the cover page, the research proposal should contain the title of the research project, the name, address phone number and E-mail address of the lead investigator along with the name of the institution where the genotyping will be conducted, and the category of proposal (A, B or C) submitted. Office of Human Research Protections assurance numbers for the institutions engaged in the research project should be included. CDC investigators need to include their Scientific Ethics Verification Number. E-mail submission of the proposal is encouraged.

The proposals should be a maximum of 20 single-spaced typed pages, excluding figures and tables, using ten cpi type density. Please use appendices sparingly. If a proposal is approved, the title, specific aims, name, and phone number of the author will be maintained by NCHS and released if requested by the public. Unapproved proposals will be returned to the investigator and will not be maintained by NCHS.

Since the number of sets of DNA is limited, proposals will be reviewed by the technical panel and then will be reviewed by a secondary review panel composed of CDC officials. The technical panel will determine if the proposal is technically sound and if so, the technical panel will rank the proposal on a scale of 0–100. Proposals that are rejected will not be scored.

Applications will also be reviewed by an internal Secondary Review Committee which will perform a programmatic review based on the results of the first level review. The Secondary Review Committee considers the scientific and technical merit results from the first level review, important programmatic considerations such as program priorities, program relevance, and other criteria germane to this announcement and to CDC. The Secondary Review Panel will be comprised of senior CDC scientists. Approved proposal will then be reviewed by the CDC/NCHS Ethics Review Board (ERB) to ensure appropriate human subjects protections are provided, in compliance with 45 CFR 46.

Category A, B and C Proposals should include the following information:


2. Background and Public Health Significance: (A) Describe the public health significance of the proposed research. (B) Discuss how the results will be used. Analyses should be consistent with the NHANES mission to assess the health of the nation. The Panel will ensure that the proposed project does not go beyond either the general purpose for collecting the samples in the survey or the specific stated goals of the proposal.

3. Design, Method, and Output: (A) Research Design and Methods: Describe the analytic and statistical methods to be employed. Include power calculations. For all proposal categories, include a detailed description of the laboratory methods. The characteristics of the laboratory assay, such as reliability, validity, should be included with appropriate references. The potential difficulties and limitations of the proposed procedures should also be discussed. Address adequate methods planned for handling and storage of samples. (1) Category A proposals will be provided with approximately 480 quality control samples at no additional cost. Approved projects must run these quality control samples and submit the results from the NHANES DNA samples.

4. Abstract: Please limit the abstract to 300 words.

5. Specific Aims: List the broad objectives; describe concisely and realistically what the research is intended to accomplish, and state the specific hypotheses to be tested.

6. Methodology: Provide a logical and comprehensive description of the approach that will be used in the project. Emphasize the experimental design and the methods that will be used to achieve the goals as stated in the specific aims.

7. Population or Study Design: Describe the population on which the study will be conducted. Specify the methods used to select the sample.

8. Data handling and storage of samples: The proposal should contain a discussion of additional quality control samples. The proposal should contain a discussion of additional quality control samples and submit the results from the NHANES DNA samples.

9. Assurances: Include a discussion of appropriate human subjects protections. The proposal should include a detailed description of the laboratory assay, such as reliability, validity, should be included with appropriate references. The potential difficulties and limitations of the proposed procedures should also be discussed. Address adequate methods planned for handling and storage of samples. (1) Category A proposals will be provided with approximately 480 quality control samples at no additional cost. Approved projects must run these quality control samples and submit the results from the NHANES DNA samples. (2) Category B proposals will be required to use residual quality control samples. The proposal should contain a discussion of additional quality control procedures the laboratory will use to assure the validity of the test results. Address adequate methods planned for handling and storage of samples. (B). Output: Please describe any output that you would like to take out of the RDC. Please be detailed as this section helps...
the Review Committee assess disclosure risk. Include detailed examples of table
tables, models, and/or graphs. How will
you present the results of this project?
(C). Data Dictionary: Includes (1) NCHS
Restricted Data Dictionary (2) NCHS
Public Use Data Dictionary (3) Non-
NCHS Data Dictionary see: http://
The appropriateness and adequacy of the
methodology proposed to reach the
research aims as well as 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.
(6) Additional information for
NHANES: (A) Discussion Regarding the
Race/Ethnicity Variables: If the research
is limited to specific race or ethnic
groups (only applicable for a subsample
request) or if information about the race
or ethnicity of the subjects is requested,
indicate the reason for analyzing race/
ethnicity and how the results will be
interpreted. Discuss the potential for
group-specific stigmatization. (B) Clinical Relevance of
Research Findings: The samples under
this Plan are available for genetic
research, not genetic testing. Therefore,
it is the intent of the program to approve
only those proposals that would yield
meaningful research, but not clinically
relevant information for the
participants. Researchers should justify
that the test results should not be
reported to the subjects. (C) Period of
Performance: Specify the project period.
The period may be up to three years. At
the end of the project period, any
unused DNA samples must be returned to the
NHANES DNA Specimen Bank in
accordance with instructions from the
Division of Environmental Laboratory
Science. Extensions to the period of
performance may be requested. (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 samples (See table).
Also, in general information for RDC.
(7) References
(8) Re¨sume´s/CV: Please include a 2-
page CV for each member of the
research team in this document (not as
attachments).
Public Availability of Data
Genetic test results from all studies
using NHANES DNA samples will be
made available to the public for
secondary data analyses. After the
NCHS quality control review is
completed, researchers will be given up
to six months to conduct a more
comprehensive quality assurance
review. The final quality control review
timeframe will be negotiated between
the researcher and the NCHS Project
Officer and will depend on the number
and characteristics of the genetic tests
submitted. This time for final review is
provided before the announcement is
made to the public that the test results
are available for submission of
proposals for secondary data analyses.
The list of currently available genotypes
will be outlined on: http://www.cdc.gov/
nchs/nhanes/genetics/
genetic_types.htm.
Proposals for secondary data analyses linking
NHANES public use data with genetic
variation data will be reviewed by the
Research Data Center on a rolling basis
see: http://www.cdc.gov/rdc/B3Proposal/
PP320.htm for proposal guidelines.
Requirements for the Inclusion of
Women and Racial and Ethnic
Minorities in Research
In NHANES III, NHANES 1999–2002,
and NHANES 2007–2008 race/ethnicity
was derived by combining responses to
questions on race and Hispanic origin.
For NHANES III, These categories are
defined as non-Hispanic white, non-
Hispanic black, or Mexican American.
For NHANES 1999–2002, and NHANES
2007–2008, these categories are defined
as non-Hispanic white, non-Hispanic
black, Mexican American or Other
Hispanics. Individuals who did not self-
select into these categories were
classified as “other”. If proposal requests
a subsample and excludes one or more
race/ethnic groups or a gender, this
exclusion must be justified.
CDC is also sensitive to the
stigmatization of racial/ethnic specific
populations through inappropriate
reporting and interpretation of findings.
For all proposals that request
information on race/ethnicity for the
samples selected, the investigator
should discuss the reason for analyzing
race/ethnicity, how the results will be
interpreted, and the potential for group
harm.
Submission of Proposals
Proposals can be submitted
immediately. The review process will
begin approximately 60 days from the
publication of the notice and will
include all proposals submitted as of
that date.
Electronic submission of proposals is
encouraged. Please submit proposals to:
Geraldine McQuillan, PhD, Division of
Health and Nutrition Examination
Surveys, National Center for Health
Statistics, Centers for Disease Control
and Prevention, 3311 Toledo Road,
Room 4204, Hyattsville, MD 20782,
Phone: 301–458–4840, Fax: 301–458–
4028 E-Mail: Nhanesgenetics@cdc.gov.
Approved Proposals
The genetic results will be sent back
to NCHS so they can be linked to the
requested NHANES III, NHANES 1999–
2002 or NHANES 2007–2008 public use
data. Analysis will be done in the
Research Data Center.
Agency Agreement
A formal signed agreement in the
form of a Materials Transfer Agreement
(MTA) with individuals who have
projects approved and funding has been
secured will be completed before the
release of the samples. This agreement
will contain the conditions for use of
the DNA as stated in this document and
as agreed upon by the investigators and
CDC. A key component of this
agreement is that no attempt will be
made to link the results of the proposed
research to any other data, including,
but not limited to, the NHANES public
use data sets outside the Research Data
Center. Also, the investigator agrees that
the samples cannot be used for
commercial purposes. A list of genes
generated from the testing of the
NHANES samples will be made
available to the public for potential
solicitation of proposals for secondary
data analysis after the quality control
process has been completed
(approximately six months after NCHS
receives the genetic variation results).
These secondary data analysis proposals
must also be reviewed by the ERB.
Progress Reports
A progress report will be submitted
annually. CDC/NCHS/ERB continuation
reports are also required annually if
testing is not completed within a year.
An ERB continuation form will be sent
to the researcher each year for project
update.
Termination of ERB Protocol
At the end of laboratory testing the
Ethics Review Board Protocol will be
closed. All data analysis will be
conducted through the NCHS Research
Data Center (RDC). For secondary data
analysis project an analytic plan must
be submitted to the RDC to set up the
analytic data set. See: http://
www.cdc.gov/nchs/rdc/rdc.htm for
guidelines.
Disposition of Results and Samples
No DNA samples provided can be
used for any purpose other than those
specifically requested in the proposal
and approved by the Genetics Technical
Panel, the Secondary Review Committee
and the NHANES EB. No sample can be
shared with others, including other
investigators, unless specified in the
proposal and so approved. Any unused
samples must be returned upon completion of the approved project. These results, once returned to NCHS and quality controlled, will be part of the public domain. Genetic test results from all studies using NHANES DNA samples will be made available to the public for secondary data analyses. After the NCHS quality control review is completed, researchers will be given up to six months to conduct a more comprehensive quality assurance review. The final quality control review timeframe will be negotiated between the researcher and the NCHS Project Officer and will depend on the number and characteristics of the genetic tests submitted. Data analyses will be conducted at the NCHS’ Research Data Center or similar environment provided by NCHS. Proposals for secondary data analyses are accepted on a rolling basis (http://www.cdc.gov/nchs/nhanes/genetics/genetic_types.htm).

Send Requests for Information

Geraldine McQuillan, PhD, Division of Health and Nutrition Examination Surveys, National Center for Health Statistics, Centers for Disease Control and Prevention, 3311 Toledo Road, Room 4204, Hyattsville, MD 20782. Phone: 301–458–4371, Fax: 301–458–4028, E-mail: NHANESgenetics@cdc.gov.


Tanja Popovic,
Deputy Associate Director for Science, Centers for Disease Control and Prevention.

BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention

Procedures and Costs for Use of the Research Data Center

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

ACTION: Notice and request for comments.

Authority: Section 306 of the Public Health Service Act, as amended (42 U.S.C. 242k) and Public Law 103–333.

SUMMARY: This notice provides information about the Research Data Center (RDC) operated by the National Center for Health Statistics (NCHS) within the Centers for Disease Control and Prevention (CDC). The Research Data Center was established in 1998 to provide a mechanism whereby researchers can access detailed data files in a secure environment, without jeopardizing the confidentiality of respondents. Historically, the data files accessed in the RDC have consisted of NCHS survey data and vital statistics.

RDC has recently begun accepting data files that were not produced from NCHS survey data in order to assure that all data files are processed in a consistent manner, the original guidelines for accessing files in the RDC are being reviewed and revised as necessary. As part of the revision process, potential users are being given the opportunity to provide input on how the procedures of the RDC can best serve their research needs. This notice describes how to submit proposals requesting use of the data, mechanisms to access the RDC, requirements, use of outside data sets, costs for using the RDC, and other pertinent topics. We are seeking comments on these procedures and will post the final procedures on the NCHS Web site.

ADDRESSES: Send comments concerning this notice to Peter Meyer, National Center for Health Statistics, 3311 Toledo Road, Room 4113, Hyattsville, MD 20782, or e-mail to pmeyer1@cdc.gov.

FOR FURTHER INFORMATION CONTACT:

SUPPLEMENTARY INFORMATION:

Operational Procedures for Use of the Research Data Center; National Center for Health Statistics; Centers for Disease Control and Prevention

Table of Contents

Background

Methods of Access to Data
Submission of Research Proposals Using NCHS Data
Proposal Review
Researcher Supplied Data
General Procedures for Onsite Access
General Procedures for Remote Access
Confidentiality and Human Subjects Protection
Disclosure Review Process
Costs for Using the RDC

National Center for Health Statistics Research Data Center Procedures

Background

The National Center for Health Statistics (NCHS) releases and hosts a range of statistical data products on the health and well-being of the nation and its health care system. Statistical tabulations (tables) present data in predetermined categories such as age, race, sex or geographic region that are important to describe health status and trends. In addition, statistical microdata containing health and related variables are published so that outside analysts may conduct original research and special studies to address issues of public health science and policy.

Section 308 (d) of the Public Health Service Act and the NCHS Staff Manual on Confidentiality do not permit the release of data that are either identified or identifiable to persons outside of NCHS. In order to preserve privacy and confidentiality, details that might identify or facilitate the identification of persons and entities participating in NCHS surveys and data systems either owned or hosted by NCHS are not released in published data products.

Examples of data elements that might be abridged or suppressed to prevent reidentification are geographic identifiers, genetic data, details of sample design, and variables such as age or income that might exist in other databases.

Despite the wide dissemination of NCHS data through publications, Web releases, etc., the inability to release files with these sensitive variables limits the utility of NCHS data for research, policy, and programmatic purposes and sets a boundary on one of the Department of Health and Human Service’s goals: to increase our capacity to provide state and local area estimates. In pursuit of this goal and in response to the public research community’s interest in restricted data, NCHS established the NCHS Research Data Centers (RDCs), a place where Guest Researchers can access detailed data files in a secure environment, without jeopardizing the confidentiality of respondents. Access for Guest Researchers is regulated by the Confidential Information Protection and Statistical Efficiency Act (CIPSEA) and other Federal statutes. The RDCs provide restricted access to NCHS data and non-NCHS data. Guest Researchers function under the supervision of NCHS employees and are subject to the same provisions of law with regard to confidentiality as NCHS employees.

Instructions for developing a research proposal can be found in Appendix II. Special requirements for use of non-NCHS data can be found in Appendix III, Project-Specific Requirements.

Methods to Access Data

Restricted NCHS data or data hosted by NCHS can be made accessible through the RDC. To gain access to these data, Guest Researchers must submit a proposal for review and approval. Once the proposal is approved, Guest Researchers meeting certain criteria are allowed access, under strict supervision, to restricted statistical microdata file(s). There are four modes of access: (1)