NIMH CENTER FOR GENETIC STUDIES

RFP NO. NIMH-98-DB-0004
ISSUED BY: Patricia L. Gibbons, Contracting Officer
National Institute of Mental Health
Contracts Management Branch
5600 Fishers Ln., Rm. 9C-15
Rockville, MD 20857-8030

DATE ISSUED: Monday, April 20, 1998

PROPOSAL DUE DATE: Monday, June 22, 1998

Dear Sirs:

The National Institute of Mental Health (NIMH) invites you to submit a proposal in accordance with the requirements and instructions of Request for Proposals (RFP) No. NIMH-98-DB-0004 entitled: "NIMH Center for Genetic Studies." Proposals are being solicited under Full and Open Competitive procedures.

It is expected that an award will be made on or before September 30, 1998.

The RFP does not commit the Government to pay costs for the preparation and submission of a proposal. It is also brought to your attention that the Contracting Officer is the only individualwho can legally commit the Government to the expenditure of public funds in connection with any acquisition action.

SPECIAL ATTENTION SHOULD BE DIRECTED TO THE TECHNICAL PROPOSAL INSTRUCTIONS AND BUSINESS PROPOSAL INSTRUCTIONS CONTAINED IN ATTACHMENT 4. Questions pertaining the Government's requirement or proposal preparation should be referred only to Patricia L. Gibbons, Contracting Officer, Contracts Management Branch, NIMH, who may be called on (301) 443-2696 or email: pgibbons@nih.gov

The documents included with this electronic RFP package are as follows:

I.Streamlined RFP

a.Statement of Work (SOW) (Attachment 1)
b.Deliverables and Reporting Requirements (Attachment 2)
c.Evaluation Factors for Award (Attachment 3)

II.Specific RFP Instructions and Provisions (Attachment 4)

III.Applicable RFP References (Attachment 5)

The attachments listed above represent all the necessary information required for the submission of a proposal for this acquisition.

Your proposal must be signed by an official authorized to contractually bind your organization and must indicate that it is valid for a period of at least 120 days. One (1) original and ten (10) copies of your technical proposal, and one (1) original and four (4) copies of your Business/Cost Proposal, must be received by the Contracting Officer NO LATER THAN 3:30 P.M., LOCAL PREVAILING TIME, ON MONDAY, JUNE 22, 1998, at the following address:

Patricia L. Gibbons, Contracting Officer
National Institute of Mental Health
Contracts Management Branch
5600 Fishers Ln., Rm. 9C-15
Rockville, MD 20857-8030

In addition, you are reminded that the "Technical Proposal Cover Sheet" (Attachment 5) must be completed in full detail and used as the cover sheet for each copy of your technical proposal. New policies require submission of more detailed information than what has been previously required. It is important that you list all professional personnel and organizations named in the proposal who will have any role in the proposed work, including: staff of the primary organization (offeror), subcontractors, collaborating organizations, and consultants. Organizational affiliation(s) must be indicated for every person named. You may use additional sheets, as needed, following the format shown in the Technical Proposal Cover Sheet. This information will be used to ensure that there will be no conflicts of interest when selecting review committee members.

Your attention is further directed to the "Proposal Intent Response Sheet" contained in Attachment 4. Please complete this form and return it to this office or notify me at the following internet address: pgibbons@nih.gov on or before Wednesday, May 13, 1998. This will allow us to expedite preparations for the peer review of proposals.

ALL AMENDMENTS TO THIS SOLICITATION WILL BE AVAILABLE ON THE INTERNET ON THE NIMH HOME PAGE AT: http://www.nimh.nih.gov. Notification of solicitation amendments to this RFP will be provided to those who submit the Proposal Intent Response Sheet.

Questions concerning any areas of uncertainty which in your opinion require clarification or correction, must be furnished in writing, (Fax or email is also acceptable) to Patricia L. Gibbons, and marked "Offeror's Questions, RFP No. NIMH-98-DB-0004". If you have any additional questions regarding this RFP, please contact me by email: pgibbons@nih.gov by phone (301) 443-2696 or by Fax at (301) 443-0501. Collect calls will not be accepted. ANY DISCUSSION OF THIS RFP WITH ANY INDIVIDUAL(S) OUTSIDE THE CONTRACTS MANAGEMENT BRANCH, NIMH, MAY RESULT IN DISQUALIFICATION OF THE OFFEROR AND REJECTION OF ANY PROPOSAL SUBMITTED.

Sincerely,

/s/

Patricia L. Gibbons, Contracting Officer
Contracts Management Branch, ORM
National Institute of Mental Health, NIH

Attachments: 1-5

RFP No. NIMH-98-DB-0004

I.STREAMLINED RFP

STATEMENT OF WORK

I. Background

The role of genetic factors in the familial aggregation of serious brain disorders is well supported by twin and adoption studies. In the late 1980's, the NIMH developed a program to study the genetic basis of vulnerability to three such disorders - schizophrenia, Alzheimer disease, and bipolar disorder. Ten data collection sites were funded as cooperative agreements in Fiscal Year (FY) 1989 to ascertain pedigrees with at least two affected individuals. Clinical, diagnostic, and pedigree structure data, as well as blood samples for extracting DNA for subsequent genetic analyses, were collected from affected individuals and their relatives.

The primary goals of the program were to: (1) develop a set of common protocols to assess subjects; (2) develop a comprehensive set of reliable and valid assessment instruments and to adopt a common protocol and criteria for diagnosing subjects across centers; (3) design and implement an ascertainment plan for systematic pedigree collection; and (4) create and maintain comprehensive electronic databases, as well as DNA samples and cell lines, as a national resource of data and biological materials for wide distribution to qualified investigators in the scientific community. The ultimate objective of this effort was the identification of genes that confer susceptibility to schizophrenia and major mood disorders. Data collection at seven sites ended in FY 1997, and will continue for bipolar disorder at three sites until the end of FY 1998. Further background on this effort, termed the NIMH Human Genetics Initiative, may be found on the World Wide Web (WWW) at http://www-grb.nimh.nih.gov/gi.html.

Despite several reports of linkages to schizophrenia and mood disorders, no chromosomal region has been convincingly replicated. It is clear that the effects of genes that confer susceptibilities to these disorders are of weaker magnitude than anticipated a decade ago. Consequently, identification of these susceptibility genes will require additional large-scale pedigree ascertainment and data collection efforts. A genetics workgroup of the National Advisory Mental Health Council reviewed the NIMH portfolio of funded genetic research in 1997. Their specific recommendations for how the Institute should proceed include: (1) the funding of large-scale data collection efforts, in which affected individuals and their relatives are clinically well-characterized; and (2) the continued maintenance of a cell repository and electronic files of clinical, diagnostic, and pedigree structure data that are widely distributed to qualified investigators in the scientific community. The full report of the workgroup can be found on the WWW at http://www.nimh.nih.gov/research/genetics.htm.

A Request for Applications (RFA) was issued in March 1998 (MH-98-010) for multidisciplinary and collaborative research projects, employing state-of-the-art diagnostic procedures and analytic methods, to collect large samples of pedigrees for the genetic analysis of schizophrenia and mood disorders. Another RFA (MH-99-xxx) will be issued later in 1998 that will support genetic analyses and re-diagnosis in existing pedigree samples collected in prior NIMH-supported genetic research projects. The goal of these RFAs is the identification of chromosomal regions harboring genes that confer susceptibility to these disorders, as a crucial first step in the effort to positionally clone precise genes. Clinical, diagnostic, and pedigree structure information collected in projects funded under these RFAs over the next four years will augment existing resources to be widely distributed by NIMH for genetic analyses by qualified investigators in the scientific community.

In FY 1990, NIMH awarded a competitive contract for the NIMH National Cell Repository to the Coriell Institute for Medical Research, Camden, New Jersey, to serve the ten original data collection sites and the scientific community by creating high-quality, well-characterized cell lines from which DNA was extracted. Another competitive contract was awarded to the Coriell Institute in FY 1997 to complete these tasks for bipolar family data being collected at three sites. In FY 1990, NIMH also awarded a competitive contract for a Data Management Center to SRA Technologies, Falls Church, VA, to serve the data collection sites and the scientific community by developing a remote data entry system, facilitating the development of new diagnostic and family interview instruments, and creating electronic data files for wide distribution to qualified investigators in the scientific community. This contract was recompeted in FY 1995, which resulted in another award to SRA Technologies.

This contract will integrate all of the functions currently performed under these two contracts, as well as data distribution and several monitoring functions currently performed by NIMH staff. The objective of this contract will be to establish the NIMH Center for Genetic Studies, in order to accomplish in a highly efficient, rapid, and cost-effective manner the following: (1) receive clinical, diagnostic, pedigree structure, and other data and blood samples from approximately 25 new R01 projects expected to be funded under RFAs MH-98-010 and MH-99-xxx; (2) process these data and materials to create databases, cell lines, and DNA samples that are incorporated with comparable existing data and materials in the NIMH Human Genetics Initiative; and (3) widely distribute all data and materials in the NIMH Human Genetics Initiative to qualified investigators in the scientific community. There are no grants, cooperative agreements, or contracts currently funded by NIMH that can perform all of the required work, create all of the required deliverables, and widely distribute clinical data and biological materials to the scientific community.

II. Purpose and Objectives

A. Summary of Requirements

For this one-year contract (with options of up to four additional years), the contractor shall receive and process data and biological materials collected from individuals with serious brain disorders and their relatives. These data and biological materials shall be added to those currently distributed under the NIMH Human Genetics Initiative. Cell lines, DNA, and electronic files suitable for immediate genetic analysis will be prepared. Given that this is a highly technical endeavor, the contractor shall have prior experience in preparing pedigree files and using those files to conduct statistical genetic analyses that would be suitable for publication in peer-reviewed scientific journals. This contractor shall also widely distribute this information, for use exclusively in genetic research on serious brain disorders, to qualified investigators in the scientific community (including scientists in industry, the NIH intramural program, and public and private universities) granted access by NIMH. Specifically, the following tasks shall be performed on data and biological materials received from grants supported under RFAs MH-98-010 and MH-99-xxx:

1. Receive blood samples collected from patients and their relatives and create cell lines via Epstein-Barr virus transformation of lymphocytes from these blood samples, with a success rate of 95% or greater.

2. Expand these lymphoblastoid cell lines to extract DNA samples.

3. Receive clinical, diagnostic, pedigree structure, and other data, for incorporation into phenotypic databases that are suitable for immediate genetic analysis.

4. Receive data obtained from any and all genetic analyses of these materials, for incorporation into genotypic databases.

5. Maintain, store, and distribute all databases, cell lines, and DNA samples for immediate genetic analysis by qualified investigators granted access by the GPO to these data and materials.

6. Continue to distribute data and biological materials already collected under the NIMH Human Genetics Initiative.

B. Cell Lines and DNA

The contractor shall receive and process blood drawn at one encounter from each subject and shall establish high-quality lymphoblastoid cell lines, from which DNA shall be extracted in sufficient quantities for genetic analysis (i.e., at least 30 micrograms).

C. Phenotypic Data

1. The contractor shall receive electronic files in ASCII or another format (e.g., SAS system file) of diagnostic and pedigree structure information. Data for each subject will minimally include a unique subject and pedigree identification number (ID), parental IDs, sex status, death status, ethnicity, age, twin status, all final best estimate diagnoses established according to the criteria in the fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and a best estimate of the age at onset of illness.

2. The contractor shall receive electronic files in ASCII or another format (e.g., SAS system file) of comprehensive clinical data obtained from the administration to subjects of a structured diagnostic interview (e.g., Diagnostic Interview for Genetic Studies). Data will be received without personal identifiers and thus are unlinked to their sources; such materials are "anonymous" samples.

3. All information in the database required to establish pedigree structure and to establish final best estimate diagnoses shall have been carefully verified by the contractor in collaboration with staff on the projects where the data were collected.

4. All of this phenotypic data shall be maintained in electronic databases in a format that permits rapid and efficient production of files for distribution.

5. A file of pedigree structure produced from the databases shall be immediately suitable for linkage and other genetic analyses. Given that this is a highly detailed and complex task, the contractor shall ensure that the contract is staffed at all times by personnel who are well-recognized as experts in the creation of such files and in the conduction of statistical genetic analyses published in peer-reviewed scientific journals.

D. Genotypic Data

1. When genotyping has been conducted, the contractor shall minimally receive electronic files of all available genotypes completed for each subject and also DNA marker names, allele sizes in base pairs and corresponding frequencies, and relative map distances for each marker.

2. The contractor also shall receive results from sequence and mutation analyses, and from any and all other genetic analyses performed on these data and biological materials.

3. All of this genotypic data shall be maintained in electronic databases in a format that permits rapid and efficient production of files for distribution.

4. A file of genotypic data produced from the databases shall be immediately suitable for linkage and other genetic analyses. Given that this is a highly detailed and complex task, the contractor shall ensure that the contract is staffed at all times by personnel who are well-recognized as experts in the creation of such files and in the conduction of statistical genetic analyses published in peer-reviewed scientific journals.

E. Subject Recruitment

Each investigator whose research project is funded under RFAs MH-98-010 and MH-99-xxx is responsible for the recruitment of pedigrees from which blood samples and clinical, diagnostic, pedigree structure, and other data are obtained. Family members who agree to participate may live in several different states, requiring the investigator to travel to one or more states for data and blood collection. Due to the difficulties in obtaining families, investigators often have little control over timing of the collection and shipment of blood samples. For example, a subject who agreed to be interviewed may initially refuse to participate when the investigator arrives, postponing the interview and blood collection one or more days. The reverse situation is also common: additional family members may arrive who were not originally scheduled and ask to participate in the study. Many samples are being collected from patients with brain disorders that for a variety of reasons may never again be available for the investigator to draw blood and collect important diagnostic information.

F. Subject Confidentiality

Traditional personal identifiers that may be utilized to establish the identity of individual subjects (e.g., surname, address, social security number, etc.) shall never be provided or accepted by the contractor. All data and biological materials received by the contractor thus shall be unlinked to their original sources. All biological materials generated under this contract (cell lines, DNA samples) shall also remain unlinked to their original source. While current and future technologies may allow DNA to be used as a personal identifier in conjunction with other data to establish an individual's identity, there is no information that will be contained in the contractor's databases that would permit the contractor as the keeper of a record system to retrieve an individual record based on the DNA samples maintained by the contractor. Thus, the contractor will not be able to use information collected under this contract to establish the identity of a given subject or query the databases and retrieve information for an individual subject whose identity is known from some other source. NIMH shall distribute information only for use in scientific research projects and shall prohibit in the Distribution Agreement signed by the contractor and qualified investigators any efforts to use data or biological materials to establish individual identities.

The contractor shall have a constituted Institutional Review Board (IRB), which will approve the distribution of data and biological materials to qualified investigators. NIMH shall assure that any necessary information required by the IRB is provided to the contractor. The contractor shall apply to the Office for Protection From Research Risks (OPRR) at the National Institutes of Health (NIH) for a project assurance number, if such a number has not been assigned to the contractor by OPRR. Obtainment of a project assurance number represents a binding commitment to minimum standards for the protection of human subjects, which safeguards the

rights and welfare of all human research subjects.

G. Number of Subjects

Since investigators cannot determine the exact number of subjects over a 12-month period of time, estimates are used for predicting the number of subjects per year. For the purpose of constructing fixed price schedules, the contractor shall anticipate receiving blood samples from the following minimum - maximum number of subjects: 500 – 2,750 subjects in year 1; 750 – 3,500 in option year 2; 750 - 3,500 in option year 3; 250 – 2,000 in option year 4, and 100 – 1,000 in option year 5. For the purpose of constructing a budget/cost proposal, the expected number of blood samples to be received are as follows: year 1, 2,000; option year 2, 2,500; option year 3, 2,500; option year 4, 1,500; option year 5, 500. The contractor shall have a skilled staff on site when shipments are scheduled to arrive Monday - Friday and Saturdays when necessary.

H. Access to Data and Biological Materials

Researchers other than those projects are funded under RFAs MH-98-010 and MH-99-xxx shall be granted access to data and biological materials maintained by the contractor under one of two conditions: (1) the researcher receives funding under a peer-reviewed NIMH research grant application to analyze these data; or (2) the researcher is certified by NIMH as a qualified investigator. Under condition 2, the contractor shall charge an access fee per cell line or DNA sample. Additional details are available on the WWW at http://www-grb.nimh.nih.gov/ newinstr.html. The contractor shall provide clinical, diagnostic, and pedigree structure data, As well as DNA samples and cell lines, to all researchers who have been granted access by NIMH. An appropriate system for the accounting and reporting of fees shall be established, and shall follow the fee schedule established by NIMH.

I. Specific Major Responsibilities of the Contractor

The contractor shall not use data, cell lines, and DNA for any purpose, other than that specified in this contract, without written approval of the GPO. Major responsibilities include the following:

1. Ensure the receipt of approximately 30 mls of whole blood from individuals enrolled for study in research projects supported under RFAs MH-98-010 and MH-99-xxx.

2. Transform blood samples to establish high-quality permanent lymphoblastoid cell lines. These cell lines shall be generated in a cost-effective manner with a minimum rate of 95%, and shall be free of contamination by bacteria, fungi, mycoplasma, other cells, etc.

3. Extract and store DNA from each cell line.

4. Ensure on a monthly basis the receipt of clinical, diagnostic, and pedigree structure for all individuals for whom blood has been received and transformed to create cell lines. Diagnostic information shall at a minimum include all best estimate final DSM-IV diagnoses.

5. Ensure the receipt of genotyping results from each project funded under RFAs MH-98-010 MH-99-xxx before its completion. These results include genotypes for each subject, DNA marker names, allele sizes in base pairs and corresponding frequencies, and relative map distances for each marker.

6. Ensure the receipt of genotyping results, if available, from each qualified investigator

provided with data and biological materials. These results include genotypes for each subject, DNA marker names, allele sizes in base pairs and corresponding frequencies, and relative map distances for each marker. In addition, the contractor shall receive results from sequence and mutation analyses and any and all other genetic analyses, if available.

7. Create an electronic database of clinical, diagnostic and pedigree structure information, such that all data have been carefully verified by the contractor in collaboration with the Principal Investigator on the grants under which the data were collected. Pedigree structure shall be verified, such that files generated from this database shall be ready for immediate genetic analysis and will not produce fatal errors when run through pedigree structure verification programs currently available (e.g., MAKEPED in the LINKAGE package, FSP in the SAGE package). All such phenotypic and pedigree structure information shall be maintained in electronic databases in a format that permits rapid and efficient distribution of files.

8. Create electronic databases of all available genotypic information for each subject. This includes all genotyping information, as well as DNA marker names, allele sizes in base pairs and corresponding frequencies, and relative map distances for each marker. In addition, the contractor shall receive results from sequence and mutation analyses. All such genotypic information shall be maintained in electronic databases in a format that permits rapid and efficient production of files for distribution.

9. Distribute electronic files of clinical, diagnostic, genotypic, and pedigree structure data, as well as cell lines and DNA, only with the expressed written approval of the Government Project Officer (GPO), and in accordance with current state or federal laboratory procedures assuring appropriate usage of genetic material.

10. Distribute such data and biological materials within two weeks of notification by the GPO that an investigator is authorized to receive such information.

11. Only accept with the expressed written approval of the GPO blood samples or data from investigators not funded under RFAs MH-98-010 and MH-99-xxx. This is expected to occur infrequently. Such data and materials shall not be treated any differently from data and materials received from grants funded under RFAs MH-98-010 and MH-99-xxx.

12. Maintain an electronic database containing detailed information for all shipments of data and biological materials to qualified investigators. This will minimally include the investigator's e-mail, telephone and fax number, mailing address, number of DNA and/or cell lines sent, and the number of pedigrees on which information was sent.

13. Distribute genotypic information and periodic updates, if available, of clinical, diagnostic, and pedigree structure data to qualified investigators who receive data.

14. Create and maintain, on a WWW site, tables of descriptive information describing the current status of the database for each disorder included in the NIMH Human Genetics Initiative. The information contained in these tables shall be comparable to those currently available on the WWW at http://www-grb.nimh.nih.gov/ gi.html.

15. Create and maintain a WWW site by which software and files for the administration of the Diagnostic Interview for Genetic Studies (DIGS) and the Family Interview for Genetic Studies (FIGS) shall be widely distributed. This site shall have a format

comparable to that currently available on the WWW at http://www-grb.nimh.nih.gov/interviews.html.

III. Services to be Performed

A. General Requirements

1. The GPO, whose position is defined in Section G of the contract, shall monitor all work under this contract.

2. Independently, and not as an agent of the federal government, the contractor shall furnish all necessary labor, services, equipment, materials, and supplies (except as otherwise specified herein) and perform the work set forth below.

B. Specific Requirement

All of the data and biological materials to be created, maintained, and distributed under the scope of work for this contract shall be included under the rubric of the NIMH Human Genetics Initiative. Descriptive information on the Initiative is available on the WWW at http://www-grb.nimh.nih.gov/gi.html. All of the current data and biological materials currently existing in the Initiative shall be received by the contractor and integrated with the data and biological materials received and created over the life of this contract.

The contractor shall conduct all aspects of the contract, as specified in the tasks listed below.

1. Task I. Management Transition

   (a) Within 1 calendar week of the contract award date, the contractor's project director shall meet with the GPO and the project directors from contracts N01 MH50003 and N01 MH70002, to discuss a plan for the smooth transition of any and all software, data files, databases, cell lines, and DNA.

   (b) The contractor shall review all data and materials received from the prior contractors to ensure the smooth transition of all data and materials.

   (c) Within 1 calendar week of this meeting the contractor shall finalize the work plan to successfully complete the transition and set-up of all equipment, files, and biological materials.

   (d) The contractor shall meet with the GPO and the prior contractors to resolve any remaining issues, if necessary.

   (e) All current electronic files of clinical, diagnostic, and pedigree structure data, genotypic data (if available), and all DIGS files, FIGS files, and DIGS software shall be received by the new contractor from the prior contractor within 2 calendar weeks of the contract award date. The contractor shall insure the integrity of these files and create phenotypic databases. Data collected from nearly 600 pedigrees shall be received.

   (f) All cell lines and DNA samples shall be received by the new contractor from the prior contractor within 4 calendar weeks of the contract award date. Approximately 4,800 cell lines are expected to be received. The new contractor shall pay for all moving costs incurred in the transfer and set-up of cell lines and DNA samples.

The contractor shall ensure the integrity and viability of these materials and store them accordingly.

(g) The contractor shall be responsible for maintenance of all equipment, including computer software, throughout the period of this contract and shall purchase maintenance contracts when necessary.

2. Task II. Training & Preparation

The Contractor shall perform these tasks to ensure staff are highly trained and that the contractor is prepared to receive blood and data:

(a) Purchase the following equipment:

i. Two four-gigabyte disks to store electronic data.

ii. One tape back-up drive to archive databases.

iii. Four –80°C freezers to store cell lines and DNA samples.

(b) Prepare blood collection kits as needed for shipment to investigators supported under RFAs MH-98-010 and MH-99-xxx. Blood samples shall be sent to the contractor via overnight express delivery. All shipments of blood from these projects shall be paid for by the contractor and charged to the contract.

(c) Ensure the capacity for receiving blood for processing within 4 calendar weeks of contract award. Set up laboratory and test equipment, if necessary, for the establishment of cell lines and extraction of DNA.

(d) Submit, within 2 calendar weeks of award, a detailed protocol for quality control measures to ensure that all cultures remain free of contamination by bacteria, mycoplasma, and other agents, and to prevent sample mix-ups. The GPO will review the final protocol, which will be in place by 4 calendar weeks after the contract award.

(e) A draft protocol shall be delivered to the GPO within 2 calendar weeks of the contract award date for quality control to ensure that both acceptable safety standards and the viability of biological materials are maintained during shipping. The GPO shall return the draft within one week of receipt. The contractor shall obtain GPO approval of the final protocol prior to receiving any blood under the contract.

(f) Assure the creation of processing algorithms and software needed to integrate datafiles received from the previous contractor and from the GPO, in order to assure the creation of phenotypic and genotypic databases. The data management protocol shall be submitted to the GPO within 2 calendar weeks after the contract award.

(g) Hire and train personnel, if necessary, to ensure the capacity for receiving and processing data for incorporation into databases and files suitable for immediate statistical genetic analysis, and which are distributed to qualified investigators as determined by the GPO, within 4 calendar weeks of contract award.

(h) Receive from the GPO within 2 calendar weeks contact information for each of the grants awarded under RFAs MH-98-010 that shall provide data and blood samples. Information shall subsequently be provided about grants awarded under RFA MH-99-xxx.

(i) Receive from the GPO within 2 calendar weeks information for each of the qualified investigators to whom data and biological materials have already been distributed by the prior contractors.

3. Task III. Establishment and Storage of Permanent Cell Lines

(a) A blood sample of approximately 30 mls drawn at one encounter from each subject shall be received. Epstein-Barr virus transformation of lymphocytes shall be used to create cell lines at a fixed price, using a protocol that specifies a single transformation.

(b) The contractor shall pay the shipping costs for receipt of the blood sample, which shall be charged to the contract.

(c) The contractor shall perform in accordance with the fixed price schedule of this contract, which covers the following tasks:

i. Transformation of lymphocytes, including the cost of PCR or hybridization to test for contamination by mycoplasma, fungi, etc. (year 1: 500 - 2,750; option year 2: 750 - 3,500; option year 3: 750 - 3,500; option year 4: 250 - 2,000; option year 5: 100 - 1,000).

ii. Cell line storage on an annual basis (year 1: 5,300 - 7,500; option year 2: 6,050 - 11,050; option year 3: 6,800 - 14,550; option year 4: 7,050 - 16,550; option year 5: 7,150 - 17,050).

iii. Regrowth of cell lines (year 1: 450 - 2,475; option year 2: 675 - 3,150; option year 3: 675 - 3,150; option year 4: 225 - 1,800; option year 5: 90 - 450).

iv. Shipping costs to receive a blood sample (year 1: 500 - 2,750; option year 2: 750 - 3,500; option year 3: 750 - 3,500; option year 4: 250 - 2,000; option year 5, 100 - 1,000).

v. Any and all other tasks required to establish and store cell lines not covered above.

(d) Lymphoblastoid cell lines shall be established with a minimum success rate of 95%.

(e) A portion of the blood received from each subject shall be cyropreserved for back-up in the event of transformation failure.

(f) The work plan shall document the precise transformation methods that will be employed, a rationale for their selection, reliability, feasibility, and documented evidence that the method has been successful (minimum success rate of 95%) in a sufficiently large number of samples. The work plan shall also specify actions that shall be taken to maximize the transformation success rate and to ensure that

it is maintained at a minimum of 95% during the performance of the contract.

(g) The contractor shall detail how cell cultures will be grown and shall divide each of these cell cultures among a number of ampules as required to maintain an adequate level of access to the cell lines. These will be frozen and stored under conditions in which the maximal viability is retained.

(h) The contractor shall obtain a written statement from each grantee collecting pedigree data that contains appropriate confirmation that the individual from whom the blood was obtained had consented to their use for research purposes by the wider scientific community. No personal identifiers of any kind will be included in the consent. The subjects will not know their cell line identification numbers, and the contractor will not have the subjects' identity.

4. Task IV . Cell Line Transformation Failures and Corrective Action

(a) In the event of cell transformation failure, where a cell line cannot be established for a subject from a blood sample received by the contractor (including the use of cyropreserved blood), the contractor shall notify the GPO within 2 calendar weeks of the determination of failure and shall request that the project that submitted the blood sample to obtain additional blood from the subject.

(b) Any problems in the contractor's protocols that are responsible for transformation failure shall be detected and corrected as rapidly as possible. The Contractor shall closely monitor its success rate.

5. Task V. Cell Line Quality Control

(a) The protocol shall ensure that cell lines are established using procedures that ensure freedom from contamination by bacteria, fungi, mycoplasma, other cells, etc.

(b) A sample of unprocessed whole blood shall be cyropreserved in order to resolve questions that may arise regarding sample mix-ups and pedigree structure.

(c) DNA samples obtained from a subsequent cell line expansion shall be compared against the sample obtained from the previous cell line expansion. This shall be done in every case to confirm that both DNA samples were derived from the same individual.

(d) The contractor shall maintain a suitable off-site facility (this need not be a separate building but must include separate storage facilities and power source) for storage of an adequate number of ampules of each cell line as a safeguard against accidental loss of cell lines. The back-up ampules of each cell line will be sent to the off-site facility at the time they are ready for storage, thus allowing for parallel storage of all cell lines in the Repository. The lines will be stored at both sites for the life of this contract and prepared for transfer to any subsequent contractor at the expiration of this contract. All contract provisions applying to the use and handling of biological material in the contractor's facility shall apply to any and all biological materials stored at the off-site facility.

6. Task VI. DNA Extraction

   (a) At least 30 micrograms of DNA shall be extracted at a fixed price from each cell line established by the contractor.

   (b) The contractor shall perform in accordance with the fixed price schedule of this contract, which covers the following tasks:

      i. Isolation, preparation, and storage of DNA from each cell line that is established (year 1: 500 - 2,750; option year 2: 750 - 3,500; option year 3: 750 - 3,500; option year 4: 250 - 2,000; option year 5: 100 - 1,000).

      ii. Any and all other tasks required to extract, prepare, and store DNA not covered above.

7. Task VII . Unique ID Numbers

   (a) A unique Cell Repository ID number shall be assigned consecutively by the contractor to each subject on whom a blood sample is received and a cell line successfully established.

   (b) A unique site ID number shall be assigned by the contractor to each project supported under RFA MH-98-010 and MH-99-xxx. All subjects for whom clinical data is received from that project shall also be assigned this site ID number.

   (c) A unique subject ID number shall be assigned by the contractor to each subject on whom clinical data is received from each project supported under RFA MH-98-010 and MH-99-xxx. This shall represent a concatenation of the site ID number and subject ID number assigned by each project, and shall result in an ID number that is unique within the entire database of all subjects across all projects.

   (d) The unique Cell Repository ID and concatenated subject/site IDs shall be used to retrieve all data for a subject across databases of clinical, diagnostic, pedigree structure, and genotypic data, and shall be used by qualified investigators to request biological materials.

8. Task VIII . Clinical, Diagnostic, and Pedigree Structure Databases

   (a) The contractor shall receive on a regular basis from research grants supported under RFA MH-98-010 and MH-99-xxx electronic files in ASCII or another format (e.g., SAS system file) containing clinical, diagnostic, and pedigree structure information.

   (b) Separate databases shall be maintained for each disorder (schizophrenia, Alzheimer disease, bipolar disorder, early-onset recurrent unipolar depression) on which data is contributed from the research grants supported under RFA MH-98-010 and MH-99-xxx.

   (c) The contractor shall create and maintain a database of clinical, diagnostic, and pedigree structure information that for each subject minimally includes:

      i. Subject ID number.

ii. Family ID number.

iii. Site ID number.

iv. Parental ID numbers.

v. Sex.

vi. Death Status.

vii. Ethnicity.

viii. Age.

ix. Twin Status.

x. Final best estimate DSM-IV diagnosis.

xi. Source of information to establish diagnosis (medical records, interview, etc).

xii. Best estimate of the age at onset of illness.

(d) The contractor shall create a database sufficient to contain all clinical information derived from administration to subjects of a structured psychiatric diagnostic interview.

(e) The contractor shall maintain all data without personal identifiers. Data, cell lines, and DNA are thus unlinked to their original sources.

9. Task IX . Data Verification

(a) The contractor shall initially verify that data are suitable for immediate genetic analysis. Pedigree structure shall be verified, such that generated datafiles will not produce fatal errors in existing pedigree structure verification programs currently available, e.g., MAKEPED in the LINKAGE package, FSP in the SAGE package.

(b) The contractor shall exchange information with grantees and their staff who collected the data, in order to verify all diagnostic and pedigree structure information as described in Task VIII (c).

(c) The contractor shall not verify the extensive array of clinical information derived from the administration of a structured psychiatric diagnostic interview to subjects, as described in Task VIII (d). Grantees who collect such data shall be responsible for the verification of such data.

10. Task X . Final (Laboratory) Verification of Pedigree Relationships

(a) The contractor, only as directed by the GPO for approximately 5% of subjects for whom blood is received, shall obtain final verification of pedigree relationships by genotyping subjects on a predetermined set of highly polymorphic markers.

(b) A fixed price schedule shall be submitted along with the work plan that specifies

the cost per subject for final (laboratory) verification of pedigree relationships.

(c) The contractor shall specify a cost-effective protocol for genotyping subjects on this predetermined set of markers, and establish a fixed price per subject.

(d) In circumstances where genotyping results are inconsistent with pedigree structure information as provided by the grantee who collected the data, and only as directed by the GPO, the contractor shall exchange information with staff on the projects who provided the pedigree structure information. The contractor shall work with project personnel to resolve the cause for the discrepancy, i.e., sample mix-up, nonpaternity, etc.

(e) In circumstances where genotyping results are inconsistent with pedigree structure information as provided by the research project in which the data were collected, and only when scientifically appropriate and as directed by the GPO, the contractor shall contact the research project and request a blood re-draw.

(f) Upon resolution of the inconsistency between the contractor's genotyping results and the initial pedigree structure provided by a grantee, and only as directed by the GPO, the contractor shall use the results from genotyping analyses to update and modify pedigree structure in all databases. If no resolution is obtained, the contractor shall discard data on the subject, modify databases accordingly, demarcate the subject, or pursue another course of action, as directed by the GPO.

(g) The contractor shall catalog all inconsistencies in pedigree structure that are detected by qualified investigators gaining access to data and materials and who provide genotypic results to the contractor. The contractor shall use the results from these genotyping analyses to update and modify pedigree structure in all databases, only as directed by the GPO.

11. Task XI . <u>Genotypic Databases</u>

(a) The contractor shall receive electronic files containing genotypic data from research grants supported under RFA MH-98-010 and MH-99-xxx, and also from qualified investigators in the wider scientific community who gain access to data and biological materials.

(b) The contractor shall create an extensive database of such genotypic data that includes:

i. DNA marker names, allele sizes in base pairs and corresponding frequencies, and relative map distances, for genotyping projects.
ii. Gene sequence.

iii. Mutation analysis results.

iv. Results from any and all other genetic analyses of data and biological materials.

(c) The contractor shall provide grantees and other qualified investigators sending data a precise file format (e.g., ASCII, SAS system file) to assure that the data may be easily and rapidly incorporated within the genotypic databases maintained

by the contractor.

12. Task XII . Database Quality Control

(a) The contractor shall maintain accurate databases that are regularly updated and verified.

(b) The contractor shall thoroughly document all variables and all updates, changes, or corrections to database information.

(c) Databases shall be organized to permit rapid and efficient downloading and uploading of information.

(d) The contractor shall assure that ASCII files and other formats (e.g., SAS system files) can be rapidly and efficiently generated from all databases.

(e) The contractor shall maintain a daily backup of all electronic databases to protect against the accidental data loss.

13. Task XIII. Distribution of Data and Biological Materials

(a) A fixed price schedule shall be submitted along with the work plan that specifies the cost per cell line and DNA sample for shipment to qualified investigators. This schedule shall include the following:

i. Room temperature shipments of biological materials (extracted DNA and cultures of transformed cells).

ii. Frozen (dry ice) shipments of biological materials (viable cells).

(b) Any and all data (clinical, diagnostic, pedigree structure, and genotypic information) and biological materials (cell lines and/or DNA samples) shall be distributed by the contractor to grantees and other qualified investigators, only upon written authorization by the GPO. Approximately 5 – 10 requests are expected in year 1.

(c) All data distributed and maintained by the contractors are unlinked to their original sources. As the keeper of databases and materials, the contractor shall not attempt to establish the identity of individual subjects because all biological materials (DNA, cell lines) and data are unlinked to other personal identifiers that would establish an individual's identity.

(d) The contractor shall distribute within two calendar weeks of a request by the GPO high-quality documentation and datafiles in ASCII or other formats (e.g., SAS system files) that have been most recently updated. It is anticipated that 10 –20 requests may occur annually. This shall include the following:

i. Updated and verified diagnostic and pedigree structure information, as provided by the approximately 25 grantees supported under MH-98-010 and MH-99-xxx.

ii. Comprehensive clinical information from a structured diagnostic interview, as provided by the grantees supported under MH-98-010 and

MH-99-xxx.

iii. Genotypic information provided by grantees supported under MH-98-010 and MH-99-xxx, and provided by all qualified investigators given access to data and biological materials by the GPO.

iv. Complete documentation of all variables and their coding.

(e) The contractor shall distribute high-quality biological materials. These include the following:

i. Lymphoblastoid cell lines.

ii. At least 30 micrograms of DNA.

(f) The contractor shall prepare drawings of all pedigrees contained in the datafile provided to qualified investigators, by using an existing pedigree drawing program (e.g., CYRILLIC).

(g) The contractor shall develop and maintain a secure password-protected site on the WWW, in order to permit the rapid and efficient distribution of electronic datafiles to qualified investigators granted access by the GPO.

(h) All investigators given access to data and biological materials shall be approved by the GPO, in accordance with the most recent procedures described on the WWW at http://www-grb.nimh.nih.gov/newinstr.html.

(i) All qualified investigators given access to data and biological materials by NIMH shall sign with NIMH the most recent version of the Distribution Agreement available on the WWW at http://www-grb.nimh.nih.gov/distribution.html. The contractor also shall be a co-signatory of each Distribution Agreement.

(j) The GPO retains the right to modify existing access procedures and the Distribution Agreement.

(k) The government shall own cell lines and all other products (e.g., DNA, databases, documentation) produced under this contract.

(l) NIMH shall provide access to DNA samples for each of the grantees supported under MH-98-010 and MH-99-xxx that provides blood samples and data to the contractor. The contractor should expect that each such grantee will request one DNA sample from each subject contributed. In this case, the requestor shall not be charged for a single 50 microgram DNA sample and its shipment. Any other additional shipments shall be subject to access costs and shipping charges incurred by the requestor, as determined by the GPO.

(m) The contractor shall ship cell lines and/or DNA samples to requestors approved for access by NIMH within 2 calendar weeks of receipt by the contractor of the GPO's approval and request for shipment.

(n) Biological material will be shipped in a way that shall ensure the viability of the cells or satisfactory condition of the DNA.

(o) The contractor shall package and ship biological and hazardous materials in accordance with all state and federal safety and shipping regulations, and with the Center for Disease Control and Prevention procedures for packaging and shipping biological materials.

(p) The contractor shall charge the recipient of data and biological materials all reasonable shipping charges, except as indicated in paragraph (l) above. These fees shall not be charged to the contract.

(q) The GPO and CO shall establish a schedule of fees to be charged by, and payable to, the contractor for access to cell lines and DNA samples. The GPO retains the right to waive the access charge for a recipient. In these cases, the contractor shall pay any and all shipping charges. The current access fee schedule established by NIMH is described in the most recent Distribution Agreement on the WWW at http://www-grb.nimh.nih.gov/ distribution.html. The contractor shall establish a process, with CO approval, to ensure that all such fees are promptly collected and accounted for accurately, and offset against contract costs in a proper and timely manner.

(r) If the access charge is not waived by NIMH, the contractor shall not distribute materials before payment in full is received. Payment shall be in the most expeditious format (e.g., check, purchase order) possible.

(s) The contractor shall only provide data and biological materials to a recipient biomedical research institution for use by a designated principal investigator in a scientific research project specified in the signed and completed Distribution Agreement, and only when authorized by the GPO. Data and biological materials shall by provided to recipient biomedical research organizations and not to individuals.

(t) Income received from fees charged for access to cell lines and DNA shall be utilized to offset contract costs. Such income shall be reflected on the contractor's invoice for the month it is received. The contractor shall establish a system, with the CO's approval, separate from other contract costs to account for such fees.

14. Task XIV . <u>Provision of Data Updates</u>

(a) The contractor shall provide quarterly updates of phenotypic and genotypic data, as directed by the GPO, to qualified investigators who receive data and biological materials.

(b) The updates shall include, but not be limited to, changes in diagnostic status, pedigree structure, and recently received genotypic data provided by other qualified investigators.

(c) The format of these updates shall permit recipients to easily identify which subjects have an updated or modified diagnosis, and which have newly available DNA samples that may be obtained from the contractor.

(d) Updates shall be rapidly and efficiently distributed via a secure password-protected site on the WWW.

15. Task XV . <u>Receipt of Data from Qualified Investigators</u>

a) Executed Distribution Agreements shall stipulate that qualified investigators who receive data and biological materials from the contractor are obliged to provide the results of any and all genetic analyses derived from these data and materials one year after receipt or upon publication, whichever comes first. The contractor shall oversee the compliance of investigators with this requirement.

b) As stated under Task XI (a) above, the contractor shall also receive comparable data from research projects supported under RFAs MH-98-010 and MH-99-xxx.

c) The contractor shall develop and provide to the qualified investigator submitting data a precise electronic format by which these data are to be received.

d) All data shall be indexed by the unique concatenation of the subject and site ID number.

e) All genotypic data provided by qualified investigators shall remain unlinked to their original sources.

f) The contractor shall receive from qualified investigators data relevant to the establishment of paternity and laboratory verification of pedigree structure.

g) The contractor shall rapidly and efficiently incorporate all verified data received from qualified investigators into existing clinical, diagnostic, pedigree structure, and genotypic databases.

h) The contractor shall distribute these data to other qualified investigators requesting access who are approved by NIMH, as described under Task XIII (d) and (e) above.

16. Task XVI. <u>Qualified Investigator Database</u>

(a) The Contractor shall maintain a database of information about qualified investigators given access by NIMH who receive data and biological materials.

(b) The database shall minimally include for each investigator the following information: name and title of the research project's principal investigator, mailing address, telephone number, fax number, e-mail address, and recipient institution.

(c) For each investigator, the database shall also include the date of access notification given by NIMH to the contractor, number of DNA samples and/or cell lines provided, repository ID numbers of subjects from whom cells lines and/or DNA were sent, the date when genotypic data were requested, the date when genotypic data were shipped, the fee charged, and when the fee was received by the contractor and offset against contract costs.

(d) This database shall be continuously updated with information including, but not limited to, subsequent shipments of cell lines and/or DNA as authorized by the GPO.

(e) This database shall also include creation and maintenance of an e-mail list of all qualified investigators, to enable rapid and efficient electronic communication among the investigators, the contractor, and the GPO.

17. Task XVII . WWW Resources

(a) Access procedures, descriptive data, and other relevant information about the data and biological materials currently distributed through the NIMH Human Genetics Initiative are described on a site maintained by NIMH on the WWW at http://www-grb.nimh.nih.gov/gi.html. The contractor shall maintain pages on the WWW that link to NIMH's pages.

(b) The contractor shall maintain on a WWW site descriptive information about the NIMH Human Genetics Initiative databases created and maintained by the contractor. This information shall minimally include the following: number of pedigrees, number of affected sibling pairs, number of affected subjects with DNA available, numbers of sibships of varying sizes of affected subjects, etc. These pages shall be modeled on those currently available for the NIMH Human Genetics Initiative at http://www-grb.nimh.nih.gov/gi.html, and shall be updated at least monthly.

(c) The contractor shall create and maintain a WWW site by which software and files for the administration of the Diagnostic Interview for Genetic Studies (DIGS) and the Family Interview for Genetic Studies (FIGS) shall be widely distributed. This site shall have a format comparable to that currently available on the WWW at http://www-grb.nimh.nih.gov/interviews.html.

(d) The contractor shall maintain secure password-protected sites on the WWW that permit downloading of updates and datafiles and updates, as described in Tasks XIII (g) and XIV (d) above.

18. Task XVIII. Other Activities

a) Three months prior to the completion of the contract, a full inventory of cell lines, DNA, and plasma shall be provided to the GPO. A system for the transfer of all cell lines and biological materials to a storage facility or successor contractor shall be provided at least twelve months before the expiration date of this contract. If there is a successor contractor or if this function is be to taken over by the Government, the contractor shall inform and assist the GPO or successor contractor in the transition and day-to-day operation to enable the successor to gain detailed working knowledge of procedures utilized in order to assure proper and successful transition.

b) Three months prior to the completion of the contract, a full inventory of all genotypic and phenotypic electronic databases shall be provided to the GPO and any successor contractor. A system for the transfer of all electronic databases and files to a successor contractor shall be provided at least twelve months before the expiration date of this contract. If there is a successor contractor or if this function is be to taken over by the federal government, the contractor shall inform and assist the GPO or successor contractor in the transition and day-to-day operation to enable the successor to gain detailed working knowledge of procedures utilized in order to assure proper and successful transition.

c) The contractor may conduct statistical genetic and molecular genetic analyses of any and all data and biological materials created, collected, and maintained under the scope of work of this contract. Under these circumstances, the contractor

shall be required to sign the Distribution Agreement. Any and all shipping charges shall be at the contractor's expense.

IV. Special Requirements

A. Fees are expected to be collected by the contractor, according to a fee schedule established by the GPO and CO, which shall be used as offset revenue against contract charges for the month in which the offset revenue was received.

B. The budget estimate should assume the following amounts of offset revenue in each year: year 1, $50,000; option year 2, $100,000; option year 3, $150,000; option year 4, $200,000; option year 5, $250,000.

C. The budget estimate should include storage of 4,800 cell lines in year 1 and each of the 4 option years, received from the previous contractor. Fixed unit price schedules shall be established for year 1 and each of the 4 option years for each of the following, assuming the minimum and maximum quantities specified:

YEAR 1

		QUANTITY		
DESCRIPTION	UNIT	MINIMIUM	MAXIMUM	EXPECTED
Transform lymphocytes (including PCR or hybridization for mycoplasma)	cell line	500	2,750	2,000
Extract and prepare DNA	vials	500	2,750	2,000
Cell line and DNA shipments	parcels	500	2,750	2,000
Store cell lines	cell line	5,300	7,550	6,800
Regrow cell lines	cell line	450	2,475	1,800
Establish pedigree relationship	DNA	25	138	100
Receive blood shipments	tubes	500	2,750	2,000

YEAR 2

		QUANTITY		
DESCRIPTION	UNIT	MINIMIUM	MAXIMUM	EXPECTED
Transform lymphocytes (including PCR or hybridization for mycoplasma)	cell line	750	3,500	2,500
Extract and prepare DNA	vials	750	3,500	2,500
Cell line and DNA shipments	parcels	750	3,500	2,500
Store cell lines	cell line	6,050	11,050	9,350
Regrow cell lines	cell line	675	3,150	2,250
Establish pedigree relationship	DNA	38	175	125
Receive blood shipments	tubes	750	3,500	2,500

YEAR 3

		QUANTITY		
DESCRIPTION	UNIT	MINIMIUM	MAXIMUM	EXPECTED
Transform lymphocytes (including PCR or hybridization for mycoplasma)	cell line	750	3,500	2,500
Extract and prepare DNA	vials	750	3,500	2,500
Cell line and DNA shipments	parcels	750	3,500	2,500
Store cell lines	cell line	6,800	14,550	11,800

Regrow cell lines	cell line	675	3,150	2,250
Establish pedigree relationship	DNA	38	175	125
Receive blood shipments	tubes	750	3,500	2,500

YEAR 4

		QUANTITY		
DESCRIPTION	UNIT	MINIMIUM	MAXIMUM	EXPECTED
Transform lymphocytes (including PCR or hybridization for mycoplasma)	cell line	250	2,000	1,500
Extract and prepare DNA	vials	250	2,000	1,500
Cell line and DNA shipments	parcels	250	2,000	1,500
Store cell lines	cell line	7,050	16,550	13,300
Regrow cell lines	cell line	225	1,800	1,350
Establish pedigree relationship	DNA	13	100	75
Receive blood shipments	tubes	250	2,000	1,500

YEAR 5

		QUANTITY		
DESCRIPTION	UNIT	MINIMIUM	MAXIMUM	EXPECTED
Transform lymphocytes (including PCR or hybridization for mycoplasma)	cell line	100	1,000	500
Extract and prepare DNA	vials	100	1,000	500
Cell line and DNA shipments	parcels	100	1,000	500
Store cell lines	cell line	7,150	17,550	13,800
Regrow cell lines	cell line	90	900	450
Establish pedigree relationship	DNA	5	50	25
Receive blood shipments	tubes	100	1,000	500

D. The data management functions will be funded as a cost reimbursement component. The cell line creation, DNA extraction, and other laboratory functions will be funded as a fixed cost component.

E. The contractor is expected to work as needed in a collaborative and interactive fashion to exchange information with the grantees funded under RFAs MH-98-010 and MH-99-xxx, in order to establish pedigree structure and diagnostic information.

F. The contractor shall not use data and biological materials that are received or produced under this contract, alone or in conjunction with any other information, in any effort to establish the individual identities of research subjects.

G. Phenotypic and genotypic data and biological materials (cell lines, DNA samples) received or generated under this contract are to be widely distributed to qualified investigators in the scientific community, as determined by the GPO.

H. The contractor shall have, or shall establish, an Internal Review Board that will approve the distribution of data and biological materials to qualified investigators.

I. The contractor shall be a co-signatory with NIMH and with qualified investigators approved for access to data and biological materials the most recent version of the Distribution Agreement available on the WWW at http://www-grb.nimh.nih.gov/distribution.html.