This manual is one of a series of protocols and manuals of operation for the Jackson Heart Study (JHS). The complexity of the JHS requires that a sizeable number of procedures be described, thus this rather extensive list of materials has been organized into the set of manuals listed below. Manual 1 provides the background, organization, and general objectives of the JHS Study. Manuals 2 and 3 describe the operation of the Cohort Procedures and Family Study Components of the study. Detailed Manuals of Operation for specific procedures, including those of reading centers and central laboratories, make up Manuals 3 through 9. Manual 10 describes the Cohort Surveillance Component of the study and Manual 11 details the Data Management System.

**JHS Study Protocols and Manuals of Operation**

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JHS Manual 3: Family Study

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1.0 INTRODUCTION, BACKGROUND AND HYPOTHESES

It is generally accepted that most common cardiovascular diseases and associated risk factors are the result of the complex interplay between multiple environmental and genetic factors. The excess CVD risk experienced by African-Americans relative to their white counterparts in the United States may be the result of disproportionate exposure to harmful environmental factors (e.g., diet and stress), increased frequency of deleterious genes or the complex interplay between these risk factors. Improvement in molecular techniques and findings from the Human Genome Project makes it possible to study the contributing influence of genetic factors to the pathophysiology of common complex diseases including most forms of CVD. Evidence from ongoing studies of the genetic epidemiology of CVD shows that differential distribution of CVD and associated risk factors may in part be due to ethnic differences in gene variants. Recent molecular evidence shows that the influence of some gene variants is similar across ethnic groups while other variants are more important in specific ethnic groups including African-Americans. The Jackson Heart Study (JHS) promises to contribute to our understanding of the genetic variants relevant to increased susceptibility and/or resistance to heart, lung and blood disorders in African-Americans and other ethnic populations in the US and across the globe.

Extensive work has been undertaken to better explain the genetics of CVD and associated risk factors including hypertension, obesity, and diabetes. Findings from the renin-angiotensin aldosterone system, an important pathway in water and salt regulation, have identified several genetic variations that may increase susceptibility to hypertension in certain ethnic groups. In comparison to Caucasians, some of these genetic variations are more common in ethnic minority populations including African-Americans. However, the significance of these genetic variants in the pathophysiology of hypertension and other CVDs has been inconsistent within and between populations.

In addition, several investigators have uncovered specific single-gene defects leading to hypo and hypertension in small populations. These defects, which obey simple Mendelian principles, include glucocorticoid remediable aldosteronism, apparent mineralocorticoid excess and Liddle’s syndrome. However, these and other forms of inherited hypertension account for only a small fraction of essential hypertension. Similarly, work in diabetes and obesity has uncovered rare forms of disease that are explained by a single gene defect. Despite explaining only a small proportion of the observed genetic variations, these advances have provided invaluable insight into the pathophysiology of these diseases, which may lead to novel therapeutic and preventive strategies in the future.

The proposed JHS genetic research seeks to identify new genes important to heart, lung and blood disorders in African-Americans. In addition, knowledge of candidate genes will be used to investigate the effect of known variants on disease risk in African-Americans. To date there have been few large biomedical studies involving families of African origin. Therefore, replication of genetic findings from other populations of African origin is also an important goal of the JHS. Because of the complex interaction of risk factors for heart, lung and blood disease, a major goal of the JHS is investigation of genotype-environment interaction in determining disease risk.

The JHS genetic research is further defined to focus on heart, lung and blood disorders where there is a disproportionate risk in African-Americans. For example, hypotheses focus on genetic and environmental risk for obesity, particularly in African-American women. The JHS will have a unique opportunity to identify new genes involved in the development of renal disease and hypertension. Other areas of interest include identification of new genes predisposing to left ventricular hypertrophy and disentangling the genetic and environmental factors leading to diabetes in African-Americans.
1.1 Cultural Sensitivities

There is a long history of mistrust of the medical scientific community among African-Americans. This mistrust manifests itself in several ways including low rates of involvement of African-Americans and other minorities in medical research and skepticism in adopting the resulting recommendations. In addition, the willingness of some investigators to use genetics to explain ethnic differences (e.g., performance on IQ tests and mental illness), especially in the absence of rigorous evidence, has unquestionably contributed to further alienation of ethnic minority populations with respect to participation in biomedical research activities.

It is obvious that any investigations of racial/ethnic differences in cardiovascular or other diseases (like cancer or mental illness) have to be undertaken in such a way as to preserve the dignity of all participants. This may be particularly true of genetic studies given the widespread belief that genetic determinants of disease cluster in racial/ethnic groups. In this regard, the JHS must be conducted in a manner that adheres to the desires and concerns of the greater Jackson area African American community. The JHS investigators have engaged in dialogue with the community concerning this issue and will continue this dialogue as the study progresses and newer genetic techniques evolve.

The JHS investigators will pay particular attention to issues of race and privacy whenever dealing with genetic materials. The primary use of the data will be to attempt to better explain CVD and to identify potential preventative and therapeutic strategies. As there may be differences from one racial or ethnic group to another in the genetic and environmental contributions to CVD, we may discover genes that are more or less important in African-Americans than in other groups. There must be care to foresee what may be implied or inferred, yet not stated, when genetic data are reported. These steps are absolutely necessary for the JHS data to be accepted and effectively applied for the reduction of CVD morbidity and mortality in African-Americans.
2.0 DESCRIPTION OF THE JHS FAMILY STUDY

The JHS Family Study is designed to detect new genes influencing risk factors for a variety of heart, lung and blood disorders. To this end, family enrollment is based on a random ascertainment strategy. In addition, the Family study will be nested within the JHS population-based sample, such that each participant eligible to participate in the JH cohort study is a potential proband (initial family contact) for the family study. This will ensure that results obtained from the Family Study are generalizable to the greater JHS community.

1. To be eligible, a proband should be between the ages of 35-84 years;
2. Live in the Jackson tri-county area;
3. Self identify as African American; and
4. Have an appropriate family structure and family members who are willing to participate in the JHS family study.
5. In addition, attempts will be made to enroll equal numbers of male and female probands to ensure that there are no subtle biases in family structure.

Figure 1 shows a schematic diagram of the relationship between the random population-based sample and the family sample. It may be necessary to sample outside of our age range to obtain families of sufficient size. However, we would restrict the lower bound of age to 21 years of age and make all efforts to stay within the 35-84 year age range. In addition, some family members may not be of African descent. These members will be included in the family study as they clearly bear on familial determinants of CVD.

The total number of individuals in the family study is expected to be 2,000. Efforts will be made to recruit the largest families available with an optimum family size of at least twelve, resulting in approximately 160 families depending on the family size.
3.0 COMMUNITY INVOLVEMENT IN GENETIC RESEARCH

The success of the Family Study of the JHS rests, in large measure, on the co-involvement of the Jackson metropolitan community as partners with the research team. This partnership and sharing of power includes sharing in decision-making on central aspects of the design, ongoing evolution and monitoring of the Family Study. Creating opportunities for the community and research partners to think together about new solutions for the age-old issues of suspicion and mistrust surrounding the gathering and use of genetics materials is central to informed community co-participation. Two exemplar opportunities are addressed below as community decision-making and community education. Additional opportunities will be incorporated as appropriate throughout the course of the JHS.
Figure 1. Family Study

Potential Pool of Probands
ARIC participants and randomly ascertained men and women using Accudata List
N ~ 4,700
Ages 35 - 84

Eligible probands (approximately 200 men and women)

1. 35-84 years of age
2. Live in the Jackson tri-county area
3. Self identify as African American.
4. Have required family structure and family members who are willing to participate in the JHS family study

1. Optimum family size is at least 12 (i.e., 2 full siblings of the proband and 9 additional first degree relatives of the proband).
2. Priority will be given to families in which each of a pair of parental partners have 11 mutually exclusive first-degree relatives.
3. Priority should be given to family members who are between 35 to 84 years of age.
4. If necessary, choose first-degree relatives who are closest to the age requirements of 35 to 84 years. For example, choose a 30 year old before choosing a 25 year old irrespective of their sex.
5. For families with 8 or fewer first-degree relatives refer to the additional eligibility requirements in section 5.1 of this manual.

Total number of participants for the JHS

Randomly ascertained 4,700 (including ~ 200 probands)
Family members of probands 1,800

6,500
3.1 Community Decision-making

A process for community decision-making in the JHS is described in Manual 1 in the section defining the “Community Council (CC)”. The CC is designed to serve as the “voice” of the community with power to influence decision-making on JHS issues vested in its two voting Steering Committee members. In keeping with this process model, one or more representatives of the CC will participate in the Genetics Committee (GC). This representative(s) will act as a liaison between the GC and the CC to assure community co-participation in all decisions regarding the Family Study. Such level of involvement will allow the representatives attending the GC meetings to relay information on issues, discussions and recommendations reciprocally between the GC and the CC. The process will make provisions for sufficient time for input and dissemination of information to the full CC in order to provide its two Steering Committee voting representatives the opportunity to express the desires of the community during Steering Committee meetings.

A specific process for time-sensitive decisions will be developed by the GC and CC to assure community co-participation within realistic time constraints, which will not jeopardize elements of study protocol.

3.2 Community Education

Community capacity building is a major goal of the JHS. Improving community knowledge and understanding of key issues in cardiovascular health through ongoing interactive community education is an expected outcome of this study. Providing opportunities for educational dialogue regarding issues of family history and genetics creates another opportunity for shared learning and new research partnerships with the community at-large. As researchers and community come together to learn more about genetic and environmental aspects of disease, possibilities for new conversations about community concerns such as cloning, opening themselves to DNA identification for other than research purposes, the ongoing legacy of Tuskegee, and others emerge.

Education and community dialogue about issues of family history and genetics will be enacted as one component of the Community Mobilization Health Education Plan. In keeping with the overall design of this plan, education will occur on multiple levels including dissemination of educational materials, “train the trainer” family/genetics sessions, community education forums on family history and genetics as CV risk factors, among others. As few materials are available for this type of programmatic effort, initial efforts will be directed to developing culturally sensitive materials with input from collaborating consultants and community co-investigators. Sample educational materials from other projects including a family/genetics component will be sought as models. Input regarding community education needs and desires specific to the JHS will be obtained from the CRC, the Community Mobilization Advisory Committee and the Council of Elders throughout the process. These materials will be disseminated widely to the JHS cohort and the community at-large.

Genetics training workshops were initiated in March, 2000 as an ongoing component of community education. These workshops, which will include a train the trainer component, will be conducted periodically by genetics collaborators and consultants. These efforts will include JHS investigators and staff and select community members. The CC, as both representatives of and liaisons to the community at-large, along with interested members of the Council of Elders and the Community Mobilization Advisory Committee will be invited to take part in the next series of family/genetics workshops. These sessions will serve to both increase understanding of the key issues among the co-investigators and to establish a “train the trainer” model for conducting ongoing community forums for genetics information and discussion. It is anticipated that at least two rounds of these sessions will be conducted to create a large enough cadre of community/investigator teams to conduct these forums.

Ongoing community education and dialogue forums will be offered throughout the study area in places where the local community gathers. These forums will be co-led by a community trainer and a JHS investigator/staff to provide opportunities for information dissemination about family/genetics and
community discussion of issues of importance. A record of community discussions and issues will be kept from these sessions with a summary provided to both the CC and the GC on a quarterly basis to assure ongoing consideration of community concerns in the Family Study.
4.0 COLLECTING FAMILY INFORMATION

4.1 Protocol

Information regarding potential eligibility for the Family Study will be gathered from all eligible JHS participants (ARIC, random community sample and family sample) during the initial Home Induction Interview. Select questions (items 10-19) on the Eligibility (ELG) Form (see Manual 2) will ascertain the number of family members (grandparents, parents, siblings, children, aunts and uncles, nieces and nephews) living in the tri-county sampling area for the JHS who are 21 years of age or older.

A family score will be calculated from data in the Eligibility Form using a defined point system (see “Data Management”). If an informant shares biological children with someone who (1) lives in the same household; (2) has family in the tri-county area; and (3) has participated in JHS, then the informant’s “family score” will be increased to reflect this (see “Data Management”).

If a participant’s family score is above a threshold level, his/her record will be flagged to identify eligibility for the family sample and the participant’s family will be assigned a FAMILY ID number (FAMID). FAMIDs will be derived from a pool of numbers that has been partitioned for this purpose by the JHS Coordinating Center, and will consist of a “P” followed by a unique six-digit number. When a FAMID has been assigned, clinic staff will be alerted to gather additional family information during the initial clinic visit, including production of a graphical pedigree (using Progeny2000; see “Data Management”) and completion of a Parental Identification Form (PIF) (see Forms Appendix).

The graphical pedigree will include the full name and age of each person in the pedigree, to the extent known by the participant. “Jr.”, “Sr.”, “III”, etc., will be included where appropriate. Members of the pedigree who live in the tri-county area will be identified in the graphical pedigree and this information will be recorded automatically to a tabular data field in Progeny2000. If family members other than the informant have participated in JHS, this will be indicated adjacent to their symbol(s) in the pedigree. In addition, their name(s) will be recorded in designated spaces on the PIF. Before the participant leaves the clinic a Family Contact Form (FCF; see Forms Appendix) will be printed. The name, age, and gender of each person in the pedigree who is at least 21 years old and lives in the tri-county area will be printed to the FCF automatically through an interface between Progeny2000 and Microsoft Word. Row number for entry into the FCF will correspond to position in the pedigree, working from left to right beginning in the earliest generation and moving sequentially from left to right through subsequent generations. Clinic staff will then instruct the participant in the completion of the FCF. If exactly duplicate names are encountered within a family then street addresses will be completed for these “duplicate” individuals before the participant leaves the clinic. The participant will then take the form home and complete the “permission to contact”, address, and telephone number portions. The form will be collected from the participant simultaneous with the 24-hour exam components. If the form has not been completed before the 24-hour collection visit, the sample coordinator will assist the participant in completing the missing information. If this is not possible, an addressed, stamped envelope will be provided for mailing the form to the JHS and a notation will be made to schedule telephone follow-up if the form has not been received within one week.

Names and ages will be deleted from copies of the graphical pedigree, and the anonymized pedigrees will be reviewed at quarterly intervals by the Genetics Committee, who will select families for recruitment based on eligibility scores and family structure. If a family is selected for recruitment, each family member listed in the FCF will be assigned a JHS ID number and will be approached regarding participation in the JHS Family Study. Each family member who then participates will complete a PIF during her/his initial clinic visit.
Once a family has been selected for recruitment, efforts to extend the pedigree will begin immediately. The index participant will be asked which relative(s) are likely to know most about the extended family, and efforts to recruit these relatives will be given priority. If they agree to participate, a pedigree for the extended family will be completed during their initial clinic visit, without reference to that obtained from the index participant. The resulting pedigrees will be merged. Family relationships will be verified first based on data in the PIFs of study participants and eventually by molecular markers. As additional family relationships are identified during the JHS, data from the smaller of any two related families will be copied/merged to the larger family through a “drag-and-drop” mechanism. The combined family will retain the FAMID of the larger family, and that of the smaller family will become inactive. Family merger history will be tracked by Progeny2000. Definitive pedigrees will be derived from data in the PIFs of JHS participants having the same final FAMID (See Section 8.4, “Progeny2000 Database”). In certain cases during generation of definitive pedigrees study participants may be contacted to determine whether a parent may sometimes go by another name. If inconsistencies cannot be reconciled, data for the pedigree will be referred to the Genetics Committee or to a designated committee member for review.
Figure 2. Family Study Data Collection Flow Chart

HOME INDUCTION INTERVIEW
Recruiter completes Eligibility Form for each JHS participant.

Eligibility scores are calculated before the initial clinic visit.

For all participants whose eligibility scores are above a selected threshold, a graphical pedigree is drawn during the initial clinic visit, a Parental Identification Form is completed, and a Family Contact Form is filled in with the name, age, and gender of each family member living in the tri-county area. This form is sent home with the participant.

Graphical pedigrees are reviewed quarterly by the Genetics Committee and families are selected for recruitment.

Participant completes address and permission to contact portions of the Family Contact Form at home. Form is picked up from home 24 hours after initial clinic visit (along with BP monitor and urine).

Additional family members are recruited. Participating family members complete a Parental Identification Form during their initial clinic visit. Definitive pedigrees are generated from a spreadsheet by Progeny2000 based on data in the Parental Identification Form.
4.2 Instructions to Interviewers

4.2.1 Gathering Family Information

For the African-American community the family has a wider circle of members than the word suggests in European cultures. In traditional European society, the family includes children, parents, grandparents, uncles, aunts, brothers and sisters who may have their own children, and other immediate relatives. In many other cultures, including African and African-American the most common concept is extended family. The range of family members can be extensive and even include non-blood/biological members. In this kind of familial relationship, family members, often children are sent to live with relatives, and these children are counted as members of the families where they happen to live. Also the blending of families has always been prevalent in the A/A communities, with there being children from prior relationships from either parent, common-law relationships, grandparents raising their grandchildren or an array of configurations of the extended family unit. Terms such as adopted, step or half are generally not used because the sense of family diffuses beyond the Western concept of blood or biological kinship. This kinship system is like a vast network stretching laterally (horizontally) in every direction, to embrace everybody in any given local group. This means that each individual is a brother, or sister, father or mother, grandmother or grandfather, or cousin, or brother-in-law or sister-in-law, uncle or aunt or something else to everybody else. That means that everybody is related to everybody else, and there are many kinship terms to express the precise kind of relationship pertaining between two individuals. With this in mind, understanding the dynamic definition of family and relationships is key in completing a graphical pedigree for the African-American community.

Thus in these kinds of alternative family arrangements, terms such as adopted, step and half are not conceptualized for the average African American. Below are the terms defined by Webster's dictionary in reference to the terminology used by researchers:

- Stepfather-one’s mother’s husband who is not one’s natural father
- Stepmother-one’s father’s wife who is not one’s natural mother
- Stepson-the son of one’s spouse by an earlier marriage
- Stepparent-the daughter on one’s spouse by an earlier marriage
- Stepdaughter-the son of one’s stepparent by an earlier marriage
- Stepbrother-the son of one’s stepparent by an earlier marriage
- Stepsister-the daughter of one’s stepparent by an earlier marriage
- Half brother-a brother related through only one parent
- Half sister-a sister related through only one parent
- Adopted-to take a child into one’s family legally and raise as one’s own.

Most of these terms are based upon the ideal of a legal marriage. In the African-American community this is not necessarily a prerequisite for defining the official family structure. There may be blended families, common-law relationships, or children/adults inherited (by various ways and raised as one’s own, but not necessarily involving the formal legal procedures). There are no literal word substitutions for the aforementioned terms; however there will be stories and phrasing for the same concepts. And these concepts can be captured through a culturally relevant understanding of the dynamic familial relationships that exist in the African-American community.

This concept of African American family was discussed with several African-American psychologists (Drs Cynthia Ford, Pamela Banks, Mary Ann Jones-Gali) and clinical a psychologist, Dr. Althea Henry from Syracuse. Dr. Henry commented on the search to define family relationships by saying, “It’s not
until you dig a little deeper do you find that siblings have different mothers or fathers. So people will usually say as an example, “my sister on my father’s side”. One has to probe to get further clarification. They all agreed that using the Western terminology of the traditional family unit was not useful in discovering blood relationships.

They all thought that asking people initially “name your children/siblings” then asking each person’s parents name would be a non-invasive and indirect way of getting the same information without using the non-descriptive, and insensitive terminology of adopted, half and step. This would allow people to become comfortable with the subject matter, feel at ease to disclose private information, and tell the story of their complex and extended pattern of family relationships. With the information the interviewer and researcher would be able to appropriately discern the graphical pedigree or family tree for the individuals.

By changing the way in which you ask the family tree or graphical pedigree questions, such as administering the table framework and allowing the participant to include all siblings and children (as the participant defines) you can then query on the possible differences in the family framework and relationships. Phrasing such as “there are different ways in which people define and call family and we want to know how distinct and unique your family is…” can be utilized to frame the discussion.

A full and accurate understanding of the African-American family for the purposes of the JHS will occur only when it is conceptualized, studied and evaluated in terms of its own intrinsic definition. This task requires in itself, new theory, new analytical frameworks and new research models.

Questions about family relationships should be asked with sensitivity to each family member’s background. Caution must be used if the interviewer has information of which the family member is unaware. It is important that the interviewer identify questions that need to be asked with care (or not at all if information can be gained elsewhere) at the start of the interview.
4.3 Constructing the Family Tree

A preliminary graphical pedigree will be produced by the clinic staff during the initial clinic visit using Progeny2000. A definitive pedigree will be generated automatically by Progeny2000 from information in a spreadsheet derived from the PIF. A brief description of symbols used in family trees is provided below:

**males** are represented by squares:

**females** are represented by circles:

Arrow pointing to a male or female symbol represents the **proband**:

A solid symbol represents **affected persons** (e.g., participants with hypertension):

Square for male:

Circle for female:

**Deceased** individuals are represented with a line through the symbol:

Square for male:

Circle for female:

**Partners** who share biological children are represented by a horizontal line joining a square & circle:

**A sibship** is represented by a horizontal line with vertical lines dropping from it to the symbols:

The example above represents two brothers and a sister.
A vertical line connects parents with their children:

The example above represents a family that includes both parents and their three children, who are full siblings (all have the same mother and father).

Multiple unions and half siblings (siblings who only share one parent) are represented as follows:

The example above represents a family where the mother has children from two different relationships. One relationship resulted in three full sibs and the other resulted in one daughter who is a half sib to the previous three full sibs.

Twins (dizygotic):

Twins (monozygotic):

Adoption:
4.4 Sample Script for Clinic Staff Drawing an Initial Graphical Pedigree

“As you know, the JHS is trying to help scientists understand why diseases like high blood pressure, stroke, diabetes and heart disease run in some families. By studying the occurrence of these diseases across family generations, scientists may be able to identify factors in our environment (e.g., diet and stress) and factors that we may have inherited from our parents (genes) which put us and family members at greater risk of developing these diseases. To be successful, JHS scientists need to know exactly how family members are related. To do this we need to draw a diagram that shows as clearly as possible how the members of your family are related by blood.”
5.0 CHOOSING FAMILIES FOR THE STUDY

Basic family size and structure can be obtained from the Eligibility Form (ELG) and Household Enumeration Form (see Manual 2) completed at the home interview. An eligibility score will be calculated from the data in the ELG and study participants having sufficiently high scores will be selected to have graphical pedigrees drawn during their initial clinic visit. These participants will also complete PIF and FCF. Final selection of families for recruitment will be made by the Genetics Committee every three months, based on eligibility scores and family structures depicted in the graphical pedigrees.

5.1 Eligibility Criteria

Families of all JHS participants are potentially eligible for the JHS family study. Families will be selected for recruitment based on scores calculated from participants' ELG questions, using the point system described in section 8.1 of this manual, and on preliminary graphical pedigrees. Relatives to be recruited do not necessarily need to meet the other recruitment requirements for JHS participants. Parental partners should be counted among the first-degree relatives if they have eligible, natural children with a JHS participant. An optimum family size of at least twelve was selected based on an average sibship size of three in the ARIC Jackson cohort. For example, a simple pedigree might consist of the participant and two siblings (sibship of three) each having three offspring and a parental partner, for a total family size of 12-15 (with all partners).

There are other considerations in choosing families for the study. We would like to recruit families that are as large as possible; thus priority should be given to families with twelve or more members. If we have difficulty recruiting families of this size, we will then consider recruiting smaller families. In addition, willingness to participate in the study will influence our choice of families. The initial study participant will be asked for permission to contact his or her relatives. Therefore we will choose to recruit those families where we have permission to contact all members first.
In the event that it is not feasible to collect families of size 12 or more, we have set a minimum acceptable family size. A family size of five may be acceptable if the family consists of: a proband, their parental partner, one sibling and 2 offspring. The family tree would look as follows:

**Figure 3. Minimal Family Structure**

![Minimal Family Structure](image)

For family sizes of fewer than nine, the pedigree must consist of the minimal family structure (Figure 3) plus one to three first-degree relatives of any pedigree member. These one to three first-degree relatives should be blood relatives of the proband (not relatives by marriage) if possible. In all pedigrees of fewer than nine individuals both parents of each child should be collected. Examples of the possible pedigree structures are shown below:

**Figure 4. Examples of Family Structures**

(a) family size = 8  
(b) family size = 6  
(c) family size = 7

For families of size nine to eleven individuals, the structure should consist of either (in this priority):

1. A proband eligible for the JHS with 2 full siblings who meet recruitment criteria AND six to eight additional first degree relatives of the proband and siblings who live in the Jackson recruitment area.

2. A proband eligible for the JHS with 1 full sibling who meets recruitment criteria AND seven to nine additional first degree relatives of the proband and sibling (including their parents) who live in the Jackson recruitment area.
5.2 Criteria for reviewing pedigree structure by the genetics committee

1. All pedigrees with family size less than 9 that do not have the minimum family structure (i.e., proband, spouse, one sibling and two offspring of the proband) will be reviewed by the Genetics Committee before attempting to recruit those family members.

2. Since the minimum eligibility age for the overall study is 35 years, enrollment of younger family members has to be reviewed by the Genetics Committee. The inclusion of persons younger than 35 years of age may be necessary to increase the informativeness of some otherwise eligible families. However, the minimum allowable age is 21 years.
6.0 RECRUITING FAMILIES

Our success in recruiting families depends on our ability to explain the goals of the Family Study in a way that makes its value clear. The following narrative may help.

Heart disease and high blood pressure are serious health problems for African-Americans and other Americans. Research has established that heart disease and high blood pressure run in families, although the reasons why are not clear. Family members tend to live together for part of their lives and as a result share eating habits, exercise patterns and exposure to cigarette smoke. Family members also share genes and we think that some of these genes may increase the risk of heart disease and high blood pressure. The pattern of heart disease and high blood pressure in a family is the result of both shared genes and environmental factors such as diet and smoking.

One of the goals of the JHS is to study the causes of family patterns of disease in African-Americans. The participation of families in your community, including parents, children, brothers, sisters, aunts, uncles, and possibly grand children or grand parents in the JHS can help us learn about family patterns of disease. For each participating family we will draw a family tree, give each member an extensive physical exam and ask questions about health-related habits that may influence risk of heart disease and high blood pressure. All of the information collected will be coded so that confidentiality of individuals and families can be strictly maintained.

We will analyze family patterns of traits related to heart disease and high blood pressure to determine what factors, including genes, influence these traits. If the effects of a gene can be detected we will try to locate the gene by studying genetic material (DNA) from your blood sample.

Discovering genes that contribute to the risk of developing heart disease and high blood pressure is very important for reducing the burden of these diseases on African American families and communities. If these genes can be identified, new treatments and ways of preventing disease can be found and individuals and families at risk of developing high blood pressure or heart disease can be helped before they become ill. We will also be able to help people change their lifestyles so that the effect of harmful genes is lessened. In keeping with the JHS legacy of health, these genetic discoveries will enhance our knowledge of cardiovascular disease risk factors and help in developing new treatments for future generations of African-Americans.
7.0 CLINIC EXAM

7.1 Sample Collection

During the clinic exam two 10 ml ACD tubes will be collected for isolation of genomic DNA. With the participant’s specific consent, two 5 ml CPT tubes will be collected for lymphocyte cryopreservation and either immediate or selective transformation of lymphocytes at a later date. Genomic DNA will be prepared for all JHS participants. Lymphocyte cryopreservation will be done for all participants who are selected to have a graphical pedigree drawn, whether or not their family is eventually chosen for recruitment. Immortalized cell lines will provide essentially unlimited amounts of DNA from a single sample, eliminating the need for additional blood draws for research where DNA is needed. Tubes will be bar coded and will not be identified by the participant’s name. Samples will be shipped to the Central Laboratory at ambient temperature the same day, by overnight carrier. Any blood drawn for lymphocyte cryopreservation of participants who are not ultimately selected for inclusion in the Family Study will be discarded.

7.2 Tracking of Samples

Each sample will receive a bar code and will be recorded into a database prior to shipping to the Central Laboratory. Details of sample database management can be found in the Manual 9, Specimen Collection and Processing.

7.3 Destruction of Samples

As provided in the informed consent, some study participants may choose to withdraw from JHS genetic studies and may request that all samples of their genomic DNA and cryopreserved cells be destroyed. Upon receipt of such a request, the contractor responsible for handling and storing these samples will be contacted by electronic mail, will destroy the designated samples and record their destruction in the sample log, and will notify the JHS by electronic mail that the samples have been destroyed. Paper copies of these electronic mail messages will be printed and retained in the participant’s JHS file, and a letter will be sent notifying the participant that his/her samples have been destroyed. Genotype data for the participant that have been stored in the JHS Database will be deleted, and the participant’s genotype will be recorded as “deleted by request”. Published or submitted manuscripts that have included analysis of the participant’s DNA will not be altered.
8.0 DATA MANAGEMENT

8.1 Eligibility Scoring System

Only relatives ≥21, in the tri-county area, with permission to contact will be scored.

Scoring criteria:

1. Desired family structure includes at least an informant, parental partner, two children, and a sibling of one parent. All of these individuals must be at least 21 years old: 10 points

2. Three-generation families: Add 5 points.

3. Each generation > 3: Add 5 points.

4. Each additional first-degree relative, grandchild, grandparent of either parental partner (beyond desired family structure; include half-siblings): 1 point.

5. Each aunt, uncle, niece, or nephew: 0.5 points.

If an informant’s parental partner (1) lives in the same household; (2) has family in the tri-county area; and (3) has participated in JHS, then the informant’s eligibility score will be increased by an amount equal to the average eligibility score for the first 30 participants, minus 4 points (to adjust for double-counting children and the informant).

8.2 Validation of Eligibility Scoring System

Thirty consecutive participants will be selected and graphical pedigrees will be completed for all 30. These pedigrees will be ranked by the Genetics Committee for their degree of informativeness, and this ranking will be compared with the rank order of the Eligibility Scores for the participants. The Eligibility Scoring system will be revised based on the results of this analysis, with iterative retesting on the same data set.

8.3 Progeny2000® Master File

Each participant’s information will occupy one line.

Required columns:

FAMID
JHS ID
Participant age
Participant gender
Mother first name
Mother middle name
Mother last name
Mother maiden name
Mother age
Father first name
Father middle name
Father last name
Father age
Mother ID (MA)
Father ID (PA)
8.4  Progeny2000® Database

The master file of all tabular pedigree data items will be maintained in Progeny2000®. The Progeny2000® database will be used to generate and analyze preliminary and definitive family trees. In addition to other variables, the tabular master file (section 8.3) will contain the following standard genetic analysis identifying information: FAMID, participant ID (J+ six digit unique identifier for each individual in the JHS), MA (mother ID - identifies the mother of each person within a family), PA (father ID - identifies the father of each person within the family), SEX (male=1, female=2). All data except MA and PA will be entered automatically from the graphical pedigree and PIF. MA and PA will be entered manually based on other data in the spreadsheet (section 8.3) to allow for differences in spelling, etc. (e.g. Johnny vs. Johnnie). Any number of independently developed data files with the unique ID is easily merged as needed with the Master File. Furthermore, the Progeny2000® software generates printable ASCII characters, which makes it very easy to import data developed on other database systems and to export data to other programs or computers for analysis. The following example will illustrate the ID numbering system.
Figure 5. Example of ID Numbering System

The above information is what is needed for linkage and other family analyses. The table also contains all the information you need to know how individuals are related and therefore the ability to correctly deduce the family tree. It is remarkably straightforward.
8.5 Interface of Progeny2000 with ClinTrial

Family data will be entered in ClinTrial only if a family is selected for recruitment by the Genetics Committee. At that point, each person listed on the Family Contact Form is assigned a JHS ID number. Data sharing between Progeny2000 and ClinTrial can occur at two levels. At the level of primary data management, Progeny2000 data will be accessed by ClinTrial through a “Central Agency” function. Alternatively, data sharing can occur downstream in the analytic process as a SAS function. To allow database interactions at the level of primary data management, a single relational table will be created in ClinTrial, having three data fields, including (1) Family ID number; (2) JHS ID number; and (3) a code indicating whether the participant is the index family member (code=1) or a secondary family member (code=2). When it occurs that more than one family member has been recruited through ARIC or by random selection, each such family member will be coded as an “index” participant.

Certain functions, including contact tracking and rates of recruitment for the Family Study, will occur at the data management level. Efforts to contact family members will be logged using the same “Home Induction Record of Contact” (HIRC) form that is used for ARIC and randomly ascertained participants. It is likely that most contact efforts involving family members will be by telephone rather than home visit, and appropriate codes for telephone contacts (but no additional data fields) will be added to the HIRC. Until this is done, contacts will be logged as “other”, and specific narrative qualifying terms will be used by recruiters so that when telephone codes are developed they can be assigned to the data. Standing reports based on data in the “Home Induction Record of Contact” and “Home Induction Interview Form” will be created in ClinTrial to allow family-specific contact tracking and analysis of rates of recruitment for the Family Study.

8.6 Quality Assurance

8.6.1 Pedigrees

Family structure programs (including S.A.G.E®, Progeny2000®, Pedsys®, etc.) will be used for error checking on the pedigree data structure. Several structural errors may be detected including married persons with the same sex code, an individual who is his or her own ancestor, more than one person having the same ID. These programs may also identify certain types of consanguineous matings and loops in the pedigree.

8.6.2 Samples

See Manual 9, Sample Collection and Processing for quality assurance in handling DNA and blood samples for immortalized cell lines.

8.6.3 Genotypes

As genotype information becomes available, marker-typing incompatibilities will be checked. Given an individual's genotype, inconsistencies with parents and offspring data will be verified. For example, we will consider the following inconsistencies:

a. Parent and child alleles are incompatible.
b. There more than 4 alleles in a sibship (brothers and sisters).
c. A sibship has more than 3 alleles in the presence of a homozygous child.
d. Males homozygous for an X-linked allele.

Mendelian consistency will be verified for all pedigrees. It may be necessary to set the genotype of some individuals to missing to save a family.
9.0 DATA SHARING POLICIES

9.1 Sharing Genetic Information with Participants

Results generated from the Family Study component of the JHS will be handled in the same manner as other JHS results considered to be of research value only. They will not be routinely reported. If a participant requests them, these values will be provided on an *ad hoc* basis only after completion of a written request form (Appendix 1).

If during the course of the JHS a genetic polymorphism is discovered which has clear clinical relevance for a treatable condition, participants will be notified by study wide approaches. A description of the polymorphism, its health risk and treatment will appear in the JHS newsletter along with a phone number to receive more information and a referral for gene testing if available. All referrals will be at the cost of the participant.

9.2 Sharing Data with non-JHS Scientists

Genetic data (pedigrees, genotypes and DNA samples) will be shared with JHS approved investigators who agree to maintain participant confidentiality and follow JHS publication clearance procedures for ancillary genetic studies of heart, lung and blood disorders and their risk factors. All investigators will be subject to the procedures outlined for ancillary studies prior to access to JHS data. A specific process for ancillary genetic studies involving JHS samples will be developed by the Genetics Committee within the first year of the study. Participants have the option in the informed consent to specify that their samples not be used for research by non-JHS investigators.
APPENDIX
Appendix 1. Request For JHS Results Not Previously Reported

REQUEST FOR JHS RESULTS NOT PREVIOUSLY REPORTED

Participant's name
Date of request
Result requested
Date exam performed
Reason for request (to be completed by participant)

I understand that the requested result was not originally reported to me as it was considered by JHS investigators to be of insignificant or undetermined clinical usefulness. Although the Exam Center will not provide an interpretative explanation of the requested result, I will be provided the result as it was reported to the Exam Center.

____________________________
Participant’s signature

____ Approved
____ Not Approved

____________________________
Exam Center PI