

Chapter 16

Pedigree and Family Structure

INTRODUCTION

Construction and documentation of the Family Pedigree is completed in three phases and utilizes multiple forms and worksheets. A written summary of these phases of the study is provided; please also refer to *Figure 1* below:

| Phase I – Screening Phase | | |
|---|---------------------|--|
| Instrument | Abbreviation | Purpose |
| Proband Telephone Screening Interview | TS1 | <ul style="list-style-type: none"> • Determine interest of Proband • Obtain information on Proband & Family to calculate FRS Score |
| Relative Contact Information Form | TS2 | <ul style="list-style-type: none"> • Identification of Proband's Sibship to construct Family Pedigree • Determination of "Index Person" for each branch of family structure • To obtain contact information and verbal consent to contact Proband's other relatives who may wish to participate (rolling process) • Designation of a Family Reporter, if necessary |
| Family Member Telephone Screening Interview | TS1a | <ul style="list-style-type: none"> • Determine interest of each of Proband's family members • Obtain information to see if this family meets the Minimum Family Size/FLoSS criteria • Identification of potential spouses of offspring for enrollment as control subjects |

| Phase II – Collection of Pedigree Information | | |
|--|---------------------|--|
| Instrument | Abbreviation | Purpose |
| Relative Contact Information Form | TS2 | <ul style="list-style-type: none"> • Section 1 of this instrument, which obtains Proband's sibship, is carried over into Phase II • The sibship identified is the basis from which to start a PIF Form for each "Index Person" in a given family (i.e. the Proband and each sibling) |
| Pedigree Information Form | PIF | <ul style="list-style-type: none"> • To obtain all necessary information, via a telephone interview with each Index Person in a family (including Proband), for each 3-generational branch pedigree |
| Family Structure Worksheet | FSW | <ul style="list-style-type: none"> • To apply the information obtained above and sketch out each branch pedigree |

| Phase III – In-Home Visit(s) / Pedigree Verification | | |
|---|---------------------|---|
| Instrument | Abbreviation | Purpose |
| Section 1: Relative Contact Information Form; Pedigree Information Form; and Family Structure Worksheet | TS2, PIF, FSW | <ul style="list-style-type: none"> • A formal review of each drawn branch pedigree to verify the accuracy of information provided; this is to be done in conjunction with the in-home visit for each Index Person identified |
| Family Structure Worksheet | FSW | <ul style="list-style-type: none"> • After all branch pedigrees for a family are verified, compile into one "Family Pedigree" |

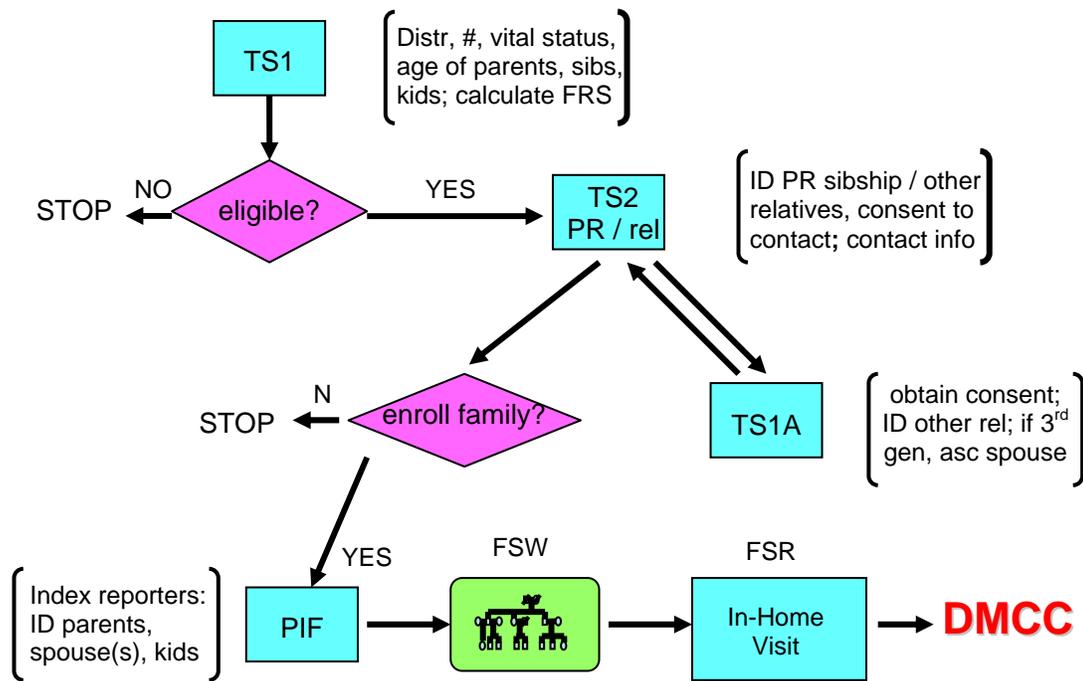


Figure 1. Process Overview

1. **Phase I** consists of a series of telephone interviews to determine interest and eligibility. During this Screening Process (TS1, TS2, TS1a), a significant amount of general family information is gathered. In TS1, the basic family history is reported by the Proband to determine suitability for further screening. For the promising families, the Proband is asked to obtain consent from his/her siblings and offspring to be contacted by LLFS. TS2 is a second telephone interview, during which an LLFS staff member follows-up with the Proband as to whether his/her family members have agreed to be contacted and, if so, obtains contact information. TS2 is also the first step of the LLFS Pedigree Collection process, via [Section 1](#) of this form. Here the Proband is asked to identify his/her entire sibship, including full- or half-siblings, as well as any siblings who may be deceased. All of this information is then entered into the LLFS Data Entry System and serves as an outline to begin **Phase II**. (For more detail on the completion of TS1, TS2 and TS1a, please refer to *Chapter 2: Recruitment*.)
2. **Phase II** has three steps: (a) Summarizing and transferring the family structure information obtained during **Phase I** to the PIF; (b) scheduling and conducting a telephone interview with Proband and each of the identified "Index Persons" (*i.e. siblings of Proband*) to complete the PIF for their individual 3-generation branch (parents/self-spouse/offspring); and, (c) compiling this information and transferring it to the Family Structure Worksheet (FSW) to construct and draw a "branch Pedigree" representing the Proband and each Index Person in this family.
3. **Phase III** of this process, coinciding with **Phase III** of the LLFS protocol, occurs during the in-home visit. **Phase III** occurs during the interview portion of the in-home visit with the Proband and each "Index Person"; it is at this time, that the Pedigree Information is reviewed (Family Structure Review) and verified with the corresponding "Index Person" for that branch, using the FS-Worksheet as a reference. (See *Chapter 1, p. 4 of the LLFS MOP*). During this interview, the relationships depicted in the pedigree are confirmed, revised, and/or updated. Once all branch Pedigrees are verified, they should then be assembled to create the complete Family Pedigree.

OVERVIEW OF CONSTRUCTING A FAMILY PEDIGREE

For each family selected to participate in **Phase III** of LLFS, a pedigree is constructed based on information obtained during **Phases I and II**. A review of this information occurs at the in-home visit (a/k/a "enrollment

visit") with each Reporter in the family that originally provided the information, usually the Proband and each of his/her siblings. If the person who completed Phase II does not or is not able to participate in an in-home examination (i.e. due to death, incapacitation, etc.), an alternate family member may be identified to confirm the pedigree structure for this family branch; however, every effort should be made to confirm each branch of the pedigree structure with the corresponding informant.

It is important to note here, that there will be multiple Family Structure Reviews (FSRs) conducted for each family enrolled in LLFS. The total number of FSRs to be done will correspond with the total number of "Index Persons" identified (i.e. *Proband plus his/her siblings*). In addition, the pedigree for each "Index Person" should contain 3 generations: (1) Parents (to Proband/Siblings); (2) Spouse(s) (of Probands/Siblings); and (3) Children of "Index Persons". In addition to the aforementioned, Proband will also need to verify his/her sibship, as reported on the TS2. (*Please refer to Figure 2 below*). Also, as depicted in *Figure 2*, it is important to ascertain the availability of marry-ins to the third generation subjects for use as potential controls. This information is obtained as part of the Telephone Family Screener (TS1a).

The LLFS staff responsible for collecting and compiling the information for the branch and family pedigrees must be trained and certified for this task. The LLFS staff responsible for the Family Structure Review during the field examination must be trained and certified as an interviewer, as well as in the techniques for completing a pedigree. Familiarity with the LLFS Manual of Procedures, the key of symbols used in pedigree construction (refer to *Appendix 1 at the end of this Chapter*), the training materials, and proficiency in pedigree construction, including importing/exporting of ".txt" files, drawing and correction of pedigrees using *Progeny Clinical v.7* software, are required elements in the certification of staff for the use of this form. (*Please refer to Appendix D at the end of this MOP for a tutorial in using Progeny Clinical v.7*)

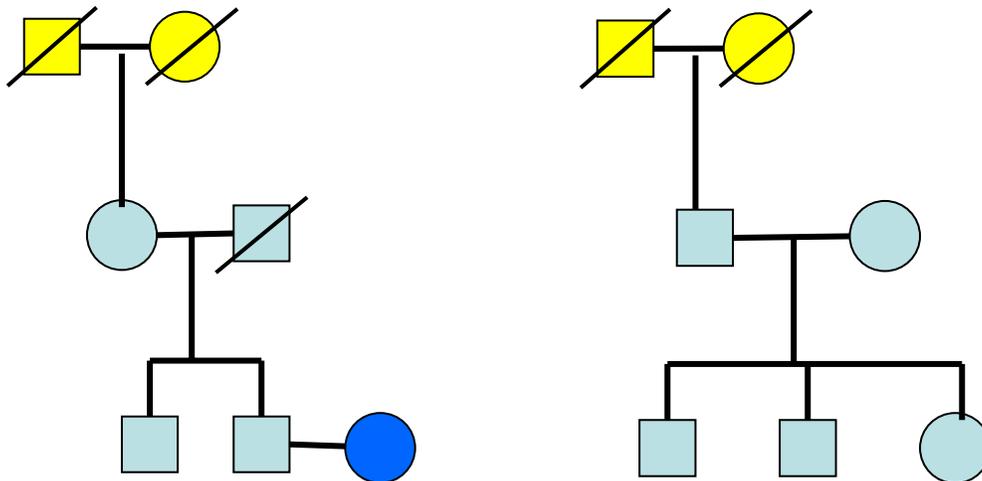


Figure 2. Sample 3-Generational Branch Pedigrees

PEDIGREE INFORMATION FORM (PIF)

Fully Consented Participant as Reporter: Once a family has been selected for enrollment into the LLFS Study, and the Proband has identified his/her Sibship, a telephone interview should be scheduled with each Proband and "Index Person" (i.e. sibling), or their designated family reporter, to complete the PIF for their respective family branch. The following procedures are to be used with any individual who actually provides full written consent and will participate in an assessment visit. See the next section should the family reporter be an individual OUTSIDE of the sampling frame (e.g. a grandchild to the Proband's

generation). At the time the appointment is scheduled, the reporter should be notified that this should take approximately 15-30 minutes, depending upon the size of the family.

To complete the header portion of the PIF, affix the provided label containing the Index Person's Participant ID and Participant Name Code in the designated area (in the instance a label is not available, please fill in this information by hand).

Prior to conducting the interview, identify the "Index Person" (Proband or his/her sibling) or the Name of the Reporter (if not "Index Person") on the first page of the PIF. Additionally, at this time, a review of the information obtained in Phase I, for each "Index Person", should be completed, a PIF Form should be created for each "Index Person" and the corresponding information should be transferred over. Whenever prior information is available, this should be verified during the actual interview to avoid redundancy.

Sample Script(s):

- *You are a younger sister to our participant, John Smith. Is this correct?*
- *Your parents were Sarah Rebecca Jones and James Edward Smith. Is this correct?*
- *You have four siblings, two brothers and two sisters. Is this correct?*

NOTE: On every page of this form, there is a header in which the Index Person's LLFS ID, Name Code and Name **MUST** be filled out. This is necessary to keep all of the pages of this form together, in the instance that one or more of the pages become misplaced.

Section 1: Page 2. This page of the PIF is devoted to obtain basic information on the Index Person's biological parents(s). **Please Note:** It is important to ask the "Index Person" (i.e. sibling) information about his/her parents, not Proband's parents. It is important to flag any inconsistency in the reporting of the parents by the siblings. The information to be obtained includes:

- (a) **Name(s):** Last, First, Middle Initial, Maiden (if applicable);
- (b) **Relationship:** Father or Mother of the "Index Person";
- (c) **Date of Birth:** Probe for date of birth or best estimate. Enter the date in the standard format used for this study (i.e. June 16, 1908 is 08/JUN/1908).
- (d) **Vital Status:** Living or Deceased; If deceased, check the box for deceased and then go to (e). If alive, check the box for alive and then skip to the column for Parent #2.
- (e) **Date of Death:** Probe for date of death or best estimate; proceed to (f) Enter the date in the standard format used for this study (i.e. June 16, 1908 is 08/JUN/1908).
- (f) **Health Conditions:** If deceased, inquire whether this individual suffered from any of the specified health conditions. **Check all that apply.**

Each page contains a space for the interviewer to make any notations which are felt to be important or relative to any information on this page.

Section 2: Page 3. This page of the PIF is devoted to obtaining basic information on the Index Person's Spouse(s). Information to be obtained includes:

- (a) **Name(s):** Last, First, Middle Initial, Maiden (if applicable);
- (b) **Relationship:** Husband or Wife to the Proband;
- (c) **Date of Birth:** Probe for date of birth or best estimate. Enter the date in the standard format used for this study (i.e. June 16, 1908 is 08/JUN/1908).
- (d) **Vital Status:** Living or Deceased; If deceased, check the box for deceased and then go to (e). If alive, check the box for alive and then skip to the column for Spouse #2; if no additional spouse(s), then proceed to the next section.

- (e) **Date of Death:** Probe for date of death or best estimate; proceed to (f) Enter the date in the standard format used for this study (i.e. June 16, 1908 is 08/JUN/1908).
- (f) **Health Conditions:** If deceased, inquire whether this individual suffered from any of the specified health conditions. **Check all that apply.**
- (g) **Children:** By checking the box for 'Yes' or 'No', indicate whether the "Index Person" had any children with the respective spouse. If yes, go to Section 3.

Each page contains a space for the interviewer to make any notations which are felt to be important or relative to any information on this page. Please add additional pages as needed.

Section 3: Pages 4-7. This section of the PIF is devoted to obtaining basic information on the Index Person's biological children, with each spouse (if more than one). **Note:** In Section 3, for each spouse identified, please start a new page to record the Index Person's children with that respective spouse. Information to be obtained includes:

- (a) **Name(s):** Last, First, Middle Initial, Maiden (if applicable);
- (b) **Relationship:** Son or Daughter to the Proband;
- (c) **Date of Birth:** Probe for date of birth or best estimate
- (d) **Vital Status:** Living or Deceased; If deceased, go to (e). If alive, skip to the cell for the next child or proceed to the next section.
- (e) **Date of Death:** Probe for date of death or best estimate; proceed to (f)
- (f) **Health Conditions:** If deceased, inquire whether this individual suffered from any of the specified health conditions.
- (g) **Biological Children:** Inquire as to the number of biological children this child has and write the number on the line provided.
- (h) **Another Spouse:** Indicate whether the "Index Person" had another spouse by checking the box for Yes or No. If 'Yes', then go back to Section 2 and repeat the steps outlined for Section 2 above. Continue with this process until no additional Spouses or Children are identified.
- (i) **Other Partners:** Allowing for the possibility that biological children might have resulted from unions with partners who may not have been spouses, query whether the Index has had children with another partner and check the box for Yes or No. If 'Yes', then go back to Section 2 and repeat the steps outlined for Section 2 above. This additional partner would be treated like a spouse for the purposes of obtaining a pedigree.

When possible, each page contains a space for the interviewer to make any notations which are felt to be important or relative to any information on this page. Please add additional pages as needed.

Family Reporter Out of Sampling Frame: In some cases, the proband or an index subject (proband's sib) might designate someone else to report the family structure. The most likely such designated reporter will be a grandchild of anyone in the proband generation. It is also possible that some unrelated person (friend or spouse) may be designated as a family reporter. The sampling frame for LLFS families can be defined as including the following relatives:

- (a) proband and all living parents and siblings
- (b) the spouses and offspring of all subjects in the proband generation
- (c) the living spouses of the family members in the offspring generation (controls)

The PIF will be administered to such family reporters using the same procedure described above – the reporting will be with respect to an "Index Person" in the proband generation, and will seek to identify the same set of individuals (parents, spouses, offspring, offspring's spouses). However, IF the designated family reporter is NOT within the sampling frame as defined above, then special procedures may become

necessary in order to meet consenting standards. In these cases, a verbal consent should be administered according to the individual field center's IRB regulations. A script to obtain this verbal consent is provided as Appendix A to the actual PIF Form.

FAMILY STRUCTURE WORKSHEET (FSW)

Preparing for the Index Person's In-home Visit(s): Once a PIF interview and form have been completed by each "Index Person" within a family, a Family Structure Worksheet is prepared, for this specific 3-generational branch of the family, by a certified LLFS staff member based on the information provided in Phases I and II. (*Refer to Figure 2 on page 3*). This is done prior to the assessment visit of this individual.

To complete the header portion of the FSW, affix the provided label containing the Participant's ID and Name Code in the designated area (in the instance a label is not available, please fill in this information by hand). Complete the name of the Proband, "Index Person" who completed the PIF and use the lines provided to note any relevant comments. Next, a pedigree is constructed and sketched using the information obtained and recorded on the PIF, during Phase II, as described in the next section. The staff person who prepares the pedigree records his/her Interviewer Code at the top of page 1 of the Family Structure Worksheet, along with the date of completion (i.e. June 16, 1908 is 16/JUN/1908. The space for comments on page 1 of the form is used to record elements of the PIF/FSW information that need clarification during the Family Structure Review, and notes that would be considered useful during the verification of the family pedigree over the course of the interview.

Page 2 of the Family Structure Worksheet, the family pedigree, is completed by transferring the information on the PIF, as described in General Instructions for Completing a Family Pedigree, below. The pedigree is drawn in dark pencil; changes and corrections to the pedigree prior to the Family Structure Review are erased and re-drawn. Interviewers must be provided with a clean copy of the pedigree for review with the study participant. During the interview, changes to the pedigree are made with a red pen; large "X" marks are used to cross out inappropriate elements or linkages in the pedigree identified during the interview, and replacement symbols/linkages are to be drawn in red pen.

Important: Once all of the separate 3-generational pedigrees have been drawn and verified with the appropriate Family Reporter, the LLFS staff member will then need to assemble all of the branch-pedigrees into one complete Family Pedigree. Refer to *Figure X* below.

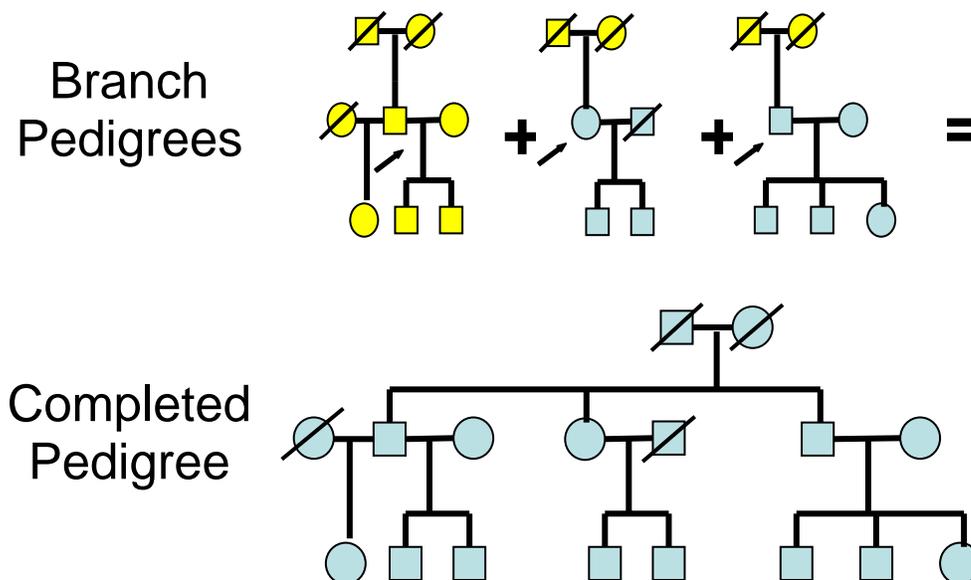


Figure X. Branch Pedigrees and Family Pedigree

FORMAL/FINAL CONSTRUCTION OF A PEDIGREE

Once a Family Pedigree is compiled, the FC should contact the DMCC and request that a ".txt" file, containing all of the associated IDs for this Proband's family, be forwarded to them. [**Note:** If preferred, FCs can wait to request these files until they have 5-6 pedigrees to be constructed.] Once this information is forwarded by the DMCC, the FC staff should then:

- Import the ".txt" file using *Progeny Clinical v.7* software'
- Draw/construct the pedigree within the program
- Review the final drawing for accuracy, linkage and singletons, etc.
- Upon review and verification based on available information, the FC should then export this file back to the DMCC for a final review.
- The DMCC then checks the pedigree one more time for any errors or problems and, if any are identified, requests correction by the Field Center. Otherwise, the pedigree is considered completed.

In addition to allowing for an accuracy check of the individual pedigree, this method also provides for an additional quality control check of the data contained in the LLFS DES.

Note: The process for the Danish cohort differs somewhat. Currently, they are providing the DMCC with a tripllett file from which the pedigrees are constructed at the DMCC.

THE FAMILY STRUCTURE REVIEW (FSR)

The Family Structure Review is always conducted as a review of a previously constructed pedigree, corresponding to information collected during TS2-Section 1 and the PIF conducted with each "Index Person". Thus, the branch pedigree structures are verified separately within each brand of the family.

The review should be conducted with the individual who acted as the reporter for the PIF. Other members of this Index Person's family cannot substitute for the person who completed Phase II, except in the cases where: a) the "Index Person" has since died or become incapacitated, or b) the PIF reporter for that family branch is not within the sampling frame. If the latter case applies, then a family member undergoing consent and assessment should be asked to do the family structure review. For this purpose, we prefer 1) someone within the family branch, 2) someone in the proband generation, and 3) cousins from other family branches. Only one alternate person should be tapped to conduct the review.

For each family taking part in Phase III of LLFS, the pedigree (on the Family Structure Worksheet) is kept in the Proband's folder. If another member of the family serves as a Reporter for the Proband or one of his/her siblings, i.e. has completed Phase II and the Family Structure Review, the pedigree is still kept in the Proband's folder instead of that person's folder. Pedigrees are not shown to, nor discussed with, other study participants, nor are they to be accessed by LLFS staff who are not responsible for processing this information.

Conducting the Family Structure Review: When conducting the FSR, it is important that, throughout the course of the interview, the interviewer shows interest in the responses from the participant, using a pleasant and non-judgmental attitude. The name of the participant should be confirmed against the "Index Person" name recorded on page 1 of the FS-Worksheet. The interviewer then explains that the purpose of the Family Structure Review is to review and update the information provided during Phase II (PIF). The interviewer also indicates that he/she is aware of the confidential nature of this information.

During this interview, the only family relationships reviewed are the ones provided by the interviewee during the PIF he/she participated in. Questions from the participant about relationships reported by a sibling should not be answered nor discussed. If asked, the interviewer indicates that the information provided by each study participant is kept separate and politely indicates that all information provided to LLFS is personal and confidential.

During the interview, all changes to the pedigree prepared prior to the in-home visit are made in a different colored pen or pencil (red is preferred). The following is a prototype script for the review of the family structure pedigree. The interviewer can use his/her own words, but the order of the review should not be changed. For the Proband, the review should include: Proband's parents (biological, step), spouse(s)/partner(s), siblings (full, half, step and adopted), and children (full, half, step and adopted). For the family's remaining Index Person(s) (i.e. Proband's siblings), the review should include: parents (biological, step), spouse(s)/partner(s) and children (full, half, step and adopted).

Script: " During this part of the LLFS visit, we want to review the information you provided to us about the structure of your family. As you recall, you provided us with information about your family during a telephone interview. You provided information regarding your parents, spouse(s), [Proband Only: brother(s)/sister(s)], and son(s)/daughter(s).

At this time, we want to make sure that this information is correct and up to date. We do not need to review any information related to their health. In this review, you will notice that the information you provided has been recorded in a drawing of your family pedigree, which we will review together.

This is your family pedigree, and this symbol represents you. In this pedigree, females are recorded as circles and males are recorded as squares. Related individuals are linked together using lines. I will explain this as we go.

First we will talk about your parents. [Point to the corresponding symbol on the pedigree as you proceed]. You indicated that your biological mother, _____(name) is living/deceased. You reported that your biological father, _____(name) is living/deceased. As far as you know, are/were your parents related by blood? [Record this on the pedigree (see Key) and specify the type of consanguineous relationship in the comment section. Update vital status as shown on the pedigree]. Are these the same biological parents of all of your brother(s)/sister(s) that we discussed?

You reported [no or #] of step-parents, [Point to the symbols, list names, ask whether they are related through the Proband's biological mother or father and update vital status]. As far as you know, is/are/was/were (any of) your step-parent(s) related by blood to your biological parent? [If so, record using double horizontal lines (see Key) and record the exact type of consanguineous relationship in the comment section].

Interviewer Note: Complete this section with the **Proband Only**; skip this section for all "Index Persons" other than Proband.

You indicated that you have [no or #] full brothers or sisters. [If more than one:] Let's start with your oldest full sibling. [Point to the symbols as you name each, their relationship (brother/sister) and their vital status (living/deceased). Inquire as to the number of twins, if any, in the sibship, and verify the exact nature of the twins (identical, fraternal), even if already reported]. Have we missed any full brothers or sisters?

You indicated that you have [no or #] adopted brothers or sisters in your family. [Point to each symbol, record name and vital status. Determine if there is any genetic relationship between the Proband and each

of his/her adopted siblings. If there is, record the exact genetic relationship in the comments section. If the Proband has more than one adopted sibling, determine if the adopted siblings are genetically related to each other. If they are, record the type of genetic relationship in the comments section]. *Have we missed any adopted brothers or sisters?*

You report having [no or #] half-brothers or sisters. [Name each as you point to the corresponding symbol, verify their biological parents and their vital status]. You indicated that you have [no or #] step-brothers or sisters [Name each, confirm that the pedigree appropriately displays their biological parent(s) and verify their vital status]. Have we missed any half-brothers or sisters?

Interviewer Note: Repeat this section for each Spouse/Partner and respective Offspring.

Now we will discuss your marital status. You reported [no or #] spouse(s)/partner(s). Your spouse(s)/partner(s) name(s) is/was/are/were [list spouses or partners in order from first to last and point to the corresponding symbol on the pedigree as you proceed; in each case, indicate their status whether living or deceased]. Are you related by blood to [any of] your spouse(s)/partner(s)? [If so, indicate with a double horizontal line joining the mating/relationship (see key). Record the specific type of consanguineous relationship in the comment section (e.g. first cousins)].

As a result of this marriage, you indicated that you and _____ (name of first spouse/partner) have [no or #] children together. Their names are [name each, verify that the pedigree appropriately displays their relationship, and confirm their vital status]. Have we missed any children with [Name of first spouse/partner]?

If applicable:

You reported [no or #] step-children. [Establish that this information is correct on the pedigree]. These are the biological children of _____ (name of this spouse/partner). If more than one child: Do these children share the same mother/father or do they have different mothers/fathers? [Verify that the pedigree shows this information correctly]. Have we missed any step-children?

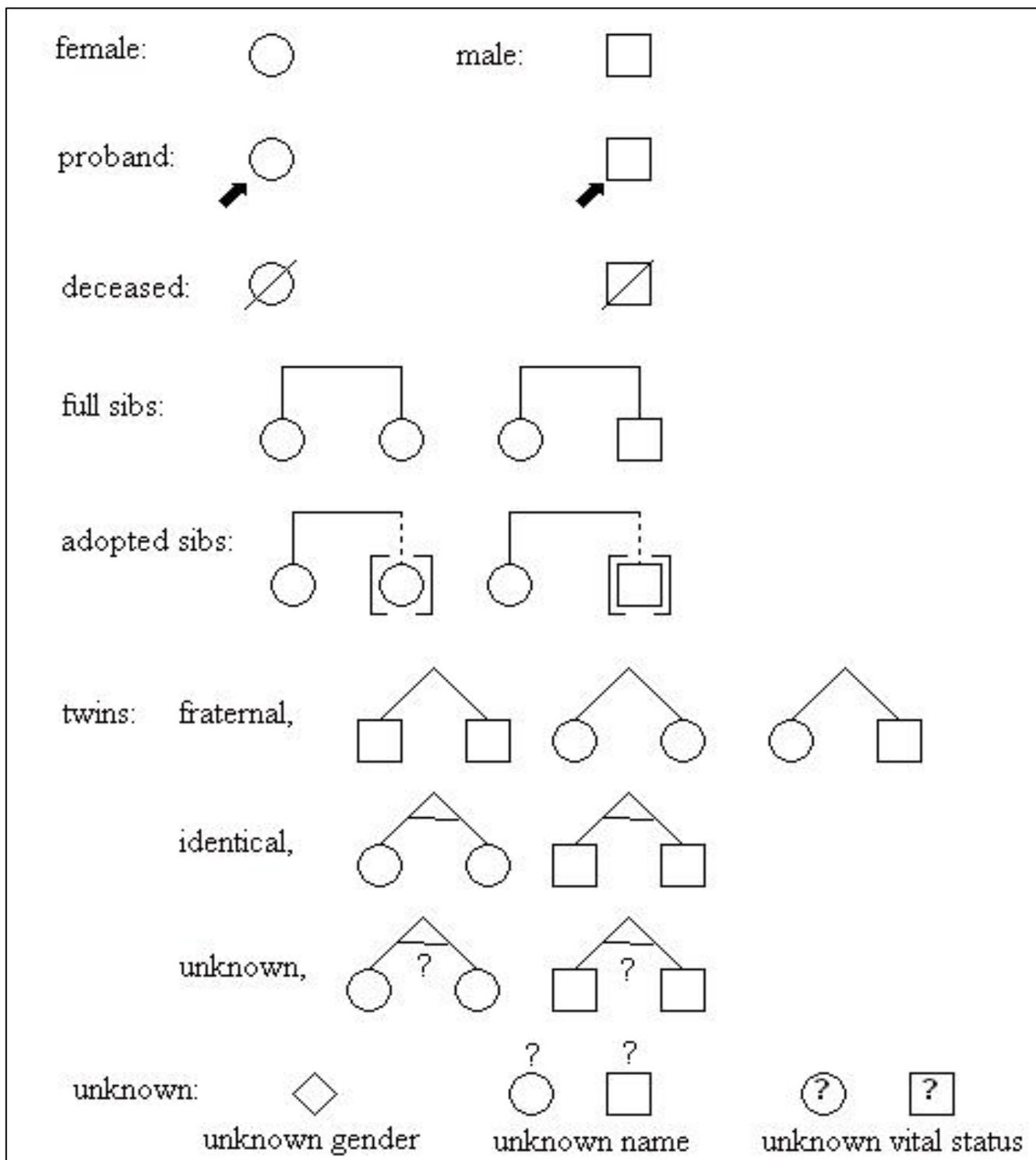
Interviewer Note: Go back to the beginning of this section and complete for next Spouse/Partner and respective Offspring, if applicable. Complete this for as many Spouse(s)/Partner(s) as were reported.

Finally, you reported [no or #] of adopted children. [Verify name(s) and vital status on the pedigree. Determine if there is any genetic relationship between the Proband and his/her adopted children. If there is, record the exact genetic relationship in the comments section. If the Proband has more than one adopted child, determine if the adopted children are genetically related to each other. If they are, record the type of genetic relationship in the comments section]. Are there any adopted children we have missed?

Is there any additional information, or changes you would like to make to the family structure information? [If yes, record other changes or additions]. If no: Thank you for your help in reviewing your family pedigree. This information is very important in helping us understand why some people live long-lives.

Chapter 16 – Appendix 1

Key Symbols for Constructing a Pedigree



Chapter 16 – Appendix 2

General Instructions For Completing A Family Pedigree

Important Note: The instructions below provide a general outline as to how to approach the sketching of the Proband's 3-generational Pedigree. For each of the corresponding Index Person(s), these same steps should be followed, but approaching it as though the "Index Person" were the "Proband". Please note that not all of these relationships will be encountered in preparing the LLFS Pedigrees.

The main purpose of a family tree or pedigree in the LONG LIFE Family Study is to serve as a record of both biological and social relationships. Pedigrees may also be used during analysis as a template for other relevant facts and medical history. If constructed appropriately, the family pedigree can assist in identifying patterns of inheritance and at-risk individuals. The most widely utilized and accepted standards in pedigree format were established early in the twentieth century. Charles Davenport, a noted biologist, established the Eugenics Record Office (ERO) in Cold Spring Harbor, New York, as a center for the development of eugenic ideology (Allen, 1986; Resta, 1992). It was from this Office that Davenport published a number of articles describing the ERO pedigree style which is very similar to the format used today (Davenport et al., 1911; Davenport, 1212a).

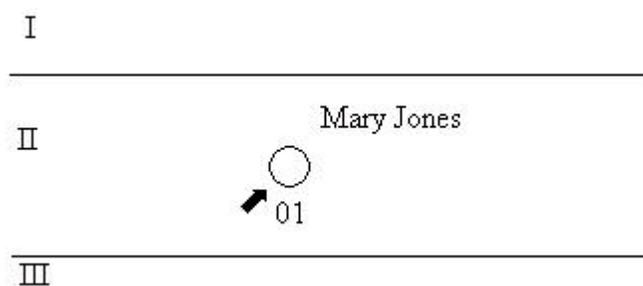
There remain many areas in which family pedigrees are not standardized, although there is a generally perceived need for a standard pedigree nomenclature that encompasses the expanding number of reproductive options and social relationships, as well as one that establishes standards for frequently used symbols. The nomenclature and Key established in LLFS for use on the FS-Worksheet has utilized the ERO style, but has included some non-standardized symbols based on the investigator's preference. Although it is not the only taxonomy in wide-spread use, the nomenclature and symbols used in this Manual of Operations provides the means for standardization within LLFS.

Pedigrees consist of two basic elements: (1) pedigree symbols, and (2) relationship lines (see Pedigree Structure Key on FSW). A pedigree symbol represents a single member of a family. Hence, one pedigree symbol is drawn for each family member. The pedigree symbol indicates the sex and vital status (living, deceased) of the family member; sex is indicated by the shape of the pedigree symbol (squares for males; circles for females), and deceased individuals are denoted by a diagonal line drawn through the corresponding square/circle. The study Proband is identified by an arrow pointing to his/her pedigree symbol. Relationship lines are a system of horizontal and vertical lines that define the relationships between family members. By tracing the relationship lines that connect any two individuals within a pedigree, it is possible to unambiguously determine their genetic relationship.

The name of each pedigree member is recorded above the symbol and slightly to the right to avoid, as much as possible, having to cross the names with vertical relationship lines (care must be exercised not to off-set the names too far to the right). The LLFS Participant ID number, corresponding to each pedigree member (if one has been assigned), is recorded below the appropriate pedigree symbol. If an LLFS ID has not been assigned, an equal sign (=) is placed below the pedigree symbol. Pedigree members that have not been assigned an LLFS ID, will receive one at a later stage from the DMCC. ID numbers for such individuals should not be assigned by Field Center staff, even if the family relationship is clearly defined and confirmed during the Family Structure Review.

Before drawing the pedigree, the PIF is completed and entered into the DES, resulting in a simplified summary report to aid in assessing the size of the sibship and the complexity of the pedigree. This is helpful in spacing the elements of the pedigree and prevents the need for extensive erasing or redrawing of the pedigree. The pedigree should be drawn in the order indicated below. Each of the specified relationships refer to the relationship between the Proband and his/her family members (i.e., spouse(s) refers to the spouse(s) of the Proband). Construction of the pedigree in this manner ensures standardization and completeness of the family structure data.

Proband: The pedigree symbol for the Proband is drawn in the center of Generation II. Indicate the gender of the Proband by the shape of the pedigree symbol. Draw an arrow pointing to this symbol, to indicate that this is the study Proband. Write the Proband's first and last name above and to the right, and his/her LLFS ID below and to the right of the symbol. If the Proband is deceased, draw a diagonal line through the symbol. See Example 1. ***Important Note:*** in this example, '01' is the identifying number for Mary Jones. For the LLFS Pedigree, '01' will be replaced with that individual's LLFS Participant ID #.



Example 1

Proband's Relatives:

General Instructions: Indicate the gender of each of the Proband's relatives by the shape of the pedigree symbol.

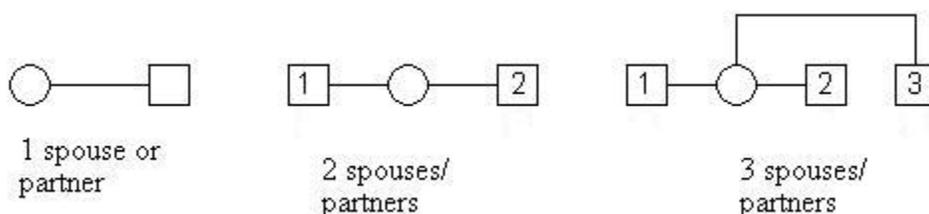
Record the first and last name of each relative above and slightly to the right, and the LLFS ID for each relative below and to the right of the appropriate symbol. If a relative's name is unknown, place a question mark (?) above and to the right of his/her pedigree symbol. If an LLFS ID has not been assigned, place an equal sign (=) below and to the right of the pedigree symbol.

If the relative is deceased, draw a diagonal line through his/her symbol. If the vital status of the relative is unknown, place a question mark (?) inside the pedigree symbol. Indicate twin pairs using the appropriate symbol from the Pedigree Structure Key.

Specific Instructions:

A. Spouse(s)/Partner(s) – Generation II

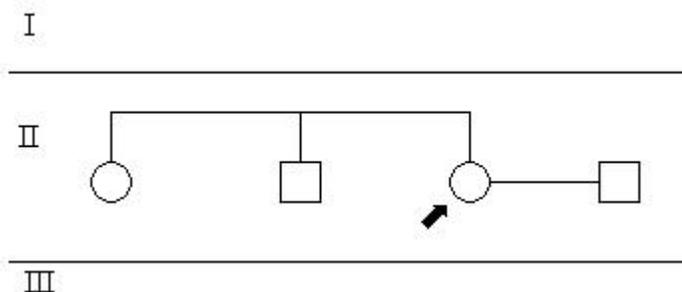
Draw a pedigree symbol for each spouse/partner of the Proband in Generation II. Indicate the relationship between the Proband and each spouse/partner by drawing a horizontal mating line between their pedigree symbols. If a Proband has had more than two partners, a squared line can be drawn between the pedigree symbol for the Proband and his/her third, fourth, etc. partner. When a Proband has more than one partner, record the order of the relationships by placing a "1" in the pedigree symbol for the first partner, a "2" in the pedigree symbol for the second partner, etc. *See Example 2 below.*



Example 2

B. Full Siblings – Generation II

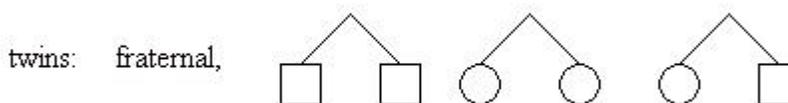
Draw a pedigree symbol for each full sibling of the Proband in Generation II. Indicate the relationship between the Proband and his/her full sibling(s) by drawing a vertical line up from the center of the Proband's pedigree symbol and the symbols for each of his/her full siblings (toward, but not to the Generation I boundary). Use a horizontal sibship line to connect all of the individuals within the Proband's sibship. See Example 3 below.



Example 3

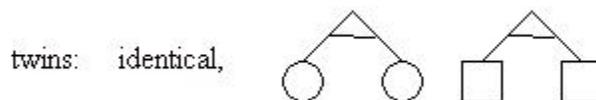
C. Twins – Generation II

- Fraternal: Draw a pedigree symbol for each twin. Indicate that it is a twin ship by drawing diagonal lines up from the center of each symbol, to meet at a point at the top. See Example 4 below.



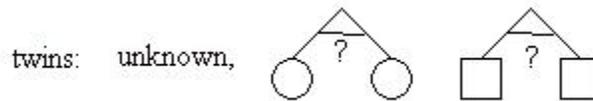
Example 4

- Identical: Draw as with fraternal twins, but add a horizontal line connecting the pedigree symbols. See Example 5 below.

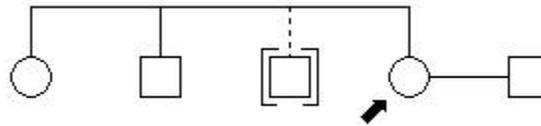


Example 5

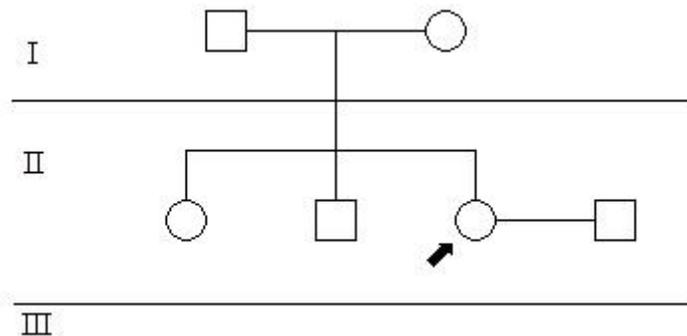
- **Unknown:** If the Proband (or his/her proxy) does not know if the twins are fraternal or identical, draw as with identical twins, but then add a question mark (?) below the horizontal line. See *Example 6 below*.

**Example 6****D. Adopted Siblings – Generation II**

Draw a pedigree symbol for each adopted sibling of the Proband in Generation II. Adopted siblings are placed within the Proband's sibship by connecting the appropriate symbol to the Proband and his/her siblings with a solid line, and then identifying the adopted sibling by a dotted-line circle surrounding his/her symbol. See *Example 7 below*.

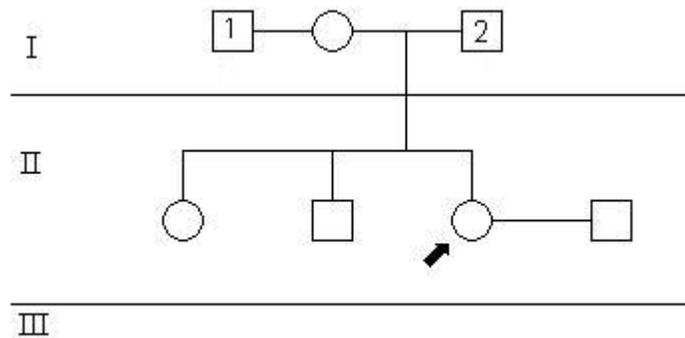
**Example 7****E. Biological Parents – Generation I**

Pedigree symbols for the biological mother and father of the Proband are drawn in Generation I. To place the biological parents in the pedigree, draw a vertical line from the center of the line connecting the Proband's sibship, into Generation I. Draw a female symbol to the left and a male symbol to the right of the line. Connect these two symbols with a mating line. See *Example 8 below*.

**Example 8****F. Step-Parents – Generation I**

Pedigree symbols for any additional spouse/partner of the Proband's biological parents (i.e. the Proband's step-parents) are drawn in Generation I. Indicate the relationship between the Proband's parents and each of their additional spouses/partners by connecting their pedigree symbols with an arched mating line. Record the order of the relationships by placing a "1" in the pedigree symbol for the first partner, a "2" in the pedigree symbol for the second partner, etc.

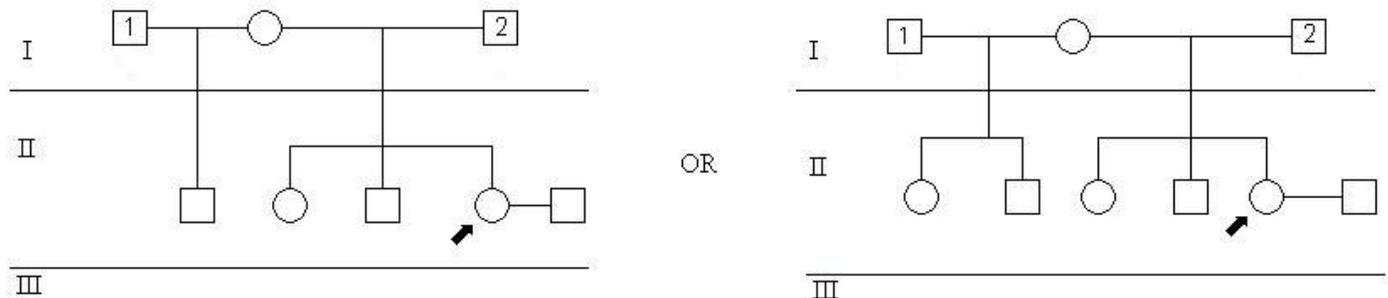
Determine if there is a genetic relationship between the Proband's biological parent and any of his/her additional spouses/partners. If there are, indicate this on the pedigree by drawing a second mating line (parallel to the first) between the Proband's parent and the appropriate spouse/partner (see Example 2). Record the exact genetic relationship in the comments section. *See Example 9 below.*



Example 9

G. Half-Siblings – Generation II

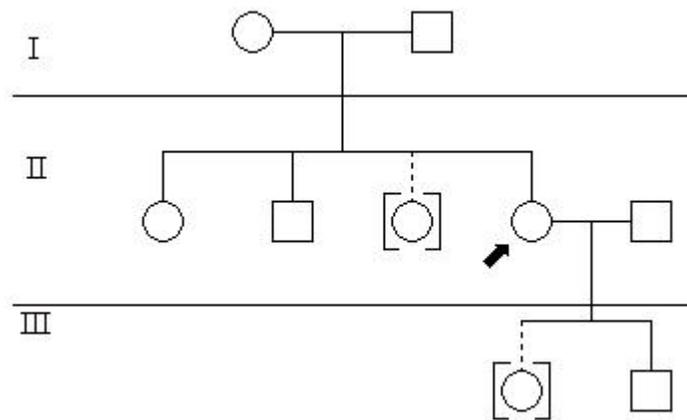
Pedigree symbols for the half-siblings of the Proband are drawn in Generation II. To place the half-siblings in the pedigree, draw a vertical line down from the center of the mating line that connects the half-siblings' parents. This line should extend to the level of the line connecting the Proband's sibship. If these parents have a single child, the appropriate pedigree symbol should be centered below, and connected to this line. If they have more than one child, a horizontal sibship line should be drawn at the base of the line. A pedigree symbol for each of their children should be drawn below and connected (with a vertical line) to the horizontal line. *See Example 10 below.*



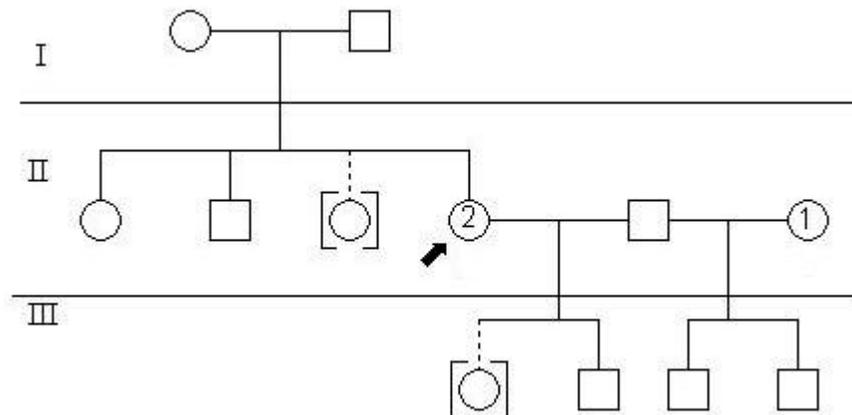
Example 10

H. Step-Siblings – Generation II

Pedigree symbols for the step-siblings of the Proband are drawn in Generation II. Prior to placing step-siblings in the pedigree, the second parent (i.e. the spouse/partner of the Proband's step-parent) of these individuals must be added to the pedigree. Pedigree symbols for such individuals should be drawn in Generation I, and a mating line should be drawn between these individuals and the appropriate step-parent of the Proband. Step-siblings are then added to the pedigree in a manner analogous to that outlined for half-siblings. *See Example 11 below.*

**Example 13****K. Step-Children – Generation III**

Pedigree symbols for the step-children of the Proband are drawn in Generation III. Prior to placing step-children in the pedigree, the second parent of these children must be added to the pedigree. Pedigree symbols for such individuals are drawn in Generation II, and a mating line is drawn between these individuals and the appropriate spouse/partner of the Proband. Record the order of the relationships by placing a "1" in the pedigree symbol for the first spouse/partner, etc. Step-children are then added to the pedigree in a manner analogous to that outlined for full-siblings. *See Example 14 below.*

**Example 13**