# Appendices

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# Appendix I

## The Process

The GAP Committee began meeting in June 2000 and continued until January 2002.

Different members of the committee took responsibility for drafting particular components of the recommendations. All committee meetings were recorded and transcribed. Each draft was reviewed twice, and then finalized, by the entire committee.

### Committee Members

Members of the committee represented a variety of backgrounds and perspectives, and included researchers, clinicians, clergy, lawyers, and nurses.

Co-chairs:

Elizabeth Hohmann, MD, Partners HealthCare System
Bruce Korf, MD, PhD, Harvard-Partners Center for Genetics and Genomics
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Scott Weiss, MD, Brigham & Women's Hospital

Members:

A.G. Breitenstein, Attorney
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Rosalyn Gray, Partners HealthCare System
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Appendix 2:

## General Guidelines for Subject Recruitment in Genetic Studies

**Purpose:**

To provide guidance on how to recruit volunteers to participate in genetic studies.

**Background:**

According to Federal regulations, an IRB must review and approve methods that investigators propose to use to recruit subjects, to ensure that the methods are not coercive and that the confidentiality and privacy of potential subjects are protected. Potential subjects can be identified in a number of ways: through medical records; by referring physicians; from the medical practices of one or more of the investigators; or by advertisements in various media.

The key issues to consider in preparing, or reviewing, the recruitment section of a protocol are as follows:

1. Volunteers must understand the purpose of the study, the expected outcome (a new genetic test? identification of a gene?), all benefits and all risks, and these must be explained in an informed consent process and documented in a consent form. Volunteers must also understand how their identifiable information will be used and possible disclosed for the purposes of the study. These details must be documented in an authorization. (N.b., the informed consent and the authorization can either be two separate documents, or more commonly, at Partners the required elements of both are merged into a single document.)

2. If a new treatment is being tested, the volunteers must understand that the drug or device being tested is investigational or being used for research.

3. Steps must be taken to avoid coercion. The participants must be provided with a way to decline participating if they do not want to participate.

4. Steps must be taken to maintain a person's confidentiality and privacy. The privacy and confidentiality issues are particularly important – and may require additional safeguards – if the subject of the research involves particularly sensitive issues such as:

    - Sexual behavior
    - Mental illness
    - Substance abuse (drugs, alcohol)
    - Illegal behavior

The IRB carefully considers all aspects of the identification, recruitment and enrollment of research subjects during its review. Investigators can facilitate the review process and avoid unnecessary delays by describing all aspects of these processes in detail as part of the research protocol. The guidelines listed below may not be applicable to every situation that arises in the research process. Carefully justified alternative approaches will be considered on a case-by-case basis. IRB staff will offer guidance to investigators upon request.

**Guidelines for Recruitment:**

Note: These guidelines must be followed in addition to the subject recruitment guidelines stipulated in Partners' standard recruitment policy.

Every protocol must include a Recruitment section that clearly describes:

- How potential subjects are identified
- How and by whom subjects are approached about participation
- When consent is obtained in relation to the start of the study procedures
- Whether any third parties may be involved in screening subjects or otherwise participating in recruitment

For additional guidance, see applicable section in the categories that follow.

**Identification of Potential Subjects**

Investigators frequently seek to identify and recruit individuals known to have a specific medical condition for participation in a study. Sometimes the easiest way to find potential study participants is to search medical records, patient registries and clinical databases, but investigators using these methods should exercise special precautions to respect patient privacy. All identifiable medical information is private and must be handled confidentially under federal and state laws and institutional policies.
The IRB will review specific plans for subject identification to ascertain compliance with the Common Rule and with the HIPAA Privacy Rule.

**How to Contact Potential Subjects About Participation in Research**

The patient's primary caregiver must be an active participant in the recruitment process. This ensures that consideration will be given as to whether it is appropriate for an individual patient to participate in a particular investigation.

As a general principle, only someone who has first-hand knowledge of a patient's medical history should initiate contact with that individual. For instance, if a potential subject is identified through a medical record or by referral, the investigator must obtain permission from the individual's primary caregiver, usually a physician, to contact

his/her patient for research purposes. So called "cold calls" by investigators – in which investigators identify subjects through hospital records, clinic charts or other databases independently, and then contact them by phone – are not permissible unless the subject is already under the medical care of the investigator.

Potential subjects may be contacted in person by their own physicians, during an office visit or while receiving medical care. If the patient gives his or her verbal permission to be contacted about the study, his/her physician can then contact the investigator for follow up.

The patient may also be contacted by letter. If a recruitment letter is used, it should be signed either by the patient's physician, or by the patient's physician and the study investigator, but not the investigator alone. In some cases, it may be appropriate for a representative from a practice group or clinic to contact patients on behalf of the clinic staff. It is not appropriate for recruitment letters to come from study staff, such as research assistants or data managers.

In the letter, the physician should indicate that one of his/her medical colleagues is conducting a research study. The letter should explain the purpose of the research, and provide a brief description of the nature and extent of involvement, e.g., duration of participation and study procedures. For practical purposes, recruitment letters are frequently written and prepared by the study staff, but must be signed by the patient's physician, not the investigator. It is not sufficient to simply obtain permission to contact the patient from the patient's physician.

Recruitment letters must be submitted for review by the IRB.

**Provide Participants with the Choice to Opt Out or Opt In**

Potential subjects must be allowed to "opt out" or "opt in," depending upon the nature of the research. When the research involves sensitive or personal information, such as illegal behaviors, drug or alcohol use, mental illness, sexual behavior or other sensitive issues, etc., the IRB may require that the more stringent "opt in" procedure be followed.

> **OPT OUT Procedure:** In this procedure, the assumption is that the individual is willing to participate in the research, unless he/she actively opts out. The recruitment letter should include a telephone number to call or a postcard to return if subject is *not* interested in participating in the study. If no telephone call is received or postcard returned, the subject may then be contacted by the investigator to determine whether or not the subject is interested in learning more about and/or participating in the study.
>
> **OPT IN Procedure:** In this procedure, the assumption is that the individual is not willing to participate unless the individual actively opts in. The recruitment letter should include a telephone number to call or a postcard to return if the subject *is* interested in learning more about and/or participating in the study. The

investigator may *not* contact subjects who have not called or returned a postcard indicating interest learning more about the study.

In either case, care should be taken to ensure that letters are properly addressed to avoid delivery to an incorrect party, and return postcards must not contain information regarding the patient's medical condition, medication or diagnosis.

**Notices or Letters Sent to Other Health Care Providers**

When asking colleagues to refer patients to you, include additional information about study design, placebo, risks, and benefits. Provide enough information for colleagues to reasonably present the study to their patients.

Notices to clinical colleagues seeking study referrals require IRB approval. Such notices include, but are not limited to, letters, electronic and other postings, and notices in professional publications.

**Incentives and Rewards for Recruitment of Patients and Referral to Clinical Investigators**

Timely enrollment of patients into approved trials is desirable, but care must be taken to ensure that the interests of patients are not jeopardized during the recruitment process. Cash payments or other financial or non-monetary incentives to physicians for referral of patients, otherwise known as "finder's fees," pose a conflict of interest and are not permissible. Financial incentives to physician-investigators to accelerate enrollment of their own patients in their own clinical trials pose a similar conflict of interest and are not acceptable.

The IRB requires full disclosure of any financial arrangements that may encourage physicians to recruit patients for research studies that may not be in their best interests. Physicians who actively participate in the research process by identifying potential subjects, conducting screening examinations or tests, participating in the consent process or performing other specific research-related activities may be reasonably compensated for their time and effort. Such arrangements should be clearly detailed and justified in the research protocol.

**Recruitment of Subjects through Advertisements**

The text of all direct advertising for research subjects must be reviewed and approved by the IRB prior to distribution, posting, publication, or broadcasting. Direct advertising encompasses any notice that will be seen or heard by prospective subjects and includes, but is not limited to, notices placed in newspapers, radio, TV, bulletin boards and the Internet. Advertisements developed by coordinating centers for multicenter study recruitment also require IRB approval if the MGH or BWH sites intend to enroll from among the pool of prospective subjects responding to these ads. Use of calling centers or other third parties to assist with recruitment also requires review and approval.

**Advertisements Should Include:**

- Name of research facility
- Purpose of the research and eligibility criteria (briefly stated)
- Time commitment and remuneration
- Contact person for more information
- The word “research” somewhere prominent in the advertisement

**Advertisements Should Not Include:**

- Claims, explicit or implicit, that the drug, biologic or device is safe or effective for the purposes under investigation or that the test article (drug, biologic, device) is known to be equivalent or superior to any other drug, biologic or device; and

- References to “new treatment”, “new medication” or “new drug” without explaining that the drug, biologic or device is investigational.

All advertisements should be tastefully composed and not inappropriately emphasize monetary remuneration. If you wish to use BWH/MGH/Partners logos, contact Public Affairs for relevant guidelines.

**Do:**

- Use the word "Research" in your advertisement. The terms "Study" or "Treatment Study" do not convey the same message.

- Provide information prospective subjects need to determine interest, such as eligibility, significant study procedures, and time commitment. Specific information to include:

  - Who is eligible to participate? (males, females, adults, children, age range, taking no medications, etc.)

  - What medical tests will be involved? (X-rays, MRIs, exercise testing, overnight stays, frequent blood sampling, etc.)

  - How long will the study last? (duration of study, number of visits and/or length of visits, if only one or two visits)

- Use the phrase "healthy volunteers" instead of "normal volunteers."

- Use simple lay language without acronyms or abbreviations unless these are well known to the public or to the special patient group you are targeting (e.g., patients with ALS or women with PMS will understand these abbreviations).

- List symptoms caused by the disorder you are studying if you are looking for subjects who have not yet been diagnosed.
- Provide basic exclusion criteria whenever possible to reduce unnecessary calls.
- Use the word “investigational” rather than “experimental.”
- Name drugs used if approved an/or known to the public, e.g. aspirin, St. John’s Wort.
- Use the words "at no cost" rather than "free" where relevant.
- Specify amount of monetary compensation (if you wish).
- Use the words "up to" if pro-rated compensation is likely.
- Specify hospital affiliation (e.g. Cardiovascular Division, BWH).
- Indicate where the ad is going to be placed/posted, if the same text will be used for e-mail, newspaper, T-stops, etc.
- Submit printed ads as they will appear in print (or as close as possible) so the reviewer can assess the visual impact, emphasis and graphic message.
- Submit the full text of radio or television ads.

**Don't:**

- Feature monetary compensation as a lead in before describing study purpose and procedures.
- Bold, italicize, underline or enlarge fonts on type describing monetary compensation.
- Imply treatment benefit if the *primary* focus of the study is basic physiological processes or genetic risk.
- Provide detailed lists of risks and benefits (this should be done in person).
- "Hype" the study with overly optimistic or effusive language implying benefit (commercially designed radio ads occasionally do this).
- Use words describing broader affiliations (e.g., "Harvard researchers" or "Harvard Medical School study") which tend to mistakenly convey endorsement and/or direct oversight of study treatments and procedures by the university or medical school.

**Sample Patient Recruitment Letter**
**(A single letter, co-signed by patient's physician and researcher)**

Joan R, Patient
29 High Street
Boston MA

Dear Ms. Patient,

I am writing to tell you about a research study being conducted at Massachusetts General Hospital by Dr. Expert in the Diabetes Unit. I am letting my patients with diabetes who are under 40 years old know about this research project, in case they would like to participate.

Dr. Expert is studying environmental and genetic causes of diabetes. Diabetes may run in certain families, but many other things like diet and exercise can influence a person's risk of developing this disorder. This research project is designed to find out whether diabetes in some people can be linked to specific genes (genes are made up of DNA, inherited from your parents, and passed on to your children).

The researchers are looking for patients under 40 years old, with diabetes, who have a brother or sister who also has diabetes. Participation would involve 2 visits to the Clinical Research Center at Mass. General, each lasting about half a day. There are no medications involved. Participation includes a dietary evaluation, questionnaires, a medical and family history, a physical exam by a study doctor and blood and urine tests. Researchers will isolate your DNA from one of your blood samples, so they can look at genes that seem to be associated with diabetes. As part of the study you will be asked to contact close family members to see if they would also like to participate. Even if they don't want to participate, your participation is still important to us. People who complete the entire study will receive $100 for their time. The study will also pay for parking for necessary visits, and for lunch during visits.

You will not receive any personal health benefits as a result of your participation in this research study. We hope that the results will help us understand diabetes better, and benefit patients with diabetes in the future

Please contact the study coordinator Jane Helper, RN, at 716-724-XXXX or Dr. Expert if you would like to learn more about the study. Your participation is voluntary. Whether you participate or not will have no effect on the medical care you receive here at Mass. General. If you definitely don't want to participate or hear any more about the study, please return the enclosed postage-paid card. If we don't receive the card within 2 weeks, Dr. Expert's staff may send you another letter or phone you to see if you might wish to hear more about the study

Thank you in advance for considering this request,

Sincerely,

Primary Care Physician, MD
Medical Associates
(XXX) XXX-XXXX
*Note: PCP could also be a specialist known to patient.*

Jane Q. Expert, MD
Diabetes Research Unit
(617) XXX-XXXX

**Sample Recruitment Letter**

(Letter from patient's physician that encloses a second letter from researcher. Some physicians feel that this two letter approach allows them to assist with enrollment without entirely "endorsing" or promoting participation.)

**Letter #1: from patient's physician**

Joan R, Patient
29 High Street
Boston MA

Dear Ms. Patient

As you may know, Brigham and Women's Hospital is an academic medical center, dedicated to excellence in both patient care and research.

I am personally involved in both treating patients and furthering research activities in order to understand and reduce surgical and medical problems. In supporting research activities, I always consider my patients' needs and health first and foremost.

Accompanying this letter is a request from a colleague, Dr. Stewart Researcher, who is studying the effects of a blood hormone. I am not a member of his research team, but I am allowing him to approach some of my patients to see if they would be interested in joining his study. He has discussed the goals, the risks and the potential benefits of this project with me, and has received approval of his study by a hospital review board. The surgery that we have discussed and your condition enable you to be a potential subject in this study.

It would not be appropriate for me to promote this study, but if you are interested in it, feel free to contact Dr. Researcher or me with any questions that you may have.

Sincerely yours,

(Dr. Personal Physician to sign)

Enclosure: Letter from Dr. Researcher

**Letter #2: From Dr. Researcher**

Joan R, Patient
29 High Street
Boston MA

Dear Ms. Patient

I am contacting you because you are scheduled to have spine surgery in several weeks. I am an anesthesiologist who often works with your surgeon, and he has signed below to indicate his approval of this letter. I would like to ask you to consider participating in a research study I am conducting.

The study involves an FDA-approved medication (Procrit) very similar to a normal hormone made by your kidney that acts to build up the amount of red blood cells circulating in your bloodstream. Procrit is often used to reduce the need for blood transfusions from other people. The purpose of my study is to see whether Procrit reduces blood transfusions safely in people having spine surgery.

I am looking for 24 people who have moderately low red blood cell levels to join in this study. Your surgeon has indicated you may be eligible.

I am including a stamped postcard for you to mail to indicate if you are interested in having me contact you. Indicating "Yes" does not mean that you have any obligation to join the study; it simply means you would like to receive more information. If I do not receive the postcard within a week, then I will try to contact you by telephone to see if you are interested.

If you have questions or need more information about this study, please feel free to contact me at the hospital during weekdays, (617) XXX-XXXX, or my research nurse John Assistant RN at (617) XXX-XXXX.

Sincerely yours,

Stewart Researcher, MD, PhD

Dr. Patient's Physician
Department of What, Hospital

## Appendix 3:

## Issues Concerning Children Who Display A Specific Phenotype

The following points, taken from the American Society of Human Genetics/American College of Medical Genetics statement "Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents" should be taken into account when the study involves children who display the specific phenotype under investigation (*Am. J. Hum. Genet. 57:1233-1241, 1995)*.

**The Impact of Potential Benefits and Harms on Decisions about Testing**

1. *Timely medical benefit to the child should be the primary justification for genetic testing in children and adolescents.* Under this condition, genetic testing is similar to other medical diagnostic evaluations. Medical benefits include preventive measures and therapies, as well as diagnostic information about symptomatic children. If the medical benefits are uncertain or will be deferred to a later time, this justification for testing is less compelling.

2. *Substantial psychosocial benefits to the competent adolescent also may be a justification for genetic testing.* The benefits and harms of many genetic tests are psychosocial rather than physical. Relevant issues include anxiety, self-image, uncertainty, and the impact on decisions relating to reproduction, education, career, insurance, and lifestyle.

3. *If the medical or psychosocial benefits of a genetic test will not accrue until adulthood, as in the case of carrier status or adult-onset diseases, genetic testing generally should be deferred.* Exceptions to this principle might occur when the adolescent meets conditions of competence, voluntary participation, and adequate understanding of information. Further consultation with other genetic services providers, pediatricians, psychologists, and ethics committees may be appropriate to evaluate these conditions.

4. *If the balance of benefits and harms is uncertain, the provider should respect the decision of competent adolescents and their families.* These decisions should be based on the unique circumstances of each family. The provider should enter into a thorough discussion about the potential benefits and harms and should assess the family's understanding of these issues.

5. *Testing should be discouraged when the provider determines that potential harms of genetic testing in children and adolescents outweigh the potential benefits.* A health-care provider has no obligation to provide a medical service for a child or adolescent that is not in the best interest of the child or adolescent.

**The Family's Involvement in Decision Making**

1. *Education and counseling for parents and the child, commensurate on maturity, should precede genetic testing.* Follow-up genetic counseling and psychological

counseling also should be readily available. Providers of genetic testing should be prepared to educate, counsel, and refer, as appropriate.

2. *The provider should obtain the permission of the parents and, as appropriate, the assent of the child or consent of the adolescent.* Decisions about competence should not depend arbitrarily on the child's age but should be based on an evaluation of the child's cognitive and moral development. The provider should also attempt to establish that the child's decision is voluntary.

3. *The provider is obligated to advocate on behalf of the child when he or she considers a genetic test to be - or not to be - in the best interest of the child.* Continued discussion about the potential benefits and harms - and about the interests of the child - may be helpful in reaching a consensus.

4. *A request by a competent adolescent for the results of a genetic test should be given priority over parents' requests to conceal information.* When possible, these issues should be explored prior to testing. When a younger child is tested and the parents request that the provider not reveal results, the provider should engage the parents in an ongoing discussion about the benefits and harms of the nondisclosure, the child's interest in the information, and when and in what manner the results should be disclosed.

# Appendix 4
## Suggested language for Research Consent Forms

Suggested Standard Language for Genetics

***Directions to investigator:*** *The language below is generally considered acceptable to the IRB. If used as is, assuming it fits your research protocol, it is likely to be acceptable in consent forms. Modify the language as appropriate to fit your study design and planned procedures. Don't include language not relevant to your study. For example, if it's not possible for people to have their blood drawn off site and shipped to you, don't include the language which describes that. Areas in italics denote where investigator choice or input is needed. Please proof-read your consent forms carefully. We strongly recommend review that you ask for a review of your form by colleagues, lay people and native English speakers before you submit with your protocol. Consent forms should be written for people with no medical background, at an 8-9$^{th}$ grade reading level. The headers are only meant to guide investigators to specific language and not to be included in your final form.*

**General statement on purpose of a genetic study**
We would like permission to enroll you as a participant in a research study**.** The purpose of the study is to search for hereditary causes of *[Investigator: insert genetic or medical disorder; expand upon this with additional sentences to truly inform subjects of the nature of the study and/or define the syndrome in lay language]*. You have been asked to be in this study because your doctor has told you that you have *[disorder]*, or you are a family member of a person with *[disorder or condition]. [Investigator: if this does not fit your population, or study goals, modify!]*

**Taking blood for a genetic study**
If you agree to join the study, a blood sample of *45 ml [about 3 tablespoons]* will be drawn. *[Specify the volume in ml and household measures. smaller age appropriate volumes if children are involved!] [If relevant, offer as an option if you wish:* The inside of your cheek will be swabbed if you do not wish to have your blood drawn*.]* Blood cells will be isolated from your blood sample and DNA will be removed from the cells. [*If relevant*: Other parts of the blood sample will also be saved for research also.] DNA is your genetic material, the material from which your genes are made. Your genes are inherited from your parents and passed on to your children. Genes determine important things about you like your height or hair color, and also influence your health. Your DNA will be stored in a freezer in the research lab. Your DNA will be labeled with a code number that links the sample to you, but not labeled with your name. Your sample will be saved for *(investigator, specify duration; for example: indefinitely, for at least 5 years, for a maximum of 25 years. We recommended that a finite time be given wherever possible).*

**Cell lines**
A "cell line" will be developed from your blood sample. This means that cells from your sample will be made to grow in the research laboratory continuously, or saved frozen for growing later. This is sometimes called an "immortalized" cell line. This cell line can provide an endless source of your cells and DNA for research for many years. Cell lines will be labeled with a code that links the samples to you, but not labeled with your name. This cell line will be saved indefinitely.

*[Investigator: consider whether your study design accomodates this as an optional vs. mandatory activity, and whether you really need to maintain a link to the individual long term to accomplish your research goals.]*

**Ongoing review of medical records as part of a genetic study**
Your medical records will be reviewed and results of tests associated with the diagnosis of *[genetic disorder]* will be recorded for the study. Your medical record will continue to be reviewed for at least X years to collect any new clinical information important for the study of *(disorder)*. Autopsy results related to *[disorder]* will also be recorded, if you die and your family agrees to an autopsy. This information is helpful in connecting the research results with medical findings. We may ask you to provide medical records from outside hospitals or doctors. If so, you will be asked to sign a separate release form so that the outside hospital or doctor knows that you want them to send us that information.

## Coding of samples or data

All information and samples obtained for this study will be assigned a code number. No names or important numbers like hospital medical record number or social security number will be kept on samples to link them easily to you. A key to the code will be kept in a separate locked file or password protected computer in the investigator's office.

## Anonymizing samples or data

Samples which we collect will be assigned an anonymous code number. Anonymous means that it will not be possible for us or anyone else to trace the samples back to you, once it is placed in our collection. We will keep several important pieces of medical information attached to the sample: for example your age, gender, medical diagnosis, and some medical test results. It will not be possible for you to remove your sample from the tissue collection, because we will not be able to tell which sample came from you.

**Putting information into a database**
The research results *[including the data collected from the medical charts]* may be entered into a computer database. *If relevant:* This database may be used by other researchers studying inherited causes of *[genetic disorder]*. OR: This database will only be used by members of our research group. [If used by others: No names are entered into this database, only the codes assigned to the research record.] (*Investigator: clarify whether the database will be access by other researchers not affiliated with your group, or who will have access to the data. If it is only you and your research group, state that.).*

## Recruitment of family members

You may be asked if you are willing to tell other family members about this research. We want to enroll your family members *[investigator fill in reason(s)]*. If you agree to contact family members, you will be given written information describing the study. You do not *have* to ask your family members to participate. If you do ask family members, maybe some of them will not want to participate. If you choose to ask, and a relative is interested, you should tell that person to call Dr. *Investigator*. Or, you can tell Dr. *Investigator* that it is okay to call the family member if that person says it's OK. Information about who does, and does not, decide to join the study will be kept private by the investigator so that nobody feels they must join because of family pressure.

**Withdrawal of samples** *[This should be in all forms EXCEPT where samples are made anonymous.]*

Your participation is voluntary. You may stop being in the study at any time or decide not to join the study. If you change your mind and want to withdraw your sample *[and/or cell line]* from further research you should contact Dr. *Investigator* at *[provide phone and/or address; it is preferable to ask people to submit withdrawal request in writing],* and your sample [*and/or cell line*] will be destroyed. Any information obtained from the samples will also be withdrawn except to the extent to which the information has already been used in analyses. If you decide not to participate, you will not be penalized in any way, and you will not lose any benefits to which you are otherwise entitled. *[Investigator: if samples are anonymized, clarify that the subject can't withdraw such samples. It is possible to offer people the option to de-identify or anonymize their sample if they wish, but this may be cumbersome, and difficult to explain.]*

**Costs**
No charges will be billed to your insurance company or to you for this study. *If relevant:* If you choose to have your blood drawn by someone other than the investigator, 1) A pre-paid blood kit and mailing envelope will be sent to you, 2) You should be sure that no charges for the blood draw are to be filed with your insurance company; and 3) If the person who draws your blood intends to bill you, you should pay for this yourself and send a copy of the bill to the investigator, who will reimburse you.

**RETURN OF INFORMATION TO YOU**

**Fill in one of the approved optional statements about return of information to research subjects.**

**Possible commercialization of research results**
The sample you provide may be used to develop new medical tests or treatments. It is possible that the researchers, hospitals, or companies sponsoring the research might benefit financially if the tests or treatments can be patented and sold. There are no plans to provide you with payments or royalties if these discoveries are marketed or licensed. *Investigator: If you have no intention of sharing samples with others, you should state this explicitly. It is best to include these statements if there is any possibility of commercialization of your research for diagnostic or therapeutic purposes.*

**OPTIONS TO CHOOSE (please circle and initial your choice)**

1. *If relevant***:** We may wish to collect more blood from you in the future for more genetic research on *[disorder].* Is it okay to contact you for additional samples in the future?

   _____YES, it's OK to contact me. _____NO, don't contact me in the future.

2. *If relevant:* Would you like to receive our research group's newsletter describing general research results?

   _____YES, please send me a newsletter. _____NO, don't send me a newsletter.

**Sharing of research samples for related research use.**
*(Note to investigator: this can be either an optional activity, which people can agree to or not, OR, you may wish to simply make this a part of the project and if people don't wish to allow this*

*they should not participate. Samples may be coded or de-identified, please specify which; outside researchers should NEVER get keys to code or identities.)*
Your sample and/or cell line may be shared with investigators not associated with this project for research on *[Investigator fill in relevant boundaries of the research projects: e.g: asthma, inflammation and chronic obstructive lung disease].* These researchers will not know who you are, but will have some information about you in order to link their research findings to the disorder being studied. For example, they would know your age, gender, and non-identifying information about your medical condition. A key to the code linking the sample and information to you will never be provided to outside investigators and they must agree that they will not try to find out who you are. *If relevant:* Information regarding research results done by other investigators will not be shared with the investigators of this study, and will not be available to you or your doctor. Do you agree to this?

_____YES, It's OK for others to use my sample for related research.

_____NO, don't share my sample others for related research.

**Sharing of research samples for UNRELATED research use.**

*(Note to investigator: Sharing of identifiable samples for UNRELATED research use is always an optional activity. Subjects must agree to this specifically, or it cannot be done. It is required that samples de-identified before providing to an outside researcher for an unrelated project. If a code is maintained, this must be scientifically justified. Outside resarchers should NEVER get keys to code or identities, and should agree to this in writing.)*

Your sample and/or cell line may be shared with investigators not associated with this project who wish to study [*investigator fill in your area/study*] and also other **unrelated** illnesses. Before your sample is used for unrelated research, all codes and number linking the samples to you will be removed. It will not be possible for outside researchers to find out who you are. These researchers will not know who you are, but will have some information about you in order to link their research findings to the disorder being studied. For example, they might know your age, gender, and non-identifying information about your medical condition. Research results done by other investigators will not be shared with the investigators of this study, and will not be available to you or your doctor. Do you agree to this?

_____YES, It's OK to use my sample for unrelated research.

_____NO, I don't want my sample used in, unrelated research.

*The investigator may wish to ask for specific consent to perform either related or both related AND unrelated research. If you have no intention of sharing samples outside your research group, or no intention of sharing outside your research group, you should state this in order to reassure people. If you commit to not sharing samples in consent forms you will be held to this commitment. Investigators are reminded that PHS is increasingly encouraging and mandating that investigators share valuable resources or collections obtained with funding from the PHS with other researchers. You should always stipulate that you will NOT provide outside researchers with access to identity or keys to codes and outside or secondary investigators must sign a letter of agreement documenting that they will not seek such information.*

**Absence of any plans to share samples or data.**
Your samples and information will not be shared with other investigators outside of our research group.

### Nonmedical risks of the genetics

If you choose to participate in this research, there is a small risk that your confidential medical information could be disclosed or discovered by mistake (due to human error). Information about your participation in a genetic study, if disclosed, may influence insurance companies and/or employers regarding your health status. To help prevent disclosure, information about your participation and the results of the research will not be placed in your medical records. In addition, your samples and information will be coded and the key to the code kept in a separate locked file. No information will be released or published in a way that will identify a specific individual. If you choose to receive the Newsletter, no remarks or statements will be made that indicates that you participated in a genetic study. Any materials mailed to you will not identify you as a participant in a genetic study. Not sharing information about your participation in this study with others will minimize these risks. Although every effort will be made to keep your participation confidential, the investigators cannot guarantee absolute confidentiality.

### Risks of blood drawing

There are minor risks and discomforts associated with blood sampling, including a small amount of pain and possibly bruising at the needle site. Occasionally a person feels faint when their blood is drawn. Rarely an infection develops, which can be treated.

### Risks of the cheek swab

There are no risks to a cheek swab. There may be a very small amount of discomfort when the cheek is swabbed.

**Lack of personal health benefits of genetic studies**
There are no direct health benefits to you as a result of your participation in this research. It is possible that genetic or inherited susceptibility to *[genetic disorder]* may be found. This may help other people or families with *[disorder]* in the future.

**Alternatives**
This research does not involve medical treatment or diagnosis. Your alternative is to not participate in this research study.

### Return of medical and genetic information to subjects

See the section on this in the GAP report. Specific situations and language relevant to each one is presented there.

## Appendix 5:

# IRB Terms Glossary

**Aliquot:** Portion of a tissue sample, such as blood, that is stored or tested separately from the original donated sample.

**Amendment:** A request to the IRB to modify an existing protocol.

**Analytical Validity:** The accuracy of a genetic test, how well it measures a particular trait or characteristic. An analytically valid genetic test is positive if the gene mutation is present and negative when the gene mutation is absent. Analytical validity is not enough, by itself, to assess a genetic test's risks or benefits, however. To do so, the test's *clinical validity* and *clinical utility* must be determined (see definitions below).

**Anonymized:** Previously identifiable data that have been deidentified and for which a code or other link no longer exists. An investigator would not be able to link anonymized information back to a specific individual.

**Anonymous Samples:** Tissue or blood samples that were *never* linked to a specific person – even by the researchers involved in the study. No key exists to link the sample and its assigned code back to the person who donated the sample. Demographic and clinical data of importance may be retained with an anonymous sample.

**Authorization (HIPAA term):** HIPAA document designating permission. The HIPAA Privacy Rule requires authorization or waiver of authorization for the use or disclosure of identifiable health information for research (among other activities). The authorization must indicate if the health information used or disclosed is existing information and/or new information that will be created during the research. The authorization form may be free-standing or combined with the informed consent form, so that a subject need sign only one form. An authorization must include the following specific elements: a description of what information will be used and disclosed and for what purposes; a list of who will disclose the information and to whom it will be disclosed; an expiration date for the disclosure; a statement that the authorization can be revoked; a statement that disclosed information may be redisclosed and no longer protected; a statement that if the individual does not provide an authorization, s/he cannot receive research-related treatment; the subject's signature and date.

**Benefits:** The positive results of a research study (or genetic test). These include: health benefits (being able to take steps to prevent a disease in certain cases, or to institute lifestyle changes to prevent disease); psychological benefits; and societal benefits

**Biomarker:** Any biological trait that is used as an indicator of some trait or disorder of interest. (If this refers to a gene, use the word "gene.")

**Certificate of Confidentiality:** A confidentiality certification provided by the federal government, upon application by a researcher, for a specific project or sample collection. This certificate makes it possible for a researcher to withhold confidential research information from outside parties. Such a certificate may protect information requested by

subpoena. Typically certificates of confidentiality are requested for studies involving sensitive or stigmatizing information, such as research involving drug use, illegal behaviors or violence and abuse. It is not recommended that researchers over-utilize certificates of confidentiality on genetic research which does not meet these criteria. There are some genetic studies where certificates of confidentiality are warranted and should be obtained. For FAQs on certificate of confidentiality, see: http://grants1.nih.gov/grants/policy/coc/index.htm

**Child Assent Form:** A simplified "consent form" for children ages 7 through 14 to 15, which contains all important elements of an adult consent form. Children read and sign an assent form to agree to study participation, rather than a consent form because they have not yet reached legal age of providing their own informed consent. A template and suggested language is available, but investigators are also free to make their own assent forms. Older teens may more appropriately read and sign an adult form, but in all instances, a parent or legal guardian must provide written informed consent for the participation of their child in a research study. Anyone under 18 is considered a minor/child.

**CLIA (Clinical Laboratory Improvement Amendments):** A set of regulations, administered through the federal Health Care Financing Administration (HCFA), which sets minimum requirements for any laboratory that conducts tests (including genetic tests) communicated to a patient, physician, or any other health care provider. HCFA conducts periodic inspections to renew a CLIA certification. Laboratories that are not CLIA certified can still conduct genetic tests, but they should not communicate such information for routine clinical use.

**Clinical Reporting of Results:** Sharing of results with patients, physicians or other health care providers, or including the information in a patient's medical record.

**Clinical Utility:** The usefulness of the test to an individual, a family, or to society. In determining clinical utility, consider the relative benefits and risks of the test, as well as the degree to which it guides clinical decision making.

**Clinical Validity:** The accuracy of a test in diagnosing a particular medical condition, or in assessing the risk of developing that condition. To determine the clinical validity of a test, ask the following three questions:

- How *sensitive* is the test? How well does it detect the presence or absence of a genetic mutation?
- How *specific* is the test? Does it detect a particular gene or mutation? Or does it provide only general information?
- How *predictive* is the test? Do the researchers understand enough about how a particular health condition develops, and how it is linked to the

mutation being tested? Or do questions remain about how the mutation is (or is not) linked to the development of a disease?

**Coded Samples:** Tissue or blood samples which carry a code that allows someone (usually the researcher in charge of the study) to link the sample back to a specific person. A code may be a number, alphanumerical, or a bar code. As long as a link exists, data are considered indirectly identifiable and not anonymous or anonymized. Coded data are not covered by the HIPAA Privacy Rule – but note that the linking code itself is protected by the Privacy Rule. Also, note that coded information is protected under the Common Rule.

**Common Rule** – Also known as 45 CFR 46. Outlines requirements of federally supported research with regards to human subjects protections and places the responsibility of these protections on institutions, their Institutional Review Boards (IRBs), and investigators. Among other requirements, the Common Rule mandates that all researchers obtain informed consent from human subjects to participate in research, unless the IRB has approved a waiver of the requirement for informed consent.

**Continuing Review:** Ongoing review of a project which is already IRB approved and underway. Studies that undergo initial review by expedited procedures and still pose only minimal risks to subjects may undergo an expedited continuing review by a committee chair.

**Data Sheets:** The initial part of the IRB application describing study staff, study populations funding sources, etc. These sheets also include attestations in which investigators and departments acknowledge their familiarity with the study and accept relevant responsibilities.

**Deidentified (HIPAA definition):** Under the HIPAA Privacy Rule, data are deidentified if either (1) an experienced expert determines that the risk that certain information could be used to identify an individual is "very small" and documents and justifies the determination, or (2) the data do not include any of the following eighteen identifiers (of the individual or his/her relatives, household members, or employers) which could be used alone or in combination with other information to identify the subject: names, geographic subdivisions smaller than a state (including zip code), all elements of dates except year (unless the subject is greater than 89 years old), telephone numbers, FAX numbers, email address, Social Security numbers, medical record numbers, health plan beneficiary numbers, account numbers, certificate/license numbers, vehicle identifiers including license plates, device identifiers and serial numbers, URLs, internet protocol addresses, biometric identifiers, full face photos and comparable images, and any unique identifying number, characteristic or code; note that even if these identifiers are removed, the Privacy Rule states that information will be considered identifiable if the covered entity knows that the identity of the person may still be determined.

**Designated Record Set (HIPAA term):** A health care provider's medical and billing records about individuals and any records used by the provider to make decisions about

individuals. Individuals, including research subjects, have the right under the HIPAA Privacy Rule to access and amend protected health information in a Designated Record Set.

**Deviation or Violation Report:** Retrospective notification of the IRB of the deviation or violation from protocol-specified procedures that has already occurred. If the deviations or violations are remediable systems issues (for example: wrong study medications dispensed), the IRB will usually request a plan for how the difficulties will be avoided in the future. If the deviations are unavoidable, such as the patient being unable to comply with the visit schedule because of inclement weather, the deviations are simply noted by the IRB and remedial action is not expected.

**Directly Identifiable** – Any information that includes personal identifiers. To determine what data may be considered identifiable, please see items that must be removed under the HIPAA Privacy Rule's definition of *deidentified*.

**Disclosure (HIPAA term):** A release of identifiable health information to anyone or any entity *outside* of the covered entity (i.e., outside of Partners).

**Exculpatory Language:** Language in consent form that asks, appears to ask or implies that the subject is waiving rights, benefits or privileges. Exculpatory language is explicitly prohibited by federal regulations. Language of this nature will be stricken from consent forms or edits will be recommended by the IRB. Guidance from OHRP sets a fairly high standard here. For example, OHRP does not allow consent forms to state that a patient has given up ownership of a blood sample: this is viewed as exculpatory language.

**Expedited Review:** Review conducted on behalf of the IRB by an IRB chairperson or other designee, rather than by the full panel at a convened meeting. Expedited review is only possible for protocols that pose minimal risk to *subjects as defined by federal regulations*. Minimal risk is defined within federal regulations governing IRBs. Some examples of minimal risk studies include: questionnaire studies, limited blood draws in healthy adults, ultrasound and MRI if performed without contrast agents, within FDA approved parameters of use. Amendments which do not alter the risk/benefit ratio of a study are also reviewed by expedited procedures. IRBs are required to consider social and psychological risks, as well as physical risks, in making their assessments.

**Food and Drug Administration:** The federal agency in charge of approving new drugs and medical devices before they can be marketed to the public. The FDA must approve any laboratory test (including genetic tests) that will be sold as kits to the public or to multiple laboratories or hospitals. (The tests are considered diagnostic devices.) Although technically the FDA has the power to regulate genetic tests while they are in development, the agency has not exercised that authority. It relies on the IRB at an institution to provide oversight.

**Genetic Research:** Any study which attempts to correlate a person's physical traits or *phenotype* (including the presence or absence of disease) with the particular genes he or she possesses, or *genotype*. Genetic research includes two types of studies – genetic identification and testing and experimental genetic therapy, both described below.

**Genetic Testing:** An analysis performed on human genetic material (including DNA, RNA, genes and/or chromosomes, and the proteins encoded by genes) to detect inherited or acquired mutations, a person's genetic profile (genotype), physical characteristics (phenotype), or chromosomal profile (karyotype). Genetic tests are generally performed to detect genetic material that causes or is likely to cause a specific disease or condition.

**Gene Therapy:** Treatment of medical condition based on introduction of a specific genetic sequence, or its protein product, into a cell.
**HIPAA** [pr: *hip'-ah*]: The Health Insurance Portability and Accountability Act of 1996. HIPAA is a federal law that was designed to allow portability of health insurance between jobs. In addition, it required the creation of a federal law to protect personally identifiable health information; if that did not occur by a specific date (which it did not), HIPAA directed the Department of Health and Human Services (DHHS) to issue federal regulations with the same purpose. DHHS has issued HIPAA privacy regulations (the HIPAA Privacy Rule) as well as other regulations under HIPAA.

**Identifier:** Anything used to identify a tissue or blood sample. The use of a name or social security number will enable a direct link to be made between the tissue sample and a specific person. The use of a code (such as a number, or a letter/number combination) with a corresponding key will provide some protection of privacy, but people with access to the code will be able to link the sample back to a person. The only way to insure complete anonymity of samples is to randomly assign identifiers, where there is no key linking the identifying number to a specific person.

**Immortalized Cell Lines:** Transformed lymphoblasts capable of continuous replication within the laboratory. Cell lines of this nature are able to provide large, potentially inexhaustible supplies of DNA for research study. Such cell lines may be defined in consent forms as: "cell lines capable for living many years in the research laboratory and providing large supplies of DNA for ongoing research." Note that cell lines may represent a greater potential risk to confidentiality than finite DNA samples.

**Indirectly Identifiable** – Data that do not include personal identifiers, but link the identifying information to the data through use of a code. These data are considered identifiable by the Common Rule and not identifiable by the Privacy Rule. To determine what data may be considered identifiable, please see *deidentified*.

**Information Sheets**: A lay language summary of a research study for potential subjects, or their families in the case of genetic studies seeking family member participation. Information sheets are typically presented as a 1-page summary or 3-fold brochure which describes a study in more detail than a simple advertisement. An information sheet should

contain the same elements as a recruitment letter (see below). Information sheets should be made available to probands for distribution to family members. Include contact numbers for interested parties to reach investigators directly.

**Informed Consent:** Permission as required by the Common Rule. A person's consent to voluntarily participate in a research study after he or she has been fully informed about the purpose of the study, and its procedures, risks and potential benefits. Informed consent is obtained after the potential subject has learned about all aspects of the study, and indicates that he or she is willing to participate in the study. An individual's signature on an IRB-approved consent form is one important component of informed consent, but it is not the only one. Investigators must also demonstrate that they have taken steps to truly educate subjects about the study, and advised them of their right to withdraw at any time.

**Institutional Review Board (IRB)** – Common Rule-mandated method of peer review to protect human subjects. HIPAA privacy regulations require an IRB also to protect the privacy rights of research subjects in specific ways.

**Keys to Coded Samples:** A key that can be used to identify the person who provided sample that has been coded in some way. If a key exists, coded samples are NOT anonymous or not non-identifiable.

**Limited Data Set (HIPAA term):** Set of data that may be used for research, public health or health care operations without an authorization or waiver of authorization. The limited data set is defined as PHI that excludes the following direct identifiers of the individual or of relatives, employers or household members of the individual: names; postal address information, (other than town or city, State and zip code); telephone and FAX numbers; electronic mail addresses; SSN; medical record numbers; health plan beneficiary numbers; account numbers; certificate/license numbers; vehicle identifiers and serial numbers, including license plates; device identifiers and serial numbers; web universal resource locators (URLs); internet protocol (IP) address; biometric identifiers, including finger and voice prints; full face photos, and comparable images. A covered entity must enter into a data use agreement with the recipient of a limited data set.
It should be noted that although a limited data set is subject to only select provisions of the HIPAA Privacy Rule, it may be covered by the Common Rule.

**Medical Risk:** A risk to someone's health or well-being.

**Minimum Necessary (HHIPAA term):** A HIPAA Privacy Rule standard requiring that when protected health information is used or disclosed, only the information that is needed for the immediate use or disclosure should be made available by the health care provider or other covered entity. This standard does not apply to uses and disclosures for treatment purposes (so as not to interfere with treatment) or to uses and disclosures that an individual has authorized, among other limited exceptions. Justification regarding what constitutes the minimum necessary will be required in some situations (*e.g.*, disclosures with a waiver of authorization and non-routine disclosures).

**Nongenetic Uses of Samples**: Any research that does not involve analysis of genes. Such uses might include experiments on immune system function, cell cultures, etc.

**Office for Human Research Protection (OHRP):** An office within the Department of Health and Human Services which has responsibility for protecting people who participate in research funded by DHHS. OHRP regulates individual researchers, institutions receiving federal funding and IRBs.

**Planned Deviation:** A prospective request to the IRB to deviate from the protocol specified procedures for individual subjects.

**Polymorphism:** Variation in gene that is common in the population. Because most laypeople (such as those who participate in studies or serve on IRBs) are unlikely to know what a polymorphism is, it's better to call it a "gene" or "variant" in the protocol summary, consent form and other documents intended for lay readers, to avoid confusion. "Mutation" or "mutant" may be unfavorably received by the public and perhaps avoided in some settings.

**Privacy Notice (HIPAA term):** Institution-wide notice describing the practices of the covered entity regarding protected health information. Health care providers and other covered entities must give the notice to patients and research subjects and should obtain signed acknowledgements of receipt. Internal and external uses of protected health information are explained. It is the responsibility of the researcher to provide a copy of the Privacy Notice to any subject who has not already received one. If the researcher does provide the notice, the researcher should also obtain the subject's written acknowledgement of receipt.

**Protected Health Information (HIPAA term):** Individually identifiable health information transmitted or maintained in any form.

**Protocol Summary:** A 3 page summary in lay or simplified medical language which summarizes a research study concisely. The summary should provide details about the conduct of the study which are unique to this performance site in the case of a multicenter study.

**Recruitment Letter:** Letter to a potential research subjects requesting consideration of a research project. A recruitment letter should contain, briefly, the purpose of the study, what procedures will take place, costs or stipends provided, and risks and potential benefits of the research study. State how many visits and what type of time commitment is required. Recruitment letters which are sent to a patient based on a confidential medical information, for example the diagnosis of Type II diabetes with moderate renal impairment, should be cosigned by a clinician who has a medical reason to be aware of the confidential medical information. Such a clinician could be either the primary care physician or specialist involved in the patients care. Recruitment letters for "routine" studies which are not evaluating highly sensitive information typically contain an "opt out" return postcard, in which a subject can decline any further contact.

**Risks**: The risks of a genetic test are any negative impacts the test or knowledge of its results may bring. These include:

- Psychological risks, such as depression or despair that can result when an individual learn he has a mutation that puts him at risk for a disease which currently lacks treatment, or for a disease where the treatment options are not good
- Social risks
- Employment discrimination that may result if the test results become known
- Insurance discrimination that may result if the test results become known
- Family discord over whether to be tested for an inherited condition, and differing views about whether to learn the results
- Economic consequences, such as lost wages if the individual loses his or her job

**Secondary Uses of DNA:** Research or study related to the original project, by other affiliated researchers either inside or outside the institution. Such uses must fall within the boundaries designated within a consent form and approved by the IRB.

**Social Consequences:** The impact a test has on an individual's (or a group's) standing in the community. Negative social consequences include: stigma (leading to social rejection) and discrimination (in employment, health insurance, life insurance, housing, etc.). Both individuals and social, ethnic or racial groups of people can suffer social consequences from a genetic test, especially if a genetic mutation is common in that particular group.

**Standard Language:** Language appended to every consent form that is required by the institutions. This language is required because it addresses many of the standard elements of consent, for example confidentiality, injury, ability to withdraw from a research study. These elements are required by federal law and are often omitted from "home grown" consent forms. Additionally injury statements may be complicated and it is recommended that the injury statements approved by the hospital lawyers be the one that is included. (New HIPAA standards will be met with modifications to the standard language.) The language and wording put forth as "standard language" and appended automatically to each consent form after the investigator written segments has already been viewed and is acceptable to the IRB and legal counsel and cannot be altered, except in unusual circumstances: For example, there is a version of the standard language which addresses the study with a certificate of confidentiality and a version of the standard

language approved by studies funded by the Department of Defense which has specific requirements.

**Tertiary uses of DNA:** A new use of DNA beyond that approved by the IRB. Any new use of DNA must be approved by the IRB before it can take place. With exceptions considered individually, the IRB will typically allow completely unrelated uses to be permitted only if samples are completely stripped of identifiers before such uses are undertaken, or if specific consent for unrestricted use was sought and provided by the individual donating the sample. In some instances, tissue repositories or studies may describe in consent forms who oversees such potential future uses and safeguards the rights and welfare of subjects who provided samples (e.g. the IRB or other independent ethical review board).

**Tissue Bank or Sample Bank:** Prospective collection of samples (buffy coat, DNA, serum, tumor or normal tissue) stored for an extended period for research use. A researcher should seek specific consent for long-term storage, define future uses specifically or generally as needed and provide an option for withdrawal of samples should be individual wish to do so. Samples which are obtained anonymously retain no link to an individual and therefore cannot be withdrawn from the sample collection. A bank may be comprised of samples which are originally removed for clinical care (leftover tumor after completion of pathology) or originally removed exclusively for research (blood sample for DNA extraction or "extra" aspiration of bone marrow at the time of a diagnostic procedure).

**Use (HIPAA term):** The sharing of individually identifiable health information *within* a covered entity. [*See Affiliated Covered Entity; Compare Disclosure*]

**Waiver of Authorization (HIPAA term):** Under some circumstances, a waiver of the requirement for authorization for use or disclosure of private health information may be obtained from the IRB by the researcher. A waiver of authorization can be approved only if specific criteria have been met. [*See Authorization*]

## Appendix 6:

# Genetics Glossary

**Acquired Mutations:** Changes to genetic material that occur over a person's lifetime, often as a result of exposure to environmental factors such as radiation, or as a result of the aging process. Also known as somatic mutations.

**Adenine or "A":** One of the four bases of DNA. Pairs with thymine or uracil (in RNA).

**Age-Dependent Penetrance:** The increased likelihood that someone will show signs or symptoms of a genetic disorder as he or she grows older.

**Alpha-Fetoprotein (AFP):** Protein secreted by fetus during development. AFP levels that are not within normal limits can indicate an abnormality of fetus, such as Down syndrome.

**Alleles:** Different forms of a particular gene.

**Amino Acids:** Chemical building blocks that together form proteins.

**Amniocentesis:** A diagnostic test that removes fluid from the amniotic sac to determine whether a developing fetus may suffer from certain abnormalities, such as Down syndrome. Typically performed at 16 to 18 weeks' gestation.

**Animal Model**: An animal (e.g., mouse, Drosophila, etc.) that has been bred to show the characteristics of a human disease. Sometimes researchers create animal models by introducing particular genes into them or by knocking out particular genes.

**Anonymous Marker:** A DNA segment whose function is not understood, but which can be used as a landmark for genetic mapping.

**Anticipation:** Situation in which a genetic disorder worsens as it is inherited by successive generations. Usually a characteristic of disorders associated with triplet repeat expansion mutations

**Antisense:** The strand of DNA that does not contain information for making proteins, but which serves as a template for making mRNA. (Also referred to as non-coding DNA.)

**Apoptosis:** Also called programmed cell death or cell suicide; this is the way that the body rids itself of cells that are defective, unnecessary or no longer needed.

**Association:** Traits that often appear together, suggesting that the causes may be closely related.

**Autosomal Dominant Disorder:** A disorder that is produced by a change in a single dominant gene on an autosome , even when its counterpart on another chromosome is not mutated.

**Autosomal Recessive Disorder:** A disorder that develops when someone inherits two copies of a recessive gene mutation on an autosome that causes the disorder. (See recessive genes.)

**Autosome:** Any chromosome that is not one of the sex chromosomes. Usually people have 46 chromosomes, 22 pairs of autosomes and 2 sex chromosomes.

**Bacterial Artificial Chromosome:** Long segments of DNA that has been cloned into bacteria. This is a way of making many copies of the foreign DNA, since bacteria multiply quickly.

**Base Pairs:** The molecular units of DNA, which are bound together by weak chemical bonds. Base pairs help to form the twin strands of DNA so that it resembles a double helix.

**Bias of Ascertainment:** The process of selecting individuals to participate in a study because they possess a particular characteristic or trait, which can then inflate the estimate of how frequently that trait appears in the larger population.

**Birth Defect:** Some type of abnormality that is present at birth, caused either by genes or something in the environment (such as prenatal exposure to a toxin, like radiation or certain medications).

**Buffy Coat DNA:** DNA isolated from the white blood cells from whole blood, which form a layer on top of red cells when the blood sample is sedimented by gravity.

**Candidate Gene:** A gene suspected of causing a specific trait or genetic disorder, based either on DNA mapping or other types of evidence.

**Carrier:** A person who has inherited a mutated copy of a recessive gene along with a normal copy of the gene. People who are carriers do not usually develop a particular disease themselves, but they can pass the gene mutation on to their children. And if their spouse has the same mutation, the child may be at increased risk of getting a disease by inheriting a mutated pair.

**Carrier Testing:** Genetic testing of a healthy person to determine if he or she has inherited a mutated gene. This may be done to better inform a person of his or her risk of passing an inherited disorder onto offspring. It might also be done so that the individual can take advantage of further diagnostic tests or intervention to prevent the disorder from occurring (or to diagnose it as early as possible).

**Cascade Testing:** Genetic testing of relatives of someone who has an inherited disorder, to see if they are carriers of the disorder themselves.

**cDNA Library:** A collection of DNA sequences that contain instructions for making proteins. (Because this library is made from mRNA, it does not include any non-coding DNA.)

**Cell:** The basic unit of any living organism. Each cell has a nucleus which contains genetic material, as well as other chemicals (amino acids, proteins, etc.) which enable it to function.

**Centimorgan:** A way to measure the distance between genes. One centimorgan corresponds with a frequency of recombination of 1%, roughly equivalent to 1 million base pairs.

**Chemical Base:** Each strand of DNA is made from combinations of chemical base pairs: adenine, thymine, cytosine, guanine (ATCG).

**Chorionic Villus Sampling (CVS):** Sampling of the placenta to detect certain or particular abnormalities in the developing fetus. Usually performed at 10 to 12 weeks gestation.

**Chromatid:** One of the two arms of a chromosome that has replicated.

**Chromosomal Abnormality:** A change in the structure of a chromosome, or in the total number of chromosomes. Some people are born with chromosomal abnormalities (as in the case of Down syndrome, in which there is an extra copy of chromosome 21); others may acquire them over time (as is the case with certain cancers).

**Chromosomes:** Structures that contain genes. In people, a normal cell contains 46 chromosomes in its nucleus. 44 consist of 22 sets of exact pairs, each containing the same genes. The remaining 2 are sex chromosomes, X and Y.

**Cloning:** The process of copying a particular segment of DNA or a gene. This is different from making a genetically identical copy of an organism by replicating a single ancestor cell.

**Codon:** A set of three bases, contained in a larger segment of DNA or RNA, which provide the instructions for insertion of a particular amino acid into a protein.

**Cofactor:** A substance that joins with an enzyme to cause a chemical reaction.

**Complementarity:** Tendency for A to pair with T (or U) and G to pair with C in DNA or RNA to form a double stranded structure.

**Complex Inheritance:** A model used to explain the development of disease as resulting from several factors, genetic and environmental, and how they interact.

**Congenital:** Existing from birth (refers to birth defects, traits, conditions, genetic characteristics).

**Contig:** A group of overlapping DNA clones that together cover a large region.

**Couple Testing:** Genetic screening of a couple to determine if one or both is a carrier for a disorder.

**Critical Region:** Portion of a chromosome thought to contain a gene or genes that may result in a particular trait or disorder.

**Cytogenetics:** The study of the structure and inheritance patterns of chromosomes.

**Cytogenetic Banding:** Distinct regions on a chromosome that are revealed as light and dark bands once the chromosome is stained and viewed under a microscope. There are several methods of staining, such as G-banding or Q-banding.

**Cytoplasm:** The part of a cell where most proteins are made.

**Cytosine or "C":** One of four bases of DNA; pairs with guanine.

**Deletion:** The loss of DNA, or an entire gene, which can lead to the development of a disease or other abnormality.

**DNA:** The abbreviation for deoxyribonucleic acid, a molecule that is the basis for heredity. DNA contains genetic information which cells need in order to function and reproduce (or replicate).

**DNA Replication**: The process by which DNA makes a copy of itself.

**DNA Sequencing:** Finding out the order of base pairs in DNA.

**Dominant Gene (or Allele):** A gene that is expressed regardless of its companion gene on the other chromosome is dominant or recessive.

**Double Helix:** The phrase used to describe the structural appearance of DNA, which resembles a ladder twisted into a coil. The rungs of the ladders consist of base pairs, the sides of sugar and phosphate molecules.

**Duplication:** A type of genetic mutation that occurs when one or more segments of DNA, a gene, or an entire region of a chromosome is repeated.

**Electrophoresis:** The application of an electrical current to DNA or RNA fragments in order to separate them.

**Enzyme:** A protein that fosters a chemical reaction within the body.

**Exon:** The portion of a gene that contains instructions for making a protein. A gene can have multiple exons, each of which produces a particular part of the protein. Exons are separated by introns, which do not encode protein.

**Exon Skipping Mutation:** A mutation that alters the way a gene is spliced, so that an exon is removed when the transcript is processed into mRNA.

**Expressivity:** The degree or manner in which a phenotype (a physical characteristic) is observed.

**Fluoresence in Situ Hybridization (FISH):** The use of fluorescent molecules to mark sites on chromosomes that are homologous with specific DNA sequences. FISH analysis greatly improved on other staining methods because it allows the detection of deletions and other chromosomal abnormalities that are too small to be detected otherwise. Several types of FISH probes exist.

**Functional Gene Test:** A test to determine whether a particular gene is active, by detecting a protein that gene produces.

**Gene:** A subunit of DNA that encodes the sequence of an RNA molecule, which in most cases leads to the production of a specific protein.

**Gene Amplification:** The copying of particular segments of DNA beyond the usual number. Amplification of DNA often occurs in cancerous cells.

**Gene Chips:** Array of multiple DNA sequences attached to a glass chip, used for rapid detection of patterns of sequence expression or mutation

**Gene Expression**: The process by which a chemical (usually a protein) is created out of the instructions contained in a gene.

**Gene Knockout:** The deletion or inactivation of a particular gene to determine its function. (Researchers see what happens after the gene is knocked out.)

**Gene Pool:** The total number of genes (including all their variations) for a particular population.

**Gene Therapy:** An experimental approach to treating disease by inserting a DNA sequence or protein product into a cell. This document does not cover gene therapy.

**Gene Transfer:** The introduction of foreign DNA into another organism by means of a vector such as a virus. Used in some types of gene therapy.

**Genetic Code:** The instructions, spelled out in chemical letters, for making a protein. Each gene combines four chemical bases (adenine, thymine, guanine, and cytosine, represented by the letters A,T,G,C) into specific chemical formulas.

**Genetic Counseling:** Counseling of a person (or a family) who either has a genetic disorder or is at risk for developing a disorder or disease. The goal is to provide information to help the individuals involved better understand their risk and make informed decisions about testing, treatment, and the risk of passing the disorder onto children.

**Genetic Linkage Maps:** Maps of the relative location of particular genetic landmarks on a chromosome, based on how often they are inherited together.

**Genetic Mapping:** Identifying where genes are located on a particular chromosome.

**Genetic Marker:** A genetic variation that may be inherited along with a target gene, or a segment of DNA that can serve as a landmark. Markers serve as signposts for gene mapping.

**Genetic Testing**: Testing a blood sample, tissue sample, or some other fluid for the presence or absence of a particular gene or a change in the gene. Researchers may also look for the protein a particular gene produces, which provides indirect evidence that it is present.

> **Direct Testing:** If the gene has been identified, researchers will test an individual's gene for any mutations. DNA sequencing, Southern blot, or PCR assay are all methods of direct testing.
>
> **Indirect Testing:** This type of testing is used when the gene that causes a disease is not known, or the gene has been identified but it is not clear which mutation produces the disease. In these situations, linkage analysis based on known markers will be used to measure a person's risk.

**Genetics:** The study of how particular traits (including susceptibility to disease) are passed from parents to children.

**Genome:** All the genes in a particular organism.

**Genotype:** A person's particular collection of genes, which cannot be discerned from outward traits. (This is different from a phenotype, the physical characteristics that result when instructions from the genes are decoded.)

**Germline Change:** A genetic change in the egg or sperm cell, which unite to create a fertilized egg cell. As a result, these genetic changes become incorporated into every cell in the person who develops out of this single fertilized egg.

**Guanosine or "G":** One of four bases of DNA; pairs with cytosine.

**Haploinsufficiency:** A situation in which one of the two copies of a gene is nonfunctional, resulting in deficient level of production of the gene product.

**Haplotype:** A group of alleles (variations of genes) located together on a particular chromosome, and usually inherited together. Haplotype analysis is used to determine if individuals affected by a disease have inherited the same region of a chromosome – which is useful in some types of genetic testing and in the search for genes.

**Heterozygous:** Having two different alleles of the same gene. Usually refers to having one normal allele and one disease allele.

**Highly Conserved Sequence:** A segment of DNA or gene that varies only slightly from one organism to the next. Such similarities indicate that the gene may perform a function essential to life, so that it has been conserved throughout evolution.

**Homologous Recombination:** The process that occurs as egg and sperm cells are formed, when the two copies of a chromosome shuffle segments of DNA between them. This ensures genetic diversity.

**Homozygous**: Having a pair of identical alleles for the same gene. Usually refers to two normal alleles or two disease alleles.

**Housekeeping Genes:** Genes that control common and fundamental cell functions.

**Human Artificial Chromosome:** A vector that includes essential elements of a human chromosome, and is used to transfer or express large segments of DNA.

**Human Genome Project:** The research effort underway to identify all human genes and sequence their base pairs. A preliminary mapping, or draft, was completed in June 2000.

**Hybridization:** Formation of a double helix from complementary strands of DNA or RNA, which originated from different sources.

**Hypermutability:** High rate of mutation or change during DNA replication.

**Immortal Cell Lines:** Cells capable of unlimited cycles of replication.

**Imprinting:** The inheritance of a condition or trait from only one parent, usually because only the maternal or the paternal form of the gene is expressed.

**Inherited:** Passed from parents to offspring by means of genes.

**Insertion:** A type of mutation that results when one or more bases are inserted into a DNA sequence.

**In Situ Hybridization:** A technique to identify the region of a chromosome that contains a DNA sequence that will complement a cloned segment of DNA.

**Intellectual Property Rights:** Law that protects any test, product, or method that is the result of creative or intellectual effort. Includes patents, copyrights, and trademarks.

**Intron:** A section of DNA without function (also known as "non-coding" or "junk" DNA).

**Inversion:** A type of mutation that results when the sequence of base pairs that make up a segment of DNA are in reverse order.

**Karyotype:** An individual's chromosomal profile, including the number of chromosomes and any deviations from the norm.

**Label:** When geneticists use this term, they mean the use of a segment of DNA that will bind with DNA they are trying to study by pairing of complementary bases.

**Liability:** The tendency to exhibit a trait that is the result of both genes and external or "environmental" factors.

**Linkage:** The proximity of one or more genes or markers on the same chromosome.

**Linkage Analysis:** An analysis of the hereditary patterns of any pair of gene loci to determine the frequency of recombination between them. Used in genetic mapping.

**Linkage Disequilibrium Analysis:** The search for shared haplotypes (groups of genes or traits inherited together) among different individuals.

**Locus:** The location of a DNA sequence on a chromosome.

**LOD Score:** Acronym for "log of the odds"; a mathematical expression that measures the frequency of recombination between a pair of loci in families.

**Marker:** A segment of DNA whose location on a chromosome is known, which can be used in determining the locations of other genes. Scientists track the inheritance of markers, and use them to home in on genes whose approximate locations are known but whose exact location remains a mystery.

**Mendelian Inheritance:** A pattern of transmission of genes in families. There are several types of patterns of Mendelian inheritance, the main ones being autosomal dominant, autosomal recessive, and sex-linked.

**Messenger RNA (mRNA):** A blueprint for a protein. mRNA comes about after the process of *transcription*. It functions as a messenger in that it ferries the genetic instructions to the cytoplasm of a cell, where the protein is actually assembled.

**Metaphase:** The phase of cell division when chromosomes line up along the center of the cell, just before the cell splits. At this point in the cell cycle, chromosomes are concentrated and condensed, making it more efficient for scientists to identify chromosomal abnormalities.

**Metastasis:** The spread of cancerous cells from their original location to other tissue.

**Micro-Array Technology:** Technology that enables rapid analysis of patterns of expression of multiple genes.

**Mitosis:** Cell division in somatic cells.

**Monosomy:** A situation in which there is only one copy of a particular chromosome instead of two. This is generally lethal in people.

**Multifactorial Inheritance:** Traits that result from the combination of several genes and/or external ("environmental") factors.

**Mutation:** A change in a gene. Used especially to refer to a change that leads to disease or puts someone at risk for developing a disease.

**Neoplasm:** Abnormal cells that grow and replicate rapidly; may develop into cancerous cells.

**Non-Coding DNA:** The strand of DNA that does not carry instructions for making a protein. (DNA consists of two strands that form a double helix.)

**Nonpenetrance:** The absence of a particular trait or "phenotype" in a person known to be carrying a mutated gene that affects that trait.

**Nonsense Mutation:** A substitution of a single base chemical that leads to premature termination of translation of the protein product (a *stop codon*).

**Northern Blot:** A technique that identifies mRNA sequences that are complementary to a DNA probe.

**Nucleotide:** A building block of DNA or RNA, which contains a base (such as adenine or thymine), a molecule of sugar and a molecule of phosphoric acid.

**Nucleus:** The structure in a cell that contains chromosomes.

**Oligonucleotide:** A short sequence of single-stranded DNA or RNA.

**Oncogene:** A mutation of a gene that usually helps to control the growth or replication of cells. Once mutated, the oncogene contributes to the out of control growth typical of cancer cells.

**P arm:** The short arm of a chromosome.

**Pathogenic Mutation:** A mutation that results in a genetic disorder.

**Pedigree:** A diagram of a family using standard symbols showing the relationship of members to one another and what traits have been passed on.

**Penetrance:** The expression of a particular trait by a gene.

**Peptide:** Two or more amino acids joined by covalent bonds.

**Percutaneous Umbilical Blood Sampling (PUBS):** A blood sample taken from the fetal umbilical cord. Usually done after 18 weeks' gestation to sample for a specific fetal disorder.

**Pharmacogenetics:** A new field that uses information about genetic variations to guide medical treatment. (Certain drugs will be more effective in people who have, or do not have, particular gene mutations. This helps physicians and pharmacists to determine how effective a drug may be in a particular person, and to reduce the risk of adverse reactions.)

**Phenotype:** The physical characteristic resulting from expression of a particular gene.

**Physical Map:** A map of a particular species' chromosomes, showing physical locations of genes and markers. Used in positional cloning and in hunting for genes.

**Plasmid:** A type of DNA that can replicate in bacteria; used in cloning.

**Pleiotropy:** Various physical characteristics that result from a single genetic trait.

**Point Mutation:** A change in one base in a DNA sequence.

**Polygenic Inheritance:** A model of inheritance for diseases or traits that develop because of more than one altered genes, each of which contributes something to the trait or disease process. None of the genes acting alone could produce the trait.

**Polymerase Chain Reaction (PCR):** A rapid and low cost technique to make copies of DNA segments for research.

**Polymorphism:** A frequently occurring variation in DNA sequences from one person to the next. Usually does not result in disease.

**Population Genetics:** Study of the frequency of specific genetic traits in a population.

**Positional Cloning:** The use of gene mapping techniques to identify a disease gene, even when little or nothing is known about the biochemical alterations involved in that disease.

**Predictive test:** A test to identify the risk that a person will develop a disorder.

**Preimplantation Diagnosis:** Genetic diagnosis of an embryo before it implants in the uterus.

**Premutation:** A variation in a DNA sequence that makes that segment of DNA vulnerable to mutation.

**Prenatal Testing:** Test of the unborn fetus for a specific disorder. May involve genetic testing using fetal cells obtained by amniocentesis, chorionic villus biopsy, or umbilical blood sampling, or may involve structural studies by ultrasound or MRI.

**Primer:** A short segment of single-stranded DNA (an *oligonucleotide)* used in polymerase chain reaction or DNA replication.

**Proband:** Individual whose condition brings his family to medical attention.

**Probe:** A segment of DNA, RNA, or an antibody used to determine the function of a gene or protein.

**Promoter:** The portion of a gene where RNA polymerase and regulatory molecules bind, involved in the control of gene expression.

**Pronucleus:** The nucleus of a sperm or egg before fertilization occurs. Each pronucleus contains half the number of chromosomes, but when fertilization occurs, sperm and egg fuse to form a single nucleus with the full complement of chromosomes.

**Protease:** An enzyme that catalyzes the breakdown of proteins into amino acids.

**Protein:** A molecule that is essential to cell function and regulation composed of a string of specific amino acids.

**Proto-oncogene:** A gene that normally helps to control growth and replication in cells, but can mutate into an oncogene and contribute to cancer.

**Pseudogene:** A sequence of DNA that is similar to a function gene, but is itself not able to produce a protein.

**Pulsed Field Gel Electrophoresis:** A technique that separates large DNA fragments according to size.

**Purine:** The chemical structure of the bases adenine and guanosine.

**Pyrimidine:** The chemical structure of thymine, cytosine, and uracil.

**Q Arm:** The long arm of a chromosome.

**Recessive Gene:** A gene alteration that only results in a phenotype if both alleles are mutated.

**Recombinant DNA:** Refers to a number of different techniques used to manipulate DNA to study the structure and function of genes.

**Repair Genes:** Normally these genes help to repair damage to a cell's DNA that can occur in the normal process of replication, or because of environmental influences such as radiation. When repair genes themselves become damaged, genetic mutations and changes can accumulate within a cell.

**Restriction Enzymes:** Sometimes referred to as "molecular scissors," these are enzymes that cut DNA only at specific base sequences.

**Restriction Fragment-Length Polymorphism (RFLP):** A common genetic variant that occurs at the location where a restriction enzyme would normally cut a segment of DNA. As a result, the cut segments vary in length and can be used as markers.

**Retrovirus:** Virus with single-stranded RNA as its genetic material. When such a virus infects a cell, the RNA is translated into DNA integrates into the host cell's DNA. Some cancers and AIDS are caused by infection with retroviruses.

**Ribosome:** A structure in the cell that is involved in the translation of mRNA into protein.

**RNA:** RNA is an abbreviation for ribonucleic acid. RNA is similar to a single strand of DNA, except that uracil (U) is substituted for thymine (T).

**Screening:** A test that detects any evidence of disease in a person who does not have any symptoms. Some screening tests are genetic; others include X-rays, mammograms, colonoscopies, urine and blood tests.

**Sequence Tagged Site:** A DNA segment whose location is known and which occurs only once in the human genome. This unique segment serves as a landmark for gene mapping.

**Sex Chromosomes:** The X or Y chromosomes, which determine sex.

**Sex-linked Disorders:** Disorders related to genetic mutations on the X chromosome. Usually such disorders are seen in men, who inherit only one copy of the X chromosome (women inherit two.)

**Shotgun Sequencing:** A method of decoding an entire genome by breaking it down into smaller segments of DNA, sequencing them, and then piecing the segments back together by matching overlaps.

**Single Nucleotide Polymorphisms (SNPs):** A common but tiny variation that involves one base in DNA sequences. SNPs can be used to determine patterns of inheritance in families.

**Single Stranded Conformational Polymorphism:** A technique to identify a DNA sequence that contains a genetic mutation.

**Somatic Changes:** Changes in genes that are not inherited, but occur over time, either because of exposure to environmental toxins, like radiation, or because of internal errors that may occur as a matter of chance as someone ages.

**Southern Blot:** A technique to identify DNA segments separated by size and hybridized to complementary base sequences ("probes").

**Spectral Karyotype:** A method of making an organism's chromosomes visible by labeling each one with a different color. Useful for detecting chromosomes that differ from the norm.

**Splicing:** The removal of introns and joining of exons during RNA processing.

**Splicing Mutations:** Mutations that affect the pattern of RNA splicing.

**Stepwise Testing:** A genetic screening of one member of a couple at a time. If the first is found to be a carrier of a genetic disorder, the second is tested.

**Stop Codon:** A codon (set of three bases) that terminates translation of RNA.

**Substitution:** The replacement of one nucleotide with another in DNA.

**Syndrome:** Symptoms or other characteristics that may be caused by a common underlying mechanism.

**Tandem Mass Spectrometry:** Method of analysis of abnormal metabolites, used in diagnosis of metabolic disorders.

**Telomere:** A DNA structure located at the end of chromosomes.

**Teratogen:** A substance that interferes with normal embryonic development.

**Threshold Model of Inheritance:** A theory of disease development which posits that the disease will develop only after a certain level or *threshold* of risk factors has been exceeded.

**Thymine or "T":** One of the four bases of DNA; pairs with adenine.

**Transcription:** A crucial step in the formation of a particular protein that begins when information encoded in DNA is transcribed into messenger RNA (mRNA), which functions as a blueprint for the desired protein.

**Transfection:** Introduction of a foreign DNA segment into a cell.

**Transgenic:** An organism (anything from a simple organism like yeast to something more complex, like a mouse or sheep) which contains foreign DNA introduced shortly after fertilization and incorporated into its germline.

**Transition:** A mutation in which one pyrimidine base is exchanged for another (i.e., A to G or G to A), or one purine base is exchanged for another (C to T or T to C).

**Translation:** The process by which mRNA forms a protein.

**Translocation:** The removal of a DNA segment from one chromosome and its relocation on a different chromosome, or the swapping of material between two different chromosomes.

**Transversion:** A mutation in which a purine base is exchanged with a pyrimidine base, or vice versa (i.e., T to G, or C to A).

**Triple Screen:** A blood test which analyzes three substances (alpha fetoprotein, unconjugated estriol, and human chorionic gonadotrophin) in a mother's blood, to screen for Down syndrome and several other disorders.

**Triplet Repeat Expansion:** A mutation in which a gene segment containing multiple copies of a triplet of bases is expanded in length.

**Trisomy:** A situation in which there are three copies of a particular chromosome rather than two.

**Tumor Suppressor Gene:** Normally, a tumor suppressor gene limits the growth of cells, but if such a gene changes (mutates), cancer can result. One example is *BRCA1*, which when mutated can lead to the development of breast cancer.

**Uracil or "U":** A base that substitutes for thymine in RNA and pairs with adenine.

**Vector:** An agent, such as a retrovirus, used to deliver a gene to a target cell.

**Western Blot:** A technique to identify proteins, based on how binding proteins separated by molecular weight to particular antibodies.

**Wild Type:** The most common form of a gene (allele) at a particular location.

**X Chromosome:** One of the sex chromosomes.

**Y Chromosome:** One of the sex chromosomes.

**Yeast Artificial Chromosome:** The grafting of segments of DNA from one species into the DNA of a yeast cell. Process is used to clone large quantities of foreign DNA.

## Appendix 7:

## SOURCES:

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