1. Description of the research aspects of the study

2. Signing the informed consent document, to formally enroll in the family study

3. Genetics and testicular cancer education

4. Medical evaluations

5. Specimen collection
Testicular Cancer: What We Know

- Accounts for ~1% of all cancer in men
- Incidence of testicular cancer is on the rise
- Most frequent in Northern Europe and North America
- ~ 9,000 new cases in US in 2004
- Incidence varies with ethnic background (blacks at lower risk than whites)
- The first step in the process that leads to testicular cancer probably occurs during pregnancy
- Tumors begin to appear during adolescence
Testicular Cancer Risk Factors

- Sex - male
- Age - 15 to 35
- Race - Caucasian
- Family history
- Prior testicular cancer
- Infertility
- Undescended testicle (cryptorchidism)

- Inguinal hernia
- Abnormal development of testes
- HIV/AIDS
- Carcinoma-in-situ
- Klinefelter syndrome
Testes Development

- Testes develop adjacent to the kidneys and from the same tissue in the fetus (therefore, it is possible that abnormalities of the kidneys may be found in males with testicular cancer)

- Testes descend into the scrotum through the inguinal canal

- Undescended testicles (cryptorchidism) occurs in 3% of full-term and 30% of premature deliveries

Adapted from: http://lpc1.clpccd.cc.ca.us/lpc/zinng/anat/alects.shtml - Chapter 27 - Figure 27-3
Mature Male Urogenital System

http://lpc1.clpccd.cc.ca.us/lpc/zingg/anat/alecture/ach27m/sld004.htm
Genes

- What are genes?
- Where are they located?
- How do they work?
- What happens when they don’t work?
What are genes?

- A small bit of DNA that contains the information needed to make a protein
- Proteins are what tell our cells how to function
- Genes are inherited from our parents
- Genes can be passed on to our children

Where are the genes located?

- Our bodies are composed of organs and tissues
- Organs and tissues are made up of many cells
- Cells contain chromosomes
- Chromosomes come in pairs (one from each parent)
- Each chromosome contains thousands of genes (like beads on a string)
- Genes make proteins
- Proteins tell our cells what to do: grow, divide, secrete hormones, etc.

http://school.discovery.com/clipart/clip/in-body.html
Chromosomes, DNA, and Genes

Adapted from Understanding Gene Testing, NIH, 1995
Chromosomes Come in Pairs

Normal Karyotype
How You Get Your Genes

- Adapted from: Essential Cell Biology, Chapter 9, Figure 9-34, ©1998 by Alberts, Bray, Johnson, Lewis, Raff, Roberts, Walter. http://www.essentialcellbiology.com
- Published by Garland Publishing, a member of the Taylor & Francis Group.
The DNA Double Helix

Sugar phosphate backbone

Bases

Base pair

Adenine (A)
Cytosine (C)
Thymine (T)
Guanine (G)
The DNA Double Helix and the Genetic Code

Sugar phosphate backbone

Base pair

Bases

ATT ATG AGT AAC CCA

Isoleucine - Methionine - Serine - Asparagine - Proline
Disease-Associated Mutations
Alter Protein Function

Functional protein

Functional protein - polymorphism

Nonfunctional or missing protein - deleterious mutation

ASCO, modified 12/02
The Development of Cancer Depends on Multiple Genetic Changes
“Sporadic” Mutations

- Mutations in testicular cell cause cancer
- Both mutations occur in target organ
- Causes cancer later in life
- Mutation cannot be passed on

Genetic “hit” or mutation

ASCO, modified 1/03
Inherited mutations = “Hereditary Cancer”

Parent:
- Parent has mutation present in all cells of the body

Offspring:
- Offspring inherits first mutation from parent and may get second “hit” leading to testicular cancer
- All cells have mutation from birth
- Second mutation permits cancer
- Mutation passes through egg/sperm to some offspring

Genetic “hit” or mutation

ASCO, modified 1/03
Possible Inheritance Patterns

- Autosomal Dominant
- Autosomal Recessive
- X-Linked Recessive
Inheritance from Your Parents

Alleles: variant forms of the same gene (A a)
Autosomal Dominant Inheritance

- Each child of a person with a mutation has 50% chance of inheriting the mutation.
- Even though the cancer may appear to “skip generations,” the mutation does not. This occurs because not everyone with a mutation will actually develop cancer.
- Equally transmitted by men and women.

ASCO, modified 12/02
Autosomal Recessive Inheritance

- Family members with one copy of the abnormal gene appear to be healthy. They are called “carriers.”

- Males who inherit two germline mutations (one from each parent) are at risk of developing testicular cancer

- Females, in this example, may have two abnormal copies of the gene, but they cannot get the disease, because they lack the critical target – they are “genetically affected,” but clinically normal, females.

- Equally transmitted by men and women

ASCO, modified 12/02
The mutated gene is on the X (sex) chromosome

1 **Females who carry a mutation:**
   - Half (50%) of their sons will inherit the mutation and be at increased risk of developing testicular cancer;
   - Half (50%) of their daughters will inherit the mutation, and they will be carriers.

2 **Males who carry a mutation (whether or not they have cancer):**
   - All of their daughters will inherit the mutation;
   - NONE of their sons will inherit the mutation.

Females or males who do not inherit a mutation cannot pass it on to their children.
The Genetics of Testicular Cancer
The Human Genome and Cancer

- The Human Genome Project is helping us to discover new cancer genes and to develop:
  - Predictive tests to identify genetic predisposition
  - Diagnostic tests to detect cancer in its earliest stages
  - Treatments that target gene abnormalities in cancer cells
CGB’s Testicular Cancer Genetic Research Program

- Identify gene(s) associated with testicular cancer to:
  - Develop gene mutation tests for testicular cancer
  - Determine who is at higher risk of testicular cancer
  - Determine the risk of developing testicular and/or other cancers based on the genetic mutation
  - Improve testicular cancer prevention, screening and treatment for those men at increased risk
How Much of Testicular Cancer is Hereditary?

- The majority of testicular cancer is isolated (or “sporadic”), i.e. it occurs only once in a family.
- ~2% of men with testicular cancer also have a relative with testicular cancer.
- Brothers of men with testicular cancer are 8-10 times more likely to develop the disease.
- Sons of men with testicular cancer are 4-6 times more likely to develop the disease.
- However since testicular cancer is relatively rare, there are still not a large number of familial cases.
- The genes for familial testicular cancer have not yet been discovered.
What are Linkage Studies?

- Linkage analysis is a way to estimate the chance that a person has inherited a mutated gene from one of their parents.
- Linkage analysis involves tracking genetic markers close to or within a disease gene.
- It is used when the specific gene has not yet been discovered and cloned.
- It is not always possible to use, due to family structure and the unavailability of key family members.
Requirements for Linkage Studies

- Families with multiple living people, who have the condition in question
- Blood samples from both affected and unaffected family members, to identify maternal & paternal chromosomes
- Availability of testable genetic markers from the same chromosome on which the gene of interest is thought to be located
- These markers must have sufficient genetic variation from person to person to permit distinguishing their chromosomes from one another
Testicular Cancer and Xq27

- Study of 134 families with at least 2 cases of testicular cancer
- Linkage to Xq27 was found when:
  - The family history was compatible with X-linked recessive inheritance
  - There was at least one bilateral case in the family (tighter linkage)
  - Some family members had undescended testicles (a higher percentage of families linked to Xq27)
- The gene has not yet been found – work is ongoing
- It is estimated that only 20% of familial testicular cancer families may be linked to this area of Xq27
- Therefore, there are other genes for testicular cancer yet to be discovered

Sporadic and Familial Testicular Cancer

Sporadic Testicular Cancer

Familial Testicular Cancer

Familial Testicular Cancer For Which No Gene Has Yet Been Found (80%)

Familial Testicular Cancer Linked To Xq27 (20%)
Once a Testicular Cancer Gene Has Been Found, Genetic Testing Becomes a Possibility

Pretest Genetic Counseling

- Consider your:
  - Personal and family medical history
  - Motivation for, and feelings about, genetic testing
- Learn about
  - Testicular cancer genetics & your personal risk
  - The inheritance pattern of testicular cancer in your family
- Discuss the:
  - Risks, benefits, and limitations of testing
  - Testing procedure
  - Alternatives to genetic testing
  - Management options

ASCO, Modified 12/02
Anticipatory Guidance

Have you thought about how you’d feel if your result is positive?

I’d be worried—but at least I would know what type of screening to do.
Medical Issues – Considering the Options
Screening Recommendations – General Population

- **American Cancer Society**
  - Examine testicles during a cancer-related checkup every three years for men older than age 20 and annually after age 40

- **American Academy of Family Physicians**
  - Palpation of testicles for men aged 13 to 39 who fall into a higher risk group due to a history of cryptorchidism, orchiopexy or testicular atrophy

- **United States Preventive Services Task Force**
  - Concluded that there is insufficient evidence to recommend for or against routine screening
Testicular Self-Examination

- Should be seriously considered for men with:
  - History of undescended testicle ("cryptorchidism")
  - Previous germ cell tumor in one testicle
  - Family history of testicular cancer

- Should be performed:
  - Monthly, during or after taking a shower or bath
  - By examining the testicles, epididymis and vas deferens separately
Cautions Regarding Testicular Self-Examination

- Risk vs. benefit is not established: no randomized trials have tested the efficacy of testicular examination, performed either by physicians or individuals themselves, to see if this procedure results in fewer deaths from testicular cancer.

- Finding testicular cancer at its earliest stages may allow curative treatment to be achieved using much less toxic therapy. In some instances, for example, chemotherapy may be avoided completely.
Studies We Plan to Do

- **Males**
  - Physical examinations
  - Ultrasound of the kidneys
  - Laboratory studies
  - Testicular ultrasound

- **Females**
  - Physical examinations
  - Ultrasound of the kidneys
  - Laboratory studies
  - Transvaginal ultrasound – ovaries*

* Physiologic changes, such as ovarian cysts, occasionally need follow-up
Vertical section of the testis, to show the arrangement of the ducts and mediastinum testis.

http://www.bartleby.com/107/illus1149.html
Normal Sonogram of Testes

Mediastinum testis
Normal Color Doppler Ultrasound
Normal Testis with Benign Cyst
Calcifications in the Testes
Testicular Mass - Seminoma
What’s Next?

1. Description of the research aspects of the study
2. Signing the informed consent document, to formally enroll in the family study
3. Genetics and testicular cancer education
4. Medical evaluations
5. Specimen collection