**Native Cancer 101 Module 4: The Role of Genes in Cancer**

**Assumptions**
- This is a workshop that should follow several other topics (e.g., overview of cancer among AI/ANs, importance of cancer screening, etc.).
- Thus, it is not an introductory topic.
- This includes scientific and cultural information specific to biobanks and biospecimens.
- The workshop facilitator / faculty is/are NOT interested to collecting biospecimens from you.

**Introduction and overview**

**Genetics is not new information for AIANs**
- Our ancestors knew how to
  - Breed horses (Pintos, Appaloosa) so that their coloring blended with rocks, ground or aspens during the winter
  - Grow stronger, more disease-resistant crops (e.g., corn and squash)

**QUESTION: Why is this important for AI/AN communities?**
- Cancer = increased among AI/ANs
- People may learn their cancer risk, but:
  - Is there an effective cure or treatment?
  - Are there people trained to explain the cancer risk (is the risk real?)
- New treatments are at the genetic and molecular level and the information may impact patient care.
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Objective 1: Define basic genetics terminology

- genes, chromosomes, DNA, mutation, heredity

What are “genetics”? What are “genes”? 

- “Genetics” is the study of “genes”
- “Genes” contain the information for the body to function
- Some genes make bones strong
- Other genes help prevent cancer (tumor suppressor)
- A gene is a segment within a chromosome

Chromosomes

- Organized by researchers from the largest/longest (number 1) to the smallest (number 22).
- The longer the chromosome, the more genes

Chromosomes (continued)

- DNA (Deoxyribonucleic Acid) molecules refer to the genetic information that is within the chromosomes
- Chromosomes are in the “nucleus” (braim) of the cell
- Chromosomes are packed with thousands of genes
- Genes tell our cells what to be and how to act

“Genes” and “Mutations”

- The pattern of information within genes needs to follow a specific sequence for the cell to function correctly.
- When the sequence differs, it is called a “mutation” (or SNP, pronounced “snip”)
- Everybody has mutations (or SNPs) that may cause:
  - A different effect or function of the gene
  - The gene to continue having the normal function

Example: p53 (“The Big Guy”)

- Human chromosomes have a segment containing a gene called “p53”
- Dr. Bemis calls “p53”, “The Big Guy”
- More than half of all tumors have damage in the area of the gene that makes up “p53”
- p53 helps protect the body against cancer
- p53 is a tumor suppressor
  - Unless it is damaged (mutation)
More about “Genes” (continued)

- The nucleus has genetic information provided from your mother and from your father.
- The human body has about 20,000 genes.
- Every human being is 99.9% similar to any other human being.
- That 0.1% of genetic information is why and how we look and are different from one another.

QUESTION: What does “heredity” mean?

- Heredity means that the characteristic came from the sperm and egg (from your dad and mom) when you were conceived in the womb.
- 23 chromosomes from dad (sperm) and 23 from mom (egg); a copy of each chromosome to fertilized egg.

Causes of Cancer

- **Daily Behavior / Lifestyle** (not enough physical activity, unhealthy food, excess alcohol, habitual use of tobacco) = cause changes in genes within body cells.
- **Environment** (exposure to contaminants, e.g., asbestos) = cause changes in genes within body cells.
- **Heredity** (chromosomes from mother and father that created the fertilized egg that resulted in the child) = only 5-10% of all cancers.

Objective 2: Describe role of genes in cancer

Role of genes in cancer

- Only a small group of mutations directly associated with cancer risk are inherited from the parents.
- Other (i.e., “most”) mutations are acquired over the life span.
- Multiple injuries occur to the same cell to evolve or result in cancer.
- “Injuries” can be from alcohol abuse, exposure to commercial tobacco, bacteria, virus, inactivity, unhealthy diet.

Role of genes: mutations

- The injury is a mutation resulting in damage that is passed on from the first body (somatic) cell as it divides into additional cells.
- It gives the cells harboring the mutation an advantage to outgrow other cells.
- For example in lung cancer the carcinogens in cigarette smoke may cause damage in several genes.

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Role of genes: mutations (continued)

- One change may allow the cells to grow out of control while another may cause the cells to be resistant to therapy.
- Multiple injuries are required before the cells are changed enough to allow them to grow out of control.
- For most solid tumors, 5-10 separate "injuries" occur before the cell becomes cancer.

Role of genes in cancer (continued)

- A variety of genes are known to be "injured" in cancer.
- Two overall types of injuries occur:
  - Those that block the expression of "Tumor suppressor" genes like p53, BRCA1 and BRCA2
  - Those that activate oncogenes (genetic markers / SNPs that contribute to cancer)

Tumor Suppressors

- Those genes whose normal function is to suppress the overgrowth of cells.
- For example:
  - p53 is known as the guardian of genome
  - p53 is a guardian because it protects the cell from damages such as radiation or other stress.

Oncogenes and Adapted Cancer Treatments

- Oncogenes are genes that are over-expressed, allowing the growth of the tumor or increases the aggressive nature of a tumor.
- Mutations in BRAF are a good example in melanoma because it allows for the uncontrolled growth of melanoma cells.
Oncogenes and Adapted Cancer Treatments

- Mutations must be detected for patient to receive drug targeting BRAF because if given to patients without a BRAF mutation they may become more sick due to the effects of the drug.
- Obviously learning more about these oncogenes can predict more effective cancer treatments with fewer side effects.

Researchers Study Molecular Pathways

- Researchers study “pathways” for how oncogenes reach the cancer tumor cells.
- These are molecular pathways that tell the tumor cell to grow (also called “amplification”).

Researchers Study Molecular Pathways

- Researchers try to find other molecules that would block that pathway so that the cell never receives the signal to grow.

Cancer Treatment: cetuximab

- Cetuximab is an antibody (protein acceptable to human body) that attacks receptors on cancer cell so that the cancer cell cannot multiply.
- Attacks oncoproteins such as Epidermal Growth Factor Receptor (EGFR).

Based on this type of Research

- If you give the patient cetuximab, the cetuximab goes to the EGFR protein and blocks its ability to send “grow grow grow” signals.
- Patient is tested for KRAS mutation prior to CRC treatment.
- Currently the clinical lab needs a biopsy of the tumor.
- The test for KRAS is a blood test.
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95% of pancreas cancers have KRAS Mutation

This is why cetuximab cannot be used to treat pancreas cancer
Likely to need a different drug—(e.g., mTOR inhibitors) to target this signal

Chromosomal changes in Cancer

- There are frequent mutations in cancer cells
- Sometimes there are large rearrangements
- Sometimes there are deletions of part of a chromosome
- Sometimes there are small changes that may only be detected with PCR or other genetic tests.

NOTE: PCR stands for polymerase chain reaction. This is the method that allows researchers to copy and amplify almost any piece of DNA to better understand it. Many of the genetic tests currently in use require PCR as part of the process of determining if the patient has a SNP.

Chromosomal Changes in Cancer

- Sometimes a test can be developed that looks at large regions of DNA changes
- Other times a few regions of a gene are examined
- BRCA1 and BRCA2 are very large genes known to harbor many mutations that may be passed from the parent to child

QUESTION: What is a BRCA2 mutation?

- BRCA2 is a protein that helps to repair certain kinds of damage to DNA
- BRCA2 is a very large gene composed of 84,188 base pairs
- Hundreds of mutations have been discovered in BRCA2 and some are associated with certain ethnic groups

SEE YELLOW LAMINATED SHEETS WITH BRCA2 SUMMARY INFO

Objective 3: Describe potential benefits and drawbacks of genetics testing

Using BRCA2 As An Example

- Having the marker (BRCA2) does not mean you will develop cancer
- The marker indicates a predisposition
- Every single person has a BRCA2 gene, but only a few have a mutation
- Populations at risk are on following page
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### Using BRCA2 As An Example

<table>
<thead>
<tr>
<th>Populations who may carry the mutation</th>
<th>BRCA2 mutation(s)</th>
<th>Result of the mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish</td>
<td>6174delT</td>
<td>A deletion of a T base results in a shorter than normal protein</td>
</tr>
<tr>
<td>Dutch</td>
<td>5579insA</td>
<td>An extra base (A) causes altered expression of the protein</td>
</tr>
<tr>
<td>French Canadians</td>
<td>8765delAG</td>
<td>In this case two base pairs are missing</td>
</tr>
</tbody>
</table>

### Possible Personal Benefits of Genetic Testing

- **QUESTION:** What are examples of some ways that an individual may *personally benefit* from participating in genetic tests?
  - Medical and lifestyle choices are available for selected conditions
  - Learns whether s/he does or does not have an altered gene
  - Learns to cope with the personal risk

### How Might the Tribe or Other Native Americans Benefit by an Individual Participating in Genetic Testing?

- Information about common conditions may be helpful to others
- Communities can focus on behavior changes rather than assume “fatalistic” attitude about a disease

### Possible Drawbacks to Genetic Testing

- A genetic “mutation” that NEVER results in a disease (i.e., worry about “nothing”)
- What does “lifetime risk” mean? How does “lifetime risk” relate to tribal beliefs or cultural mores?
- Genetic “mutation” may be present, but there may not be “treatment”
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Possible Drawbacks to Genetic Testing

- The test may be limited to only one part of a gene, and not the part of the gene that has the mutation (the test is “limited”)
- The test may be inaccurate
- “false positives” or “false negatives”
- Negative test results may provide a false sense of security
- An individual may find it harder to cope with the cancer risk when s/he knows the test results

Possible Drawbacks to Genetic Testing

- You may be asked to disclose genetic test findings that may result in the participant:
  - Losing health insurance coverage
  - Other family members losing their health insurance
  - Losing his/her job

NOTE: Federal and state laws are supposed to protect against such outcomes, but they are imperfect

Genetic Information Nondiscrimination Act of 2008 (GINA), a Federal law

- Prohibits discrimination in health coverage and employment based on genetic information
- Generally prohibits health insurers or health plan administrators from requesting or requiring genetic information of an individual or the individual’s family members, or using it for decisions regarding coverage, rates, or preexisting conditions.
- The law also prohibits most employers from using genetic information for hiring, firing, or promotion decisions, and for any decisions regarding terms of employment

How Might My Tribe or Other Native Americans be Harmed by My Participating in Genetic Testing?

- Tribal ordinances against participating in “genetic research” (genetic testing may be included in genetic research)
- “Genetic testing” is an individual decision, there should be little opportunity for harm to the Tribal community

Native American Cultural and Ethical Issues related to Genetic Testing

- NOTE: Due to projects such as HGDP targeting Aboriginal Peoples, communities are suspicious of any program involving “genetics”
- Native people being encouraged to take part in genetic testing by being given rewards ... without being told the risks of genetic tests.

Native American Cultural and Ethical Issues related to Genetic Testing

- Native people being tested without being given enough information to make an “informed” decision
- Native people being tested without having their rights to privacy and confidentiality “protected”
- Native people being tested without having test results clearly explained (no genetic counseling)
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Objective 4: Discuss the benefit of recording your family health history

Reasons Family Histories May be Important

- Helps the genetic counselor work with the patient to decide whether or not the patient is genetically at high risk for a condition and should have a genetic test (most cancer genetic tests are expensive)
- Helps explain why some members of the family are not affected
- Clarifies daily behaviors versus inherited risks for people who are adopted
- Helps the provider make a diagnosis
- Clarifies family myths regarding who in the family is at risk
- Accurate Family Histories are needed to determine if a cancer risk is likely to be hereditary or from other causes (daily behaviors, exposure to environmental contamination)

Reasons Family Histories May be Important (cont.)

- Helps explain why some members of the family are not affected
- Accurate Family Histories are needed to determine if a cancer risk is likely to be hereditary or from other causes (daily behaviors, exposure to environmental contamination)
- Helps the genetic counselor work with the patient to decide whether or not the patient is genetically at high risk for a condition and should have a genetic test (most cancer genetic tests are expensive)
- Helps clarify family myths regarding who in the family is at risk
- Helps the provider make a diagnosis
- Clarifies daily behaviors versus inherited risks for people who are adopted

Sample Cancer Family History Questionnaire

1. Name
2. Date
3. Age
4. Ethnic Background
5. Do you have any specific concerns about cancer in yourself or your family?
6. Do you or any members of your family have a history of cancer?

Example of Culturally Inappropriate Family History Data Collection by Epidemiologists during the Hanta Virus Infection

- CDC scientists demanded to interview the surviving family members immediately following the patient’s death
- Researchers unaware / unwilling to be educated by local Native physician of local cultural beliefs requiring no discussion of the deceased for 3 days
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Example of Culturally Inappropriate Family History Data Collection by Epidemiologists during the Hanta Virus Infection

- Family forced to violate cultural practices = very difficult ceremony
- Researchers given inaccurate information
- Alienated the local AI community

Family History Data Collection Cautions

- Asking the patient and/or family members personal information about their ancestors and immediate family
- Some tribes are prohibited from discussing family members who have “walked on” / “passed away” / died
  - Cannot use their name
  - Cannot refer to them directly via relationship (“mother”, “father”)

“First Degree Relative” vs. Indian Adoption

- Note: some tribes use maternity for tribal affiliation rather than paternity
- Cancer risk genetic tests typically focus on first degree relatives (FDRs)
  - Mother, Father
  - Sisters, Brothers
  - Children
- Spiritually, adopted children are regarded as FDR by AIANS, but NOT so for genetic family trees …
  - question: “did you come from the same womb as your brother?”

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Mayo Clinic’s “Spirit of EAGLES Community Network Programs 2” [P.I. Kaur; U54CA153605]
Summary / Take Home Messages

Healthy body (somatic) cells are damaged by daily behaviors or sometimes by exposure to environmental contaminants.

The same cells are injured 5-10 times before the cells begin to become cancer.

Researchers are using the new, detailed genetic and molecular information to tailor cancer treatments.

Some of these treatments are available already (e.g., colon, melanoma).

Information collected during your family history can help the researchers understand your genetic or molecular information better.

Collecting family histories in Indian Country is challenging, in part because:

Some tribal cultures prohibit the use of family relations who have passed on (e.g., you cannot say, “father” or “sister”).

Most of our tribal Nations practice casual adoption of nieces, neighbors and others who need a home.

Once adopted, they are of our family spiritually …

We do not distinguish siblings as coming from the same womb, but spiritually we are sisters.

Thank you for allowing us to share Native Cancer 101 module with you.

Reference:
Bemis, UMN-Duluth, Burhansstipanov, Native American Cancer Initiatives, Incorporated (NACI)
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NACI’s Edited Background Information
BRCA2 Summary Fact Sheet
Date Discovered: 1995
Location 13q12
- Very large gene
- Tumor suppressor
Genetics:
- Autosomal dominant transmission of germline alteration (mutation)
- Transmission of germline mutation by EITHER parent

NACI’s Edited Background Information
BRCA2 Summary Fact Sheet (cont.)
Germline mutation increases RISK for breast and ovarian cancers
- Cancer is a progressive process of different mutations that alter cell function.
- Eventually, cell function is altered so much that it becomes “cancerous”.

NACI’s Edited Background Information
BRCA2 Summary Fact Sheet (cont.)
An inherited susceptibility to cancer, like a germline mutation in BRCA2 gene, means that a person has inherited a “damage” which decreases the number of further acquired mutations needed for a cell to become cancerous.
- i.e., most “cancer” evolves after at least “two” damages

NACI’s Edited: Increased Cancer Risks for Mutations in BRCA2:
- Women
  - Breast cancer
  - Ovarian cancer (not as high as BRCA1 mutations)
- Men
  - Breast cancer
  - Prostate cancer

NACI’s Edited Increased Cancer Risks for Mutations in BRCA2:
- Other Cancers (risk for these may be slightly elevated over the general population)
  - Colon cancer
  - Pancreatic cancer
  - Stomach cancer
  - Cancer of the gallbladder
  - Melanoma