Objectives

• Describe genetic counseling and risk assessment
• Understand patterns of inheritance
• Review important aspects of genetic testing
What is Genetic Counseling?

• Process:
  • Obtaining pertinent personal and family medical history information (genetic pedigree)
  • Risk assessment
  • Patient education
    • Counseling: provide differential diagnosis with discussion of associated health risks and medical management options, review inheritance and risk to family members, discuss genetic testing options, and address legal, privacy, psychosocial issues
    • +/- genetic testing
Who are Genetic Counselors?

• GC’s are Master’s level trained medical providers specializing in hereditary disorders
• National board certification; state level licensure in some areas
• Multiple subspecialties
  • Cancer
  • Neurology
  • Cardiac
  • Pediatric
• Typical new patient consultations take 60-90 minutes
Principals of Genetic Counseling

- respect for patient autonomy
- non-maleficence
- beneficence
- veracity
- cultural sensitivity
- non-directiveness
GCs most important tool - Pedigree

- Pictorial representation of a family
  - Males (squares)
  - Females (circles)
  - Lines connecting represent biological relationships
  - Depicts first-, second-, and third-degree relatives (three generations)

- Documents
  - Common health conditions (diabetes, heart disease)
  - Focused (i.e. cancers, birth defects, etc.)

Family History

• UPDATE YEARLY!
• Clearly document:
  • Relationship
  • Age of onset of symptoms/ age of diagnosis
  • Current age/ age of death
  • Genetic testing performed/ results
Targeted questioning isn’t enough!

- **Urology clinic**
  - Ask about MORE than prostate cancers
  - Breast, ovarian, pancreatic, colon, etc.

- **GYN clinic**
  - Ask about MORE than “female” cancers (breast, ovarian, uterine)
  - Colon, prostate, pancreatic, etc.

- Ask about more than immediate family members!
Implications

- Proactive management
  - Enhanced/ earlier screenings
- Risk reduction
  - Lifestyle
  - Medicines
  - Surgical
- Life saving for family members!
- Family planning - recessive risks
- Personalized medicine
  - Match treatment to genetic defect
Genetics Basics

• Types of genetic disease
• Inheritance patterns
• Genotype vs phenotype correlations
Types of Genetic Disease: Chromosomal Abnormality

- Chromosomal abnormalities include an increase or reduction in the number of chromosomes, or a translocation of part of one chromosome to another.

- Common conditions caused by chromosomal abnormalities include:
  - Trisomy 21 or Down syndrome:
    - distinct facial appearance, intellectual disability, developmental delays, and may be associated with thyroid or heart disease.
  - 45X or Turner syndrome:
    - one of the two X chromosomes in females is either missing or incomplete causing short stature and gonadal dysgenesis, which can cause incomplete sexual development, ovarian failure and infertility.
“Advanced” maternal age

• Increasing maternal age is directly correlated with increased risk for numerical chromosomal abnormalities

• Risk for baby born* with Down syndrome (Trisomy 21; +21)

<table>
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<th>AGE 31</th>
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<td>1/1400</td>
<td>1/900</td>
<td>1/350</td>
<td>1/85</td>
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* The rate is higher during a pregnancy as there will be fetal losses
Types of Genetic Disease: Single Gene Disorder

- Also known as Mendelian inheritance disorders
  - In these disorders a single gene is responsible for a defect, abnormality or disease
  - Single gene disorders usually have greater risks of inheritance

- Common single gene disorders include
  - Marfan syndrome
    - A connective tissue disorder causing long limbs and heart defects
  - Cystic fibrosis
    - A disorder of the glands causing excess mucus in the lungs and problems with pancreatic function
  - Hemophilia
    - Bleeding disorder caused by low levels, or absence of, a blood protein that is essential for clotting
  - Cancer
Inheritance Pattern: Autosomal Dominant

• Equal inheritance between males and females
• 50% chance of inheritance for each child of an affected individual

• Example - mutations in the BRCA1 and BRCA2 genes associated with Hereditary Breast and Ovarian Cancer syndrome
  • Associated with significantly increased risk for breast and ovarian cancer, as well as increased risk for male breast cancer, prostate and pancreatic cancer
• Majority of hereditary cancer syndrome mutations are inherited in a dominant manner, yet tumor suppressor genes represent a recessive pattern of expression
Inheritance Pattern: Autosomal Recessive

• BOTH parents are unaffected carriers
  • 25% chance with each pregnancy for child to be affected
• All children of an affected individual will be carriers (unaffected)

• Example - Fanconi Anemia
• Caused by mutations in at least 15 genes, including BRCA2
• Condition primarily associated with bone marrow failure, physical abnormalities (e.g. malformed thumbs or forearms), organ defects (e.g. absent or malformed kidneys) and an increased risk of certain cancers (e.g. AML)
Inheritance Pattern: X-linked

- Recessive
  - Carrier females
    - Each male child will have a 50% chance of being affected
    - Each female child will have a 50% chance of being an unaffected carrier
  - Affected males
    - Each male child will be unaffected
    - Each female child will be an unaffected carrier

- Example - Hemophilia
  - Caused by mutations in the F8 or F9 gene
  - Features
    - Bleeding disorder that slows the blood clotting process
Inheritance Pattern: X-linked

• Dominant
  • Affected females
    • Each child will have a 50% chance of being affected*
  • Affected males
    • Each male child will be unaffected
    • Each female child will be affected*

• Example - Fragile X
  • Caused by mutations in the FMR1 gene - causes a range of developmental problems including learning disabilities and cognitive impairment

• Recent study identified x-linked ovarian cancer susceptibility - with higher risk for ovarian cancer in women with a paternal grandmother with ovarian cancer versus a maternal grandmother with ovarian cancer

Genotype vs Phenotype

- Same genotype (genetic makeup) different phenotype (observed features)
  - Pleiotropy (single gene influences multiple phenotypic traits)
    - Ex. MLH1 mutation assoc. w/ colon ca, endometrial ca, ovarian ca, ureter ca, etc.
  - Expression (different degrees of presentation)
    - Ex. APC mutation - classic vs. attenuated
Genotype vs Phenotype

• Same phenotype different genotype
  • Ex. Breast cancer assoc. w/ mutations in BRCA, PTEN, TP53

• Phenocopy = Normal genotype with disease phenotype
• Penetrance = Mutant genotype with no disease phenotype
  • Thus, susceptibility (rather than predisposition)
  • Majority of hereditary cancer syndromes are NOT 100% penetrant
Genetic Screening & Testing: Important Considerations

• Who to test?
• Clinical vs Research testing
• Type/Method
  • Biochemical - protein product
  • Cytogenetic - all/part of chromosome
  • Molecular - gene/DNA/RNA
    • Site specific (known mutation in family)
    • Common mutations/ targeted (ex. Factor V Leiden)
    • Full gene
    • Multi-gene panel
    • Whole exome (coding regions)
    • Whole genome (coding and noncoding regions)
• Germline vs. somatic
Genetic Testing - additional considerations

- Sample source: blood, saliva, skin biopsy
- Results: sensitivity, specificity

- Technology and quality varies lab to lab - easy testing option not necessarily the best
  - Inconclusive rates, reclassification criteria

- MORE testing is not necessarily better

- Direct to consumer - patient comes in with result!
Result Interpretation

- **No Mutation** (Negative)
- **VUS** - Likely Benign
- **Uncertain Significance** (VUS)
- **VUS** - Likely Pathogenic
- **Pathogenic** (Positive)

- **Medical management based on personal and family history.** Uncertain results do not influence recommendations for care.
- **Do not test unaffected relatives based on VUS.**

- **Medical management based on cancer risks linked with gene where mutation found.**
- **Testing for relatives specific to familial mutation.**
Result Interpretation (cont.)

• Negative vs true negative

• Full disclosure of result
  • VUS - while treated as a “negative”, it may be reclassified in the future

• VUS - clinic’s policy of re-contacting patients - notification - ordering providers responsibility!

• Communicating to patient the importance of cascade testing
  • Testing other relatives to determine inheritance and refining risks
Responsibilities

• Obtain informed consent - NYS law require written documentation

• Be prepared to counsel on the result of the test you ordered
  • If you don’t know - REFER!

• Re-referral
  • Testing (and family history) change over time - update fhx. every year and offer updated testing as it becomes available
Need for periodic reassessment

- For patients with a past positive genetic test result
  - Newly identified cancer risks
  - Change in screening recommendations

- For patients with a past negative genetic test result
  - Consideration for additional testing
    - ALL patients with negative BRCA testing prior to 2012 are likely candidates for further testing!

- For patients who were previously not candidates for genetic testing
  - Changes in personal and/or family history
  - New/updated testing criteria
Ethics: Testing Minors

• Consent vs. Assent
  • Legal consent obtained from parent/ legal guardian
  • Depending on patient age, appropriate for them to receive age-appropriate counseling and obtain their “assent”

• Adult onset conditions
  • Typically do not test minors for conditions with symptom-onset in adulthood
  • Wait for age 18 for consent from that individual

• Includes those with limited capacity
Ethics: Legal

- Privacy of genetic information
  - HIPAA
  - Release of information in writing

- Discrimination
  - GINA

- Life insurance
• Yes rare, but for those patients and their families, there are huge consequences

• Information may impact immediate treatment planning and future screening/prevention recommendations

• Aides patient decision making

• Although provider may not see immediate value for patient, failure to refer may be a liability
Referrals to Roswell Park CGS

• Patient referred from RPCI, community providers and through self-referral
• Internal referrals - consult request placed in EMR
  • **Routine** - seen in ~8-10 weeks (current treatments will not be influenced by results)
  • **Time sensitive** - seen in 4-6 weeks (ex. receiving neoadjuvant chemotherapy prior to surgery)
  • **ASAP** - seen within 1 week (surgical plans pending)
• Non-urgent patients - mailed an appointment offer - they must call to confirm the offered date/time
QUESTIONS?

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