Introduction to Evaluating Hereditary Risk

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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?

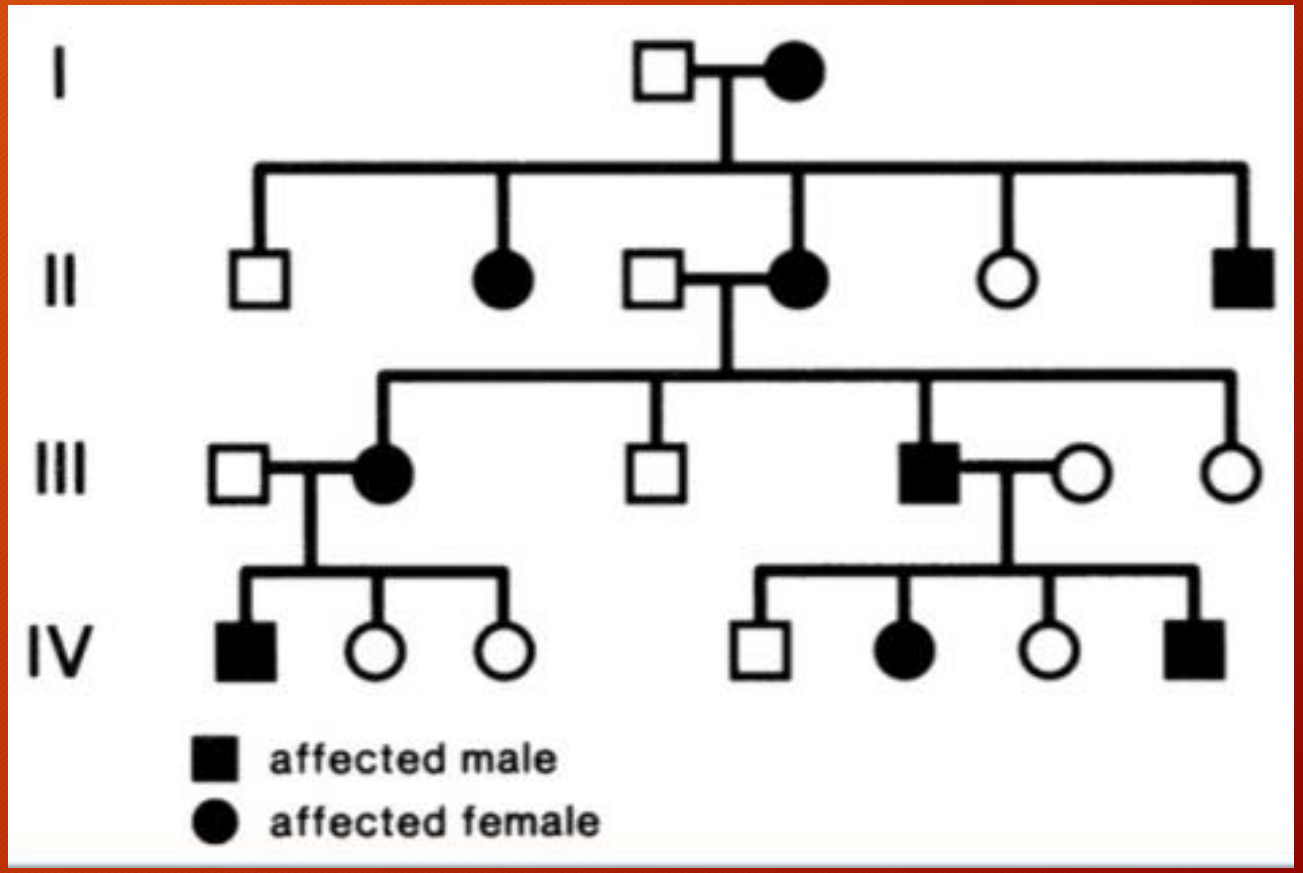
- GC's are Master's level trained medical providers specializing in hereditary disorders
- National board certification; state level licensure in some areas
- Multiple subspecialties
  - Cancer
  - Neurology
  - Cardiac
  - Pediatric
- Typical new patient consultations take 60-90 minutes

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.)



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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)

AGE 21	AGE 31	“AGE 35”	AGE 41
1/1400	1/900	1/350	1/85

* The rate is higher during a pregnancy as there will be fetal losses

Types of Genetic Disease: Single Gene Disorder

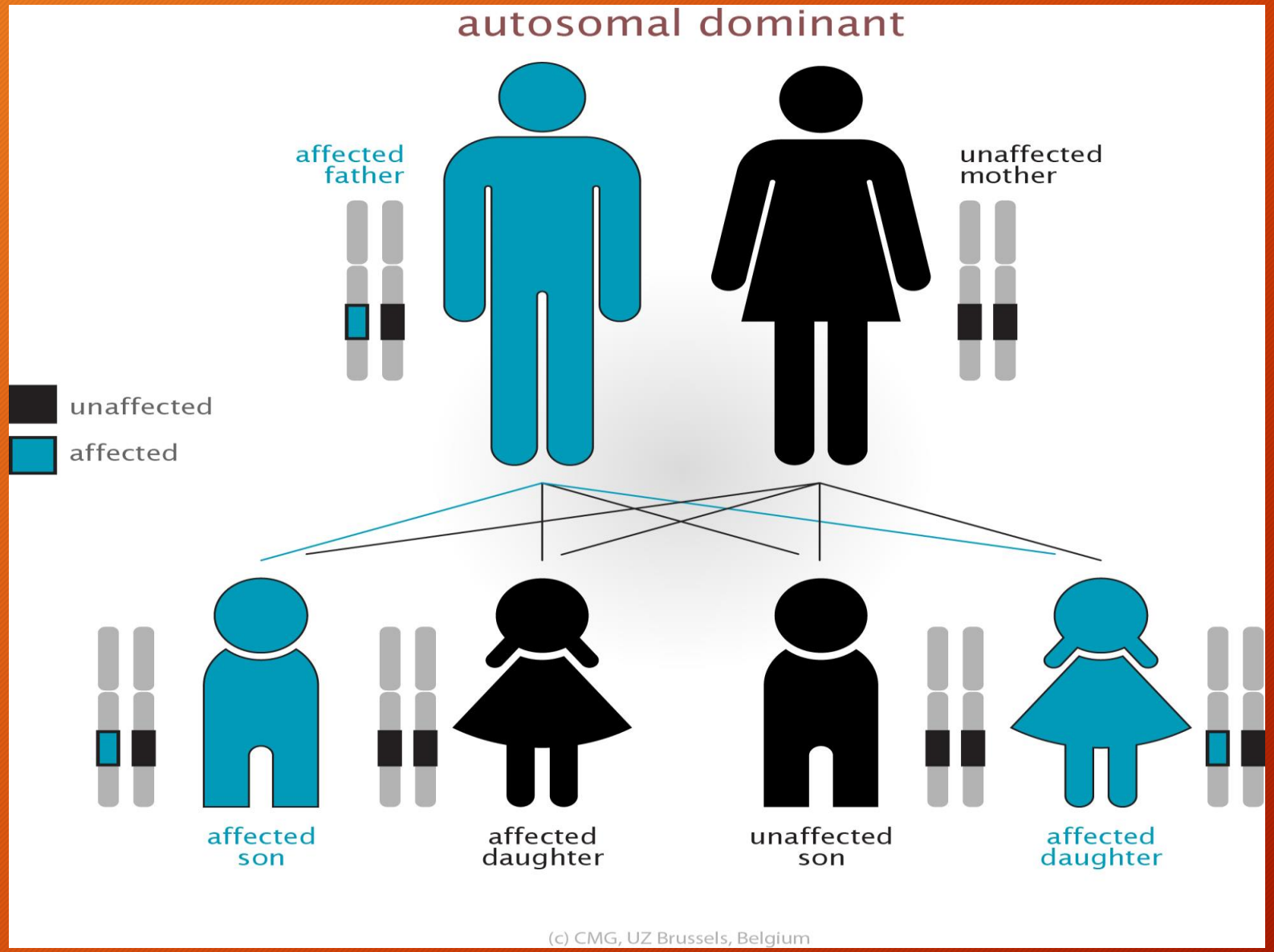
- Also known as Mendelian inheritance disorders
  - In these disorders a single gene is responsible for a defect, abnormality or disease
  - Single gene disorders usually have greater risks of inheritance

- 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



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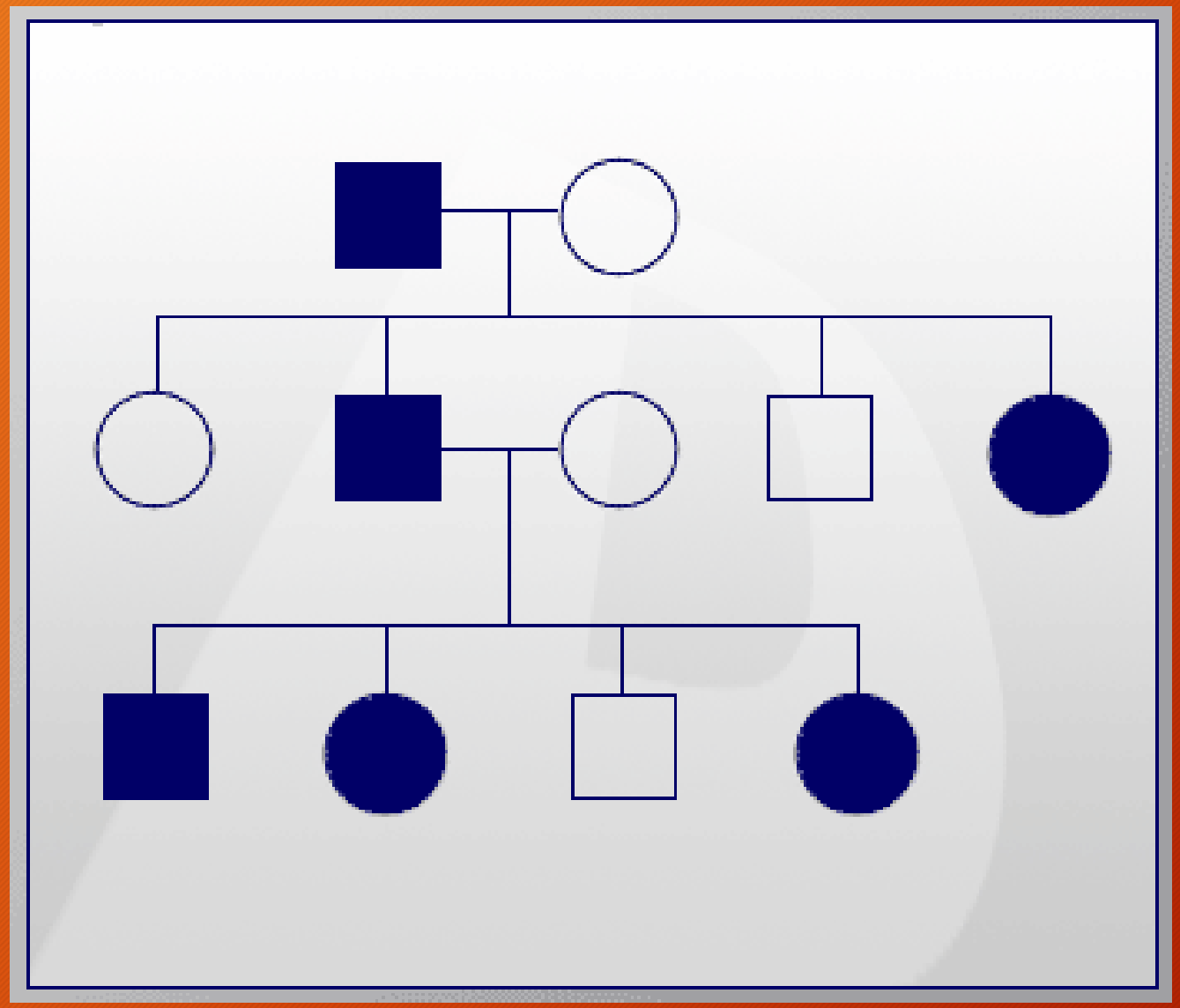

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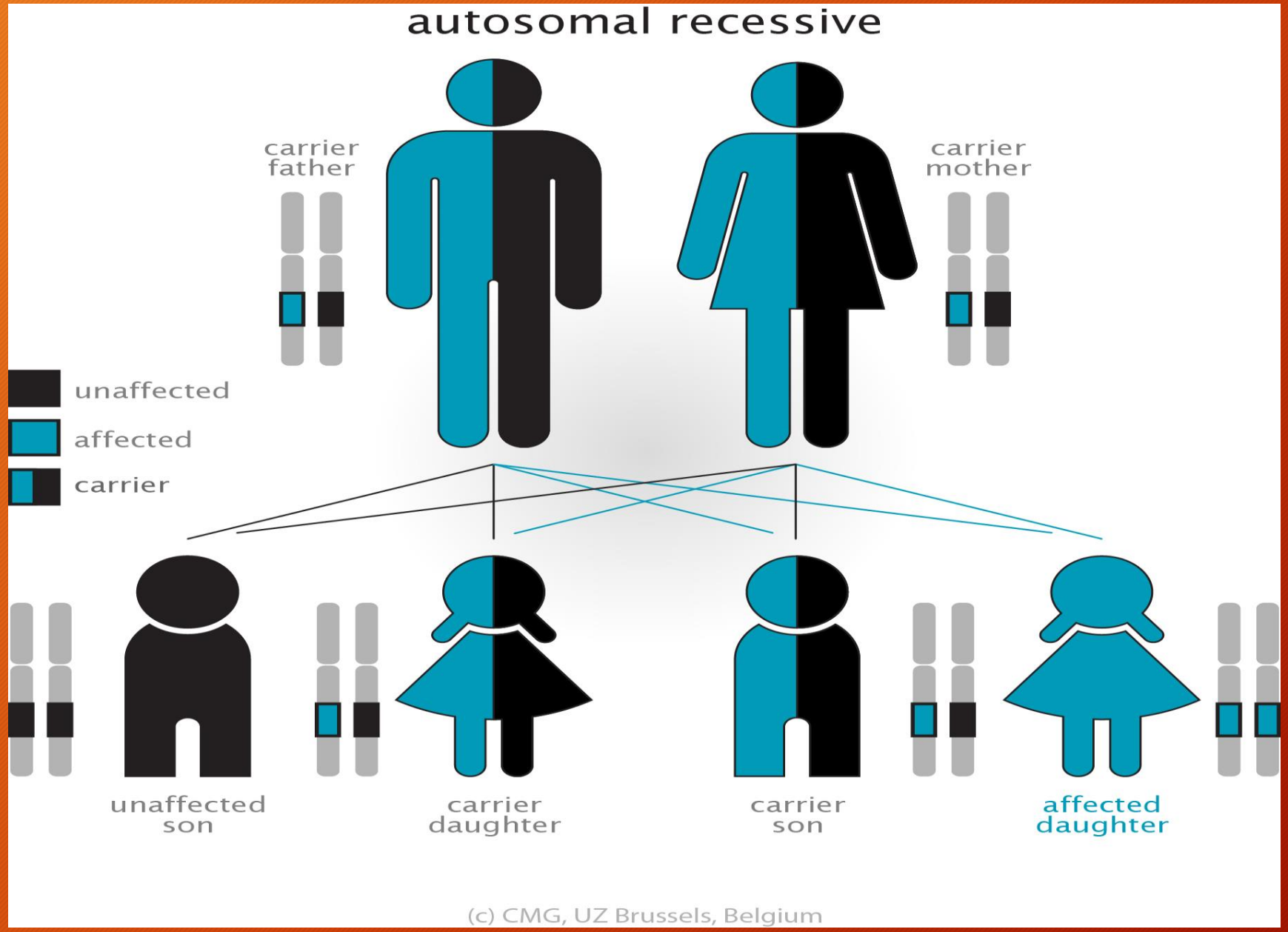
Inheritance Pattern: Autosomal Recessive

- 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)



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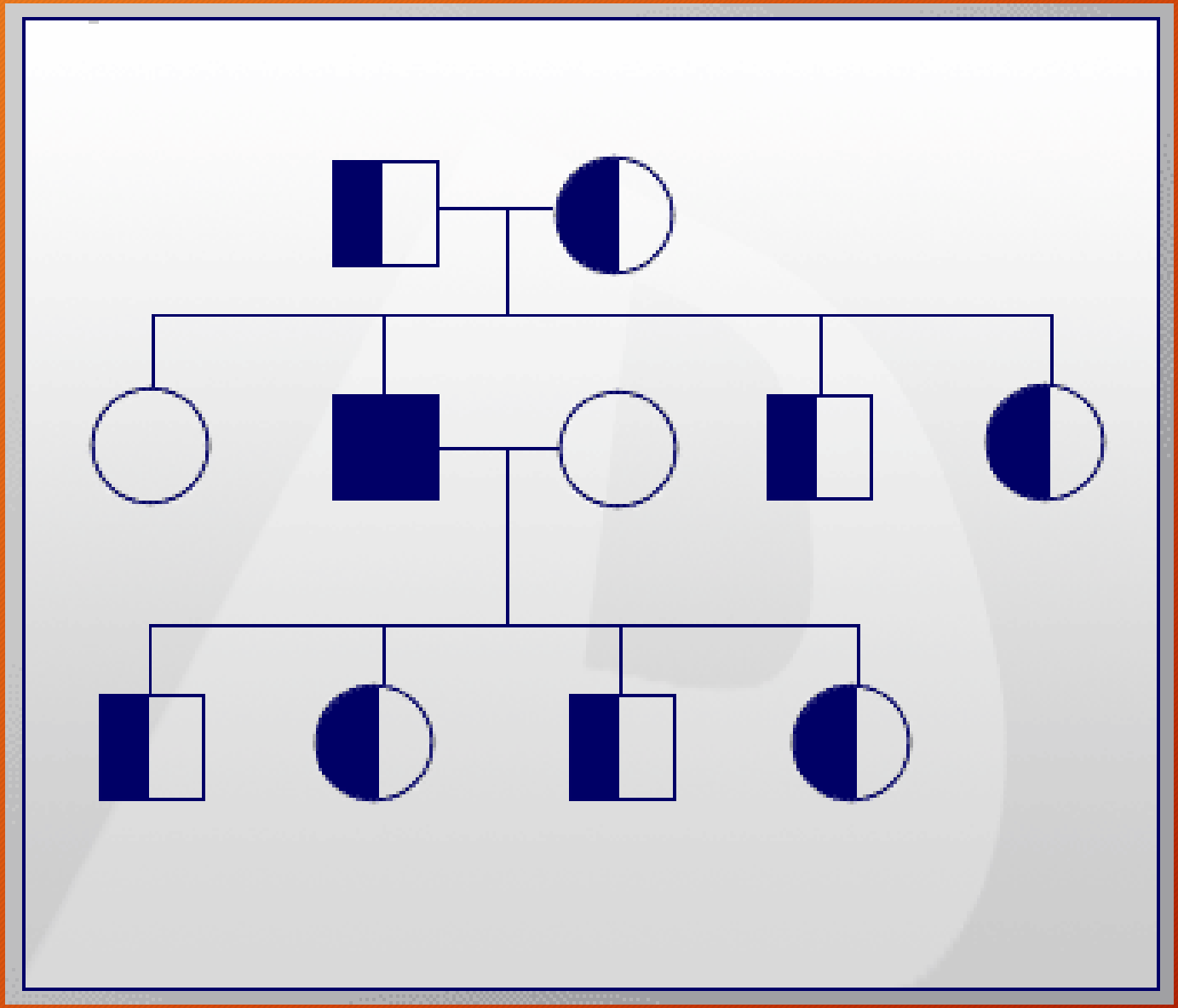

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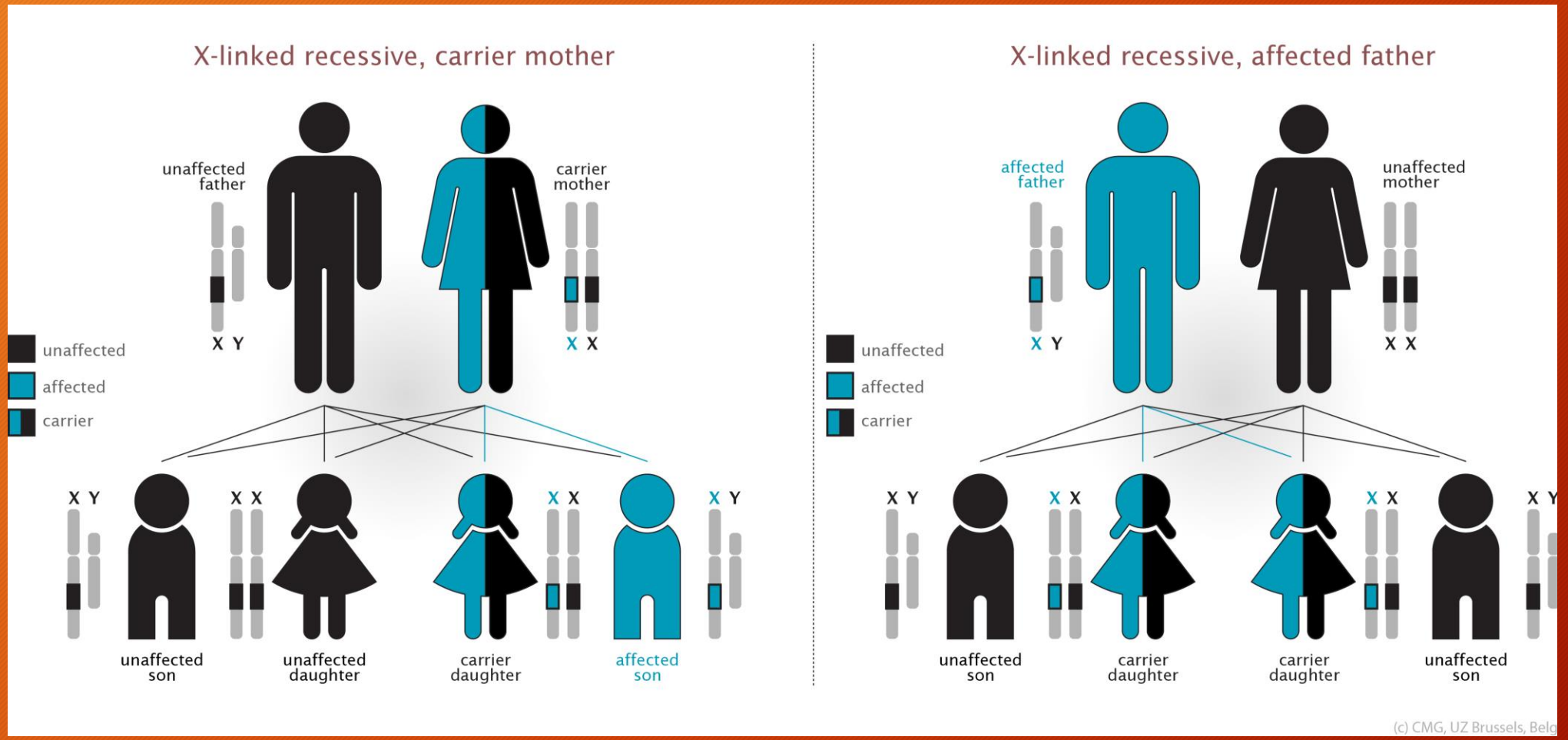
Inheritance Pattern: X-linked

- 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



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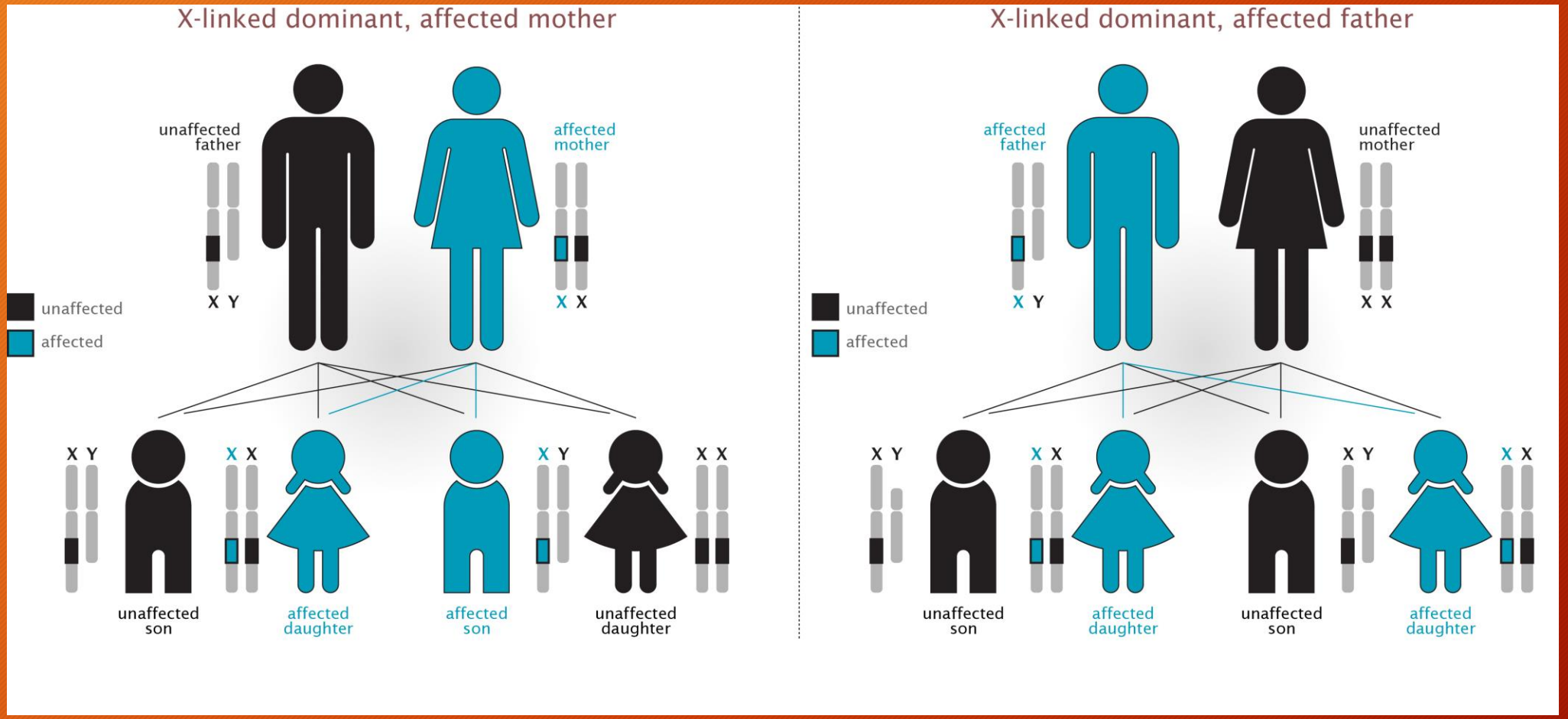
Inheritance Pattern: X-linked

- 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

Eng KH, Szender JB, Etter JL, Kaur J, Poblete S, Huang R-Y, et al. (2018) Paternal lineage early onset hereditary ovarian cancers: A Familial Ovarian Cancer Registry study. PLoS Genet 14(2): e1007194. https://doi.org/10.1371/journal.pgen.1007194



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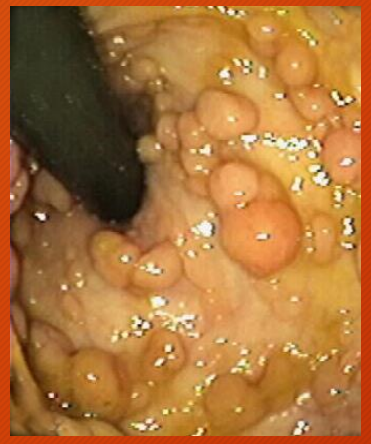
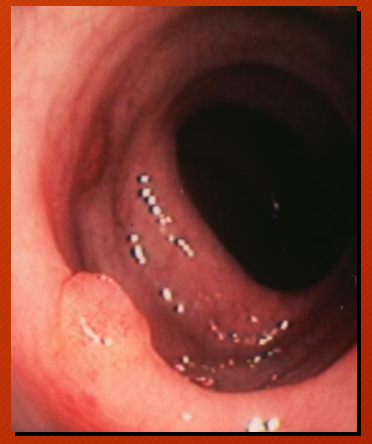
Genotype vs Phenotype

- 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

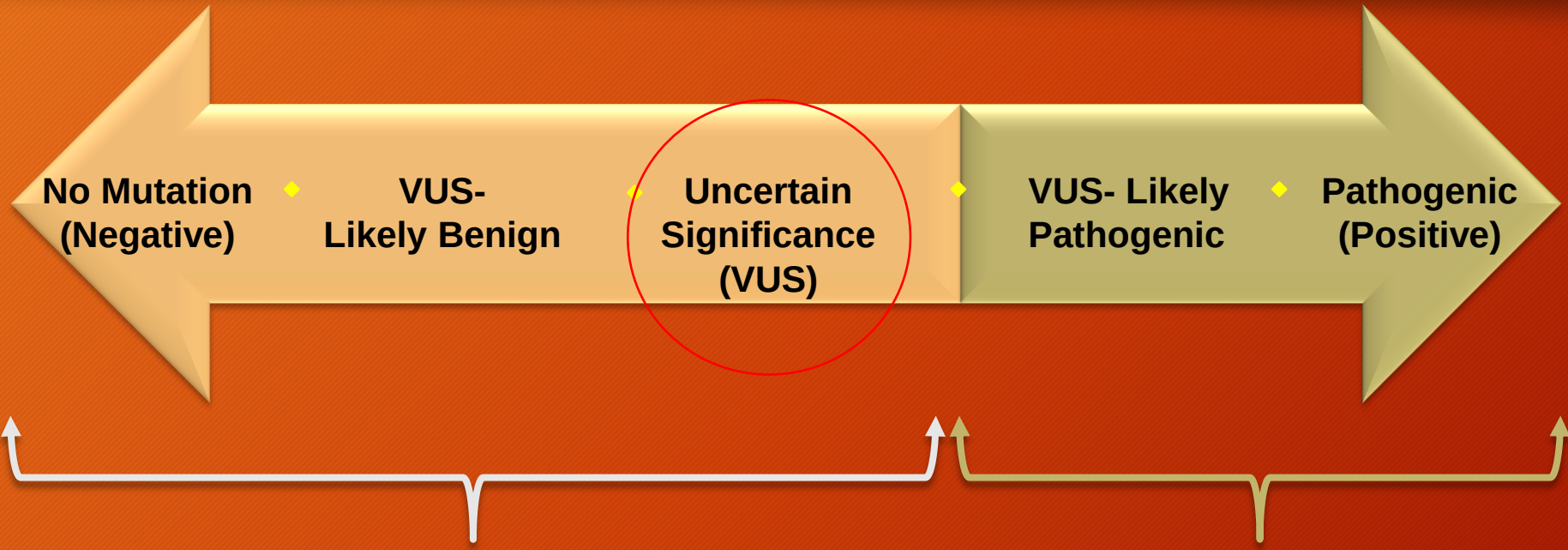
- Sample source: blood, saliva, skin biopsy
- Results: sensitivity, specificity

- 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



- 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

Value

- 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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