GENETIC COUNSELING

What the heck is a genetic counselor?

Krista Krol-Buch, MS, LGC
Licensed Genetic Counselor
Nemours Children's Health

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What is a Genetic Counselor

A genetic counselor is a specialized medical professional who:

- Educates about genetics
- Estimates risk for disease
- Provides emotional support
- Guides you through the genetic testing process
- Gives you information to make an informed decision
- Interprets genetic testing results
- Connects with groups and resources
- Explains treatment or management options
- Describes surveillance, prevention, and research

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CAREER OPPORTUNITIES

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Specialty Areas

Prenatal

- Preconception
- Fertility
- MFM
- High Risk

Pediatric

- General Genetics
- Neurology
- Cardiology
- Developmental
- ENT
- Endocrinology
- Metabolic
- Mitochondrial
- Ophthalmology
- Psychiatry
- Immunology
- Hematology

Oncology

- Adult
- Pediatric

There are more and more emerging fields and subspecialties!

Genetic Counselor was named one of the “25 Amazing Healthcare Support Jobs” and one of the “100 Best Jobs” in 2020

- *U.S. News and World Report*

92% of Genetic Counselors report that they are satisfied with their job

- *NSGC 2020 Professional Status Survey*

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Rankings

Genetic Counselors rank #1 in Best Health Care Support Jobs. Jobs are ranked according to their ability to offer an elusive mix of factors. Read more about how we rank the best jobs.

- **#1** in **Best Health Care Support Jobs**
- **#14** in **100 Best Jobs**

Scorecard	6.0
Salary	5.4
Job Market	3.6
Future Growth	8.4
Stress	5.8
Work Life Balance	5

HOW WE RANK JOBS »

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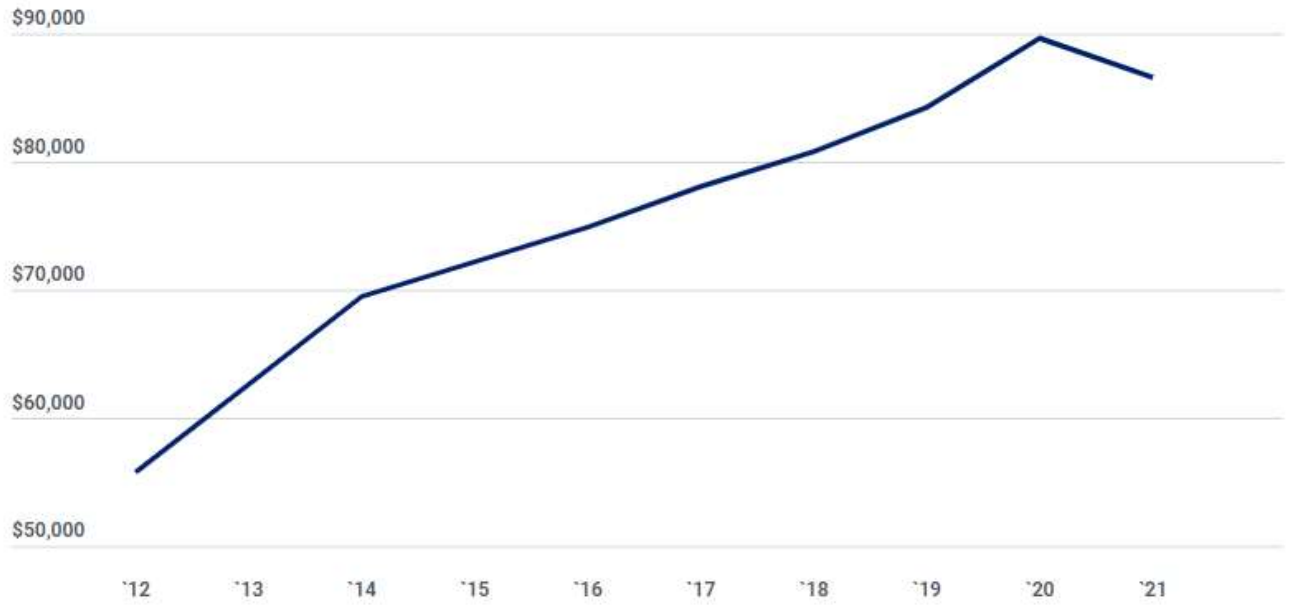
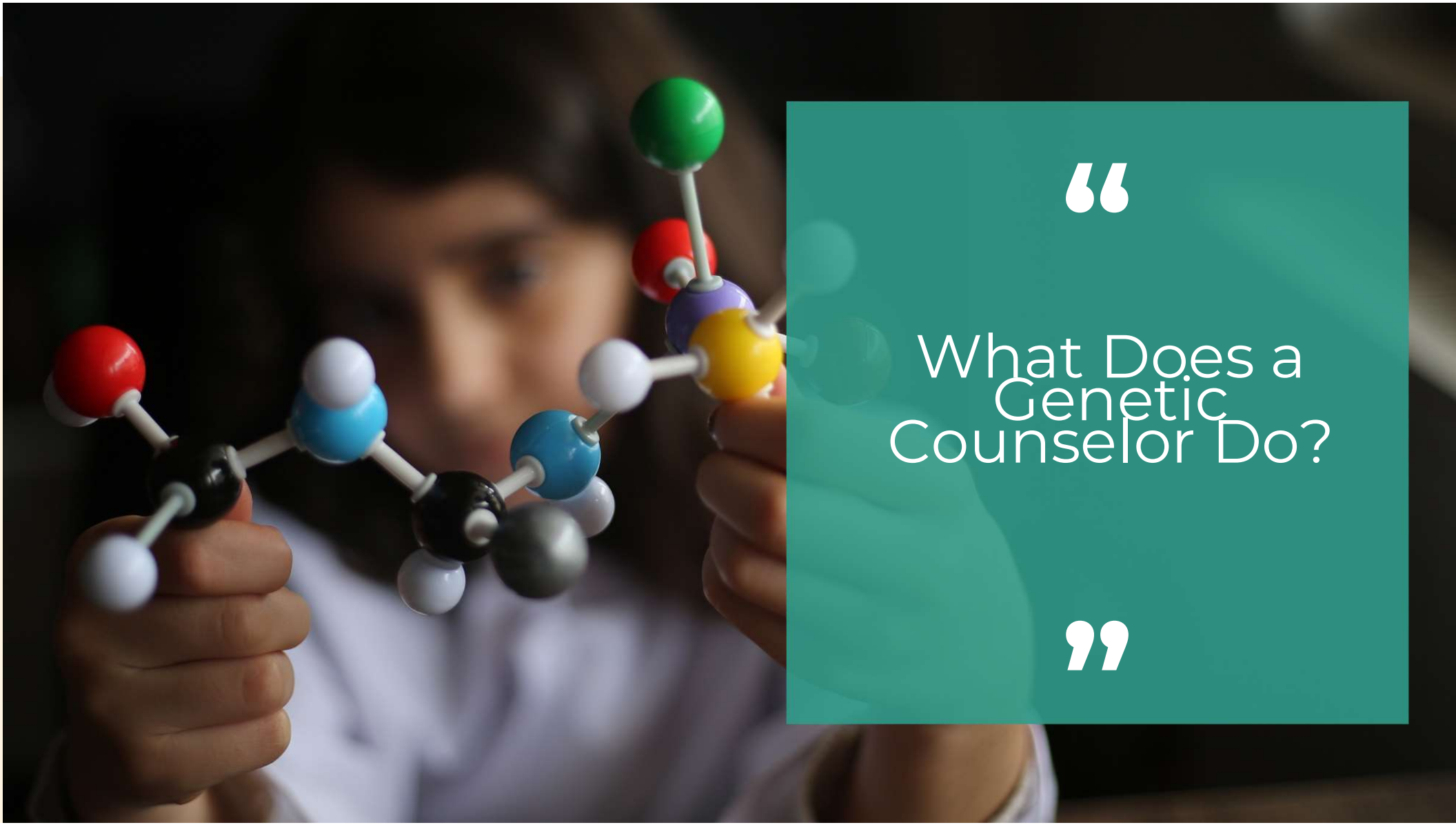
Salary Outlook

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What Does a Genetic Counselor Do?
”

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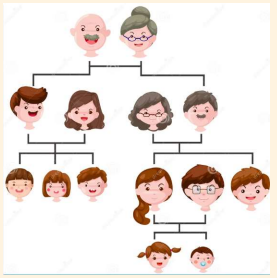
Reasons to see a Genetic Counselor

- You are pregnant or considering pregnancy
- You were diagnosed with cancer or have a significant family history of cancer
- You, your child, or a family member was recently diagnosed with a genetic condition
- You, your child, or a family member have a medical history concerning for a genetic condition
- You, your child, or a family member have physical differences, developmental concerns, or cognitive impairments concerning for a genetic condition



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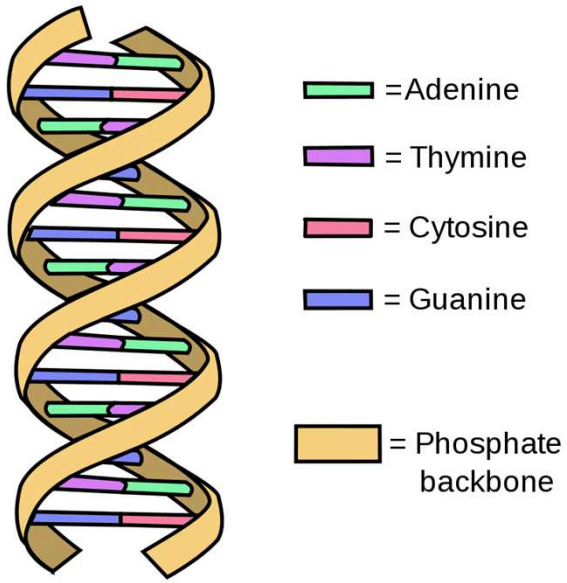
Common conditions with a genetic cause



DNA

- Cancer
- Heart disease
- Hearing loss
- Seizures
- Cleft lip/palate
- Developmental Delay
- Bleeding/clotting issues
- Stroke
- Early onset Alzheimer's disease

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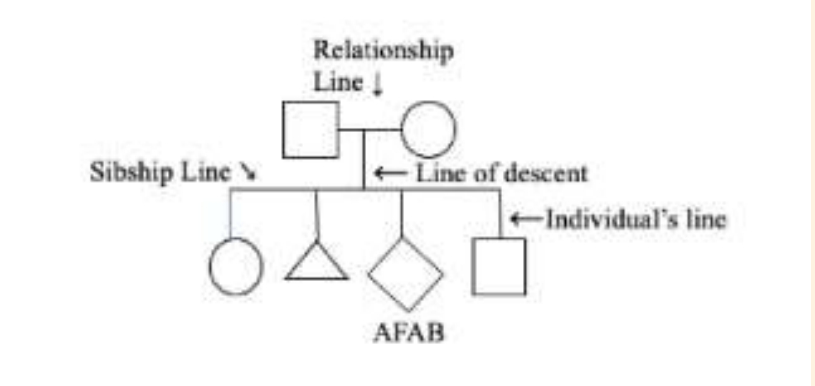
What Happens During an Initial Visit?

1. Review personal medical history
2. Review family history
3. Discuss why patient was referred for genetic counseling
4. Review basic genetic concepts (DNA and genes)
5. Risk assessment
6. Discuss genetic testing options and types of results
7. Assist in decision making
8. Informed consent
9. Psychosocial counseling
10. Help coordinate genetic testing sample
11. Test requisition

Family History

Gender	Sex		
	Male	Female	Unassigned at Birth
Man/Boy	56y	AFAB 34y	UAAB 28y
Woman/Girl	AMAB 56y	34y	UAAB 28y
Non-binary/Gender Diverse	AMAB 56y	AFAB 34y	UAAB 28y



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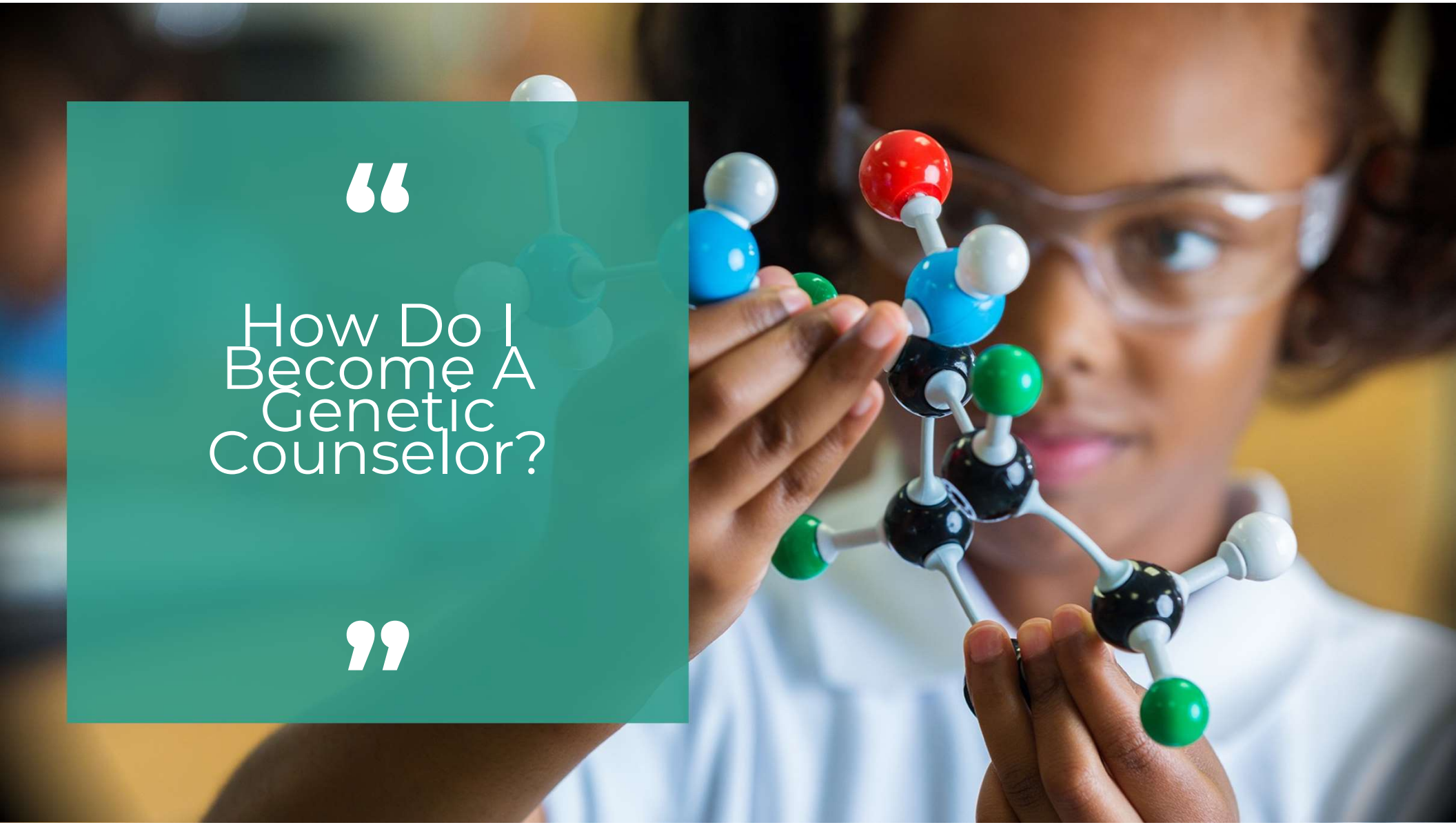
What Happens During a Results Visit?

1. Walk you through your test results
2. Help guide you through the emotional impact of results
3. Review recommended medical management
4. Review surveillance/screening guidelines
5. Discuss impact on other family members and cascade testing if needed
6. Refer you to the correct healthcare providers
7. Plan follow up visits if needed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How Do I Become A Genetic Counselor?
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Academic Pathway to Genetic Counseling

* Always check Genetic Counseling Program requirements, some require additional experiences to apply (shadowing, counseling, advocacy)

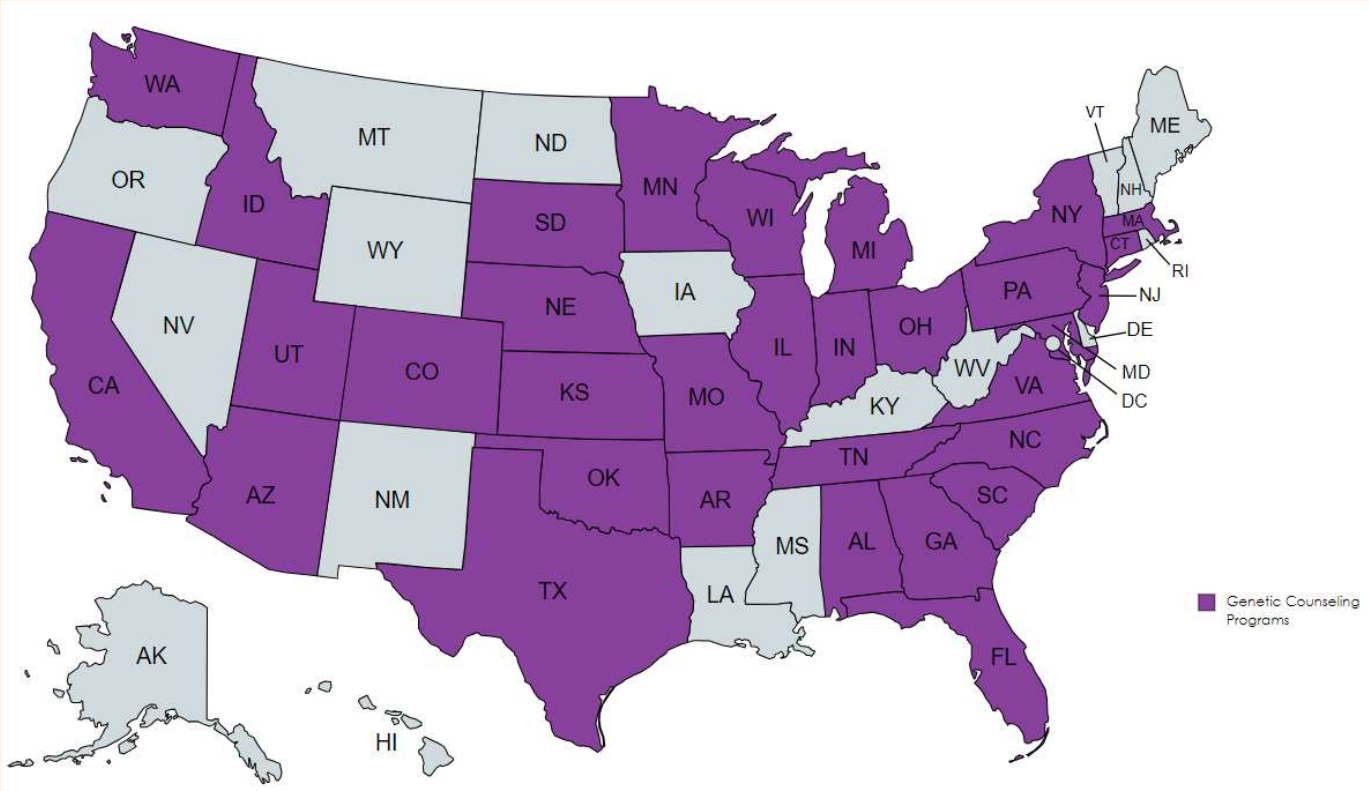
GC Programs

PA
- Thomas Jefferson University
- University of Pennsylvania

NJ
- Rutgers University
- Kean University

MD
- University of Maryland
- Johns Hopkins University

NY
- Mt Sinai School of Medicine
- Columbia University
- Sarah Lawrence College



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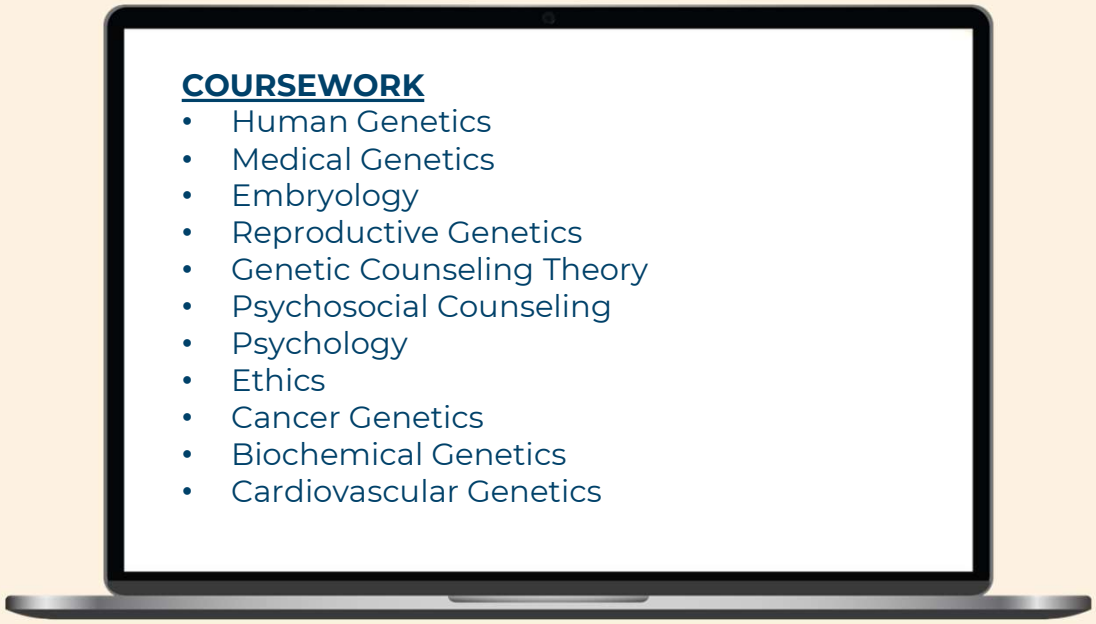
GC Programs Curriculum



CLINICAL ROTATIONS

- Prenatal
- Adult Cancer
- Pediatrics
- Specialty

RESEARCH

- Class to teach you research concepts
- Thesis

Boards Examination

Topic	Number of Questions
Clinical Information, Human Development, and Genetic Conditions	34
Risk Assessment and Principles of Human Genetics and Genomics	32
Testing Interpretation, Testing Options, and Reproductive Risk Management	35
Counseling Skills, Communication, and Education	30
Financial/Reimbursement Issues, Resources and Services for Clients, Legal and Regulatory Requirements, and Professional Frameworks	39

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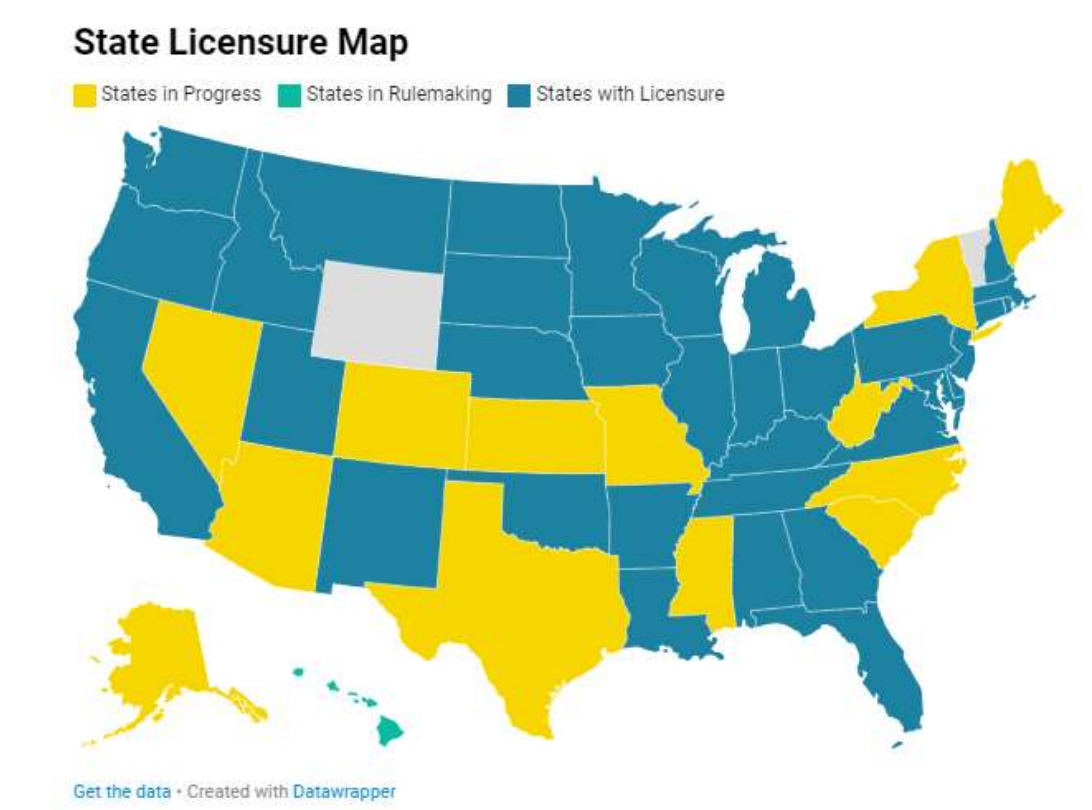
Licensure



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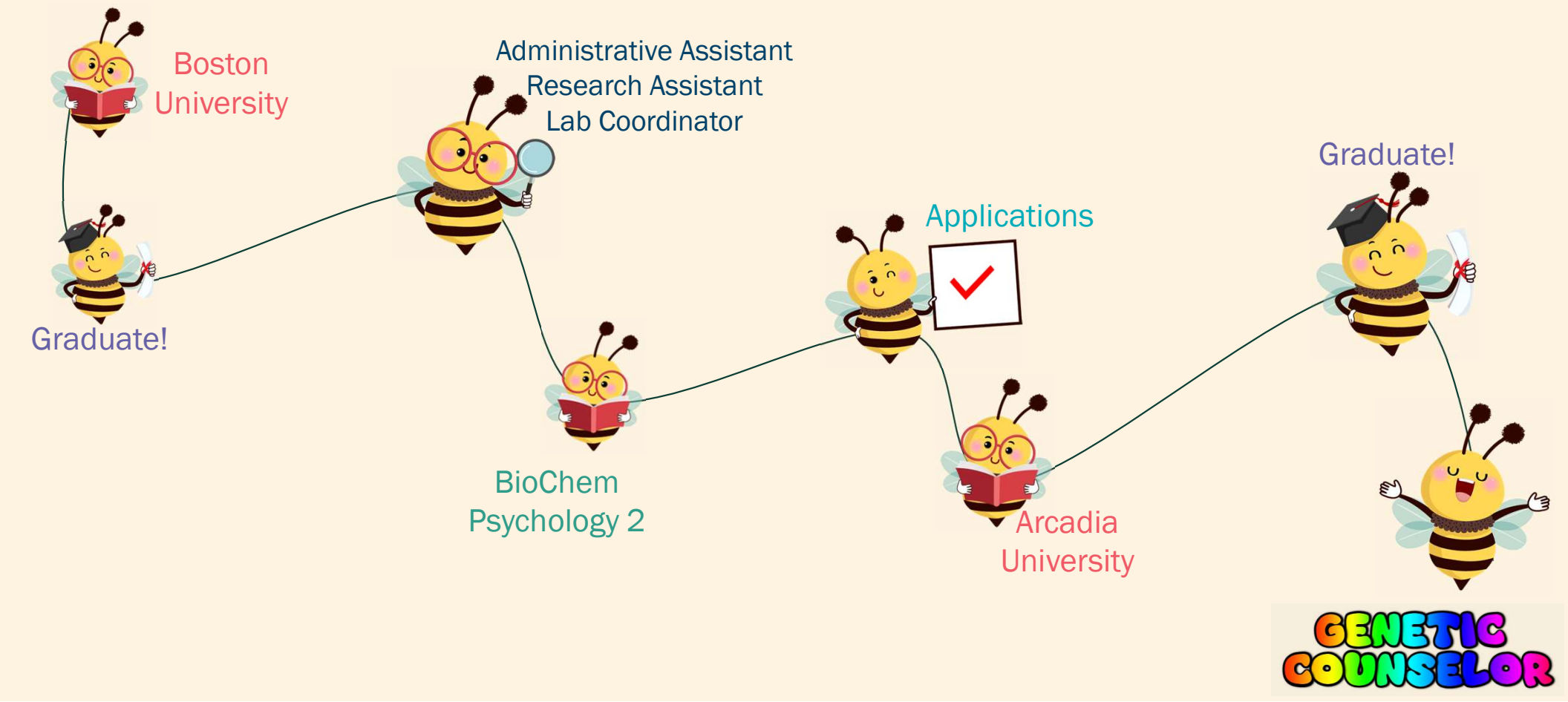
My Career Path!



What do I do?

Roles

- Seeing patients suspicious for a cancer predisposition
- Organizing somatic (tumor testing) and germline (DNA you are born with) testing
- Providing education to providers, families, and the public

Patients I see:

- Children and young adults who have cancer
- Children and young adults with a family history of cancer
- Children and young adults with physical features indicative of a cancer predisposition

Cases!

Pediatric Case

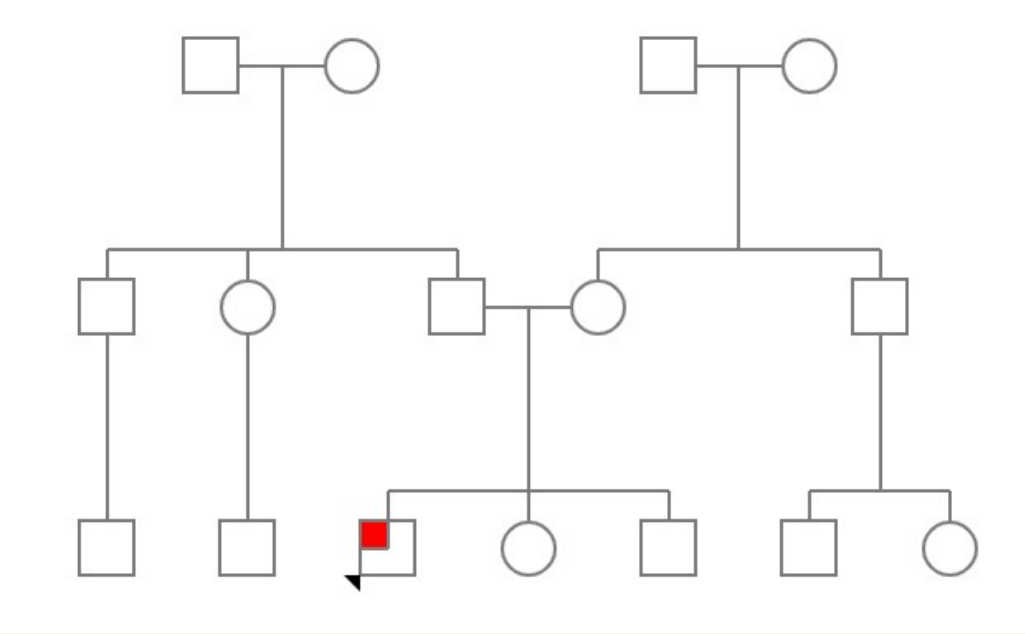
15 month old male

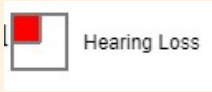
- referred to ENT due to failed newborn hearing screen

- audiology testing determined patient has bilateral sensory neural hearing loss

- referral for genetic counseling was made

Family History





What do we know?

- Patient has bl SNHL
- 80% chance to be genetic
- Either autosomal recessive or de novo
- No other relative medical history/concerns
  - MRI was normal
  - No infection history

What testing do we send?

- Targeted hearing loss panel?
- Broad hearing loss panel?
- Microarray?

[redacted]

GeneDx | sema4

DOB [redacted] Accession [redacted]

Submitter Patient ID(s) [redacted]

Sample	Testing	Provider
Source: OraCollect Buccal Date Collected: [redacted] Date Received:	Date Started: [redacted] Date Reporte	[redacted]

Test(s) Requested

Hearing Loss Panel

Result: Positive

Gene	Mode of Inheritance	Variant	Zygosity	Classification
[redacted]			Heterozygous	Pathogenic Variant
USH2A	Autosomal recessive	Partial Gene Deletion	Heterozygous	Pathogenic Variant
USH2A	Autosomal recessive	c.2299del p.(E767Sfs*21)	Heterozygous	Pathogenic Variant
[redacted]			Heterozygous	Variant of Uncertain Significance

Interpretation

[redacted]. Although this gene is associated with both autosomal dominant and autosomal recessive disorders, the variant identified in this individual is predicted to be associated with the autosomal recessive disorder. As no second variant was identified, this finding does not establish a molecular diagnosis of autosomal recessive [redacted]ng loss.

This individual is heterozygous for two pathogenic variants in the USH2A gene, which is consistent with autosomal recessive USH2A-related Usher syndrome in this individual if these variants are on different alleles (in trans).

This individual is heterozygous for a variant of uncertain significance in the DIAPH1 gene, which does not establish a molecular diagnosis in this individual.

Recommendation(s)

- Genetic counseling is recommended to discuss the implications of these results.
- Correlation of these findings with the clinical features of this individual is recommended.
- Targeted carrier testing may be considered for family members, and molecular prenatal diagnosis may be considered for the parents of this individual, if desired, for the variants in the USH2A gene. GeneDx requires targeted carrier testing of both parents prior to or concurrently with any carrier testing or predictive testing in this family to evaluate whether the two variants were inherited on separate alleles (in trans) or inherited on one allele (in cis).
- Targeted carrier testing for th[redacted]
- Targeted testing of the parents of this individual and/or other family members, if available, may help determine if the variant in the DIAPH1 gene occurred de novo or segregates with the phenotype and may assist in further interpretation.

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GeneDx.com

USH2A

GENE SUMMARY

The USH2A gene encodes the usherin protein, a transmembrane protein that is involved in protein-matrix interactions. Specifically, usherin has been localized to the synaptic region of stereocilia in the inner ear and to connecting cilium at the synaptic terminals of cone and rod

GeneDx | sema4

photoreceptor cells in the retina (PMID: 16545802). Pathogenic variants in the USH2A gene are associated with Usher syndrome type II and non-syndromic retinitis pigmentosa; both are autosomal recessive disorders with onset in the first to second decade of life which share the phenotype of progressive retinal degeneration. Usher syndrome type II is also characterized by a moderate to severe congenital hearing impairment (PMID: 16545802, 19165952). A wide range of pathogenic variants in the USH2A gene, including missense, nonsense, splice site, frameshift, and deep intronic changes as well as gross deletions of the USH2A gene, have been reported in association with USH2A-related disorders (PMID: 16545802, 19165952, 26629787). Heterozygous PDZD7 variants have been reported in combination with biallelic pathogenic variants in the USH2A gene in a small number of patients with Usher syndrome, in which the presence of the PDZD7 variant correlated with a more severe retinal phenotype (PMID: 20440071). This suggests a possible role for PDZD7 as a modifier of the retinal disease phenotype, however, additional evidence is needed to further characterize the association of variants in PDZD7 with Usher syndrome.

c.2299del:p.(Glu767Serfs*21) in exon 13 of the USH2A gene (NM_206933.2) The sequence with the altered base(s) in brackets is: GTGT[delG]AGTG

- Identified in multiple unrelated patients tested at GeneDx and in the published literature with Usher syndrome type II, atypical Usher syndrome, and non-syndromic autosomal recessive retinitis pigmentosa who were homozygous or had different pathogenic variants on the opposite allele (Eudy et al., 1998; Dreyer et al., 2001; Aller et al., 2004; Seyedahmadi et al., 2004; Aller et al., 2010)
- Common pathogenic variant, accounting for 16%-44% of USH2A variants (Dreyer et al., 2001)
- Frameshift variant predicted to result in protein truncation or nonsense mediated decay in a gene for which loss-of-function is a known mechanism of disease
- mRNA studies showed that this variant alters gene splicing leading to skipping of exon 13 and/or exons 12 and 13 (Lenassi et al., 2014)
- Observed in large population cohorts (gnomAD; internal data)

We interpret this as a Pathogenic Variant.

Deletion including exon 62-64 of the USH2A gene [NM_206933.2]. Genomic coordinates: chr1:215844298_215853788 [GRCh37]

- Deletion, predicted in-frame, involving exon(s) encoding a functionally important protein region
- Not observed at significant frequency in large population cohorts (Database of Genomic Variants)
- A smaller deletion within this region has been reported as pathogenic at GeneDx in association with USH2A-related Usher syndrome
- Has not been previously published as pathogenic or benign to our knowledge

We interpret this as a Pathogenic Variant.

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Usher Syndrome

USHER SYNDROME TYPES AND SYMPTOMS

SENSE	Type 1	Type 2	Type 3
Hearing 	Profound deafness in both ears from birth.	Moderate to severe hearing loss from birth.	Normal at birth; progressive loss in childhood or early teens.
Vision 	Decreased night vision before age 10, then a gradual loss of peripheral vision.	Decreased night vision begins in late childhood or teens, then a gradual loss of peripheral vision.	Varies in severity; night vision problems begin in teens, then a gradual loss of peripheral vision.
Balance 	Balance problems from birth.	Normal.	Normal to near normal; chance of later problems.

Source: NIH/NIDCD

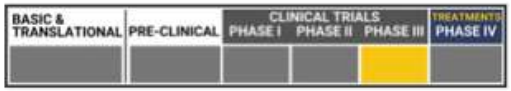
Advances in treatment

Usher Type 2A

ProQR's Stellar Clinical Trial

Pre-clinical USH2A c.2299delG mutation gene editing using the CRISPR system

Gene Independent Treatment



NAC Attack: Oral N-acetylcysteine for Retinitis Pigmentosa

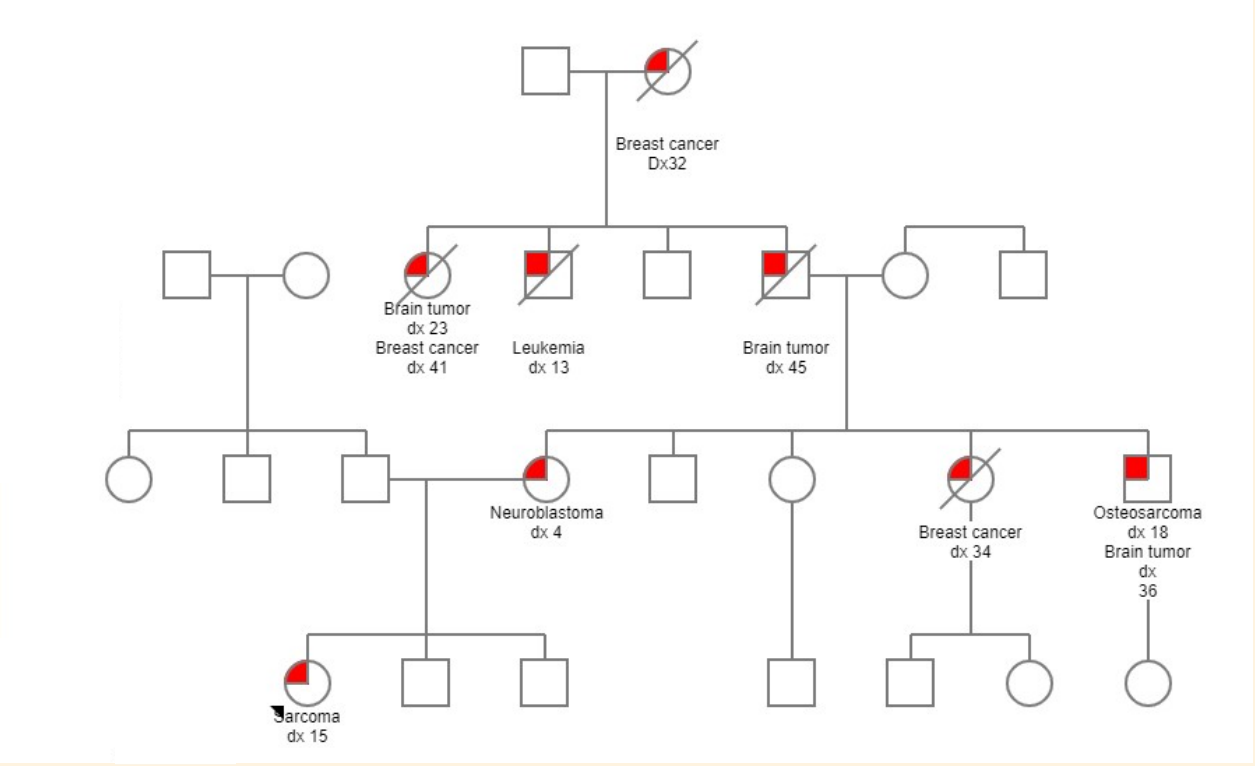
Nacuity: Safety and Efficacy of NPI-001 Tablets for RP Associated With Usher Syndrome (SLO RP)

Cancer Case

15 year old female

- - presented to the ER due to increasing leg pain and swelling
- -imaging identified a mass on left leg
- - through pathology mass was determined to be a sarcoma
- - referred for genetic counseling

Family History



What do we know?

- Patient has a sarcoma
- Family history of early onset cancers
- Chrompret criteria

What testing do we send?

- Somatic tumor testing
  - Dedicated sarcoma panel?
  - Research based?
- Germline testing
  - Targeted testing for Li-Fraumeni?
  - Broad cancer panel?

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GENETIC TEST REPORT

GeneDx an OPKO Health Company

PHYSICIAN	PATIENT	SAMPLE
[redacted]		

Additional Healthcare Provider: KRISTA KROL-BUCH

TEST REQUESTED

Comprehensive Common Cancer Panel

GENES EVALUATED

APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCC, FANCM, FH, FLCN, HOXB13, MET, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, POT1, PTEN, RAD51C, RAD51D, RECQL, SCG5/GREM1, SDHB, SDHC, SDHD, SMAD4, STK11, TP53, TSC1, TSC2, VHL (47 genes)

CLINICAL INDICATION

Personal history [redacted]

RESULTS: POSITIVE

Gene	Variant	Zygosity	Classification
TP53	c.733G>A p.(Gly245Ser)	Heterozygous	Pathogenic

No additional reportable variants were detected in any of the genes on this panel by sequencing or deletion/duplication analysis.

Li-Fraumeni Syndrome

- Lifetime cancer risk of >70% for XY individuals and >90% risk for XX individuals
- Caused by mutations in the TP53 gene
  - The TP53 gene codes for a protein that is one of the key players in controlling cell growth
- Risk to develop cancer:
  - In childhood = ~25% or ¼ (one in 4 individuals)
  - By age 30 = ~50% or ½ (half of individuals)
  - By age 60 = ~80-90%
- Increased risk of certain cancer types
  - The Bs (bone, brain, breast, blood, and sarcomas)

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Li-Fraumeni Syndrome Screening 0-18

Tumor Risk	Intervention and Screening Interval in Pediatric Patients
General Assessment	• Complete physical exam: every 3-4 months • Includes: blood pressure, anthropometric measurements, cushingold appearance, signs of virtualization, and full neurological assessment
Adrenal cortical carcinoma	• Ultrasound of abdomen and pelvis: every 3-4 months • In case of unsatisfactory u/s, blood tests may be performed.
Brain tumor	• Brain MRI : annually
Soft tissue and bone sarcoma	• Whole body MRI: annually

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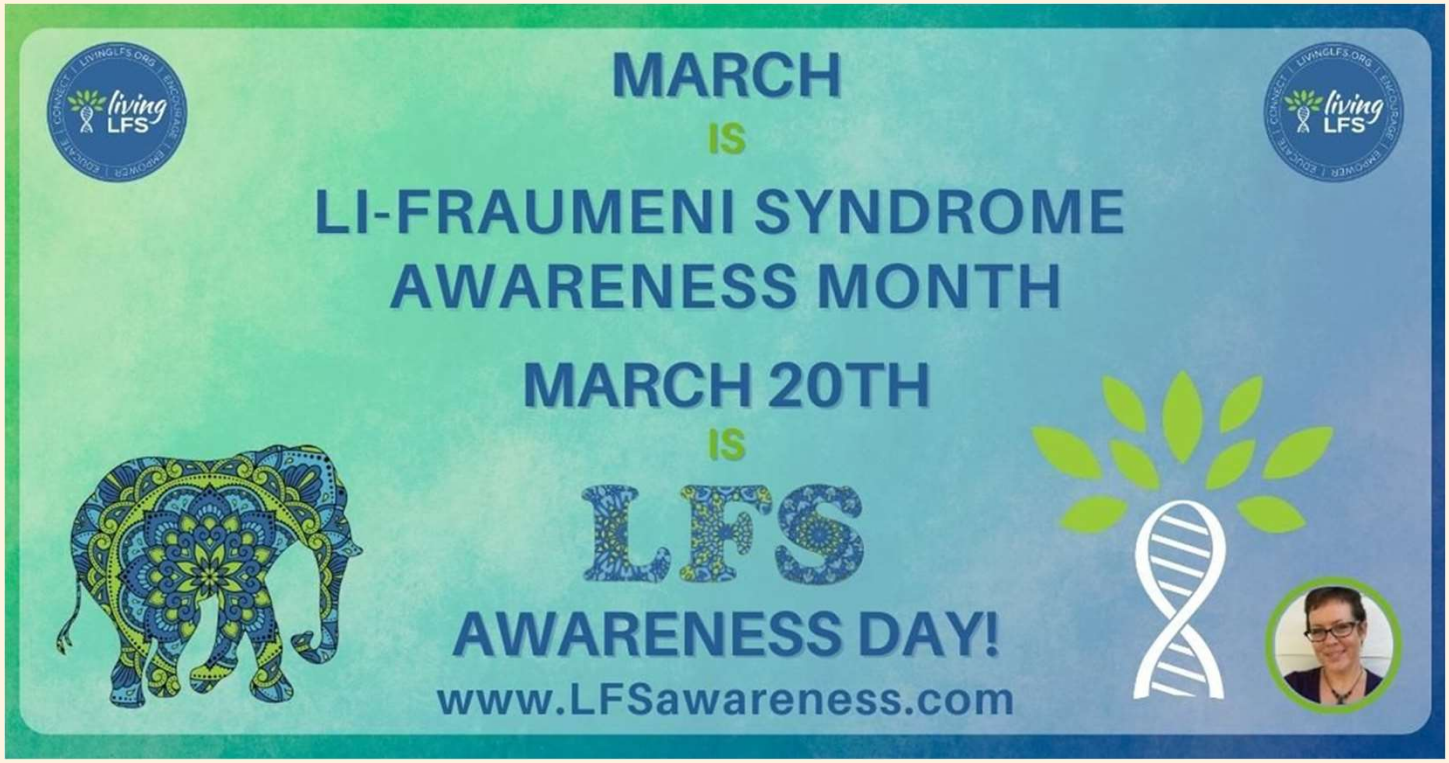
Li-Fraumeni Syndrome Screening Adults

Tumor Risk	Intervention and Screening Interval in Adult Patients
Breast Cancer	• Breast awareness – start at 18 years of age • Clinical breast exam – every 6-12 months starting at 20 years of age • Screening: breast MRI & mammogram – annual MRI starting at 20-29 (or earliest age of breast CA in the family). At 30, annual MRI and mammogram • Option of risk-reducing mastectomy
Other cancer risks	• Comprehensive physical exam: every 6-12months • Colonoscopy and upper endoscopy: every 2-5 years starting at 25 (or 5y before earliest colon CA in the family). • Dermatologic exam: annually starting at 18 • Whole body MRI: annually • Brain MRI: annually


MARCH
IS
LI-FRAUMENI SYNDROME
AWARENESS MONTH
MARCH 20TH
IS
LFS
AWARENESS DAY!
www.LFSawareness.com

Prenatal Case

36 year old female; G2P0010

- (G2 = two pregnancies, P = Pregnancies to term, pregnancies to preterm, terminations/miscarriages, living children)
- Second trimester ultrasound showed heart defect

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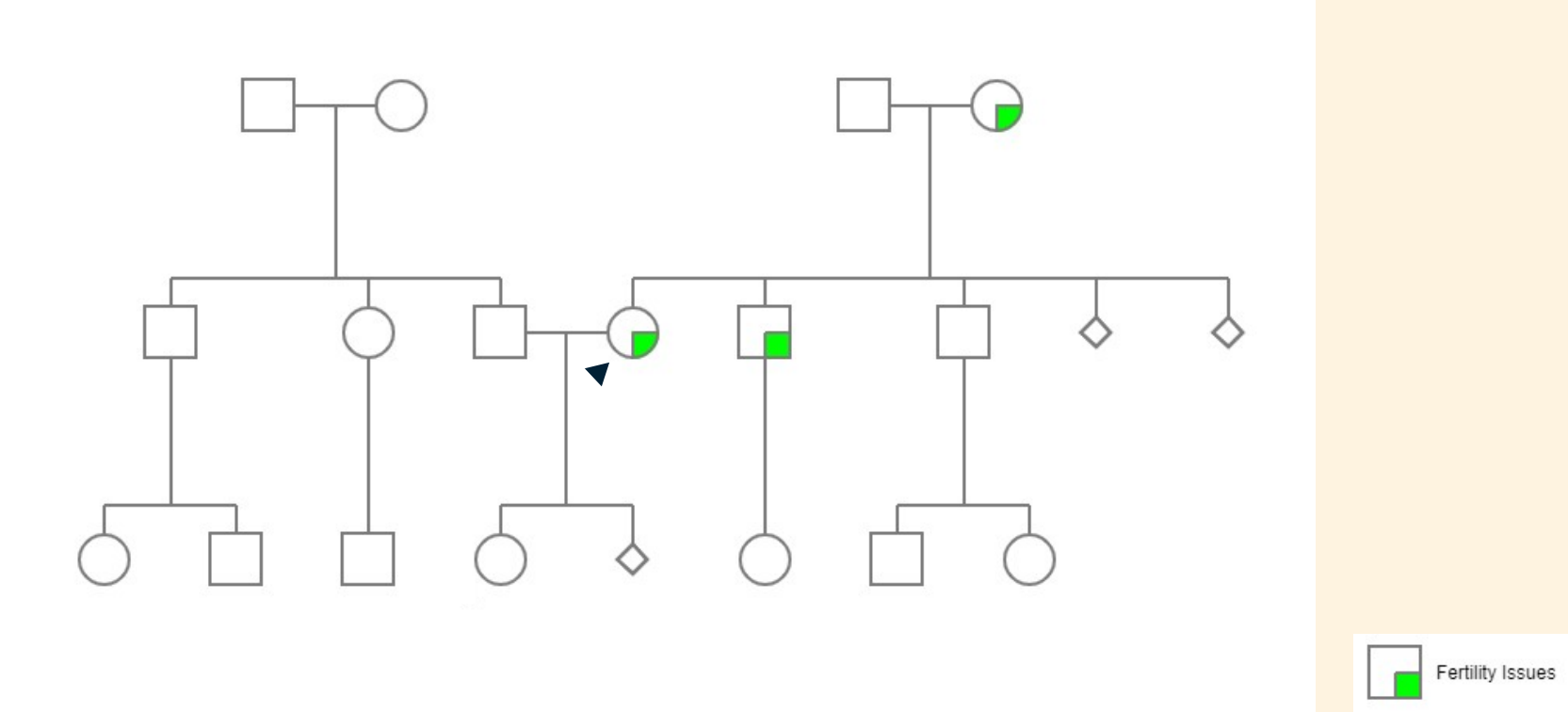
Family History



What do we know?

- Patient had fertility struggles
- First trimester screen was normal
- Second trimester ultrasound identified heart defect, repeat ultrasound showed conotruncal heart defect

What testing do we send?

- Microarray is a standard test to order on amniocentesis

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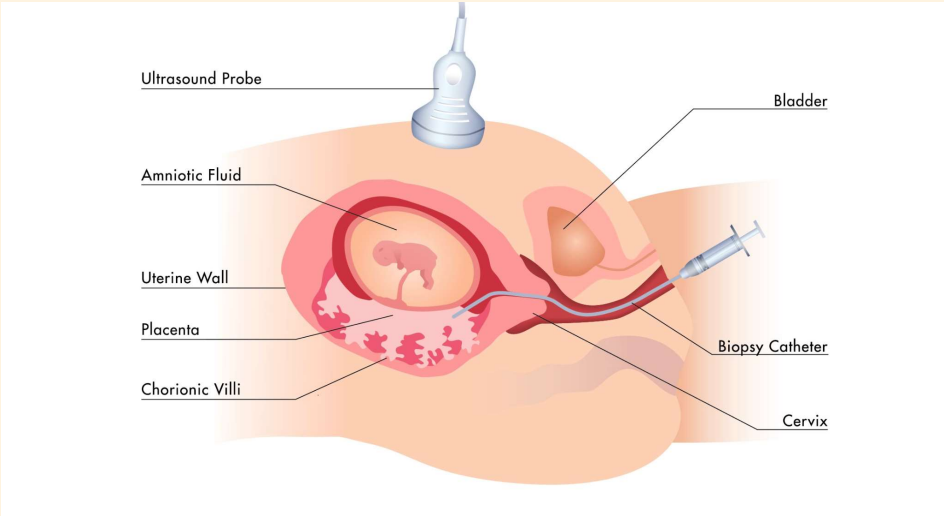
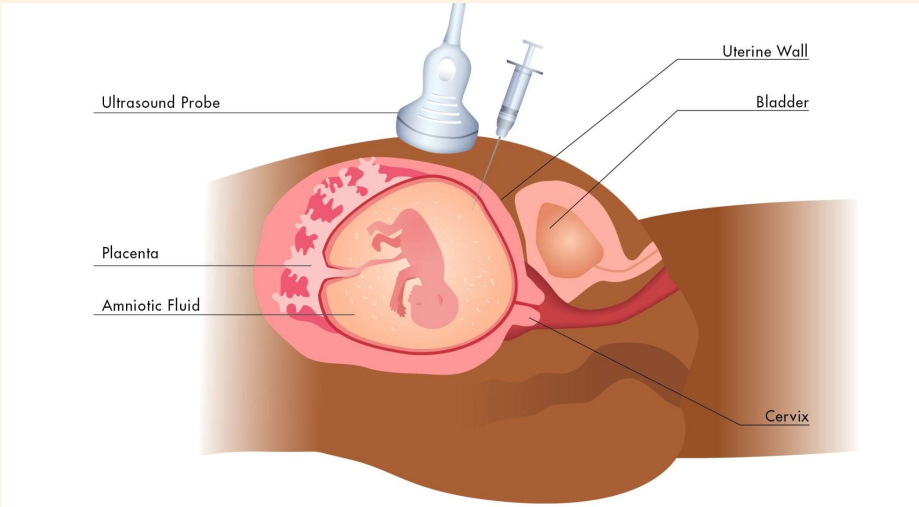
Chorionic Villus Sampling (CVS)



Amniocentesis (Amnio)



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MICROARRAY RESULT: **16.2 MB INTERSTITIAL DUPLICATION OF 9P21.3->9P13.1; 13.2 MB INTERSTITIAL DELETION OF 9Q21.11->9Q21.31**

INTERPRETATION: **FEMALE WITH POSSIBLE PATHOGENIC DUPLICATION AND DELETION**

MCC RESULT: NO SIGNIFICANT MATERNAL CELL CONTAMINATION WAS DETECTED. LINKED SPEC#10722520580 (NO MATERNAL CELL CONTAMINATION DETECTED)

arr [hg19] 9p21.3p13.1(22,537,254-38,771,831)x3, 9q21.11q21.31(69,977,403-83,134,354)x1

The whole genome SNP microarray (Reveal) analysis has detected a **female** with an interstitial duplication and deletion of the chromosomal segments listed above.

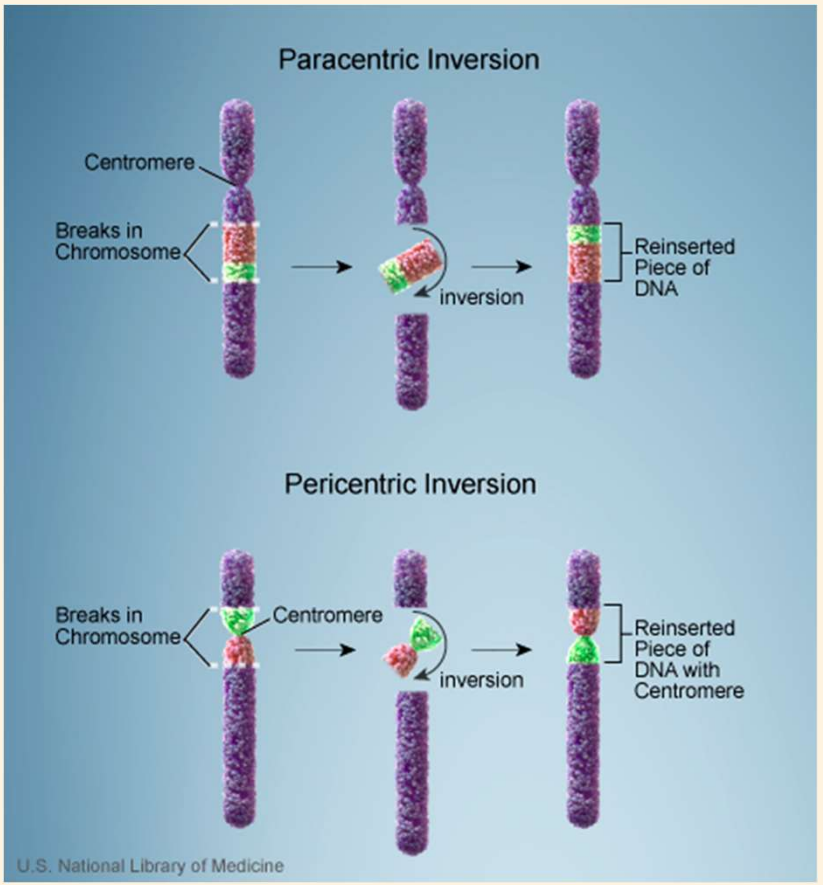
The duplication interval includes numerous OMIM genes [start: *ELAVL2* to end: *IGFBPL1*]. The deletion interval includes numerous OMIM genes [start: *CBWD3* to end: *TLE4*].

The 9q deletion includes the 9q21 deletion syndrome region. Clinical features may include intellectual disability, speech delay, epilepsy, and characteristic facial features (see references). There is limited literature regarding duplication of the interstitial 9p region, case reports suggest overlapping duplications are associated with speech/language delays and some dysmorphic features(see reference).

Patient	1	2	3	4	5	6	7	8	9
Autism	Y	Y	Y	Y	Y	Y	N	Y	Y
ID	Y	Y	Y	Y	Y	Y	Y	Y	Y
Cardiac anomalies	N	N	N	N	N	N	N	N	N
CNS anomalies	Chiari type 1	N	N	N	Hippocampal asymmetry	Corpus callosum hypoplasia	N	N	Delayed myelination, arachnoid cyst
Seizures	Y	N	Y	Y	Y	Y	Y	Y	Y
Dysmorphic facies	Y	Y	Y	Y	Y	Y	N	Y	Y
Prenatal anomalies	N	N	N	Increased NT	N	N	N	N	N

What do we know now?

- Patient has a deletion AND a duplication
- This likely means one of the parents has an inversion



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A pericentric inversion includes the centromere

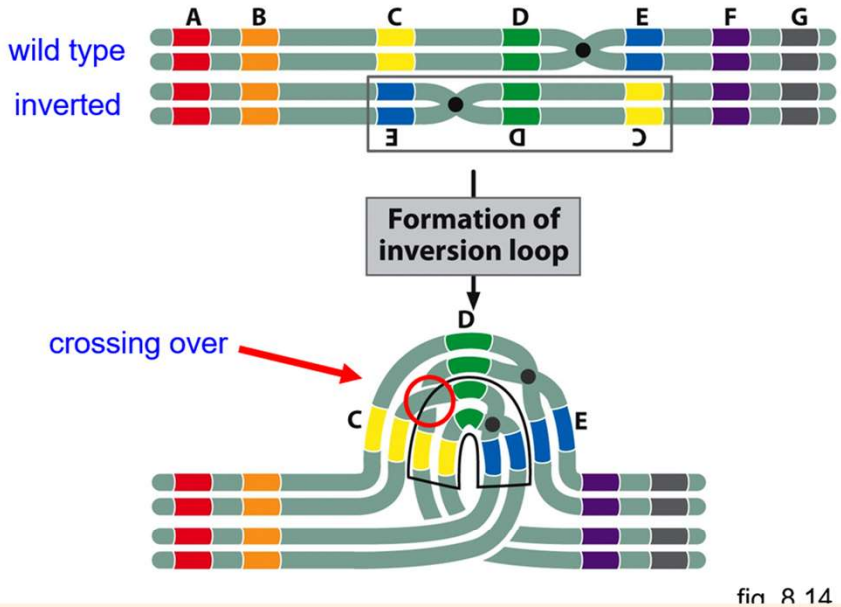
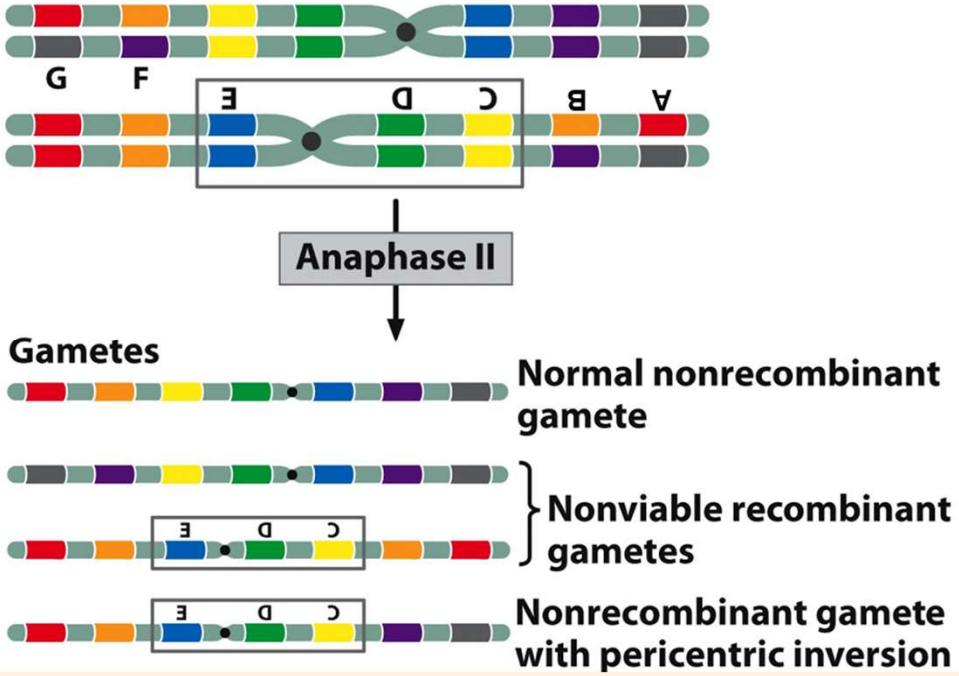


fig. 8.14



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Metaphases Counted:	20			**Banding Technique:**	GTW
Metaphases Analyzed:	5	**Number of Cultures:**	2	**Banding Resolution:**	550
Metaphases Karyotyped:	4			**Dept. Section:**	B1

RESULTS: 46,XX,inv(9)(p21.3q21.3)
Inversion karyotype, female

INTERPRETATION:

Cytogenetic analysis shows an apparently balanced pericentric inversion of one chromosome 9.

RECOMMENDATION:

A balanced rearrangement carried by a parent can result in unbalanced gametes, and can lead to decreased fertility, miscarriage, or chromosomally abnormal offspring. Prenatal diagnosis should be offered in future pregnancies.

Cytogenetic analysis should be offered to family members who could also be carriers.

Genetic counseling is recommended for this family.

Questions?