Genetics for the Non-Geneticist: What Role can PCPs Play in Their Adult Patients' Genetics Care?

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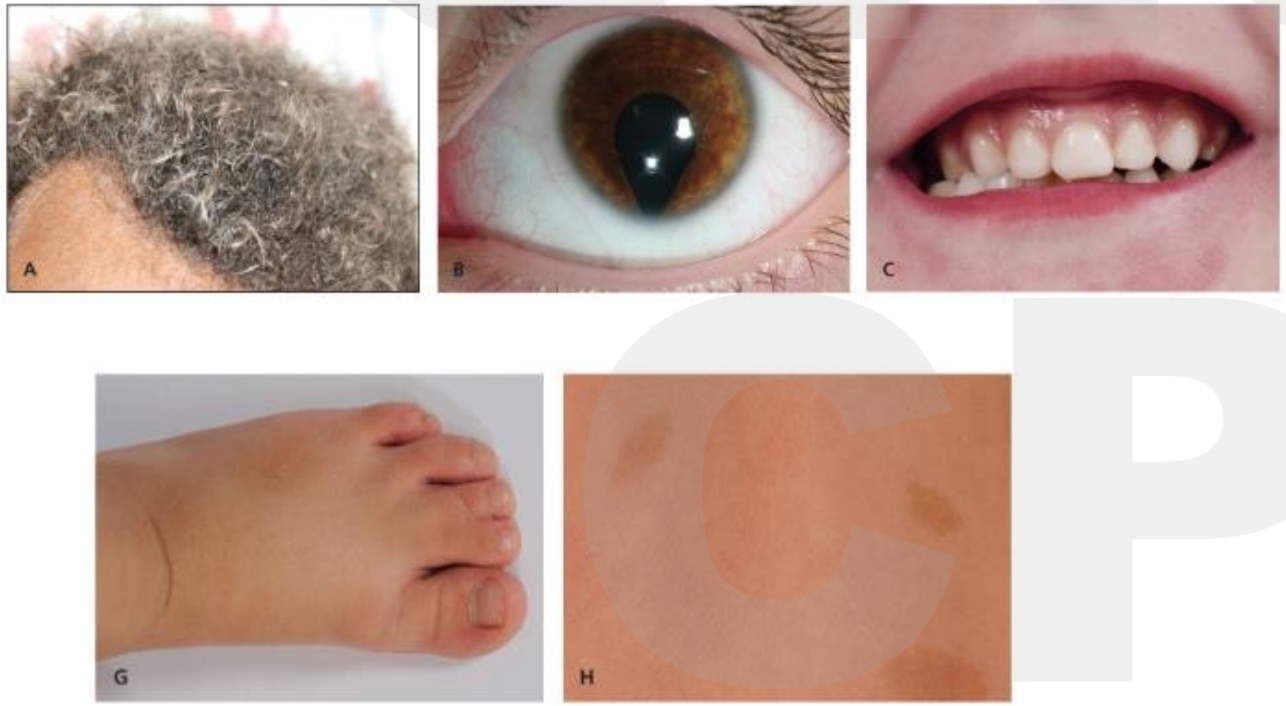
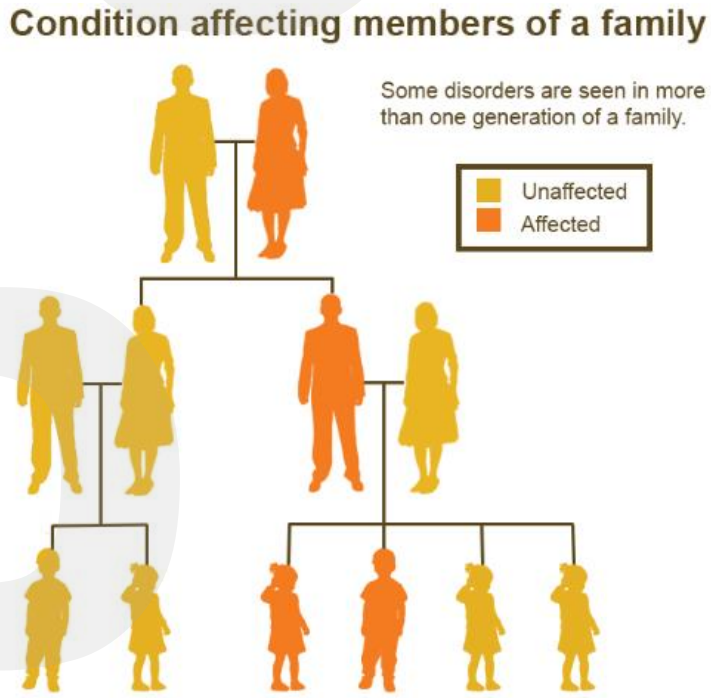
Outline

- Describe role of medical genetics in medicine
- Discuss basics of genetics
- Understand genetic testing and result interpretation
- Recognize indication for genetic testing and need for referral

Medical genetics

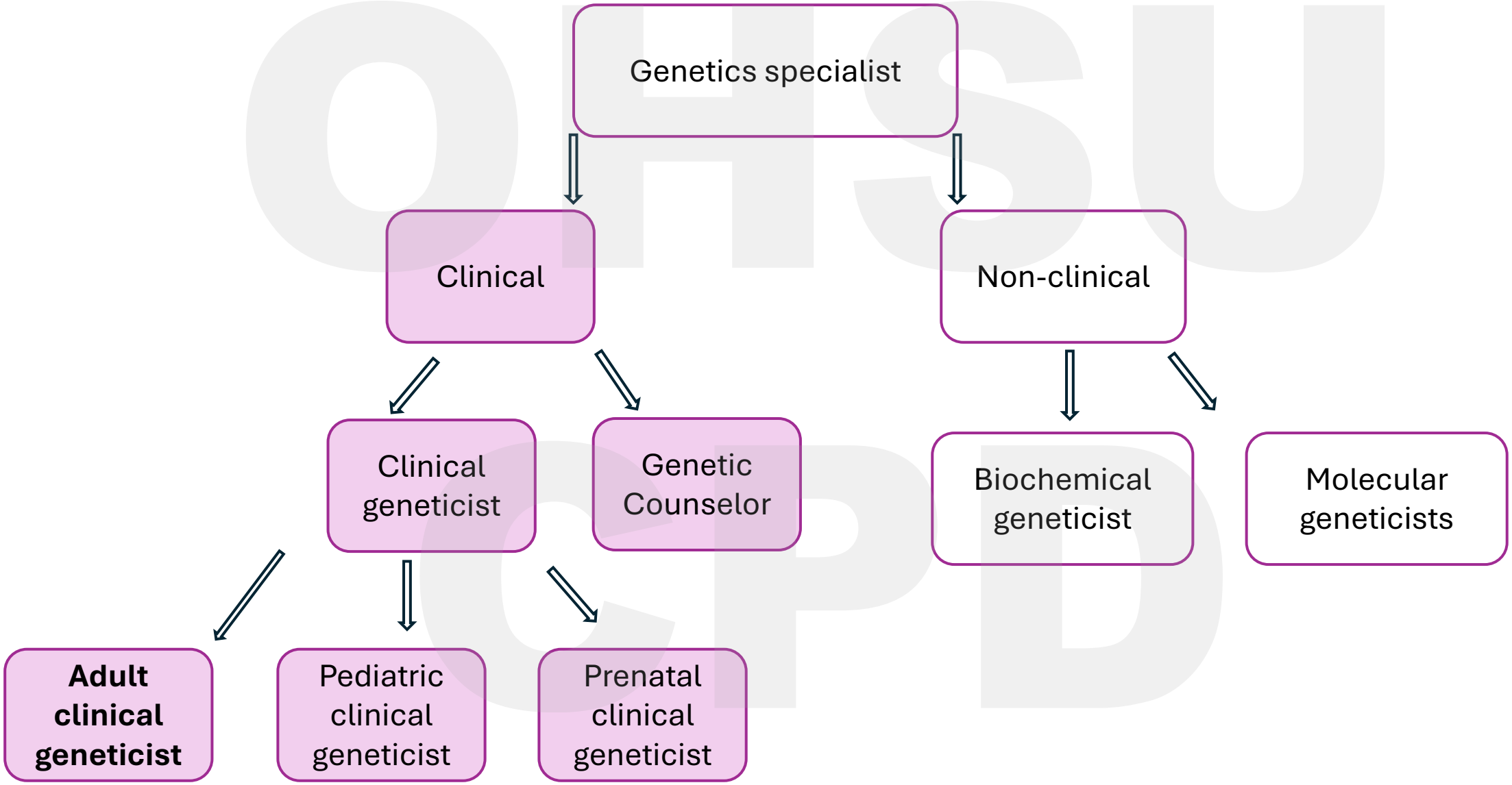
Medical genetics is a clinical specialty focused on diagnosing, managing, and preventing disorders arising from genetic variations.





AAFP. (2012). *Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer.* Am Fam Physician, 86(9), 826-831.
HealthyChildren.org. *Inheriting mental disorders.*

The specialty



Medical Genetics at OHSU

Medical genetics at OHSU

Portland clinics supported by Molecular and Medical Genetics

- Cancer Genetics
- Cardio Genetics
- General Adult Genetics
- Metabolic Genetics
- Neuro Genetics
- Neuro Oncology Genetics
- Pediatric Genetics
- Pediatric Oncology Genetics
- Predictive Neuro Genetics

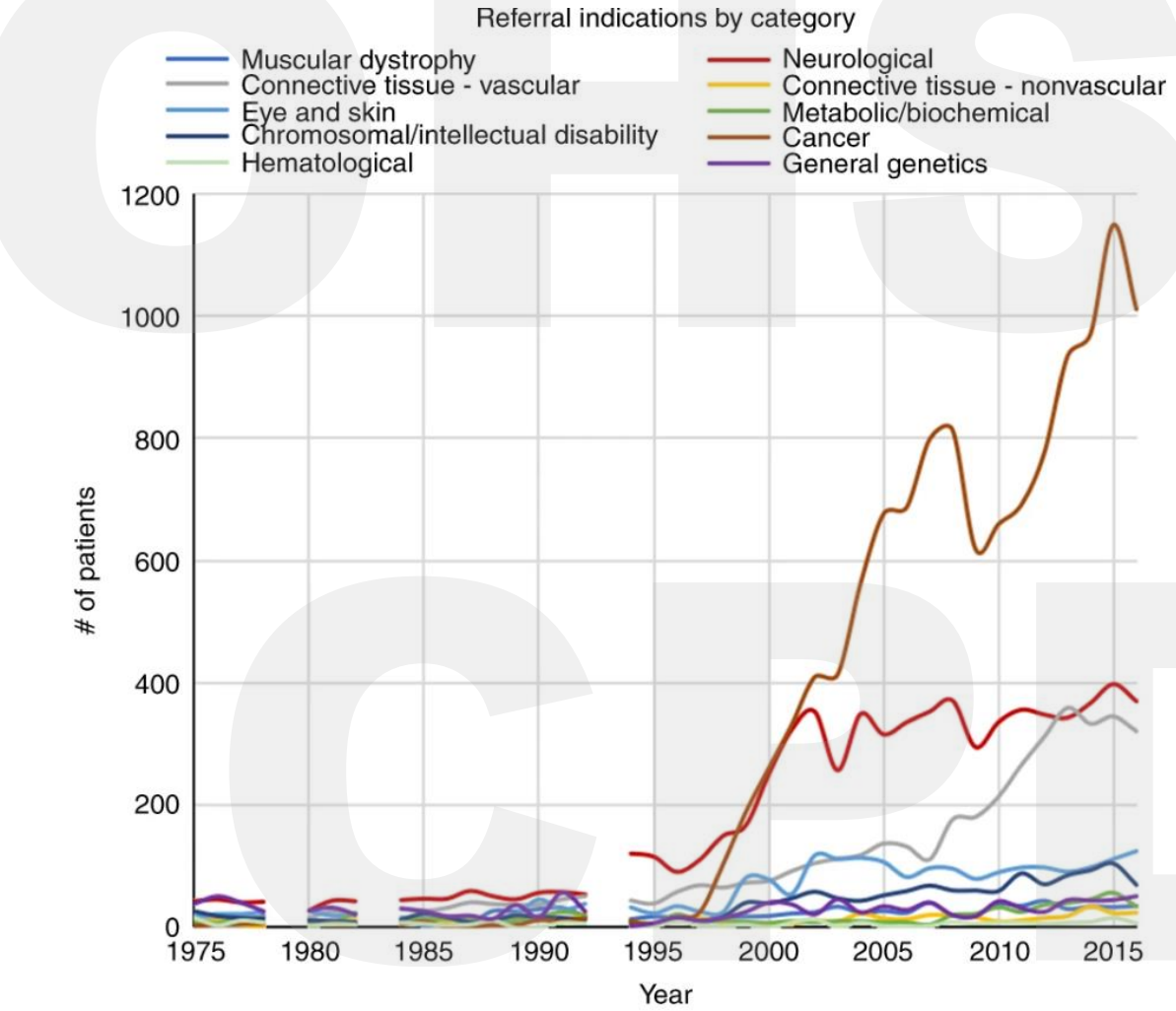
Outreach clinics

- Ambulatory Telemedicine Cancer Genetics
  Rogue Regional Medical Center
- Ambulatory Metabolic Genetics Clinics
  State of Alaska Department of health and human services
- Inpatient NICU consultations
  OHSU Telemedicine (Transitions of care programs)

Other specialties at OHSU

- Prenatal genetics
  OHSU Center for Women's Health
- Opthalmic genetics
  Casey Eye Institute

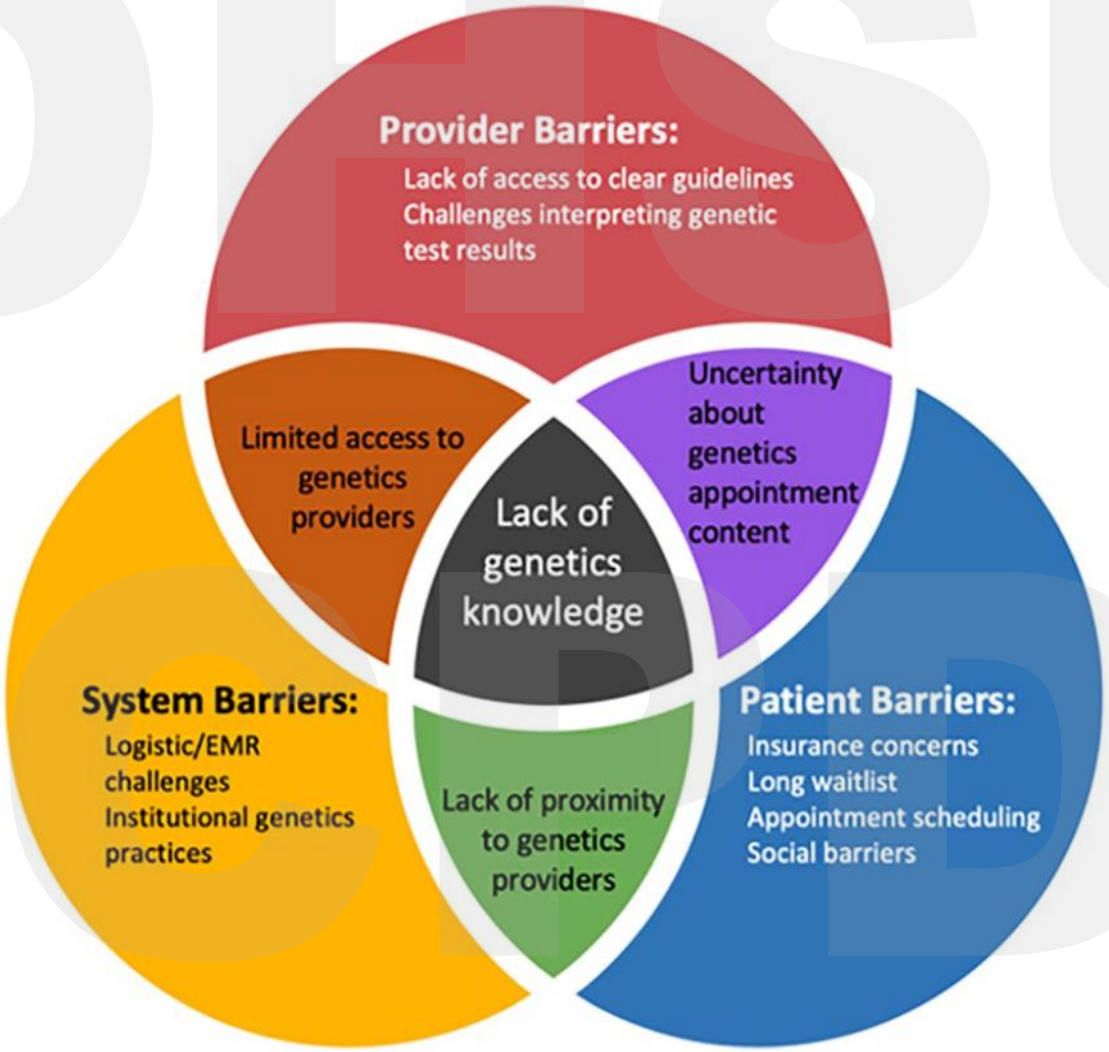
Common indications for genetics referral



s seen at the University of Washington Adult Genetic Medicine Clinic (UWAGMC) from 1975 to 2016 binned into categories fro

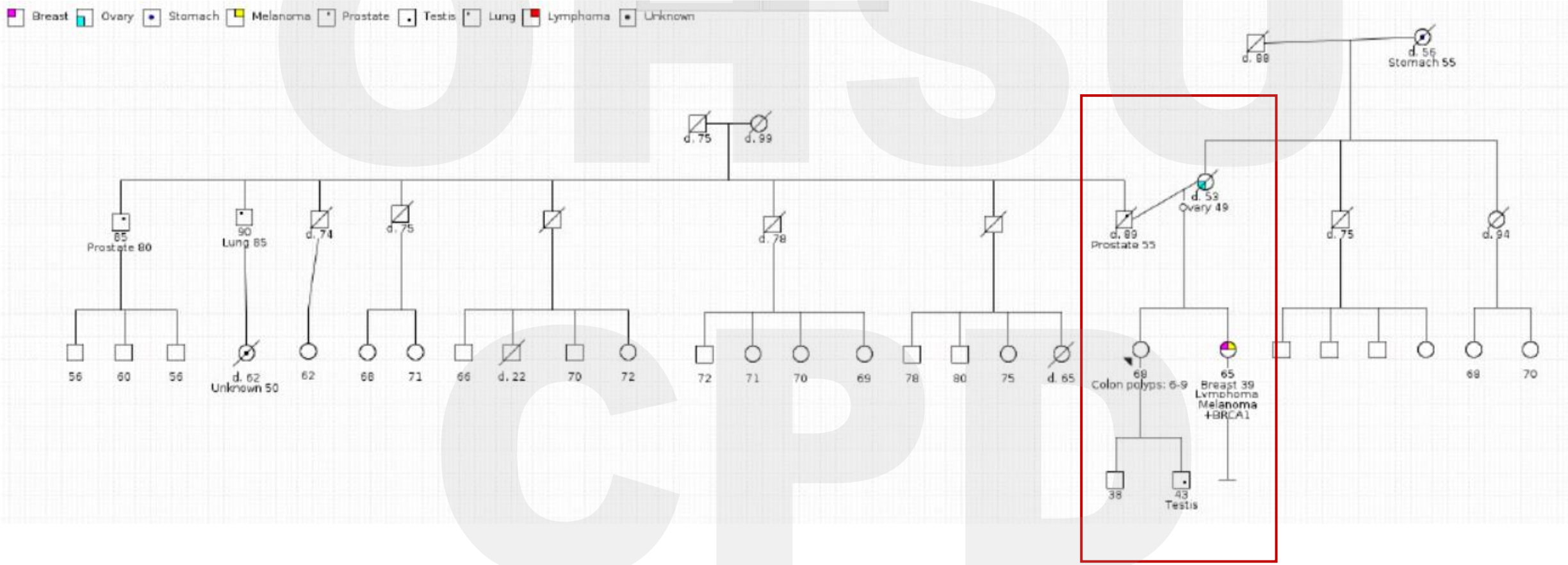
Sukumar S., Linnér R.K., Hägg S. (2021). *Genetics of lifestyle and aging-related traits.* Adv Genet, 109, 255-298.

Barriers noted in providing genetic service

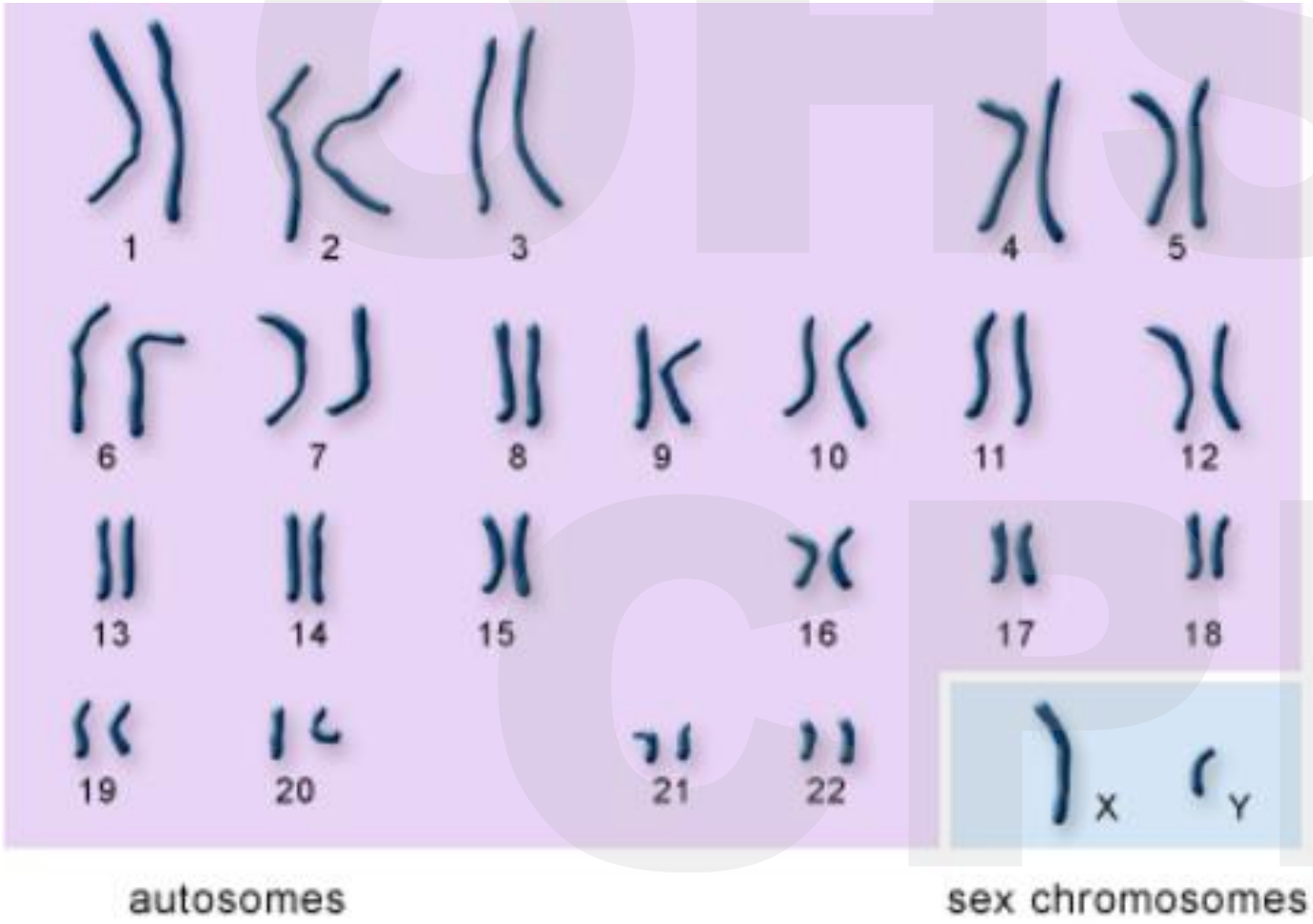


Kuehn B.M. (2022). *Experts outline new clinical genetic testing guidelines*. JAMA, 328(22), 2177.

Family history

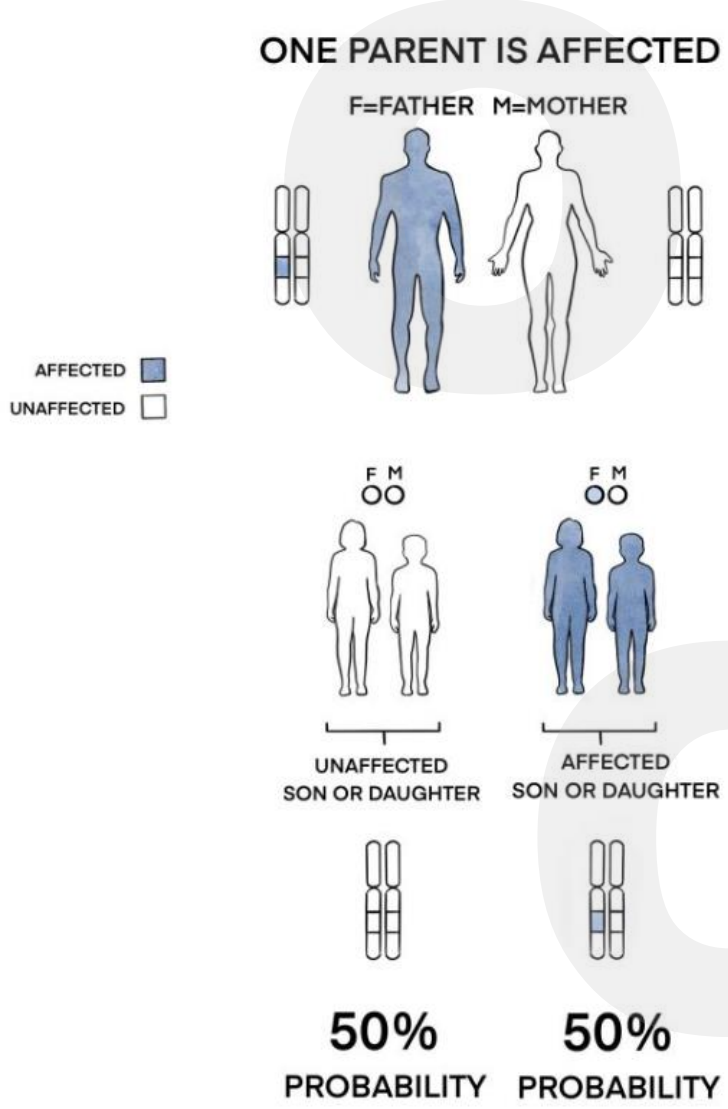


Basics of genetics and inheritance

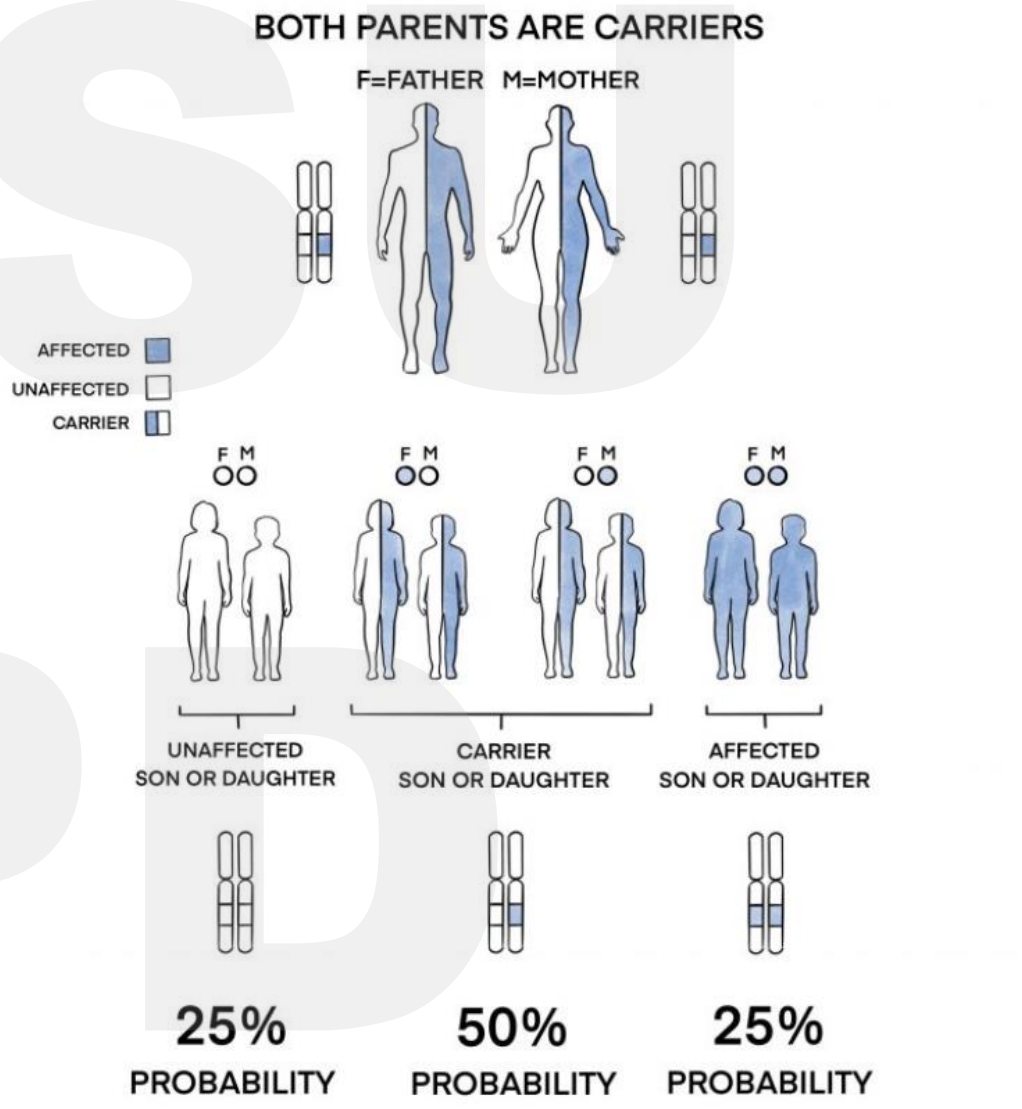


Gene Vision. *Genetic basics and inheritance patterns*. Retrieved from https://gene.vision/knowledge-base/genetic-basics-and-inheritance-pattern/

AUTOSOMAL DOMINANT

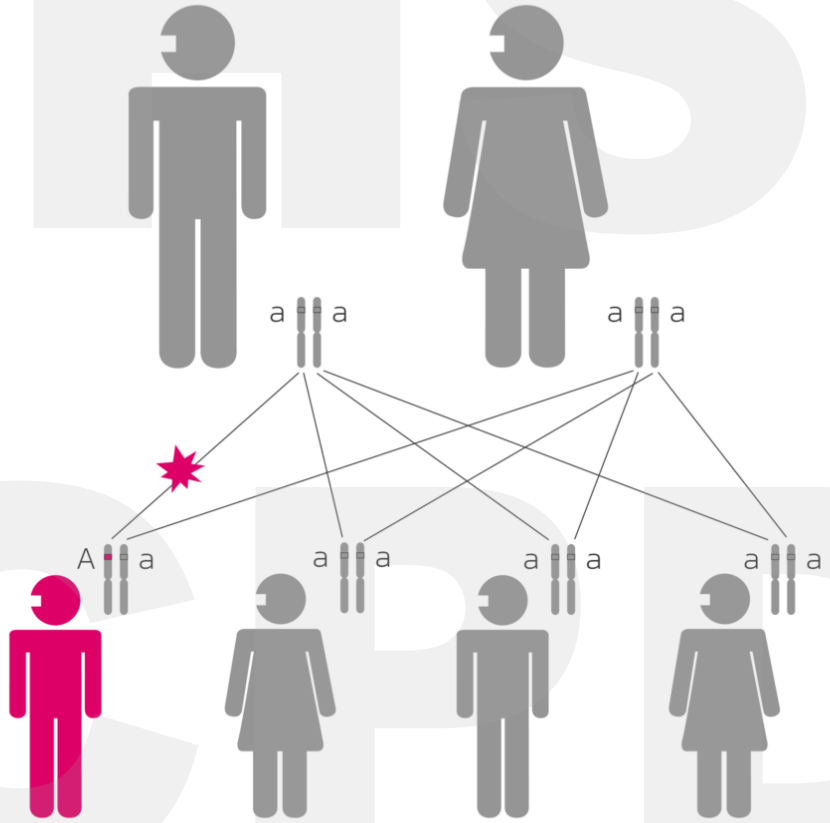


AUTOSOMAL RECESSIVE



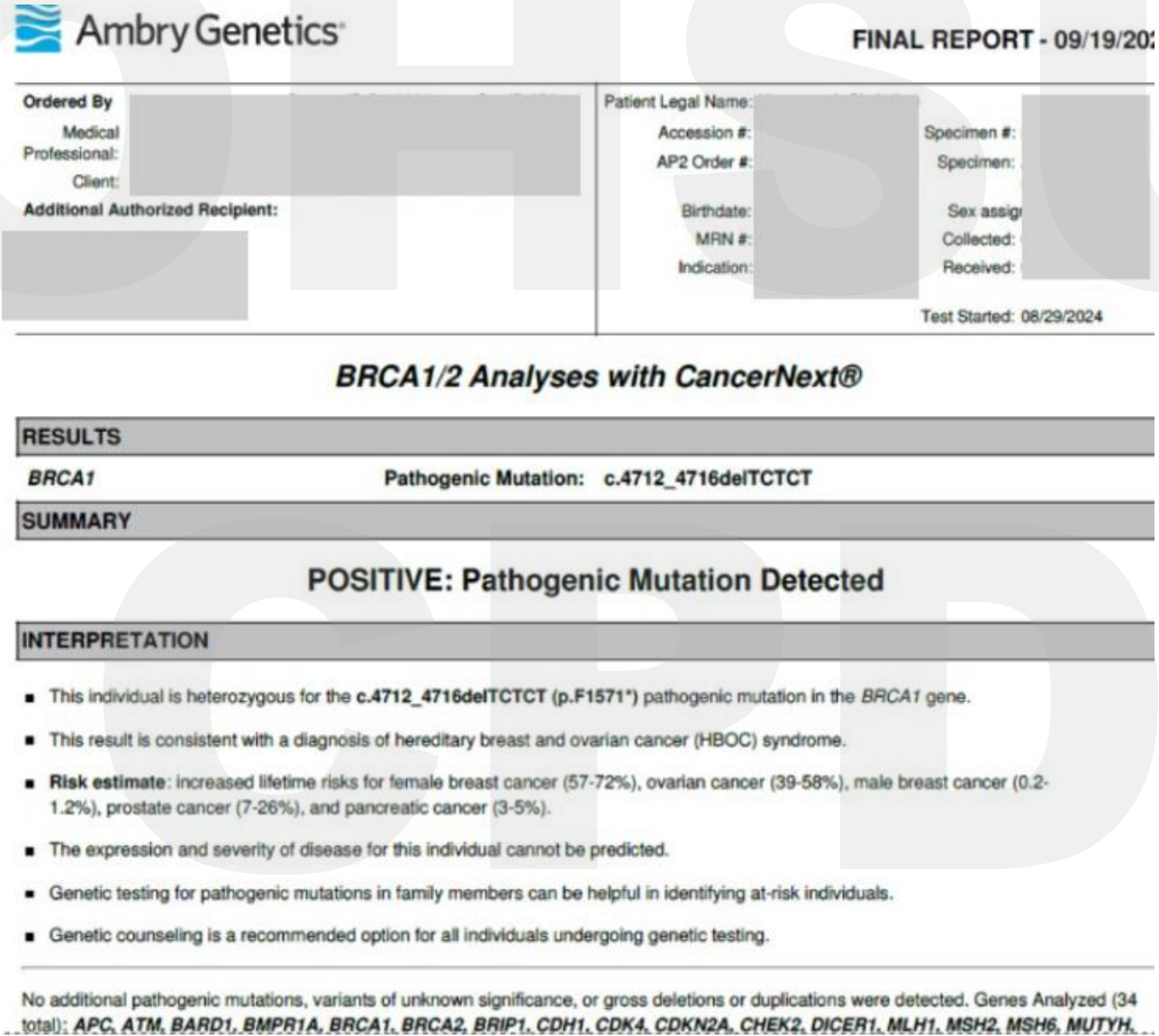
Gene Vision. *Genetic basics and inheritance patterns*.

De novo



Gene Vision. *Genetic basics and inheritance patterns*.

Interpreting genetic test report



Ambry Genetics

FINAL REPORT - 09/19/202

Ordered By	Patient Legal Name:
Medical Professional:	Accession #: / Specimen #:
Client:	AP2 Order #: / Specimen:
Additional Authorized Recipient:	Birthdate: / Sex assig
	MRN #: / Collected:
	Indication: / Received:
	Test Started: 08/29/2024

BRCA1/2 Analyses with CancerNext®

RESULTS

BRCA1 **Pathogenic Mutation: c.4712_4716delTCTCT**

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the **c.4712_4716delTCTCT (p.F1571*)** pathogenic mutation in the *BRCA1* gene.
- This result is consistent with a diagnosis of hereditary breast and ovarian cancer (HBOC) syndrome.
- **Risk estimate**: increased lifetime risks for female breast cancer (57-72%), ovarian cancer (39-58%), male breast cancer (0.2-1.2%), prostate cancer (7-26%), and pancreatic cancer (3-5%).
- The expression and severity of disease for this individual cannot be predicted.
- Genetic testing for pathogenic mutations in family members can be helpful in identifying at-risk individuals.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

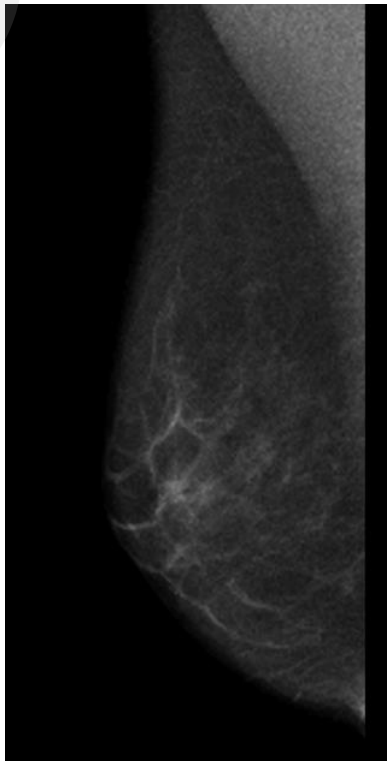
No additional pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected. Genes Analyzed (34 total): ***APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, DICER1, MLH1, MSH2, MSH6, MUTYH,***

How would the presence of a *BRCA* mutation change management for our patient?

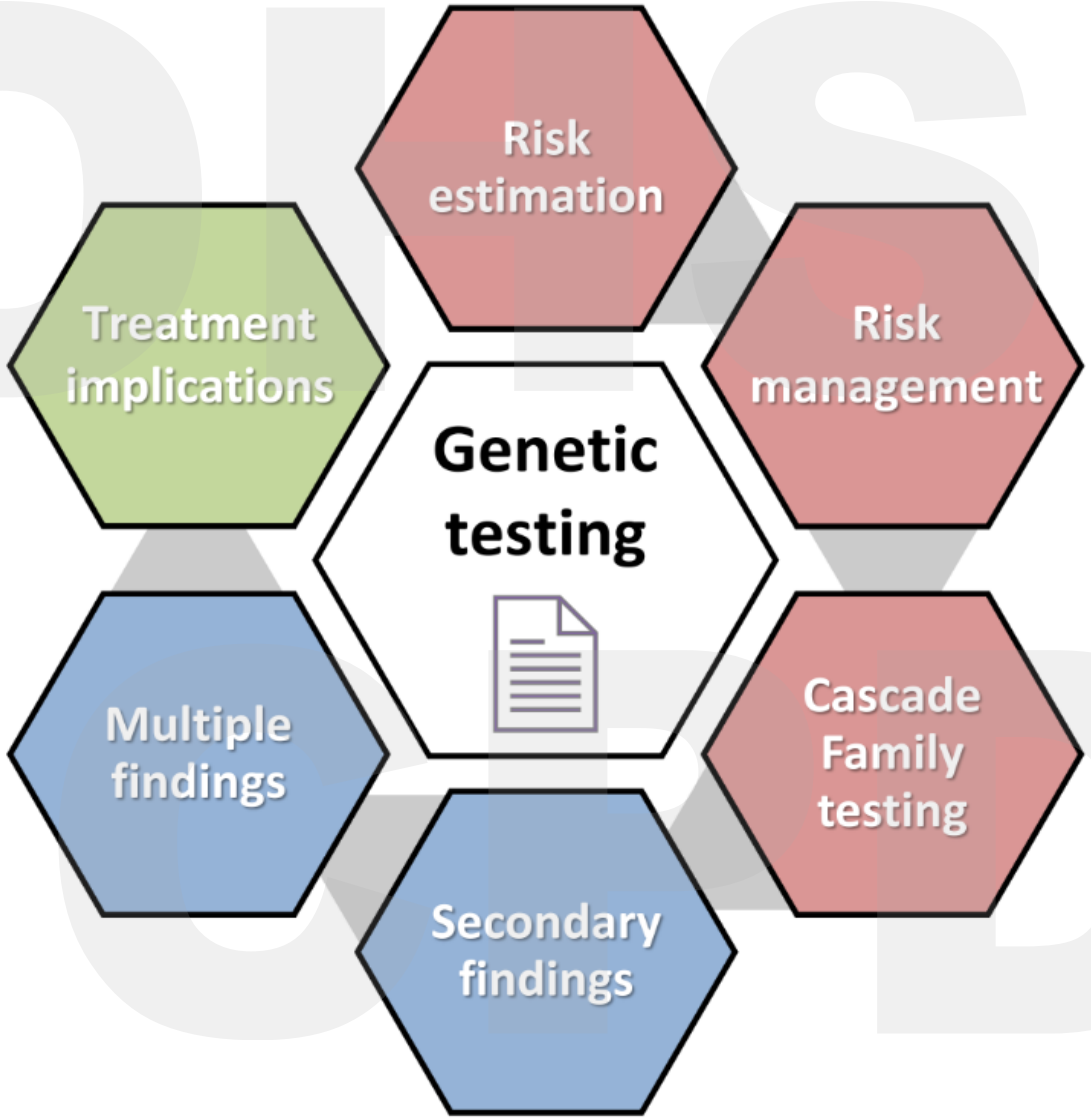
Screening for breast cancer is recommended and begins at an earlier age than recommended for the general population.

Monthly breast exams should be started at age 18 with semiannual clinical breast exams from age 25. **Annual breast MRI should begin at age 25 with annual mammogram from age 30.**

Men with BRCA1/2 variants should also be screened with annual clinical breast exam from age 35 along with monthly self-breast exams. **Prostate cancer screening should begin at age 45.**



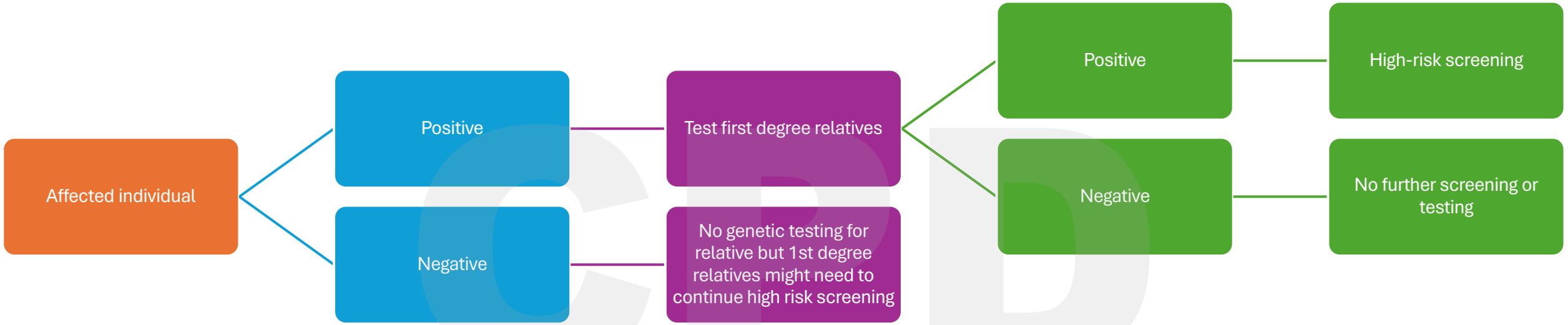
How does genetic testing help?



Tsaousis G.N., et al. *Revisiting the implications of positive germline testing results using multi-gene panels in individuals with personal and/or family history of breast cancer.* Preprint.

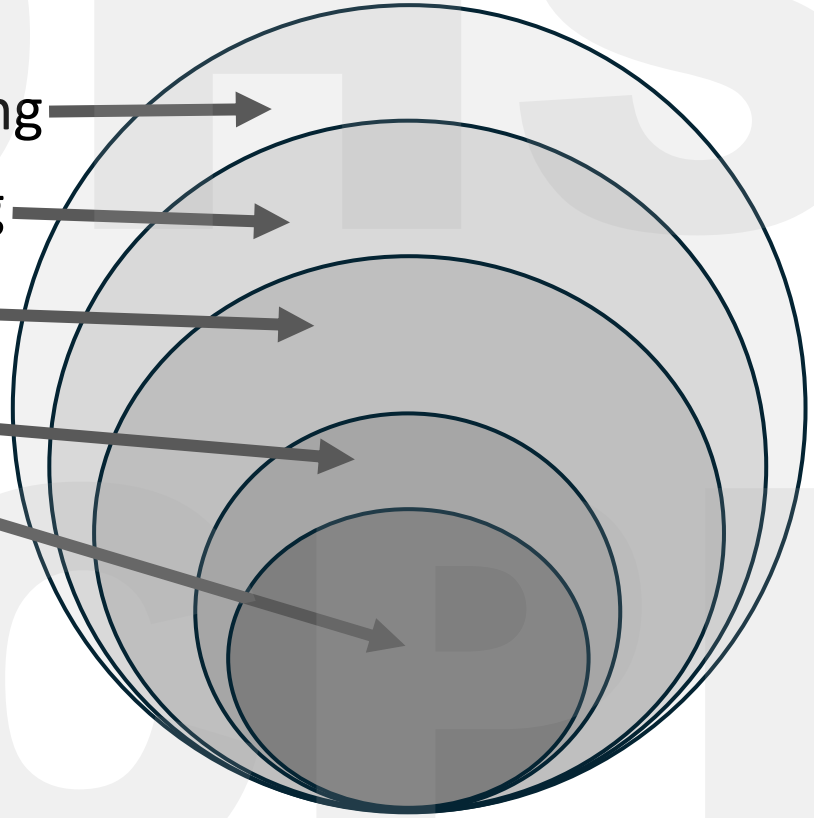
Who should undergo genetic testing first?

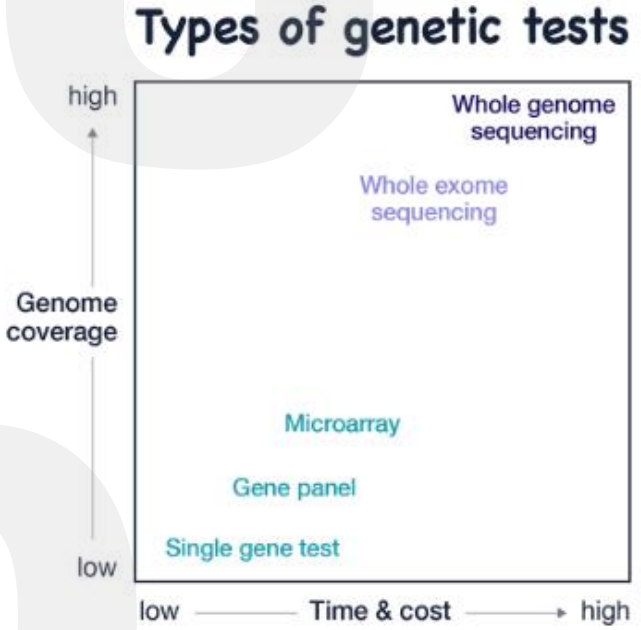
- Always the best person to be tested is the person who is affected by the condition (as opposed to unaffected family members)



Different types of genetic testing

- Whole genome sequencing
- Whole exome sequencing
- Gene panel
- Single gene
- Targeted single variant





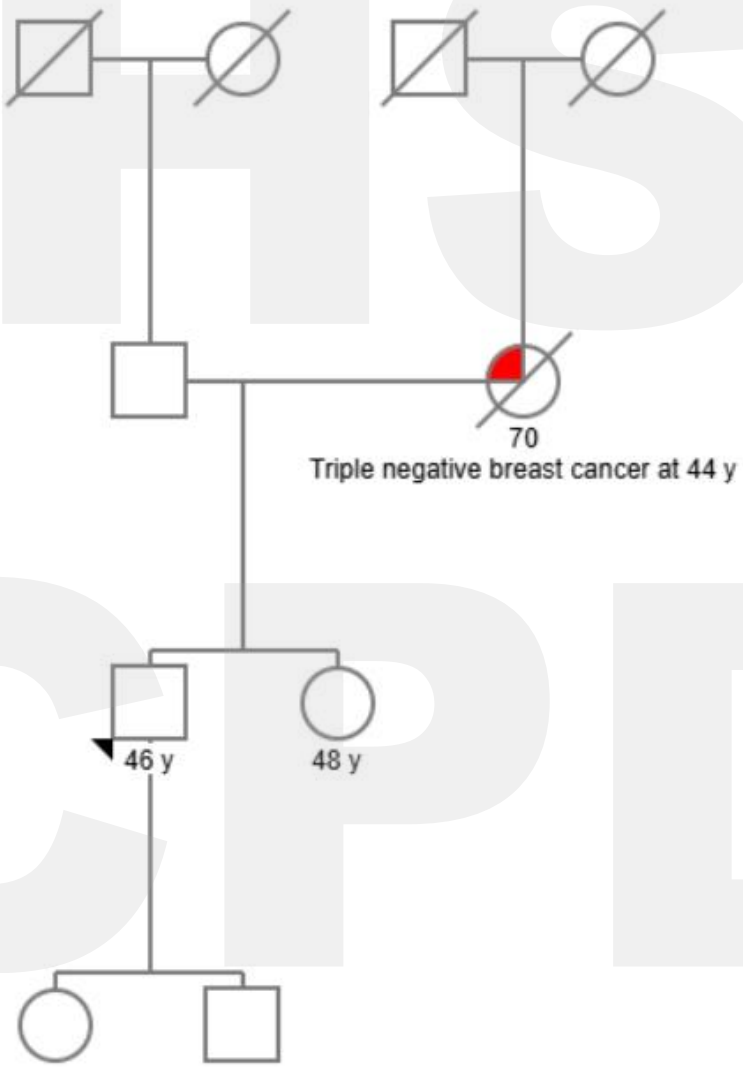
Types of variants reported in genetic test results

- Pathogenic or likely pathogenic (positive/ disease causing)
- Variant of uncertain significance (VUS)
  - **NOT necessarily pathogenic** – majority are ultimately reclassified as benign or likely benign
- Benign or likely benign (negative)
- Positive result may change medical management (eg – increased screening, chemoprevention, risk reducing surgeries)
- Negative and uncertain result – no change in medical management

Question 3

A **46-year-old male** with **no past medical history** presents for an initial visit to establish care. He has a **family history of triple-negative breast cancer (TNBC) in his mother**, who was diagnosed at **44 years of age** and is now deceased. He inquires whether his **sister** should undergo genetic testing due to their mother's history of breast cancer.

Pedigree – Family History

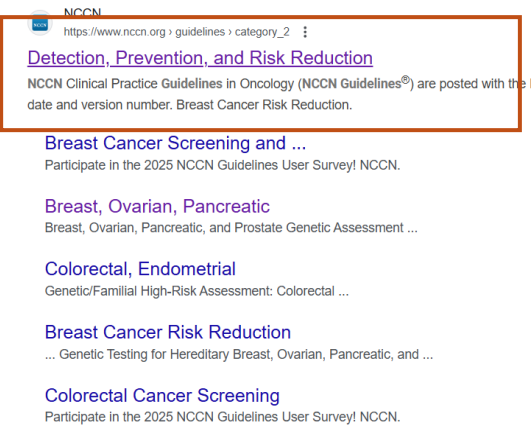


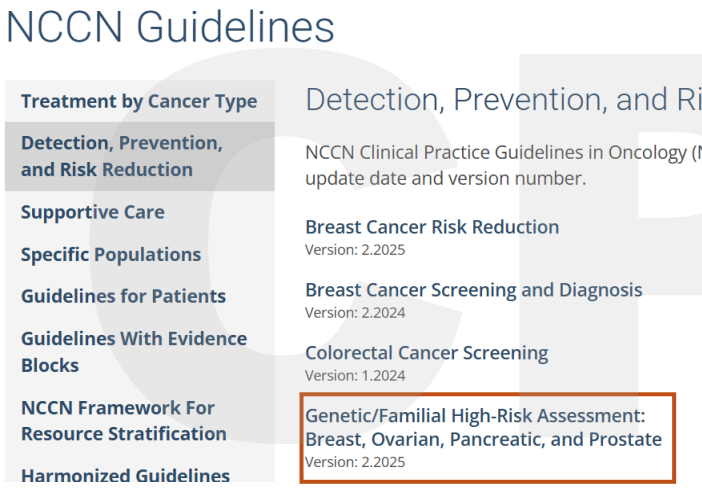
Cancer risk with HBOC syndrome as compared to the general population

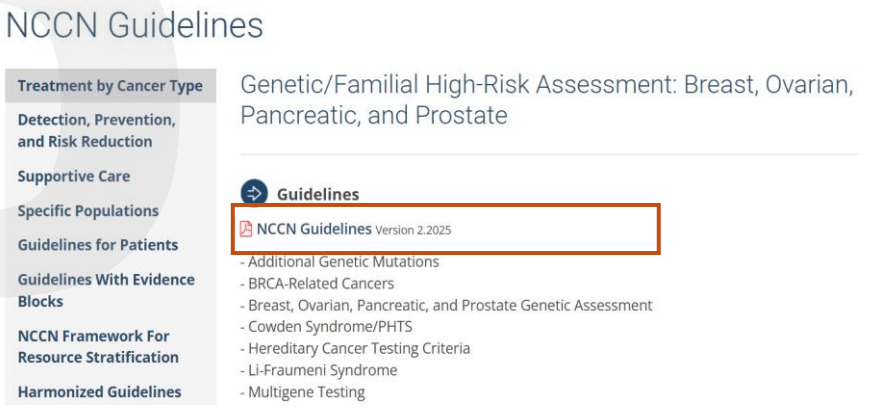
Cancer	General population risk	Risk because of *BRCA1* variants	Risk because of *BRCA2* variants
Female breast	12.3%	46%–87%	38%–84%
Male breast	<1%	1.2%	8.9%
Ovarian	1.6%	39%–63%	16.5%–27%
Pancreatic	0.5%	1%–3%	2%–7%
Prostate	11%	8.6% (by age 65)	15% (by age 65)
Melanoma	1.6%	No increase	Increased

Criteria for genetic evaluation in cancer syndromes

- NCCN guidelines are an excellent resource for recommendations on genetic testing
- https://www.nccn.org/guidelines/category_2







Navigating NCCN guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Hereditary Cancer Testing Criteria

NCCN Guidelines Index
Table of Contents
Discussion

GENERAL TESTING CRITERIA[a]

Testing is clinically indicated in the following scenarios:

- Individuals with any blood relative with a known P/LP variant in a cancer susceptibility gene
- Individuals meeting the criteria below but who tested negative with previous limited testing (eg, single gene and/or absent deletion duplication analysis) and are interested in pursuing multigene testing
- A P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline
- To aid in systemic therapy and surgical decision-making[b]
- Individual who meets Li-Fraumeni syndrome (LFS) testing criteria (CRIT-7) or CS/PHTS testing criteria (CRIT-8) or Lynch syndrome (LS)
  NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric
- For personal or family history of
  - Breast cancer — Testing Criteria for High-Penetrance Breast Cancer Susceptibility Genes (CRIT-2)
  - Ovarian cancer — Testing Criteria for Ovarian Cancer Susceptibility Genes (CRIT-4)
  - Pancreatic cancer — Testing Criteria for Pancreatic Cancer Susceptibility Genes (CRIT-5)
  - Prostate cancer — Testing Criteria for Prostate Cancer Susceptibility Genes (CRIT-6)
  - Colorectal cancer — NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

Testing *may be* considered in the following scenario (with appropriate pre-test education and access to post-test management):

- An individual of Ashkenazi Jewish ancestry[c] without additional risk factors[d]
- Personal history of serous endometrial cancer[e]

For a list of NCCN Guidelines that include content focused on inherited cancer conditions, including criteria for testing and/or cancer risk management based on a genetic test result, see Summary of Genes and/or Syndromes Included/Mentioned in Other NCCN Guidelines (SUMM-1).

Question 4

A 47-year-old female with a history of developmental delay, bipolar disorder, type 2 diabetes mellitus (diagnosed in her 20s), renal agenesis (single kidney), and dyslipidemia presents for a follow-up visit with her primary care physician. During the visit, the patient's mother expresses concern about the possibility of Prader-Willi syndrome (PWS) and requests an evaluation for the condition.

Genetic testing in intellectual disability

- **Exome sequencing/ genome sequencing is considered as a first- or second-tier test for patients with congenital anomalies/ developmental delay/ intellectual disability**

Genetics inMedicine

www.nature.com/gim

Check for updates

ACMG PRACTICE GUIDELINE

Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG)

Kandamurugu Manickam[1,2], Monica R. McClain[3], Laurie A. Demmer[4], Sawona Biswas[5], Hutton M. Kearney[6], Jennifer Malinowski[7], Lauren J. Massingham[8,9], Danny Miller[10], Timothy W. Yu[11,12], Fuki M. Hisama[13] and ACMG Board of Directors[14]*

Cardiovascular disorders

Left ventricular hypertrophy – wall thickness > 15 mm (not explained by secondary causes)	LDL-C > 190 mg/dl in adults and > 160 mg/dl in children
• Diagnostic of **hypertrophic cardiomyopathy (AD)** • Prevalence -1 /500 (50%-60% has mutations) • Genetic testing indicated	• Consider **familial hypercholesterolemia (AD)** • Early CAD, PE findings (xanthoma or corneal arcus) • Prevalence 1/250 to 1/500

Renal disorders

Multiple bilateral renal cyst

- ADPKD ultrasound diagnostic criteria:
  - 15-39 y: at least 3 unilateral or bilateral cysts
  - 40-59 y: 2 cysts in each kidney
  - ≥ 60 y: 4 cysts in each kidney
- Rx goal – preventing progression of renal disease
- Monitoring of ICA in those with FHx

Early or bilateral renal cell carcinoma

- Think of Von-Hippel Lindau (AD)
- Other features - Hemangioblastomas, pheochromocytomas, pancreatic cysts, neuroendocrine tumors, or retinal angiomas
- Familial screening indicated

Gastrointestinal disorders

Recurrent Pancreatitis (2-3% hereditary)

- **Hereditary pancreatitis** - pancreatitis at young age, multiple episodes without clear trigger (AD and rarely AR)
- FHx of pancreatitis in 2 first-degree relatives or multiple second-degree relatives

Elevated ferritin or transferrin saturation > 45%

- **Hemochromatosis**
- Other features -hepatomegaly, cirrhosis, diabetes mellitus, cardiomyopathy

Neurological disorders

Peripheral Neuropathy

- **Charcot-Marie-Tooth** (typical onset in adolescent or childhood and slowly progressive)
- **Fabry disease** (periodic episode of burning pain)

Dementia

- Onset before 60 y of age – think of **early onset AD, frontotemporal dementia**
- **CADASIL** – dementia with early onset TIA

Connective tissue disorders

Connective tissue disorders associated with vascular anomalies -

- Marfan syndrome
- Ehlers Danlos syndrome
- Loeys- Dietz syndrome

Patient with aortic root dilatation

- If aortic root dilatation or dissection present in a patient, then consider asking FHx or look for any other associated symptoms or features of Marfan syndrome

- Marfan syndrome diagnostic criteria

Without FH

1. Ao ($Z \geq 2$) AND EL = MFS
2. Ao ($Z \geq 2$) AND FBN1 = MFS1
3. Ao ($Z \geq 2$) AND systemic score (≥7pts) = MFS[a]
4. EL AND FBN1 with known Ao = MFS

Ao, aortic root dilatation or dissection.
EL, ectopia lentis.
FH, family history.

In the presence of FH

5. EL AND FH of MFS (as defined above) = MFS
6. Systemic score (≥7 pts) AND FH of MFS = MFS
7. Ao ($Z \geq 2$ in adults ≥ 3 in children) + FH of MFS = MFS

Systemic score

Feature	Value
Wrist AND thumb sign	3
Wrist OR thumb sign	1
Pectus carinatum deformity	2
Pectus excavatum or chest asymmetry	1
Hindfoot deformity	2
Plain flat foot (pes planus)	1
Pneumothorax	2
Dural ectasia	2
Protrusio acetabulae	2
Reduced upper segment/lower segment AND increased arm span/height ratios	1
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
3/5 facial features	1
Skin striae	1
Myopia	1
Mitral valve prolapse	1
(positive ≥7)	Total

Patient with aortic dissections and aneurysms

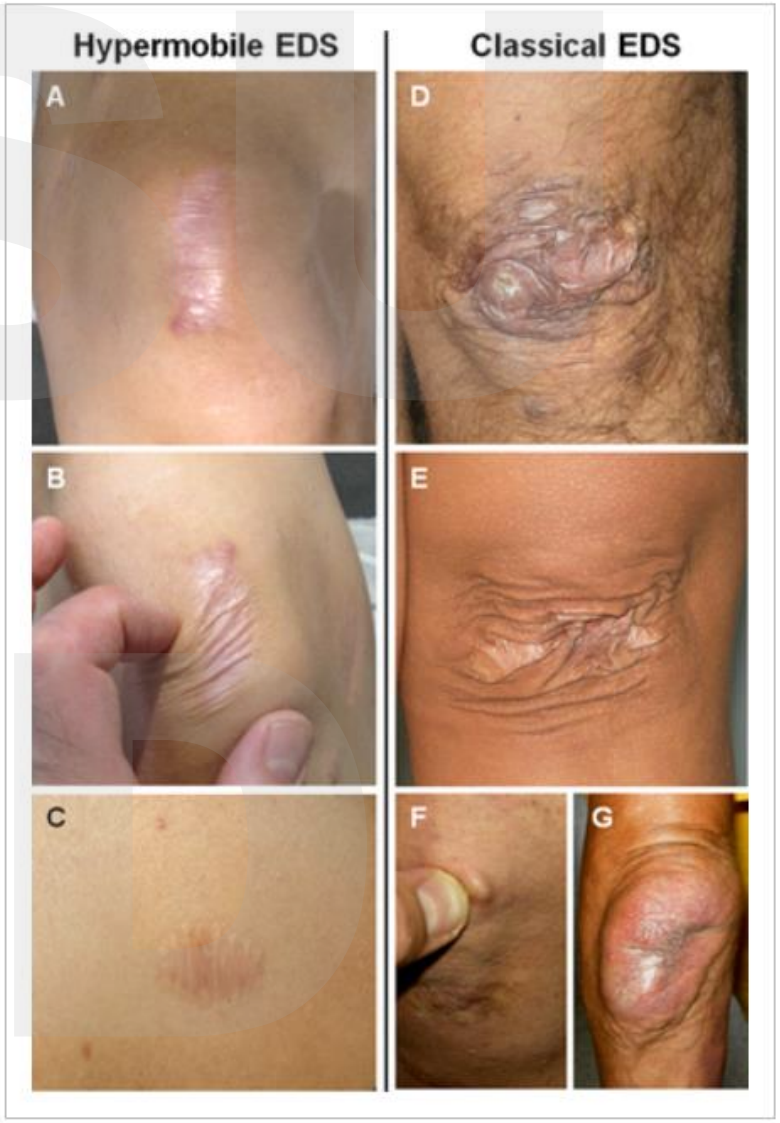
- If secondary cause ruled out, consider genetic evaluation
- **Patients with Loeys-Dietz syndrome (LDS) are prone to aortic dissections and aneurysms in various locations**
- Other features of LDS – hypertelorism, cleft palate, bifid uvula (but not all patients will have it)
- Dr. Sherene Shalhub at OHSU focuses on treating patients with genetically triggered aortopathies and arteriopathies such as Marfan, Loeys Dietz, and Vascular Ehlers-Danlos syndromes

Ehlers-Danlos syndrome (EDS)

- Different types based on the genes involved and clinical features
- **Hypermobile EDS does not have a genetic basis** while vascular (vEDS) and classic EDS with similar features to hypermobile has genetic basis and hence will need genetic evaluation
- vEDS - **widespread arterial fragility, often accompanied by thin, translucent skin and easy bruising**.
- Patients with features of chronic pain and features of hypermobility are not typically evaluated by genetics

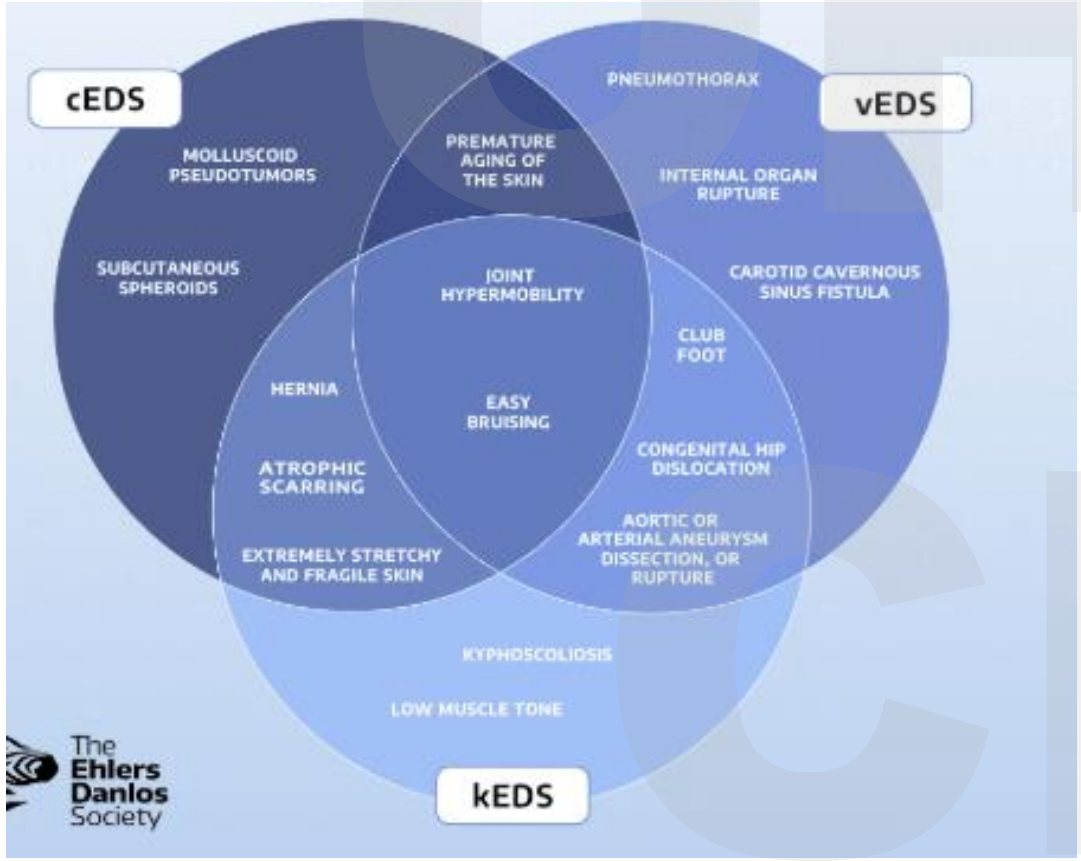
EDS subtypes

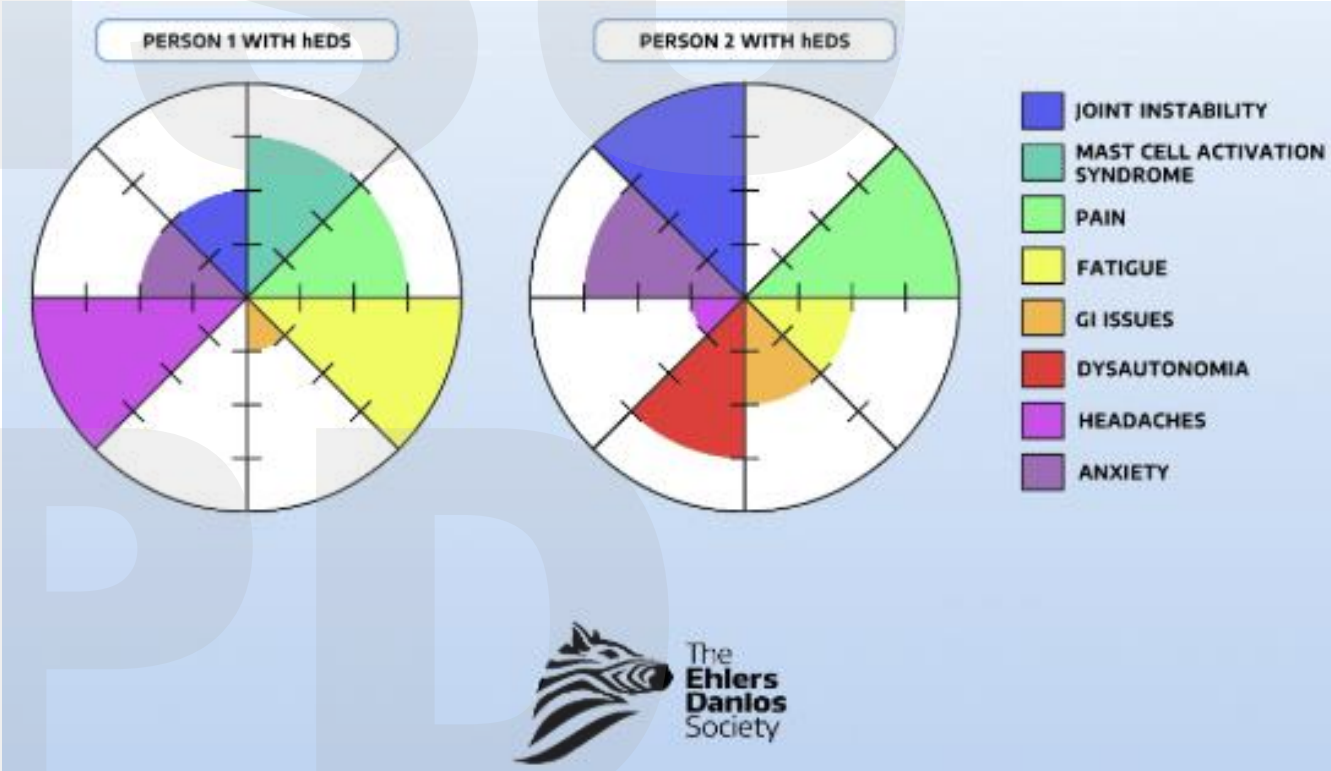
Type of EDS (In order of estimated prevalence)	Approximate Prevalence	Associated Gene(s)	Affected Protein(s)
Hypermobile EDS (hEDS)	1 in 3,100 – 5,000	Unknown	Unknown
Classical EDS (cEDS)	1 in 20,000 – 40,000	*COL5A1*	Type V collagen
		COL5A2	Type V collagen
		COL1A1	Type I collagen
Vascular EDS (vEDS)	1 in 100,000 – 200,000	*COL3A1*	Type III collagen
		COL1A1	Type I collagen
Periodontal EDS (pEDS)	Less than 1 in 1,000,000	*C1R*	C1r
		C1S	C1s
Kyphoscoliotic EDS (kEDS)	Less than 1 in 1,000,000	*PLOD1*	LH1
		FKBP14	FKBP22



Ehlers-Danlos Society. *What is EDS?* https://www.ehlers-danlos.com/what-is-eds/; Malfait F. et al. (2017). *The 2017 international classification of the Ehlers–Danlos syndromes.* Am J Med Genet C.

EDS spectrum





Ehlers-Danlos Society. (n.d.). *What is EDS?* https://www.ehlers-danlos.com/what-is-eds/

Should non-geneticist order genetic testing?

Not typically expected, but for those interested, here are key considerations before proceeding:

- Do I have the time to conduct a comprehensive genetic evaluation, including:
  - Gathering a detailed family history
  - Obtaining medical records of key family members
- Do I possess the knowledge and confidence to accurately interpret genetic test results?
- Am I prepared to provide thorough pre- and post-test counseling?
- Am I aware of insurance coverage policies and variations among testing laboratories?
- Genetic testing ordered by a geneticist is more likely to be covered by insurance.

Labs offering genetic testing

- Examples of laboratories offering genetic testing: Invitae, Prevention Genetics, Ambry, GeneDx.
- Genetic testing costs are typically covered by insurance.
- Some laboratories verify insurance coverage and out-of-pocket costs before initiating testing.
- Discounted rates may be available for family member testing.
- Self-payment is also an option.

Direct to consumer (DTC) testing

- Marketed directly to consumers without the involvement of a health care provider
- Different companies offer different tests (23 and me, ancestry, sequencing.com, dante labs)
- Interpretation of results may vary across companies.
- FDA has granted marketing authorization to limited number of these tests
- Clinical genetics at OHSU typically does not see patients for DTC test results

Resource to share with patients about DTC testing - https://medlineplus.gov/genetics/understanding/dtcgenetictesting/directtoconsumer/

Considerations for medical genetics referrals

When referring to medical genetics, specify the affected family member, underlying condition, and their genetic testing status.

Referrals for pregnancy planning and preconception counseling should be directed to the prenatal genetics team.

Urgent referrals may be placed if genetic test results are needed for surgical decision-making (include the indication for urgency).

Genetic Information Non-discrimination Act

The Genetic Information Nondiscrimination Act (GINA) of 2008 is a federal law that prevents discrimination based on genetic information in employment and health coverage

Resources

- **NCCN guidelines**

- **GeneReviews** - peer-reviewed articles about genetic diagnoses with a focus on diagnosis and management

- **Genetic and Rare Diseases Information Center** (GARD) - Patient-friendly information about rare or genetic diseases in English and Spanish

Summary of indications to consider genetic evaluation

Family history of disease

Multiple affected family members

- 2 affected first-degree relatives

Early onset of disease

- Dementia (<60 yo)
- T2DM (< 40 yo)
- Stroke (< 50 yo)
- CAD (males < 55 yo and females ,65 yo)

Hereditary cancer syndrome

- Early onset (<50 y in breast, ovarian, endometrial, prostate and colon)
- Breast cancer in a male
- Bilateral cancers (in paired organs)
- Multiple or multifocal tumor in same organ
- Synchronous/ metachronous tumors
- Constellation of cancers in same patient or multiple members of same family

Sudden cardiac death in healthy individual

Summary and key points

Family history is important

Affected individual should be the first to undergo genetic testing

Variant of uncertain significance (VUS) does not indicate a positive test result (VUS ≠ pathogenic or likely pathogenic variant)

Consider genetic evaluation for unusual presentation without a secondary cause

References and acknowledgement

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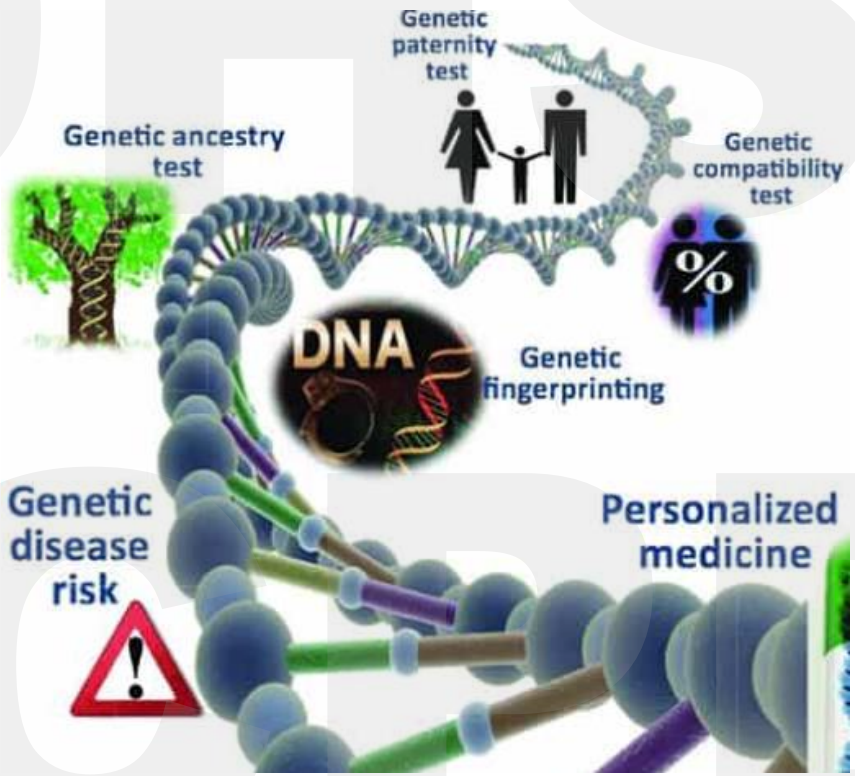
- Hisama, F. (2017, June 6). *Medical Genetics in the Age of Genomics and Precision Medicine.* https://www.youtube.com/watch?v=xEJyPRvGz-E

- Mary Pat Bland, MS., CGC. Genetic Counselor. OHSU

Questions?



https://stemcellthailand.org/genetics/dna-testing/