# *Genetics for the Endocrinologist*

## *A Clinical Approach to the Application of Genetic Testing in Endocrine Conditions*

*A CSEM Knowledge Transfer Activity*

*Thursday, April 25, 2024*

*7:00 pm ET*

# Faculty

Dr. Jane Green
Memorial University, St. John's, NL
Speaker

Dr. Ari Morgenthau
University of Toronto, Toronto, ON
Speaker

Dr. Sandra Cooke-Hubley
Memorial University, St. John's, NL
Moderator

Dr. Liz Rosolowsky
University of Alberta, Edmonton
CSEM CPD Chair

# Sponsors

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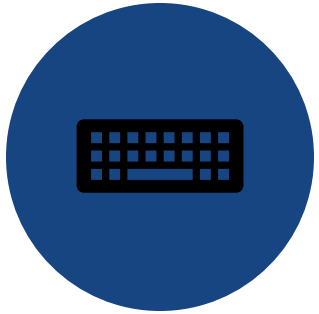
# Interaction

- Pre & post tests via Slido – be sure to sign in for your Section 3 credits
- Use the Q&A in Slido to ask questions during presentations
- Live discussion at 8:30 in Zoom room. Click the **JOIN ZOOM MEETING button** under your video player.

Scan, login to to Slido

# Section 3 Self-Assessment Credits



SIGN IN TO SLIDO

PRE-TEST

POST-TEST

REVIEW AND REFLECT

# Pre-test Questions

- Ensure you are signed in to Slido: Name, Email
- Slido.com with code: **#3559013**

Scan, login to to Slido

# Agenda

7:00 pm Welcome and Introductions – Sandra Cooke-Hubley

7:05 pm Pre-test Questions 1-2 MEN

7:10 pm Multiple Endocrine Neoplasia, Type1 (Burin): Lessons for Newfoundland and Elsewhere - Jane Green

7:25 pm Post-test Questions 1-2 & Discussion

7:35 pm Pre-test Questions 3 Genetics

7:40 pm Introduction to Genetics Part 1 – Ari Morgenthau

8:00 pm Pre-test Questions 4-5

8:05 pm Introduction to Genetics Part 2 – Ari Morgenthau

8:25 pm Post-test Question 3-5

8:30 pm Live Panel Discussion and Q&A (Join Zoom room)

8:55 pm Take-away messages and Wrap Up

# CONFLICT OF INTEREST DECLARATION – Sandra Cooke-Hubley

I **DO NOT** have a relationship with for-profit/not-for-profit organizations to disclose.

| Nature of relationship(s) | Name of for-profit or not-for-profit organization(s) | Description of relationship(s) |
|---|---|---|
| Any direct financial payments including receipt of honoraria | | |
| Membership on advisory boards or speakers' bureaus | | |
| Funded grants or clinical trials | | |
| Patents on a drug, product or device | | |
| All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity | | |

# Learning Objectives

At the end of this session, participants will be able to:

- Develop a clinical approach to detecting familial conditions in endocrine patients, such as MEN1.
- Develop an approach to reviewing and applying genetic test results, using MEN syndromes as an example.
- Determine how to investigate variances of unknown significance and best practices in following patients.

# Multiple Endocrine Neoplasia, Type1 (Burin): Lessons for Newfoundland and Elsewhere

Jane Green, OC, NOL, PhD, FCCMG (Honorary)

Develop an approach to reviewing and applying genetic test results, using MEN syndromes as an example

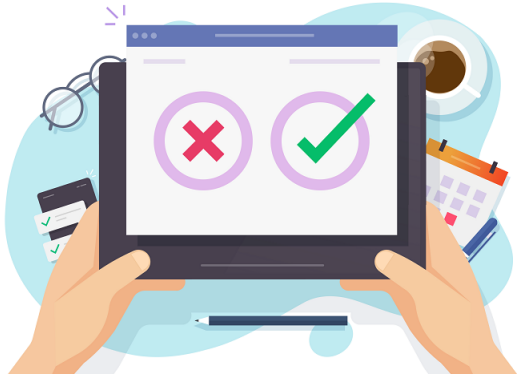
# Post-test Question #1 - Answer

**When do you suspect a hereditary condition?**

a) patient has a specific surname

**b) early age at onset**

c) person comes from a certain community



REFERENCE

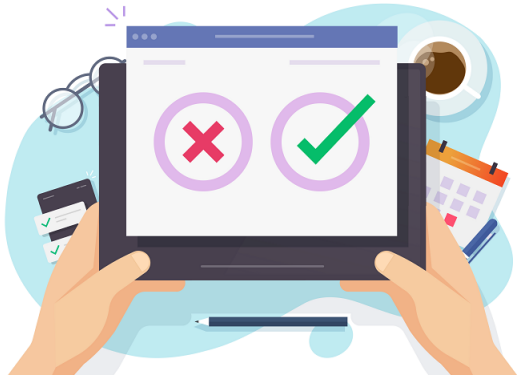
# Post-test Question #2 - Answer

**Does every patient with MEN1 have multiple manifestations?**

a) Every genetic condition has multiple manifestations

**b) Some MEN1 patients have multiple manifestations**

c) MEN1 patients have only one manifestation



REFERENCE

# An endocrinologist focused approach to genetic testing reports

Dr. Ari Morgenthau

Pre-Test Question #3

# Dr. Ari Morgenthau Presentation Title

An endocrinologist focused approach to genetic testing reports

# CONFLICT OF INTEREST DECLARATION – Ari Morgenthau

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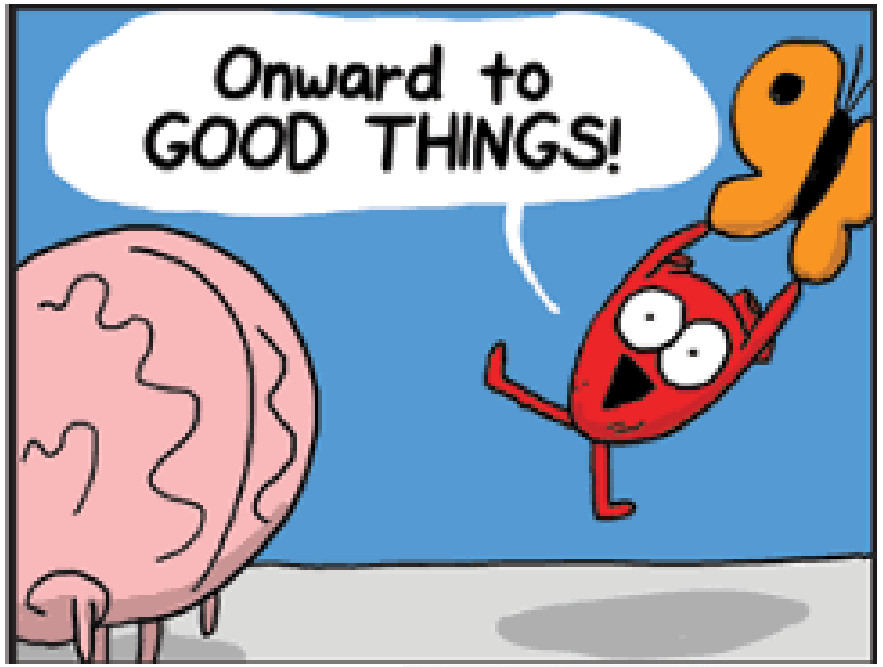
# Objectives

- By the end of todays talk you will be able to:
  - Understand the types of genetic test results that can be obtained
  - Develop an approach to reviewing genetic test results
  - Improve understanding and comfort with variants of uncertain significance

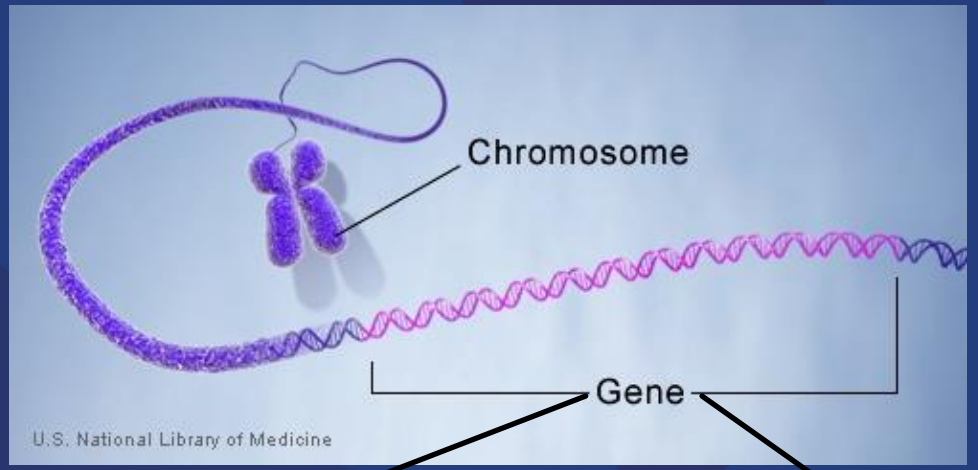
# Outline

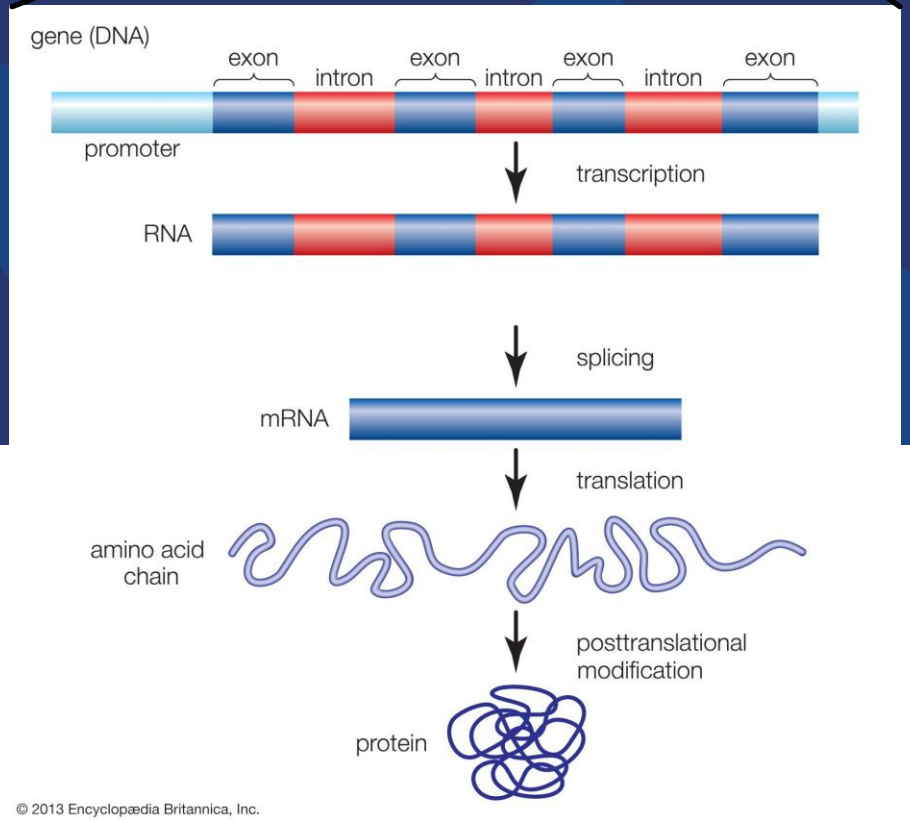
- Brief introduction to genetics
- The Case: a 28 year old with a prolactinoma and hyperparathyroidism
  - Version 1: An approach to positive results
  - Version 2: An approach to negative results
  - Version 3: An approach to variants of uncertain significance  (VUS)

# Introduction to Genetics



# Our genetic information is made up of approximately 22,000 genes on 23 paired chromosomes



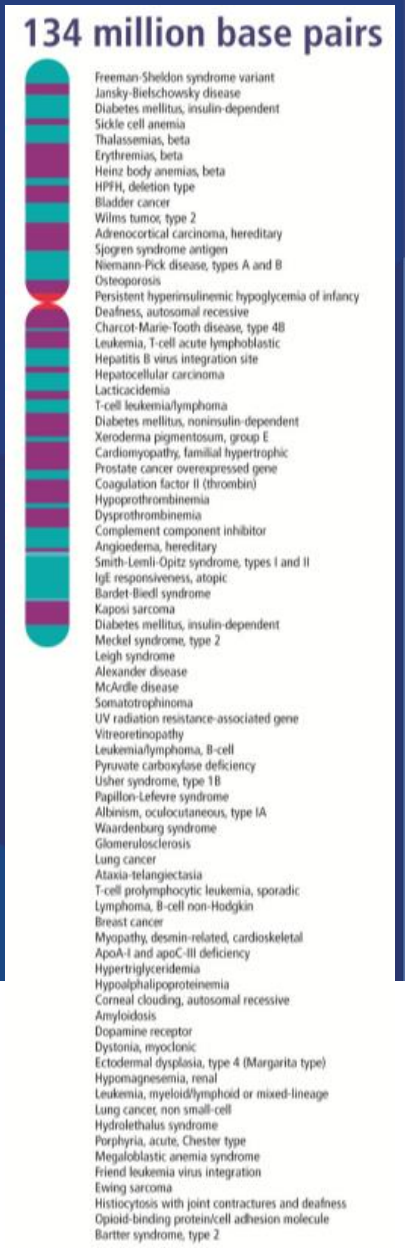




Image of Ch 11 from Wikipedia

# Main clinically available gene-based tests

- Single gene sequencing
- Multiple gene sequencing (panels)

Looking at all of one gene or the exons of specific genes

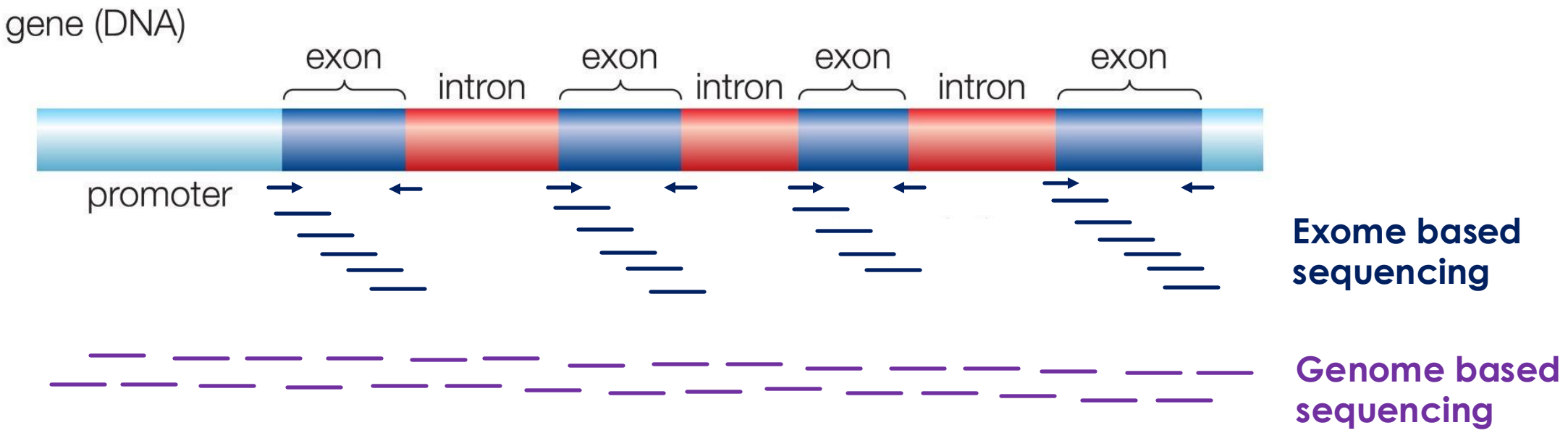
- Deletion/Duplication testing (MLPA)

Looking to see if there are multiple exons (within an individual gene that is missing or added)

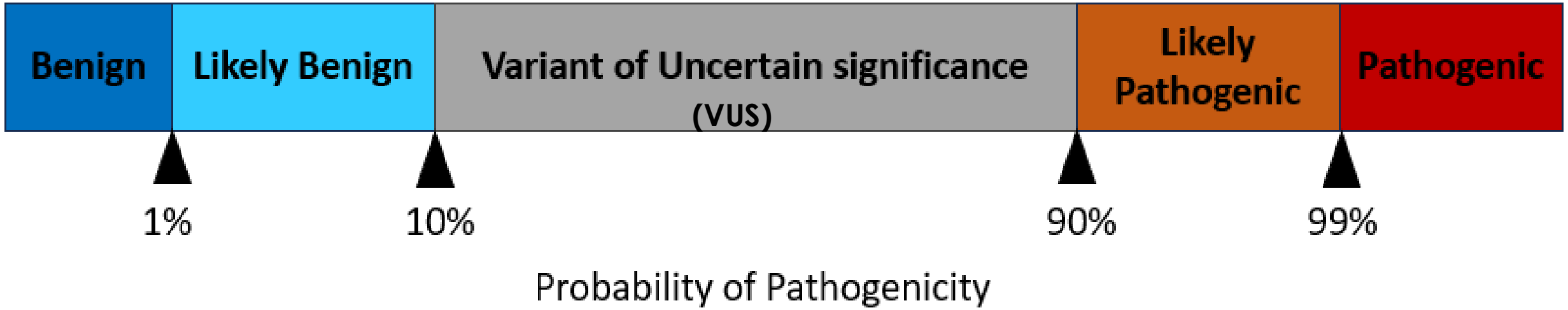
- Whole exome sequencing (WES)

Looking at all exons of all clinically relevant genes - Limited access in Ontario

# The majority of commercial panels use exome based sequencing



# Genetic test results are reported on a spectrum



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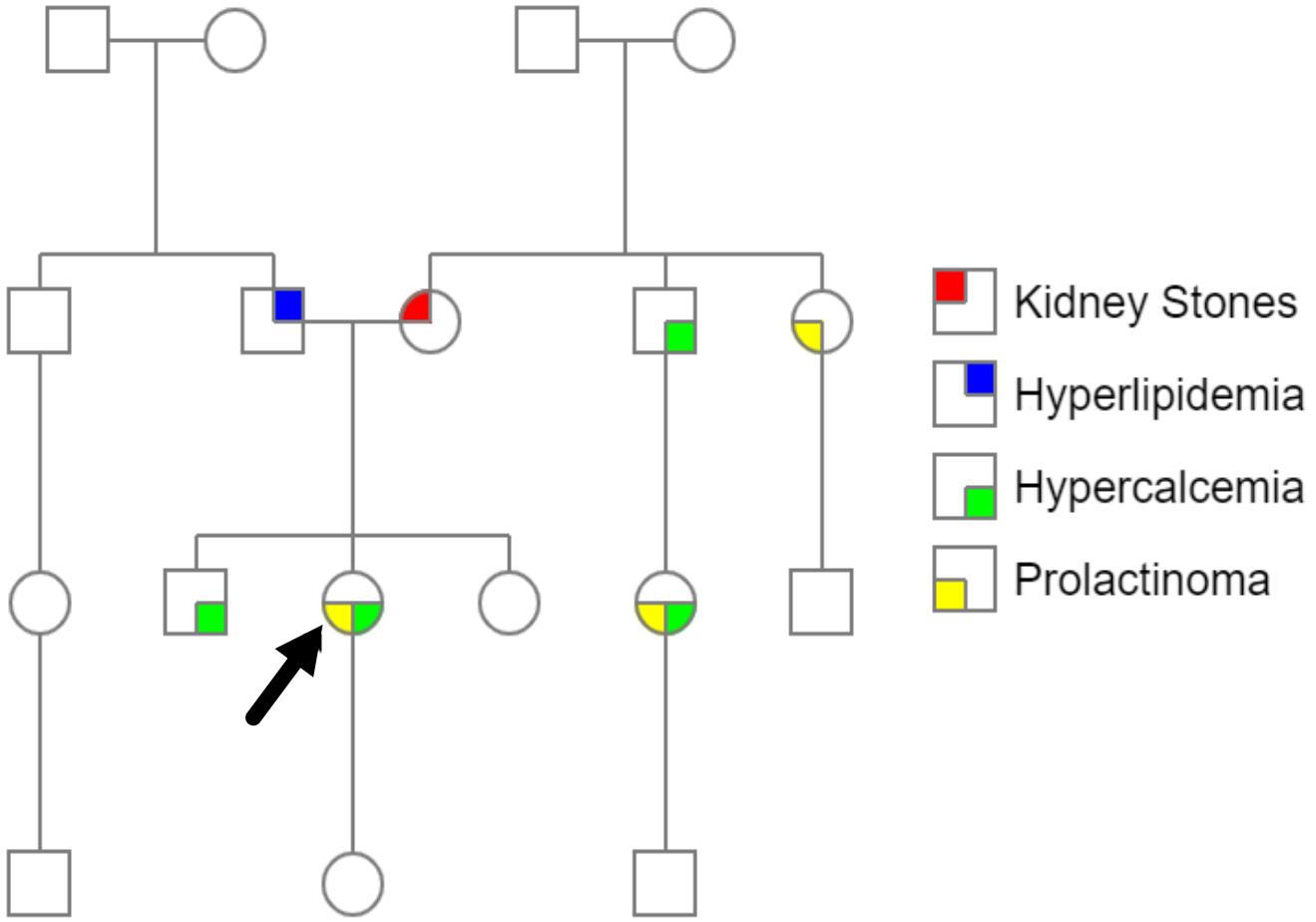
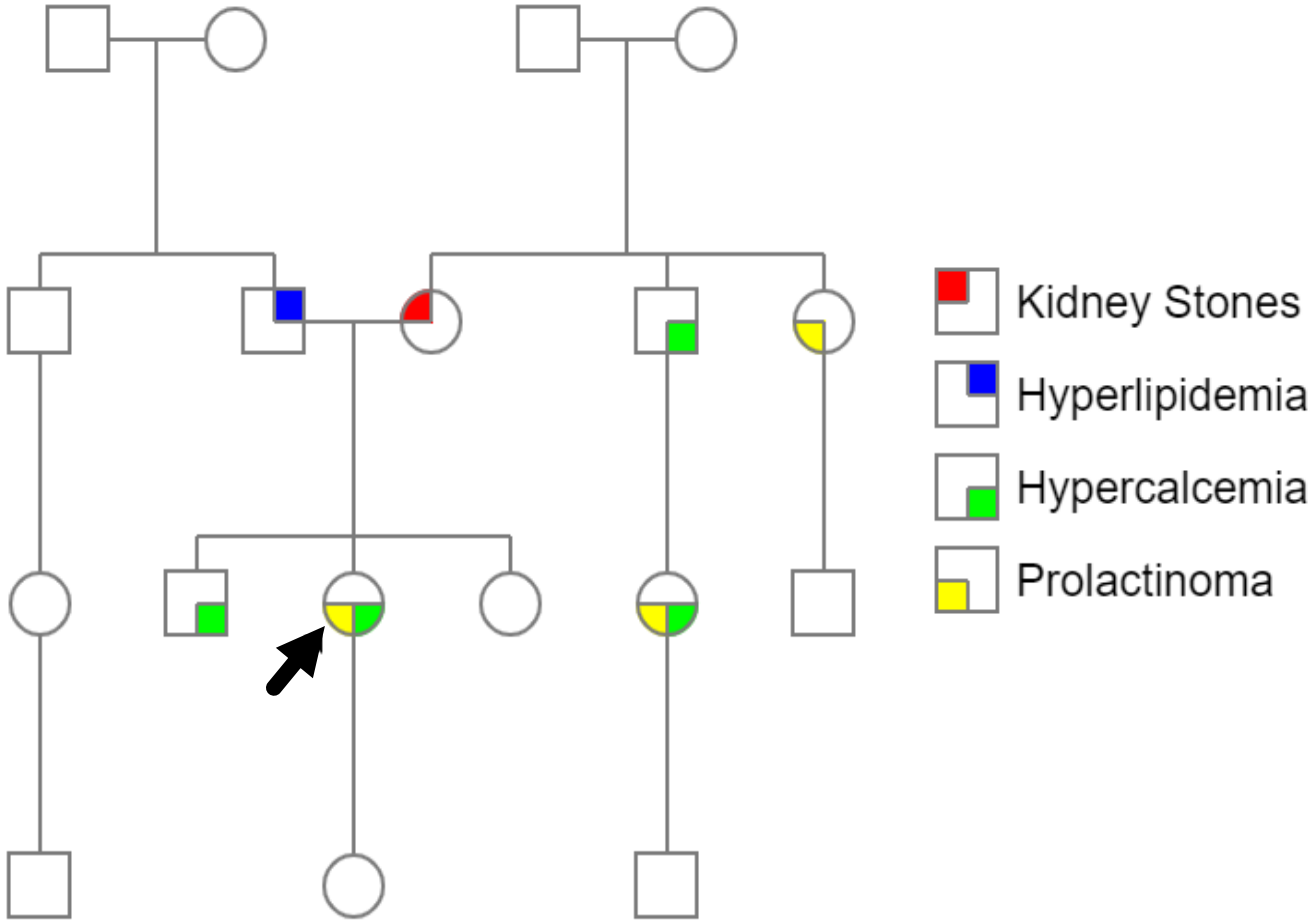
# 28 year old mother referred with hyperparathyroidism and a prolactinoma

- Referred with elevated:
  - Calcium, PTH and Prolactin
  - No Galactorrhea or vision changes
  - LMP 3 weeks ago
- Past Medical History:
  - 0.9cm Prolactinoma treated with cabergoline x1.5 years
  - PCOS
  - Kidney stones

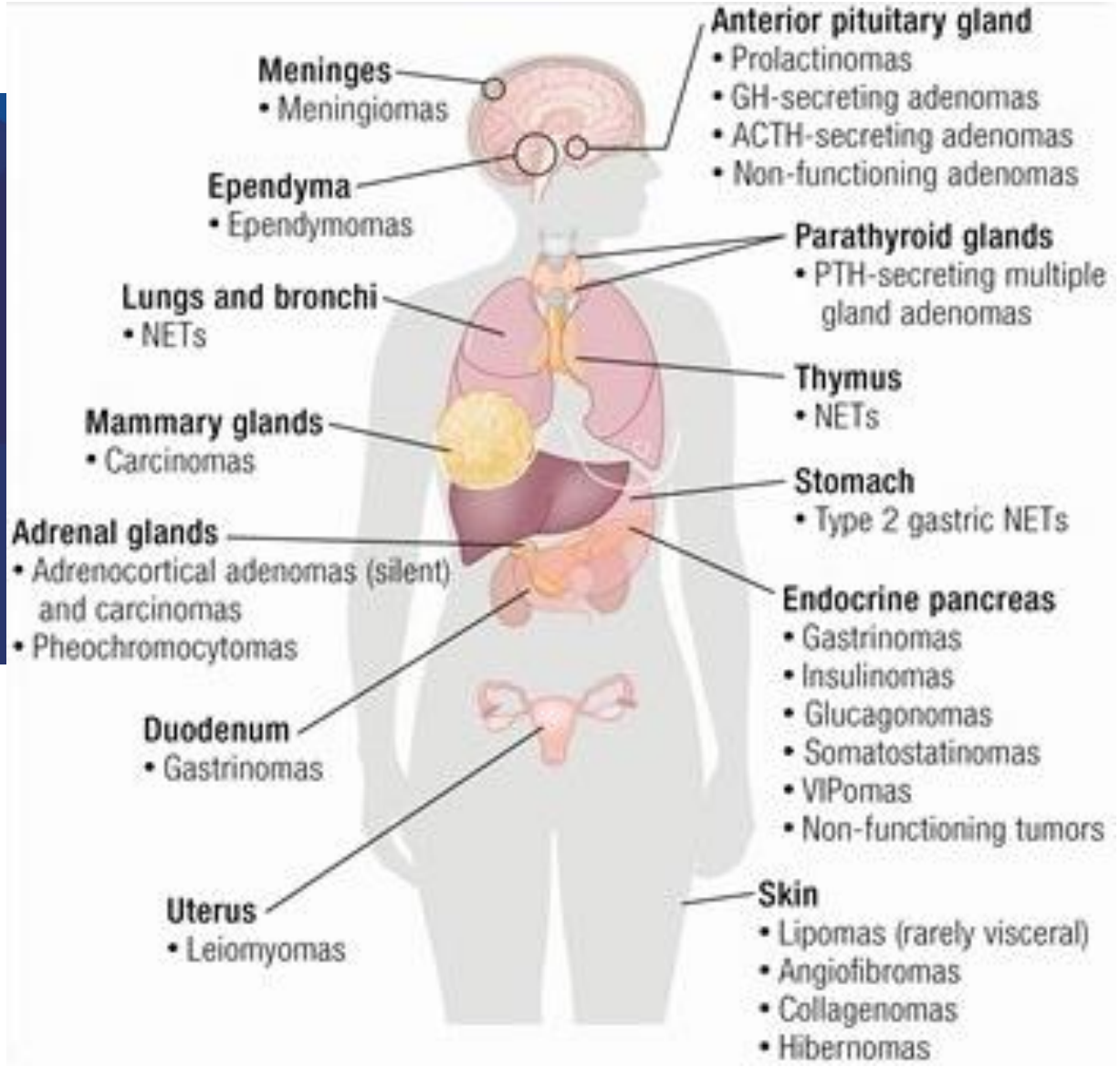


# Would you clinically diagnosis the patient with MEN1?

- Yes
- No
- Unsure



# MEN1 is diagnosed clinically in someone two or more MEN1 associated tumors



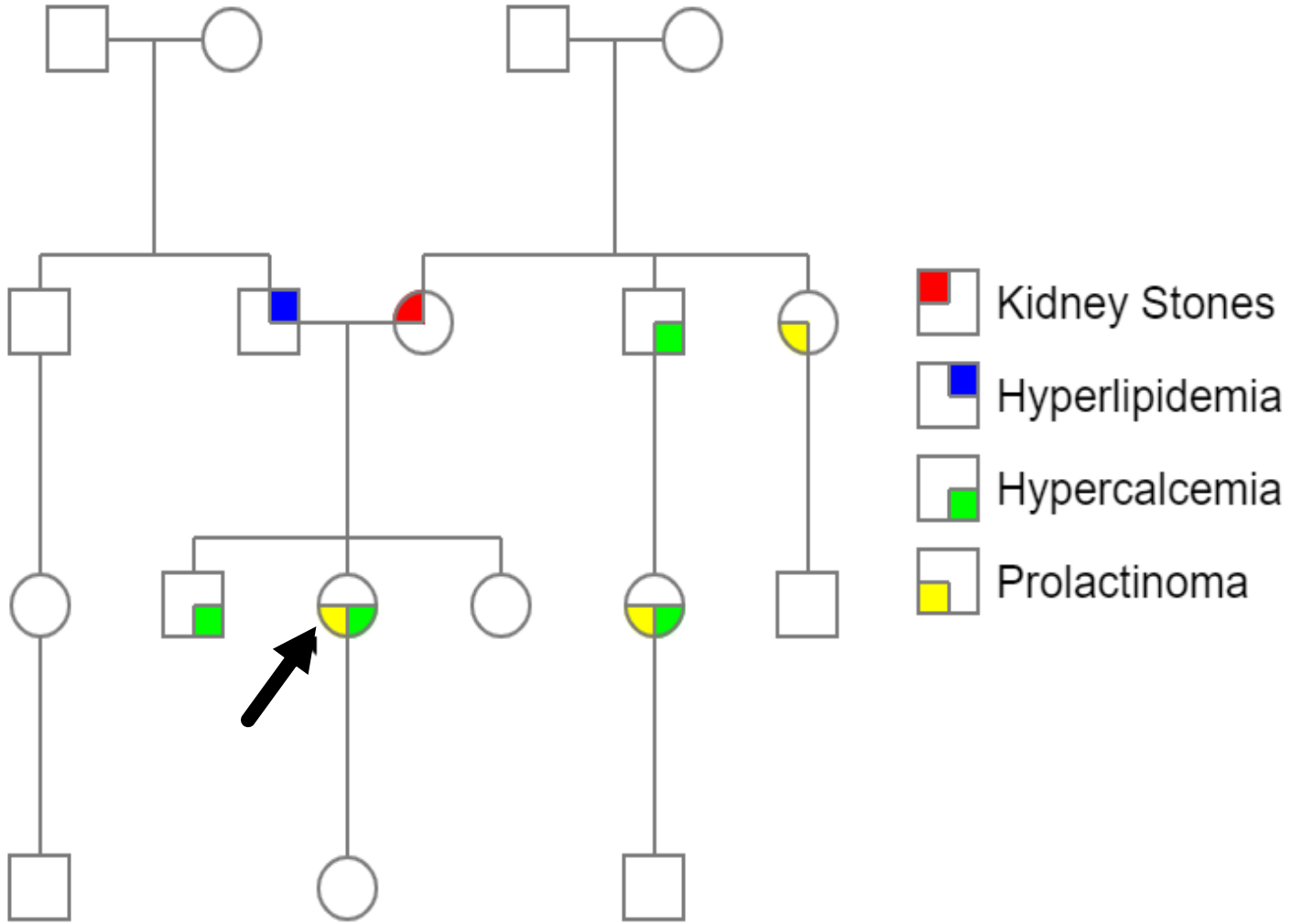

Brandi et al 2021 Endo Rev

# Should this patient be offered genetic testing?

A: Yes

B: No

C: Unsure



# When the endocrine society recommends testing for MEN1 (Thakker et al 2012 JCEM)

- An individual with two or more MEN1-associated tumors
- An individual with a first-degree relative with a known pathogenic MEN1 variant
- An individual with a suspicious or atypical presentation:
  - Multigland parathyroid disease
  - Parathyroid adenomas before the age of 30
  - Gastrinoma or multiple pancreatic islet tumors at any age

# When the endocrine society recommends testing for MEN1 (Thakker et al 2012 JCEM)

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# Positive Test

## MEN1 Report

| Sample ID | Specimen | Result* | Classification |
|---|---|---|---|
| MD-21-0000487 / PA016637 | Blood | MEN1 c.292delc (p.Arg98Glufs*21) | Pathogenic |

**Sample Received: 2021/01/14 15:27**

**Pathogenic Variant(s) Identified:**

**MEN1 (NM_130799.2):c.292delC (p.Arg98Glufs*21)**

Germline pathogenic variants in MEN1 are known to cause multiple endocrine neoplasia type 1 (MEN1) which includes varying combinations of more than 20 endocrine and non-endocrine tumors (PMID: 33249439, 23279763). Based on the following evidence, the MEN1 c.292delC (p.Arg98Glufs*21) variant is classified as pathogenic: 1) this frameshift variant is predicted to result in an altered protein product or absence of protein due to nonsense-mediated decay; 2) this variant is not present in gnomAD; 3) this variant has been reported in individuals with pituitary tumors, insulinoma and/or hyperthyroidism as well as in an asymptomatic individual (PMID: 18601604, 37390813); 4) another MEN1 truncating variant affecting the Arg81 residue (p.Arg81*) has been reported in individuals with MEN 1 (PMID: 17879353, 12112656, 2311764) and has been classified in ClinVar as pathogenic by 3 clinical labs. Based on currently available information, this variant is classified as pathogenic according to the ACMG 2015 variant classification guidelines (PMID: 25741868).

**Gene(s)/ Panel Tested:**

**Multiple Endocrine Neoplasia, Type 1**: MEN1 (NM_130799.2), CDKN1B (NM_004064.4)

**Methodology:** Genomic DNA was analyzed using UHN Hereditary Panel version 4.0 to examine the exonic coding regions (+/- 10bp of the intron) of the listed genes, using the Illumina DNA Prep with enrichment hybrid capture followed by paired-end sequencing with the Illumina sequencing platform. Variant calls are generated using the UHN Clinical Laboratory Genetics custom bioinformatics pipeline with alignment to the reference genome sequence build GRCh37/hg19, and variants assessed using Alissa Interpret. For panels that include the *EPCAM* or *GREM1* genes, only copy number variants are evaluated. Long-range PCR and Sanger sequencing were performed for confirmation of variants identified in PMS2 due to regions of high homology. Minimum acceptable coverage for all reported genomic regions is >25x. Exon level deletions or duplications were analyzed using DECoN [PMID: 28459104] or using multiplex ligation-dependent probe amplification (MLPA) assays by MRC Holland. The reportable range is 20%-100% variant allele frequency. Test sensitivity for this assay is >98%. Current methodology may not detect all variants or CNV changes present in the tested genes

# Breaking down the report

# The summary

## MEN1 Report

| Sample ID | Specimen | Result* | Classification |
|---|---|---|---|
| MD-21-0000487 / PA016637 | Blood | MEN1 c.292delc (p.Arg98Glufs*21) | Pathogenic |

**Sample Received: 2021/01/14 15:27**

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# The evidence

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# Genes tested

**Gene(s)/ Panel Tested:**

**Multiple Endocrine Neoplasia, Type 1**: MEN1 (NM_130799.2), CDKN1B (NM_004064.4)

# The technical details

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# Understanding the evidence

ACMG and AMP standards and guidelines for interpretation of sequence variants (2015)

Richards et al. Genet Med

| | Benign | | Pathogenic | | | |
|---|---|---|---|---|---|---|
| | **Strong** | **Supporting** | **Supporting** | **Moderate** | **Strong** | **Very Strong** |
| **Population Data** | MAF is too high for disorder *BA1/BS1* **OR** observation in controls inconsistent with disease penetrance *BS2* | | | Absent in population databases *PM2* | Prevalence in affecteds statistically increased over controls *PS4* | |
| **Computational And Predictive Data** | | Multiple lines of computational evidence suggest no impact on gene /gene product *BP4*<br>Missense in gene where only truncating cause disease *BP1*<br>Silent variant with non predicted splice impact *BP7* | Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3* | Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5*<br>Protein length changing variant *PM4* | Same amino acid change as an established pathogenic variant *PS1* | Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1* |
| **Functional Data** | Well-established functional studies show no deleterious effect *BS3* | | Missense in gene with low rate of benign missense variants and path. missenses common *PP2* | Mutational hot spot or well-studied functional domain without benign variation *PM1* | Well-established functional studies show a deleterious effect *PS3* | |
| **Segregation Data** | Non-segregation with disease *BS4* | | Co-segregation with disease in multiple affected family members *PP1* | Increased segregation data → | | |
| **De novo Data** | | | | *De novo* (without paternity & maternity confirmed) *PM6* | *De novo* (paternity & maternity confirmed) *PS2* | |
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| **Other Database** | | Reputable source w/out shared data = benign *BP6* | Reputable source = pathogenic *PP5* | | | |
| **Other Data** | | Found in case with an alternate cause *BP5* | Patient's phenotype or FH highly specific for gene *PP4* | | | |

# Understanding the evidence

- 1) this frameshift variant is predicted to result in an altered protein product or absence of protein due to nonsense-mediated decay
- 2) this variant is not present in gnomAD
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Richards et al 2015 Genet Med

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Richards et al 2015 Genet Med

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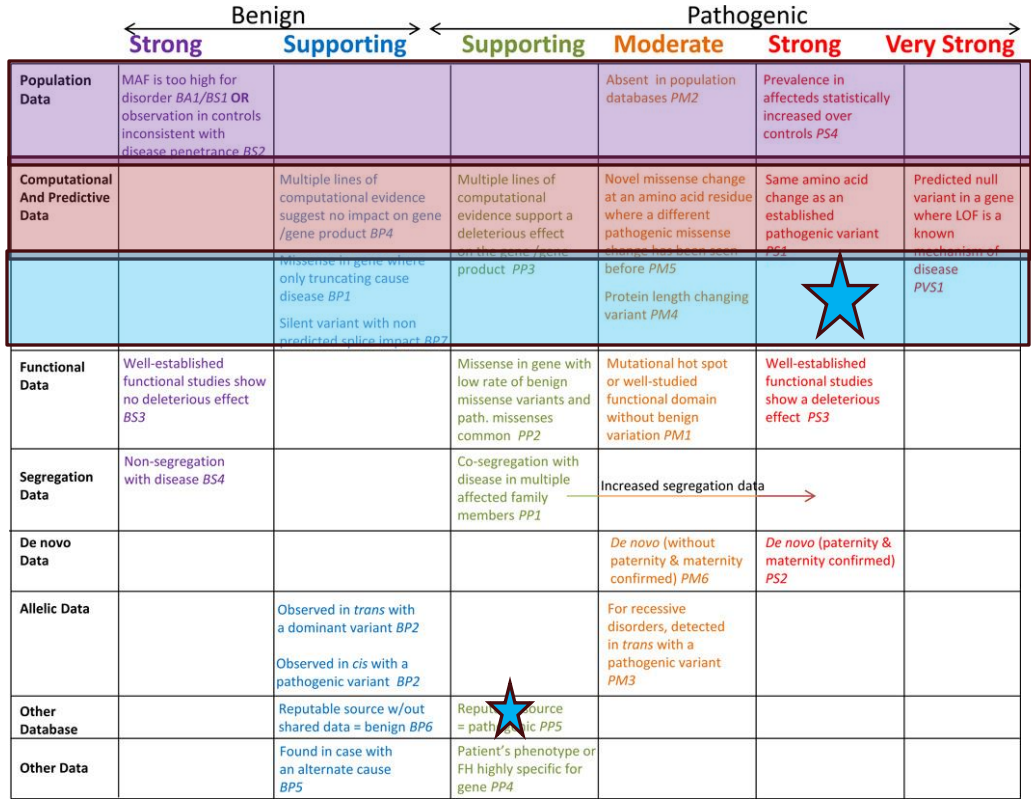
- 4) another MEN1 truncating variant affecting the Arg81 residue (p.Arg81*) has been reported in individuals with MEN 1 (PMID: 17879353, 12112656, 2311764) and has been classified in ClinVar as pathogenic by 3 clinical labs.

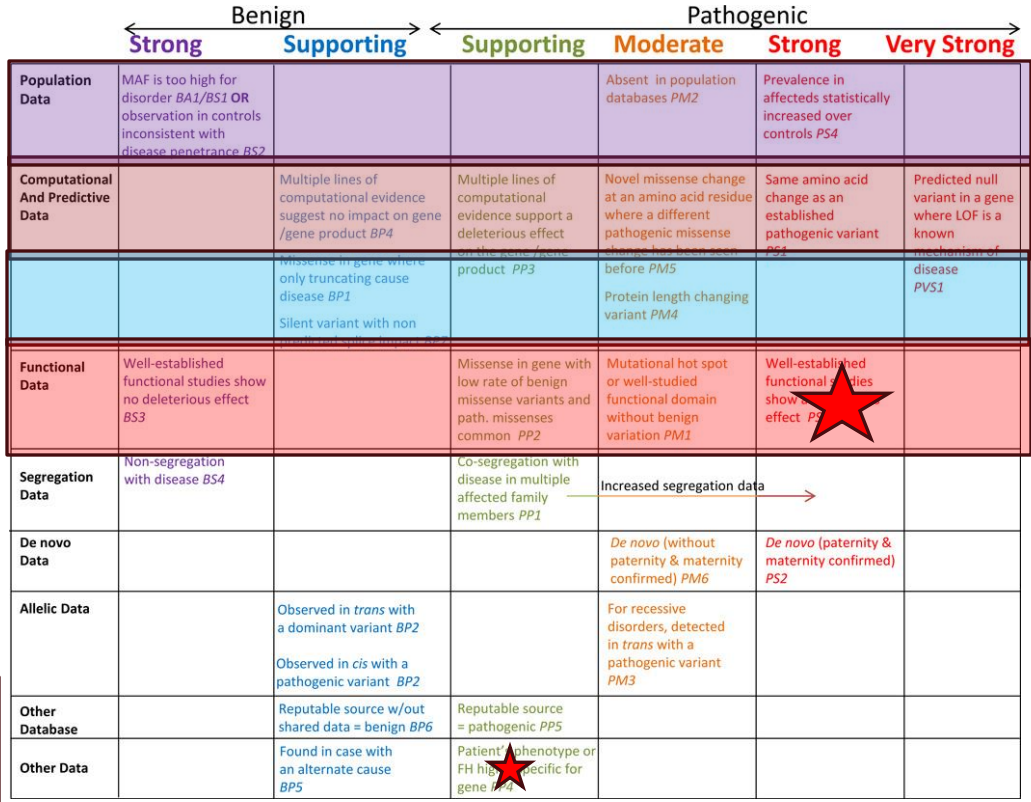


| | Benign | | Pathogenic | | | |
|---|---|---|---|---|---|---|
| | Strong | Supporting | Supporting | Moderate | Strong | Very Strong |
| Population Data | MAF is too high for disorder *BA1/BS1* OR observation in controls inconsistent with disease penetrance *BS2* | | | Absent in population databases *PM2* | Prevalence in affecteds statistically increased over controls *PS4* | |
| Computational And Predictive Data | | Multiple lines of computational evidence suggest no impact on gene /gene product *BP4*<br>Missense in gene where only truncating cause disease *BP1*<br>Silent variant with non predicted splice impact *BP7* | Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3* | Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5*<br>Protein length changing variant *PM4* | Same amino acid change as an established pathogenic variant *PS1* | Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1* |
| Functional Data | Well-established functional studies show no deleterious effect *BS3* | | Missense in gene with low rate of benign missense variants and path. missenses common *PP2* | Mutational hot spot or well-studied functional domain without benign variation *PM1* | Well-established functional studies show a deleterious effect *PS3* | |
| Segregation Data | Non-segregation with disease *BS4* | | Co-segregation with disease in multiple affected family members *PP1* | Increased segregation data → | | |
| De novo Data | | | | *De novo* (without paternity & maternity confirmed) *PM6* | *De novo* (paternity & maternity confirmed) *PS2* | |
| Allelic Data | | Observed in *trans* with a dominant variant *BP2*<br>Observed in *cis* with a pathogenic variant *BP2* | | For recessive disorders, detected in *trans* with a pathogenic variant *PM3* | | |
| Other Database | | Reputable source w/out shared data = benign *BP6* | Reputable source = pathogenic *PP5* | | | |
| Other Data | | Found in case with an alternate cause *BP5* | Patient's phenotype or FH highly specific for gene *PP4* | | | |

Richards et al 2015 Genet Med

# Understanding the evidence

- 1) this frameshift variant is predicted to result in an altered protein product or absence of protein due to nonsense-mediated decay
- 2) this variant is not present in gnomAD
- 3) this variant has been reported in individuals with pituitary tumors, insulinoma and/or hyperthyroidism as well as in an asymptomatic individual (PMID: 18601604, 37390813)
- 4) another MEN1 truncating variant affecting the Arg81 residue (p.Arg81*) has been reported in individuals with MEN 1 (PMID: 17879353, 12112656, 2311764) and has been classified in ClinVar as pathogenic by 3 clinical labs.



| | Benign | | Pathogenic | | | |
|---|---|---|---|---|---|---|
| | Strong | Supporting | Supporting | Moderate | Strong | Very Strong |
| Population Data | MAF is too high for disorder *BA1/BS1* OR observation in controls inconsistent with disease penetrance *BS2* | | | Absent in population databases *PM2* | Prevalence in affecteds statistically increased over controls *PS4* | |
| Computational And Predictive Data | | Multiple lines of computational evidence suggest no impact on gene /gene product *BP4*<br>Missense in gene where only truncating cause disease *BP1*<br>Silent variant with non [illegible] *BP7* | Multiple lines of computational evidence support a deleterious effect [illegible] product *PP3* | Novel missense change at an amino acid residue where a different pathogenic missense [illegible] before *PM5*<br>Protein length changing variant *PM4* | Same amino acid change as an established pathogenic variant *PS1* | Predicted null variant in a gene where LOF is a known [illegible] disease *PVS1* |
| Functional Data | Well-established functional studies show no deleterious effect *BS3* | | Missense in gene with low rate of benign missense variants and path. missenses common *PP2* | Mutational hot spot or well-studied functional domain without benign variation *PM1* | Well-established functional [illegible] show [illegible] effect *PS3* | |
| Segregation Data | Non-segregation with disease *BS4* | | Co-segregation with disease in multiple affected family members *PP1* | Increased segregation data → | | |
| De novo Data | | | | *De novo* (without paternity & maternity confirmed) *PM6* | *De novo* (paternity & maternity confirmed) *PS2* | |
| Allelic Data | | Observed in *trans* with a dominant variant *BP2*<br>Observed in *cis* with a pathogenic variant *BP2* | | For recessive disorders, detected in *trans* with a pathogenic variant *PM3* | | |
| Other Database | | Reputable source w/out shared data = benign *BP6* | Reputable source = pathogenic *PP5* | | | |
| Other Data | | Found in case with an alternate cause *BP5* | Patient's phenotype or FH highly specific for gene [illegible] *PP4* | | | |

Richards et al 2015 Genet Med

# Understanding the evidence

- 1) this frameshift variant is predicted to result in an altered protein product or absence of protein due to nonsense-mediated decay
- 2) this variant is not present in gnomAD
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- 4) another MEN1 truncating variant affecting the Arg81 residue (p.Arg81*) has been reported in individuals with MEN 1 (PMID: 17879353, 12112656, 2311764) and has been classified in ClinVar as pathogenic by 3 clinical labs.

**Table 5** Rules for combining criteria to classify sequence variants Richards et al 2015 Genet Med

| | |
|---|---|
| Pathogenic | (i) 1 Very strong (PVS1) *AND*<br>(a) ≥1 Strong (PS1–PS4) *OR*<br>(b) ≥2 Moderate (PM1–PM6) *OR*<br>(c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) *OR*<br>(d) ≥2 Supporting (PP1–PP5)<br>(ii) ≥2 Strong (PS1–PS4) *OR*<br>(iii) 1 Strong (PS1–PS4) *AND*<br>(a)≥3 Moderate (PM1–PM6) *OR*<br>(b)2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR*<br>(c)1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5) |
| Likely pathogenic | (i) 1 Very strong (PVS1) *AND* 1 moderate (PM1–PM6) *OR*<br>(ii) 1 Strong (PS1–PS4) *AND* 1–2 moderate (PM1–PM6) *OR*<br>(iii) 1 Strong (PS1–PS4) *AND* ≥2 supporting (PP1–PP5) *OR*<br>(iv) ≥3 Moderate (PM1–PM6) *OR*<br>(v) 2 Moderate (PM1–PM6) *AND* ≥2 supporting (PP1–PP5) *OR*<br>(vi) 1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5) |
| Benign | (i) 1 Stand-alone (BA1) *OR*<br>(ii) ≥2 Strong (BS1–BS4) |
| Likely benign | (i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR*<br>(ii) ≥2 Supporting (BP1–BP7) |
| Uncertain significance | (i) Other criteria shown above are not met OR<br>(ii) the criteria for benign and pathogenic are contradictory |

# What to do with a positive test results

- Disclose the results to the patient
  - What does it mean for their care?
- Discuss implications for family members
  - Autosomal Dominant vs Recessive
  - Sporadic vs Inherited
  - Risk of passing on the variant to children
- Provide recommendations for cascade screening
  - Genetic testing for family members at risk
  - Clinical screening for those who decline or can not access genetic testing

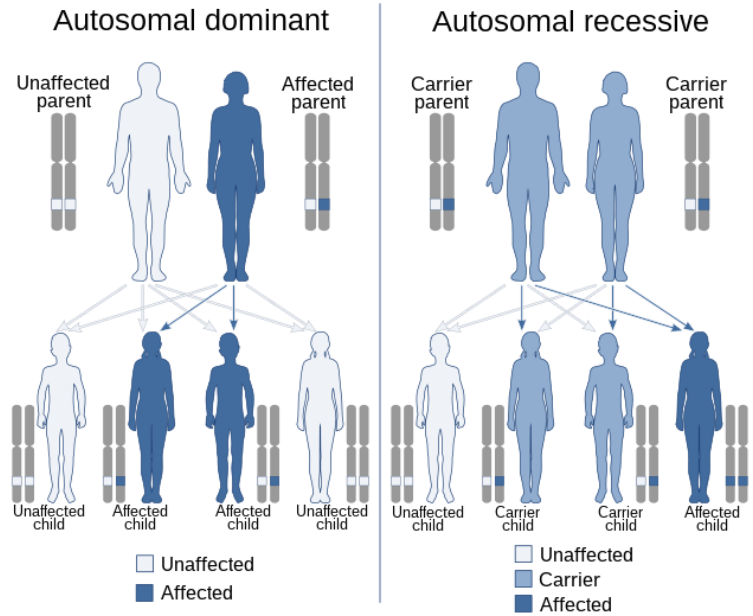


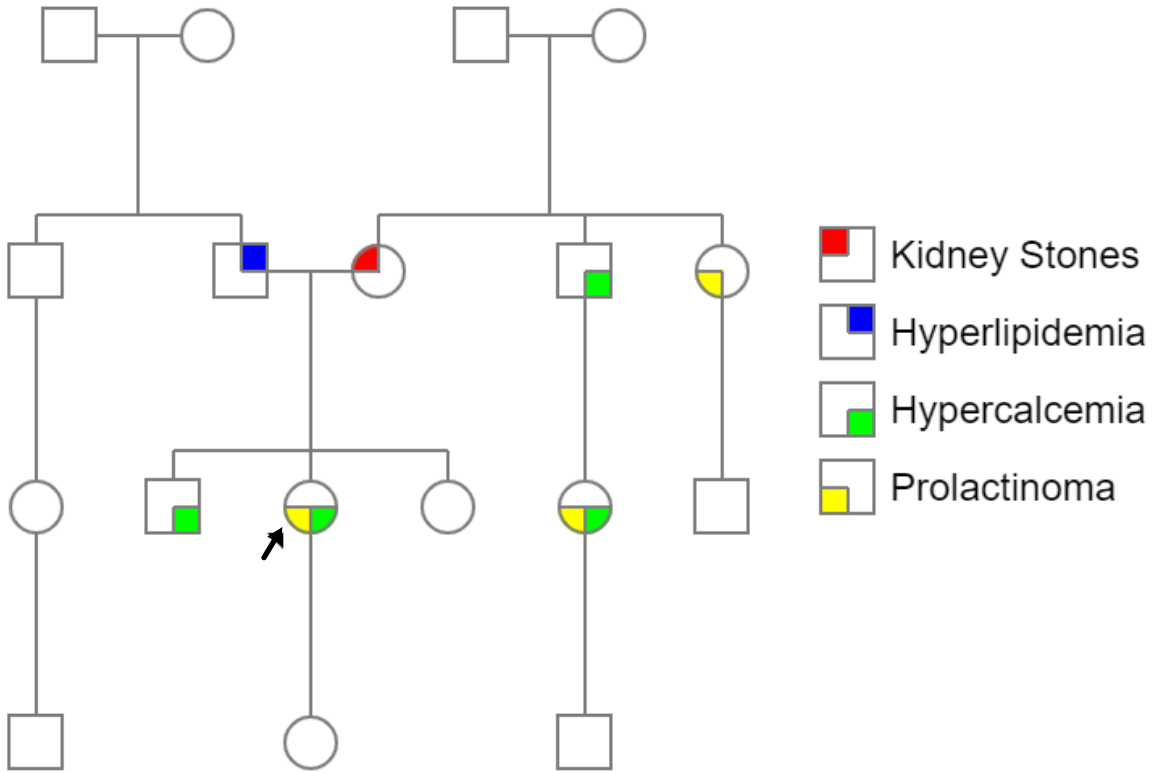

Figure from Wikipedia last accessed April 01 2024

# Outline

- Brief introduction to genetics
- The Case: a 28 year old with a prolactinoma and hyperparathyroidism
  - Version 1: An approach to positive results
  - **Version 2: An approach to negative results**
  - Version 3: An approach to variants of uncertain significance (VUS)

# 28 year old mother referred with hyperparathyroidism and a prolactinoma

- Referred with elevated:
  - Calcium, PTH and Prolactin
  - No Galactorrhea or vision changes
  - LMP 3 weeks ago
- Past Medical History:
  - 0.9cm Prolactinoma treated with cabergoline x1.5 years
  - PCOS
  - Kidney stones



# Case version 2: the negative report

## MEN1 Report

| Sample ID | Specimen | Result* | Classification |
|---|---|---|---|
| MD-21-0000487 / PA016637 | Blood | No Pathogenic Variants Detected | No Pathogenic Variants Detected |

**Sample Received: 2021/01/14 15:27**

*Heterozygous unless otherwise indicated

Genes Tested (hg19;HGVS nomenclature):MEN1(RefSeq Isoform2 NM_130799.2)

**Interpretation: No pathogenic variants and exon deletion or duplications detected.**

**Disease Characteristics:** Multiple endocrine neoplasia type 1 (MEN 1) is a familial cancer syndrome characterised by parathyroid hyperplasia, pituitary adenomas, and neuroendocrine tumours of the pancreas and duodenum. In 1997, the MEN1 tumour suppressor gene was identified, and since then numerous germline mutations have been reported to be distributed throughout the gene (PMID:15714081, PMID:10090472, PMID:16595707, PMID:17342152). These mutations include missense, nonsense, and frameshift mutations, as well as mutations potentially responsible for abnormal RNA splicing, and highlight the need to investigate the entire MEN1 gene when characterizing new MEN 1 families. Coding sequence mutations that may disrupt the MEN1 gene can be screened for by direct sequence analysis of PCR-amplified fragments encompassing each of the exons, including flanking 5'(20bp) and 3'(10bp) intronic sequence, comprising the coding region of the MEN1 gene. Less common deleterious mutations consisting of genomic rearrangements of the MEN1 gene may be detected by the Multiplex Ligation-dependent Probe Amplification method (MLPA)5, which may be confirmed by LR-PCR, (unless the genomic deletion occurs at the extreme 5' or 3' ends of the gene), or by gene dosage determination (e.g. using a quantitative PCR-based approach). The approach described above is expected to provide an efficiency of MEN1 gene mutation detection approaching 100%.

# Breaking down a negative test report

The summary

## MEN1 Report

| Sample ID | Specimen | Result* | Classification |
|---|---|---|---|
| MD-21-0000487 / PA016637 | Blood | No Pathogenic Variants Detected | No Pathogenic Variants Detected |

**Sample Received: 2021/01/14 15:27**

*Heterozygous unless otherwise indicated

Genes tested

Genes Tested (hg19;HGVS nomenclature):MEN1(RefSeq Isoform2 NM_130799.2)

The summary

**Interpretation: No pathogenic variants and exon deletion or duplications detected.**

**Disease Characteristics:** Multiple endocrine neoplasia type 1 (MEN 1) is a familial cancer syndrome characterised by parathyroid

The technical details

**Methodology:** All coding exons and 20 bp of flanking intronic sequence are enriched using an LHSC custom targeted hybridization protocol (Roche Nimblegen), followed by high throughput sequencing (Illumina). Sequence variants and copy number changes are assessed and interpreted using clinically validated algorithms and commercial software (SoftGenetics: Nextgene, Geneticist Assistant, Mutation Surveyor; and Alamut Visual). All exons have >300x mean read depth coverage, with a minimum 100x coverage at a single nucleotide resolution. This assay meets the sensitivity and specificity of combined Sanger sequencing and MLPA copy number analysis. All variants interpreted as either ACMG category 1, 2, or 3 (pathogenic, likely pathogenic, VUS; PMID: 25741868) are confirmed using Sanger sequencing, MLPA, or other assays. ACMG category 4 and 5 variants (likely benign, benign) are not reported, but are available upon request. This assay has been validated at a level of sensitivity equivalent to the Sanger sequencing and standard copy number analysis (>99%; PMID: 27376475).

**Disclaimer:** This test was developed and its performance determined by this laboratory, which is accredited under the Institute for Quality Management in Healthcare (IQMH) program. Utilization of the reported results for clinical purposes remains the full responsibility of the practitioner. Testing is highly accurate, however, rare diagnostic errors can arise from specimen mishandling or misinterpretation; and it has been reported that as much as 0.5% error rate may occur in any of the pre-analytical/analytical or post analytical phases of the test (PMID:11978595).

# Gene deletions and duplications are not detected by all sequencing technologies

**MEN1 Report**

| Sample ID | Specimen | Result* | Classification |
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| MD-21-0000487 / PA016637 | Blood | No Pathogenic Variants Detected | No Pathogenic Variants Detected |

**Sample Received: 2021/01/14 15:27**

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Genes Tested (hg19;HGVS nomenclature):MEN1(RefSeq Isoform2 NM_130799.2)

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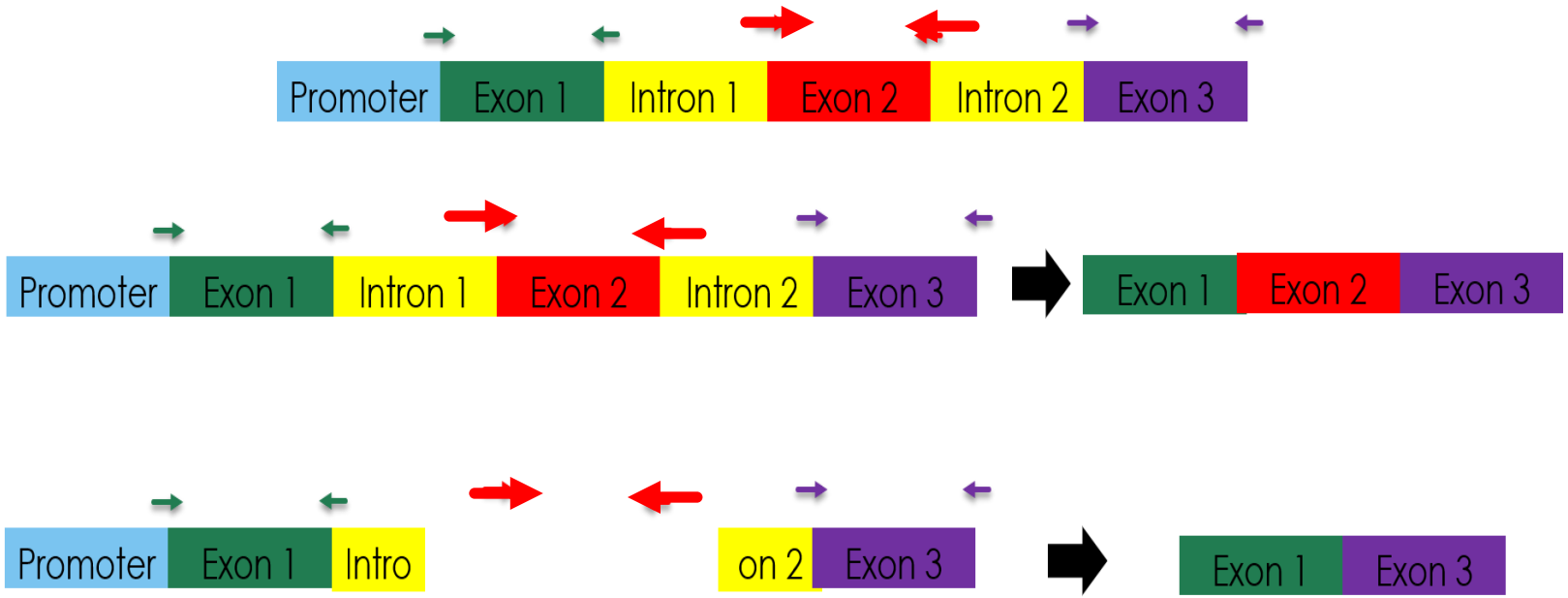

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**Sample Received: 2021/01/14 15:27**

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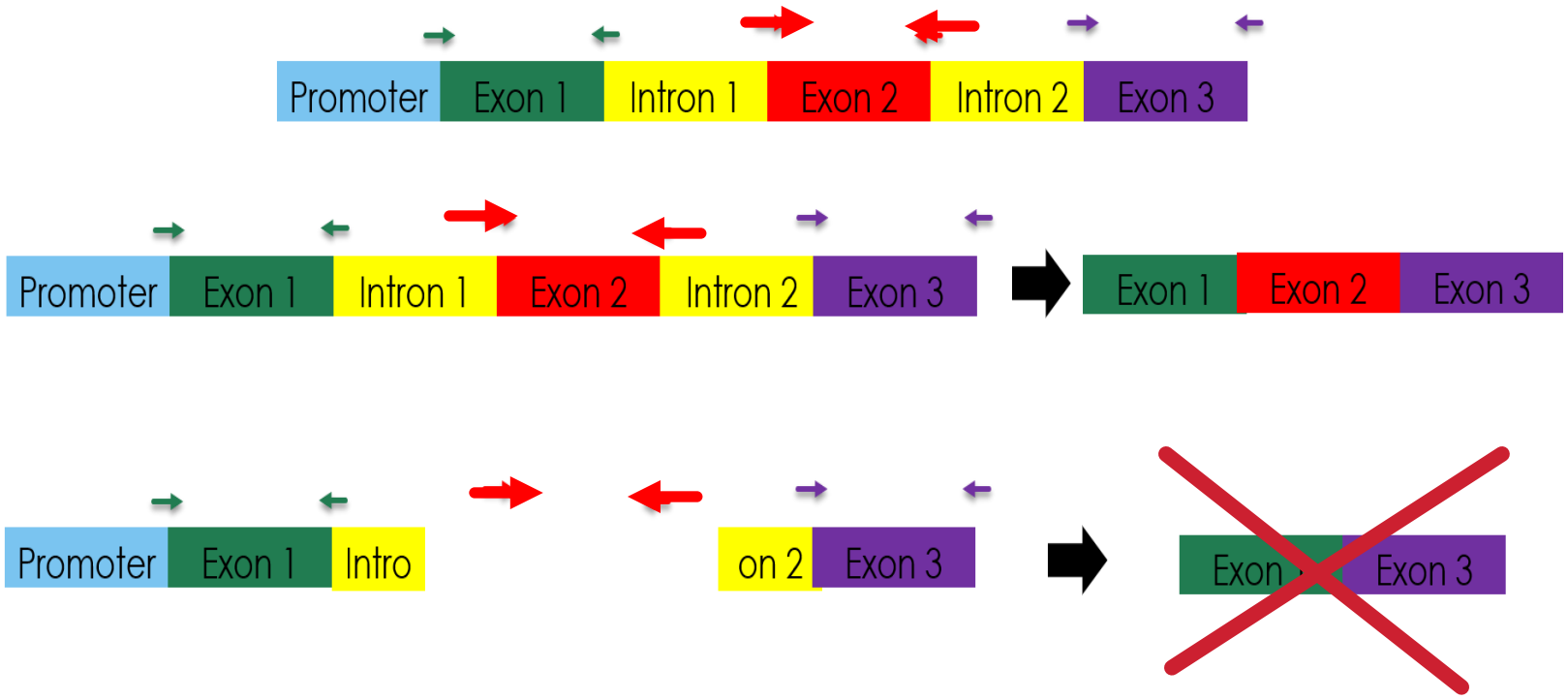


# Did we test for the right part of the gene?

**MEN1 Report**

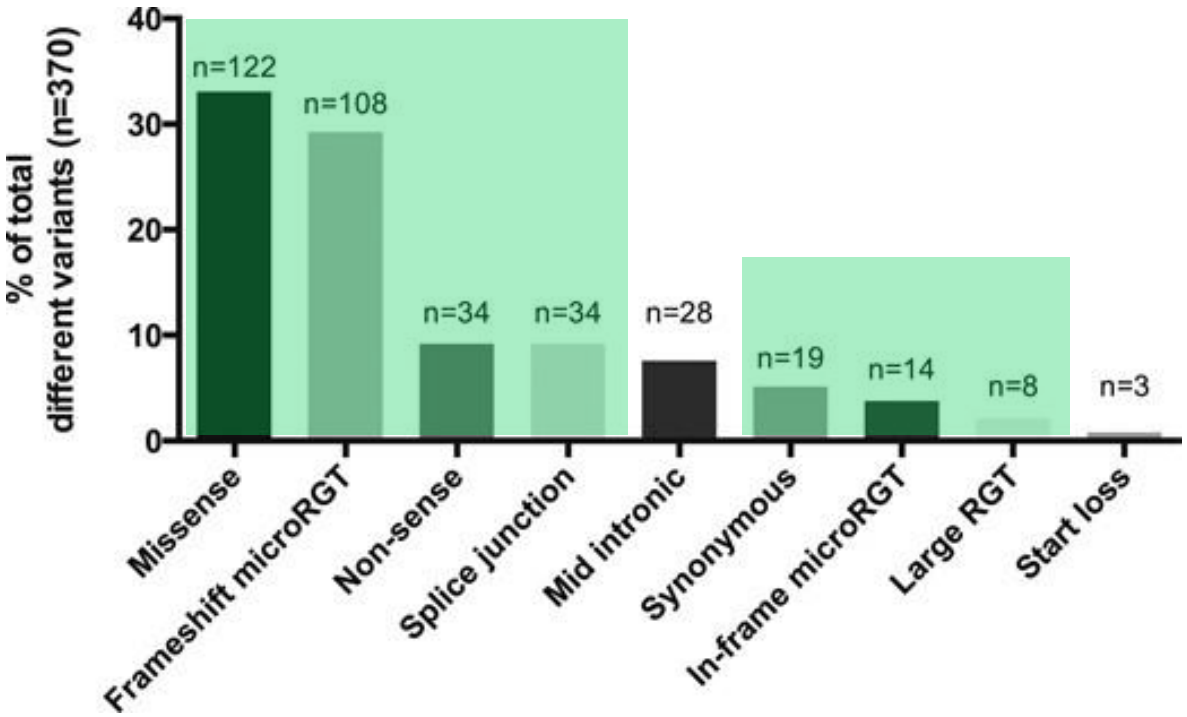
| Sample ID | Specimen | Result* | Classification |
|---|---|---|---|
| MD-21-0000487 / PA016637 | Blood | No Pathogenic Variants Detected | No Pathogenic Variants Detected |

**Sample Received: 2021/01/14 15:27**
*Heterozygous unless otherwise indicated
Genes Tested (hg19;HGVS nomenclature):MEN1(RefSeq Isoform2 NM_130799.2)

**Interpretation**: **No pathogenic variants and exon deletion or duplications detected.**

**Disease Characteristics:** Multiple endocrine neoplasia type 1 (MEN 1) is a familial cancer syndrome characterised by parathyroid

**Methodology:** All coding exons and 20 bp of flanking intronic sequence are enriched using an LHSC custom targeted hybridization protocol (Roche Nimblegen), followed by high throughput sequencing (Illumina). Sequence variants and copy number changes are assessed and interpreted using clinically validated algorithms and commercial software (SoftGenetics: Nextgene, Geneticist Assistant, Mutation Surveyor; and Alamut Visual). All exons have >300x mean read depth coverage, with a minimum 100x coverage at a single nucleotide resolution. This assay meets the sensitivity and specificity of combined Sanger sequencing and MLPA copy number analysis. All variants interpreted as either ACMG category 1, 2, or 3 (pathogenic, likely pathogenic, VUS; PMID: 25741868) are confirmed using Sanger sequencing, MLPA, or other assays. ACMG category 4 and 5 variants (likely benign, benign) are not reported, but are available upon request. This assay has been validated at a level of sensitivity equivalent to the Sanger sequencing and standard copy number analysis (>99%; PMID: 27376475).




Romanet et al 2019 JCEM

# Did we test for the right genes?

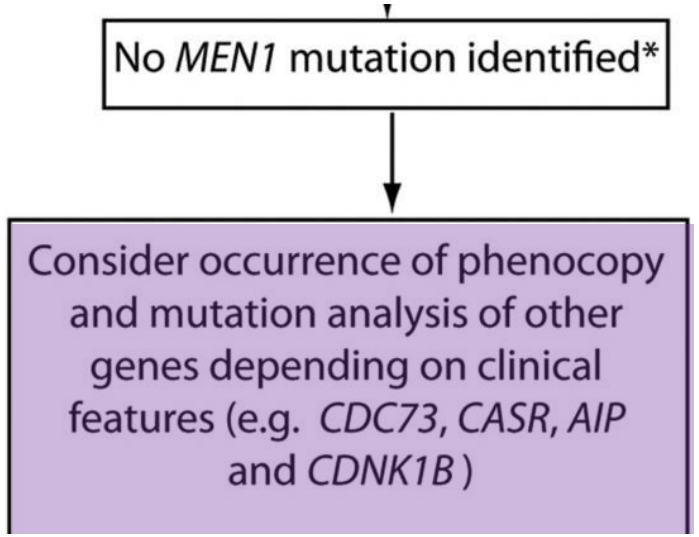
**MEN1 Report**

| Sample ID | Specimen | Result* | Classification |
|---|---|---|---|
| MD-21-0000487 / PA016637 | Blood | No Pathogenic Variants Detected | No Pathogenic Variants Detected |

**Sample Received: 2021/01/14 15:27**

*Heterozygous unless otherwise indicated

Genes Tested (hg19;HGVS nomenclature):MEN1(RefSeq Isoform2 NM_130799.2)




Thakker et al 2012 JCEM

# What to do with a negative test results

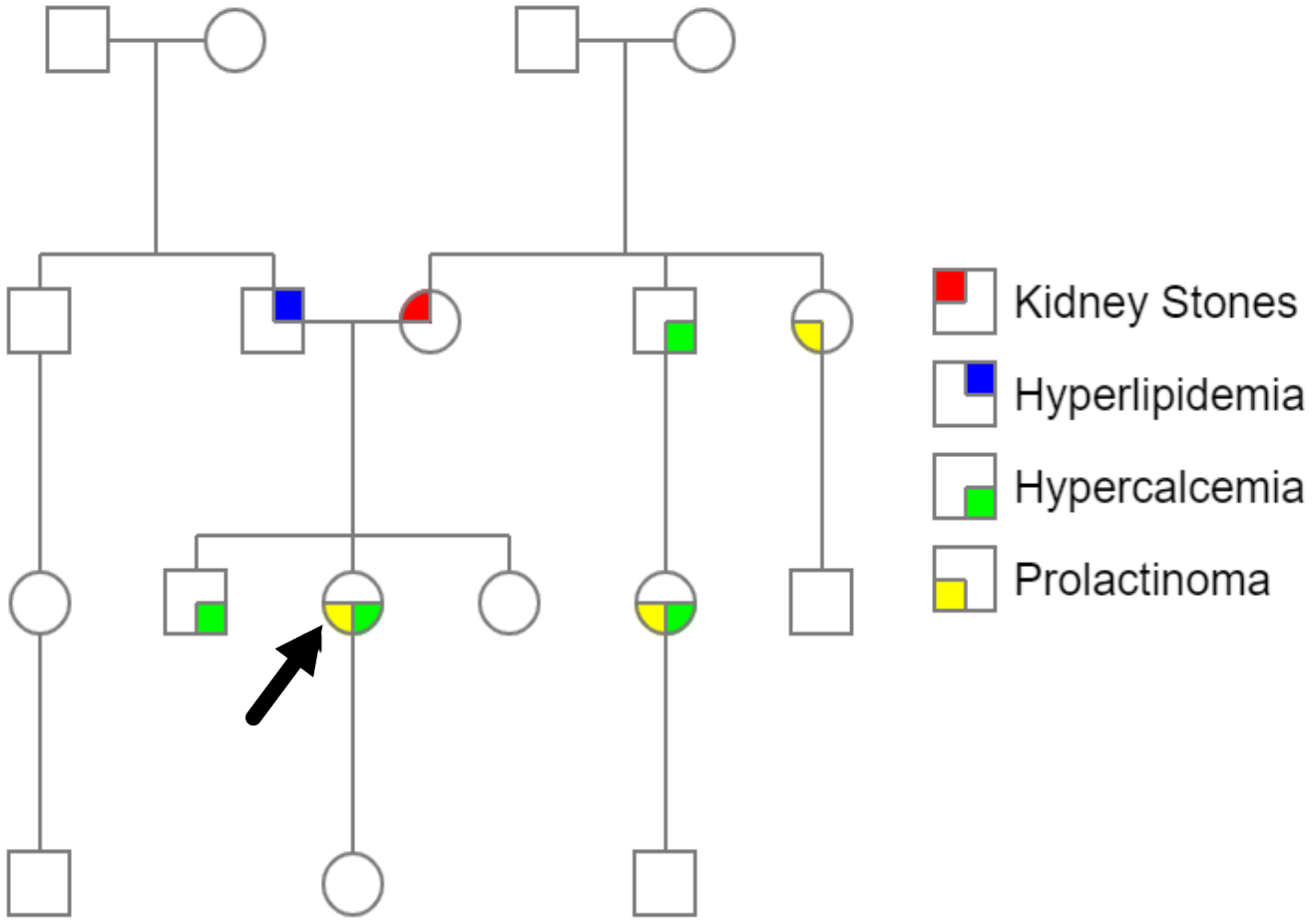
- Review the test details and if further testing is needed:
  - Deletion and Duplication analysis
  - Exome or Genome backbone
  - Is genetic testing for other conditions on the differential necessary
- Disclose the results to the patient:
  - **A negative test does not rule out a genetic condition**
  - Review the patient indicated clinical management
- Provide recommendations for clinical cascade screening if appropriate
- Consider re-valuating genetic testing in 5+ years

# Outline

- Brief introduction to genetics
- The Case: a 28 year old with a prolactinoma and hyperparathyroidism
  - Version 1: An approach to positive results
  - Version 2: An approach to negative results
  - **Version 3: An approach to variants of uncertain significance (VUS)**

# 28 year old mother referred with hyperparathyroidism and a prolactinoma

- Referred with elevated:
  - Calcium, PTH and Prolactin
  - No Galactorrhea or vision changes
  - LMP 3 weeks ago
- Past Medical History:
  - 0.9cm Prolactinoma treated with cabergoline x1.5 years
  - PCOS
  - Kidney stones



# Case Version 3: a Variant of Uncertain Significance

**MEN1 Report**

| Sample ID | Specimen | Result* | Classification |
|---|---|---|---|
| MD-21-0000487 / PA016637 | Blood | MEN1 c.466G>A (p.G156S) | Uncertain Significance |

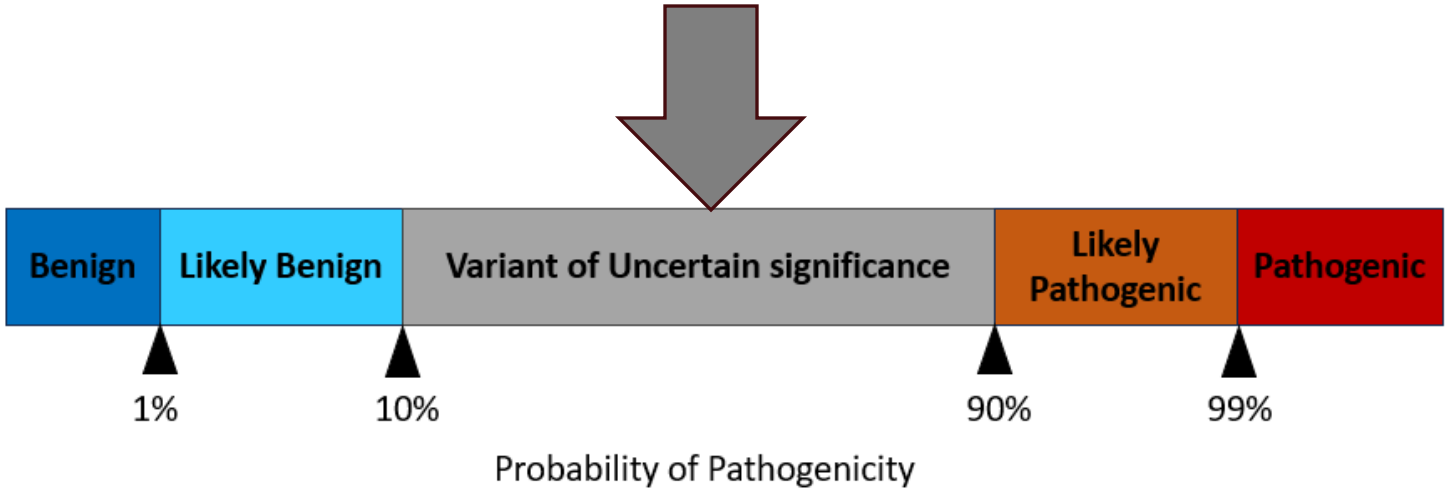
The p.G156S variant (also known as c.466G>A), located in coding exon 2 of the MEN1 gene, results from a G to A substitution at nucleotide position 466. The glycine at codon 156 is replaced by serine, an amino acid with similar properties. This alteration has been identified in an individual with multiple endocrine neoplasia type 1 (MEN1); however, this individual also had another identified alteration in MEN1 (p.A160P), which has been identified in multiple probands with MEN1 phenotype (Tham E et al. J Clin Endocrinol Metab 2007 Sep;92(9):3389-95; Agarwal SK et al. Hum. Mol. Genet., 1997 Jul;6:1169-75; Wautot V et al. Hum. Mutat., 2002 Jul;20:35-47; Bassett JH et al. Am. J. Hum. Genet., 1998 Feb;62:232-44). This amino acid position is highly conserved in available vertebrate species. In addition, this alteration is predicted to be deleterious by in silico analysis. Since supporting evidence is limited at this time, the clinical significance of this alteration remains unclear.

# What is a Variant of Uncertain Significance

GRAY

VS

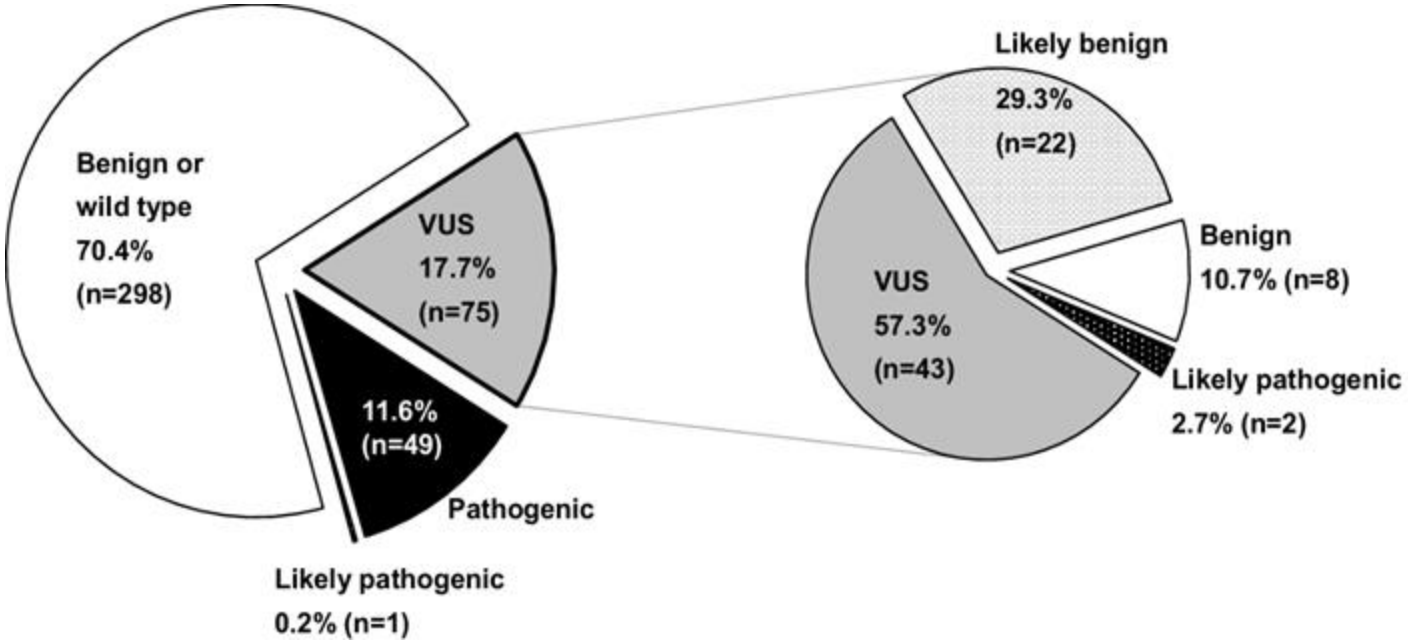
GREY



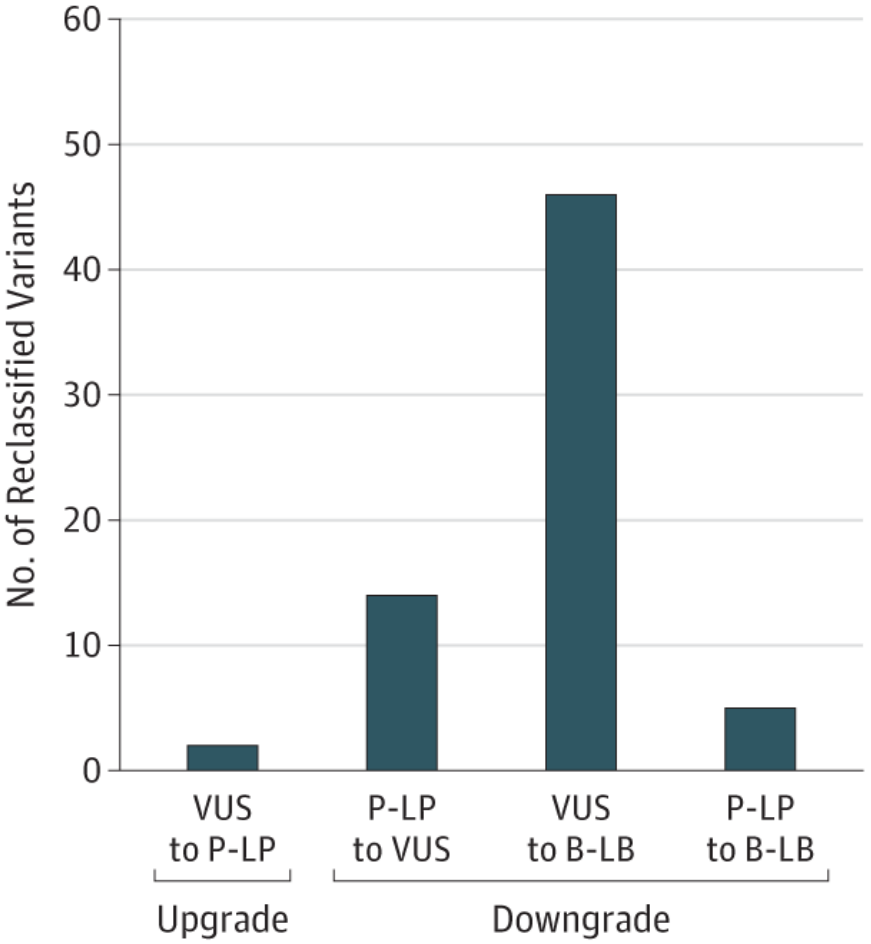

GRAY

VS

# Variants of Uncertain Significance get reclassified over time

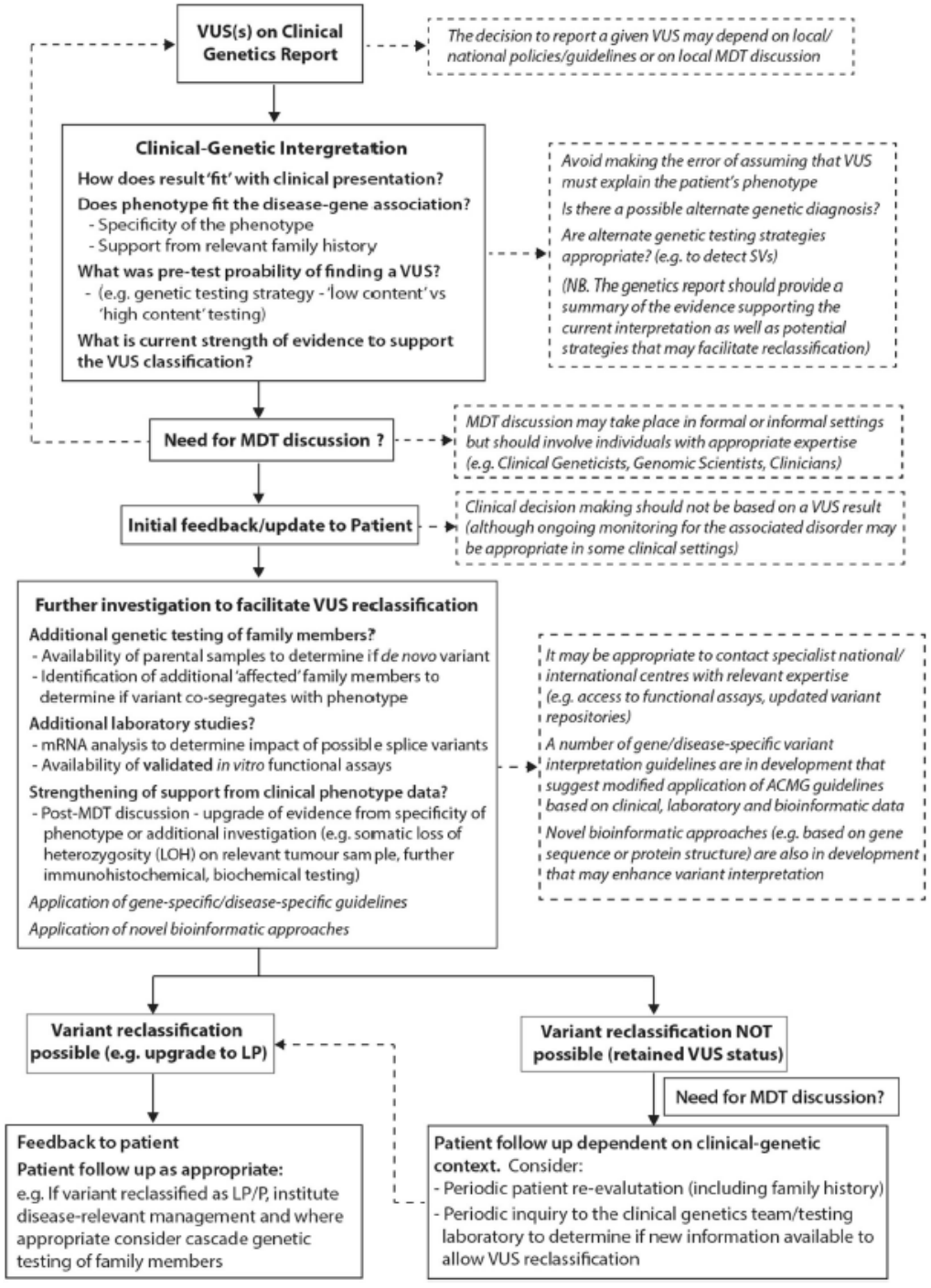



So et al 2019 Breast Cancer




SoRelle et al 2019 JAMA Peds

# How to approach a variant of uncertain significance




**Newey 2022 Clinical Endo**

# How to approach a VUS: Does it fit the clinical picture?

**Clinical-Genetic Intergretation**

**How does result 'fit' with clinical presentation?**

**Does phenotype fit the disease-gene association?**
- Specificity of the phenotype
- Support from relevant family history

**What was pre-test proability of finding a VUS?**
- (e.g. genetic testing strategy - 'low content' vs 'high content' testing)

**What is current strength of evidence to support the VUS classification?**

*Avoid making the error of assuming that VUS must explain the patient's phenotype*

*Is there a possible alternate genetic diagnosis?*

*Are alternate genetic testing strategies appropriate? (e.g. to detect SVs)*

*(NB. The genetics report should provide a summary of the evidence supporting the current interpretation as well as potential strategies that may facilitate reclassification)*

**Newey 2022 Clinical Endo**

# How to approach a VUS: Evaluate the evidence

- MEN1 c.466G>A (p.Gly156Ser)
  - Glycine is replaced by an amino acid with similar properties (serine)
  - The amino acid position is hlighly conserved among vertebrate species
- In silico modelling is predicted to be deleterious
- The variant has been reported in an individual with an additional MEN1 Variant (p.Ala160Pro)
  - MEN1 p.Ala160Pro has been published to affect multiple individuals with MEN1

# Approach to VUS: Involve genetics to see if additional testing may help reclassify the variant

**Further investigation to facilitate VUS reclassification**

**Additional genetic testing of family members?**
- Availability of parental samples to determine if *de novo* variant
- Identification of additional 'affected' family members to determine if variant co-segregates with phenotype

**Additional laboratory studies?**
- mRNA analysis to determine impact of possible splice variants
- Availability of **validated** *in vitro* functional assays

**Strengthening of support from clinical phenotype data?**
- Post-MDT discussion - upgrade of evidence from specificity of phenotype or additional investigation (e.g. somatic loss of heterozygosity (LOH) on relevant tumour sample, further immunohistochemical, biochemical testing)

*Application of gene-specific/disease-specific guidelines*

*Application of novel bioinformatic approaches*

**Newey 2022 Clinical Endo**

# Additional testing may help reclassify the variant

- The variant has been reported in an individual with an additional MEN1 Variant (p.Ala160Pro)
  - MEN1 p.Ala160Pro has been published to affect multiple individuals with MEN1

**Further investigation to facilitate VUS reclassification**

**Additional genetic testing of family members?**
- Availability of parental samples to determine if *de novo* variant
- Identification of additional 'affected' family members to determine if variant co-segregates with phenotype

**Additional laboratory studies?**
- mRNA analysis to determine impact of possible splice variants
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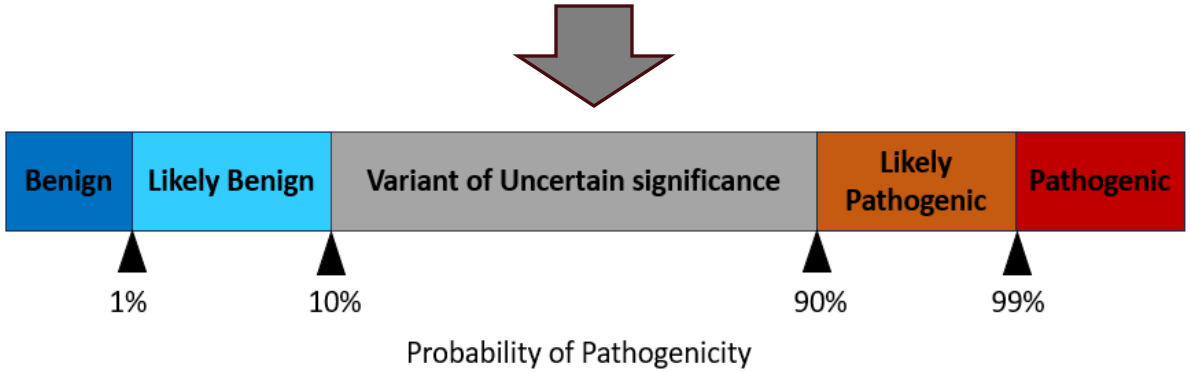
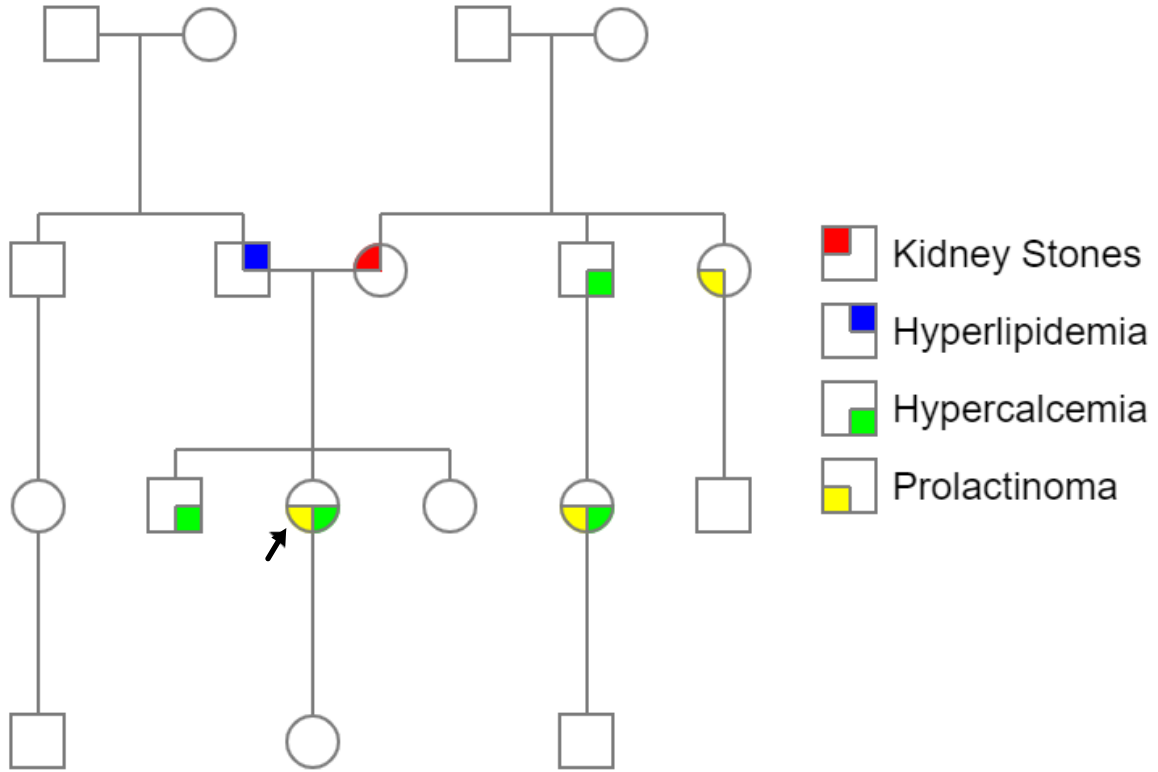
**Strengthening of support from clinical phenotype data?**
- Post-MDT discussion - upgrade of evidence from specificity of phenotype or additional investigation (e.g. somatic loss of heterozygosity (LOH) on relevant tumour sample, further immunohistochemical, biochemical testing)

*Application of gene-specific/disease-specific guidelines*

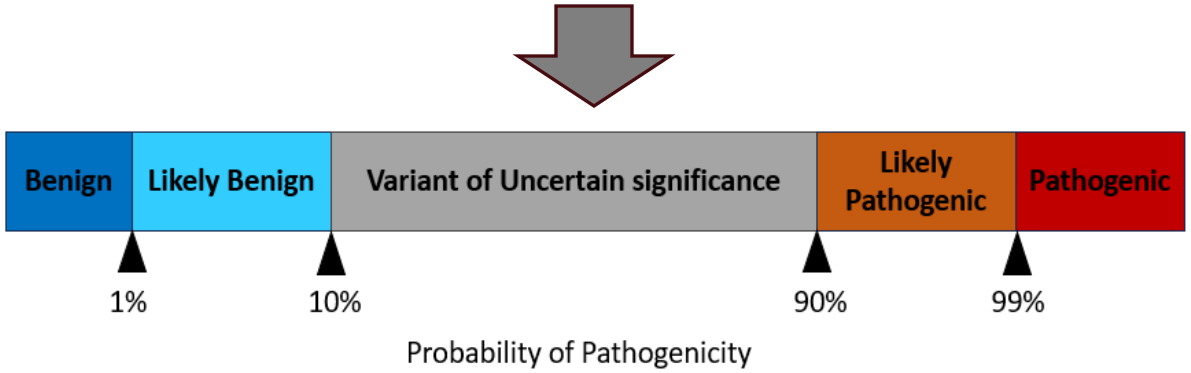
*Application of novel bioinformatic approaches*

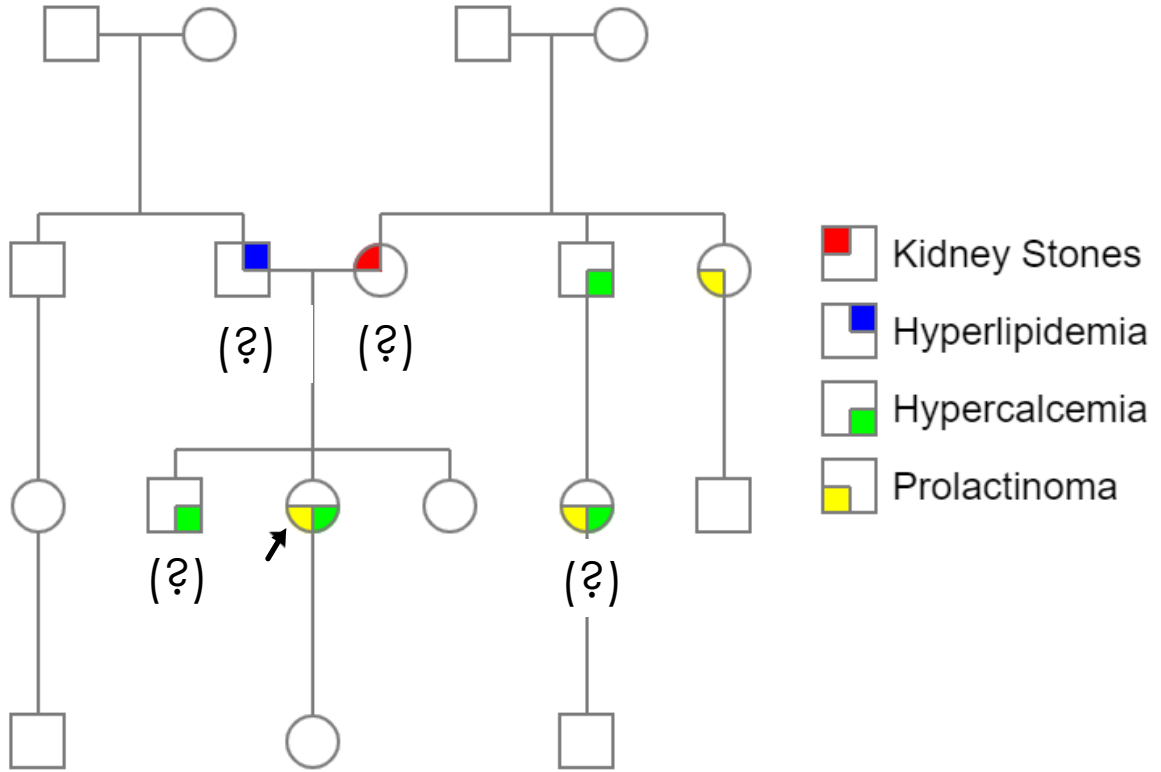
# Selective testing of other family members may help move the needle



# Selective testing of other family members may help move the needle



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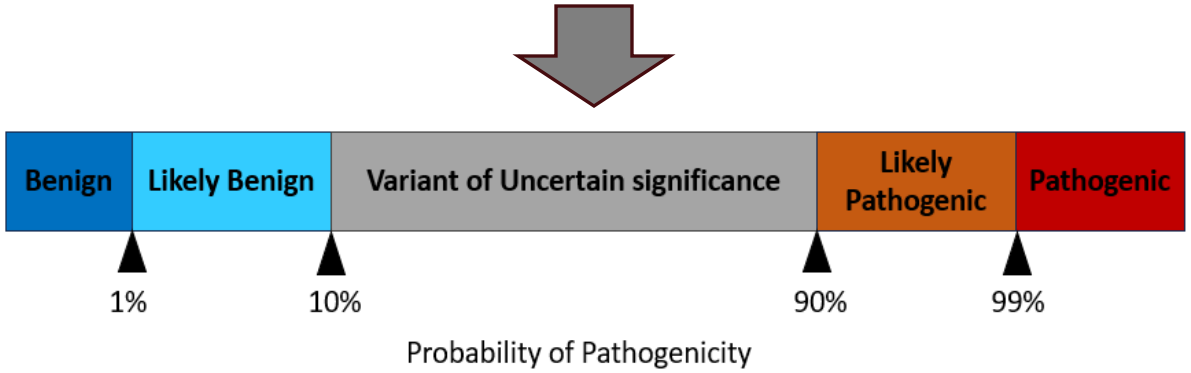


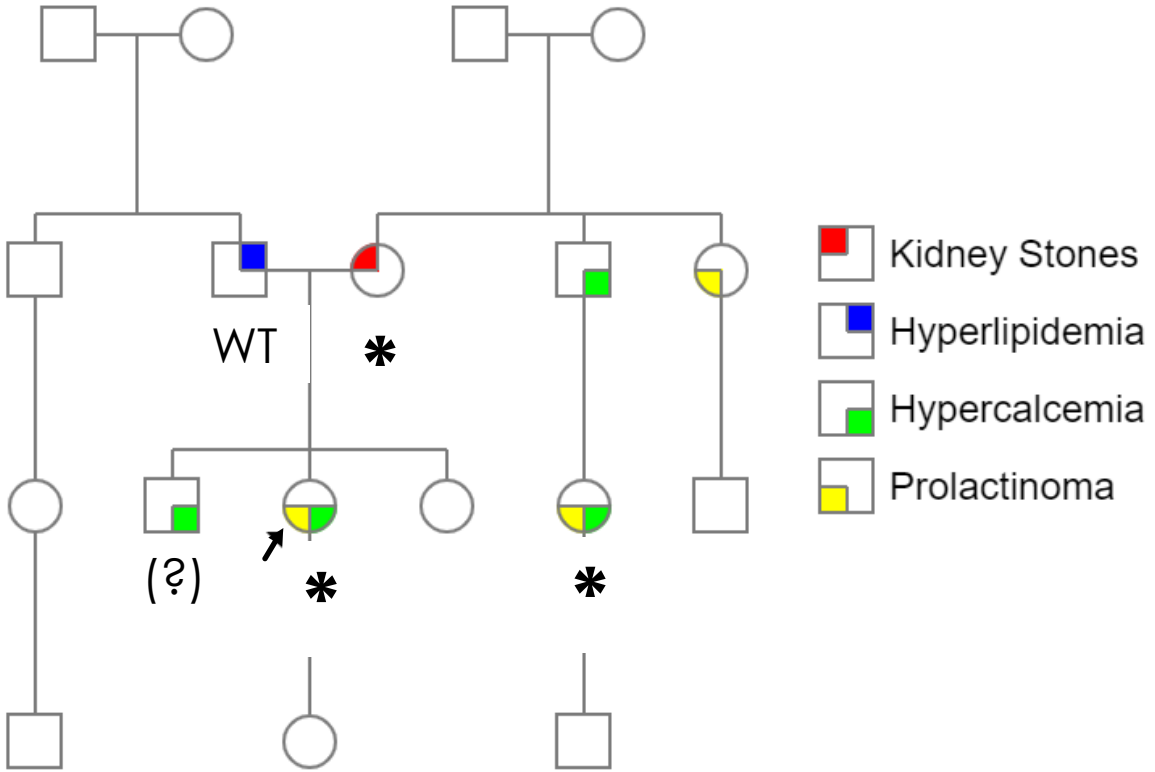

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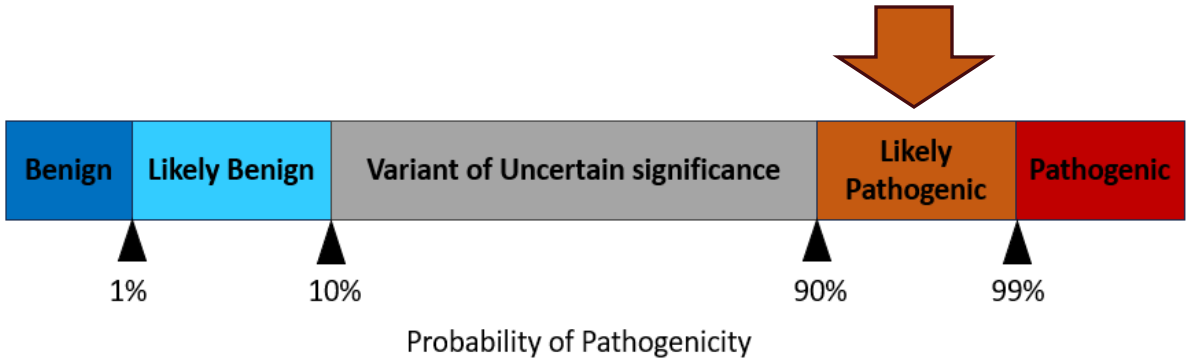
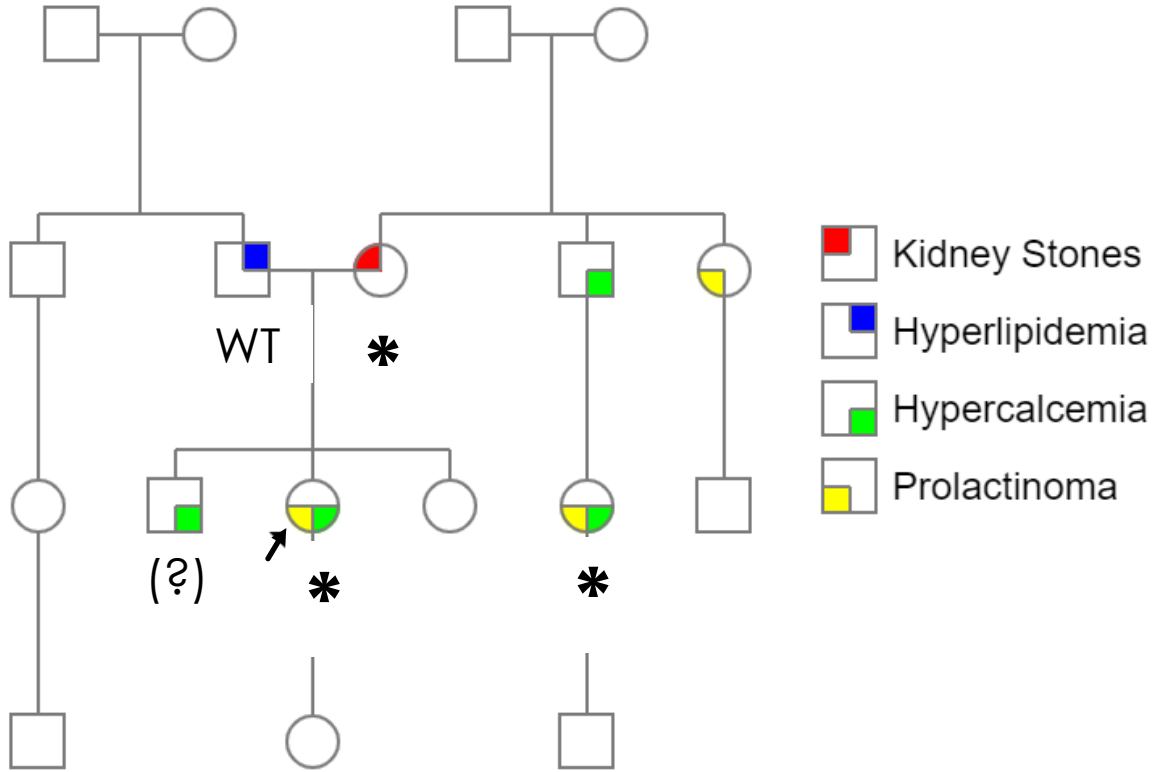
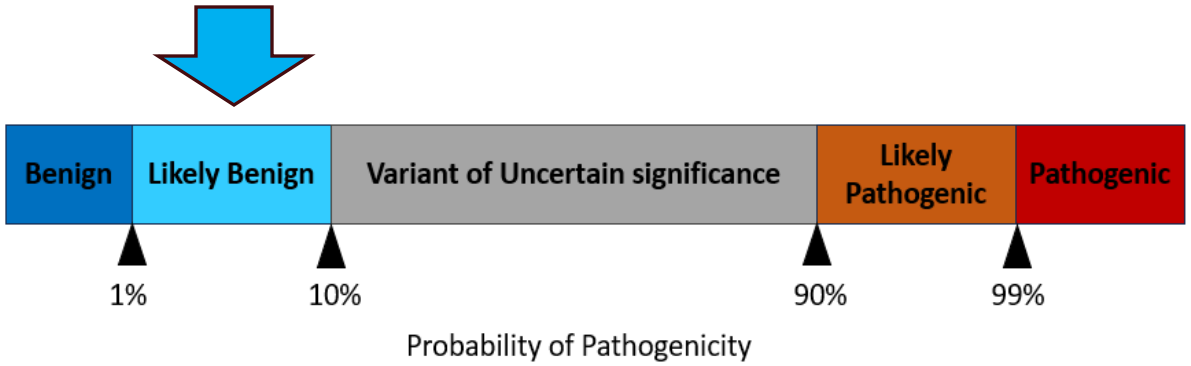
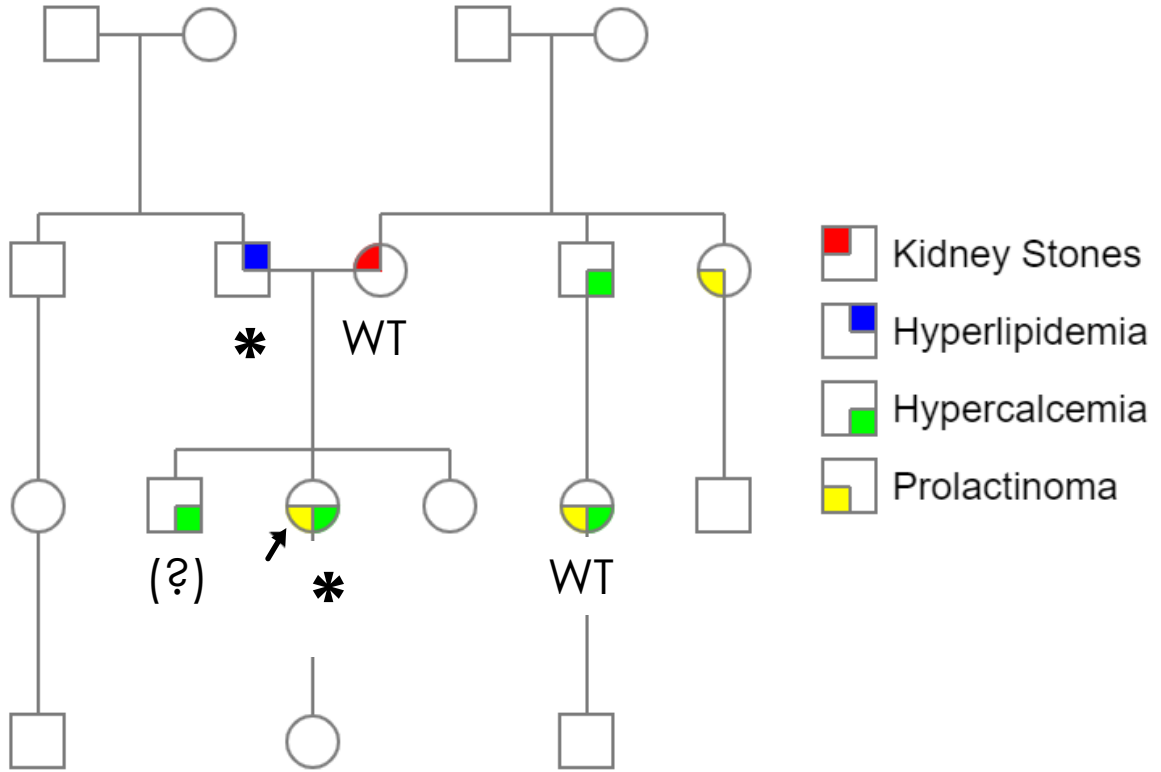


# Selective testing of other family members may help move the needle



# What to do with a Variant of Uncertain Significance

- Review the test details and see if you can provide more information to move the needle:
  - Additional clinical phenotyping
  - Work with genetics to facilitate testing  of other family members (segregation analysis)
  - Additional molecular testing options (often requires collaboration with researchers)

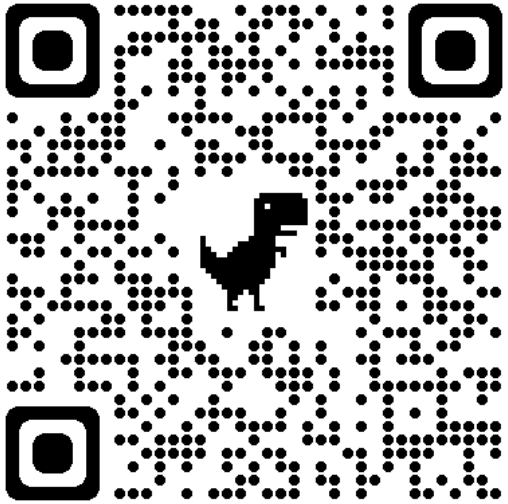
- Disclose the results to the patient, and highlight that they still have a clinical diagnosis
  - A VUS is an inconclusive result for which clinical evidence is lacking
  - It neither confirms or eliminates a genetic condition
  - Re-evaluate in 3-5+ years

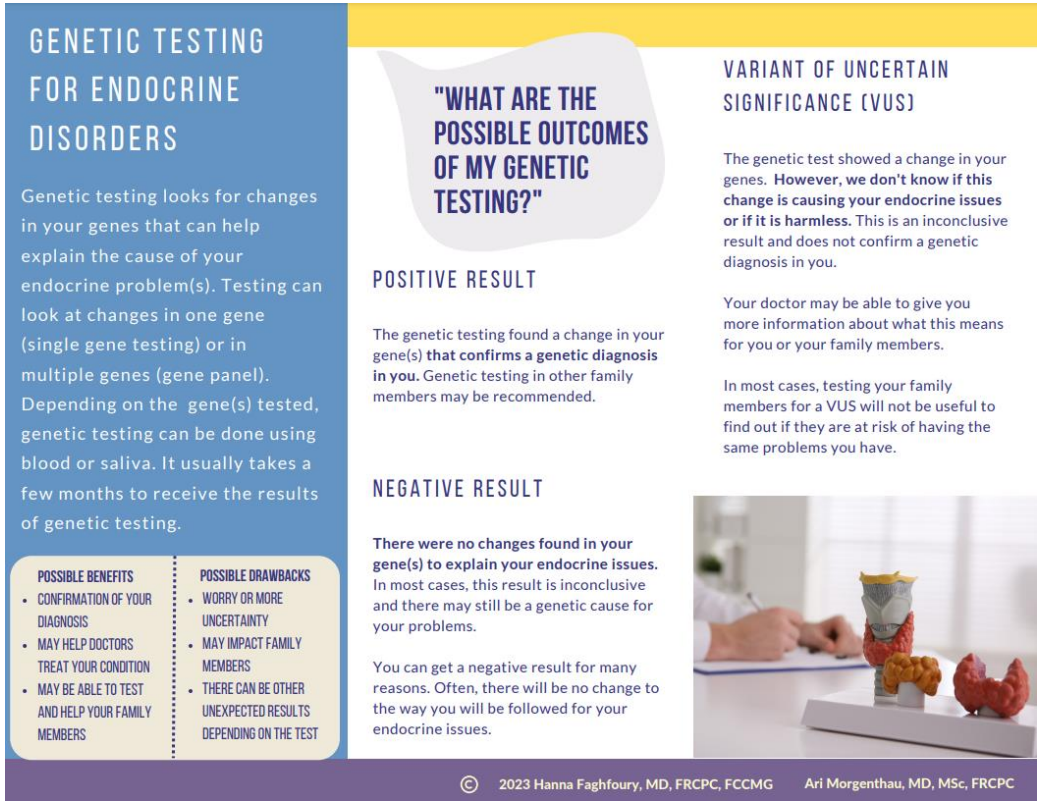
- Provide recommendations for ongoing clinical management and cascade screening if appropriate

# Take home points

- Genetic test results can help guide patient management but do not replace a clinical diagnosis
- Genetic test results are reported on a spectrum
  - Positive, Negative and Uncertain
  - The only conclusive result is a positive genetic test results (likely pathogenic/pathogenic)
- Not all genetic tests are equal: When reviewing genetic test reports it is important to consider the genes including and the testing methods
- Refer to genetics for expert help with reclassifying variants of uncertain significance
  - Endocrinologists have a role in clinical phenotyping

# Genetic testing for endocrine disorder results pamphlet





## GENETIC TESTING FOR ENDOCRINE DISORDERS

Genetic testing looks for changes in your genes that can help explain the cause of your endocrine problem(s). Testing can look at changes in one gene (single gene testing) or in multiple genes (gene panel). Depending on the gene(s) tested, genetic testing can be done using blood or saliva. It usually takes a few months to receive the results of genetic testing.

**POSSIBLE BENEFITS**

- CONFIRMATION OF YOUR DIAGNOSIS
- MAY HELP DOCTORS TREAT YOUR CONDITION
- MAY BE ABLE TO TEST AND HELP YOUR FAMILY MEMBERS

**POSSIBLE DRAWBACKS**

- WORRY OR MORE UNCERTAINTY
- MAY IMPACT FAMILY MEMBERS
- THERE CAN BE OTHER UNEXPECTED RESULTS DEPENDING ON THE TEST

## "WHAT ARE THE POSSIBLE OUTCOMES OF MY GENETIC TESTING?"

### POSITIVE RESULT

The genetic testing found a change in your gene(s) **that confirms a genetic diagnosis in you.** Genetic testing in other family members may be recommended.

### NEGATIVE RESULT

**There were no changes found in your gene(s) to explain your endocrine issues.** In most cases, this result is inconclusive and there may still be a genetic cause for your problems.

You can get a negative result for many reasons. Often, there will be no change to the way you will be followed for your endocrine issues.

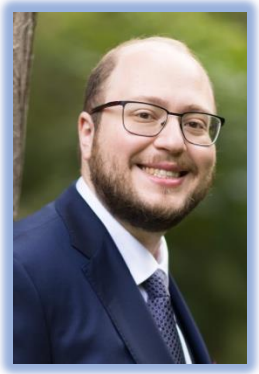
### VARIANT OF UNCERTAIN SIGNIFICANCE (VUS)

The genetic test showed a change in your genes. **However, we don't know if this change is causing your endocrine issues or if it is harmless.** This is an inconclusive result and does not confirm a genetic diagnosis in you.

Your doctor may be able to give you more information about what this means for you or your family members.

In most cases, testing your family members for a VUS will not be useful to find out if they are at risk of having the same problems you have.

# Post-test questions 3-5



# Post-test Question #3 - Answer

Which of the following clinical presentations should be offered genetic testing for MEN1

**a) A 20-year-old presenting with a parathyroid adenoma?**

b) A 22-year-old presenting with a pheochromocytoma

**c) An individual presenting with a non-functional pancreatic neuroendocrine tumor and a past medical history of a prolactinoma**

**d) An individual with breast cancer with a meningioma resected in childhood, and multiple lipomas on physical exam**

e) An individual presenting with a pituitary adenoma with a parent who also had a pituitary adenoma

**Correct answers A C, D**

- B should have testing for MEN2 and hereditary pheochromocytoma and paraganglioma syndrome (also VHL)
- D depending on age of onset could consider testing of the AIP gene

REFERENCE: https://academic.oup.com/jcem/article/97/9/2990/2536740

# Post-test Question #4 - Answer

**You are seeing a 50 year old man in follow up with a pituitary adenoma, and a history of multigland hyperparathyroidism. At last visit you ordered MEN1 genetic test which was negative, what investigations do you recommend:**

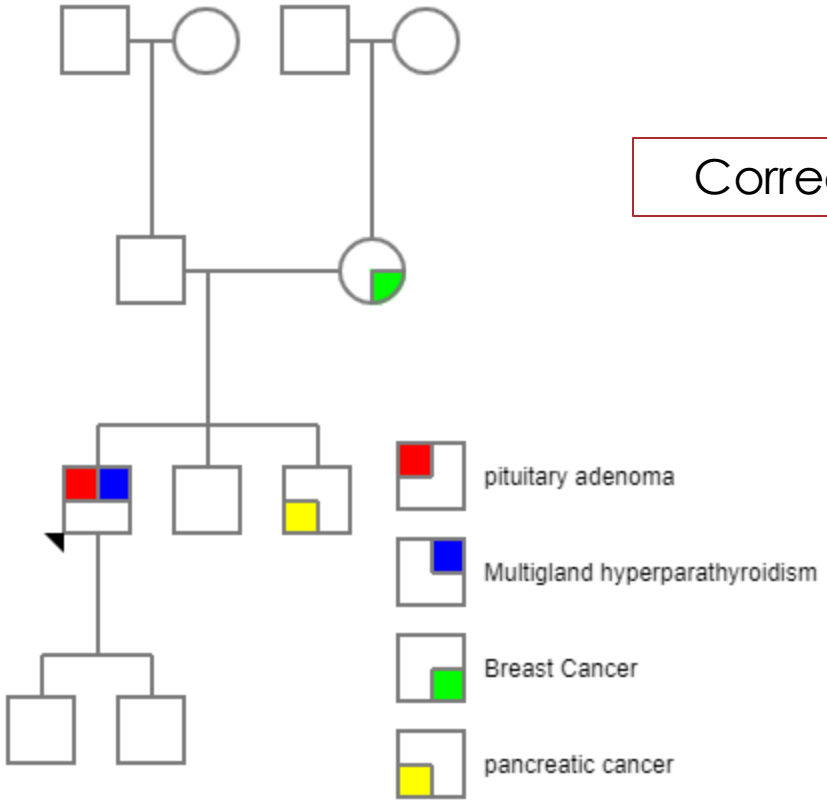
A: follow up pituitary imaging

B: MRI Chest and Abdomen

C: No further investigation

D: Ca, PTH, Prolactin, IGF1 and imaging for his first degree relatives

**E: B and C**




Correct answer: E

https://academic.oup.com/jcem/article/104/3/753/5134196 Romanet et al 2019 JCEM
https://academic.oup.com/jcem/article/97/9/2990/2536740 (MEN1 screening guidelines)

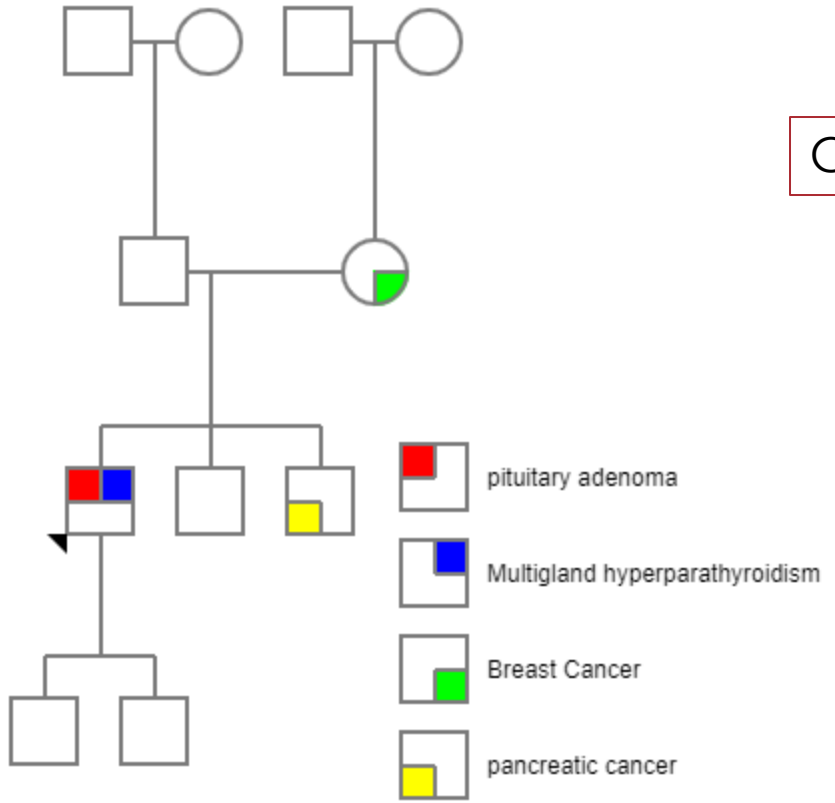
# Post-test Question #5 - Answer

**You are seeing a 50-year-old man in follov up with a pituitary adenoma, and a history of multigland hyperparathyroidism. At last visit you ordered MEN1 genetic testing which identified a variant of uncertain significance, what investigations do you fo his first-degree family members:**

A: No investigations at all

B: Genetic testing for the MEN1 Variant to determine need for MEN1 screening

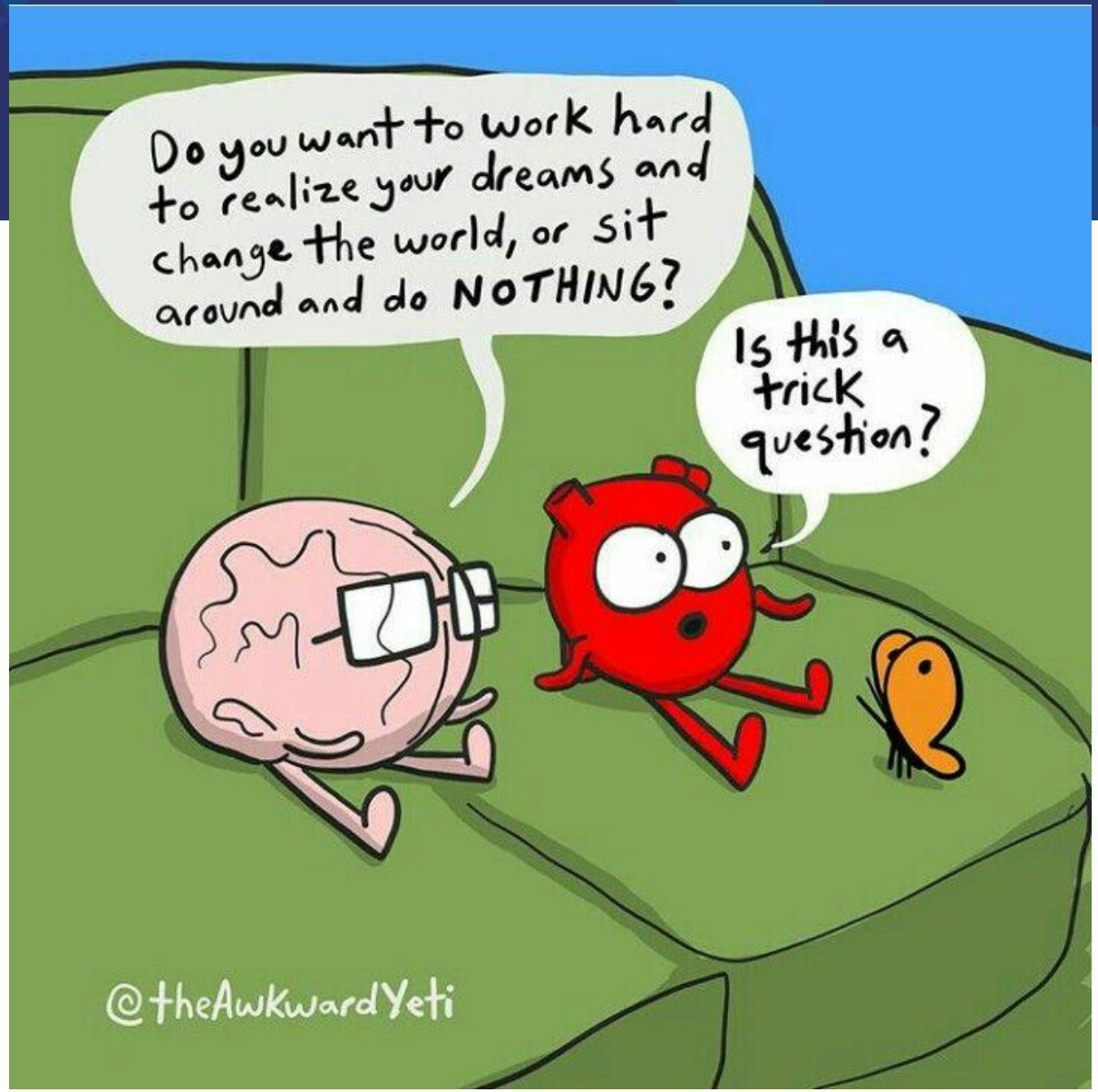
**C: PTH, Ca, Prolactin, IGF1, FBG, Insulin and MRI Brain, Chest, Abdomen**




Correct answer: C

REFERENCES: https://academic.oup.com/jcem/article/97/9/2990/2536740 (MEN1 screening guidelines)
https://onlinelibrary.wiley.com/doi/abs/10.1111/cen.14818 (Approach to VUS)

# Questions


Do you want to work hard to realize your dreams and change the world, or sit around and do NOTHING?
Is this a trick question?
@theAwkwardYeti

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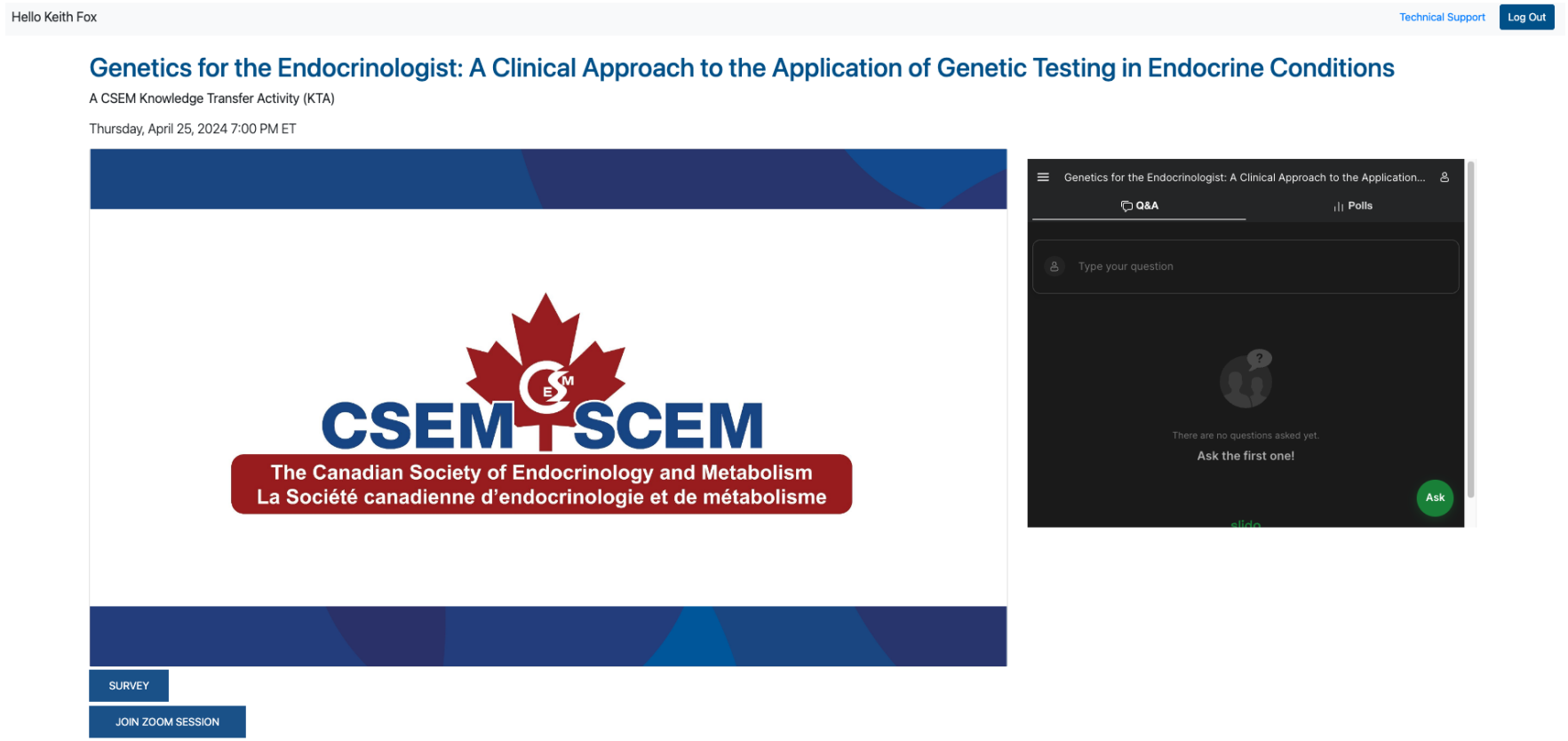
Click the **JOIN ZOOM MEETING button** under your video player.



# Wrap Up

# Accreditation

This activity is an accredited group learning activity under Section 3 as defined by the Royal College of Physicians & Surgeons of Canada for the Maintenance of Certification program.

Approved by CSEM for a maximum of **2.0 hours (credits are automatically calculated)**

**CREDITS**

- Complete the evaluation
- 2 weeks post-session, we'll email your results and personal reflection tool
- Review your results
- Reflect using the tool
- Enter your learning outcomes into Mainport

# Evaluation

- Scan the QR code now
- Visit the website for the evaluation link
- Check your email tomorrow for link

# Upcoming Webinar-Unaccredited

Thyroid Foundation of Canada
La Fondation canadienne de la Thyroïde

Hosted by the Thyroid Foundation of Canada,

a CSEM patient partner organization

***Rethinking Hypothyroidism***

***Dr. Antonio Bianco, University of Chicago***

**April 28, 2024; 1:00 pm ET**

REGISTER at thyroid.ca

(this presentation is for a medical audience)

# Upcoming CSEM KTA

**Challenging Cases in Osteoporosis**

June 18, 2024; 7:00 pm ET

REGISTER via your membership portal

# Thank You

Thank you to:

- Our faculty for sharing their expertise.
- Our sponsors.
- You – our participants and CSEM members!