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Institut-Hôpital neurologique de Montréal
Montreal Neurological Institute-Hospital

November 28th, 2022

1st National Neurogenetic Variant Interpretation Course

Lecture by:

Sali Farhan, PhD, FCCMG (Assistant Professor, Clinical Molecular Geneticist)
Allison Dilliott, PhD (Post-Doctoral Scholar)
Alana Mistry, MSc, **Nellie Fotopoulos**, PhD, and **Kayla Horowitz**, MSc
(Genetic Counsellors at The Neuro)

McGill
Centre universitaire de santé McGill
McGill University Health Centre

Meet Our Genetic Counselling Team

Alana Mistry, MSc, CGC

Clinical Genetic Counsellor

Kayla Horowitz, MSc, GC

Clinical/Research Genetic Counsellor

Nellie Fotopoulos, PhD, CCGC

Clinical/Research Genetic Counsellor

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Meet Our Genome Analysis Team

Sali Farhan, PhD, FCCMG

Assistant Professor and Clinical Molecular Geneticist

Allison Dilliott, PhD

Post-Doctoral Scholar

- **Isabela Bucco,** Genome Analyst
- **Mia Ginsberg**, Genome Analyst

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Outline - Learning Objectives

Part I:

1. Understand the role of genetic counsellors in neurology.
2. Recognize when an underlying genetic cause should be considered.
3. Become familiar with the process of gene panel selection and lab report interpretation.

Part II:

4. From DNA to data - the process of generating meaningful results.
5. Review ACMG criteria for variant classification and VUS interpretation.
6. Introduction to frequently used variant interpretation resources.

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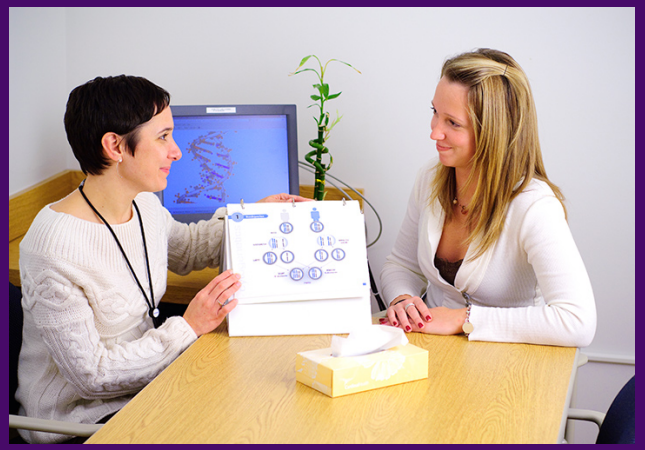
What is Genetic Counselling?

"Genetic counselling is the process of ***helping*** people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease"

– NSGC Definition Task Force, 2006.



Genetic counselling ≠ Genetic testing

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Genetic Counsellors can work in…

Oncology

Ophthalmology

Pediatrics

Neurology

Research

Prenatal care & family planning

Cardiology

Personalized medicine

Lab

Education

and more…

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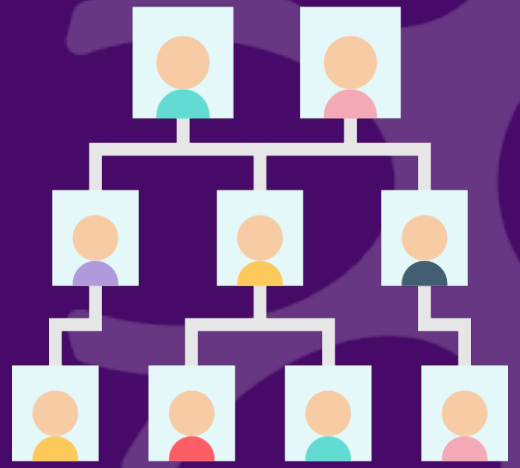
Why take a family history?

Eliciting the family history can allow for recognition of inheritance patterns and the opportunity for **diagnosis**, **counselling**, potential targeted **prevention and treatment**, and the **identification of at-risk relatives**



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When to Consider a Referral to Neurogenetics

- Two or more family members with the same disease on same side of the family
  - ++ suspicion for rare diseases in multiple relatives (i.e. ALS)
- Vertical transmission of disease in a family
- Earlier age of onset than expected in the general population
- A hereditary condition reported in a close relative (i.e. Huntington's)

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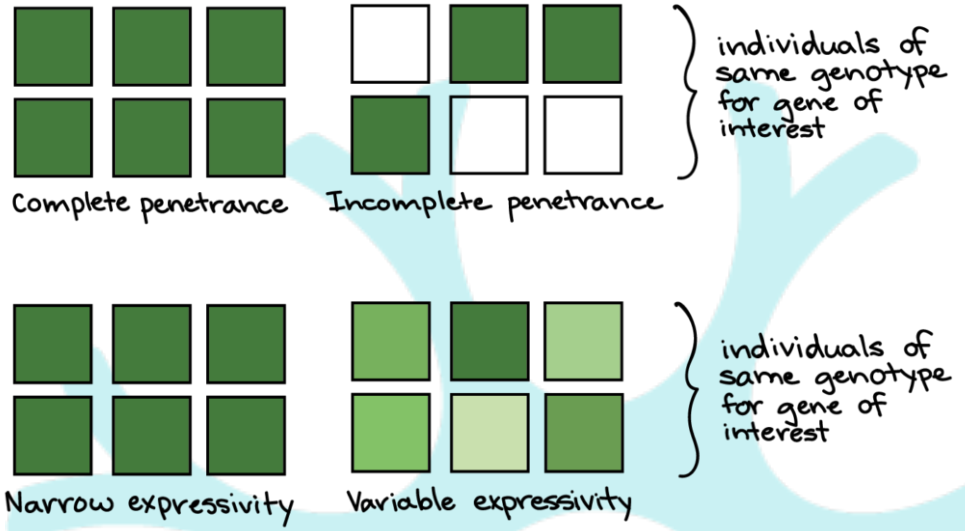
Factors that complicate the interpretation of a pedigree

- Incomplete or reduced penetrance
- Variable expressivity

- Small families
- Premature death of relatives
- *De novo* (“new”) mutation
- Recessive disorders
- Genetic anticipation
- Complex sociocultural factors



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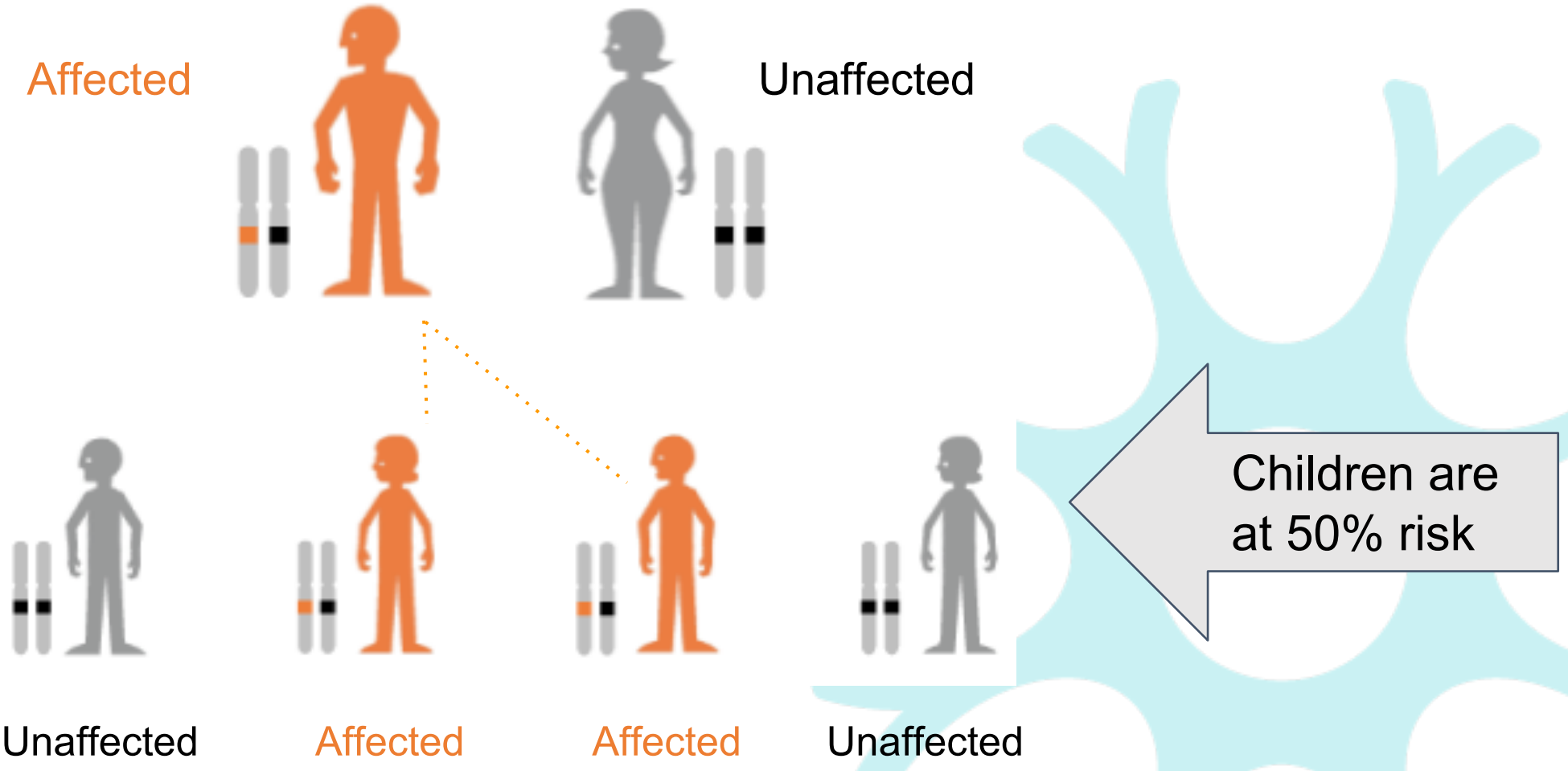
Inheritance pattern - Autosomal Dominant (AD)



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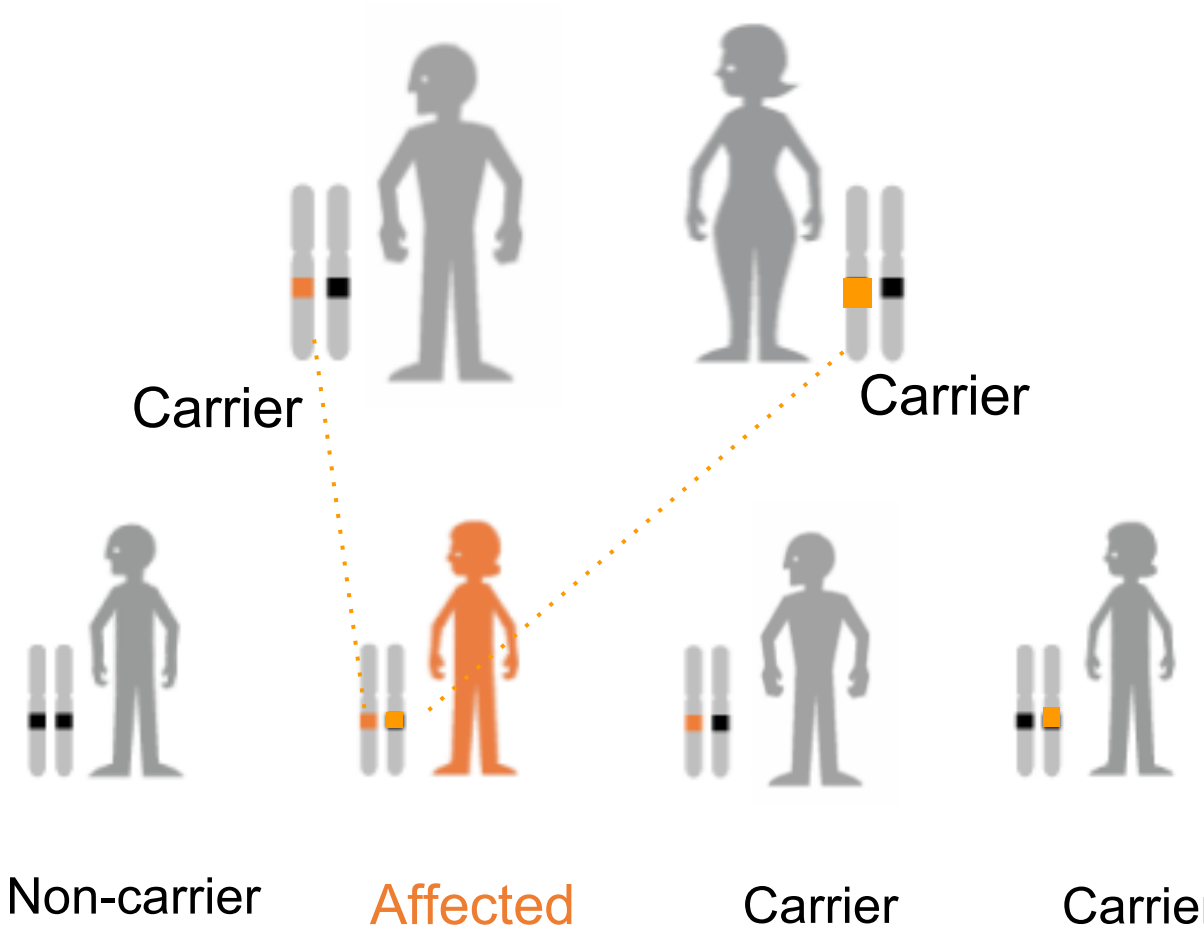
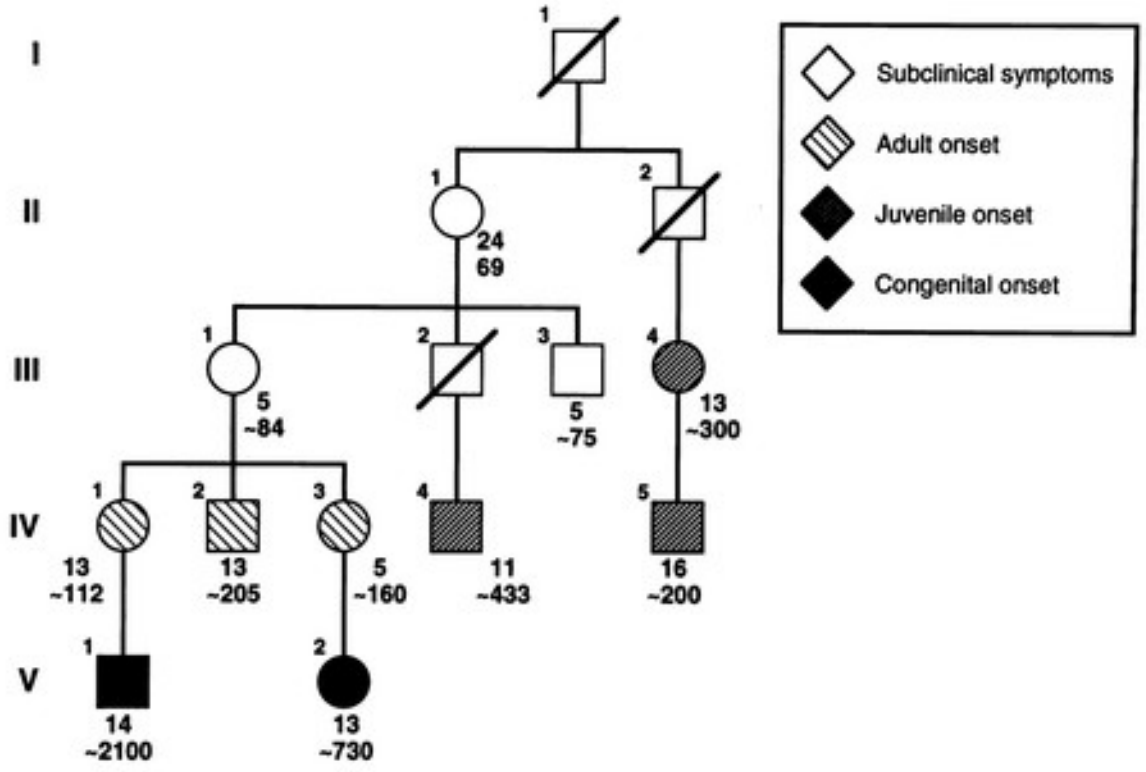
Inheritance pattern - Autosomal Recessive (AR)

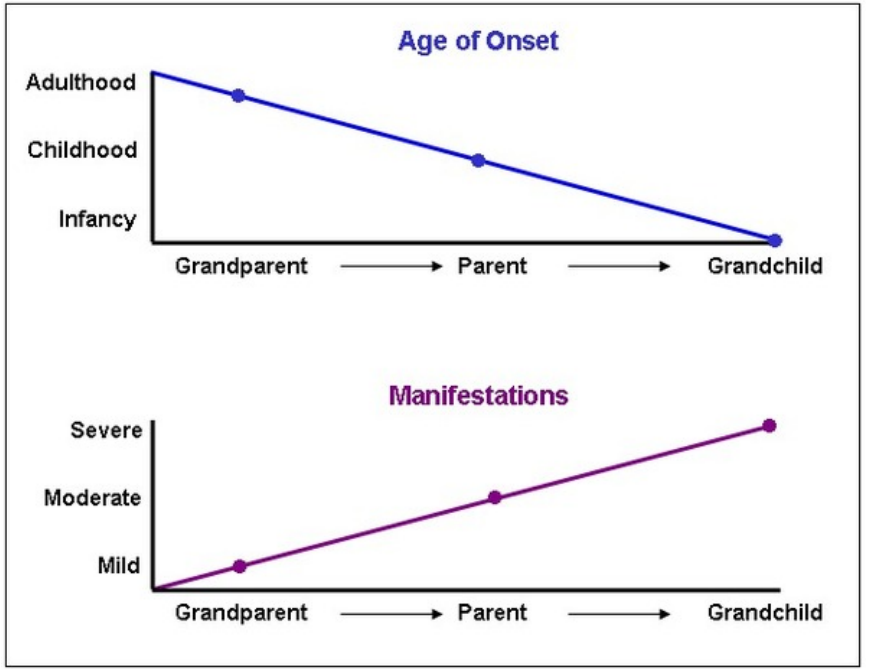


- ➔ Carriers are typically unaffected
- ➔ Often no family history seen
- ➔ Consanguinity is a key risk factor

Children are at 25% risk

Genetic Anticipation





Common Neurogenetic Indications

Condition	Genes	Type of Variant
CADASIL	*NOTCH3*	Sequence (~95%)
Alzheimer's	*APP, PSEN1, PSEN2; APOe4*	Sequence; risk allele; late-onset
Frontotemporal Dementia (FTD)	*C9orf72, GRN, MAPT*	>60 G_4C_2 rpt expansion; sequence
Parkinson's disease (AD or AR)	*GBA, LRRK2, SNCA, PARK2, PARK7,PINK1, VPS35,* etc.	Sequence
OPMD	*PABPN1*	11 to 18 GCN rpt exp (99%)
FSHD	*D4Z4*	<9 rpt contraction
Huntington's	*HTT*	>40 CAG rpt expansion
ALS (AD, AR)	*C9orf72, SOD1, FUS, ATXN2,* etc.	>60 G_4C_2 rpt expansion; sequence; risk allele
SCA (>60 types) (AD, AR, X-linked)	*ATN1, ATXN1, ATXN2, ATXN3, CACNA1A,* etc.	CAG rpt exp; # pathogenic rpts depend on gene
HSP (AD, AR, X-linked)	*SPAST, ATL1, SPG31, KIF1A, REEP1* etc.	Sequence (~80%)
CMT (AD, AR, X-linked)	*PMP22*	Duplication (80%)
Myotonic Dystrophy Type 1, 2	*DMPK; CNBP*	>100 CTG rpt exp; 75-11K CCTG rpt exp

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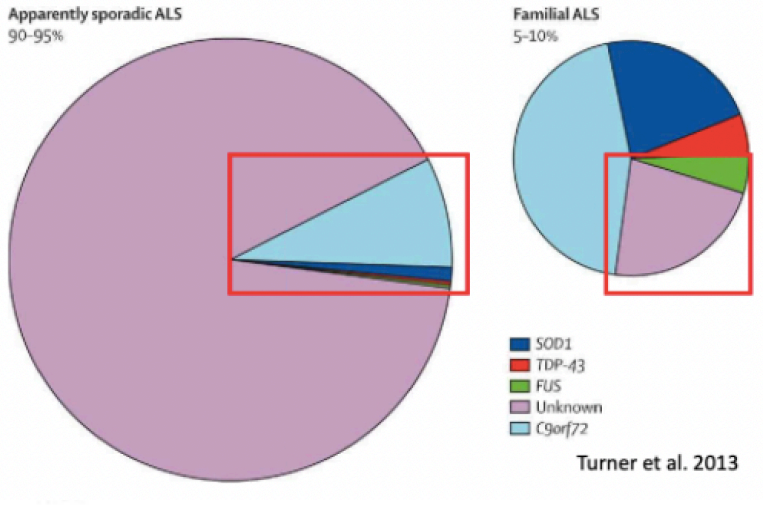
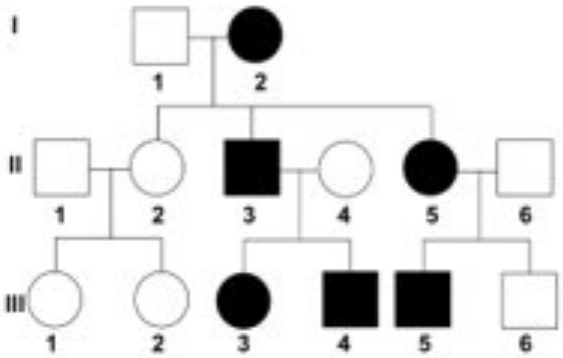
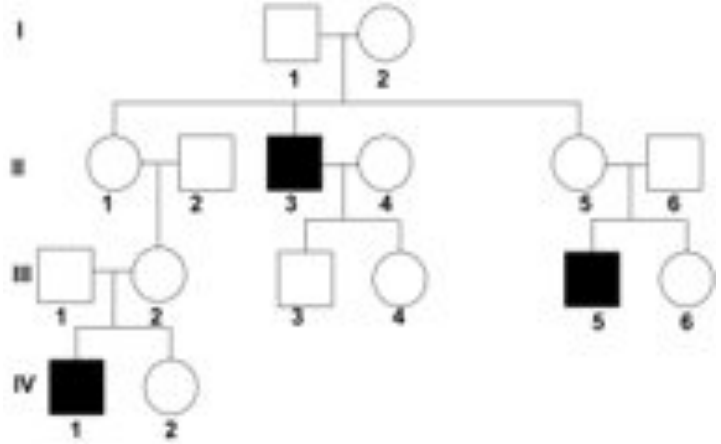
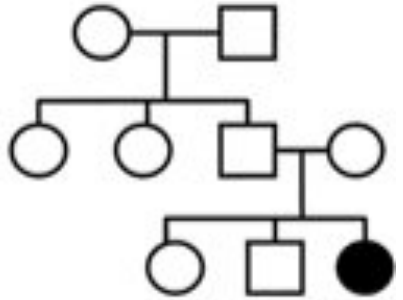
Sporadic vs. Familial ALS









"Familial"/Hereditary ALS

Family with reduced penetrance

Isolated case with an identified gene variant

"Sporadic" ALS

MNI Criteria for Genetic Testing in Alzheimer's Disease

For patients with a diagnosis of Alzheimer's:

- Offer testing to all early-onset cases (diagnosed before age 65) with or without family history and those diagnosed older than 65 with at least 1 close relative with early-onset diagnosis

- For those diagnosed after age 65 without a family history of early-onset, genetic testing is generally not offered but clinical judgement can be used in cases of many relatives with late-onset diagnosis

Genetic testing for symptomatic patients only. If clinical trials or treatments become available, then asymptomatic patients with a significant family history could be tested. Can quote empiric lifetime risk based on family history.

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Recommended Components of HD Predictive Testing Process:

1. **Telephone Contact**
2. **Visit 1**
   - Genetic Counseling
   - Sign Informed Consent Document
   - Mental Health Assessment
   - Neurological Exam
   - Draw Blood
3. **Visit 2**
   - Disclosure of Results in Person
   - Arrange Post-result Follow-up
4. **Follow-Up**
   - Prearranged phone call or in-person visit

"Predictive patient":
an asymptomatic at-risk individual for an incurable neurodegenerative disease (i.e. Huntington's, genetic ALS/FTD, CADASIL, etc.)

Please always refer these cases to Genetics for pre-test counselling!

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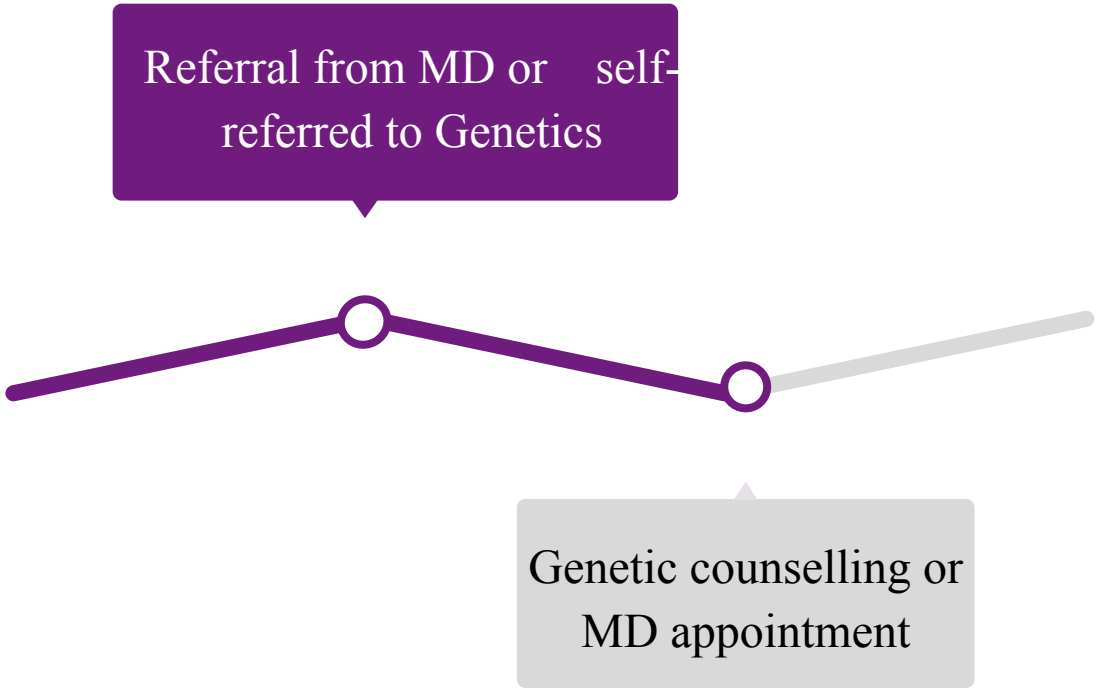
Typical Genetic Testing Process



Historically, almost all genetic testing ordered in Medical Genetics

Now, mainstreaming has become more common in neurology and other specialties

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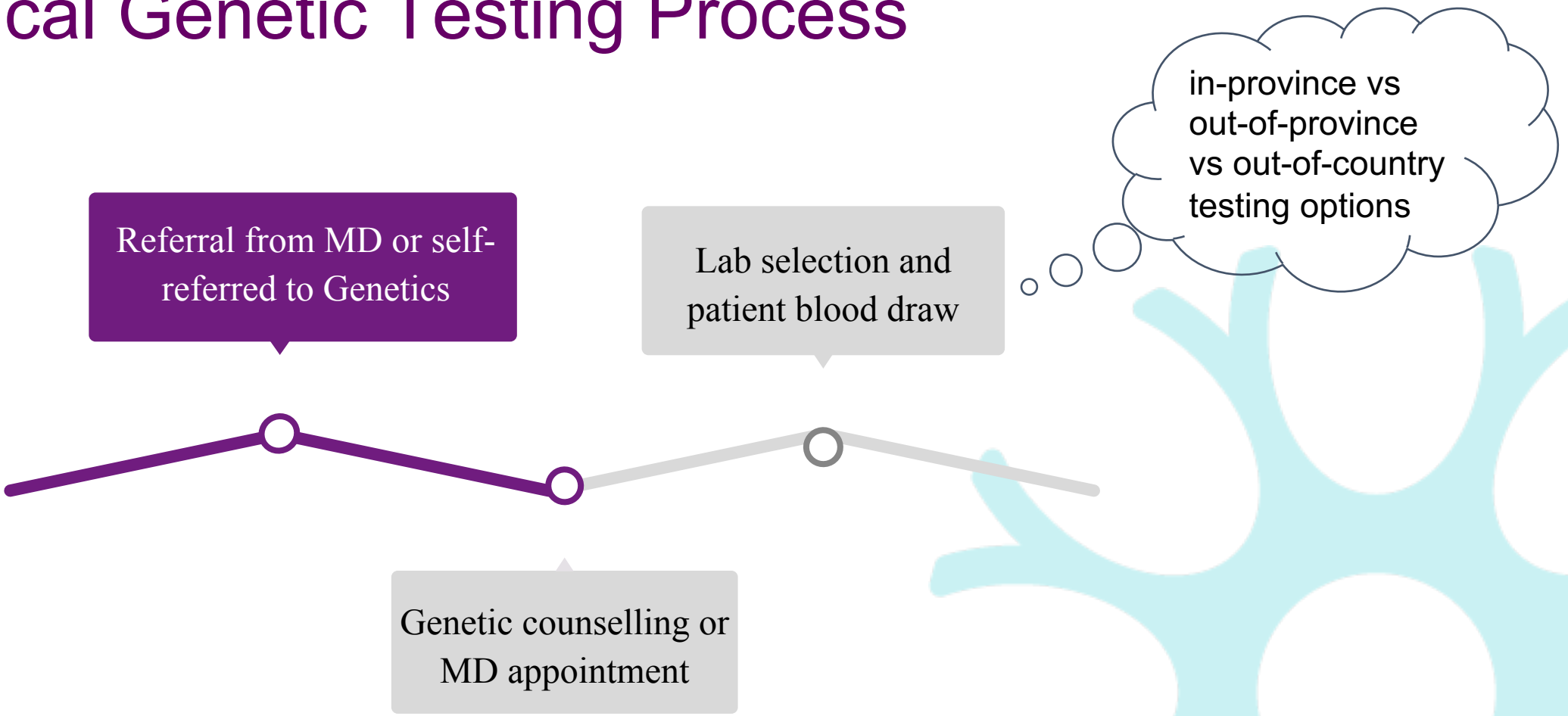
Typical Genetic Testing Process



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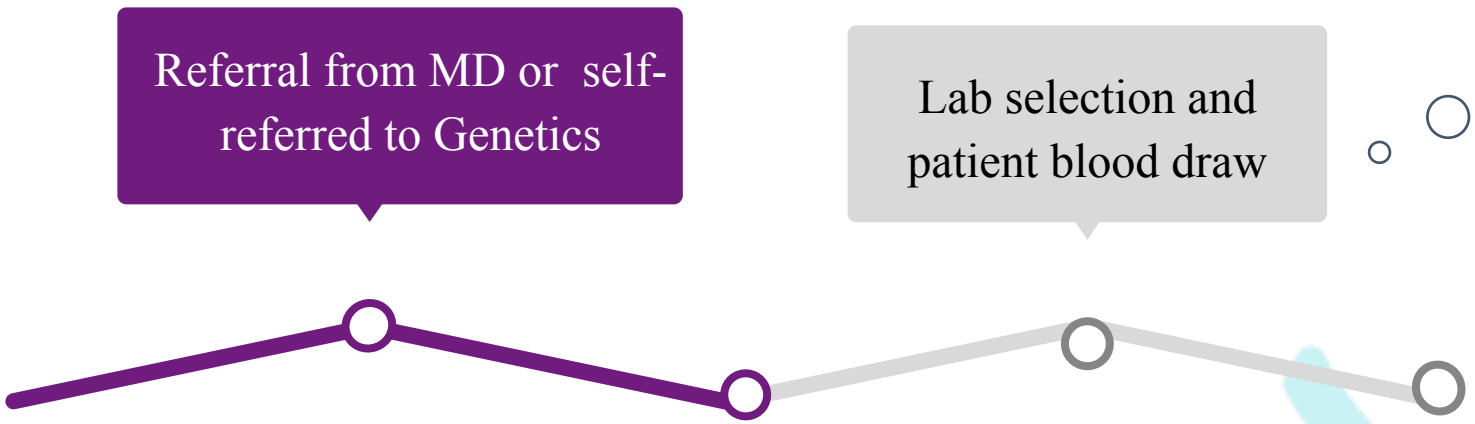
Typical Genetic Testing Process



Referral from MD or self-referred to Genetics

Genetic counselling or MD appointment

Lab selection and patient blood draw

Result disclosure and family letter if indicated

If +, referral from MD to Genetics

in-province vs out-of-province vs out-of-country testing options

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Type of results

Pathogenic/ Likely Pathogenic Variant identified

Can confirm diagnosis

Testing available for all relatives

Variant of uncertain significance identified

Result is inconclusive

Recontact clinic in 1-2 years

Negative

(benign or likely benign changes identified)

Based on current knowledge

May or may not lead to more testing

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Example Report: Positive

PATIENT INFORMATION	SPECIMEN INFORMATION	PROVIDER INFORMATION
LAST, First ID#: DOB: Month, Day, Year Sex:	Type: Collected: Month, Day, Year Received: Month, Day, Year PG ID: ####-###-###	Physician Genetic Counselor Institution

MOLECULAR GENETICS REPORT:
Huntington Disease Testing via the *HTT* Repeat Expansion Test

SUMMARY OF RESULTS **POSITIVE: Heterozygous for 42 CAG Repeats (One Full Penetrance Allele)**

RESULTS AND INTERPRETATIONS: This patient is heterozygous for one *HTT* normal allele with 17 CAG repeats and one expanded *HTT* allele with 42 CAG repeats. An expanded *HTT* allele of this size is consistent with this individual developing Huntington disease with variable age of onset (see for example Jama et al. 2013. PubMed ID: 23414820; Bean & Bayrak-Toydemir. 2014. PubMed ID: 25356969).

These results should be interpreted in the context of clinical findings, family history and other laboratory data. All genetic tests have limitations. Please see limitations and other information for this test on the following pages.

NOTES: Genetic counseling is recommended. Testing for the *HTT* CAG repeat expansion is available for at-risk, adult family members.

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Example Report: Negative

PATIENT INFORMATION	SAMPLE INFORMATION	PROVIDER INFORMATION
LAST, First ID#: DOB: Month, Day, Year Sex:	Type: Collected: Month, Day, Year Received: Month, Day, Year PG ID: ####-###-###	Physician Genetic Counselor Institution

MOLECULAR GENETICS REPORT:

Huntington Disease Testing via the *HTT* Repeat Expansion Test

SUMMARY OF RESULTS **NEGATIVE**

RESULTS AND INTERPRETATIONS: This patient is heterozygous for two normal *HTT* alleles, one with 17 CAG repeats and one with 18 CAG repeats.

These results should be interpreted in context of clinical findings, family history and other laboratory data. All genetic tests have limitations. Please see limitations and other information for this test on the following pages.

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Example Report: Variant of Uncertain Significance (VUS)

MOLECULAR GENETICS REPORT:
Glycogen Storage Disease and Disorders of Glucose Metabolism Panel

SUMMARY OF RESULTS **Heterozygous for a Variant of Uncertain Significance in *PHKG2***

Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variations, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
PHKG2, NM_000294.2	AR, 172471	c.1187T>A, p.Ile396Lys, Heterozygous	Not listed in ClinVar	Not Present	Conflicting	UNCERTAIN

Mode of Inheritance: Autosomal Dominant=AD, Autosomal Recessive=AR, X-Linked=XL
ClinVar ID: Variant accession (www.ncbi.nlm.nih.gov/clinvar)
GnomAD: Allele Frequency registered in a large population database (gnomad.broadinstitute.org). Value listed is the highest allele frequency reported within one of seven population categories recognized in gnomAD v.2.0 (The "Other" population is excluded).
Missense Predictions: Summarized output (Damaging, Conflicting, or Tolerated) via PolyPhen-2, SIFT, MutationTaster, and FATHMM (PMID: 26555599).

RESULTS AND INTERPRETATIONS: This patient is heterozygous in the *PHKG2* gene for a sequence variant designated c.1187T>A, which is predicted to result in the amino acid substitution p.Ile396Lys. To our knowledge, this variant has not been reported in literature. Although it is possible that the *PHKG2* c.1187T>A (p.Ile396Lys) variant could be pathogenic, at this time its clinical significance is uncertain due to the absence of conclusive functional and genetic evidence.

This patient is also apparently negative for copy number variants (CNVs) within the genomic regions of this test.

These results should be interpreted in context of clinical findings, family history and other laboratory data.
All genetic tests have limitations. Please see limitations and other information for this test on the following pages.

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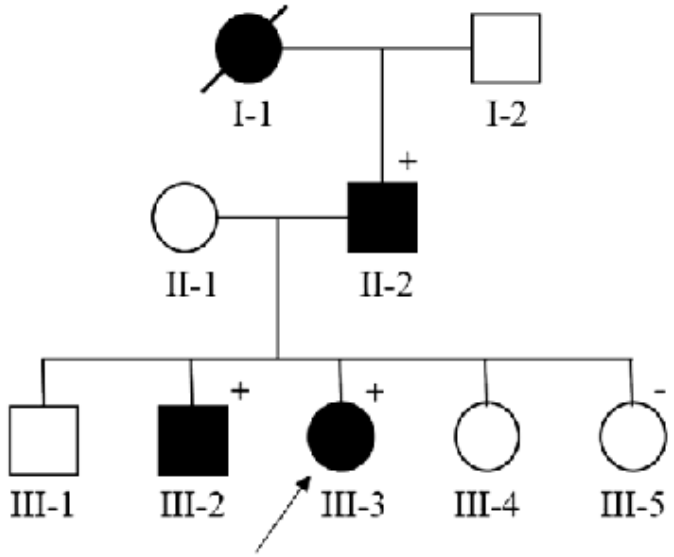
What to do with VUS?

ACMG guidelines:

VUS should not be used in clinical decision-making. All clinical decisions should be based on personal and family history alone.



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Part I: Q&A

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Part II

1. From DNA to data - the process of generating meaningful results

2. Review ACMG criteria for variant classification and VUS interpretation

3. Introduction to frequently used variant interpretation resources

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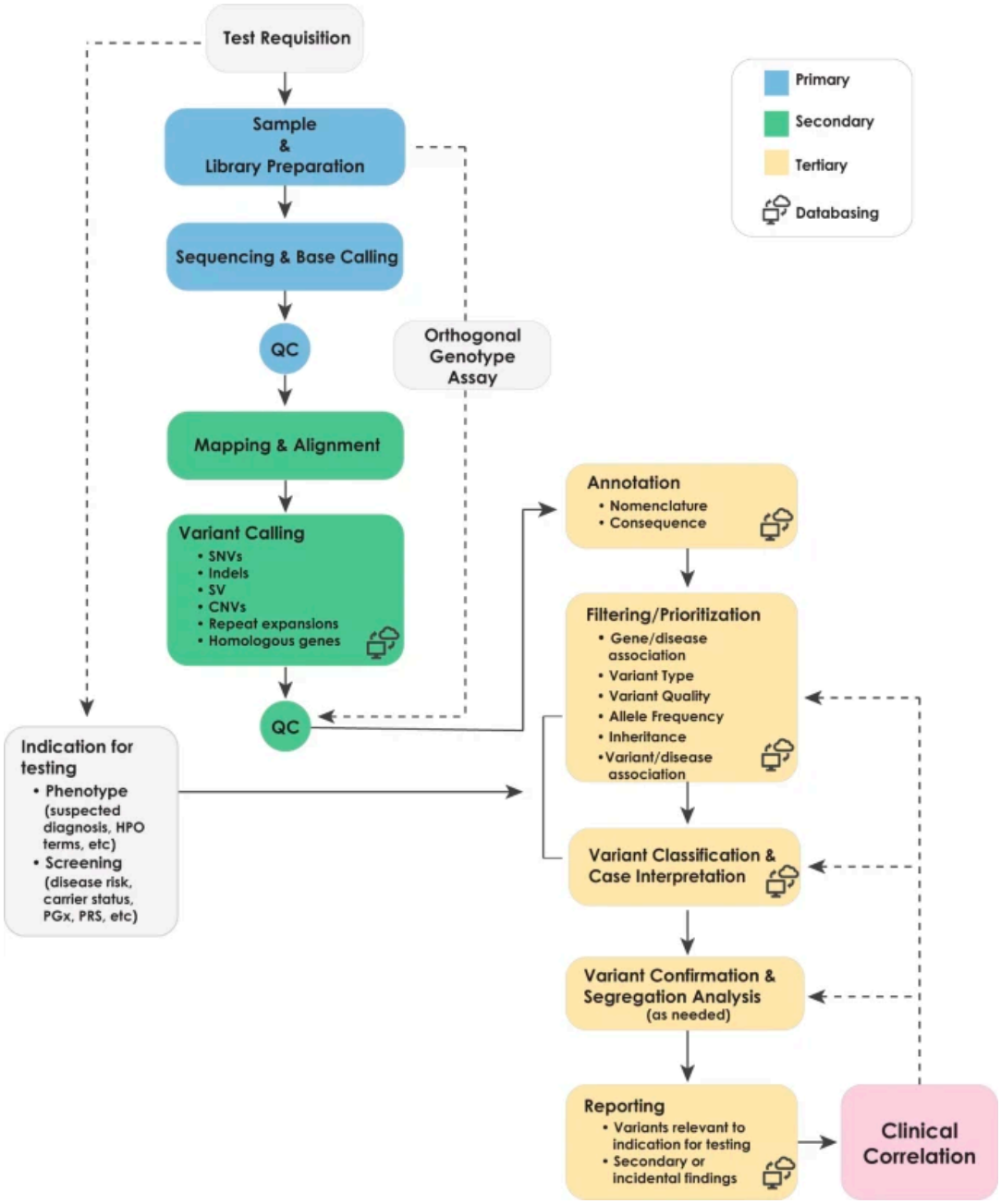


Marshall et al., 2020. PMID: 33110627

Example of supplementary information in a clinical lab report:

GENES ANALYZED: *AIP, ALK, ANKRD26, APC, ARMC5, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN1C, CDKN2A, CEBPA, CHEK2, DDX41, DICER1, DIS3L2, EPCAM, ETV6, EXT1, EXT2, FANCC, FH, FLCN, GALNT12, GATA2, GPC3, GREM1, HOXB13, HRAS, KIF1B, KIT, LZTR1, MAX, MEN1, MET, MITF, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PALLD, PDGFRA, PHOX2B, PMS2, POLD1, POLE, POT1, PRKAR1A, PRKAR1A, PTCH1, PTCH2, PTEN, RAD50, RAD51C, RAD51D, RB1, RECQL, REST, RET, RUNX1, SAMD9L, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, SRP72, STK11, SUFU, TERC, TERT, TMEM127, TP53, TRIP13, TSC1, TSC2, VHL, WT1, XRCC2*

SUMMARY STATISTICS:

Pipeline	Version	Average NGS Coverage	Fraction Bases Covered with NGS
Titanium	1.1.0	275x	99.7%

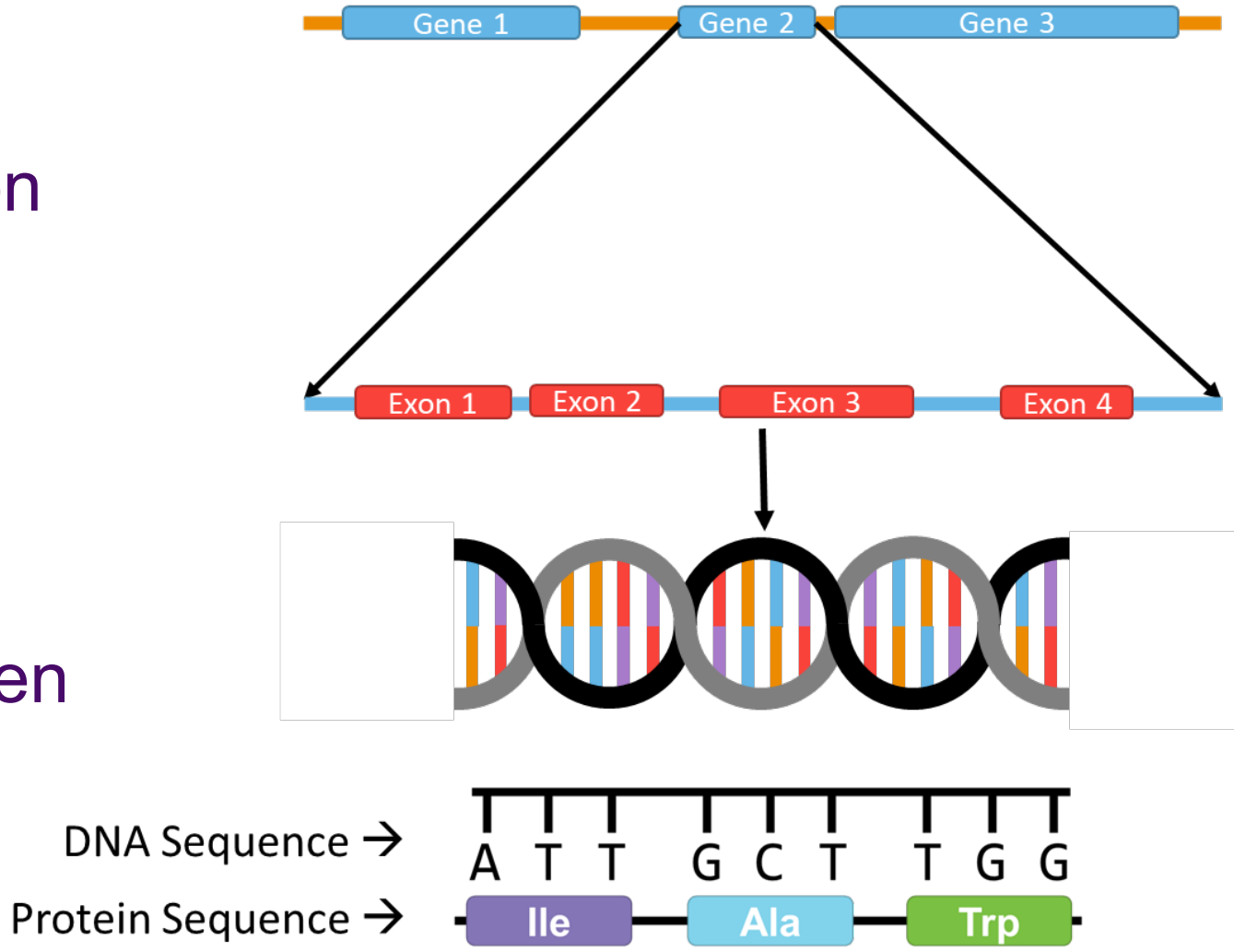
Minimum NGS coverage is ≥20x for all exons and +/-10bp of flanking DNA, and ≥10x from 11-20bp of flanking DNA.

- Test limitations
- Test methods
- Sensitivity (true positive) and specificity (true negative) metrics of test
- Recommendations

Genetic testing methodology

- Genetic testing typically encompasses next-generation sequencing:
  - Genome
  - Exome
  - Targeted gene panels

- Most tests are built on an exome backbone, but are often offered as disease-specific panels that sequence pre-determined gene sets



Genetic testing methodology

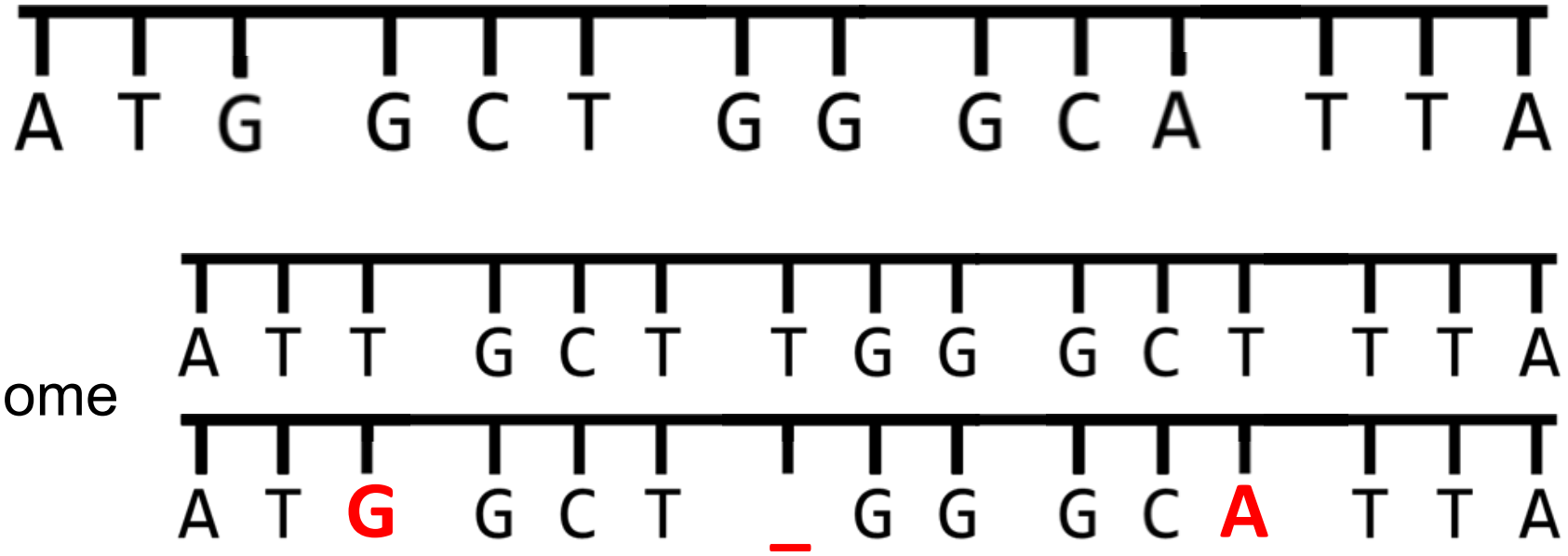
FASTQ:
Raw sequencing data

↓

BAM:
Alignment to the human genome
"reference sequence"

↓

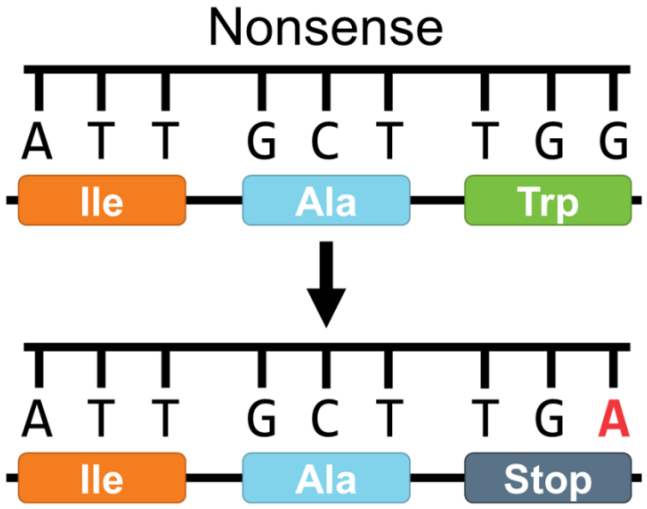
VCF:
Variant calls



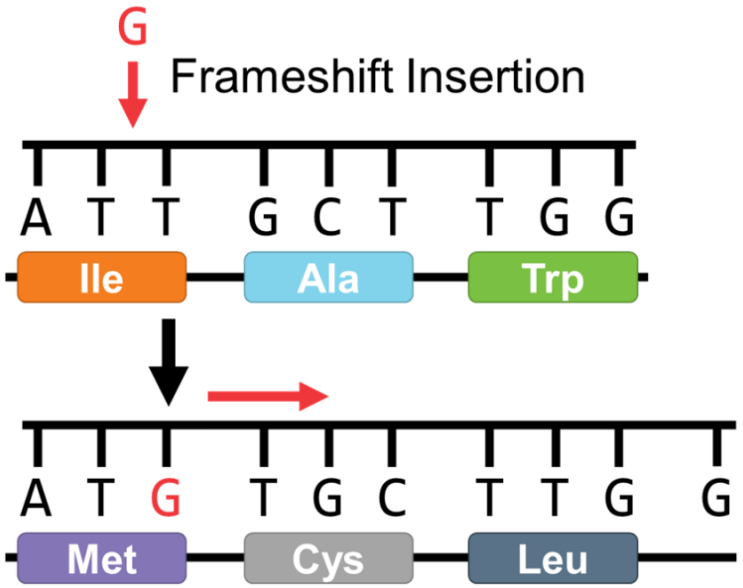
#CHROM	POS	REF	ALT	QUAL	FILTER
22	6,352,492	T	G	52	PASS
22	6,352,496	TG	G	7	q10
22	6,352,501	T	A	29	PASS

Variant types detected from sequencing data

Protein truncating variants

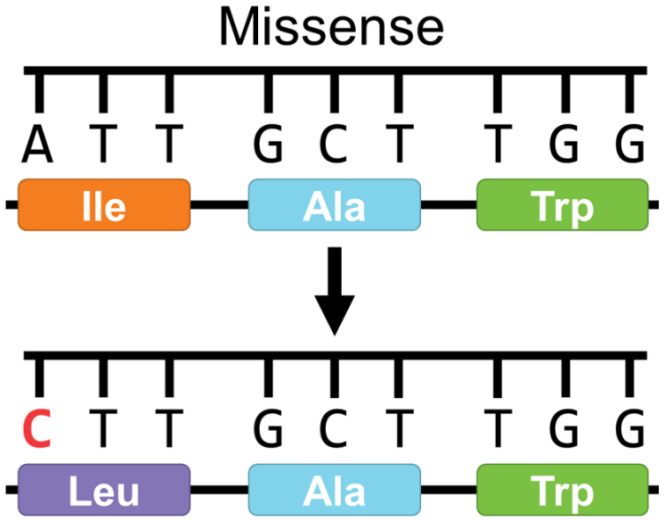


c.126G>C
p.Trp42Ter



c.119_120insG
p.Ile40fs

Missense variants



c.A118C
p.Ile40Leu

Additional variation detected from genome sequencing

Variant type	Gene(s) (if applicable)	Disorder(s)	References (if applicable)
SNVs and small insertions and deletions[a] (1–50 base pairs)	N/A	Heritable disease	Zook et al.[37] Eberle et al.[58]
Copy number variation[a] (deletions and duplications)	N/A	Heritable disease including known microdeletion/duplication syndromes	Gross et al.[33] Stavropoulos et al.[27] Lindstrand et al.[45]
Mitochondrial variation[b] (SNVs, deletions, duplications, and heteroplasmy of at least 5%)	N/A	Known mitochondrial disorders	Duan et al.[56]
Structural variants[b]	N/A	Heritable disease including those caused by translocations, inversions, and other genomic rearrangements	Lindstrand et al.[45]
Repeat expansions[c]	*FMR1*	Fragile X and related disorders	Dolzhenko et al.[43]
	HTT	Huntington disease	
	SCA1	Spinocerebellar ataxia 1	
	DMPK	Myotonic dystrophy 1	
	C9orf72	Amyotrophic lateral sclerosis	
Selected pseudogenes[c]	*SMN1 and SMN2*	Spinal muscular atrophy	Chen et al.[57]
	CYP21A2	21-Hydroxylase deficiency	
	CYP2D6	Codeine sensitivity	
	HBA1 and HBA2	Alpha thalassemia	
	PMS2	Colorectal cancer	
	PKD1	Polycystic kidney disease 1	

[a]Recommended minimum variant types for clinical validation of WGS. Copy number variation is defined here as unbalanced changes (deletions and duplications) that are at the resolution of chromosomal microarray analysis.

[b]Some initiative groups have clinically validated. Structural variants are defined here as any genomic alteration >50 base pairs, including balanced and unbalanced changes.

[c]Examples of targeted loci that could be validated and reported as part of a clinical WGS test.

Marshall et al., 2020. PMID: 33110627

Variant Annotations

Gene-disease associations

- Online Mendelian in Man (OMIM®)
- ClinGen gene curations

General population databases - minor allele frequencies

- GnomAD - WES > 125,000 samples; WGS > 76,000 samples

In silico prediction tools

- Apply biochemical properties and conservation to predict variant pathogenicity

ClinVar - variant-level previous disease associations

Gene-disease associations

OMIM®

*147450
Table of Contents

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  - Animal Model
- Allelic Variants
  - Table View
- See Also
- References
- Contributors
- Creation Date
- Edit History

* 147450

SUPEROXIDE DISMUTASE 1; SOD1

Alternative titles; symbols

SUPEROXIDE DISMUTASE, CYTOSOLIC
SUPEROXIDE DISMUTASE, SOLUBLE
SOD, SOLUBLE
SUPEROXIDE DISMUTASE, COPPER-ZINC
INDOPHENOL OXIDASE A; IPOA

HGNC Approved Gene Symbol: SOD1

Cytogenetic location: 21q22.11 Genomic coordinates (GRCh38): 21:31,659,693-31,668,931 (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype (View Clinical Synopses)	Phenotype MIM number	Inheritance	Phenotype mapping key
21q22.11	Amyotrophic lateral sclerosis 1	105400	AD, AR	3
	Spastic tetraplegia and axial hypotonia, progressive	618598	AR	3

ClinGen Expert Panels

Amyotrophic Lateral Sclerosis Spectrum Disorders Expert Panel

23 Total Curations Return to Listing

Click on below to view hidden columns

Search in table

Showing 1 to 23 of 23 rows 25 rows per page

Gene	Disease	MOI	SOP	Contribution	Classification	Last Eval.
ANG	amyotrophic lateral sclerosis type 9	AD	SOP8	Primary	Limited	02/08/2022
ANXA11	amyotrophic lateral sclerosis type 23	AD	SOP8	Primary	Definitive	11/12/2021
C9orf72	frontotemporal dementia and/or amyotrophic lateral sclerosis 1	AD	SOP8	Primary	Definitive	09/21/2021
CCNF	frontotemporal dementia and/or amyotrophic lateral sclerosis 5	AD	SOP8	Primary	Limited	04/05/2022
CHMP2B	frontotemporal dementia and/or amyotrophic lateral sclerosis 7	AD	SOP8	Primary	Definitive	07/12/2022
DAO	amyotrophic lateral sclerosis	AD	SOP8	Primary	Refuted	04/12/2022

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General population databases

SOD1 (gnomAD v2.1.1)

GnomAD

- WES > 125,000 samples; WGS > 76,000 samples
- Disease exclusion cohorts available, e.g. non-neurological
- Multiple ancestral populations, although largely European

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In silico prediction tools

PolyPhen-2

- Score that incorporates biochemical/physical properties

SIFT

- Score that incorporates amino acid conservation information

REVEL

- Score that predicts the pathogenicity of missense variants based on a combination of scores from 13 individual tools

- Genomic variants are typically classified on a five-point scale to indicate the likelihood that the particular variant is associated with disease
- Pathogenic variants in disease genes related to phenotype (or symptoms) means that a cause of the patient's symptoms has been identified
- Clinically, both pathogenic and likely pathogenic variants are treated the same—as if they are likely disease causing
- Variants of Uncertain significance (VUS) have an uncertain relationship to disease
- It is not recommended that Variants of Uncertain Significance be used for clinical decision making
- International efforts are underway to reclassify VUS variants as benign or pathogenic
- Finding a VUS is common among large-scale tests like gene panels, whole exome, and whole genome sequencing

Evidence Framework:

"Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology"

Richards et al., 2015.
PMID: 25741868

	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 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	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 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	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 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			

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Rules for Combining Criteria to Classify Sequence Variants

Richards et al., 2015.
PMID: 25741868

Pathogenic

1. 1 Very Strong (PVS1) *AND*
   - **a.** ≥1 Strong (PS1–PS4) *OR*
   - **b.** ≥2 Moderate (PM1–PM6) *OR*
   - **c.** 1 Moderate (PM1–PM6) and 1 Supporting (PP1–PP5) *OR*
   - **d.** ≥2 Supporting (PP1–PP5)
2. ≥2 Strong (PS1–PS4) *OR*
3. 1 Strong (PS1–PS4) *AND*
   - **a.** ≥3 Moderate (PM1–PM6) *OR*
   - **b.** 2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR*
   - **c.** 1 Moderate (PM1–PM6) *AND* ≥4 Supporting (PP1–PP5)

Likely Pathogenic

1. 1 Very Strong (PVS1) *AND* 1 Moderate (PM1–PM6) *OR*
2. 1 Strong (PS1–PS4) *AND* 1–2 Moderate (PM1–PM6) *OR*
3. 1 Strong (PS1–PS4) *AND* ≥2 Supporting (PP1–PP5) *OR*
4. ≥3 Moderate (PM1–PM6) *OR*
5. 2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR*
6. 1 Moderate (PM1–PM6) *AND* ≥4 Supporting (PP1–PP5)

Benign

1. 1 Stand-Alone (BA1) *OR*
2. ≥2 Strong (BS1–BS4)

Likely Benign

1. 1 Strong (BS1–BS4) and 1 Supporting (BP1–BP7) *OR*
2. ≥2 Supporting (BP1–BP7)

*Variants should be classified as Uncertain Significance if other criteria are unmet or the criteria for benign and pathogenic are contradictory.

Variant level previous disease associations

ClinVar

- Public archive of relationships among human variations and phenotypes, with supporting evidence
- Submissions have differing levels of complexity

	Variation *Location*	Gene(s)	Protein change	Condition(s)	Clinical significance (Last reviewed)	Review status
61.	NM_000454.5(**SOD1**):c.50G>C (p.Gly17Ala) *GRCh37:* Chr21:33032132 *GRCh38:* Chr21:31659819	**SOD1**	G17A	Amyotrophic lateral sclerosis type 1, not provided	Pathogenic/Likely pathogenic (Aug 27, 2021)	criteria provided, multiple submitters, no conflicts
62.	NM_000454.5(**SOD1**):c.56T>C (p.Ile19Thr) *GRCh37:* Chr21:33032138 *GRCh38:* Chr21:31659825	**SOD1**	I19T	Amyotrophic lateral sclerosis type 1	Uncertain significance (Sep 1, 2021)	criteria provided, single submitter
63.	NM_000454.5(**SOD1**):c.59A>G (p.Asn20Ser) *GRCh37:* Chr21:33032141 *GRCh38:* Chr21:31659828	**SOD1**	N20S	not specified, Amyotrophic lateral sclerosis type 1	Conflicting interpretations of pathogenicity (Dec 17, 2021)	criteria provided, conflicting interpretations

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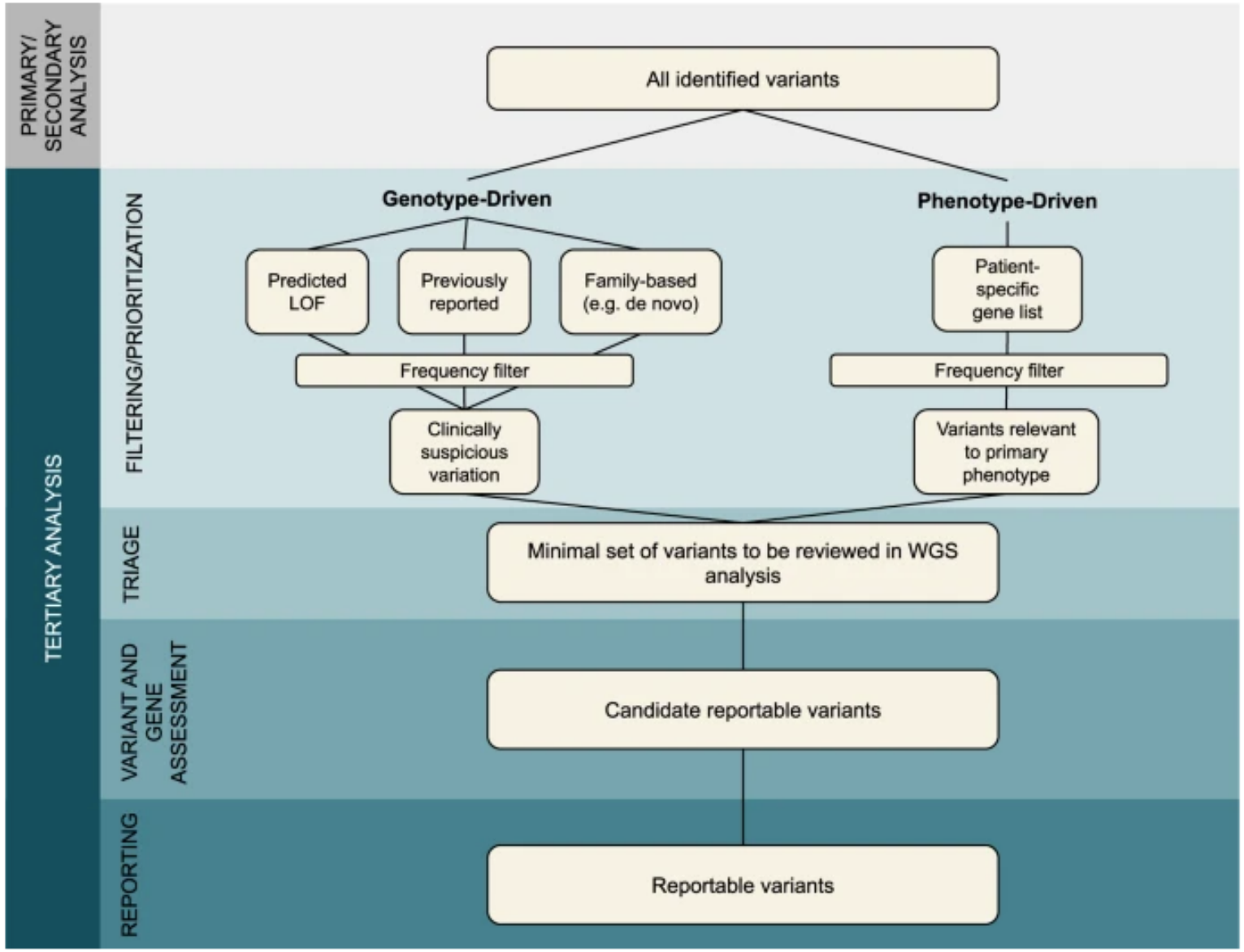
Conventional analytical approach:

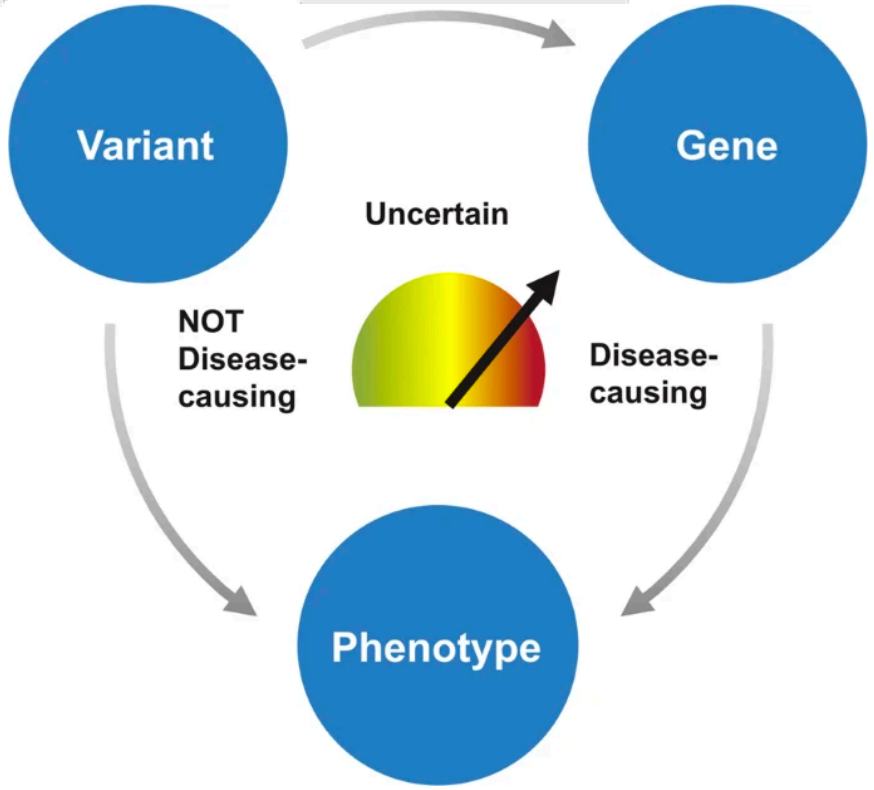
1) genotype-driven
2) phenotype-driven



Marshall et al., 2020. PMID: 33110627

Conventional analytical approach:

- What gene(s) does the variant impact?
- Is the variant expected to impact the function of the gene(s) and if so, does it cause a human phenotype?
- How well does the variant or gene's disease association match that of the patient?
- Has this particular variant (or this variant type, e.g. LOF variants) been shown to cause a phenotype?
- Is the variant returnable as a secondary or incidental finding?



Marshall et al., 2020. PMID: 33110627

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Limitations of variant interpretations:

Our variant interpretations are only as good as the resources available

- Not all ancestries are adequately represented
- Not all types of variation are captured (somatic, mosaic, deep intronic); and even if captured, we do not fully know how to interpret them
- Not all genes are characterized
- Tissue and development-specific expression

What populations are represented in the gnomAD data?

gnomAD v2

Population	overall		controls		non-cancer		non-neuro		non-TOPMed	
	exomes	genomes	exomes	genomes	exomes	genomes	exomes	genomes	exomes	genomes
African/African American	8,128	4,359	3,582	1,287	7,451	4,359	8,109	1,694	6,013	4,278
Amish	0	0	0	0	0	0	0	0	0	0
Latino/Admixed American	17,296	424	8,556	123	17,130	424	15,262	277	17,229	405
Ashkenazi Jewish	5,040	145	1,160	19	4,786	145	3,106	123	4,999	69
East Asian	9,197	780	4,523	458	8,846	780	6,708	780	9,195	761
European (Finnish)	10,824	1,738	6,697	581	10,816	1,738	8,367	582	10,823	1,738
European (non-Finnish)	56,885	7,718	21,384	2,762	51,377	7,718	44,779	6,813	55,840	5,547
South Asian	15,308	*	7,845	*	15,263	*	15,304	*	15,308	*
Other	3,070	544	957	212	2,810	544	2,433	367	3,032	506
XX	57,787	6,967	25,645	2,508	53,850	6,967	47,831	4,799	55,662	6,299
XY	67,961	8,741	29,059	2,934	64,629	8,741	56,237	5,837	66,777	7,005
Total	**125,748**	**15,708**	**54,704**	**5,442**	**118,479**	**15,708**	**104,068**	**10,636**	**122,439**	**13,304**

gnomAD v3

Population	overall	controls/biobanks	non-cancer	non-neuro	non-TOPMed	non-v2
African/African American	20,744	4,554	20,583	16,253	12,431	14,377
Amish	456	30	456	431	56	455
Latino/Admixed American	7,647	2,345	7,553	7,424	6,460	6,878
Ashkenazi Jewish	1,736	68	1,651	1,694	499	1,538
East Asian	2,604	1,215	2,486	2,604	1,883	1,414
European (Finnish)	5,316	2,750	5,316	3,495	5,270	3,662
Middle Eastern	158	123	152	155	136	154
European (non-Finnish)	34,029	3,427	32,411	31,966	10,533	25,988
South Asian	2,419	1,558	2,403	2,418	2,405	1,946
Other	1,047	395	1,012	1,002	760	932
XX	38,947	6,717	38,060	35,271	16,438	30,110
XY	37,209	9,748	35,963	32,171	23,995	27,234
Total	**76,156**	**16,465**	**74,023**	**67,442**	**40,433**	**57,344**

…more likely to see ‘rare’ variants in patients from an under-represented population

Neurogenetic VUS Rounds at the Neuro

1 hour virtual bi-weekly meeting with our team to review and internally classify VUS identified in our patients

All Canadian neurologists and genetic counsellors are welcome to submit cases and participate in our meetings!

If interested, please contact:

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Final Q&A

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Additional resources

- Clinical variant interpretation: https://www.youtube.com/watch?v=VqrEtABxvhY&t=3s
- gnomAD tips: https://www.youtube.com/watch?v=Bh8AKkI-DhY
- Variant classification: https://www.youtube.com/watch?v=xVAnjg_AqSg; https://www.youtube.com/watch?v=wTBxyT8a2PI
- General genome analysis: https://www.youtube.com/watch?v=yeUETPbzgGw
- ClinGen Resource videos, refreshers, etc: https://www.youtube.com/channel/UCsn4nEVUTpVQz70rClgMMsQ ; in silico tools: https://www.youtube.com/watch?v=MJtgahM5Zak
- Guide to Interpreting Genomic Reports: A Genomics Toolkit: https://www.genome.gov/sites/default/files/media/files/2020-04/Guide_to_Interpreting_Genomic_Reports_Toolkit.pdf