Application of Genetics in Clinical Practice

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Presenter

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Clesson Turner, M.D. is a pediatrician, clinical geneticist, and clinical-molecular geneticist at the Uniformed Services University of the Health Sciences. He is particularly interested in implementation of genomic medicine in the military health system. Prior to retiring from the Army, Dr. Turner served as the Chief of Genetics at Walter Reed National Military Medical Center and the Chief of Cancer Genetics at the Murtha Cancer Center. He is currently Interim Director of the Uniformed Services University initiative in precision medicine, PRIMER (**PR**ecision medicine **I**nitiative for **M**ilitary **E**ducation and **R**esearch).

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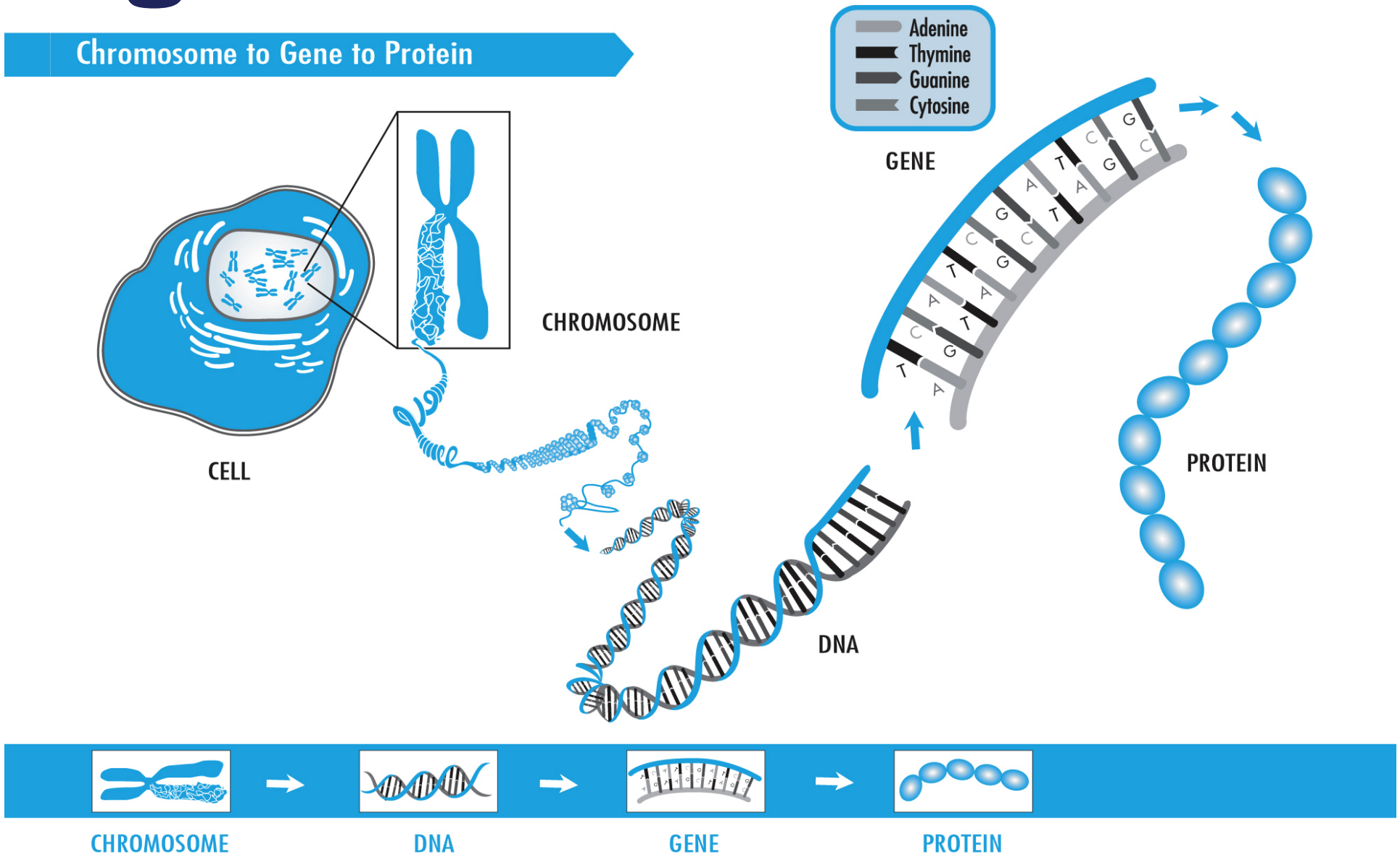
Learning Objectives

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

1. Identify the role of a genomics in primary care.
2. Discuss circumstances in which genetic testing may be beneficial.
3. Summarize current genetic testing options.
4. Explain when to refer a patient to a geneticist or genetic counselor.

BACKGROUND

Background


Chromosome to Gene to Protein
Adenine
Thymine
Guanine
Cytosine
GENE
CHROMOSOME
CELL
DNA
PROTEIN
CHROMOSOME
DNA
GENE
PROTEIN

Genome Analogy

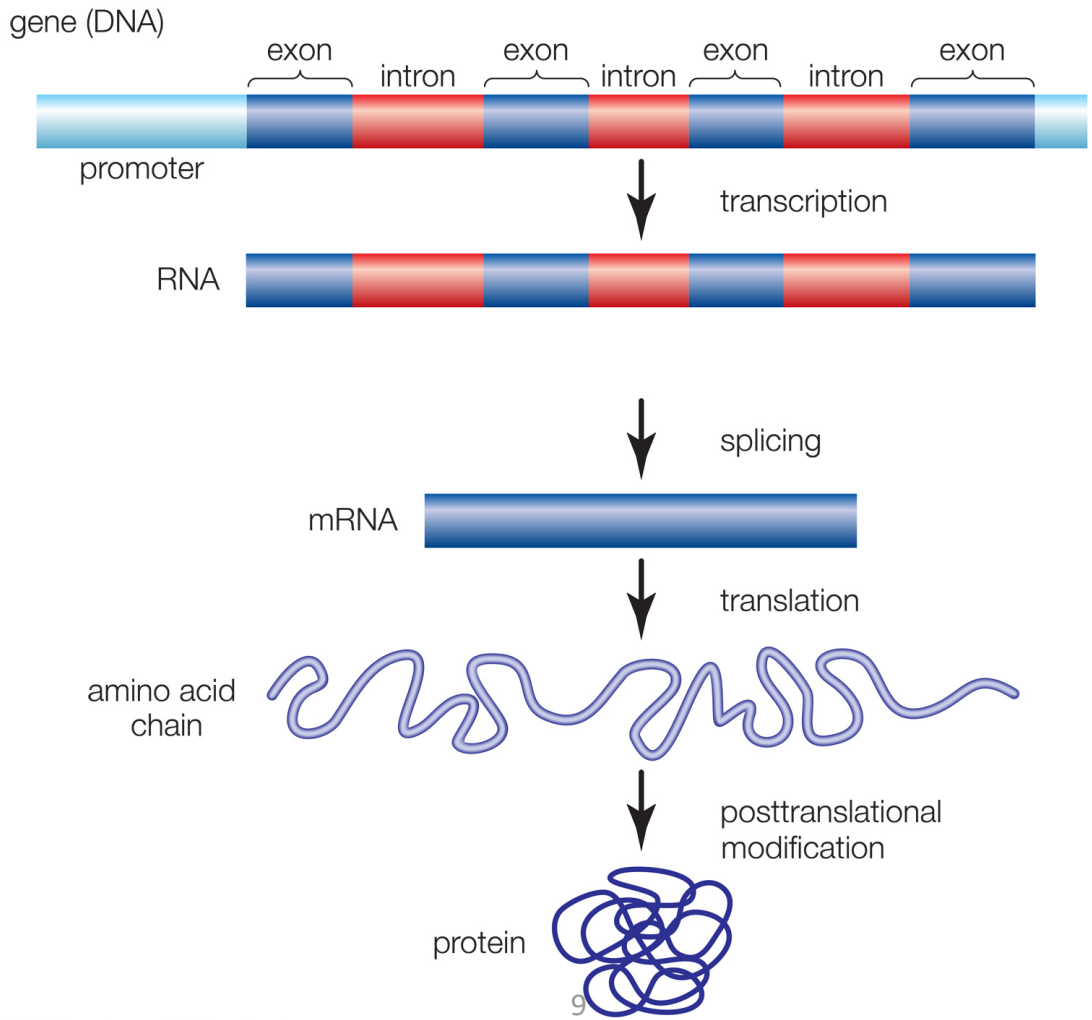
Genome

Chromosome

Gene

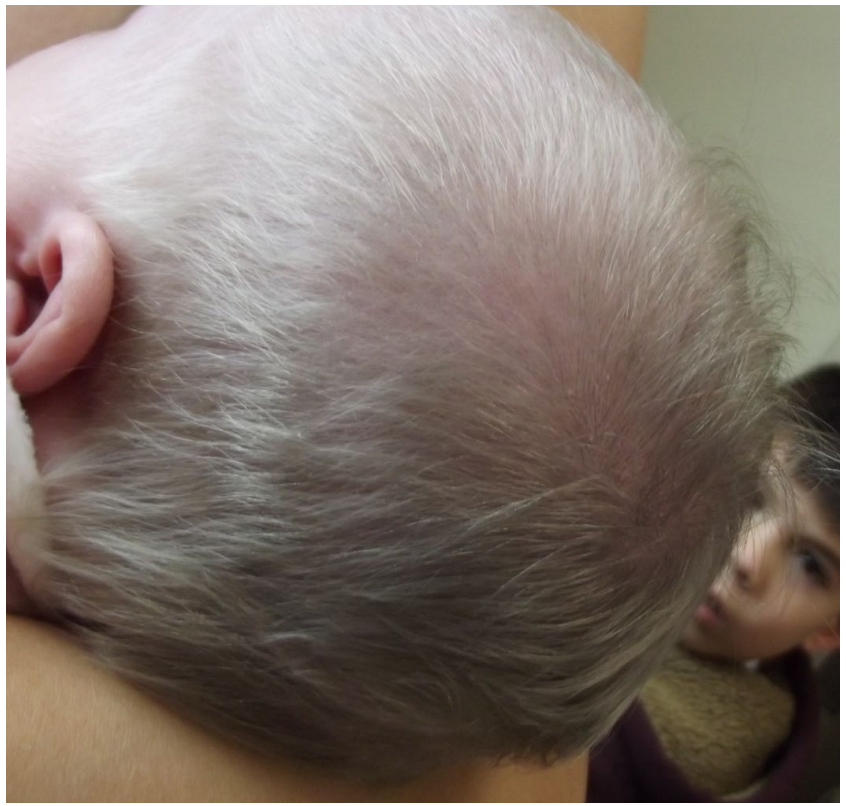
(Themuseumtimes.com, 2015)
(Meraresult.com, n.d.)
(Etsy.com, n.d.)

Basic Structure of Gene



Cases

- Case 1

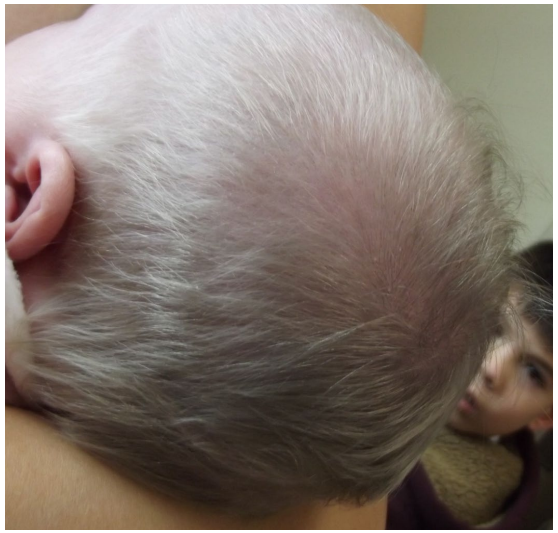


(Courtesy of Dr. Turner, n.d.)

- Case 2 - Five year old male with Autism

Cases-History and Exam

- Case 1
  - Platinum Hair
  - Albinism

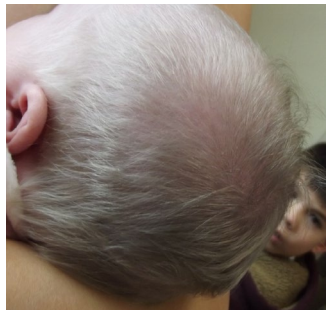


- Case 2
  - Autism
  - Occipitofrontal circumference (OFC) - >>+2 standard deviation (SD) above mean for age

Cases-Clinical Testing

- Case 1
  - Peripheral Smear - normal
  - Immunology
    - Normal T and B cell subsets
    - Natural killer (NK cell) Function
      - 0.0 Lytic units (normal >2.6)

(Courtesy of Dr. Turner, n.d.)

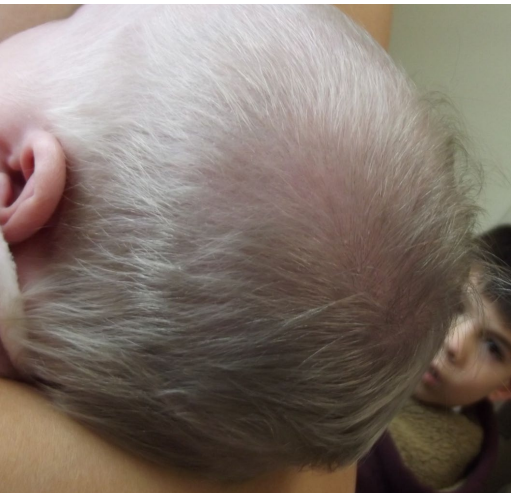


- Case 2
  - None

- T and B Cell – T and B lymphocytes
- NK cell – Natural Killer Cell

Cases-Clinical Diagnosis

- Case 1
  - Griscelli Syndrome
    - about 100 cases a year in the US
    - Autosomal Recessive (AR)
      - intracellular trafficking genes
    - Clinical features:
      - Partial oculocutaneous albinism
      - Neutropenia and thrombocytopenia
      - Hemophagocytic lymphohistiocytosis (HLH)
      - Progressive neurologic involvement *(cerebral lymphohistiocytic infiltration)*

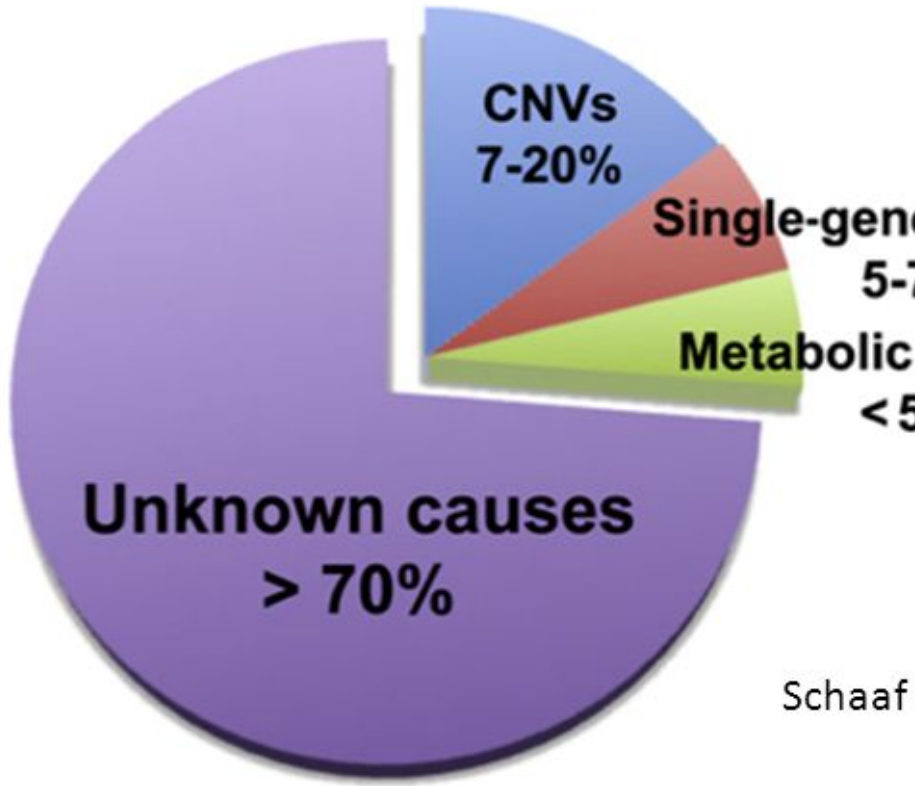


(Courtesy of Dr. Turner, n.d.)

- Case 2
  - Autism
    - > 1000 genetic associations
  - Macrocephaly

Autism Spectrum Disorders

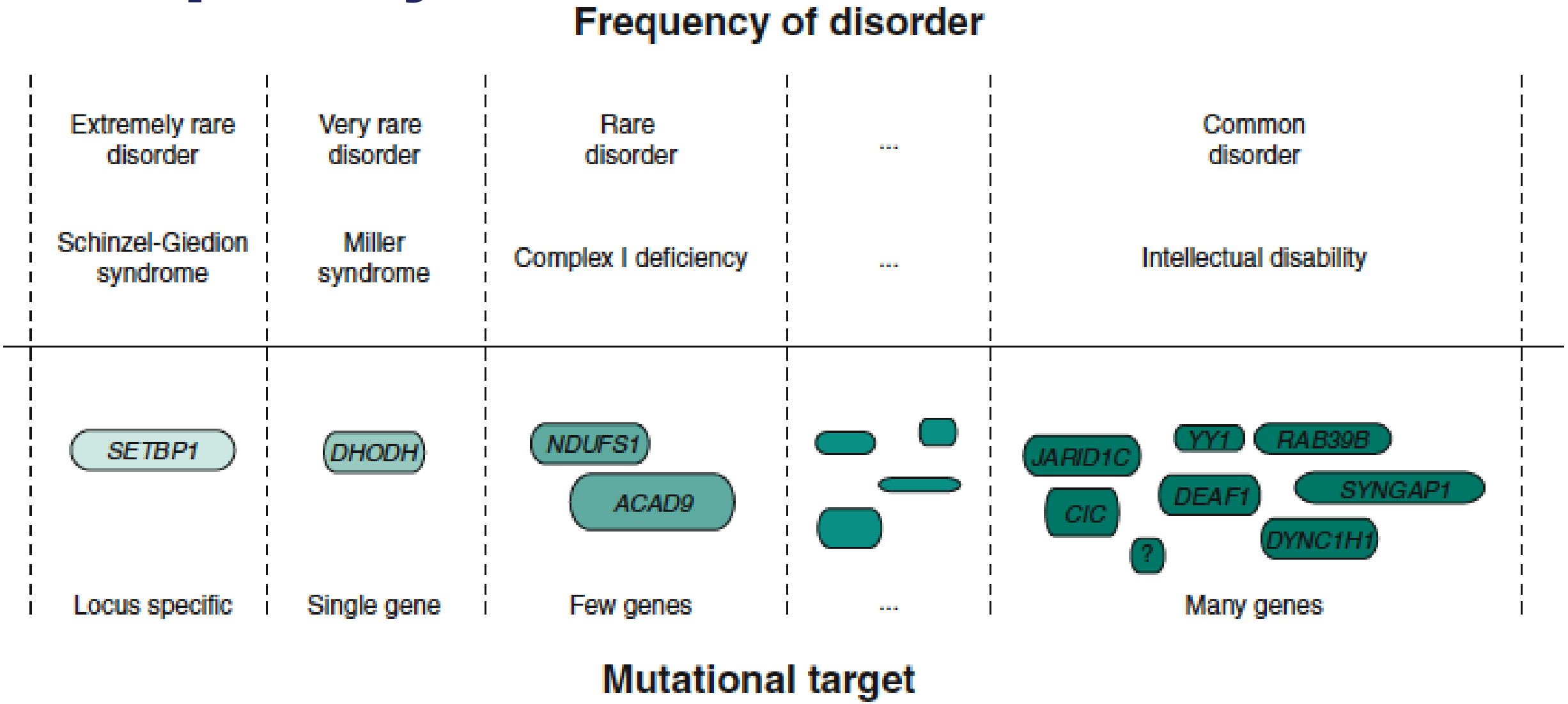
Highly heritable – twin studies estimate 85-92%



Schaaf and Zoghbi, 2011

- The most genetic of all developmental neuropsychiatric syndromes
- Risk of 2-8% among siblings (20-80X higher than in general population)

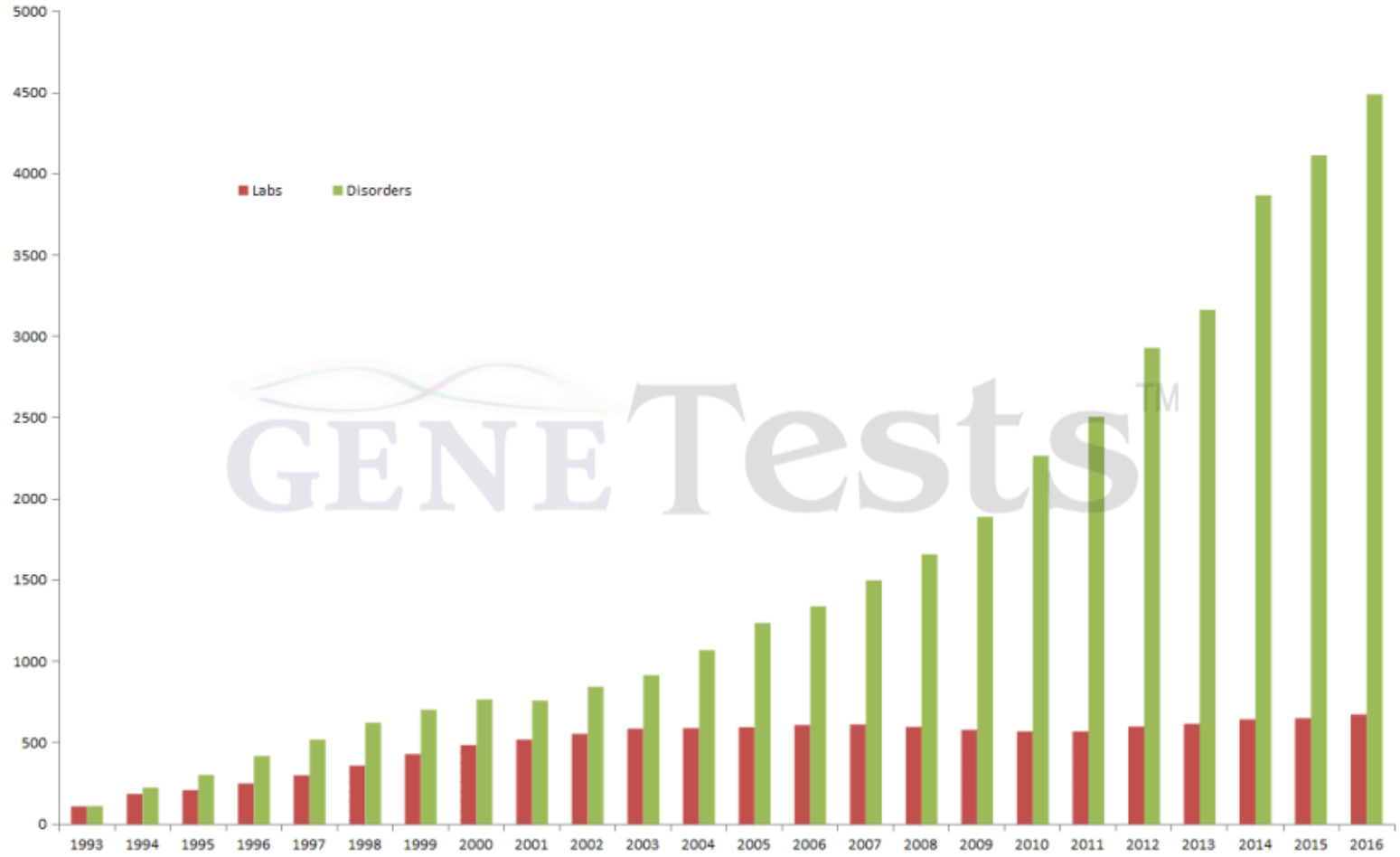
Frequency of Disorder



(Gilissen et al., 2011)

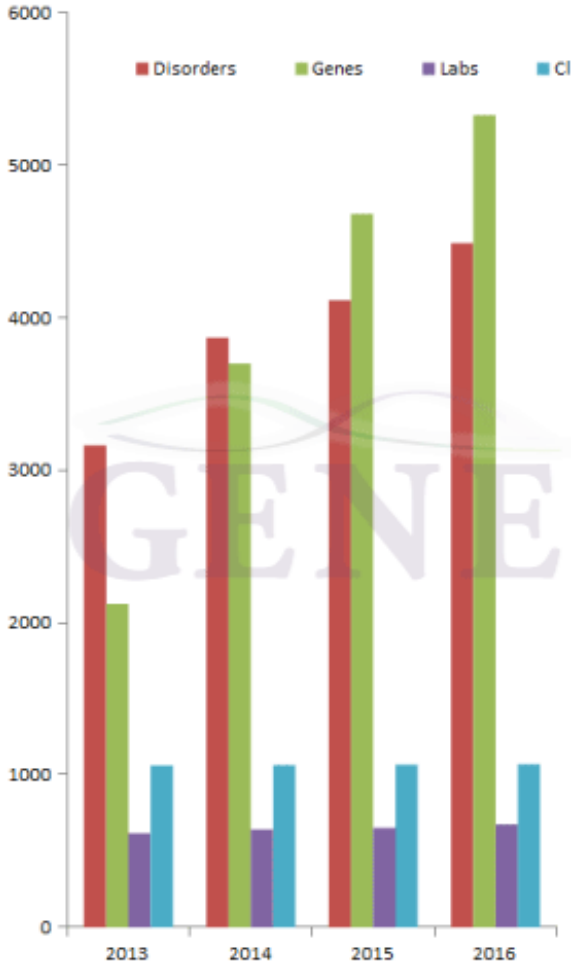
WHAT TEST TO ORDER?

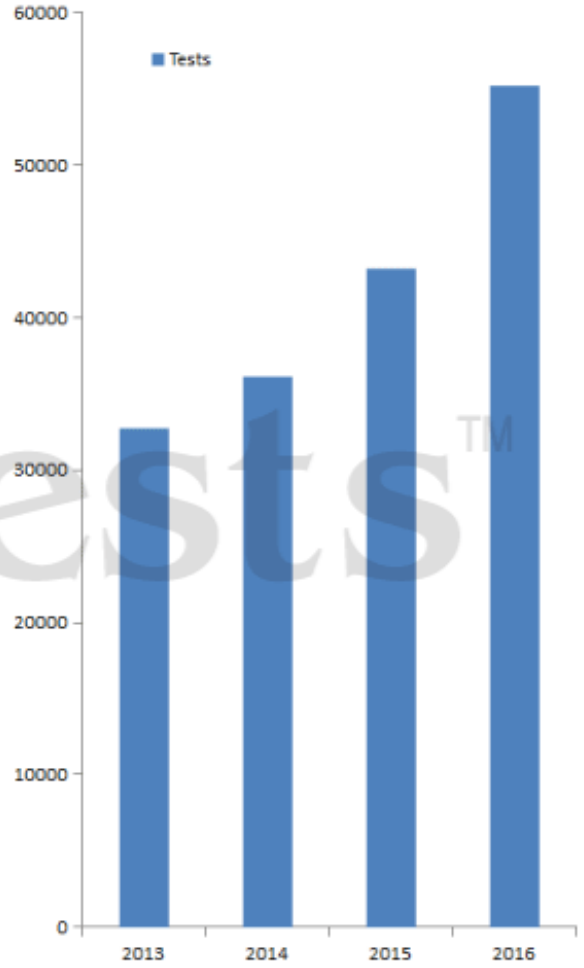
Available Genetic Tests



(genereviews.org, 2018)

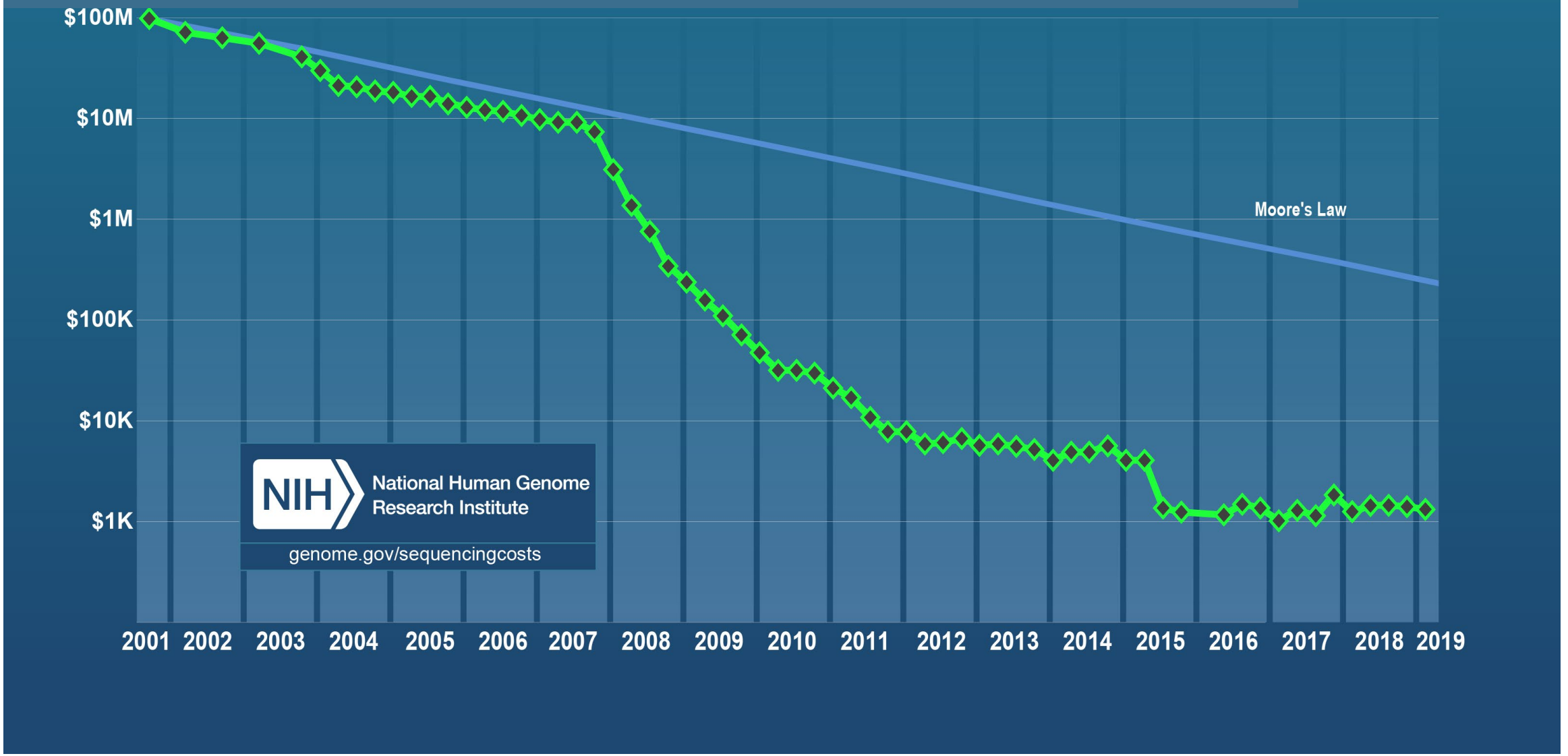
Available Genetic Tests





(genereviews.org, 2018)

Cost of Genome Sequencing



Caution

(Paulclaireaux.com, n.d.)

Genomic Variation

Panel 3: Types of clinically important genomic variation

Single nucleotide variants (one base replaced by another)

- Synonymous: no change in the encoded amino acid
- Missense: change in the encoded amino acid
- Nonsense: premature termination of the peptide chain
- Splice site: variant occurring at the boundary of an exon and an intron (splice site), which can disrupt RNA splicing and result in the loss of exons or inclusion of introns and an altered protein-coding sequence[28]

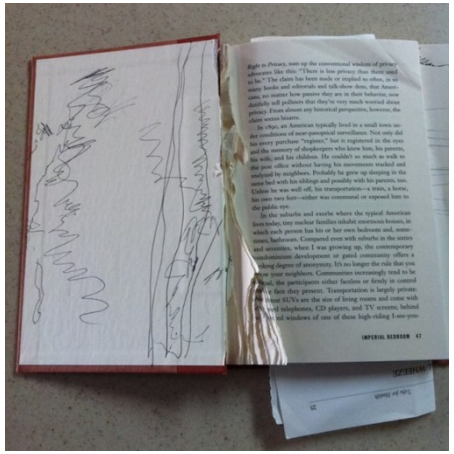
Structural variants

- Deletion: one or more bases deleted from the sequence
- Insertion: one or more bases added to the sequence
- Duplication: segment of DNA copied abnormally one or more times
- Frameshift: addition or deletion of one or two bases (or any number that is not a multiple of three) that shifts the reading frame of three bases per amino acid, producing an altered or truncated protein
- Expansion: short DNA sequences repeated many times
- Inversion: a chromosomal segment reversed end to end

(Manolio et al., 2019)

Genetic Tests

Chromosome Analysis	Fluorescence In situ Hybridization (FISH)	Chromosomal Microarray (CMA)	Sequencing
5-8 Mb	1-5 Mb	50-100 Kb	Single Base pair



(Flickr.com, n.d.)
(Countrybooks.com, n.d.)
(Vice.com, 2012)
(Pinterest.com, n.d.)

Types of Genetic Test

	Example
Single gene	
Minimal locus heterogeneity (only one or a small number of genes is known to cause the condition)	*CFTR* for cystic fibrosis
Distinctive clinical findings that clearly indicate a specific gene	*PAH* for phenylketonuria
Gene panel	
Locus heterogeneity (multiple genes are known to cause the same condition or similar conditions)	Muscular dystrophy panel
Disorders with overlapping phenotypes	Cardiomyopathy panel
Disorders that share one manifestation but can have very different presentations	Epilepsy panel
Disorders associated with genes from a common pathway or structure	RASopathy panel
Exome	
Extreme heterogeneity and de novo mutations common	Autism, intellectual disability
Two or more unrelated phenotypes in one patient	Oculocutaneous albinism and neutropenia
No distinctive phenotypic features present	Kabuki syndrome
Phenotype indistinct and underlying cause is not clear	Congenital diarrhoea, Zellweger syndrome
Genome*	
Non-coding variation is suspected as a cause	Hypertrophic cardiomyopathy[37]
Structural variation is suspected as a cause	DiGeorge syndrome[29]
Exome sequencing has already been performed and was non-diagnostic	Undiagnosed Diseases Network[38]
Rapid generation of sequencing data needed for patients who are critically ill	Neonates in intensive care[5]

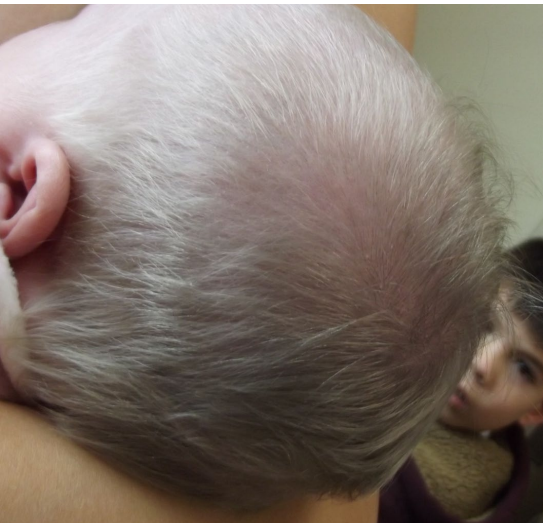
*Indications for exome also apply to genome, with the addition of those listed below.

Table 1: **Indications for single gene, gene panel, exome, and genome sequencing[39]**

(Manolio et al., 2019)

Cases-Test Selection

- Case 1
  - Traditional Approach
    - Key on specific features or diagnosis
    - Test for specific associated mutations

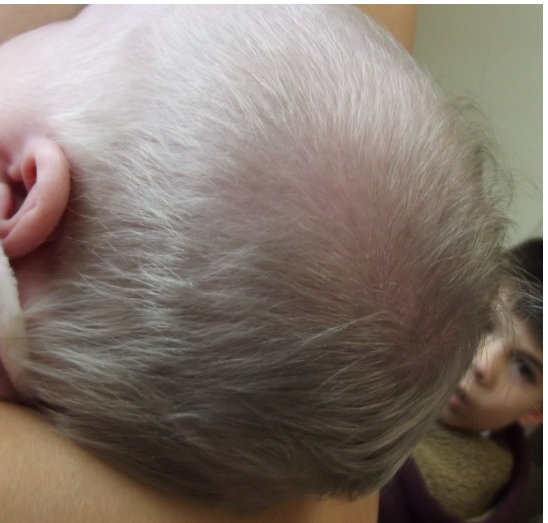


(Courtesy of Dr. Turner, n.d.)

- Case 2
  - Autism
    - Baseline
      - Microarray, Fragile X
    - Further testing if above negative

Cases-Test Ordered

- Case 1
  - Traditional Approach
    - Sequencing Panel for three genes associated with Griscelli Syndrome



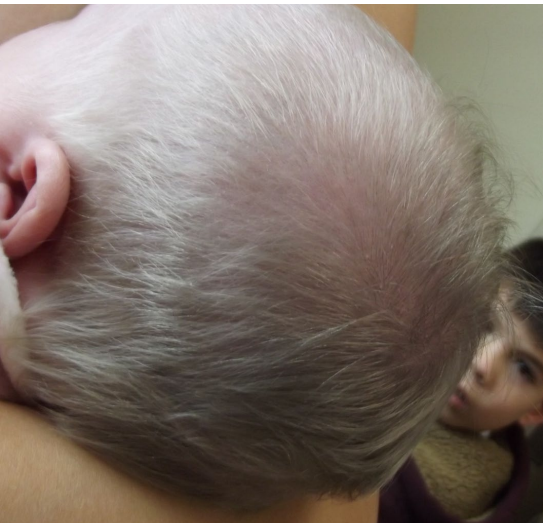
(Courtesy of Dr. Turner, n.d.)

- Case 2
  - Autism
    - Baseline
      - Microarray, Fragile X
    - Autism/ID sequencing Panel considered
      - >2,000 genes

Cases-Results

- Case 1
  - *RAB27A*
    - Apparently homozygous

      c.37T>G, p.Leu13Val



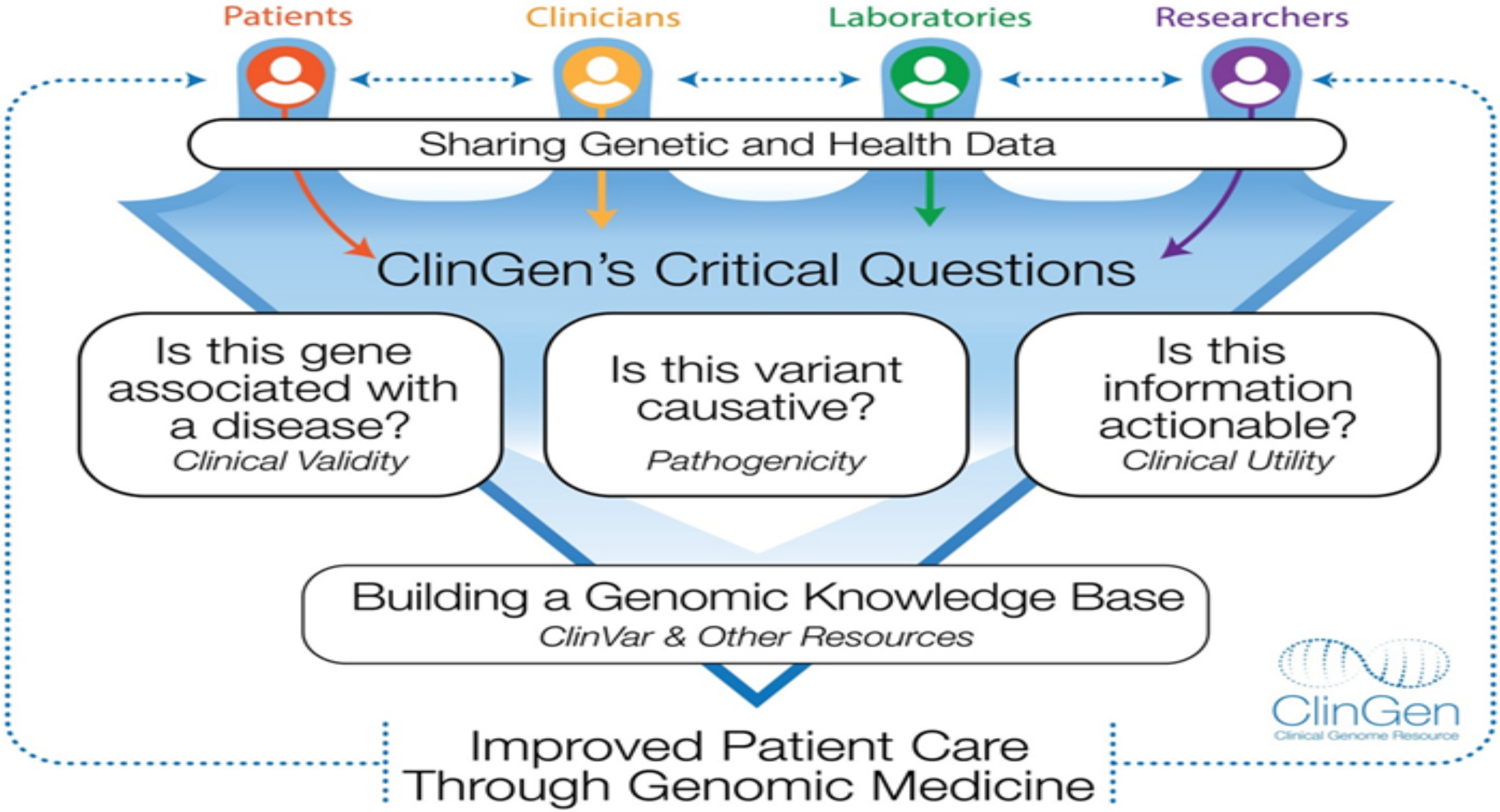
(Courtesy of Dr. Turner, n.d.)

- Case 2
  - Microarray, Fragile X
    - No change found
  - Autism/ID sequencing

    Panel
    - *PTEN*
      - c.203A>G,

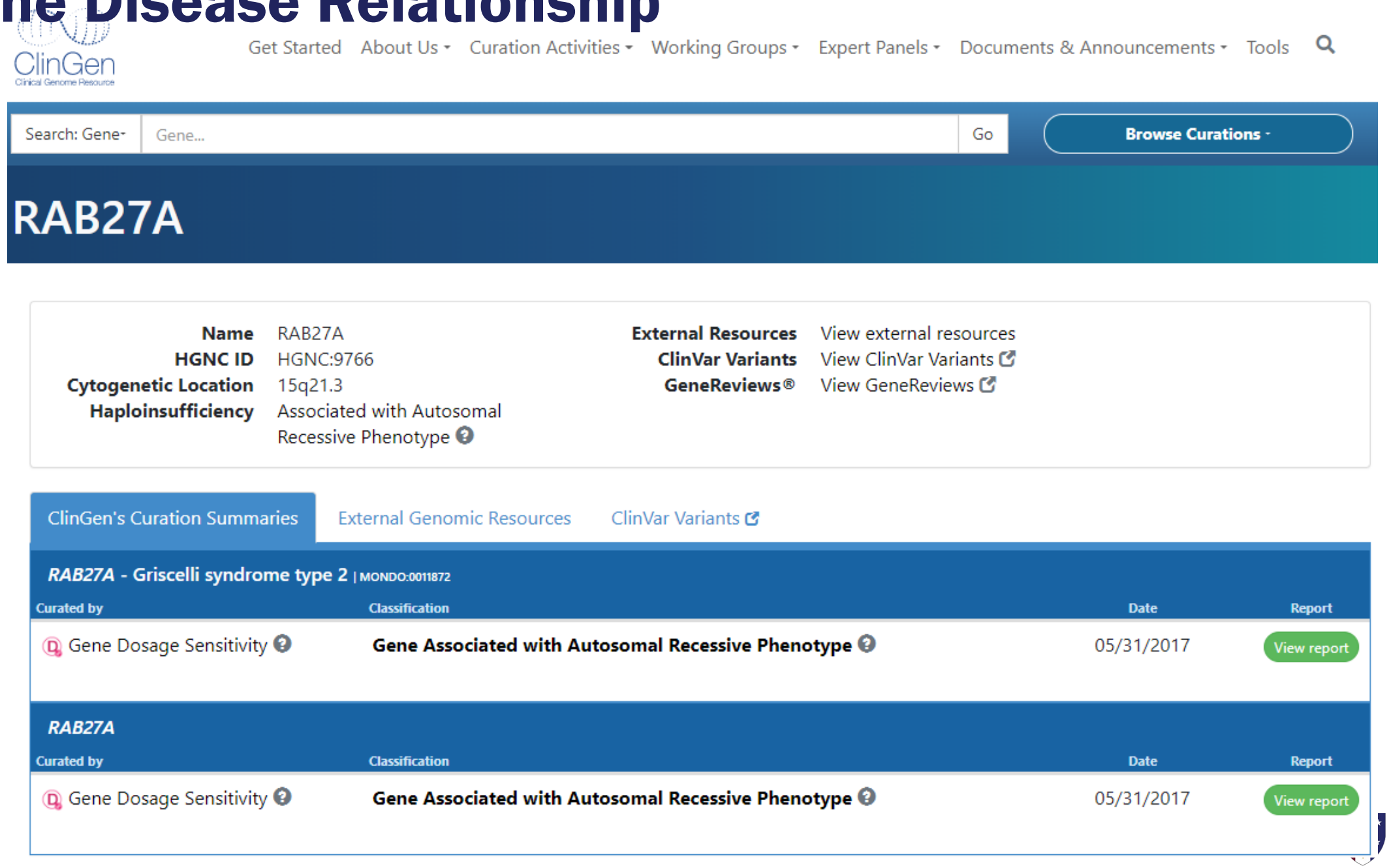
        p.Tyr68Cys

Genomic Medicine

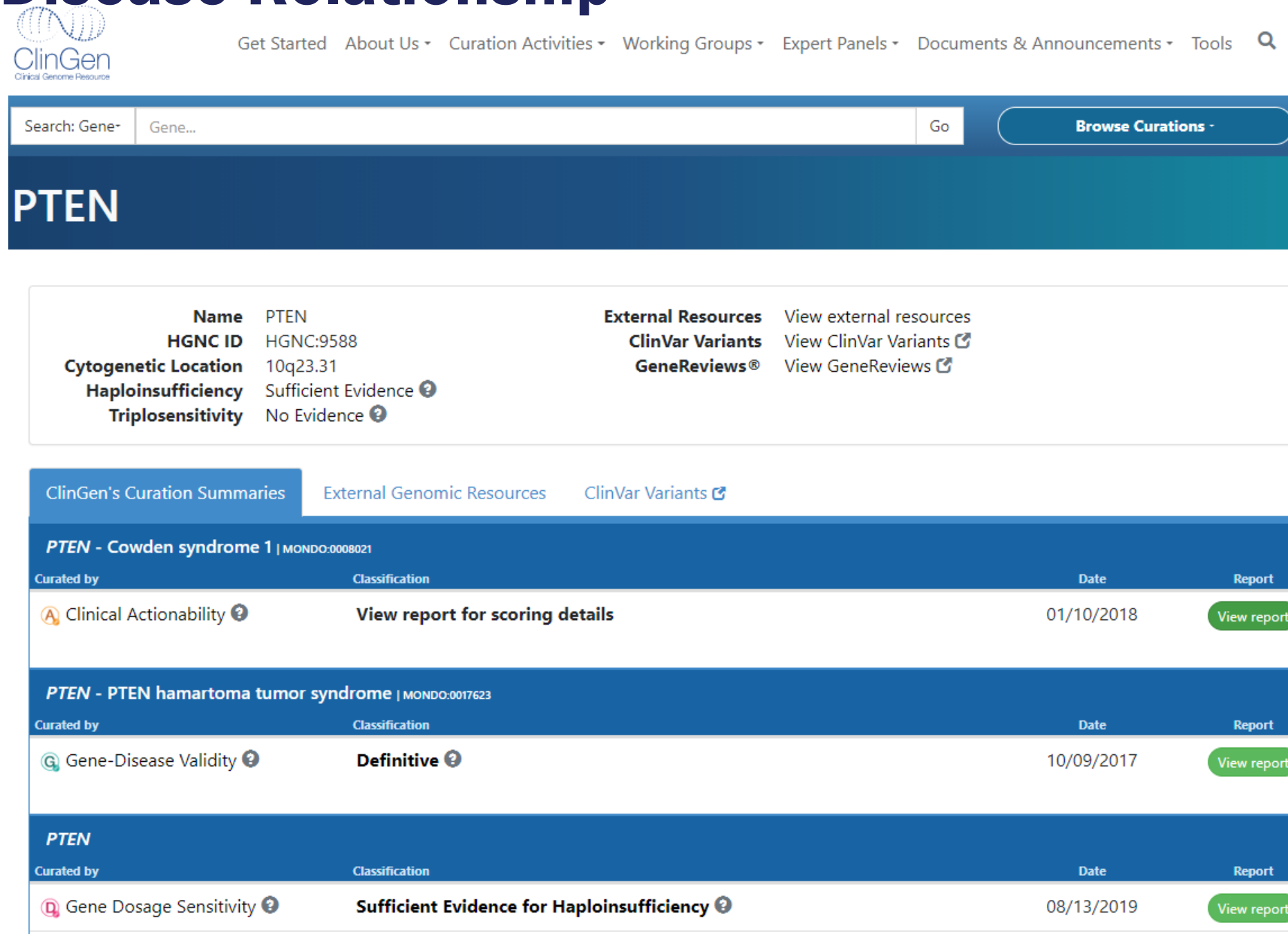


GENE DISEASE RELATIONSHIP

Gene Disease Relationship



Gene Disease Relationship



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VARIANT INTERPRETATION

Variant Interpretation

	Definition
Pathogenic	>99% certainty of being disease-causing
Likely pathogenic	>90% certainty of being disease-causing
Unknown significance	10–90% certainty of being disease-causing
Likely benign	>90% certainty of not being disease-causing
Benign	>99% certainty of not being disease-causing

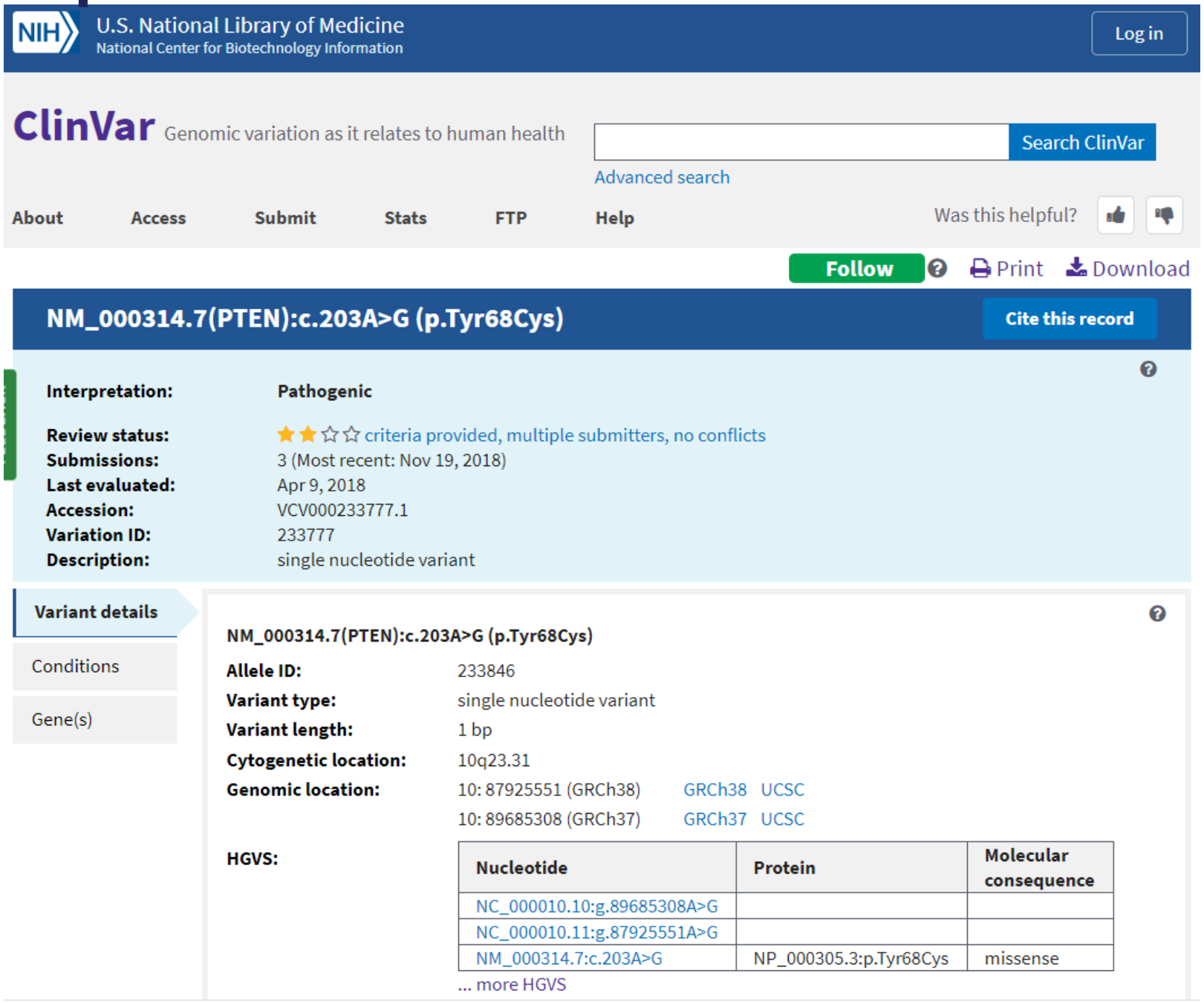
Table 2: Classifications of pathogenicity for genomic variants[48]

(Manolio et al., 2019)

Variant Interpretation

	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			

Variant Interpretation



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National Center for Biotechnology Information

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NM_000314.7(PTEN):c.203A>G (p.Tyr68Cys)

Cite this record

Interpretation: Pathogenic

Review status: ★★☆☆ criteria provided, multiple submitters, no conflicts
Submissions: 3 (Most recent: Nov 19, 2018)
Last evaluated: Apr 9, 2018
Accession: VCV000233777.1
Variation ID: 233777
Description: single nucleotide variant

Variant details
Conditions
Gene(s)

NM_000314.7(PTEN):c.203A>G (p.Tyr68Cys)

Allele ID: 233846
Variant type: single nucleotide variant
Variant length: 1 bp
Cytogenetic location: 10q23.31
Genomic location: 10: 87925551 (GRCh38) GRCh38 UCSC
10: 89685308 (GRCh37) GRCh37 UCSC

HGVS:

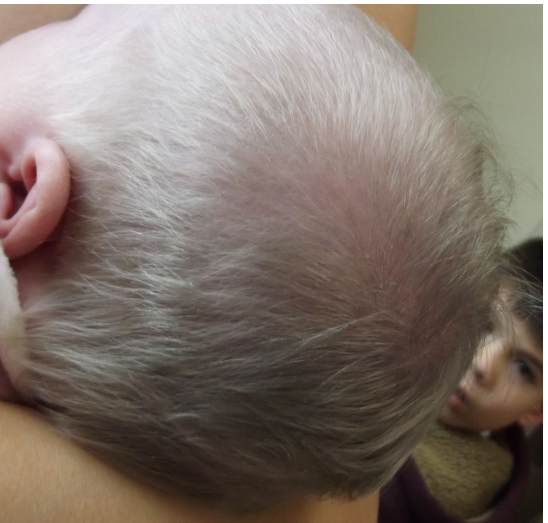
Nucleotide	Protein	Molecular consequence
NC_000010.10:g.89685308A>G		
NC_000010.11:g.87925551A>G		
NM_000314.7:c.203A>G	NP_000305.3:p.Tyr68Cys	missense

... more HGVS

USU
Uniformed Services University

Cases-Variant Interpretation

- Case 1
  - *RAB27A*
    - c.37T>G, p.Leu13Val
      - Variant of uncertain significance (VUS)



(Courtesy of Dr. Turner, n.d.)

- Case 2
  - *PTEN*
    - c.203A>G, p.Tyr68Cys
      - Pathogenic

CLINICAL UTILITY

Clinical Utility

	Patients and family members	Clinicians	Geneticists and genetic counsellors	Diagnostic laboratory scientists	Genomics researchers
Clinical reference resources	Genetics Home Reference	MedGen, Genetic Testing Registry, Clinical Pharmacogenetics Implementation Consortium	Online Mendelian Inheritance in Man	Clinical Genome Resource, ClinVar	GeneCards, PharmGKB, The Cancer Genome Atlas
Educational resources	NHGRI Talking Glossary of Genetic Terms, Your Genome, Genetic Alliance	Genetics/Genomics Competency Center, GeneReviews	NA	NA	NA
Data resources	GenomeConnect, MyGene2	NA	Matchmaker Exchange	Genome Aggregation Database	Gene-Tissue Expression Project, Monarch Initiative, Alliance of Genome Resources

NHGRI=National Human Genome Research Institute. NA=not applicable.

Table 3: **Examples of resources for reference, education, and data sharing by user group**

(Manolio et al., 2019)

Clinical Utility

GeneReviews® [Internet].

< Prev Next >

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GeneReviews by Title

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PTEN Hamartoma Tumor Syndrome

Synonym: PHTS

Charis Eng, MD, PhD.

Author Information

Initial Posting: November 29, 2001; Last Update: June 2, 2016.

Estimated reading time: 30 minutes

Summary

Go to:

Clinical characteristics. The ***PTEN*** hamartoma tumor syndrome (PHTS) includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), ***PTEN***-related Proteus syndrome (PS), and Proteus-like syndrome.

- CS is a multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, and endometrium. Affected individuals usually have macrocephaly, trichilemmomas, and papillomatous papules, and present by the late 20s. The lifetime risk of developing breast cancer is 85%, with an average age of diagnosis between 38 and 46 years. The lifetime risk for thyroid cancer (usually follicular, rarely papillary, but never medullary thyroid cancer) is approximately 35%. The risk for endometrial cancer may approach 28%.
- BRRS is a congenital disorder characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, and pigmented macules of the glans penis.
- PS is a complex, highly variable disorder involving congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses.
- Proteus-like syndrome is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

Diagnosis/testing. The diagnosis of PHTS is established in a proband by identification of a heterozygous germline ***PTEN*** pathogenic variant on molecular genetic testing.

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New in *GeneReviews*

DIAGNOSTIC YIELD

Clinical Utility

	Diagnostic rate, n/N (%)
Splinter et al (2018)[3]	
Paediatric and adult	132/382 (35%)
Yang et al (2014)[14]	
Fetus	6/11 (55%)
<5 years	247/900 (27%)
5–18 years	210/845 (25%)
>18 years	41/244 (17%)
All ages	504/2000 (25%)
Lee et al (2014)[15]	
Paediatric and adult	213/814 (26%)
Bick et al (2017)[16]	
Paediatric	8/22 (36%)

(Wise et al., 2019)

Clinical Utility

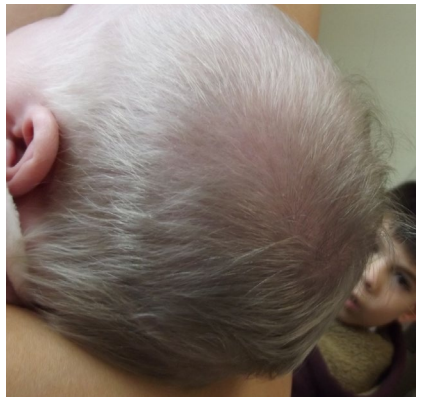
	Age group	Management changes
Splinter et al (2018)[3]	Paediatric and adult	28 (21%) of 132 patients had change in therapy; 49 (37%) of 132 had change in care other than therapy; 48 (36%) of 132 had variant-specific genetic counselling
Bick et al (2017)[16]	Paediatric	Six (75%) of eight patients had change to medical management or surveillance; four (50%) of eight had changes in medication; six (75%) of eight had medical surveillance
Retterer et al (2016)[17]	Paediatric and adult	Five (1%) of 876 diagnosed patients had suggested intervention or treatment
Stark et al (2016)[18]	0–2 years	15 (33%) of 46 patients had change to clinical management (three started additional treatment, five had treatments stopped or modified, nine had additional surveillance for known complications, one had surveillance stopped)
Stavropoulos et al (2016)[19]	<1 month to 18 years	32 (94%) of 34 patients had a change in clinical management
Normand et al (2018)[22]	Prenatal	Four of 19 cases with information had medical management changes; 15 of 19 had reproductive planning; 10 had recurrence risk information
Meng et al (2017)[24]	Infant (<100 days)	Medical management affected for 53 (52%) of 102 infants

Table 3: Examples of management changes after diagnosis

(Wise et al., 2019)

Cases-Follow up Testing

- Case 1



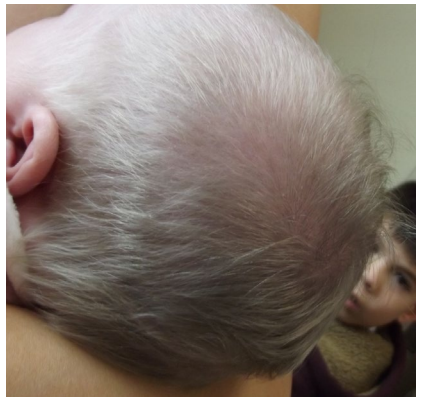
  - *RAB27A* Deletion/Duplication
    - negative
  - Parental testing
    - Father Heterozygous for mutation
    - Mother negative
  - Microarray
    - upd(15)pat.arr[hg19]15q11.2q14(23,706,111- 102,398,213)x2 hmz

- Case 2
  - *PTEN*
    - c.203A>G, p.Tyr68Cys
      - Pathogenic

(Courtesy of Dr. Turner, n.d.)

Cases-Final Diagnoses

- Case 1



  - Autosomal recessive (AR) Griscelli Syndrome secondary to homozygosity for *RAB27A* mutation
  - Paternal UPD15
  - Angelman Syndrome

- Case 2
  - *PTEN*-Hamartoma Tumor Syndrome
    - Patient and mother

(Courtesy of Dr. Turner, n.d.)

Cases-Clinical Follow Up

- Case 1
  - Human leukocyte antigen (HLA) matched bone marrow transplant (BMT) from donor list

- Case 2
  - *PTEN*-Hamartoma Tumor Syndrome
    - National Comprehensive Cancer Network (NCCN) guidelines for enhanced screening
    - Mother-risk reduction mastectomy

(Courtesy of Dr. Turner, n.d.)

SECONDARY FINDINGS

Clinical Utility

	Associated genes†	Pathogenic variant rate among unselected population‡	Process outcomes	Intermediate outcomes	Clinical outcomes
Hereditary breast and ovarian cancer	*BRCA1, BRCA2*	0·5%[17]	Breast cancer screen modality and schedule	Breast biopsy findings	Prophylactic mastectomy or oophorectomy; diagnosis of breast or ovarian cancer and presenting stage
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*	0·4%	Colorectal cancer screen modality and schedule	Colonoscopy findings, polypectomy	Bilateral salpingo-oophorectomy; incidence and presenting stage of colorectal cancer, ovarian cancer, or endometrial cancer
Familial hypercholesterolaemia	*LDLR, ABOB, PCSK9*	0·4%[18]	Measurement of LDL cholesterol	Initiation or intensification of statin or *PCSK9* inhibitor therapy	Atherosclerotic disease: myocardial infarction, cerebrovascular accident, or peripheral vascular disease
Familial hypertrophic and dilated cardiomyopathy	*TTN, TNNT2, LMNA, MYH7*	0·2%[19,20]	Echocardiogram screening, creatine kinase measurement	Left ventricular wall thickness; implantation of defibrillator or pacemaker	Diagnosis of cardiomyopathy; incidence and presenting stage of congestive heart failure
Familial arrhythmia	*SCN5A, KCNH2, KCNQ1, RYR2*	0·03%§[21]	Electrocardiogram or electrophysiology studies	Medical prophylaxis; defibrillator placement	Incidence of ventricular arrhythmia or sudden death
Hereditary haemochromatosis	*HFE*	0·5%	Ferritin, transferrin saturation measurement	Liver biopsy	Diagnosis of iron overload, cirrhosis, diabetes, or dilated cardiomyopathy

*Subset of returnable conditions. Distinct genes and genomic diagnoses are grouped by related phenotypes. †Partial list of genes associated with condition. ‡Approximate pathogenic and likely pathogenic rate; variant rates vary by ethnicity. §Additional data from the Genome Aggregation Database.

Table 1: **Examples of process, intermediate, and clinical outcomes potentially resulting from sequencing studies by generic syndrome(s)***

(Peterson et al., 2019)

CHALLENGES

Challenges

Panel 2: Challenges to implementation of genomic medicine[1]

- Lack of familiarity and understanding by patients and clinicians
- Poor access to genomic medicine expertise and testing
- High cost and lack of reimbursement for genetic or genomic tests and services
- Accessibility and relevance of genetic or genomic testing and interpretation to under-represented and non-European populations
- Potentially overwhelming and rapidly evolving nature of genomic information
- Need for extensive informatics and infrastructure to integrate genomic results into electronic medical records and provide clinical decision support
- Little evidence of the effectiveness of using genomic information in clinical care
- Non-acceptance of genomic medicine by institutions and clinicians
- Potential burden of following up genotyped patients when the clinical significance of genomic variants changes or becomes clear
- Potential responsibility for outreach to at-risk family members
- Community perceptions and concerns regarding consent, patient privacy and confidentiality, and discrimination

(Manolio et al., 2019)

Key Takeaways

- Resources to answer genetic counseling questions include ClinVar and ClinGen.
- Single gene, Gene panel, Exome and Genome are all types of genetic testing.
- There are various challenges to utilizing Genetics in Primary Care, however being aware of resources can alleviate some of the obstacles.

QUESTIONS?

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