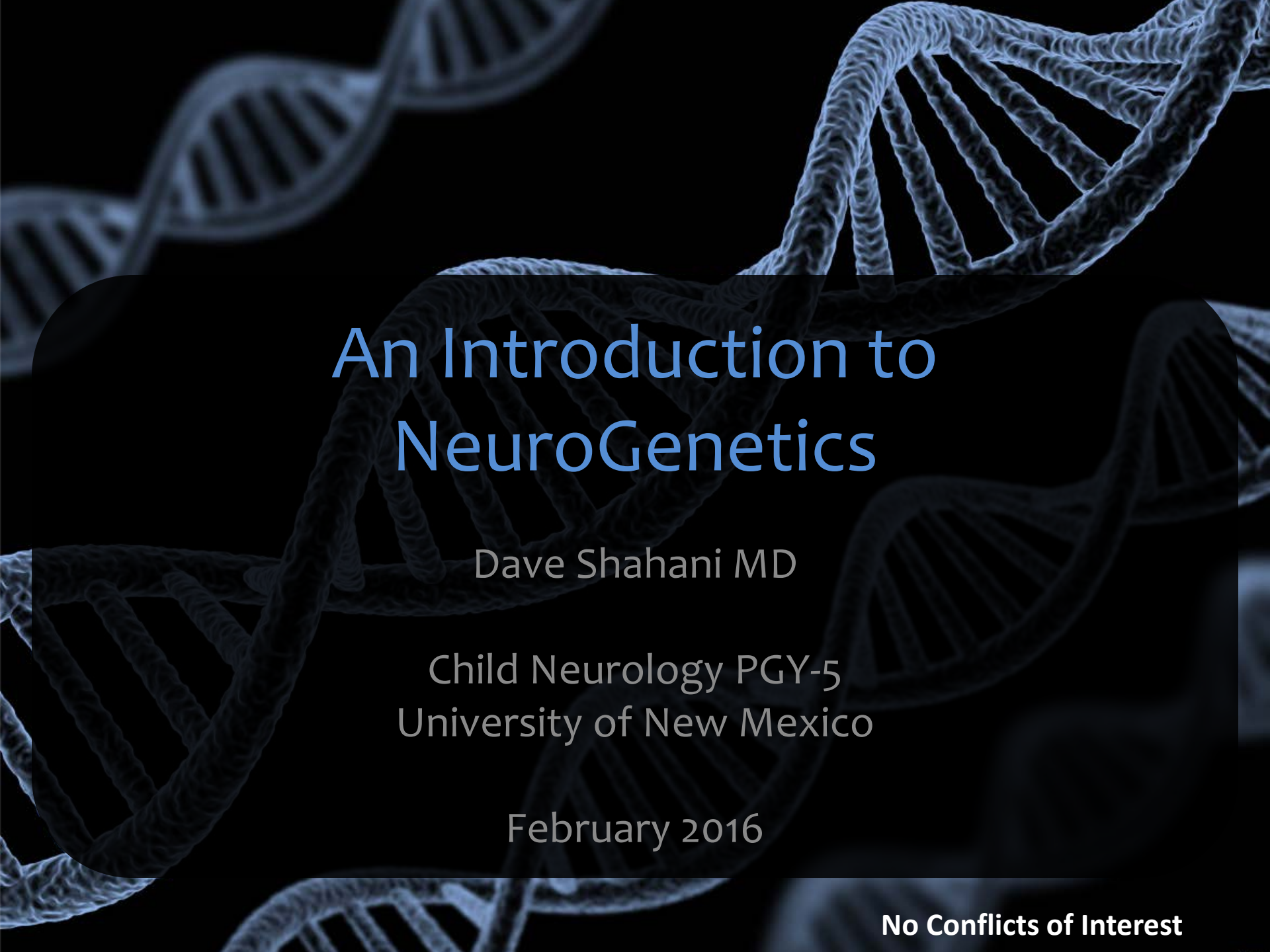


An Introduction to NeuroGenetics

Dave Shahani MD

Child Neurology PGY-5
University of New Mexico

February 2016

No Conflicts of Interest

Don't know what it is…
send a genetic test!

An estimated **30-40 %** of genetic tests in the US are ordered or interpreted incorrectly

There are over **1,000** different genetic tests in use

Genetics tests are complex and **$$$$**

Why should we test?

Molecular Medicine = **Personalized Medicine**

Diagnosing the previously unknown

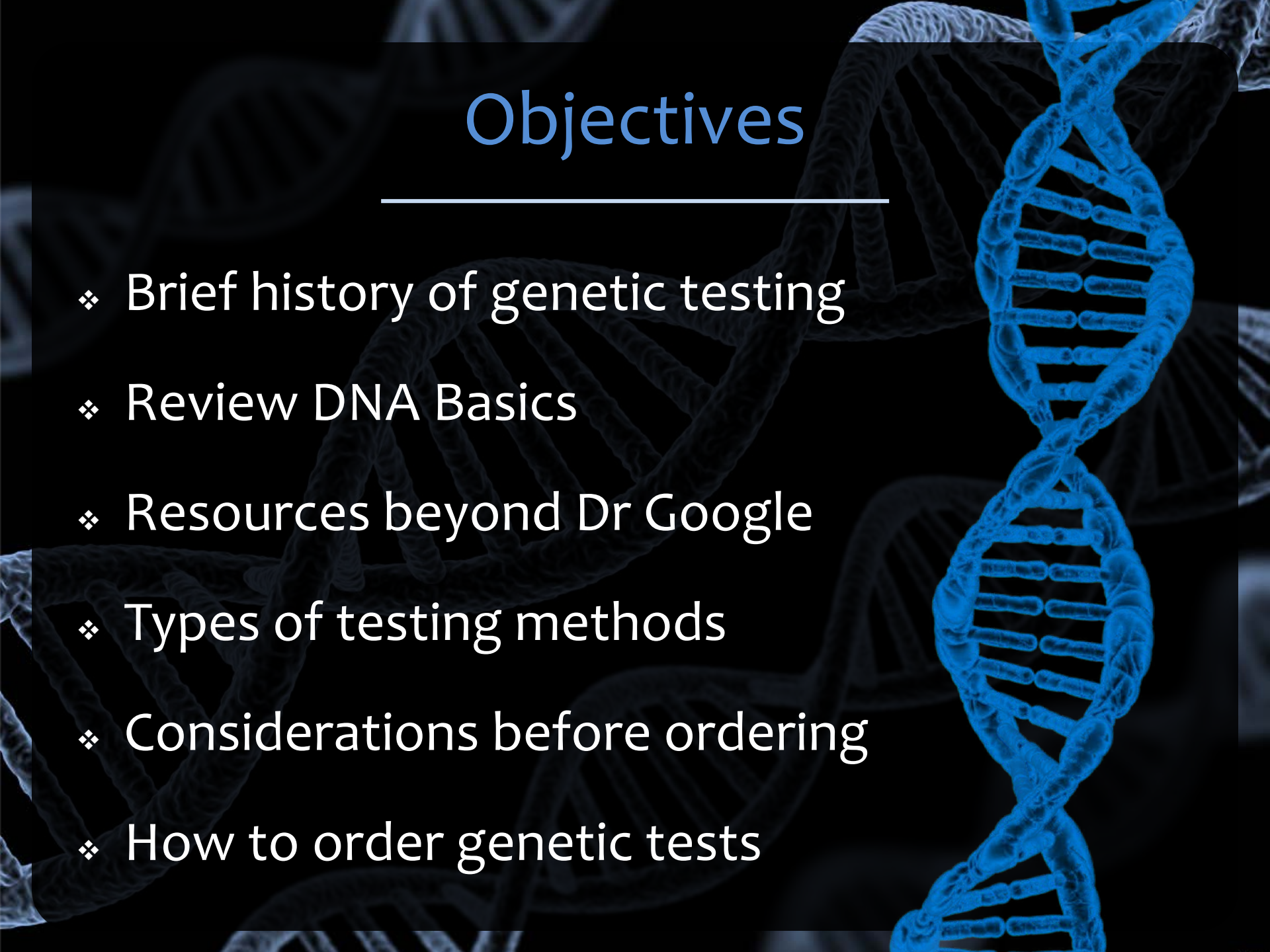
Pharmacogenomics

Cancer prognostics

Family planning

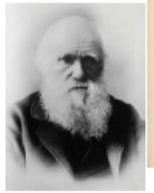
Objectives

- Brief history of genetic testing
- Review DNA Basics
- Resources beyond Dr Google
- Types of testing methods
- Considerations before ordering
- How to order genetic tests



"He who asks a question is a fool for five minutes; he who does not ask a question remains a fool forever."

- Chinese proverb



Charles Darwin published *"On the Origin of Species by means of Natural Selection,"* 1859

Gregory Mendel introduced the fundamental laws of inheritance 1865

Chromosomes and cancer relationship has been proposed by Boveri 1902

James Watson and Francis Crick described the structure of DNA 1953

Sanger sequencing method was developed 1977

Invention of "polymerase chain reaction" by Kerry Mullis 1985

Applied biosystems (USA) marketed the first automated sequencing machine 1987

"Human Genome Project" was launched 1990

The first draft of "Human Genome Project" was reported 2001

"Human Genome Project" was officially completed 2003

Applied biosystems, Illumina, Roche Company, Pacific Biosciences, Oxford Technologies Nanopore, Helicos Biosciences, and Solexa launched 2nd and 3rd generation sequencing platforms 2004 -

Invention of single-lens optical microscope by Janssen 1595

1665 "Cell" was described by Robert Hooke

Walther Flemming 1882

1888 "Chromosome" was described by Waldeyer

1910 Thomas Hunt Morgan showed that genes are located on chromosomes

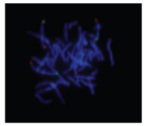
1956 Levan and Tijo reported the human chromosome number was 46

1959 Trisomy 21 was described in Down syndrome by Lejeune

21

1980 Maxam-Gilbert sequencing method was developed

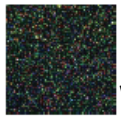
1982 Fluorescence in situ hybridization (FISH) was developed



1992 Comparative genomic hybridization (CGH) was developed

2000 Massively parallel sequencing (MPS) was developed by Lynx Therapeutics

Chromosomal Microarray Clinically Available 2006



Whole Exome Sequencing Clinically Available 2011

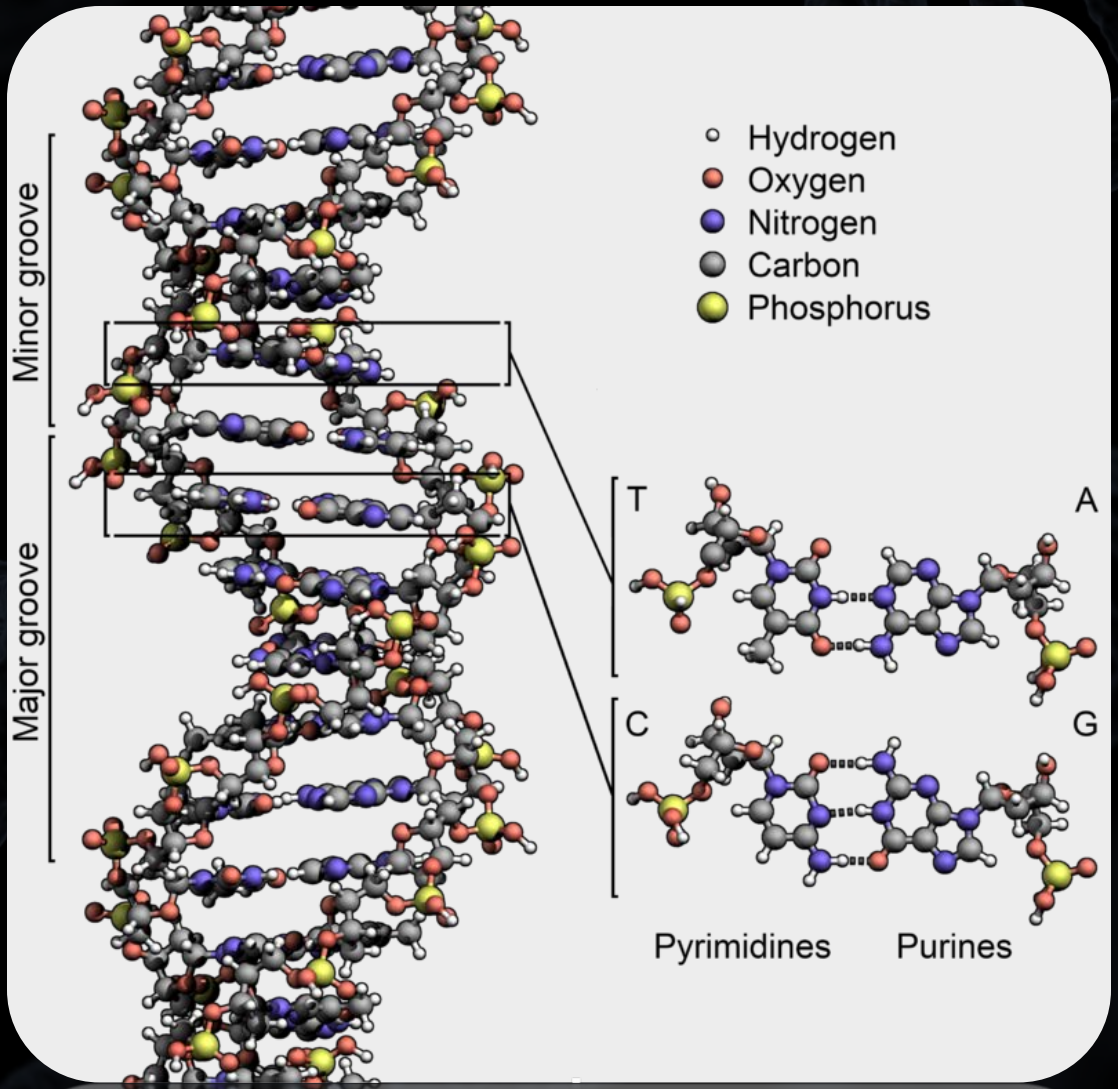
13 years ago…

- The Human Genome Project
  - Completed in 2003 after 13 years of research
  - Identified about 25,000 genes
    - Now estimated to have 35,000 genes
  - Cost: $ 2.7 billion

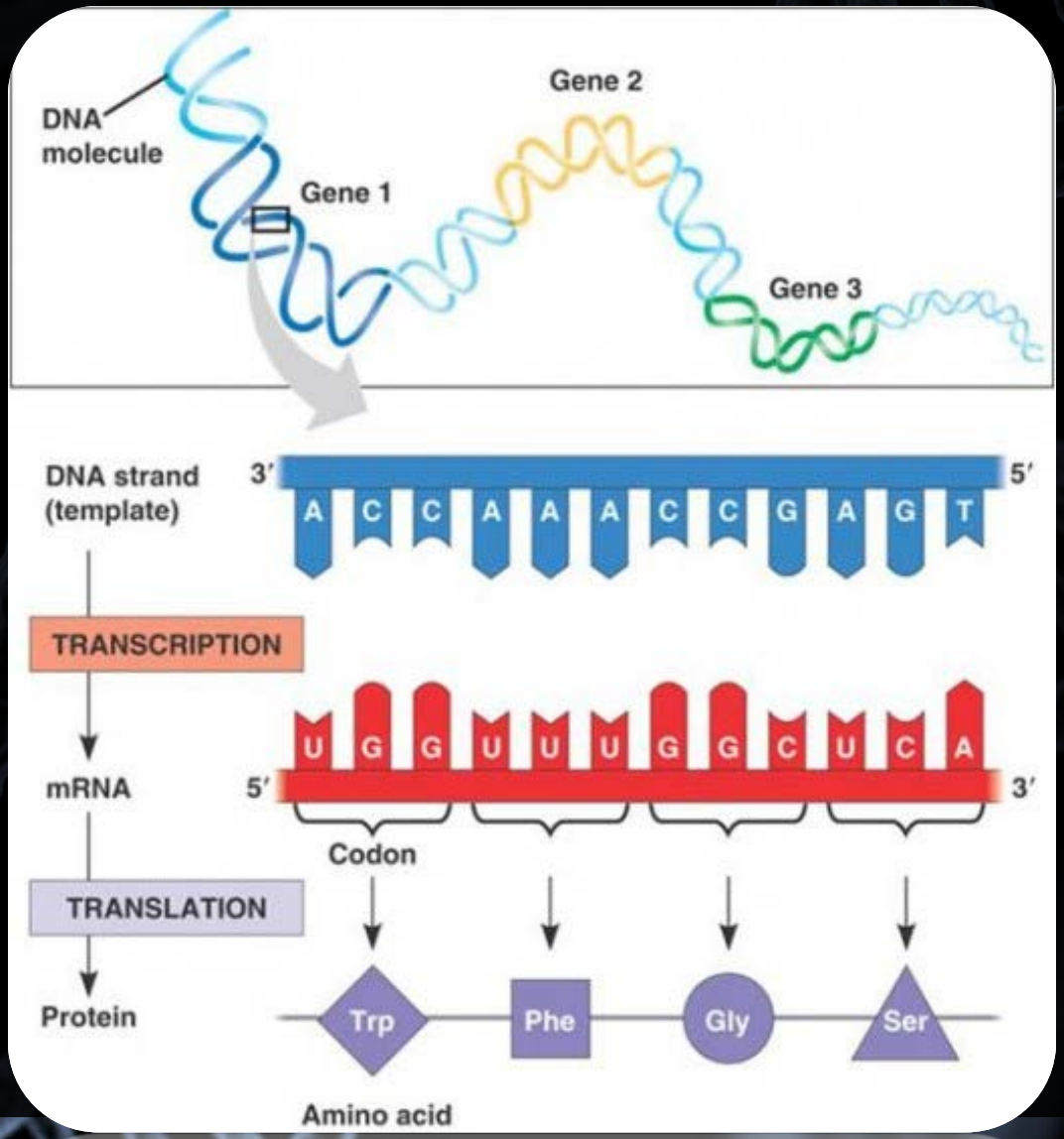
- The International HapMap Project
  - First completed in 2005
  - Haplotype – a set of genes that are closely linked and tend to be inherited together


DNA Basics

Deoxyribonucleic Acid



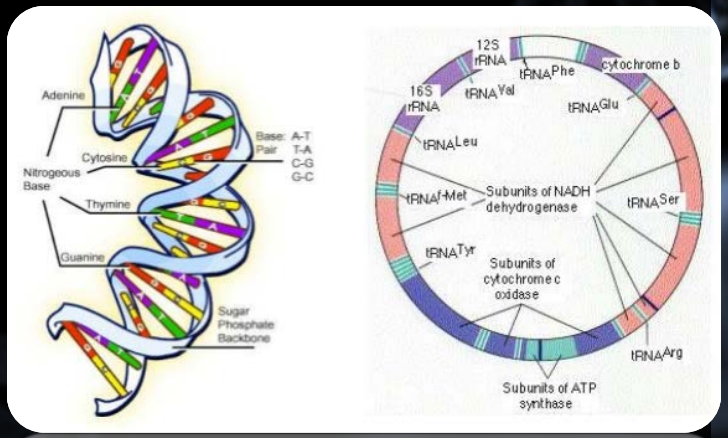
Transcription & Translation



Interesting Numbers

Nuclear DNA

- The human genome contains **3.2** billion nucleotide pairs
- Only **1.5 %** encode proteins !
- Little is known about the rest



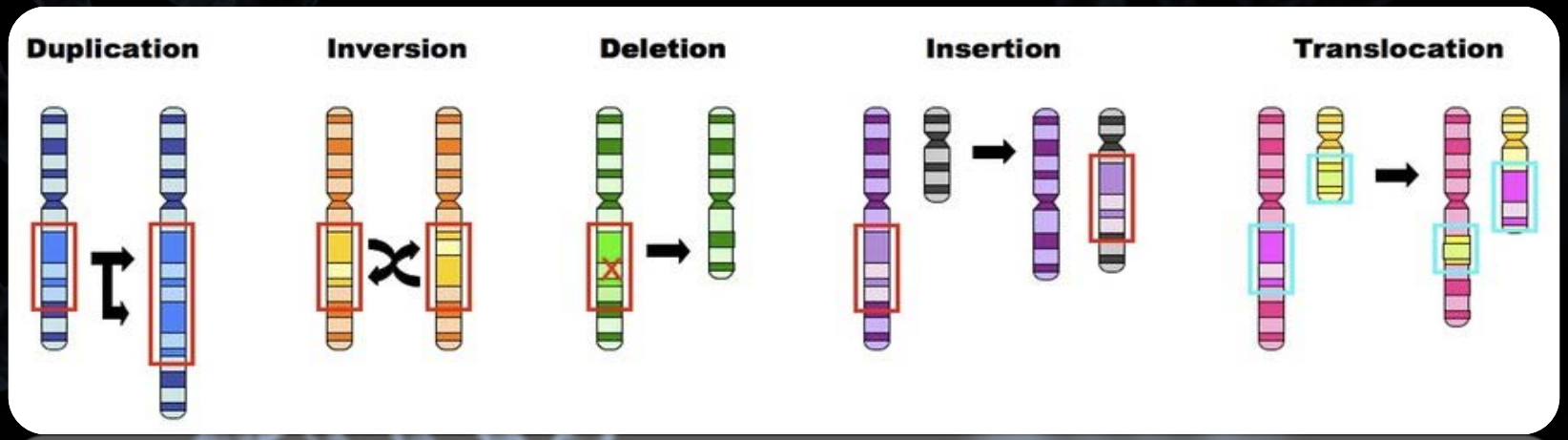
Mitochondrial DNA

- 16,600 nucleotide pairs
- Codes for 37 genes
- Over 100 nuclear genes necessary for mitochondrial function

Types of DNA Mutations

Insertion
Deletion
Point Mutations
Duplication
And more ??

Frameshift
Missense
Nonsense
Repeat Expansions



Case

A family of 5 come to your clinic for genetic counseling .

Dad was diagnosed with Huntington Disease at 42.

His three kids have already been tested.

They're coming to you because you mistakenly took a job where there is no genetic counselor within 200 miles.

Question

How is Huntington Disease inherited?

AD CAG Nucleotide Repeats

10 yo has 43 CAG Repeats

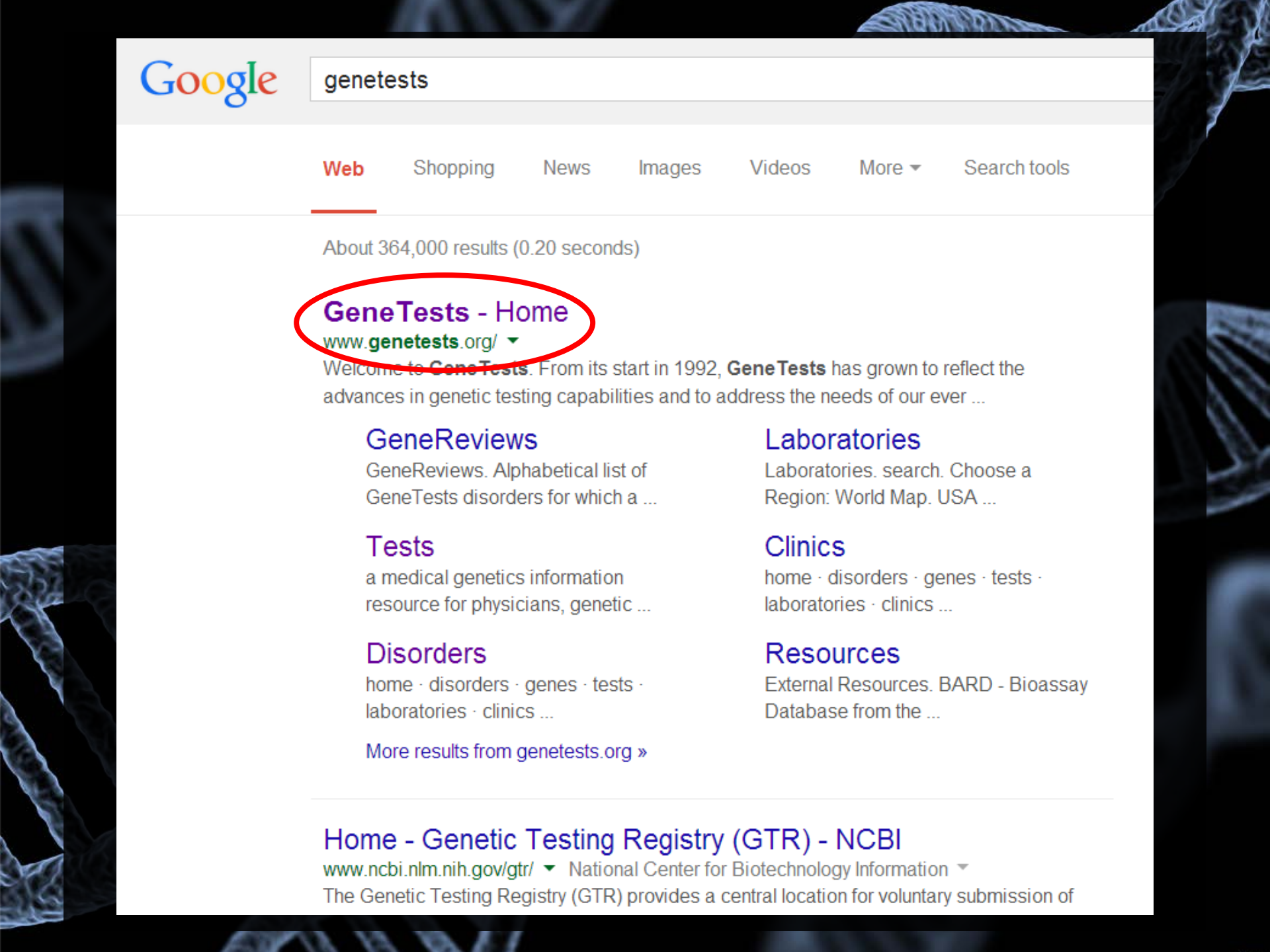
6 yo has 32 CAG Repeats

4 yo has 37 CAG Repeats

Do they have the different risks of developing HD?

Yes or No


I have no idea.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The Genetic Testing Registry (GTR) provides a central location for voluntary submission of

GENETests™

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Huntington Disease

Welcome to **GeneTests**, a medical genetics information resource.

NEW TESTS

Welcome

The GeneTests website

Welcome to GeneTests. From its start in 1992, GeneTests has grown to reflect the advances in genetic testing capabilities and to address the needs of our ever widening user community. We invite you to explore, try some of your favorite searches, and let us know what you think. Your feedback will help shape GeneTests into the indispensable tool you want for your practice.

What's New

Labs Continue to Add Tests Daily

Laboratories from around the world are adding new tests to their listings on GeneTests daily. Since the major upload and publication of tests at the end of May 3,583 new tests have been published of which 140 are for disorders not previously listed in GeneTests. Check the New Tests button to find the most recently added tests every day.

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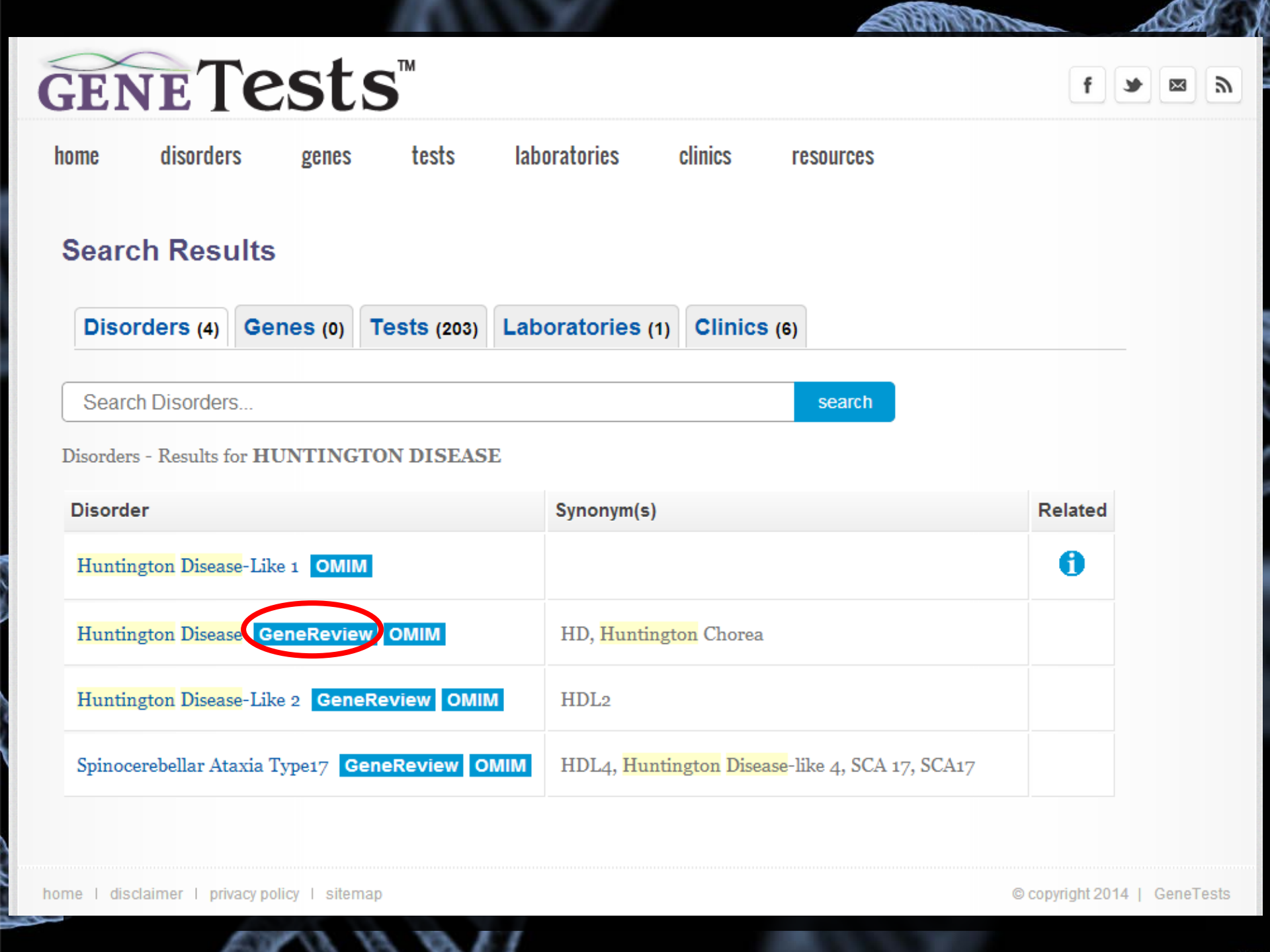
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Huntington Disease

Synonym: Huntington Chorea

Simon C Warby, PhD, Rona K Graham, PhD, and Michael R Hayden, MB, ChB, PhD, FRCP(C), FRSC.

Author Information

Initial Posting: October 23, 1998; Last Update: April 22, 2010.

Summary

Go to:

Disease characteristics. Huntington disease (HD) is a progressive disorder of motor, cognitive, and psychiatric disturbances. The mean age of onset is 35 to 44 years and the median survival time is 15 to 18 years after onset.

Diagnosis/testing. The diagnosis of HD rests on positive family history, characteristic clinical findings, and the detection of an expansion of 36 or more CAG trinucleotide repeats in *HTT*.

Management. *Treatment of manifestations:* Pharmacologic therapy including typical neuroleptics (haloperidol), atypical neuroleptics (olanzapine), benzodiazepines, or the monoamine depleting agent tetrabenazine for choreic movements; anti-parkinsonian agents for hypokinesia and rigidity; psychotropic drugs or some types of antiepileptic drugs for psychiatric disturbances (depression, psychotic symptoms, outbursts of aggression); valproic acid for myoclonic hyperkinesia. Supportive care with attention to nursing needs, dietary intake, special equipment, and eligibility for state and federal benefits.

Views

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Illustrated Glossary

Diagnosis

Go to:

Clinical Diagnosis

The diagnosis of Huntington disease (HD) is suspected clinically in the presence of the following:

- Progressive motor disability featuring chorea; voluntary movement may also be affected
- Mental disturbances including cognitive decline, changes in personality, and/or depression
- Family history consistent with autosomal dominant inheritance

Note: The appearance and sequence of motor, cognitive, and psychiatric disturbances can be variable in HD. The test for CAG repeat size in *HTT* is used to determine the risk status for HD. The diagnosis and age of onset of the disease is determined clinically, usually based on motor signs.

Molecular Genetic Testing

Gene. *HTT* (*HD*) is the only gene known to be associated with Huntington disease. A trinucleotide CAG repeat expansion is the only mutation observed.

Allele sizes. Alleles in *HTT* are classified as normal, intermediate, or HD-causing depending on the number of CAG repeats. The disease is inherited in a dominant fashion and a single HD-causing allele is sufficient to cause the disease.

- **Normal alleles.** p.Gln18(<26), 26 or fewer CAG repeats.
- **Intermediate alleles.** p.Gln18(27_35), 27-35 CAG repeats. An individual with an allele in this range is not at risk of developing symptoms of HD, but because of instability in the CAG tract, may be at risk of having a child with an allele in the HD-causing range [Semaka et al 2006]. Exact estimates of risk are low, but currently unknown. Alleles in the intermediate range have also been described as "mutable alleles" [Potter et al 2004].
- **HD-causing alleles.** p.Gln18(>36), 36 or more CAG repeats. Persons who have an HD-causing allele are considered at risk of developing HD in their lifetime. HD-causing alleles are further classified as:
  - **Reduced-penetrance HD-causing alleles.** p.Gln18(36_39), 36-39 CAG repeats. An individual with an allele in this range is at risk for HD but may not develop symptoms. In rare cases, elderly asymptomatic individuals have been found with CAG repeats in this range [Langbehn et al 2004].
  - **Full-penetrance HD-causing alleles.** p.Gln18(>40), 40 or more CAG repeats. Alleles of this size are associated with development of HD with great certainty.

Clinical testing

At risk for developing HD

10 yo has 43 CAG Repeats and has full penetrance HD

6 yo has 32 CAG Repeats and is ‘not at risk’ carrier

4 yo has 37 CAG Repeats has reduced penetrance HD

What do you do next?

Useful Internet Resources

For Direct Patient Care

- GeneTests www.genetests.org
  - This links you to GeneReviews & OMIM
- TreatableID www.treatable-id.org

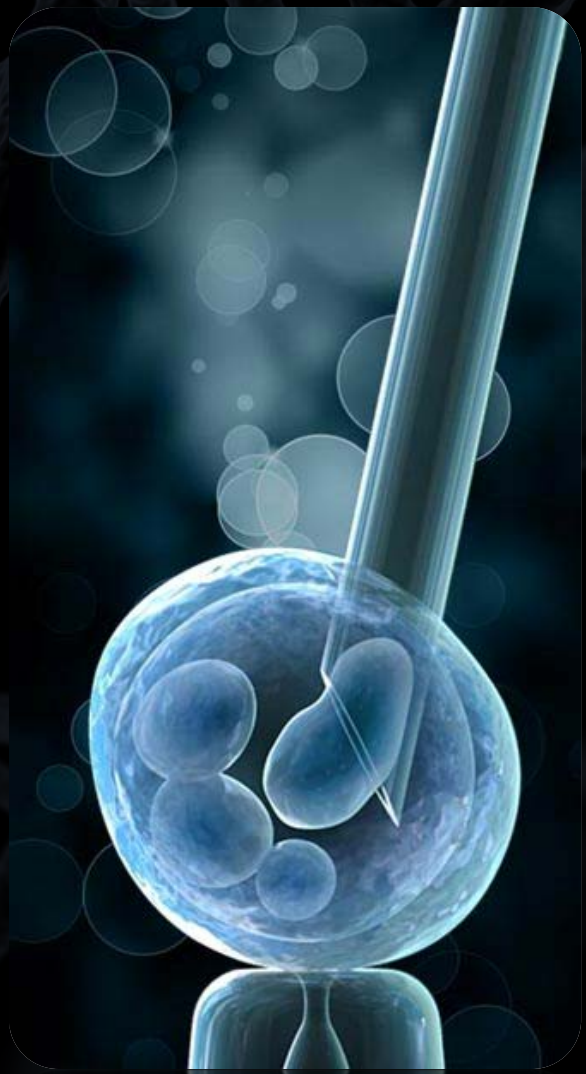
For individual gene investigations

- OMIM www.ncbi.nlm.nih.gov/omim
- GeneCards www.genecards.org


Genetic Testing Options

Types of Clinical Testing

- Newborn screening
- Diagnostic testing
- Carrier testing
- Prenatal testing
- Preimplantation testing
- Predictive testing



Clinically Available Testing Methods

- Biochemical Testing
- Chromosomal Banding (Karyotype)
- Comparative Genomic Hybridization (CGH)
- FISH
- Single Gene or Gene Panel Testing
- Mitochondrial DNA Tests
- Whole Exome Sequencing
- Whole Genome Sequencing

Biochemical Testing

Specific tests to assess the presence, absence, or function of downstream effects of genetic changes

Cannot distinguish between various genetic etiologies and often influenced by time of evaluation.

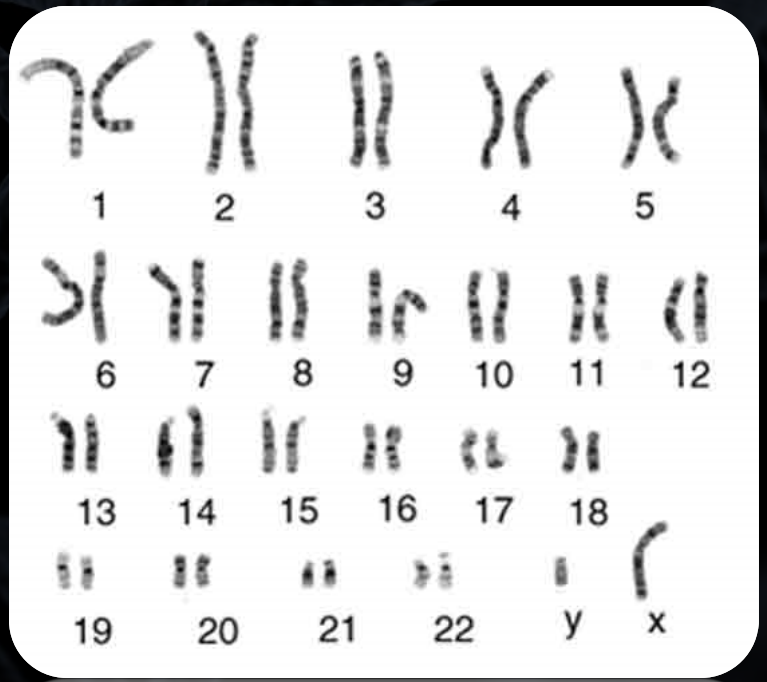
$50 - 1000

Chromosomal Banding (Karyotype)

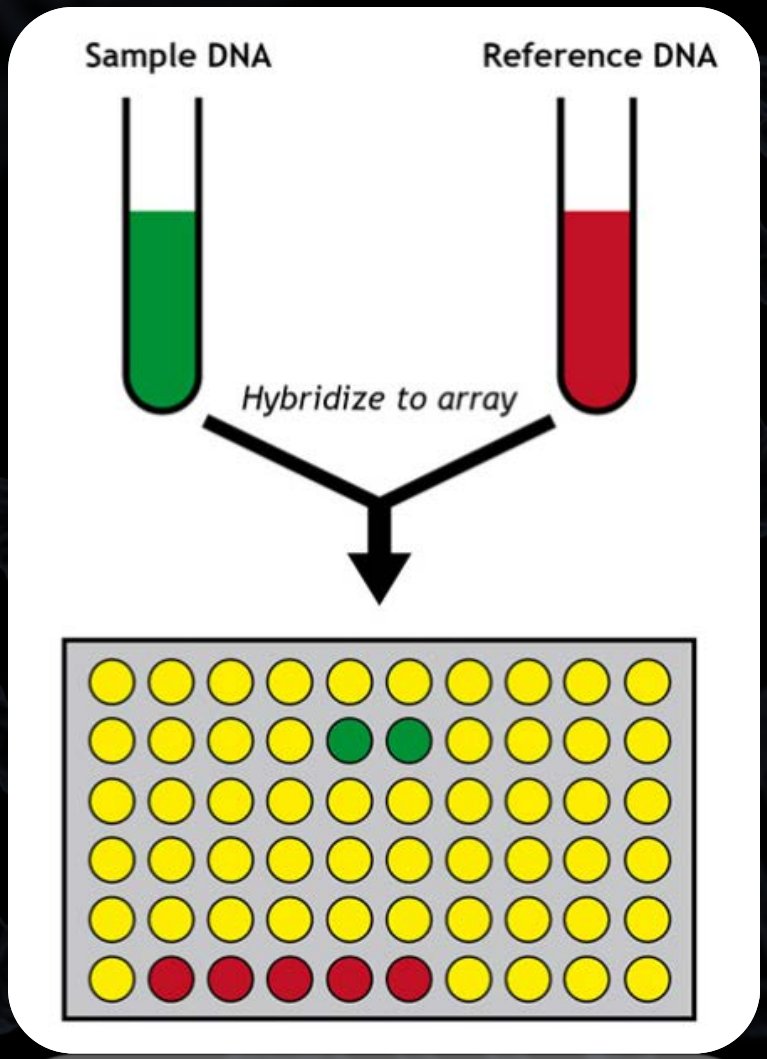
Detects large segments of missing, extra, or rearranged DNA

Misses small changes. Some rearrangements are not clinically significant.

$300 - 500



Comparative Genomic Hybridization (Chromosomal Microarray)



Detects small deletions or duplications of specific segments of the genome

Rare mutations and chromosomal rearrangements are often missed.

$1500 - 2000

ARTICLE

Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies

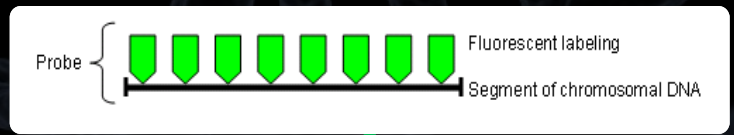
David T. Miller,[1,*] Margaret P. Adam,[2,3] Swaroop Aradhya,[4] Leslie G. Biesecker,[5] Arthur R. Brothman,[6] Nigel P. Carter,[7] Deanna M. Church,[8] John A. Crolla,[9] Evan E. Eichler,[10] Charles J. Epstein,[11] W. Andrew Faucett,[2] Lars Feuk,[12] Jan M. Friedman,[13] Ada Hamosh,[14] Laird Jackson,[15] Erin B. Kaminsky,[2] Klaas Kok,[16] Ian D. Krantz,[17] Robert M. Kuhn,[18] Charles Lee,[19] James M. Ostell,[8] Carla Rosenberg,[20] Stephen W. Scherer,[21] Nancy B. Spinner,[17] Dimitri J. Stavropoulos,[22] James H. Tepperberg,[23] Erik C. Thorland,[24] Joris R. Vermeesch,[25] Darrel J. Waggoner,[26] Michael S. Watson,[27] Christa Lese Martin,[2] and David H. Ledbetter[2,*]

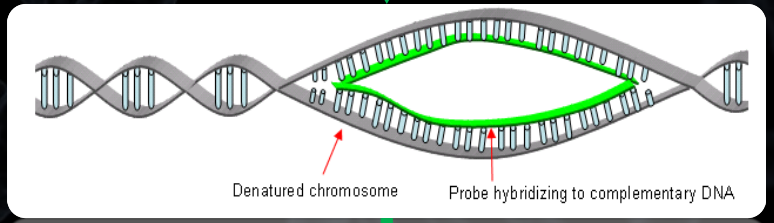
Fluorescent in Situ Hybridization

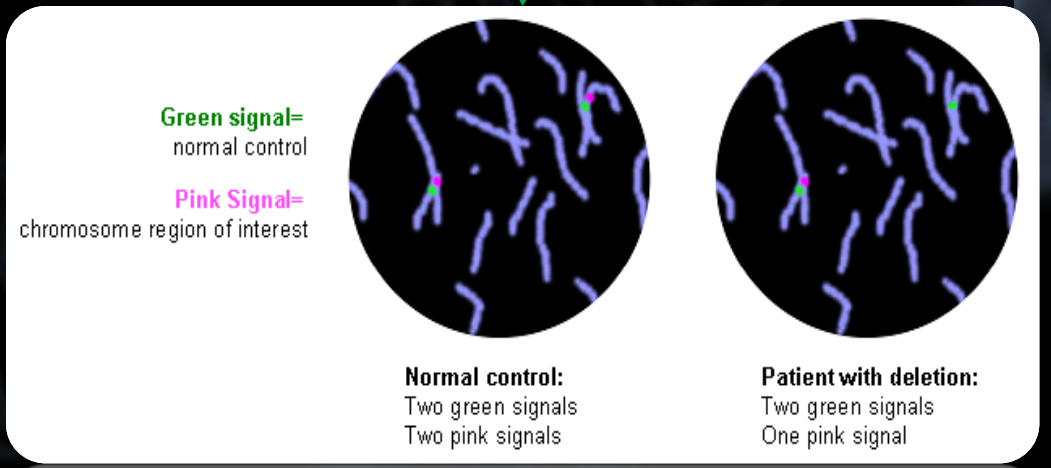
Detects large specific rearrangements, deletions, or duplications

Specific mutation in question must be known.

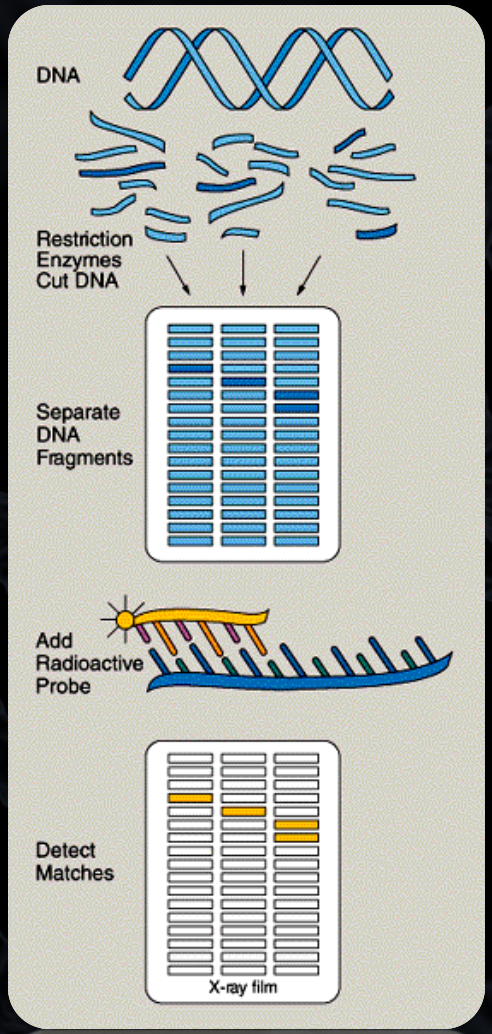
$100 - 800







Sequencing or Direct DNA Testing



Many ways to test including probes, PCR gene amplification, or other 'next generation sequencing' techniques

When you have a specific constellation of symptoms or a unique clinical symptom

Only tests for known clinically significant mutations depending on each lab's panels

$300 – 10,000

Whole Exome Sequencing

Evaluates each base of protein encoding regions of DNA

Can miss Trinucleotide Repeats and large deletions or duplications.

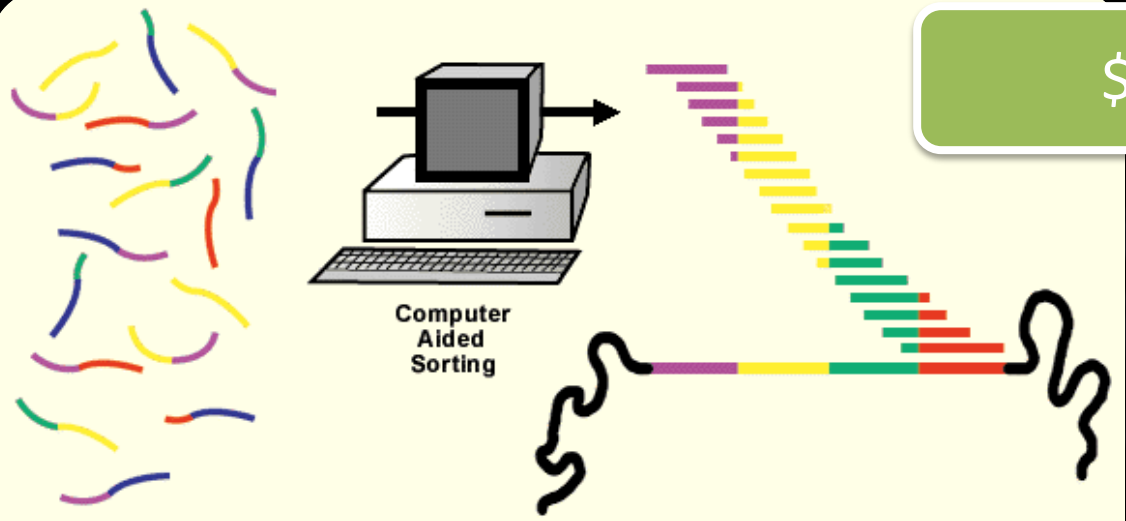
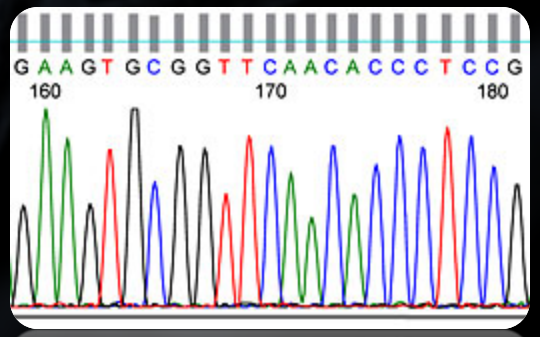


Fig 2: Short fragments of DNA sequence are ordered by overlapping data to recreate the whole genome sequence

$8,000 – 12,000




So shouldn’t we all get our genetic testing and be done with it?

Consider the Challenges

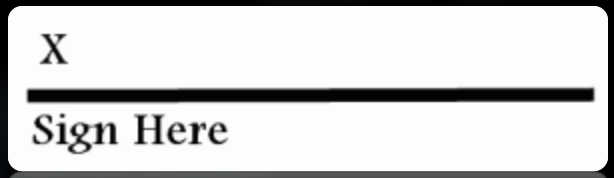
We're collecting a large amount of information about patients that we have a limited understanding of.

Genetic mutations can cause the activation or deactivation of downstream products in variable degrees of unknown clinical significance.

Informed Consent for Data

For the first time, patients will need to choose beforehand what portions of the test results they wish to receive or not receive.

- Receive *all* information (Pamphlet, Website, CD, DVD?)
- Receive information regarding target of interest
- Receive medically actionable information for patient's today, in the future, or for their relatives



Not to mention…

- Revelation of nonpaternity, consanguinity
- Huge number of variants of unknown significance
- Finding unexpected mutations
- Possible forensic uses of data
- Data storage and privacy
- Costs of genetic counseling
- Need for other follow-up

Should the test be made widely available?

10 minutes counseling pre and post test

If 3 million tests are done: 2,820,000 unaffected

Totaling 940,000 hours of counseling for normal studies!

(That's 470 full-time genetic counselors)

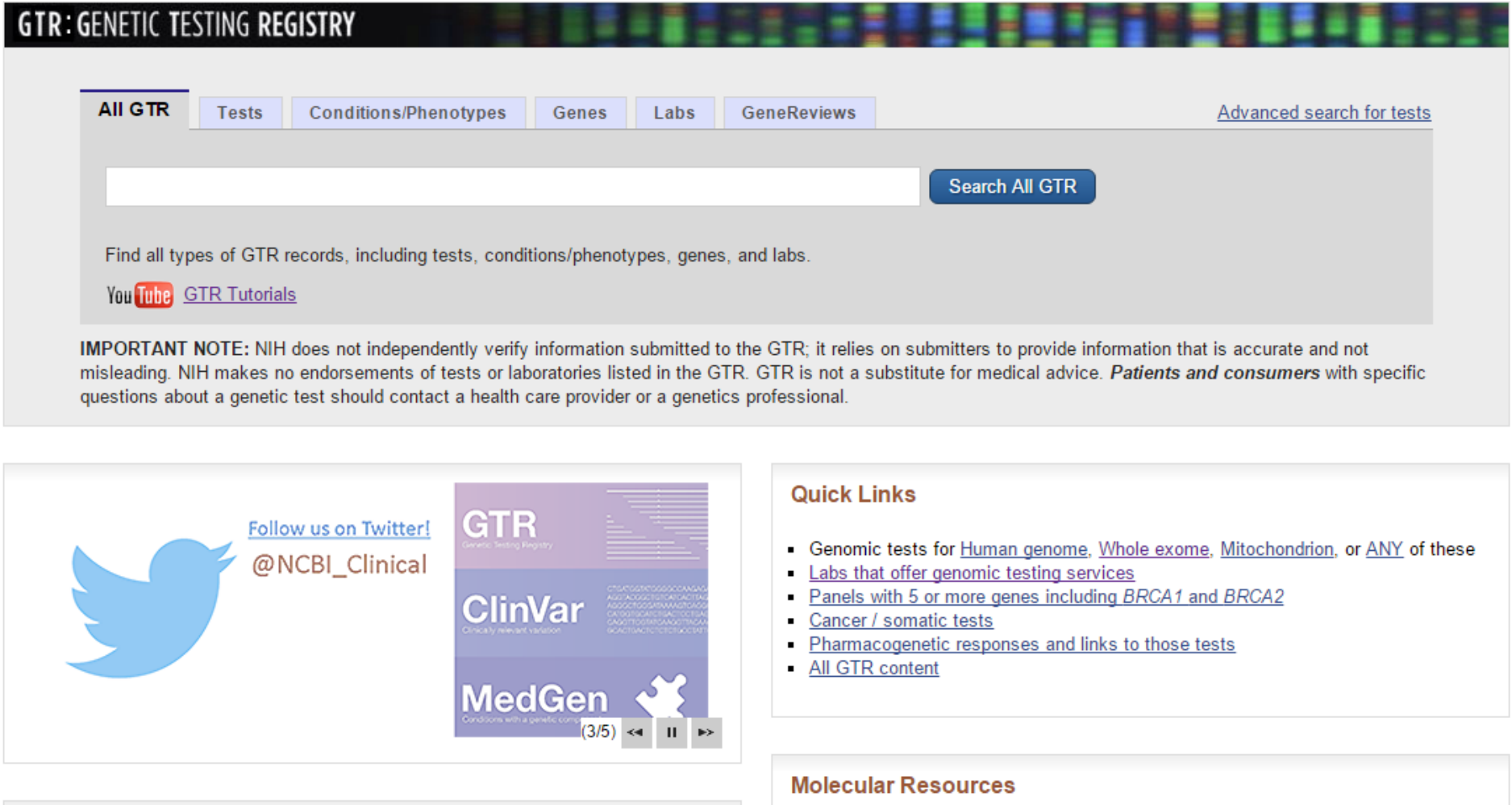

How do we find the right test?

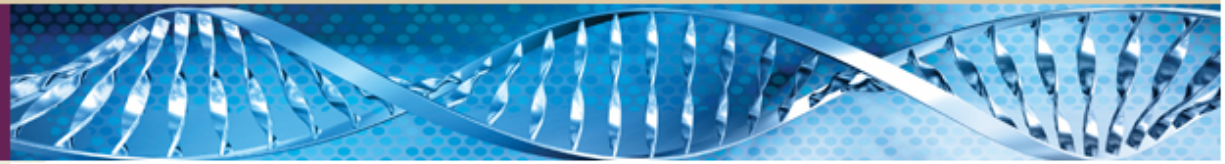
That Depends…

Clinical

Direct to Consumer

www.ncbi.nlm.nih.gov/gtr/





Whole Genome Laboratory (WGL)

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The development and clinical implementation of the Whole Exome Sequencing test derives from a joint effort by Baylor's Human Genome Sequencing Center and the Medical Genetics Laboratories of the Department of Molecular and Human Genetics to establish a clinical laboratory dedicated to state-of-the-art next generation sequencing. The collaboration between these groups brings together genomic scientists, clinical laboratory scientists, and clinicians to provide reliable genome-wide analyses that are carefully annotated and interpreted for clinical significance by medical geneticists. Whole Exome Sequencing is the first test to be offered by the WGL and is focused on the evaluation of underlying genetic causes of disease. In the near future, the WGL will implement additional clinical tests, including Whole Genome Sequencing (WGS) that will bring this technology to other aspects of medical care and treatment.

WGL
WHOLE GENOME LABORATORY

The Whole Exome Sequencing for the Evaluation of Mendelian Disorders applies the power of next generation sequencing technology to clinical genetics in a CLIA approved setting with clinical interpretation of the sequence information. Whole Exome Sequencing (WES) is poised to change the current paradigm of genetic testing for Mendelian disorders, pharmacogenetic traits, and potentially complex traits. Rather than limiting testing to a single gene or panel of genes and incurring diagnostic delays and escalating costs, the Whole Exome Sequencing test will sequence nucleotide by nucleotide, the human exome to the depth of coverage required to achieve a consensus sequence with high accuracy. Point mutations, insertions, deletions, inversions, and rearrangements of the exome are potentially discoverable and could be considered pathologic depending on the defect. The reporting of the Whole Exome Sequencing test will focus on known or predicted deleterious mutations in genes known to be associated with human disorders, however, significant potentially medically actionable findings in other genes of interest will also be communicated for future reference.

List of Selected Positive Cases Reported by Whole Exome Sequencing (WES)

TEST CATALOG | ORDERING & BILLING | DIAGNOSTIC EDUCATION | REQUEST MATERIALS | NEUROLINK | SITE SEARCH

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Testing that Makes a Difference.

LATEST TESTS: #4500 Paraneoplastic Neurological Syndromes, I

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Enter a symptom, disease type, test name or code.

Need help?

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Need help?

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Access forms, resources, shipping materials and educational info.

ANNOUNCEMENTS:

Next Generation Sequencing Testing for Epilepsy Available April 2, 2014
Athena Diagnostics is pleased to announce the availability of next-generation sequencing for epilepsy, starting April 2, 2014. Epilepsy is one of the most common serious neurological diseases, characterized by multiple unprovoked seizures (surges of electrical activity in the brain that disrupt function).
Read More >

Athena Diagnostics Announces New Genetic Testing Services for Rare Neurological Disorders
Tests to be unveiled at the American Academy of Neurology | Annual Meeting in San Diego, March 16-23, 2013
Read More >

NEUROLINK™
by Athena Diagnostics, Inc.

CDC Report Suggests Increase in Autism Spectrum Disorder
A new Centers for Disease Control and Prevention (CDC) summary report estimates an increase in the United States of some 30 percent in children with autism spectrum disorder (ASD), bringing the ratio ... Read Article >

athena diagnostics

Request Materials

- Get Requisition
- Get Materials
- Algorithms
- Letters of Medical Necessity
- Virtual Grand Rounds

Test Catalog

SEARCH | BROWSE

Enter symptom, disease type, test name or code

search

need help? click here ►

Request Materials

Athena Diagnostics is pleased to offer you the following resources to make ordering easy. We offer shipping kits with prepaid airbills, requisition forms, reprints & references, literature that details the many testing services we offer, and much more.

Email this page

Get Requisitions
Download a requisition form

Get Materials
Shipping kits, product literature and blank requisitions

Algorithms
Testing algorithms for CMT, Ataxia and Spastic Paraplegia based on published practice parameters and guidelines

[back to top]

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Complete this requisition form when Athena will directly bill hospitals, laboratories or clinics.

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Complete this requisition for all international samples.

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Athena Diagnostics Neurology Testing Services (June 2014)

Important: Please be sure to write in test code and test name in the Tests Ordered section on front.

Test Code		Pref. Spec.	Min. Vol.	Tube Type
Cerebrovascular Disease (Stroke)				
☐ 421	Complete CADASIL Evaluation* (Notch3 Sequencing)	B	10 mL	L
☐ 442	HTRA1 DNA Sequencing Test* (CARASIL)	B	10 mL	L
☐ 424	COL4A1 DNA Sequencing Test* (CSVD)	B	10 mL	L
☐ **692**	**Complete Cerebral Cavernous Malformation (CCM) Evaluation*** (KRIT1 Seq./Del., CCM2 Seq./Del., PDCD10 Seq./Del.)	B	10 mL	L
☐ **683**	**KRIT1 (CCM1) Evaluation*** (KRIT1 Sequencing/Deletion)	B	10 mL	L
☐ **686**	**CCM2 Evaluation*** (CCM2 Sequencing/Deletion)	B	10 mL	L
☐ **689**	**PDCD10 (CCM3) Evaluation*** (PDCD10 Sequencing/Deletion)	B	10 mL	L
☐ 681	KRIT1 (CCM1) DNA Sequencing Test*	B	10 mL	L
☐ 682	KRIT1 (CCM1) Deletion Test*	B	10 mL	L
☐ 684	CCM2 DNA Sequencing Test*	B	10 mL	L
☐ 685	CCM2 Deletion Test*	B	10 mL	L
☐ 687	PDCD10 (CCM3) DNA Sequencing Test*	B	10 mL	L
☐ 688	PDCD10 (CCM3) Deletion Test*	B	10 mL	L
Dementia				
☐ **178**	**ADmark® Alzheimer's Evaluation*** (ApoE, Phospho-Tau, Total-Tau, Aβ42) (Symptomatic for Dementia) (CSF must be in polypropylene tube and arrive on cold pack)	C B	2 mL 10 mL	P L
☐ 109	ADmark® ApoE Genotype Analysis & Interpretation* (Symptomatic for Dementia)	B	10 mL	L
☐ 177	ADmark® Phospho-Tau/Total-Tau/Aβ42 CSF Analysis & Interpretation (CSF must be in polypropylene tube and arrive on cold pack)	C	2 mL	P
☐ **179**	**ADmark® Early-Onset Alzheimer's Evaluation*** (PS-1, APP Seq./Dup., PS-2)	B	10 mL	L
☐ 167	ADmark® PS-1 DNA Sequencing Test*	B	10 mL	L
☐ 168	ADmark® APP DNA Seq./Dup. Test*	B	10 mL	L
☐ 169	ADmark® PS-2 DNA Sequencing Test*	B	10 mL	L
☐ **281**	**Frontotemporal Dementia (FTD) Evaluation*** (MAPT, GRN, C9orf72)	B	10 mL	L
☐ 209	C9orf72 DNA Test*	B	10 mL	L
☐ 204	GRN DNA Sequencing Test*	B	10 mL	L
☐ 205	MAPT DNA Sequencing Test*	B	10 mL	L
Developmental Disabilities				
☐ **788**	**Primary Microcephaly Evaluation*** (ASPM, MCPH1, WDR62)	B	10 mL	L
☐ 784	ASPM DNA Sequencing Test*	B	10 mL	L
☐ 786	MCPH1 DNA Sequencing Test*	B	10 mL	L
☐ 787	WDR62 DNA Sequencing Test*	B	10 mL	L
☐ 742	SHANK3 DNA Sequencing Test*	B	10 mL	L
☐ 724	SHANK2 DNA Sequencing Test*	B	10 mL	L
☐ 744	PTEN DNA Sequencing Test*	B	5 mL	L
☐ **795**	**Joubert Syndrome Evaluation*** (TMEM67, TMEM216, AHI1, CEP290, NPHP1, CC2D2A)	B	10 mL	L
☐ 792	TMEM67 DNA Sequencing Test*	B	10 mL	L
☐ 789	TMEM216 DNA Sequencing Test*	B	10 mL	L
☐ 790	AHI1 DNA Sequencing Test*	B	10 mL	L
☐ 791	CEP290 DNA Sequencing Test*	B	10 mL	L
☐ 793	NPHP1 DNA Deletion Test*	B	10 mL	L
☐ 794	CC2D2A DNA Sequencing Test*	B	10 mL	L
☐ 737	Smith-Lemli-Opitz Syndrome (DHCR7) DNA Test*	B	5 mL	L
☐ 729	Cohen Syndrome (COH1) DNA Seq. Test*	B	5 mL	L
☐ **153**	**Complete Rett Syndrome Evaluation*** (MECP2 Seq., MECP2 Duplication/Deletion)	B	10 mL	L
☐ 142	Rett Syndrome (MECP2) DNA Seq. Test*	B	10 mL	L
☐ 148	Rett Syndrome (MECP2) Dup./Del. Test*	B	10 mL	L
☐ **773**	**ARX Evaluation*** (ARX DNA Seq., ARX Dup./Del.)	B	10 mL	L
☐ 141	ARX DNA Sequencing Test*	B	10 mL	L
☐ 041	ARX Duplication/Deletion Test*	B	10 mL	L
☐ **785**	**CDKL5 Evaluation*** (CDKL5 Seq., CDKL5 Dup./Del.)	B	10 mL	L
☐ 149	CDKL5 DNA Sequencing Test*	B	10 mL	L
☐ 049	CDKL5 Duplication/Deletion Test*	B	10 mL	L
☐ 771	SYNGAP1 DNA Sequencing Test*	B	10 mL	L
☐ **7540**	**MEF2C Evaluation*** (MEF2C DNA Seq., MEF2C Del.)	B	4 mL	L
☐ 754	MEF2C DNA Sequencing Test*	B	4 mL	L
☐ 077	MEF2C Deletion Test*	B	4 mL	L
☐ **7410**	**FOXG1 Evaluation*** (FOXG1 DNA Seq., FOXG1 Del.)	B	4 mL	L
☐ 740	FOXG1 DNA Sequencing Test*	B	4 mL	L
☐ 074	FOXG1 Deletion Test*	B	4 mL	L
NOTE: Pediatric minimum for all Developmental Disabilities tests is 2 mL.				
Epilepsy				
☐ **5000**	**Epilepsy Advanced Sequencing Evaluation***	B	7 - 10 mL	L
☐ **5001**	**Epilepsy Advanced Sequencing Evaluation – Generalized, Absence, Focal and Myoclonus Epilepsies***	B	7 - 10 mL	L
☐ **5002**	**Epilepsy Advanced Sequencing Evaluation – Epileptic Encephalopathies***	B	7 - 10 mL	L
☐ **5003**	**Epilepsy Advanced Sequencing Evaluation – Neuronal Migration Disorders***	B	7 - 10 mL	L
☐ **5004**	**Epilepsy Advanced Sequencing Evaluation – Epilepsy in X-Linked Intellectual Disability***	B	7 - 10 mL	L
☐ **5005**	**Epilepsy Advanced Sequencing Evaluation – Neuronal Ceroid Lipofuscinosis***	B	7 - 10 mL	L
☐ **5006**	**Epilepsy Advanced Sequencing Evaluation – Epilepsy Associated with Migraine***	B	7 - 10 mL	L
☐ **5007**	**Epilepsy Advanced Sequencing Evaluation – Syndromic Disorders with Epilepsy***	B	7 - 10 mL	L
☐ **5008**	**Epilepsy Advanced Sequencing Evaluation – Infantile Spasms***	B	7 - 10 mL	L
Please see website for the list of genes in each panel.				
☐ **5100**	**Autoimmune Epilepsy Evaluation** GAD65 Neurological Syndrome, VGKC, CASPR2, LGI1, NMDA (NR1-subunit) Autoantibody Test	S	2 mL	R
☐ 5101	GAD65 Neurological Syndrome Autoantibody Test (Epilepsy) (Single)	S	2 mL	R
☐ 5102	VGKC Autoantibody Test (Epilepsy) (Single)	S	2 mL	R
☐ 5103	CASPR2 Autoantibody Test (Epilepsy) (Single)	S	2 mL	R
☐ 5104	LGI1 Autoantibody Test (Epilepsy) (Single)	S	2 mL	R
☐ 5105	NMDA Receptor (NR1-subunit) Autoantibody Test (Epilepsy) (Single)	S	2 mL	R
☐ **556**	**Complete Tuberous Sclerosis Evaluation*** (TSC1 Seq., TSC1 Del., TSC2 Seq., TSC2 Del.)	B	20 mL	L
☐ 521	TSC1 DNA Sequencing Test*	B	20 mL	L
☐ 508	TSC1 DNA Deletion Test*	B	20 mL	L
☐ 522	TSC2 DNA Sequencing Test*	B	20 mL	L
☐ 524	TSC2 DNA Deletion Test*	B	10 mL	L
☐ 523	TSC Familial DNA Seq. Mutation Evaluation* Proband Accession # _____ Relationship _____	B	10 mL	L
☐ **573**	**SCN1A Complete Evaluation*** (SCN1A Sequencing, SCN1A Deletion)	B	10 mL	L
☐ 537	SCN1A Deletion Test*	B	10 mL	L
☐ **674**	**CSTB (EPM1) Evaluation*** (CSTB (EPM1) DNA Test, CSTB (EPM1) Seq.)	B	10 mL	L
☐ 410	CSTB (EPM1) (Unverricht-Lundborg) DNA Test*	B	10 mL	L
☐ **797**	**ARX Evaluation*** (ARX Seq., ARX Dup./Del.)	B	10 mL	L
☐ **799**	**CDKL5 Evaluation*** (CDKL5 Seq., CDKL5 Dup./Del.)	B	10 mL	L
☐ 065	ARX Duplication/Deletion Test*	B	10 mL	L
☐ 067	CDKL5 Duplication/Deletion Test*	B	10 mL	L
☐ 549	Alexander Disease (GFAP) DNA Seq. Test*	B	10 mL	L
☐ 443	POLG DNA Seq. Test* (Alpers Syndrome)	B	10 mL	L
NOTE: Pediatric minimum for all Epilepsy tests is 2 mL.				
Family Testing				
☐ 185	Familial DNA Sequence Evaluation* This test detects previously identified sequence variants in at-risk family members. This test cannot be applied to the TTR gene. For Familial TSC mutations, please order Code 523. Proband Accession # _____ Relationship _____	B	10 mL	L
Hearing Loss				
☐ **329**	**Connexin Related Deafness Evaluation*** (Connexin 26, Connexin 30)	B	10 mL	L
☐ 321	Connexin 26 DNA Sequencing Test*	B	10 mL	L
☐ 319	Connexin 30 DNA Deletion Test*			
Hereditary Motor Neuron Diseases				
☐ **655**	**Complete Hereditary Spastic Paraplegia Evaluation*** (Includes all individual HSP DNA tests, see below.)	B	20 mL	L
☐ **653**	**Autosomal Dominant Hereditary Spastic Paraplegia Evaluation*** (SPG3A, SPG4, SPG4 Del., SPG6, SPG8, SPG17, SPG31, KIF5A (SPG10), REEP1 (SPG31) Del.)	B	20 mL	L
☐ **654**	**Autosomal Recessive Hereditary Spastic Paraplegia Evaluation*** (SPG7, SPG11, CYP7B1 (SPG5), Spastizin/ZFYVE26 (SPG15))	B	10 mL	L
Individual HSP DNA Tests:		B	10 mL	L
☐ 530	Spastin (SPG4)*	☐ 532	NIPA1 (SPG6)*	
☐ 531	Atlastin (SPG3A)*	☐ 533	Strumpellin (SPG8)*	
☐ 529	REEP1 (SPG31 Seq.)*	☐ 632	Paraplegin (SPG7)*	
☐ 661	Spastin (SPG4 Del.)*	☐ 633	Spatacsin (SPG11)*	
☐ 631	BSCL2 (SPG17)*	☐ 612	CYP7B1 (SPG5A)*	
☐ 613	KIF5A (SPG10)*	☐ 665	REEP1 (SPG31 Del.)*	
☐ 614	Spastizin/ZFYVE26 (SPG15)*			
☐ **215**	**Complete SMA Evaluation (Reflexive)*** This is a reflexive test. Tests will be run in succession until either a positive result is detected or the profile is completed. Testing is performed in this order: 1. SMN1 Del.; 2. SMN1 Seq.; 3. IGHMBP2 (SMARD), UBE1 Exon15 (XLSMA)	B	2 - 4 mL	L
☐ **214**	**SMA Plus (Reflexive)*** This is a reflexive test. Tests will be run in succession until either a positive result is detected or the profile is completed. Testing is performed in this order: 1. SMN1 Del.; 2. SMN1 Seq.	B	2 - 4 mL	L
☐ 1110	Spinal Muscular Atrophy Deletion – Diagnostic* (Including SMN2 Copy Number)	B	2 - 4 mL	L
☐ 211	Spinal Muscular Atrophy – SMN1 DNA Seq. Test* (only order if deletion testing has already been performed)	B	2 - 4 mL	L
☐ 212	Spinal Muscular Atrophy with Respiratory Distress (SMARD) IGHMBP2 DNA Seq. Test*	B	2 - 4 mL	L
☐ 213	X-Linked Spinal Muscular Atrophy (XLSMA) UBE1 DNA Sequencing Test* (Exon 15 only)	B	2 - 4 mL	L
☐ 444	Spinal Muscular Atrophy – Carrier SMN1 Del. Test*	B	2 - 4 mL	L
☐ 117	Kennedy's Disease (SBMA) DNA Test*	B	10 mL	L
☐ **643**	**Complete ALS Evaluation*** (C9orf72, SOD1, OPTN, VCP, UBQLN2, FUS, TARDBP, ANG, FIG4)	B	20 mL	L
☐ 670	C9orf72 DNA Test*	B	10 mL	L
☐ 620	SOD1 DNA Sequencing Test*	B	10 mL	L
☐ 609	OPTN DNA Sequencing Test*	B	10 mL	L
☐ 610	VCP DNA Sequencing Test*	B	10 mL	L
☐ 611	UBQLN2 DNA Sequencing Test*	B	10 mL	L
☐ 619	FUS DNA Sequencing Test*	B	10 mL	L
☐ 621	TARDBP DNA Sequencing Test*	B	10 mL	L
☐ 622	ANG DNA Sequencing Test*	B	10 mL	L
Leukodystrophy				
☐ 421	Complete CADASIL Evaluation* (Notch3 Sequencing)	B	10 mL	L
☐ **6106**	**Leukoencephalopathy with Vanishing White Matter Evaluation*** (EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5)	B	10 mL	L
☐ 6101	EIF2B1 DNA Sequencing Test*	B	10 mL	L
☐ 6102	EIF2B2 DNA Sequencing Test*	B	10 mL	L
☐ 6103	EIF2B3 DNA Sequencing Test*	B	10 mL	L
☐ 6104	EIF2B4 DNA Sequencing Test*	B	10 mL	L
☐ 6105	EIF2B5 DNA Sequencing Test*	B	10 mL	L
☐ 6107	ARSA DNA Sequencing Test*	B	10 mL	L
☐ 6108	ABCD1 DNA Sequencing Test*	B	10 mL	L
☐ **6110**	**PLP1 Evaluation*** (PLP1 Seq., PLP1 Dup.)	B	10 mL	L
☐ 6112	PLP1 DNA Sequencing Test*	B	10 mL	L
☐ 6111	PLP1 Duplication Test*	B	10 mL	L
☐ 6109	GJC2 DNA Sequencing Test*	B	10 mL	L
☐ 549	Alexander Disease (GFAP) DNA Seq. Test*	B	10 mL	L

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*Medicare ABN Required

Test Code		Pref. Spec.	Min. Vol.	Tube Type
Migraine				
☐ **190**	**Hemiplegic Migraine Evaluation*** (CACNA1A, ATP1A2, SCN1A)	B	10 mL	L

Mitochondrial Disorders				
☐ **575**	**Common Mitochondrial Disorders Evaluation*** (POLG, MELAS, MERRF, NARP)	B	10 mL	L
☐ **576**	**Progressive External Ophthalmoplegia (PEO) Evaluation*** (POLG, TWINKLE, ANT1, OPA1, MELAS)	B	10 mL	L
☐ **577**	**Mitochondrial Neurogastrointestinal Encephalopathy (MNGIE) Evaluation*** (TYMP, RRM2B, MELAS)	B	10 mL	L
☐ **578**	**Mitochondrial Hepatoencephalopathic Evaluation*** (POLG, DGUOK, MPV17, TWINKLE)	B	10 mL	L
☐ **579**	**Mitochondrial Encephalomyopathic Evaluation*** (TK2, RRM2B, POLG)	B	10 mL	L
☐ **515**	**LHON mtDNA Evaluation*** (LHON 11778, 3460, 14484)	B	10 mL	L

Multiple Sclerosis				
☐ 112	NAbFeron® (IFN-ß) Neutralizing Antibody Test	S	2 mL	R
☐ 194	BAbScreen®/NAbFeron® (IFN-ß) Antibody Test (Binding Antibody positive confirmed by NAbFeron® Test)	S	2 mL	R
☐ 197	TYSABRI® (Natalizumab) Antibody Test (must arrive on cold pack)	S	2 mL	R
☐ 193	Neuromyelitis Optica (NMO) Autoantibody Test	S	2 mL	R

Paraneoplastic & Other Antibody Disorders of the CNS				
☐ **4500**	**Paraneoplastic Neurological Syndromes Initial Assessment (PNS-IA)**	S	2 mL	R
		or		
	(Hu, Yo, CV2, MaTa, Ri, Amphiphysin)	C	2 mL	P**
☐ **467**	**NeoComplete Paraneoplastic Evaluation with Recombx® (Reflexive)** Hu, Yo, Zic4, CV2, MaTa, Ri, CAR, VGCC, VGKC, Amphiphysin, gnAChR, NR1, GAD65 Neurological Syndrome, LGI1, CASPR2.	S	2 mL	R
☐ **438**	**NeoCerebellar Degeneration Paraneoplastic Evaluation with Recombx®** (Hu, Yo, Zic4, CV2, MaTa, Ri, Amphiphysin, GAD65 Neurological Syndrome)	S	2 mL	R
☐ **447**	**NeoEncephalitis Paraneoplastic Evaluation with Recombx®** (Hu, CV2, MaTa, VGKC, Amphiphysin, NR1, GAD65 Neurological Syndrome, LGI1, CASPR2)	S	3 mL	R
☐ **436**	**NeoSensory Neuropathy Paraneoplastic Evaluation with Recombx®** (Hu, CV2, Amphiphysin)	S	2 mL	R
☐ **494**	**Neuromyotonia Evaluation** (CASPR2, VGKC)	S	2 mL	R

Peripheral Neuropathy: Autoimmune				
☐ **287**	**SensoriMotor Neuropathy Evaluation** (Co-GM1 Quattro®, MAG 'Dual Antigen'®, Hu, GALOP™, Sulfatide)	S	2 mL	R
☐ **263**	**Sensory Neuropathy Evaluation** (MAG 'Dual Antigen'®, Hu, GALOP™, Sulfatide)	S	2 mL	R
☐ **288**	**Motor Neuropathy Evaluation** (Co-GM1 Quattro®, MAG 'Dual Antigen'®)	S	2 mL	R
☐ **276**	**Multifocal Motor Neuropathy Evaluation*** (Co-GM1 Quattro®, PMP22 Dup./Del.)	S	2 mL	R
		B	10 mL	L

Epilepsy				
☐ 5000	Epilepsy Advanced Sequencing Evaluation*	B	7 - 10 mL	L
☐ 5001	Epilepsy Advanced Sequencing Evaluation - Generalized, Absence, Focal and Myoclonus Epilepsies*	B	7 - 10 mL	L
☐ 5002	Epilepsy Advanced Sequencing Evaluation - Epileptic Encephalopathies*	B	7 - 10 mL	L
☐ 5003	Epilepsy Advanced Sequencing Evaluation - Neuronal Migration Disorders*	B	7 - 10 mL	L
☐ 5004	Epilepsy Advanced Sequencing Evaluation - Epilepsy in X-Linked Intellectual Disability*	B	7 - 10 mL	L
☐ 5005	Epilepsy Advanced Sequencing Evaluation - Neuronal Ceroid Lipofuscinosis*	B	7 - 10 mL	L
☐ 5006	Epilepsy Advanced Sequencing Evaluation - Epilepsy Associated with Migraine*	B	7 - 10 mL	L
☐ 5007	Epilepsy Advanced Sequencing Evaluation - Syndromic Disorders with Epilepsy*	B	7 - 10 mL	L
☐ 5008	Epilepsy Advanced Sequencing Evaluation - Infantile Spasms*	B	7 - 10 mL	L

☐ **5002 Epilepsy Advanced Sequencing Evaluation – Epileptic Encephalopathies*** B 7 - 10 mL L

ARHGEF9, ARX, CDKL5, CNTNAP2, FOXG1, GABRG2, GRIN2A, KCNT1, MECP2, NRXN1, PCDH19, PNKP, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, SCN1A, SCN1B, SCN2A, SCN8A, SCN9A, SLC25A22, SLC2A1, SLC9A6, SPTAN1, STXBP1, SYNGAP1, TCF4, TREX1, UBE3A, ZEB2

- Angelman syndrome
- Rett Syndrome
- Generalized Epilepsy with Febrile Seizures Plus (GEFS+)
- Early infantile epileptic encephalopathy
- Pitt-Hopkins-like syndrome
- Aicardi-Goutieres syndrome 1-5
- Epilepsy and Mowat-Wilson syndrome
- Cortical dysplasia-focal epilepsy syndrome
- Christianson syndrome
- Severe epileptic encephalopathy with autonomic dysfunction

☐	5008	Epilepsy Advanced Sequencing Evaluation – Infantile Spasms*	B 7 - 10 mL	L

ARX
CDKL5
FOXG1
GABRB3
GRIN2A
MEF2C
SCN2A
SLC25A22
SPTAN1
STXBP1

- X-linked infantile spasms syndrome (ISSX)
- West syndrome (WS)
- Infantile spasms associated with Rett syndrome congenital variant
- Early onset epileptic spasms associated with epilepsy with neurodevelopmental defects
- Infantile spasms associated with intellectual disability, stereotypic movements, and/or cerebral malformations
- West syndrome associated with early infantile epileptic encephalopathy (EIEE)

Future of Genetics

Will likely become cheaper and more widely available

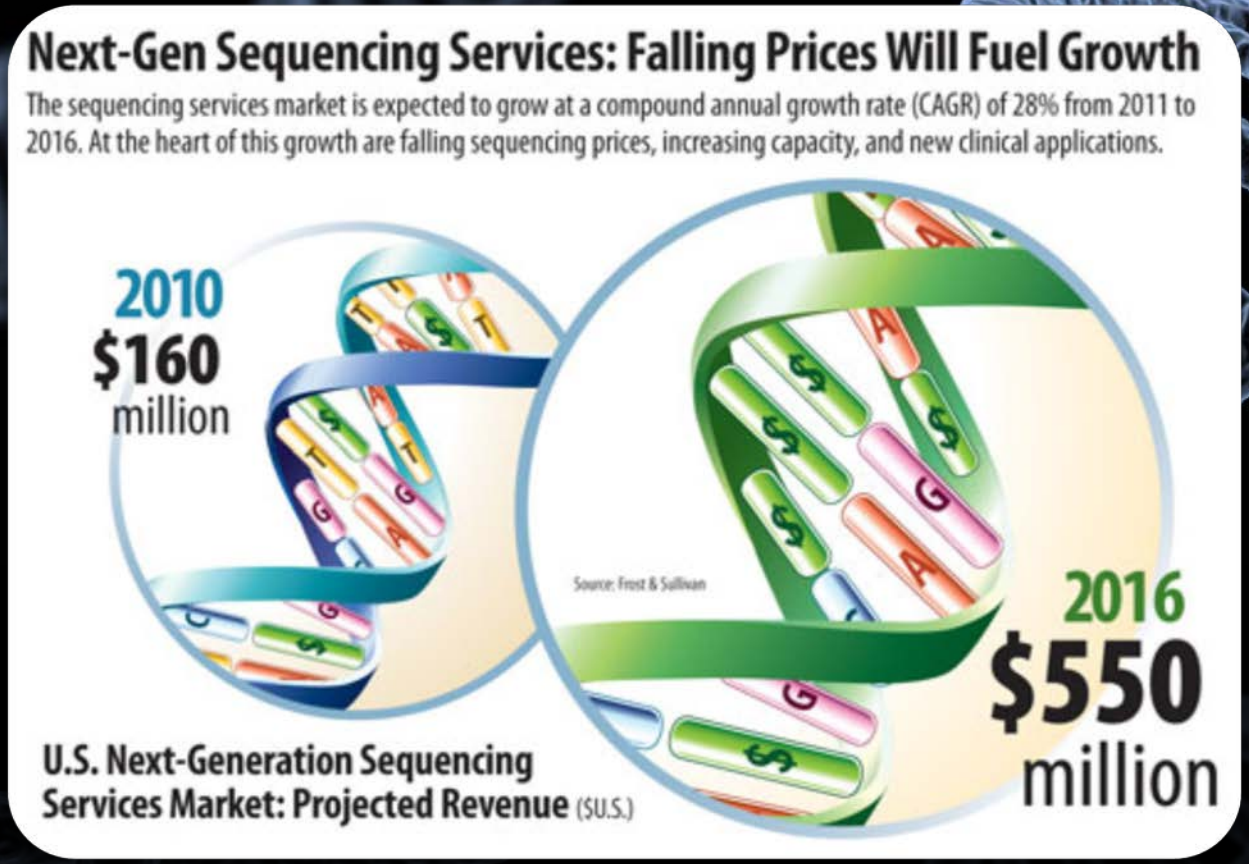
Will guide the development of gene specific therapies

An overflow of information and increasing challenges with clinical application

- Expanding need for clinical databases

Take Home Points

- Genetic tests should be considered when they are useful in the diagnosis and care of a patient.
- Testing should be chosen carefully. You may not require the newest or most sophisticated testing.
- All patients who pursue genetic testing must have adequate pre and post discussions.



QUESTIONS OR COMMENTS ??

Thank you for your attention!

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2. International HapMap Project. 2013. <http://hapmap.ncbi.nlm.nih.gov/>
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