
# Genetics and Genomics 101: What you absolutely need to know, and not a drop more

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# Disclosures

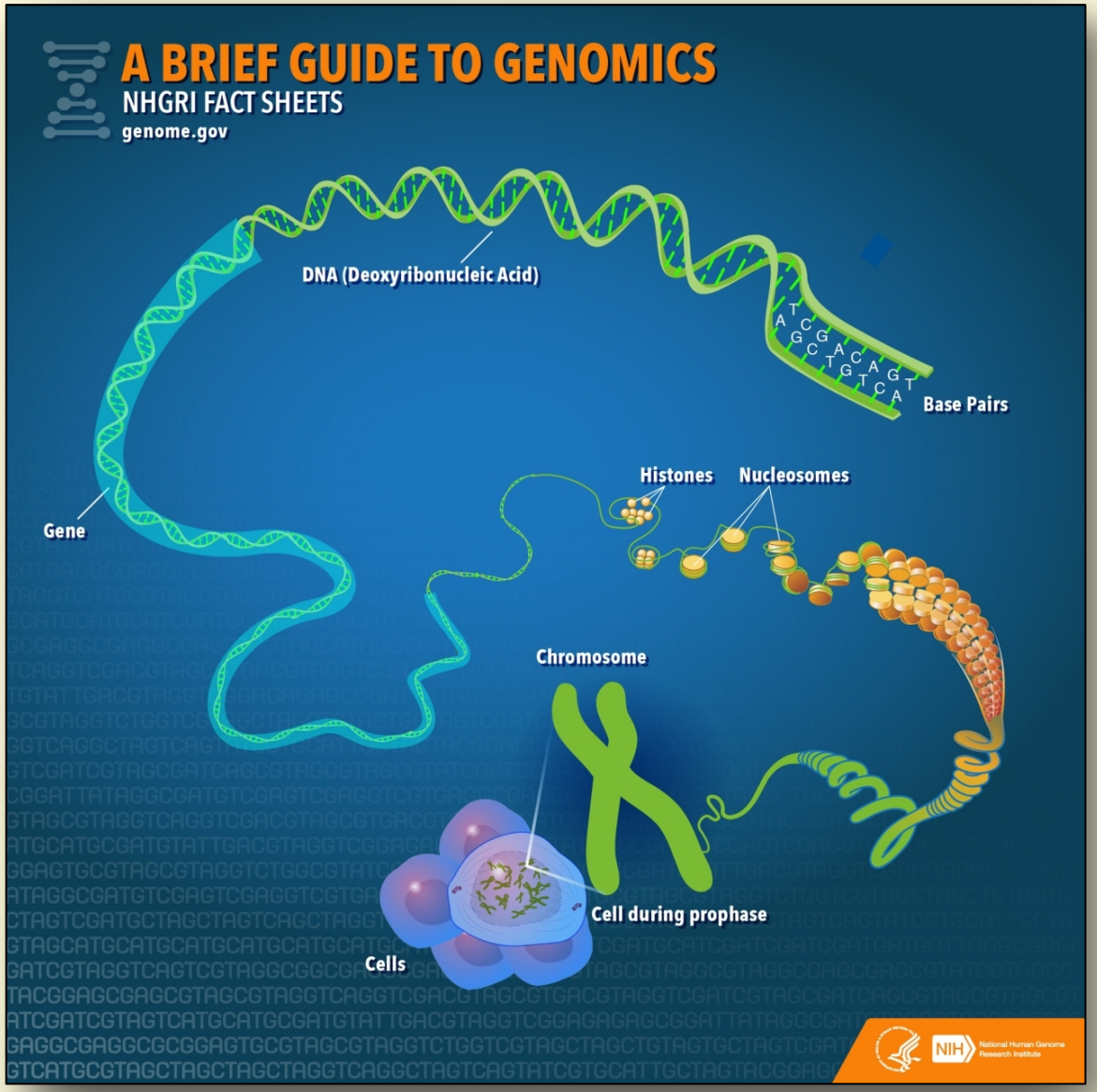
- Nothing to declare

# Impetus for this topic

- Clinicians are often unfamiliar with genetic/genomic terminology, which may be intimidating

- Clinical management of patients with heritable thoracic disease relies on accurate interpretation of results of genetic testing

# A Few Basic Facts




- Genome: complete set of DNA
- Human genome:
  - 3.05 billion base-pairs
  - 23 chromosome pairs (one set from each parent)
- Number of protein coding genes: ~ 20,000
  - Only 1-2% of entire genome
  - 2 copies of each gene – one from each parent
  - Most genes are the same in all individuals, with only 1% variation

# Building Blocks of DNA

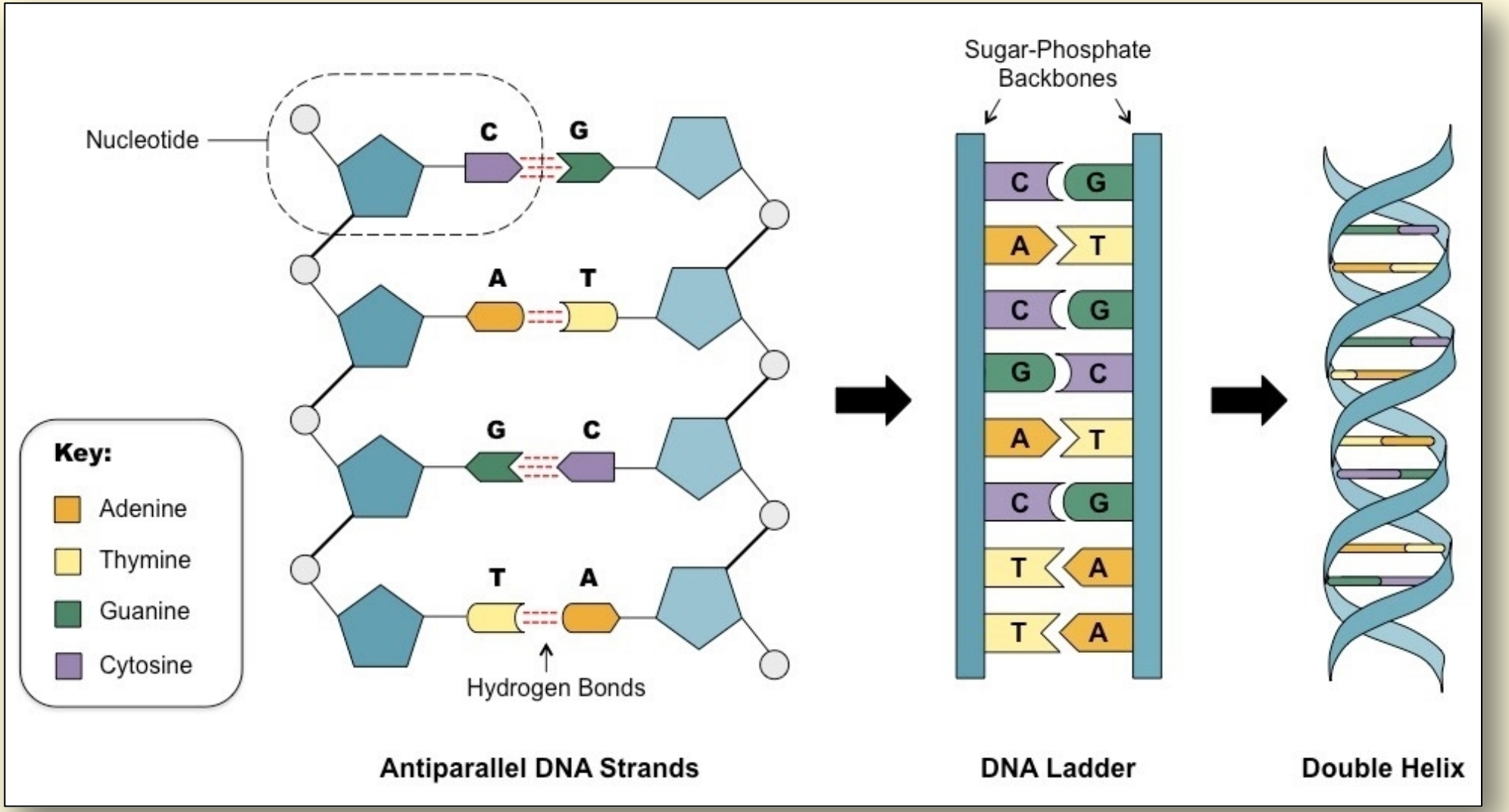



Image source: https://ib.bioninja.com.au/standard-level/topic-2-molecular-biology/26-structure-of-dna-and-rna/dna-structure.html, May 14, 2022

# DNA to RNA to Protein

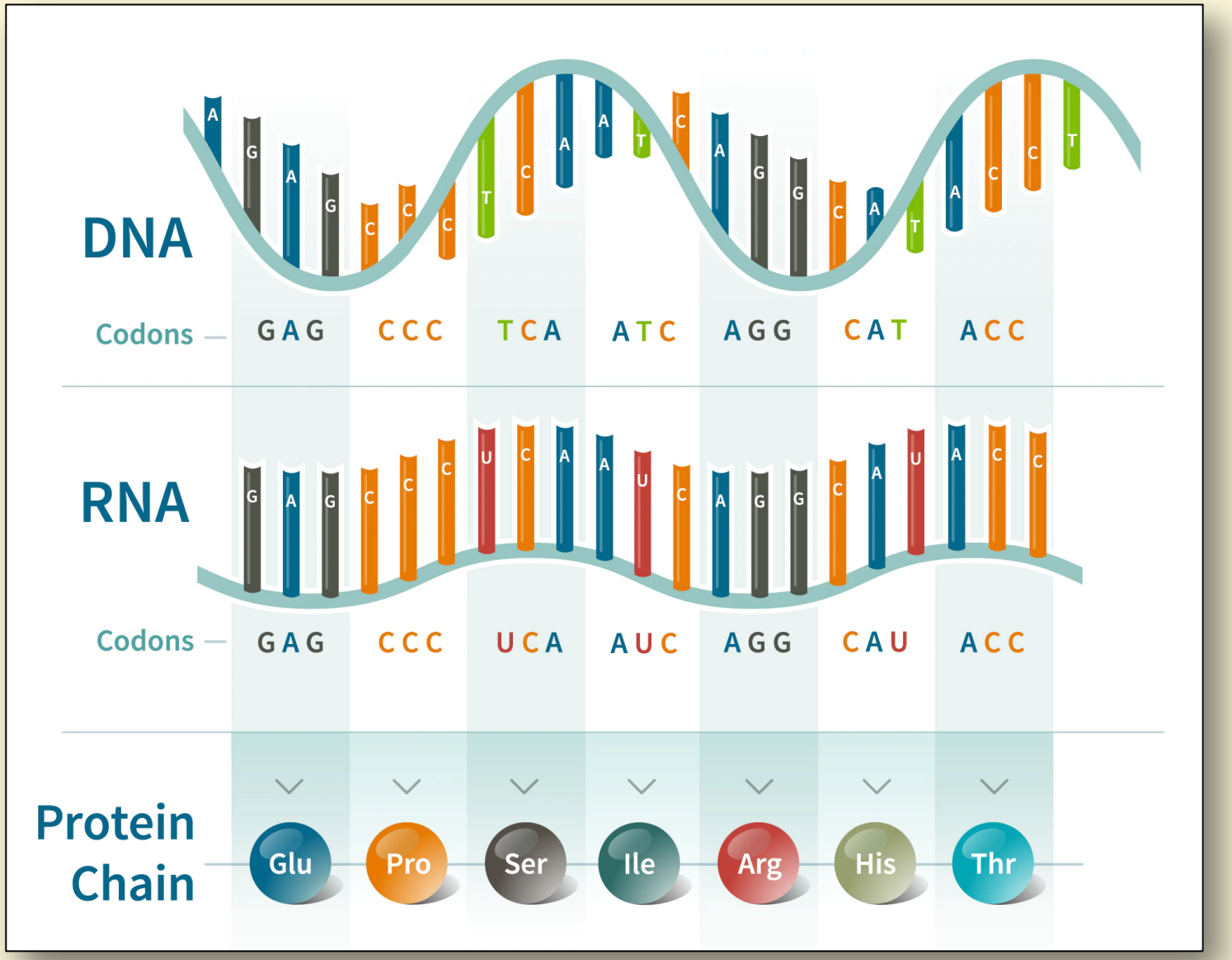
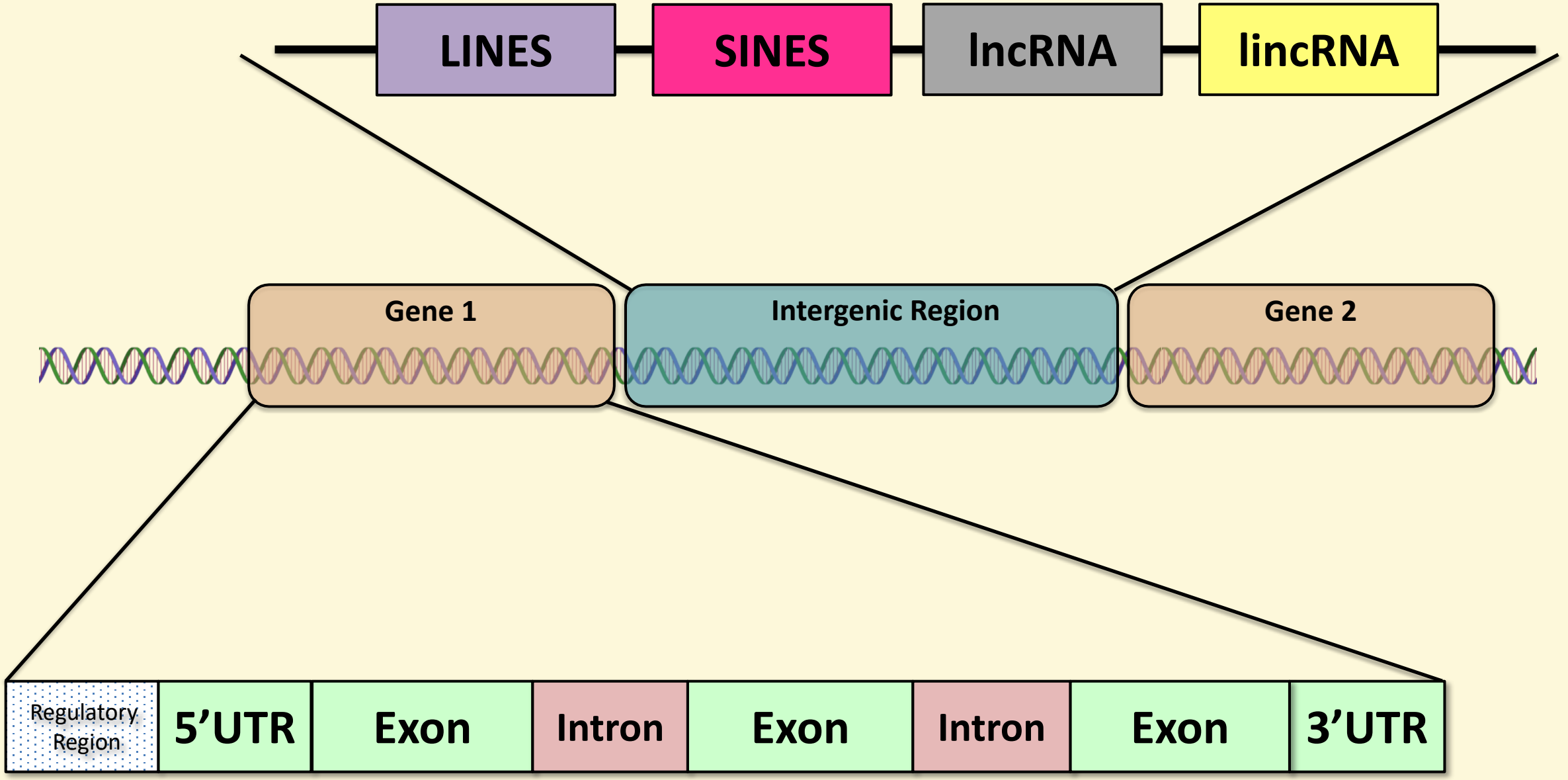
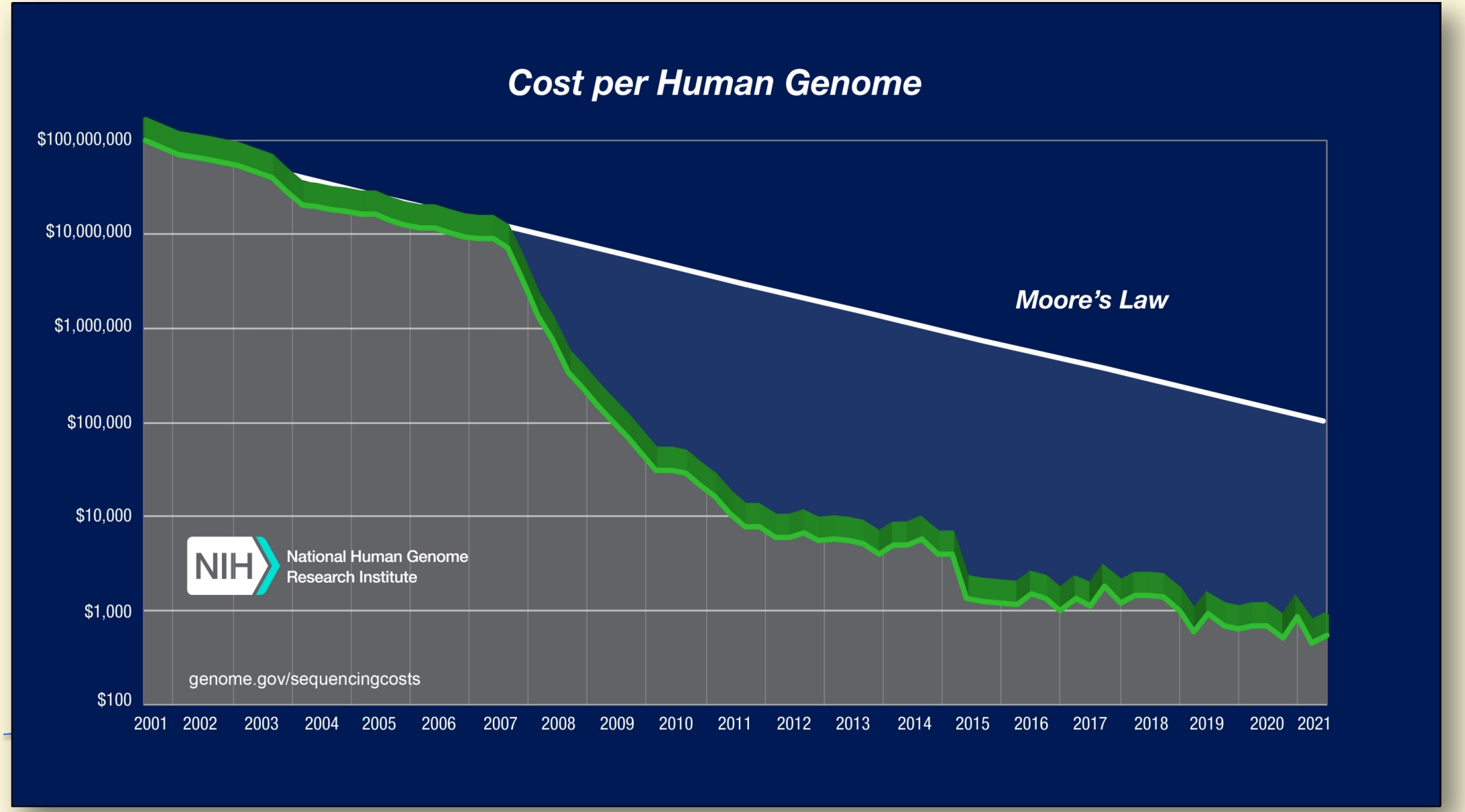



Image source: https://www.ancestry.com/c/dna-learning-hub/dna-code-codons, May 14, 2022

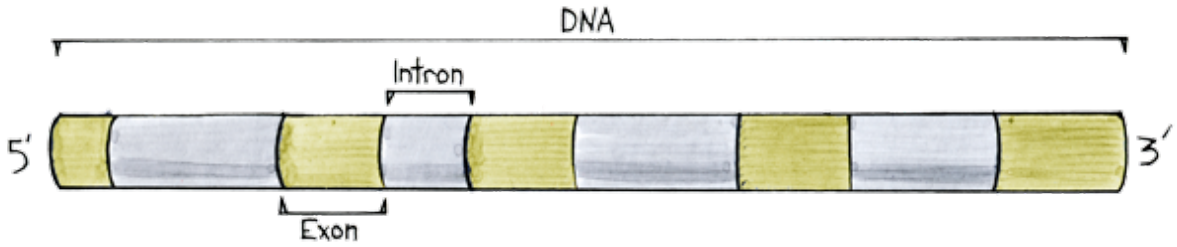
# Genes and Intergenic Regions of DNA



# Reading the Genome: “Next Generation” Sequencing



# Whole Genome vs Whole Exome sequencing

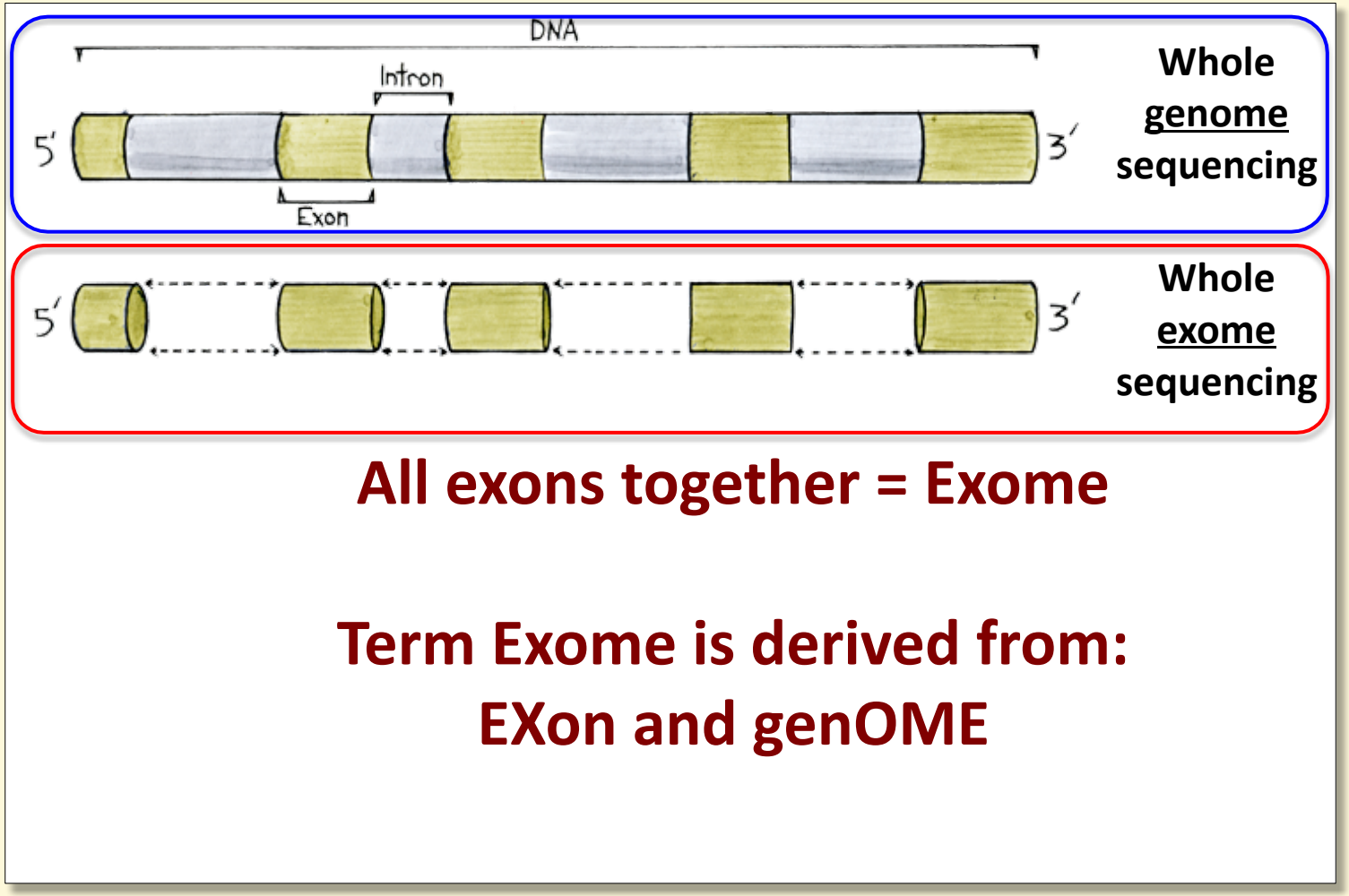



**Exons – protein coding regions of the DNA**

**Introns – noncoding DNA regions**

Image Source: University of Washington, 2012

# Whole Genome vs Whole Exome sequencing




**All exons together = Exome**

**Term Exome is derived from:**
**EXon and genOME**

Image Source: University of Washington, 2012

# Whole Genome vs Whole Exome sequencing

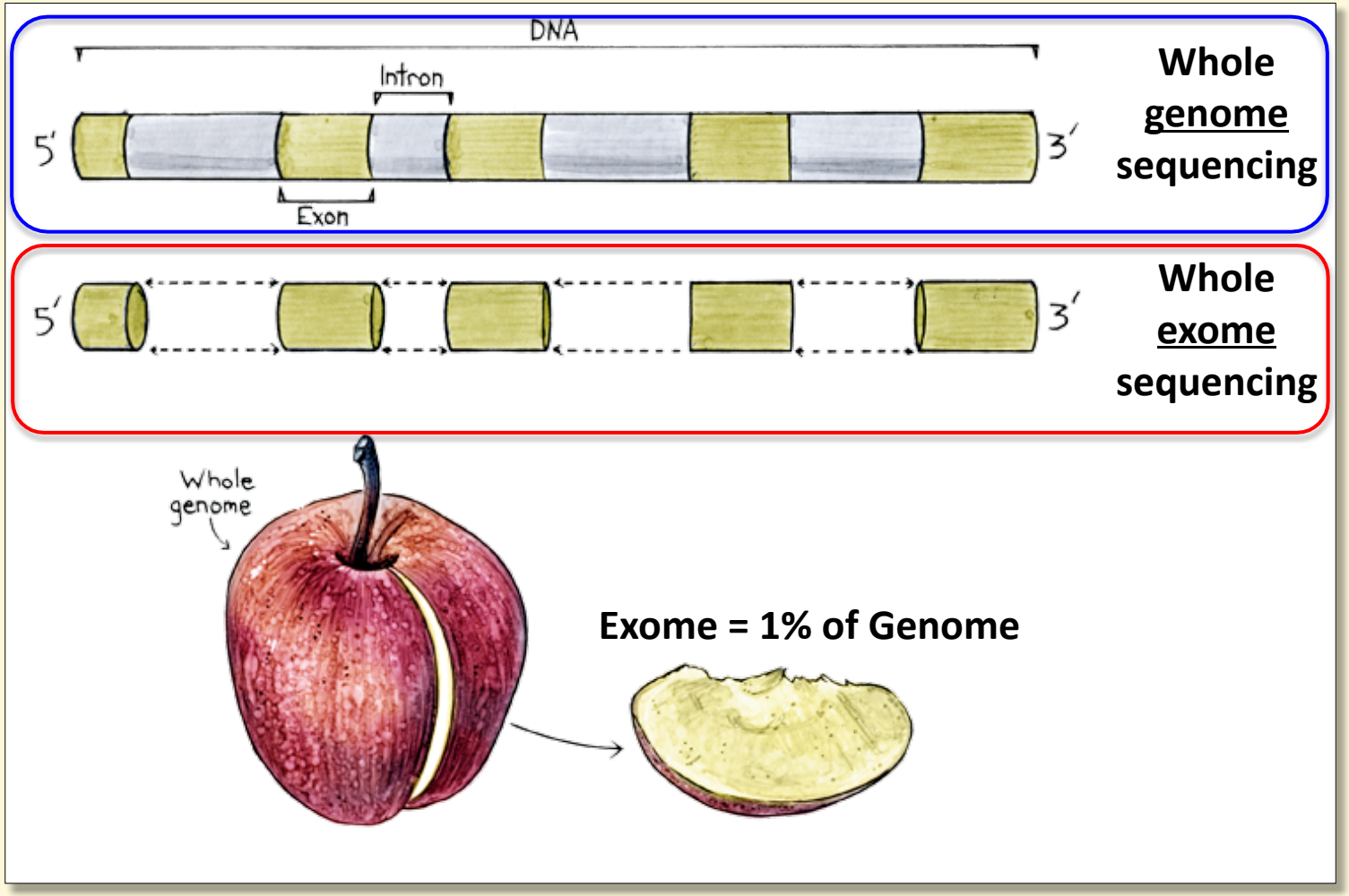
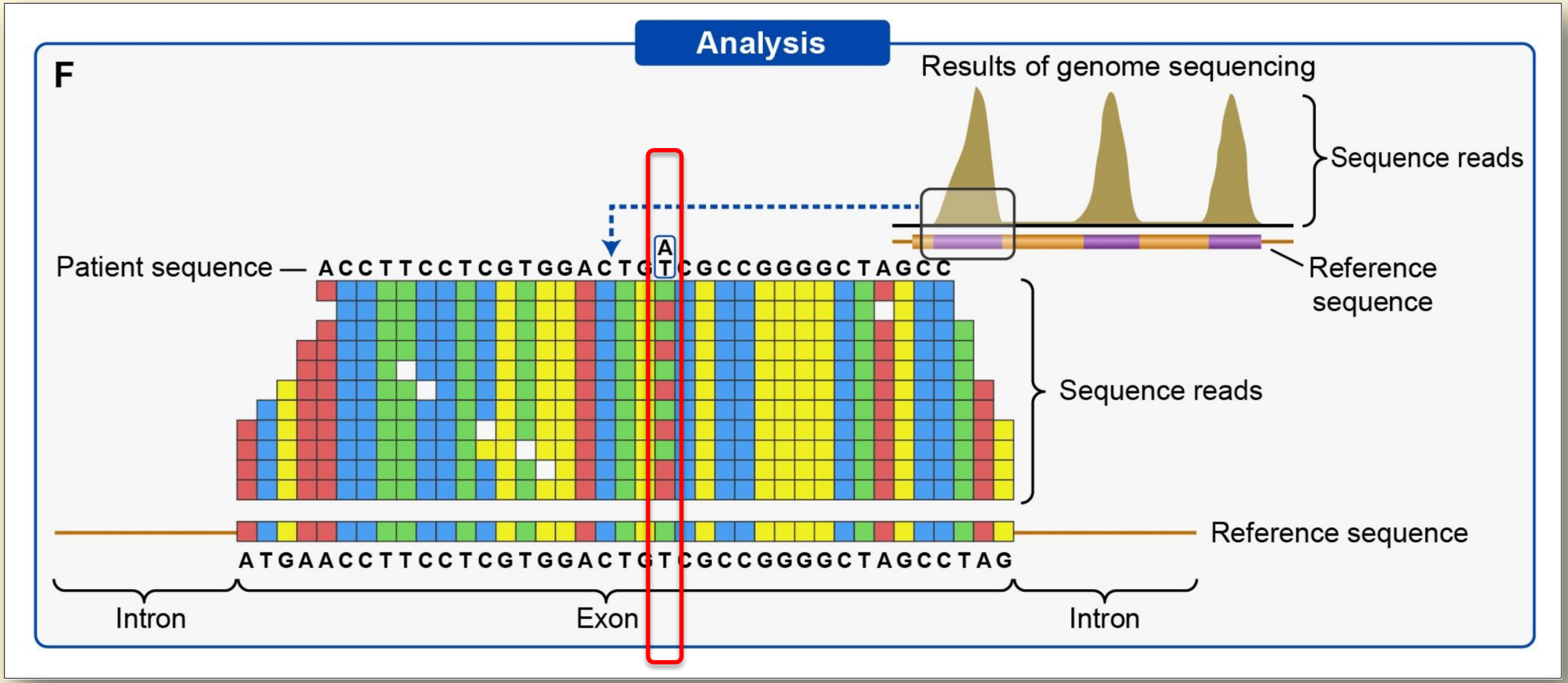



Image Source: University of Washington, 2012

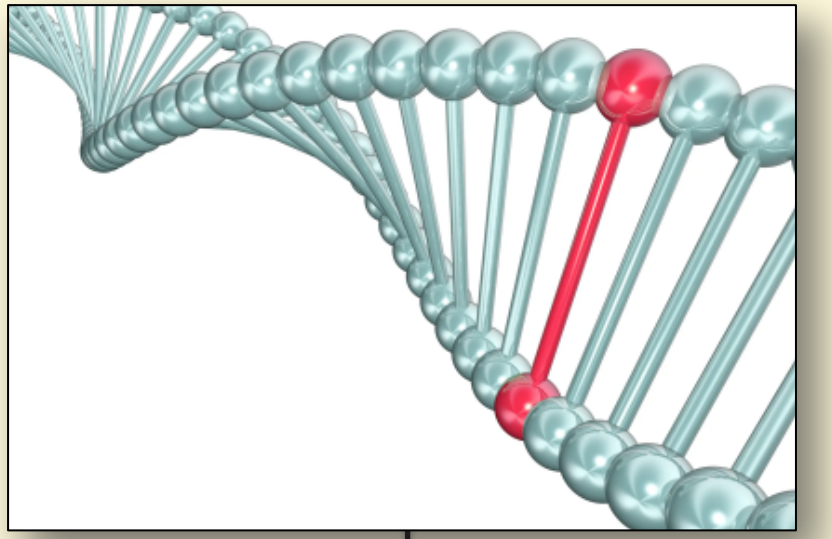
# Analysis of Whole Exome Sequencing




Modified from Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. *N Engl J Med* 2014;370:2418-2425

# Mutations vs Variants

- Permanent changes to the DNA sequence in a particular gene
- Mutations – changes typically causative of disease
- Variants – changes that do not necessarily lead to disease (more accurate term)



**Inherited**

**One or both parents carry the variant**

**De novo**

**Neither parent carries the variant**

Image source: https://newatlas.com/biology/evolution-dna-mutations-less-random/, May 14, 2022

# Most Basic Types of Variants

- Normal Sequence: A-A-A-T-T-T-C-C-C-G-G-G
- Substitution: A-A-A-T-T-A-C-C-C-G-G-G
- Insertion: A-A-A-T-T-T-C-C-A-C-G-G-G
- Deletion: A-A-T-T-T-C-C-C-G-G-G

# How Common are Variants in the General Population?

- Large sequencing databased provide frequency information

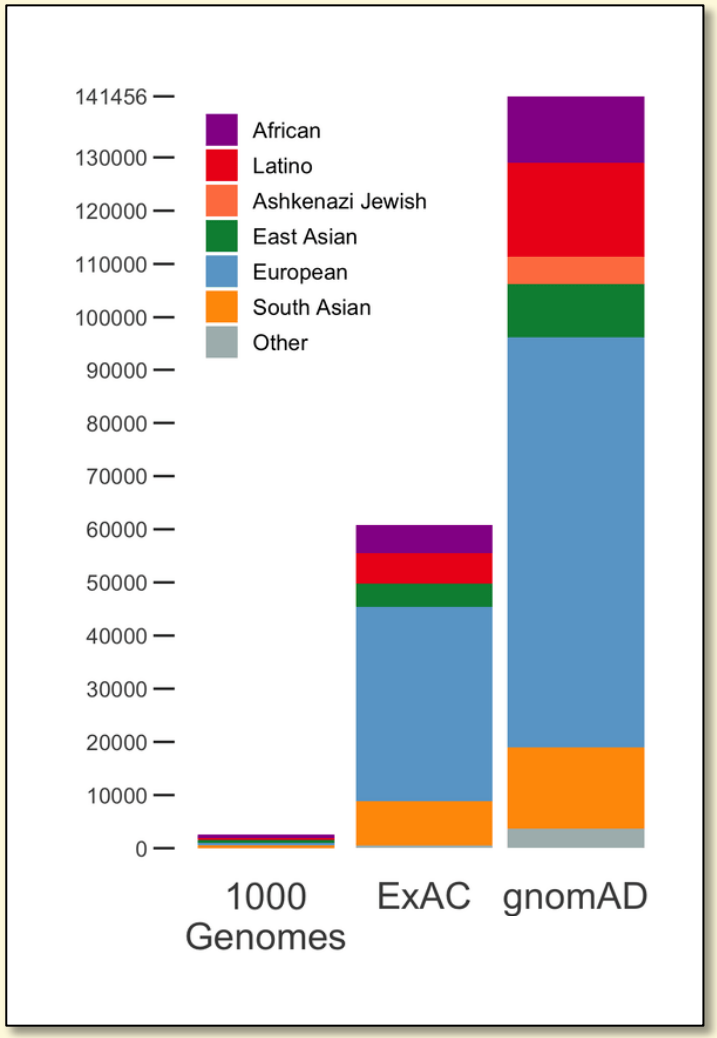



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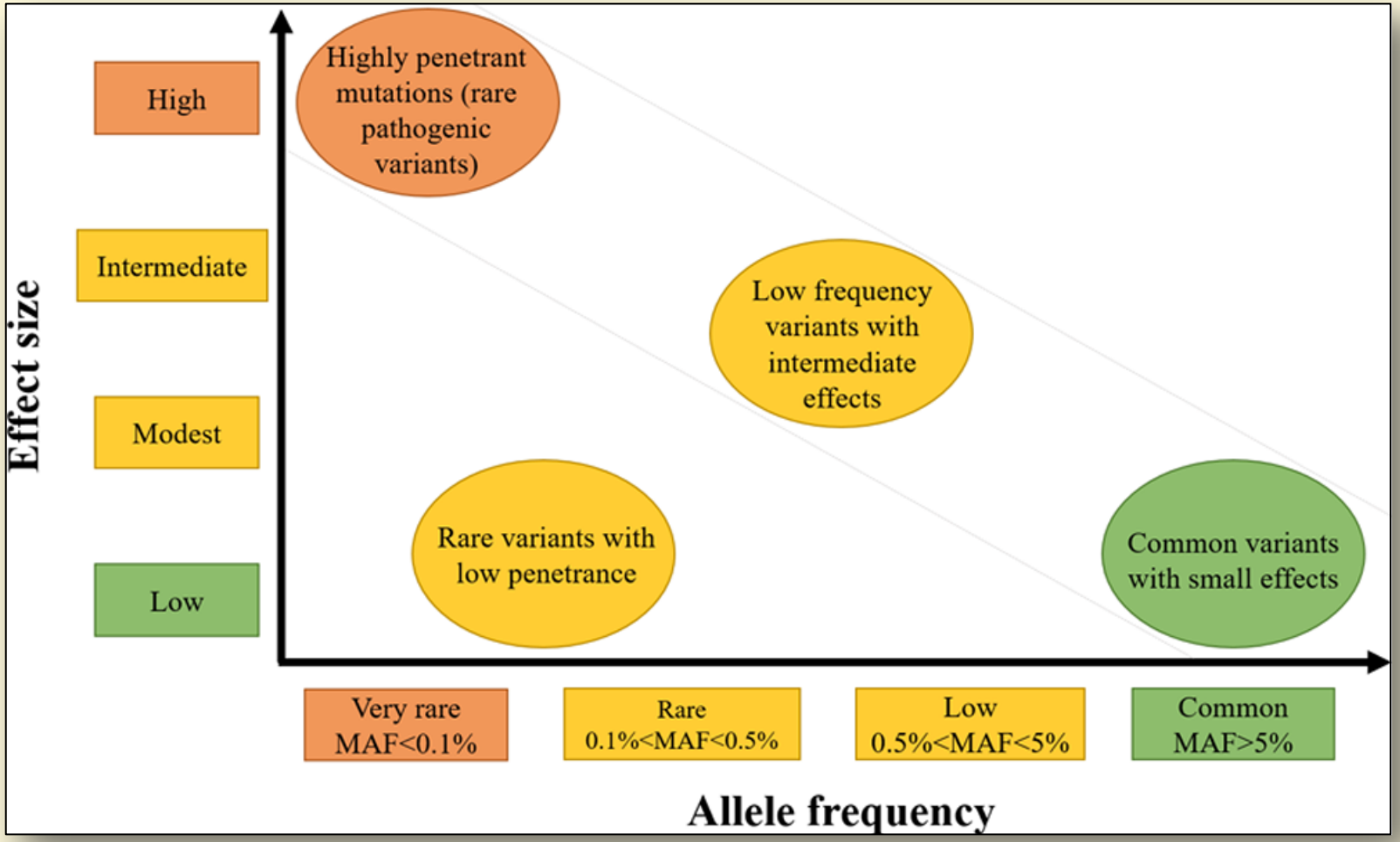
Image source: https://gnomad.broadinstitute.org/news/2018-10-gnomad-v2-1/, May 14, 2022

# Variant Frequency vs Effect Size Relationship






Pinard A, Jones GT, Milewicz DM. Genetics of Thoracic and Abdominal Aortic Diseases. Circ Res 2019;124:588-606.

# Interpreting Variants



ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

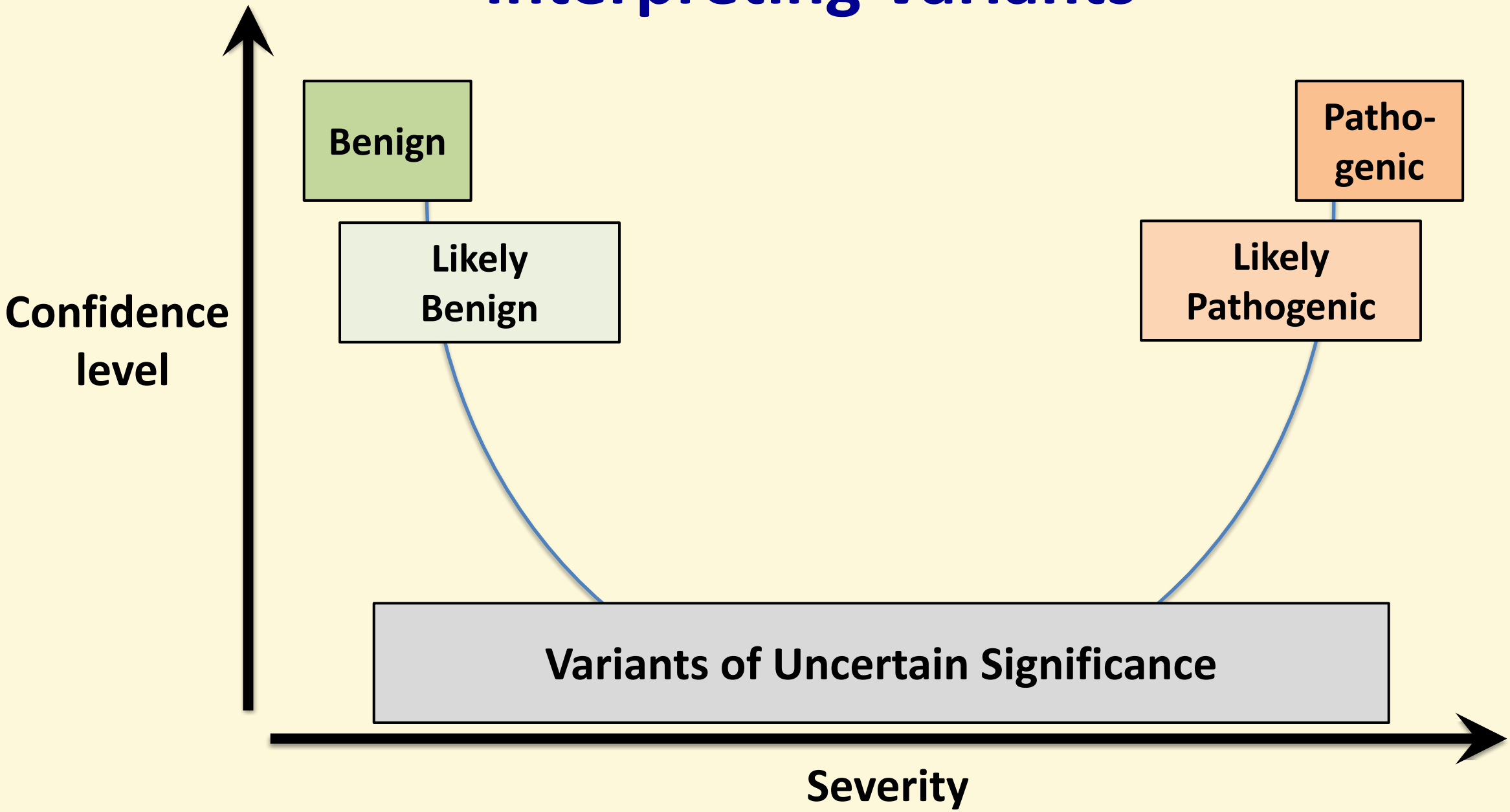
## Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

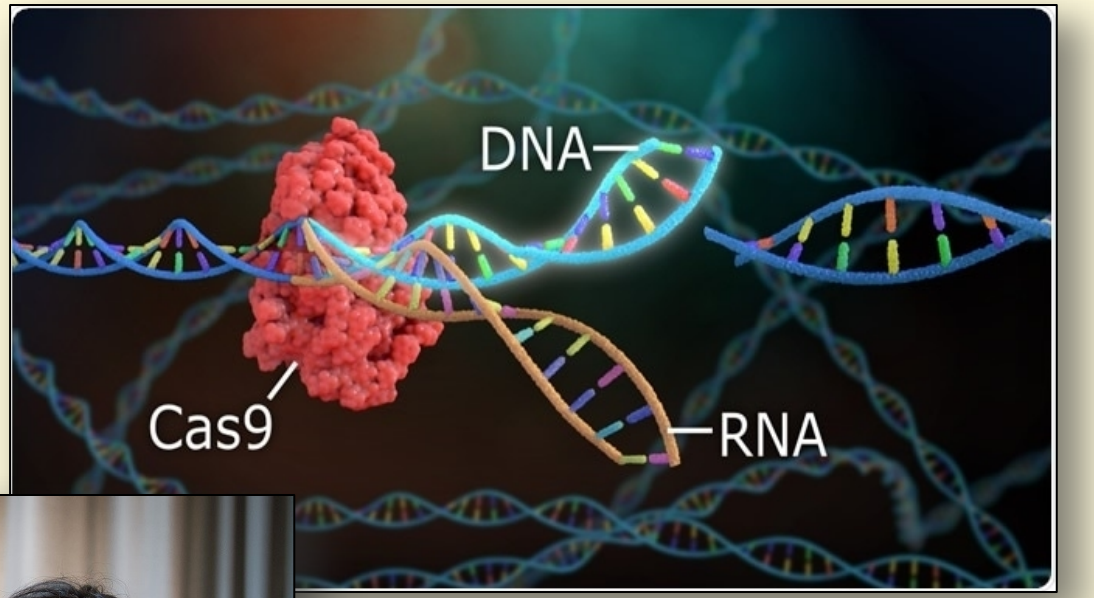
**Table 5** Rules for combining criteria to classify sequence variants

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

# Interpreting Variants



# Gene Editing using CRISPR




Ledford H, Callaway E. Pioneers of revolutionary CRISPR gene editing win chemistry Nobel. Nature. 2020 Oct;586(7829):346-347.

Image source: https://uw.manifoldapp.org/read/final-keyword-essay-gene-editing/section/256e2447-bf30-4e5a-8b06-d12a1067ec14

# Conclusions and Public Health Significance

- Genetics and genomics are likely to play a dominant role in healthcare over the next decade.
- Genomic data provides additional information resources regarding specific diseases.
- Great potential for prevention and treatment of human disease using gene-editing technology.
- Ethical concerns regarding privacy, use of genomic information and genome editing exist and must be taken into account.