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The Era of Personalized Medicine using Next Generation Sequencing(NGS)

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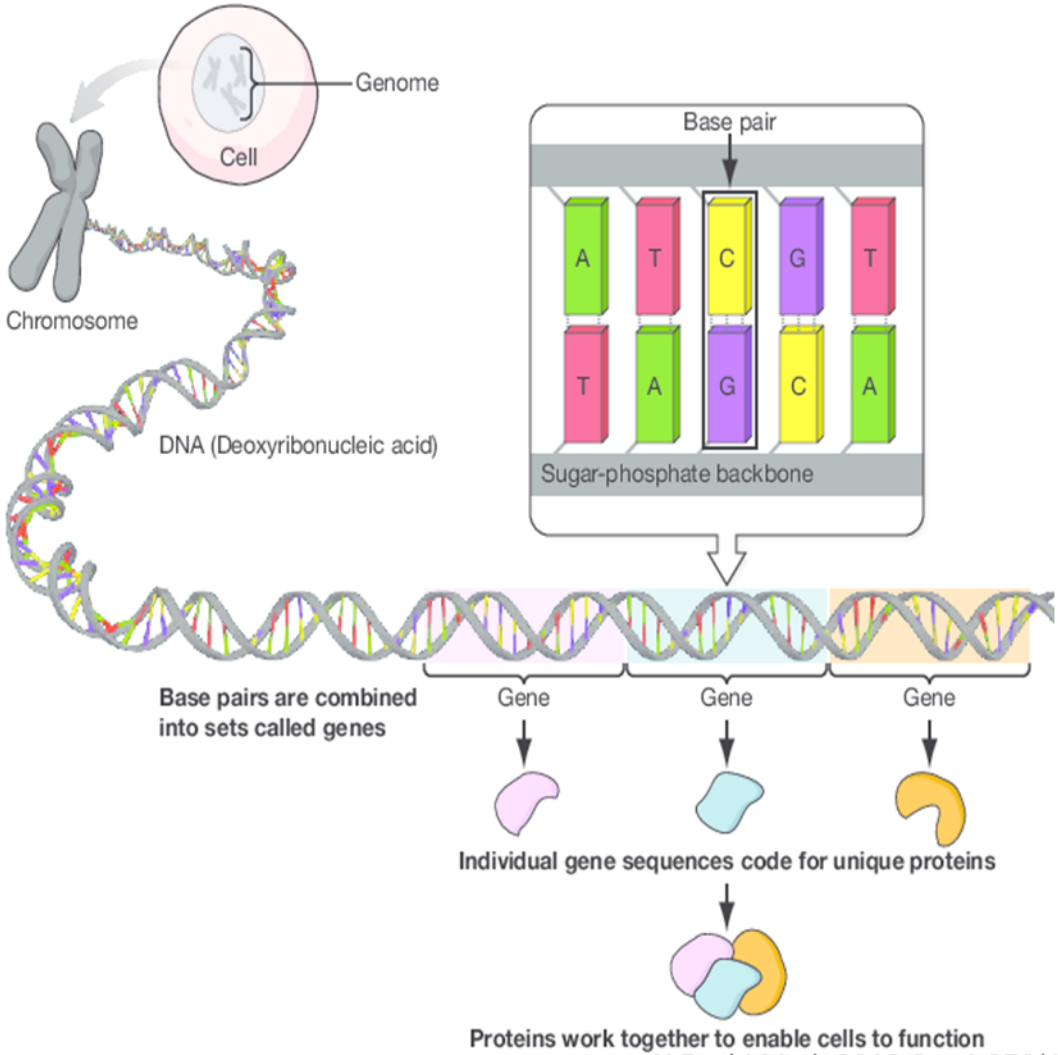
Disclosure

This presenter has no financial interest or other relationships with manufacturers of commercial products, suppliers of commercial services, or commercial supporters.

Objectives

- Definition
- Analyses and Interpretation
- Clinical Utility
- Advantages/Limitations
- Test Costs/Reimbursements

Genes



Nucleotides and base pairs that make up a sequence to encode proteins and instructions to turn a gene on or off

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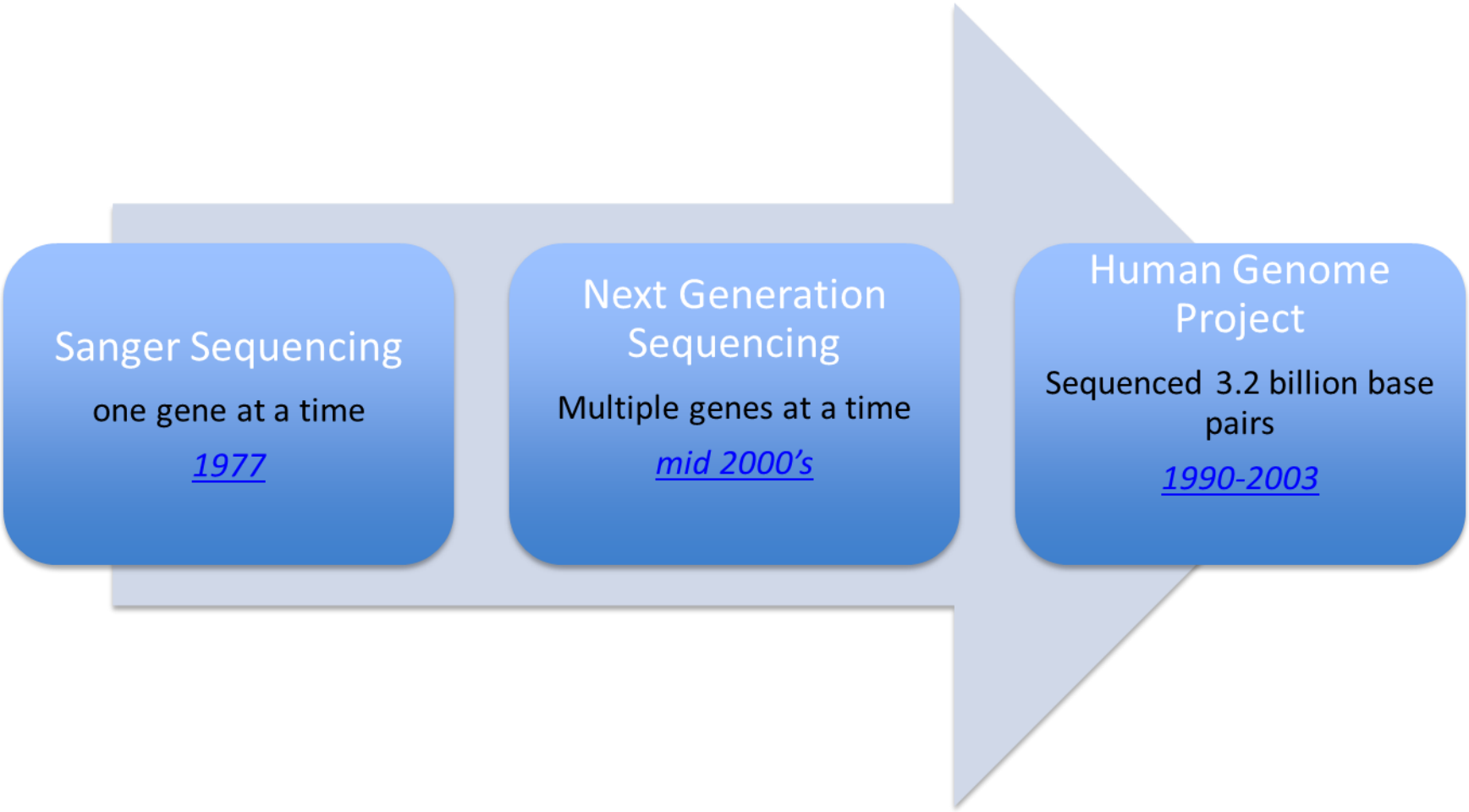
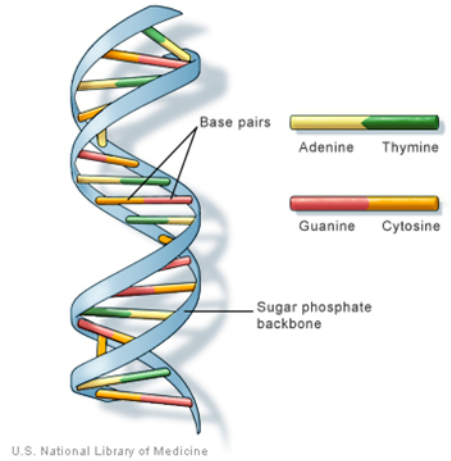
Goal of a genetic test

- Identify DNA sequence “variants” that may be confidently associated with presenting signs and symptoms of a disease

Development of technology





NGS

- Number of different modern sequencing technologies
- Powerful platform that has enabled the sequencing of thousands to millions of DNA molecules and genes simultaneously
- Target genes “of interest” to sequence instead of whole genome

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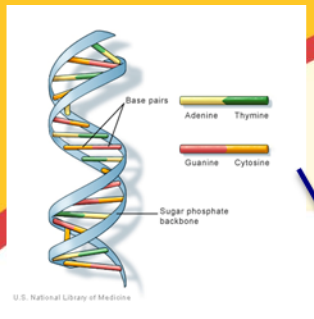
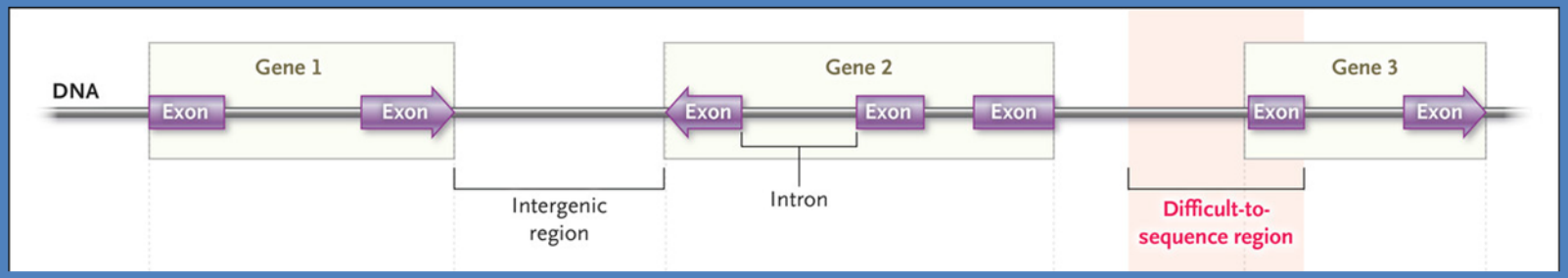


Analysis

DNA fragmentation: used to break the targeted DNA into many short segments and extracted using specific probes or by polymerase chain reaction amplification (PCR)



Analysis

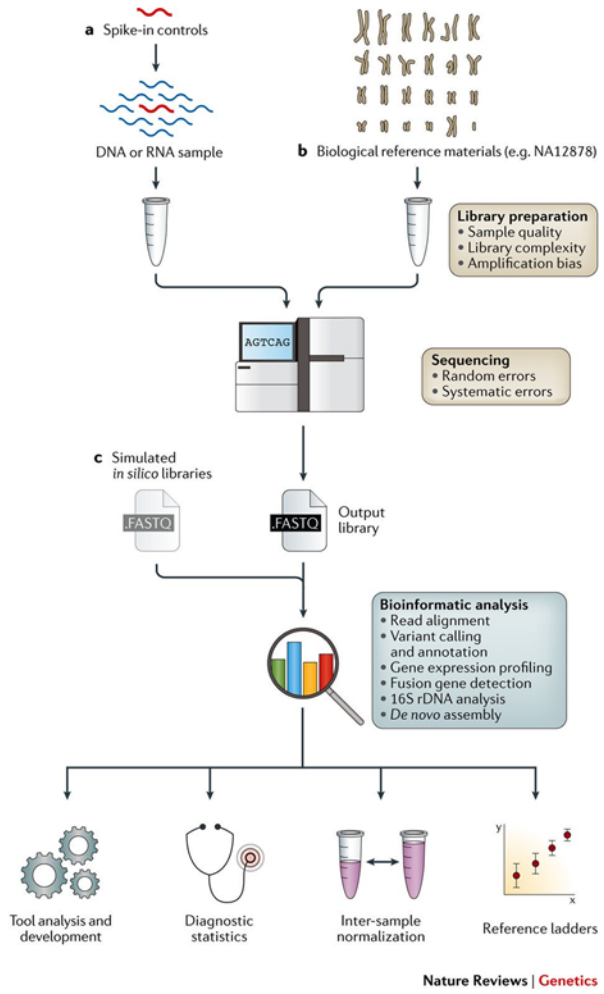
DNA fragmentation: used to break the targeted DNA into many short segments and extracted using specific probes or by polymerase chain reaction amplification (PCR)

Library preparation: DNA segments are modified so that each DNA sample can have identification specific to each patient

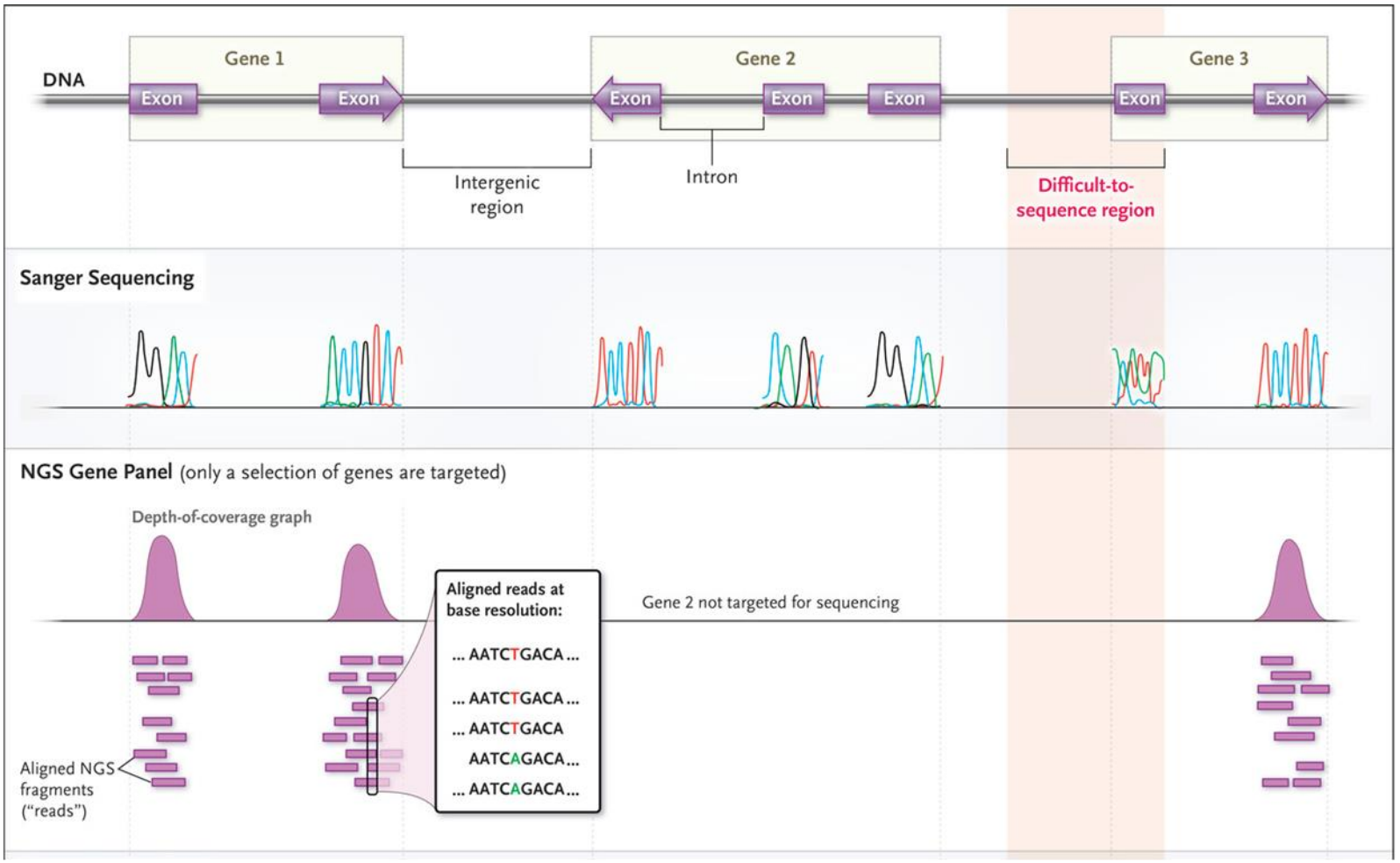
Sequencing: massive parallel sequencing of all DNA segments at the same time

Bioinformatics analysis: process of base calling, read alignment, variant identification and variant annotation

Final sequence is referenced to Genome Reference Consortium



Interpretation



Target sequences are compared to reference sequences in the and differences are annotated as variant cells which are further interpreted by qualified laboratory staff.

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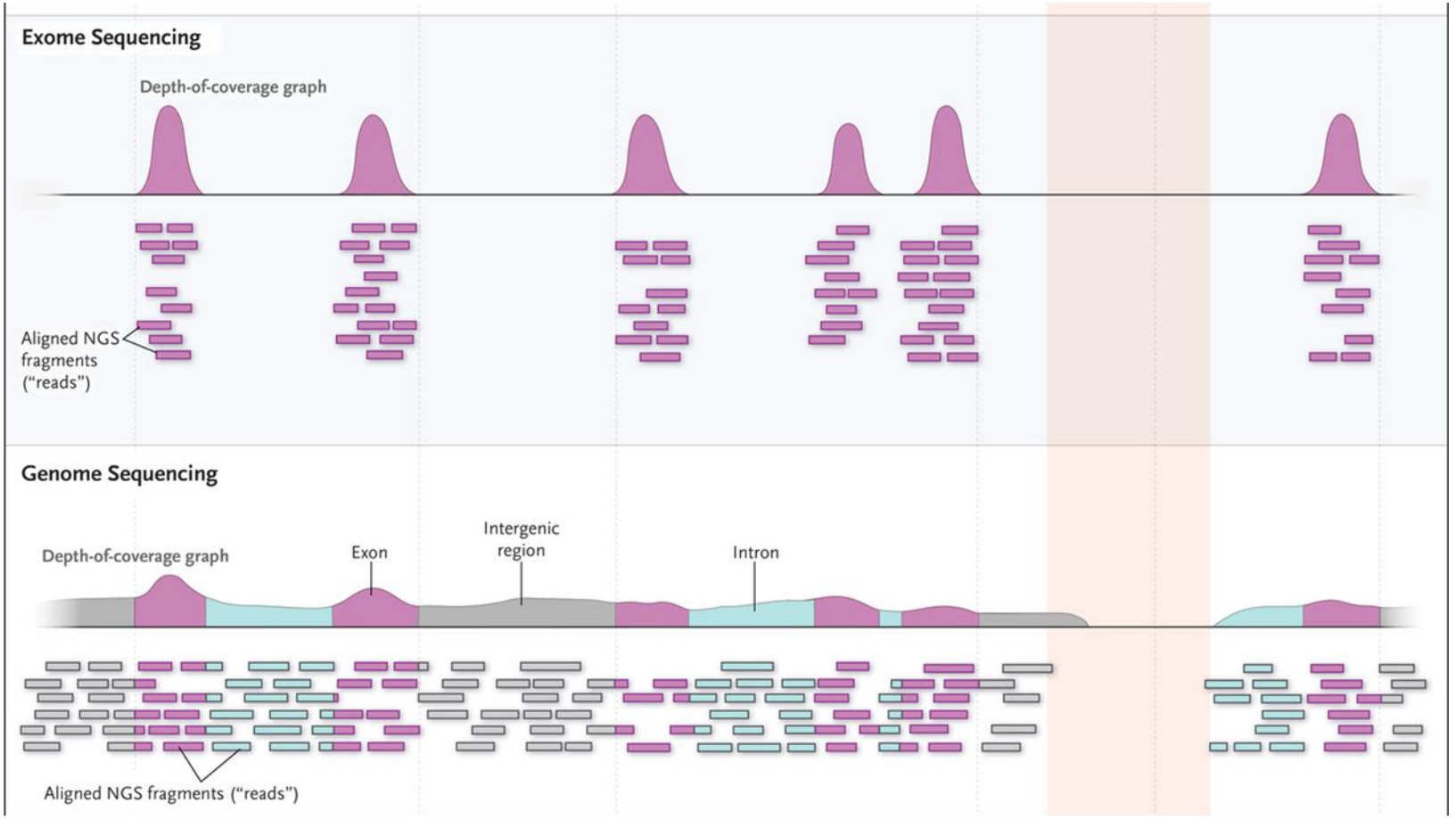
Exome sequencing



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Results

- Pathogenic, likely pathogenic, likely benign, benign, and variant of unknown significance
- Clinical laboratories primarily report variants for genes with well known disease associations
- GeneMatcher, (*https://genematcher.org/*)or DECIPHER (*https://decipher.sanger.ac.uk/)*

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Advantages

- No limitations on number of genes analyzed, large stretches of DNA can be analyzed (can be 1 million bases or more!)
- Detects low level gene mutations, deletions, insertions, substitutions, rearrangements, microsatellite instability (MSI) and tumor mutational burden
- Cost effective, fast, accurate

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Limitations

- Certain regions in genome can be missed by sequencing or miss intergenic mutations due to lack of non-coding data
- Lack of knowledge of genes & variants
- Increase number of false positive rates
- Storage of genomic data in electronic medical records
- Inadequate sampling
- Risk of false associations with genes and diseases is regularly reclassified as improvements are made to databases→ Data reanalysis

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- So is it reliable?

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Clinical Utility

- Defining therapeutic targets to improve patient outcomes and personalize treatments
- Modify future disease risk
- Examining gene regulation in disease
- Determining development of heart disease, diabetes, and different inherited diseases

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Clinical Utility

- NGS is not a stand alone test, it is combined with secondary and tertiary confirmatory methods that improve analytical power (Sanger Sequencing)
- Most clinical laboratories are confirming relevant changes by secondary methods before reporting results
- If confirmed, results can be *reliable* and interpreted for clinical purposes

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What do you do with positive results?

- Lead to diagnosis with appropriate clinical correlation
- Testing family members, prenatal screenings and counseling and communication
- Tailor treatment
- Pharmacogenomics
- Diagnose late onset diseases

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What about Negative Results?

- Pathological mutations may be in genes that are not analyzed
- Disease is caused by a gene that has not been identified
- Can perform whole exome sequencing
  - Without a diagnosis; rate of which testing reveals a molecular diagnosis ranges from 25-52%

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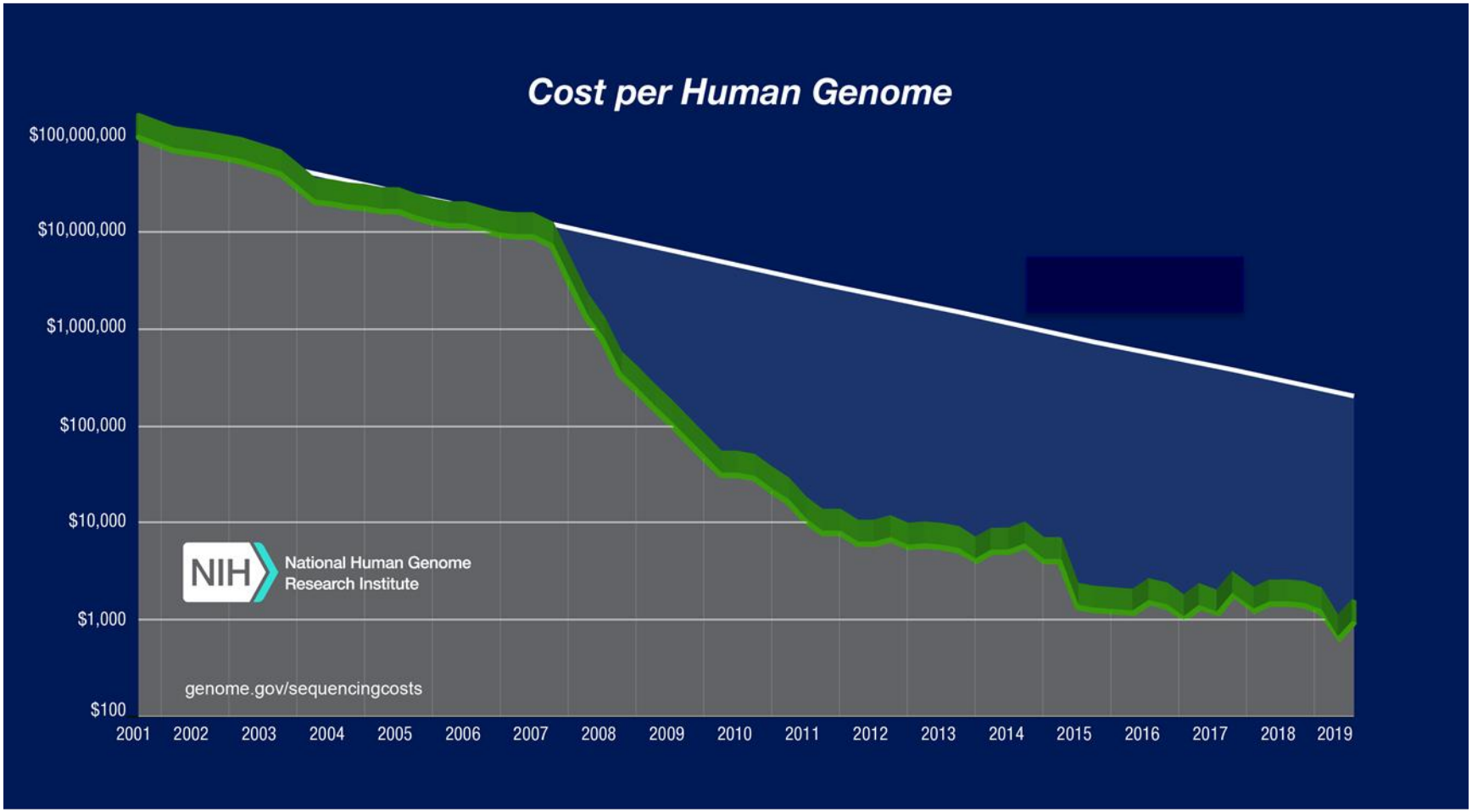
Costs



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Reimbursements

- Analytical and clinical validity of the test
- Guidelines from professional societies and evidence based scientific literature
- Coverage based on if test is used for experimental, investigational or medical necessity
- May differ based on carriers and plans and priorauthorization is typically required
- Self pay and financial assistance

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FDA approved Genetic Tests

- FoundationOne; 287 cancer related genes
- FoundationOne Heme; 405 genes and variants
- 21-gene Oncotype DX Breast Recurrence Score Test
- myRisk Hereditary cancer (ex:*BRCA1,BRCA2, CDH1,ATM,PALB2,CHEK2*)

Healthy Individuals

- In one study, genome sequence of 100 healthy individuals resulted in 22% of monogenic disease risk with uncertain clinical usefulness
- *Research ongoing for utility of genomic data to assess common risk diseases*

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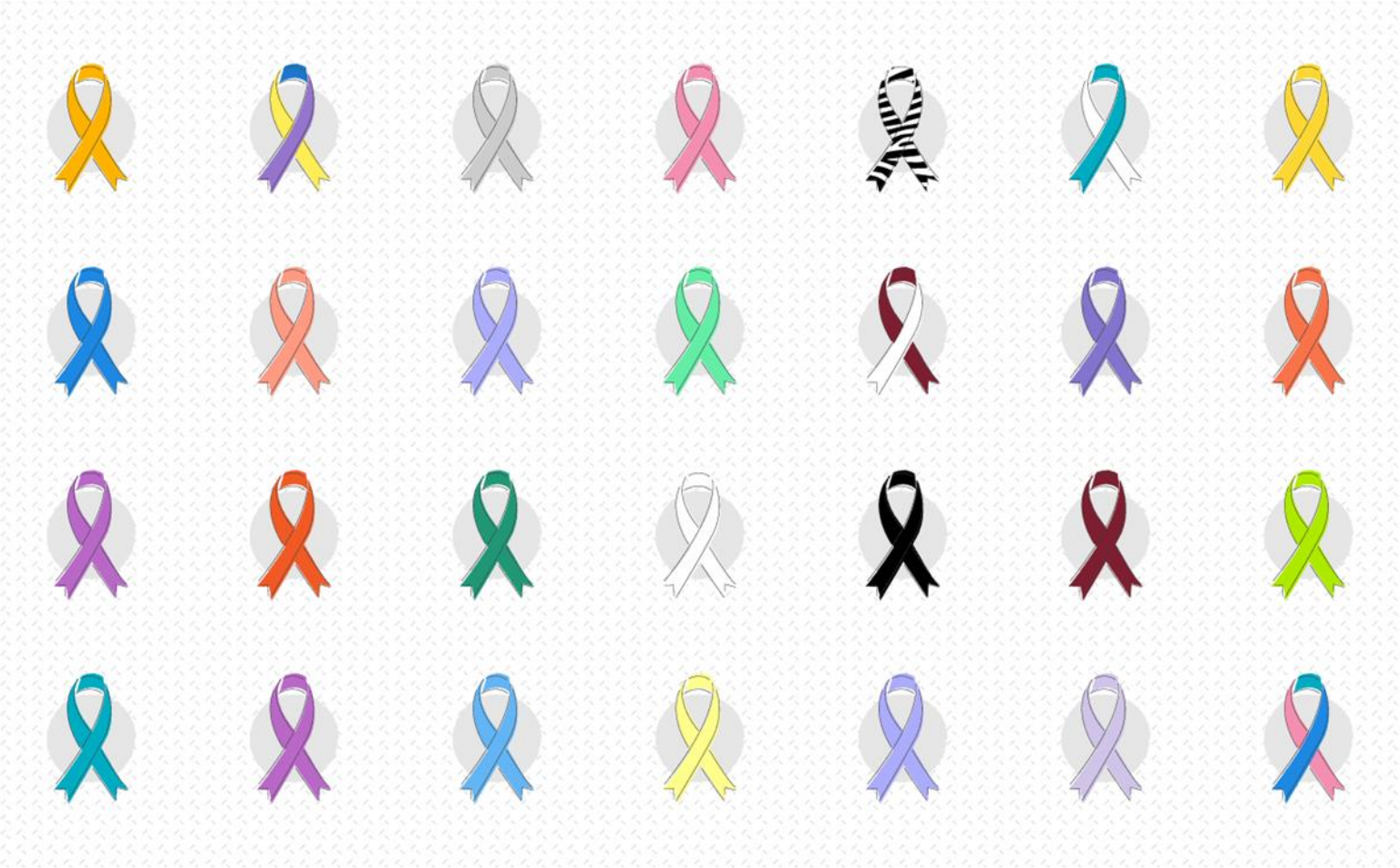
Future Frontiers

- Which tests to order, gene panels, exome sequencing, genome testing
- Creation of databases of genomic variation in global populations
- Cost, ethics and standards will shape trajectory of clinical NGS into routine medical practice

Thank you!



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