Laboratory Perspective on Whole Genome Sequencing

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Presentation Outline

- **Progression of Next Generation Sequencing**
- **A Technical Moving Target**
- **What is Needed Going Foward**

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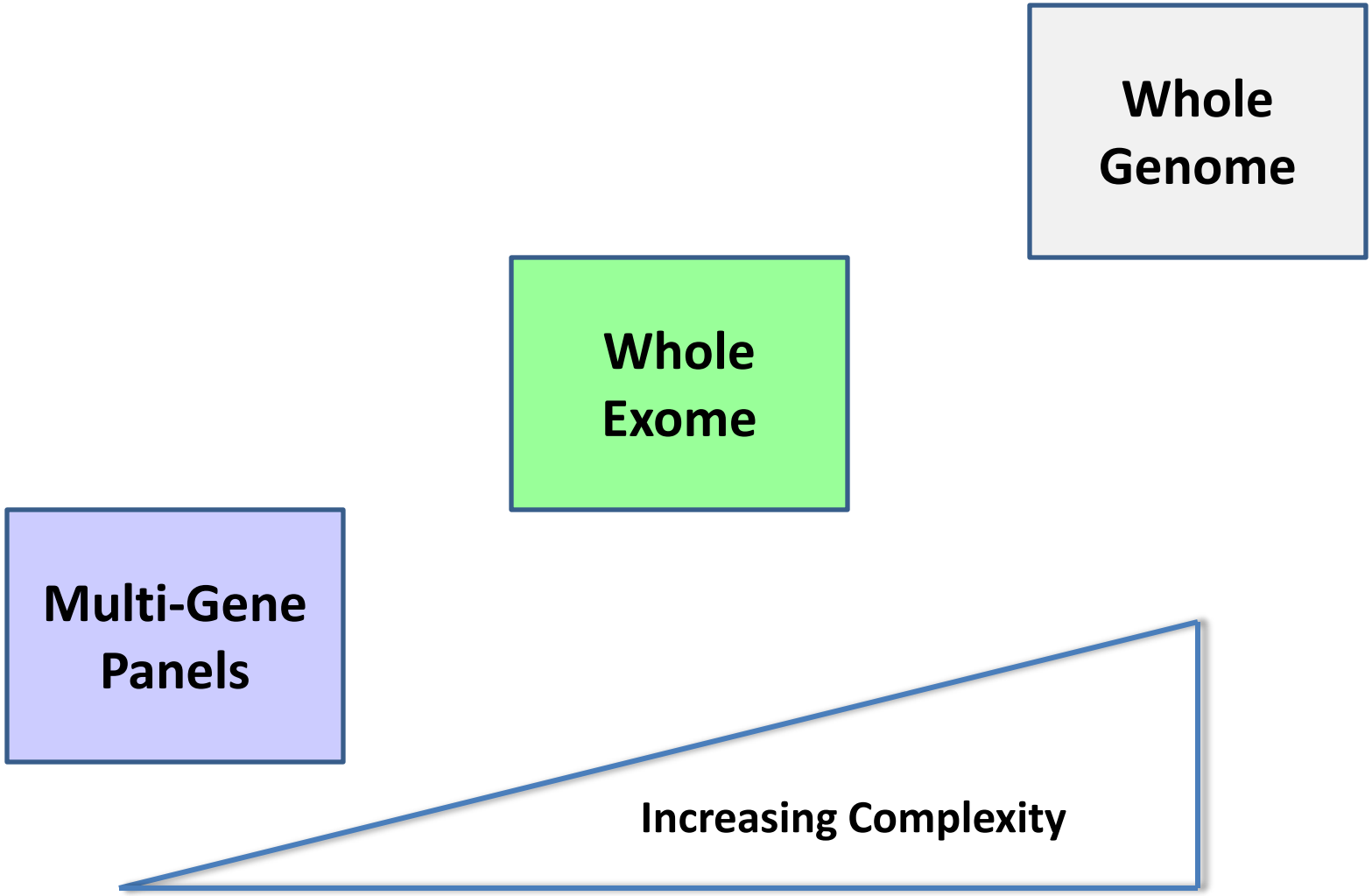
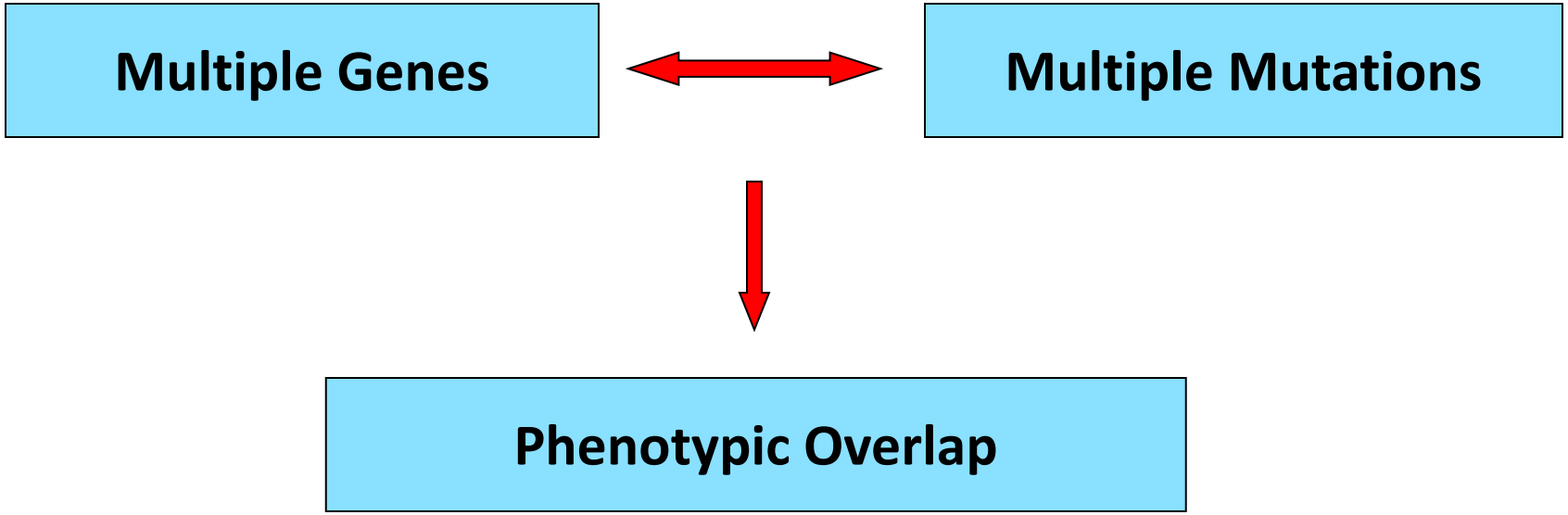
Progression of Next Generation Sequencing



Multi-Gene Panels



Multi-Gene Panels

Cardiomyopathies

- Hypertrophic
- Dilated
- Arrythmias

} 10-30 Genes

Mitochondrial Disorders

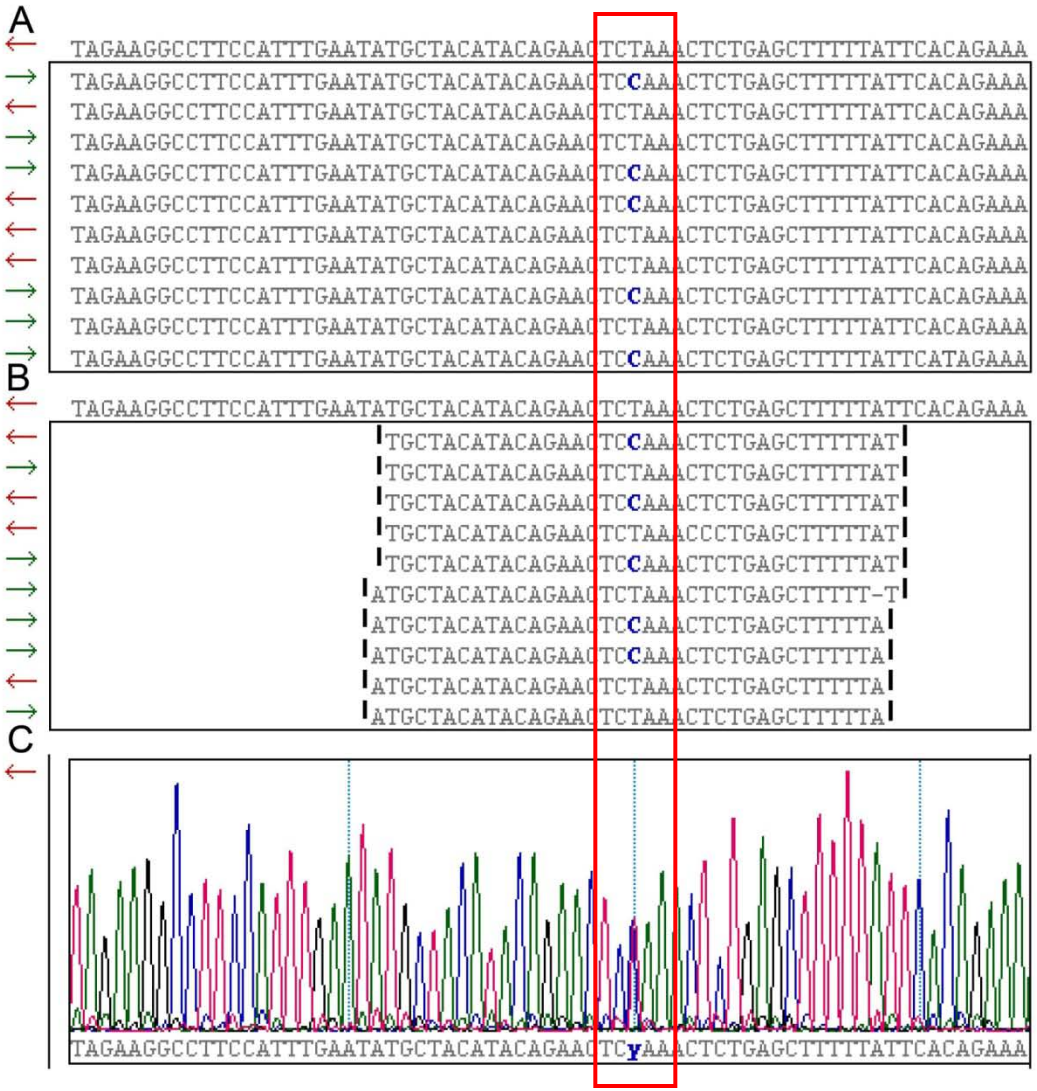
- Mitochondrial Genome
- Nuclear Genes > 100 Genes

X-Linked Mental Retardation → ~ 95 Genes

Snapshot of NGS Diagnostic Development

	Gene Panels	Exome	Genome
ARUP	X		
Mayo Clinic	X		
Emory	X		
Harvard	X		
Ambry	X		
GeneDx	X		
NCGR	X		

Concordant Variant g.5871488T>C in *ACTC1*



Roche 454
50%

Illumina
52%

Dames et al. 2010
J BioMol Tech
20(2): 73-80

Progression of Next Generation Sequencing

Whole
Exome

Human Exome

"Journey to the Center of the Genome"

~ 30 Megabases (~ 1% of the genome)

~ 180,000 exons (~ 20,500 genes)

Harbors majority of Mendelian mutations

Gene Discovery and Diagnostics
In
Probands/Kindreds

TPM1

Variant g.34142190T>C

Reference

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GAGGCCAAGCACATTGCTGAAGATGCCGACCGCAAATATGAAGAGGTCAGATCCTGGGGCCCAAAGCCTTGTGGACACCCAG
```

Gene Panel 47%

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GCCAAGCACATTGCTGAAGATGCCGACCGCAAGTACGAAGAGGTCAGATCCTGGGGCCCAAAGCCTTGTGGACACC
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```

Exome 47%

```
GAGGCCAAGCACATTGCTGAAGATGCCGACCGCAAATATGAAGAGGTCAGATCCTGGGGCCCAAAGCCTTGTGGACACCCAG
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CAAGCACATTGCTGAAGATGCCGACCGCAAATATGAAGAGGTCAGATCCTGGGGCCCAAAGCCTTGTGGACACCCA
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TGCCGACCGCAAATACGAAGAGGTCAGATCCTGGGGCCCAAAGCCTTGTGGACACCCAG
CGACCGCAAATACGAAGAGGTCAGATCCTGGGGCCCAAAGCCTTGTGGACACCCAG
GACCGCAAATATGAAGAGGTCAGATCCTGGGGCCCAAAGCCTTGTGGACACCCAG
```

Sanger

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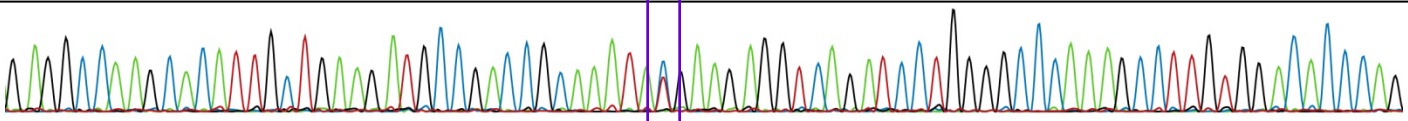
```



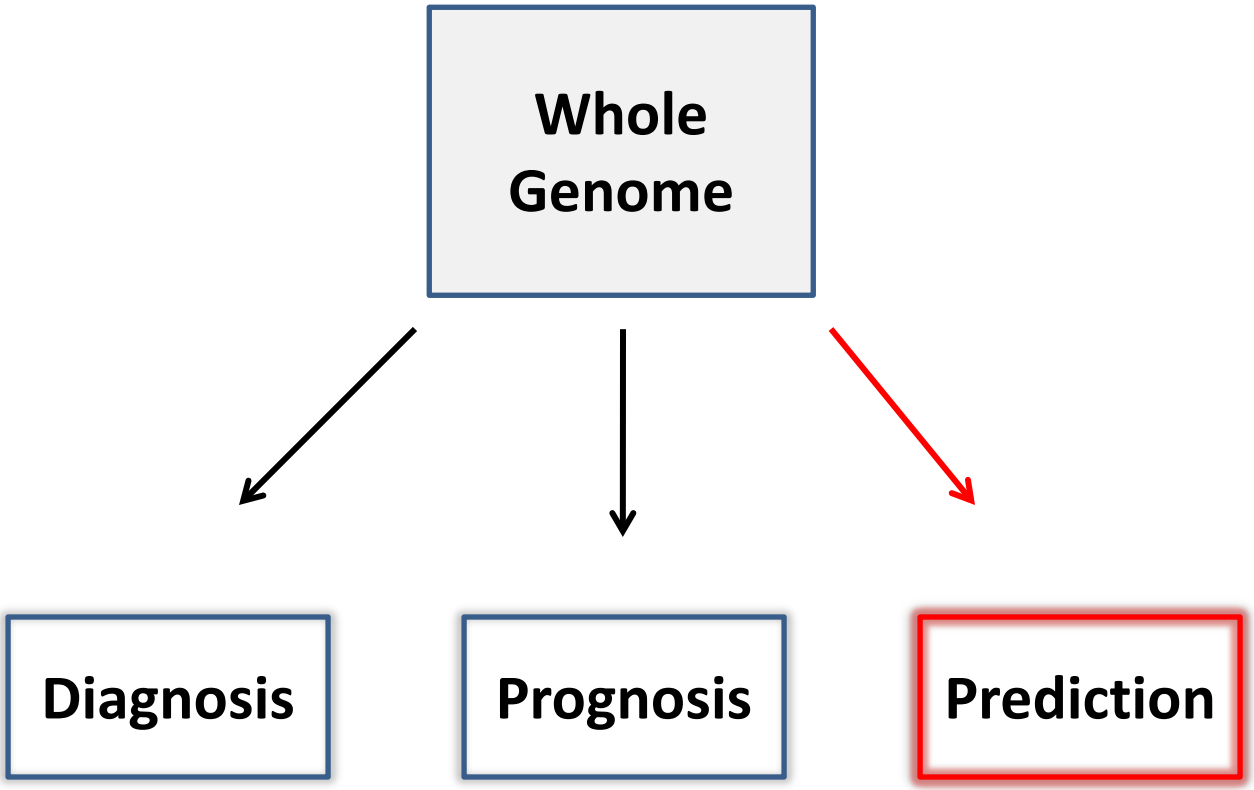
Snapshot of NGS Diagnostic Development

	Gene Panels	Exome	Genome
ARUP	X	X	
Mayo Clinic	X		
Emory	X		
Harvard	X		
Ambry	X		
GeneDx	X		
NCGR	X		
Medomics		X	
Knome		X	

Progression of Next Generation Sequencing

Whole Genome

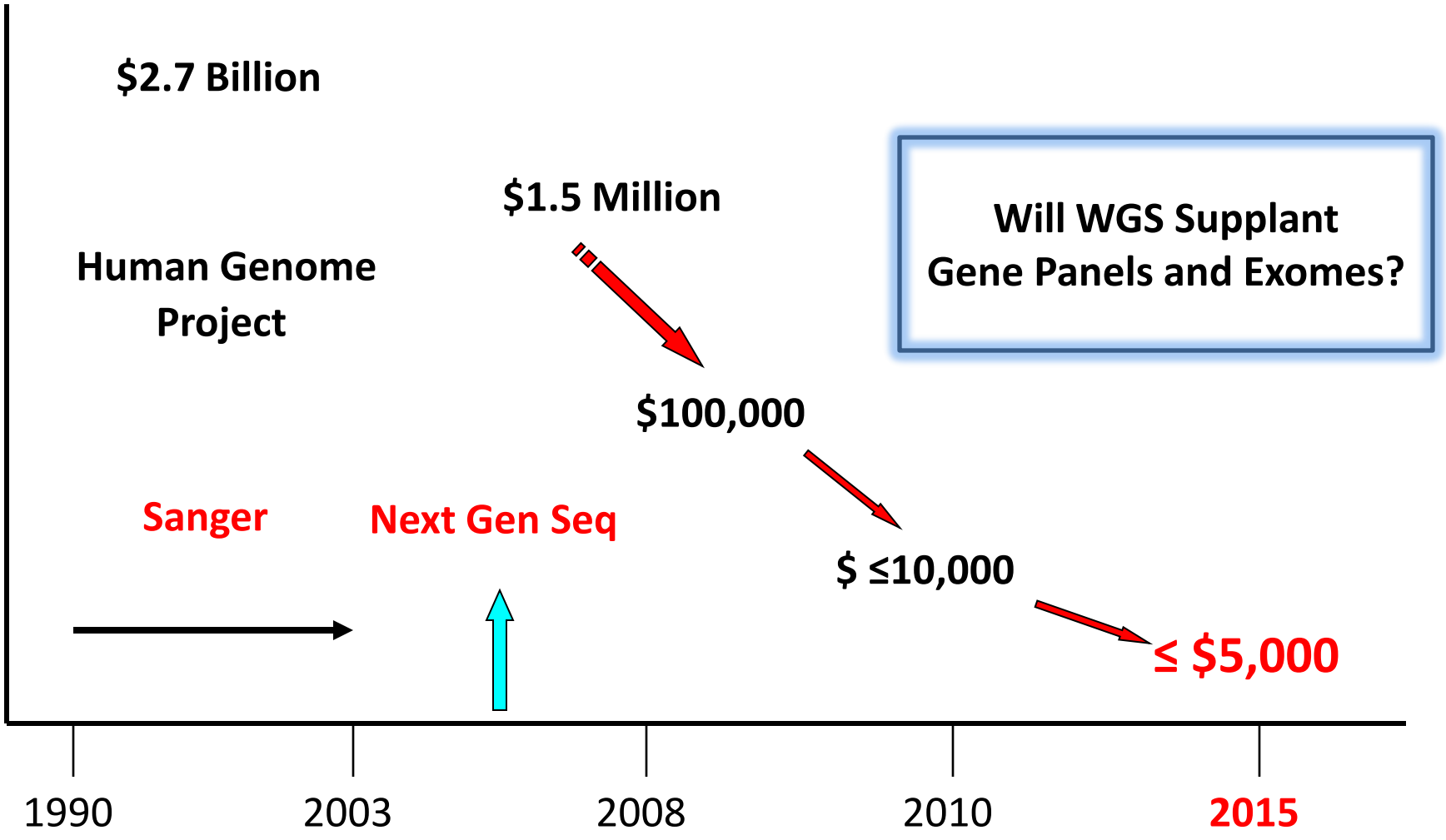
Progression of Next Generation Sequencing



Snapshot of NGS Diagnostic Development

	Gene Panels	Exome	Genome
ARUP	X	X	Groundwork
Mayo Clinic	X		
Emory	X		
Harvard	X		
Ambry	X		
GeneDx	X		
NCGR	X		
Medomics		X	
Knome		X	X
CGenomics			X
Illumina			X

Human Genome Sequencing Cost



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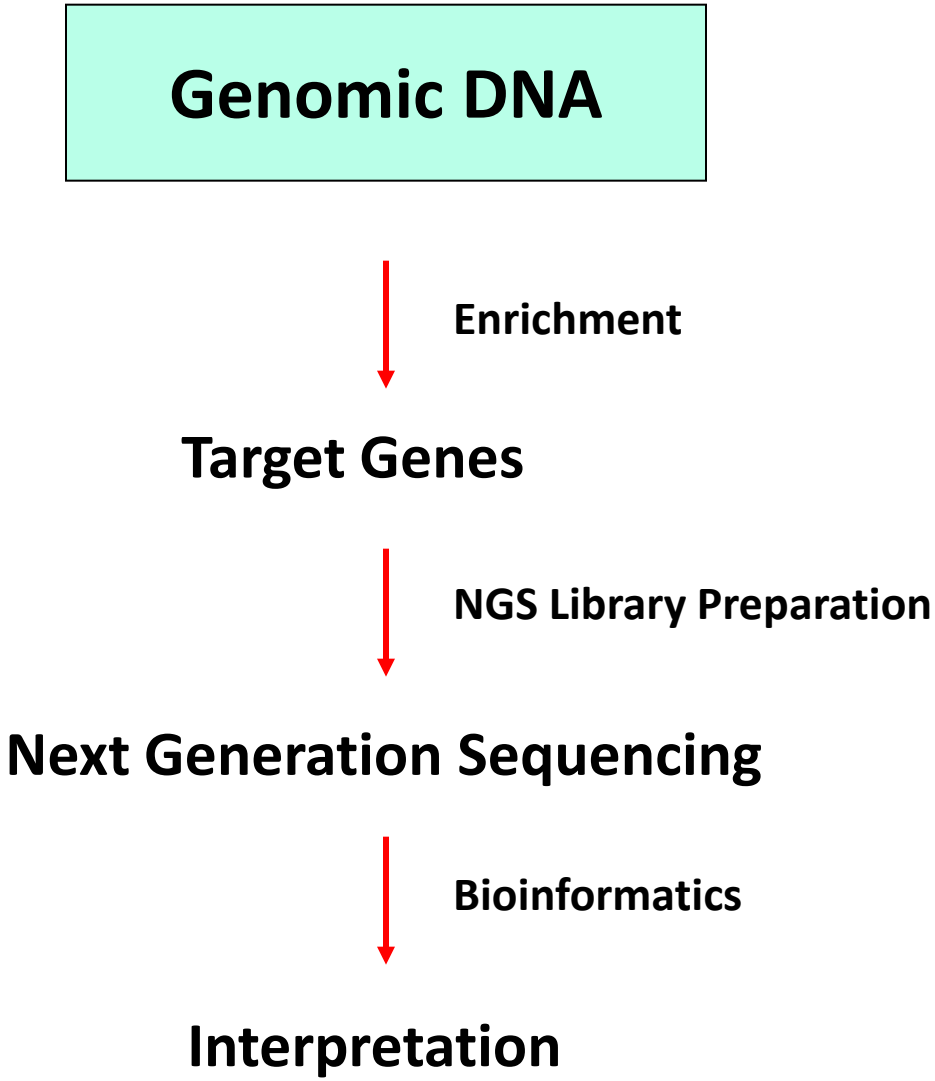
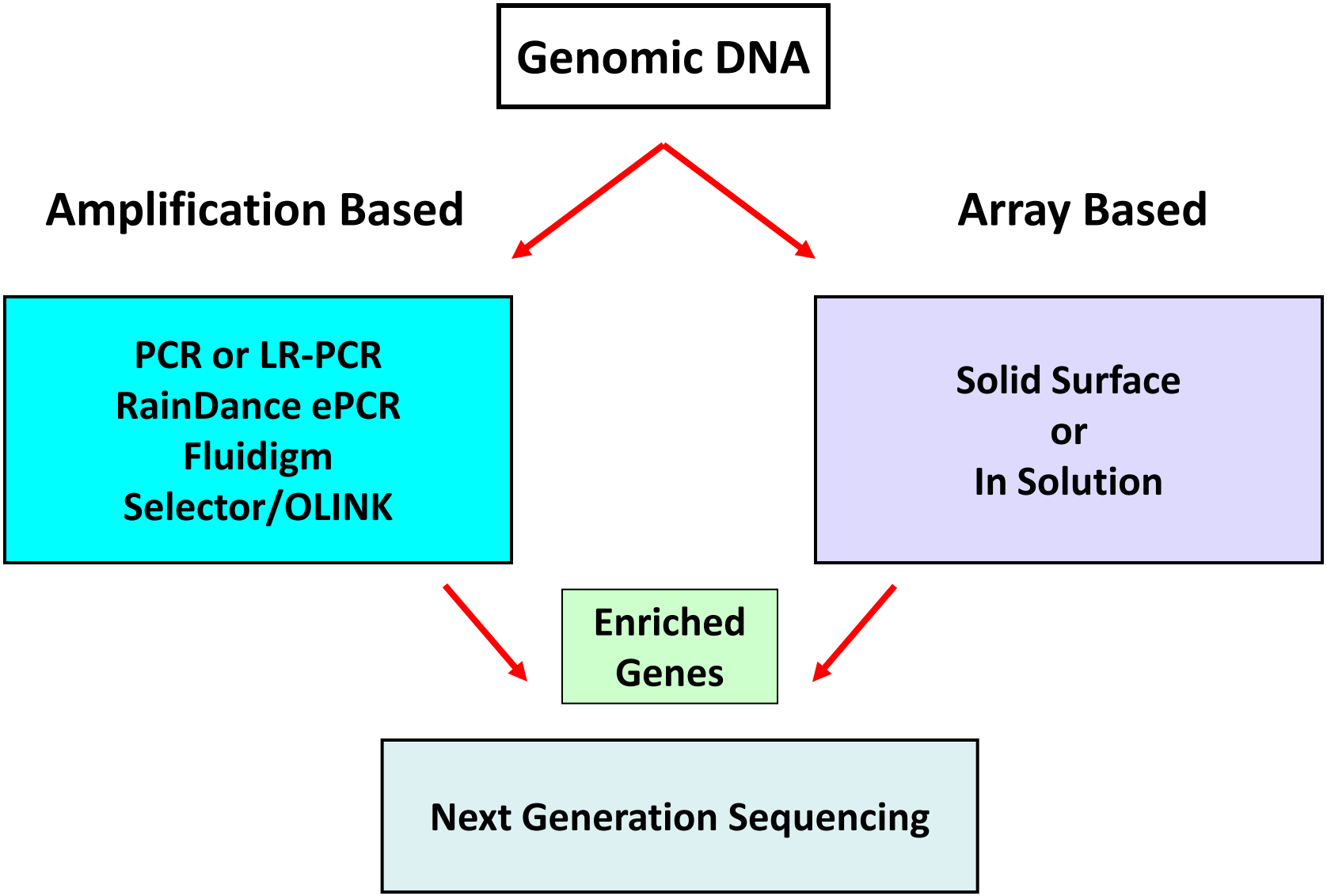
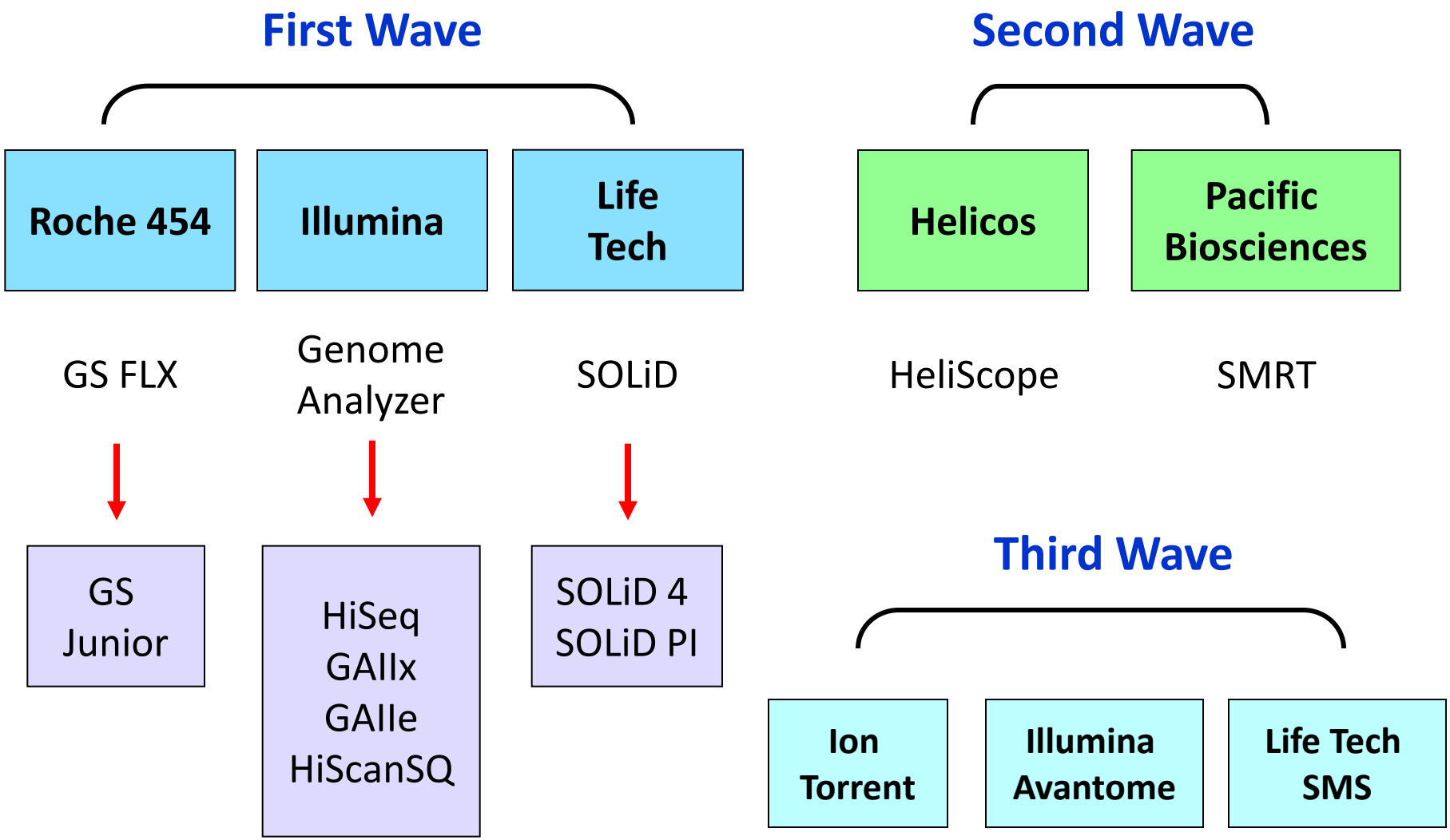

Genomic DNA
Enrichment
Target Genes
NGS Library Preparation
Next Generation Sequencing
Bioinformatics
Interpretation

Gene Enrichment Strategies



Next Generation Sequencers



A Bioinformatic World

Algorithms - Alignments - Assemblies

Software – Academic/Commercial/Custom

Computational Power and Storage

Diagnostic Databases and Interpretation

Convergence of Chemistry and Bioinformatics

Large Cognitive Component

TCGAAGTCTGCCTAGCTGT

CCGTACGTCTGATGCGTA

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What is Needed Going Forward

Historical Perspective and Fostering of Innovation

Next Generation Sequencing is a New Technology as were PCR and Arrays

Expand Education and Training

Medical Profession is on a Learning Curve

What is Needed Going Forward

Develop Technical Standards and Guidelines

Leverage Existing Infrastructure within Professional Organizations

Develop Genome Wide Genotype Phenotype Database

Coalesce Existing Databases and Integration of New Knowledge

What is Needed Going Forward

Promote Appropriate Medical Use

Understand our Limitations in Knowledge

Address Genomic Information Access and Portability

Incorporate into Evolving Electronic Health Record Principles and Practice

Questions?

The capacity to blunder slightly is the real marvel of DNA. Without this special attribute, we would still be anaerobic bacteria and there would be no music.

Lewis Thomas