



Built To Adapt

Comprehensive next-generation sequencing promotes efficiencies in rare disease analysis

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illumina®

Move

The pace of genomic discovery in rare disease is breathtaking. Two hundred and fifty new gene-disease associations are identified annually. Over nine thousand new variant-disease associations are reported per year.¹

Deeper understanding of the genome is being uncovered with each new day.

omal microarrays (CMA) are a traditional method used by investigators in s with unexplained developmental s.²

profiling of chromosomal abnormalities,uplications and microdeletions, down to size.³ While highly effective, CMA only a portion of the genome and does e interrogation of sequence variants.

— traditional methods

S and WES offer higher diagnostic utility than CMA



ven studies comprising 20,068 children published between January 2011 and December 2017 were reviewed for the diagnostic utility of CMA, WES, and WGS. $P = 0.0001$.⁴

Evidence-based guidelines issued by the American College of Genetics and Genomics (ACMG) have recognized the value of whole-genome sequencing (WGS) or whole-exome sequencing (WES) in first or second tier use. Improved management, higher diagnostic yield, and improved costs were cited as support to using early in a genomic evaluation.⁵

TAGCTACTTGTCTAGC
TTGCTTTAACTGATCTAC
TAGCTTAACATCTACTTAGC
AGGCTACT TGCTAGCT
TAGCTAC TTAGCTAC
TTGCTAG CTTCTTA
TGCCTGAT CTGGGAG
CTTGTCTA GCTTAAC
CTAGCTT AACTGAT
ATGCTTGTCTGGGAGAGCA
CTAGCTTAACTGATCTACT
TCTTAAC AGCTTCTT
GCTTAAC TGATCTTA
GTC TAGC
TAGCTAC TTGCTAG
GATGCTT GATCTGG
CTAGCTT CTAGCTTA
CTAGACC TTAACCTA
GGAGAGCAGCTTACCTAGC
CTACTTAGCTACTTGCTAC
AGAGCAGCTTAC

TTAACTGA TCTCTACT TAGCTACT TGCTACTC
TTAGCTAC TTAGCTAC TTAGCTAC TTAGCTAC
TAAGCTGAT TAAGCTGAT CTTAACTG ATCTCTT
TTGCTAG TTGCTAG CTTAACTG ATCTTAAAC
GCTGAGAG CTTAACTG ATCTTAAAC TGACTCA
AGCAGCT ACTTACG ACTTACG ACTTACG
TGATCCAT GATGCTT GCTACTTG TCTAGCTT
CTTACTTA GCTACTTA GCTACTTG TCTAGCTT
GCTACTTA GCTACTTA GCTACTTG TCTAGCTT
TAGCTACT TGCTAGCT TAGCTACT TAGCTACT
AGCTACTT AGCTACTT GTCTAGCT TCTAGCTA
ACTGATCT ACTGATCT TCTTAGCT ACTTGTCT
TAGCTACT TGCTAGC TTAAGCTA TCTTAAC
TAGCTACT TGCTAGC TCTGATCT GGGAGAG
GAGAGCA GCTACTTA GCTACTTG TCTAGCTT
ACTGATCT ACTGATCT CTACTTAG CTAGCTAG
TCTTAAC TCTTAAC GATCTCT TAGCTACT
TGCTAGCTTAACTGATCTAC TTAGCTAC TTGCTAG
TTAACTGATCTAACTGATCTAC CTTCTAG CTTAACTG
CTACTTGCTAG CTACTTGCTAC

TAGCTACTTAGCTAC GCTACTTAGCTACTTG
TTAGCTAC TTAGCTAC GATCTGG GAGCATGA
TGATCTTA CTTAGCTA CTAGCTA CTACTTG
CTACTTAG CTAGCATG TAACTGAG TAACTGAG
TGCTAGCT TAACTGAG CTTAGCTA AGCTTCTT
CTTAGCTA CTTGCTA AGCTTCTT AGCTACTT
GATCTCT TAGCTACT CAGCCAT GATCCAT
GGGAGAG AACTGATG AACTGATC TTACTTAG
TCTAGCTT CTAGCTAG CTACTTG TGCTAGC
ACTTACGCTTGTCTAGCT AGCTTACGTTAGCT
TCACTTAGCTACTTGCTAGCT ATCTTACTTAGCTACTTGCTAC

The burden of multigene panels

The velocity of change brings challenges for the modern molecular genomics laboratory to stay current. One lab found 23% of positive WES findings were in genes described within the last two years, while 7% of positive variants were in novel gene discoveries.⁶

Labs face a continuous cycle of new panel design and validation with every new gene or variant association with rare disease, requiring significant expenditure of time and resources, all while being unable to engage in gene discovery themselves.

for the future

In contrast, with WGS and WES labs can create a comprehensive assay, amenable to the latest genomic discoveries. New findings can be incorporated into existing workflows and “future-proof” the test menu.

Re-analysis of existing data sets can identify novel associations without the need to re-sequence samples or re-validate an assay. “Virtual panels” can be created out of a genome or exome output, providing ordering health care providers a bespoke panel of their choosing (Figure 2).

Create “virtual panels” with a genome or exome foundation

Use of whole-genome or whole-exome sequencing as an assay foundation enables dynamic creation and modification of “virtual panels” as more is understood about the genome.

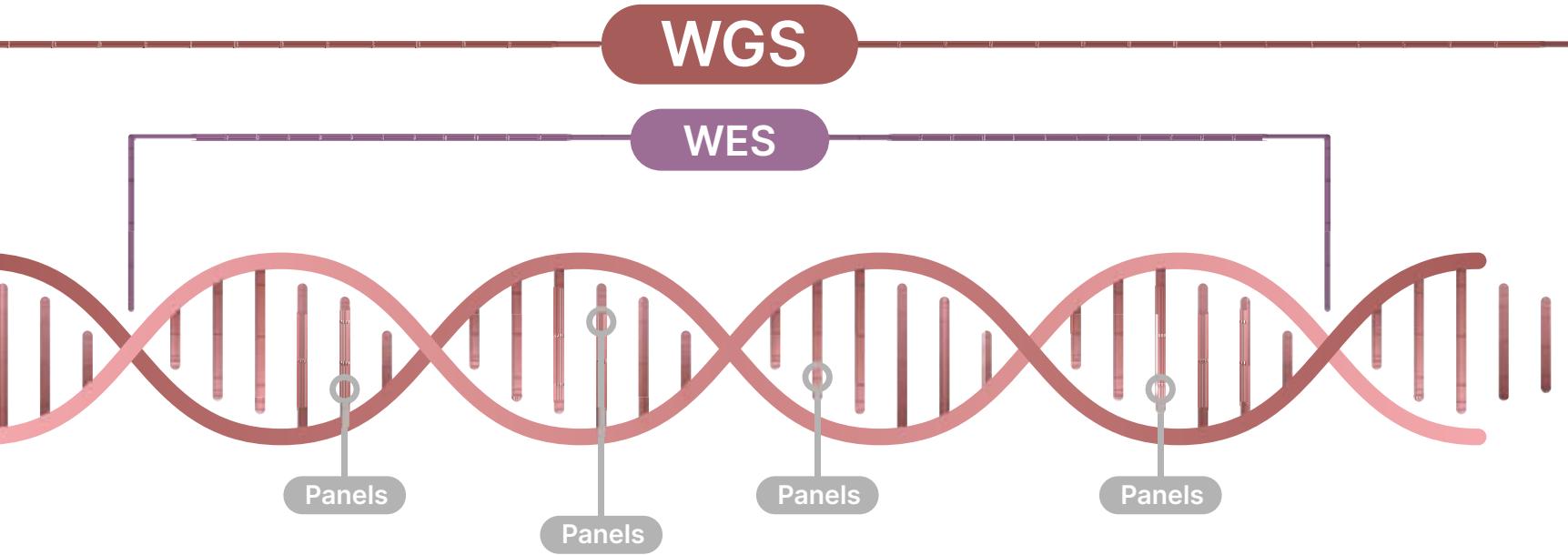


Figure 2: Genome as a foundation

CTACTTGTCTAGCTTA	GATCTCTACTTAGCTACTG	TCTAGCTAGCTACTT	AGCTAAC	TTAACTGATCTTACTTAG	CTACTTGCCTGATCTGGGA	GAGCAGCTA	CTTAGCT
ACTTGTCAGCTTA	ACTTAGCTACTGCTAGCTTA	ACTGATCTACTAGCTTA	TGATCTTA	CTTGTAGCTA	GCTACTCTTA	TCTAGCTAC	TCTAGCTA
CTTGTCTA	GCTCTGAC	TACTTGC	GGAGCAT	AGAGCA	AGAGCA GCTACTT	GCTACTTA	TGAGCTA
GCTACTC	ATGATGC	TGATCTG	TGATCTGG	GAGAGCA	GCTACT TGCTA	GCTACTTGTC	TGAGCTGT
AGCTTAA	CTGATCC	ATGATGCT	TGATCTGG	TACTTAC	TGATCTG	TGAGCTA	TGAGCTAA
TACTTGC	TAGCATG	ATGCTGA	TCTGGGA	GAGCAC	TACTTGT	ATCTTACT	CTGATGC
TTAGCTA	CTTGTCT	AGCTAGC	TACTTAG	TACTTAGC	ACTGTT	TACTTAG	CTAGCTTA
AGCTACT	TGCTAG	CTTAACTG	ATCTTAC	CTAGCTTA	ACTGAT CTTA	GATCTCT	TGCTAGCTA
AGCTTA	ACTTCTA	ATCTCTAGCTACTAGCTAC	TTGCTAG	TTAGCTAC	TTAGCTA	AGCTCTT	TGCTAGCTAA
TACTTGTAGCTTA	CTTACTTAGCTACTGCTA	GCTTA	TCTTCTAC	TCTAGAT	AGCTGTC	AGCTACTT	CTGATGCT
CTACTTA	GCTACTGT	CTAGCTTGTAGCTGGGAGAG	GAGCTACT	TAGCTAC	TAGCTG	CTGGGAG	GGAGCA
AGCTACT	TAGTACT	TGTCTAGC	TAACTGA	TCTTA	GATCTCT	ATCTTACT	TGAGCTACT
GCTACTT	GTCAGC	TAACTGA	TCTTAC	GTCTAGC	GTCTAG	TAGCTACT	AGCTACTT
TAACCTGA	TCTCTTA	GCTACTTA	GCTACTT	GTCTAGC	TAAGCT	AGCTACTT	AGCTACT
TTAACTG	ATCTCTAC	TTAGCTAC	TTGCTAG	TTAGCTAC	TTAGCTA	TTAGCTA	AGCTACT
TTAGCTA	CTTGTCTA	GCTTA	GATCTAC	TTGCTAG	TTGCTT	TTACTT	GGGAGCA
CTTAACT	GATCTAA	CTGATTT	CTTGTCTA	CTTGTCTA	TAACTGA	ACCTACTT	ACTTAGC
ACTTAGCTACTTGTCTAGCTCT	TAGCTACT	TGCTAG	CTAGCTACTCATGATGCTGA	TCTGGGA	GATCTAC	AGCTAGC	ACTTAA
ACTTGTCTAGCTTA	CATGATG	CTGATCT	GGGAGACCACTTA	GCTACTT	GCTAGAT	TACTGCT	CTGATC
TGCTTGATCTGGGAG	AGCAGCT	ACTTAGC	TACTTGCTAG	CTTAACT	GATCTTG	AGCTTA	TCTTAGCT

your analysis with WES

Scale variant interpretation
and benefit from
Next-Generation Sequencing
(NGS)

For labs that want to increase capabilities and gain proficiency in comprehensive NGS analysis, WES is a targeted sequencing approach that enables them to focus resources on genes likely to affect the phenotype.

WES targets protein-coding regions, which comprise less than 2% of the genome but contain ~90-95% of known disease-related variants.⁶ It produces a manageable data set for focused analysis that can help build competencies.



Enhance laboratory proficiencies associated with data management and interpretation at scale.



Offer greater opportunity for re-analysis or discovery potential than CMA or gene panels.

With WES
~30%
find a molecular
etiology⁷

WES can:

CTTGTCTA
TACTTGTCTA
GCAGCTAC
TGTCTAGC

Provide the laboratory professional a broad view of coding variants.



For Research Use Only.

Not for use in diagnostic procedures.

No single test is more

WGS offers unparalleled analysis

For labs that want to streamline operational efficiency, WGS provides the most comprehensive view of the human genome.

WGS enables simultaneous analysis of thousands of genes with known or suspected associations with rare disease, as well as discovery of novel causative variants. Enabling uniform coverage of coding regions, WGS provides advantages evaluating exons compared to WES. As a single assay, there is no other test that can detect as many diverse variant types (Table 1).

Comprehensive variant calling can result in greater opportunities to interrogate the genome, as 13% of WGS diagnoses in a large national pilot study were not expected to be discovered with exome sequencing.⁷ WGS also provides a foundational assay for other emerging applications including pharmacogenomics, human leukocyte antigen (HLA) typing, and polygenic risk scores.

TAGCT GAGCAGCTA ACTTG CTTAGCTAC TCTAGC TTAGT GACTCTAA GATCTCTA CTTAGCTA CTTGCTAGCTA GCTA CTTA GCTACTTGTCT TAATC GATC TTACT TAGC TACTT GTCG CTTGATCTGGGA
TGAT CTTC TTAG CTAC TTGCTA GCTTA AGCTTACTTA CTTGCTCT AGCT TCTA GCTA CTTA GCTA TGAT CTGG GAGC ATGATG CTG ATCT GACT AACTGAGC AGCT GAGC AGCT ATCT TTGT CTAG CTTA ACTGATCTAAC
TACT TGTC TAGC TTCT TAGCTA CTTGCTCT AGCT AGCT ACTC ATGA TGCT TGAT CTGG GAGC ATGATG CTG ATCT GAGC GAGA GCAG CTAC TTAG CTC TACT TAGC
AGCT ACTT GTCT AGCTTAA CTG ATCT TACT TAGC TCTG TAGC TTAA CTGA TGAT GCTAGC TGATGCTGATC TGG GAG AGCTAC TTAG CTAC TTGT CTAGCTTAAC
CTAC TTGT CTAG CTTA ACT GAT CTTA CTTA GCTA CTG TCTA GCTTAACGTATG TGATGCTGATC TGG GAG AGCTAC TTAG CTAC TTGT CTAGCTTAAC
ATCT TACT TAGC TACT TGT CTA GCTT AACTGATCTCT AACTGACTCT TGCTAGCTAGC TACTTAGCTACTTG TCTAGCTTAAC TGATCTTC GATC TTA ACT GATCTC TTAG CTAC TTAG CTAGCTGTTAG
CTTC TAGC TACT TAGC TAC TTG TCTA GCTT AACT GATC TTAA CTGA CTTA ACTG ATCT TAAC TGAT CTTC TTAGCT ACTT AGCT ACTT GTC TAGC
ACTT GTCT AGCT AGCT ACTTAG CTAC TTGT CCAT GATG CCAT GATG AGCT GAGC GCTA CTTA GCTA CTTGTC TCTAA CTGA TCTAA CTGATCTCTTA
TTAC TACT CATG ATGC TTG TCTGG GAGA GCAG CCAT GATG CCAT GATG AGCT GAGC GCTA CTTA GCTA CTTGTC TCTAA CTGA TCTAA TTAACGTATCTCTA
TTAAC TGAT CTTAC TTAGC TACT TGCT AGCT TAAC TGAT CTCT ACTTAGCTACTT GTCT AGCTACTTAGCT GCTA CTGT CTAGCTTAAC TGATCTTC AGCTAC TTGT CTAGC TTAACGTATCTCTA

WGS provides the most comprehensive analysis of genomic variants among all clinical genomic testing methods⁹

	Sanger*	Targeted NGS*	PCR*	CMA*	WES*	WGS*
Single-Nucleotide Variants (SNVs)	✓	✓	✓	✓	✓	✓
Insertions & Deletions (Indels)	✓	✓	✓	✓	✓	✓
Copy Number Variants (CNVs)	✓	✓	✓	✓	✓	✓
Repeat Expansions			✓			✓
Structural Variants (SVs)				✓	✓	✓
Mitochondrial	✓	✓		✓	✓	✓
Paralogs	✓		✓			✓

Table 1: Comparison of WGS to Standard Testing

✓ Limited capabilities ✓ Capable

It is clear whole-genome sequencing is contributing significantly to end diagnostic odysseys in rare disease. With guidelines advocating use as a first-tier test⁵, inclusion in national health care systems⁷, and increasing evidence of economic value when used as a first-tier test⁸, genome sequencing appears to be on the path toward standard of care.

*Variant detection may vary depending on laboratory and test offering

CMA = chromosomal microarray, CNV = copy number variant, FISH = fluorescence in-situ hybridization, indel = small insertion deletion, NGS = next-generation sequencing, PCR = polymerase chain reaction, SNV=single nucleotide variant, WES = whole-exome sequencing, WGS = whole-genome sequencing

TAGCTA CTTGCT AGCTT AACTGATCTCTAGCTA CTTGCTAGCTAGCTAC TTAGTACT CTTAGCTACTGCTTAAC TGATCTCTAGCTAAGCTA CTTGCTACTGCTAGCTAC TTAGTACT CTTAGCTACTGCTAGCTAC TTAGTACT CTTAGCTACTGCTAGCTAC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 AGCTTA ACTATCT CTTGT AGCTT AACTGATCTCTAGCTA CTTGCTAGCTAGCTAC TTAGTACT CTTAGCTACTGCTTAAC TGATCTCTAGCTAAGCTA CTTGCTACTGCTAGCTAC TTAGTACT CTTAGCTACTGCTAGCTAC TTAGTACT CTTAGCTACTGCTAGCTAC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 TAGCTA CTAGCTA CTTGT AGCTT AACTGATCTCTAGCTA CTTGCTAGCTAGCTAC TTAGTACT CTTAGCTACTGCTTAAC TGATCTCTAGCTAAGCTA CTTGCTACTGCTAGCTAC TTAGTACT CTTAGCTACTGCTAGCTAC TTAGTACT CTTAGCTACTGCTAGCTAC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 TAGCT AACTGCTT CTTGT AACTG AACTGA CTTAGT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 CTACTT GTCTACTT CTTGT AACTG AACTGA CTTAGT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 GCTACT TAGCTACTT CTTGT AACTG AACTGA CTTAGT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 ACTCTG CTTACTT GTCT AACTG AACTGA CTTAA GATCT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 CTTAGC TACTCT GTCT AACTG AACTGA CTTAA GATCT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
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 AACCTG TGTCT AGCTT AGCTA GCTAC TGTAC AGCTT AACTG AACTGA CTTAA GATCT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 AGCAGC TACTT AGCTT AGCTA GCTAC TGTAC AGCTT AACTG AACTGA CTTAA GATCT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 GATCTT AACTG AACTGA CTTAA GATCT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 TAGCT TGTCT AGCTT AGCTA GCTAC TGTAC AGCTT AACTG AACTGA CTTAA GATCT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 TACTG AACTG AACTGA CTTAA GATCT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 ACTCTG TGTCT AGCTT AGCTA GCTAC TGTAC AGCTT AACTG AACTGA CTTAA GATCT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 GCTACT GCTCT AGCTT AGCTA GCTAC TGTAC AGCTT AACTG AACTGA CTTAA GATCT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 ACTCTG GAGAG CAGCTACTT AGCTAC TGTCT AGCTT AACTG AACTGA CTTAA GATCT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 GCTCT AGCTC TACTCTAGC TACTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 AGCTAC TTGTC TAGCTAA CTGATC TTAACCTGCTCTAGCTAAGCTA CTTGCTACTGCTAGCTAC TTAGTACT CTTAGCTACTGCTAGCTAC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 CTTGAT CTGGG AGAGCAG CTTACTT TGATGCTAC TGTCT AGCTT AACTG AACTGA CTTAA GATCT CTTAGC TTAGT ACTCTG TCTAGC TCTTACTT AGCTACTTGCGCTTGATCT GGGAGAGCAGCTACTT AGCTACTGTCT
 TAGCT TAATC GATCTTA CTTAGC TACTTGTCTAGCTTAAC TGATGCTAC TTGTC TAGCAT GATGC TTGATC GATCC TGATGC AGCAGC TACTTAGCTACTGTCT AGCTTAAGTGTCT

workflows for NGS methods

Illumina offers investigators integrated, streamlined workflows for WES and WGS research that follow the same three steps labs may be familiar with and already use for targeted sequencing (Figure 4). Regardless of the method, prepared libraries are loaded onto an Illumina platform for sequencing.

WES research can be performed on a range of Illumina systems from the benchtop MiSeq™ System to the NovaSeq™ 6000 System. The output capabilities and scalability of the NextSeq™ 1000, NextSeq 2000, and NovaSeq 6000 Systems make them ideal for WGS investigations.

Illumina sequencing systems are powered by the same sequencing by synthesis (SBS) chemistry, so data generated across systems can be compared and integrated, enabling labs to transition to new methods with confidence.

The Illumina NGS workflow

Regardless of the specific method used, all Illumina NGS workflows consist of three basic steps: library prep, sequencing, and data analysis.



Figure 4:
The Illumina NGS workflow

TCTAGCTT	ACTTGCTC	CTGATCTA	TCTTAGCTACT
CTTAGCTACTT	GCTAGCTAA	CTTAACCTG	TGTCTAGCTCTAGCTA
TACTTGT	GGGAGA	GCTAGCTA	CTTAGCTA
TTGATCT	ACTTGT	ACTAGC	GCAGCT
CTTAGCT	GCTACTT	ACTGATC	AGCTTA
GCTACTT	ACTTGT	AGCTACT	TCTAGCT
CTACTTG	ATGCTTGAT	AGCTGAG	CTGGAG
CTTAACGTACT	TCTAGCTAGCTA	TACTTAG	TCTAGCT
TCTAGCTAGCTA	TACTAGCTAC	CTTAGCT	ACTAGT
TACTAGCTAC	AGCTTAAC	TTAGCTA	ACTTGT
AGCTTAAC	TGCTCTAG	ACTTGT	CTAGCT
TGCTCTAG	AGCTTAA	ACTGAT	TAACTG
CTTTCTA	CTCATGA	AGCTACT	GATCTTA
GATCTGG	GAGAGC	TCTGGG	CTCTTA
CTACTTG	TCTAGCT	TAACTGA	CTGATCT
GCTACTTGCTAGACCTA	GCTACTGCTAGCTT	TCTCTAC	ACTGATCTAACGTACT
GCTACTGCTAGCTT	CTTAGCTT	TTAGCT	AACTGATCTACTT
CTTAGCTACT		TTAGCT	TGCTCTAGCTT
		AACTGAT	AACTGAT
		CTTAAC	CTTAAC

with automated interpretation and XAI

The cornerstone of rare disease analysis is interpretation. With variability in the method, the genes interrogated, and the output generated by an application, a software solution to provide an investigator a complete view of the data is crucial.

Illumina's Emedgene tertiary analysis platform has been designed to translate the vast amounts of data produced by WGS, WES and virtual panels into meaningful insights, enabling rapid analysis.

Illumina's Emedgene intuitive genomic analysis platform enables 2-5x improvement in efficiency:

- Streamline interpretation and automate evidence curation with explainable artificial intelligence (XAI) and machine-learning
- Integrate with the cloud-based DRAGEN™ Bio-IT Platform to enable comprehensive, streamlined secondary and tertiary analysis workflows and ultrarapid variant calling

Illumina offers users an ecosystem of end-to-end high-throughput products, designed for diverse researcher needs. Whether it is including automation to increase efficiency, ensuring quality of a run, or providing a seamless experience with scalable software for sample-to-report generation, laboratories can have confidence knowing they have the very latest to equip them in their search for answers.

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