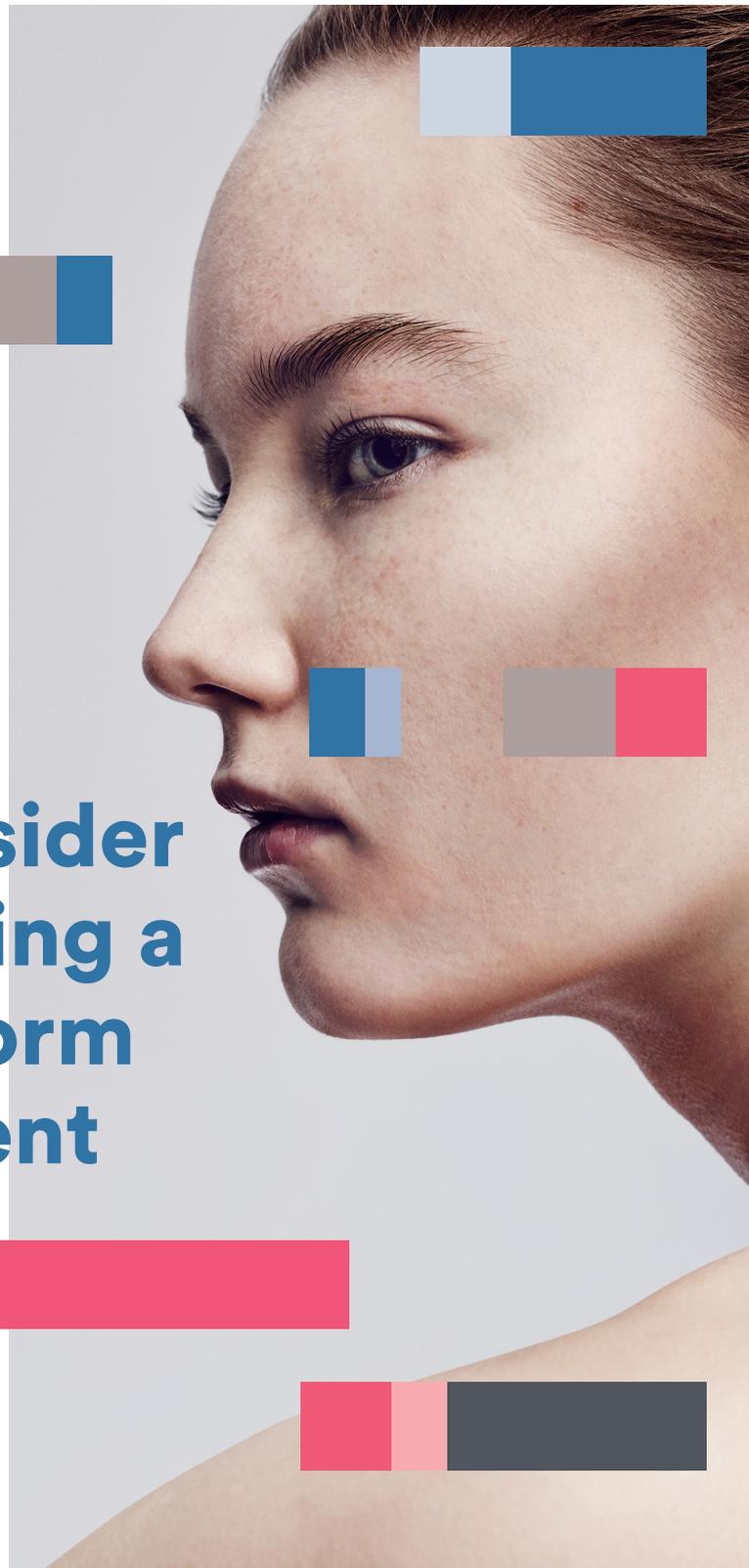


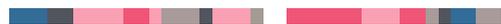
# What to Consider When Choosing a Testing Platform for Your Patient



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Blueprint Genetics



### How many genes are included in the whole exome sequencing platform?

	Blueprint Genetics	Lab A*	Lab B*	Lab C*	Lab D*
<b>Number of genes</b>	~20,000 genes	~20,000 genes	>18,000 genes	~20,000 genes	~6,700 genes

\* information provided on laboratory websites

### How well are the genes covered? How is this demonstrated?

	Blueprint Genetics	Lab A*	Lab B*	Lab C*	Lab D*
<b>% coverage of target regions</b>	99.4%-99.7% at 20x**	~95% at 10x, >98% at 1x	>99.4% at 20x	97% at >20x	~97-98% at 10x
<b>Mean read depth</b>	174x->244x**	Not provided	150x	>120x	100x
<b>Validation study</b>	Yes	Not provided	Not provided	Not provided	Not provided

\* information provided on laboratory websites

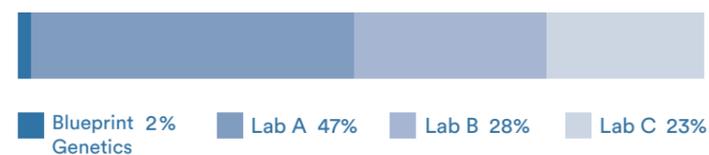
\*\*lower value in publicly available validation samples of varying quality, higher value in patient samples

### Why do these numbers matter? What do they really mean? What is the difference between 99.7% versus 95% coverage?

	Blueprint Genetics	Lab A	Lab B	Lab C
<b>% coverage of target region</b>	99.7% >20x	95% >10x	97% >20x	97.5% >10x
<b># bp covered &lt;20x (or &lt;10x)*</b>	60,000 bp <20x	1,500,000 bp <10x	900,000 bp <20x	750,000 bp <10x
<b># exons/genes covered &lt;20x (or &lt;10x)*</b>	414 exons 45 genes	10,345 exons 1,119 genes	6,207 exons 672 genes	5,100 exons 550 genes

\*Estimates intended for illustrative purposes

### Genes Covered Suboptimally



### How does this translate to the clinic?

#### CASE 1:

27-year-old with polydactyly and early onset retinitis pigmentosa. Previous testing, including the Bardet-Biedl syndrome 2 (*BBS2*) gene, was negative.

#### Blueprint Genetics results

Sequence analysis revealed two variants in the *BBS2* gene, c.1895G>C (pathogenic) and c.534+1G>T (likely pathogenic) resulting in a diagnosis of Bardet-Biedl syndrome.

#### Blueprint Genetics advantage

High-quality sequencing with uniform coverage reduces the risk of false-negative results. In this case previous testing had low-coverage in some regions, resulting in a failure to detect the patient's variants.

#### CASE 2:

A 12-year-old male with clinical suspicion of X-linked retinitis pigmentosa due to a strong family history of maternally related affected male relatives. Testing performed at another lab was negative.

#### Blueprint Genetics results

A deletion was discovered in the retinitis pigmentosa GTPase regulator (*RPGR*) gene, c.2426\_2427del (p.[Glu809Glyfs\*25]), specifically in the ORF15 region. As a result, a diagnosis of *RPGR*-related X-linked retinitis pigmentosa was made.

#### Blueprint Genetics advantage

Improvements to capture kit, sequencing platform, mapping quality, and bioinformatic pipeline increase the sensitivity of variant detection in genes difficult to sequence by NGS, including *RPGR*, *PKD1*, *GBA*, and others.

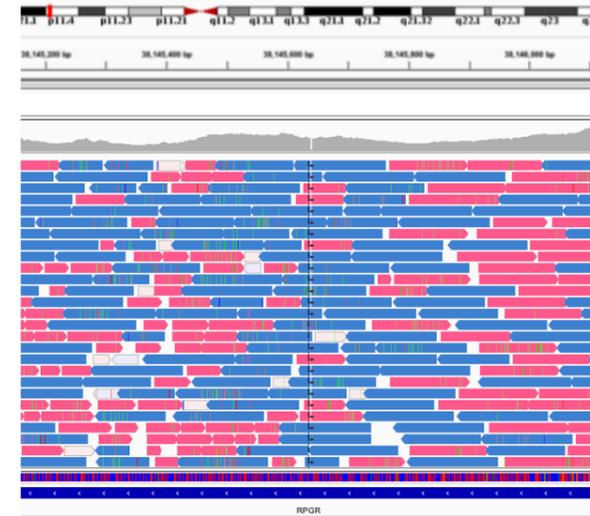


Figure 1. The new NovaSeq technology with custom oligo design shows improved coverage in the *RPGR*-ORF15 region.

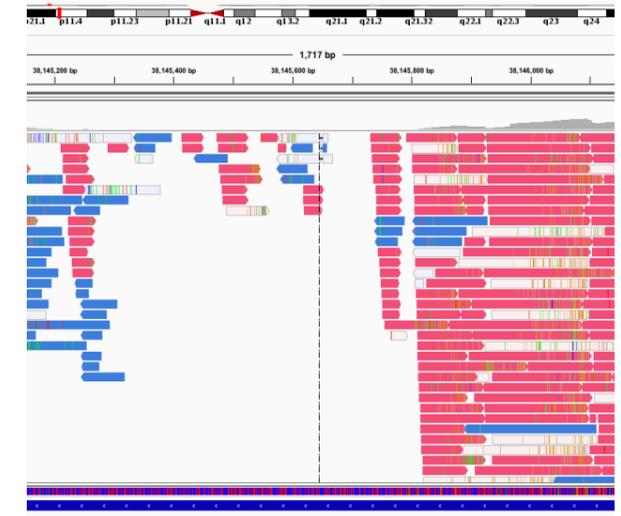


Figure 2. Coverage in the *RPGR*-ORF15 region using the previous NGS technology.

### What types of variants can be detected using this test?

	Blueprint Genetics	Lab A*	Lab B*	Lab C*	Lab D*
<b>Deep intronic variants</b>	20 bps from exon-intron boundary + >1,500 disease causing deep intronic variants included	Not provided	Not provided	Not provided	Not provided

\* information provided on laboratory websites

#### CASE 3:

A 4-year-old with bilateral choanal atresia, bilateral lacrimal duct obstruction, abnormal eyelids, and moderate unilateral conductive hearing loss. Sequence analysis at another lab revealed the genetic variant *TXNL4A* c.88\_110del23 (likely pathogenic) which is associated with Burn-McKeown syndrome, but insufficient for an autosomal recessive disease diagnosis.

#### Blueprint Genetics results

Sequence analysis revealed the previously described *TXNL4A* c.88\_110del23 variant as well as c.-222\_-189del (pathogenic), a previously described 34 bp deletion in the promoter. As a result, the Burn-McKeown syndrome diagnosis was confirmed, and another relevant variant was identified.

#### Blueprint Genetics advantage

More than 1,500 previously described disease-causing deep intronic variants are included in our panels and whole exome sequencing.

	Blueprint Genetics	Lab A*	Lab B*	Lab C*	Lab D*
<b>SNV detection</b>	99.7%	Not provided	Not provided	Not provided	~93.2%
<b>Indel detection</b>	1-10 bp 96.9% 11-20 bp 98.9% 21-30 bp 100% 31-40 bp 100%	Not provided	<50 bp reliably detected	Not provided	Not provided
<b>CNV detection</b>	1 exon del 92.3% 2 exon del 100% 3 exon del 93.3% Microdeletion syndromes 100%	May detect CNV 3 exons or larger.	Reliable detection of CNVs 4 exons or larger with high confidence. Not intended to detect large CNVs.	1, 2, and 3 exon CNVs ~ 70%; 4 or more exon CNVs >95%	Not provided

\* information provided on laboratory websites  
SNV, single nucleotide variant; CNV, copy number variant.

#### CASE 4:

An 11-month-old baby with abnormal soft tissue calcification at joints, mild global developmental delay, and failure to thrive. Parents are consanguineous and chromosomal microarray (CMA) testing was normal.

#### Blueprint Genetics results

Genetic testing showed that the patient was homozygous for a one exon (~273 bp) deletion in the *ENPP1* gene, c.1091+1\_1092-1\_1164+1\_1165-1 (likely pathogenic), while the parents are both heterozygous. The resulting diagnosis was generalized arterial calcification of infancy.

#### Blueprint Genetics advantage

NGS-based CNV analysis able to detect CNV missed by CMA.

#### CASE 5:

A 4-month-old with clinical and laboratory features consistent with propionic acidemia.

#### Blueprint Genetics results

Sequencing analysis identified *PCCA* c.1746G>A (pathogenic). CNV analysis revealed a deletion of exons 7-18 in the *PCCA* gene. These variants, confirmed to be in trans, are consistent with a diagnosis of propionic acidemia.

#### Blueprint Genetics advantage

The combination of SNV and CNV detection in one test decreases the need to resort to non-NGS deletion/duplication assays when only one SNV is identified.

### A quick and easy checklist for quality testing platforms

- High-quality sequencing platform with >20X coverage across >99.4% of targets
- Publicly available analytic validation that demonstrates sensitivity to detect SNVs, indels, and CNVs across all genes
- Inclusion of disease-causing deep intronic variants
- High-quality bioinformatics pipeline and rigorous variant interpretation
- Clinical statement that includes all data and evidence used to evaluate variants
- Competitive turnaround time and price