Quality matters

- 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

Blueprint Genetics

How many genes are included in the whole exome sequencing platform?	Blueprint Genetics
Number of genes	~20,000 genes

How well are the genes covered?	Blueprint Genetics
% coverage of target regions	99.4%-99.7%
Mean read depth	174x->244x*
Validation study	Yes

Why do these numbers matter?	Blueprint Genetics
% coverage of target region	99.7% >20x
# bp covered <20x (or <10x)*	60,000 bp <20x
# exons/genes covered <20x (or <10x)**	414 exons 45 genes

*Lower value in publicly available validation samples of varying quality, higher value in patient samples.
**Estimates intended for illustrative purposes.

How does this translate to the clinic?

	Results	Blueprint Genetics Advantage
Case 1 27-year-old with polydactyly and early onset retinitis pigmentosa. Previous testing, including the Bardet-Biedl syndrome 2 (*BBS2*) gene, was negative.	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.	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.	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.	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 NovaSeq technology with custom oligo design shows improved coverage in the *RPGR*-ORF15 region.

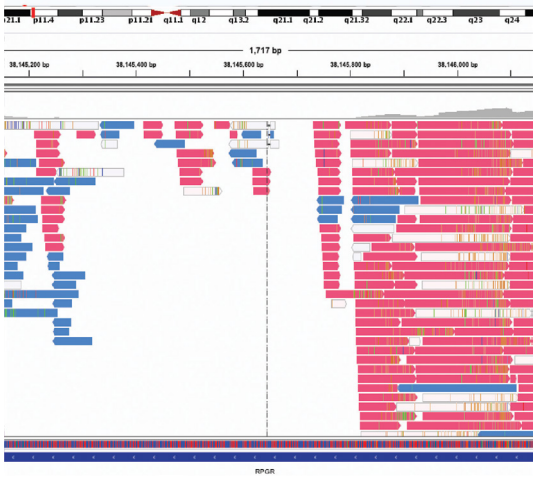


Figure 2. Coverage in the *RPGR*- ORF15 region using the NGS technology.

	Blueprint Genetics
Deep intronic variants	20 bps from exon-intron boundary + 1,500 disease-causing deep intronic variants included

	Results	Blueprint Genetics Advantage
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) that is associated with Burn-McKeown syndrome, but insufficient for an autosomal recessive disease diagnosis.	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.	More than 1,500 previously described disease-causing deep intronic variants are included in our panels and whole exome sequencing.

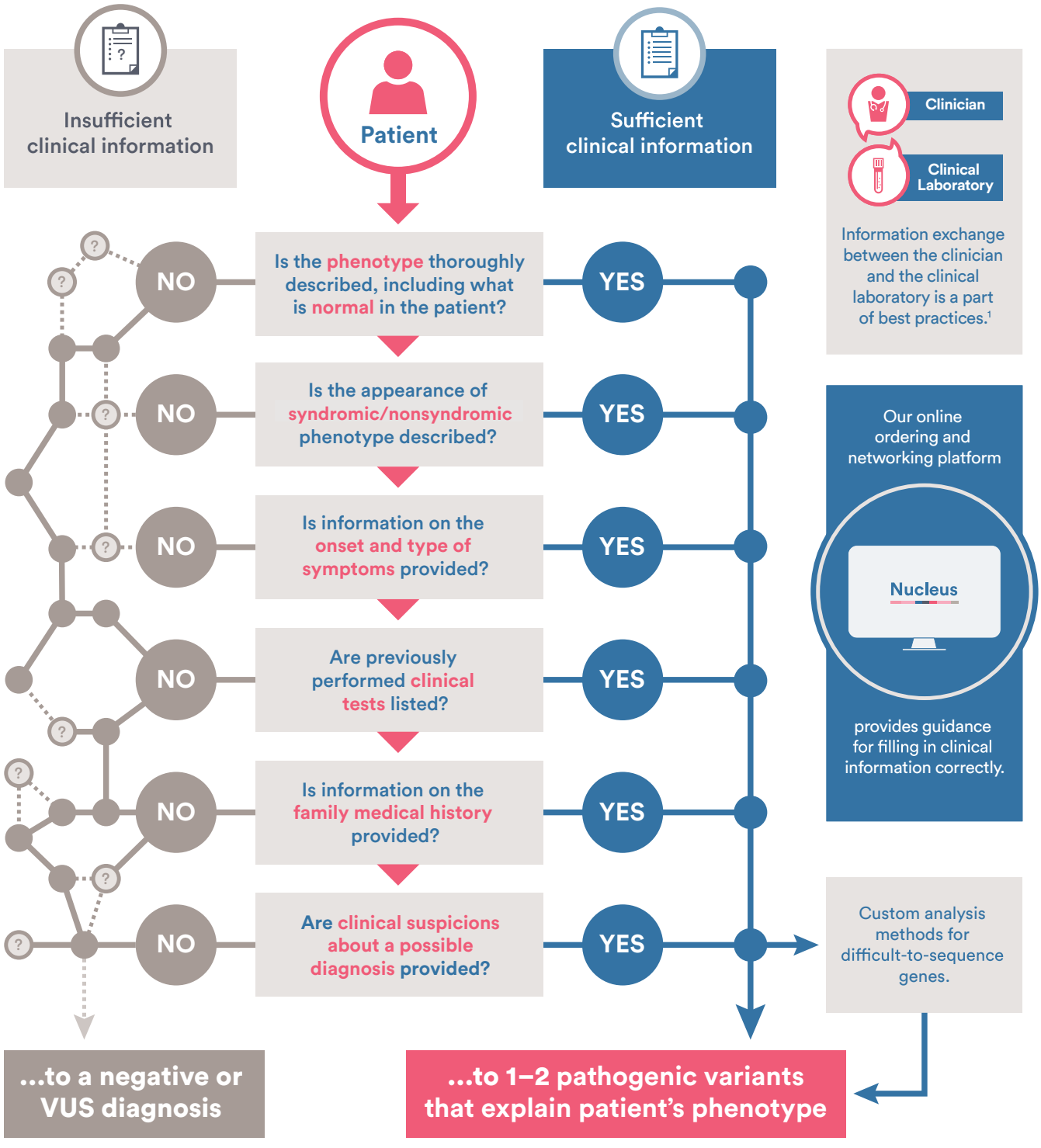
	Blueprint Genetics
SNV detection	99.7%
Indel detection	1–10 bp 96.9%, 11–20 bp 98.9%, 21–30 bp 100%, 31–40 bp 100%
CNV detection	1 exon del 92.3%, 2 exon del 100%, 3 exon del 93.3%, microdeletion syndromes 100%

	Results	Blueprint Genetics Advantage
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.	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.	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.	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.	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.

SNV, single nucleotide variant; CNV, copy number variant.

Clinical information can lead to finding a variant that might otherwise be missed

From 20,000–35,000 possible variants explaining the phenotype...



[1] Bush et al on behalf of the ACMG SELI committee. *Genet Med.* 2018;20(2):169-171.