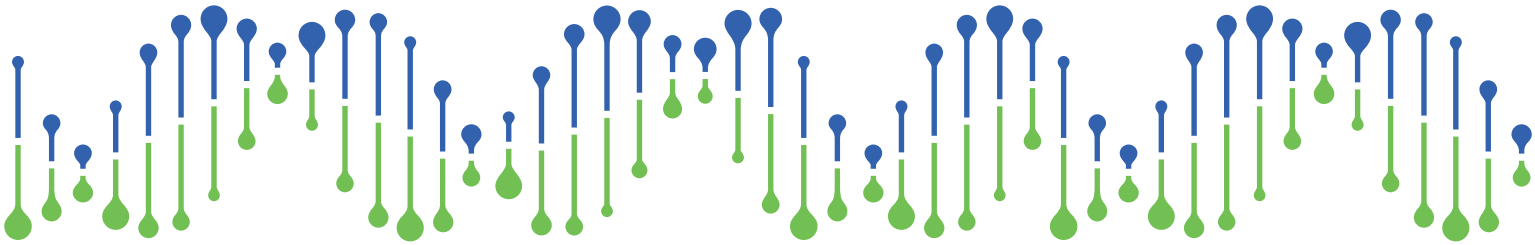

Cell3™ Target: Nexome

Clinically enhanced exome capture designed to detect SNVs, indels and CNVs in a single, clinical-grade assay.

Highlights

Comprehensive clinically relevant content
Maximise your diagnostic yield with coverage of important clinical targets from the major genetic databases (RefSeq, CCDS, GenCode and ClinVar) including CNVs and non-coding regions associated with prenatal and postnatal disease.

Streamlined workflow
Validate and run one workflow for all variants including SNVs, Indels and CNVs in a single, clinical-grade assay giving you the confidence to replace your array and MLPA-based CNV analysis.

Robust calling of all variants
Confidently call SNVs, Indels and CNVs with high recall and precision from as little as 10ng of DNA, unlocking prental or limited samples without compromising on quality or robustness.

Maximise diagnostic yield without increasing sequencing costs
Call many more variants and increase your diagnostic yield without increasing the amount of sequence per sample.

Introduction

Current clinical cytogenomics workflows consist of multiple tests including Chromosomal Microarrays (CMA), Multiplex Ligation Probe Amplification (MLPA), fluorescent in situ hybridization (FISH) and next generation sequencing (NGS) Exome Sequencing. Undertaking multiple tests with different technologies increases associated test cost, time to result and has negative implications for the required amount of sample input and the cost to process a given sample.

Cell3 Target: Nexome is a clinically enhanced human exome capture panel enabling laboratories to detect all variants (SNVs,Indels and CNVs) in a single, clinical-grade test, suitable for constitutional postnatal and prenatal analysis.

Combining our experience of exome panel design and input from experts in the field, Nexome has been augmented with baits for genes associated with prenatal and postnatal disease and additional pharmacogenomics (PGx) markers to maximise coverage of clinically relevant targets for constitutional genetics. Designed to cover exon level deletions and duplications as well as SNVs and indels, it provides an exome alternative to CMA and MLPA based CNV analysis.

NONACUS
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Coverage of clinically relevant genes

Larger than most exome products, Cell3 Target: Nexome targets not only the protein coding regions of the human genome but clinically relevant non-coding regions and has probe enhancement to enable CNV detection at loci with known gene and exon level rearrangements. It is designed to offer excellent coverage of CCDS, GENCODE, RefSeq and ACMG73 databases (Figure 1) with enhanced probes for clinically relevant genes and CNV calling.

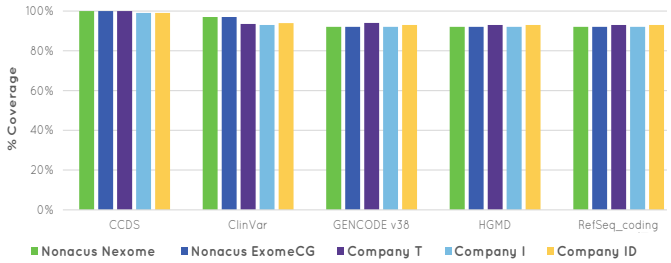

Figure 1: Coverage of different databases by Nexome compared to other commercially available kits.

The clinically enhanced regions include;

- addition RefSeq transcripts across the OMIM morbid set of 4090 genes[1]
- exon level deletions and duplications currently targeted by commercially available kits, such as MLPA, enabling SNV calling and CNV-detection in a single test
- genes associated with prenatal phenotypes (fetal anomalies) for prenatal diagnosis
- transcripts and extra exons associated with Early Infant Epileptic Encephalopathy (EIEE) genes for enhanced epilepsy diagnosis

As well as enhanced regions, the Nexome panel includes:

- promoter, 5' and 3' UTR sequences for current OMIM morbid genes
- non-coding, disease-causing variants[2,3]
- pharmacogenomic (PGx) markers for drug response prediction
- sample tracking variants

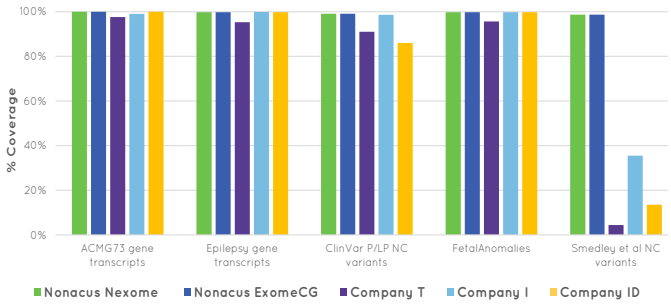

Figure 2: Coverage of targeted gene panels and variant sets by Nexome compared to other commercially available kits

Precision and recall of SNVs and indels

Nexome covers almost 30% more variants present in the HG001 human genome reference standard than other exome captures and at comparable precision and recall for both SNVs and indels (Figures 3 and 4).

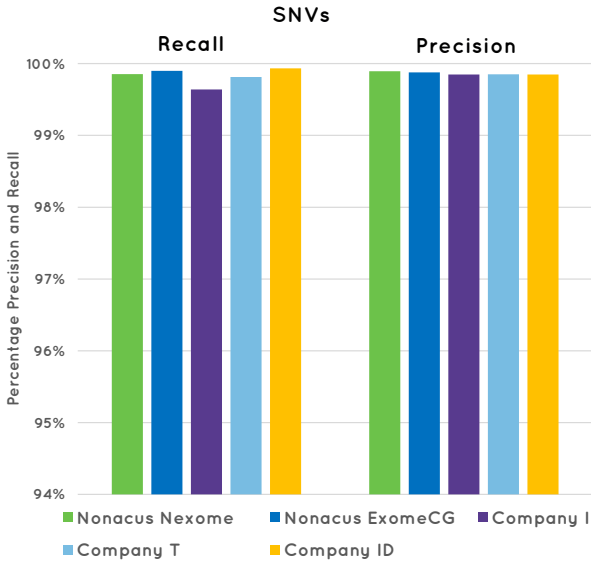

Figure 3a: Precision and recall of SNVs detected by Nexome and other commercially available exome panels.

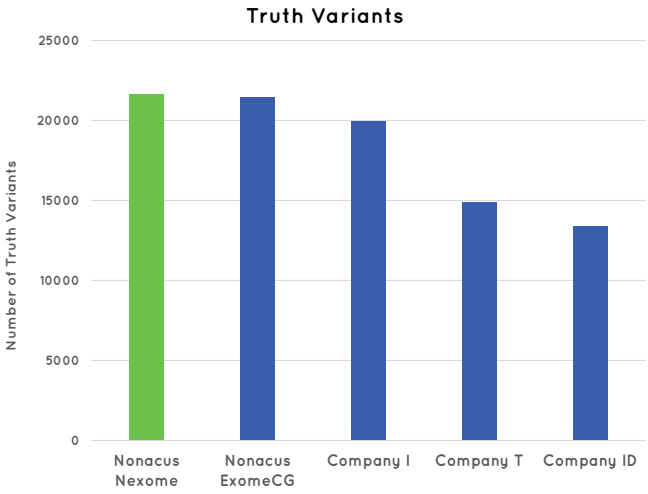

Figure 3b: Total number of truth variants (SNVs) detected by Nexome and other commercially available exome panels.

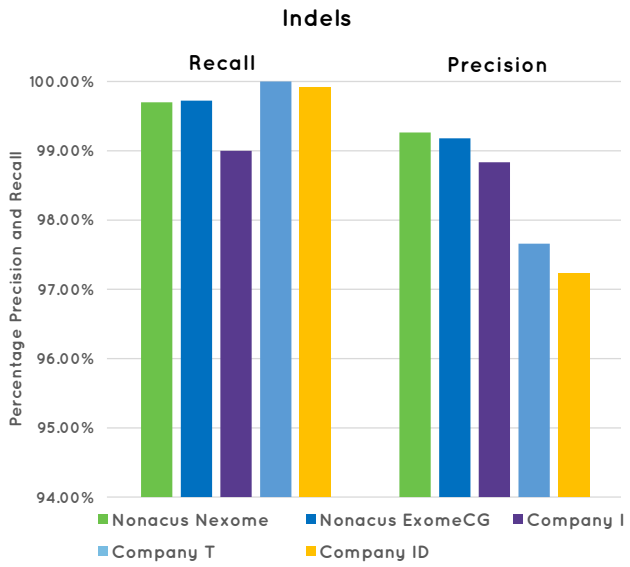

Figure 4a: Precision and recall of Indels detected by Nexome and other commercially available exome panels.

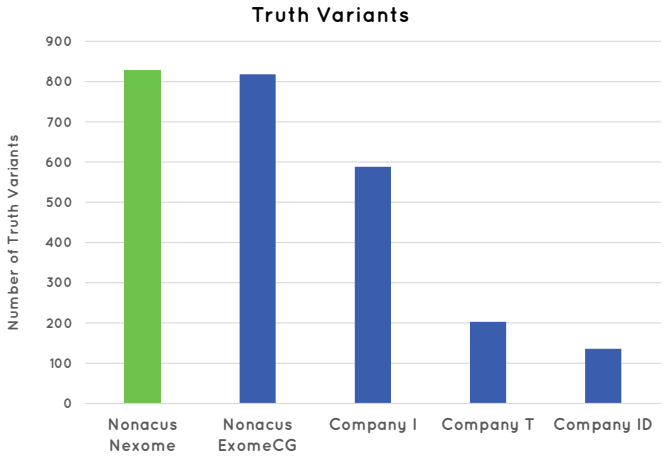

Figure 4b: Total number of truth variants (Indels) detected by Nexome and other commercially available panels.

Reliable CNV calling

Enhanced coverage across the whole panel means that Cell3 Target Nexome is capable of detecting CNVs with sizes spanning from just a few exons up to multiple contiguous genes (~100 bp–40 Mb); detection of clinically relevant events is achieved with superior precision and recall (Tables 1a and 1b).

Table 1a. Detection of MLPA-confirmed CNVs.

Affected Gene	CNV region	CNV size (bp)	CNV exons	CNV type	Bayes factor
FBN1	exons 29-65	74632	37	deletion	320.0
BRCA1	exons 1-23	77841	24	deletion	190.0
FBN1	exons 1-17	142063	18	deletion	300.0
BRCA1	exons 1-17	57876	18	deletion	200.0
BRCA1	exons 8-13	17956	6	deletion	40.4
BRCA1	exons 8-13	17956	6	deletion	82.4
BRCA2	exons 5-7	513	3	deletion	22.1
NSD1	exons 7-9	6034	3	deletion	34.5
FBN1	exons 60-62	3934	3	deletion	32.8
NSD1	exons 1-3	58095	3	deletion	54.8
BRCA2	exons 1-2	1054	2	deletion	28.3
BRCA1	exons 7-8	311	2	deletion	4.7
BRCA1	exons 8-9	1444	2	deletion	7.5
BRCA1	exon 16	211	1	deletion	14.5
BRCA1	exon 20	84	1	deletion	9.4

Table 1b. Detection of CMA-confirmed multi-gene CNVs.

CNV region	CNV size (Mb)	CNV genes	CNV type	Bayes factor
13q14.2q32.1	42.0	367	deletion	2410
4p16.3p15.2	22.9	339	deletion	4620
20q11.22q13.12	11.3	244	deletion	7000
7p14.1p11.2	15.9	182	deletion	5040
1p36.32	3.7	140	deletion	2710
22q11.21	2.0	83	deletion	2890
8q23.1q24.12	11.8	71	deletion	1330
22q11.21	2.2	64	duplication	1430
11p12p11.2	2.3	54	deletion	1240
7q11.23	1.4	38	deletion	2080
15q11.2	0.9	31	deletion	494
17p12	1.3	24	deletion	275
14q22.1	0.7	20	deletion	508
15q11.2	0.5	4	duplication	370
13q12.11	0.2	2	deletion	75

High on-target rates deliver more efficient sequencing

Despite being larger than other commercially available exome products, Cell3 Target: Nexome delivers >94% of on target reads. So, for approximately the same amount of sequence data generated per sample, users can detect many more clinically relevant variants

Table 2: Mb required to achieve mean coverage of 100x for Nexome and other commercially available exome products. *[Comparable data was generated by randomly down sampling the available sequencing reads for all samples to 100x mean coverage depth and analysing through the Nonacus analysis pipeline].*

	Panel Size (Mb)	Percentage target covered at 1x	Gb Required for mean 100x coverage	Percent Bases on or near bait
Nexome	51.90	98.78%	6.63	94.18%
Exome CG	51.60	98.78%	6.57	94.07%
Company T	36.70	97.42%	6.85	85.89%
Company I	45.20	98.15%	7.16	86.18%
Company I.D	34.10	98.49%	6.04	93.09%

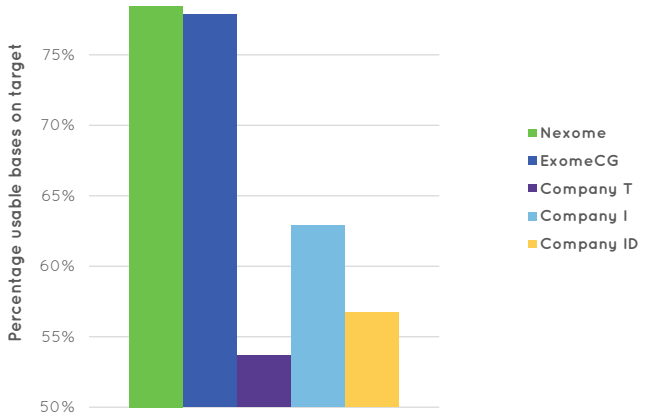

Figure 5: Percentage of usable bases on target for Nexome and other commercially available exome products.

Simple, automatable protocols

The kit contains all reagents for both library preparation and hybridization and capture and enables laboratories to validate and run just one workflow for all variants including SNVs, Indels and CNVs in a single, clinical grade assay giving you the option to replace your array and MLPA-based CNV analysis. The Cell3 Target workflow is simple and easy and requires as little as 10ng of DNA. Taking less than 10 hours, with less than 2 hours hands-on time, itis designed with multiple stop points to provide flexibility within laboratory processing.

Library preparation can be run manually or automated (up to 96 samples in a single batch). Indexes are available for up to 384 samples to facilitate high through put laboratories, allow for flexible batch sizes and provide scalability across all Illumina sequencers.

Summary

Cell3™ Target: Nexome is an hybridization and capture panel designed to target 51.9 Mb of clinically relevant genes for pre and postnatal analysis. Its robust performance enables laboratories to confidently call SNVs, Indels and CNVs with high recall and precision. This provides the option to replace array and MLPA-based CNV analysis with just one validated workflow for all variants in a single, clinical-grade assay.

The content has been carefully selected to maximise diagnostic yield and the high usable on-target rate means that many more variants can be called for the same amount of sequencing data when compared with other exome capture products.

Learn more

To learn more about Cell3™ Target: Nexome Panel and to download the protocols, application notes and white papers please visit: **www.nonacus.com**

References

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2. Smedley D et al. 2016; A Whole-Genome Analysis Framework for Effective Identification of Pathogenic Regulatory Variants in Mendelian Disease. Am J Hum Genet. 99(3): 595-606 (2016). https://doi.org/10.1016/j.ajhg.2016.07.005

3. Landrum, MJ et al. ClinVar: improving access to variant interpretations and supporting evidence, Nucleic Acids Research, Volume 46, Issue D1, (2018) D1062–D1067. https://doi.org/10.1093/nar/gkx1153

Ordering information

Product	Catalogue No.
Cell3™ Target: Nexome (16 Sample)	C3230NX
Cell3™ Target: Nexome (96 Sample) (Includes fragmentation library prep kit (for gDNA (blood or saliva) or FFPE DNA))	C3231NX

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