Patient Name	Date of Birth	Test	Genetic Sex
Albana Qemali	Nov 13 2013	202639147 / 70147	Female

Results: NEGATIVE

No pathogenic or likely pathogenic variants sufficient to cause disease were identified that have been associated with the clinical symptoms provided.

No variants were identified in the American College of Medical Genetics and Genomics (ACMG) list of genes to be reported as secondary findings.

However, variants were identified in this analysis that were not considered to impact the interpretation of this report and are listed in the supplementary tables below: 'Previously Reported Results' and 'Regions of Homozygosity (ROH)'.

Ordering Physician
Richard Frye

NPI
1891730461

Provider
Neurodevelopmental Precision Medicine

Test Performed
Trio

Type
Blood

Collected
Nov 21 2023

Received
Nov 24 2023

Processed
Jan 18 2024

Additional Information

The patient's clinical notes mentioned that previous genetic testing from another diagnostic laboratory identified variants in the following genes: *NGLY1, CLPB, DHTKD1, CSGALNACT1, ACAD9, CPS1, COQ4, BSCL2*. However, these variants could not be identified with the information provided and, therefore, are not included in this report. This report includes analysis and classification of any variants that meet our reporting criteria.

Follow Up Recommendations

Genetic counseling is recommended to review both positive and negative results, as well as secondary and incidental findings, if identified. Test results may benefit from periodic reevaluation for new clinical associations to variants and updated variant classification.

Consider family studies for UPD should there be any clinical correlation with conditions that arise due to UPD of chromosome 11.

Indication for Testing (Phenotype)

Behavioral abnormality, Cognitive impairment, Arachnoid cyst, Delayed speech and language development, Insomnia, Feeding difficulties, Recurrent singultus, Autism, EEG abnormality, Skeletal muscle atrophy, Hypotonia, Hyporeflexia, Encephalopathy, Global developmental delay, Recurrent ear infections

Likely Diagnostic Findings

This section contains variant(s) in genes partially or fully consistent with the clinical phenotype.
No findings were identified.

ACMG Secondary Findings

This section of the report includes variants identified in a list of genes recommended by the American College of Medical Genetics and Genomics (ACMG) for reviewing and reporting secondary findings.
No variants meeting the ACMG recommendations for reporting secondary findings were identified. Note that in some cases variants in genes listed by the ACMG may be reported in other sections of this report if the associated disorder is consistent with the patient's phenotype.

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Regions of Homozygosity (ROH)

Regions of homozygosity, also known as loss of heterozygosity (LOH) or absence of heterozygosity (AOH), are genomic segments showing a continuous stretch of homozygous variants with no statistically significant intervening heterozygous variants. ROH may be representative of uniparental disomy (UPD), ancestral homozygosity or regions inherited from a more recent common ancestor that are identical by descent (IBD). If the analysis includes sequence analysis, these regions will be interrogated for homozygous pathogenic or likely pathogenic variants and reported as indicated. Consider family studies for UPD if there is clinical correlation with the reported imprinted chromosome. Reporting ROH follows the ACMG guidelines for ROH and UPD (PMID: 23328890, 32296163).

LOCATION	VARIANT	DISEASE / INHERITANCE
11p11.2p11.11 NC_000011.10: g.45,800,981_51,182,410	5.38 Mb	Region of Homozygosity

Previously Reported Results

This section of the report includes variants reported by previous genetic testing, either in this individual or in a family member, that do not otherwise meet our clinical diagnostic reporting criteria. Disease associations for the gene(s) in this table are not provided in the absence of clinical and/or molecular correlation. Variants are only included in the report if sufficient variant information was provided at the time of testing. For previously reported structural variants, if identified, see additional comments below. Any previously reported variants that meet our clinical diagnostic reporting criteria will appear in other sections of this report. Any differences in variant nomenclature from previous results may be due to differences in reference transcript, genome build, testing methodology, and/or bioinformatics platforms used.

LOCATION	VARIANT
MTHFR NM_005957.5	c.1286A>C p.Glu429Ala rs1801131 Homozygous in proband Heterozygous in father Heterozygous in mother
MTRR NM_002454.3	c.66A>G p.Ile22Met rs1801394 Heterozygous in proband Not detected in father Heterozygous in mother

Sample Information

PATIENT	SEX	DATE OF BIRTH	SPECIMEN TYPE	DATE COLLECTED	DATE RECEIVED
Proband Albana Qemali 202639147	F	Nov 13 2013	Blood	Nov 21 2023	Nov 24 2023
Mother 202639129	F	-	Blood	Nov 21 2023	Nov 24 2023
Father 202639138	M	-	Blood	Nov 21 2023	Nov 24 2023

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General Information

The Genomic Unity® Whole Genome Analysis is a whole genome sequence based test designed to identify genetic variants that correlate with the patient's clinical symptoms. This test includes sequence analysis (single nucleotide variants, deletions/insertions, intronic, regulatory and intergenic variants); analysis of copy number variants, duplications, deletions, regions of homozygosity, uniparental disomy, mobile element insertions, inversions, and aneuploidy; mitochondrial genome sequence analysis with heteroplasmy and large deletions; and short tandem repeat expansion analysis in select genes.

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Methods

Whole genome short read sequencing was performed using the Illumina® DNA PCR-Free Prep, Tagmentation followed by next generation sequencing (NGS). Analyses were performed to detect, analyze and report clinically relevant variants using the Variantyx Genomic Intelligence® platform version 3.13.0.0. Orthogonal confirmation is performed as needed by Oxford Nanopore Technologies (ONT) PromethION 24.

Statistics

The sensitivity, specificity and positive predictive value of the assay is greater than 0.99 for single nucleotide variants. The sensitivity and positive predicted value of small insertions and deletions of fewer than 50 base pairs is greater than 0.95 and 0.92, respectively. The analytical sensitivity for copy number variants reported in this assay is greater than 0.80 for variants greater than 300 base pairs, while the clinical sensitivity for copy number variants of any size is greater than 0.96. The clinical sensitivity of this test is greater than 0.99 for pathogenic short tandem repeats.

Report Standards

Variants are reported using Human Genome Variation Society (HGVS) recommendations, when available. Variants are classified using one of five interpretation categories recommended by the American College of Medical Genetics and Genomics (ACMG): pathogenic, likely pathogenic, uncertain, likely benign, and benign (PMID: 25741868). Benign and likely benign variants are typically not reported. Variants of uncertain clinical significance are reported in select cases where there is a strong clinical correlation to the provided clinical symptoms of the patient and/or the family history. The genetic results are interpreted in the context of the provided personal medical and family history. Accurate interpretation of results is dependent on complete and accurate clinical information. Variants of uncertain clinical significance will only be reported if found to be associated with patient phenotype. Variants of uncertain clinical significance will not be reported in targeted analysis (phenotypic based analyses) unless sufficient clinical information was provided.

Regions of homozygosity (ROH) and uniparental disomy (UPD) are detectable with this analysis. ROH for non-imprinted autosomal chromosomes and the X chromosome is reported for regions greater than or equal to 10 Mb. ROH is reported for regions greater than or equal to 5 Mb for imprinted chromosomes (6, 7, 11, 14, 15 and 20). Multiple regions of ROH can be indicative of shared common ancestry or consanguinity. Although the results of ROH are not interpreted, variants in genes associated with autosomal or X-linked recessive conditions related to the patient phenotype or severe early onset disorders will be reported if detected. UPD will only be determined when testing is run as a trio analysis (i.e. both parental samples are available). UPD will be reported for clinically relevant regions on the imprinted chromosomes. If relevant, additional testing may aid in diagnosis.

Previously Reported Variants

Variantyx reviews clinical notes and copies of previous test results provided with the test submission. The detection and reporting of previously reported results depends on the provided detailed variant information accompanying the test requisition and on Variantyx reporting criteria. Of note, discordant results may be due to differences in technical methods or due to reference sequence errors.

Annotations

To maintain the most up-to-date annotations, the Variantyx database is updated quarterly and, as a result, variant classification and/or interpretation may change over time as more information becomes available. Sequence variation is compared to reference data using genome build GRCh38 and the lab cannot guarantee the accuracy of this data nor the accuracy of databases listed below. The following databases and tools are included in Variantyx Genomic Intelligence® platform:
1. Disease association: HGMD Professional (http://www.hgmd.cf.ac.uk/), ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), OMIM (http://www.omim.org/), Orphanet (www.orpha.net/), GeneTests (https://www.genetests.org/).
2. Population frequencies: gnomAD (http://gnomad.broadinstitute.org/), dbSNP (http://www.ncbi.nlm.nih.gov/SNP/), ensembl (www.ensembl.org/), 1000 Genomes Project (www.1000genomes.org/), DGV (http://dgv.tcag.ca/) and the Variantyx allele frequency database (http://variantyx.com/).
3. In silico pathogenicity prediction: REVEL (PMID: 36413997, 27666373)
4. Gene Essentiality: According to published work 10.1371/journal.pgen.1003484
5. Gene tolerance: RVIS score, according to published work 10.1371/journal.pgen.1003709
6. Haploinsufficiency and Triplosensitivity using ClinGen Dosage Sensitivity Map(https://dosage.clinicalgenome.org)
7. Pathogenicity scoring - ACMG classification for SV based on ClinGen CNV Pathogenicity Calculator (https://cnvcalc.clinicalgenome.org/cnvcalc/)
8. Human Genome Variation Society (http://varnomen.hgvs.org/)
9. International System for Human Cytogenomic Nomenclature 2020 (ISCN 2020)
10. MITOMAP - A human mitochondrial genome database (https://mitomap.org/MITOMAP)
11. SFARI - Simons Foundation Autism Research Initiative (https://www.sfari.org/)

A glossary of terms can be found at https://www.variantyx.com/glossary/

Single Nucleotide Variants

Single nucleotide variants and small deletion/insertions (<50 bp) are reported if there is clinical correlation to the patient's clinical symptoms.

Structural Variants

Structural variants classified as pathogenic, likely pathogenic and uncertain are reported if there is clinical correlation with the genes and or region. Parental inheritance will be reported for structural variants when both parents are available for testing.

Short Tandem Repeats

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Short tandem repeats (e.g. trinucleotide repeat expansions) in pathogenic ranges, when identified and reported for the following genes: *AFF2, AR, ARX, ATN1, ATXN1, ATXN2, ATXN3, ATXN7, ATXN8OS, ATXN10, C9ORF72, CACNA1A, CNBP, CSTB, DMPK, DIP2B, FGF14, FMR1, FOXL2, FXN, GIPC1, GLS, HTT, JPH3, LRP12, NOP56, NOTCH2NLC, PABPN1, PPP2R2B, RFC1, SOX3, TBP, PHOX2B, TCF4, VWA1, ZIC2*.

Mitochondrial Variants
Mitochondrial variants are reported in the mitochondrial genome if they are pathogenic/likely pathogenic, or a variant of uncertain clinical significance if there is correlation to the patient's clinical symptoms. Heteroplasmy is reported for single nucleotide variants if above 5%, however, heteroplasmy is not reported for large deletions and duplications are not detected. The false negative rate for mitochondrial large deletions have not been determined.

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Limitations

Technical Limitations

A negative result from this analysis does not rule out the possibility that the tested individual carries a rare, unexamined pathogenic variant or a pathogenic variant in an undetectable region. All next generation sequencing (NGS) technologies, including whole genome sequencing analysis, may generate false positive and false negative results. Results are applicable to the tissue type used for this sequence test and may not reflect the variation in other tissue types. The minimum average on-target read depth is 30X. At the variant level, read depths fewer than 8X are not reported, which for any given test is approximately 0.5% of the reference genome (GRCh38). Each individual may have slightly different coverage yield distributions within the genome. While most structural variants are detectable, some genetic aberrations, such as gross genomic rearrangements or variants in portions of genes with highly homologous pseudogenes (including HBA1/HBA2), mosaicism (with the exception of full chromosomal mosaic aneuploidy), are identified with a lower efficiency. Deletions and duplications in the range of 50-300 base pairs are detected with a reduced sensitivity (0.19). For short tandem repeat expansions, due to possible somatic expansion in the tissue being tested and/or sampling bias, the median size of the expanded allele may not be representative of the actual event in the biologically relevant tissue. In addition, this test detects direct DNA sequence changes, and not indirect changes and aberrations, such as gene expression, epigenetic modifications, fusion, chromosome conformational changes, and other unknown abnormalities. This test may not detect variants in regions homologous to pseudogenes. Variants are not reported if they are not uniquely mappable, are of low coverage or are otherwise determined to be of low quality. Variantyx is not responsible for specimen errors (e.g. labeling, extraction) of samples received that may have occurred prior to our receipt. This test will not typically report variants related to infertility, carrier status of autosomal recessive disease, carrier status of X-linked recessive diseases, or variants that increase a statistical risk for a disease. Variants are not confirmed unless stated and confirmations are not included in published turnaround times.

Annotation Limitations

Sequence variation is compared to reference data using genome build GRCh38 and the lab cannot guarantee the accuracy of this data nor the accuracy of databases listed in the 'Annotations' section of this report.

Parental Analysis

When parental samples are submitted, they are used in the evaluation of the patient (proband) only and no specific parental results are issued under the family member's name, however, parental inheritance is reported for the proband and therefore will reveal parental results for select genes.

ACMG Secondary Findings

The American College of Medical Genetics and Genomics (ACMG) recommends reporting pathogenic and likely pathogenic variants in a list of genes in both a gene-specific and variant-specific manner. Variantyx evaluates the secondary findings list of genes V3.2, which can be found on the Variantyx website (ACMG Secondary Findings). These variants are not typically reviewed during routine processing of patient samples, but are actively sought and reported to the patient. The ACMG recommends reviewing variants in the genes in their recommended list because the genes are related to conditions that are considered 'actionable', meaning that there are steps that can be taken to mitigate the onset or severity of the clinical outcome. It is important to understand that it is possible to have a pathogenic variant, but to have it not detected by the assay. In addition, variants of uncertain significance are not reported in these genes. If a variant is of uncertain significance, and later is considered pathogenic, it cannot be determined without a reanalysis of the data. Variantyx secondary findings are not reported with this assay. ACMG secondary findings are reported if opted-in.

Incidental Findings

Incidental findings are likely pathogenic/pathogenic variants detected unexpectedly during routine processing of patient samples. These variants are in genes apparently unrelated to the patient's reported phenotype, but with some degree of clinical actionability. These genes are not restricted to a specific list (such as the ACMG Secondary Findings list), but are similar in that they could impact medical management and decision making. Incidental findings are not actively sought and therefore all incidental findings may not be identified during processing. Variants of uncertain clinical significance are not reported in these genes. Some examples of these findings are pathogenic/likely pathogenic variants in high penetrance oncogenic related genes, polycystic kidney related genes with increased surveillance recommendations, and/or genes associated with conditions for which possible treatment is available.

Reanalysis and Reclassification of Variants

Variant classification and/or interpretation may change over time as more information becomes available on the clinical symptoms associated with the genes/variants. Variants of uncertain significance identified by sequencing are typically not reported in this test, however may be reported when they are rare and in genes associated with diseases with symptoms that partially or completely correlate with the patient's disease spectrum and severity. Variants of uncertain significance are neither pathogenic nor benign, but are likely to be reclassified as such over time as more evidence becomes available. Variants in 5' or 3' untranslated regions are typically not reported. New associations of symptoms to diseases and genes are likely to occur with time. In addition, if the clinical symptoms reported to Variantyx were incomplete or if there has been a change in symptoms, new correlations may be revealed upon reanalysis. Therefore, it is recommended that results be reinterpreted periodically to determine if they may be related to disease.

Use of Test Results by Clinician

Results should be interpreted by the ordering clinician in the context of the patient's personal medical and family history. Genetic counseling is recommended to assist in the interpretation of genetic results. Genetic counselors in your area may be found by visiting the National Society of Genetic Counselors (NSGC) website at https://www.nsgc.org/ or at https://www.findageneticcounselor.com/.

FDA Notes

This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 as qualified to perform high complexity laboratory testing. The US Food and Drug Administration (FDA) does not require this test to go through premarket clearance. This lab developed test (LDT) was

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developed and its performance characteristics determined by Variantyx, Inc. to be used for clinical purposes and not as investigational or as research. These results should be used in the context of the patient's clinical findings and family history and not as the sole basis for diagnosis and/or treatment.

Electronically signed by
Christian Antolik PhD, FACMG

Patient Name	Date of Birth	Test	Genetic Sex
Albana Qemali	Nov 13 2013	202639147 / 70147	Female

Patient Name	Date of Birth	Test	Genetic Sex
Albana Qemali	Nov 13 2013	202639147 / 70147	Female

Ordering Physician	Provider	Type	Received
Richard Frye	Neurodevelopmental Precision Medicine	Blood	Nov 24 2023
NPI	**Test Performed**	**Collected**	**Processed**
1891730461	Trio	Nov 21 2023	Jan 18 2024

Pharmacogenomics Results

Antidepressants

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Amitriptyline Elevil®	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.
Citalopram Celexa®	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Clomipramine Anafranil®	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.
Desipramine Norpramin®	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.
Doxepin Sinequan®	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Doxepin Sinequan®	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.
Escitalopram Lexapro®	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Fluvoxamine Luvox®	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Imipramine Tofranil®	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.
Nortriptyline Pamelor®	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.

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Psychology / Psychiatry (Antidepressants, Anti-psychotics)

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Amphetamine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Aripiprazole	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Aripiprazole Lauroxil	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Atomoxetine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Brexpiprazole	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Citalopram Celexa®	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Clozapine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Iloperidone	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Pimozide	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Thioridazine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Venlafaxine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Vortioxetine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Perphenazine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Amitriptyline Elevil®	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.
Amoxapine	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.
Clomipramine Anafranil®	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.
Desipramine Norpramin®	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.
Doxepin Sinequan®	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Doxepin Sinequan®	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.
Escitalopram Lexapro®	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Fluvoxamine Luvox®	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Imipramine Tofranil®	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.
Nortriptyline Pamelor®	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.

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Paroxetine	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.
Protriptyline	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Risperidone	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Trimipramine	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. May alter systemic concentrations.

Hematology (Anticoagulants)

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Clopidogrel	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Warfarin	CYP2C9 (*1/*2)	Intermediate Metabolizer	Data Support Therapeutic Management Recommendations. Alters systemic concentrations and dosage requirements. Select initial dosage, taking into account clinical and genetic factors. Monitor and adjust dosages based on INR.
Warfarin	CYP4F2 (*1/*3 (V433M))	Indeterminate	Data Support Therapeutic Management Recommendations. May affect dosage requirements. Monitor and adjust doses based on INR.
Warfarin	VKORC1 (Reference/rs9923231 (-1639G>A))	Indeterminate	Data Support Therapeutic Management Recommendations. Alters dosage requirements. Select initial dosage, taking into account clinical and genetic factors. Monitor and adjust dosages based on INR.
Avatrombopag	CYP2C9 (*1/*2)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. Results in higher systemic concentrations.

Infectious Disease (Antifungals, Antibacterials)

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Efavirenz	CYP2B6 (*1/*1)	Normal Metabolizer	No available recommendation
Dolutegravir	UGT1A1 (*1/*80+*28)	Intermediate Metabolizer	No available recommendation
Raltegravir	UGT1A1 (*1/*80+*28)	Intermediate Metabolizer	No available recommendation
Voriconazole	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation

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Rheumatology (Anti-inflammatory)

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Amifampridine	NAT2 (*6/*6)	Indeterminate	Indeterminate metabolic status. Follow up with additional risk assesment
Amifampridine Phosphate	NAT2 (*6/*6)	Indeterminate	Indeterminate metabolic status. Follow up with additional risk assesment
Azathioprine	TPMT (*1/*1)	Normal Metabolizer	No available recommendation

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Azathioprine	NUDT15 (*1/*1)	Normal Metabolizer	No available recommendation
Celecoxib	CYP2C9 (*1/*2)	Intermediate Metabolizer	No available recommendation
Flurbiprofen	CYP2C9 (*1/*2)	Intermediate Metabolizer	No available recommendation
Piroxicam	CYP2C9 (*1/*2)	Intermediate Metabolizer	Data Support Therapeutic Management Recommendations. Results in higher systemic concentrations. Consider reducing dosage in poor metabolizers.
Cevimeline	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation

Oncology (Targeted therapies, chemotherapy)

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Belinostat	UGT1A1 (*1/*80+*28)	Intermediate Metabolizer	No available recommendation
Capecitabine	DPYD (Reference/Reference)	Normal Metabolizer	No available recommendation
Erdafitinib	CYP2C9 (*1/*2)	Intermediate Metabolizer	No available recommendation
Fluorouracil	DPYD (Reference/Reference)	Normal Metabolizer	No available recommendation
Gefitinib	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Irinotecan	UGT1A1 (*1/*80+*28)	Intermediate Metabolizer	No available recommendation
Mercaptopurine	TPMT (*1/*1)	Normal Metabolizer	No available recommendation
Mercaptopurine	NUDT15 (*1/*1)	Normal Metabolizer	No available recommendation
Thioguanine	TPMT (*1/*1)	Normal Metabolizer	No available recommendation
Thioguanine	NUDT15 (*1/*1)	Normal Metabolizer	No available recommendation
Nilotinib	UGT1A1 (*1/*80+*28)	Intermediate Metabolizer	No available recommendation
Pazopanib	UGT1A1 (*1/*80+*28)	Intermediate Metabolizer	No available recommendation
Tamoxifen	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only. Results in lower systemic active metabolite concentrations. The impact of CYP2D6 intermediate or poor metabolism on efficacy is not well established.

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Neurology (AEDs, antiemetics, dementia medications)

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Brivaracetam	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Clobazam	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Deutetrabenazine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Meclizine	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Support Therapeutic Management Recommendations. May affect systemic concentrations. Monitor for adverse reactions and clinical effect.
Siponimod	CYP2C9 (*1/*2)	Intermediate Metabolizer	Data Support Therapeutic Management Recommendations. Results in higher systemic concentrations. Adjust dosage based on genotype. Do not use in patients with CYP2C9 *3/*3 genotype. Refer to FDA labeling for specific dosing recommendations.
Tetrabenazine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Valbenazine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Donepezil	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Galantamine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation

Anesthesiology (Pain Medications, muscle relaxants, paralytics)

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Codeine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Dronabinol	CYP2C9 (*1/*2)	Intermediate Metabolizer	Data Support Therapeutic Management Recommendations. May result in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Lofexidine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Tramadol	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Carisoprodol	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Diazepam	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation

Patient Name	Date of Birth	Test	Genetic Sex
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Pediatrics (Rare Congenital Diseases)

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Eliglustat	CYP2D6 (*1/*4)	Intermediate Metabolizer	Data Support Therapeutic Management Recommendations. Alters systemic concentrations, effectiveness, and adverse reaction risk (QT prolongation). Indicated for normal, intermediate, and poor metabolizer patients. Ultrarapid metabolizers may not achieve adequate concentrations to achieve a therapeutic effect. The recommended dosages are based on CYP2D6 metabolizer status. Coadministration with strong CYP3A inhibitors is contraindicated in intermediate and poor CYP2D6 metabolizers. Refer to FDA labeling for specific dosing recommendations.

Gynecology

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Flibanserin	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Elagolix	SLCO1B1 (*1/*15 (521C))	Decreased Function	No available recommendation

Gastroenterology (Antacids)

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Metoclopramide	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Pantoprazole	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Dexlansoprazole	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Esomeprazole	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Omeprazole	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation
Rabeprazole	CYP2C19 (*1/*17)	Rapid Metabolizer	No available recommendation

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Cardiology

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Propafenone	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Carvedilol	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Simvastatin	SLCO1B1 (*1/*15 (521C))	Decreased Function	Data Indicate a Potential Impact on Safety or Response. Results in higher systemic concentrations and higher adverse reaction risk (myopathy). The risk of adverse reaction (myopathy) is higher for patients on 80 mg than for those on lower doses.
Metoprolol	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Nebivolol	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Propranolol	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Rosuvastatin	SLCO1B1 (*1/*15 (521C))	Decreased Function	No available recommendation

Transplant Medicine

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Tacrolimus	CYP3A5 (*3/*3)	Poor Metabolizer	No available recommendation

Urology

DRUG	GENE ANALYZED FOR IMPACT	METABOLIZER STATUS	FDA USAGE NOTES
Tolterodine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Darifenacin	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Fesoterodine	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Mirabegron	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation
Tamsulosin	CYP2D6 (*1/*4)	Intermediate Metabolizer	No available recommendation

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Patient Genotype

GENE	GENOTYPE	METABOLIZER STATUS
CYP2B6	*1/*1	Normal Metabolizer
CYP2C19	*1/*17	Rapid Metabolizer
CYP2C9	*1/*2	Intermediate Metabolizer
CYP2D6	*1/*4	Intermediate Metabolizer
CYP3A5	*3/*3	Poor Metabolizer
CYP4F2	*1/*3 (V433M)	Indeterminate
DPYD	Reference/Reference	Normal Metabolizer
NAT2	*6/*6	Indeterminate
NUDT15	*1/*1	Normal Metabolizer
SLCO1B1	*1/*15 (521C)	Decreased Function
TPMT	*1/*1	Normal Metabolizer
UGT1A1	*1/*80+*28	Intermediate Metabolizer
VKORC1	Reference/rs9923231 (-1639G>A)	Indeterminate

General Information

The Genomic Unity® Pharmacogenomics Analysis is a whole genome based test designed to identify common variants associated with drug metabolism and pharmacogenetics response, as outlined by the FDA Table of Pharmacogenetic Associations (2022) and can be found at https://www.variantyx.com/pharmacogenomics. The test includes sequence analysis of known star alleles in 13 genes and copy number variants analysis of selected genes, listed below, that were recommended by the FDA for predicted adverse drug reactions and drug response. This test was designed to provide gene-drug associations and was not designed to diagnose health conditions. The information provided in this report does not contain medication recommendations, and any dosage adjustments or other changes to medications should be evaluated by the ordering healthcare provider with consideration of current prescriptions, family and patient's history, presenting symptoms, and other factors.

Test Description and Methods

Methods

Whole genome short read sequencing was performed using the Illumina® DNA PCR-Free Prep, Tagmentation followed by next generation sequencing (NGS). Analyses were performed to detect, analyze and report pharmacogenomic variants using the Variantyx Genomic Intelligence® platform version 3.13.0.0 augmented with PYPGX V0.15.0 (with MIT license - https://github.com/sbslee/pypgx/blob/master/LICENSE).

Statistics

The detection sensitivity of pharmacogenomic diploid genotypes (star alleles and copy number variants) in this assay is greater than 0.96; specificity and positive predictive values are greater than 0.98.

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Reporting Standards

Pharmacogenomics results and recommendations are based on current guidance and are not reviewed when guidelines are updated. Patients are not notified if changes impact their results. Research data evolves and amendments to the prescribing information of the drugs listed might change over time as more information becomes available.
Sequence variation is compared to reference data using genome build GRCh38 and the lab cannot guarantee the accuracy of this data nor the accuracy of databases listed below. Additional limitations regarding the provided results can be found here (https://public4.pagefreezer.com/browse/FDA/19-04-2022T16:13/https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations).

Pharmacogenomic star allele definitions (apply to SNVs, combinations of SNVs, and structural variants) and the metabolizer status estimation used in this assay are based on the following databases:
1. Clinical Pharmacogenetics Implementation Consortium (CPIC, https://cpicpgx.org/)
2. The Pharmacogene Variation Consortium (PharmVar https://www.pharmvar.org/)
3. PharmKGB resource (https://www.pharmgkb.org/)
4. Arylamine N-acetyltransferases (NATs) database (http://nat.mbg.duth.gr/)
5. FDA's Table of Pharmacogenetic Associations (https://public4.pagefreezer.com/browse/FDA/19-04-2022T16:13/https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations)

Limitations and Disclaimers

Limitations
The detection or absence of results does not replace the need for therapeutic monitoring by healthcare providers. The report is based on the genotype to phenotype mappings and FDA usage guidelines and includes a set of specific genes, star alleles, and select copy number variants as described below. This test will not detect all known variants that result in altered gene activity and drug metabolism. The patient's unique genotype is only one factor used in the evaluation of drug metabolism, concentration and response. In addition, this report is limited to certain pharmacogenetic associations only and does not include all of the information necessary for safe and effective use of a drug. For example drug-drug interactions may alter the metabolizer phenotype.
Inconclusive results may be due to low coverage or poor quality and therefore the genotype(s) cannot accurately be determined.

Technical Limitations
The absence of a positive test result for all variants listed may result in the default assignment of a *1 (wild-type) status with exception of *4 for the *NAT2* gene, *38 for the *CYP2C19* gene, and "Reference" for the *VKORC1* gene. Only listed alleles are tested, and absence of a detected allele does not rule out the possibility of sensitivity to a specific drug due to the presence of other variants or other environmental factors. When two or more pharmacogenomic star alleles are detected on the same haplotype, they are prioritized based on the impact on the metabolizer status defined in CPIC/PharmVar and the most impactful (or one of the equally impactful) is reported. Additional genetic testing might uncover other functional variations that the individual may carry that also affect the medication response, but were not detected in this analysis. This test uses statistical genotype imputation, based on population data, for phasing of variants. Therefore, a misassignment of phasing may result in erroneous assignment of star allele status.

Use of Test Results by Clinician
Healthcare providers should refer to FDA-approved labeling for prescribing information, including monitoring instructions and information on other factors that may affect drug concentrations, benefits, and risks. Results should be interpreted by the ordering clinician in the context of the patient's personal medical and family history.

FDA Notes
This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 as qualified to perform high complexity laboratory testing. The US Food and Drug Administration (FDA) does not require this test to go through premarket clearance. This lab developed test (LDT) was developed and its performance characteristics determined by Variantyx, Inc. to be used for clinical purposes and not as investigational or as research. These results should be used in the context of the patient's clinical findings and family history and not as the sole basis for diagnosis and/or treatment.

Patient Name	Date of Birth	Test	Genetic Sex
Albana Qemali	Nov 13 2013	202639147 / 70147	Female

Genes and Alleles Tested

GENE	ALLELES TESTED
CYP2B6	*1 (reference), *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *17, *18, *19, *20, *21, *22, *23, *24, *25, *26, *27, *28, *29 (CYP2B7-CYP2B6 hybrid), *30 (CYP2B6-CYP2B7 hybrid), *31, *32, *33, *34, *35, *36, *37, *38, and copy number variations (*xN).
CYP2C9	*1 (reference), *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *17, *18, *19, *20, *21, *22, *23, *24, *25, *26, *27, *28, *29, *30, *31, *32, *33, *34, *35, *36, *37, *38, *39, *40, *41, *42, *43, *44, *45, *46, *47, *48, *49, *50, *51, *52, *53, *54, *55, *56, *57, *58, *59, *60, *61, *62, *63, *64, *65, *66, *67, *68, *69, *70, *71
CYP2C19	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *17, *18, *19, *22, *23, *24, *25, *26, *28, *29, *30, *31, *32, *33, *34, *35, *36 (Whole gene deletion), *37 (Partial gene deletion), *38 (reference), *39
CYP2D6	*1 (reference), *2, *3, *4, *5 (Whole gene deletion), *6, *7, *8, *9, *10, *11, *12, *13 (CYP2D7-CYP2D6 hybrid), *14, *15, *17, *18, *19, *20, *21, *22, *23, *24, *25, *26, *28, *29, *30, *31, *33, *34, *35, *36 (CYP2D6-CYP2D7 hybrid), *37, *38, *39, *40, *41, *42, *43, *44, *45, *46, *47, *48, *49, *50, *51, *52, *53, *54, *55, *56, *57, *58, *59, *60, *61 (CYP2D6-CYP2D7 hybrid), *62, *63 (CYP2D6-CYP2D7 hybrid), *64, *65, *68 (CYP2D6-CYP2D7 hybrid), *69, *70, *71, *72, *73, *74, *75, *81, *82, *83, *84, *85, *86, *87, *88, *89, *90, *91, *92, *93, *94, *95, *96, *97, *98, *99, *100, *101, *102, *103, *104, *105, *106, *107, *108, *109, *110, *111, *112, *113, *114, *115, *116, *117, *118, *119, *120, *121, *123, *124, *125, *126, *128, *129, *130, *132, *133, *134, *135, *136, *137, *138, *140, *141, *142, *143, *144, *145, and copy number variations (*xN)
CYP3A5	*1 (reference), *3, *6, *7, *8, *9
CYP4F2	*1 (reference), *2, *3 (V433M)
DPYD	Reference, c.1905+1G>A (*2A), c.1898delC (*3), c.1601G>A (*4), c.1627A>G (*5), c.2194G>A (*6), c.295_298delTCAT (*7), c.703C>T (*8), c.85T>C (*9A), c.2657G>A (*9B), c.2983G>T (*10), c.1003G>T (*11), c.1156G>T (*12), c.1679T>G (*13), c.1129-5923C>G, c.1236G>A (HapB3), c.2846A>T, c.557A>G, c.62G>A, c.496A>G, c.1218G>A, c.1896T>C, c.46C>G, c.61C>T, c.313G>A, c.343A>G, c.451A>G, c.498G>A, c.601A>C, c.632A>G, c.775A>G, c.868A>G, c.929T>C, c.934C>T, c.967G>A, c.1024G>A, c.1057C>T, c.1108A>G, c.1181G>T, c.1180C>T, c.1260T>A, c.1278G>T, c.1294G>A, c.1314T>G, c.1349C>T, c.1358C>G, c.1403C>A, c.1475C>T, c.1484A>G, c.1519G>A, c.1543G>A, c.1577C>G, c.1615G>A, c.1682G>T, c.1775G>A, c.1774C>T, c.1777G>A, c.1796T>C, c.1905C>G, c.1906A>C, c.1990G>T, c.2021G>A, c.2161G>A, c.2186C>T, c.2195T>G, c.2279C>T, c.2303C>A, c.2336C>A, c.2482G>A, c.2582A>G, c.2623A>C, c.2639G>T, c.2656C>T, c.2872A>G, c.2915A>G, c.2921A>T, c.2933A>G, c.2978T>G, c.2977C>T, c.3049G>A, c.3061G>C, c.3067C>A, c.525G>A, c.1371C>T
NAT2	*4 (reference), *5, *6, *7, *10, *11, *12, *13, *14, *17, *18, *19, *20, *21, *22, *23, *24, *25
NUDT15	*1 (reference), *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *17, *18, *19, *20
SLCO1B1	*1 (*1A, reference), *37 (*1B), *2, *3, *4, *5 (521C), *6, *7, *8, *9, *10, *11, *12, *13, *14, *15 (521C), *16, *19, *20, *23, *24, *25, *26, *27, *28, *29, *30, *31, *32, *33, *34, *36
TPMT	*1 (reference), *2, *3A, *3B, *3C, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *17, *18, *19, *20, *21, *22, *23, *24, *25, *26, *27, *28, *29, *30, *31, *32, *33, *34, *35, *36, *37, *38, *39, *40, *41, *42, *43, *44
UGT1A1	*1 (reference), *6, *27, *28, *36, *37, *80, *80+*28, *80+*37
VKORC1	Reference, rs9923231 (-1639G>A)

Gene Specific Limitations

Orthogonal confirmation may be required for the *CYP2D6* gene if a tandem duplication is identified involving *36 and *10 alleles, and/or to verify phasing of variants in complex alleles (eg, *7 = *5+*6 in *CYP2D6*).