The most comprehensive and accurate newborn screening test that gives early insight into baby's health

What is newborn screening?

Almost every child is screened for certain medical conditions shortly after birth. Commonly known as newborn screening, this public health program helps identify babies who may be at an increased risk for serious, but treatable, inherited conditions soon after birth or in childhood.

Most babies who are born with these conditions appear healthy at first. Without early screening, a condition may not be discovered until symptoms appear and it may be too late to prevent serious health consequences. Proactive screening can help parents and pediatricians to identify conditions early in life, so that treatment can be started immediately.

Newborn screening is currently performed only for selected conditions which can be analyzed by biochemical assays from blood, and for which treatment options exist[1]. Each country determines which conditions babies will be screened for, so different countries may test for different conditions. In general, most countries screen for 34 conditions that are recommended. This is also known as the Recommended Uniform Screening Panel (RUSP) [2,3]. Life Baby Test is a more extensive newborn screen. It screens for every condition on the RUSP and all state panels, as well as 188 additional conditions that can benefit from early detection.

The newborn screening covered by the National Health System (NHS) primarily uses biochemical analysis to look at analytes and markers in the blood. Life Baby Test is a genetic test that analyzes DNA to check for variations, or changes that may cause certain diseases. Since many diseases cannot be detected via biochemical blood analysis, Life Baby Test is able to screen for a wider range of conditions than current NHS newborn screening.

Life Baby Test

Life Baby Test is a highly accurate newborn screening test that analyses baby's DNA for more than **200 conditions**, as well as providing personalized genetic information on the metabolism of more than **30 medications.**

Life Baby Test is a **genetic test** and it only screens for conditions that can be treated with medication, dietary modification, or other therapies.

Early screening with Life Baby Test can help parents and pediatrician to know whether to take proactive steps, sooner, to care for baby's health.

There are two types of Test:

Standard – It analyses 86 genes for 87 diseases (including 34 conditions of the Recommended Uniform Screening Panel RUSP) and 12 genes for more than 30 medications.

Extended – It analyses 220 genes for 222 diseases (including 34 conditions of the Recommended Uniform Screening Panel RUSP) and 12 genes for more than 30 medications.

Indications relative to Life Baby Test

- Individuals presenting with the most common symptoms of a metabolic disease, typically include neurological symptoms such as developmental delay, seizure, lethargy, ataxia, behavioural abnormalities, deafness, blindness, and additionally organomegaly and ophthalmologic findings.
- Individuals with a positive family history of metabolic disease[4,5]
- Individuals without a positive family history but with symptoms resembling the specific disease indication
- Individuals with a negative, but suspected, family history in order to perform proper genetic counselling (prenatal analyses are recommended in families of affected individuals)

What is the procedure for Life Baby Test?

The DNA isolated from cells collected by a buccal swab is then amplified by PCR. Through a state-of-the-art technological process, named massive parallel sequencing (MPS), which uses Next Generation Sequencing (NGS) techniques with ILLUMINA/Thermo Fisher sequencing instruments, genes included in Life Baby panels are completely sequenced (exons and adjacent intronic regions, ± 5 nucleotides) (Table 1 and 2) at high read depth. The resulting genetic sequences are analysed via an advanced bioinformatics analysis, to check the presence of potential mutations in the genes under investigation.

Results of Lafe Baby Test

“POSITIVE“

Pathogenic / Likely Pathogenic mutation(s) detected

Indicates that a well characterized disease-causing mutation(s) was identified. This result can indicate the best way to treat the disease.

Only **known pathogenic** and **likely pathogenic** mutations are reported

“NEGATIVE“

NO Pathogenic / Likely Pathogenic mutation(s) detected

Indicates that no disease causing mutations have been detected in the target genes screened.

A negative test result reduces, but doesn’t eliminate, a child’s risk of being affected by these genetic conditions or any other genetic conditions not covered by this test.

Life Baby test is only intended to identify mutations in DNA that are very likely to cause genetic conditions (pathogenic or likely pathogenic). Variants of uncertain clinical significance (VOUS), i.e. findings with insufficient evidence available for unequivocal determination of clinical significance, are not reported with Life Baby test.

No single genetic test can detect all of the possible gene variants that could cause a condition. Parental DNA is only analyzed using targeted testing if indicated by the child's test results. A separate report will not be issued to the parent.

Parameters used to report the genetic variations

The test analyses only the genes listed in Table 1 and 2. Only mutations classified as "known pathogenic" in accordance with the relevant scientific literature and the current classification in the Human Gene Mutation Database (HGMD), updated on the date of the sample collection, will be reported. Moreover, in compliance with the indications of the American College of Medical Genetics (ACMG)[6], only mutations with a Minor Allele Frequency (MAF) <5% (1000 Genomes Project) are considered as pathogenic or possibly pathogenic; this measurement refers to the frequency in which the less common allele is present in the general population.

Target Coverage

Life Baby test is a highly accurate newborn screening test that gives early insight into a baby's health. Life Baby test uses an advanced DNA sequencing technology, named Next Generation Sequencing (NGS), coupled with a leading bioinformatic analysis, to detect mutations in 220 genes associated with 222 genetic disorders, with > 99% accuracy. Many of these conditions cannot be detected by carrier screening, standard prenatal tests, or state newborn screening.

Accuracy of Life Baby Test

Present DNA sequencing techniques are more than 99% accurate. Even though this test is very accurate, the limitations of this examination are always to be taken into consideration. Please read below.

Limits of Life Baby Test

This examination analyses only genetic diseases and genes listed in Table 1 and 2. The test does not detect other genetic diseases or genes that were not specifically targeted.

Moreover, the test cannot detect:

- Mutation located into intronic regions beyond +/- nucleotides from the breakpoints.
- Deletions, inversions or duplications of more than 20 bps.
- Germline mosaicism (i.e. mutations occurring only in the gametes)

The intrinsic limitation of the NGS methodology is the lack of coverage uniformity of each examined genetic region. Quantity and quality of the DNA extracted from samples is one of the potential causes of such lack of uniformity, which may lead to the lack of detection of gene mutations. Due to this limitation, NGS tests may not detect specific genetic mutations in the selected genes.

Some of these variations may not be identified or validated yet by the scientific community and, therefore, may not be classified as pathogenic variations at the time of analysis. For a correct interpretation of results, we need to have accurate information on the health of the patient and any pathology in the clinical history of the couple and their relatives. This information allows our geneticists to have a better iterpretation of genetic results.

Newborn screening with unmatched detection of serious disorders

The true goal of newborn screening is to detect serious, prevalent, and clinically-actionable diseases. That's why the Life Baby test has been methodically designed by the genetic experts to maximize detection rates for the diseases that matter the most.

The Life Baby test screens for the most clinically relevant and impactful genetic conditions that typically affect health in infancy or childhood. The disorders included in the Life Baby test panel have been carefully selected based on carrier rate, clinical severity, and availability of treatment options. This test only includes conditions that may be treated with medication, dietary modification, or other therapies, so proactive steps can be taken with a pediatrician to care for the child's health.

Every Life Baby test also includes an additional pharmacogenetic analysis of a child's response to more than 30 medications, thus allowing a personalized treatment throughout life. This test is offered at no additional cost and can be completed using the same DNA sample collected for Life Baby.

List of genes and genetic disorders screened

Life Baby includes genes to cover all ACMG core panel phenotypes for newborn screening

Table 1: Genes analysed in the Life Baby **STANDARD** and **EXTENDED** Panel

ABCD1	Adrenoleukodystrophy	**Standard Panel**
ACAD8	Isobutyryl-CoA dehydrogenase deficiency	**Standard Panel**
ACADM	Acyl-CoA dehydrogenase, medium chain, deficiency of	**Standard Panel**
ACADS	Acyl-CoA dehydrogenase, short-chain, deficiency of	**Standard Panel**
ACADSB	2-methylbutyrylglycinuria	**Standard Panel**
ACADVL	very long-chain acyl-CoA dehydrogenase deficiency	**Standard Panel**
ACAT1	Alpha-methylacetoacetic aciduria	**Standard Panel**
ADA	Severe combined immunodeficiency due to ADA deficiency	**Standard Panel**
ADK	Hypermethioninemia due to adenosine kinase deficiency	**Standard Panel**
AHCY	Hypermethioninemia with deficiency of S-adenosylhomocysteine hydrolase	**Standard Panel**
ARG1	Argininemia	**Standard Panel**
ASL	Argininosuccinic aciduria	**Standard Panel**
ASS1	Citrullinemia Type 1	**Standard Panel**
AUH	3-methylglutaconic aciduria, type I	**Standard Panel**
BCKDHA	Maple syrup urine disease, type Ia	**Standard Panel**

BCKDHB	Maple syrup urine disease, type Ib	**Standard Panel**
BTD	Biotinidase deficiency	**Standard Panel**
CBS	Homocystinuria, B6-responsive and nonresponsive types	**Standard Panel**
CFTR	Cystic fibrosis	**Standard Panel**
CPS1	Carbamoylphosphate synthetase I deficiency	**Standard Panel**
CPT1A	Carnitine palmitoyltransferase type I deficiency	**Standard Panel**
CPT2	Carnitine palmitoyltransferase type II deficiency	**Standard Panel**
CYP21A2	Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency	**Standard Panel**
DBT	Maple syrup urine disease, type II	**Standard Panel**
DNAJC19	Hyperphenylalaninemia, mild, non-BH4-deficient	**Standard Panel**
ETFA	Glutaric acidemia IIA	**Standard Panel**
ETFB	Glutaric acidemia IIB	**Standard Panel**
ETFDH	Glutaric acidemia IIC	**Standard Panel**
FAH	Tyrosinemia, type I	**Standard Panel**
G6PD	Hemolytic anemia, G6PD deficient (favism)	**Standard Panel**
GAA	Glycogen storage disease II - Pompe disease	**Standard Panel**
GALC	Krabbe disease	**Standard Panel**
GALE	Galactose epimerase deficiency	**Standard Panel**
GALK1	Galactokinase deficiency with cataracts	**Standard Panel**
GALT	Galactosemia	**Standard Panel**
GBA	Gaucher disease, type I	**Standard Panel**
GCDH	Glutaricaciduria, type I	**Standard Panel**
GCH1	Hyperphenylalaninemia, BH4-deficient, B	**Standard Panel**
GJB2	Deafness, autosomal recessive 1A	**Standard Panel**
GJB3	Deafness, digenic, GJB2/GJB3	**Standard Panel**
GJB6	Deafness, digenic GJB2/GJB6	**Standard Panel**
GLA	Fabry disease	**Standard Panel**
GSS	Glutathione synthetase deficiency - 5-oxoprolinuria	**Standard Panel**
HADH	Short-chain hydroxyacyl-coenzyme A dehydrogenase deficiency	**Standard Panel**

HADHA	long-chain hydroxyacyl-CoA dehydrogenase deficiency	**Standard Panel**
HADHB	Trifunctional protein deficiency	**Standard Panel**
HBA1	Thalassemia, alpha-	**Standard Panel**
HBA2	Thalassemia, alpha-	**Standard Panel**
HBB	Sickle cell anemia	**Standard Panel**
HLCS	Holocarboxylase synthetase deficiency	**Standard Panel**
HMGCL	HMG-CoA lyase deficiency	**Standard Panel**
HPD	Tyrosinemia, type III	**Standard Panel**
IDUA	Mucopolysaccharidosis type Ih	**Standard Panel**
IL2RG	Severe combined immunodeficiency, X-linked	**Standard Panel**
IVD	Isovaleric acidemia	**Standard Panel**
LMBRD1	Methylmalonic aciduria and homocystinuria, cblF type	**Standard Panel**
MAT1A	Hypermethioninemia, due to methionine adenosyltransferase I/III deficiency	**Standard Panel**
MCCC1	3-Methylcrotonyl-CoA carboxylase 1 deficiency	**Standard Panel**
MCCC2	3-Methylcrotonyl-CoA carboxylase 2 deficiency	**Standard Panel**
MLYCD	Malonyl-CoA decarboxylase deficiency	**Standard Panel**
MMAA	Methylmalonic aciduria, vitamin B12-responsive	**Standard Panel**
MMAB	Methylmalonic aciduria, vitamin B12-responsive, due to defect in synthesis of adenosylcobalamin, cblB complementation type	**Standard Panel**
MMACHC	Methylmalonic aciduria and homocystinuria, cblC type	**Standard Panel**
MMADHC	Methylmalonic aciduria and homocystinuria, cblD type	**Standard Panel**
MUT	Methylmalonic aciduria, mut(0) type	**Standard Panel**
NADK2	2,4-dienoyl-CoA reductase deficiency	**Standard Panel**
NAGS	N-acetylglutamate synthase deficiency	**Standard Panel**
OAT	Gyrate atrophy of choroid and retina with or without ornithinemia	**Standard Panel**
OPA3	3-methylglutaconic aciduria, type III	**Standard Panel**
OTC	Ornithine transcarbamylase deficiency	**Standard Panel**
PAH	Phenylketonuria	**Standard Panel**
PAX8	Hypothyroidism, congenital, due to thyroid dysgenesis or hypoplasia	**Standard Panel**

PCBD1	Hyperphenylalaninemia, BH4-deficient, D	**Standard Panel**
PCCA	Propionic acidemia	**Standard Panel**
PCCB	Propionic acidemia	**Standard Panel**
PTS	Hyperphenylalaninemia, BH4-deficient, A	**Standard Panel**
QDPR	Hyperphenylalaninemia, BH4-deficient, C	**Standard Panel**
SLC22A5	Carnitine deficiency, systemic primary	**Standard Panel**
SLC25A13	Citrullinemia, type II, adult-onset - neonatal-onset	**Standard Panel**
SLC25A15	Hyperornithinemia-hyperammonemia-homocitrullinemia syndrome	**Standard Panel**
SLC25A20	Carnitine-acylcarnitine translocase deficiency	**Standard Panel**
SLC37A4	Glycogen storage disease Ib	**Standard Panel**
SMPD1	Niemann-Pick disease, type A	**Standard Panel**
TAT	Tyrosinemia, type II	**Standard Panel**
TAZ	3-methylglutaconic aciduria, type II - Barth syndrome	**Standard Panel**
TSHR	Hypothyroidism, congenital, nongoitrous, 1	**Standard Panel**
ABCC8	Familial hyperinsulinism ABCC8-related	**Extended panel**
ABCD1	Adrenoleukodystrophy	**Extended panel**
ABCD4	Methylmalonic aciduria and homocystinuria, cblJ type	**Extended panel**
ACAD8	Isobutyryl-CoA dehydrogenase deficiency	**Extended panel**
ACAD9	acyl-CoA dehydrogenase-9 (ACAD9) deficiency	**Extended panel**
ACADM	Acyl-CoA dehydrogenase, medium chain, deficiency of	**Extended panel**
ACADS	Acyl-CoA dehydrogenase, short-chain, deficiency of	**Extended panel**
ACADSB	2-methylbutyrylglycinuria	**Extended panel**
ACADVL	very long-chain acyl-CoA dehydrogenase deficiency	**Extended panel**
ACAT1	Alpha-methylacetoacetic aciduria	**Extended panel**
ACSF3	Combined malonic and methylmalonic aciduria	**Extended panel**
ADA	Severe combined immunodeficiency due to ADA deficiency	**Extended panel**
ADK	Hypermethioninemia due to adenosine kinase deficiency	**Extended panel**
AGL	Glycogen storage disease, type III	**Extended panel**
AGXT	Primary hyperoxaluria, type 1	**Extended panel**

AHCY	Hypermethioninemia with deficiency of S-adenosylhomocysteine hydrolase	**Extended panel**
AK2	Reticular dysgenesis	**Extended panel**
AKR1D1	Bile acid synthesis defect, congenital, 3	**Extended panel**
ALDH4A1	Hyperprolinemia, type II	**Extended panel**
ALDH7A1	Epilepsy, pyridoxine-dependent	**Extended panel**
ALDOB	Fructose intolerance, hereditary	**Extended panel**
ALPL	Hypophosphatasia	**Extended panel**
ANK1	Spherocytosis, type 2	**Extended panel**
AQP2	Diabetes insipidus, nephrogenic	**Extended panel**
ARG1	Argininemia	**Extended panel**
ARSA	Metachromatic leukodystrophy	**Extended panel**
ARSB	Mucopolysaccharidosis type VI (Maroteaux-Lamy)	**Extended panel**
ASL	Argininosuccinic aciduria	**Extended panel**
ASS1	Citrullinemia Type 1	**Extended panel**
AUH	3-methylglutaconic aciduria, type I	**Extended panel**
AVPR2	Nephrogenic syndrome of inappropriate antidiuresis / Nephrogenic diabetes insipidus AVPR2-related	**Extended panel**
BCKDHA	Maple syrup urine disease, type Ia	**Extended panel**
BCKDHB	Maple syrup urine disease, type Ib	**Extended panel**
BTD	Biotinidase deficiency	**Extended panel**
BTK	Agammaglobulinemia, X-linked 1	**Extended panel**
CASR	Neonatal hyperparathyroidism / Autosomal dominant hypocalcemia	**Extended panel**
CBS	Homocystinuria, B6-responsive and nonresponsive types	**Extended panel**
CD247	Immunodeficiency 25	**Extended panel**
CD320	Methylmalonic aciduria, transient, due to transcobalamin receptor defect	**Extended panel**
CD3D	Immunodeficiency 19	**Extended panel**
CD3E	Immunodeficiency 18	**Extended panel**
CFTR	Cystic fibrosis	**Extended panel**
COL4A3	Alport syndrome COL4A3-related	**Extended panel**

COL4A4	Alport syndrome, autosomal recessive	**Extended panel**
COL4A5	Alport syndrome	**Extended panel**
CPS1	Carbamoylphosphate synthetase I deficiency	**Extended panel**
CPT1A	Carnitine palmitoyltransferase type I deficiency	**Extended panel**
CPT2	Carnitine palmitoyltransferase type II deficiency	**Extended panel**
CTH	Cystathioninuria	**Extended panel**
CTNS	Cystinosis	**Extended panel**
CYBA	Chronic granulomatous disease, autosomal, due to deficiency of CYBA	**Extended panel**
CYBB	Chronic granulomatous disease CYBB-related	**Extended panel**
CYP11B1	Congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency	**Extended panel**
CYP11B2	Corticosterone methyloxidase deficiency	**Extended panel**
CYP21A2	Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency	**Extended panel**
CYP27A1	Cerebrotendinous xanthomatosis	**Extended panel**
DBT	Maple syrup urine disease, type II	**Extended panel**
DCLRE1C	Omenn syndrome / Severe combined immunodeficiency, Athabaskan-type	**Extended panel**
DECR1	2,4-dienoyl-CoA reductase deficiency	**Extended panel**
DLD	Dihydrolipoamide dehydrogenase deficiency	**Extended panel**
DNAJC19	Hyperphenylalaninemia, mild, non-BH4-deficient	**Extended panel**
DUOX2	Thyroid dyshormonogenesis 6	**Extended panel**
DUOXA2	Thyroid dyshormonogenesis 5	**Extended panel**
EPB42	Spherocytosis, type 6	**Extended panel**
ETFA	Glutaric acidemia IIA	**Extended panel**
ETFB	Glutaric acidemia IIB	**Extended panel**
ETFDH	Glutaric acidemia IIC	**Extended panel**
ETHE1	Ethylmalonic encephalopathy	**Extended panel**
F9	Factor IX deficiency	**Extended panel**
FAH	Tyrosinemia, type I	**Extended panel**
FBN1	Marfan syndrome and other FBN1-related disorders	**Extended panel**
FBP1	Fructose-1,6-bisphosphatase deficiency	**Extended panel**

FOLR1	Neurodegeneration due to cerebral folate transport deficiency	**Extended panel**
FTCD	Glutamate formiminotransferase deficiency	**Extended panel**
G6PC	Glycogen storage disease, type Ia	**Extended panel**
G6PD	Hemolytic anemia, G6PD deficient (favism)	**Extended panel**
GAA	Glycogen storage disease II - Pompe disease	**Extended panel**
GALC	Krabbe disease	**Extended panel**
GALE	Galactose epimerase deficiency	**Extended panel**
GALK1	Galactokinase deficiency with cataracts	**Extended panel**
GALNS	Mucopolysaccharidosis IVA	**Extended panel**
GALT	Galactosemia	**Extended panel**
GAMT	Cerebral creatine deficiency syndrome 2	**Extended panel**
GATM	Cerebral creatine deficiency syndrome	**Extended panel**
GBA	Gaucher disease, type I	**Extended panel**
GCDH	Glutaricaciduria, type I	**Extended panel**
GCH1	Hyperphenylalaninemia, BH4-deficient, B	**Extended panel**
GJB2	Deafness, autosomal recessive 1A	**Extended panel**
GJB3	Deafness, digenic, GJB2/GJB3	**Extended panel**
GJB6	Deafness, digenic GJB2/GJB6	**Extended panel**
GLA	Fabry disease	**Extended panel**
GLIS3	Diabetes mellitus, neonatal, with congenital hypothyroidism	**Extended panel**
GLUD1	congenital hyperinsulinic hyperammonemia (HI/HA) syndrome	**Extended panel**
GNAS	Pseudohypoparathyroidism Ia	**Extended panel**
GNMT	Glycine N-methyltransferase deficiency	**Extended panel**
GRHPR	Hyperoxaluria, primary, type II	**Extended panel**
GSS	Glutathione synthetase deficiency - 5-oxoprolinuria	**Extended panel**
GYS2	Glycogen storage disease 0, liver	**Extended panel**
HADH	Short-chain hydroxyacyl-coenzyme A dehydrogenase deficiency	**Extended panel**
HADHA	long-chain hydroxyacyl-CoA dehydrogenase deficiency	**Extended panel**
HADHB	Trifunctional protein deficiency	**Extended panel**

HAL	Histidinemia	**Extended panel**
HAX1	Neutropenia, severe congenital 3, autosomal recessive	**Extended panel**
HBA1	Thalassemia, alpha-	**Extended panel**
HBA2	Thalassemia, alpha-	**Extended panel**
HBB	Sickle cell anemia	**Extended panel**
HGD	Alkaptonuria	**Extended panel**
HLCS	Holocarboxylase synthetase deficiency	**Extended panel**
HMGCL	HMG-CoA lyase deficiency	**Extended panel**
HMGCS2	HMG-CoA synthase-2 deficiency	**Extended panel**
HOGA1	Hyperoxaluria, primary, type III	**Extended panel**
HPD	Tyrosinemia, type III	**Extended panel**
HSD17B10	17-beta-hydroxysteroid dehydrogenase X (HSD10) deficiency	**Extended panel**
HSD3B2	Adrenal hyperplasia, congenital, due to 3-beta-hydroxysteroid dehydrogenase 2 deficiency	**Extended panel**
HSD3B7	Bile acid synthesis defect, congenital, 2	**Extended panel**
IDS	Mucopolysaccharidosis II	**Extended panel**
IDUA	Mucopolysaccharidosis type Ih	**Extended panel**
IL2RG	Severe combined immunodeficiency, X-linked	**Extended panel**
IL7R	Severe combined immunodeficiency, T-cell negative, B-cell/natural killer cell-positive type	**Extended panel**
INS	Diabetes mellitus, permanent neonatal	**Extended panel**
IVD	Isovaleric acidemia	**Extended panel**
IYD	Thyroid dyshormonogenesis 5	**Extended panel**
JAG1	Alagille syndrome 1 / Tetralogy of Fallot	**Extended panel**
JAK3	Severe combined immunodeficiency	**Extended panel**
KCNJ11	Familial hyperinsulinism	**Extended panel**
KCNQ2	Early Infantile epileptic encephalopathy 7 / Benign neonatal seizures 2	**Extended panel**
LDLR	Familial hypercholesterolemia	**Extended panel**
LHX3	Combined pituitary hormone deficiency 4	**Extended panel**

LIG4	LIG4 syndrome	**Extended panel**
LIPA	Wolman disease / Cholesteryl ester storage disease	**Extended panel**
LMBRD1	Methylmalonic aciduria and homocystinuria, cblF type	**Extended panel**
LPL	Lipoprotein lipase deficiency	**Extended panel**
MAT1A	Hypermethioninemia, due to methionine adenosyltransferase I/III deficiency	**Extended panel**
MCCC1	3-Methylcrotonyl-CoA carboxylase 1 deficiency	**Extended panel**
MCCC2	3-Methylcrotonyl-CoA carboxylase 2 deficiency	**Extended panel**
MCEE	Methylmalonyl-CoA epimerase deficiency	**Extended panel**
MLYCD	Malonyl-CoA decarboxylase deficiency	**Extended panel**
MMAA	Methylmalonic aciduria, vitamin B12-responsive	**Extended panel**
MMAB	Methylmalonic aciduria, vitamin B12-responsive, due to defect in synthesis of adenosylcobalamin, cblB complementation type	**Extended panel**
MMACHC	Methylmalonic aciduria and homocystinuria, cblC type	**Extended panel**
MMADHC	Methylmalonic aciduria and homocystinuria, cblD type	**Extended panel**
MPI	Congenital disorder of glycosylation, type Ib	**Extended panel**
MPL	Congenital amegakaryocytic thrombocytopenia	**Extended panel**
MTHFR	Homocystinuria due to MTHFR deficiency	**Extended panel**
MTR	Homocystinuria-megaloblastic anemia, cobalamin G type	**Extended panel**
MTRR	Homocystinuria, cobalamin E type	**Extended panel**
MTTP	Abetalipoproteinemia	**Extended panel**
MUT	Methylmalonic aciduria, mut(0) type	**Extended panel**
MVK	Mevalonic aciduria	**Extended panel**
NADK2	2,4-dienoyl-CoA reductase deficiency	**Extended panel**
NAGS	N-acetylglutamate synthase deficiency	**Extended panel**
NHEJ1	Severe combined immunodeficiency with microcephaly, growth retardation, and sensitivity to ionizing radiation	**Extended panel**
NKX2-1	Choreoathetosis, hypothyroidism, and neonatal respiratory distress	**Extended panel**
NKX2-5	Hypothyroidism, congenital nongoitrous, 5	**Extended panel**
NPC1	Niemann-Pick disease, type C1	**Extended panel**

NPC2	Niemann-pick disease, type C2	**Extended panel**
OAT	Gyrate atrophy of choroid and retina with or without ornithinemia	**Extended panel**
OPA3	3-methylglutaconic aciduria, type III	**Extended panel**
OTC	Ornithine transcarbamylase deficiency	**Extended panel**
PAH	Phenylketonuria	**Extended panel**
PAX8	Hypothyroidism, congenital, due to thyroid dysgenesis or hypoplasia	**Extended panel**
PC	Pyruvate carboxylase deficiency	**Extended panel**
PCBD1	Hyperphenylalaninemia, BH4-deficient, D	**Extended panel**
PCCA	Propionic acidemia	**Extended panel**
PCCB	Propionic acidemia	**Extended panel**
PHGDH	3-phosphoglycerate dehydrogenase deficiency	**Extended panel**
PHKB	Glycogen storage disease, type IXb	**Extended panel**
PNP	Immunodeficiency due to purine nucleoside phosphorylase deficiency	**Extended panel**
PNPO	Pyridoxamine 5'-phosphate oxidase deficiency	**Extended panel**
POU1F1	Combined pituitary hormone deficiency 1	**Extended panel**
PPARG	peroxisome proliferator–activated receptorgamma (PPAR-g) ligand resistance syndrome (PLRS) or familial partial lipodystrophy type 3	**Extended panel**
PRF1	Hemophagocytic lymphohistiocytosis, familial, 2	**Extended panel**
PRODH	Hyperprolinemia, type I	**Extended panel**
PROP1	Combined pituitary hormone deficiency 2	**Extended panel**
PRRT2	Familial infantile convulsions with paroxysmal choreoathetosis	**Extended panel**
PTPRC	Severe combined immunodeficiency PTPRC-related	**Extended panel**
PTS	Hyperphenylalaninemia, BH4-deficient, A	**Extended panel**
PYGL	Glycogen storage disease, type VI	**Extended panel**
QDPR	Hyperphenylalaninemia, BH4-deficient, C	**Extended panel**
RAG1	Omenn syndrome and other RAG1-related disorders	**Extended panel**
RAG2	Omenn syndrome RAG2-related	**Extended panel**
RB1	Retinoblastoma	**Extended panel**
SCN2A	Early infantile epileptic encephalopathy 11 / Benign familial infantile seizures 3	**Extended panel**

SCN8A	Early infantile epileptic encephalopathy 13 / Benign familial infantile seizures 5	**Extended panel**
SLC22A5	Carnitine deficiency, systemic primary	**Extended panel**
SLC25A13	Citrullinemia, type II, adult-onset - neonatal-onset	**Extended panel**
SLC25A15	Hyperornithinemia-hyperammonemia-homocitrullinemia syndrome	**Extended panel**
SLC25A20	Carnitine-acylcarnitine translocase deficiency	**Extended panel**
SLC26A4	Pendred syndrome	**Extended panel**
SLC2A1	Glucose transporter 1 deficiency syndrome and other SLC2A1-related disorders	**Extended panel**
SLC3A1	Cystinuria	**Extended panel**
SLC37A4	Glycogen storage disease Ib	**Extended panel**
SLC39A4	Acrodermatitis enteropathica	**Extended panel**
SLC4A1	Distal renal tubular acidosis and other SLC4A1-related disorders	**Extended panel**
SLC5A5	Thyroid dyshormonogenesis 1	**Extended panel**
SLC7A7	Lysinuric protein intolerance	**Extended panel**
SLC7A9	Cystinuria	**Extended panel**
SMPD1	Niemann-Pick disease, type A	**Extended panel**
SPR	Sepiapterin reductase deficiency	**Extended panel**
STAR	Lipoid adrenal hyperplasia	**Extended panel**
STX11	Hemophagocytic lymphohistiocytosis, familial, 4	**Extended panel**
SUCLA2	Mitochondrial DNA depletion syndrome 5 (encephalomyopathic with or without methylmalonic aciduria)	**Extended panel**
SUCLG1	Mitochondrial DNA depletion syndrome 9 (encephalomyopathic type with methylmalonic aciduria)	**Extended panel**
TAT	Tyrosinemia, type II	**Extended panel**
TAZ	3-methylglutaconic aciduria, type II - Barth syndrome	**Extended panel**
TCIRG1	Osteopetrosis 1	**Extended panel**
TG	Thyroid dyshormonogenesis 4	**Extended panel**
TH	Segawa syndrome	**Extended panel**
THRA	Congenital nongoitrous hypothryoidism 6	**Extended panel**
TMEM70	Mitochondrial complex V (ATP synthase) deficiency, nuclear type 2	**Extended panel**

TPO	Thyroid dyshormonogenesis 2°	**Extended panel**
TRHR	Generalized thyrotropin-releasing hormone resistance	**Extended panel**
TRMU	Acute infantile liver failure	**Extended panel**
TSHB	Congenital nongoitrous hypothryoidism 4	**Extended panel**
TSHR	Hypothyroidism, congenital, nongoitrous, 1	**Extended panel**
TTPA	Ataxia with isolated vitamin E deficiency	**Extended panel**
UGT1A1	Crigler-Najjar syndrome, types 1 and 2 / Gilbert syndrome	**Extended panel**
UNC13D	Hemophagocytic lymphohistiocytosis, familial, 3	**Extended panel**
ZAP70	Immunodeficiency 48	**Extended panel**
WT1	Wilms tumor, type 1 and other WT1-related disorders	**Extended panel**

Additional pharmacogenetic analysis

Every Life Baby test includes an additional pharmacogenetic analysis of a child's response to more than **30 medications** that may be prescribed during childhood. This analysis can help doctors to personalize treatments throughout the child's life.

This pharmacogenetic analysis is offered at no additional cost and can be completed using the same DNA sample collected for Life Baby.

This test is included with every Life Baby test, a genetic screening of **222** childhood genetic conditions.

Table 2: List of medications and genes screened

Analgesics

- Celecoxib *(CYP2C9)*
- Codeine *(CYP2D6)*
- Hydrocodone *(CYP2D6)*
- Oxycodone *(CYP2D6)*
- Tramadol *(CYP2D6)*

Anticoagulants

- Warfarin *(CYP2C9, VKORC1)*

Anticonvulsant

- Fosphenytoin *(CYP2C9)*
- Phenytoin *(CYP2C9)*

Antiemetics

- Ondansetron *(CYP2D6)*

Antifungal Agents

- Voriconazole *(CYP2C19)*

Antidepressant

- Amitriptyline *(CYP2D6, CYP2C19)*
- Citalopram *(CYP2C19)*
- Clomipramine *(CYP2D6, CYP2C19)*
- Desipramine *(CYP2D6)*
- Doxepin *(CYP2D6, CYP2C19)*
- Escitalopram *(CYP2C19)*
- Fluoxetine *(CYP2D6)*
- Fluvoxamine *(CYP2D6)*
- Imipramine *(CYP2D6)*
- Nortriptyline *(CYP2D6)*
- Paroxetine *(CYP2D6)*
- Sertraline *(CYP2C19)*
- Trimipramine *(CYP2D6, CYP2C19)*

Antilipemic Agents

- Simvastatin *(SLCO1B1)*

Antineoplastic Agents

- Capecitabine *(DPYD)*
- Fluorouracil *(DPYD)*
- Mercaptopurine *(TPMT)*
- Thioguanine *(TPMT)*

Antiplatelet Agents

- Clopidogrel *(CYP2C19)*

Antipsycotics

- Aripiprazole *(CYP2D6)*
- Iloperidone *(CYP2D6)*
- Pimozide *(CYP2D6)*

Antiretrovirals

- Atazanavir *(UGT1A1)*

Immunosuppressant

- Azathioprine *(TPMT)*
- Tacrolimus *(CYP3A5)*

Enzyme Inhibitors

- Eliglustat *(CYP2D6)*

Psychotropics

- Atomoxetine *(CYP2D6)*

Please note that almost all individuals will test positive for a variant in at least one of the 12 genes on this panel.

Pharmacogenetic test reporting.

Enzymes codified by the genes in table 2 are drug-metabolizing enzymes (DMEs). DMEs are responsible for the drugs metabolic biotransformation and their body elimination. Different relevant polymorphisms have been identified in the gene coding sequences of DMES enzymes causing loss of therapeutic effects or excessive drug response.

Based on the presence of genetic variants on genes codifying for DMEs enzymes patients can be divided in four phenotypes:

- **Poor Metabolizer - PMs**: PMs have gene inactivating variations on both alleles that result in inactive enzyme or no enzyme at all. PMs have a reduced response or no response and may have increased side effects if treated with standard drug dose.

- **Intermediate Metabolizer – IMs**: IMs have an allele with normal function and a non-functional allele. IMs may require a lower drug dose for a therapeutic effect.

- **Extensive Metabolizer - EMs**: EMs usually have normal drug response as they have two active alleles of the gene.

- **Ultra rapid-Metabolizer - UMs:** UMs usually have an increased expression of genes involved in drug metabolism. UMs may have a reduced or no drug response and may require a higher drug dosage to obtain the therapeutic response. UMs may have three or more active alleles caused by a duplication of the normal allele, or a mutation on one or both alleles causing increased activity.

Eurofins Genoma Group will report the subgroup for the specific drug-metabolizing enzymes identified as polymorphic.

Based on the polymorphisms identified by the pharmacogenetic Life Baby test, the physician can evaluate the adequate drug dosage for the patient. To this purpose, the physician should be aware about metabolic pathway of the specific drug to compare it with the metabolic genetic profile of the patient.

Polymorphisms investigated:

***1**		None (wild type)	None	**Normal function**
***2**	6	2850 C-T	R296C	**Normal function**
***3**	5	2549delA	frameshift	**No function**
	3 5	1749A>G 2549delA	N166D, frameshift	**No function**
***4**	4	1846G>A	splicing defect	**No function**
***5**		Gene deletion	No protein	**No function**
***6**	3	1707delT	frameshift	**No function**
***7**	6	2935A>C	H324P	**No function**
***8**	3	1758G>T	Stop codon	**No function**
***9**	5	2613-2615delAGA	K281del	**Decreased function**
***10**	1	100C>T	Pro34Ser	**Decreased function**
***11**	intr. 2	883G>C		**No function**
***12**	1	124G>A	Glu42Arg	**No function**
***14**	3	1758G>A	G169R	**No function**
***17**	2	1023C>T	T107I, R296C	**Decreased function**

	6	2850C>T		
*20	4	1973insG	frameshift	No function
*21	5	2573insC	frameshift	No function
*24	6	2853A>C	I297L	
*38	5	2587-2590delGACT	frameshift	No function
*44	intron 6	2950G>C	splicing defect	No function
*XN		gene amplification	increased protein	Increased function
				Poor metabolizer
*XN (Gene Duplication)				Increased function

CYP2D6 *1 and *2 alleles are associated with a normal enzymatic function, while **CYP2D6 *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *17, *20, *21, *38, *44**, correspond to non-functional or decreased activity alleles. Polymorphisms associated to **CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6** alleles are found in 97% of the PM. **CYP2D6*4** represents the most common allele (21.5-28.6%), followed by the **CYP2D6*3** (2.7%) and **CYP2D6*5** (2.6%). Others rare alleles (**CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*11, CYP2D6*12, CYP2D6*14, CYP2D6*20, CYP2D6*31, CYP2D6*38, CYP2D6*44**), are associated to non-functional enzyme.

CYP2C19 gene mutations investigated				
CYP2C19 Allele	Exon/intron	Mutation	Effect on protein	Effect on enzymatic function
*1		Nessuna (wild type)	None	Normal function
*2	5	681G>A	splicing defect	No function
*3	4	636G>A	W212X	No function
*4	1	1A>G	start codon mutation	No function
*5	9	1297G>A	R433W	No function
*6	3	395G>A	R132Q	No function
*7	5	1VS5+2T>A	splicing defect	No function
*8	3	358T>C	W120R	No function
*9	3	431G>A	R144H	Decreased function
*10	5	680C>T	P227L	Decreased function
*11	3	449G>A	R150H	
*2, *3, *4, *5, *6, *7, *8, *9, *10, *11				poor metaboliser

CYP2C19*1 allele is associated with normal enzymatic function; individuals homozygous for this allele are **extensive metabolizer** (**EM**). **CYP2C19 *2,*3, *4, *5, *6, *7, *8, *9, *10, *11** correspond to non-functional or decreased alleles activity (**poor metabolizer** – **PM**).
Polymorphisms associated with **CYP2C19*2**, **CYP2C19*3**, **CYP2C19*4**, **CYP2C19*5**, **CYP2C19*6** and **CYP2C19*7** occurs in 98% of the PM. The most common alleles are **CYP2C19*2** (75-85% of the Asiatics and 15% of the Europeans and Afro-americans), and **CYP2C19*3** (6-10% of the Asiatics and rare in Europeans and Afro-americans).

CYP2C9 gene mutations investigated				
CYP2C9 Allele	Exons/intron	Mutation	Effect on protein	Effect on enzymatic function
*1		None (wild type)	None	Normal
*2	3	430C>T	R144C	Decreased function
*3	7	1075A>C	I359L	Decreased function
*4	7	1076T>C	I359T	Decreased function
*5	7	1080C>G	D360E	Decreased function
*6	5	818delA	frameshift	No function
*8	3	449G>A	R150H	Increased function
*9	5	752A>G	H251R	
*10	5	815A>G	E272G	
*11	7	1003C>T	R335W	Decreased function
*14	3	374 G-A	R125H	Decreased function
*18	7	1075A>C	I359L	Decreased function
*2, *3, *4, *5, *6, *11, *14, *18				poor metaboliser

CYP2C9*1 allele is associated with normal enzymatic activity; individuals homozygous for this allele are considered to be **extensive metabolizers (EM).** Alleles **CYP2C9*2 (R144C)** and **CYP2C9*3 (I359L)**, were found to be the most common ones in the Caucasian population with frequencies of 8-18% and of 4-10% respectively. The same alleles were found less frequently in Asiatics and Afro-Americans (0.5 – 4%). **CYP2C9*4** allele was found only in the Japanese population, while **CYP2C9*5** and **CYP2C9*6** alleles were found in almost the 2% of the Afro-Americans. Only the 1-2% of European population is homozygous for the CYP2C9*2 and CYP2C9*3 alleles.

Individuals carrying **CYP2C9 *2, *3, *4, *5, *6, *11, *14, *18** alleles, are found to be poor metabolizers- PM (decreased enzymatic function or no enzymatic function).
Genotype-phenotype correlation for a better patient management:

- Individuals with CYP2C9*1/*1 genotype (70% of the Caucasian population) are normal metabolizes.
- Individuals with CYP2C9*1/ *2 (16% of the Caucasian population) and *1/*3 (10% of the Caucasian population) genotypes are poor metabolizers.
- Individuals with CYP2C9*2/*2 (frequency 1%), *2/*3 (frequency 1%), *3/*3 (frequency 0.3%) genotypes are found to be very poor metabolizers.

CYP2C9 *2, CYP2C9 *3, CYP2C9 *4, CYP2C9 *5 and **CYP2C9 *6** alleles are found in almost 98% of PM individuals.

CYP1A2 gene mutations investigated				
CYP1A2 Allele	Exon/intron	Mutation	Effect on protein	Effect on enzymatic function
*1A	1	None (wild type)	None	Normal
*1C	1	g.-3860G>A		Decreased function
*1F	1	g.-164C>A		Elevated inducibility

CYP1A2*1A allele is considered the reference allele to which all variants are compared (normal induction). Two relevant polymorphisms were identified for the **CYP1A2*1** allele causing **CYP1A2** enzymatic functional alteration**: CYP1A2*1C allele**, due to **-3860 G>A** point mutation and associated with a decreased metabolic activity; **CYP1A2*1F allele**, due to **-163 C>A** point mutation, associated with an increased enzymatic induction,

mostly in smokers. CYP1A2 alleles are distributed in the population as follow: **1F/*1F ~ 46 %; *1A/*1F ~ 44%**; ***1A/*1A ~ 10%**, indicating that the most common phenotype observed is the inducibility increment.

Some of the medications influenced by the CYP450 system activity

Generic medication (Brand)	CYP450 genes				Generic medication (Brand)	CYP450 genes			
				2D6		1A2	2C9		2D6
Amitriptyline (Elavil®)	✓	✓	✓	✓	diphenhydramine				✓
Aripiprazole (Abilify®)				✓	hydroxyzine				✓
Atomoxetine (Strattera®)				✓	loratadine {Alavert®, Claritin®}				✓
Citalopram (Celexa®)			✓		terfenadine				✓
Clomipramine (Anafranil®)	✓		✓	✓					
Desipramine (Norpramin®)				✓	alprenolol				✓
Diazepam (Diazepam Intensol®, Valium®)			✓		amiodarone	✓	✓	✓	✓
Escitalopram (Lexapro®)			✓		atorvastatin		✓		✓
Fluoxetine (Prozac®)	✓	✓		✓	brofaramine	✓			
Fluvoxamine (Luvox®)	✓			✓	Carvedilol (Coreg®)		✓		✓
Haloperidol (Haldol®)	✓			✓	cerivastatin			✓	✓
Imipramine (Tofranil®)	✓		✓	✓	Flecainide (Tambocor®)	✓			✓
Maprotiline (Ludiomil®)	✓			✓	Fluvastatin (Lescol®)		✓	✓	✓
Nortriptyline (Pamelor®, Aventyl®)	✓			✓	Irbesartan (Avalide®, Avapro®)		✓		
Paroxetine (Paxil®)	✓			✓	lidocaine	✓			
Perphenazine (Trilafon®)	✓			✓	Losartan (Cozaar®, Hyzaar®)		✓		
Phenytoin (Dilantin®)		✓			lovastatin		✓	✓	
Risperidone (Risperdal®)				✓	nicardipine				✓
Sertraline (Zoloft®)	✓	✓	✓		Metoprolol (Lopressor®, Toprol XL®)				✓
Thioridazine (Mellaril®)	✓			✓	Mexiletine (Mexitil®)	✓			✓
Trimipramine (Surmontil®)		✓	✓	✓	nicardipine		✓	✓	
Venlafaxine (Effexor®)				✓	nifedipine			✓	
Zuclopenthixol (Clopixol®)				✓	Propafenone (Rythmol®)	✓			✓
					propranolol	✓		✓	✓
ciprofloxacin	✓				quinidine		✓		✓
enoxacin	✓				simvastatin		✓	✓	✓
grepafloxacin	✓				Timolol (Betimol®, Timoptic®, Blocadren®, Istalol®)				✓
norfloxacin	✓				verapamil	✓			✓
ofloxacin	✓				Warfarin (Coumadin®)		✓		
rifampin		✓							
sparfloxacin	✓				acetaminophen	✓			✓
					Celecoxib (Celebrex®)		✓		✓
carbamazepine	✓		✓		Codeine				✓
Diazepam (Valium®)			✓		diclofenac		✓		✓
felbamate			✓		flurbiprofen		✓		
mephenytoin			✓		hydrocodone				✓
phenobarbitone			✓		ketoprofen		✓		
Phenytoin (Dilantin®)		✓	✓		Ibuprofen (Advil®, Motrin®)		✓		
topiramate			✓		indomethacin		✓		

Some of the medications influenced by the CYP450 system activity

Generic medication (Brand)	CYP450 genes				Generic medication (Brand)	CYP450 genes			
Anti-Diabetics					**Analgesics/ Anti-inflammatories**				
					meloxicam		✓		
Glimepiride (Amaryl®)		✓			methadone		✓	✓	✓
Glipizide (Glucotrol®)		✓			Naproxen (Aleve®, Naprosyn®)	✓	✓		
Glyburide (Diabeta®, Micronase®, Glynase®)		✓	✓		perhexiline				✓
nateglinide		✓			phenacetin				✓
Pioglitazone (Actos®)		✓			piroxicam		✓		
Rosiglitazone (Avandia®)		✓			propranolol				✓
Tolbutamide		✓	✓		suprofen		✓		
Chemioterapici					Oxycodone (Oxycontin®)				✓
Ondansetron (Zofran®)				✓	Tramadol (Ultram®)				✓
Tamoxifen (Nolvadex®)				✓	**Antacids**				
Tropisetron				✓	Esomeprazole (Nexium®)			✓	✓
Antihistamines					Lansoprazole (Prevacid®)			✓	✓
Astemizole				✓	Omeprazole (Prilosec®)		✓	✓	✓
Azelastine				✓	Pantoprazole (Protonix®)			✓	
chlorpheniramine				✓	Rabepranole (Aciphex®)			✓	
					HIV Antiviral				
					amprenavir		✓	✓	✓
					delavirdine	✓	✓	✓	✓
					efavirenz	✓	✓	✓	✓
					indinavir				✓
					nelfinavir			✓	✓
					ritonavir	✓	✓	✓	✓
					saquinavir				✓

CYP3A4 gene mutations investigated				
CYP3A4 Allele	Exon/intron	Mutation	Effect on protein	Effect on enzymatic function
*1A		Wild-type	None	Normal function
*2	7	g.15713T>C	S222P	Decreased function
*6		g.17662-17663insA	frameshift	Premature transcription termination
*8	5	g.13908G>A	R130Q	Decreased function
*11	11	g.21867C>T	T363M	Decreased function
*12	11	g.21896C>T	L373F	Decreased function
*13	11	g.22026C>T	R416L	Decreased function
*16	7	g.15603C>G	T185S	Decreased function
*17	7	g.15615T>C	F189S	Decreased function
*18	10	g.20070T>C	L293P	Increased function
*20		25889_25890insA	488Frameshift	No function
*26		17633C>T	R268X	Decreased function

Dugs metabolised by CYP3A4

The most important enzymatic substrates, inhibitors and inductors of the CYP3A4 cytochrome are listed in the tables below:

Substrates, inhibitors and inductors of the CYP3A4		
SUBSTRATES	INHIBITORS	INDUCTORS
Antidepressants (Imipramine, amitriptyline, sertraline, venlafaxine, nefazodone) **Benzodiazepine** (alprazolam, triazolam, midazolam) **Antimycotics** (ketoconazole, astemizole) **Protease inhibitors** (ritonavir, indinavir, nelfinavir, saquinavir)	**Antidepressant** (Nefazodone > fluvoxamine > Fluoxetine > sertraline, paroxetine, venlafaxine) **Azole antifungal** (Ketoconazole, itraconazole, fluconazole)	Carbamazepine Dexamethasone Phenobarbital Phenytoin Rifampicin
Others Terfenadine Verapamil Testosterone Theophylline Carbamazepine Cisapride Dexamethasone Erythromycin Ethinyl estradiol Glyburides Cyclosporine Lovastatin	**Others** Cimetidine Clarithromycin Diltiazem Protease Inhibitors	

Examples of drug-drug interaction between drugs metabolised by CYP3A4		
Interfering drugs	***Interaction mechanism***	***Clinical consequences***
Fluoxetine-calcium antagonists	Fluoxetine, by its metabolite norfluoxetine, inhibits the CYP3A4 activity, limiting the calcium-antagonist agents metabolisation.	Nausea, flushing, oedema, headache.
Fluoxetine-alprazolam	Fluoxetine, by its metabolite norfluoxetine, inhibits the CYP3A4 activity, which normally metabolise alprazolam. This dug-drug interaction does not affect the activity of triazolam, which is mainly metabolised in the gastrointestinal tract.	Cognitive or psychomotor function impairment.
Astemizole-ketoconazole	Ketoconazole is a strong selective CYP3A4 inhibitor, able to inhibit the astemizole metabolism almost entirely.	Cardio toxicity.

TPMT gene mutations investigated				
TPMT Allele	**Exon/intron**	**Mutation**	**Effect on protein**	**Effect on enzymatic function**
***1**		None (wild type)	None	**Normal function**
***2**		c.288G>C	A80P	**Decreased function**
***3A**		c.460G>A c.719A>G	A154T Y240C	**Decreased function**
***3B**		c.719A>G	Y240C	**Decreased function**

At least 20 polymorphisms have been identified on the *TMPT* gene, four of them are associated to decrement or loss of enzymatic function. **TPMT*3A** and **TPMT*3C** polymorphisms (Poor Metabolizer) are the most common defective alleles (almost 90% of the defective alleles in the European population).
These polymorphisms are transmitted as an autosomal codominant trait and their combination lead to four different alleles associated to different enzymatic activity levels.

CYP3A5 gene mutations investigated			
CYP3A5 Allele	***Mutation***	***Effect on protein***	***Effect on enzymatic function***
CYP3A5*1A	None (wild type)	None	**Normal function**
CYP3A5*3A	6986A>G; 31611C>T	Splicing defect	**Severely decreased function**
CYP3A5*3B	3705C>T; 3709_3710insG; 6986A>G; 31611C>T	H30Y; Splicing defect	**Severely decreased function**
CYP3A5*3C	6986A>G	Splicing defect	**Severely decreased function**
CYP3A5*3D	6986A>G; 7249T>G	Splicing defect; L82R	**Severely decreased function**

*CYP3A5*3E*	6986A>G; 27050A>G; 31611C>T	Splicing defect	**Severely decreased function**
*CYP3A5*3F*	6986A>G; 31551T>C; 31611C>T	Splicing defect; I488T	**Severely decreased function**
*CYP3A5*3G*	6986A>G; 12952T>C; 31611C>T	Splicing defect	**Severely decreased function**
*CYP3A5*3H*	6986A>G; 13108T>C; 31611C>T	Splicing defect	**Severely decreased function**
*CYP3A5*3I*	6986A>G; 16903A>G; 31611C>T	Splicing defect	**Severely decreased function**
*CYP3A5*3J*	6986A>G; 29782A>G; 31611C>T	Splicing defect; I456V	**Severely decreased function**
*CYP3A5*3K*	6986A>G; 29753T>C; 31611C>T	Splicing defect; F446S	**Decreased function**
*CYP3A5*3L*	3775A>G; 6986A>G	Y53C; Splicing defect	**Decreased function**
*CYP3A5*6*	14690G>A	Splicing defect	**No function or severely decreased function**
*CYP3A5*8*	3699C>T	R28C	**Decreased function**
*CYP3A5*9*	19386G>A	A337T	**Decreased function**

CYP3A7 gene mutations investigated				
Gene	Allele	Mutation	Effect on protein	Effect on enzymatic function
CYP3A7	*1C	c.-291G>T -284T>A -282T>C -281A>T -270T>G -262T>A -232A>C		Increased function
	*2	c.1226C>G	T409R	Increased function

UGT1A1 gene mutations investigated				
Allele	Exon/intron	Mutation	Effect on protein	Effect on enzymatic function
*1		promoter repeat [TA] **6**	wild type	
*28		promoter repeat [TA] **7**		Decreased function
*36		promoter repeat [TA] **5**		Increased activity
*37		promoter repeat [TA] **8**		Decreased function

Three principal genotypes in the promoter region of the **UGT1A1** gene have been observed in the general population: the wild type homozygous genotype**,** characterised by 6 thymine-adenine dinucleotide repeats **(TA) 6/6**, the homozygous genotype with **7 TA** dinucleotide repeats **(TA) 7/7**, and the heterozygous **(TA) 6/7** genotype carrying a wild-type allele and the 7 TA expanded allele.
The presence of the 7TA expanded allele lead to a **decreased enzymatic activity**.

DPYD

Different polymorphisms in the DPYD gene have been found to decrease or abolish the DPD enzymatic function, with the consequent increased risk of severe toxicity, potentially fatal. The most common is the point mutation **G→A** in a splicing site of the exon 14 (**IVS14+ 1G>A**). This nucleotide substitution results in exon loss and the production of a non-functional incomplete protein. Approximately the 1% of the general population carries this allelic variant (known as ***DPYD*2A)*** corresponding to almost the 50% of DPD-deficiency. In particular, patients heterozygous for these polymorphisms show partial DPD enzymatic activity, while patients carrying homozygous mutation show DPD enzymatic deficiency. A dose reduction should be considered for patients carrying these variants.

VKORC1 gene mutations investigated		
VKORC1 allele	Mutations	Effect on enzymatic function
-1639	**-1639G>A**	Decreased Transcription

The **-1639G>A** polymorphism in the promoter of the **VKORC1** (Vitamin K epOxide Reductase Complex subunit 1) gene, target of dicumarolic drugs, is found to be associated to a decreased gene expression. As dicumarolic drugs act by inhibiting Vitamin K epoxide reductase, the presence of the genetic variant (which induce a lower enzyme product resulting in increased drug sensitivity) requires a reduction in drug dose.

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