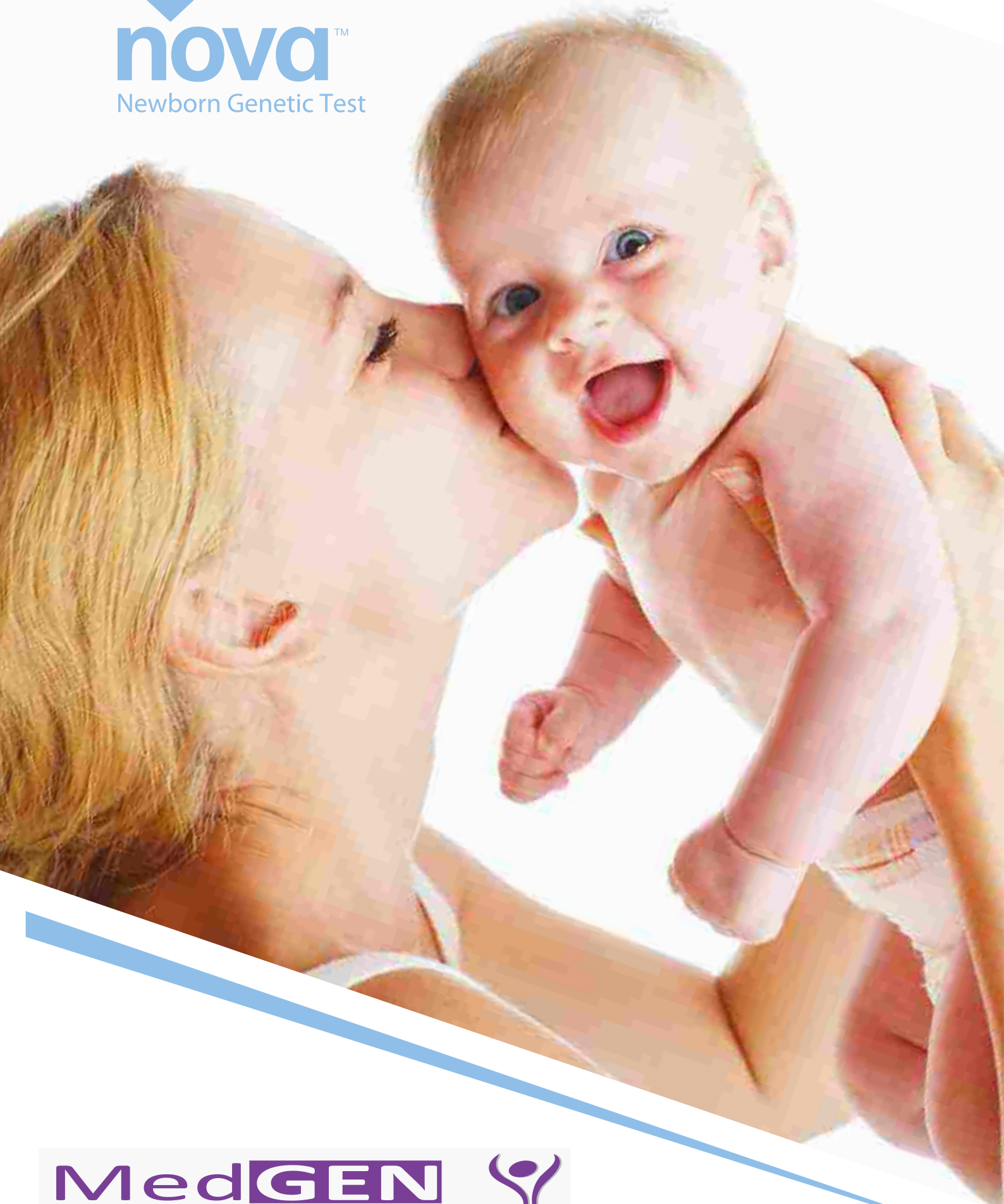
nova™

Newborn Genetic Test



MedGEN

Introduction

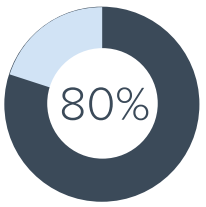
We are proud to offer the Nova™ Newborn Genetic Test, a comprehensive screening test that determines a babys risk for 50 inherited disorders , as well as providing personalized genetic information on the likely response of 20 pediatric drugs . Utilizing Next Generation Sequencing technology and with access to BGIs industry leading genetics bioinformatics software, NOVA offers the most comprehensive and accurate newborn screening test on the market with a positive predictive value (PPV) of >99%.*

Why Nova Newborn Genetic Testing?

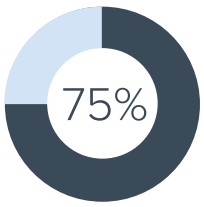
Each year worldwide, over **7.9 million babies** are born with birth defects[*], many of which appear perfectly healthy at birth and come from families with no history of the disorder. Many affected babies are not identified until the appearance of severe and often irreversible symptoms later in life. Many countries run publicly funded programmes to screen newborns for inherited disorders. However, most countries include only 516 disorders on their programmes, leaving thousands of newborns unscreened for any number of potentially manageable disorders every year. In addtion,certain gene mutations may make a baby more sensitive to particular drugs and it may be much safer to use lower doses or avoid them completely. Usually there is no way of anticipating the response to these drugs until after they have been given and had an unexpected effect.

The Nova Newborn Genetic Test screens for 50 inherited disorders, which have a combined estimated prevalence rate of **1/400 births**. These disorders have been selected based off the core panel and secondary targets of the American College of Medical Genetics Newborn Screening Expert Group report[**]. All conditions on the Nova Newborn Genetic Test panel have been carefully selected based on clinical characteristics of the disease inlcuding incidence, burden if not treated, and management of the disease in acute and chronic forms. The Nova Newborn Genetic Test aims to help healthcare providers achieve early detection, referral and treatment of all babies identified as at high risk of these disorders.

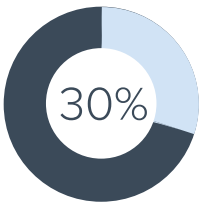
In additon to disease screening, the Nova Newborn Genetic Test provides pharmocogeneomic information realting to 20 pediatric drugs. All drugs have been FDA approved for pediatric use and selected according to the potential severity of the drug response to different gene mutations.[***]



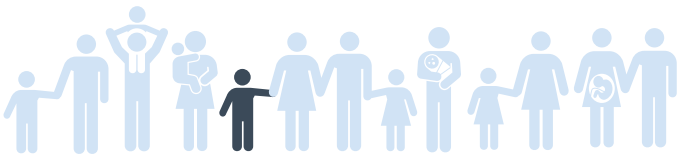
of rare diseases have identified genetic origins



of rare diseases affect children



of rare disease patients die before the age of 5



1/17 will be affected by rare disease at some point in their life

eurodis.org, raredisease.org.uk, European Council

[*] Christianson A., Howson C., Modell B, March of Dimes, Global Report On Birth Defects, p2, March of Dimes Birth Defects Foundation White Plains, New York 2006

[**] Watson M. et al, Newborn Screening: Toward a Uniform Screening Panel and SystemExecutive Summary, American College of Medical Genetics Newborn Screening Expert Group, PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275); published in the public domain by the American Academy of Pediatrics

[***] The Pharmocogenomics Knowledge Database (pharmgkb.org) was used to determine the impact of genetic variation on drug response.

What Does The Test Screen For?

50 Inherited Disorders (see table below)

Inherited Metabolic Diseases (40) / Congenital Hearing-impairment (1) / Immunodeficiency (6) / Other Monogenic Diseases (3)

20 Pediatric Pharmacogenomics

Neurology Drugs (5) / Anti-infection Agents (10) / Rheumatology Drugs (1) / Gastroenterology Drugs (2) / Cardiology Drugs (1) / Oncology Drugs (1)

Condition Category	No.	Condition Name	Gene	Inherited Mode
Amino Acid Disorders	1	Phenylketonuria	PAH	AR
	2	Tetrahydrobiopterin(BH4)-deficient Hyperphenylalaninemia	FAH	AR
	3	Maple Syrup Urine Disease	BCKDHA	AR
			BCKDHB	AR
			DBT	AR
			DLD	AR
	4	Argininosuccinic Acidemia	ASL	AR
	5	Citrullinemia Type I	ASS1	AR
	6	Arginase Deficiency	ARG1	AR
	7	Carbamoylphosphate Synthetase I Deficiency	CPS1	AR
	8	N-Acetylglutamate Synthase Deficiency	NAGS	AR
	9	Ornithine Transcarbamylase Deficiency	OTC	XL
	10	Citrin Deficiency	SLC25A13	AR
	11	Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency	CBS	AR
	12	Tyrosinemia Type 1	PTS	AR
Organic Acid Disorders	13	Methylmalonic Acidemia	MUT	AR
			MMAA	AR
			MMAB	AR
			MCEE	AR
			MMADHC	AR
	14	Propionic Acidemia	PCCA	AR
			PCCB	AR
	15	Isovaleric Acidemia	IVD	AR
	16	Carbamoylphosphate Synthetase I Deficiency	MCCC1	AR
			MCCC2	AR
	17	Glutaric Acidemia Type I	GCDH	AR
	18	Beta-Ketothiolase Deficiency	ACAT1	AR
	19	Beta-Ketothiolase Deficiency	BTD	AR
				AR
			HLCS	AR
Fatty Acid Oxidation Disorders	20	Glutaric Acidemia type II	ETFDH	AR
			ETFA	AR
			ETFB	AR
	21	Systemic Primary Carnitine Deficiency	SLC22A5	AR
	22	Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency	HADHA	AR
	23	Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency	ACADM	AR
	24	Trifunctional Protein Deficiency	HADHA	AR
			HADHB	AR

The Nova Newborn Genetic Test screens for mutations which have been linked to the specific genetic conditions listed on the testing panel. The purpose of the Nova Newborn Genetic Test is to identify babies as more likely to have one of the listed genetic conditions. If the test result returns as positive for one of the mutations, definitive diagnosis of the condition should only be undertaken by a qualified healthcare professional. Further, confirmatory diagnostic testing is recommended.

Condition Category	No.	Condition Name	Gene	Inherited Mode
Fatty Acid Oxidation Disorders	25	Very Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency	ACADVL	AR
	26	Carnitine Palmitoyltransferase II Deficiency	CPT2	AR
	27	Carnitine Palmitoyltransferase 1A Deficiency	CPT1A	AR
	28	Short-Chain Acyl-CoA Dehydrogenase Deficiency	ACADS	AR
Copper Metabolism Disorder	29	Wilson Disease	ACADS	AR
Carbohydrate Disorders	30	Glucose-6-Phosphate Dehydrogenase Deficiency	G6PD	XL
	31	Hereditary Fructose Intolerance	ALDOB	AR
	32	Galactosemia	GALT	AR
			GALE	AR
			GALK1	AR
Lysosomal Storage Diseases	33	Fabry Disease	GLA	XR
	34	Glycogen Storage Disease Type Ia	G6PC	AR
	35	Glycogen Storage Disease Type Ib	SLC37A4	AR
	36	Glycogen Storage Disease Type II (Pompe Disease)	GAA	AR
	37	Mucopolysaccharidosis Type I	IDUA	AR
	38	Mucopolysaccharidosis Type II	DLD	XR
	39	Krabbe Disease	GALC	AR
	40	Niemann-Pick Disease	SMPD1	AR
			NPC1	AR
			NPC2	AR
Hearing Impairment	41	Nonsyndromic Hearing Loss and Deafness	GJB2	AD/AR
			SLC26A4	AR
			GJB3	AD/AR
			MT-RNR1	Mitochondrial Inheritance
Primary Immunological Deficiency	42	Severe Combined Immunodificiency	IL2RG	XR
			JAK3	AR
			IL7R	AR
			PTPRC	AR
			CD3D	AR
			CD3E	AR
			CD247	AR
			RAG1	AR
			RAG2	AR
			DCLRE1C	AR
			AK2	AR
			ADA	AR
			LIG4	AR
			NHEJ1	AR
			PNP	AR
			ZAP70	AR
	43	Beta-Ketothiolase Deficiency	BTK	XR
	44	Ataxia-Telangiectasia	ATM	AR
	45	Nijmegen Breakage Syndrome	NBN	AR
	46	Cartilage Hair Hypoplasia	RMRP	AR
	47	Familial Hemophagocytic Lymphohistiocytosis	PRF1	AR
			UNC13D	AR
			STX11	AR
			STXBP2	AR
Miscellaneous Genetic Conditions	48	Cystic Fibrosis	CFTR	AR
	49	Severe Myoclonic Epilepsy of Infancy	SCN1A	AD
	50	Tuberous Sclerosis	TSC1	AD
			TSC2	AD

*AD: Autosomal Dominant, AR: Autosomal Recessive, XR: X Chromosome Recessive; XL: X-linked

Who Is Testing Suitable For?*

Nova is par ticularly suitable for:

- Parents who want a comprehensive genetic screen for their baby

- Parents who would like to learn their babys drug-related genetic status

- Babies who have missed out on regular screening

- Babies from parents with a family history of inherited disorders or from a population identified as at higher risk for genetic disease

Nova is not suitable for:

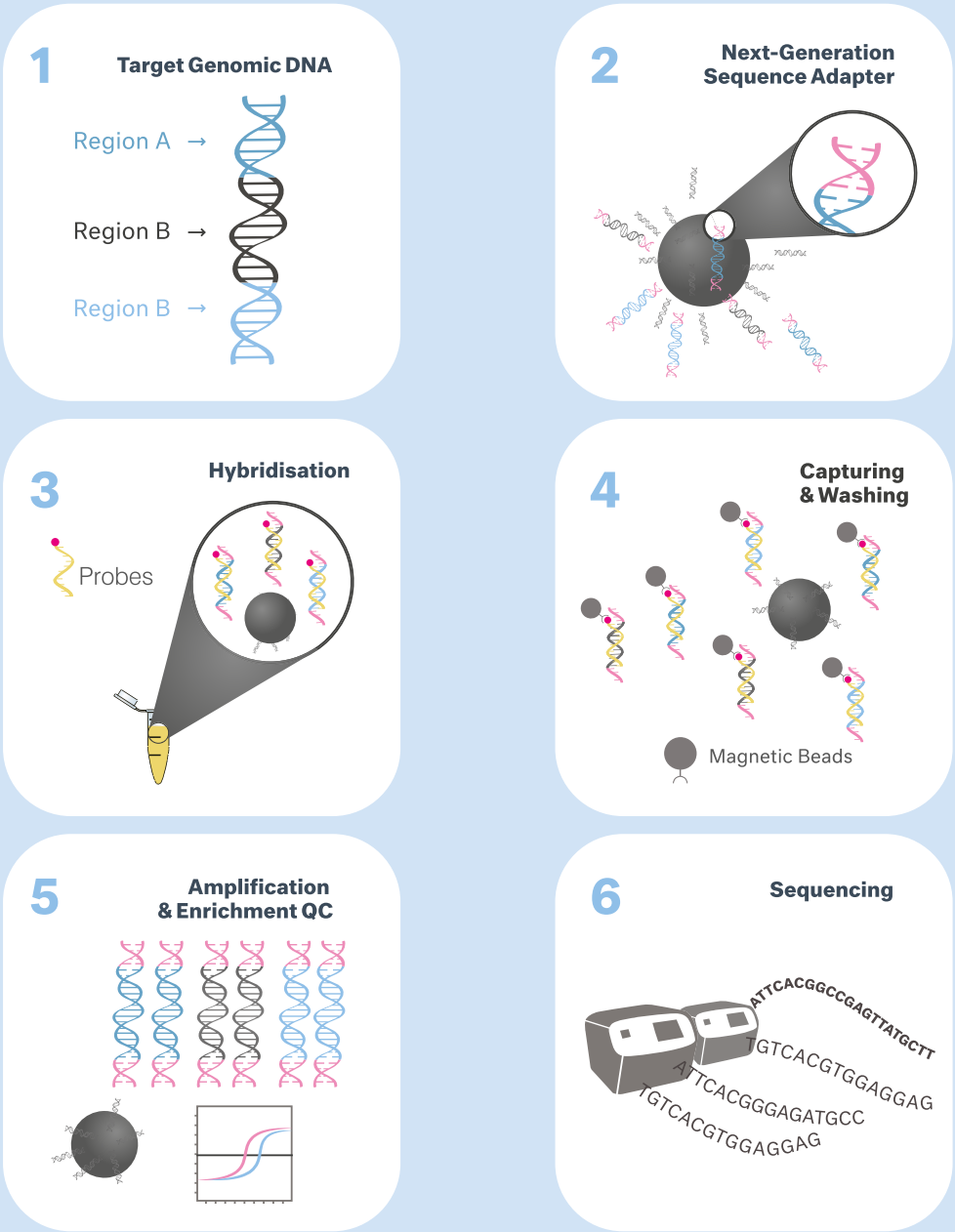
- Definitive diagnosis of a disorder

- Newborns with numerical or structural changes of the chromosome, copy number variations and/or germ cell mosaicism

- Newborns who have received blood transfusions, organ transplants or stem cell therapy

*Healthcare providers should refer to the patient consent form for a full list of test limitations and to determine whether or not a patient is suitable for testing.

Methodology



Unique targeting sequencing

Library with trace DNA: can obtain >100ng DNA from 4 blood spots and build library on just 50ng DNA (1ug=1000ng is the minimal requirement for standard library)

DNA is captured by a BGI manufactured capture chip, with equivalent capture efficiency to other leading capture chips on the market.

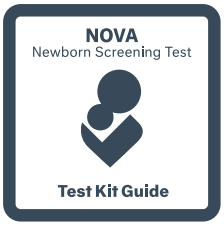
A comprehensive database comprising 12,000 mutations of all listed genes is used to generate report automatically.

Test Kit Contents

1

Consent Form

2

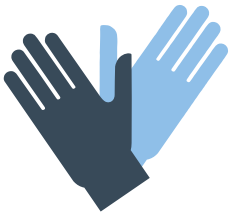


NOVA T est Kit Guide

3

Test Request Form/
Blood Spot Card

4



Latex gloves

5

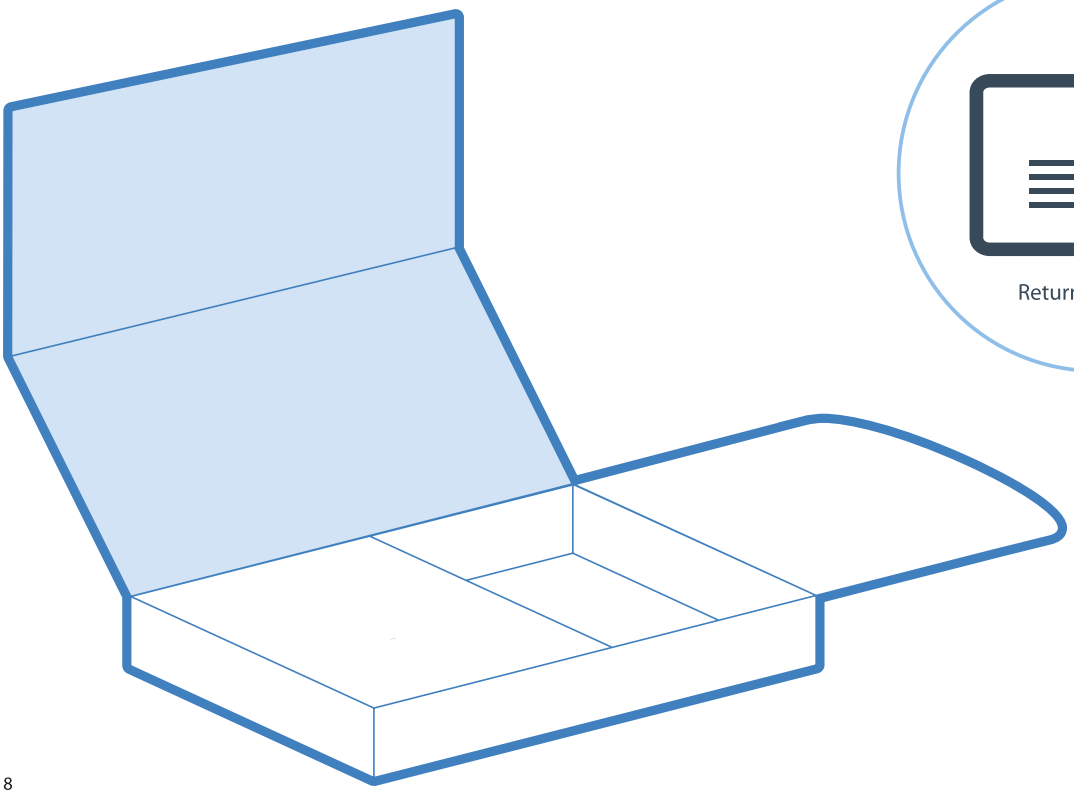
Heel puncture needle

6

Blood Spot Sample Bag

7

Return Envelope



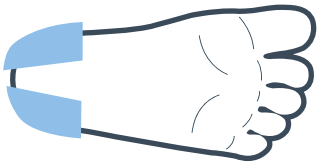
Sample Requirements

- 4 blood spot samples from the baby that can be safely obtained from a simple heel prick.
- Cord blood, heel blood and peripheral blood (children under 5 years of age) are all acceptable.
- A detailed step-by-step explanation of the sampling process is provided with every test kit.

Heel pricking is a safe, easy and widely practised clinical procedure.

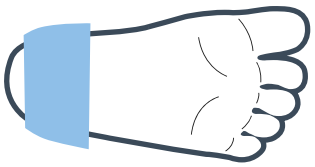
Blood Spot Samples

Puncture Site Visual Guide



For full-term and pre-term infants

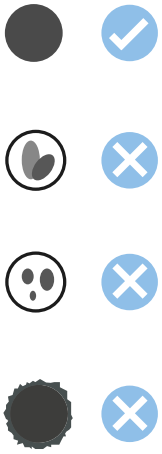
Skin puncture must be no deeper than 2.0 mm



For infants who have had repeated heel punctures

An automated incision device with a penetrative depth of no more than 1.0 mm is recommened

Blood Spot Visual Guide



Circle filled and evenly saturared

Layering

Insufficient, multi applications

Serum ring present

Do Not Touch The Blood Collection Area To Avoid Contaminating Results

Drying the sample

Air dry on clean, flat surface for three to four hours away from heat or light

Do not stack or allow the blood spots on the filter paper to touch other surfaces while drying

When dry, return the fold over flap to its original position

Providing a correctly applied blood spot sample is important in order to avoid delay and/or resampling

Workflow

1

Conduct pre-test genetic counseling, provide full explanation of the test and obtain informed consent from the patient/guardian.

2

Discuss, fill in and sign the NOVA Consent Form and Test Request Form/Blood Card with the patient/guardian.

3

Send scanned copies of Consent Form, Test Request Form/Blood Card and information sheet to Medgen

4

Arrange collection of blood sample with Medgen Courier

5

Send Consent Form, Test Request Form/Blood Card (with blood spot samples) to laboratory

6

Receive results back in 15 days

7

Conduct post test genetic counselling and provide drug guidance advice as required

Rare Disease Information Resources

Even those with severe rare diseases can sometimes be identified and treated at an early stage to reduce the impact of their disease (for example through surgery nutrition or medication). Antenatal and new born screening (for example newborn blood spot screening) has an important role to play.

Source: UK Strategy For Rare Diseases, p14

Rare diseases are characterised by a wide diversity of symptoms and signs that vary not only from disease to disease but also from patient to patient suffering from the same disease. Relatively common symptoms can hide underlying rare diseases, leading to misdiagnosis.

Source: www.eurordis.org/content/what-rare-disease

A rare disease is defined by the European Union as one that affects less than 5 in 10,000 of the general population. There are between 6,000 and 8,000 known rare diseases. Around five new rare diseases are described in medical literature each week.

Source: www.raredisease.org.uk/about-rare-diseases

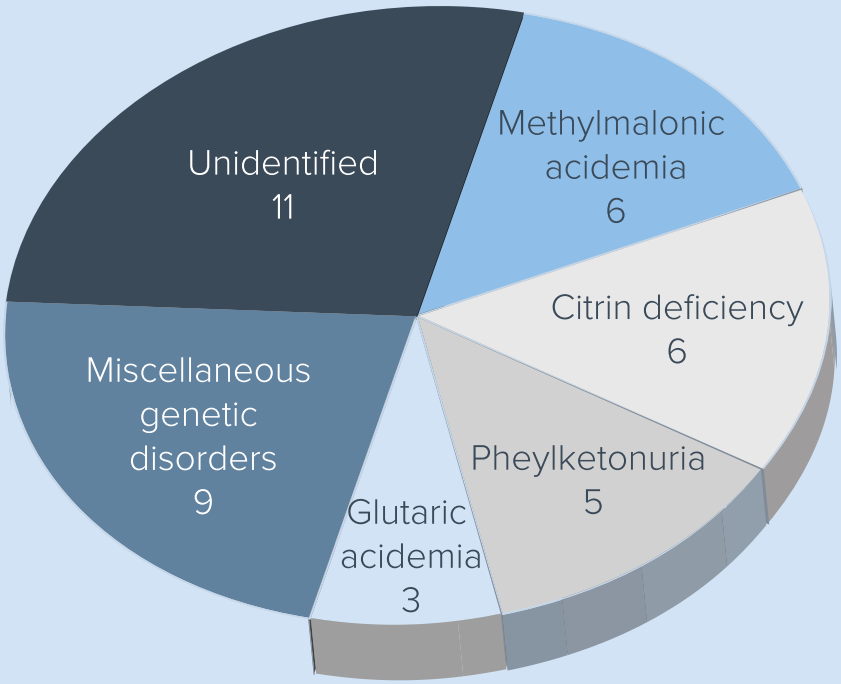
Clinical Validation

Study based on 40 independently provided samples
Childrens Hospital of Fudan University

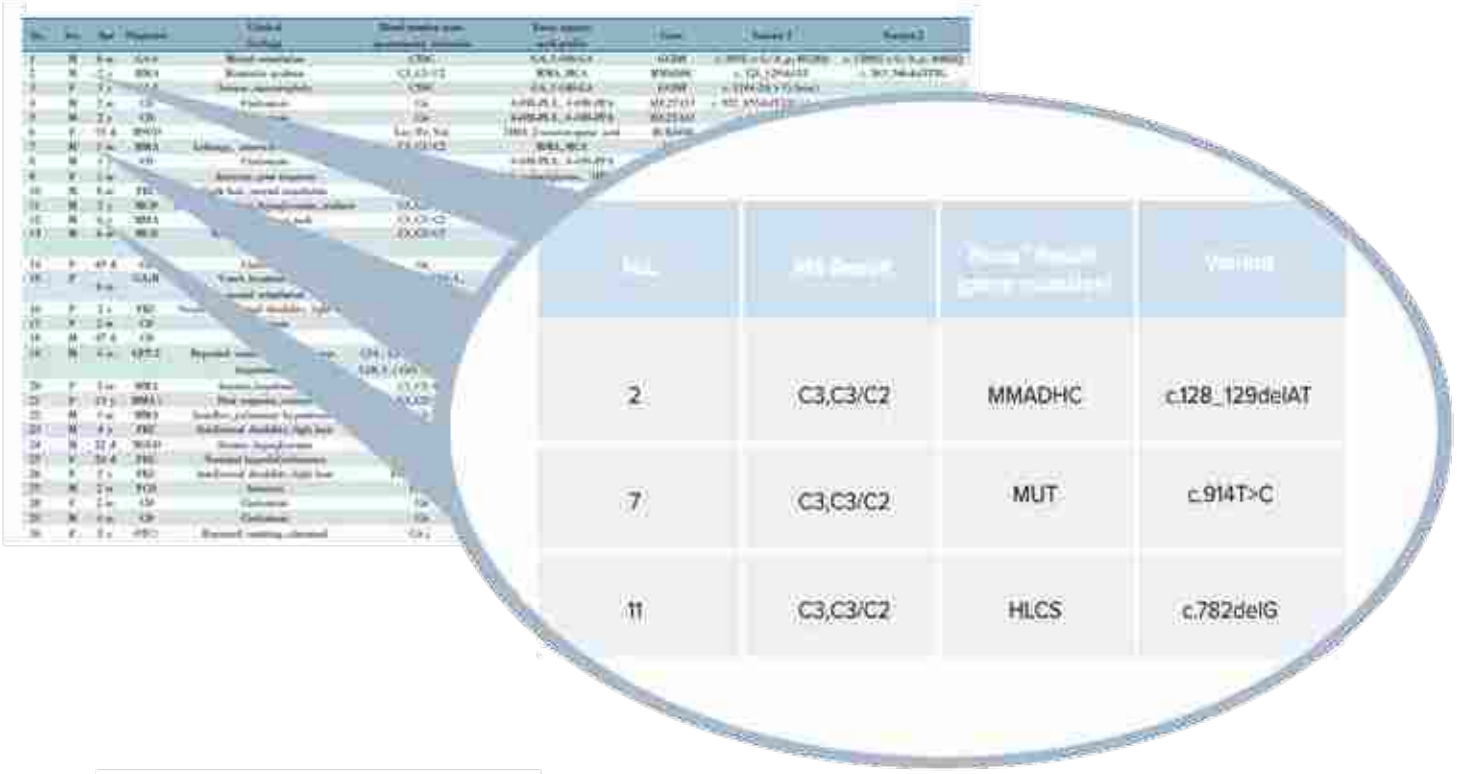
22 males

18 females

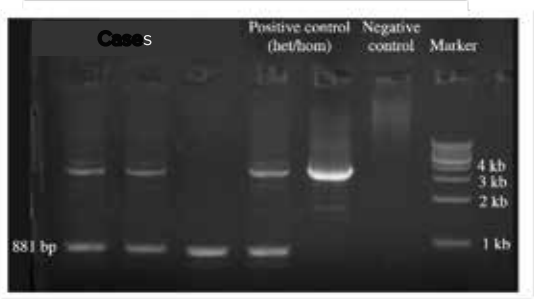
Gene mutations consistent with clinical phenotypes were discovered in **29 samples (72.5%).** The other samples were only discovered to have common pathogenic mutations or SNPs.



Case 2, 7 and 11 out of the samples received had the same outcomes in Mass Spectrometry results but actually were determined to be caused by three different gene mutations. The therapy strategies for these three mutations are very different.



No.	MS Result	Gene mutation	Variant
2	C3,C3/C2	MMADHC	c.128_129delAT
7	C3,C3/C2	MUT	c.914T>C
11	C3,C3/C2	HLCS	c.782delG



Electrophoretogram of long range PCR
All mutations confirmed by Sanger sequencing

Conclusion

Application of targeted NGS in children with high risk of inherited metabolic disorders can potentially provide reliable molecular diagnosis in a cost and time-efficient manner. Identification of disease-causing mutations may have benefit in clinical practice and is essential for genetic counseling.

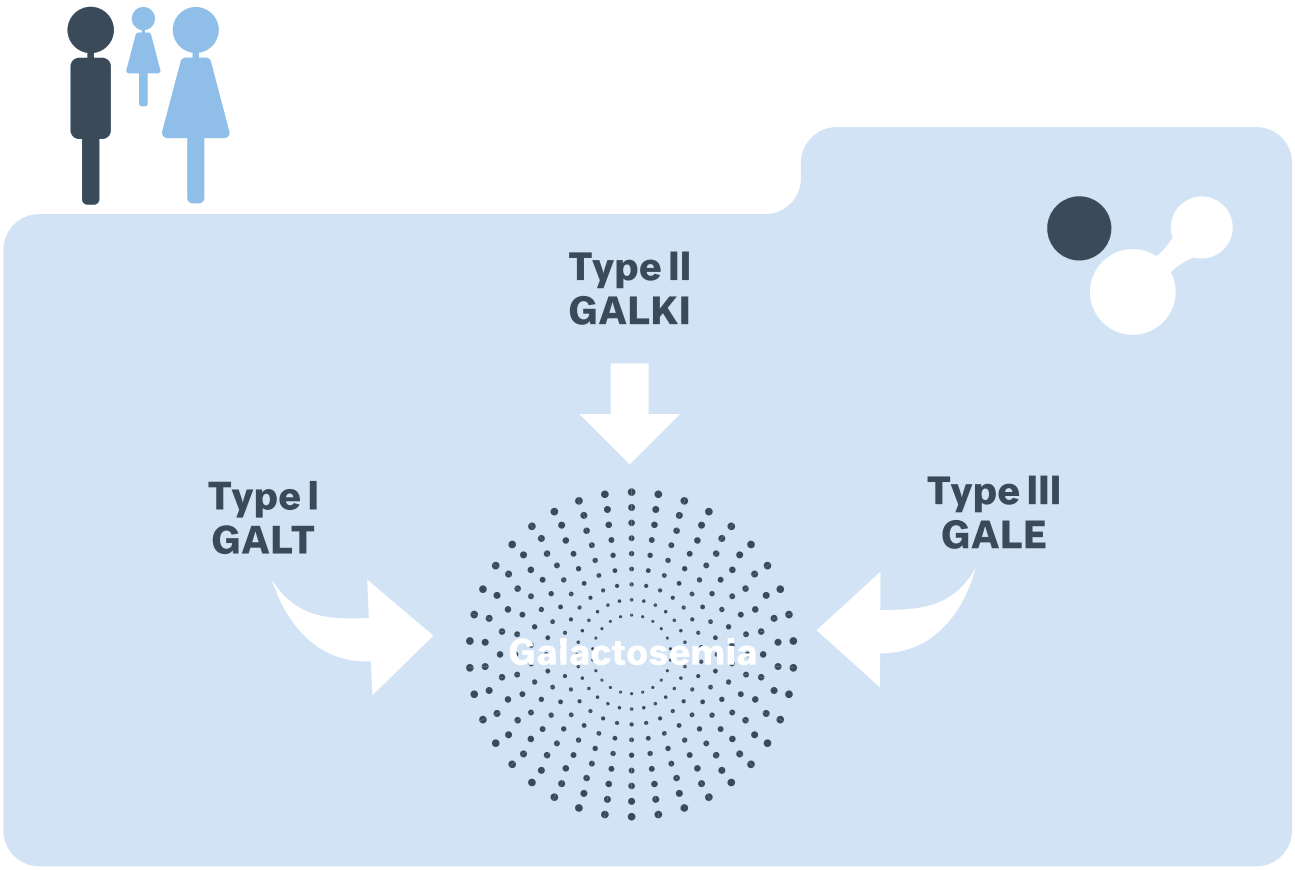
Study Reference

Wu BB, Gao Rui. et. al. Application of targeted next generation sequencing in the molecular diagnosis of abnormal mass spectrometry analysis findings. Chin J Evid Based Pediatr. 2015 Feb, Vol10, No1.doi:10.3969/j.issn.1673-5501.2015.01.007

Case Studies For Clinical Reference

Case 1 / Galactosemia

Babies with galactosaemia usually present in the first days and weeks of life with feeding difficulties, vomiting, jaundice, failure to thrive, liver and kidney disease due to their inability to convert galactose, a sugar present in milk, into glucose, the sugar used by the body.
If the disorder is not treated promptly there is a risk of death due to liver failure, bleeding or infection. Older children usually have some difficulties with learning and speech development. Most girls with galactosaemia have a delay in their pubertal development and as women are infertile. There are three types of galactosemia which are caused by different gene mutations.



Case Report:
A sample from a patient with severe clinical symptoms was sent to BGI.
Two mutations (c.505C>T and c.452G>A) on gene GALE were detected by NOVA. They were inherited from each parent respectively.
The patient was diagnosed as the first GALE caused galactosemia in China.

Case 2 / Familial Chylomicronemia

Familial Chylomicronemia (type I hyperlipidemia) is a rare autosomal recessive disease due mainly to rare variants in the lipoprotein lipase (LPL) gene sequence. The disorder usually presents in childhood and is characterized by very severe hypertriglyceridemia with episodes of abdominal pain, recurrent acute pancreatitis, eruptive cutaneous xanthomata, and the plasma exhibiting a lipemic (milky ") appearance.

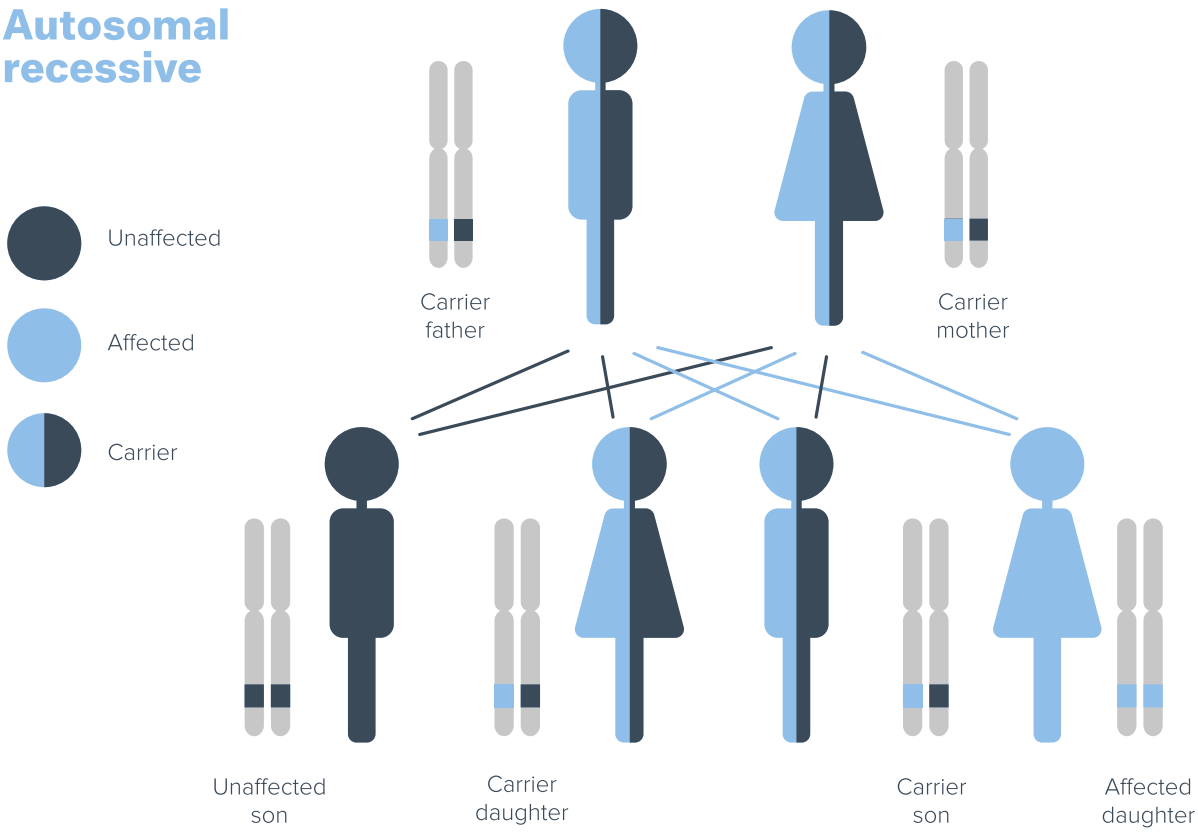
Method: We used a monogenic dyslipidemias panel paralleled next generation sequencing assay to detect disease causing mutations in two infants displaying symptoms of hypertriglyceridemia and lipemic plasma.

Case Report A:

A 30-day-old Chinese boy was admitted to hospital with a persistent cough. His blood was found to be pink in color. Fasting serum lipids, which included triglyceride (TG) and cholesterol (CHOL) were abnormal, total cholesterol (TC) and triglyceridemia (TG) was 1270 and 757mg/dL, respectively. Subsequent genetic testing of the boy revealed compound heterozygosity of p.Arg270His and p.Trp421* mutations on LPL gene, both of which were known pathogenic mutations. A low-fat/low-cholesterol diet was introduced. Subsequently, the boys serum cholesterol level decreased dramatically, and normalized in 2 months.

Case Report B:

A 48-day-old Chinese boy exhibited symptoms of milk choking and polypnea. His triglyceride (TG) was 557mg/dL, but cholesterol (CHOL) was normal. Genetic testing of the patient revealed compound heterozygosis of two known pathogenic mutations: p.Leu279Arg and a large fragment deletion on exon8/exon9/exon10. With a low fat, vitamin enriched diet, TG level was controlled and the boy continued normal development.



Clinical References

Wu BB, Gao Rui. et. al. **Application of targeted next generation sequencing in the molecular diagnosis of abnormal mass spectrometry analysis findings.** Chin J Evid Based Pediatr. 2015 Feb, Vol10, No1.doi:10.3969/j.issn.1673-5501.2015.01.007[Chinese]

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Christianson A., Howson C., Modell B, **March of Dimes, Global Report On Birth Defects,** p2, March of Dimes Birth Defects Foundation White Plains, New York 2006

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Please visit our website for
more information

www.medgen.com.pk

Information is for qualified healthcare professionals only.

Information is not meant to substitute qualified medical advice and is for reference only.

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Any patient treatment plans, including drug guidance, should only be recommended and provided by a qualified healthcare professional.

BGI recommends that non-directive genetic counseling and guidance always be provided to patients prior to undertaking any genetic testing and when reviewing results with the patient.

Accuracy of genetic testing may be affected by certain clinical factors. Therefore, test results should always be interpreted in the context of other clinical and family information of the patient.

Informed consent should always be obtained from the patient prior to testing.

MedGEN
Complete Health Solution

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