Invitae Elevated Very Long Chain Fatty Acids Panel (including X-ALD): Disorders Tested

The Invitae Elevated Very Long Chain Fatty Acids Panel (including X-ALD) analyzes genes that are associated with elevated very long chain fatty acids on newborn screening or plasma very long chain fatty acid analysis including but not limited to X-linked adrenoleukodystrophy, Zellweger Spectrum disorders, bile acid synthesis disorders and Aicardi-Goutieres syndrome. These genes were selected based on the available evidence to date to provide a broad panel for conditions associated with elevated very long chain fatty acids. Conditions associated with elevated very long chain fatty acids are genetically heterogeneous, and broad panel testing allows for an efficient evaluation of many potentially relevant genes based on a single clinical indication.

Disorders Tested	Disorder Description	PMID	Gene
Achalasia-Addisonism-Alacrima syndrome (Triple A)	Achalasia-Addisonism-Alacrima (Triple A) syndrome is an autosomal recessive neurological condition primarily caused by dysfunction of the autonomic nervous system. The majority of affected individuals manifest the three key features of the condition: alacrima, which is typically the first outward sign of the condition; achalasia; and Addison disease. Achalasia can lead to feeding difficulties and hypoglycemia, while Addison disease, also known as primary adrenal insufficiency, can result in fatigue, failure to thrive, hypotension, and hyperpigmentation. Additional features can include developmental delay and intellectual disability, dysarthria, microcephaly, muscle weakness, movement problems, peripheral neuropathy, short stature, osteoporosis, optic atrophy, and dermatological abnormalities. The clinical presentation and age of onset of this condition can vary among affected individuals and even among members of the same family (PMID: 11159947, 16609705, 12429595).	11159947, 16609705, 12429595	AAAS
X-linked adrenoleukodystrophy (X-ALD)	X-linked adrenoleukodystrophy is a metabolic disorder (X-ALD) caused by impaired peroxisomal beta oxidation that leads to the accumulation of saturated very long chain fatty acids (VLCFA) in numerous tissues throughout the body (PMID: 16380594). The condition has a broad range of clinical phenotypes, including adrenocortical insufficiency, progressive myelopathy, peripheral neuropathy and fatal childhood-onset cerebral demyelinating disease, cerebral adrenoleukodystrophy (PMID: 25115486). Individuals with the same ABCD1 variant can have entirely different neurological and neuropathologic symptoms (PMID: 7811247, 8048932). Females typically present at a later age than males, and rarely develop adrenocortical insufficiency or cerebral adrenoleukodystrophy (PMID: 25115486). Elevated levels of VLCFA in plasma and/or cultured skin fibroblasts can be detected in males and in 85% of females (PMID: 9894883). X-ALD is included in the RUSP newborn screening panel.	7811247, 8048932, 25115486, 9894883	ABCD1
ABCD3-related disorder of bile acid biosynthesis	The ABCD3 gene currently has no well-established disease association; however, there is preliminary evidence supporting a correlation with a disorder of bile acid biosynthesis (PMID: 25168382).	25168382	ABCD3
Cone-rod dystrophy and white matter disease	Pathogenic ACBD5 variants have been found in patients with syndromic features characterized by retinal dystrophy and severe white matter disease, including progressive leukodystrophy (PMID: 23105016). The symptoms typically become evident in the first two years of life. Some affected individuals were reported to have additional symptoms of spastic paraparesis, cleft palate, or ataxia (PMID: 23105016, 27799409). Emerging studies indicated that ACBD5 defect leads to accumulation of very long-chain fatty acids (VLCFAs) as a result of impaired peroxisomal β-oxidation (PMID: 27799409, 27899449). The disorder is inherited in an autosomal recessive fashion.	23105016, 27799409, 27899449	ACBD5
Acyl-CoA oxidase deficiency	Acyl-CoA oxidase deficiency is a severe, autosomal recessive peroxisomal leukodystrophy, which manifests in the neonatal period with seizures and hypotonia, which develops into hyperreflexia. Characteristic features include hypertelorism, low nasal bridge, low-set ears, polydactyly, and hepatomegaly. Some affected individuals have hearing and vision loss and experience developmental regression between 1 and 3 years of age (PMID: 18536048, 17458872). Progressive white matter demyelination with abnormal signals in the brainstem and cerebellum have been reported (PMID: 2894756, 8279468, 15065573). Laboratory findings include elevated liver enzymes and very long-chain fatty acids in plasma. The penetrance of this condition is high and death occurs in early childhood (PMID: 18536048, 17458872).	18536048, 17458872, 2894756, 8279468, 15065573	ACOX1
ACOX2-related disorder of bile acid biosynthesis	The ACOX2 gene currently has no well-established disease association; however, there is preliminary evidence supporting a correlation with autosomal recessive bile acid synthesis defect (PMID: 27647924).	27647924	ACOX2
Aicardi-Goutieres syndrome	Aicardi Goutieres syndrome (AGS) associated with ADAR is an autosomal recessive early-onset inflammatory encephalopathy characterized by basal ganglia calcification, white matter abnormalities and a chronic cerebrospinal fluid lymphocytosis with elevated interferon-alpha (PMID: 23622384, 22149989). AGS can be broadly divided into neonatal and later-onset forms. The neonatal form often manifests with neurologic findings including jitteriness, seizures, poor feeding, hepatosplenomegaly and thrombocytopenia with anemia requiring transfusions. The later-onset form presents with a sub-acute encephalopathy and developmental regression anytime after the first few weeks of life following a period of normal development. Premature death occurs before 20 years of age in approximately 25% of affected individuals (PMID: 22149989). Brain calcifications have also been identified prenatally (PMID:15662687). Brain MRI findings include bilateral striatal necrosis, signal changes in the caudate and putamen, and intracranial calcifications (PMID: 24262145).	23622384, 22149989, 15662687	ADAR

Alpha-methylacyl-CoA racemase deficiency (AMACR)	Alpha-methylacyl-CoA racemase (AMACR) deficiency is an autosomal recessive peroxisomal disorder characterized by accumulation of pristanic acid and bile acid intermediates. Age of onset ranges from infancy to adulthood. Individuals may present in infancy with coagulopathy and cholestasis due to bile acid abnormalities. Those presenting later in life typically experience seizures in the second decade and subsequent central and peripheral nervous system involvement including encephalopathy, sensorimotor neuropathy, pyramidal tract signs, and migraines. Primary hypogonadism has been observed in males, and ophthalmologic abnormalities have also been reported (PMID: 12512044, 20821052). Biochemical findings include elevated serum pristanic acid and elevated pristanic/phytanic ratio (PMID: 20821052). Brain MRI may reveal deep white matter changes in the pons, basal ganglia, thalami, and cerebral peduncles in affected individuals (PMID: 20821052, 15249642).	12512044, 20821052, 15249642	AMACR
Metachromatic leukodystrophy	Metachromatic leukodystrophy is an autosomal recessive neurodegenerative lipid storage disorder caused by the accumulation of sulfatides in the nervous system, which results in the destruction of the myelin sheath surrounding nerves in both the central and peripheral nervous systems (PMID: 19989245, 25987178). Earlier onset forms generally become apparent during the second year of life with loss of developmental milestones, gait disturbances, muscle weakness, seizures, behavioral issues and peripheral neuropathy (PMIDs: 14206875, 5110535). Later onset forms of the condition may present initially with changes in behavior and/or psychiatric symptoms followed by muscle weakness, peripheral neuropathy, tremor, seizures, and dementia (PMID: 2876627, 3813937, 15710861). Sulfatide accumulation also occurs in visceral organs and has been associated with gallbladder dysfunction and pathology (PMIDs: 25569213, 29494779, 27993207). Affected individuals exhibit decreased arylsulfatase A (ARSA) activity in various tissues, leukocytes and fibroblasts, along with increased urinary sulfatide excretion (PMIDs: 4953831, 4192207, 6054756).	19989245, 25987178, 14206875, 5110535, 2876627, 3813937, 15710861, 25569213, 29494779, 27993207, 4953831, 4192207, 6054756	ARSA
X-linked deafness, dystonia, and cerebral hypomyelination syndrome	X-linked deafness, dystonia, and cerebral hypomyelination syndrome are characterized by intellectual disability, dyskinetic movements, failure to thrive, hearing loss, and hypomyelinating white matter abnormalities (PMID: 24011989). Heterozygous females were previously thought to be asymptomatic; however, there is a report of one affected female with sensorineural hearing loss (PMID:11992258, 31330203, 28332767).	24011989, 11992258, 31330203, 28332767	BCAP31
Neuronal ceroid lipofuscinosis type 3 (CLN3)	Neuronal ceroid lipofuscinosis 3 (CLN3) is an autosomal recessive condition characterized by the storage of autofluorescent material in neurons and other cells, resulting in neurodegeneration. Juvenile-onset CLN3 presents between the ages of four and ten with rapidly progressive vision loss, followed by seizures and developmental regression affecting intellectual and motor abilities. Lifespan is reduced with most individuals living into the second or third decade. Case reports of individuals with protracted disease and one case of infantile-onset disease have been reported (PMID: 21990111, 20301601). Retinitis pigmentosa (RP) is a genetically heterogeneous group of inherited eye conditions with degeneration of the retina, beginning in the midperiphery and advancing toward the macula and fovea (PMID: 17296890). CLN3-related non-syndromic RP occurs without signs or symptoms of neurologic involvement, with age of onset ranging from childhood to the fifth decade in reported cases (PMID: 28542676). Symptoms include night blindness followed by constriction of peripheral visual fields, which leads to tunnel vision and eventually loss of central vision (PMID: 28542676, 17296890).	21990111, 20301601, 17296890, 28542676	CLN3
Encephalopathy due to defective mitochondrial and peroxisomal fission 1 (EMPF1)	Encephalopathy due to defective mitochondrial and peroxisomal fission 1 (EMPF1) is an autosomal recessive condition associated with infantile to childhood-onset encephalopathy, microcephaly, developmental delay, hypotonia, refractory seizures, structural brain abnormalities, and optic atrophy/hypoplasia (PMID: 26825290, 27328748, 15791210, 17682056).	26825290, 27328748, 15791210, 17682056	DNM1L
Krabbe disease	Krabbe disease is an autosomal recessive lysosomal storage disorder caused a deficiency of the enzyme galactosylceramidase, which is involved in the production of the myelin sheath surrounding nerve cells. It is characterized by damage to the brain due to progressive loss of myelin and the symptoms vary in age of onset and severity. Two main presentations are recognized based on age of onset and symptoms, including early infantile (onset under 12 months), and late-onset (at 12 months or older) (PMID: 24384330). The early-infantile phenotype, which constitutes 85-95% of Krabbe disease, is characterized by initial symptoms such as crying and irritability, poor feeding and failure to thrive, stiffness, poor head control, seizures, hyperpyrexia, exaggerated startle, fisting, and loss of smiling. It is followed by a rapidly progressive stage, which can include optic atrophy and slow pupillary reflexes, hypertonia and extension of the limbs, myoclonic jerks, hyper- or hyporeflexia, psychomotor regression, and point opisthotonus. The average life expectancy of the early infantile presentation is 24 months, and end-stage symptoms include vision and hearing loss, decerebrate posturing, loss of ability to feed, and loss of voluntary movement. The late onset form is more variable and can include late infantile, juvenile, and adult ages of onset and presentations (PMID: 24384330). Clumsiness, frequent falls, ataxia, hemiparesis, motor deterioration, spasticity, peripheral neuropathy, cognitive decline, and vision loss are common symptoms. Life expectancy can range depending on the severity of the disease.	24384330	GALC

D-bifunctional protein deficiency (DBP), Perrault syndrome	The HSD17B4 gene is associated with autosomal recessive D-bifunctional protein (DBP) deficiency and autosomal recessive Perrault syndrome. DBP deficiency is an inborn error of peroxisomal fatty acid oxidation with variable clinical presentation (PMID: 16385454, 24553428). Severely affected individuals typically present with neonatal hypotonia, severe psychomotor delay, and seizures within the first month of life and do not survive past the age of 2 years; visual impairment, deafness, and dysmorphic features are also common, as well as elevated plasma very long chain fatty acids (PMID: 16385454). Those with a juvenile-onset form typically have relatively normal development in early childhood and then develop progressive cerebellar and sensory ataxia, deafness, retinitis pigmentosa, and cognitive and language deficits in late childhood or adolescence. Additionally, variants in the HSD17B4 gene are associated with Perrault syndrome, a sex-influenced autosomal recessive disorder (28830375, 20673864). Perrault syndrome is characterized by premature ovarian failure in females and normal pubertal development and fertility in males. Affected individuals typically develop sensorineural hearing loss, with a slowly progressive peripheral neuropathy, cerebellar ataxia and cognitive decline with variable age of onset, and normal very long chain fatty acids (PMID: 28830375, 20673864).	16385454, 24553428, 28830375, 20673864	HSD17B4
Aicardi-Goutieres syndrome	Aicardi Goutieres syndrome (AGS) associated with IFIH1 is an autosomal dominant early-onset inflammatory encephalopathy characterized by basal ganglia calcification, white matter abnormalities and a chronic cerebrospinal fluid lymphocytosis with elevated interferon-alpha (PMID: 23622384, 22149989). AGS can be broadly divided into neonatal and later-onset forms. The neonatal form often manifests with neurologic findings including jitteriness, poor feeding, seizures, hepatosplenomegaly, and thrombocytopenia with anemia requiring transfusion. Brain calcifications have also been identified prenatally (PMID:15662687). The later-onset form presents with a sub-acute encephalopathy and developmental regression anytime after the first few weeks of life following a period of normal development. Premature death occurs before 20 years of age in approximately 25% of affected individuals (PMID: 22149989).	23622384, 22149989, 15662687	IFIH1
Encephalopathy due to defective mitochondrial and peroxisomal fission (EMPF2)	Encephalopathy due to defective mitochondrial and peroxisomal fission (EMPF2) is an autosomal recessive condition characterized by early onset encephalopathy, hypotonia, seizures, hypsarrhythmia, developmental delay, developmental regression, microcephaly, optic atrophy, external ophthalmoparesis, spasticity and abnormally brisk reflexes (PMID: 26783368, 22499341). Affected individuals have difficulty sitting independently or walking. Speech is typically absent or limited. Swallowing is difficult (dysphagia) and individuals may require feeding support, such as a feeding tube. Life span and prognosis are dependent upon the severity of symptoms. Blood lactate levels may be normal or increased. Fibroblasts show evidence of abnormal mitochondrial and peroxisomal fission with elongation of both structures in most affected individuals. Brain MRI typically reveals lesions in the basal ganglia and cerebellar atrophy.	26783368, 22499341	MFF
NR0B1-related conditions	The NR0B1-related conditions are associated with X-linked congenital adrenal hypoplasia and disorders of sex development. Males with X-linked congenital adrenal hypoplasia (CAH) typically present with adrenal insufficiency manifesting as salt wasting and failure to thrive in infancy or childhood. However late-onset adrenal insufficiency has been reported (PMID: 10022408, 12519885). Hypoglycemia and seizures may be the first symptom and complications affecting neurological development may occur if adrenal insufficiency is untreated. Hypogonadotropic hypogonadism is a common feature of X-linked CAH during adolescence and results in delayed puberty and incomplete sexual maturation, while precocious puberty can occur in infants (PMID: 19508677). Heterozygous female carriers may have symptoms of delayed puberty (PMID: 10210708, 10599709). Duplications of the NR0B1 gene have been associated with disorders of sex development due to failure of testis development (PMID: 20685758).	10022408, 12519885, 19508677, 10599709, 20685758	NR0B1
Zellweger spectrum disorder (ZSD)	Zellweger spectrum disorders (ZSD) are autosomal recessive peroxisomal biogenesis disorders comprised of 3 overlapping clinical subtypes: Zellweger syndrome, which presents neonatally with dysmorphic facial features, respiratory complications, liver dysfunction, brain abnormalities, and profound neurological symptoms including developmental delay, seizures, hypotonia and ataxia; neonatal adrenoleukodystrophy, which presents with predominantly neurological symptoms; and infantile Refsum disease, which presents with predominantly gastrointestinal signs including failure to thrive, hypercholesterolemia and cholestasis (PMID: 22483868, 22871920). ZSDs are progressive and typically result in a shortened lifespan; however, age of onset and severity are highly variable (PMID: 26750748, 15098234, 22871920, 26287655). Elevated plasma very long chain fatty acids, increased pipecolic acid, increased phytanic acid and decreased plasmalogens are characteristic of ZSD (PMID: 26750748).	22483868, 22871920, 26750748, 15098234, 26287655	PEX1, PEX10, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6
Zellweger spectrum disorder (ZSD)	Zellweger spectrum disorder (ZSD), an autosomal recessive condition caused by PEX11B, has an atypical, milder presentation, characterized by congenital cataracts, poor growth, sparse hair, dry skin, gastrointestinal issues, with varying degrees of intellectual and motor delays (PMID: 22581968, 28129423). While only a limited number of affected individuals have been reported to date, all have had normal or only minimally perturbed very long chain fatty acids, phytanic acid, pipecolic acid, and plasmalogens (PMID: 31724321).	22581968, 28129423, 31724321	PEX11B

Rhizomelic chondrodysplasia punctata	Rhizomelic chondrodysplasia punctata is an autosomal recessive disorder of peroxisome metabolism characterized by rhizomelic shortening of the upper extremities, contractures, bilateral congenital cataracts, dysmorphic facial features, seizures, and severe growth and developmental delay (PMID: 9536089, 12687664). Punctate epiphyseal calcifications, metaphyseal dysplasia and vertebral coronal clefts are seen on skeletal X-rays. Brain anomalies have been reported on cranial MRI (white matter abnormalities, cerebral and cerebellar atrophy) (PMID: 21990100). Life expectancy is usually shortened and affected children may only survive the first decade; however, milder phenotypes have been reported (PMID: 21990100, 12325024). Biochemical findings include plasmalogen deficiency, with the most severely affected individuals typically having the lowest erythrocyte plasmalogen levels. However, in rare cases normal plasmalogen levels have been reported (PMID: 27089543). In addition, phytanic acid levels are elevated in type 1 and type 5 RCDP (PMID: 27089543).	9536089, 12687664, 21990100, 12325024, 27089543	PEX7
Refsum disease	Refsum disease is an autosomal recessive condition caused by impaired function of phytanoyl-CoA hydroxylase, which is a peroxisomal protein involved in the metabolism of the branched chain fatty acid called phytanic acid (PMID: 9326939). Clinical symptoms are variable, with onset between the first and third decade of life and can include: retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, elevated protein levels in the cerebrospinal fluid, cardiac dysfunction, nerve deafness, ichthyosis, and multiple epiphyseal dysplasia (PMID: 2433405, 2433405). Biochemical features include: accumulation of phytanic acid and pipecolic acid in tissue and blood, and increased C26-C22 fatty acid ratios (PMID: 2433405, 2452736).	9326939, 2433405, 2452736	PHYH
Neuronal ceroid lipofuscinosis 1 (CLN1)	Neuronal ceroid lipofuscinosis 1 (CLN1) is an autosomal recessive condition characterized by storage of autofluorescent material in neurons and other cells, resulting in neurodegeneration. Classic infantile CLN1 disease typically presents between six and 24 months of age with decline of motor and cognitive abilities, hypotonia, ataxia, vision loss, white matter abnormalities, and seizures (PMID: 5706364, 8576553, 4698309). Lifespan is significantly reduced with few individuals living beyond the early-teen years. Late-infantile CLN1 disease typically presents between 18 months and three years of age (PMID: 8576553). Juvenile CLN1 disease typically presents between four and ten years of age with learning difficulties followed by regression of motor and intellectual abilities, vision loss, and seizures (PMID: 7668323). Adult CLN1 disease has been reported in three cases which presented in the late teens, early thirties, and late thirties (PMID: 21990111, 20301601). The palmitoyl-protein thioesterase 1 (PPT1) enzyme is deficient is CLN1. Historically, electron microscopy was also utilized to aid in diagnosis.	5706364, 8576553, 4698309, 7668323, 21990111, 20301601	PPT1
Aicardi-Goutieres syndrome	Aicardi Goutieres syndrome (AGS) is an autosomal recessive early-onset inflammatory encephalopathy characterized by basal ganglia calcification, white matter abnormalities and a chronic cerebrospinal fluid lymphocytosis with elevated interferon-alpha (PMID: 23622384, 22149989). AGS can be broadly divided into neonatal and later-onset forms. The neonatal form often manifests with neurologic findings including jitteriness, poor feeding, seizures, hepatosplenomegaly and thrombocytopenia with anemia requiring transfusion. Brain calcifications have also been identified prenatally (PMID:15662687). The later-onset form presents with a sub-acute encephalopathy and developmental regression anytime after the first few weeks of life following a period of normal development. Premature death occurs before 20 years of age in approximately 25% of affected individuals (PMID: 22149989).	23622384, 22149989, 15662687	RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1
Sterol carrier protein x deficiency, Leukoencephalopathy with dystonia and motor neuropathy	The SCP2 gene is associated with autosomal recessive leukoencephalopathy with dystonia and motor neuropathy and autosomal recessive sterol carrier protein x deficiency. Leukoencephalopathy with dystonia and motor neuropathy is an adult-onset condition characterized by dystonic head tremor, spasmodic torticollis, hypergonadotropic hypogonadism, hyposmia, saccadic eye movemen,t and hypoacusis (PMID: 16685654, 26497993). Brain imaging in affected individuals has revealed bilateral hyperintensities in the thalamus with lesions in the pons and occipital regions (PMID: 16685654). Sterol carrier protein x deficiency is characterized by adult onset ataxia and brain iron accumulation (PMID: 26497993).	16685654, 26497993	SCP2
Neuronal ceroid lipofuscinosis 2 (CLN2)	Neuronal ceroid lipofuscinosis 2 (CLN2) is an autosomal recessive condition characterized by neurodegeneration resulting from storage of autofluorescent material in neurons and other cells (PMID: 15965709). Classic late-infantile CLN2 typically presents between two and four years of age with seizures followed by cognitive decline, myoclonus, ataxia, and vision loss (PMID: 12376936). Three cases of infantile CLN2 have been reported with onset within the first year of life (PMID: 21990111, 20301601). Juvenile CLN2 typically presents between the ages of six and ten years (PMID: 20301601). Lifespan is significantly reduced with few affected individuals living beyond the early teen years (PMID: 20301601). Biochemical analysis of deficient TPP1 enzyme activity in leukocytes, fibroblasts or dried blood spots is diagnostic (PMID: 27553878).	15965709, 12376936, 21990111, 20301601, 27553878	TPP1

Aicardi-Goutieres syndrome 1 (AGS1), Retinal vasculopathy with cerebral leukodystrophy	The TREX1 gene is associated with autosomal dominant retinal vasculopathy with cerebral leukodystrophy and autosomal recessive Aicardi Goutieres. Retinal vasculopathy is an adult-onset neuro-vascular condition characterized by central nervous system degeneration and retinal vasculopathy which results in cognitive decline, stroke, progressive loss of vision, and motor impairment (PMID: 25213617, 17660820). Periventricular white matter lesions, progressive subcortical contrast-enhancing lesions with surrounding edema, mimicking tumors have been observed on brain imaging (PMID: 11438888, 2817001). Aicardi Goutieres is a neonatal onset encephalopathy characterized by cerebral atrophy, intracranial calcifications, leukodystrophy, and chronic cerebrospinal fluid lymphocytosis with elevated alpha-interferon (PMID: 16845398, 17846997, 22149989). Affected infants typically present with jitteriness, poor feeding, seizures, hepatosplenomegaly and thrombocytopenia with anemia requiring transfusions (PMID: 17846997). While typically associated with autosomal recessive inheritance, affected individuals with heterozygous TREX1 mutations have been reported (PMID: 20799324). Symptoms include painful, cold- and wet-induced skin lesions (chilblains) primarily affecting acral areas (PMID: 17357087, 25517357).	16845398, 17846997, 22149989, 20799324, 17357087, 25517357, 25213617, 17660820, 11438888, 2817001	TREX1

Invitae Elevated Very Long Chain Fatty Acids Panel (including X-ALD): Clinical Summary

Indications for Invitae Elevated Very Long Chain Fatty Acids Panel (including X-ALD)			
Signs and Symptoms	The Invitae Elevated Very Long Chain Fatty Acids Panel (including X-ALD) analyzes genes that are associated with elevated very long chain fatty acids on newborn screening or plasma very long chain fatty acid analysis including, but not limited to X-linked adrenoleukodystrophy, Zellweger Spectrum disorders, bile acid synthesis disorders, and Aicardi-Goutieres syndrome. Additional biochemical features can include differences in phytanic acid, pristanic acid, plasmologens and pipecolic acid. The conditions on this panel exhibit variable phenotypes and can have onset in infancy, childhood, adolescence or adulthood.		
Clinical Sensitivity	The clinical sensitivity of this test is dependent on the individual's underlying genetic condition. For each condition, the table below shows the percentage of clinical cases in which a pathogenic variant is expected through analysis of the genes on this panel. Conditions resulting in elevated very long chain fatty acids are genetically heterogeneous.The percentage of patients with conditions resulting in elevated very long chain fatty acids and a pathogenic variant in one of the genes offered in this panel has not been determined. A negative genetic test result does not rule out the possibility that an individual may have a genetic condition associated with elevated very long chain fatty acids.		

Clinical Sensitivity of Invitae Elevated Very Long Chain Fatty Acids Panel (including X-ALD)

Disorder	Gene	% of Disorder Attributed to Gene	References
X-linked adrenoleukodystrophy (X-ALD)	ABCD1	>99%	20301491
Cone-rod dystrophy and white matter disease	ACBD5	Rare	27799409, 23105016
Alpha-methylacyl-CoA racemase deficiency (AMACR)	AMACR	Rare	10655068, 12512044
Metachromatic leukodystrophy	ARSA	90-95%	10477432
Krabbe disease	GALC	>99%	26795590
D-bifunctional protein deficiency (DBP), Perrault syndrome	HSD17B4	Unknown, 7% of Perrault syndrome	16385454, 27650058, 26970254
Encephalopathy due to defective mitochondrial and peroxisomal fission (EMPF2)	MFF	<1%	26783368
Zellweger spectrum disorder (ZSD)	PEX1	58-68%	21031596
	PEX10	3-4.6%	
	PEX12	4.1-9%	
	PEX13	~1%	
	PEX14	~0.5%	
	PEX16	0.5-1%	
	PEX19	~0.5%	
	PEX2	1-4%	
	PEX26	3-6.6%	
	PEX3	~1-1.5%	
	PEX5	1.5-2%	
	PEX6	10.7-16%	
	PEX11B	Rare	RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1
Rhizomelic chondrodysplasia punctata	PEX7	97%	11781871, 12325024
Aicardi-Goutieres syndrome	ADAR	7%	25604658, 27643693
	RNASEH2A	5%	
	RNASEH2B	36%	
	RNASEH2C	12%	
	SAMHD1	13%	
	TREX1	23%	
	IFIH1	3%	
Sterol carrier protein X deficiency Leukoencephalopathy with dystonia and motor neuropathy	SCP2	Rare	26497993
Neuronal ceroid lipofuscinosis	CLN3	51%	27553520
	TPP1	30%	
	PPT1	9%	