Table S1. Rare genetic conditions for which the KD is contraindicated

Clinical Snapshot

Why KD is contraindicated?

These rare mutations lead to defects in ketone production (ketogenesis) or breakdown (ketolysis) that impair the body's ability to use ketones as fuel. **Clinical signs and symptoms** These disorders manifest with acute episodes of metabolic decompensation during any condition that causes hypoglycemia and subsequent increase in increase the body's demand for ketone bodies and fatty acids (e.g. carbohydrate restriction or prolonged fasting, exercise, and times of physiologic stress, such as illness, sleep deprivation, or extreme weather). These episodes present with abnormal levels of ketones and/or glucose in the blood (hypoketotic hypoglycemia or ketoacidosis), metabolic acidosis, and toxic effects on the brain leading to vomiting, dehydration, difficulty breathing, lethargy, seizures and coma.

Therapeutic considerations

Carbohydrates

While affected individuals should consume carbohydrates as part of their diets, especially before and during exercise, those who over-consume carbohydrates in hope of preventing acute attacks may be at higher risk of developing obesity and associated disorders with no proven benefit for the underling metabolic issue.

Dietary fatty acids and MCT supplementation for FAODs

Long-chain FAODs (i.e. deficiency of CPT2, CACT, VLCAD, and LCHAD) may benefit from reduction of dietary long-chain fatty acids and supplementation with MCT (15%– 18% of total calories) — which can bypass the block in long-chain FAO and improve exercise tolerance when administered before exercise (0.5 g/kg lean body weight) [PMID: 21763168, PMID: 22030098]. For LCHAD patients, MCT preparations with a higher ratio of decanoate to octanoate may be most effective to reduce the accumulation of potentially toxic long-chain 3-hydroxy-fatty acid [PMID: 12621125]. Infant formula should have reduced content of long-chain fatty acids plus MCT with continuous feeds for CACT neonates or every 2–3 hours during the day and continuous at night. In patients with primary carnitine deficiency, carnitine supplementation may be provided at a dose of 200 to 300 mg per kilogram of body weight divided throughout the day. In patients with pyruvate carboxylase deficiency, supplementation with thiamine has been shown to ameliorate symptoms likely by facilitating an alternative mechanism for pyruvate oxidation. Thiamine pyrophosphate is the coenzyme for pyruvate dehydrogenase, a key enzyme for an alternate route of pyruvate

Inborn errors of ketogenesis and ketolysis

Condition	Prevalence	Gene & best characterized mutations	Enzyme function & clinical signs	BHB levels	Blood Glucose
Mitochondrial HMG-CoA synthase 2 deficiency	< 20 patients reported worldwide	HMGCS2 rs137852636 rs137852637 rs137852638 rs137852639 rs28937320 rs137852640	Mitochondrial HMG-CoA synthase 2 catalyzes the condensation of acetyl-CoA and acetoacetyl-CoA to form HMG-CoA in the first steps of ketogenesis in the liver. Patients are generally asymptomatic unless during fasting or infection, which makes the diagnosis very difficult. Clinical manifestations include severe hypoketotic hypoglycemia, encephalopathy, and hepatomegaly. Genetic testing is required to confirm the diagnosis.	Low	Low
HMG-CoA lyase deficiency	About 100 cases reported in Saudi Arabia, Portugal, Spain	HMGCL rs752137615 rs121964996 rs121964997 rs121964998 rs786205431	HMG-CoA lyase catalyzes the formation of acetoacetate from HMG-CoA within the mitochondria in the liver and is required for the catabolism of the amino acid leucine in dietary proteins. Clinical acute symptoms usually appear within the first year of life often triggered by fasting, infection, or other types of stress. However, some patients can develop hypoglycemic crises and neurological symptoms even in adolescence or adulthood. They include: hypoketotic hypoglycemia due to	Low	Low

			impaired ketone production, organic acid buildup and metabolic acidosis due to defective breakdown of leucine, vomiting, seizures, and lethargy. If untreated, the disorder can lead to breathing problems, convulsions, coma, and death.		
SCOT deficiency	< 35 cases reported	OXCT1 rs121909299 rs121909300 rs267606930 rs75134564 rs121909301 rs121909302 rs121909303	SCOT/OXCT1 plays a central role in extrahepatic ketone body catabolism by catalyzing the reversible transfer of coenzyme A (CoA) from succinyl-CoA to acetoacetate. Impaired function of SCOT/OXCT1 results in inability to break down ketones outside the liver. This can result in permanent ketosis and attacks of ketoacidosis during illness or stress. While patients with "mild" SCOT mutations may be asymptomatic and have non-ketotic periods, those with more severe enzymatic defects can present persistent ketonemia and ketonuria.	High/ very high	High or low
Beta-ketothiolase deficiency	1 in 1 million	ACAT1 rs120074140 rs120074141 rs727503796 rs145229472 rs1131691567 rs1280110907 rs120074142 rs120074143 rs120074144 rs387906282 rs387906283 rs120074145 rs120074146 rs120074147 rs120074148 rs779565865	Mitochondrial ACAT1, also known as beta-ketothiolase or T2, carries out the last step of ketolysis in extra-hepatic tissues. In this reversible reaction acetoacetyl-CoA is broken down into two molecules of acetyl-CoAa, which can be used to produce energy. In the liver, ACAT1 carries out this chemical reaction in reverse, which is the first step in ketogenesis, and helps break down the amino acid isoleucine. Acute symptoms manifest during ketoacidotic attacks between the ages of 6 months and 24 months, which are often triggered by fasting, infection, or increased intake of protein-rich foods. Affected children present hyperketotic hypoglycemia and metabolic acidosis due to buildup of organic acids in the blood, which can damage the body's tissues and organs, particularly the nervous system. The resulting toxic encephalopathy can lead to vomiting, dehydration, difficulty breathing, lethargy leading to coma, and seizures. The clinical outcome greatly improves if the disease is diagnosed in the first ten days of life.	High/ very high	High or low
Fatty acid oxidation disorders (FAODs)					
Condition	**Prevalence**	**Gene & best characterized mutations**	**Enzyme function & clinical signs**	**BHB levels**	**Blood Glucose**
Primary carnitine deficiency	(1:200,000)	SLC22A5 rs72552727 rs121908887 rs386134217 rs72552735 rs121908888 rs121908889	Solute Carrier Family 22, Member 5 (SLC22A5) is a transmembrane protein that transports carnitine into cells in a sodium-dependent manner. Cells need carnitine to bring fatty acids into mitochondria to produce energy in form of ATP. Mutations in the SLC22A5	Low	Low

		rs121908890 rs68018207 rs121908891 rs121908892 rs121908893 rs267607054 rs267607053 rs267607052	gene result in an absent or dysfunctional SLC22A5 transporter leading to low intracellular and blood levels and urinary loss of carnitine. This results in reduced energy production within mitochondria, muscle weakness and hypoglycemia. Fatty acids may also build up in cells and damage the liver, heart, and muscles leading to hypertrophic cardiomyopathy, congestive heart failure, arrhythmias, sudden death, hypotonia, muscle weakness. Symptoms typically appear during infancy or early childhood but some people are asymptomatic.		
CPT1A deficiency	(1:50–100,000)	CPT1A rs80356778 rs80356787 rs80356774 rs80356790 rs80356791 rs80356798 rs1169875761 rs28936374 rs80356800 rs80356780 rs80356779	The CPT1A enzyme attaches carnitine to long-chain fatty acids to form acylcarnitines that can cross the inner membrane of mitochondria. Once these fatty acids are inside the mitochondria, they can be metabolized to produce energy after the remotion of carnitine. Mutations in the CPT1A gene reduce or eliminate the activity of the CPT1A enzyme (residual enzyme activity between 0 and 10%). As a result, carnitine is not attached to long-chain fatty acids, which cannot enter mitochondria and be converted into energy. This leads to low levels of ketones and glucose in blood (hypoketotic hypoglycemia). Fatty acids may also build up in cells and damage the liver, heart, and brain leading to cardiomyopathy (infantile form), congestive heart failure, muscle weakness, rhabdomyolysis, and exercise intolerance.	Low	Low
CPT2 deficiency	Myopathic form: >300 cases; severe infantile form (hepatocardiomuscular): ~30 families; lethal neonatal form: ~18 families.	CPT2 rs74315293 rs74315294 rs28936375 rs28936376 rs28936673 rs28936674 rs74315295 rs74315296 rs397509431 rs74315297 rs74315298 rs74315299 rs74315300 rs121918528 rs2229291 rs1799821	The CPT2 enzyme removes carnitine from fatty acids that have entered the mitochondria (acylcarnitines) and adds coenzyme A to form acyl-CoA esters that can be broken down to produce energy. Mutations in the CPT2 gene reduce the activity of the CPT2 enzyme. As a result, long-chain fatty acids remain attached to carnitine as acylcarnitines and cannot be metabolized to produce energy. This leads to low levels of ketones and glucose in blood (hypoketotic hypoglycemia). Fatty acids and long-chain acylcarnitines may also build up in cells and damage the liver, heart, and muscles causing the other signs and symptoms of the disorder. Mutations that lead to extremely reduced enzyme activity typically cause the more severe forms of CPT II deficiency (a lethal neonatal form and a severe infantile hepatocardiomuscular form), while those that result in partially reduced enzyme	Low	Low

			activity usually lead to a less severe myopathic form of the disorder. [1]		
CACT deficiency	~30 cases	SLC25A20[1] rs587776759 [1]rs1553686314 rs151340616 rs587776760 rs541208710 rs28934589 rs587777286 rs587777287	CACT transports long-chain fatty acids attached to carnitine (long-chain acylcarnitines) across the inner mitochondrial membrane as part of the carnitine shuttle system. Once acylcarnitines are inside the mitochondria, CACT removes carnitine, and transports it back out of mitochondria.[1][2]Mutations in the SLC25A20 gene reduce the activity of the CACT protein. As a result, long-chain fatty acids cannot be transported into mitochondria and converted to energy. This leads to low levels of ketones and glucose in blood (hypoketotic hypoglycemia). Fatty acids and long-chain acylcarnitines may also build up in cells and damage the liver, heart, and muscles leading to hypertrophic cardiomyopathy, congestive heart failure, arrhythmias, and muscle damage. Because neonates depend largely on metabolism of long-chain fatty acids for energy, children with severe CACT deficiency have a poor prognosis, with most dying before 1 year of age. Some affected individuals have a less severe form of the condition and do not develop signs and symptoms until early childhood. These individuals are at risk for liver failure, nervous system damage, coma, and sudden death.	Low (neonatal, severe)	Low (neonatal, severe)
MCAD deficiency	(1:10–15,000)	ACADM[1] rs77931234[1]rs1225471006 rs121434274 rs121434275 rs121434276 rs121434277 rs387906297 rs864621963 rs121434278 rs121434279 rs121434280 rs121434281 rs121434282 rs121434283 rs74090726	MCAD is required to metabolize a group of fats called medium-chain fatty acids (MCTs). These fatty acids are found in foods and body fat and are produced when longer fatty acids are metabolized. MCAD catalyzes the initial reaction in the beta-oxidation of C4 to C12 straight-chain acyl-CoA esters. [1][2]Mutations in the ACADM gene reduce the activity of the MCAD protein. The resulting defect in the oxidation of MCTs to acetyl-CoA, which is used to produce ketones, can lead to hypoketotic hypoglycemia and lack of energy (lethargy), particularly during periods of fasting, although some individuals remain completely asymptomatic in absence of significant metabolic stress. MCTs or partially metabolized fatty acids may build up in tissues, damage the liver and brain, inhibit gluconeogenesis, and produce metabolic acidosis. This abnormal buildup causes the other signs and symptoms of MCAD deficiency. These include muscle weakness, exercise intolerance, rhabdomyolysis. Symptoms typically appear during infancy or early childhood.	Lack or only trace of urinary ketones	Low

			Possible complications include seizures, breathing difficulties, liver problems, brain damage, coma, and sudden death.		
VLCAD deficiency	(1:40-80,000)	ACADVL rs113690956 rs118204014 rs387906249 rs387906251 rs387906252 rs118204015 rs2309689 rs118204016 rs387906253 rs28934585 rs118204017 rs118204018 rs118204016	VLCAD is bound to the inner mitochondrial membrane, where it catalyzes the first intramitochondrial step of the oxidation of long-chain fatty acids to acetyl-coA for the production of ketones and energy.Mutations in the ACADVL gene severely reduce or abolish the activity of the VLCAD enzyme. Like with other FAO disorders, this leads to hypoketotic hypoglycemia and lethargy, particularly during periods of fasting. Very long-chain fatty acids or partially metabolized fatty acids may build up in tissues and damage the heart, liver, and muscles leading to the other signs and symptoms of VLCAD deficiency. These include hypertrophic ardiomyopathy, arrhythmias, sudden death, muscle weakness, exercise intolerance, recurrent rhabdomyolysis, hypoketotic hypoglycemia, and “Reye-like” hepatic syndrome.	Lack or only trace of urinary ketones	Low or normal
SCAD deficiency	(1:35,000-50,000)	ACADS rs121908003 rs61732144 rs121908004 rs57443665 rs28940872 rs1800556 rs1799958 rs121908005 rs387906308 rs28940874 rs121908006 rs28941773 rs28940875 rs147442301 rs387906950 rs387906951	Acyl-CoA dehydrogenase short chain (ACADS) or SCAD catalyzes the first steps in the oxidation of short-chain fatty acids (SCFA) to acetyl-CoA, which is used to produce ketone bodies that can supply the energy needs to compensate for the lack of adequate glucose in presence of hypoglycemia.SCAD deficiency is viewed as a biochemical phenotype rather than a disease, and some people never develop any symptoms. When SCAD activity is reduced, short-chain fatty acids are not converted into energy, whereas some ketone formation can still occur. This can lead to hypoglycemia with normal or elevated ketones, lethargy, and muscle weakness. Metabolic decompensation is typically triggered by low blood sugar (e.g. fasting or increased energy expenditure due to a catabolic state such as infection, surgery, fever, etc.), which mobilizes FFAs for oxidation to acetyl-CoA and production of ketone bodies. The accumulation of fatty acid intermediates can also inhibit gluconeogenesis leading to metabolic acidosis with elevated ketone levels and toxic effect on the liver. Two distinct clinical phenotypes have been identified. One type has been observed in infants with acute acidosis and muscle weakness (generalized); the other has been observed in middle-aged patients with chronic myopathy (skeletal muscles).	High	Low

LCHAD	1: 62,000 (Finnish population, probably much lower in US)	HADHA rs137852769 rs137852770 rs786205088 rs781222705 rs137852771 rs137852772 rs137852773 rs137852774 rs137852775	Hydroxyacyl-Coa Dehydrogenase, Alpha Subunit (HADHA) is part of a protein complex called mitochondrial trifunctional protein, which is required to break down long-chain fatty acids. Four alpha subunits are produced from the HADHA gene, and four beta subunits are produced from the HADHB gene. Like other FAO disorders, LCHAD deficiency due to HADHA mutations leads to hypoketotic hypoglycemia and lethargy, particularly during periods of physiological stress such as fasting, illnesses, or weather extremes. Long-chain fatty acids or partially metabolized fatty acids may also build up in the liver, heart, muscles, and retina, inhibit gluconeogenesis, and produce metabolic (including lactic) acidosis. Affected infants and children usually present by 2 years of age. Muscle, particularly myocardium, requires a lot of energy and, therefore, becomes functionally impaired resulting in lethargy, hypotonia, cardiomyopathy, and risk of sudden death. Early-onset symptoms include cardiomyopathy, hypoglycemia, neuropathy, and pigmentary retinopathy. Later in childhood, people may experience muscle pain, breakdown of muscle tissue, and a loss of sensation in their arms and legs (peripheral neuropathy).	Lack or only trace of urinary ketones	Low
Pyruvate carboxylase deficiency	1 in 250,000	PC rs28940589 rs28940590 rs28940591 rs113994143 rs119103241 rs119103242	Pyruvate carboxylase is active in mitochondria, where it is involved in gluconeogenesis in kidneys, liver, and pancreas, where it helps regulate insulin secretion, lipogenesis in adipose tissue, and synthesis of neurotransmitters and myelin in the brain. In newborns, acetyl-CoA derived from pyruvate metabolism is an important source of energy. Pyruvate carboxylase deficiency leads to defective production of glucose through gluconeogenesis and accumulation of lactic acid and ammonia, which damages organs and tissues. Ketone levels are increased, especially during any condition leading to hypoglycemia such as carbohydrate restriction and prolonged fasting. Myelin formation and neurotransmitter production are also impaired, contributing to the neurologic features of pyruvate carboxylase deficiency.	High	Low
ALAD deficiency porphyria	Only ~10 cases, all males, have been reported worldwide. This is in contrast to	ALAD rs121912980 rs121912981 rs1800435 rs121912982	ALAD combines two molecules of delta-aminolevulinic acid (ALA) to form porphobilinogen (PBG) for the production of heme. Heme is vital for all of the body's organs, although it is found	Not affected	Not affected

	the other acute porphyries, in which more women are symptomatic.	rs121912983 rs121912984 rs749066913	mostly in the blood, bone marrow, and liver. [1] [2] Hereditary ALAD deficiency is extremely rare whereas acquired forms due to enzymatic inhibition through heavy metal (e.g. lead) poisoning, are more common. ALAD deficiency results in build-up of toxic levels of ALA in the body leading to acute attacks characterized by abdominal pain, vomiting, muscle weakness, seizures, fever, and neurological symptoms such as anxiety and hallucinations. These signs and symptoms can be life-threatening, especially if the muscles that control breathing become paralyzed. Any condition leading to hypoglycemia such as prolonged fasting and very low carbohydrate diets, can trigger acute attacks in some undiagnosed and non-symptomatic individuals by increasing excretion of heme precursors.

Abbreviations. SNP identification numbers (noted as "rs...") are the unique SNP identifiers from the NCBI dbSNP database. HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA; SCOT: Succinyl-CoA:3-ketoacid CoA transferase; OXCT1: 3-oxoacid CoA-transferase 1; ACAT1: Acetyl-CoA acetyltransferase 1; FAOD: fatty acid oxidation disorders; FFAs free fatty acids; CPT1A: Carnitine palmitoyltransferase 1A; CPT2: carnitine palmitoyltransferase 2; CACT: carnitine-acylcarnitine translocase; MCAD: medium-chain acyl dehydrogenase; VLCAD: very long-chain acyl dehydrogenase deficiency; SCAD: short-chain acyl dehydrogenase; LCHAD: long-chain 3-hydroxyacyl-CoA deficiency; MCTs: medium-chain fatty acids; ALAD: Delta-aminolevulinic acid dehydratase; BHB: beta-hydroxybutyrate. Blood levels of BHB and glucose refer to those observed during metabolic decompensation unless otherwise stated.

Table S2. Rare genetic conditions for which KD may be indicated

Clinical Snapshot

Why KD is indicated?
KD is a first-line therapy in children with GLUT1-DS and PDCD, which impair the production of energy from glucose thus leading to alterations in brain development and function. In both conditions, KD provides ketones as an alternative fuel for the brain and the body thus producing significant improvements in neurological symptoms (motor function, seizures, cognitive performance).

KD can also ameliorate symptoms and laboratory parameters in other rare conditions such glycogen storage disease, disorders of mitochondrial energy supply, urea cycle, purine metabolism and amino acid metabolism, and drug resistant epilepsy. In glycogen storage disease, the reduction of blood insulin levels and use of ketones as an alternative energy source likely underlies the reduction in glycogen storage and improvements in exercise tolerance observed in patients treated with KD. In the other conditions, KD leads to reduction or elimination of seizures and improvement of brain function and neurological symptoms through complex yet not fully elucidated mechanisms [PMID: 18266755].

Clinical signs and symptoms
These conditions have different etiology and clinical presentation. Please see the "Enzyme function and clinical signs" column for further details.

Therapeutic considerations
Therapeutic ranges of BHB and utility of using exogenous ketone supplementation differ among these conditions. Please refer to the "KD benefits and case reports" column for further details.

Genetic conditions in which KD directly targets the underlying metabolic defect

Condition	Prevalence	Gene & best characterized mutations	Enzyme function & clinical signs	Benefits of KD/exogenous ketones and case reports
GLUT1 deficiency syndrome	1:90000 (Australia)	SLC2A1 rs80359829 rs80359828 rs80359822 rs80359816 rs80359814 rs80359816 rs121909739 rs121909740 rs80359812 rs267607060 rs267607061 rs80359818 rs202060209 rs267607059 rs387907312 rs387907313 rs397514564 rs13306758 rs398123069 rs864309514 rs864309522	GLUT1 transports glucose into cells for use as fuel. In the brain, the GLUT1 protein is involved in moving glucose across the blood-brain barrier and between glia cells, which protect and support neurons. Impaired function of GLUT1 leads to reduced glucose available to brain cells and defects in brain development and function. In addition to mutations in the SLC2A1 gene, other gene mutations can lead to GLUT1 deficiency syndrome and explain a favorable response to KD.	KD is the first line therapy for GLUT1 deficiency. Ketone bodies bypass the GLUT1 defect and enter the brain by a monocarboxylic acid transporter (MCT1). Therapeutic ranges of blood ketones are 2-4 mM in presence of very low blood glucose levels (<40 mg/dL). Exogenous ketones have not been shown to provide additional benefits as adjunct therapy, possibly because MCT1 is already saturated at physiological levels of blood ketones typically induced by a ketogenic diet (1-3 mM) [PMID: 28510035, PMID: 25415176, PMID; 12555938; PMID 16217704; PMID 15622525; PMID: 25914049. Review: PMID 19304421].

PDC deficiency (PDCD)	Rare, ~500 reported cases, likely under-diagnosed	PDHA1 (80% of cases) rs606231184 rs606231185 rs137853250 rs137853251 rs606231186 rs606231187 rs606231188 rs137853259 rs137853252 rs606231189 rs137853253 rs137853254 rs137853255 rs137853256 rs2229137 rs606231190 rs137853257 rs606231191 rs137853258 rs1555935690 rs121917898 PDHB rs28935769 rs28933391 DLAT rs119103240 rs797044957 PDHX rs1554989996 rs724159828 rs724159829 rs724159830 rs724159979 rs113309941 rs387906998 rs1135402725 PDP1 rs1554572756 rs267606938	PDC converts pyruvate, which is formed from the breakdown of carbohydrates to acetyl-CoA. PDC is made up of several enzymes including pyruvate dehydrogenase or E1 (PDHA1 and PDHB genes), E2 (DLAT gene), E3, as well as the PDHX, PDP1 enzymes, which regulate the activity of the complex. Defects in any of these enzymes impair the function of PDHC resulting in decreased conversion of glucose-derived pyruvate into acetyl-CoA, buildup of lactate, and severe defects in brain development and function.	KD is the first line therapy for PDC deficiency [PMID: 30407699; PMID: 824610; PMID: 12621116]. Due to its low-carbohydrate content, KD lowers the production of lactate from pyruvate while providing ketones as an alternative fuel for energy production. Ketone bodies bypass the oxidation of pyruvate in mitochondria and provide an alternative route for the production of acetyl-CoA. Therapeutic ranges of BHB are 0.2-2 mM in presence of blood glucose levels <85 mg/dL. Exogenous ketones have been shown to have some efficacy as adjunct treatment to KD in PDCD children [PMID: 28510035].
Genetic conditions in which KD ameliorates clinical symptoms and laboratory parameters				
Condition	**Prevalence**	**Gene & best characterized mutations**	**Enzyme function & clinical signs**	**Benefits of KD/exogenous ketones and case reports**
Disorders of carbohydrate metabolism				

GSD type III (Forbes or Cori disease)	1 in 5,400 (North African Jewish population); 1 in 100,000 (United States)	AGL rs387906244 rs113994126 rs113994129 rs113994127 rs113994134 rs113994133 rs369973784 rs199922945 rs118203964 rs113994132 rs387906246 rs780504025 rs113994128 rs267606639 rs267606640	The glycogen debranching enzyme breaks down the side chains of glycogen, which stores energy from carbohydrates in muscle and liver. Different mutations in the AGL gene can affect different isoforms of this enzyme producing two clinical phenotypes: GSD IIIa, which involves liver and muscle, and GSD IIIb, which involves only the liver (Dagli et al 2010).	KD may reduce glycogen storage in muscle and liver through the reduction of blood insulin levels and provide an alternative fuel for energy through the induction of ketone bodies production. A few case studies reported that KD (classical KD or Modified Atkins Diet), with or without supplementation of exogenous ketones, significantly improved cardiomyopathy in GSD IIIa [PMID: 25308556 (n=2, cKD); PMID: 25431232 (n=2, MAD); PMID: 21857385 (n=1, 2:1 KD)].
GSD type V (McArdle's disease)	1:100,000	PYGM rs116987552 rs119103251 rs119103252 rs267606993 rs119103253 rs119103254 rs144081869 rs119103255 rs119103256 rs786200874 rs267606993 rs119103257 rs119103258 rs119103259 rs119103260 rs764313717 rs397514631	Myophosphorylase breaks down glycogen in muscle cells. Enzymatic defects can cause exercise intolerance with muscular pain and myoglobinuria.	KD may reduce glycogen storage in muscle and liver through the reduction of blood insulin levels and provide an alternative fuel for energy through the induction of ketone bodies production. A few case studies reported that KD induced a marked improvement in exercise tolerance and quality of life in both children and elderly patient [PMID: 18425888, PMID: 16049943, PMID: 17915573]
Disorders of mitochondrial energy supply				
mtDNA depletion syndromes (MDS)	Unknown. Together, mitochondrial diseases occur in about 1 in 4,000 people.	POLG rs113994099 rs113994095 rs121918044 rs121918045 rs121918046 rs113994098 rs113994094 rs121918047 rs121918048 rs121918049 rs113994096 rs121918050 rs113994097 rs121918051 rs41549716 rs121918052 rs1567185775 rs121918053 rs121918054 rs121918055 rs121918056 rs267606959	Polymerase gamma is one of the enzymes catalyzing mtDNA replication. Enzymatic defects can cause intractable epilepsy with variable associated clinical symptoms.	KD may reduce seizures. In a case study in 6 patients with POLG mutations, 5 of them experienced a substantial seizure reduction [PMID: 26109259].

MELAS	Unknown. Together, mitochondrial diseases occur in about 1 in 4,000 people.	MTTL1 rs199474657 rs199474658 rs199474659 rs199474660 rs199474661 rs199474662 rs199474663 rs199474664 rs199474665 rs199474666 rs199474667 rs199474668	Mitochondrial transfer-RNA, leucine, 1 (MTTL1) incorporates the amino acid leucine into mitochondrial proteins. MTTL1 mutations impair the ability of mitochondria to make proteins, use oxygen, and produce energy leading to neurological problems and other specific symptoms of MELAS.	KD may reduce seizures. The use of KD and magnesium citrate as add-on therapy to anti-epileptic drugs lead to complete remission of seizures in a 22-year old patient carrying the rs199474663 MTTL1 mutation [n=1; PMID: 24656211].
Disorders of the mitochondrial respiratory chain (MRC)				
Isolated complex I deficiency (NADH ubiquinone oxidoreductase deficiency)	1 in 8500	NDUFV1 rs121913659 rs768050261 rs121913660 rs121913661 rs199683937 ACAD9 rs387906242 rs387907041 rs387907042 rs368949613 rs115532916 rs377022708 rs762521317 rs1057518752 FOXRED1 rs267606829 rs267606830 rs387907087 Other genes involved: MTND1-6 MTFMT NDUFA1-2, 9-13 NDUFAF1-6 NDUFB3,9-11 NDUFS1-8 NDUFV1-2 NUBPL ELAC2 PPA2 TIMMDC1 TMEM126B MTTL1	Complex I is the first of five mitochondrial complexes that carry out a multi-step process called oxidative phosphorylation, through which cells derive much of their energy. Mutations in any of the components or regulators of Complex I can cause a wide variety of symptoms affecting many organs and systems of the body, particularly the nervous system, the heart, and skeletal muscle. They can also cause Leigh syndrome and Leber hereditary optic neuropathy.	MRC defects are one of the most common causes of childhood epilepsy PMID: 18266755. KD may reduce seizures. Compared to carbohydrate oxidation, beta-oxidation of fatty acids provides more FADH2, thereby bypassing complex I of the mitochondrial respiratory chain. A few case studies reported that KD may reduce seizure frequency (4:1 KD) (n=24; Lee et al 2008); n=9, Kang et al 2007; n=1, Seo et al 2010; n=1, Yoon et al 2014).), normalize cognitive function (n=1; Kang et al 2006), and improve ophthalmoplegia [n=1, PMID: 17162199]

Isolated complex II and IV deficiency and complex I/IV deficiency	Unknown	TMEM70 rs183973249 rs387907070 ATP5F1A rs587776960 rs587777788 ATP5F1E rs387906929 ATPAF2 rs104894554 MT-ATP6 rs199476133 rs199476135 MT-ATP8 rs267606881	Mutations in in mtDNA genes as well as in the nuclear gene TMEM70 can cause complex V deficiency. The resulting reduction in oxidative phosphorylation can lead to cell death by reducing the amount of energy available in the cell. Energy demanding organs, such as the nervous system, heart, liver, kidneys, and skeletal muscles, are most affected.	KD reduced or eliminated seizures in a few case studies of patients with different types of MRC deficiencies including isolated complex II, complex IV and complex I/IV deficiency [n=5, PMID: 17241212; n=24, PMID: 18266755]
Urea cycle disorders				
ASL deficiency	1 in 70,000 to 218,000	ASL rs28940585 rs28941472 rs28940287 rs28940286 rs28941473 rs28940287	ASL is an enzyme of the urea cycle, which processes excess nitrogen into urea. Urea is excreted by the kidneys preventing the buildup of nitrogen in the form of ammonia. ASL deficiency results in a buildup of ammonia, which damages the brain and other tissues causing frequent epilepsy, neurological problems, and other signs and symptoms of argininosuccinic aciduria.	KD with ongoing protein restriction may reduce seizure without aggravating hyperammonemia [n=2; PMID: 23430928].
Disorders of purine metabolism				
ADSL deficiency	Fewer than 100 cases reported	ADSL rs119450941 rs119450942 rs119450943 rs28941471 rs119450944	ADSL is a component of the purinosome, a protein complex involved in purine synthesis. ADSL deficiency impairs purine metabolism causing an accumulation of succinylaminoimidazole carboxamide riboside (SAICAr) and succinyladenosine (S-Ado), which are toxic to the brain and cause neurological problems. Approximately 50% of such patients present with epilepsy, which is often resistant to drugs.	KD reduced or eliminated seizures in two case studies of ADSL patients [n=1, PMID: 22140128; n=1, PMID: 23504561].

Disorders of aminoacid metabolism				
Non ketotic hyperglycinemia (NKH)	1 in 55-76000	GLDC rs121964974 rs121964975 rs121964976 rs386833549 rs121964977 rs121964978 rs121964979 rs121964980 AMT rs121964981 rs121964982 rs121964983 rs121964984 rs121964985 rs121964986 rs181134220 rs769468125	The glycine cleavage system (GCS) degrades the neurotransmitter glycine in the mitochondria. Mutations in the components of the GCS (GLDC, AMT, GCSH) cause accumulation of glycine in body fluids leading to severe neurological symptoms, including seizures, myoclonic jerks, and encephalopathy in the first days of life (neonatal form).	In a few reports, classical KD (4:1) in combination with antiepileptic drugs reduced seizures and glycine concentrations in cerebrospinal fluid and plasma, and improved quality of life. [n=3; PMID: 22261077, PMID: 26962342, PMID: 30108280].
Drug-Resistant Epilepsy				
Tuberous sclerosis complex (TSC)	1 in 6000	TSC1 rs118203447 rs118203597 rs118203557 rs118203426 rs118203396 rs137854251 rs137854083 TSC2 rs45512692 rs137854337 rs45517179 rs28934872 rs45517214 rs121964862 rs45483392 rs45516293 rs45517349 rs137854218 rs45517259 rs45517258 rs45517258 rs137854250 rs45515894	Hamartin (TSC1) and tuberin (TSC2) are tumor suppressors proteins that down regulate protein synthesis and cell growth in presence of cellular stress or DNA damage. Mutations in TSC1-2 can cause the formation of benign tumors in many parts of the body as well as brain problems such as seizures, hyperactivity and aggression, and intellectual disability.	KD should be considered as a therapeutic option for seizure reduction, along with other modalities such as surgical resection of one or more tubers, corpus callosotomy, and vagal nerve stimulation [PMID: 16996395: study population: 12 children aged 8 months to 18 years with drug-resistant epilepsy].

Developmental and epileptic encephalopathy (DEE)	Unknown; 60-65% of cases are undiagnosed due to genetic heterogeneity	SCN1A rs121918624 rs121918625 rs121918629 rs121918630 rs397514458 rs397514459 SCN2A rs387906683 rs387906684 rs387906685 rs387906686 KCNQ2 rs397514581 rs397515420 rs397514582 rs587777219 STXBP1 rs121918317 rs121918318 rs121918319 rs121918320 rs121918321 rs587776641	Developmental and epileptic encephalopathies (DEE) are a group of genetically heterogeneous disorders characterized by early-onset drug-resistant seizures, electroencephalographic abnormalities, and developmental delay. Dravet syndrome (DS) is one of the most genetically homogeneous DEEs, with more than than 80% of DS cases are attributable to variants in SCN1A.	The use of KD has been shown to produce a ≥90% seizure reduction in 77-100% of patients carrying mutations in SCN1A, SCN2A, KCNQ2, or STXBP1. [PMID: 30061856]
ATP1A3-Related Neurologic Disorders	1 in 1 million people	ATP1A3 rs80356537 rs387907281 rs387907282 rs398122887 rs398122887 rs587777771 rs267606670 rs80356532 rs606231441	The ATP1A3 gene encodes the alpha-3 catalytic subunit of the Na+/K(+)-ATPase transmembrane ion pump. It plays a key role in the regulation of electrical activity and neurotransmitter re-uptake in neurons. Mutations in ATP1A3 can cause rare neurological conditions such as alternating hemiplegia of childhood (AHC).	In a case report, KD reduced epileptic seizures and episodes of hemiplegia or uncontrolled movements, and produced long-term improvement of neurological development [n=1, PMID: 29395663].
MED23-associated refractory epilepsy	Unknown	MED23 rs370667926	Med23 is a component of the Mediator complex, a key regulator of protein-coding gene expression. Mutations in MED23 can cause neurological problems characterized by developmental delay and refractory epilepsy such as mental retardation, autosomal recessive 18 (MRT18).	KD eliminated seizures on the first day of administration in a case report in a 2.5 year old child with MED23 refractory epilepsy [PMID: 27311965].

Abbreviations. SNP identification numbers (noted as "rs...") are the unique SNP identifiers from the NCBI dbSNP database. GLUT1: Glucose transporter protein type; PDC: pyruvate dehydrogenase; GSD: glycogen storage disease type III; mtDNA: mitochondrial DNA; MELAS: mitochondrial encephalopathy with lactic acidosis and strokelike episodes syndrome;

ASL: argininosuccinate lyase; ADSL: adenylosuccinate lyase; AGL: amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase; TMEM70: transmembrane protein 70; GLDC: glycine decarboxylase; AMT: aminomethyltransferase; GCSH: glycine cleavage system, H protein; SCN1A: sodium channel, voltage-gated, type i, alpha subunit; SCN2A: sodium channel, voltage-gated, type ii, alpha subunit; KCNQ2: potassium channel, voltage-gated, kqt-like subfamily, member 2; STXBP1: syntaxin-binding protein 1. ATP1A3: ATPase, Na+/K+, Alpha 3. BHB: beta-hydroxybutyrate. Blood levels of BHB and glucose refer to those observed during metabolic decompensation.

Table S3: Candidate SNPs for the selection of KD as therapeutic option with no evidence from intervention studies of KD.

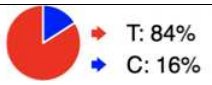
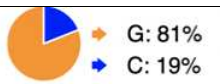
Clinical Snapshot

Are these SNPs ready for clinical implementation?
No. The strength of scientific evidence for the use of this SNPs for the prediction of KD response is "not demonstrated" using a scoring system based on recent guidelines for the interpretation of nutrigenetic variants[1]. These SNPs should be considered as candidate gene variants to evaluate and validate in research studies employing KD or exogenous ketone sources.

How can clinicians use these SNPs?
Clinicians can test the below associations as exploratory outcomes in clinic-based research of KD response. Please refer to the "Trait" column for a list of possible associations to test.

How can clinicians help accelerate the clinical implementation of these SNPs?
Clinicians can contribute to the building of a nutrigenomics knowledge base and accelerate the clinical implementation of these SNPs by testing them in clinic-based research, keeping records of their research data, and promoting the establishment of curated databases of nutrigenetic SNPs where they can submit their research data.

SNPs within ketone/fat metabolism genes associated with metabolic traits in observational studies

Effect allele	Allele frequency	Trait	Effect on trait in observational studies
HMGCS2 rs9943291-G		Blood glucose Hypertension	Increased[2]
SLC22A5 rs10060615-C		DBP	Increased[3]
SLC22A5 rs274555-C		Lean body mass	Increased[4]
CPT1A rs2924679-A		Fat oxidation	Increased[5]
CPT1A rs7938117-A		TC LDL-C HDL-C	Decreased Decreased Decreased[6]
CPT1A rs597539-G		CAC	Decreased[7]
ACADM: rs11161521-T		Carnitine metabolites	Increased[8]
ACADVL rs2286963-T		Carnitine metabolites	Increased[9 10]
ACADS rs1799958-C		Kidney disease serum metabolites (butyrylcarnitine)	Increased[11]
ACADS rs3916-C		Disease serum metabolites (cancer, coronary heart disease)	Increased[12]

Abbreviations: SNP identification numbers (noted as "rs...") are the unique SNP identifiers from the NCBI dbSNP database; HF: high fat diet (fat 40%; carbohydrate 35% or 40%); LF: low fat diet (fat 20%; carbohydrate 60% or 65%); HDL-C: HDL cholesterol; RQ: respiratory quotient; TC: Total cholesterol, LDL-C: LDL cholesterol, TG: triglycerides; MetS: metabolic syndrome; WC: waist circumference; CAC: coronary artery calcification; DBP: diastolic blood pressure.

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