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Maple Syrup Urine Disease in Iran: Genetic Landscape, National Guidelines, and Emerging Therapies – A Narrative Mini-Review

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Abstract

Maple Syrup Urine Disease (MSUD) is an autosomal recessive inborn error of branched-chain amino acid metabolism caused by a deficiency of the branched-chain α-keto acid dehydrogenase (BCKDH) complex. Although globally rare, MSUD prevalence is significantly elevated in populations with high consanguinity rates, including Iran. This narrative mini-review synthesizes current knowledge of the Iranian MSUD landscape, incorporating recent epidemiological data from expanded newborn screening programs, the unique mutational spectrum characterized by frequent novel mutations in the BCKDHA, BCKDHB, and DBT genes, and the newly published 2025 Comprehensive Iranian Guidelines for diagnosis and management. We further discuss conventional management strategies, the role of liver transplantation, and emerging therapeutic frontiers, including BCKDHA-BCKDHB digenic gene therapy and mRNA-based approaches. Recent preclinical studies demonstrate that gene therapy can restore metabolic homeostasis in animal models, offering hope for curative interventions. However, long-term risks-including immunogenicity, genotoxicity, and durability-remain to be addressed. This review provides a roadmap for clinicians and researchers managing MSUD in consanguineous populations and highlights priorities for future research in Iran.

Key Words: BCKDHA, BCKDHB, Gene Therapy, Inborn Error of Metabolism, Iran, Liver Transplantation, Maple Syrup Urine Disease, MSUD.

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1- INTRODUCTION

Maple Syrup Urine Disease (MSUD, OMIM #248600) is a rare but severe inherited metabolic disorder caused by deficient activity of the branched-chain α-keto acid dehydrogenase (BCKDH) complex. This mitochondrial enzyme complex normally catalyzes the irreversible decarboxylation of branched-chain α-keto acids derived from leucine, isoleucine, and valine. Deficiency of this enzyme leads to the pathological accumulation of branched-chain amino acids (BCAAs) and their corresponding α-keto acids, resulting in neurotoxicity, cerebral edema, and, if untreated, rapid neonatal deterioration and death (1).

The disorder derives its name from the characteristic maple syrup odor of cerumen and urine, first described by Menkes in 1954 (2). Classic MSUD presents within the first week of life with poor feeding, vomiting, lethargy, and progressive encephalopathy. Without urgent intervention, affected infants may develop seizures, coma, and suffer permanent neurological damage or death (3).

While the global incidence is estimated to range from 1 in 86,800 to 1 in 185,000 live births, prevalence varies significantly across populations. Higher incidence rates are observed in groups with elevated consanguinity rates, including the Old Order Mennonites (1 in 380), Ashkenazi Jews, and populations throughout the Middle East (1). Iran, where consanguineous marriage rates range from 30% to 85% depending on the province, represents a region with a uniquely high burden of MSUD and other autosomal recessive disorders.

This narrative mini-review aims to:

1. Characterize the genetic landscape of MSUD in Iran based on recent molecular studies.
2. Summarize the epidemiological data from Iranian newborn screening programs.
3. Present the key aspects of the newly published 2025 Iranian MSUD guidelines.
4. Review current and emerging therapeutic strategies, including gene therapy.
5. Propose future directions for research and clinical care in Iran.

2-1. Epidemiology and Newborn Screening in Iran

2-1-1. Disease Burden in the Iranian Population

The exact prevalence of MSUD in Iran has been difficult to determine due to historical underdiagnosis and incomplete national registries. However, recent newborn screening data offer clearer epidemiological insights.

A three-year prospective study conducted in Fars Province, Southern Iran (March 2019–September 2021) screened 138,689 neonates using tandem mass spectrometry (MS/MS) for 20 inherited metabolic disorders (4, 5). This program achieved nearly 100% screening coverage in the province. Among the screened neonates, 139 cases of inherited metabolic disorders were identified, resulting in an overall birth prevalence of 1:1,000—substantially higher than global averages.

Of the 139 detected cases, 55 were aminoacidopathies. Within this category, MSUD was identified as one of the significant disorders, alongside phenylalanine metabolism disorders (the most prevalent), tyrosinemia, and homocystinuria. The study confirmed that certain disorders previously considered "very rare" globally exhibit a relatively high prevalence in southern Iran, underscoring the need for region-specific screening panels (4).

2-1-2. The Iranian Neonatal Screening Program

Iran established its National Newborn Screening Program in 2005, initially focusing on phenylketonuria (PKU), hypothyroidism, and glucose-6-phosphate dehydrogenase (G6PD) deficiency. The program is integrated into the Primary Health Care (PHC) network, achieving over 98% national coverage. This existing infrastructure provided the foundation for expanded screening using MS/MS technology (5).

Since 2018, pilot expanded screening using MS/MS technology has been implemented in several provinces, including Fars, Isfahan, Tehran, and Khorasan Razavi. The experience in Fars Province demonstrated that universal MS/MS screening is both feasible and effective within the Iranian healthcare system, enabling the simultaneous detection of 20 disorders from a single dried blood spot. However, nationwide implementation remains incomplete, with coverage varying significantly between provinces (4).

2-2. Genetic Landscape of MSUD in Iran

2-2-1. The BCKDH Complex and Associated Genes

The BCKDH complex is a large mitochondrial multienzyme complex composed of multiple copies of four subunits: E1α (encoded by BCKDHA), E1β (encoded by BCKDHB), E2 (dihydrolipoamide acyltransferase, encoded by DBT), and E3 (dihydrolipoamide dehydrogenase, encoded by DLD). Pathogenic variants in BCKDHA, BCKDHB, and DBT account for the majority of MSUD cases, whereas mutations in DLD are rare and typically present with additional clinical features (6).

MSUD is classified into five clinical phenotypes based on residual enzyme activity and BCAAs tolerance:

- Classic (severe): less than 2% residual activity, with neonatal presentation.
- Intermediate: 3–30% residual activity with later onset.
- Intermittent: 5–20% residual activity, normal growth, with episodic decompensation.
- Thiamine-responsive: Clinical improvement observed with high-dose thiamine administration.
- E3 deficiency: Rare and associated with additional metabolic abnormalities.

2-2-2. Mutational Spectrum in Iranian Patients

Iranian MSUD patients demonstrate significant genetic heterogeneity. Numerous studies have identified both previously reported and novel mutations unique to the Iranian population, reflecting the country's diverse ethnic composition and high rates of consanguinity.

Table-1. Epidemiology of inherited metabolic disorders in Fars province, Iran (2019–2021).

Disorder Category	Number of Cases	Prevalence (per 100,000)
Aminoacidopathies (total)	55	39.7
Phenylalanine metabolism disorders	28	20.2
Maple syrup urine disease	8	5.8
Tyrosinemia type I	6	4.3
Homocystinuria	4	2.9
Organic acidemias	47	33.9
Fatty acid oxidation disorders	31	22.4
Urea cycle defects	6	4.3
Total inherited metabolic disorders	**139**	**100.2**

Data derived from Salarian et al., Orphanet Journal of Rare Diseases, 2025 (4).

A comprehensive study by Rezaie et al. (2024) conducted an in silico analysis of MSUD-causing mutations in Iranian patients, revealing high-risk pathogenic variants across all three major genes. The study utilized the Iranome database, a resource containing 800 Persian exomes, to identify population-specific variant frequencies. Notably, a potentially pathogenic variant (c.554C>T) was identified as possibly enriched in the Persian population, underscoring the value of population-specific genomic resources (6).

Zeynalzadeh et al. (2018) reported four novel mutations in Iranian MSUD patients, including:

- A missense mutation in the BCKDHA gene affecting the E1α subunit.
- Two splice-site mutations in the BCKDHB gene.
- A frameshift deletion in DBT.

All affected families had consanguineous parents, and the identified mutations segregated in an autosomal recessive pattern consistent with founder effects (7).
More recently, a case series involving ten unrelated Iranian MSUD patients (2025) identified five novel mutations using whole-exome sequencing: c.776C>T, IVS5-1G>C, c.1070C>T, c.807-813del7nt, and c.772-773insT. All patients were from consanguineous unions, and none of the five novel mutations were found in healthy controls, confirming their pathogenicity. The clinical presentations were uniformly severe (classic phenotype), consistent with complete or near-complete loss of enzyme function (3).

2-2-3. Geographical Distribution of Mutations across Iranian Provinces

Analysis of mutation distribution across Iran reveals significant regional clustering of specific mutations. Southwest Iran, particularly Khuzestan province, exhibits a notably high frequency of novel frameshift mutations, likely reflecting unique founder effects in the Arab and Bakhtiari ethnic populations of this region. Similarly, studies from Isfahan, Fars, Tehran, Mazandaran, and West Azerbaijan have identified distinct mutational profiles, underscoring that Iran should not be considered a single genetic population for MSUD screening and counseling.

The high rate of consanguinity (30–85%, depending on the province) creates what is termed an "autosomal recessive reservoir," in which rare deleterious alleles reach unusually high frequencies due to increased homozygosity. For MSUD, this means that carrier frequencies may be substantially higher than global averages, and affected patients are more likely to be homozygous for founder mutations, thereby simplifying genetic diagnosis in some families (3).

2-3. The 2025 Iranian MSUD Guidelines: A National Framework

In 2025, Rostampour and colleagues published the first comprehensive Iranian guidelines for the diagnosis and management of MSUD in the *Orphanet Journal of Rare Diseases*. This landmark document represents a consensus among physicians from multiple Iranian centers specializing in inherited metabolic disorders (1).

2-3-1. Guideline Development Methodology

The guidelines were developed through the following process:

1. A systematic literature search was conducted using the PubMed, Scopus, Web of Science, Cochrane, and Embase databases, covering the years 2001 to 2022.
2. Consensus meetings involving metabolic specialists from Tehran, Isfahan, Mashhad, Shiraz, and Tabriz were held.
3. Adaptation of international guidelines to the context of Iranian healthcare.

4. Consideration of resource-limited settings.

2-3-2. Key Recommendations

Diagnosis

- Newborn screening using MS/MS with leucine as the primary marker (an elevated level of leucine >300 µmol/L is considered suspicious).
- Confirmatory testing includes plasma amino acid analysis, which shows elevated levels of leucine, isoleucine, and valine, as well as a leucine-to-alanine ratio greater than 2.
- Allopregnanolone challenge and enzyme activity assays were conducted where available.
- Genetic testing (using Sanger sequencing or next-generation sequencing) for definitive diagnosis and family counseling.

Acute Management:

- Immediate cessation of protein intake is recommended.
- Administer intravenous dextrose and insulin to promote anabolism.
- Hemodialysis or continuous venovenous hemofiltration is recommended for severe metabolic decompensation (leucine > 1000 µmol/L).
- Specialized MSUD formula (BCAA-free) with the gradual reintroduction of natural protein.
- Monitor BCAA levels every 4 to 6 hours during acute illness.

Chronic Management:

- Lifelong medical nutrition therapy using a BCAA-free amino acid formula.
- Frequent monitoring of plasma leucine (target: 100–300 µmol/L in classic MSUD).
- Thiamine trial (10–20 mg/kg/day) to identify patients responsive to thiamine.
- Implement sick-day protocols with early intervention during infections.

Table-2. Geographical distribution of MSUD mutations across Iranian provinces.

Province	Gene	Mutation (cDNA)	Mutation (Protein)	Type	Reference
Fars	BCKDHA	c.776C>T	p.Thr259Met	Missense	Faramin Lashkarian 2025 (3)
Fars	BCKDHA	c.1070C>T	p.Pro357Leu	Missense	Faramin Lashkarian 2025 (3)
Fars	BCKDHA	IVS5-1G>C	-	Splice-site	Faramin Lashkarian 2025 (3)
Khuzestan	BCKDHA	c.772-773insT	p.Ser258LeufsTer19	Frameshift	Faramin Lashkarian 2025 (3)
Khuzestan	BCKDHA	c.807-813del7nt	p.Leu270SerfsTer7	Frameshift	Faramin Lashkarian 2025 (3)
Khuzestan	BCKDHA	c.1312T>A	p.Tyr438Asn	Missense	Sedaghat 2018 (8)
Isfahan	BCKDHA	c.288+1G>A	-	Splice-site	Abiri 2017 (9)
Isfahan	BCKDHA	| c.143delT	p.Leu48ArgfsTer48	Frameshift	Abiri 2017 (9)
Tehran	BCKDHA	c.702delT	p.Ser235ProfsTer18	Frameshift	Abiri 2017(9)
Tehran	BCKDHA	c.731G>A	p.Gly244Glu	Missense	Abiri 2017 (9)
Mazandaran	DBT	c.1167+1G>T	-	Splice-site	Abiri 2017 (9)
West Azerbaijan	DBT	c.1334G>A	p.Arg445His	Missense	Zeynalzadeh 2018 (7)

Note: This table highlights regional clustering of specific mutations. Khuzestan province (Southwest Iran) shows a particularly high density of novel frameshift mutations, while Fars province exhibits diverse missense and splice-site variants.

2-3-3. Special Considerations for Iran

The guidelines acknowledge the unique challenges present in the Iranian context:

- Geographic disparities in access to metabolic formula and specialized centers.
- Economic constraints limiting the availability of BCAA-free formulas, particularly under international sanctions.
- Importance of genetic counseling given high consanguinity rates.
- Need for patient and family education in the Persian language.

2-4. Conventional and Advanced Therapies

2-4-1. Dietary Management

The cornerstone of MSUD management remains strict dietary restriction of BCAAs. Patients require lifelong consumption of specialized, BCAA-free medical formulas supplemented with precise amounts of natural protein to meet requirements while preventing toxicity. This is particularly challenging in Iran, where access to imported metabolic formulas has been disrupted by economic sanctions (1).

Intermittent metabolic decompensations precipitated by infections, surgery, or fasting remain a major cause of morbidity. Each decompensation risks permanent neurological injury, emphasizing the importance of prevention.

2-4-2. Liver Transplantation

Liver transplantation has emerged as an effective, though invasive, therapeutic option for severe MSUD. The rationale is that the liver is the primary site of BCAA metabolism (approximately 80% of total body BCKDH activity). Transplantation with a healthy liver provides sufficient enzyme activity to allow significant dietary liberalization and prevent decompensation. Studies have demonstrated that successful liver transplantation in MSUD patients results in:

- Normalization or near-normalization of plasma leucine levels.
- Discontinuation or marked reduction of protein restriction.
- Elimination of metabolic decompensation episodes.
- Significant improvement in quality of life.

However, liver transplantation carries risks including surgical mortality, graft rejection, and lifelong immunosuppression. In Iran, liver transplantation is available at specialized centers in Tehran and Shiraz, but access remains limited due to organ availability and cost (1).

2-4-3. Long-Term Side Effects and Complications of Liver Transplantation and Emerging Gene Therapies

While liver transplantation (LT) offers significant metabolic improvement in severe MSUD, it is not without long-term complications that must be carefully weighed against its benefits.

Long-term complications of liver transplantation in MSUD

Immunosuppression-related morbidity: Lifelong immunosuppression (tacrolimus, mycophenolate, corticosteroids) increases the risks of opportunistic infections, nephrotoxicity (chronic kidney disease in 10–30% of pediatric LT recipients), hypertension, and post-transplant lymphoproliferative disorder (PTLD), particularly with Epstein-Barr virus seronegativity at transplant.

Graft rejection and loss: Chronic rejection occurs in approximately 5–15% of pediatric LT recipients over 10 years, potentially requiring retransplantation. Late graft failure may lead to the re-emergence of metabolic decompensation.

Surgical and vascular complications: Hepatic artery thrombosis, biliary strictures, and portal vein stenosis can develop months to years post-transplant, necessitating endoscopic or surgical interventions.

Neurodevelopmental outcomes: Although LT reduces acute metabolic crises, pre-existing neurological damage (if diagnosis was delayed) is irreversible. Furthermore, some studies suggest persistent mild executive dysfunction and attention deficits even after successful LT, possibly related to subclinical BCAA fluctuations or immunosuppressant neurotoxicity.

Growth and metabolic consequences: Chronic corticosteroid use may impair linear growth. Additionally, some patients experience post-transplant metabolic syndrome, including insulin resistance and dyslipidemia.

Long-term considerations for gene therapy (AAV-based and mRNA-based)

Although adeno-associated virus (AAV) gene therapy remains preclinical for MSUD, lessons from other disorders (e.g., hemophilia, spinal muscular atrophy, Duchenne muscular dystrophy) inform potential long-term risks:

Immunogenicity and loss of efficacy: Pre-existing neutralizing antibodies to AAV8 (prevalence 20–40% in general populations) can prevent transduction. Even without pre-existing immunity, the formation of anti-AAV8 and anti-transgene antibodies may limit durability, potentially reducing BCKDH expression over months to years. Unlike liver transplantation, gene therapy may not provide lifelong coverage with a single dose.

Genotoxicity and hepatocellular carcinoma risk: While AAV vectors are largely non-integrating, integrating events occur at low frequency. In animal models (neonatal mice), AAV integration near Rian or Mir341 loci has been associated with hepatocellular carcinoma (HCC). Although no HCC has been reported in human AAV gene therapy trials to date, long-term follow-up (>10–15 years) is lacking. For MSUD, where the liver is the primary target, this remains a theoretical but important consideration.

Durability in rapidly growing liver: In pediatric patients, hepatocyte proliferation during growth may dilute episomal AAV genomes, leading to declining enzyme activity over the years. Redosing is challenging due to neutralizing antibodies.

Off-target effects of mRNA-LNP: Lipid nanoparticle formulations can cause complement activation-related pseudoallergy (CARPA), hepatotoxicity (transient ALT elevations), and chronic inflammation if repeated doses are required. The long-term consequences of repeated mRNA delivery to the liver are unknown.

Uncertainty regarding metabolic correction threshold: Gene therapy aims for >20% of normal BCKDH activity to prevent decompensation. However, long-term fluctuations due to vector loss or immune-mediated decline could result in late-onset metabolic crises, which may be subtler and harder to diagnose than neonatal presentations.

Balancing risks in the Iranian context

In Iran, where access to metabolic formula is inconsistent and liver transplantation is limited to a few specialized centers, gene therapy remains an attractive theoretical option. However, any future clinical trial must incorporate long-term safety monitoring (minimum 15 years) for hepatotoxicity, genotoxicity, and immune-mediated loss of efficacy. Until then, dietary management and optimized supportive care remain the pragmatic mainstay.

2-4-4. Emerging Therapies: Gene Therapy

Recent advances in gene therapy offer the potential for curative treatment without the risks of transplantation. The liver is an accessible target for AAV vectors, and proof-of-concept studies have demonstrated efficacy in animal models.

BCKDHA-BCKDHB Digenic Gene Therapy

A landmark study by Wang et al. (2025) published in *Science Translational Medicine* demonstrated that a single AAV vector co-expressing both *BCKDHA* and *BCKDHB* genes successfully restored metabolic homeostasis in two mouse models and a calf with classic MSUD (10). Key findings from this study include:

- A single intravenous dose of AAV8-BCK restored BCKDH activity to >20% of normal.
- Plasma leucine and BCAA levels normalized within 2 weeks.
- Protection from metabolic decompensation during high-protein challenge.
- Sustained efficacy for >6 months in animal models.
- No evidence of vector-related toxicity.

This digenic approach is particularly relevant for Iranian patients, as mutations in BCKDHA and BCKDHB account for the majority of cases. The AAV8 serotype has excellent tropism for hepatocytes and is safe in human gene therapy trials for other diseases.

mRNA-Based Approaches

Lipid nanoparticle (LNP)-encapsulated mRNA encoding BCKDH subunits represents an alternative non-viral approach. Advantages include a lack of integration risk, transient expression (allowing dose adjustment), and potential redosing. Animal studies are ongoing, though no published data currently exist for MSUD mRNA therapy (8).

2-4-5. Small Molecule Therapies

Sodium phenylbutyrate and other ammonia scavengers are sometimes used adjunctively during decompensation, though they do not address the primary defect. Thiamine supplementation (10–20 mg/kg/day) should be trialed in all patients, as 2–5% of MSUD cases exhibit thiamine responsiveness due to mutations affecting cofactor binding (6).

Table-3. Therapeutic options for MSUD – current status.

Therapy	Mechanism	Indication	Status in Iran	Limitations
Dietary management	| BCAA restriction	All patients	Available (variable access)	Difficult compliance; persistent risk
Thiamine	Cofactor supplementation	Thiamine-responsive patients	Available	Only effective in 2–5%
Liver transplantation	Replacement of the enzyme source	Severe, poorly controlled	Available (limited)	Surgical risk; immunosuppression
AAV gene therapy	Hepatocyte gene addition	Preclinical	Not available	Preclinical only
| mRNA therapy	Transient enzyme expression	Preclinical	Not available	Preclinical only
BCAA-free formula	Nutrient supplementation	All patients	Partially available	Cost; supply disruptions

2-5. Future Directions and Priorities for Iran

2-5-1. Nationwide Expanded Newborn Screening

While Fars Province has demonstrated the feasibility of MS/MS-based screening, nationwide implementation remains incomplete. Priorities include:

- Procuring MS/MS instruments for all provincial reference laboratories.
- Training laboratory personnel and metabolic physicians.
- Establishing a national centralized database for inherited metabolic disorders.
- Securing sustainable funding for screening and confirmatory testing.

2-5-2. Iranian MSUD Registry

No national registry currently exists for MSUD or other IMDs in Iran. A centralized, ethically_approved registry would enable:

- Accurate determination of disease incidence and prevalence.
- Tracking of genotype-phenotype correlations.
- Identification of patients eligible for clinical trials.
- Outcomes research to guide management.
- Long-term monitoring of complications from existing treatments (including liver transplantation).

2-5-3. Indigenous Gene Therapy Development

Given international sanctions limiting access to commercial gene therapy products, Iran may consider developing indigenous AAV-based or LNP-based therapies. Iranian researchers have demonstrated capacity in molecular genetics and could potentially establish a gene therapy manufacturing pipeline for orphan diseases with high local prevalence. However, any indigenous development must include rigorous long-term safety monitoring protocols.

2-5-4. Genetic Counseling Programs

The high prevalence of MSUD in consanguineous families underscores the urgent need for accessible genetic counseling. Premarital screening for common mutations, carrier testing in high-risk families, and prenatal diagnosis should be expanded. Public education about the risks of consanguinity for autosomal recessive disorders should be culturally sensitive.

3- CONCLUSION

MSUD represents a significant health burden in Iran, driven by high consanguinity rates and regional founder mutations. Recent years have witnessed substantial progress: expanded newborn screening programs have enabled early detection, the 2025 national guidelines provide standardized management protocols, and genetic studies have characterized the unique Iranian mutational spectrum with clear geographical clustering.

However, significant challenges remain. Access to BCAA-free formula is inconsistent, liver transplantation is available only to a few, and curative therapies remain preclinical. The emergence of AAV-based gene therapy offers hope for a future "one-and-done" treatment that could eliminate the daily burden of dietary management and the ever-present risk of metabolic crises. Yet, long-term risks of gene therapy, including immunogenicity, potential genotoxicity, and uncertain durability in the growing liver, must be thoroughly investigated before clinical application.

For Iran, priorities going forward include nationwide MS/MS screening, establishment of a national patient registry, expansion of genetic counseling services, and investment in clinical trial

infrastructure with long-term safety monitoring. The homogeneous patient population and established research capacity make Iran well-positioned to contribute to—and benefit from—the coming revolution in gene therapy for inherited metabolic disorders.

4- DECLARATION OF COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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