Stage I: Rule-Out Dashboard

Secondary Findings in Adults

GENE/GENE PANEL: *MUT, MMAA, MMAB, MMADHC, MCEE*
HGNC ID: 7526, 18871, 19331, 25221, 16732

DISORDER: Methylmalonic aciduria (MMA)
OMIM ID: 251000, 251100, 251110, 277410, 251120

ACTIONABILITY

1. **Is there a qualifying resource, such as a practice guideline or systematic review, for the genetic condition?**

☒ **YES** ☐ **NO**

2. **Does the practice guideline or systematic review indicate that the result is actionable in one or more of the following ways?**

Yes	No	
☒	☐	Patient Management
☐	☒	Surveillance or Screening
☐	☒	Family Management
☒	☐	Circumstances to Avoid

☒ **YES (≥ 1 of above)** ☐ **NO**

3. **Is the result actionable in an undiagnosed adult with the genetic condition?**

☒ **YES** ☐ **NO**

PENETRANCE

4. **Is there at least one known pathogenic variant with at least moderate penetrance (≥40%) or moderate relative risk (≥2) in any population?**

☐ **YES** ☐ **NO** ☒ **UNKNOWN**

SIGNIFICANCE/BURDEN OF DISEASE

5. **Is this condition an important health problem?**

☒ **YES** ☐ **NO**

NEXT STEPS

6. **Are Actionability (Q2-3), Penetrance (Q4), and Significance (Q5) all "YES"?**

☒ **YES (Proceed to Stage II)**

☐ **NO (Consult Actionability Working Group)**

- ☐ **Exception granted, proceed to Stage II**
- ☐ **Exception not granted, STOP**

Stage II: Summary Report

Secondary Findings in Adults

Non-diagnostic, excludes newborn screening & prenatal testing/screening

GENE/GENE PANEL: *MUT, MMAA, MMAB, MMADHC, MCEE, MMACHC*		**DISORDER:** Methylmalonic aciduria (MMA)	
Topic		**Narrative Description of Evidence**	**Ref**
1. What is the nature of the threat to health for an individual carrying a deleterious allele?			
Prevalence of the genetic disorder		Prevalence of methylmalonic aciduria (MMA) has been estimated between 1/50,000 to 1/100,000.	(1;2)
Signif/Burden of Condition	**Clinical Features** (Signs/symptoms)	MMA is an inborn error of vitamin B12 metabolism characterized by gastrointestinal and neurometabolic manifestations resulting from decreased function of the mitochondrial enzyme methylmalonyl-CoA mutase. Clinical signs, which typically present neonatally or during infancy, include lethargy, failure to thrive, recurrent vomiting, dehydration, respiratory distress, and muscle hypotonia, as well as developmental delay, intellectual disability, hepatomegaly and coma. Long-term consequences of the disorder include neurological damage due to metabolic stroke affecting the brain stem, and end stage renal failure. The adult or "benign" form of MMA is associated with a mildly increased urinary excretion of methylmalonate, but it is uncertain if some of these individuals will develop symptoms. This form of MA is not well understood, though patients are typically viewed as stable, but may be prone to acute metabolic decompensation.	(1;2)
	Natural History (Important subgroups & survival/recovery)	Onset ranges from the neonatal period to adulthood. The most common MMA phenotype presents during infancy where infants are normal at birth, but rapidly develop clinical manifestations. All phenotypes demonstrate periods of relative health and intermittent metabolic decompensation, usually associated with intercurrent infections and stress. Survival expectancy depends on the MMA subtype.	(1)
2. How effective are interventions for preventing the harm? **Information on the effectiveness of the recommendations below was not provided unless otherwise stated.**			
Patient Management		To establish the extent of disease in an individual diagnosed with isolated MMA, the following evaluations are recommended: - serum chemistry panel (Na , K , Cl , glucose, urea, creatinine, AST, ALT, alkaline phosphatase, bilirubin [T/U], triglycerides, and cholesterol) - complete blood count with differential - arterial or venous blood gas - plasma ammonium concentration - formal urinalysis - quantitative plasma amino acids - urine organic acid analysis by gas chromatography and mass spectrometry (GC-MS) - if possible, measurement of plasma concentrations of methylmalonic acid, methylcitrate, free and total carnitine, and an acylcarnitine profile to document propionylcarnitine (C3 species) concentration. **(Tier 4)**	(1)
		Nutritional management should include a low-protein, high-calorie diet. **(Tier 4)**	(1)
		Patients who are vitamin B12 responsive, should be administered hydroxocobalamin injections every day to every other day. This regimen should be adjusted for the patient's age and weight. **(Tier 4)**	(1)
		Carnitine can be given daily as a dietary supplement to increase intracellular CoA pools and enhance the excretion of propionylcarnitine. **(Tier 4)**	(1)
		Antibiotics can be used to reduce the production of proprionate from gut flora, though the recommended types, dosage, frequency may vary. **(Tier 4)**	(1)
		Medic Alert bracelets allow for easily accessed detailed emergency treatment protocols to facilitate care in the event of an episode. **(Tier 4)**	(1)

Stage II: Summary Report

Secondary Findings in Adults

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Surveillance	Information on surveillance was not identified.	
Family Management	Siblings of patients should be evaluated using biochemical testing. Genetic testing is possible when the mutation is known. **(Tier 4)**	(1)
Circumstances to Avoid	Patients are recommended to avoid fasting and increased dietary protein and to regulate their stress. **(Tier 4)**	(1)

Description of sources of evidence:

Tier 1: Evidence from a systematic review, or a meta-analysis or clinical practice guideline clearly based on a systematic review
Tier 2: Evidence from clinical practice guidelines or broad-based expert consensus with non-systematic evidence review
Tier 3: Evidence from another source with non-systematic review of evidence with primary literature cited
Tier 4: Evidence from another source with non-systematic review of evidence with no citations to primary data sources
Tier 5: Evidence from a non-systematically identified source

GENE/GENE PANEL: *MUT, MMAA, MMAB, MMADHC, MCEE* **DISORDER:** Methylmalonic aciduria (MMA)		
Topic	**Narrative Description of Evidence**	**Ref**
1. What is the chance that this threat will materialize?		
Mode of Inheritance	Autosomal recessive	
Prevalence of Genetic Mutations	Virtually all cases are attributed to a mutation in *MUT*, *MMA*, *MMAB*, *MCEE*, or *MMADHC*. Thus the prevalence of genetic mutations should be similar to prevalence estimates for methylmalonic aciduria (between 1/50,000 to 1/100,000). **(Tier 4)**	(1)
Penetrance **OR** **Relative Risk** (include high risk racial or ethnic subgroups)	Information on penetrance was not available.	
	Information on relative risk was not available.	
Expressivity	Clinical presentation of methylmalonic aciduria can vary and may present with severe manifestations during the neonatal period or as an atypical or "benign" form with onset during adulthood with mild clinical outcomes.	(1)
2. What is the nature of the intervention?		
Nature of Intervention	Identified interventions include Medic Alert bracelets, B12 administration, avoidance of fasting and increased dietary protein, and stress regulation.	
3. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?		
Chance to Escape Clinical Detection	Without newborn screening, an individual with the adult onset form would likely escape detection prior to their first episode. **(Tier 4)**	(1)

Stage II: Summary Report

Secondary Findings in Adults

Non-diagnostic, excludes newborn screening & prenatal testing/screening

Final Consensus Scores						
Gene(s)	**Outcome/intervention pair**	**Severity**	**Likelihood**	**Effectiveness**	**Nature of the Intervention**	**Total Score**
MUT *MMAA* *MMAB* *MCEE*	Reduced morbidity/Protein restriction (Vitamin B12 responsive)	2	3D	1C	2	8DC
	Reduced morbidity/Monitor kidney function (Vitamin B12 responsive)	2	3D	2D	3	10DD
	Reduced morbidity/Vitamin B12 (Vitamin B12 responsive)	2	3D	2C	3	10DC
	Reduced morbidity/Protein restriction (Vitamin B12 non-responsive)	2	3D	1C	2	8DC
	Reduced morbidity/Monitor kidney function (Vitamin B12 non-responsive)	2	3D	2D	3	10DD

To see the scoring key, please go to: https://clinicalgenome.org/working-groups/actionability/projects-initiatives/actionability-evidence-based-summaries/.

Date of Search (MM.DD.YYYY): 08.18.2015

Reference List

1. GeneReviews. Methylmalonic Acidemia. 2010.
Ref Type: Online Source

2. OrphaNet. Methylmalonic acidemia without homocystinuria. 2014.
Ref Type: Online Source