Frequently Asked Questions

1. What is the role of folate in cancer?

At this time, there is no peer reviewed literature associating L-methylfolate with cancer risk. For further information please request a medical letter by contacting pamlab@pamlab.com.

2. Why L-methylfolate instead of folic acid?

EXECUTIVE SUMMARY

- L-methylfolate is 7x more bioavailable than folic acid.¹
- L-methylfolate is unaffected by an inborn error of metabolism that as many as 70% of depressed individuals have that compromises their ability to metabolize folic acid to L-methylfolate.²
- Evidence in both human and animal studies has demonstrated high dose folic acid led to an increase in serum and RBC folate, and a decrease in CSF folate.³
- Low CNS L-methylfolate is associated with low production of serotonin, norepinephrine and dopamine.⁴-⁶

FULL SUMMARY

- Unmetabolized folic acid (especially doses > 800mcg) binds to the “folate receptor” transport mechanism with a greater affinity than L-methylfolate resulting in a reduction in the transfer of L-methylfolate across the BBB.⁷,⁸ This can lead to a lowering of the CNS L-methylfolate level. Synthetic folic acid competes with the same binding site needed by L-methylfolate, and can reduce the brain’s level of L-methylfolate simply by competing with the uptake of L-methylfolate. This results in a reduction in the transfer of L-methylfolate across the blood-brain barrier and potentially lowering CNS L-methylfolate levels.⁷,⁹
- What might be the clinical effect of prolonged oral administration of high dose synthetic folic acid? In a recent study appearing in JAMA, in a multi-centered, randomized, double-blind, placebo controlled clinical trial, 5mg folic acid administered over 18 months in older patients with cognitive impairment led to a significant increase in depressive symptoms.¹⁰
- L-methylfolate is unlikely to mask pernicious anemia.⁸,¹¹,¹² L-methylfolate may be more appropriate than folic acid as a fortificant, because it is unlikely to mask vitamin B12 deficiency. Unlike folic acid, L-MTHF has to be converted into tetrahydrofolate (THF) via the vitamin B12-dependent enzyme methionine synthase before it can participate into other folate-dependent reactions. When vitamin B12 is deficient, L-MTHF is not converted into THF and thus is not able to ameliorate megaloblastic anemia.¹³
<table>
<thead>
<tr>
<th>Overview of L-methylfolate vs Folic Acid</th>
<th>L-MTHF</th>
<th>Folic Acid</th>
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<tbody>
<tr>
<td>Unlikely to mask pernicious anemia from a B-12 deficiency[^14]</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Unlikely to decrease immune system (NK cells)[^15] or proliferate colon cancer cells[^16]</td>
<td>Yes</td>
<td>No</td>
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<td>Superior reduction in homocystein (p = 0.02)[^17,18]</td>
<td>21.3%</td>
<td>7.7%</td>
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<td>Unaffected by NTHFR C&gt;T polymorphism (~50% general population)[^1,19]</td>
<td>Yes</td>
<td>No</td>
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<td>Able to cross blood-brain barrier &amp; aid in the synthesis of neurotransmitters[^20–22]</td>
<td>Yes</td>
<td>No</td>
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<td>Does not bind to BBB receptors inhibiting L-methylfolate absorption into the CNS[^23–25]</td>
<td>Yes</td>
<td>No</td>
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### 3. What is a Medical Food?

**EXECUTIVE SUMMARY**

A food that is:

- formulated for oral or enteral administration
- used only under medical supervision
- intended for specific dietary management of a disease or condition that
- has distinctive nutritional requirements
- is established by medical evaluation
- is based on recognized scientific principles

**FULL SUMMARY**

US Orphan Drug Amendment states:

“The term *medical food* means a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.”

That definition was subsequently incorporated into the FDC Act by the Nutrition Labeling and Education Act of 1990 (“NLEA”).
FDA requires that ALL ingredients of a medical food formulation be GRAS (Generally Recognized As Safe), or an approved food additive.

Under sections 201(s) and 409 of the Act, and FDA's implementing regulations in 21 CFR 170.3 and 21 CFR 170.30, “the use of a food substance may be GRAS either through scientific procedures or, for a substance used in food before 1958, through experience based on common use in food.”

FDA regulations further redefine the concept of a medical food, limiting it to a food that:

1. is a “specially formulated and processed product (as opposed to a naturally occurring foodstuff used in its natural state) for the partial or exclusive feeding of a patient by means of oral intake or enteral feeding by tube”;
2. is “intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone”;
3. provides “nutritional support specifically modified for the management of the unique nutrient needs that result from the specific disease or condition, as determined by medical evaluation”;
4. is intended “to be used under medical supervision”; and
5. is “intended only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food.”

References

17. College of Medicine, University of South Alabama (data on file).