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Press Release

Regarding FDA's Proposed Changes for Leucovorin as a Treatment for Autism Spectrum Disorder

About Leucovorin as a Treatment for Autism Spectrum Disorder (ASD)

Leucovorin is a prescription form of folate (vitamin B9) that has been used for over 80 years to rescue the body from the harmful effects of chemotherapy. While it is best known for its role in oncology, for the past two decades Dr. Richard Frye, MD, PhD, cofounder of the Autism Discovery and Treatment Foundation (ADTF), has been investigating its off-label use as a therapy for ASD and other neurodevelopmental disorders.

In 2005, Cerebral Folate Deficiency (CFD) was first described in a landmark *New England Journal of Medicine* article by Ramaekers et al. The study reported children with low folate levels in their cerebrospinal fluid (CSF) who experienced symptom improvement after receiving leucovorin.

In this early study, as well as in related investigations, treatment with leucovorin produced measurable improvements. These included normalization of 5-MTHF levels, resolution of myelination abnormalities observed on MRI (1), and most importantly, improvement of neurological symptoms such as movement disorders, seizures, cognitive impairments, and other deficits (see Appendix A). The therapeutic effect was particularly pronounced in children who began treatment at an earlier age. These encouraging findings prompted Dr. Frye to investigate leucovorin as a potential treatment for ASD, given that several patients with CFD also exhibited autistic features.

Dr. Frye subsequently identified several patients with ASD and CFD who responded positively to leucovorin. This led him to collaborate with Dr. Dan Rossignol, MD, cofounder of ADTF, and director of Rossignol Medical Center, a large multi-state autism medical clinic, to systematically test and treat autistic patients.

By this time, multiple causes of CFD had been recognized (see Appendix B), including the presence of Folate Receptor Autoantibodies (FRAAs) that block folate transport into the brain, a discovery made by Dr. Edward Quadros, PhD. While measuring folate levels in the brain requires a lumbar puncture, FRAAs can be detected with a simple blood test, making the presence of FRAAs a more accessible biomarker.

In 2010, Drs. Frye and Rossignol launched a study to determine the frequency of FRAAs in children with ASD. Additionally, they compared the FRAA levels in the blood with folate levels in the CSF for patients who consented to a lumbar puncture. They also used a waitlist control treatment design, offering leucovorin to FRAA-positive patients. Their findings were striking: approximately 75% of children tested (n = 93) were FRAA positive. For children who consented to the lumbar puncture (n=16), they also found that FRAA levels correlated with lower normative folate concentrations in CSF.

Treatment with leucovorin led to significant improvements in receptive and expressive language, verbal communication, stereotyped behaviors, and attention, with about two-thirds of children demonstrating a positive response (mean duration of treatment was 4 months). These results were published in 2013 in *Molecular Psychiatry*, one of the leading psychiatric journals worldwide (2).

Building on these findings, Dr. Frye conducted the first double-blind, placebo-controlled trial of leucovorin in patients with ASD, using verbal communication as the primary outcome measure.

Children with ASD treated with leucovorin (n = 23) demonstrated significant improvements in language as well as in other symptoms, including stereotyped behavior, social withdrawal, and hyperactivity as compared to placebo (n = 25). Overall, 65% of children with ASD responded to treatment regardless of FRAA status, while 77% responded if they were FRAA-positive. This study was published in 2018 in *Molecular Psychiatry* (3) and was rated as the second most important autism research finding that year by Autism Speaks. Even though this study had a smaller number of children, the effect size of leucovorin was large, indicating leucovorin had a robust effect in ASD.

Since then, independent researchers in four different countries have conducted randomized, blinded, placebo-controlled trials that have largely replicated and validated these initial results (4–7).

Strength of Research

In response to the leucovorin announcement, many critics have argued that the evidence remains insufficient, pointing to the small scale of existing studies, variability in dosing, and the heterogeneity of autism populations included in the research.

Overall, there seems to be a misunderstanding about what constitutes a "typical" study size or duration for the ASD population, as well as a dismissal of the clinical reality that this treatment has already benefited thousands of families over many years.

While the team at ADTF fully supports, and is actively conducting, larger and longer studies on leucovorin and other ASD treatments, it is important to place current research on leucovorin into context by comparing it with the studies that led to FDA approval of existing medications for ASD.

The only drugs currently approved for ASD patients are atypical antipsychotics, which are prescribed to manage the associated symptoms of irritability and aggression, not core symptoms, in children and adolescents with ASD. Both were approved on the basis of relatively small, short-term trials. These drugs are considerably less safe than leucovorin, repeatedly causing significant side effects, including movement disorders, weight gain, and metabolic changes including diabetes.

Risperidone was approved in 2006 based on two 8-week studies involving 156 children, of whom 76 received treatment. Similarly, aripiprazole was approved in 2009 following two 8-week studies involving 316 children, with 204 receiving treatment at varying doses (see Appendix C). By comparison, leucovorin has been evaluated in five blinded, controlled clinical trials including 293 children with ASD, with one trial extending up to 24 weeks (3–7). The ADC maintains that the heterogeneity of participants in the leucovorin trials is a strength rather than a limitation, as it highlights the robustness of leucovorin's effects across different subsets of children with ASD. Furthermore, leucovorin targets core symptoms of autism and, given its biological mechanism, holds potential as a disease-modifying treatment.

In addition, the first double blind placebo-controlled trial demonstrated a number needed to treat (NNT) for FRAA-positive children was 1.8, meaning that only 1.8 children need to be treated to obtain significant improvement in language over 12 weeks. This translates to 42% of children with ASD responding significantly to leucovorin treatment in this initial study. This is compared to the risperidone study where the number needed to treat was 3, suggesting that 3 children needed to be treated to see a significant response.

Important Information about Using Leucovorin as a Treatment for Autism

While initial research on leucovorin has been promising, Drs. Frye, Rossignol, and many other practicing physicians have also gained valuable experience using it in clinical practice and observing long-term patient outcomes. Some patients have been treated successfully with leucovorin for more than a decade.

Through this clinical experience, they have also identified real-world complications and nuances that must be considered when recommending leucovorin for broader use across larger populations. Some examples of these nuances include:

1. **Drug Interactions** – Many children with ASD have comorbidities, including epilepsy. While leucovorin is not contraindicated for epilepsy (in some cases may even help control seizures) certain antiepileptic drugs (AEDs) alter folate metabolism. Careful coordination of medications and monitoring for drug interactions are essential in these patients. The same caution applies to those taking methotrexate or other antifolate drugs.

2. **Over-the-Counter (OTC) Supplements** – Because leucovorin's active ingredient is folinic acid, some assume that over-the-counter (OTC) folinic acid supplements can be substituted with the same effect. We caution parents against this approach. Unlike FDA-approved medications, OTC supplements are not subject to rigorous monitoring or regulation. They often contain additional ingredients that may vary in quality and consistency. Another important concern is dosage. Most OTC folinic acid products are measured in micrograms (mcg), while leucovorin is prescribed in milligrams (mg). For reference, 1 mg equals 1,000 mcg: dosages that are too low are unlikely to be therapeutic. Additionally, it is critical not to confuse **folinic acid** with **folic acid**. Folic acid is a synthetic form of folate that is often sold as a supplement. **Folic acid** is metabolized differently than leucovorin and should not be used as a treatment for CFD or ASD.

3. **Formulations** – Leucovorin is currently available as a generic drug, and each brand uses different inactive ingredients such as milk derivatives, binders, and artificial dyes. These variations are often poorly tolerated by children with ASD, who frequently have gastrointestinal issues and other metabolic abnormalities, leading to reduced effectiveness and/or behavioral side effects.

4. **Shortages** – Generic leucovorin brands are prone to shortages, which may force families to switch products or interrupt treatment. Such disruptions, especially sudden discontinuation, can cause adverse side effects and possible regression in children who rely on consistent dosing.

5. **Substitution** – Because leucovorin is generic, a pharmacist can switch brands of leucovorin without notifying the family. As some brands are better tolerated than others, this can lead to sudden regression or behavioral problems which are typically unexplainable to the family.

6. **Uptake** – Many children with ASD cannot tolerate current tablet formulations due to sensory sensitivities and aversions to taste and texture. Avoidant/Restrictive Food Intake Disorder (ARFID), which is commonly diagnosed in children with ASD, further complicates medication acceptance and adherence. This is especially true for young children who cannot swallow pills. Compounded versions can reduce additives, but the taste and texture can be barriers for uptake.

7. **Cost** – Leucovorin can be prohibitively expensive. In situations where insurance does not cover the drug, the cost for ASD treatment may reach several thousand dollars monthly. As of September 2025, the retail price for sixty 25 mg tablets (a typical one-month supply at 50 mg daily) is approximately $1,225 (based on GoodRx Estimates). Even with rebates and coupons, the cost often ranges from $100 to $800 per month. For children who cannot tolerate commercial brands, compounded liquid formulations are required, costing hundreds of dollars monthly, generally not covered by insurance.

Recent Announcements by the White House Regarding Leucovorin

When President Trump was elected and Robert F. Kennedy Jr. was considered for Secretary of Health and Human Services, many ASD researchers felt a sense of optimism, believing that this administration might finally prioritize autism initiatives. Historically, research into autism outside of genetic studies has been significantly underfunded.

In response to this promising shift, a diverse group of scientists, researchers, clinicians, parents, and advocates came together to form the Autism Discovery Coalition (ADC) as an outreach arm of the ADTF. The ADC unites key stakeholders who have already developed impactful programs that have significantly improved the lives of individuals with ASD.

ADC reached out to the NIH to share information about these advancements since their formation. Two months ago, the ADC, met with Dr. Jay Bhattacharya to discuss some of our most promising findings.

Upon learning that the positive effects of leucovorin in children with ASD had been replicated in four additional blinded, controlled studies, Dr. Bhattacharya expressed strong interest in this treatment. His team then connected the researchers with the FDA to explore the possibility of developing a leucovorin formulation specifically for children with ASD. For that reason, the ADC was surprised when the FDA announced a collaboration with GlaxoSmithKline (GSK), and that the NIH indicated it would pursue further studies. ADTF and our coalition are ready to work with NIH and/or GSK to help design and/or execute the studies if needed.

Response to Recent Changes

There has been considerable confusion surrounding the recent announcement about leucovorin, largely due to media mischaracterizations of it as a proposed "cure" for autism. In addition, some have reported that leucovorin was previously "pulled from the market" in the 1990s, referencing a GSK's decision to stop production when the medication became generic. This was a decision based on lack of profitability, not due to safety or efficacy.

Beyond the sensational and misleading headlines, there has also been confusion about the labeling changes, which initially suggested that leucovorin would be recognized as an "on-label" treatment for ASD. However, according to the Federal Register (8) and GSK's press release (9), the FDA's new changes

recognize leucovorin for the treatment of **genetically confirmed Cerebral Folate Deficiency (CFD)**, not ASD.

A diagnosis of CFD requires a lumbar puncture showing low 5-MTHF levels, a test that is particularly challenging to administer in children with severe ASD. In addition, the requirement for a "genetically confirmed" case of CFD implies the presence of a pathogenic FOLR1 mutation. The FOLR1 gene encodes folate receptor alpha (FRα), the primary mechanism by which folate is transported into the CSF.

Although FOLR1 mutations are exceedingly rare with only 35 documented cases to date (10), they are highly informative. These cases provide the clearest link between disrupted folate transport, the resulting neurological manifestations, and the potential for symptom resolution with leucovorin treatment. The FDA's initial decisions in this space were strongly influenced by evidence demonstrating that low CSF 5-MTHF levels correspond with neurological symptoms, including ASD features, and that leucovorin administration can normalize these levels with resulting clinical improvement.

While FOLR1 mutations represent the most clear-cut, genetically confirmed cases of CFD, several other genetic conditions, such as mitochondrial disease or mutations affecting ATP production and enzymes in folate metabolism, are also associated with secondary CFD. Importantly, the majority of CFD cases are non-genetic, most commonly arising from folate receptor autoantibodies or mitochondrial dysfunction.

This distinction between genetic and non-genetic etiologies of CFD, and their overlap with ASD, highlights significant gaps in knowledge and creates regulatory challenges. Specifically, it risks limiting "on-label" access to leucovorin for the broader ASD population, despite compelling evidence of benefit.

While we appreciate the FDA's careful attention to this important field, our goal is to ensure that any regulatory pathway meaningfully addresses the needs of the thousands of American families managing ASD. To this end, we have initiated discussions with the FDA on the design of a registration trial for a pediatric formulation of leucovorin tailored specifically for children with ASD: one that ensures safety, tolerability, and a high likelihood of therapeutic success.

Formulation Considerations:
For a broader rollout, we believe it is essential to develop a specialized formulation of leucovorin tailored for children with ASD. This formulation should accommodate the diverse needs of the community in terms of delivery methods and precision dosing, and it must be consistently available without risk of substitutions for formulas with different additives and fillers.

Levo-Leucovorin Research:
ADTF has been exploring levo-leucovorin, a purified form of leucovorin, that could offer greater safety and effectiveness at lower doses. This formulation is particularly well-tolerated by children with ASD, including very young children, because it is a tasteless, textureless, odorless liquid that can be easily mixed into water. These studies have previously received support from the National Institutes of Health, the Department of Defense, and Autism Speaks. Although progress was delayed by the COVID-19 pandemic, this research is now advancing toward completion.

Clinician Education on Biological Treatments:
We believe it is critical for physicians considering leucovorin treatment to understand the specific biomarkers that identify children likely to benefit from the therapy. Additionally, for physicians who are

unfamiliar with biological treatments for ASD, it is essential to raise awareness of mitochondrial dysfunction and other metabolic abnormalities, which may require identification and adjunct treatments to ensure the effectiveness of leucovorin.

To help educate clinicians on many of these nuances of treatment, Dr. Frye recently published a book titled ***The Folate Fix: Exploring the Role of Folate in Autism and Neurodevelopmental Disorders*** which serves as a guide for clinicians and patients interested in the use of leucovorin as a treatment for ASD, CFD, and related conditions. In addition, Dr Frye has launched the Metabolic Learning Resource which is developing online content and resources for health care practitioners.

Developing Better Biomarkers:
Over the last two years, ADTF has clarified the role of one of the FRAAs called the binding FRAA (11) and discovered the role of the soluble folate receptor protein (12). ADTF is continuing to pursue further research into better defining these and other biomarkers. Our goals are: to identify which children are most likely to benefit from leucovorin, to determine the optimal dosing for each patient based on their personal metabolic markers, and to determine which adjunctive therapies may enhance leucovorin's efficacy.

Looking Towards Prevention
Additionally, the ADTF team is researching the role of FRAAs in parents. Our recent preliminary research suggests children's outcomes may be impacted by the FRAA status of the parents (13). In another recent paper, we have found that some parents share mitochondrial abnormalities with their children with ASD (14). Although these studies are preliminary, the identification of **non-genetic, treatable inherited conditions** paves the way to investigate preventative treatments for parents prior to conception.

Changing the Narrative
Unfortunately, many mainstream physicians still believe that ASD is purely genetic because of the high heritability and, therefore, untreatable - both of which are false. First, although ASD does have a strong genetic component, most of the mutations found are *de novo*, meaning new and not inherited (15). So, although there is a prominent genetic component it does not account for the strong heritability. Rather, we have recently found the FRAAs are primary found in multiplex families – families with multiple children with ASD, potentially explaining the high heritability (13). Furthermore, as documented in **The Folate Fix**, there are many children with primary genetic conditions that have CFD and respond positively to leucovorin.

In Conclusion
We are deeply grateful to President Trump, Secretary Kennedy, Dr. Bhattacharya, Dr. Makary, and Dr. Oz for helping to raise awareness that treatments for ASD are available. These efforts reinforce the growing evidence that ASD, regardless of its underlying causes, is a treatable condition.

Leucovorin targets core biological deficits in ASD, offering the potential for disease-modifying effects. Recognition by the administration that such a treatment exists brings hope to countless families. While these are exciting developments, there is still work to be done. Exceedingly few children with ASD will meet the strict criteria of "genetically confirmed CFD." Even if this definition is expanded, many children with ASD struggle to tolerate commercially available forms of leucovorin. If they are prescribed brands that cause side effects or lack effectiveness, it could lead to confusion and frustration for families.

Moreover, leucovorin is not an "autism pill." For it to be effective, physicians must understand how to prescribe it, which patients are most likely to benefit, and which formulations are suitable for children

with ASD. Without this knowledge, even regulatory approval may fall short of ensuring children receive safe and effective treatment.

ADTF stands by ready to serve this incredible population of patients and families with our long history and dedication to developing treatments that improve lives for patients with neurodevelopmental disorders.

For questions or comments, please contact: media@autismdiscovery.org

Appendix A. Selected Studies of Cerebral Folate Deficiency

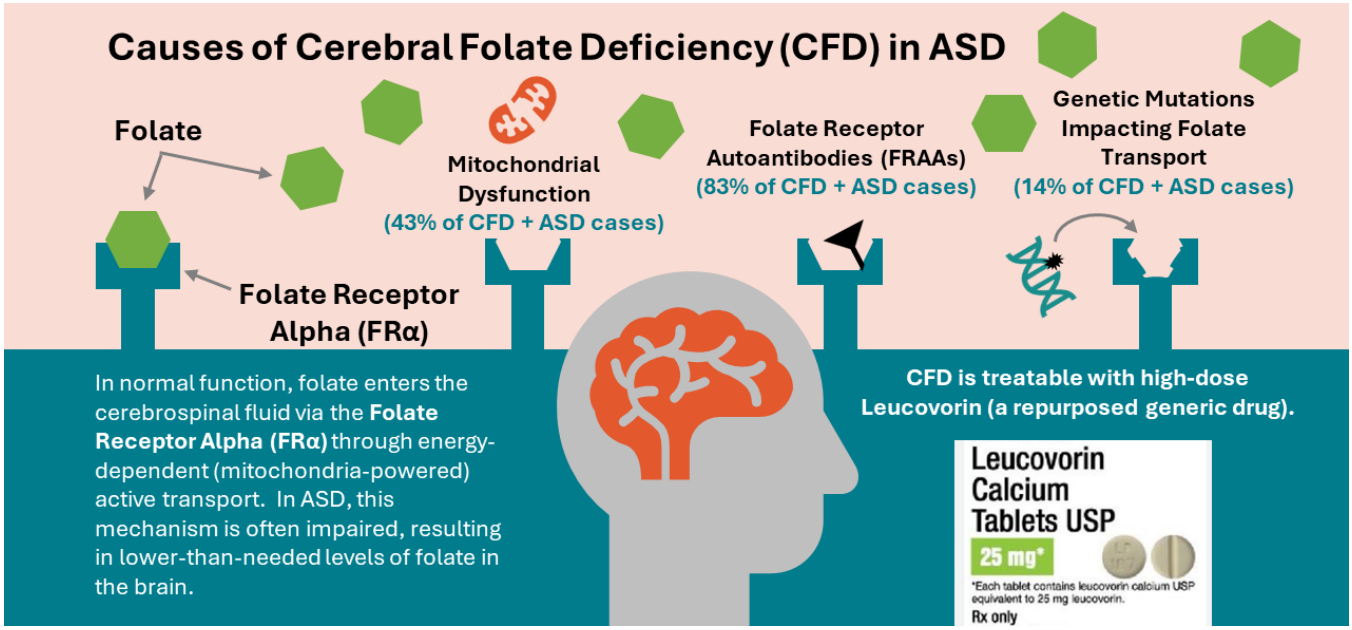
Population Size	**28 Patients**	**35 Patients (Various Initial Studies, Summarized in One Comprehensive Study)**
Population Features	-Low 5-MTHF in CSF -25/28 had FRAAs -0/28 age-matched controls had FRAAs -Multi-faceted neurological symptoms including epilepsy -6 with Autism -8 with seizures	FOLR1 Mutations leading to loss of function of Folate Receptor Alpha and Cerebral Folate Transport Deficiency -Developmental Delay – 100% -Cognitive Impairment > 90% -Movement Disorder > 90% -Seizures > 90% -Speech Impairment > 65% -Hypomyelination on MRI > 90%
Treatment	Leucovorin 0.5-1 mg/kg/day	Various doses of oral, intramuscular, and intravenous Leucovorin
Result	-Normalization of the 5-MTHF levels in the CSF at 6 months -Symptom improvement	-Normalization of the 5-MTHF -Improvement on imaging -Improvement up to reversal of symptoms
	Ramaekers VT, Rothenberg SP, Sequeira JM, Opladen T, Blau N, Quadros EV, Selhub J. Autoantibodies to folate receptors in the cerebral folate deficiency syndrome. N Engl J Med. 2005 May 12;352(19):1985-91. doi: 10.1056/NEJMoa043160. PMID: 15888699.	Goldman ID. FOLR1-Related Cerebral Folate Transport Deficiency. 2024 Jan 11. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.

Population Size	**72 Patients**	**71 Patients**
Population Features	Low 5-MTHF in CSF Neurological symptoms 10 patients w/FORL1 mutations -Developmental Regression -Ataxia -Cerebral Atrophy	Low 5-MTHF in CSF 35/71 – Abnormal amines and pterins in CSF Causes included: FOLR1 defects, Rett syndrome, Kearns-Sayre syndrome
Treatment	N/A	19 Patients in study received leucovorin treatment at varying doses
Result	N/A	Symptom improvement – most notably was seizure reduction
	Grapp M, Just IA, Linnankivi T, Wolf P, Lücke T, Häusler M, Gärtner J, Steinfeld R. Molecular characterization of folate receptor 1 mutations delineates cerebral folate transport deficiency. Brain. 2012 Jul;135(Pt 7):2022-31. doi: 10.1093/brain/aws122. Epub 2012 May 13. PMID: 22586289.	Pérez-Dueñas B, Ormazábal A, Toma C, Torrico B, Cormand B, Serrano M, Sierra C, De Grandis E, Marfa MP, García-Cazorla A, Campistol J, Pascual JM, Artuch R. Cerebral folate deficiency syndromes in childhood: clinical, analytical, and etiologic aspects. Arch Neurol. 2011 May;68(5):615-21. doi: 10.1001/archneurol.2011.80. PMID: 21555636.

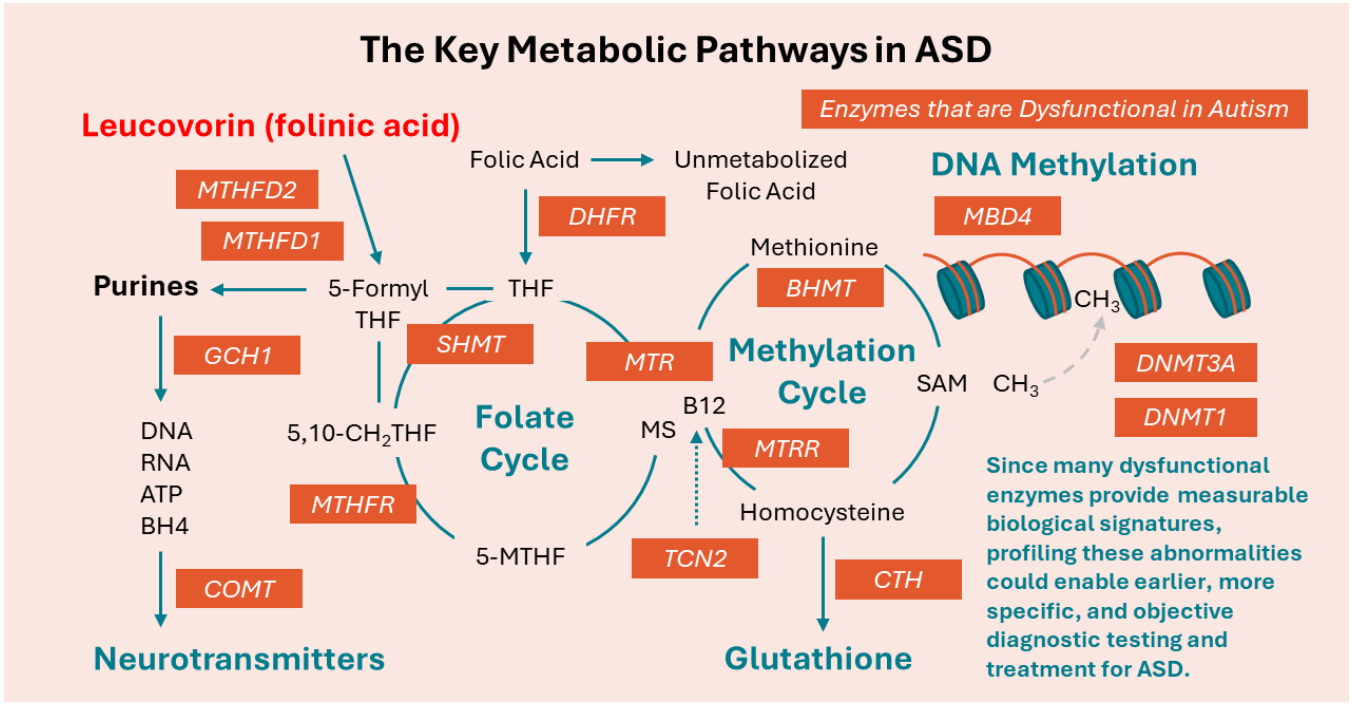
Also See Case Summary Table from Wang Q, Yang J, Yu C, Deng Y, Wen Q, Yang H, Liu H, Luo R. Case Report: Cerebral folate deficiency caused by *FOLR1* variant. Front Pediatr. 2024 Sep 12;12:1434209. Table: https://pmc.ncbi.nlm.nih.gov/articles/instance/11424398/bin/Table1.pdf

Appendix B. The Causes Cerebral Folate Deficiency in ASD

Folate metabolism can be disrupted through several, often overlapping, mechanisms, including immune dysfunction (83%), mitochondrial dysfunction (43%), and genetic variants (14%) (percentages add to more than 100% as some children have more than one condition) [16]. The Folate Receptor Alpha (FRα) is encoded by the FOLR1 gene. Mutations in this gene lead to Cerebral Folate Deficiency (CFD) because the receptor is often unable to function properly. FOLR1 mutations are exceedingly rare. Genetic mutations that impact the function of mitochondria are more common and can also indirectly cause CFD. Most commonly, CFD is caused by non-genetic autoantibodies against the folate receptor (83% of cases).



Even with leucovorin treatment, other metabolic factors may impact its effectiveness in ASD patients. The diagram below shows key metabolic pathways that are abnormal in ASD. This helps to illustrate why different individuals may respond differently to treatment based on their personal genetic variations.



Appendix C. Current FDA-Approved Medications for Autistic Individuals Compared to Leucovorin

For the Treatment of Irritability and Aggression in ASD:

Risperidone (Risperdal)

Drug/Trial	Risperidone Trial 1	Risperidone Trial 2
Dosages	0.5-3.5 mg/day	0.02 – 0.06 mg/kg/day
Treatment Group(s)	**49 children ages 5-17**	**27 children ages 5-12**
Placebo Group(s)	52 children ages 5-17	28 children ages 5-12
Total Patients	101 children (26 dropped out, 75 finished)	55 children (10 dropped out, 45 finished)
Duration	**8 weeks**	**8 weeks**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020588s046lbl.pdf

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Aripiprazole (Abilify)

Drug/Trial	Aripiprazole Trial 1	Aripiprazole Trial 2
Dosages	2mg, 5mg, 10mg, 15mg	5mg, 10mg, 15mg
Treatment Group(s)	**43 children ages 6-17**	**161 children ages 6-17**
Placebo Group(s)	55 children ages 6-17	57 children ages 6-17
Total Patients	98 children (8 dropped out, 90 finished)	218 children (5 dropped out, 213 finished)
Duration	**8 weeks**	**8 weeks**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021436s038,021713s030,021729s022,021866s023lbl.pdf

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Leucovorin

Drug/Trial	Leucovorin – Open-Label Waitlist Controlled Trial	Leucovorin – Double-Blind, Placebo-Controlled Trial
Dosages	2mg/kg/day, max 50mg	2mg/kg/day, max 50mg
Treatment Group(s)	**23 children ages 2-15**	**23 children ages 3-14**
Placebo Group(s)	26 children (Waitlist control)	25 children ages 3-14
Total Patients	49 children (4 dropped out, 44 finished)	48 children (5 dropped out, 43 finished)
Duration	**Average 4 months**	**12 weeks**
Published Results	Frye RE, Sequeira JM, Quadros EV, James SJ, Rossignol DA. Cerebral folate receptor autoantibodies in autism spectrum disorder. Mol Psychiatry. 2013 Mar;18(3):369-81. doi: 10.1038/mp.2011.175. Epub 2012 Jan 10. PMID: 22230883; PMCID: PMC3578948.	Frye, R., Slattery, J., Delhey, L. *et al.* Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial. *Mol Psychiatry* **23**, 247–256 (2018). https://doi.org/10.1038/mp.2016.168

Drug/Trial	Leucovorin – Placebo-Controlled, Randomized Trial	Leucovorin – Placebo-Controlled, Randomized Trial
Dosages	2mg/kg/day	2mg/kg/day, max 50mg +Risperidone in both groups
Treatment Group(s)	**9 children**	**33 children ages 4-12**
Placebo Group(s)	10 children	33 children ages 4-12
Total Patients	19 children	66 children (11 dropped out, 55 finished)
Duration	**12 weeks**	**10 weeks**
Published Results	Renard E, Leheup B, Guéant-Rodriguez RM, Oussalah A, Quadros EV, Guéant JL. Folinic acid improves the score of Autism in the EFFET placebo-controlled randomized trial. Biochimie. 2020 Jun;173:57-61. doi: 10.1016/j.biochi.2020.04.019. Epub 2020 May 7. PMID: 32387472.	Batebi N, Moghaddam HS, Hasanzadeh A, Fakour Y, Mohammadi MR, Akhondzadeh S. Folinic Acid as Adjunctive Therapy in Treatment of Inappropriate Speech in Children with Autism: A Double-Blind and Placebo-Controlled Randomized Trial. Child Psychiatry Hum Dev. 2021 Oct;52(5):928-938. doi: 10.1007/s10578-020-01072-8. Epub 2020 Oct 7. PMID: 33029705.

Drug/Trial	Leucovorin – Randomized, Double-Blind, Placebo-Controlled Trial	Leucovorin – Randomized, Blind, Placebo-Controlled Trial
Dosages	2mg/kg/day, max 50mg	2mg/kg/day, max 50mg
Treatment Group(s)	**40 children ages 2-10**	**50 children ages 3-6**
Placebo Group(s)	40 children ages 2-10	30 children ages 3-6
Total Patients	80 children (2 dropped out, 78 finished)	80 children (4 dropped out, 76 finished)
Duration	**24 weeks**	**12 weeks**
Published Results	Panda PK, Sharawat IK, Saha S, Gupta D, Palayullakandi A, Meena K. Efficacy of oral folinic acid supplementation in children with autism spectrum disorder: a randomized double-blind, placebo-controlled trial. Eur J Pediatr. 2024 Nov;183(11):4827-4835. doi: 10.1007/s00431-024-05762-6. Epub 2024 Sep 7. PMID: 39243316.	Zhang C, Chen Y, Hou F, Li Y, Wang W, Guo L, Zhang C, Li L, Lu C. Safety and Efficacy of High-Dose Folinic Acid in Children with Autism: The Impact of Folate Metabolism Gene Polymorphisms. Nutrients. 2025 May 7;17(9):1602. doi: 10.3390/nu17091602. PMID: 40362912; PMCID: PMC12073535.

References

1. Potic A, Perrier S, Radovic T, Gavrilovic S, Ostojic J, Tran LT, Thiffault I, Pastinen T, Schiffmann R, Bernard G. Hypomyelination caused by a novel homozygous pathogenic variant in FOLR1: complete clinical and radiological recovery with oral folinic acid therapy and review of the literature. Orphanet J Rare Dis. 2023 Jul 13;18(1):187. doi: 10.1186/s13023-023-02802-6. PMID: 37443037; PMCID: PMC10339608.
2. Frye RE, Sequeira JM, Quadros EV, James SJ, Rossignol DA. Cerebral folate receptor autoantibodies in autism spectrum disorder. Mol Psychiatry. 2013 Mar;18(3):369-81. doi: 10.1038/mp.2011.175. Epub 2012 Jan 10. PMID: 22230883; PMCID: PMC3578948.
3. Frye RE, Slattery J, Delhey L, Furgerson B, Strickland T, Tippett M, Sailey A, Wynne R, Rose S, Melnyk S, Jill James S, Sequeira JM, Quadros EV. Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial. Mol Psychiatry. 2018 Feb;23(2):247-256. doi: 10.1038/mp.2016.168. Epub 2016 Oct 18. PMID: 27752075; PMCID: PMC5794882.
4. Batebi N, Moghaddam HS, Hasanzadeh A, Fakour Y, Mohammadi MR, Akhondzadeh S. Folinic Acid as Adjunctive Therapy in Treatment of Inappropriate Speech in Children with Autism: A Double-Blind and Placebo-Controlled Randomized Trial. Child Psychiatry Hum Dev. 2021 Oct;52(5):928-938. doi: 10.1007/s10578-020-01072-8. Epub 2020 Oct 7. PMID: 33029705.
5. Panda PK, Sharawat IK, Saha S, Gupta D, Palayullakandi A, Meena K. Efficacy of oral folinic acid supplementation in children with autism spectrum disorder: a randomized double-blind, placebo-controlled trial. Eur J Pediatr. 2024 Nov;183(11):4827-4835. doi: 10.1007/s00431-024-05762-6. Epub 2024 Sep 7. PMID: 39243316.
6. Renard E, Leheup B, Guéant-Rodriguez RM, Oussalah A, Quadros EV, Guéant JL. Folinic acid improves the score of Autism in the EFFET placebo-controlled randomized trial. Biochimie. 2020 Jun;173:57-61. doi: 10.1016/j.biochi.2020.04.019. Epub 2020 May 7. PMID: 32387472.
7. Zhang, C.; Chen, Y.; Hou, F.; Li, Y.;Wang,W.; Guo, L.; Zhang, C.; Li, L.; Lu, C. Safety and Efficacy of High-Dose Folinic Acid in Children with Autism: The Impact of Folate Metabolism Gene Polymorphisms. Nutrients 2025, 17, 1602. Doi: 10.3390/nu17091602
8. Approval of Previously Withdrawn New Drug Application for WELLCOVORIN (Leucovorin Calcium) Tablets. FDA on 9/24/2025. https://www.federalregister.gov/documents/2025/09/24/2025-18510/approval-of-previously-withdrawn-new-drug-application-for-wellcovorin-leucovorin-calcium-tablets
9. GSK to submit label update for Wellcovorin (leucovorin) at US FDA's request. 9/22/2025. https://www.gsk.com/en-gb/media/press-releases/gsk-to-submit-label-update-for-wellcovorin-leucovorin-at-us-fda-s-request/
10. Goldman ID. FOLR1-Related Cerebral Folate Transport Deficiency. 2024 Jan 11. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK599286/
11. Frye RE, McCarty PJ, Werner BA, Scheck AC, Collins HL, Adelman SJ, Rossignol DA, Quadros EV. Binding Folate Receptor Alpha Autoantibody Is a Biomarker for Leucovorin Treatment Response in Autism Spectrum Disorder. J Pers Med. 2024;14(1):62. doi: 10.3390/jpm14010062. PMID: 38248763; PMCID: PMC10820361.
12. Frye RE, Lane A, Worner A, Werner BA, McCarty PJ, Scheck AC, Collins HL, Adelman SJ, Quadros EV, Rossignol DA. The Soluble Folate Receptor in Autism Spectrum Disorder: Relation to Autism Severity and Leucovorin Treatment. J Pers Med. 2022 Dec 8;12(12):2033. doi: 10.3390/jpm12122033. PMID: 36556254; PMCID: PMC9786140.
13. Frye RE, Cohen IL, Sequeira JM, Hill Z, Espinoza A, Brown WT, Mevs C, Marchi E, Flory M, Jenkins EC, Velinov MT, Quadros EV. Transgenerational Effects and Heritability of Folate Receptor Alpha Autoantibodies in Autism Spectrum Disorder. Int J Mol Sci. 2025 Aug 26;26(17):8293. doi: 10.3390/ijms26178293. PMID: 40943215; PMCID: PMC12428755.
14. Frye RE, McCarty PJ, Werner BA, Rose S, Scheck AC. Bioenergetic signatures of neurodevelopmental regression. Front Physiol. 2024 Feb 19;15:1306038. doi: 10.3389/fphys.2024.1306038. PMID: 38449786; PMCID: PMC10916717.
15. Boles RG, Bar O, Boles PT, Hill ZR, Frye RE. De Novo Variants Predominate in Autism Spectrum Disorder. Genes (Basel). 2025 Sep 17;16(9):1099. doi:10.3390/genes16091099. PMID: 41010044.

16. Rossignol, D.A.; Frye, R.E. Correction: Rossignol, D.A.; Frye, R.E. Cerebral Folate Deficiency, Folate Receptor Alpha Autoantibodies and Leucovorin (Folinic Acid) Treatment in Autism Spectrum Disorders: A Systematic Review and Meta-Analysis. J. Pers. Med. 2021, 11, 1141. *J Pers Med* **2022**, *12*, doi:10.3390/jpm12050721.