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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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BEYOND THE GENETIC CODE: SYSTEMIC REGULATORY MELTDOWN AS A FRAMEWORK FOR PRIMARY EPIGENETIC DISEASES

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Abstract.

Background: Modern medicine is increasingly encountering multisystemic disorders that do not fit into traditional genetic or organ-specific nosologies. This study proposes and validates the concept of "primary epigenetic disease" (PED) as a distinct clinical entity.

Objective: to define the molecular mechanisms, genetic foundations, and clinical manifestations of PED, and to establish a standardized diagnostic framework using autism spectrum disorder (ASD) and chronic fatigue syndrome (CFS) as primary models.

Materials and Methods: A narrative review was conducted using PubMed and Scopus databases (predominantly 2021–2026). Evidence was synthesized from meta-analyses, randomized controlled trials, and large-scale genomic studies focusing on DNA methylation, histone modifications, and microRNA networks.

Results: We identified that PED emerges from a synergistic failure of the epigenetic machinery, often driven by a high load of common single nucleotide polymorphisms (SNPs) in genes such as MTHFR, DNMTs, and HDACs. We established a 30-point diagnostic matrix comprising 15 clinical criteria (e.g., developmental delays, connective tissue dysplasia, and paradoxical drug sensitivity) and 15 laboratory criteria (e.g., SAM/SAH imbalance, mitochondrial dysfunction markers, and global DNA hypomethylation). The application of this matrix to ASD and CFS demonstrates a shared pathogenic core: systemic biological desynchronization, barrier failure, and persistent low-grade inflammation.

Conclusion: Primary Epigenetic Disease represents a "regulatory meltdown" of the genome. Effective management requires a paradigm shift from symptomatic treatment to "epigenetic rehabilitation," which combines systemic genomic modulation with precision biochemical correction of identified bottlenecks. This framework provides a robust toolkit for the identification and management of multisystemic patients in the era of systems medicine.

Key words. DNA methylation, histone code, non-coding RNA networks, single nucleotide polymorphisms, mitochondrial dysfunction.

Introduction.

In recent years, the paradigm of human pathology has shifted from purely genetic determinism toward a complex interplay between the genome and the epigenome. Unlike genetic mutations, epigenetic alterations are reversible yet heritable changes in gene expression that do not involve alterations in the DNA sequence itself. These mechanisms, primarily including DNA methylation and histone post-translational modifications, play a pivotal role in the pathogenesis of various chronic disorders [1,2].

The classical view of human genetics, once dominated by the 'DNA-as-destiny' paradigm, has been fundamentally reshaped by the emergence of epigenetics. Epigenetic regulation represents a complex layer of biochemical information that orchestrates gene expression without altering the underlying nucleotide sequence. While essential for cellular differentiation and homeostasis, disruptions in this delicate balance—often termed epigenetic aberrations—are now recognized as hallmarks of numerous human diseases. Unlike irreversible genetic mutations, the inherent plasticity of the epigenome offers a promising avenue for pharmacological intervention, making it a focal point of modern precision medicine [3,4].

Traditionally, epigenetic changes have been viewed as intermediary responses to genetic or environmental triggers. However, we propose a paradigm shift: in certain contexts, the collapse of the epigenetic regulatory machinery constitutes a distinct disease entity. This 'epigenetic disease' is characterized by a loss of homeostatic control over the chromatin state, leading to a cascade of multi-organ dysfunctions. By examining ASD in pediatrics, CFS and post-infectious syndromes in adults, and metabolic syndrome in the elderly, we demonstrate a unified trajectory of epigenetic failure across the human lifespan [5,6].

It is time to systematize knowledge about the phenomenon of epigenetic disorders in humans, demonstrating its diversity and universal pathogenetic and clinical features and common approaches to treatment.

Aim of the study: To propose and validate the concept of "primary epigenetic disease" by synthesizing current data on molecular mechanisms (DNA methylation, histone code, ncRNA networks) and genetic vulnerabilities (SNPs). The work aims to define a comprehensive clinical and pathogenic phenotype that integrates multisystemic failures—from metabolic and mitochondrial dysfunction to neurodevelopmental and immune dysregulation—into a single diagnostic framework.

Objectives of the study:

1. To systematize the molecular drivers of epigenetic instability, focusing on the synergistic interaction between DNA methylation, histone post-translational modifications, and non-coding RNA networks in the maintenance of genomic homeostasis;
2. To identify high-frequency genetic polymorphisms (SNPs) in the epigenetic machinery (such as MTHFR, DNMTs, HDACs, and miRSNPs) that serve as foundational substrates for "primary epigenetic vulnerability";
3. To synthesize a comprehensive pathogenic model of the epigenetic syndrome, integrating key drivers such as hyperhomocysteinemia, mitochondrial dysfunction, persistent systemic low-grade inflammation, and the failure of histo-hematic barriers;

4. To delineate the multisystemic clinical phenotype of epigenetic disease across the lifespan, mapping the transition from early neurodevelopmental markers to late-stage metabolic and structural erosion;

5. To validate the "primary epigenetic disease" framework using clinical models, specifically analyzing autism spectrum disorder (ASD) in pediatrics and chronic fatigue syndrome (CFS) in adults;

6. To establish working diagnostic criteria and outline available therapeutic approaches for managing primary epigenetic diseases, emphasizing personalized epigenetic rehabilitation, nutritional support for biochemical cycles, and the restoration of homeostatic buffers.

Materials and Methods.

General data:

To ensure a high level of scientific rigor and objectivity in the formulation of the "primary epigenetic disease" concept, this narrative review was conducted using a structured approach to literature selection and analysis. The search strategy was designed to identify high-quality evidence that establishes the link between molecular epigenetic mechanisms, common genetic polymorphisms, and systemic clinical phenotypes.

Search strategy and data sources:

A comprehensive search of the literature was performed across the PubMed/MEDLINE and SCOPUS databases. The search focused on publications released predominantly within the last five years (2021–2026) to prioritize the most recent advancements in epigenomics and systems medicine. However, seminal historical studies and fundamental works in the field of molecular biology were included where necessary to provide essential context. Search terms included combinations of keywords such as "epigenetic regulation," "DNA methylation," "histone code," "non-coding RNA," "single nucleotide polymorphisms (SNPs)," "MTHFR," "autism spectrum disorder," "chronic fatigue syndrome", "metabolic syndrome", "mitochondrial dysfunction," and "systemic inflammation."

Inclusion and exclusion criteria:

Priority was given to studies of the highest evidentiary value, specifically: meta-analyses and systematic reviews that synthesize large-scale genomic data, randomized, placebo-controlled clinical trials (RCTs) investigating biochemical and epigenetic interventions, large-scale epidemiological studies and genome-wide association studies (GWAS) that identify prevalent SNPs, expert consensus statements and authoritative reviews in the fields of pediatrics, neurology, and endocrinology.

The exclusion criteria focused on studies with insufficient sample sizes, case reports without molecular confirmation, and publications in non-peer-reviewed or predatory journals.

Data synthesis and analysis:

Information was extracted from the selected sources and synthesized using a multisystemic integration approach. We analyzed the data not as isolated pathological events, but as interconnected components of a single regulatory network. The synthesis aimed to align molecular findings (genotype and epigenotype) with the pathogenic and clinical manifestations (phenotype) described in the study. This methodological framework allowed for the transition from traditional organ-specific nosology to a holistic model of "epigenetic syndrome," ensuring that the proposed diagnostic and therapeutic approaches are grounded in evidence-based medicine (Figure 1).

We argue that these conditions share a common denominator: a disrupted epigenetic landscape that persists even after the initial trigger (pathogen, toxin, or stressor) is removed. When the regulatory mechanisms themselves — such as the writer, eraser, and reader proteins of the histone code — become dysfunctional, the resulting state should be classified as a primary epigenetic disorder. This classification is crucial for developing 'epi-drugs' aimed at resetting the cellular memory rather than merely treating downstream symptoms.

Risk of Bias and Methodological Quality Assessment:

To ensure the validity and robustness of the synthesized evidence supporting the PED framework, a stringent risk of bias (RoB) assessment was performed. Given the hybrid nature of the synthesized literature—incorporating both clinical observational data and mechanistical/translational laboratory studies—two distinct validation tracks were utilized.

Clinical and Observational Evidence: for clinical cohorts validating the convergent phenotypes (ASD, CFS, and MS), the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) and adapted Newcastle-Ottawa Scale (NOS) were applied. Primary domains evaluated included confounding factors (e.g., genetic background heterogeneity, environmental exposures), selection of participants, and misclassification of exposures. Studies with an overall evaluation of "Serious" or "Critical" risk of bias under ROBINS-I were systematically excluded.

Mechanistic and In Vitro/In Vivo Evidence: methodological quality for basic science and epigenetic mapping studies (e.g., chromatin remodeling, DNA methylation landscapes) was assessed using customized checklists focusing on analytical validity, replication consistency, and the mitigation of technical artifacts (e.g., batch effects in high-throughput sequencing).

To minimize selection and synthesis bias, the review process adhered to a multi-investigator consensus protocol. Disagreements regarding the risk of bias or data extraction adjustments for any given study were resolved through collaborative reconciliation (panel).

Software: AI Gemini 3 flash.

PRISMA 2020 Aligned Methods Summary.

1. Eligibility Criteria:

Study Design: Systematic reviews, meta-analyses, and high-impact clinical trials (Q1, Q2 journals).

Timeframe: Focus on the "Modern Epigenetic Era" (2024–2026) to ensure clinical relevance.

Target Models: Studies must address at least one of the three validation models: Autism Spectrum Disorder (ASD), Chronic Fatigue Syndrome (CFS), or Metabolic Syndrome (MetS).

Mechanistic Focus: Inclusion required evidence of epigenetic aberrations (DNA methylation, histone modifications, or miRNA dysregulation).

2. Information Sources:

Databases: PubMed/MEDLINE, Scopus.

Search Strategy: Applied keywords including "Epigenetic Disease", "Epi-Shield failure", “Methylation disorders”, “Histone machinery disorders”, “microRNA network”, “Oxidative Stress”, "Sterile Inflammation" and "Mitochondrial dysfunction".

3. Selection Process:

Screening: Titles and abstracts were screened for relevance to the "Paradigm Shift" from genetic determinism to epigenetic plasticity.

Full-text Review: Articles were assessed for their ability to validate the 15 pillars of the PED pathogenetic architecture.

4. Data Collection & Synthesis:

Thematic Mapping: Data was extracted to populate the multi-layered visual model (The Wheel).

Synthesis Method: A convergent synthesis approach was used to align disparate clinical phenotypes (pediatric ASD, adult CFS, geriatric MetS) into a unified trajectory of epigenetic failure.

5. Quality Assessment:

Methodological quality was prioritized by selecting journals with high impact factors and rigorous peer-review processes (e.g., Nature, Lancet, Cell).

Results.

Mechanism 1: DNA Methylation and Its Regulatory Dynamics.

DNA methylation is arguably the most extensively characterized epigenetic mechanism, acting as a stable yet reversible "switch" for genomic activity. In the human genome, this process predominantly involves the covalent attachment of a methyl group (–CH_3) to the 5th carbon position of the cytosine ring, resulting in 5-methylcytosine (5mC). This modification occurs almost exclusively at CpG dinucleotides, which are often clustered in high-density regions known as CpG islands located within or near gene promoters [7].

The orchestration of this landscape is managed by a specialized class of enzymes: DNA methyltransferases (DNMTs). De novo methylation, established during embryonic development or cellular differentiation, is catalyzed by DNMT3a and DNMT3b, while DNMT1 ensures the faithful maintenance of these patterns during DNA replication, preserving cellular identity across cell divisions. From a functional perspective, dense methylation at promoter regions is typically associated with transcriptional silencing. This is achieved through two primary pathways: first, by physically impeding the binding of transcription factors to their cognate sequences, and second, by recruiting Methyl-CpG-binding domain (MBD) proteins. These MBDs act as molecular scaffolds that attract histone deacetylases (HDACs) and chromatin-remodeling complexes, inducing a transition from an open, active euchromatin state to a condensed, inactive heterochromatin state [8].

In the context of the "epigenetic disease" hypothesis, DNA methylation is not merely a reactive state but a critical regulatory layer susceptible to "noise" or erosion. Aberrant methylation—characterized by focal hypermethylation of tumor-suppressor genes or global hypomethylation leading to genomic instability—represents a primary breakdown in cellular logic. When the DNMT-mediated equilibrium is disrupted by environmental

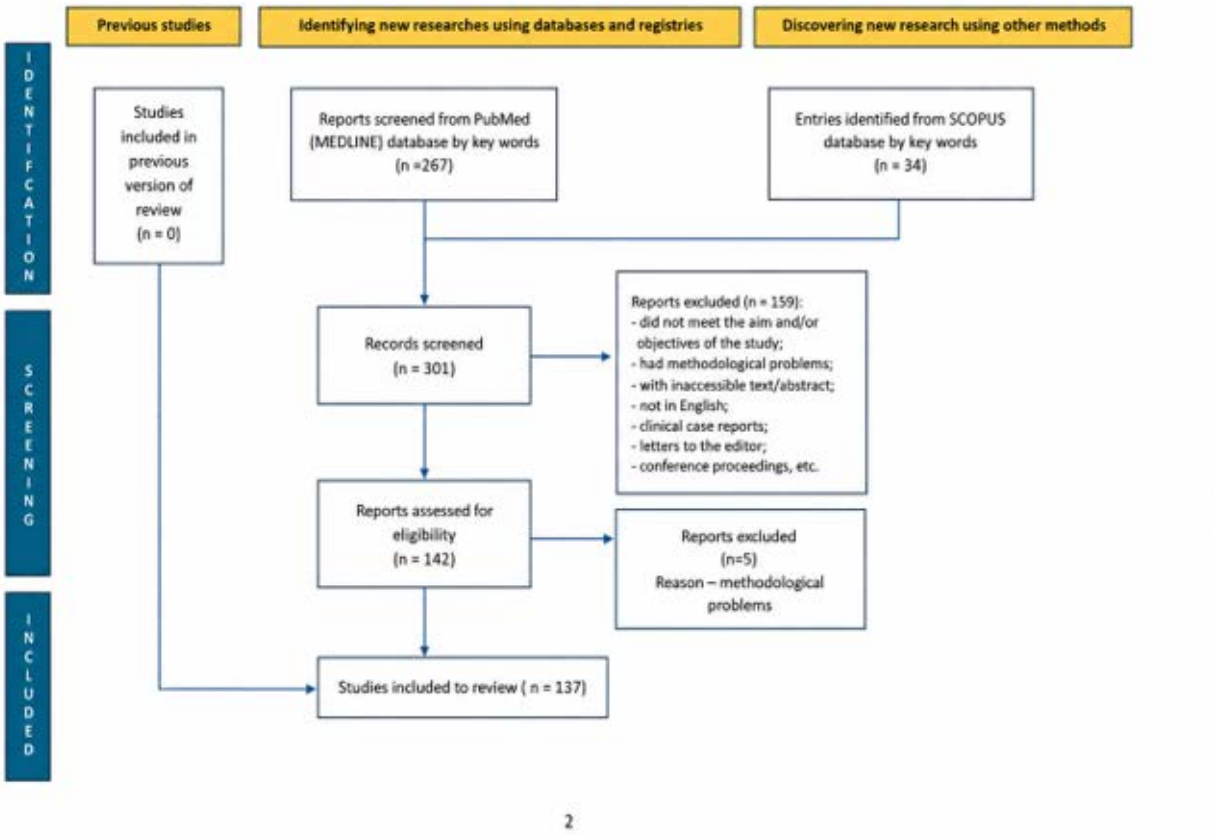

Figure 1. *Scheme of the research structure (PRISMA flow diagram 2020) Panel.*

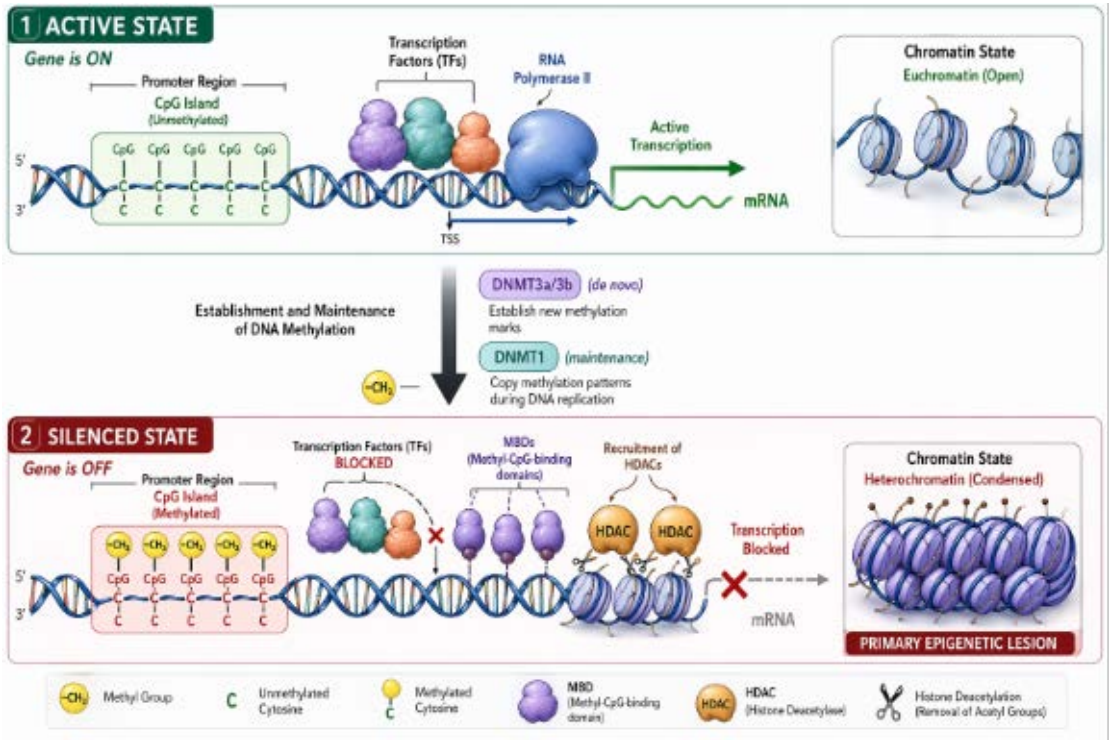

Figure 2. *The Dynamics of DNA Methylation and Transcriptional Silencing.*
Conceptual model of DNA methylation. (A) Homeostatic state with unmethylated CpG islands allowing transcription. (B) Aberrant hypermethylation catalyzed by DNMTs triggers the recruitment of MBDs and HDACs, leading to chromatin compaction and stable gene silencing.

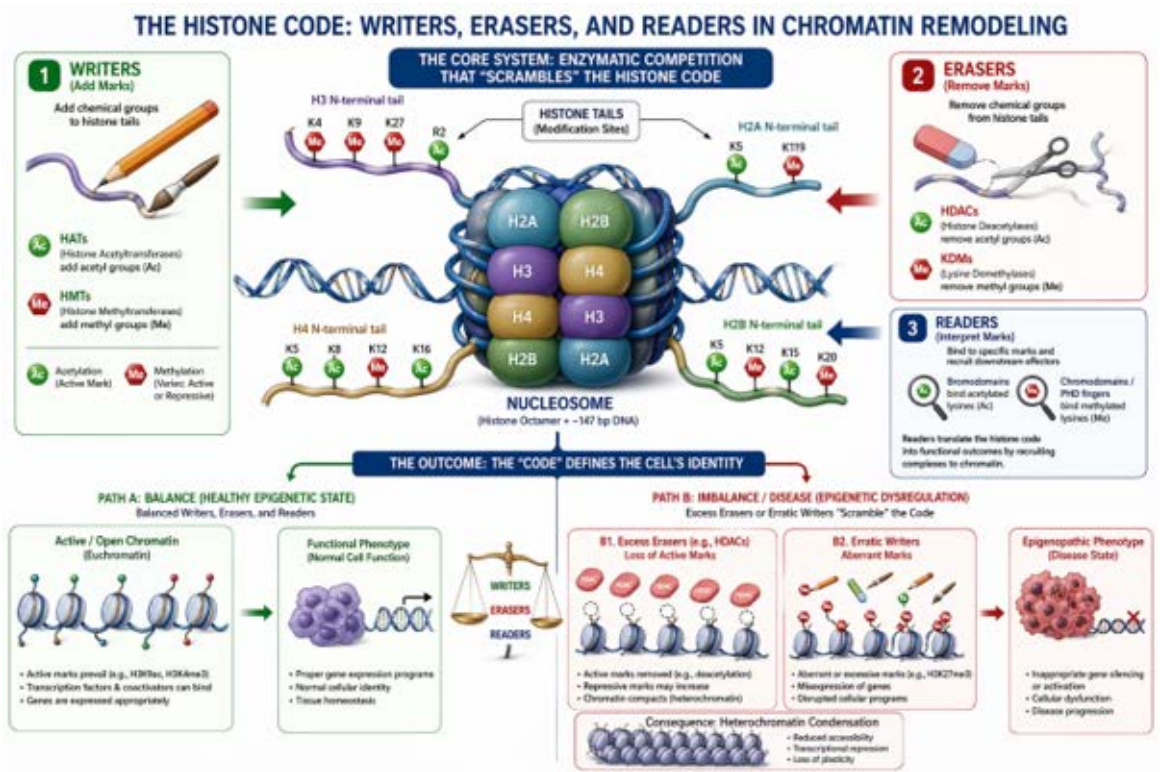

Figure 3. *The Histone Code: Writers, Erasers, and Readers in Chromatin Remodeling. The interplay of the 'histone code' regulatory machinery. Epigenetic health relies on the equilibrium between "writers" (adding PTMs) and "erasers" (removing PTMs), which are interpreted by "readers". We hypothesize that a chronic tilt in this balance—the "scrambling" of the code—is the foundational event in primary epigenetic disorders*

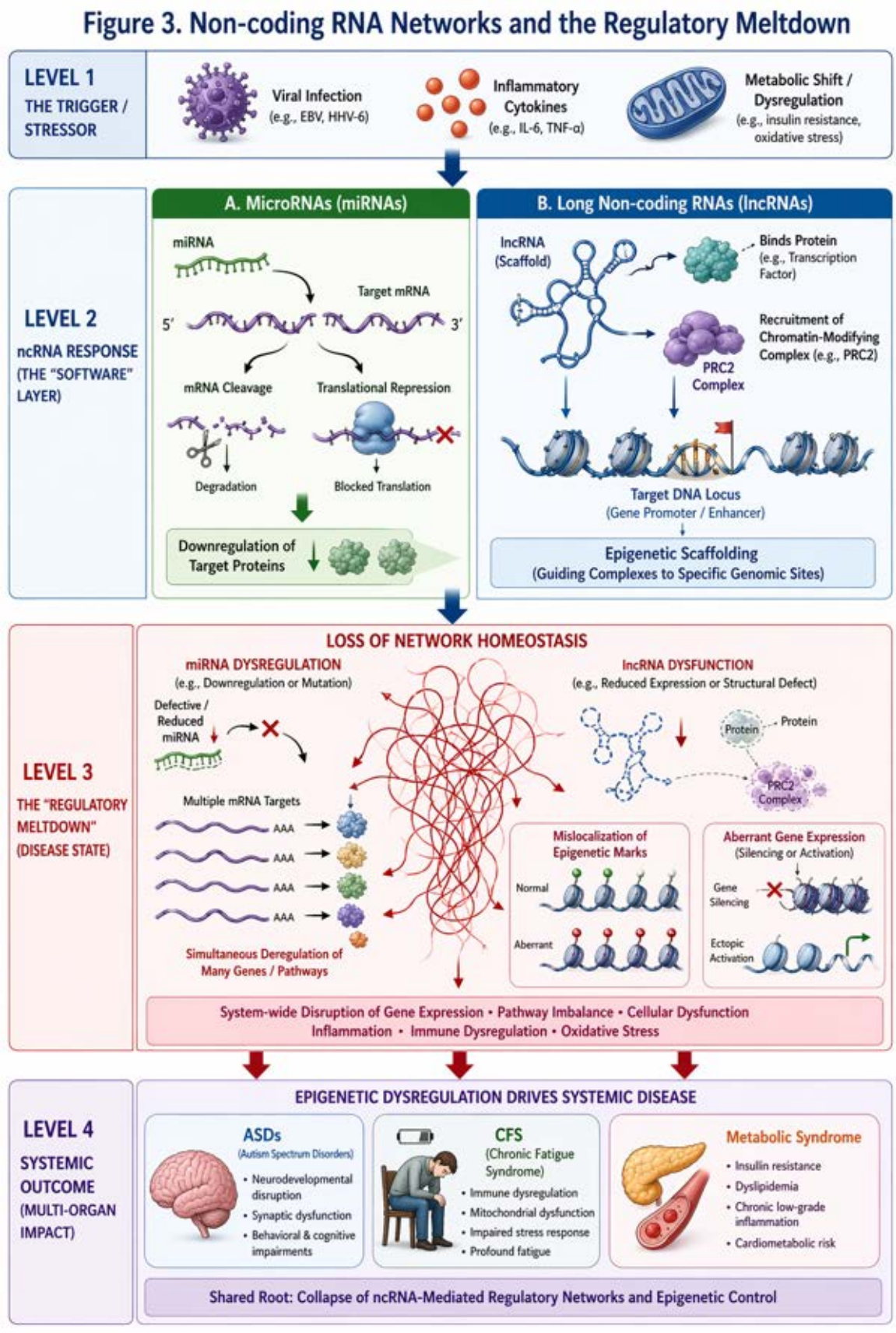

Figure 4. *Non-coding RNA Networks and the Regulatory Meltdown. Non-coding RNAs as systemic orchestrators. (A) MiRNAs provide rapid post-transcriptional silencing, while (B) lncRNAs provide spatial scaffolding for chromatin modifiers. In primary epigenetic diseases, a localized failure in this ncRNA 'genomic software' catalyzes a systemic 'regulatory meltdown,' affecting broad gene networks.*

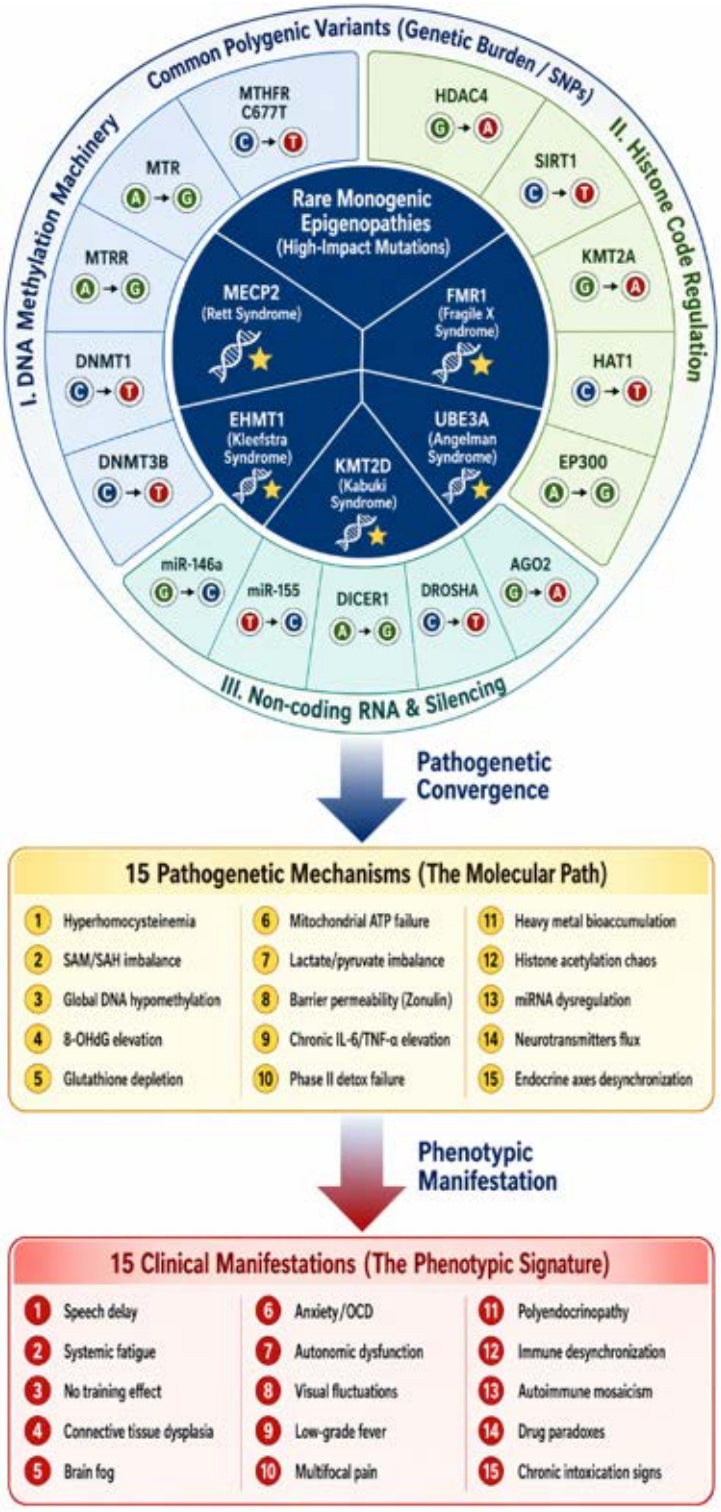

Figure 5. *The Hierarchical Model of Epigenetic Dysregulation (The "Convergence Wheel").*
This diagram illustrates the structural hierarchy of epigenetic dysregulation and the convergence of diverse genetic inputs into a unified clinical phenotype.

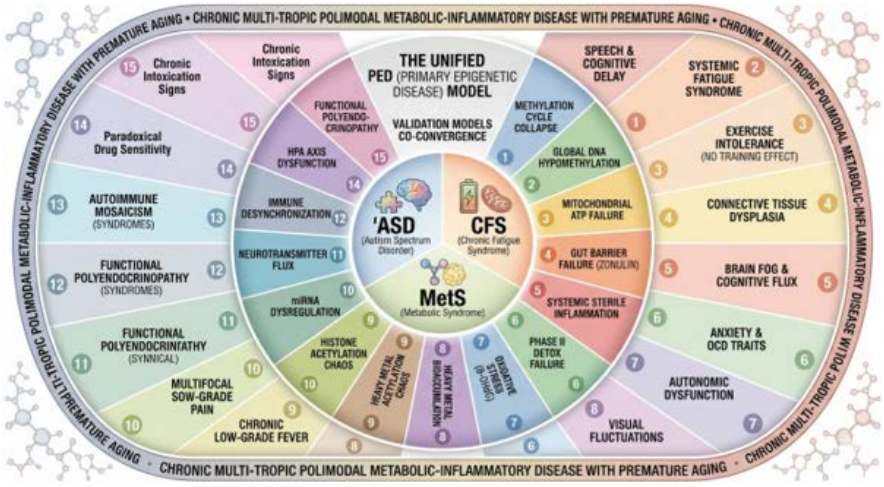

Figure 6. *The Multidimensional Architecture of Primary Epigenetic Disease: From Clinical Models to Systemic Degeneration. This circular hierarchical model illustrates the integrated structure of PED on ASD, CFS, MS examples, demonstrating how diverse clinical entities converge into a unified metabolic and inflammatory phenotype.*

Table 1. *Comprehensive Diagnostic Matrix for Primary Epigenetic Disease.*

№	Clinical Manifestations (Phenotype)	Pathogenetic Mechanism (Process)	Laboratory & Instrumental Biomarkers
1	Communication & Speech & Cognitive Delay	Failure of synaptic pruning & neuronal synchronization	miRSNP dysregulation (miR-146a), Altered EEG patterns & Psychometry [56]
2	Systemic Fatigue Syndrome & Developmental delay & Liver Dysfunction	Mitochondrial ATP production collapse & Multiple Biochemical Abnormalities From Genetic Burden	Index Ritter, Abnormal Lactate/Pyruvate ratio, Low CoQ10 & Bicarbonates; Organic Acids disbalance, MitoSwab evaluation [57] & Multiple deviations of Biochemical Tests (Cholesterol, Urea, Ureic acid, Ammonium, AF, GGTP etc.) [58]
3	Absence of "Training Effect"	Maladaptive epigenetic response to physical stress	Blunted Cortisol response, Persistent CK & LDH elevation [59]
4	Connective Tissue Dysplasia	Epigenetic erosion of the extracellular matrix	High TGF-β, Low Vitamin C/Silicon status & High Hydroxyproline in urea [60]
5	Brain Fog & Cognitive Flux & Gut dysfunction	Histo-hematic barrier instability & "Leaky Gut" & Microbiota-Gut -Brain axis activation	High Protein S100B, Neuron-specific enolase & Zonulin; Gut Dysbiosis test [61]
6	Anxiety & OCD & Panic attacks & Depression	Neurotransmitter methylation/ demethylation failure & Hypovitaminosis of Methyl-Donors and D3	Hyperhomocysteinemia, SAM/SAH imbalance & Low 5-HIAA in urine; Neurotransmitters Panel evaluation [62] &: Chronic deficiency of B12, B6, D3 and Folates despite adequate intake [63].
7	Autonomic Dysfunction	Dysregulation of the HPA and autonomic axes	Reduced Heart Rate Variability (HRV), Orthostatic test & NT-proBNP elevation [64]
8	Visual Acuity Fluctuations	Retinal and optic nerve metabolic instability	Fluctuating intraocular pressure, Retinal scans & Non-Neuronal Enolase elevation [65]
9	Chronic Subfebrile Fever (37.1–37.5°C)	Persistent systemic "sterile" Low-Grade inflammation, Oxidative stress	High-sensitivity CRP (hs-CRP), IL-6, TNF-α, Calprotectin, TumorM2pyruvatkinase & Ferritin [66]
10	Multifocal Somatic Pain	Pro-inflammatory "oxidative stress scarring" of nociceptors	Elevated 8-OHdG (Oxidative DNA damage) & Malonic Dialdehyde, Low levels of reduced glutathione, High Mg, Ca, Cu, Zn, Ceruloplasmin & Transferrin [67]
11	Functional Polyendocrinopathy	Epigenetic silencing of endocrine receptor genes	Subclinical TSH/T4/T3, Sex hormones, Insulin, Leptin, Parathormone and Prolactin fluctuations, Low Androstenedione etc. [68]
12	Immune Desynchronization/ dysregulation & lymphoproliferation	Loss of gain control in leukocyte gene expression	Hematopoietic Instability, Altered CD4+/CD8+ ratio, Low NK-cell activity, IgG Subclasses Deficiencies, Opportunistic Infections, IgE to allergens, Eosinophilic Cationic Protein etc. [69]
13	Autoimmune Mosaicism	Failure of self-tolerance due to DNA hypomethylation	Global DNA methylation (5-mC) levels & ANA, Polymyositis & Systemic Sclerosis. Immunoblots & Ab to neurons, myelin etc. [70]
14	Paradoxical Drug Sensitivity	Cytochrome P450 & Phase II epigenetic silencing	Impaired Glucuronidation/Sulfation profile tests [71]
15	Chronic Intoxication Signs	Detoxification failure & xenobiotic "locking"	Heavy metals (Pb, Hg etc.) in hair/urine & Mycotoxin panel [72]

Table 2. *Main disorders in PED and possible therapeutical interventions according to multitargeted strategy.*

№	Disorder	Possible intervention
1	Hypomethylation	Methylcobalamin, 5-MTHF [115]
2	Hypermethylation	SAM(e) [116]
3	Transsulforation disorder	N-acetylcysteine, L-glutathione reduced [117]
4	Deficiencies of vitamins	Supplementation with vitamins [118]
5	Deficiencies of microelements	Supplementation with microelements [119]
6	Ornithine cycle disorder	Phenylbutyrate, malate citrulline [120]
7	Mitochondrial dysfunction	Mitochondrial triad: L-carnitine, coenzyme Q10, alpha-lipoic acid [121]
8	Hyperuricemia	Febuxostat [122]
9	Hyperlipidaemia	Statins, fibrates [123]
10	Low tolerance to glucose, hyperglycaemia	Metformin [124]
11	Functional polyendocrinopathy	Substitution with hormones (in low function) or specific blockers (in high function) [125]
12	Immunodeficiency	Substitution of immunodeficiency as IVIG in humoral immunodeficiencies and opportunistic infections treatment [126]
13	Autoimmune 8mosaicism	Methylprednisolone, immunosuppressants, immunomodulatory drugs [127]
14	Neurotransmitter disorders	Psychotropic drugs [128]
15	Chronic intoxication	Detoxification therapy [129]
16	Chronic inflammation	Anti-inflammatory drugs [130]
17	Oxidative stress	Antioxidants, such as Curcumin, Quercetin, vit C [131]
18	Epileptic attack and/or epileptic activity on EEG	Anticonvulsants [132]
19	Gut dysbiosis	Pre/probiotics [133]
20	Pathogenic gut bacteria overgrowth	Gut antiseptics, such as rifaximin [134]

triggers or metabolic shifts, the resulting "epigenetic scars" can permanently alter the phenotypical expression of a cell, serving as the foundational driver for complex disorders across the lifespan, from neurodevelopmental shifts to age-related metabolic decline [9] (Figure 2).

Mechanism 2: Histone Post-Translational Modifications and the Histone Code.

While DNA methylation provides a long-term epigenetic memory, histone post-translational modifications (PTMs) offer a more nuanced and dynamic layer of gene regulation. In the eukaryotic nucleus, DNA is packaged into chromatin, the basic unit of which is the nucleosome—an octamer consisting of pairs of histones H2A, H2B, H3, and H4. The N-terminal "tails" of these histones protrude from the nucleosome core and are subject to a diverse array of enzymatic modifications, including acetylation, methylation, phosphorylation, ubiquitination, and sumoylation. These PTMs collectively constitute the "histone code," a complex regulatory language that dictates the accessibility of the underlying genetic sequence to the transcriptional machinery [10].

The functional outcome of these modifications depends on the specific residue involved and the type of chemical group added. For instance, histone acetylation, catalyzed by histone acetyltransferases (HATs), typically neutralizes the positive charge on lysine residues, weakening the electrostatic interaction between histones and the negatively charged DNA. This results in an open, transcriptionally permissive chromatin structure (euchromatin). Conversely, the removal of these groups by histone deacetylases (HDACs) leads to chromatin condensation and gene repression. Histone methylation is even more complex; depending on the site (e.g., H3K4 vs. H3K27) and the degree of methylation (mono-, di-, or tri-methylation), it can either activate or silence transcription. These processes are tightly regulated by "writers" (enzymes that add marks), "erasers" (enzymes that remove them), and "readers" (proteins that recognize and bind to specific marks to recruit further regulatory complexes) [11].

In the framework of our proposed concept, the breakdown of this enzymatic equilibrium represents a primary epigenetic pathology. When the balance between "writers" and "erasers" is chronically tilted—due to metabolic stress or systemic inflammation—the histone code becomes "scrambled." Such dysregulation does not merely modulate existing disease pathways but establishes a self-sustaining state of aberrant gene expression. In disorders like ASD or chronic fatigue, the failure of the chromatin-remodeling machinery to reset these marks leads to persistent cellular dysfunction, effectively "locking" the cell into a pathological phenotype that defines the disease itself [12] (Figure 3).

Mechanism 3: Non-coding RNAs as Orchestrators of Epigenetic Networks.

Beyond the chemical modifications of DNA and histones, the epigenome is governed by an expansive layer of functional transcripts known as non-coding RNAs (ncRNAs). While these molecules do not encode proteins, they act as critical regulatory nodes that fine-tune gene expression at both transcriptional and post-transcriptional levels. Based on their size and function, ncRNAs are broadly categorized into small non-coding RNAs, primarily microRNAs (miRNAs), and long non-coding RNAs (lncRNAs), each contributing uniquely to the stability or erosion of the epigenetic landscape [13].

MicroRNAs (~22 nucleotides) typically function by binding to the 3' untranslated regions (3' UTR) of target messenger RNAs (mRNAs), leading to their degradation or the inhibition of their translation. This allows for a rapid, systemic response to physiological shifts. In contrast, lncRNAs (>200 nucleotides)

possess a more complex structural versatility, enabling them to act as molecular "scaffolds" or "guides." They can recruit chromatin-modifying enzymes, such as Polycomb Repressive Complexes (PRC), to specific genomic loci, thereby facilitating either the silencing or activation of large gene clusters. Through these interactions, ncRNAs bridge the gap between transient signaling and permanent epigenetic marks, creating a self-reinforcing regulatory loop [14].

Within the framework of primary epigenetic diseases, ncRNAs represent a high-level control system that, when compromised, leads to a "regulatory meltdown." In conditions like ASD or post-infectious inflammatory syndromes, the dysregulation of specific "epi-miRNAs" or lncRNAs can lead to a state of chronic cellular desynchronization. Because ncRNAs often regulate hundreds of downstream targets simultaneously, a single lesion in this network—whether triggered by viral interference or metabolic imbalance—can catalyze a multi-system failure. Thus, rather than being a side effect of pathology, the collapse of the ncRNA-mediated "genomic software" constitutes a foundational disease state, where the cell loses its ability to interpret and execute its own genetic instructions [15] (Figure 4).

The Interplay Between Genetic Burden and Epigenetic Buffering: The Mechanism of Phenotypic Unmasking.

A fundamental paradox in systems medicine is why identical epigenetic dysregulations lead to vastly different clinical outcomes. A central tenet of the primary epigenetic disease hypothesis is the existence of a "genetic burden" (genetic load)—a cumulative collection of deleterious or suboptimal genetic variations present in every human genome [16]. This burden is not a collection of rare mutations, but a unique "genomic fingerprint" of vulnerabilities that every individual carries from birth.

No human genome is perfect. Each individual possesses thousands of minor genetic flaws, including single nucleotide polymorphisms (SNPs), copy number variations (CNVs), and "silent" mutations in metabolic, structural, and regulatory genes. In a state of health, this genetic burden remains clinically silent. It is effectively "masked" or "buffered" by a robust epigenetic system that compensates for these genetic gaps through precise gene expression control [17].

The epigenetic machinery acts as a homeostatic shield. For instance, if a person has a genetically "weak" enzyme in a metabolic pathway, the epigenetic system can upregulate the expression of that gene or activate alternative pathways to maintain biochemical balance. This creates a state of compensated genetic vulnerability, where the person remains healthy despite their genetic burden [18].

The clinical phenotype of an epigenetic disease is determined not just by the primary "breakdown" of the regulatory machinery (e.g., MTHFR or HDAC SNPs), but by the unmasking of the underlying genetic burden. When the epigenetic "shield" fails due to systemic desynchronization, the individual's unique genetic flaws begin to manifest clinically [19].

This explains the extraordinary diversity of the epigenetic syndrome: two patients with the same epigenetic failure (e.g., systemic hypomethylation) may show different symptoms because their underlying genetic burdens are different. One might develop neurodevelopmental issues because of "weak" synaptic genes, while another develops cardiovascular pathology due to "weak" lipid metabolism genes [20].

While the genetic burden is unique to each individual, there are typical human vulnerabilities—conserved evolutionary bottlenecks in the folate cycle, mitochondrial DNA, and immune signaling—that are frequently affected in almost all cases of epigenetic disease.

In summary, the clinical picture of an epigenetic disease is the realization of the latent genetic burden. The disease is not "caused" by a single mutation; it is the state where the genome's "buffer capacity" is exhausted, allowing the accumulated weight of minor genetic flaws to dictate the pathological trajectory of the organism.

Mendelian Genetic Aberrations in the DNA Methylation Machinery: rare extreme "experiments" of nature.

The classification of epigenetic dysregulation as a primary disease entity is best supported by mutations in the genes encoding the DNA methylation apparatus. When the "writers" or "readers" of the methyl code are genetically compromised, the resulting phenotype is not merely a secondary symptom but a direct manifestation of an epigenopathic state.

DNMT3B (DNA methyltransferase 3 beta) mutations: Mutations in the de novo methyltransferase DNMT3B lead to Immunodeficiency, Centromeric instability, and Facial anomalies (ICF) syndrome. This is a classic example of a primary epigenetic disease where the loss of methylation at satellite DNA triggers global genomic instability and immune failure [21].

MECP2 (methyl-CpG-binding protein 2) mutations: The MECP2 gene encodes a key "reader" protein that binds to methylated CpG sites. Mutations in MECP2 cause Rett Syndrome, a severe neurodevelopmental disorder. Here, the DNA marks may be present, but the cell's inability to "read" and translate them into transcriptional silencing leads to a catastrophic breakdown in neuronal maturation [22].

DNMT3A (DNA methyltransferase 3 alpha) germline mutations: Overgrowth syndromes, such as Tatton-Brown-Rahman Syndrome (TBRS), result from mutations in DNMT3A. These mutations cause global shifts in the epigenetic landscape during early development, demonstrating how a primary defect in a methyltransferase dictates a systemic developmental trajectory [23].

MBD5 and MBD6 (methyl-CpG binding domain proteins) polymorphisms: Variations in methyl-CpG binding domain proteins are increasingly linked to ASD. These polymorphisms alter the affinity of readers for methylated DNA, leading to "epigenetic noise" in genes responsible for synaptic pruning [24].

DNMT1 (DNA methyltransferase 1) mutations: Mutations in the maintenance methyltransferase DNMT1 cause Hereditary Sensory and Autonomic Neuropathy with Dementia and Hearing Loss (HSAN1E). This highlights that even minor deficits in preserving the methylome during cell division can lead to progressive neurodegeneration [25].

TET2 (tet methylcytosine dioxygenase 2, or ten-eleven

translocation 2) mutations: Although TET2 is an "eraser" (involved in DNA demethylation), its mutations are hallmarks of clonal hematopoiesis. A defect in removing methyl groups leads to a "locked" epigenetic state that prevents hematopoietic stem cell differentiation, serving as a primary driver for myelodysplastic syndromes [26].

In these instances, the pathology is defined by the dysfunction of the epigenetic editor itself. These mutations create a stable, pathological "epi-genotype" that persists throughout the individual's life, validating the concept of epigenetic mechanisms as primary disease-causing agents.

These rare monogenic abnormalities support the very principled possibility of a primary epigenetic disease. However, due to their low frequency in humans, these extreme experiments of nature can not represent primary epigenetic disease at the population level. Therefore, it is necessary to consider common genetic abnormalities in the population that lead to clinically manifest epigenetic disorders.

Common Genetic Polymorphisms of Epigenetic Systems: frequent regulatory disorders represent epigenopathy on population scale.

Below are the pathogenic polymorphisms common in the population that cause disruption of the three basic mechanisms of epigenetic control, which collectively create a significant burden on the health of the modern person, society, states and humanity, representing epigenetic disease as a serious population problem. Due to their high prevalence in the population, these polymorphisms can combine in a single individual in any order, creating a harmful genetic network of hidden epigenetic disease, which currently affects a significant part of humanity, often being beyond the scope of diagnostic search and therapeutic interventions.

Common single-nucleotide polymorphisms (SNPs), such as MTHFR C677T/A1298C and HDAC4, presents as the basis for primary epigenetic vulnerability. However, according to the current consensus in clinical genetics (such as the ACMG guidelines), these common SNPs are not considered to cause disease on their own; rather, they are regarded as low-impact risk factor in the general population. Without statistical support, such as polygenic risk scores (PRS), there remain strong concerns about placing these at the core of a pathophysiological model as a “trigger for disease” (genetic burden).

Unlike mendelian mutations, such polymorphisms alone cannot cause disease, but their abnormal accumulation either within one mechanism of epigenetic control, or in two or even three mechanisms at once can significantly disrupt epigenetic regulation, acquiring clinical significance on a polygenic basis. In addition, pathogenic polymorphisms can be aggravated by monogenic mendelian mutations that induce epigenetic disorders, and other mutations that do not relate to epigenetic control, but can determine the development of the clinical phenotype of the associated nosology, for example, ASD, in some patients.

Common Genetic Polymorphisms with DNA Methylation disorders as Drivers of the Epigenetic Disease State.

In the context of the "epigenetic disease" hypothesis, the focus shifts from rare monogenic syndromes to high-frequency single nucleotide polymorphisms (SNPs) that compromise the robustness of the epigenetic machinery. These variations do not constitute distinct clinical nosologies but rather create a persistent state of epigenetic vulnerability, where the cell’s ability to maintain its methylome is chronically impaired.

MTHFR (methylenetetrahydrofolate reductase) C677T and A1298C (folate cycle "bottleneck"): These are the most prevalent SNPs affecting the synthesis of S-adenosylmethionine (SAM). The C677T variant leads to a thermolabile enzyme, while A1298C affects the regulatory C-terminal domain. In compound heterozygotes, the resulting reduction in SAM availability acts as a primary "metabolic-epigenetic" lesion, causing systemic DNA hypomethylation and predisposing individuals to neurodevelopmental and cardiovascular desynchronization [27].

DNMT3B (DNA methyltransferase 3beta) -149C>T (promoter variation): Unlike the severe mutations seen in ICF syndrome, this common polymorphism in the promoter of the de novo methyltransferase DNMT3B significantly alters gene expression levels. This variation creates a "fluctuating" methylome, where the precision of de novo methylation during cellular stress is compromised, potentially serving as a primary driver for the aberrant silencing of protective genes [28].

COMT (catechol-O-methyltransferase) Val158Met (methylation competition): The Catechol-O-methyltransferase polymorphism (Val158Met) is a crucial node where neurotransmitter metabolism competes for methyl donors. The "High-activity" Val-allele consumes a disproportionate amount of SAM for catecholamine degradation, effectively "robbing" the epigenetic machinery of methyl groups. This competition creates a state of epigenetic drift, especially in the prefrontal cortex, linking it to the pathogenesis of ASD and chronic fatigue [29].

MTR (methionine synthase) A2756G and MTRR (methionine synthase reductase) A66G (remethylation defects): Polymorphisms in methionine synthase (MTR) and its reductase (MTRR) impair the efficient recycling of homocysteine back to methionine. These SNPs act as "silent" epigenetic modifiers that ensure a suboptimal pool of methyl groups, locking the epigenome into a state of low plasticity and high susceptibility to environmental stressors [30].

BHMT (betaine-homocysteine S-methyltransferase) G742A (alternative methylation pathway): The betaine-homocysteine S-methyltransferase polymorphism disrupts the backup pathway for SAM production. In individuals with co-existing MTHFR defects, this SNP becomes a decisive factor in the collapse of epigenetic homeostasis, illustrating the concept of a multi-hit epigenetic disease [31].

By integrating these common variants, we demonstrate that an "epigenetic disease" can arise from a cumulative deficit in the methyl-donor network, rather than a single genetic mutation.

Common Genetic Polymorphisms in Histone Modifying Machinery.

In the framework of primary epigenetic pathology, common polymorphisms in genes encoding "writers" and "erasers" of the histone code represent a significant source of inter-

individual variation in chromatin stability. These SNPs do not manifest classic Mendelian disorders but predispose the cellular machinery to chromatin desynchronization, particularly under conditions of chronic stress or systemic inflammation.

HDAC4 (histone deacetylase 4) rs12452272 (deacetylation efficiency): This common polymorphism in the Histone Deacetylase 4 gene is linked to altered brain-derived neurotrophic factor (BDNF) expression. The variation affects the efficiency of HDAC4 nuclear-cytoplasmic shuttling, creating a state of "epigenetic rigidity" in neurons. This SNP is a silent driver of impaired synaptic plasticity, providing a foundational substrate for neurodevelopmental disorders without being a direct genetic cause [32].

SIRT1 (NAD-dependent protein deacetylase sirtuin-1) rs7069102 (metabolic-epigenetic link): Sirtuin 1 is a NAD+-dependent deacetylase that bridges metabolism and epigenetics. The rs7069102 polymorphism reduces SIRT1 activity, leading to a failure in the "metabolic reset" of histones. This results in persistent hyperacetylation of pro-inflammatory genes, effectively "locking" the individual into a state of chronic systemic inflammation, typical of metabolic syndrome and chronic fatigue [33].

CLOCK (circadian locomotor output cycles kaput) and BMAL1 (brain and muscle ARNT-Like 1) polymorphisms (circadian histone acetylation): SNPs in these core circadian genes (e.g., CLOCK rs1801260) disrupt the rhythmic acetylation of histones H3 and H4. This leads to a loss of temporal coordination in gene expression. In our concept, this is a "temporal epigenopathy," where the cell lose its ability to synchronize metabolic processes with environmental cues, a hallmark of metabolic and post-infectious syndromes [34].

P300/CBP (EP300) (CREB-binding protein and E1A-associated protein p300) variations: Common variants in these histone acetyltransferases (HATs) reduce the global "acetylation reserve." While not causing Rubinstein-Taybi syndrome, these SNPs lower the threshold for epigenetic silencing, making the genome more susceptible to environmental "scars" and reducing the plasticity required for normal immune and cognitive responses [35].

KMT2A (MLL1) (lysine methyltransferase 2, mixed-lineage leukemia 1) Ars17420 (methylation patterning): This polymorphism in a major histone H3K4 methyltransferase alters the fine-tuning of gene activation marks. It creates "epigenetic noise" in the regulation of homeobox genes, subtly shifting the developmental trajectory and contributing to the multifaceted phenotype of ASD [36].

By examining these high-frequency variants, we emphasize that epigenetic disease often arises from a diminished capacity of the histone-modifying machinery to maintain chromatin homeostasis, rather than from a single catastrophic mutation.

Common Genetic Polymorphisms in Non-coding RNA Regulatory Networks.

In the paradigm of epigenetic disease, polymorphisms affecting non-coding RNA (ncRNA) pathways represent a "regulatory meltdown" of the genomic software. These variations, often termed miRSNPs, occur in microRNA sequences, their target binding sites, or the enzymatic machinery responsible for RNA processing. Unlike structural mutations, these high-frequency variants subtly alter the "gain control" of entire gene networks, driving systemic desynchronization.

MIR146A (microRNA-146a) rs2910164 (the inflammation switch): This is one of the most studied polymorphisms in immune-epigenetics. The C>G variation in the precursor of miR-146a reduces the production of the mature microRNA. Since miR-146a is a primary brake on pro-inflammatory signaling (targeting IRAK1 and TRAF6), this SNP creates a state of epigenetic hyper-reactivity. It serves as a foundational substrate for post-infectious inflammatory syndromes and chronic fatigue, where the "off-switch" for inflammation is genetically underpowered [37].

DICER1 rs3742330 (processing efficiency): Dicer is the core enzyme that crops pre-miRNAs into their functional mature forms. A common polymorphism in its 3' UTR is associated with altered miRNA global profiles. In our framework, this is a "biogenesis epigenopathy," where a slight reduction in Dicer efficiency leads to a reduced "repertoire" of regulatory RNAs, limiting the cell's ability to buffer environmental stress [38].

MIR155 (microRNA-155) rs767649 (immune-metabolic hub): miR-155 is a master regulator of both immune response and adipocyte function. Polymorphisms in its flanking regions alter its expression levels, creating a predisposition to the metabolic syndrome. By shifting the epigenetic set-point of macrophages and adipocytes, this SNP locks the system into a pro-inflammatory metabolic state [39].

MIR499 (microRNA-499) rs3746444 (mitochondrial-epigenetic link): This SNP affects the targeting of genes involved in mitochondrial dynamics and muscle metabolism. It is a silent driver of the "fatigue phenotype," where the epigenetic regulation of energy production is compromised, contributing to the persistent energy deficits seen in CFS [40].

Target-site SNPs, e.g., in the 3' UTR of BDNF (3'-untranslated region of the brain-derived neurotrophic factor gene). Polymorphisms that destroy or create new miRNA binding sites (e.g., for miR-124 or miR-132) can lead to "gene-specific epigenetic escape." Such variants are highly relevant in ASD, where the loss of miRNA-mediated control over synaptic genes leads to uncontrolled dendritic pruning [41].

These ncRNA-related polymorphisms demonstrate that epigenetic diseases can emerge from a failure in regulatory fine-tuning. By altering the "density" and "connectivity" of RNA networks, these variants establish a stable, pathological state that defines the disease's trajectory across the lifespan.

The Generalized Phenotype of Primary Epigenetic Disease.

The clinical manifestation of a primary epigenetic disease is not confined to a single organ system but rather presents as a multisystemic "epigenetic syndromocomplex". This phenotype emerges from the chronic failure of cellular memory and regulatory feedback loops, leading to a state of systemic biological desynchronization.

The conceptualization of epigenetic dysregulation as a primary disease entity necessitates a shift toward a multisystemic clinical paradigm. Unlike classical Mendelian disorders, the "epigenetic syndrome" manifests as a progressive decay of the

organism's regulatory buffer, where the accumulation of sub-threshold biochemical failures leads to a stable, yet profoundly pathological, state. This phenotype is characterized by its extraordinary breadth, spanning from early neurodevelopmental shifts to terminal age-related structural erosion, all united by a common thread of genomic desynchronization.

The core of this phenotype is defined by several interlocking pathogenic pillars.

1. Metabolic and Biochemical Instability:

The foundational hallmark is hyperhomocysteinemia (or, less frequently, hypohomocysteinemia), signaling a collapse of the folate and sulfur-amino acid cycles. This disruption radiates through the metabolic landscape, manifesting as multiple anomalies across various pathways, including impaired transsulfuration and methylation. This metabolic chaos is further exacerbated by mitochondrial dysfunction, leading to a persistent energy deficit and the systemic accumulation of reactive oxygen species (oxidative stress) [42].

2. Chronic Inflammation and Barrier Breakdown:

The epigenetic phenotype is characterized by Persistent Systemic Low-Grade Inflammation (inflammaging). This is not localized but involves specific neuro-inflammatory and gastrointestinal axes, manifesting as chronic inflammation in the gut and brain. This state is intrinsically linked to the failure of histo-hematic barriers, including increased intestinal and blood-brain barrier permeability ("leaky" barriers), which allows for the translocation of inflammatory triggers and the development of profound intestinal dysbiosis [43].

3. Neuro-Endocrine and Structural Dysregulation:

At the regulatory level, the syndrome presents as a functional polyendocrinopathy, where hormonal imbalances arise from altered epigenetic programming of endocrine axes rather than primary glandular failure. This is mirrored in the central nervous system by complex neurotransmitter imbalances, affecting mood, cognition, and autonomic function. Furthermore, the pathology extends to the structural framework of the body, characterized by abnormalities in the connective tissue matrix, reflecting disrupted epigenetic control over collagen and extracellular matrix remodeling [44].

4. Detoxification and Immune Failure:

The PED phenotype includes a profound dysfunction of detoxification systems, leading to the bioaccumulation of endogenous and exogenous toxins. This occurs alongside immune dysregulation, marked by a deficiency in key immune factors and a loss of self-tolerance [45].

5. Developmental and Neuro-Psychiatric Manifestations:

The earliest clinical markers of the epigenetic disease are often observed in the pediatric population, primarily presenting as a disruption of psycho-speech development. In these children, the epigenetic programming of neuronal networks fails to meet developmental milestones, leading to delayed language acquisition and cognitive maturation. While physical growth retardation may occur, it is the structural integrity of the connective tissue that serves as a more frequent "silent" marker [46]. The connective tissue dysplasia syndrome, manifested by marked joint hypermobility, reflects an early-stage epigenetic aberration in the synthesis of the extracellular matrix [47].

As the pathology progresses into adolescence and adulthood, the focus shifts toward a profound neurotransmitter dysregulation. The clinical picture is dominated by a diverse array of neuropsychiatric symptoms, reflecting the instability of the neuro-epigenetic landscape. Patients frequently experience chronic anxiety, depression, and obsessive-compulsive disorders, often accompanied by panic attacks and emotional lability. At the physiological level, this neuro-instability manifests as intracranial hypertension, leading to fluctuating visual acuity and persistent autonomic dysfunction. These symptoms are not isolated psychiatric events but are symptomatic of a deeper failure in the epigenetic "gain control" of the central and autonomic nervous systems [48].

6. Immune-Inflammatory Synergies and Immune Dysregulation:

A cornerstone of the epigenetic phenotype is the paradox of immune dysregulation. The clinical trajectory is defined by a simultaneous state of immune deficiency and autoimmune hyper-reactivity. On one hand, patients suffer from persistent opportunistic infections, chronic anemia, and neutropenia, indicating a failure of the hematopoietic and immune-proliferative machinery. On the other hand, there is a progressive emergence of multiple autoimmunization against antigens of various organs and tissues. This is frequently accompanied by polyvalent allergies and complex immunoinflammatory syndromes [49].

This immune chaos is exacerbated by the chronic failure of histo-hematic barriers. The "leaky gut" syndrome (increased intestinal permeability) acts as a primary driver of systemic endotoxemia, manifesting clinically as persistent intestinal dyspepsia. This breakdown of barrier integrity allows for a continuous influx of pro-inflammatory triggers, fueling a state of persistent systemic low-grade inflammation and oxidative stress. This is clinically observable as chronic subfebrile temperature, persistent fatigue, and a constellation of somatic pain including arthralgia and myalgia [50].

7. Musculoskeletal System Damage:

The epigenetic disease phenotype further manifests as a functional polyendocrinopathy, where the dysfunction is rooted in altered gene expression axes rather than primary glandular destruction. Clinical manifestations are widespread, including fluctuating thyroid function (primarily hypothyroidism, though hyperthyroidism may occur), hypo- or hyperparathyroidism, and hyperprolactinemia. Patients often exhibit glucose intolerance and hormonal imbalances such as hypogonadism (or less frequently, hypergonadism) and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [51].

This endocrine instability contributes to the metabolic decay observed in older populations. The epigenetic "memory" of metabolic stress translates into premature atherosclerosis, arterial hypertension, and a heightened risk of acute cardiovascular events. This is mirrored in the musculoskeletal system by a transition from early hypermobility to secondary osteoporosis, osteochondrosis, and deforming osteoarthritis. The structural failure is further complicated by myomalacia and

chondromalacia, reflecting the total exhaustion of the epigenetic control over tissue repair and mineral homeostasis [52].

8. Mitochondrial Exhaustion and Detoxification Failure:

The energetic hallmark of the epigenetic syndrome is a profound mitochondrial dysfunction. Patients describe a sense of "insurmountable fatigue" and psycho-emotional lability that is not relieved by rest. Crucially, there is an absence of the training effect from physical activity; instead of adaptation, exertion leads to further systemic depletion [53]. This mitochondrial failure is intrinsically linked to the collapse of the detoxification systems. Clinically, this manifests as a paradoxical hypersensitivity to medications (poor drug tolerance) and the systemic bioaccumulation of heavy metals, xenobiotics, and mycotoxins. The organism loses its ability to biotransform toxins, leading to a state of chronic self-poisoning that reinforces the epigenetic lesions [54].

9. Hematopoietic disorders:

Finally, the persistence of chronic anemia and neutropenia underscores the failure of the epigenetic regulation of the bone marrow niche [55].

In conclusion, the generalized phenotype of the primary epigenetic disease represents an organism that has lost its biological "homeostatic anchor." It is a state of multisystemic desynchronization where the breakdown of biochemical cycles, the erosion of barriers, and the scrambling of regulatory codes converge into a single, complex clinical entity. Understanding this generalized phenotype is essential for moving beyond symptomatic treatment toward a systemic, epigenetic-based therapeutic intervention.

Working Diagnostic Criteria for PED.

The diagnosis of PED is established through a multi-dimensional analysis, requiring a combination of genetic, biochemical, and clinical findings. We propose a set of 15 criteria divided into three diagnostic tiers.

Tier I: Genetic and Epigenetic Vulnerability (The "Hardware" Layer)

1. **High-frequency SNP Load:** Identification of functionally significant polymorphisms in the folate cycle (MTHFR C677T/A1298C) and remethylation pathway (MTR, MTRR).
2. **Epigenetic Machinery Variations:** Presence of SNPs in genes encoding "writers" (DNMTs), "erasers" (HDACs, SIRT1), or "readers" (MBDs) of the epigenetic code.
3. **miRSNP Profile:** Detection of polymorphisms in microRNA sequences (e.g., miR-146a, miR-155) or their binding sites that disrupt gene silencing networks.
4. **Family History of Multi-systemic Dysfunction:** A pedigree demonstrating non-Mendelian, "fluctuating" pathologies across generations (e.g., ASD in children, autoimmune issues in parents, early CVD in grandparents).

Tier II: Biochemical and Metabolic Dysregulation (The "Software" Layer)

5. **Methylation Cycle Imbalance:** persistent hyperhomocysteinemia (or significant hypohomocysteinemia) and an altered SAM/SAH (S-adenosylmethionine to S-adenosylhomocysteine) ratio.
6. **Chronic Oxidative Stress Markers:** elevated levels of 8-OHdG (oxidative DNA damage) and a reduced glutathione (GSH) index.
7. **Mitochondrial Insufficiency:** abnormal lactate/pyruvate ratios and markers of impaired fatty acid oxidation.
8. **Histo-Hematic Barrier Permeability:** elevated serum zonulin or calprotectin (gut barrier) and evidence of altered blood-brain barrier integrity (via neuro-specific markers).
9. **Systemic Low-Grade Inflammation:** chronic elevation of highly sensitive C-reactive protein (hs-CRP) and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) without an acute infectious cause.
10. **Detoxification Failure:** bioaccumulation of heavy metals or mycotoxins and impaired phase I/II liver detoxification profiles.

Tier III: Clinical and Phenotypic Manifestations (The "Output" Layer)

11. **Neuro-Psychiatric Spectrum:** presence of developmental delays (psycho-speech), chronic anxiety, obsessive-compulsive traits, or cognitive "fog."
12. **Connective Tissue and Structural Erosion:** a spectrum ranging from joint hypermobility (dysplasia) in youth to early-onset osteoarthritis and osteoporosis in adulthood.
13. **Functional Polyendocrinopathy:** subclinical fluctuations in thyroid, adrenal, or gonadal axes that lack a primary glandular lesion.
14. **Immune Desynchronization:** a combination of opportunistic infections (immune deficiency) and multiple autoimmunization or polyvalent allergies.
15. **Therapeutic Paradox and Fatigue:** the absence of a training effect from physical activity, paradoxical reactions to standard medications, and insurmountable systemic fatigue.

In table 1 the original 30-fold diagnostic matrix of 15 main pathogenetic and 15 associated clinical branches for PED diagnosis is presented.

These working criteria should be tested for relevance and validity in further research. In this publication, we have created a 30-component diagnostic matrix as a working material for further research. If such criteria show their validity, we will have an effective universal tool for identifying the epigenetic nature of the disease for all clinical cases, regardless of their complexity.

Figure 5 integrates data on genetic diversity, key pathogenic links, and associated clinical syndromes of the general epigenetic syndrome complex of PED.

It is necessary to clarify that currently there are results of meta-analyses, systematic reviews, narrative reviews, which indicate the association of each component of the 30-component matrix of PED diagnosis, however, these components have not been collected together into a single matrix. It is in this work that we combine the data, proposing a transition from studies of separate relationships between genetic abnormalities and clinical or laboratory outcome, to integral studies that would validate the entire known complex as a single representative PED matrix.

Since the studies of separate associations between genetic factors and clinical and laboratory data are positive, the

application of the 30-component matrix model to the phenotypes of ASD, CFS and MS does not lead to the phenomenon of circular reasoning. This is not about the insufficient evidence of the key clinical and laboratory signs of epigenetic disorders, but about the need to form a promising integral diagnostic matrix for further studies. Without a doubt, this is a proposal, not a complete proof. However, without the formation of such a proposal on the basis of the evidence accumulated so far, it is impossible to move from the level of separate to multi-complex integral studies.

Clinical nosologies that have signs of primary epigenetic disease.

Such nosological entities as ASD, CFS, and MS have all the characteristic features of PED. It currently remains an open question whether PEH is root cause of the pathophysiology of ASD and CFS. Much of the presented data (such as generalized DNA hypomethylation or elevated oxidative stress markers) does not fully rule out the possibility that these are “reactive (secondary)” changes resulting from environmental factors, chronic inflammation, or secondary metabolic abnormalities. It is needed to prove that the molecular mechanisms that epigenetic changes are the “true cause” rather than merely a “consequence.” Considering the results of meta-analyses and systematic reviews, which indicate the association of the above-mentioned nosologies with pathogenic polymorphisms that disrupt epigenetic regulation, at this stage we cannot say that PED is an etiological factor, but only that in ASD, CFS, MS the phenomenon of PED is determined, which may affect the severity of the condition, prognosis, and sensitivity to treatment.

We attempt to integrate childhood ASD, adult CFS, and metabolic syndrome in the elderly into a single spectrum under the common label of “primary epigenetic disease.” While these conditions do share common biomarkers such as chronic low-grade inflammation and mitochondrial dysfunction, it is not possible to conclude that they constitute a single disease entity (PED). No doubt, there is a risk of downplaying the unique etiological backgrounds of each condition (such as neurodevelopmental specificity). Therefore, correct positioning is essential. We do not limit ASD, CFS, and MS to PED alone, but we will point out that its signs are strongly present in these conditions and, probably, should be considered in diagnosis and clinical management.

Model 1: Primary Epigenetic Disease in Autism Spectrum Disorder.

ASD has traditionally been viewed through the lens of genetic determinism or isolated neurobiology. However, the lack of a single "autism gene" in the majority of cases and the systemic nature of the disorder suggest a more complex etiology. We propose that ASD is a prototypical primary epigenetic disease, representing a developmental "regulatory meltdown" where the epigenome fails to synchronize neuronal maturation with systemic homeostasis.

I. Clinical Validation: Mapping ASD to the 15 Phenotypic Criteria:

In pediatric practice, ASD demonstrates a near-perfect correlation with the proposed clinical criteria for PED. The hallmark delay in psycho-speech development (criterion 1) is not merely a neurological symptom but an epigenetic failure of synaptic pruning and plasticity [73]. This is frequently accompanied by connective tissue dysplasia (criterion 4), manifesting as joint hypermobility and hypotonia, which points to a systemic defect in matrix regulation rather than a localized brain issue [74].

Children with ASD often exhibit histo-hematic barrier instability (criterion 5), specifically the "leaky gut" phenotype, which drives chronic neuro-inflammation [75]. This systemic desynchronization is further evidenced by immune desynchronization/dysregulation (criterion 12) [76], where the child suffers from recurrent infections [77] while simultaneously showing high levels of autoantibodies against brain proteins [78]. The presence of autonomic dysfunction (criterion 7) [79] and systemic fatigue (criterion 2) [80]—often dismissed as "behavioral issues"—reflects the underlying mitochondrial failure and the absence of a physiological "training effect" in response to environmental stimuli.

II. Laboratory Validation: The Molecular Fingerprint of ASD:

The laboratory profile of children with ASD provides definitive evidence of an epigenopathic state. Hyperhomocysteinemia and SAM/SAH imbalance (criteria 1, 2) are almost universal findings in this population, indicating a fundamental collapse of the methylation cycle. This biochemical bottleneck is often driven by a High SNP Load (criterion 3) in the folate cycle, particularly the MTHFR C677T and A1298C variants, which deprive the developing brain of essential methyl donors [81].

Furthermore, ASD is characterized by chronic oxidative stress (criterion 5), with significantly elevated 8-OHdG [82] and a depleted glutathione index (criterion 6) [83]. This creates a feedback loop where oxidative stress further damages the epigenetic machinery (DNMTs, SIRT1), leading to global DNA hypomethylation (criterion 13) [84]. The bioaccumulation of heavy metals and xenobiotics (criterion 11) [85], such as lead or mercury, in ASD children is not merely an environmental accident but a direct consequence of impaired phase II detoxification (criterion 10) [86].

III. The Epigenetic Mechanism of Synaptic "Scrambling":

At the molecular level, ASD represents a failure of the histone code and ncRNA networks. In our model, polymorphisms in "reader" proteins like MECP2 or MBDs prevent the cell from interpreting epigenetic marks correctly. This results in "epigenetic noise," where genes that should be silenced during specific developmental windows remains active, leading to the characteristic "over-connectivity" or "under-connectivity" in the autistic brain [87].

Moreover, the collapse of ncRNA regulation (miRSNPs) leads to the loss of "gain control" over inflammatory pathways (e.g., miR-146a), transforming a normal immune response into a state of persistent systemic low-grade inflammation (criterion 9) [88]. This inflammation, in turn, disrupts the hormonal axes, resulting in functional polyendocrinopathy (criterion 11), including the frequently observed TSH and prolactin fluctuations in these children [89].

Conclusion of the model. By applying the 30-point diagnostic matrix, it becomes evident that ASD is a systemic epigenopathy.

The neuro-behavioral symptoms are merely the most visible "output" of a deeper failure in biological synchronization. Recognizing ASD as a primary epigenetic disease shifts the therapeutic focus from behavioral management to epigenetic rehabilitation—targeting the methylation cycle, restoring barrier integrity, and neutralizing oxidative stress to "re-program" the developmental trajectory.

Model 2: Systemic Epigenopathic Failure in Chronic Fatigue Syndrome.

CFS has long remained a diagnostic challenge due to its multisystemic nature and the lack of a single structural lesion. However, through the lens of our proposed framework, CFS emerges as a primary epigenetic disease — a state of persistent biological desynchronization where the organism loses its ability to exit a "defensive" metabolic mode. This model demonstrates how the 30-point diagnostic matrix identifies the underlying regulatory collapse in adult patients.

I. Clinical Validation: The Phenotypic Signature of CFS:

The clinical presentation of CFS provides a comprehensive match for the PED criteria. The defining feature, systemic fatigue syndrome (criterion 2), is not merely tiredness but a fundamental breakdown of the cellular energy "buffer." This is inextricably linked to the absence of a "training effect" (criterion 3): patients with CFS do not experience physiological adaptation to exercise; instead, physical or cognitive exertion triggers "post-exertional malaise" (PEM), a hallmark of mitochondrial-epigenetic failure [90].

Patients consistently demonstrate histo-hematic barrier instability (criterion 5) [91], with the "leaky gut" phenotype driving the translocation of endotoxins that fuel neurotransmitter imbalance (criterion 6) [92]. This manifests as "brain fog," chronic anxiety, and autonomic dysfunction (criterion 7), including orthostatic intolerance and fluctuating intracranial pressure [93]. Furthermore, the presence of multifocal somatic pain (criterion 10) — arthralgia and myalgia—reflects the epigenetic erosion of the connective tissue matrix and persistent low-grade inflammation, rather than localized injury [94].

II. Laboratory Validation: The Biochemical "Locked" State:

The laboratory profile of CFS patients mirrors the molecular pathology seen in ASD, but with an emphasis on metabolic exhaustion. methylation cycle imbalance (criteria 1, 2) is a frequent finding, where an altered SAM/SAH ratio prevents the effective silencing of pro-inflammatory retrotransposons and genes. This is often underpinned by a high SNP load (criterion 3) in the MTHFR and MTR/MTRR genes, limiting the availability of methyl donors required for mitochondrial DNA repair [95].

A critical laboratory finding in CFS is mitochondrial insufficiency (criterion 7), evidenced by an abnormal lactate/pyruvate ratio and impaired oxygen consumption at the cellular level [96]. This state is reinforced by chronic oxidative stress (criterion 5) [97] and a severely depleted glutathione (GSH) index (criterion 6) [98]. The resulting "oxidative scarring" of the epigenome maintains the cells in a pro-inflammatory state, confirmed by the chronic inflammatory profile (criterion 9) (elevated hs-CRP, IL-6) [99]. Additionally, the bioaccumulation of mycotoxins and xenobiotics (criterion 11) [100], due to impaired phase II detoxification (criterion 10), acts as a persistent epigenetic "anchor" that prevents recovery [101].

III. The Epigenetic "Lock": From Infection to Chronic Disease:

In CFS, the transition from a healthy state to a pathological one is often triggered by an infection (e.g., EBV, COVID-19). This trigger causes a "regulatory meltdown" where ncRNA networks (criterion 1), specifically miR-146a and miR-155, fail to "turn off" the inflammatory response [102]. This leads to immune desynchronization/dysregulation (criterion 12) [103] and autoimmune mosaicism (criterion 13) [104], where the body continues to fight a "ghost" of an infection long after the pathogen is cleared.

The epigenetic "lock" is further maintained by functional polyendocrinopathy (criterion 15), characterized by a flattened cortisol curve and subclinical thyroid fluctuations. This is not a failure of the glands themselves, but an epigenetic reprogramming of the HPA axis to a "low-energy" survival mode [105].

Conclusion of the model. Applying the 30-point matrix to CFS reveals that it is not a "psychosomatic" condition but a systemic epigenopathy of exhaustion. The patient is "locked" in a state of mitochondrial and epigenetic depletion. Therapeutic success in CFS, therefore, requires more than symptomatic relief; it demands "manual" biochemical correction to restore the glutathione pool and methylation capacity, combined with systemic epigenetic modulation to "re-program" the organism out of its pathological defensive state.

Model 3: Epigenetic disorders in Metabolic Syndrome.

Metabolic syndrome includes hypercholesterolemia, hypertriglyceridemia, dyslipoproteinemia, hyperuricemia and hyperglycemia. This syndrome is often observed in elderly people as a manifestation of aging. Metabolic syndrome is linked in such cases with atherosclerosis of the arteries and associated cardiac and neurological atherothrombotic acute events, which is the main cause of death of modern humans. The reason is the age-related weakening of epigenetic control over the affected genes of the genetic burden that regulate lipid and carbohydrate metabolism. In addition, this syndrome may not only be an isolated phenomenon, but also a component of a broader metabolic phenotype of ASD and CFS in early age. Therefore, it can be said that ASD and CFS are characterized by the phenomenon of premature aging [106] (Figure 6).

Therapeutic Strategies: From Systemic Epigenetic Modulation to Precision "Manual" Correction.

If PED is a monogenic pathology, then correction is theoretically possible with one specific drug. The introduction the trofinetide into clinical practice in Rett syndrome is a good example of such success [107]. However, in most cases, a polygenic pattern with multiple biochemical disorders is formed in PED. So, multitargeted polymodal therapy is needed.

The recognition of primary epigenetic disease as a multisystemic regulatory failure mandate a dual-track therapeutic approach. While the long-term goal is to achieve systemic re-programming of the epigenome, current clinical practice relies on high-precision biochemical correction to restore homeostatic buffers.

I. Systemic Epigenetic Modulation: The Frontier of Molecular Therapy:

The first approach focuses on the direct modification of the epigenetic "machinery" (writers, erasers, and readers). This represents the systemic correction of the genomic software.

1. DNA Methyltransferase (DNMT) Modulators: Beyond oncology, low-dose DNMT inhibitors and synthetic methyl-donors are being explored to "re-set" global hypomethylation patterns [108].
2. Histone Deacetylase (HDAC) Inhibitors: Medications that target specific HDAC classes (e.g., Valproic acid derivatives or new selective SIRT1 activators) aim to restore the "Histone Code." By promoting an open chromatin state in repressed neuroprotective genes, these agents can theoretically reverse the "epigenetic rigidity" seen in ASD and neurodegenerative disorders [109].
3. RNA-interference (RNAi) and Antisense Oligonucleotides (ASOs): The most promising systemic frontier is the use of synthetic ncRNA analogues to suppress pathological "epigenetic noise." Targeting specific microRNAs (e.g., antagomirs against miR-155 or miR-146a) allows for the systemic quenching of chronic low-grade inflammation [110].

II. Precision "Manual" Management: Targeted Biochemical Restoration:

The second, and currently more accessible, approach is the "manual" correction of identified biochemical aberrations. This method views the epigenetic syndrome as a collection of faulty circuits that must be repaired individually to restore the collective system.

1. Restoration of the Methylation Cycle

Based on the high SNP load (e.g., MTHFR, MTR), therapy involves the use of "pre-activated" methyl donors. Instead of folic acid, clinicians utilize 5-MTHF (methylfolate) and Methylcobalamin (B12), bypassing the genetic bottlenecks to directly supply the SAM pool [111].

2. Mitochondrial and Antioxidant Rehabilitation

To neutralize systemic oxidative stress and mitochondrial failure, a complex of co-factors is required. This includes L-carnitine, Coenzyme Q10, and PQQ, which aim to restore the "training effect" and energy production. The replenishment of the Glutathione (GSH) pool through N-acetylcysteine (NAC) or liposomal GSH is essential to protect the DNA from further epigenetic "scarring" [112].

3. Barrier Integrity and Detoxification Support

Manual management includes the aggressive restoration of the intestinal barrier ("leaky gut") using glutamine, zinc carnosine, and specific probiotics to normalize the zonulin levels. Simultaneously, Phase II detoxification is supported by sulfur-containing compounds (sulforaphane, taurine) to facilitate the clearance of bioaccumulated heavy metals and xenobiotics [113].

4. Neuroendocrine and Connective Tissue Support

Correction of neurotransmitter imbalances is achieved through precursors (e.g., psychotropic drugs, 5-HTP, GABA) and magnesium threonate, while the connective tissue matrix is supported by collagen peptides and silicon, addressing the dysplasia component of the phenotype [114].

III. The Integrated Model: Epigenetic Rehabilitation:

The ultimate clinical success lies in the synergy of these two approaches. By combining systemic modulators with meticulous "manual" biochemical support, we achieve what can be termed "epigenetic rehabilitation." This approach does not merely treat symptoms but "re-teaches" the organism to maintain its own homeostatic boundaries.

In this framework, the clinician acts as a "system administrator" of the genome, identifying specific errors in the methylation, histone, and RNA networks and applying a multi-component therapeutic protocol to stabilize the patient's biological trajectory (Table 2).

It should be clarified that table 2 lists the most promising agents for the correction of clinical and laboratory abnormalities in patients with epigenetic disorders. These agents have now undergone a number of placebo-controlled clinical trials. Undoubtedly, the data in table 2 are not final clinical recommendations for general medical practice. Rather, these data summarize the diversity of clinical trials conducted to date in the field of multitarget correction of epigenetic disorders, show the current state of affairs and indicate promising directions for further research. And it is in this vein that this information should be perceived. There is no doubt that only a consensus treatment guideline can be a direct indication for the routine administration of certain drugs.

IV. Existing guidelines.

At the moment, three guidelines of a multitargeted therapeutic strategy for ASD as a model of PED have been developed and published. The biomarker-based strategy was first introduced by Bradstreet J et al in 2010. The protocol contains all known biomarkers at that time to open access the full spectrum of examinations and determine the individual list of biochemical disorders in each patient for multitarget correction [135]. The guidline BaS-BiSTOR (collect Baseline data, search for Symptoms, measure Biomarkers, Select Treatment, Observe for Response) was proposed by Frye R. in 2022 and is based on a biomarker-based strategy. This protocol additionally discusses the work of a multidisciplinary group of medical experts in a multidisciplinary hospital to implement a personalized treatment in compound clinical approach [136]. The guidline GBINS (Genetic-Biochemistry-Immunology-Neurology-Symptoms) was proposed by Maltsev D. in 2024. It is based on the two previous ones, supplementing with data on the pathogenesis of the disease, the main mechanisms of disease development, and the hierarchical structure of multitropic polymodal lesions, expanding the possibilities of a multitargeted personalized treatment strategy [137].

Discussion.

Toward a New Paradigm in Systems Medicine.

General Concept: The transition from a symptom-based nosology to a mechanism-based understanding of "primary epigenetic disease" represents a fundamental shift in clinical medicine. Our findings suggest that conditions as diverse as (ASD) and CFS share a common molecular "understructure"—a state of systemic biological desynchronization driven by a compromised epigenetic buffer.

The Synergistic Failure of the Epigenome: The core strength of the proposed concept lies in its ability to integrate the "three pillars" of epigenetic regulation: DNA methylation, histone modifications, and non-coding RNA networks. We demonstrate that a primary epigenetic disease is rarely the result of a single catastrophic mutation. Instead, it arises from the cumulative effect of high-frequency SNPs (e.g., MTHFR, HDAC4, miR-146a). This "polygenic epigenetic vulnerability" remains silent until triggered by environmental stressors, at which point the regulatory machinery collapses into a pathological stable state.

A Holistic Phenotype vs. Fragmented Diagnosis: By establishing 15 clinical and 15 laboratory criteria, we address one of the most significant gaps in modern medicine: the fragmentation of multisystemic patients. The current diagnostic model often forces clinicians to view "leaky gut," "mitochondrial dysfunction," and "neurotransmitter imbalance" as separate comorbidities. Our framework proves they are, in fact, synchronized outputs of the same epigenetic failure. The presence of connective tissue dysplasia alongside neurodevelopmental delays in ASD, or the absence of a "training effect" in CFS, serves as a phenotypic signature of a genome that has lost its homeostatic anchor.

The "System Administrator" Approach to Therapy: The discussion of therapeutic strategies highlights a crucial realization: treating the symptoms of an epigenetic disease is equivalent to treating the "output" of a corrupted software without fixing the code. The dual-track approach—combining systemic epigenetic modulators with precision "manual" biochemical correction—offers a path toward genuine rehabilitation. While systemic modulators represent the future of pharmacology, the manual restoration of methylation cycles and mitochondrial buffers provides an immediate, evidence-based toolkit for the modern clinician.

Future Research Directions.

Validation and Standardization of the PED Framework:

The introduction PED concept necessitates a rigorous, multi-stage validation process to transition from a theoretical framework to a globally recognized clinical standard. Future research must prioritize large-scale, longitudinal cohort studies designed to establish the statistical relevance and diagnostic validity of the proposed 30-point matrix. Central to this effort is the formal verification of the "30-point diagnostic matrix," which requires assessing the sensitivity and specificity of each clinical and laboratory criterion across diverse populations, including pediatric (ASD-focused) and adult (CFS-focused) cohorts.

A critical direction for future inquiry lies in the structural analysis of clinical syndromes. We must move beyond simple observation to employ advanced machine learning algorithms and cluster analysis to determine how specific combinations of the 15 clinical markers correlate with distinct "epigenetic signatures." This will allow for the identification of sub-phenotypes within the PED spectrum, enabling more precise prognostic modeling. Simultaneously, the validation of associated biomarkers is paramount. Future trials should aim to establish "gold standard" reference ranges for pivotal indicators such as the SAM/SAH ratio, global DNA methylation levels (5-mC), and specific miRSNP profiles. It is essential to correlate these molecular findings with objective instrumental data, such as heart rate variability (HRV) and neuroimaging markers of barrier permeability, to confirm the causal link between epigenetic "unmasking" and physiological dysfunction.

Furthermore, research must address the dynamic nature of the epigenetic shield. Prospective studies are required to track the stability of these biomarkers over time and in response to the proposed "Epigenetic Rehabilitation" protocols. Establishing a standardized "PED Severity Score" will facilitate international multi-center trials, ensuring that diagnostic criteria remain robust across different healthcare systems and ethnic backgrounds. Ultimately, validating the interplay between the latent genetic burden and measurable epigenetic decay will not only solidify PED as a formal nosological entity but also pave the way for the inclusion of these criteria into future iterations of international classification systems (ICD), fundamentally transforming the management of multisystemic chronic disorders.

Limitations.

Despite the robustness of the proposed framework, several limitations must be acknowledged. First, the dynamic nature of the epigenome means that biomarkers may fluctuate based on circadian rhythms, acute stress, or nutritional status, potentially complicating single-point diagnostic assessments. Second, while the 30-point matrix is based on synthesized evidence, the weighting of individual criteria remains to be refined through prospective clinical trials. Furthermore, the accessibility of advanced epigenetic testing, such as global 5-mC quantification or specific miRSNP profiling, may be limited in standard clinical settings, necessitating the development of more affordable surrogate markers. Finally, the role of the microbiome-epigenome axis and its contribution to the "genetic burden unmasking" requires deeper integration into the model. These factors underscore the need for standardized, multi-center longitudinal studies to harmonize diagnostic protocols across diverse populations.

Conclusion.

This work presents a phenomenological characterization of primary human epigenetic disease in all its diversity.

Epigenetic disease is a multisystemic and polymodal nosological entity driven by the synergistic failure of DNA methylation, histone code maintenance, and ncRNA regulatory networks.

The susceptibility to this condition is determined by a high load of common polymorphisms (SNPs) in the epigenetic machinery, which create a state of "epigenetic fragility" rather than direct structural damage.

The disease is characterized by a stable pathological core, including hyperhomocysteinemia, oxidative stress, persistent low-grade inflammation, autoimmunization, mitochondrial failure, gut dysbiosis and the breakdown of histo-hematic barriers.

Multiple biochemical disorders are noted in various metabolic pathways and cycles, reflecting the manifestation of individual genetic burden in conditions of insufficient epigenetic control.

Across the lifespan, the disease manifests through a consistent 30-point diagnostic matrix (15 clinical and 15 laboratory

criteria), allowing for the identification of the "epigenetic syndrome complex" regardless of the primary medical specialty.

The application of this framework to ASD (pediatric model) and CFS (adult model) validates the universality of the concept, demonstrating that these diverse conditions are manifestations of the same underlying regulatory meltdown.

Effective management requires "epigenetic rehabilitation"—a combination of systemic genomic modulation and high-precision biochemical correction to restore the organism's homeostatic buffers and developmental/functional trajectory.

REFERENCES

1. Burgio E, Porru A, Pettini C, et al. From Genetic Determinism to Epigenetic Regulation: Paradigm Shifts in the Understanding of Neurodevelopmental Disorders. Curr Issues Mol Biol. 2026;48:163.
2. Silva AMPD, Torres EDS, Santos do Nascimento MDV, et al. Genetic and Epigenetic Biomarkers in Hypertension Impact on the Effectiveness of Individualized Therapy: A Systematic Review. J Cardiovasc Pharmacol. 2025;86:321-329.
3. Aung TL, Kan Y, Aung YW, et al. Meta-analysis of long non-coding RNA expression profile in Parkinson's disease. Brain Res. 2025;1863:149838.
4. Katrinli S, Wani AH, Maihofer AX, et al. Epigenome-wide association studies identify novel DNA methylation sites associated with PTSD: a meta-analysis of 23 military and civilian cohorts. Genome Med. 2024;16:147.
5. Zhang XX, Wei M, Wang HR, et al. Mitochondrial dysfunction gene expression, DNA methylation, and inflammatory cytokines interaction activate Alzheimer's disease: a multi-omics Mendelian randomization study. J Transl Med. 2024;22:893.
6. Li S, Spitz N, Ghantous A, et al. A Pregnancy and Childhood Epigenetics Consortium (PACE) meta-analysis highlights potential relationships between birth order and neonatal blood DNA methylation. Commun Biol. 2024;7:66.
7. Balfour D, Kleinig Z, Mittinty M, et al. Human DNA methylation and the cortisol response to an acute psychological stressor: A systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2026;146:111708.
8. Caramaschi D, Fernández-Barrés S, Casey E, et al. Breastfeeding association with DNA methylation in the pregnancy and childhood epigenetics (PACE) consortium. Clin Epigenetics. 2026;18:63.
9. Sinke L, van Dongen J, Delerue T, et al. Epigenome-wide association study of circulating interleukin-6 connects DNA methylation to immunometabolic and inflammatory health. Commun Biol. 2026;9:242.
10. Wang H, Langlais D, Nijnik A. Histone H2A deubiquitinases in the transcriptional programs of development and hematopoiesis: a consolidated analysis. Int J Biochem Cell Biol. 2023;157:106384.
11. Li S, Shen L, Chen KN. Association between H3K4 methylation and cancer prognosis: A meta-analysis. Thorac Cancer. 2018;9:794-799.
12. Yadav P, Tanweer S, Garg M, et al. Structural inscrutabilities of Histone (H2BK123) monoubiquitination: A systematic review. Int J Biol Macromol. 2024;280:135977.
13. Yang L, Lv Y. The role of non-coding RNAs in exosome-mediated wound healing: A systematic review and meta-analysis. Int J Biol Macromol. 2026;356:151474.
14. Panina A, Sokolov AV, Jonsson J, et al. Integrative transcriptomic meta-analysis reveals immune, synaptic, and non-coding RNA dysregulation in bipolar disorder across brain and blood. Neurobiol Dis. 2026;221:107339.
15. Xie H, Li Y, Zhao W, et al. Polymorphisms of long non-coding RNA HOTAIR and susceptibility to gastrointestinal cancers: A meta-analysis. Medicine (Baltimore). 2026;105:e47733.
16. Ozturk FN, Keskin E. Non-COL1A1/2 genetic burden and osteoporosis-overlap in patients referred with osteogenesis imperfecta phenotype. Arch Osteoporos. 2026;21:76.
17. Berry BC, Rodriguez T, Hou CC, et al. Epigenetic buffering of proteotoxic stress by EHMT2 enables meningioma growth. Neurooncol Adv. 2026;8:vdag037.
18. Bakermans-Kranenburg MJ, van Ijzendoorn MH. Research Review: genetic vulnerability or differential susceptibility in child development: the case of attachment. J Child Psychol Psychiatry. 2007;48:1160-73.
19. Wei EQ, Fatkin D, Kim Y. Unmasking the Hidden Genetic Burden of Heart Failure: A Call to Action. JACC Heart Fail. 2025;13:102628.
20. Huang WC, Bennett K, Gregg C. Epigenetic and Cellular Diversity in the Brain through Allele-Specific Effects. Trends Neurosci. 2018;41:925-937.
21. Ali ZA, Al-Ali KF, Bader F, et al. Epigenetic disruption meets immune deficiency: a case report of ICF syndrome linked to DNMT3B mutation. Front Immunol. 2026;16:1742293.
22. Good KV, Strickfaden H, Muhammad T, et al. MeCP2 NID interaction with RNA: implications for Rett syndrome-relevant protein regulation. Hum Mol Genet. 2026;35:ddag031.
23. Ferreira L, Sorrell M, Raskin SI, et al. DNMT3A R882C variant in a patient with a presumed pineal gland tumor, highlighting potential tumor susceptibility in Tatton-Brown-Rahman syndrome. Cancer Genet. 2026;302-303:162-165.
24. Meguro-Horike M, Iwata K, Matsuzaki H, et al. Haploinsufficiency of MBD5 and MBD6 impairs mitochondrial respiration through chromatin-mediated gene regulation. Biochem Biophys Res Commun. 2026;800:153288.
25. Tamura M, Sugiyama A, Hirano S, et al. Hummingbird sign in a patient with DNMT1-related disorder. Neurocase. 2025;31:239-244.
26. Heavican-Foral TB, Li Y, Lone W, et al. Tet2 deficiency alters CD4+ T cell function and promotes T cell lymphoma with a TFH cell immunophenotype. J Exp Med. 2026;223:e20250194.
27. Fang Y, Cui Y, Yin Z, et al. Comprehensive systematic review and meta-analysis of the association between common genetic variants and autism spectrum disorder. Gene. 2023;887:147723.
28. Chen B, Wang J, Gu X, et al. The DNMT3B -579G>T Polymorphism Is Significantly Associated with the Risk of Gastric Cancer but not Lung Cancer in Chinese Population. Technol Cancer Res Treat. 2017;16:1259-1265.
29. Lee YH, Song GG. Association of catechol-O-methyltransferase Val158Met polymorphism with fibromyalgia risk and FIQ scores: an updated meta-analysis. Clin Exp Rheumatol. 2025;43:1002-1009.

30. Li F, Qi JJ, Li LX, et al. MTHFR C677T, MTHFR A1298C, MTRR A66G and MTR A2756G polymorphisms and male infertility risk: a systematic review and meta-analysis. Reprod Biol Endocrinol. 2024;22:133.
31. Singh PR, Lele SS. Folate gene polymorphisms MTR A2756G, MTRR A66G, and BHMT G742A and risk for coronary artery disease: a meta-analysis. Genet Test Mol Biomarkers. 2012;16:471-5.
32. Dou B, Ma F, Jiang Z, et al. Blood HDAC4 Variation Links with Disease Activity and Response to Tumor Necrosis Factor Inhibitor and Regulates CD4+ T Cell Differentiation in Ankylosing Spondylitis. Front Med (Lausanne). 2022;9:875341.
33. Bešić M, Letonja J, Globočnik Petrovič M, et al. SIRT1 rs7069102 Polymorphism Confers Increased Risk of Diabetic Retinopathy in T2DM. Genes (Basel). 2026;17:221.
34. Oladghaffari M, Bandehagh H, Malekinejad F, et al. Polymorphisms in CLOCK and ARNTL/BMAL-1 genes in multiple sclerosis: a systematic review and meta-analysis. Eur J Med Res. 2026;31:204.
35. Wang R, He Y, Robinson V, et al. Targeting Lineage-specific MITF Pathway in Human Melanoma Cell Lines by A-485, the Selective Small-molecule Inhibitor of p300/CBP. Mol Cancer Ther. 2018;17:2543-2550.
36. Batayneh O, Moein M, Naji NS, et al. Characterizing KMT2A Rearrangement in Acute Myeloid Leukemia: A Comprehensive Genomic Study. Cancers (Basel). 2026;18:161.
37. Alikhani MY, Khoobbakht F, Khazaei S, et al. Association Between miR-146a rs2910164 Polymorphism and Tuberculosis Susceptibility: A Comprehensive Meta-Analysis. Int J Mol Cell Med. 2025;14:1084-1098.
38. Rania L, Djalila C, Brahim D, et al. Potential risk factors for hypospadias and negative correlation with DICER1 (rs3742330) A>G variant in Algerian population: A case-control study. Birth Defects Res. 2024;116:e2365.
39. Icduygu FM, Oguz ID, Akgun E, et al. Genetic Polymorphisms of miR-146a and miR-155 in Psoriasis and Psoriatic Arthritis: Evidence from a Turkish Case-Control Study. Dermatol Pract Concept. 2026;16:5977.
40. Lee YH, Song GG. Association between miRNA polymorphisms and rheumatoid arthritis susceptibility: a meta-analysis. Biomark Med. 2025;19:947-955.
41. Liu D, Fan Z, Zhang T, et al. Rs12516 A allele elevates the risk of colorectal cancer via functional CeRNA network of BDNF-AS, miR-4704-5p and BRCA1. BMC Cancer. 2026;26:229.
42. Huang M, Wu Q, Jiang ZH. Epigenetic Alterations under Oxidative Stress in Stem Cells. Oxid Med Cell Longev. 2022;2022:6439097.
43. Ashrafi F, Advani S, Pinto-Tomás AA, et al. Oxidative Stress-Microbiota-Epigenetics Crosstalk: A Missing Link Between Cognition and Social Behavior in Metabolic and Neuropsychiatric Disorders. Cells. 2025;15:3.
44. Zatterale F, Raciti GA, Prevenzano I, et al. Epigenetic Reprogramming of the Inflammatory Response in Obesity and Type 2 Diabetes. Biomolecules. 2022;12:982.
45. Schnekenburger M, Karius T, Diederich M. Regulation of epigenetic traits of the glutathione S-transferase P1 gene: from detoxification toward cancer prevention and diagnosis. Front Pharmacol. 2014;5:170.
46. Liu M, Liu R, Wang R, et al. Lead-induced neurodevelopmental lesion and epigenetic landscape: Implication in neurological disorders. J Appl Toxicol. 2023;43:1256-1271.
47. Harsanyi S, Zamborsky R, Krajciova L, et al. Developmental Dysplasia of the Hip: A Review of Etiopathogenesis, Risk Factors, and Genetic Aspects. Medicina (Kaunas). 2020;56:153.
48. Liu D, Zusman BE, Shaffer JR, et al. Decreased DNA Methylation of RGMA is Associated with Intracranial Hypertension After Severe Traumatic Brain Injury: An Exploratory Epigenome-Wide Association Study. Neurocrit Care. 2022;37:26-37.
49. Liu Z, Yang F, Pan Z. Epigenetic alterations in WDFY4 DNA methylation are linked to immunoinflammatory processes in rheumatoid arthritis: insights from a case-control study. Clin Rheumatol. 2026.
50. Ronca A, Bellelli F, Proietti M, et al. Fatigue, muscle fatigability, and the Hallmarks of Aging: a narrative review. J Nutr Health Aging. 2026;30:100844.
51. Xiao S, Hu Y, Wang X, et al. Epigenetic Mechanisms in Autoimmune Thyroid Diseases: Bridging Research and Clinical Applications. Int J Mol Sci. 2025;26:11823.
52. Xu P, Cheng S, Yang X, et al. Integrative single-cell analysis reveals transcriptional and epigenetic regulatory features of human developmental dysplasia of the hip. Osteoarthritis Cartilage. 2026;34:343-357.
53. Chen Z, Rasheed M, Deng Y. The epigenetic mechanisms involved in mitochondrial dysfunction: Implication for Parkinson's disease. Brain Pathol. 2022;32:e13012.
54. Jin J, Zhong XB. Epigenetic Mechanisms Contribute to Intraindividual Variations of Drug Metabolism Mediated by Cytochrome P450 Enzymes. Drug Metab Dispos. 2023;51:672-684.
55. Du C, Li SW, Singh SX, et al. Epigenetic Regulation of Fanconi Anemia Genes Implicates PRMT5 Blockage as a Strategy for Tumor Chemosensitization. Mol Cancer Res. 2021;19:2046-2056.
56. Masini E, Loi E, Vega-Benedetti AF, et al. An Overview of the Main Genetic, Epigenetic and Environmental Factors Involved in Autism Spectrum Disorder Focusing on Synaptic Activity. Int J Mol Sci. 2020;21:8290.
57. Sharma J, Kumari R, Bhargava A, et al. Mitochondrial-induced Epigenetic Modifications: From Biology to Clinical Translation. Curr Pharm Des. 2021;27:159-176.
58. Ajoolabady A, Aslkhodapasandhokmabad H, Zhou Y, et al. Epigenetic modification in alcohol-related liver diseases. Med Res Rev. 2022;42:1463-1491.
59. García-Giménez JL, Cánovas-Cervera I, Pallardó FV. Oxidative stress and metabolism meet epigenetic modulation in physical exercise. Free Radic Biol Med. 2024;213:123-137.
60. Baghdadi T, Nejadhosseinian M, Shirkoohi R, et al. DNA hypermethylation of GDF5 in developmental dysplasia of the hip (DDH). Mol Genet Genomic Med. 2019;7:e887.
61. Mostafavi Abdolmaleky H, Zhou JR. Gut Microbiota Dysbiosis, Oxidative Stress, Inflammation, and Epigenetic Alterations in Metabolic Diseases. Antioxidants (Basel). 2024;13:985.
62. Girault JA. Epigenetic tinkering with neurotransmitters. Science. 2020;368:134-135.

63. Liu H, Lu N, Cui M, et al. Role of epigenetic modifications mediated by vitamins and trace elements in inflammatory bowel disease. Epigenomics. 2023;15:839-843.
64. Dos Santos Oliveira NC, Serpeloni F, Gonçalves de Assis S. The interplay between DNA methylation and cardiac autonomic system functioning: a systematic review. Int J Environ Health Res. 2023;33:54-70.
65. Gao Q, Lai Y, He S, et al. Lysine acetyltransferase 5 contributes to diabetic retinopathy by modulating autophagy through epigenetically regulating autophagy-related gene 7. Cytojournal. 2025;22:22.
66. Erdik S, Solmaz Avcikurt A, Bolat H. Epigenetic regulators and inflammation antagonists in familial Mediterranean fever: the role of hsa-miR-335-5p, hsa-miR-26b-5p, hsa-miR-16-5p miRNAs and IL-36Ra levels in pathogenesis. Immunol Res. 2026;74:36.
67. Occhigrossi F, Mosca J, Micheli F, et al. Pulsed Radiofrequency and Epigenetic Modulation of Pain Pathways: A Systematic Review Based on Preclinical Evidence. J Pain Res. 2026;19:582117.
68. Meeks KAC, van der Linden EL, Bentley AR, et al. Causal relationship between epigenetic markers and type 2 diabetes in West African populations: a Mendelian randomisation analysis. Diabetologia. 2026.
69. Merlo Pich LM, Ziogas A, Netea MG. Genetic and epigenetic dysregulation of innate immune mechanisms in autoinflammatory diseases. FEBS J. 2024;291:4414-4432.
70. Mu S, Wang W, Liu Q, et al. Autoimmune disease: a view of epigenetics and therapeutic targeting. Front Immunol. 2024;15:1482728.
71. Zhang T, Pilko A, Wollman R. Loci specific epigenetic drug sensitivity. Nucleic Acids Res. 2020;48:4797-4810.
72. Yu G, Wu L, Su Q, et al. Neurotoxic effects of heavy metal pollutants in the environment: Focusing on epigenetic mechanisms. Environ Pollut. 2024;345:123563.
73. Wang T, Chen B, Luo M, et al. Microbiota-indole 3-propionic acid-brain axis mediates abnormal synaptic pruning of hippocampal microglia and susceptibility to ASD in IUGR offspring. Microbiome. 2023;11:245.
74. Baeza-Velasco C, Vergne J, Poli M, et al. Autism in the context of joint hypermobility, hypermobility spectrum disorders, and Ehlers-Danlos syndromes: A systematic review and prevalence meta-analyses. Autism. 2025;29:1939-1958.
75. Nalbant K, Erden S, Yazar A, et al. Investigation of the Relation between Epithelial Barrier Function and Autism Symptom Severity in Children with Autism Spectrum Disorder. J Mol Neurosci. 2022;72:741-747.
76. Robinson-Agramonte MLA, Noris García E, Fraga Guerra J, et al. Immune Dysregulation in Autism Spectrum Disorder: What Do We Know about It? Int J Mol Sci. 2022;23:3033.
77. Maltsev D, Solonko I, Sydorenko O. The assessment of microbial infection in children with autism spectrum disorders and genetic folate cycle deficiency. BMC Pediatr. 2024;24:200.
78. Halepoto DM, Al-Ayadhi LY, Alhowikan AM, et al. Role of autoimmunity in Neuronal damage in children with Autism spectrum disorder. Pak J Med Sci. 2023;39:1858-1864.
79. Owens AP, Mathias CJ, Iodice V. Autonomic Dysfunction in Autism Spectrum Disorder. Front Integr Neurosci. 2021;15:787037.
80. Li Y, Xie T, Vos M, et al. Shared genetic architecture and causality between autism spectrum disorder and irritable bowel syndrome, multisite pain, and fatigue. Transl Psychiatry. 2024;14:476.
81. Avram OE, Bratu EA, Curis C, et al. Modifiable Nutritional Biomarkers in Autism Spectrum Disorder: A Systematic Review and Meta-Analysis of Vitamin D, B12, and Homocysteine Exposure Spanning Prenatal Development Through Late Adolescence. Int J Mol Sci. 2025;26:4410.
82. Usui N, Kobayashi H, Shimada S. Neuroinflammation and Oxidative Stress in the Pathogenesis of Autism Spectrum Disorder. Int J Mol Sci. 2023;24:5487.
83. Bjørklund G, Doşa MD, Maes M, et al. The impact of glutathione metabolism in autism spectrum disorder. Pharmacol Res. 2021;166:105437.
84. lshamrani AA, Alshehri S, Alqarni SS, et al. DNA Hypomethylation Is Associated with Increased Inflammation in Peripheral Blood Neutrophils of Children with Autism Spectrum Disorder: Understanding the Role of Ubiquitous Pollutant Di(2-ethylhexyl) Phthalate. Metabolites. 2023;13:458.
85. Chatterjee D, Maparu K, Singh S. Exploring pathological targets and advancing pharmacotherapy in autism spectrum disorder: Contributions of glial cells and heavy metals. Histol Histopathol. 2025;40:979-991.
86. Carter CJ. The barrier, airway particle clearance, placental and detoxification functions of autism susceptibility genes. Neurochem Int. 2016;99:42-51.
87. LaSalle JM, Yasui DH. Evolving role of MeCP2 in Rett syndrome and autism. Epigenomics. 2009;1:119-30.
88. Roe K. Autism Spectrum Disorder Initiation by Inflammation-Facilitated Neurotoxin Transport. Neurochem Res. 2022;47:1150-1165.
89. De Luca F. Endocrinological Abnormalities in Autism. Semin Pediatr Neurol. 2020;35:100582.
90. Zhao L, Gou B, Zhang M. The efficacy of exercise in patients with myalgic encephalomyelitis/chronic fatigue syndrome: A systematic review and meta-analysis. J Psychosom Res. 2026;207:112677.
91. Chojnacki C, Mędrek-Socha M, Chojnacki J, et al. Multi-Strain Probiotic Improves Tryptophan Metabolism and Symptoms in Chronic Fatigue Syndrome Patients with Co-Occurring Irritable Bowel Syndrome: An Open-Label Pilot Study. Nutrients. 2026;18:174.
92. Zhu Y, Quan P, Yamazaki T, et al. Metabolic neuroimaging of myalgic encephalomyelitis/chronic fatigue syndrome and Long-COVID. Immunometabolism (Cobham). 2025;7:e00068.
93. Barr J, Marsden L, Dassanayake T, et al. Testing a Personalised Dysautonomia Management Protocol in Patients with Orthostatic Intolerance and a Diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome or Long COVID. J Clin Med. 2026;15:2510.
94. Chen E, Rudder T, Nwankwere C, et al. Fatigue, interoplastic and nociplastic distress in myalgic encephalomyelitis/chronic fatigue syndrome, Gulf War Illness, and chronic idiopathic fatigue. Front Neurosci. 2025;19:1530652.
95. Peppercorn K, Sharma S, Edgar CD, et al. Comparing DNA Methylation Landscapes in Peripheral Blood from Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long COVID Patients. Int J Mol Sci. 2025;26:6631.

96. Keele GR, Enger M, Barnette Q, et al. Systematic Examination of Gene Expression and Proteomic Evidence Across Tissues Supports the Role of Mitochondrial Dysregulation in ME/CFS. Int J Mol Sci. 2026;27:1997.
97. Herman ME. How pandemics reshape our brain: Common links and targets between long-haul COVID-19, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), oxidative stress, and neurodegeneration. Neuroprotection. 2025;3:280-287.
98. Godlewska BR, Williams S, Emir UE, et al. Neurochemical abnormalities in chronic fatigue syndrome: a pilot magnetic resonance spectroscopy study at 7 Tesla. Psychopharmacology (Berl). 2022;239:163-171.
99. Shirole RL, Khalane MR, Nage VP, et al. Immunomodulatory and locomotor regulations via Diosgenin treatment in lipopolysaccharide-induced chronic fatigue syndrome (CFS)/ depressive despair symptom: an in vivo assessment. Naunyn Schmiedebergs Arch Pharmacol. 2026.
100. Caccamo D, Cesareo E, Mariani S, et al. Xenobiotic sensor- and metabolism-related gene variants in environmental sensitivity-related illnesses: a survey on the Italian population. Oxid Med Cell Longev. 2013;2013:831969.
101. Erasmus E, Steffens FE, van Reenen M, et al. Biotransformation profiles from a cohort of chronic fatigue women in response to a hepatic detoxification challenge. PLoS One. 2019;14:e0216298.
102. Al-Rawaf HA, Alghadir AH, Gabr SA. MicroRNAs as Biomarkers of Pain Intensity in Patients with Chronic Fatigue Syndrome. Pain Pract. 2019;19:848-860.
103. Maya J, Unger ER, Lin JS, et al. Genetic Insights into Circulating Complement Proteins in Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: A Potential Inflammatory Subgroup. Int J Mol Sci. 2026;27:1574.
104. Liu Z, Hollmann C, Kalanidhi S, et al. Immunoglobulin G complexes from post-infectious ME/CFS, including post-COVID ME/CFS disrupt cellular energetics and alter inflammatory marker secretion. Brain Behav Immun Health. 2026;52:101187.
105. Bansal R, Gubbi S, Koch CA. COVID-19 and chronic fatigue syndrome: An endocrine perspective. J Clin Transl Endocrinol. 2022;27:100284.
106. Dollin C, Ward M, Stafford MYC, et al. Accelerated epigenetic age in hypertension: a systematic review and meta-analysis. Hypertens Res. 2026;49:1265-1303.
107. Neul JL, Percy AK, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study. Nat Med. 2023;29:1468-1475.
108. Campisi M, Cannella L, Visioli F, et al. A Systematic Review of Food-Derived DNA Methyltransferase Modulators: Mechanistic Insights and Perspectives for Healthy Aging. Adv Nutr. 2025;16:100521.
109. Theodoropoulou MA, Mantzourani C, Kokotos G. Histone Deacetylase (HDAC) Inhibitors as a Novel Therapeutic Option Against Fibrotic and Inflammatory Diseases. Biomolecules. 2024;14:1605.
110. Germain ND, Chung WK, Sarmiere PD. RNA interference (RNAi)-based therapeutics for treatment of rare neurologic diseases. Mol Aspects Med. 2023;91:101148.
111. Román GC, Mancera-Páez O, Bernal C. Epigenetic Factors in Late-Onset Alzheimer's Disease: MTHFR and CTH Gene Polymorphisms, Metabolic Transsulfuration and Methylation Pathways, and B Vitamins. Int J Mol Sci. 2019;20:319.
112. Galicia-Moreno M, Monroy-Ramirez HC, Caloca-Camarena F, et al. A new opportunity for N-acetylcysteine. An outline of its classic antioxidant effects and its pharmacological potential as an epigenetic modulator in liver diseases treatment. Naunyn Schmiedebergs Arch Pharmacol. 2025;398:2365-2386.
113. Long J, Liao X, Tang Z, et al. Investigating the clinical efficacy, safety and molecular mechanism of sulforaphane in autism spectrum disorder: an integrated study combining meta-analysis, network pharmacology, and computational biology. BMC Pharmacol Toxicol. 2025;26:217.
114. Oberman LM. mGluR antagonists and GABA agonists as novel pharmacological agents for the treatment of autism spectrum disorders. Expert Opin Investig Drugs. 2012;21:1819-25.
115. Rossignol DA, Frye RE. The Effectiveness of Cobalamin (B12) Treatment for Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. J Pers Med. 2021;11:784.
116. Peng TR, Cheng HY, Wu TW. S-Adenosylmethionine (SAMe) as an adjuvant therapy for patients with depression: An updated systematic review and meta-analysis. Gen Hosp Psychiatry. 2024;86:118-126.
117. Ma X, Yang Y, Liu S, et al. Meta-analysis of the efficacy and safety of L-carnitine and N-acetylcysteine monotherapy for male idiopathic infertility. Rev Int Androl. 2025;23:1-12.
118. Pan H, Xu W, Liu M, et al. The relationship between antioxidant vitamins and mental disorders: a meta-analysis. Food Funct. 2026;17:89-105.
119. Bjørklund G. Zinc deficiency and zinc/copper ratio imbalance in autism spectrum disorder: a reanalysis of six multinational studies. Biometals. 2026;39:285-296.
120. Tang W, Cai D, Song Y, et al. The effect of 4-phenylbutyrate and sodium 4-phenylbutyrate on genetic mutation diseases: A meta-analysis. Medicine (Baltimore). 2025;104:e40818.
121. Hill Z, McCarty PJ, Boles RG, et al. A Mitochondrial Supplement Improves Function and Mitochondrial Activity in Autism: A Double-Blind Placebo-Controlled Cross-Over Trial. Int J Mol Sci. 2025;26:2479.
122. Chen X, Chen Y, Xu W, et al. Influencing Factors and a Predictive Model for Cardiovascular Events in Patients with Hyperuricemia Treated with Febuxostat. Br J Hosp Med (Lond). 2026;87:52969.
123. Abdelhamid A, Nasrallah D, Ahmed E, et al. Beyond cardiovascular health: The pharmacotherapeutic potential of statins in oncology. Semin Cancer Biol. 2025;117:1-22.
124. Shen Y, Yu L, Wang L, et al. Biomimetic ferritin nanocages for synergistic co-delivery of metformin and rapamycin restore neurodevelopmental homeostasis in autism spectrum disorders. J Nanobiotechnology. 2025;23:670.
125. Tunc-Ozcan E, Ullmann TM, Shukla PK, et al. Low-dose thyroxine attenuates autism-associated adverse effects of fetal alcohol in male offspring's social behavior and hippocampal gene expression. Alcohol Clin Exp Res. 2013;37:1986-95.
126. Zhang Z, Zhang L, Zhu G, et al. Efficacy and Safety of Intravenous Immunoglobulin in Children with Autism Spectrum

Disorder with Immune Dysregulation: A Prospective, Open-Label, Single-Arm Study. Neurol Ther. 2026.
127. Rossignol DA, Frye RE. A Systematic Review and Meta-Analysis of Immunoglobulin G Abnormalities and the Therapeutic Use of Intravenous Immunoglobulins (IVIG) in Autism Spectrum Disorder. J Pers Med. 2021;11:488.
128. Meza N, Franco JV, Sguassero Y, et al. Atypical antipsychotics for autism spectrum disorder: a network meta-analysis. Cochrane Database Syst Rev. 2025;5:CD014965.
129. James S, Stevenson SW, Silove N, et al. Chelation for autism spectrum disorder (ASD). Cochrane Database Syst Rev. 2015;5:CD010766.
130. Tufano M, Pinna G. Is There a Future for PPARs in the Treatment of Neuropsychiatric Disorders? Molecules. 2020;25:1062.
131. Lan S, Zhou X, Xiang Y, et al. Curcumin Treatment for Metabolic Dysfunction-Associated Steatotic Liver Disease: Mechanism Exploration, Clinical Application Strategies, and Application Limitations Challenges. Phytother Res. 2026.
132. Hirota T, Veenstra-Vanderweele J, Hollander E, et al. Antiepileptic medications in autism spectrum disorder: a systematic review and meta-analysis. J Autism Dev Disord. 2014;44:948-57.
133. Wen YH, Liang SC, Sun CK, et al. Therapeutic Effects of Probiotics on Symptoms of Anxiety in Children and Adolescents: A Systematic Review and Meta-Analysis of Placebo-Controlled Trials. J Child Adolesc Psychopharmacol. 2026;36:45-52.
134. Michalczuk MT, Longo L, Keingeski MB, et al. Rifaximin on epigenetics and autophagy in animal model of hepatocellular carcinoma secondary to metabolic-dysfunction associated steatotic liver disease. World J Hepatol. 2024;16:75-90.
135. Bradstreet JJ, Smith S, Baral M, et al. Biomarker-guided interventions of clinically relevant conditions associated with autism spectrum disorders and attention deficit hyperactivity disorder. Altern Med Rev. 2010;15:15-32.
136. Frye RE. A Personalized Multidisciplinary Approach to Evaluating and Treating Autism Spectrum Disorder. J Pers Med. 2022;12:464.
137. Maltsev D. Integrative concept of pathogenesis and GBINS personalized multidisciplinary approach to clinical management of children with neuropsychiatric syndromes, associated with genetic deficiency of folate cycle. Acta Biomed. 2024;95:e2024041.