nuttall women's health

D^3

Drivers, Diagnostics and Drug Development in Endometriosis

Issued by: Nuttall Women's Health

Funding Scope and Duration

D³ offers flexible support for projects ranging in duration from **one to three years**, with total funding requests **ranging from $500,000 up to $5,000,000 US dollars for each awarded project. NWH expects to fund several projects in the D³ RFP.** Proposed budgets and timelines should be commensurate with the scope, ambition and stage of development of the project. Applicants are encouraged to carefully align their proposed work with the overall goals of the RFP and to demonstrate how the requested resources will enable meaningful scientific or technological advancement.

Goal

D³ aims to transform the landscape of endometriosis research and care by catalyzing mechanistically grounded translational science. Through targeted investment in studies that elucidate the biological underpinnings of endometriosis, D³ seeks to accelerate the development of reliable diagnostics and novel, non-hormonal therapeutics—ultimately reducing the diagnostic delay, improving treatment outcomes and alleviating the burden of disease for millions of individuals.

Desired Clinical Impact

Women affected by endometriosis will no longer endure years of unrecognized suffering. The future envisioned by the D³ Initiative includes: 1) Timely Diagnosis: non-invasive, clinically validated diagnostics that can reliably detect endometriosis and distinguish it from other causes of chronic pelvic pain; 2) Therapeutic Precision: biomarkers that predict disease subtype and treatment response, enabling more personalized and effective care; and 3) Expansion of therapeutic landscape: therapeutic approaches that intervene at the level of root biological mechanisms—including immune dysfunction, microbial imbalance and uterine tissue remodeling—replacing the current reliance on symptomatic hormonal treatments.

The Problem

Endometriosis is a chronic, inflammatory condition that affects over 190 million individuals globally. Despite its prevalence, it remains one of the most under-researched diseases in women's health, with limited diagnostic tools and no curative therapies. Patients often endure a diagnostic delay of seven (7) to 10 years, chronic pain, infertility and systemic symptoms that impact nearly every domain of life.

In the United States, federal research funding for endometriosis remains disproportionately low relative to disease burden—receiving less than $1 per affected individual annually. This underinvestment has hindered progress in understanding the root biological mechanisms of the disease and in developing effective, targeted therapies.

Endometriosis is classically defined by the presence of endometrial-like tissue outside of the uterus. The clinical presentation is varied, and the location of extra-uterine lesions is heterogeneous. An obstacle in prompt diagnosis is that endometriosis does not have pathognomonic signs or symptoms; in fact, common symptoms associated with endometriosis overlap with other gynecological and gastrointestinal conditions. The clinical presentation of individuals with endometriosis is diverse with pelvic pain being a common and troubling symptom. Individuals with endometriosis are much more likely to have infertility than individuals without endometriosis. Physical examinations findings may be suggestive of endometriosis but none of these are thought to be diagnostic. Similarly, while imaging may be suggestive of the presence of endometriosis,

negative findings on imaging do not rule out the presence of endometriosis. While there are some biomarkers (e.g., CA-125) that are used clinically, they are not specific and have poor predictive performance. Currently, there is no reliable biomarker to identify individuals with endometriosis.

Many studies across different populations have clearly demonstrated the impact of endometriosis on individuals, noting significant impact on quality-of-life metrics. Among the varied symptoms, pain is a common presenting symptom. Our lack of understanding of what drives pain in individuals with endometriosis is highlighted by the fact that the stage of endometriosis does not always correlate with patient reported pain. Research aimed at addressing this gap in knowledge has focused on characterizing the nerves present in the endometriotic lesions and surrounding tissues, with recent approaches focused on applying the conceptual framework of exoneural biology to endometriosis. Within this context, there are efforts to understand how specific metabolites—*which are increased in individuals with endometriosis*—can activate neural receptors. Adding to this growing line of research, recent results support the involvement of inflammatory mediators as either promoting hyperinnervation of endometriosis lesions and/or by releasing ligands that stimulate pain pathways in peripheral nerves.

The first line of treatment for individuals with endometriosis is control of hormonal fluctuations through the common use of oral contraceptive pills. While over 70% of individuals with a diagnosis of endometriosis are prescribed oral contraceptive pills, this is an off-label use, and they are not approved for the treatment of endometriosis—*reflecting the paucity of high-quality clinical trials for this disease*. In over one-third of patients, oral contraceptive pills fail to improve symptoms, suggesting that symptoms and progression of endometriosis are not solely due to hormonal shifts. While the global burden from endometriosis is quite high, including pain and loss of work and wages, only two new drugs have been approved for endometriosis is the last two decades in the United States. While these specific drugs are new to the market, the target—*hormonal suppression*—is not novel and represents the mainstay of current treatment for endometriosis.

State Of Current Knowledge

Despite significant advances in understanding endometriosis, its precise developmental origins remain elusive. Sampson's theory of retrograde menstruation continues to be the most widely accepted explanation, supported by evidence that retrograde flow is common and that reproductive tract outlet obstructions—which enhance retrograde flow—are associated with a significantly increased risk of endometriosis. However, the presence of endometriotic lesions in remote sites, including the lungs and brain challenges this theory as a singular mechanism.

Over the past decade, alternative hypotheses have gained traction, particularly the role of stem cells—either from bone marrow or other sources—in seeding ectopic lesions. Although some studies suggest that bone marrow-derived cells may contribute to endometriotic tissue, findings are inconsistent and often lack definitive mechanistic validation. More compelling is the hypothesis that intrinsic disruptions in uterine biology—*such as altered endometrial cell behavior, aberrant glandular development or changes in adhesion and migration*—may prime cells for ectopic implantation. These uterine-centric abnormalities, while increasingly documented, remain poorly defined in terms of molecular drivers and triggers.

In parallel, there is a growing consensus that inflammation is not just a consequence but a central feature of endometriosis pathophysiology. Immunological dysregulation appears to play a pivotal role in lesion development and persistence. Theories range from global immune hyper-reactivity and impaired clearance of ectopic cells to mechanisms akin to autoimmune diseases. Multiple immune cell types have been implicated including macrophages, natural killer (NK) cells, CD8+ T cells and Regulatory T cells (Tregs). Recent research highlights Tregs and macrophages as particularly important actors, with data pointing to their altered abundance and function both in lesions and in the surrounding immune microenvironment. However,

current studies are limited by several key design flaws: small sample sizes, lack of lesion sampling beyond ovarian sites, failure to compare eutopic and ectopic tissues within the same individuals and only inclusion of hormonally treated patients. Importantly, high-throughput genomic and transcriptomic studies—*while promising*—have not yet achieved the depth or rigor necessary to resolve these gaps.

The immune abnormalities observed in endometriosis may themselves be influenced by other upstream drivers. One such candidate is the microbiome, which has well-documented roles in modulating systemic immunity and inflammation in conditions such as inflammatory bowel disease and rheumatoid arthritis. In endometriosis, initial studies have explored the vaginal, cervical and peritoneal microbiota, identifying alterations in microbial diversity and abundance. However, results have been inconsistent—likely due to heterogeneous populations, small sample sizes, and the limitations of 16S rRNA sequencing, which cannot resolve microbial function or strain-level variation. In addition, studies on the vaginal microbiome have focused on the presence of non-lactobacillus dominated communities (Community State Type IV) with endometriosis. Yet, these studies provide some evidence of association without any investigation into mechanism.

The gut microbiome, a known regulator of systemic immune tone, remains understudied in endometriosis. Even less explored is the gut metabolome—*the repertoire of small molecules produced by host-microbe interactions*. These metabolites, including short-chain fatty acids, amino acid derivatives, and bile acids, have been shown to modulate inflammation and neural pain signaling in other chronic pain conditions such as interstitial cystitis, irritable bowel syndrome and inflammatory bowel disease.

Preclinical mouse studies suggest that modulating the gut microbiome can alter metabolomic profiles, reduce inflammation and suppress lesion growth. However, no human studies have yet systematically characterized the gut microbiome-metabolome in endometriosis, nor examined its potential role as a biomarker or mediator of pain and symptom heterogeneity. Given the association between visceral hypersensitivity and gut-derived metabolites in other disorders, this represents a critical frontier for discovery.

The pathogenesis of endometriosis likely reflects the convergence of multiple biological processes—*altered uterine cell behavior, immune dysfunction, inflammatory signaling and possibly microbial and metabolic dysregulation*. While each of these domains has yielded potential important insights, they remain insufficiently integrated and incompletely understood. There is a clear need for mechanistically rigorous, systems-level research that combines uterine biology, immunology, microbiome science and metabolomics—anchored in well-phenotyped, appropriately controlled human cohorts. By illuminating upstream drivers rather than downstream symptoms, such work has the potential to reshape diagnostic and therapeutic strategies for a condition that has long suffered from scientific and clinical neglect.

Broad Research Priorities

D³ is a targeted research effort designed to catalyze scientific progress in understanding and treating endometriosis. We invite proposals for transformative, high-impact research—*from discovery-stage science to technology validation and preclinical development*—focused on:

- The identification and characterization of key disease drivers
- The development of diagnostic tools for earlier and more accurate detection
- The advancement of non-hormonal therapeutic strategies that address root biological mechanisms rather than symptom suppression

By advancing this critical research agenda, D³ seeks to close long-standing gaps in the field and improve the lives of millions affected by this debilitating disease.

Specific Research Priorities

We welcome both discovery-oriented investigations and translational efforts aimed at diagnostics, therapeutic target validation or intervention development. Cross-domain proposals and those integrating multi-omics, engineering, device development or drug discovery approaches are encouraged. Applicants must address at least one of the following domains.

Uterine Biology and Its Role in Endometriosis

- Reveal how uterine function (and/or dysfunction) contribute to disease initiation, lesion seeding and symptom variability
- Investigate uterine-derived signals—*hormonal, inflammatory, cellular or extracellular vesicular*—that may influence systemic or peritoneal environments
- Demonstrate the molecular and cellular features of ectopic vs. eutopic endometrium, including menstrual and menstrual effluent tissues from individuals with and without the disease as well as correlating molecular profiles with surgical classification of disease and clinical symptoms
- Reveal molecular profile of endometriosis lesions compared to non-affected peritoneal tissues in the same individual

Immune Drivers of Disease Initiation and Progression

- Reveal specific roles of immune cells, pathways and effector molecules in driving disease initiation, progression and/or pain
- Explore immune-epithelial-stromal interactions contributing to disease progression
- Identify immune phenotypes or signatures associated with disease severity, either locally and/or systemically
- Investigate immune biomarkers with diagnostic or prognostic potential and/or their role in predicting response to treatment
- Characterize neuroimmune crosstalk and lesion innervation to reveal novel therapeutic targets
- Identify drivers of neuroinflammation and non-hormonal therapeutic targets for pain relief

Gut Microbiome-Metabolome in Disease Initiation, Progression, and Therapeutic Modulation

- Investigate the role of the gut microbiome, microbial metabolites and microbiome-host interactions in immune priming, lesion development, systemic modulation
- Conduct functional microbial assessments (e.g., metatranscriptomics) beyond compositional-only analyses (e.g., 16S or shotgun taxonomy without function)
- Explore microbial pathways and therapeutic strategies involving but not limited to probiotics, diet and nutrition, microbial metabolite-targeting agents and/or physical modalities such as targeted exercise regimens

- Assess impact of pharmacological and non-pharmacological interventions on disease symptoms, progression, and response to treatment
- Determine if the gut metabolome is associated with disease progression and/or disease symptoms; assess if metabolomics profiles are correlated with specific bacterial taxa and severity of disease
- Explore interventions aimed at restoring microbial homeostasis that normalize production of key metabolites and mitigate disease progression and/or symptoms

Development of Diagnostics or Therapeutic Targets

- Discover or validate non-hormonal therapeutic targets addressing endometrial, immune, neural or microbial pathways.
- Identify and validate systemic biomarkers to stratify patients by:
    - Disease phenotype
    - Response to therapeutic interventions
- Repurpose existing drugs with mechanisms relevant to endometriosis
- Studies focused on studying and/or repurposing immune therapeutics are particularly encouraged
- Evaluate the combined impact of immune and microbial modulation and lifestyle interventions on patient symptoms and clinical outcomes

Research Design Priorities

- Proposals from both academic and commercial entities are welcomed
- Proposals involving human subjects, biospecimens, or clinical data will receive priority, especially studies that include banking of specimens to allow for continued discovery
- Human studies must include adequate sample sizes and deep metadata to support rigorous endophenotyping and exploration of different clinical stages of disease
- Understanding that current clinical guidelines for staging endometriosis may not match biological drivers and/or signatures of the disease or specific disease phenotypes, proposed studies should be precise in the characterization of participants regarding clinical presentation, symptomatology, surgical findings and details of tissues being investigated
- Clinical trials (all phases) are allowed but must collect biospecimens to uncover biological mechanisms underlying treatment response or non-response
- Studies that dissect molecular signatures of pelvic pain without endometriosis to pelvic pain with endometriosis are encouraged
- Cohort and other research studies are encouraged; projects must include participants not currently receiving hormonal therapies and be adequately powered to stratify outcomes based on hormonal therapy status
- Animal and *in vitro* models may be included but require strong justification demonstrating their translational relevance to human disease and must be accompanied by relevant human component in the proposal

- For any non-human models, studies should explicitly address whether relevant hormones are functional in the proposed model system (e.g., animal, cell lines, organoids, etc)
- Inclusion of imaging modalities is acceptable, but proposals must also include analyses of biological samples
- Projects linking uterine biology to immune, neurological, or pain-related pathways are encouraged
- Use of human uterine tissue (ectopic, eutopic, menstrual fluid) is especially encouraged
- Proposals repurposing existing immune therapeutics or developing novel immune-targeting agents are encouraged
- For industry applications, teams with a clear path to clinical application or product development—*such as diagnostics, drug candidates, or digital/physical tools for endometriosis*—are especially encouraged to apply

Research that is not Considered Responsive

- Research focused on banked biospecimens that do not have sufficient metadata and/or only include individuals that were on hormonal medications
- Pure epidemiological studies
- Implementation studies
- Use of large databases without corresponding biological samples
- Research that does not have ample sample sizes for rigorous conclusions
- Use of existing biobanks that do not provide 1) adequate phenotyping of symptoms and outcomes and/or 2) do not have a sufficient number of individuals not receiving hormonal therapeutics.
- Research teams that are lacking sufficient women's health and/or reproductive science expertise

References and Resources for D3: Link