

What is the decision or change (e.g. clinical topic, practice guideline, system design, delivery of care) you are facing or struggling with where a summary of the evidence would be helpful?

Endometriosis, to incorporate better diagnosis and treatment algorithms, delivery of care, and critical perusal of current (conflicting, insufficient) guidelines.

Please describe the issue. Tell us about who is affected by this issue; the treatments, tests, or strategies that you are interested in; and the specific benefits or harms (outcomes) that are important to you.

Endometriosis is an incredibly complex, highly enigmatic disease with much remaining unknown about its pathogenesis and pathophysiology, even with today's robust research and scientific advances. Characterized at surgery by the presence of endometrium-like epithelium and/or stroma outside the endometrium and myometrium, usually with an associated inflammatory process, endometriosis is a spectrum disease with variety of subtypes and clinical presentations (Int'l Endometriosis Working Group, 2021). This endometrial-*like* tissue found in extrauterine environs (Saunders et al., 2021) is similar but not identical to the normal, eutopic endometrium, and its presence results in a sustained inflammatory response accompanied by angiogenesis, adhesions, fibrosis, scarring, and local and neuronal infiltration (Giudice, 2010). Although the causes of endometriosis remain uncertain, various mechanisms are implicated in its development.

The disease is authoritatively estimated to affect approximately 190 million individuals globally including an unmeasured amount of transgender and non-binary/gender nonconforming persons (World Health Organization; Jones, 2020), who must not be overlooked in this traditionally female-identified space, at annual direct and indirect costs nearing \$70 billion in just the United States alone (Soliman et al., 2018). The cost burden is comparable to other chronic yet better recognized diseases i.e., diabetes and/or rheumatoid arthritis (Cezar et al., 2018; Rogers et al., 2013), and in one recent study, healthcare costs and resource utilization in all measured categories were higher among endometriosis cases vs. controls, with authors concluding that "the economic burden of endometriosis among patients with Medicaid insurance is substantial, underscoring the unmet medical need for earlier diagnosis and cost-effective treatments" (Soliman et al., 2019). Work life and earning potential is negatively affected as well. In a time when recent research (Heymann, 2021) maintains that the United States has no national paid sick leave policy and even unpaid FMLA leave remains inaccessible to many (its minimum hours requirement disproportionately excludes women, and its tenure requirement disproportionately excludes Black, Indigenous and multiracial workers), those with endometriosis are already experiencing lower annual salaries, lower salary growth, and higher risks of work loss events as a result of the disease (Estes et al., 2020).

The impact of endometriosis on the American health system is staggering, and those affected experience a significant, even life-altering symptom burden. Dysmenorrhea, dyspareunia, dyschezia, dysuria, chronic pelvic pain, infertility, gastrointestinal, urogenital and even thoracic and other extrapelvic symptoms (to name a few) are often prevalent in those affected, with considerably negative impact on the physical, psychosocial, emotional, sexual, economic and work life of those struggling (Della Corte et al., 2020). Without question, timely diagnosis and multidisciplinary, integrative treatments are necessary to effectively manage endometriosis – yet the disease is routinely characterized by significant diagnostic delay (Cromeens et al., 2021), leaving patients to incur additional costs and further significant reduction in HRQoL. Even once diagnosed, uncertainties, frustrations and quite often, poor disease management continue unabated; likewise, definitive cure remains elusive. Universal access to quality care remains sorely limited in most settings, due in large part to dismissal of symptomology and vast, widespread disease misinformation. The disparities by race must also not be overlooked, with Black people with endometriosis and other BIPOC individuals historically and systemically ignored and race playing a role in treatment type, access and outcomes (Bougie et al., 2022; Spagnolia et al., 2020).

Laparoscopic surgery for endometriosis is an effective treatment with low rates of reoperation and high efficacy in resolving endometriosis associated infertility (Laguerre et al., 2022). Laparoscopic Excision (LAPEX), specifically, is one of the most effective therapeutic options (Htut et al., 2022; Rindos et al., 2020; Franck et al., 2018; Pundir et al., 2017). LAPEX affords biopsy-proven diagnosis and subsequent removal of lesions at the time of the surgical encounter. However, insufficient standards of care have upheld a failed reimbursement structure leading to access barriers for most with the disease, leaving them unable to obtain such necessary specialized care (see also "Better Guidelines Needed on Endometriosis, Patients Say; Bring Their Fight to ACOG Headquarters" at <https://www.medpagetoday.com/obgyn/generalobgyn/72205>). As a result, incomplete and even harmful non-excision, non-specialist surgeries are routine, lending to increased symptoms and persistent disease. This has become more prevalent than ever as a result of the publication of current guidelines in the United Kingdom and Australia, which can be expected to be used as the blueprint for other countries in their approach to the disease.

Secondary to surgery are medical therapies, none of which are curative; all have potential side effects (Rafique et al., 2017) and similar clinical efficacy in temporary reduction of pain. Some (i.e., elagolix) are so costly it prompted The Institute for Clinical and Economic Review (ICER) to issue an Affordability & Access Alert (ICER, 2018). In short, menstrual suppression does not treat endometriosis, only symptoms – and to lesser extent, further supports the perception among some that menstruation is ‘unhealthy’ and requires pharmaceutical intervention. Further, the abundance of dissimilarities between endometriosis lesions and the native endometrium present difficulties in new drug therapy development (Falcone et al., 2018).

Nor is hysterectomy the much-touted cure it is often heralded as. Despite over 100,000 hysterectomies being performed annually for a primary diagnosis of endometriosis and approximately 12% of individuals with the disease eventually undergoing hysterectomy as ‘treatment,’ there is an approximate 15% probability of persistent pain after hysterectomy, which may be due to incomplete disease removal, and a 3–5% risk of worsening pain or new symptom development (Rizk et al., 2014). Menopause is also not protective as has been suggested, with an estimated 2–4% of the endometriosis population being postmenopausal (Suchońska et al., 2018). In fact, postmenopausal endometriosis has demonstrated a predisposition to malignant change, greater tendency for extrapelvic spread, and development into constrictive and/or obstructive lesions (Tan et al., 2018).

The complexities of this multidimensional disease remain poorly elucidated in current scientific works and little progress has been made toward deciphering endometriosis (Guidone, 2020). Although research seems omnipresent, much of it is actually quite redundant in nature and/or directed at industry-supported studies merely seeking to repurpose medical suppressives which were not effective to begin with. Few qualitative studies have been conducted on the actual realities of living with the disease, and those that have lack rigor (Moradi et al., 2014). Moreover, while clinicians and scientists direct the bulk of research initiatives, data has demonstrated that their priorities differ significantly from the research priorities of patients and their families/caregivers (Brady et al., 2020).

Research on endometriosis overall remains poorly funded, even with its recent inclusion in and allocations from the Department of Defense's Congressionally Directed Medical Research Programs (review panels on which we have had the privilege of serving). Recent reports have also demonstrated that the NIH applies a disproportionate share of its resources to diseases that affect primarily men – and are doing so at the expense of those that affect primarily women. The most underfunded diseases are female-dominant - including and especially endometriosis (Mirin, 2021).

Given all of the above and much more which is outside the scope of these comments, we would respectfully request the Agency for Healthcare Research and Quality's Effective Health Care Program to cover the gaps and barriers that persist in endometriosis, namely but not limited to:

- The need to improve timely diagnosis and effective care for those impacted by the disease from adolescents to post-menopausal;
- The need for formal recognition of endometriosis care as a true medical subspecialty;
- The need to provide authoritative support and education programs in the school (i.e., EndoWhat?) and public health settings to inform on symptoms and when, where and how to obtain help at first signs;
- The need to expand fundamental components of management and achieve reduction of costs by improving access to quality treatments and standardization of care; and not least,
- The desperate need for funding of quality, unbiased, independent research that elucidates disease origins apart from the outdated Sampson model, focuses on the cancer-endometriosis connection, supports and promotes the critical need for multidisciplinary approach for improved outcomes and reduced cost burdens, and provides for truly useful non-invasive diagnoses.

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The medical community continues to fail those with endometriosis from diagnostic intervention to treatment and care access. The various current, arbitrary guidelines largely emphasize non-surgical (clinical) diagnosis with a track through stepwise medical therapy. Such therapies, while “noninvasive,” are frequently ineffective, cost prohibitive, and fraught with significant side effect profiles for many patients. Moreover, failure to diagnose and treat endometriosis through excisional biopsy means that treatment is being rendered for an inconclusive diagnosis; that is to say, it is possible the wrong disease or condition is being treated due to the assumption that it is endometriosis. By assessing the shortcomings in these guidelines - which have been formulated in part by low evidence, lack broad collaboration and perspective, are rife with conflicts of interest, and do not represent the desires of the community they serve – we hope to improve the time to diagnosis as well as remove barriers in access to best care.

Why are you struggling with this issue?

Endometriosis is a life-altering disease, one for which the great majority report being trivialized, having their symptoms dismissed, being subjected to ineffective and subpar therapies, and/or are often told there is no hope and nothing else that can be done for them. In fact, quality care does exist - but it remains largely inaccessible to the bulk of the endometriosis population due to injudicious “gatekeeping.” Data and studies continue to be largely industry-driven and hence report pro-industry results which are in conflict to the desired outcomes of the population such studies are intended to serve. Much of the research continues to lack translational benefit and there is uncertainty about benefits and harms, and certainly, a lack of patient participation in such research persists. As a result, what healthcare providers are doing in actual practice is often contradictory and inconsistent depending on where the patient obtains care.

What do you want to see changed? How will you know that your issue is improving or has been addressed?

We would like to see the creation of a truly unbiased, independent evidence report which incorporates patient desires and best practices and which casts a critical lens on the rampant disparities that persist in endometriosis diagnosis, treatment and support so that they can be addressed as outlined above. Successful outcomes of such a report would be evidenced by quicker diagnosis and increased access to patient-centric, multidisciplinary care.

When do you need the evidence report?

Understanding the vast undertaking of such an endeavor, a 2-4 year time frame is realistic.

What will you do with the evidence report?

To improve patient literacy and assist with informed healthcare decisions, to serve as a real practice guideline, to increase coverage and access, and to educate providers and patients alike.

In summary:

- This submission concerning endometriosis represents a significant healthcare intervention, including related drugs, devices, medical tests, and mechanisms of healthcare delivery in the United States;
- Endometriosis is a tremendous burden affecting a large proportion of the population;
- Endometriosis is fraught by uncertainty for decisionmakers and patients;
- This submission incorporates issues surrounding variations in practice, clinical benefits, and potential clinical harms of care for endometriosis and access thereto;
- Endometriosis is a high cost disease due to prevalence and economic burden to consumers, patients, healthcare systems, and/or payers;
- Endometriosis, to date, has not been covered by any truly high-quality evidence reports;
- The standard of care surrounding endometriosis is unclear, conflicting, and in many instances altogether absent, representing a monumental gap in information; and
- The need for evidence-based changes to review, establish and influence clinical practice and access to care is immeasurable.

Information About You

We are Board-Certified Patient Advocates living with endometriosis and working professionally in the global endometriosis space. We represent a worldwide community of patients and the dedicated providers, researchers and other advocates serving them.

What is your role or perspective?

Patient and professional.

Heather Guidone, BCPA & Kate Donahue, BCPA

Program Director, Center for Endometriosis Care & Founder, EndoGirls Blog

If you would like to have your data submittal acknowledged, please enter your email:

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Citations:

- Bougie O, Nwosu I, Warshafsky C. Revisiting the impact of race/ethnicity in endometriosis. *Reprod Fertil*. 2022 Mar 17;3(2):R34-R41.
- Brady PC, Horne AW, Saunders PTK, Thomas AM, Missmer SA, Farland LV. Research priorities for endometriosis differ among patients, clinicians, and researchers. *Am J Obstet Gynecol*. 2020 Jun;222(6):630-632.
- Cezar TC, Schweppe KW, Pletzer KR, Becker S, Krentel H, Torres-De La Roche LA, De Wilde RL. The cost-effective, but forgotten, medical endometriosis therapy: a prospective, quasi-randomized study on progestin therapy. *Facts Views Vis Obgyn*. 2018 Dec;10(4):181-190.
- Cromeens MG, Carey ET, Robinson WR, Knafl K, Thoyre S. Timing, delays and pathways to diagnosis of endometriosis: a scoping review protocol. *BMJ Open*. 2021 Jun 24;11(6):e049390.
- Della Corte L, Di Filippo C, Gabrielli O, Reppuccia S, La Rosa VL, Ragusa R, Fichera M, Commodari E, Bifulco G, Giampaolino P. The Burden of Endometriosis on Women's Lifespan: A Narrative Overview on Quality of Life and Psychosocial Wellbeing. *Int J Environ Res Public Health*. 2020 Jun 29;17(13):4683.
- EndoWhat? Web: <https://www.endowhat.com>
- Estes SJ, Soliman AM, Yang H, Wang J, Freimark J. A Longitudinal Assessment of the Impact of Endometriosis on Patients' Salary Growth and Risk of Leaving the Workforce. *Adv Ther*. 2020 May;37(5):2144-2158.
- Falcone T, Flyckt R. Clinical Management of Endometriosis. *Obstet Gynecol*. 2018 Mar;131(3):557-571.
- Franck C, Poulsen MH, Karampas G, Giraldi A, Rudnicki M. Questionnaire-based evaluation of sexual life after laparoscopic surgery for endometriosis: a systematic review of prospective studies. *Acta Obstet Gynecol Scand*. 2018 Sep;97(9):1091-1104.
- Giudice LC. Clinical practice. Endometriosis. *N Engl J Med*. 2010 Jun 24;362(25):2389-98.
- Guidone HC. The Womb Wanders Not: Enhancing Endometriosis Education in a Culture of Menstrual Misinformation. 2020 Jul 25. In: Bobel C, Winkler IT, Fahs B, Hasson KA, Kissling EA, Roberts TA, editors. *The Palgrave Handbook of Critical Menstruation Studies* [Internet]. Singapore: Palgrave Macmillan; 2020. Chapter 22.
- Heymann J, Sprague A, Earle A, McCormack M, Waisath W, Raub A. US Sick Leave In Global Context: US Eligibility Rules Widen Inequalities Despite Readily Available Solutions. *Health Aff (Millwood)*. 2021 Sep;40(9):1501-1509.
- Htut HT, Liu HM, Lee CL. Laparoscopic Excision of Severe Deep Infiltrating Endometriosis. *Gynecol Minim Invasive Ther*. 2022 Feb 14;11(1):76-77. doi: 10.4103/GMIT.GMIT_26_21.
- ICER, 2018. Web: <https://icer.org/news-insights/press-releases/elagolix-final-report>
- International Working Group of AAGL, ESGE, ESHRE and WES, Tomassetti C, Johnson NP, Petrozza J, Abrao MS, Einarsson JJ, Horne AW, Lee TTM, Missmer S, Vermeulen N, Zondervan KT, Grimbizis G, De Wilde RL. An international terminology for endometriosis, 2021. *Hum Reprod Open*. 2021 Oct 22;2021(4):hoab029.
- Jones CE. Queering gendered disabilities. *J Lesbian Stud*. 2020 Jun 22:1-17.
- Laguerre MD, Arkerson BJ, Robinson MA, Moawad NS. Outcomes of laparoscopic management of chronic pelvic pain and endometriosis. *J Obstet Gynaecol*. 2022 Jan;42(1):146-152.
- Mirin A. Gender Disparity in the Funding of Diseases by the U.S. National Institutes of Health. *Journal of Women's Health* 2021 30:7, 956-96.
- Pundir J, Omanwa K, Kovoov E, Pundir V, Lancaster G, Barton-Smith P. Laparoscopic Excision Versus Ablation for Endometriosis-associated Pain: An Updated Systematic Review and Meta-analysis. *J Minim Invasive Gynecol*. 2017 Jul-Aug;24(5):747-756.
- Rafique S, Decherney AH. Medical Management of Endometriosis. *Clin Obstet Gynecol*. 2017 Sep;60(3):485-496.
- Rindos NB, Fulcher IR, Donnellan NM. Pain and Quality of Life after Laparoscopic Excision of Endometriosis. *J Minim Invasive Gynecol*. 2020 Nov-Dec;27(7):1610-1617.e1.
- Rizk B, Fischer AS, Lotfy HA, Turki R, Zahed HA, Malik R et al. Recurrence of endometriosis after hysterectomy. *Facts Views Vis Obgyn* 2014;6(4):219-27.
- Rogers PA, D'Hooghe TM, Fazleabas A, Giudice LC, Montgomery GW, Petraglia F, Taylor RN. Defining future directions for endometriosis research: workshop report from the 2011 World Congress of Endometriosis In Montpellier, France. *Reprod Sci*. 2013 May;20(5):483-99.
- Saunders PTK, Horne AW. Endometriosis: Etiology, pathobiology, and therapeutic prospects. *Cell*. 2021 May 27;184(11):2807-2824.
- Soliman AM, Surrey E, Bonafede M, Nelson JK, Castelli-Haley J. Real-world evaluation of direct and indirect economic burden among endometriosis patients in the United States. *Adv Ther*. 2018;35(3):408-423.
- Soliman AM, Surrey ES, Bonafede M, Nelson JK, Vora JB, Agarwal SK. Health Care Utilization and Costs Associated with Endometriosis Among Women with Medicaid Insurance. *J Manag Care Spec Pharm*. 2019 May;25(5):566-572.
- Spagnolia A, Beal J, Sahnoun A. Differences in Clinical Management and Outcomes of American Indian and White Women Diagnosed With Endometriosis. *J Fam Reprod Health*. June 2020:74-80.
- Suchońska, B., M. Gajewska, A. Zyguła, and M. Wielgoś. 2018. "Endometriosis Resembling Endometrial Cancer in a Postmenopausal Patient." *Climacteric* 21, no. 1 (February): 88-91.
- World Health Organization. Web: <https://www.who.int/news-room/fact-sheets/detail/endometriosis>