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Research Priorities for Endometriosis: Recommendations From a Global Consortium of Investigators in Endometriosis

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Abstract

The 3rd International Consensus Workshop on Research Priorities in Endometriosis was held in São Paulo on May 4, 2014, following the 12th World Congress on Endometriosis. The workshop was attended by 60 participants from 19 countries and was divided into 5 main sessions covering pathogenesis/pathophysiology, symptoms, diagnosis/classification/prognosis, disease/symptom management, and research policy. This research priorities consensus statement builds on earlier efforts to develop research directions for endometriosis. Of the 56 research recommendations from the 2011 meeting in Montpellier, a total of 41 remained unchanged, 13 were updated, and 2 were deemed to be completed. Fifty-three new research recommendations were made at the 2014 meeting in Sao Paulo, which in addition to the 13 updated recommendations resulted in a total of 66 new recommendations for research. The research recommendations published herein, as well as those from the 2 previous papers from international consensus workshops, are an attempt to promote high-quality research in endometriosis by identifying and

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agreeing on key issues that require investigation. New areas included in the 2014 recommendations include infertility, patient stratification, and research in emerging nations, in addition to an increased focus on translational research. A revised and updated set of research priorities that builds on this document will be developed at the 13th World Congress on Endometriosis to be held on May 17–20, 2017, in Vancouver, British Columbia, Canada.

Keywords

endometriosis, research priorities, international workshop, consensus report

Introduction

The 3rd International Consensus Workshop on Research Directions in Endometriosis was held in São Paulo on May 4, 2014, the day following the 12th World Congress on Endometriosis (WCE). The workshop was supported by the World Endometriosis Society (WES) and the World Endometriosis Research Foundation (WERF). Previous research directions workshops have been held in conjunction with earlier WCE meetings in Melbourne in 2008 and Montpellier in 2011, both resulting in the publication of a number of research recommendations.^{1,2}

The São Paulo workshop, attended by 60 participants from 19 countries, was divided into 5 main sessions covering pathogenesis/pathophysiology, symptoms, diagnosis/classification/prognosis, disease/symptom management, and research policy. Within each session, speakers provided updates on areas of significant research progress in the past 3 years, followed by suggestions for new research directions. On each topic, discussion was opened to all workshop participants and new research recommendations were developed. Following the workshop, each speaker was asked to scrutinize a transcript of the meeting and using the 56 research recommendations from 2011 as a starting point (1) to list recommendations that are still relevant and should remain unchanged (ie, do not need updating), (2) to identify recommendations that are no longer relevant (ie, have been completed or superseded), and (3) from the transcript of the meeting, list new or updated recommendations that were suggested at the workshop. This paper records the new and updated recommendations from the workshop. The status of recommendations from 2011² is provided in Table 1.

To broaden thinking and generate new ideas, speakers were also asked to consider 3 new themes across all of the sessions: (1) novel concepts or approaches that endometriosis researchers can emulate from research successes in other complex diseases, (2) enhancing research in emerging regions, and (3) prioritization of translational research: Where should we be focusing our research efforts? Where relevant, these themes are incorporated into this report. In addition, compared to the 2011 meeting, the workshop included an enhanced focus on symptoms of endometriosis, with sessions on pain, infertility, and the patients' perspective.

Of the 56 research recommendations from the 2011 meeting in Montpellier, a total of 44 remained unchanged, 8 were updated, and only 4 were deemed to be no longer relevant, with 2 superseded and 2 completed. Fifty-three new research recommendations were made at the 2014 meeting in Sao Paulo,

which in addition to the 13 updated recommendations gives a total of 66. These are listed below.

Background

Endometriosis is a common and costly disorder affecting 6% to 10% of reproductive-age women⁵ and the most common cause of chronic pelvic pain (CPP).⁶ The financial burden of endometriosis on the health-care system is substantial, with the direct and indirect annual costs of endometriosis estimated at US\$12 419/woman affected (~€9579).⁷ The same authors reported decreased quality of life as the most important predictor of direct health-care and total costs. The economic burden associated with endometriosis is similar to other chronic diseases such as diabetes, Crohn disease, and rheumatoid arthritis.⁷

There is a delay of up to 9 years between symptom onset and definitive diagnosis of endometriosis, depending on health-care settings.^{8,9} It has been estimated that affected women lose, on average, 10.8 hours of work weekly, mainly owing to reduced effectiveness while working. Loss of work productivity translates into significant costs, ranging from US\$208 in Nigeria to US\$23 712 in Italy per woman/year.⁸ There is currently no known cure for endometriosis. Following surgical management, symptomatic recurrence ranges from 20% to 40% and many women require additional surgery at a later time.¹⁰

The research recommendations published in this report, as well as those from the 2 previous papers from international consensus workshops, are aimed at promoting high-quality research into endometriosis by identifying and agreeing on the key issues that require investigation. Although the recommendations are offered as a guide only, it is notable that the 2009 and 2013 papers have been cited 79 and 27 times, respectively (Web of Science data September 2015) by other publications, suggesting that they have been of considerable use to the endometriosis research community. Significant research effort is occurring into all aspects of endometriosis: between the 2011 and 2014 WCE meetings, a total of 2524 new scientific publications on endometriosis were recorded on PubMed. Despite this research activity, and somewhat disappointingly, only 2 of the 56 recommendations from the 2011 Research Directions Workshop were deemed to have been satisfactorily addressed.

One key area of progress since the 2011 meeting has been made in research policy. To encourage and facilitate the required large, international collaborations, the WERF launched the Endometriosis Phenome and Biobanking

Table 1. Recommendations Formulated at the 2008¹ and 2011² Workshops, with an Indication in “Status” on Whether These Were Updated at the 2014 Workshop and to What Extent Progress Has Been Made.

	Status
Diagnosis	
1 Discovery and identification of new and validation of existing endometriosis-associated biomarkers is required to develop an accurate, noninvasive method to diagnose endometriosis.	Recommendation updated in 2014.
2 The different clinical classifications of endometriosis need to be taken into consideration as part of the evaluation of predictive and diagnostic biomarkers.	WES-led consensus workshop held on April 30, 2014 to commence this process.
3 Advances in imaging techniques should be monitored for application to diagnosis of endometriosis.	Recommendation updated in 2014.
Classification and progress	
4 To collect data and evaluate across populations, the phenotypic appearance of disease, the symptomatology of disease, and attempt to more finely characterize beyond our current staging system differences between women.	WERF has developed tools (EPHect) and made these freely available to allow for consistent data collection across centers worldwide. ^{3,4}
5 WES and WERF investigators should establish a task force to consider clinical staging based on combinatorial algorithms incorporating historical findings (including prior therapies), presenting symptoms (pain and infertility), intraoperative, and biochemical findings.	This will be an outcome of WERF EPHect once sufficient data have been collected.
Clinical trials, treatment, and outcomes	
6 Center randomized controlled trials and long-term follow-up studies comparing different endometriosis treatment options against defined outcome measures.	Recommendation updated in 2014.
7 Clinical trials in endometriosis should focus on outcomes of high relevance to women, ie, quality of life and key fertility outcomes including live births.	
8 We need to transform our clinical study design to integrate treatment failure for the first agent, with subsequent rescue agents in a phased, organized, and stratified manner.	
9 Clinical trials are needed to evaluate treatment options for pelvic pain associated with endometriosis, including inflammatory nociceptive, neuropathic, and central pain.	Recommendation updated in 2014.
10 Novel medical treatments for endometriosis should be investigated.	Recommendation updated in 2014.
11 Investigate the link between dysmenorrhea and endometriosis and early intervention strategies in younger women.	
12 Studies on pregnancy and pregnancy outcomes in women with endometriosis need to be undertaken.	Recommendation updated in 2014.
Epidemiology	
13 Recruit new cohorts of patients with endometriosis and controls with more detailed phenotypic information for genetic studies.	
14 Conduct genomics research to understand gene expression in the endometrium of patients with endometriosis and controls.	
15 Research is needed to elucidate the role of diet in modifying the symptoms and underlying disease of endometriosis.	Recommendation updated in 2014.
16 Studies be undertaken to investigate the relationship between phenotypic variables, including BMI and endometriosis.	
17 Further research on the impact of environmental factors on endometriosis is warranted, with windows of susceptibility (including fetal, neonatal, childhood, and adolescent origins) being important criteria in the collection of information. Measurement of individual endocrine-disrupting chemicals and environmental contaminants, timing of exposure, dose, and duration are important to determine, if known, and should be included in databases, where possible.	
Pathophysiology	
Inflammation and immunology	
18 The potential use of immunomodulators for treatment of endometriosis should be investigated.	
19 The role of endogenous and exogenous anti-inflammatory mediators in the pathophysiology and treatment of endometriosis should be further investigated.	
20 Research should be directed toward understanding the role of macrophages in endometriosis, and in particular how increased macrophage activation and reduced phagocytotic activity coexist in women with endometriosis.	Recommendation updated in 2014.
21 WES and WERF investigators should develop/share research protocols for the study of macrophages in the context of endometriosis.	

(continued)

Table 1. (continued)

	Status
Oxidative stress	
22 A better understanding of the role of oxidative stress in the development and potential treatment of endometriosis is required.	
Nerves, neuropeptides, and pain	
23 Understanding the origins of the pain associated with endometriosis is a priority for endometriosis research: such work should include specialists in the pain field.	
24 The development of suitable animal models for endometriosis-related pain research is a priority, including a nonhuman primate model and induced and spontaneous disease models.	
25 It will be important to gain a better understanding of the function of nerve fibers in eutopic and ectopic endometrium from women with endometriosis.	
26 There is a need to investigate whether meaningful pain phenotypes can be derived from patient data and can be related to patient outcomes of interest.	Recommendation updated in 2014.
Angiogenesis and lymphangiogenesis	
27 Further studies are required on the effectiveness and safety of antiangiogenic and antivascular therapies for treating endometriosis.	
28 It is important to better understand the contribution of endometrial and endometriotic lesion lymphangiogenesis to the development of endometriosis. This includes the study of uninvolved peritoneum from women with endometriosis and correlation of lymphangiogenic parameters with detailed information on symptoms, disease stage, lesion location and appearance, and response to treatment.	
29 Given the fundamental similarities that exist in the processes that lead to growth of vascular and neural tissues and the critical role that both of these play in endometriosis, there should be increased investigation into the mechanisms of neuroangiogenesis as they apply to endometriosis.	
Stem cells	
30 Further research is required into all aspects of endometrial stem cell biology, including their role in initiating endometriosis, and whether inhibiting the recruitment of stem cells will limit the progression of endometriosis.	Recommendation updated in 2014.
Apoptosis	
31 Further work is required to determine whether manipulation of the apoptotic pathway can be harnessed as a therapeutic strategy for endometriosis.	
Endometriosis-related miRNA work	
32 More work on the role of miRNAs is required, including using miRNAs as biomarkers and therapeutic tools for endometriosis	
Animal and other preclinical models	
33 Appropriate animal and in vitro models for preclinical studies of endometriosis therapies should be agreed upon by the endometriosis research community.	
Use of targeted transgenic models	
34 Targeted gene knockout and transgenic models should be used to investigate the function of genes in the context of endometriosis.	
Progestins and endometriosis	
35 To continue clinical and basic studies to determine the effectiveness of different progestins and SPRMs as agents for treating endometriosis, as well as studies aimed at understanding progesterone resistance in eutopic and ectopic endometrium.	
Role of the ovary as a target of endometriosis	
36 Future research should consider the ovary as a target of endometriosis.	
Role of the microbiome in endometriosis	
37 Metagenomic studies should be undertaken of the microbiome of the reproductive tract and/or the gut in women with or without endometriosis.	
Unchanged recommendations from 2008 ¹	
38 Heterogeneity of endometriosis lesions should be investigated using the full range of pathological and analytical approaches to ascertain whether an association exists between different lesion types and any given symptomatology.	
39 A better understanding of the role of eutopic endometrium in the establishment and continuation of endometriosis is required.	
40 Research should be performed on menstrual tissue, including material obtained from the peritoneal cavity by laparoscopy performed at the time of menstruation. Differences in retrogradely shed menstrual material between women with and without endometriosis should be defined, including but not limited to soluble mediators, endometrial cells, and leucocytes.	

(continued)

Table 1. (continued)

	Status
41 More research is needed in order to better understand the biology and function of macroscopically normal peritoneum in women with and without endometriosis.	Recommendation updated in 2014.
42 A better understanding of the mechanisms that underlie fibrosis and adhesion formation in the peritoneal cavity of women with endometriosis is required.	
Research policy	
Data registries and biobanks	
43 That networks and/or biobanks and databases replete with patient clinical data are established to increase sample availability and improve study power for endometriosis research, including assessment and validation of biomarkers. Standard operating procedures (SOPs) should be established for tissue acquisition, processing, storage, and distribution. These activities should take account of existing databases and resources regarding patients with endometriosis.	Complete. WERF EPHect tools address this: http://endometriosisfoundation.org/ephect/ .
44 WERF should define guiding principles for establishing a global registry for endometriosis biobanks and databanks and take the lead in identifying SOP's, a consensus on clinically relevant questions and promote standardized definitions, prospective documentation, and pragmatic oriented research designs.	Complete. WERF EPHect tools address this: http://endometriosisfoundation.org/ephect/ .
45 Data from genetic and gene expression studies should be submitted to online repositories like Gene Ontology (GO) and microarray express in a standard format suitable for sharing (and use in meta analyses).	
46 A simplified questionnaire for assessment of quality of life and pain outcomes is required.	Recommendation updated in 2014.
47 WERF create a global "endometriosis phenome" with extensive and standardized annotation of patients' medical, surgical, family, social, and exposure histories, and current and evolving multidimensional knowledge networks of cellular and genetic/epigenetic proteomic, metabolomic systems for a new "taxonomy of endometriosis disease"	
Centers of expertise	
48 There should be a definition of what an endometriosis center of expertise is, based on quantifiable measures that are process and structure related, with quality indicators that are outcome related.	
Multidisciplinary approaches	
49 There is a need for a multidisciplinary approach to research in all aspects of endometriosis to include reproductive medicine physicians, reproductive surgeons, biologists, pathologists, oncologists, epidemiologists, geneticists, immunologists, toxicologists, pain specialists, infectious disease specialists, biostatisticians, bioinformaticians, and others to enable effective, accurate, and timely diagnosis, determination of those at risk, and prevention and treatment of endometriosis, and associated disorders.	
50 WES should look to educate, interact with, and involve other specialists with the purpose of gaining a better understanding of the disease, with a strong focus on translating research outcomes into better treatment and improved quality of life for women with endometriosis.	
51 Large surgical centers should participate in basic research networks and efforts should be made to maximize the amount of data that are generated from clinical trials through add-on studies and collaboration with other relevant disciplines.	
Guidelines and implementation	
52 There should be a triannual workshop of research directions in endometriosis based on a consensus approach lead by WES and WERF and based on best available scientific evidence.	Triannual workshops have been held in March 2008, September 2011, and May 2014. The next workshop is scheduled for May 21, 2017.
53 WES and WERF should formulate various task forces as required to move forward recommendations from this meeting.	
Lobbying and endometriosis organizations	
54 Women with endometriosis should be included in meetings and focus groups to develop new insights and approaches to research.	Recommendation updated in 2014. Women with endometriosis are invited to participate in WES and WERF meetings.
55 Endometriosis researchers should engage women with endometriosis and the wider community with activities that include sharing and communicating research results.	
56 Endometriosis researchers and women with endometriosis should work together to optimize funding support for endometriosis research.	

Harmonisation Project (EPHect; <http://endometriosisfoundation.org/ephect/>) led by Stacey Missmer of Harvard University and Krina Zondervan from the University of Oxford.^{3,4,11,12} The WERF EPHect team includes 34 experts from 16 countries as well as 3 industry sponsors—many of whom were present at the WES/WERF Research Workshop. Together, this group developed and published freely available clinical and surgical data collection tools along with protocols to standardize collection of biological samples to support discovery and innovation. To maximize collaborative opportunity, there is a facility for centers that use the WERF EPHect tools and protocols to identify themselves on the website above.

Pathogenesis and Pathophysiology

Epidemiology

The consensus meeting approached epidemiology from its 2 definitions: first, as the discipline focused upon determining who is at risk for endometriosis (which of a girl or woman's characteristics or exposures are associated with her developing endometriosis) and how those characteristics and exposures cause or impact endometriosis pathogenesis and pathophysiology; second, as the science underlying the methods by which valid human studies must be conducted. It matters who we choose to sample from among the population of girls and women and who we compare to whom for our studies of pathogenesis and pathophysiology. The broad consensus was that future studies need to be large and diverse to quantify and evaluate with adequate statistical power the importance or insignificance of the diversity of disease presentation, whether it be in macroscopic subtypes (superficial peritoneal, ovarian, and deep infiltrating endometriosis; propensity for scarring and adhesions), symptom presentation (dysmenorrhea, acyclic pelvic pain, dyspareunia, infertility), and treatment response.

Two topics summarize the new recommendations: (1) a need for our field to thoughtfully and actively determine what data are needed to quantify endometriosis disease burden and to facilitate discovery that takes into account phenotypic variation and (2) endometriosis must be addressed and consistent data must be collected for research and clinical needs across the life course, in adolescence, pregnancy, and throughout adulthood. Adolescents in particular are an underserved group with high morbidity and social impact, and yet this age is likely the critical window for disease etiologic discovery and intervention.¹³

Endometriosis macroscopically appears and behaves differently among patients. However, what patterns and differences are important to target for etiologic discovery, treatment development, and ultimately cure—and perhaps prevention—remain unclear. Scientific progress has been limited in part due to small studies and geographic restrictions that make identification of these unique disease groups impossible.

There were no recommendations from the 2011 meeting that are no longer relevant; 2 remain current.

Since the 2011 World Congress to this 2014 consensus meeting, only 2 epidemiological study papers evaluated

outcomes comparing and contrasting subtypes of macro-disease presentation of endometriosis. One included superficial peritoneal, ovarian, and deep infiltrating categories.¹⁴ The other applied the American Society for Reproductive Medicine (ASRM) classification system and the Endometriosis Fertility Index (EFI).¹⁵ There was nothing published comparing patients by categories of symptomatology or peritoneal lesion types. There were many publications with “stage” as a keyword; however, none published prior to the workshop evaluated stage by comparing the study outcomes among cases stratified by stage. One subsequent paper found a weak correlation between stage of endometriosis and age, concluding that minimal or mild endometriosis is equally likely to be present in women of all ages and that endometriosis in its severe form is not age dependent.¹⁶

Regarding diet, there were 7 studies published during this 3-year time period; they included focus on micronutrients, a gluten-free diet, fish oil, flavonoids, and systemic antioxidant capacity. There were a rich range of methods and expertise: animal models, small human trials, and cohort studies.¹⁷⁻²³ Among the 3 animal studies, the one using a Wistar albino rat model observed that dose-dependent vitamin C supplementation significantly reduced the volumes and weights of the endometriotic cysts.¹⁸ In a chimeric mouse model, dietary fish oil supplementation inhibited formation of endometriosis-associated adhesions,²¹ whereas in a BALB/c mouse model, xanthohumol was observed to inhibit the development of endometriotic lesions without evidence of a negative impact on the uterine horn or ovaries.²² The human studies included a small case (n = 25)–control (n = 20) study, which reported a higher current intake of fiber among the women with endometriosis and a higher polyunsaturated fat intake among the controls.²³ Also, a cohort of ~150 women reporting endometriosis-associated pain were asked to commit to a gluten-free diet for 12 months. At the end of follow-up, a significant majority reported a decrease in pain and improved physical and social functioning in unadjusted analyses.¹⁷ The largest studies (n ~100 000 participants with follow-up duration of >15 years) published from the Nurses' Health Study 2 cohort reported a significantly decreased risk of endometriosis among women who consumed larger quantities of dairy foods rich in vitamin D, calcium, or magnesium.¹⁹ They also observed a decreased risk with greater vitamin B and C intake, but from food sources, not from supplements.²⁰

Two body mass index (BMI) studies reinforced the robustly observed higher prevalence of endometriosis among lean women.^{24,25} Overall, those with lean BMI at age 18 (<18.5 kg/m²) had 20% to 25% greater risk of endometriosis compared to women with normal BMI (18.5–24.9 kg/m²), 40% greater than overweight women, and nearly double the risk of morbidly obese women (P value, test for linear trend <.0001).

Finally, with respect to environmental toxicants, only 3 studies were published between the 2011 and 2014 World Congresses.²⁶⁻²⁸ The study of environmental toxicant risk factors was the only topic that included data evaluating the importance of age at exposure, with studies that included in utero exposure, childhood exposure, and exposure during adulthood. Earlier

life exposures to toxicants may be the critical window for impacting initiation or promotion of endometriosis development, whereas later life exposures may impact symptom severity or treatment resistance. Within the French Teachers' Cohort that included ~75 000 women, Kvaskoff and colleagues observed a modest but significant increased risk of endometriosis among women who had had pets as a child or lived on a farm with livestock and a larger increased risk (up to 34%) for those who were exposed to passive cigarette smoke.²⁸ The Women's Risk of Endometriosis case-control study based in the US Pacific Northwest observed significantly higher serum concentrations of the persistent organochlorine pesticides β -hexachlorocyclohexane and mirex among case women compared to control women.²⁶ However, within the Endometriosis, Natural History, Disease, Outcome Study, the matched cohort analyses suggested no association between risk of endometriosis and exposure in utero with maternal or paternal smoking or with maternal consumption of alcohol, caffeine, or vitamins.²⁷

New Recommendations

1. *Recommendation (new)*: Facilitate and prioritize collection of country-/region-specific endometriosis prevalence data to facilitate calculation of disease burden statistics. This is particularly critical in emerging regions.
2. *Recommendation (new)*: Document the social impact of endometriosis using standardized instruments. This is particularly critical for inclusion of adolescents.
3. *Recommendation (new)*: Devise standardized questions, or tools, for participant query and medical record abstraction of endometriosis and endometriosis-related symptom data that could validly facilitate adding these data to many large ongoing international cohorts.

Genetics, Epigenetics, and Genomics

Genetic and environmental factors contribute to endometriosis risk, and the disease is inherited as a complex trait.^{29,30} Substantial progress has been made in the discovery of genomic regions contributing to endometriosis risk. New genome-wide association (GWA) studies,³¹ replication studies,^{32,33} and meta-analyses^{30,34} show remarkable consistency in the size and direction of effect for risk variants across studies and across ethnic groups. There are at least 6 genomic regions showing significant association with endometriosis of any disease stage.³⁰ In addition, association between markers near the interleukin 1A gene first reported in Japanese patients was confirmed recently.^{35,36} There is genetic overlap between endometriosis and both waste-hip ratio³⁷ and ovarian cancer,³⁸ and understanding the relationships between endometriosis and other reproductive traits will be one important direction for future studies as large data sets become available.

The combined data show the genetic contribution to endometriosis results from a large number of variants of small effect. Results from the estimated contributions of the known

genomic regions^{30,31,34} and the single-nucleotide polymorphism (SNP) heritability³⁹ suggest many more variants remain to be identified. Knowing and understanding the effects of these variants will aid understanding of disease origin and progression and the identification of biomarkers for disease as well as novel drug targets. To this end, genotyping is being completed in additional case-control samples to conduct new GWA studies and combine results in a large new meta-analysis that will increase the sample size to at least 17 000 cases. This sample size increase will increase power for gene discovery but is still modest compared with current projects of 50 000 to 100 000 cases in other diseases. In addition, an important objective for future studies is to use genetic approaches to help understand the similarities and differences between different subtypes of endometriosis including peritoneal disease, ovarian endometriomas, and deep infiltrating disease. Most of the large samples used for GWA studies lack detailed information on disease subtypes, and there is an important need for new large studies where detailed phenotypic data, medical records, and genotype data are available for combined epidemiological and genetic studies.⁴⁰

There were no recommendations from the 2011 meeting that are no longer relevant; 2 recommendations remain current.

4. *Recommendation (new)*: Establish databases for appropriate samples and clinical information to facilitate future large-scale multicenter collaborations on genetic contributions to endometriosis.
5. *Recommendation (new)*: Collect large sample sets with appropriate clinical and phenotypic information about endometriosis for future functional studies.

One objective of genetic studies is to identify the specific genes and biological pathways responsible for increasing disease risk. The gene discovery phase only identifies genomic regions associated with disease, and the next critical steps are to link the DNA sequence variation to the altered regulation and function of specific genes. Defining these molecular mechanisms for each genomic region is a major challenge.^{40,41} The general approaches include "fine mapping" of the association signal in each region with additional genotyping, functional annotation, expression quantitative trait locus studies for target-gene identification using global and local gene expression studies, and evaluation of likely causal SNPs and target genes by genomic and functional studies. Studies would be strengthened if there were comprehensive data available for global regulation of gene expression and epigenetics in relevant reproductive tissues, but these data are not currently available.

There is accumulating evidence that epigenetic mechanisms (that are able to alter the effect of genes without changing the DNA "code") may play an important role in endometriosis. Most epigenetic-focused studies to date have been investigations of promoter methylation of genes known to be differentially regulated in endometriosis: either silenced (eg, *p21*, *CDH1*, *PRB*, *HOXA10*, *17HSD2*, aromatase, and *ESR1*) or upregulated (eg, *SF1*).⁴²⁻⁴⁵ Together, these molecular

aberrations may sustain the survival and growth of ectopic implants and explain differences in disease aggressiveness and invasive properties.⁴⁶⁻⁴⁸

Genome-wide methylation signatures in isolated stromal cells obtained from eutopic endometrium and ectopic tissue from cell walls of ovarian endometriomas identified a unique epigenetic fingerprint in endometriosis, suggesting that altered DNA methylation is an integral component of the disease.⁴⁹ Results further suggest a novel role for the GATA family as key regulators of aberrant DNA methylation in endometriotic cells. Results from Illumina 450K methylation chips in DNA samples from the endometrium from 31 patients with endometriosis and 24 healthy women reported a large influence of stage of the menstrual cycle methylation patterns and a small number of significant differences between cases and controls.⁵⁰ Although further studies are required to confirm the direction of causation and role of these altered methylation signatures, large epigenetic studies offer important novel approaches. Recent analyses in other traits show environmental factors contributing to methylation differences and that genome-wide methylation signals can be combined with genome-wide genetic data to aid risk prediction.^{25,51}

Although DNA methylation has received considerable attention, little is known about the role of histone modifications in endometriosis. Histone deacetylase inhibitors (HDACi) and other epigenetic modulators are emerging as a class of promising cancer therapeutics.^{52,53} During the last decade, many drugs with histone deacetylase (HDAC)-inhibiting action have been shown to induce growth arrest, apoptosis, and differentiation of tumor cells.^{54,55} It was recently shown that different types of lesions vary in the expression of HDACs^{56,57} and that tissues (lesions and endometrium) from patients have different levels of H3K9 and H4K16 acetylation compared to control tissues.^{58,59} Thus, evidence has started to accumulate that endometriotic lesions have a characteristic histone code and that global H3 and H4 acetylation within promoter regions of candidate genes is differentially modulated in lesions.

More recently, histone methylation has been identified as another potential target for therapy, following the discovery of enzymes that modulate this specific modification of histones, histone methyltransferases (HMTs), and histone demethyltransferases.^{60,61} A growing number of HMT inhibitors (HMTi) are undergoing intense research efforts as potential treatments for cancer, based on the observation that these enzymes are at increased levels in various cancer types. It will be of interest to explore this new, promising avenue for targeted treatments of endometriosis. In conclusion, based on the data obtained to date, endometriosis may have an important epigenetic component involving nucleoside and histone modifications; as such, this disease is a good candidate for epigenetic reprogramming through HDACi and HMTi that should be explored further.^{62,63}

6. *Recommendation (new)*: Studies should be undertaken on all aspects of epigenetic regulation of endometriosis.

Functional Biology

There were a total of 25 recommendations relating to pathophysiology of endometriosis developed at the 2011 Montpellier consensus conference. The consensus of the participants was that each of these remained relevant and that none had been fully addressed. Among the earlier recommendations, some were updated in 2014 to conform more closely to evolving research concepts. Examples of this include new data emerging about the location of putative progenitor cells as well as studies in models highlighting the inherent “plasticity” of cells within the endometrium that make likely the existence of cells that may change their identity via mesenchymal/epithelial transition.

7. *Recommendation (updated)*: Further research is required into all aspects of endometrial progenitor cell biology, including their origins, their potential to adopt different cell lineages, and whether inhibiting the recruitment and differentiation of progenitor cells will limit the progression of endometriosis.
8. *Recommendation (updated)*: Research should be directed toward understanding the phenotype of immune cells such as macrophages and mast cells in endometriosis lesions.
9. *Recommendation (new)*: There should be investigation of the epithelial-to-mesenchymal transition state, well characterized in cancer metastasis, which may prove to be informative regarding the invasiveness of endometriosis lesions.⁶⁴⁻⁶⁷

Despite the many unchanged recommendations from 2011, it was noted that the literature on endometriosis continues to be compromised by studies that fail to differentiate between the location and type of lesion being studied. It was suggested that reviewers should insist on this information being included before papers are accepted and suggested that WERF EPHEct Surgical Form be utilized for harmonization of data reporting.

Several updated or new recommendations on the functional biology of endometriosis were tabled at the 2014 Sao Paulo workshop, covering animal models, imaging, immune and progenitor cells, peritoneum, and pain. A new mouse model using “menstrual” uterine tissue from a donor mouse has been developed: Insights from this model include the potential for immune cells such as macrophages that are shed into the peritoneal cavity at the time of menses persisting in lesions and contributing to the growth of both vascular (angiogenesis) and nerve cells (neurogenesis) within the lesions.⁶⁸ In the last 3 years, there has been a much greater appreciation that macrophages are not the only cell type that has the potential to play an important role in establishment of lesions and development of pain symptoms, as well as a major reevaluation within the macrophage research community of their phenotypic classification.⁶⁹

10. *Recommendation (new)*: Studies focusing on the role of macrophages should consider the contribution from

the endometrium⁷⁰ as well as the peritoneum and use new macrophage classification systems.⁷¹

11. *Recommendation (new)*: Studies on mast cells should be conducted to assess their contribution to development of pain and other symptoms,⁷² building on historical preliminary data.⁷³

New insights have been gained from studies on peritoneum highlighting changes in women with chronic pain, even if they do not have active or visible endometriosis,^{74,75} metabolic changes, and a role for transforming growth factor β .^{76,77} These studies will inform future development of nonsurgical treatments. The link between pain and pathology has only been possible because of the use of standardized measures of pain intensity.⁴

12. *Recommendation (updated)*: Studies on the peritoneum should be encouraged and used to complement those on endometriosis lesions. Cell models including mesothelium from the peritoneum of women having chronic pain should be used to extend investigations on intact human lesions/peritoneal tissue.

Symptoms

Pain

Very little progress has been made recently in either understanding the mechanisms underlying endometriosis-associated pain or in identifying effective treatment strategies for this symptom. It is now well established in the pain community (among both scientists and clinicians) that central changes occur in all chronic pain conditions and that the nervous system can both modulate pain or may itself be responsible for generating the sensation of pain.⁷⁸ There is good evidence that these changes also occur in conditions associated with pelvic pain⁷⁹⁻⁸¹ including endometriosis.^{82,83} However, in the majority, these studies are descriptive, providing no information on cause and effect nor relating central changes to potential pain generators in the periphery.

A large number of factors have been found to be altered in the pelvises of women with endometriosis when compared to controls (eg, inflammatory mediators, neoangiogenesis, nerve density, transient receptor potential cation channel subfamily V member 1 expression [TRPV1]), which may plausibly be involved in generating pain.⁸⁴ However, there is little relationship between the magnitude of these alterations and the intensity of the pain experienced.

Two recent studies have demonstrated how, by combining information about the structure or function of the nervous system with clinical descriptors and peripheral measures, insights into the mechanisms generating pain can be found. First, it was shown that levels of cytokines in the peritoneal fluid of women with endometriosis (particularly tumor necrosis factor α) were related to neurophysiological measures of central hyperexcitability in response to painful stimuli.⁸⁵ Second, brain volume

was investigated in 4 groups of women: (1) healthy controls, (2) women with CPP without endometriosis, (3) women with CPP and endometriosis, and (4) women with endometriosis but no associated pain.⁸⁶ Perhaps unsurprisingly, women with CPP had alterations in gray matter volume consistent with findings in other chronic pain conditions,⁸⁷ whether they had endometriosis. However, more interestingly, the women with endometriosis but no pain had an increased volume of the periaqueductal gray, a key region of the descending pain modulatory system (DPMS). As the DPMS acts to control the amount of information ascending to the brain from the dorsal horn of the spinal cord, and dysfunction within this system has been proposed as a potential mechanism leading to pain vulnerability,⁸⁸ this may be an example of adaptive brain plasticity preventing some women with endometriosis from experiencing pain. Of note, there is now an increased interest in dysmenorrhoea within the pain community⁸⁹ since the recent publication of 4 studies demonstrating long-lasting structural and functional changes within the brains of women with dysmenorrhoea.⁹⁰⁻⁹³ Furthermore, dysmenorrhoea was recently reclassified as a chronic pain condition by the International Association for the Study of Pain (IASP).⁹⁴

Endometriosis is unusual in the context of chronic pain conditions because of the number of different types of pain (eg, dysmenorrhoea, noncyclical pelvic pain, dyspareunia, etc) that can be experienced by any 1 woman, potentially all with different underlying mechanisms and associations. Moreover, the relative severity of this pain varies among patients and over time. Potentially one of the factors hampering progress in our understanding of endometriosis-associated pain is the use of crude or inadequate measures of pain that do not account for these differing types of pain or for the quality of the pain (stabbing, burning, aching, etc) or for variation with the menstrual cycle. The use of standardized questionnaires for data collection as proposed by EPHeC⁴ is expected to help in this respect with regard to mechanistic and biomarker studies. However, for clinical trials, the design of a novel patient report outcome measure (PROM) that is meaningful to patients is necessary. Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials have previously defined core outcome measures that should be included in any trials in chronic pain,⁹⁵ and it was proposed a few years ago that these should be adapted for clinical trials in endometriosis-associated pain rather than designing completely new unvalidated measures.⁹⁶ Any such PROM should include measures of other factors contributing to the pain experience such as psychological state and pain catastrophizing as these have also been shown to contribute to perceived quality of life^{97,98} and success of treatment.^{99,100}

Two new animal models have been used to investigate the link between estrogen and pain. Evidence that estrogenic ligands may directly regulate factors such as Slits¹⁰¹ and production of inflammatory factors by macrophages¹⁰² known to regulate nerve cell migration has been obtained using the new mouse model, demonstrating its potential as a platform for basic research and testing of potential therapies to treat

endometriosis-associated pain using Von Frey and other techniques. A rat model has been developed in which endometrial tissue is transplanted to the gastrocnemius muscle; this has subsequently been used to explore the role of leptin in estrogen-dependent chronic pain.¹⁰³⁻¹⁰⁵

Five recommendations on endometriosis-related pain were unchanged from 2011, whereas 2 were either no longer relevant or superseded.

13. *Recommendation (updated):* All studies collecting any form of biological measure (eg, inflammatory marker, gene expression, nerve density, etc) need to also collect detailed pain information rather than a single rating of “generalized pelvic pain intensity” to allow a better understanding of pain mechanisms in endometriosis.
14. *Recommendation (updated):* An endometriosis or female pelvic pain-specific PROM should be developed to capture the various different types of pain (dysmenorrhoea, dyspareunia, noncyclical pelvic pain, dyschezia, dysuria, etc), their quality (eg, burning, aching, stabbing), and any cyclicity.
15. *Recommendation (new):* Where possible, endometriosis-associated pain should be phenotyped by its underlying mechanisms (eg, inflammatory, neuropathic, central, etc).¹⁰⁶
16. *Recommendation (new):* Encourage the use of new rodent models to test existing drugs that may be suitable for repurposing as treatments for inflammation/pain in women with endometriosis.
17. *Recommendation (new):* Engage the leaders of large multinational studies launched recently to evaluate adolescent brain development with biobanking of brain imaging data and to ensure that pain and dysmenorrhea data as well as endometriosis diagnoses are included in their data collection efforts.

In common with other chronic pain conditions, potential novel treatments for endometriosis-associated pain have rarely been successful in early-phase clinical trials. One potential explanation for this observation is that the mechanisms generating pain are so variable in this heterogeneous population that there will not be a “one-size-fits-all” treatment. The strategy of sensory phenotyping, which has been proposed particularly in neuropathic pain but also applied to other chronic pain conditions, is particularly interesting in this context. This strategy uses the pattern of sensory symptoms and pain qualities derived from the completion of questionnaires and the results of quantitative sensory testing to classify patients on the basis of the potential site(s) of dysfunction of the pain processing pathways. Detailed analysis of large numbers of patients with neuropathic pain with a variety of etiologies has shown that it is feasible to subgroup patients with this strategy, and moreover, retrospective analysis of clinical trial data has shown the

sensory phenotype to predict the response to treatment.¹⁰⁷ Thus, any PROM designed for women with CPP/endometriosis should contain sufficient information to allow such stratification to be performed and to facilitate multicenter proof-of-concept studies to confirm that such a strategy is appropriate in endometriosis. It is promising, however, that in other conditions not classically considered as neuropathic, preoperative central measures have been shown to both predict the response to surgery and the development of chronic postoperative pain.¹⁰⁸⁻¹¹⁰

Although it is disappointing that endometriosis rarely features on the programs of specialist pain meetings, there is a similarly poor inclusion of pain neuroscience in the majority of Endometriosis or Women’s Health conferences. Given that CPP, with or without endometriosis, affects millions of women worldwide, inclusion of pain neuroscience more broadly in health and research meetings is essential. Furthermore, many of the topics discussed at the WCE in Sao Paulo (eg, the role of gases such as nitric oxide and hydrogen peroxide in generating pain, neurogenic inflammation, pain genetics, and patient tailored treatment) were also discussed in headache and pain meetings that same year (15th World Congress on Pain, October 6–11, 2014, Buenos Aires, Argentina. 2nd Joint Symposium of IASP/International Headache Society [IHS], April 23–26, 2014, Siena, Italy). Thus, it is proposed that the collaboration and sharing of knowledge and experience with pain neuroscientists will be key to unraveling the peripheral and central mechanisms generating the clinical experience of pain in women with endometriosis.

18. *Recommendation (new):* A joint research symposium between pain researchers and endometriosis researchers should be organized to share knowledge, identify areas of overlap, optimize potential collaborations, and avoid “reinventing the wheel.”
19. *Recommendation (new):* Research should be undertaken to analyze community attitudes to CPP using sociological methods.

Infertility

It is estimated that up to 35% to 50% of women with infertility have endometriosis.¹¹¹ Whether endometriosis contributes to infertility has long been debated, and underlying mechanisms resulting from the presence of disease and classified by stage possibly affecting fertility potential are poorly understood, although inflammation and reactive oxygen species are believed to contribute significantly.^{5,112} To date, data support abnormal folliculogenesis, including compromised granulosa cell and follicle immune homeostasis, lower oocyte quality and reduced ovarian reserve, lower fertilization rates, altered embryo development, and abnormalities in the eutopic endometrium that affect implantation success in a disease stage-specific manner.¹¹²⁻¹¹⁵ There are also consequences of anatomical distortion that may compromise fertility,¹¹² and

there are mixed data on pregnancy outcomes in women with disease.^{116,117} Human in vitro fertilization (IVF) and embryo transfer and ovum donor/recipient cycles serve to test hypotheses generated from experimental data obtained in animal models and with human endometrial and endometriosis tissues and cells.^{118,119} Overall, studies of various factors contributing to endometriosis-related infertility show conflicting results.¹²⁰ This lack of identified factors underscores the need to have rigorous epidemiological and clinical data to understand mechanisms underlying effects of endometriosis on female fertility, assess approaches to mitigate these abnormalities for treatment and also for diagnosis and prevention, and understand short-term and long-term effects of endometriosis-related infertility and treatment on the health of affected women and their offspring.

There were no previous recommendations on infertility associated with endometriosis, and 3 new recommendations were proposed.

20. *Recommendation (new)*: Research is needed to elucidate the causal relation, if one exists, between endometriosis and infertility, taking into account the importance of evaluating the relationship between pelvic pain and infertility, independent of endometriosis.
21. *Recommendation (new)*: Determine the relative contribution of anatomic versus nonanatomic endometriosis-associated lesions, including the role of adhesions, to infertility in general and embryo implantation rates in particular.
22. *Recommendations (new)*: Develop validated screening tools including clinical history and physical examination to reduce the number of patients treated by laparoscopy, so that when laparoscopy is used for endometriosis-related infertility, it is used effectively.

Oocyte Competence, Folliculogenesis, Embryo Quality, and Development

Several studies strongly support the view that oocytes from women with endometriosis have reduced competence. The proinflammatory environment in which the oocyte matures likely affects its developmental potential, and several animal studies support this view.¹²¹ Clinical IVF studies that have assessed fertilization rates, embryo quality, and implantation rates with oocytes from women with endometriosis have either not found significant differences^{122,123} or have found significantly decreased oocyte competence.¹¹⁸ Reduced oocyte competence results in early embryonic growth arrest¹²⁴ and reduced embryo quality and implantation rates.¹²⁵ A retrospective meta-analysis of IVF outcomes in patients with endometriosis has highlighted a progressive decrease in oocyte quality with increasing stage of disease¹²⁶ and more compromised oocyte quality in women with endometriomas.¹²³ Also, the latter subtype has lower ovarian reserve that can translate to lower oocyte quality/competence.

23. *Recommendation (new)*: Investigate the effects of endometriosis on folliculogenesis, oocyte competence, and subsequent fertilization and embryo quality. Studies should include detailed information on endometriosis stage and involvement of the ovaries with disease.
24. *Recommendation (new)*: Investigate the mechanisms underlying diminished ovarian reserve in women with endometriosis, the degree to which this is spontaneous due to ovarian endometriosis or endometriomas, or due to surgical intervention, and determine how much of the observed diminished ovarian reserve is reversible.

Endometrial Abnormalities and Pregnancy Outcomes

There are abundant data to suggest that the endometrium of women with endometriosis demonstrates abnormalities in gene expression, global transcriptome, signaling pathways, in response to steroid hormones, and having a proinflammatory environment.¹²⁷⁻¹²⁹ Only a few studies have looked at the influence of disease stage¹²⁹ or considered other uterine and pelvic abnormalities as confounders.¹³⁰ To date, women with more advanced compared to early-stage disease have more difficulty getting pregnant,¹³¹ significantly lower implantation rates (13.7% vs 28.3%, respectively; $P < .05$) and pregnancy rates (22.6% vs 40.0%, respectively; $P < .01$), but not fertilization or miscarriage rates,¹³² and significantly lower IVF pregnancy rates (13.84% vs 21.12%, respectively; $P < .001$),¹²⁶ underscoring a potential endometrial origin of these differences. Also, patients with advanced disease demonstrate diminished ovarian response and higher cancellation rates in IVF cycles but after surgery show improved implantation, pregnancy, miscarriage, and delivery rates, similar to those of women with tubal factor infertility,¹²² suggesting that removal of disease improves endometrial receptivity to embryonic implantation.

There is increasing evidence that endometriosis during pregnancy can present diagnostic and therapeutic challenges and can predispose to complications that can affect the mother and the outcome of the pregnancy.¹³³ For example, ovarian endometriomas with pregnancy-associated decidualization can have characteristics of malignancy, and extensive adhesions and/or disease growth can lead to bowel perforation, appendicitis, spontaneous hemoperitoneum, endometrioma infection or rupture, and other complications.¹³³ Abnormal subendometrial myometrial peristalsis and the inflammatory component of endometriosis have been proposed to predispose to abnormalities in placentation (eg, placenta previa), placenta vasculogenesis and hypertensive disorders in pregnancy, preterm birth, fetal growth restriction, and miscarriage.^{133,134} Exact mechanisms underlying these risks in the setting of a history of endometriosis in pregnant women warrant further investigation.

25. *Recommendation (updated)*: There is a need for reliable and comprehensive epidemiological data on pregnancy outcomes in women who have endometriosis who become pregnant naturally by infertility therapy and assisted reproduction.

26. *Recommendations (new)*: Data on clinical outcome after infertility treatment, whichever type, medical, surgical, expectant, should be collected with time to pregnancy as a key important event, using life table analysis and cumulative pregnancy rates at the expected level of quality in any fertility trial.
27. *Recommendations (new)*: Capture a history of endometriosis (stage, treatment to become pregnant if relevant) in obstetrical records, working with professional organizations to promote the inclusion of endometriosis as a diagnosis in the obstetrical record.

Pain and Optimal Fertility Therapies for Women With Endometriosis, Disease Status

An unmet need was identified to assess pain during fertility treatment and management of pain, including safety, efficacy, and effects on quality of life.

28. *Recommendations (new)*: There is a need to determine whether women with endometriosis experience pain during infertility therapy, and if they do, whether it is exacerbated by fertility treatment, and if/how the pain affects both quality of life and fertility. There is also a need to determine whether treatments for pain during fertility therapy are safe and efficacious, and whether they alter the efficacy of fertility treatments.

Patient Perspectives

Although previous research priorities workshops in 2008 and 2011 included consumer representatives, there were no recommendations specifically formulated toward research either into or driven by patient perspectives. The 2014 workshop sought to remedy this and agreed that future workshops should continue to include a session on the perspectives of women with endometriosis. A number of new recommendations were developed.

29. *Recommendation (updated)*: Patient views on the most pressing topics in endometriosis research and clinical priorities should be sought and subcategorized into different demographic groups including age, symptoms, ethnicity, and economic background.
30. *Recommendation (new)*: Research should be undertaken on how treatment costs, including for IVF, impact on the patients' decisions around diagnosis and treatment.
31. *Recommendation (new)*: In both developed and emerging countries, adolescent beliefs about not having periods and about the use of contraceptives when they are not sexually active should be explored. The need for improved education programs and/or patient support organizations should be quantified, particularly in emerging countries.

Diagnosis, Classification, and Prognosis

Surgery

Diagnostic surgery for endometriosis. The clinical utility of the revised American Society for Reproductive Medicine (rASRM) classification system¹³⁵ for endometriosis-related infertility, pain, and deep infiltrating endometriosis is limited. A surgical classification system for endometriosis-associated infertility¹³⁶ has been developed and its clinical prognostic usefulness validated in 10 independent trials. Classification systems for deep infiltrating endometriosis are also being developed (AAGL and ENZIAN).

The meeting recognized the need for improved education and training to increase uptake of minimally invasive diagnostic imaging technologies. Preoperative imaging will reduce the likelihood of laparoscopic procedures, which have to be abandoned because of unexpectedly severe disease. In the future, symptomatic women who have been diagnosed preoperatively with moderate to severe disease by imaging modalities should be offered excisional surgery as a first-line treatment. If imaging studies reveal no obvious signs of endometriosis, then "see-and-treat" surgery should be considered for women with pain or infertility who are refractory to nonsurgical therapies.

Diagnostic imaging modalities allow for better preoperative planning and counseling for patients scheduled to undergo excisional surgery for deep endometriosis, reducing both the morbidity and treatment cost of endometriosis.¹³⁷ Reduced reliance on diagnostic and "staging" surgery and improved education about and access to endometriosis-specific ultrasonographic and magnetic resonance imaging (MRI) techniques is desirable.¹³⁸ However, diagnostic surgery is still relevant for superficial and/or mild peritoneal disease, which remains difficult to detect using imaging modalities alone in symptomatic women.¹³⁹

Controversy also remains in young women, who are thought to have mild disease, as to the need for a surgically defined diagnosis when treating pain symptoms.¹⁴⁰ It was acknowledged that imaging techniques, such as transvaginal ultrasound (TVUS), may be inappropriate and less able to detect disease in this group.¹⁴¹ For this reason, it is still recommended that adolescents who have failed hormonal and pain therapies be offered surgery to establish a diagnosis, as more than two-thirds will likely have disease,^{142,143} with some evidence that the frequency of minimal–mild endometriosis is actually lower in adolescents than adults.¹⁴⁴

32. *Recommendation (new)*: The development, validation, and implementation of new endometriosis classification systems should continue.
33. *Recommendation (new)*: For patients at low risk of deep endometriosis, efforts should be made to improve and evaluate the development of low-cost advanced diagnostic surgical techniques (eg, single-port entry and natural orifice transluminal endoscopic surgery [NOTES] methods) in centers with advanced training and accreditation standards.

Imaging

Different imaging modalities play an essential role in the diagnosis and perioperative management of endometriosis. While operator experience as well as lack of sensitivity to detect minimal and mild endometriosis can be problematic, ovarian endometriosis (endometrioma) and deep endometriosis can be readily recognized using TVUS and/or MRI.^{145,146} Diagnostic test accuracy (DTA) studies and meta-analyses have been performed and show that TVUS and MRI techniques can diagnose endometriomas, rectosigmoid, and deep infiltrating endometriosis with a similar sensitivity and specificity to that of surgery.¹⁴⁷

At the 2011 meeting, it was recognized that technological advances in imaging were evolving rapidly and that consequently imaging techniques should be monitored on an ongoing basis for application to endometriosis. This recommendation was updated in 2014.

There have been significant advances in MRI and imaging related to pain since the 2011 meeting. Recent work in an animal model to detect endometriosis noninvasively using dynamic contrast-enhanced MRI with gadofosveset-trisodium as a contrast agent¹⁴⁸ found that contrast-enhanced MRI gave better visualization than conventional MRI. The MRI, including diffusion tensor imaging with tractography, is a noninvasive means of detecting changes in the microarchitecture of the sacral nerve roots. The MRI is increasingly used for endometriosis and CPP, and tractography can be used to show altered microstructure of sacral roots affected by endometriosis and CPP.¹⁴⁹

It is now possible under certain circumstances to image nerves and alterations in nerve properties noninvasively, to image receptor level expression and inflammatory processes in injured tissue, to image astrocyte and glial roles in neuroinflammatory processes, and to image pain conduction functionally in the trigeminal ganglion.¹⁵⁰ These advances will ultimately allow description of the pain pathway from injury site to behavioral consequence in a quantitative manner. Such a development could lead to diagnostics determining the source of pain (peripheral or central), objective monitoring of treatment progression, and, hopefully, objective biomarkers of pain.¹⁵⁰

34. *Recommendation (updated)*: More research is needed with emerging imaging modalities to define whether they are suitable for identifying lesions and peripheral pain pathways.
35. *Recommendation (new)*: More longitudinal studies are needed based just on imaging techniques to track the course of the disease and determine which patients ultimately require surgery.
36. *Recommendation (new)*: Investigate clinical outcomes in patients randomized to surgical versus nonsurgical treatment based on diagnostic imaging.
37. *Recommendation (new)*: Develop a validated screening tool based on history and physical examination to

identify women who should undergo imaging, particularly for adolescents and early-stage lesions.

38. *Recommendation (new)*: Prospective studies should be undertaken that can define changes in clinical practice and any resulting cost savings when diagnostic imaging tests are introduced into clinical algorithms.
39. *Recommendation (new)*: More high-quality DTA studies based on Quality Assessment of Diagnostic Accuracy Studies (QUADAS) are needed to ensure accurate assessment of the best diagnostic imaging modalities.

Biomarkers

Of the 2 recommendations from 2011 concerning biomarkers, both were considered still relevant and not in need of updating. In addition, a number of new recommendations were put forward. There was emphasis placed on the need for the discovery of new biomarkers to assist with diagnosis and classification of endometriosis.

Laparoscopic identification coupled with histological verification is currently the gold standard for diagnosis of endometriotic lesions.¹³⁹ Benefits of this approach include the simultaneous treatment of the condition and reassurance for both patient and clinician. However, medical treatments can also be similarly successful but may be associated with side effects, whereas surgery despite being effective in many cases is still associated with the risk of morbidity and mortality. Hence, the availability of robust biomarkers to aid clinical decision-making continues to be a major unmet need.

Two systematic reviews using well-defined QUADAS criteria summarized the results from the existing biomarker studies.^{127,151} The authors included 343 studies conducted since January 1984 on biomarkers in peripheral blood, saliva, urine, and eutopic endometrium. Despite an abundance of potential candidates, no biomarker was found to be suitable for clinical application.¹³⁹ Almost all studies were underpowered, had significant methodological issues, or demonstrated a poor choice of control patients. In addition, in some cases, different studies investigating the same marker demonstrated opposing findings, largely a result of factors such as the heterogeneity of the disease, patients and controls, different collection and processing techniques of biological samples, and nonstandardized assessment of clinical data. Many of these standardization issues have been addressed by the recent EPHeCt publications.^{3,4,11,12}

One important study tested a panel of 28 biomarkers identified from the literature in 232 women with endometriosis and 121 control women.¹⁵² A strength of this work is that the findings from a training set were then validated with the test set. A lack of validation studies was one of the main points of criticism of all the other existing studies.

40. *Recommendation (new)*: Large databases from collaborative efforts using harmonized and robust sample

and data collection tools are needed to help identify and validate the biophenome of endometriosis.

41. *Recommendation (new)*: Multicenter studies of the biophenome should incorporate well-selected control populations including women with other pelvic diseases to achieve a high sensitivity and specificity and should focus on both discovery and validation phases.
42. *Recommendation (updated)*: Efforts should be made to combine noninvasive biomarkers, imaging, and clinical characteristics to improve DTA.

It is important to emphasize the lack of data on endometriosis in adolescent girls. It has been recognized that the condition and associated symptoms are present in this age group, but that the few existing studies involve small numbers of patients, which make it impossible at present to draw any reliable clinical conclusions.¹⁴⁰ Therefore, a research focus on adolescent girls with symptoms suggestive of endometriosis is urgently needed. One such clinical observation that may point to early-onset endometriosis is neonatal uterine bleeding detected in 5% of neonatal girls around day 4. This withdrawal bleed resulting from maternal hormone withdrawal may be refluxed into the pelvic cavity due to the functional occlusion of the long neonatal cervix. Endometrial stem cells so delivered may remain dormant until menarche where they become activated to initiate growth of endometriosis lesions.¹⁵³ Although some 10 years will be required to collect these data prospectively, it will determine whether neonatal menstruation is a risk factor and potential biomarker for adolescent disease.¹⁵⁴

43. *Recommendation (new)*: In addition to adolescents and women with pain symptoms, emphasis should be placed on biomarker studies in adolescents and women with subfertility.
44. *Recommendation (new)*: Systematic registration of neonatal menstruation should be encouraged in maternity services as a potential biomarker of early-onset endometriosis.

Accumulating evidence demonstrates that genetic factors play a role in endometriosis (see above). Genome-wide association studies have identified SNPs linked to increased risk of endometriosis at a number of genetic loci in women, especially in those with extensive disease.^{30,31,34,155,156} Recent advances in laboratory techniques and network analysis now allow for large-scale functional, multiplex studies combining results from different approaches, which may not only advance our understanding of disease pathogenesis mechanisms but also identify novel target candidates for diagnosis and treatment.

45. *Recommendation (new)*: Results from large-scale genetic studies should be followed up by functional multiplex biomarker studies.

Disease and Symptom Management

Surgery

There has been significant progress made on surgery-related recommendations formulated at the 2008 Research Directions Workshop,¹ as summarized in the following 2 paragraphs.

Combined surgery and ovarian suppression results in better outcomes in patients with pain.¹⁵⁷ Laparoscopic surgery to treat mild and moderate endometriosis reduces overall pain and increases live birth or ongoing pregnancy rates. There is low-quality evidence that laparoscopic excision and ablation were similarly effective in relieving pain, although there was only one relevant study.¹⁵⁸ Reasonable data have demonstrated that laparoscopic treatment has adverse outcomes no worse than other surgical interventions. Shaving, disc resection, and bowel resection all have a role in management of bowel endometriosis, but further elucidation of their application is needed.¹⁵⁹

The EFI¹³⁶ has been validated as a useful clinical tool in 10 additional published studies. Excisional surgery improves spontaneous pregnancy rates in the 9 to 15 months after surgery compared to ablative surgery. Laparoscopic surgery improved live birth and pregnancy rates compared to diagnostic laparoscopy alone.¹⁵⁷ Ovarian reserve may be reduced with the treatment of endometriomas, but its clinical significance is variable.^{160,161}

There were 5 major recommendations relating to surgery from the 2011 workshop,² and all of these still remain relevant. In addition, 2 new recommendations have been made in 2014. Perhaps the most important of these arise from the recognition that no classification system predicts pelvic pain outcomes following surgery.¹⁵⁷

46. *Recommendation (new)*: Principles utilized in development of the EFI¹³⁶ should be utilized in development of a classification system for management of pelvic pain.
47. *Recommendation (new)*: The optimal application of surgery and specific surgical techniques, including energy techniques, need to be elucidated for endometrioma, bowel, bladder, ureter, and deep infiltrating endometriosis. Short- and long-term outcomes, including efficacy related to symptoms of infertility and pain, cost, and safety, need to be evaluated against nonsurgical techniques such as ovarian suppression, mind/body approaches, assisted reproductive technology (ART), and other medical and holistic interventions. This will provide information to develop improved comprehensive management approaches over time.

Medication

Disappointingly, there has been little research progress in medical management for endometriosis over the last 3 years due to the typically poor quality of the trials in this field. In March

2014, Brown and Farquhar published a summary of the evidence from Cochrane systematic reviews on treatment options for women with pain (or subfertility) associated with endometriosis.¹⁵⁷ They noted that the quality of the trials for specific comparisons ranged from “very low” to “moderate.” The main reason identified for the poor trial quality was bias: inadequate reporting of allocation concealment and randomization methods and a lack of blinding.

48. *Recommendation (updated)*: There is a need for more well-designed, adequately powered, multicenter randomized controlled trials and long-term follow-up studies comparing different endometriosis treatment options ideally against placebo and against defined outcome measures.

Although there were 31 “open” (recruiting or about to start) relevant trials at the time of the Sao Paulo meeting addressing treatment efficacy of endometriosis registered on ClinicalTrials.gov and the EU Clinical Trials Register, only 1 trial (PRE-EMPT <http://www.controlled-trials.com/ISRCTN97865475>) directly addresses a 2011 recommendation. This trial aims to determine whether effective medical adjuvant therapies exist to prevent or limit the recurrence of lesions and symptoms following surgery.

As a consequence of the overall lack of progress in clinical trials, most recommendations from 2011 remain substantially unchanged, although a number have been updated.

The precise mechanisms by which endometriosis causes pain are not completely understood (see above). However, there is increasing evidence that pain may be due to neuropathic, in addition to nociceptive and inflammatory, mechanisms.¹⁶² The efficacy of neuromodulatory drugs has been documented for a number of neuropathic pain conditions,^{163,164} but not for endometriosis-associated pain specifically. In some of these trials, neuromodulators also improved sleep, mood, and other elements of quality of life.

49. *Recommendation (updated)*: Clinical trials are needed to evaluate treatment options for pelvic pain associated with endometriosis, including neuromodulatory drugs used in the treatment of other chronic pain conditions.

Current treatment strategies for endometriosis are restricted to surgical excision of the lesions or suppression of ovarian function and estrogen action. In up to 75% of cases, symptoms recur after surgery, and long-term ovarian suppression is often ineffective, suppresses fertility, and has unwelcome side effects.¹⁶⁵ What women with endometriosis want is a therapy that can (1) reduce the painful symptoms associated with the condition, (2) preserve their ability to get pregnant while on medication and (3) have no, or limited, side effects. There is, therefore, an unmet clinical need for new nonhormonal treatments for endometriosis.

50. *Recommendation (updated)*: Novel nonhormonal medical treatments for endometriosis should be investigated.

The incorporation of genomic profiling into routine clinical practice has already been adopted for some tumors, such as human epidermal growth factor receptor 2 testing in breast cancer, providing a guide to treatment selection that is not afforded by histological diagnosis alone.¹⁶⁶ There is also increasing consensus that clinical trials should be more stratified for, or be performed only, in similarly “molecularly defined” subsets to avoid overtreatment and to save valuable resources.¹⁶⁷ This approach results in smaller numbers of more phenotypically and genotypically well-defined patients being eligible for such trials.

51. *Recommendation (new)*: We need to transform our clinical study design to integrate genomic profiling for patient stratification.

Other Therapies

There were no formal recommendations concerning complementary and alternative medicine (CAM) from the 2011 workshop, although it was noted that Chinese herbal medicine (CHM) was widely used in China to treat symptoms of endometriosis such as pain and infertility and that more rigorous research is required to accurately assess the potential role of CHM in treating endometriosis.^{168,169} The CAM therapies used by patients with endometriosis include herbs, acupuncture, CHM enema, microwave physiotherapy, and psychological intervention.¹⁷⁰ The same authors state that although CAM therapies have been gradually accepted in some countries, a range of issues hinders more widespread application of CAM therapies throughout the world. These include (1) selective publication of only positive results with varying study qualities and standards, (2) lack of large sample sizes and randomized controlled trials, and (3) the lack of confirmatory animal studies with therapies such as auricular acupoint, Chinese herbal enema, microwave physiotherapy, and psychological intervention.¹⁷⁰ Apart from CHM, natural products, including genistein, green tea, and resveratrol have shown effectiveness in animal studies¹⁷¹⁻¹⁷³; however, to date, no clinical trials with these agents to treat endometriosis in humans have been reported.

52. *Recommendation (new)*: There should be more research, including preclinical animal studies and randomized controlled trials, into the effectiveness of CAMs, compared to conventional therapies, for the treatment of endometriosis. These studies should include decreasing pain as well as enhancing fertility, pregnancy outcomes, and safety.

Diet and nutrition continue to be issues that women seek advice on when confronted with endometriosis. Clinical experience from practitioners present at the workshop noted that if women do modify their diet, it is often by trial and error to work out what their own triggers are. Some will find a beneficial

effect on their pain levels, but consensus on what works is not common. A similar lack of clear findings about diet and endometriosis risk is also found in the published literature, where evidence supporting a significant association between diet and endometriosis is at best equivocal.¹⁷⁴ Women with endometriosis seem to consume fewer vegetables and omega-3 polyunsaturated fatty acids and more red meat, coffee, and trans fats, but these findings could not be consistently replicated.¹⁷⁴ Others have concluded that specific types of dietary fats are associated with endometriosis and/or dysmenorrhoea, thereby indicating that there may be modifiable risk factors.¹⁷⁵ However, findings were equivocal and further research was recommended. There has also been a meta-analysis that found no evidence for an association between coffee/caffeine consumption and the risk of endometriosis.¹⁷⁶

53. *Recommendation (updated)*: Randomized controlled trials are needed to elucidate the role of diet in modifying recorded symptoms and underlying disease of endometriosis.

Patient Stratification

A number of recommendations from 2011 had some relationship to patient stratification, nearly all of which remain unchanged in this context. Patient stratification or personalized medicine is a novel concept in endometriosis. A PubMed search on May 4, 2014, using the keywords “endometriosis AND patient stratification,” identified only 13 papers, with just one linking patient stratification to outcome.¹⁷⁷ These authors reported on a clinically relevant inflammatory network that may serve as an objective measure for guiding treatment decisions for endometriosis management and in the future may provide a mechanistic end point for assessing efficacy of new agents aimed at curtailing inflammatory mechanisms that drive disease progression.

Patient stratification is an active area of research in gynecological cancer and chronic inflammatory conditions that are common in women, especially in breast and ovarian cancer but also in rheumatoid arthritis and Crohn disease. It is important to try to apply insights from patient stratification in these related diseases to patient stratification for endometriosis. A systematic review approach is warranted to stratify predefined outcomes in endometriosis research with family history, symptoms, clinical examination, dynamic imaging/pain reporting, surgical staging, and systemic or tissue biomarkers.

Standardized baseline characteristics should be reported in clinical trials evaluating reproductive outcome in women with endometriosis, specifying completed child wish (proven fertility), absent child wish, or present child wish (active child wish at present, active child wish in the future, infertile [inability to become pregnant during the last 12 months]).¹⁷⁸⁻¹⁸⁰

54. *Recommendation (new)*: To stratify reproductive outcome in women with endometriosis-associated infertility according to their current reproductive status and plans.

The phenotype of each patient needs to be determined and harmonized on the level of clinical symptoms, signs during clinical examination, imaging, and surgical staging. The WERF EPHeCT tools allow for standardized (consistent) collection of clinical symptoms and surgical findings in the context of biomarker studies,^{3,4} but harmonization is also needed with respect to definitions and reporting of data related to clinical examination and imaging, in order to relate these data (ie, ovarian mass, adhesions, deep nodules, other pathology, presence/absence of pain in specific areas during examination, coexisting morbidities such as adenomyosis and fibroids) to surgical data.

55. *Recommendation (new)*: To stratify clinical outcome data in medical or surgical therapeutic trials for endometriosis-associated pain and/or infertility according to predefined clinical symptoms, signs, imaging, and surgical staging.

The concept of recurrence is used differently by different authors in different studies, due to the lack of a universally accepted definition, which can be used in clinical research.^{180,181}

56. *Recommendation (new)*: To seek agreement on the definition of recurrence of endometriosis and endometriosis-associated symptoms after medical or surgical treatment.

Low-Income Countries and Low-Resource Settings

Previous endometriosis research priorities workshops have not considered research in low-income countries and low-resource settings.

57. *Recommendation (new)*: The Workshop on Research Priorities in Endometriosis should include statements addressing the needs of low-resource settings.

Over 2 billion people live in severe poverty (World Bank data: 2.2 billion people lived on less than US\$2 a day in 2011). The different approaches required in low-resource settings dictate that researchers appropriately consider the needs of the tens of millions of women in these situations. Challenges regarding culturally sensitive distribution of information, effective implementation of programs, the role of centers of excellence, private versus public initiatives/collaborations, and organizational collaborations play a critical role in developing successful interventions and research programs in low-resource settings. With the trend of delayed child bearing in emerging countries following similar patterns as has occurred in developed countries,¹⁸² it is expected that endometriosis prevalence will rise. However, in many emerging countries, there is a lack of awareness of endometriosis among doctors, patients, and families, and there is a huge lag between emerging and

developed countries regarding endometriosis research and centers of excellence for endoscopic surgery.

58. *Recommendation (new)*: Research programs run by emerging nations, targeting endometriosis-related issues specific to those nations, should be implemented.
59. *Recommendation (new)*: Researchers working in developed nations should ensure that progress resulting from endometriosis research will, where possible, be of benefit in low-resource settings.
60. *Recommendation (new)*: Programs and projects that provide international support and enhance regional collaboration in low-resource settings should be implemented, involving both health-care professionals and patient organizations.
61. *Recommendation (new)*: We should encourage centers of excellence in developed countries to take more active role in training and supporting research programs in centers dealing with endometriosis in emerging countries and this should be part of their accreditation process.

There are almost no data on diagnosis and classification of endometriosis in low-resource settings. There has been no organized approach to obtaining such data. An endometriosis management program involving history, physical examination, testing, and management that is culturally appropriate and cost-effective and that can be used in low-resource settings needs to be developed and taken to the World Health Organization to engage them and through them health departments in the governments of the world to bring endometriosis diagnosis and treatment into their primary and secondary health-care systems.

62. *Recommendation (new)*: Innovative approaches and tools such as WERF EPHEct, The FIGO Fertility Toolbox, the International Committee Monitoring ART registry, and low-cost IVF should be evaluated for their possible contributions to endometriosis research in low-resource settings.

In very low-resource settings, effective family and social support may be the most important intervention to reduce the burden of disease and is applicable in any setting.

63. *Recommendation (new)*: Research into culturally appropriate and cost-effective social support systems that mitigate the personal impact of endometriosis in low-resource settings should be performed.

Research Policy

Prioritization and Collaboration

At the 2011 Research Directions Workshop in Montpellier, 14 different recommendations were made under the overall banner

of research policy. Of these, significant progress has been made on several, with the most obvious being the WERF EPHEct. This initiative has been described in “Introduction” section.

Other recommendations from 2011, such as submission of genetic and genomic data into online repositories so as to be available for all researchers, are covered by the requirement from most international peer-reviewed journals that this is a prerequisite prior to publication. Some recommendations remain unchanged and were reinforced in 2014, the most notable being the need for a multidisciplinary and, where appropriate, multicenter approach to all aspects of endometriosis research.

There were 2 new recommendations under the heading of research prioritization.

64. *Recommendation (new)*: As a priority, we should undertake multidisciplinary research aimed at producing translatable patient-based outcomes, with a particular focus on pain and infertility.
65. *Recommendation (new)*: WERF should consider forming a clinical trials advisory group to provide feedback to assist researchers in developing high-quality studies that are appropriately designed and powered to achieve meaningful outcomes.

Funding Strategies

There were 3 recommendations from 2011 concerning lobbying and funding. All of these were deemed as relevant in 2014 as they were in 2011. With the global funding for research becoming more and more competitive, it has become increasingly challenging to secure funds for research in endometriosis, which despite its huge personal and health-care cost is classified as a “benign” disease. Endometriosis, however, is not benign for those who may have for decades with harsh and enduring impacts on their lives,⁸ and neither is it benign when taking into consideration the personal and societal costs.⁷

Funding sources can be divided into 3 broad categories: government, philanthropic, and industry. To successfully secure funding from any of these sources, it is necessary to position endometriosis as a disease priority and commence strategic lobbying to ensure its place in national health-care and research budgets. Specific funding requests (eg, for research initiatives) may aid this process by raising awareness about the disease. To obtain philanthropic funding, endometriosis must have its profile raised through well-directed awareness campaigns, as well as targeted proposals to wealthy individuals who have the means to support women’s health initiatives and who have a vested interest in supporting the eradication of a disease that may have impacted family and friends.

To ensure ongoing industry collaboration and financial support for investment in research into endometriosis disease mechanisms and improved treatments, convincing arguments must be collectively put forward to pharma to assist them in the

process of internal prioritization of specific disease investment. A disease affecting an estimated 176 million women worldwide,¹⁸³ which is not caused by preventive lifestyle factors, should provide tremendous potential for wider industry investment.

It is crucial that there is one, clear message from a large collective group of global collaborators of what needs to be done, how it will be done, and where money needs to be invested to make the goal of targeted treatments and prevention of endometriosis a reality.

66. *Recommendation (new)*: Develop lobbying and fundraising resources suitable to take to government, industry, and philanthropy that highlight the social and economic cost of endometriosis, as well as the need for research to improve outcomes for women with this disease.

Lobbying resources could include regularly updated fact sheets suitable for inclusion in letters to government, online resources, and videos where women and families speak about the disease and how it has affected their lives. Successful patient advocacy groups from other diseases such as breast cancer and diabetes may be able to provide guidance and examples of approaches that have been successful in the past. The meeting noted that WERF and WES may be appropriate bodies to develop and regularly update a portfolio of suitable facts and figures for groups to use in lobbying.

Discussion

The research recommendations developed by the 2014 consensus workshop provide important new insights into the evolving challenges facing endometriosis researchers, practitioners, and patients. New areas included in these recommendations include infertility, patient stratification, epigenetics, and research in emerging countries. Patient symptoms relating to pain and infertility are the 2 areas with the most new recommendations, followed by diagnosis under headings such as imaging, biomarkers, and diagnostic surgery. This shift to more translational research priorities reflects a broader focus by government funding agencies, and society in general, toward translational research. There is also a recognition of the need to involve and harness research insights in disciplines that intersect with endometriosis (eg, pain neuroscience) and the need to broaden multidisciplinary approaches to understanding and treating endometriosis.

It is interesting to follow the evolution of research priorities from the 2008 and 2011 workshops^{1,2} to present. In 2008, several of the research recommendations centered around the recognition that multidisciplinary approaches were needed and that individual silos of expertise could only make limited progress. In 2011, by far, the majority of recommendations were around functional biology and disease mechanisms, although a significant advance was the recognition of the need for more research into all aspects of endometriosis-associated pain. A

key theme for 2014 has been translation to better patient outcomes.

This 2014 research priorities consensus statement builds on earlier efforts to develop research directions in endometriosis. Forty-one of the 56 recommendations from 2011 remain current. Despite this, significant progress has been made by the international research community, with more than 2500 new scientific papers listed on PubMed between the 2011 and 2014 workshops. Of note and directly emanating from recommendations at the 2011 workshop are the publications from the EPHect.^{3,4,11,12} Lack of progress in other research areas may reflect the complexities of problems to be addressed, as well as the relatively slow pace of research and limited funding globally.

It is the hope of the workshop organizers and participants that this international consensus document will be a useful tool in aiding researchers to develop new and relevant research proposals and obtain increased funding support. The recommendations also provide a document to assist in the ongoing lobbying effort for increased research funding for endometriosis research from government, industry, and philanthropy. This is particularly important in procuring funding from nontraditional sources to support research in domains that intersect with endometriosis, such as pain.

Combining the 41 recommendations that are unchanged from 2011 with the 66 new ones from 2014 gives a total of 107 current endometriosis research recommendations. A task for the participants of the next endometriosis research priorities workshop to be held at the 13th WCE on May 17–20, 2017, in Vancouver, British Columbia, Canada, will be to consolidate and prioritize these 106 recommendations, as part of developing a revised and updated set of research priorities.

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