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Letters to the Editor

Regarding "A Call for New Theories on the Pathogenesis and Pathophysiology of Endometriosis"

To the Editor:

I read the opinion article by Abbott and the Endometriosis Initiative Group with interest [1]. Grand challenges in endometriosis remain – why is developing new drugs for endometriosis sometimes elusive? Why are fertility and pain outcomes different depending on the patient's race, ethnicity, or within the same group [2]?

The sum of a subject's observable characteristics is its phenotype. A clinical phenotype would be the presentation of a disease, such as endometriosis. While a phenotype is influenced by the genotype, genotype does not equal phenotype, the latter influenced by penetrance, dominance, expressivity, and pleiotropy [3]. I argue therefore, that the phenome be put under the investigative lens in order to further understand endometriosis.

The phenome is the expression of the entirety of phenotypic characteristics, including that of the disease phenotype. Phenomics is an interdisciplinary effort to correlate complex traits to variability not only in the genome but also in proteome, metabolome, immunome, microbiome, and environmental impacts [4,5]. Studying the phenome implicates an important point – that it is not one factor, mechanism, or theory that explains endometriosis pathogenesis and pathophysiology; rather, it is numerous acting together that elicit the pathological phenotype. If the phenome could advance the needle on understanding, preventing, and treating endometriosis, the next question would be: what should be measured, and how big is sample size? Afterall, larger and larger sample-sized Genome-Wide Association Studies studies are facing diminishing returns. There are two ways of being comprehensive: first, to sample a wide variety of phenotypes (extensive phenotyping); second, to deeply characterize a phenotype (intensive phenotyping). Both approaches can be important, but a narrowly defined disease phenotype can offer advantages over broad definitions. Thus, we believe intensive phenotyping of one of the endometriosis subphenotypes tied to well-defined physicoclinical outcomes has the potential to transform the big challenges faced in endometriosis.

Yie Hou Lee, PhD
KK Research Centre, KK Women's and Children's Hospital, Singapore, and OBGYN-Academic Medicine Programme, Duke-NUS Medical School, Singapore

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Authors' Reply

The Endometriosis Initiative Group[1]*

To the Editor:

We thank Dr Lee for his interest in our call for new theories on the pathogenesis and pathophysiology of endometriosis [1]. In the face of enigmatic endometriosis, Dr Lee offers to put phenome first into future investigative lenses. He views understanding the phemone as the key to advancing endometriosis research. Phenomics is an interdisciplinary effort to correlate complex traits to variability not only in genome but also in proteome, metabolome, immunome, microbiome, and environmental impacts [2]. In recognition of the varied disease phenotypes, Dr. Lee contrasts two possible approaches: to sample a wide variety of phenotypes (extensive phenotyping) and to deeply characterize a

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[1] The members of The Endometriosis Initiative Group are listed at the end of the article.

Corresponding authors: (On behalf of the Endometriosis Initiative Group) Michel Canis, M.D., Ph.D., Department of Obstetrics Gynecology and Reproductive Medicine, CHU Clermont Ferrand, Clermont Ferrand, France
E-mail: mcanis@chu-clermontferrand.fr

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phenotype (intensive phenotyping), proposing the second as the more attractive approach since narrowing defined disease phenotype could facilitate the identification of pathogenesis. The main tenet of his argument is that the phenotype is "influenced by penetrance, dominance, expressivity, and pleiotropy" of underlying genes, presumably endometriosis risk genes, those already identified and those yet to be discovered. This would make sense if we hypothesize that endometriosis could be a syndrome with different disease entities, phenotypes, and possibly phenomes.

We agree with Dr. Lee's point that "larger and larger sample-sized Genome wide association studies are facing diminished returns". However, not all phenotypes are determined solely by genes with various penetrances or expressivity, either dominant or recessive, pleiotropic or otherwise. More likely, there may be numerous genes with extensive gene-gene interactions, gene-environment interactions, and impactful developmental—in utero, post-natal, and adolescent—influences. Identification of these genes and factors and teasing out their individual and collective effect on the risk of developing endometriosis will or would be a formidable and challenging task that would require extensive and intensive resources. Adding one layer of complexity or more granulation in data used to study the disease could be attractive as we are developing more sophisticated research techniques with more technological, mathematical, statistical, and computing abilities. However, until now, this increase in complexity or sophistication has been rather disappointing. Hence, "in our opinion, if there is no change in the way we conceptualize the disease, no matter how much more data we accumulate and/or how we acquire these data, it will add little to our understanding" [1].

We would propose first that any novel idea is worth exploring, including those that seek to bring together an interdisciplinary approach as mentioned by Dr. Lee. We accept, we have so much to learn and explore before being able to bring tangible benefits to patients with endometriosis. Second, Dr. Lee will soon be able to propose his theory and innovative ideas on https://endo-theories.org. Lastly, we may all have to pay a closer look at clinical and personal life data of our patients over their entire disease trajectory to begin to characterize their phenome. Nonetheless, since "what we observe is not nature itself, but nature exposed to our method of questioning" (Werner Heisenberg), we still need new theories on the pathogenesis and pathophysiology of endometriosis, because extensive phenotyping or intensive phenotyping as suggested by Dr. Lee may be merely a starter.

1. Members of the Endometriosis Initiative Group

Jason Abbott (UNSW Sydney, Australia), Mauricio S Abrao (Universidade de Sao Paulo, Brazil), Moamar Al-Jefout, (United Arab Emirates University, UAE), Mohamed Bedaiwy, (The University of British Columbia, Vancouver, Canada), Giuseppe Benagiano, ("Sapienza" University of Rome, Italy), Katherine A. Burns, (University of Cincinnati College of Medicine, Ohio, U.S.A), Michel Canis, (CHU Clermont Ferrand, University Clermont Auvergne, France), Francisco Carmona (Universitat de Barcelona, Spain), Charles Chapron, (Université Paris-Cité, Faculté de Santé, Faculté de Médecine Paris-Centre, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Universitaire Paris Centre (HUPC), Centre Hospitalier Universitaire Cochin, Service de Gynécologie Obstétrique II et Médecine de la Reproduction, Paris, France), Hilary O. D. Critchley, (University of Edinburgh, UK), Dominique de Ziegler (Universite de Paris Ouest, France), Tommaso Falcone (Women's Health Institute, Cleaveland Clinic, Cleveland, Ohio, USA), Asgerally Fazleabas (Michigan State University, Grand Rapids, Michigan, USA), Simone Ferrero (University of Genova, Italy) Juan A. Garcia-Velasco, (Rey Juan Carlos University, Madrid, Spain), Caroline Gargett (Hudson Institute of Medical Research and Monash University, Melbourne, Australia), Erin Greaves (University of Warwick, Coventry, UK), Linda G. Griffith (Massachusetts Institute of Technology, USA), Sun-Wei Guo (Fudan University, Shanghai, China), Marwan Habiba (University of Leicester; Leicester Royal Infirmary, UK), Tasuku Harada (Tottori University Hospital, Tottori, Japan), Mary Louise Hull (Robinson Research Institute, University of Adelaide, Australia), Keith B Issacson (Newton-Wellesley Hospital, Newton, Massachusetts, USA), Neil P. Johnson (Flinders University, Adelaide, Australia), Yuval Kaufman (The Lady Davies Carmel Medical Center, Haifa, Israel), Khaleque N. Khan (Kyoto Prefectural University of Medicine, Japan), Mee-Ran Kim (The Catholic University of Korea, Seoul, Republic of Korea), Philippe A. Koninckx (University Hospital Gasthuisberg, Catholic University, Leuven, Belgium), Bruce A. Lessey (Atrium Health Wake Forest Baptist, Winston Salem, North Carolina, USA), Dan Martin (University of Tennessee Health Science Center, Memphis, USA), Sachiko Matsuzaki (CHU Clermont-Ferrand; Université Clermont Auvergne, France), Gita Mishra (University of Queensland, Brisbane, Australia), Yutaka Osuga (The University of Tokyo, Japan), Felice Petraglia (University of Florence, Careggi University Hospital, Italy), Alexander Popov (Moscow Regional Scientific Research Institute of Obstetrics and Gynecology, Russian Federation), Horace Roman (IFEMEndo, Clinique Tivoli-Ducos, Bordeaux, France), Andrea Romano (Maastricht University Medical Centre, Netherlands), Philippa Saunders (The University of Edinburgh, UK), Tamer Seckin (Lenox Hill Hospital, Northwell Health/Zucker School of Medicine, New York, USA), Edgardo Somigliana (Università degli Studi and Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy), Hugh S. Taylor (Yale School of Medicine, New Haven, Connecticut, USA), Paolo Vercellini (Università degli Studi and Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy), Paola Vigano (Infertility Unit, Fondazione IRCCS Ca' GrandaOspedale Maggiore Policlinico, Milan, Italy)

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Comment On: Patients' Use of Virtual Reality Technology for Pain Reduction During Outpatient Hysteroscopy: A Meta-Analysis of Randomized Controlled Trials

To the Editor:

Hysteroscopy is considered a valuable tool in the diagnosis and management of intrauterine pathology and can be performed on an outpatient basis or under general anesthesia. Virtual reality technology (VRT), a computer-controlled virtual environment experience, has been favored by many departments in recent years. However, few studies have focused on and evaluated the efficacy and safety of VRT in ambulatory hysteroscopy [1−3]. We read with great interest the recent article by Vitagliano et al in the Journal of Minimally Invasive Gynecology. The authors conducted a meta-analysis based on 5 randomized controlled trials to summarize the evidence on the efficacy of VRT in reducing pain during ambulatory hysteroscopy [4]. To further improve the quality and readability of the paper, we would like to make some comments to further improve this important study.

One of my main concerns is a possible gap in search strategies in the text. It should be recognized that an effective and adequate literature search is a prerequisite for conducting a high-quality meta-analysis. In the article, the authors mainly searched 3 databases and some registered websites. However, did the search based on only 3 databases cover most of the English literature? Importantly, I found that one of the eligible randomized controlled trials was not included in the paper [5]. Therefore, I suggest that other popular databases such as EMBASE, Scopus, Google Scholar, and Cochrane Library should also be searched extensively.

After reading the full text, I found that the authors did quite well in describing the methodology. However, I suggest that the authors should also add the following two points: (1) the authors should indicate the consistency of independent authors in literature search, quality assessment, data collection, and statistical analysis in the text; (2) the risk of publication bias should be presented in the form of figure.

Despite the heterogeneity of some of the outcomes in the paper, the authors performed a reasonable subgroup analysis based on the type of VRT. The subgroup analysis indicated that active VRT may reduce pain perception, but passive VRT had no effect, which may be the clearest and most plausible quantitative conclusion in this paper. In addition, the pain control of VRT in outpatient hysteroscopic maneuvers remains controversial due to the limitations of a small sample size and a high degree of heterogeneity. Overall, this study is an excellent preliminary study and lays the foundation for future prospective studies.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent

For this type of study, formal consent is not required.

Author Contributions

The author finished all the work for this article.

Yuan Fang*
Department of Obstetrics and Gynecology, The Central Hospital of Enshi Tujia and Miao Autonomous Prefecture, Enshi, Hubei, China
*Corresponding author: Yuan Fang, Department of Obstetrics and Gynecology, The Central Hospital of Enshi Tujia and Miao Autonomous Prefecture, 158 Wuyang Avenue, Enshi, Hubei, China.
E-mail: qpqpingaa@126.com

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