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Views and reviews

"I'm looking through you": What consumers and manufacturers need to know about non-invasive diagnostic tests for endometriosis☆

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1. The dawn of diagnostic revolution?

Laparoscopy has long been considered as the gold standard for diagnosing endometriosis; the diagnosis is made based on the visualization of pelvic implants and, in case of doubt, histology demonstrating the presence of endometrial glands and/or stroma [1]. Reluctance to recommend, perform, or accept a laparoscopy, due to the invasive nature and associated morbidity of the procedure, undoubtedly contributes to the well-documented diagnostic delay [2,3].

Following previous proposals [4–6], in 2022 the European Society for Human Reproduction and Embryology (ESHRE) finally recognized that laparoscopy is no longer necessary for the diagnosis of endometriosis and it is now only recommended for patients with negative imaging results and where empirical treatment is unsuccessful or inappropriate [7]. Thanks to the advent and spread of imaging technologies such as transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI), many endometriosis cases can be diagnosed with accuracy. TVUS in experienced hands, but also MRI in doubtful cases, can replace surgery as the gold standard for the diagnosis of ovarian endometrioma and deep endometriosis in the pelvis.

While this change in the diagnostic approach offers a non-invasive way to diagnose ovarian and infiltrating endometriosis, and further differentiate it from other disorders such as adenomyosis and uterine fibroids, the last 2–3 years have witnessed a surge in the development of

☆ "I'm looking through you": by Lennon J and McCartney P. In: Rubber Soul, Parlophone, UK, 1965.

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novel non-invasive biomarker-based tests for the detection of the disease using biological samples such as endometrial tissue, blood, menstrual or uterine fluids, saliva, or urine. Some scientific teams have already brought diagnostic tools to the market [8], promising to "improve the quality of life and the care of the patients" and claiming to be "a breakthrough for women's health" (https://ziwig.com/en/home/, accessed on May 21, 2023). Using some easily obtainable biological specimen, such as saliva, these tests promise to tell a woman, with claimed high accuracy, whether she has endometriosis, without any hassle to go to a clinic or hospital.

2. Hurdles for developing a clinically useful test

Although the development of sensitive and reliable diagnostic tools is always motivated by the idea that an early diagnosis is very important for early and more effective treatment [7], there is unavoidable and necessary testing and validation before a non-invasive test for endometriosis can be considered clinically useful [9]. Unfortunately, the development of biomarker-based diagnostic tests for endometriosis has a spotty history: without any exception, all biomarkers that were initially reported to be highly promising later ended in obscurity [10–12].

Aside from the usual requirements for a viable biomarker diagnostic test, such as sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios, specific additional requirements should be considered in the case of endometriosis:

- since symptoms and signs of endometriosis may overlap with other gynaecological diseases such as adenomyosis, uterine fibroids, pelvic inflammatory disease, and pelvic varices, the real focus also should be the differential diagnosis [13]. As such, the control group should not just merely be normal women without any disorders. Studies aimed at validating a biomarker should focus on a cohort of women with a similar baseline condition (chronic pelvic pain, infertility or even asymptomatic endometriosis) rather than comparing affected women with healthy controls. In contrast to previous studies mainly based on case-controls, only a few studies for biomarkers have managed to overcome the spectrum bias [14];
- endometriosis also co-exists with adenomyosis, uterine fibroids, or uterine polyps. As such, the test should take this into account [15–17]. The potential overlap with adenomyosis is arguably of greatest concern, for several reasons. Both endometriosis and adenomyosis are characterized by ectopic growth of tissue with hallmark features of endometrial epithelia and stroma, and thus are more likely than other conditions to share common biomarker features with endometriosis; methods to diagnose adenomyosis in the intact uterus are substantially less well-defined than those for diagnosing fibroids and polyps, thus clouding delineation of diagnostic accuracy against endometriosis alone; and, although the actual incidence of adenomyosis is still relatively unknown due to diagnostic limitations, estimated comorbidity with endometriosis is over 30% and in some populations well over 50% [18]. Adenomyosis is greatly underappreciated as a potential contributor to symptoms; hence, a diagnostic test that does not distinguish between endometriosis and adenomyosis may lead patients to an extremely frustrating clinical dead end when an evaluation for endometriosis turns out to be negative or there is no relief from removal of endometriosis found upon surgery, and the clinician does not carefully evaluate her for adenomyosis, convinced that her symptoms may be caused by endometriosis as the test suggested;
- several different subtypes of endometriosis are known (ovarian, peritoneal, and deep, as well as extrapelvic lesions), each with different clinical manifestations and severity. Due to these concerns and the vast variation in age and reproductive history, any study on biomarkers should ideally have a large sample size, covering most, if not all, the possible different combinations of demographic variables, disease subtype and stage, and symptomatology and severity [7]. The same would be true for the control group. Of relevance here, women with ovarian endometriomas or deep invasive lesions detected at ultrasound should be excluded because they are already diagnosed with the disease and the biomarker could not add significant clinical information in these situations;
- the test results, performed prior to the surgical removal of endometriotic lesions, should be different after radical removal of lesions, to make sure that the aberrations are truly due to the presence of lesions;
- aside from the reasonable test-retest consistency, and intra- and inter-individual consistency, the ideal test should be resistant to the "Hamburger effect", i.e. the test result is not affected by minor or idiosyncratic changes in mundane daily activity such as diet and sleep;
- ideally, the aberration as determined by the test should and can be biologically linked with the lesion aberrations. The test would also limn which therapies are likely to be effective–and which are not, if all possible.

These aspects are highly critical since failure to respect these requirements are likely to result in continued misdiagnosis, overdiagnosis and/or inaccuracies.

3. Caveat emptor

Unlike other consumer products/services, a diagnostic test for endometriosis could tell a woman whether she has endometriosis or not, with certain probability, and, as such, entails some benefits but also some apparent as well as unquantified or unknown risks.

Consequently, women who are contemplating to use such a test need to understand that:

- if the test has a high accuracy for diagnosing endometriosis in women who are symptomatic, it has some utility and may also prompt those who are tested positive to seek medical attention early, thus shortening the diagnostic delay;
- adverse effects can occur if diagnostic tests, validated in tertiary care, are inappropriately used for screening in general populations [19,20]. In some situations, a diagnostic test may do more harm than good. The availability of a simple – but not necessarily inexpensive – test able to detect endometriosis is expected to drive high demand [9]. The awareness that endometriosis can affect fertility and the interest of women to obtain information on their fertility status could also boost its use. In those without symptoms or signs, such as infertility, or those with occult and silent endometriosis, there would be no indication to perform diagnostic testing for endometriosis. As of now, the utility of such a test is unclear – would a positive result change the clinical management strategy when pain symptoms are absent, or infertility is not an issue [21]? Any screening test is expected to increase the number of women who are diagnosed with the disease with a consequent rise in disease prevalence and a dramatic increase of psychological burden, and, as such, likely an elevation, perhaps unnecessarily, of women's anxiety. Overdiagnosis is common when introducing a novel diagnostic test, but overdiagnosis leads to overtreatment that provides, by definition, no benefit at all but that can actually cause harm and incur unnecessary expenses [22]. An example of overdiagnosis is an asymptomatic person who would never suffer from this abnormality nor will ever need to be treated for the detected anomaly. However, importantly, once an abnormality, even if a perceived one, is identified, it would be almost impossible, and likely unethical as well, not to investigate further and not to treat the patient. Indeed, our understanding of the natural history of the disease is not well enough defined to distinguish cases, which would become symptomatic vs. those that would never need treatment;
- they may confront uncertainties. The clinical significance of early or occult endometriosis is uncertain at this moment, especially when there is no symptom. Evidence consistently demonstrated that, without treatment, peritoneal implants regress or remain stable in more than

70% of women, especially when asymptomatic, or when lesions are microscopic [21]In this context, thresholds and limits can create artificial categories that are misleading if they are mistaken as boundaries between having and not having a disease [23]. On the other hand, many tests are likely to be developed without including in the studies a group of "patients" with microscopic or occult endometriosis or having no symptom at all;
- a shadow of uncertainty always exists around every test result due to statistical variation. Results can be falsely positive, or falsely negative, or truly inconclusive. The women should know what the management options are if the result turns out to be positive, inconclusive, or negative. Patients should also understand what support can be offered if the result will be disconcerting or distressing [24].

4. Setting up the ground rules

On April 5, 2017, the European Parliament issued a new Regulation (EU) 2017/746 on diagnostic medical devices. The Regulation aims to set high standards of quality and safety for *in vitro* diagnostic medical devices by ensuring the reliability of the data generated in performance studies and the safety of subjects participating in those studies. As a general rule, devices should bear the Conformité Européenne (CE) marking to indicate their conformity with the Regulation [25]. However, this CE mark does not assure, endorse, or reflect in any way the clinical performance of a test.

The development of an *in vitro* diagnostic test from a good idea to a clinically relevant tool takes several steps, not just the conformity to the Regulation (EU) 2017/746. The manufacturer should establish a performance assessment plan in order to demonstrate (i) scientific validity, (ii) analytical performance and (iii) clinical validity and utility [24]. The ability of distinguishing patients with the target condition from patients without the target condition is only the first requirement of a diagnostic test. The technical validity addresses several aspects including the repeatability and reproducibility of the laboratory tests, analytical sensitivity and specificity, limits of detection and quantitation, determination of appropriate criteria for specimen collection and handling, and assessment of known relevant endogenous and exogenous interference and cross-reactions.

Even more important is the clinical performance. In this context, useful tools can be considered based on some observations:

- the determination of who should be tested in real life is important to establish. The patients' referral route, the healthcare setting in which they are tested and the management steps to which they will be subjected after a negative or a positive test result are crucial information. Test accuracy, including sensitivity and specificity, may vary across settings and populations. Therefore, for a correct interpretation of the study results and conclusions, the Standards for Reporting Diagnostic Accuracy (STARD) document was developed. Its guiding principle is based on a minimum list of essential items that should be included in every study report in order to improve the quality of reporting of diagnostic accuracy studies [26];
- in the case where the gold standard test cannot be applied to all participants in the study because it is invasive (i.e. laparoscopic intervention), evaluating the new test using data only from participants whose disease status is confirmed with a standard could produce verification bias. The bias would be in favour of those who are willing or require to undergo laparoscopy, due, possibly, to the severity of the disease or the urgency to seek medical attention. In this context, there are methods to be employed when only a sub-sample of the participants have their disease status verified with the gold standard [27];
- the ultimate study design aimed to assess the effect of a test on patients' health and welfare is the randomized controlled trial [26]. In this trial, one group of women will undergo the test of interest and will be further managed according to the test results, while the other group will be managed based on clinical signs and symptoms or the imaging findings.

5. Collingridge's dilemma and the responsible innovation

Many technological innovations face a well-known Collingridge's dilemma: "attempting to control a technology is difficult . . . because during its early stages, when it can be controlled, not enough can be known about its harmful social consequences to warrant controlling its development; but by the time these consequences are apparent, control has become costly and slow" [28]. In light of well-documented diagnostic delay in endometriosis [2,3], a reliable and accurate diagnostic test should minimize or even eliminate this delay, sparing women from years of unnecessary pains and suffering. However, when the test is used above and beyond its inventor's intention, its abuse, overuse, or misuse can cause havoc: a false sense of being disease-free or attributing symptoms to the wrong disease, unnecessary worries over a false positive test result with ensuing cost for unjustified treatment, denied for employment due to the condition, ruined relationship due to perceived infertility, etc. Of course, there is an urgent need for non-invasive diagnostic test for endometriosis; however, given the wide availability and acceptable accuracy in imaging diagnosis of endometrioma and deep endometriosis, and in view of the current limited and often much to be desired treatment modalities, extreme care should be exercised. Ideally, it "should be offered only when the benefits are firmly documented and considered to outweigh the harms, which should be equally well quantified" [29].

6. Mind the gaps!

As high-throughput screening and sequencing become increasingly faster and affordable, it is anticipated that there will be a swell of commercial non-invasive diagnostic tests in the coming years to fill the void. Yet, considerable knowledge gaps still exist. Considering that ovarian and infiltrating endometriotic lesions can be detected by TVUS or MRI, the only endometriosis subtype that cannot be identified with imaging techniques and would be diagnosed by using a non-invasive diagnostic test are peritoneal implants not associated with pelvic adhesions. However, the following issues must be eventually addressed before implementing these tests in everyday practice:

- no definitive data exists that characterize the histological trajectory of superficial lesions. In other words, when limited peritoneal implants do not cause symptoms and if they are not inevitably progressive, their clinical significance or impact is unclear. It cannot be excluded that, in some women, temporary presence of ectopic endometrium due to transtubal menstrual reflux may well constitute a para-physiologic condition. If this is true, detecting a non-disease has no prognostic value;
- when limited peritoneal implants cause pain symptoms, endometriosis must be promptly suspected and clinically diagnosed regardless of imaging findings and, most importantly, non-invasive diagnostic testing. History taking and correct performance of physical examination, combined with sufficient awareness of the probable presence of the disease, can and should be more than enough to clinically diagnose peritoneal endometriosis anyway. The issue here is not the search for an additional test, but rather the application of the principles of medical semeiotics and good clinical practice;
- when limited peritoneal implants do not cause pain symptoms but are associated with otherwise unexplained infertility, the overall benefit of using a non-invasive diagnostic test is unclear as of now, because management of the condition may not necessarily vary based on the result of the test. Once limited endometriosis is diagnosed, clinicians know that implant destruction at laparoscopy is associated with a marginal improvement of pregnancy rates. When infertility is otherwise unexplained, IVF generally performs better than surgery, regardless of the presence of early-stage endometriosis;
- as previously mentioned, the shift from the use of non-invasive testing for diagnostic purposes (i.e., use in symptomatic women) to screening purposes (i.e., use in asymptomatic women) is more than possible, it is

almost certain. This poses several ethical issues, because it is completely unknown whether the prognosis of asymptomatic women with superficial peritoneal implants would improve based on the detection of such early lesions that are not currently causing problems. Would endometriosis progression be prevented? If so, how? Would reproductive potential be safeguarded? Would pain symptoms be avoided? These are the outcomes that matter to consumers of the test but, unfortunately, no answers to these questions exist;

- financial and non-financial conflicts of interest of multiple stakeholders are bound to converge to push using non-invasive tests for screening beyond the diagnostic purposes as initially intended. Not only test manufacturers and their dealers, but also pharmaceutical industries producing costly GnRH antagonists or other novel drugs, manufacturers of surgical devices, administrators of private health services, and gynecologists practicing self-referral, may share the interest in expanding the boundaries of the "sick" population. Except for public health systems and the society at large, treating the healthy pays off much more profitably than treating the sick. Yet treating the healthy without clear benefit could be viewed as ethically dubious;
- the unavoidable implementation of non-invasive testing as a screening tool in asymptomatic population implies definite harms at individual and community levels. It raises many questions begging for answer. In addition to financial costs associated with the test *per se*, how could the psychological cost of diagnostic labelling be quantified? Much has been published on the emotional, relational, social, and professional consequences of a diagnosis of endometriosis. Are we willing to render innumerable women vulnerable without demonstration of definitive benefits? Moreover, who will pay for treatments that inevitably will be prescribed following a positive test? How many laparoscopies would be requested or suggested to treat the identified condition? Any medical intervention implies opportunity costs. Given that healthcare resources are finite, consuming part of those limited available resources for non-quantifiable benefits in asymptomatic women with superficial peritoneal implants means that other women with advanced, symptomatic endometriosis or patients with other severe diseases may receive less money and thus suboptimal care. Screenings need to be based on extremely robust epidemiological, comparative clinical effectiveness, cost effectiveness, and health technology assessment evidence [19,20], which is completely lacking at this time. As an example, the lesson of screening annually asymptomatic women for ovarian cancer using US and serum CA125 levels demonstrates how a medical intervention implemented at a population level with the best of intention could resulted in overtreatment with much less than expected benefits on disease-specific mortality [30]. Similar results were observed when screening men at average risk for prostate cancer using serum prostate-specific antigen levels [31,32];
- gynecologists, and all physicians, are responsible for patients' overall well-being and the community at large, and we must never abdicate the principles of proper professional conduct. This also implies that requesting a test means that we know precisely what to do in case of a positive result. Moreover, we should be able to quantify the potential benefits and risks of detecting an otherwise unidentifiable condition. Only when these circumstances are satisfied, we could provide useful counseling that may empower women to take informed decisions regarding their health based on their priorities. If this is not the case, we should strictly adhere to the sacred Hippocratic oath: "*primum non nocere*" (first, do no harm).

7. Proceed with caution

Given the issues and concerns raised above, we call upon all stakeholders of non-invasive diagnostic tests to exercise caution. In particular, we remind those test-developing companies that those that are socially responsible and held the highest quality standard are most likely to have the most benefit and commercial success in the long run.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to this work and approved it for publication.

Disclosure of interest

P.Ve. has received royalties from Wolters Kluwer for chapters on endometriosis management in the clinical decision support resource UpToDate and maintains both a public and private gynaecological practice. E.S. has a relationship with Théramex, Merck Serono and Ferring that includes funding grants. E.S. is the Editor-in-Chief of Human Reproduction Open. S.-W.G. is a member of the Scientific Advisory Board of Heranova BioSciences and has provided consultancy advice to the company, as well as to Sound Bioventures and BioGeneration, but these activities had no bearing on this work. Both P.Vi and S-W.G. are co-Editors-in-Chief of the JEUD. H.S.T. is past president of the ASRM and his university has received funding from AbbVie to support his research. F.C. declares some consultant activities for Medtronic, Myovant, Organon but these activities had no bearing on this work. C.C., F.P., L.G.G., M.D.M., D. C.M., A.N., A.R., F.R., K.A.B., P.S., M.C. and P.R.K. declare that they have no competing interest.

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