Accurate, actionable results the first time:
ERPeak℠, the advanced endometrial receptivity test you can trust

Highlights

- **Actionable results for patients and clinicians the first time**
- **~5x lower "no result" rates** compared to other test providers[1]
- Innovative approach **proactively corrects for sample variability** in endometrial biopsy
- **96% accuracy** with high classification precision for all ERPeak test samples[2]

Background

Up to 30% of infertile patients undergoing IVF may have a displaced window of implantation (WOI)[3], the short period in the monthly menstrual cycle during which an embryo is likely to implant. **The CooperSurgical ERPeak test is a molecular test used to assess the receptive state of the endometrium and define the optimal time for embryo transfer.** The test leverages unique gene expression patterns and artificial intelligence (AI) to predict the trajectory of a patient's receptivity, empowering patients and physicians with valuable information to complement embryo data. Since its launch, **the ERPeak test has been offered by 150+ clinics globally and used by thousands of patients.**

While highly accurate and robust, we saw opportunities to further improve endometrial receptivity testing. We are excited to report data demonstrating the accuracy and precision of the ERPeak test, which we hope provides greater confidence in endometrial receptivity testing and precision embryo transfer.

Optimization of ERPeak test gene panel and model

Two critical components of the ERPeak test are the gene markers and molecular signatures used to define endometrial receptivity, and AI used to classify samples.

The ERPeak test's target gene panel includes significant advancements in our understanding of the molecular pathways that drive receptivity. This reflects a better appreciation of the gene expression changes associated with specific cell types. Target genes were selected to gather information from multiple molecular pathways that converge to influence overall receptivity including proliferation, decidualization and immune response. **The relative influence of each individual gene is now more broadly distributed over the entire panel.** This enhances informative molecular signatures and allows a greater number of target genes to determine sample classification. In addition to considering new gene targets, a larger training set of 250 endometrial samples was used to finalize parameters in our machine-learning model. More training samples were included to account for the greater variability observed in clinical samples making the model a more robust predictor of receptivity.

Cross-validation confirmed improved classification accuracy, precision, and AI learning – important measures of model performance. The ERPeak test was then evaluated against a clinically accepted test from a different provider. A group of 75 independent samples was tested using both tests and the results compared (Table 1). **The ERPeak test showed a high accuracy (concordance) of 96%, 91% specificity and sensitivity of 100%.**

Table 1: Comparison of ERPeak test performance against an alternative clinically accepted test[2]

Summary: The ERPeak test gave highly accurate results in 72 of 75 (96%) samples

		Endometrial receptivity test result from other test provider			
		Pre-receptive	Receptive	Post-receptive	Non-receptive/Proliferative
ERPeak test result	Pre-receptive	29	3		
	Receptive		29		
	Post-receptive			7	
	Non-receptive				7

An important difference between the ERPeak test performance and other ER tests is observed with poor quality or difficult to classify samples. Testing challenges can also arise due to minimal biopsy volume that yields low signal for gene targets or samples with unique composition that create unexpected molecular signatures. **These samples often generate "Non-informative" or "No results" and the patient and physician are left with unactionable answers.** Six such samples from other test providers gave no results or were non-informative. These samples were evaluated with the ERPeak test. **Overall, the ERPeak test yielded usable data in all cases.**

Table 2: ERPeak test results with samples classified as "no results" with an alternative clinically accepted test[2]

Summary: The ERPeak test was able to give actionable answers for all six samples, which were unactionable with clinically accepted test.

		Endometrial receptivity test "no result" from other test provider		
		Insufficient RNA	Invalid RNA	Non-Informative
ERPeak test result	Pre-receptive	2	-	-
	Receptive	1	1	1
	Post-receptive	-	1	-

Improving accuracy and precision by reducing the impact of endometrial tissue biopsy variability

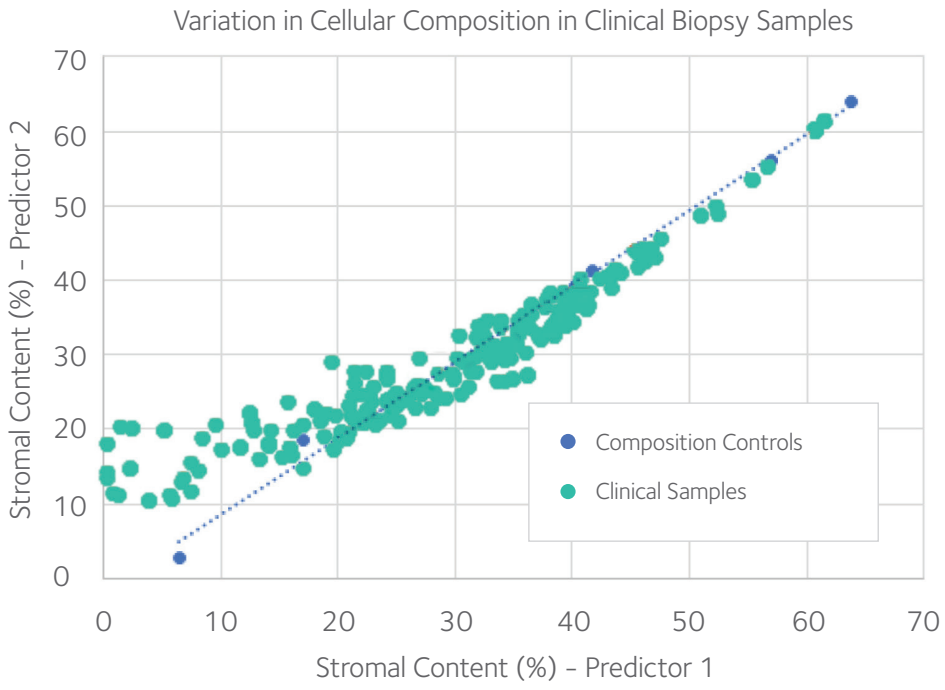
The endometrium is a dynamic tissue made up of numerous cell types. **Two principal cellular components, stromal and epithelial cells, make up approximately 95% of the endometrium – though exact proportions can vary significantly.** Importantly, epithelial and stromal cells respond differently to hormonal changes and show unique molecular signalling patterns during the window of implantation. These cell types work in concert to create an environment conducive to implantation.

Endometrial biopsy is typically performed blind and variation in biopsy collection directly impacts the cellular composition obtained from the biopsy. Samples received in the CooperGenomics laboratory indicate significant variation with stromal levels between 20 and 60% (Figure 1)[2].

It is clear the ability to account for variation in cellular composition and assign gene expression to the correct cellular type greatly impacts the accuracy of an endometrial receptivity test.

Figure 1: Cellular variability in endometrial biopsy samples[2]

Summary: Samples recieved in CooperGenomics laboratories showed significant variation in stromal cell composition between 20-60%



The ERPeak test employs a unique normalization approach (AI) to proactively correct the impact of sample variation by correlating molecular signatures with cell-type contribution. The test enables analysis of small but clinically meaningful changes in gene expression – that occur in a fraction of cells – to be considered when estimating receptivity status, improving overall accuracy and precision.

This approach makes the CooperSurgical ERPeak test unique in two ways. Firstly, it ensures an accurate receptivity classification regardless of biopsy composition. Robust accuracy prediction was assessed using paired tissue sections from 35 biopsies. Of these, 34/35 (96%) samples showed concordant test results between the paired biopsy sections (Table 3).

Table 3: Reproducibility of the ERPeak test[2]

Summary: 34 out of 35 (96%) biopsies showed reproducible results between paired tissue sections

		Biopsy section #1			
		Pre-receptive	Receptive	Post-receptive	Non-receptive/Proliferative
Biopsy section #2	Pre-receptive	16			
	Receptive		15		
	Post-receptive			3	
	Non-receptive		1		0

In a larger subset of clinical samples with two biopsy sections tested, improved concordance (84% vs 91%) and increased sample precision (+9%) were observed with the ERPeak test.

Secondly, by accounting for sample variation we were able to achieve better distinction between each ERPeak classification signature. This translates to greater precision and confidence in the classification. In a subset of 114 samples – we observed an average 4.4% increase in same-class precision (Table 4).

Table 4: High classification precision with the ERPeak test[2]

Summary: All samples returned high classification precision

	Average ERPeak test result classification precision
Pre-receptive	0.95
Receptive	0.90
Post-receptive	0.99

High confidence is further shown when challenging samples are reclassified using the ERPeak test and still give an actionable result. In a subset of 48 challenging samples, classification confidence improved by nearly 50% after reclassification (Table 5). Higher confidence scores indicate that these samples are more closely aligned with the new normalized receptivity signatures and called more accurately.

Table 5: Classification precision for challenging samples with the ERPeak test[2]

Summary: High classification precision is given with even the most challenging of samples using ERPeak test

	Average ERPeak test result classification precision
Pre-receptive	0.97
Receptive	0.92
Post-receptive	0.97

Finally, **the test virtually eliminates non-informative and non actionable results** that arise from low-confidence and challenging expression signatures. Across more than 2000 samples analyzed using the improved AI algorithm – fewer than 3 samples have been reported without a classification. A group of 19 samples previously reported as non-informative were reclassified using the new test (Table 6).

Table 6: Elimination of non-informative and non-actionable samples using the ERPeak test[2]

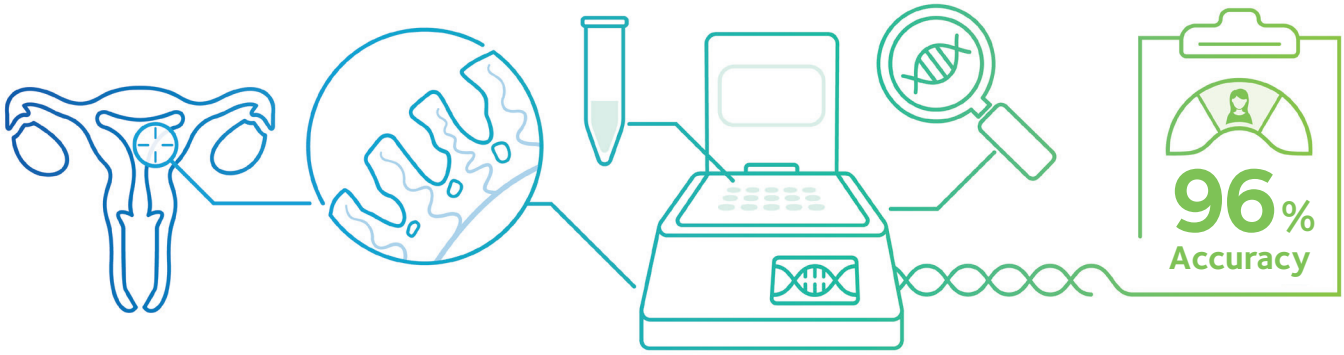
Summary: All 19 samples were reclassified to give an actionable result with the ERPeak test

	Test result with ERPeak test				
	Pre-Receptive	Receptive	Post-Receptive	Non-Receptive	Non-Informative
Number of Samples	3	11	1	4	0

Discussion & Summary

The CooperSurgical ERPeak test includes a regularly updated gene panel and proprietary data analytic approach. This approach proactively corrects for tissue variability by assigning gene expression to the correct cell type, enabling test reproducibility and low "no result" rates. These combined unique features provide the ERPeak test a 96% accuracy.

The ERPeak test also enables improved confidence in all results; providing a test result even with challenging samples, including samples that may have previously been unable to provide a result. This means, it is likely we provide accurate and actionable results the first time. The clinical impact is that embryo transfers are not delayed by the need to re-biopsy or retest samples. For patients, this greatly reduces the additional time and inconvenience of further endometrial receptivity testing, giving you an endometrial receptivity test you can trust.



The CooperSurgical ERPeak test predicts the optimal time for embryo transfer

Our AI proactively corrects for sample variability

We provide accurate and actionable results the first time

References

1. www.igenomix.com/our-services/era/#era-faqs-title, accessed 17/05/21
2. Internal CSI data
3. Katzorke N. et al., Geburtshilfe Frauenheilkd. 2016; 76:699–703

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