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From Clinical Development to Reimbursement: Real-World Evidence Is the Missing Link for In Vitro Diagnostics – A Conceptual Framework

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IDV EVIDENCE CONTINUUM : Performance | Decision Impact | Pathway Transformation | Patient Outcomes | Economic Value

01 PROBLEM

A structural evidence gap separates IVD clinical validation from reimbursement. Regulatory clearance (IVDR) establishes whether a test accurately measures an analyte. Conversely, Health Technology Assessment (HTA) asks: what actually happens when the test is integrated into routine care?

A test may display near-perfect diagnostic sensitivity/specificity, receive CE marking, and yet fail reimbursement due to unproven clinical utility, unknown decision impact, and unquantified organizational consequences.

02 OBJECTIVE

To conceptualize the evidence discontinuity between pre-market development and HTA reimbursement, defining how **Real-World Evidence (RWE)** bridges this chasm.

- Regulatory & HTA Mapping: Comparative analysis across EU IVDR 2017/746, EU HTAR 2021/2282, and national frameworks (HAS, NICE, G-BA).
- Cross-Disciplinary Benchmarks: Historical review of 3 benchmark molecular IVDs in women's oncology and prenatal screening.
- Live Empirical Case: Step-by-step evidence lifecycle of Endotest® (saliva miRNA diagnostic for endometriosis).

03 RATIONALE — IVDs RESHAPE CARE PATHWAYS

TEST → RESULT → DECISION → PATHWAY → OUTCOMES

- **Avoided Invasive procedures:** laparoscopy, biopsy, amniocentesis.
- **Changed Investigations:** less repeat imaging and lab testing
- **Changed therapeutic decisions:** avoid or select treatment
- **Shorter diagnostic journey:** fewer consultations and work-ups
- **Organisational effects:** released OR, imaging, specialist capacity
- **Societal effects:** less delay, absenteeism, productivity loss

The value of an IVD is often structural rather than transactional: accuracy says whether patients are classified correctly, not whether anyone acts on the result.

Figure 1. Three stages, three questions, two gaps.

CLINICAL DEVELOPMENT
Does the test perform as intended?
- Scientific validity
- Analytical performance
- Clinical performance
- Se - Sp - PPV - NPV - LR+/LR-

EVIDENCE GAP

CLINICAL UTILITY / RWE
What does the test change?
- Scientific validity
- Analytical performance
- Clinical performance
- Se - Sp - PPV - NPV - LR+/LR-

VALUE GAP

HTA & REIMBURSEMENT
Is the change worth paying for?
- Scientific validity
- Analytical performance
- Clinical performance
- Se - Sp - PPV - NPV - LR+/LR-

The three stages answer different questions and require different evidence; the frameworks that govern them do not naturally connect.

04 Rationale - three evidence regimes, three different questions

	STEP 1 -CE MARKING	STEP 2 -EU JCA	STEP 3 -NATIONAL HTA
Framework	EU IVDR 2017/746 [1]	EU HTAR 2021/2282 [2,3,15,16]	HAS · NICE · G-BA/IQWiG
Central question	Does the test perform as intended?	Relative clinical effects vs. comparator?	Does use of the test create enough value to reimburse?
Evidence focus	Scientific validity + analytical + clinical performance	Comparative clinical evidence addressing the EU PICO(s)	Clinical utility + economic + organisational evidence
Comparator	Reference method / clinical refere...	PICO comparator(s)	National standard of care
Economic assessment	No	No	Country-specific
Organisational impact	Not a pre-market requirement	Not a core JCA output	Increasingly relevant
Role of RWE	Complementary / post-market	Potential supportive role	**Increasing, notably under conditional access**

Each stage adds new evidence questions; it is not simply a stricter version of the preceding stage.

STEP 1 — IVDR: PERFORMANCE

1: Scientific validity: analyte linked to the clinical condition.

2: Analytical performance: precision, accuracy, limits of detection.

3: Clinical performance: clinical Se/Sp, predictive values, LR.

No systematic pre-market requirement for decision impact, pathway change, or organisational value.

Clinical performance ≠ clinical utility

STEP 2 — EU CA: HARMONISED

Mandatory EU JCA scope:
Selected class D IVDs. Class B/C not subject to mandatory JCA under Art. 7.

Does: comparative clinical assessment (PICO).

Does not: economic evaluation, price or reimbursement, organisational impact.

Less duplication, same need for national evidence on value in use.

STEP 3 — NATIONAL HTA

Three ways to manage uncertainty

FRANCE	UK (NICE)	GERMANY
HAS / Cediag	**HealthTech [10]**	**InEK / G-BA**
Linked evidence: Perf → Decision	Cost-effectiveness & NHS pathway	High bar for formal methods
Innovation Package*	**Early Use:**	**NUB / Hospital:**
Temporary access	Evidence Generation	Funding → DRG

Access with evidence generation is spreading, mechanisms are neither harmonised nor equivalent.

05 DEMONSTRATION — Three Molecular IVD Precedents

NIPT
Replaces invasive procedures

Transition:
Performance → pathway positioning → fewer invasive procedures

Value:
Avoided amniocentesis / CVS [11]

Primary HPV testing
Replaces screening test

Transition:
Performance → programme implement. → organisational outcomes

Value:
Screening effectiveness & resource use [12]

21-gene RS
Avoids costly downstream

Transition:
Prognostic validity → chemioterapy decision → real world confirm.

Value:
Chemo safely avoided (breast cancer) [13]

	NIPT	HPV	21-gene RS	Endometriosis test
Main act affected	Amniocentesis / CVS	Cytology, scr eening strategy	Adjuvant chemotherapy	**Diagnostic laparoscopy and pathway**
Performance established	✓	✓	✓	✓
Decision / pathway evidence required	✓	✓	✓	✓
Organisational consequences	Relevant	Central	Moderate	**Central: diagnostic delay + surgical capacity**

Across very different IVDs, reimbursement evidence emerges only after linking test performance to a consequential change in clinical management.

06 DISCUSSION

Four Structural Gaps

1. Population gap
Validation populations differ from values intended-use cohorts; predictive depend on prevalence.

2. Outcome gap
Accuracy does not establish utility: a if correct result creates value only it changes management.

3. Organisational gap
Avoided procedures, released capacity, in referrals and waiting times are rarely measured development.

4. Access gap
Fragmented national HTA requirements new generate evidence needs after regulatory validation.

These gaps are not failures of clinical validation: regulatory approval and HTA answer different questions.

07 ILLUSTRATIVE CASE

Figure 2. Ziwig Endotest® evidence lifecycle: from performance to value in use

PHASE A –DOES THE TEST WORK? SCIENTIFIC & CLINICAL DEVELOPMENT

1 — Biological rationale
miRNAs:stable, measurable in biofluids. Salivary signatures heterogeneous; Saliva is non-invasive & scalable. Small-RNA NGS + ML [4].
Scientific plausibility

2 — Discovery & model
ENDO-miRNA,n=200. 2,561 miRNAs →Random Forest →109-miRNA signature [4]. **Se 96.7%·Sp 100% AUC 0.98 (internal cross-validation)**
Proof of concept, internal performance

3 — External validation
Prospective multicentre,n=200 [5].
Se 96.2%·Sp 95.1%
AUC 0.96
External validity & reproducibility

4 — Full multicentre
n=971 [6].Misclassif. 4.6%vs 27.2% imaging (surgery confirmation).
Se 97.3%·Sp 94.1% PPV 98.2%·NPV 91.3%
Robust multicentre performance

HTA BREAKPOINT
HAS (Dec 2023):perf.(Se 0.95,Sp 0.94) & innovation recognised ; no direct management impact evidence on patient. Before/after change-in-management study requested [7].
Forfait Innovation: favourable opinion (18 Oct 2024)[8].
Not "is it accurate?" but "does it change what clinicians and patients do ?"

PHASE B –WHAT DOES THE TEST CHANGE ?

5 — ENDOBEST -RWE by design [9]: NCT06794424, n=2,503. Women 18–43, chronic pain, uncertain imaging. **Primary:** change in management decision; reduction in laparoscopies.
Clinical utility, practice change, patient experience

ENDOBEST DESIGN: DECISIONS RECORDED BEFORE AND AFTER THE TEST RESULT

Baseline clinical + imaging assessment → Management decision before test → **Ziwig Endotest®** → Management decision after results (Practitioner, MDT) → Shared clinician-patient decision → Actual management, 6 month follow-up

What is validated a teach iteration —successive evidence layers are complementary, not interchangeable

Scientific validity | Analytical perf. | Internal perf. | External validity | Reproduc -ibility | CE perf evidence | **VALUE GAP** | Decision impact | Pathway change | Patient experience | Clinician adoption

08 CONCLUSIONS

- Evidence requirements for IVDs evolve across the lifecycle: IVDR performance evidence is essential but does not answer HTA questions.
- NIPT, HPV testing and the 21-gene score show the same transition: from "the test performs" to "the test changes decisions, pathways and resource use".
- Endotest® illustrates it today: four studies established performance; the HTA gap was not closed by another accuracy study but by a different design, ENDOBEST study.

RWE should be planned prospectively within the IVD evidence strategy: not as a substitute for clinical validation, and not only as a response to an unfavourable HTA decision.

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*forfait innovation