Research Square

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# Honest Denominators: Post-ICSI Oocyte Degeneration Masks Conventional Laboratory KPIs, and Degeneration-Penalized and MII-Anchored Indices Reveal the True Outcome

**Emrah Onder**
Istanbul University
**Ibrahim Orcun Olcay**
Bahçeci Sağlık Grubu
**Tuba Duzcu**
Medipol University
**Mustafa Bahceci**
Bahçeci Sağlık Grubu
**Aydin Arici**
Yale University
**Ozcan Duzcu**
GOP IVF
**Murat Basar**
murat.basar@yale.edu

Yale University

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## Abstract

# Purpose.

Conventional IVF laboratory key performance indicators (KPIs) are reported as single (“sole”) ratios in which the denominator excludes mature oocytes lost to the procedure. We tested whether the blastocyst utilization rate overstates true performance by masking post-ICSI oocyte degeneration, and we developed two complementary corrections that put degeneration back into the denominator.

# Methods.

Retrospective analysis of a single pooled ICSI cohort of 7,216 cycles and 56,349 MII oocytes. Against the conventional blastocyst utilization rate (BUR = Frozen/2PN), we defined: a Degeneration-Penalized BUR (DP-BUR) that adds the degenerated oocytes back to the denominator — additive, Frozen/(2PN + ATR), and multiplicative, (Frozen/2PN) × (1 − ATR/MII) — and a True BUR (TBUR = Frozen/MII) anchored to all mature oocytes. Degeneration was stratified at < 5% versus ≥ 5%. We assessed each metric against a competence benchmark of 40% (blastocysts utilization rate) and quantified operator-level misclassification (operators anonymized).

# Results.

Conventional BUR was 41.9; DP-BUR was 40.2 (additive) and 40.5 (multiplicative); TBUR was 32.8 — bracketing the correction, with DP-BUR attributing the gap to degeneration alone (+ 4% over the true value) and TBUR to all mature-oocyte attrition (+ 28%). The corrections were degeneration-dependent and, for DP-BUR, degeneration-specific: from < 5% to ≥ 5% degeneration, DP-BUR fell from 54.4% to 42.7% while conventional BUR barely moved (54.6%→52.0%), so DP-BUR is essentially flat where degeneration is low and drops only where it is high; TBUR fell 46.1%→38.4%. Against a benchmark of 40%, conventional BUR passed 24 of 38 operators, DP-BUR passed 17 (7 flipped from pass to fail), and TBUR passed 7 (17 flipped). Two cycles with identical mature-oocyte and fertilization counts but different degeneration are scored identically by both conventional BUR and TBUR, and are separated only by DP-BUR.

# Conclusions.

Conventional blastocyst utilization overstates true performance in proportion to the degeneration it hides. A degeneration-penalized denominator (DP-BUR) isolates operator-induced oocyte damage, while an MII-anchored denominator (TBUR) reports true yield from biological starting material; both pass operators and laboratories that an honest accounting would fail.

# 1. Introduction

The In Vitro Fertilization (IVF) laboratory is increasingly judged by KPIs. Professional bodies publish competence and benchmark values for fertilization, blastocyst development, and cryopreservation [1, 2, 11, 12], and laboratories track these numbers to demonstrate quality and benchmark against peers [3, 9]. The implicit promise of a KPI is that a higher number means a better laboratory. Robust performance measurement underpins laboratory quality management, staffing, and leadership decisions [11, 12, 13, 14, 15, 16, 17, 18], and a growing literature applies statistical and machine-learning methods to these indicators [3, 7, 8].

For the blastocyst utilization rate — one of the most consequential sole KPIs — that promise is not kept. The problem is not the numerator but the denominator.

In intracytoplasmic sperm injection (ICSI), a cohort of mature (MII) oocytes is denuded and injected with sperm. Some oocytes lyse or degenerate as a direct consequence of the procedure and are recorded as post-ICSI atretic/degenerated oocytes (ATR); reported ICSI damage rates range from roughly 2–15% (median ~ 5%) [1, 6]. Blastocyst utilization is conventionally reported per 2PN zygote (BUR = Frozen/2PN) [3, 7], and because 2PN already excludes every oocyte lost to degeneration, BUR begins its accounting after the damage has been discarded. Degeneration is therefore structurally invisible to conventional BUR.

Notably, expressing fertilization itself per mature oocyte (DPFR = 2PN/MII) already absorbs degeneration acceptably, because a degenerated oocyte is simply an MII that failed to reach 2PN, and the 70–80% fertilization expectation for a competent operator presumes near-complete oocyte survival. The fertilization rate is not the problem. The correction belongs at blastocyst utilization, where the denominator has erased the damage.

We therefore develop two complementary corrections that return degeneration to the denominator — a degeneration-penalized BUR that adds the degenerated oocytes back as a penalty, and an MII-anchored TBUR that expresses yield per mature oocyte retrieved [4] — and ask: how much does conventional BUR overstate the corrected values; does the overstatement scale with degeneration; and does the correction change the performance verdict [2, 5, 19].

# 2. Materials and Methods

# 2.1 Cohort

Retrospective analysis of one pooled ICSI cohort: 7,216 cycles and 56,349 MII oocytes (44,062 2PN; 18,456 cryopreserved usable blastocysts), analyzed as a single population. A two-setting comparison (a high-workload and a lower-workload contributing center) is provided only as a closing robustness table (Table 3).

# 2.2 Variables, cleaning, and counts

Cycles required recorded MII, 2PN, and cryopreservation counts; logical-consistency filters excluded records with 2PN > MII or Frozen > 2PN. For per-cycle rate analyses, MII ≥ 4 was required. The yield numerator was the cryopreserved (usable) embryo count.

## 2.3 Degeneration

Post-ICSI degeneration (ATR/MII), recognized as a core laboratory KPI [1, 9], was directly measured in the subset of cycles for which atresia was recorded; in the remaining cycles, per-operator degeneration was modeled within the documented institutional range of 1–5% (per-cycle Binomial (MII, rate), fixed seed). **All degeneration-stratified inferences use only cycles with directly measured degeneration;** modeled values were never substituted into a stratified comparison. Strata: <5% (low) and ≥ 5% (high).

## 2.4 Conventional and corrected KPIs

| Metric | Formula | Interpretation |
|---|---|---|
| DPFR (true fertilization) | 2PN/MII | per mature oocyte retrieved |
| Conventional BUR | Frozen/2PN | per zygote (degeneration excluded) |
| DP-BUR (additive) | Frozen / (2PN + ATR) | per zygote plus the degenerated oocytes |
| DP-BUR (multiplicative) | (Frozen/2PN) × (1 − ATR/MII) | conventional BUR discounted by degeneration |
| TBUR | Frozen/MII | per mature oocyte (true biological yield) |
| Degeneration | ATR/MII | penalizing |

DP-BUR and TBUR receive equal billing throughout: DP-BUR isolates the operator's oocyte-handling damage, whereas TBUR reports the absolute yield from the starting material.

## 2.5 Rationale for a degeneration-penalized denominator

Consider two cycles that produce identical fertilization and identical usable-blastocyst counts but differ only in operator-induced damage: Cycle A (10 MII, 0 degenerated, 6 2PN, 3 usable blastocysts) and Cycle B (10 MII, 2 degenerated, 6 2PN, 3 usable blastocysts). The clinically relevant difference is that Cycle B's operator destroyed two oocytes that Cycle A's operator preserved.

| Cycle | MII | Degen. | 2PN | Frozen | Conv. BUR | DP-BUR add | DP-BUR mult | TBUR |
|---|---|---|---|---|---|---|---|---|
| A (0 degenerated) | 10 | 0 | 6 | 3 | 50 | 50.0 | 50.0 | 30 |
| B (2 degenerated) | 10 | 2 | 6 | 3 | 50 | 37.5 | 40.0 | 30 |

Conventional BUR scores the two cycles identically (50 vs 50) because it never sees the degeneration. Critically, TBUR also scores them identically (30 vs 30): when MII and the usable count are equal, Frozen/MII cannot discriminate the careful operator from the one who caused damage. Only a denominator that carries degeneration explicitly — DP-BUR — separates them (50 vs 37.5 additive; 50 vs 40.0 multiplicative). This is the minimal correction that distinguishes an operator who preserved every oocyte from one who damaged two, and it is the conceptual justification for reporting DP-BUR alongside TBUR. It also clarifies why working over MII is appropriate for the fertilization rate (where degeneration directly depresses 2PN/MII) but insufficient for blastocyst utilization when considered in isolation.

## 2.6 Statistics

Pooled rates were oocyte-weighted (summed numerators/summed denominators), with cycle and MII counts explicitly included. Operator-level analyses (≥ 150 MII per operator; operators anonymized #1, #2, …) compared each metric against a competence benchmark of 40 (out of 100). Differences among the three utilization metrics (conventional BUR, DP-BUR additive, TBUR) were tested across the 38 operators with the Friedman test followed by pairwise Wilcoxon signed-rank tests (Holm correction), with matched-pairs rank-biserial correlation and Cohen's dz as effect sizes and 95% bootstrap confidence intervals (5,000 resamples) for the mean paired differences. Rank stability used Spearman correlation. Analyses used Python (pandas, NumPy, SciPy).

# 3. Results

*The Results follow the MII: were performed using many mature oocytes entered, the true versus apparent yield, and how the corrected denominators change the verdict.*

## 3.1 In 56,349 mature oocytes, conventional BUR overstates both corrected values

The pooled cohort comprised 7,216 ICSI cycles and 56,349 MII oocytes [3, 4], yielding 44,062 2PN zygotes and 18,456 usable cryopreserved blastocysts; the overall degeneration rate was 3.4. Conventional BUR was 41.9. The degeneration-penalized BUR was 40.2 (additive) and 40.5 (multiplicative) — a modest + 4% overstatement at the cohort level, reflecting the low overall degeneration. The MII-anchored TBUR was 32.8, a + 27.9% overstatement, because TBUR additionally absorbs every non-degeneration fertilization loss. For fertilization, the survivor-based rate (80.9%) overstated the true DPFR (78.2%) by only 3%, confirming that fertilization is comparatively robust to denominator choice (Fig. 1).

## 3.2 The degeneration-penalized correction is degeneration-specific

In cycles with directly measured degeneration, DP-BUR behaved as intended — it bit only where damage occurred. Moving from low (< 5%) to high (≥ 5%) degeneration, conventional BUR scarcely moved (54.6%→52.0%), but DP-BUR fell from 54.4% to 42.7%: essentially flat where degeneration is low (no penalty) and dropping sharply where it is high. TBUR fell 46.1%→38.4%. The conventional metric absorbed almost none of the degeneration-driven loss; both corrections did, and DP-BUR did so selectively (Table 1; Fig. 2).

Table 1
Conventional vs corrected blastocyst utilization by degeneration stratum (measured-degeneration cycles; out of 100).

| Stratum | Cycles | MII | 2PN | Frozen | Degen. | Conv. BUR | DP-BUR add | DP-BUR mult | TBUR |
|---|---|---|---|---|---|---|---|---|---|
| Low (< 5%) | 992 | 8,638 | 7,290 | 3,978 | 0.2 | 54.6 | 54.4 | 54.4 | 46.1 |
| High (≥ 5%) | 560 | 5,795 | 4,279 | 2,225 | 16.0 | 52.0 | 42.7 | 43.7 | 38.4 |

# 3.3 The corrections change the verdict: benchmark misclassification

Operator rankings were largely preserved across metrics (Spearman ≈ 0.99); the effect of the corrections is recalibration of the scale, not reshuffling. Against a competence benchmark of 40%, conventional BUR passed 24 of 38 operators; the degeneration-penalized DP-BUR passed 17 (7 operators flipped from pass to fail); and the MII-anchored TBUR passed only 7 (17 flipped). The two corrections bracket the severity of the verdict: DP-BUR fails only those whose passing score was propped up by oocyte damage, while TBUR additionally fails those whose blastocyst yield per mature oocyte falls short for any reason (Fig. 3).

**Worked example.** Operator #18 (MII = 1,312; 2PN = 1,012; degenerated = 89; Frozen = 481; fertilization 2PN/MII = 77.1): conventional BUR = 481/1,012 = 47.5 (clears 40); DP-BUR additive = 481/(1,012 + 89) = 43.7 (still clears 40); DP-BUR multiplicative = 44.3; TBUR = 481/1,312 = 36.7 (fails 40). The same work, the same embryos — the verdict tightens as the denominator becomes more honest.

# 3.4 The three-utilization metrics differ significantly, and the correction is universal

Across the 38 operators, the three-utilization metrics differed highly significantly (Friedman $\chi^2 = 76.0$, $p = 3 \times 10^{-17}$). Operator-level means ± SD were 43.8 ± 8.7 (conventional BUR), 41.7 ± 7.8 (DP-BUR additive), and 34.4 ± 7.9 (TBUR). All pairwise Wilcoxon signed-rank tests were significant after Holm correction (each $p < 0.001$): conventional vs DP-BUR (mean difference 2.1 points, 95% CI 1.6–2.6; $dz = 1.29$),

conventional vs TBUR (9.4 points, 8.8–10.0; dz = 5.33), and DP-BUR vs TBUR (7.3 points, 6.8–7.8; dz = 4.16).

Because TBUR ≤ DP-BUR ≤ conventional BUR holds for every operator by construction, the ordering is deterministic — all 38 operators were ranked in the same direction (rank-biserial correlation = 1.00 for every pair). The statistical tests, therefore, confirm that the corrections are systematic and universal rather than attributable to chance, and the scientifically informative quantity is the magnitude of the gap: conventional BUR is, on average, inflated by about 2 points relative to the degeneration-specific value and by about 9 points relative to the MII-anchored value, with very large effect sizes. This is the quantitative expression of how true each metric is.

# 4. Discussion

In a single pooled cohort of more than 56,000 mature oocytes, the denominator embedded in routine blastocyst-utilization KPIs proved to be a measurement artifact with consequences. Conventional BUR overstated the degeneration-penalized value by about 4% overall and by 22% in high-degeneration cycles, and overstated the MII-anchored value by 28%. The correction flipped benchmark verdicts for between 7 and 17 of 38 operators, depending on which honest denominator was applied.

The mechanism is simple and general. Any rate that places fertilized oocytes in its denominator has already discarded the oocytes lost to the procedure, so degeneration is erased from the ledger rather than recorded as a failure. We offer two complementary remedies with deliberately different scopes. DP-BUR adds the degenerated oocytes back to the conventional denominator, isolating the one loss the operator most directly controls; it is essentially identical to conventional BUR when degeneration is low and diverges only as damage rises, which makes it a targeted, defensible competence metric. TBUR anchors yield to the mature oocyte retrieved, reporting the true biological ceiling but folding in all attrition. Reported together, they tell a laboratory both how much it lost specifically to oocyte damage and how much usable yield it extracted from its raw material.

The two-cycle comparison in Section 2.5 is the conceptual heart of the argument: when two cycles share the same mature-oocyte count and the same fertilization, conventional BUR and even MII-anchored TBUR are blind to a difference in operator-induced degeneration; only DP-BUR discriminates them. This is also why expressing the fertilization rate over MII is acceptable — degeneration depresses 2PN/MII directly, and a 70–80% fertilization expectation already presumes oocyte survival — whereas blastocyst utilization needs an explicit degeneration term.

Consistent with the recognized sensitivity of single KPIs to case mix and denominator choice [2, 30], the most important practical point is that the harm of sole KPIs is not primarily unfairness between operators — rankings were largely stable — but systematic, degeneration-dependent inflation of the entire scale. Benchmarking against published competence thresholds [1, 2] is therefore where the error bites hardest. Reporting degeneration as a first-class KPI [1, 9] and reporting blastocyst yield against a denominator that includes the degenerated oocytes [4] removes the artifact.

This is a retrospective, observational analysis. Degeneration was directly measured in part of the cohort and modeled within a documented 1–5% institutional range in the remainder; all degeneration-stratified inferences were confined to the measured cycles, and DP-BUR — which requires ATR — is exact only where degeneration was measured, approximate elsewhere, whereas TBUR is imputation-free throughout. The cryopreservation numerator reflects, in part, mixed-stage freezing and is best read as a usable-yield rate; it was applied identically across metrics. The choice between the additive and multiplicative DP-BUR forms is a transparent modeling decision; the two gave near-identical values (Table 1). Finally, we measure laboratory yield, not live birth.

# 5. Conclusion

Conventional blastocyst utilization is not a neutral measurement: by counting usable blastocysts only against fertilized oocytes, it overstates true performance in direct proportion to the post-ICSI degeneration it hides, and it passes operators and laboratories that an honest accounting would fail. Returning degeneration to the denominator — additively or multiplicatively (DP-BUR) to isolate operator-induced damage, or by anchoring to mature oocytes retrieved (TBUR) to report true yield — recovers the real outcome. In the presence of degeneration, these corrected utilization metrics are not refinements of the conventional rate; they are corrections of it.

Table 3

**— Robustness across a high-workload and a lower-workload setting** The masking is a property of the metric, not of any one center's caseload: the gap between conventional and corrected utilization appears in both a high-workload, high-volume center and a lower-workload center.

| Setting | Cycles | Operators | MII | MII/cycle | Degen. | Conv. BUR | DP-BUR add | TBUR |
|---|---|---|---|---|---|---|---|---|
| High-workload center | 5,217 | 58 | 40,981 | 7.9 | 2.1 | 37.8 | 36.8 | 29.3 |
| Lower-workload center | 1,999 | 17 | 15,368 | 7.7 | 6.7 | 52.5 | 48.5 | 41.9 |

# Declarations

**-Funding: N/A**

**-Consent to participate: N/A**

**-Consent for publication: N/A**

**-Ethical approval and its number:** Yale University Human Research Protection Program IRB# 2000032744

**-Data availability:** Data is contained within the article and could be shared upon request.

# Author Contribution

E.O. and M.Ba. conceived and designed the study. M.Ba. developed the conceptual framework for the degeneration-penalized and MII-anchored key performance indicators and supervised the project. E.O. designed and performed the quantitative and statistical analysis, including the metric derivations, significance testing, and figures. I.O.O. acquired and curated the clinical and embryological data and contributed to data interpretation. M.Bh. and A.A. provided senior scientific oversight, contributed resources, and critically revised the manuscript for important intellectual content. T.D. and O.D. contributed to data assembly and the literature review and reviewed the manuscript. M.Ba. wrote the first draft of the manuscript, and E.O. drafted the analytical sections. All authors critically revised the manuscript, and all authors read and approved the final version. M.Ba. is the corresponding author and accepts responsibility for the integrity of the work as a whole.

# Data Availability

The Ungdata surveys that support the findings of this study are available from Norwegian Social Research (NOVA), but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. The data are, however, available upon request and with the permission of Norwegian Social Research (NOVA).

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## Figures

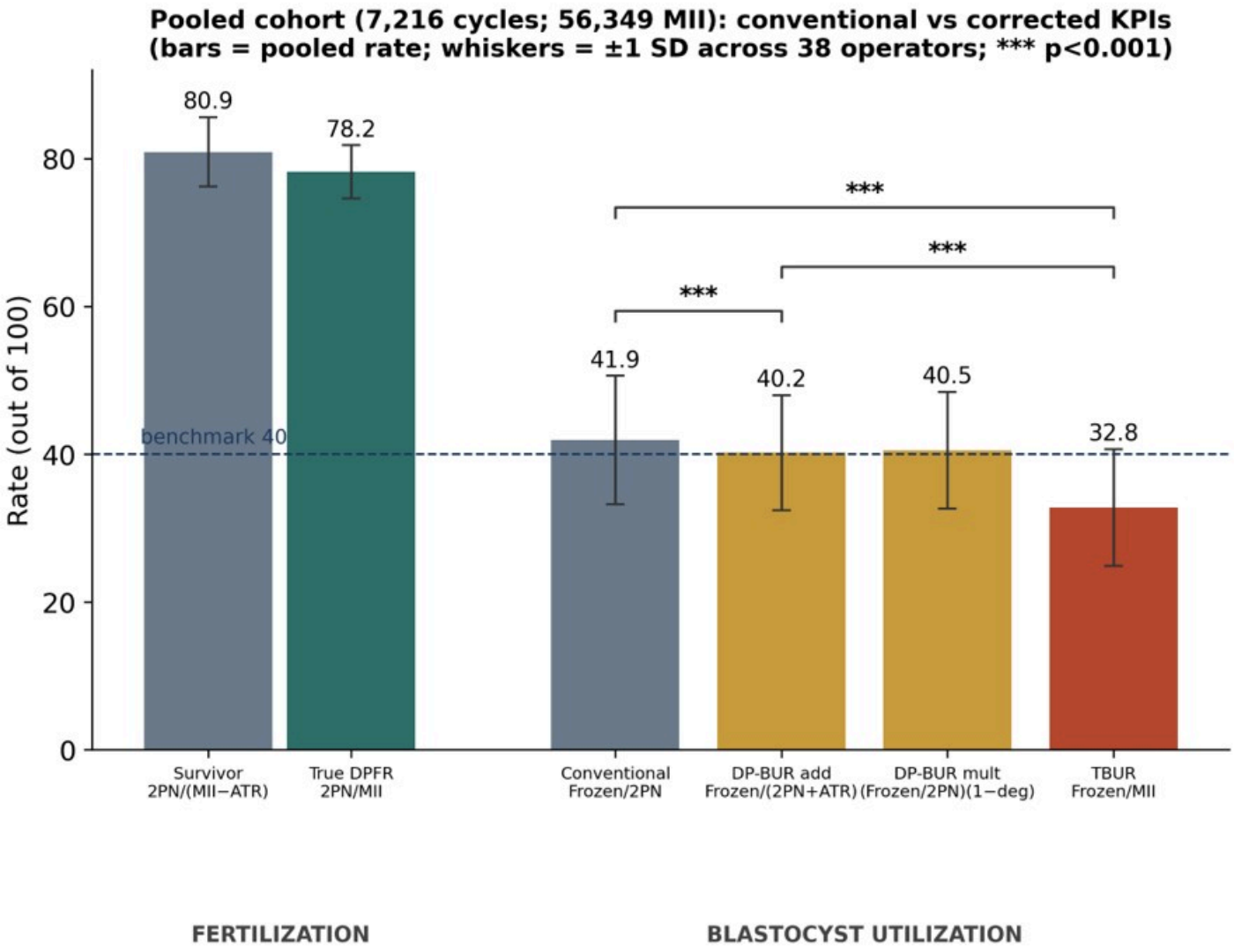



**Figure 1**

Pooled cohort (7,216 cycles; 56,349 MII): fertilization (survivor-based vs true DPFR) and blastocyst utilization (conventional vs DP-BUR additive, DP-BUR multiplicative, and TBUR). (*** p<0.001, Holm-corrected).

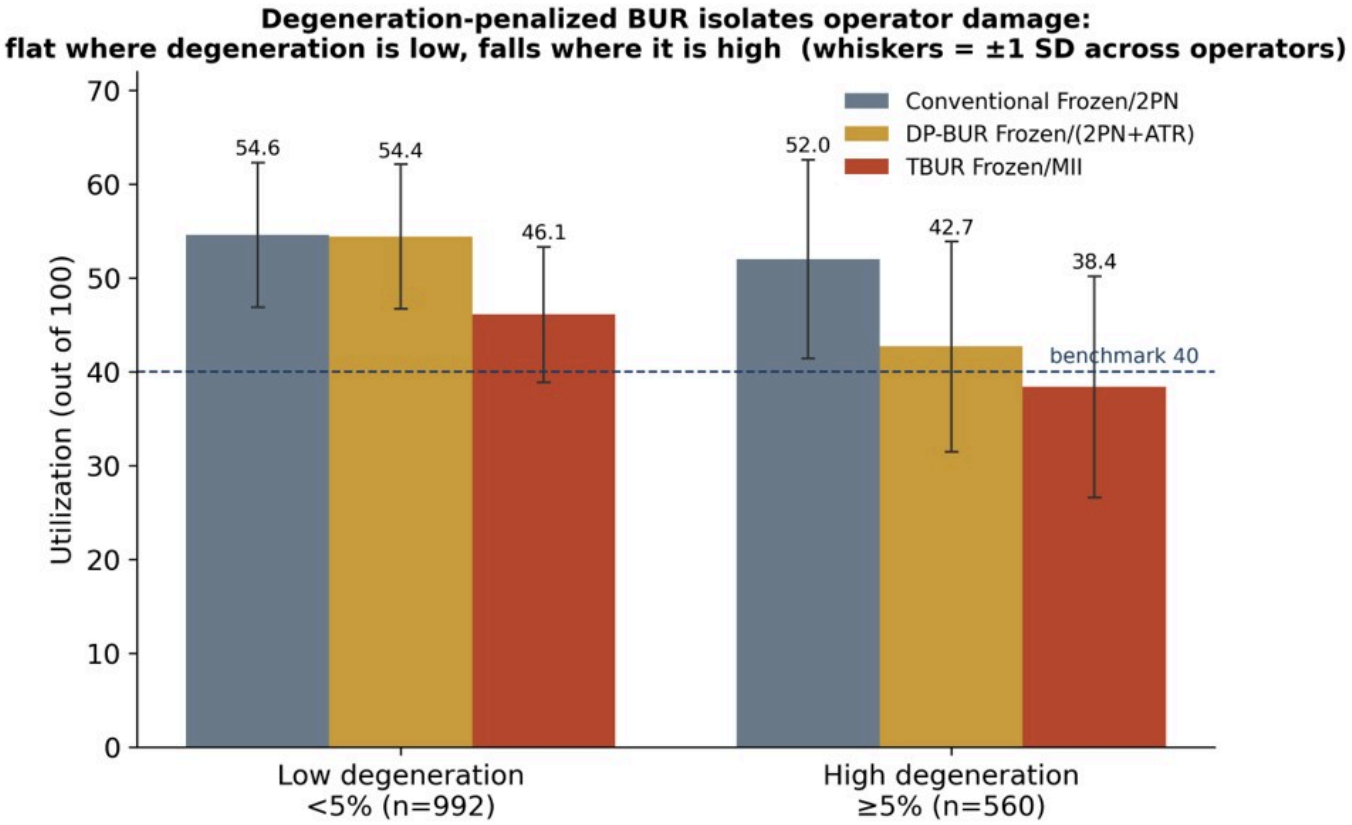



**Figure 2**

Across measured-degeneration strata, conventional BUR changes little, while DP-BUR is flat where degeneration is low (<5%) and declines where it is high (≥5%), isolating operator-induced damage; TBUR falls in both directions.

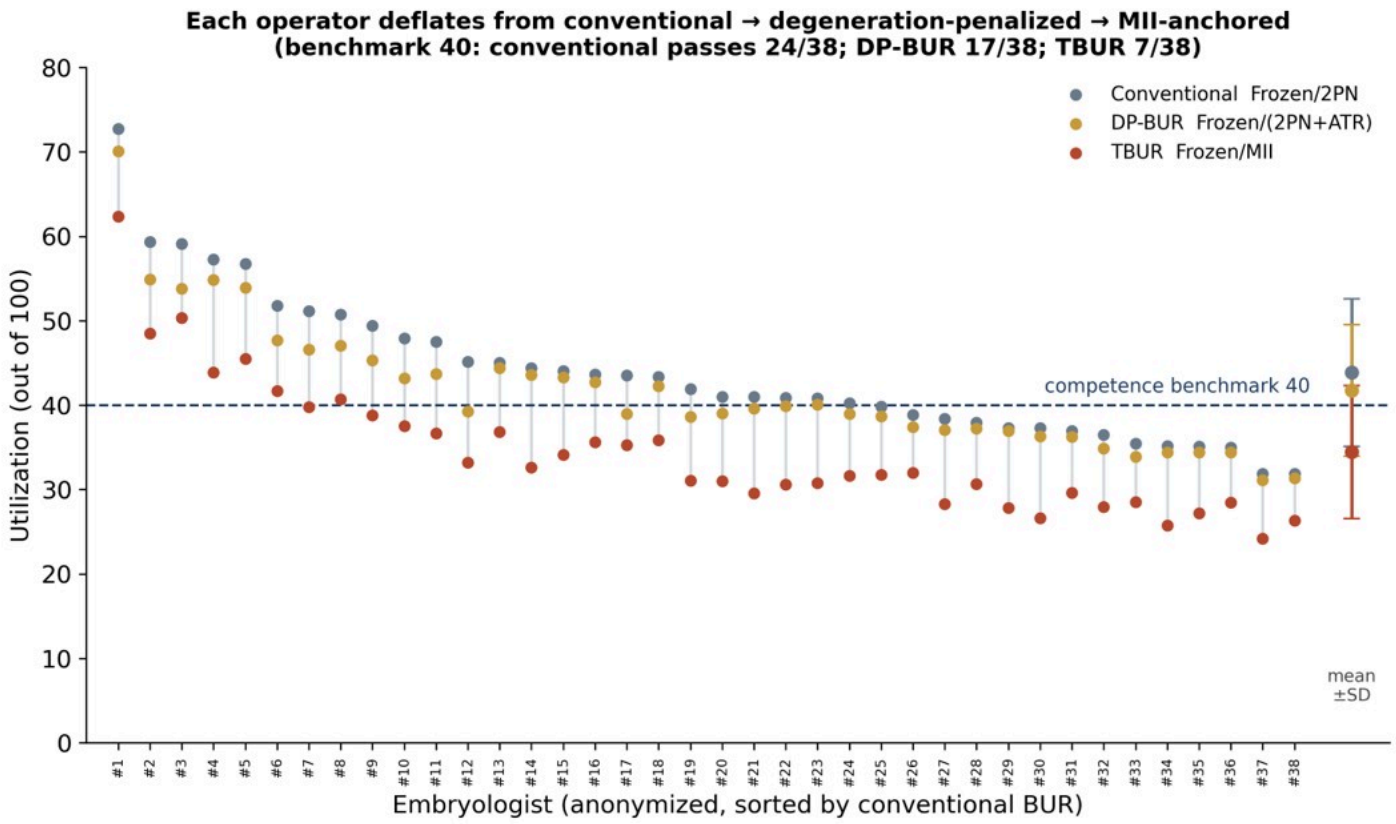



**Figure 3**

Conventional BUR, DP-BUR (additive), and TBUR for 38 anonymized operators, sorted by conventional BUR. Each operator deflates from conventional → degeneration-penalized → MII-anchored; against a 40% benchmark, conventional passes 24/38, DP-BUR 17/38, TBUR 7/38.