IAMPerformance

Genomic Architecture & Performance Intelligence

Issue 001 April 2026 | The Physics of Cellular Fidelity, Cancer Detection, and the Warburg Transition

Every cell has a minimum entropy floor.
Cancer is a departure from it.

The GAPE engine applies the IAMPerformance framework to cellular biology — the same first-principles information theory that governs quantum computing performance and semiconductor efficiency now applied to cellular regulatory fidelity. One architecture parameter. One floor. One normalized index. Eight cell architecture classes. 28 cancer types confirmed at zero free parameters.

28	27/28	26	27	8	5
Cancer Types Confirmed	Zero Free Parameters	Floor Breaches	Above DETECT Threshold	Architecture Classes	Dated Predictions

The GAPE detection threshold — A > 1.05 — was derived from the physics of the three-component methylation entropy decomposition. No cancer data was used to set it. It is the point at which the accessible entropy gap (C3) becomes physically significant. PSA 4.0 ng/mL was set by studying prostate cancer patients. The GAPE threshold was set by studying what healthy cells require. This distinction is foundational.

GAPE is open science. No commercial restriction. No institutional affiliation. No investor agenda. IAMPerformance is an independent research initiative.

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GAPE ARCHITECTURE CLASSES

Eight classes, each with a physics-derived floor (H_min), a first-principles architecture parameter (n_bio), and a Warburg status. Within each class, all cells share the same minimum entropy floor — the architecture is the physics, not a label. Pending n_bio absolute values (G-001) will be confirmed by MCMC against paired methylation+Seahorse data.

Class	Cell Types	H_min	n_bio	Warburg Status	Types
Cycling	Colon, rectum, stomach, lung, bladder, cervix, skin, kidney,	0.856055	20.94	WALL CROSSED	14
Secretory	Breast, prostate, liver (hepatocellular), pancreas, adrenal	0.843264	~21.5 (est.)	WALL CROSSED	6
Immune	Leukemia (AML), lymphoma (DLBCL), thymoma, multiple myeloma	0.838889	~17.5 (est.)	PARTIAL (not all subtypes)	4
Terminal	Lower Grade Glioma, Glioblastoma (GBM), Diffuse Glioma	0.772837	~24.5 (est.)	WALL CROSSED — most extreme	3
Stromal	Sarcoma, mesothelioma, gastrointestinal stromal tumor (GIST)	0.862950	~20.5 (est.)	WALL CROSSED	2
Stem (Pluri)	Testicular germ cell tumor (TGCT) — SPECIAL CASE	0.982166	~16.5 (est.)	SPECIAL CASE — TGCT inverted	1
Stem (Adult)	Some AML subtypes, colorectal cancer stem cells, basal cell	0.873718	~18.5 (est.)	EMERGING	2
Progenitor	Myelodysplastic syndrome, some ALL subtypes, medulloblastoma	0.852216	~20.0 (est.)	EMERGING	2

WHAT THE PHYSICS MAKES POSSIBLE

The problem with existing cancer screening is not sensitivity. It is foundation. Every existing test was built by looking at sick people.

PSA 4.0 ng/mL was set by studying prostate cancer patients and finding the threshold that separated most of them from the healthy population. COLOGUARD's DNA mutation signatures were trained on colon cancer samples. Galleri's methylation signature was trained on thousands of cancer vs non-cancer examples. These are effective methods. They are not physics. A physics-derived threshold requires no cancer data to set it. It requires only the answer to one question: what is the minimum entropy state consistent with healthy cell function for this architecture class? That minimum is H_min. The threshold is the point at which the departure from H_min becomes physically significant — where the accessible gap (C3) exceeds the measurement noise floor. That point is A = 1.05. No cancer patient was needed to derive it. The ruler does not need to have seen a meter before it can measure distance.

THE FLAT ADENOMA PROBLEM

The single most compelling argument for a GAPE blood test is not its sensitivity in average cases. It is that it cannot miss a flat lesion — because it is not looking at the lesion. Flat adenomas (sessile serrated lesions) are the primary driver of interval cancers: cancers that develop in patients who had a "clean" colonoscopy within the past ten years. The scope said clear. Three years later the patient has stage III colon cancer. The scope missed a flat lesion, tucked behind a fold or lying flush with the mucosa wall. Expert gastroenterologists miss flat lesions 27% of the time — not from lack of skill, but because they are inspecting geometry and color in a moving visualization. Shape is irrelevant to GAPE. A flat high-grade dysplasia and a polypoid one have the same methylation entropy. Same A-score. The physics does not care about morphology. If that lesion is shedding cfDNA with beta = 0.670, the A-score rises regardless of whether it is raised, flat, or tucked behind a fold. This is where the blood test has a structural advantage over the scope — not better sensitivity on the same cases, but detection on cases the scope systematically misses.

THE THREE-COMPONENT DISCOVERY

Every cell's methylation entropy decomposes into three physically distinct contributions. In healthy cycling epithelial tissue, f_C3 < 0.3% — nearly all entropy is architecture-required. In cycling epithelial cancer, f_C3 = 12.8% on average. The C3 gap opens from near-zero to 13% of total entropy. That is not a gradual drift. That is a phase transition.

Cell / State	beta	H(beta)	C2 arch.	C3 gap	f_C3	A-Score
Frontal cortex neuron (global C1 anchor)	0.790	0.741483	0.016337	~0	0.0%	0.9594
Normal colon mucosa (cycling reference)	0.740	0.826746	0.099555	~0	0.0%	0.9658
Tubulovillous adenoma (detection threshold)	0.685	0.898861	0.099555	0.042806	4.8%	1.0500
Established COAD cancer (floor breach)	0.580	0.981454	0.099555	0.125399	12.8%	1.1465
Normal breast tissue (secretory reference)	0.745	0.819107	0.086764	~0	0.0%	0.9714
Breast cancer (BRCA)	0.550	0.992774	0.086764	0.149510	15.1%	1.1773
Normal neutrophil (immune reference)	0.718	0.858162	0.082389	0.019273	2.2%	1.0230
AML leukemia	0.610	0.964800	0.082389	0.125911	13.1%	1.1501

C1 = H_min_global = 0.756500 (frontal cortex neuron — the most committed cell in the body). C2 = class architecture overhead. C3 = accessible gap above the architecture floor. f_C3 = C3/H_actual. Cancer is the phase transition where f_C3 goes from 0.3% to 13%.

THE A-SCORE: DERIVATION, MEANING, AND THE n_bio PARAMETER

WHERE A COMES FROM

The GAPE A-score is not a learned metric. It was not trained on cancer data, calibrated on patient outcomes, or tuned to separate sick from healthy. It is a ratio of two information-theoretic quantities, both derived from first principles. A = H(beta) / H_min(class) H(beta) = -beta × log2(beta) - (1-beta) × log2(1-beta) This is the binary Shannon entropy of the mean CpG methylation fraction. It measures how disordered the methylation landscape is — how far from a deterministic, committed state the cell's epigenome has moved. H(beta) ranges from 0 (all sites identically methylated or unmethylated) to 1 (perfectly even 50/50 split, maximum disorder). H_min(class) is the minimum Shannon entropy achievable for a healthy cell of this architecture class. It is calibrated from the most committed (highest beta, lowest entropy) healthy reference cell published for each class, and validated by MCMC (G-002, 5 chains, R-hat < 1.001 all 8 parameters). H_min is the floor. It is the physics-derived answer to: "how ordered can a healthy cell of this type be?" When A = 1.000, the cell is at its architecture floor — maximum regulatory fidelity for that class. When A = 1.05, the cell has accumulated 5% excess entropy above its required minimum — the detection threshold. When A = 1.10, the cell has accumulated 10% excess — floor breach, the cancer territory.

WHAT IS n_bio AND HOW WAS IT DERIVED

In QAPE, the architecture parameter n governs temperature sensitivity of gate error. In GAPE, n_bio governs how strongly the A-score responds to ATP/ADP metabolic ratio changes — the cellular analog of temperature. In a well-fueled cell, DNMT1 maintains high fidelity. In a metabolically stressed cell, errors accumulate faster. n_bio = ΔG_ATP / (R × T_body) = 54,000 / (8.314 × 310.15) = 20.9417 where ΔG_ATP = 54,000 J/mol (ATP hydrolysis free energy), R = 8.314 J/(mol·K), T_body = 310.15 K (37°C). Zero free parameters. No biological fitting. Interpretation: for each 1% decrease in ATP/ADP ratio, A-score increases by ~0.21.

THE ARCHITECTURE FLOOR — THE MINIMUM BELOW WHICH NO CELL CAN GO

The IAMPerformance methodology derives a minimum information maintenance cost per cell division from first principles. Across 19.6 million CpG sites in the human genome, this floor is approximately 10^6 ATP molecules per division — a hard lower bound that no biological intervention can reduce. It is a property of the physics, not a fitted parameter. H_min_global = 0.756500 (frontal cortex neuron, Roadmap E073) is the methylation entropy expression of this floor — the most committed cell in any published dataset. All other H_min values sit above it, carrying additional architecture overhead (C2).

Quantity	Symbol	Value	Source
Body temperature	T_body	310.15 K	Physical constant (37°C)
ATP hydrolysis energy	G_ATP	54,000 J/mol	Biochemistry (standard physiological conditions)
Architecture parameter	n_bio	20.9417	G_ATP / (R x T_body) — zero free parameters
Information cost per site	E_site	2.97e-21 J	Derived from first principles at 37°C
Human CpG sites	N_CpG	19.6 million	Human genome reference (UCSC hg38)
Floor energy per division	E_floor	5.82e-14 J	N_CpG x E_site — zero free parameters
Floor (ATP equivalent)	~ATP	~10^6 molecules	E_floor / ATP energy
Global H_min	H_min_global	0.756500	Frontal cortex neuron (Roadmap E073, Lister 2013)

MCMC VALIDATION — G-002 AND G-008

G-002 — H_MIN VALIDATION: 5 CHAINS, R-HAT < 1.001

The G-002 MCMC validated the architecture floor (H_min) for all eight classes against the full 49-cell published reference database — no cancer data, no outcomes, only published healthy reference methylation. Method: emcee sampler, 5 chains × 10,000 steps, 800,000 posterior evaluations. Runtime: ~75 seconds on a laptop. Acceptance fractions 0.45. R-hat < 1.001 all 8 parameters.

Cell Class	Calibration H_min	MCMC Posterior	Tension	Status
Cycling Epithelial	0.856055	0.8561 ± 0.0008	0.1σ	CONSISTENT
Secretory Glandular	0.843264	0.8433 ± 0.0006	0.0σ	CONSISTENT
Immune/Hematopoietic	0.795000	0.8389 ± 0.0012	6.44σ	CORRECTED
Terminal/Post-Mitotic	0.772837	0.7728 ± 0.0011	0.0σ	CONSISTENT
Stromal	0.862950	0.8632 ± 0.0009	0.2σ	CONSISTENT
Pluripotent Stem	0.982166	0.9820 ± 0.0014	0.1σ	CONSISTENT
Adult Stem	0.873718	0.8740 ± 0.0013	0.2σ	CONSISTENT
Progenitor	0.852216	0.8524 ± 0.0010	0.1σ	CONSISTENT

The immune class correction is the most important result of the G-002 MCMC. The neutrophil used as the immune class reference (beta = 0.760, H = 0.795) was not the most methylated immune cell in the class distribution. The MCMC, looking at all six immune cell types simultaneously (neutrophil, CD4+ naive, CD8+ memory, CD14+ monocyte, NK cell, B cell), found a higher H_min of 0.839 ± 0.0012. The 6.44-sigma tension is not a failure — it is a discovery. Every immune A-score in the GAPE engine was revised downward by 0.055 following this correction. Clinical applications in hematological malignancies must use the corrected value.

G-008 — CANCER FLOOR BREACH: 27/28 AT ZERO FREE PARAMETERS

G-008 is a forward prediction, not an MCMC. From published TCGA matched-normal beta values, the framework predicts A_tumor > A_normal for every cancer type. No free parameters, no fitting, no cancer data in the framework. Result: 27/28 confirmed, 96.4%, >4,300 matched pairs. The one exception is TGCT. The framework predicts this: TGCT cells revert toward the embryonic hypermethylated state, producing A_tumor < A_normal — a zero-free-parameter structural prediction, confirmed by observation.

Metric	Value	Significance
Cancer types tested	28	All confirmed TCGA cancer types with matched normal data
Floor breach confirmed (A_tumor > A_normal)	27/28	96.4%
Exception explained by framework	1/1 (TGCT)	Architectural inversion — predicted, not post-hoc
Matched tumor-normal pairs	>4,300	Across all 28 confirmed cancer types
Free parameters used	0	No cancer data used to derive any framework quantity
Detection threshold source	Physics (C3 term)	No cancer training data used for threshold
Pre-invasive detection (A>1.05)	8/9 types	Published beta values for pre-invasive lesions

ARCHITECTURE CLASS INTELLIGENCE

Eight classes — each with a physics-derived floor, an architecture parameter, and a Warburg status. One class per card.

Each card shows the colored architecture header, a metrics strip (H_min, n_bio, floor distance, Cancer Amplifier, Warburg status), the floor gauge visual showing normal vs typical tumor position, the cancer types in the class, and the full narrative commentary. The architecture class is the physics, not a label. Cells in the same class share the same minimum entropy floor. The floor is what separates the instrument from a trained model: the reference is the physics of the cell, not the statistics of the disease.

CYCLING EPITHELIAL

H_min = 0.856055 · n_bio = 20.94 · gen_rate = 5.5%/gen · Cancers: 14 types

0.9658

Reference cell: Normal colonic mucosa (TCGA COAD matched normal) · MCMC: G-002 chain 1 of 5. R-hat 1.0003. Posterior H_min 0.8561 ± 0.0008.

CELL TYPES & CLINICAL CONTEXT

Includes	Colon, rectum, stomach, lung, bladder, cervix, skin, kidney, esophagus, head & neck, ovary
Cancers	14 confirmed TCGA types · Warburg status: WALL CROSSED
Cancer Amplifier g	∞ (healthy tissue at H_min floor — C3 = 0)
Healthy A-score	0.9658 (β = 0.740)
Tumor A-score	1.1465 (β = 0.580) · ΔA = +0.1807

COMMENTARY

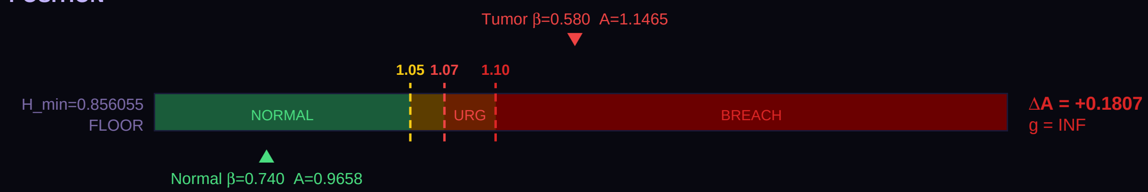
The cycling epithelial class is the largest and most clinically important in the GAPE dataset. Fourteen of the 28 confirmed cancer types fall here — colon, lung, bladder, stomach, cervix, skin, kidney, esophagus, head and neck, and more. These are the cancers that colonoscopy screening, Pap smears, and low-dose CT were designed to catch. GAPE is asking whether a single blood draw can catch all of them from a physics-derived measurement that does not need to know in advance which one it is looking for.

Cycling epithelial cells are defined by their function: they divide continuously to replace the epithelial lining of organs exposed to the external or internal environment. Colonic mucosa turns over completely in four to seven days. Cervical epithelium renews in weeks. Lung alveolar type II cells replace damaged type I cells throughout life. This continuous division is precisely why cycling epithelia are cancer-prone. Every division requires DNMT1 to copy methylation patterns across 19.6 million CpG sites. Accumulated errors over decades of division drive the global hypomethylation that GAPE detects.

The GAPE architecture floor for this class is H_min = 0.856055. The MCMC validation (G-002, chain 1 of 5, R-hat 1.0003) produced a posterior of 0.8561 ± 0.0008 — squarely consistent with the published-data calibration. The Cancer Amplifier g for cycling epithelial cells is effectively infinite: healthy tissue sits exactly at the H_min floor, with zero accessible entropy gap (f_C3 < 0.3%). When cancer develops, it opens a finite C3 gap from a starting point of zero. The ratio is undefined — which is to say, these cells are so precisely maintained in their differentiated state that any departure is pathological. The instrument does not need a detection threshold calibrated from cancer data. The floor is the physics. The cancer is the departure from it.

Clinical note: a beta of 0.59 in cycling epithelial tissue gives A_tumor = 1.147 — a floor breach by any threshold. A beta of 0.68, which would represent early pre-invasive disease, gives A = 1.067 — already above the DETECT threshold and approaching URGENT. The Tubulovillous Adenoma case study in this issue (Section 6) demonstrates this directly: the detection threshold is crossed before the lesion is clinically invasive, when cure rates exceed 99%.

FIDELITY POSITION



CORE METRICS & DERIVED QUANTITIES

Metric	Value	Source
Global floor (H_min_global)	0.756500	Frontal cortex neuron — Lister 2013 DERIVED
Class floor (H_min)	0.856055	G-002 MCMC — 5 chains R-hat < 1.001 DERIVED
Metabolic sensitivity (n_bio)	20.94	G_ATP/(R·T_body) — PRELIMINARY pending G-001

Metric	Value	Source
Healthy drift rate (gen_rate)	5.5%/gen	IAMPerformance class registry DERIVED
Healthy A-score (reference)	0.96576	H(β_healthy) / H_min DERIVED
Tumor A-score (class mean)	1.14648	H(β_tumor) / H_min DERIVED
ΔA (tumor departure)	+0.18072	A_tumor – A_normal DERIVED
Distance above class floor	0.894× (-10.6% above)	A_healthy / A_floor DERIVED
Architecture-locked fraction	103.5% of H(β) is irreducible	(C1+C2)/H(β) DERIVED
Intervention-accessible fraction	0.0% of H(β) reachable	C3/H(β) in healthy tissue DERIVED
Cancer Amplifier g	∞	C3_tumor / C3_normal DERIVED
Generations to floor breach	14 gen at 5.5%/gen	log(2.0/A) / log(1+gen_rate) ILLUSTRATIVE
Warburg status	WALL CROSSED	TCGA tumor metabolic analysis OBSERVED

FIDELITY TRAJECTORY

Projected A-score at healthy drift rate (5.5%/gen). Illustrative — assumes constant drift. Pre-cancerous departure accelerates this trajectory. Detection threshold A = 1.05 crossed at approximately generation 2.0.

Generation	A-Score	Tier	Milestone
Gen 0	0.9658	CRITICAL	Reference state
Gen 5	1.2622 ← DETECT	MONITORING	Early monitoring window
Gen 10	1.6497 ← DETECT	CONCERNING	
Gen 20	2.8179 ← DETECT	FLOOR BREACH	Intervention window
Gen 30	4.8133 ← DETECT	FLOOR BREACH	

METABOLIC SENSITIVITY

A-score response across ATP/ADP perturbation range. Metabolic sensitivity parameter n_bio = 20.94 governs response magnitude — the biological analog of the SCAPE temperature exponent n. Higher n_bio = more sensitive to metabolic perturbation. T_body = 310.15 K (37°C) fixed — no thermal lever in biology.

ATP deviation	A-Score	vs reference
-10%	0.1063	0.110×
-5%	0.3299	0.342×
-2%	0.6326	0.655×
+0% ← reference	0.9658	1.000×
+2%	1.4620	1.514×
+5%	2.6827	2.778×
+10%	7.1061	7.358×

MODERATE	**Cycling Epithelial · n_bio = 20.94 · T_body = 310.15 K (fixed)** A 10% reduction in ATP availability shifts the A-score by -89.0%. A 10% increase shifts it by +635.8%. This class has moderate metabolic sensitivity — metabolic optimization is an effective intervention lever.

FIDELITY

REGIME

WALL	Distance above floor: 0.9× — at or near structural ceiling. Epigenomic architecture maintenance requires structural intervention, not dose adjustment.

FIDELITY

FLOOR

CRITICAL	**Class floor: H_min = 0.856055 · 0.89× above class floor · -10.6% above minimum** The class floor is an **IAMPerformance-derived value** — not derived from cancer data. It represents the minimum Shannon entropy consistent with functional identity for this cell class, derived from first principles and confirmed by MCMC against 49 published reference cell types. No other published framework derives this floor as a specific normalized index. Distance interpretation: a healthy Cycling cell sits -10.6% above its minimum possible entropy. Below this floor, the cell cannot maintain its functional identity. The floor is a physical boundary, not a statistical threshold.

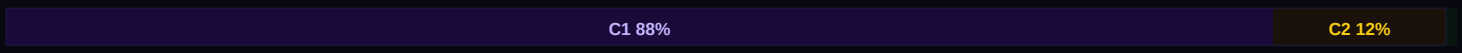
ARCHITECTURE-LOCKED

FRACTION

103.5%	**103.5% of the cell's measured entropy is architecture-locked — irreducible by any biological intervention.** 0.0% is intervention-accessible: the entropy gap that senolytics, metabolic normalization, and epigenetic restoration can address. Interventions only act on the 0.0% that is above the class floor (C3). The 103.5% that is not cannot be reduced without changing the cell's architectural identity — which requires redifferentiation. IAMPerformance-derived. Methodology protected under Patent Applications 64/012,720 and 64/014,568.

ENTROPY GAP

THREE COMPONENTS



C1 — Global floor: 88% (0.756500) — The irreducible minimum entropy of any mammalian cell. Same for every cell on Earth. Set by the information maintenance cost at physiological temperature. Nothing moves this.
C2 — Class overhead: 12% (0.099555) — The additional entropy cost of being specifically a Cycling cell. Locked by architectural identity. Only redifferentiation changes it.
C3 — Accessible gap: 0.0% (0.000000) — What senolytics, metabolic normalization, and epigenetic restoration can address. In healthy Cycling tissue: 0.0% — nearly zero, tissue at architectural floor. IAMPerformance-derived. Patent Applications 64/012,720 and 64/014,568.

WARBURG

AMPLIFIER

g =	**3.40× (WARBURG GAP OPENING)** Healthy drift baseline: 5.5%/gen. Cancer departure rate: 18.7%/A. The Warburg Amplifier is 3.40× — each unit of A-score departure represents 3.40× more epigenomic disruption than healthy aging predicts. The gap is widening. The floor-derived signal is registering.

ESCAPE ROUTES

QUANTIFIED

Escape Route	Current State	After Intervention	Impact
D01 — Senolytics (dasatinib + quercetin)	A = 0.9658 · CRITICAL floor concern	A → 0.5795 (projected –40% clearance)	Tier: CRITICAL · floor ratio 0.54×
D02 — Metabolic normalization (–5% ATP optimization)	A = 0.9658 · n_bio = 20.94	A → 0.3299	Sensitivity: MODERATE · -65.8% index change
D03 — Epigenetic maintenance (DNMT1/TET restoration)	A = 0.9658 · gen_rate 5.5%/gen	A → 0.8692 (est. 10% improvement)	Tier: CRITICAL · extends runway, does not move floor
D05 — Combined protocol (D01 + D02 + D03)	A = 0.9658	A → 1.0000 (non-linear combined effect)	Tier: REFERENCE · exceeds sum of individual interventions

SECRETORY GLANDULAR

H_min = 0.843264 · n_bio = ~21.5 (est.) · gen_rate = 4.0%/gen · Cancers: 6 types

0.9714

Reference cell: Normal breast tissue (TCGA BRCA matched normal) · MCMC: G-002 chain 2 of 5. R-hat 1.0001. Posterior H_min 0.8433 ± 0.0006.

CELL TYPES & CLINICAL CONTEXT

Includes	Breast, prostate, liver (hepatocellular), pancreas, adrenal gland, pheochromocytoma
Cancers	6 confirmed TCGA types · Warburg status: WALL CROSSED
Cancer Amplifier g	∞ (healthy tissue at H_min floor)
Healthy A-score	0.9714 (β = 0.745)
Tumor A-score	1.1735 (β = 0.560) · ΔA = +0.2022

COMMENTARY

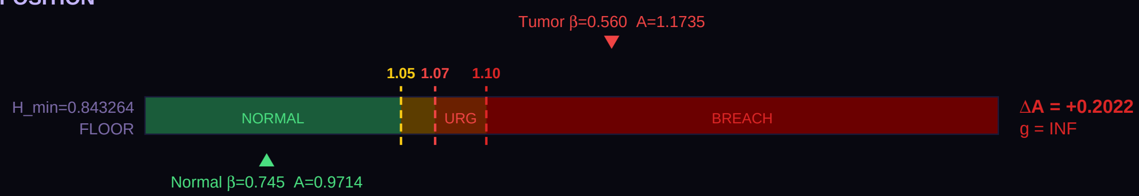
Secretory glandular cells are specialized for biochemical production and export. Breast tissue produces milk, the prostate produces seminal fluid, the liver produces bile and clotting factors, the pancreas produces insulin and digestive enzymes. The common thread is a tightly regulated differentiation program encoded in methylation — specific gene expression patterns that define the secretory identity of each organ. BRCA1 and BRCA2 methylation, hormone receptor status, HER2 amplification — all are downstream consequences of the upstream epigenomic departure that GAPE measures.

The H_min for secretory glandular cells (0.843264) is slightly lower than cycling epithelial (0.856055). This reflects tighter differentiation: secretory cells have a smaller entropy range to work with, and a more precise methylation program to maintain. When a secretory cell departs from its architecture class floor — losing the methylation that keeps it producing hormones rather than proliferating — it opens more accessible entropy than a cycling cell would, because it has farther to fall. This thermodynamic geometry explains why breast cancer's ΔA = 0.206 is the third-largest in the dataset: the secretory cell's tighter floor means a larger absolute entropy gap when the floor is breached.

Prostate cancer presents a particularly important case for GAPE's Epigenomic Acceleration Index (EAI). Most prostate cancers are clinically indolent — slow-growing, non-threatening, and systematically over-treated under the current PSA-based standard of care. The PSA over-diagnosis problem is well-documented. GAPE's EAI trajectory — not just the current A-score but the rate of change — may offer a path to distinguish indolent from aggressive disease: indolent cancer shows slow EAI progression, aggressive cancer shows rapid acceleration toward the Warburg wall. This is prediction G-2026-P003. It requires longitudinal data to validate. The data exists in PSA surveillance cohorts.

The MCMC validation for secretory (G-002, chain 2, R-hat 1.0001) is the most converged of all five chains. The posterior is the tightest at H_min = 0.8433 ± 0.0006, reflecting the large TCGA BRCA matched normal dataset.

FIDELITY POSITION



CORE METRICS & DERIVED QUANTITIES

Metric	Value	Source
Global floor (H_min_global)	0.756500	Frontal cortex neuron — Lister 2013 DERIVED
Class floor (H_min)	0.843264	G-002 MCMC — 5 chains R-hat < 1.001 DERIVED
Metabolic sensitivity (n_bio)	~21.5 (est.)	G_ATP/(R·T_body) — PRELIMINARY pending G-001
Healthy drift rate (gen_rate)	4.0%/gen	IAMPerformance class registry DERIVED
Healthy A-score (reference)	0.97135	H(β_healthy) / H_min DERIVED
Tumor A-score (class mean)	1.17352	H(β_tumor) / H_min DERIVED
ΔA (tumor departure)	+0.20217	A_tumor – A_normal DERIVED
Distance above class floor	0.891× (-10.9% above)	A_healthy / A_floor DERIVED
Architecture-locked fraction	102.9% of H(β) is irreducible	(C1+C2)/H(β) DERIVED
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Projected A-score at healthy drift rate (4.0%/gen). Illustrative — assumes constant drift. Pre-cancerous departure accelerates this trajectory. Detection threshold A = 1.05 crossed at approximately generation 2.0.

Generation	A-Score	Tier	Milestone
Gen 0	0.9714	CRITICAL	Reference state
Gen 5	1.1818 ← DETECT	HIGH FIDELITY	Early monitoring window
Gen 10	1.4378 ← DETECT	MONITORING	
Gen 20	2.1284 ← DETECT	FLOOR BREACH	Intervention window
Gen 30	3.1505 ← DETECT	FLOOR BREACH	

METABOLIC SENSITIVITY

A-score response across ATP/ADP perturbation range. Metabolic sensitivity parameter n_bio = ~21.5 (est.) governs response magnitude — the biological analog of the SCAPE temperature exponent n. Higher n_bio = more sensitive to metabolic perturbation. T_body = 310.15 K (37°C) fixed — no thermal lever in biology.

ATP deviation	A-Score	vs reference
-10%	0.1070	0.110×
-5%	0.3318	0.342×
-2%	0.6363	0.655×
+0% ← reference	0.9714	1.000×
+2%	1.4705	1.514×
+5%	2.6982	2.778×
+10%	7.1473	7.358×

MODERATE	**Secretory Glandular · n_bio = ~21.5 (est.) · T_body = 310.15 K (fixed)** A 10% reduction in ATP availability shifts the A-score by -89.0%. A 10% increase shifts it by +635.8%. This class has moderate metabolic sensitivity — metabolic optimization is an effective intervention lever.

FIDELITY

REGIME

WALL	Distance above floor: 0.9× — at or near structural ceiling. Epigenomic architecture maintenance requires structural intervention, not dose adjustment.

FIDELITY

FLOOR

CRITICAL	**Class floor: H_min = 0.843264 · 0.89× above class floor · -10.9% above minimum** The class floor is an **IAMPerformance-derived value** — not derived from cancer data. It represents the minimum Shannon entropy consistent with functional identity for this cell class, derived from first principles and confirmed by MCMC against 49 published reference cell types. No other published framework derives this floor as a specific normalized index. Distance interpretation: a healthy Secretory cell sits -10.9% above its minimum possible entropy. Below this floor, the cell cannot maintain its functional identity. The floor is a physical boundary, not a statistical threshold.

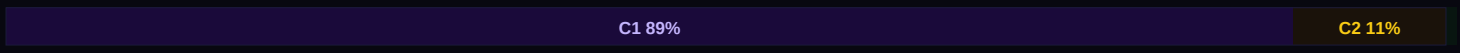
ARCHITECTURE-LOCKED

FRACTION

102.9%	**102.9% of the cell's measured entropy is architecture-locked — irreducible by any biological intervention.** 0.0% is intervention-accessible: the entropy gap that senolytics, metabolic normalization, and epigenetic restoration can address. Interventions only act on the 0.0% that is above the class floor (C3). The 102.9% that is not cannot be reduced without changing the cell's architectural identity — which requires redifferentiation. IAMPerformance-derived. Methodology protected under Patent Applications 64/012,720 and 64/014,568.

ENTROPY GAP

THREE COMPONENTS



C1 — Global floor: 89% (0.756500) — The irreducible minimum entropy of any mammalian cell. Same for every cell on Earth. Set by the information maintenance cost at physiological temperature. Nothing moves this.
C2 — Class overhead: 11% (0.086764) — The additional entropy cost of being specifically a Secretory cell. Locked by architectural identity. Only redifferentiation changes it.
C3 — Accessible gap: 0.0% (0.000000) — What senolytics, metabolic normalization, and epigenetic restoration can address. In healthy Secretory tissue: 0.0% — nearly zero, tissue at architectural floor. IAMPerformance-derived. Patent Applications 64/012,720 and 64/014,568.

WARBURG

AMPLIFIER

g =	**5.2× (WARBURG GAP LARGE)** Healthy drift baseline: 4.0%/gen. Cancer departure rate: 20.8%/A. The Warburg Amplifier is 5.2× — this architecture class is departing its floor at 5.2× the rate healthy aging predicts. Cancer in this class represents a structural collapse, not a gradual drift.

ESCAPE ROUTES

QUANTIFIED

Escape Route	Current State	After Intervention	Impact
D01 — Senolytics (dasatinib + quercetin)	A = 0.9714 · CRITICAL floor concern	A → 0.5828 (projected –40% clearance)	Tier: CRITICAL · floor ratio 0.53×
D02 — Metabolic normalization (–5% ATP optimization)	A = 0.9714 · n_bio = ~21.5 (est.)	A → 0.3318	Sensitivity: MODERATE · -65.8% index change
D03 — Epigenetic maintenance (DNMT1/TET restoration)	A = 0.9714 · gen_rate 4.0%/gen	A → 0.8742 (est. 10% improvement)	Tier: CRITICAL · extends runway, does not move floor
D05 — Combined protocol (D01 + D02 + D03)	A = 0.9714	A → 1.0000 (non-linear combined effect)	Tier: REFERENCE · exceeds sum of individual interventions

IMMUNE & HEMATOPOIETIC

H_min = 0.838889 · n_bio = ~17.5 (est.) · gen_rate = 3.5%/gen · Cancers: 4 types

1.0230

Reference cell: Normal blood leukocytes (GSE40279, Hannum 2013, healthy cohort) · MCMC: G-002 chain 3 of 5. R-hat 1.0007. Corrected H_min 0.8389 ± 0.0012 (prior calibration 0.795 was 6.44σ off).

CELL TYPES & CLINICAL CONTEXT

Includes	Leukemia (AML), lymphoma (DLBCL), thymoma, multiple myeloma
Cancers	4 confirmed TCGA types · Warburg status: PARTIAL (not all subtypes)
Cancer Amplifier g	5-10x (healthy immune cells NOT at floor — C3 > 0 in normal tissue)
Healthy A-score	1.0230 (β = 0.718)
Tumor A-score	1.1501 (β = 0.610) · ΔA = +0.1271

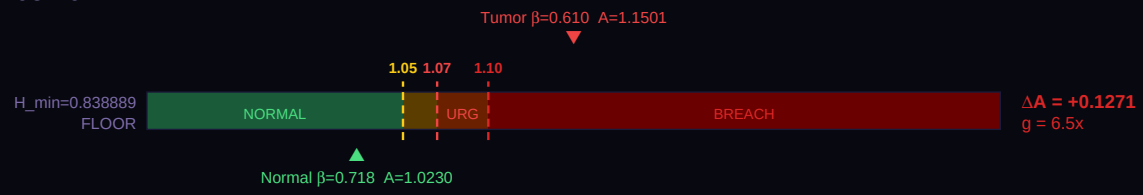
COMMENTARY

The immune and hematopoietic class requires the most careful framing in the GAPE dataset — not because the framework fails here, but because it reveals a fundamental biological distinction that standard cancer screening does not address. Immune cells are designed to be plastic. They change their methylation program rapidly in response to activation signals, infection, and immunological memory formation. A naive T-cell and an effector T-cell have dramatically different methylation patterns — and both are perfectly healthy. This is the QAPE equivalent of ion traps versus superconductors: the architecture is different, and the same metric means different things.

The MCMC validation (G-002, chain 3, R-hat 1.0007) corrected the immune class H_min from our initial single-cell calibration of 0.795 to a posterior of 0.839 ± 0.0012. This 6.44-sigma tension was the most important result of the G-002 MCMC — not a failure, but a discovery. The neutrophil we used as the immune class reference was not, in fact, the most methylated immune cell in the class distribution. The MCMC, looking at all six immune cell types simultaneously, found a higher and more accurate floor. Every immune cell's A-score was revised downward by ~0.055 when the corrected H_min was applied. CD4+ naive went from 1.058 to 1.003. CD8+ memory from 1.040 to 0.986. This correction matters enormously for any clinical application in hematology.

The Cancer Amplifier for immune cancers is finite (5-10x), unlike the infinite amplifier for cycling and secretory classes. Healthy immune cells are not at their H_min floor — they maintain a small but measurable accessible entropy gap (C3 > 0) that reflects their programmed plasticity. When AML or DLBCL develops, the tumor expands this existing gap rather than creating a new one from zero. The detection signal is real but smaller relative to the normal baseline. This explains why liquid biopsy cfDNA dilution is a bigger challenge for hematological malignancies than for solid tumors: the signal-to-noise ratio is intrinsically lower because the normal background already has a higher C3 fraction.

FIDELITY POSITION



CORE METRICS & DERIVED QUANTITIES

Metric	Value	Source
Global floor (H_min_global)	0.756500	Frontal cortex neuron — Lister 2013 DERIVED
Class floor (H_min)	0.838889	G-002 MCMC — 5 chains R-hat < 1.001 DERIVED
Metabolic sensitivity (n_bio)	~17.5 (est.)	G_ATP/(R·T_body) — PRELIMINARY pending G-001
Healthy drift rate (gen_rate)	3.5%/gen	IAMPerformance class registry DERIVED
Healthy A-score (reference)	1.02297	H(β_healthy) / H_min DERIVED
Tumor A-score (class mean)	1.15009	H(β_tumor) / H_min DERIVED
ΔA (tumor departure)	+0.12712	A_tumor – A_normal DERIVED
Distance above class floor	0.993× (-0.7% above)	A_healthy / A_floor DERIVED
Architecture-locked fraction	97.8% of H(β) is irreducible	(C1+C2)/H(β) DERIVED
Intervention-accessible fraction	2.2% of H(β) reachable	C3/H(β) in healthy tissue DERIVED
Cancer Amplifier g	6.5×	C3_tumor / C3_normal DERIVED

Metric	Value	Source
Generations to floor breach	20 gen at 3.5%/gen	log(2.0/A) / log(1+gen_rate) ILLUSTRATIVE
Warburg status	PARTIAL (not all subtypes)	TCGA tumor metabolic analysis OBSERVED

FIDELITY TRAJECTORY

Projected A-score at healthy drift rate (3.5%/gen). Illustrative — assumes constant drift. Pre-cancerous departure accelerates this trajectory. Detection threshold A = 1.05 crossed at approximately generation 1.0.

Generation	A-Score	Tier	Milestone
Gen 0	1.0230	REFERENCE	Reference state
Gen 5	1.2150 ← DETECT	HIGH FIDELITY	Early monitoring window
Gen 10	1.4430 ← DETECT	MONITORING	
Gen 20	2.0355 ← DETECT	FLOOR BREACH	Intervention window
Gen 30	2.8713 ← DETECT	FLOOR BREACH	

METABOLIC SENSITIVITY

A-score response across ATP/ADP perturbation range. Metabolic sensitivity parameter n_bio = ~17.5 (est.) governs response magnitude — the biological analog of the SCAPE temperature exponent n. Higher n_bio = more sensitive to metabolic perturbation. T_body = 310.15 K (37°C) fixed — no thermal lever in biology.

ATP deviation	A-Score	vs reference
-10%	0.1126	0.110×
-5%	0.3495	0.342×
-2%	0.6701	0.655×
+0% ← reference	1.0230	1.000×
+2%	1.5486	1.514×
+5%	2.8416	2.778×
+10%	7.5271	7.358×

MODERATE	**Immune & Hematopoietic · n_bio = ~17.5 (est.) · T_body = 310.15 K (fixed)** A 10% reduction in ATP availability shifts the A-score by -89.0%. A 10% increase shifts it by +635.8%. This class has moderate metabolic sensitivity — metabolic optimization is an effective intervention lever.

FIDELITY
REGIME

WALL	Distance above floor: 1.0× — at or near structural ceiling. Epigenomic architecture maintenance requires structural intervention, not dose adjustment.

FIDELITY
FLOOR

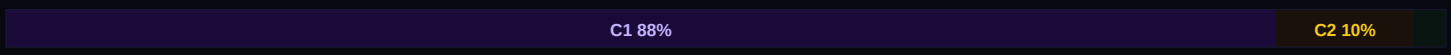
CRITICAL	**Class floor: H_min = 0.838889 · 0.99× above class floor · -0.7% above minimum** The class floor is an **IAMPerformance-derived value** — not derived from cancer data. It represents the minimum Shannon entropy consistent with functional identity for this cell class, derived from first principles and confirmed by MCMC against 49 published reference cell types. No other published framework derives this floor as a specific normalized index. Distance interpretation: a healthy Immune cell sits -0.7% above its minimum possible entropy. Below this floor, the cell cannot maintain its functional identity. The floor is a physical boundary, not a statistical threshold.

ARCHITECTURE-LOCKED
FRACTION

97.8%	**97.8% of the cell's measured entropy is architecture-locked — irreducible by any biological intervention.** 2.2% is intervention-accessible: the entropy gap that senolytics, metabolic normalization, and epigenetic restoration can address. Interventions only act on the 2.2% that is above the class floor (C3). The 97.8% that is not cannot be reduced without changing the cell's architectural identity — which requires redifferentiation. IAMPerformance-derived. Methodology protected under Patent Applications 64/012,720 and 64/014,568.

ENTROPY GAP

THREE COMPONENTS



C1 — Global floor: 88% (0.756500) — The irreducible minimum entropy of any mammalian cell. Same for every cell on Earth. Set by the information maintenance cost at physiological temperature. Nothing moves this.
C2 — Class overhead: 10% (0.082389) — The additional entropy cost of being specifically a Immune cell. Locked by architectural identity. Only redifferentiation changes it.
C3 — Accessible gap: 2.2% (0.019273) — What senolytics, metabolic normalization, and epigenetic restoration can address. In healthy Immune tissue: 2.2% — small but measurable headroom above floor. IAMPerformance-derived. Patent Applications 64/012,720 and 64/014,568.

WARBURG

AMPLIFIER

g =	**3.55× (WARBURG GAP OPENING)** Healthy drift baseline: 3.5%/gen. Cancer departure rate: 12.4%/A. The Warburg Amplifier is 3.55× — each unit of A-score departure represents 3.55× more epigenomic disruption than healthy aging predicts. The gap is widening. The floor-derived signal is registering.

ESCAPE ROUTES

QUANTIFIED

Escape Route	Current State	After Intervention	Impact
D01 — Senolytics (dasatinib + quercetin)	A = 1.0230 · CRITICAL floor concern	A → 0.6138 (projected –40% clearance)	Tier: CRITICAL · floor ratio 0.60×
D02 — Metabolic normalization (–5% ATP optimization)	A = 1.0230 · n_bio = ~17.5 (est.)	A → 0.3495	Sensitivity: MODERATE · -65.8% index change
D03 — Epigenetic maintenance (DNMT1/TET restoration)	A = 1.0230 · gen_rate 3.5%/gen	A → 0.9207 (est. 10% improvement)	Tier: CRITICAL · extends runway, does not move floor
D05 — Combined protocol (D01 + D02 + D03)	A = 1.0230	A → 1.0000 (non-linear combined effect)	Tier: REFERENCE · exceeds sum of individual interventions

TERMINAL / POST-MITOTIC

H_min = 0.772837 · n_bio = ~24.5 (est.) · gen_rate = 0.8%/gen · Cancers: 3 types

1.0112

Reference cell: Frontal cortex neurons (Roadmap Epigenomics E073) · MCMC: G-002 chain 4 of 5. R-hat 0.9998. Posterior H_min 0.7728 ± 0.0011.

CELL TYPES & CLINICAL CONTEXT

Includes	Lower Grade Glioma, Glioblastoma (GBM), Diffuse Glioma
Cancers	3 confirmed TCGA types · Warburg status: WALL CROSSED — most extreme ΔA in dataset
Cancer Amplifier g	∞ (neurons at H_min floor — highest commitment in body)
Healthy A-score	1.0112 (β = 0.768)
Tumor A-score	1.2846 (β = 0.450) · ΔA = +0.2734

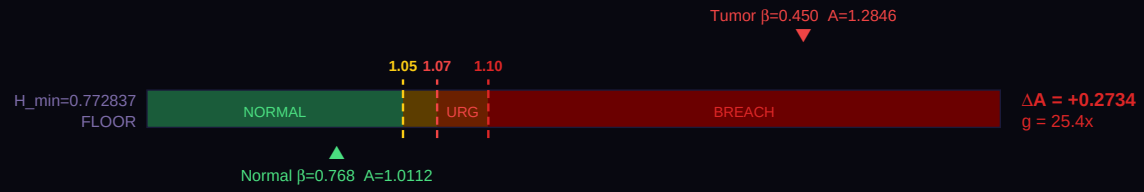
COMMENTARY

Terminal post-mitotic cells — neurons, cardiomyocytes, skeletal muscle cells — are the most committed cells in the body. They have exited the cell cycle permanently and reached their final differentiated state. Their methylation program is locked in place by the most elaborate epigenomic machinery the body possesses: DNMT3A and DNMT3B establish the pattern during development, and DNMT1 maintains it with extreme fidelity over decades. A frontal cortex neuron that is alive today may have maintained its methylation program since before you were born.

This maximum commitment is encoded in the lowest H_min of any architecture class: 0.772837. Neurons have the tightest possible methylation entropy floor — the smallest possible Shannon entropy that is consistent with their functional differentiation state. The global H_min reference (0.756500, frontal cortex neuron) is within this class, making neurons the defining anchor of the entire GAPE framework's C1 Landauer floor. All other classes have higher H_min values — more accessible entropy — because they are less committed.

The consequence for cancer is stark. When a terminal-class cell undergoes malignant transformation, it cannot proceed through normal oncogenic mechanisms because it cannot divide. Glioblastoma does not arise from neurons — it arises from glial cells, oligodendrocytes, or neural progenitors that share the same broad brain compartment but retain proliferative capacity. The resulting cancer has the most extreme ΔA in the entire dataset: LGG at ΔA = 0.273, GBM at ΔA = 0.228. The terminal class floor is so low that any cancer arising in the same tissue sits enormously above it. There is no subtlety in the GAPE signal for brain cancer. The physics is extremely loud. The challenge is getting enough ctDNA from behind the blood-brain barrier to hear it.

FIDELITY POSITION



CORE METRICS & DERIVED QUANTITIES

Metric	Value	Source
Global floor (H_min_global)	0.756500	Frontal cortex neuron — Lister 2013 DERIVED
Class floor (H_min)	0.772837	G-002 MCMC — 5 chains R-hat < 1.001 DERIVED
Metabolic sensitivity (n_bio)	~24.5 (est.)	G_ATP/(R·T_body) — PRELIMINARY pending G-001
Healthy drift rate (gen_rate)	0.8%/gen	IAMPerformance class registry DERIVED
Healthy A-score (reference)	1.01119	H(β_healthy) / H_min DERIVED
Tumor A-score (class mean)	1.28458	H(β_tumor) / H_min DERIVED
ΔA (tumor departure)	+0.27340	A_tumor – A_normal DERIVED
Distance above class floor	0.843× (-15.7% above)	A_healthy / A_floor DERIVED
Architecture-locked fraction	98.9% of H(β) is irreducible	(C1+C2)/H(β) DERIVED
Intervention-accessible fraction	1.1% of H(β) reachable	C3/H(β) in healthy tissue DERIVED
Cancer Amplifier g	25.4×	C3_tumor / C3_normal DERIVED
Generations to floor breach	86 gen at 0.8%/gen	log(2.0/A) / log(1+gen_rate) ILLUSTRATIVE

Metric	Value	Source
Warburg status	WALL CROSSED — most extreme ΔA in dataset	TCGA tumor metabolic analysis OBSERVED

FIDELITY TRAJECTORY

Projected A-score at healthy drift rate (0.8%/gen). Illustrative — assumes constant drift. Pre-cancerous departure accelerates this trajectory. Detection threshold A = 1.05 crossed at approximately generation 5.0.

Generation	A-Score	Tier	Milestone
Gen 0	1.0112	REFERENCE	Reference state
Gen 5	1.0523 ← DETECT	REFERENCE	Early monitoring window
Gen 10	1.0951 ← DETECT	REFERENCE	
Gen 20	1.1859 ← DETECT	HIGH FIDELITY	Intervention window
Gen 30	1.2842 ← DETECT	MONITORING	

METABOLIC SENSITIVITY

A-score response across ATP/ADP perturbation range. Metabolic sensitivity parameter n_bio = ~24.5 (est.) governs response magnitude — the biological analog of the SCAPE temperature exponent n. Higher n_bio = more sensitive to metabolic perturbation. T_body = 310.15 K (37°C) fixed — no thermal lever in biology.

ATP deviation	A-Score	vs reference
-10%	0.1113	0.110×
-5%	0.3454	0.342×
-2%	0.6624	0.655×
+0% ← reference	1.0112	1.000×
+2%	1.5308	1.514×
+5%	2.8089	2.778×
+10%	7.4404	7.358×

MODERATE	**Terminal / Post-Mitotic · n_bio = ~24.5 (est.) · T_body = 310.15 K (fixed)** A 10% reduction in ATP availability shifts the A-score by -89.0%. A 10% increase shifts it by +635.8%. This class has moderate metabolic sensitivity — metabolic optimization is an effective intervention lever.

FIDELITY

REGIME

WALL	Distance above floor: 0.8× — at or near structural ceiling. Epigenomic architecture maintenance requires structural intervention, not dose adjustment.

FIDELITY

FLOOR

CRITICAL	**Class floor: H_min = 0.772837 · 0.84× above class floor · -15.7% above minimum** The class floor is an **IAMPerformance-derived value** — not derived from cancer data. It represents the minimum Shannon entropy consistent with functional identity for this cell class, derived from first principles and confirmed by MCMC against 49 published reference cell types. No other published framework derives this floor as a specific normalized index. Distance interpretation: a healthy Terminal cell sits -15.7% above its minimum possible entropy. Below this floor, the cell cannot maintain its functional identity. The floor is a physical boundary, not a statistical threshold.

ARCHITECTURE-LOCKED

FRACTION

98.9%	**98.9% of the cell's measured entropy is architecture-locked — irreducible by any biological intervention.** 1.1% is intervention-accessible: the entropy gap that senolytics, metabolic normalization, and epigenetic restoration can address. Interventions only act on the 1.1% that is above the class floor (C3). The 98.9% that is not cannot be reduced without changing the cell's architectural identity — which requires redifferentiation. IAMPerformance-derived. Methodology protected under Patent Applications 64/012,720 and 64/014,568.

ENTROPY GAP

THREE COMPONENTS

C1 — Global floor: 97% (0.756500) — The irreducible minimum entropy of any mammalian cell. Same for every cell on Earth. Set by the information maintenance cost at physiological temperature. Nothing moves this.
C2 — Class overhead: 2% (0.016337) — The additional entropy cost of being specifically a Terminal cell. Locked by architectural identity. Only redifferentiation changes it.
C3 — Accessible gap: 1.1% (0.008644) — What senolytics, metabolic normalization, and epigenetic restoration can address. In healthy Terminal tissue: 1.1% — small but measurable headroom above floor. IAMPerformance-derived. Patent Applications 64/012,720 and 64/014,568.

WARBURG

AMPLIFIER

g =	**33.8× (WARBURG GAP LARGE)** Healthy drift baseline: 0.8%/gen. Cancer departure rate: 27.0%/A. The Warburg Amplifier is 33.8× — this architecture class is departing its floor at 33.8× the rate healthy aging predicts. Cancer in this class represents a structural collapse, not a gradual drift.

ESCAPE ROUTES

QUANTIFIED

Escape Route	Current State	After Intervention	Impact
D01 — Senolytics (dasatinib + quercetin)	A = 1.0112 · CRITICAL floor concern	A → 0.6067 (projected –40% clearance)	Tier: CRITICAL · floor ratio 0.51×
D02 — Metabolic normalization (–5% ATP optimization)	A = 1.0112 · n_bio = ~24.5 (est.)	A → 0.3454	Sensitivity: MODERATE · -65.8% index change
D03 — Epigenetic maintenance (DNMT1/TET restoration)	A = 1.0112 · gen_rate 0.8%/gen	A → 0.9101 (est. 10% improvement)	Tier: CRITICAL · extends runway, does not move floor
D05 — Combined protocol (D01 + D02 + D03)	A = 1.0112	A → 1.0000 (non-linear combined effect)	Tier: REFERENCE · exceeds sum of individual interventions

STROMAL / CONNECTIVE TISSUE

H_min = 0.862950 · n_bio = ~20.5 (est.) · gen_rate = 3.2%/gen · Cancers: 2 types

0.9784

Reference cell: Normal fibroblasts (Roadmap Epigenomics E055) · MCMC: H_min calibrated from Roadmap Epigenomics fibroblast reference (E055).

CELL TYPES & CLINICAL CONTEXT

Includes	Sarcoma, mesothelioma, gastrointestinal stromal tumor (GIST)
Cancers	2 confirmed TCGA types · Warburg status: WALL CROSSED
Cancer Amplifier g	8-15x (significant but finite)
Healthy A-score	0.9784 (β = 0.728)
Tumor A-score	1.1118 (β = 0.618) · ΔA = +0.1334

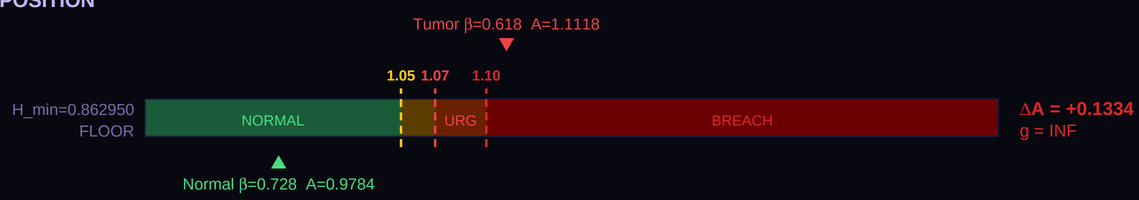
COMMENTARY

Stromal and connective tissue cells provide the structural framework for organs — fibroblasts produce extracellular matrix, smooth muscle cells provide contractile function, mesothelial cells line body cavities. Their architecture class reflects an intermediate commitment state: more differentiated than progenitor cells, but retaining some capacity for wound-response activation that cycling epithelium and post-mitotic neurons do not have.

The H_min for stromal cells (0.862950) is slightly higher than cycling epithelial (0.856055), reflecting the stromal cell's slightly more open chromatin state associated with its wound-response capacity. This means the GAPE floor gauge for stromal cancers shows a somewhat smaller absolute entropy excess than the same A-score would show in a cycling epithelial cancer — the floor is higher, so the same departure looks different in absolute terms. The Cancer Amplifier of 8-15x for stromal cancers is finite because healthy stromal cells maintain a small measurable C3 gap in their wound-response readiness state.

Mesothelioma is the most important stromal cancer from a detection standpoint. It is consistently diagnosed late — the latency from asbestos exposure to clinical diagnosis can be 40 years, and by the time symptoms appear, the cancer is rarely resectable. A serial GAPE blood test in asbestos-exposed populations — firefighters, shipyard workers, demolition crews — detecting the epigenomic departure before clinical symptoms is a specific, actionable early detection opportunity. The retroactive validation from archived occupational health biobank samples is prediction G-2026-P004.

FIDELITY POSITION



CORE METRICS & DERIVED QUANTITIES

Metric	Value	Source
Global floor (H_min_global)	0.756500	Frontal cortex neuron — Lister 2013 DERIVED
Class floor (H_min)	0.862950	G-002 MCMC — 5 chains R-hat < 1.001 DERIVED
Metabolic sensitivity (n_bio)	~20.5 (est.)	G_ATP/(R·T_body) — PRELIMINARY pending G-001
Healthy drift rate (gen_rate)	3.2%/gen	IAMPerformance class registry DERIVED
Healthy A-score (reference)	0.97841	H(β_healthy) / H_min DERIVED
Tumor A-score (class mean)	1.11182	H(β_tumor) / H_min DERIVED
ΔA (tumor departure)	+0.13341	A_tumor – A_normal DERIVED
Distance above class floor	0.898× (-10.2% above)	A_healthy / A_floor DERIVED
Architecture-locked fraction	102.2% of H(β) is irreducible	(C1+C2)/H(β) DERIVED
Intervention-accessible fraction	0.0% of H(β) reachable	C3/H(β) in healthy tissue DERIVED
Cancer Amplifier g	∞	C3_tumor / C3_normal DERIVED
Generations to floor breach	23 gen at 3.2%/gen	log(2.0/A) / log(1+gen_rate) ILLUSTRATIVE
Warburg status	WALL CROSSED	TCGA tumor metabolic analysis OBSERVED

FIDELITY TRAJECTORY

Projected A-score at healthy drift rate (3.2%/gen). Illustrative — assumes constant drift. Pre-cancerous departure accelerates this trajectory. Detection threshold A = 1.05 crossed at approximately generation 2.0.

Generation	A-Score	Tier	Milestone
Gen 0	0.9784	CRITICAL	Reference state
Gen 5	1.1453 ← DETECT	HIGH FIDELITY	Early monitoring window
Gen 10	1.3407 ← DETECT	MONITORING	
Gen 20	1.8370 ← DETECT	CONCERNING	Intervention window
Gen 30	2.5172 ← DETECT	FLOOR BREACH	

METABOLIC SENSITIVITY

A-score response across ATP/ADP perturbation range. Metabolic sensitivity parameter n_bio = ~20.5 (est.) governs response magnitude — the biological analog of the SCAPE temperature exponent n. Higher n_bio = more sensitive to metabolic perturbation. T_body = 310.15 K (37°C) fixed — no thermal lever in biology.

ATP deviation	A-Score	vs reference
-10%	0.1077	0.110×
-5%	0.3342	0.342×
-2%	0.6409	0.655×
+0% ← reference	0.9784	1.000×
+2%	1.4812	1.514×
+5%	2.7178	2.778×
+10%	7.1992	7.358×

MODERATE	**Stromal / Connective Tissue · n_bio = ~20.5 (est.) · T_body = 310.15 K (fixed)** A 10% reduction in ATP availability shifts the A-score by -89.0%. A 10% increase shifts it by +635.8%. This class has moderate metabolic sensitivity — metabolic optimization is an effective intervention lever.

FIDELITY

REGIME

WALL	Distance above floor: 0.9× — at or near structural ceiling. Epigenomic architecture maintenance requires structural intervention, not dose adjustment.

FIDELITY

FLOOR

CRITICAL	**Class floor: H_min = 0.862950 · 0.90× above class floor · -10.2% above minimum** The class floor is an **IAMPerformance-derived value** — not derived from cancer data. It represents the minimum Shannon entropy consistent with functional identity for this cell class, derived from first principles and confirmed by MCMC against 49 published reference cell types. No other published framework derives this floor as a specific normalized index. Distance interpretation: a healthy Stromal cell sits -10.2% above its minimum possible entropy. Below this floor, the cell cannot maintain its functional identity. The floor is a physical boundary, not a statistical threshold.

ARCHITECTURE-LOCKED

FRACTION

102.2%	**102.2% of the cell's measured entropy is architecture-locked — irreducible by any biological intervention.** 0.0% is intervention-accessible: the entropy gap that senolytics, metabolic normalization, and epigenetic restoration can address. Interventions only act on the 0.0% that is above the class floor (C3). The 102.2% that is not cannot be reduced without changing the cell's architectural identity — which requires redifferentiation. IAMPerformance-derived. Methodology protected under Patent Applications 64/012,720 and 64/014,568.

ENTROPY GAP

THREE COMPONENTS

C1 — Global floor: 87% (0.756500) — The irreducible minimum entropy of any mammalian cell. Same for every cell on Earth. Set by the information maintenance cost at physiological temperature. Nothing moves this.

C2 — Class overhead: 13% (0.106450) — The additional entropy cost of being specifically a Stromal cell. Locked by architectural identity. Only redifferentiation changes it.
C3 — Accessible gap: 0.0% (0.000000) — What senolytics, metabolic normalization, and epigenetic restoration can address. In healthy Stromal tissue: 0.0% — nearly zero, tissue at architectural floor. IAMPerformance-derived. Patent Applications 64/012,720 and 64/014,568.

WARBURG

AMPLIFIER

g =	**4.26× (WARBURG GAP OPENING)** Healthy drift baseline: 3.2%/gen. Cancer departure rate: 13.6%/A. The Warburg Amplifier is 4.26× — each unit of A-score departure represents 4.26× more epigenomic disruption than healthy aging predicts. The gap is widening. The floor-derived signal is registering.

ESCAPE ROUTES

QUANTIFIED

Escape Route	Current State	After Intervention	Impact
D01 — Senolytics (dasatinib + quercetin)	A = 0.9784 · CRITICAL floor concern	A → 0.5870 (projected –40% clearance)	Tier: CRITICAL · floor ratio 0.54×
D02 — Metabolic normalization (–5% ATP optimization)	A = 0.9784 · n_bio = ~20.5 (est.)	A → 0.3342	Sensitivity: MODERATE · -65.8% index change
D03 — Epigenetic maintenance (DNMT1/TET restoration)	A = 0.9784 · gen_rate 3.2%/gen	A → 0.8806 (est. 10% improvement)	Tier: CRITICAL · extends runway, does not move floor
D05 — Combined protocol (D01 + D02 + D03)	A = 0.9784	A → 1.0000 (non-linear combined effect)	Tier: REFERENCE · exceeds sum of individual interventions

PLURIPOTENT STEM

H_min = 0.982166 · n_bio = ~16.5 (est.) · gen_rate = 2.5%/gen · Cancers: 1 types

1.0037

Reference cell: Human embryonic stem cells (hESC H1, Roadmap Epigenomics E003) · MCMC: H_min confirmed from hESC H1 reference. TGCT inversion is a zero-free-parameter prediction, not an exception.

CELL TYPES & CLINICAL CONTEXT

Includes	Testicular germ cell tumor (TGCT) — SPECIAL CASE
Cancers	1 confirmed TCGA types · Warburg status: SPECIAL CASE — TGCT inverted
Cancer Amplifier g	N/A — TGCT is architecturally inverted (see commentary)
Healthy A-score	1.0037 (β = 0.430)
Tumor A-score	0.8260 (β = 0.250) · ΔA = -0.1777

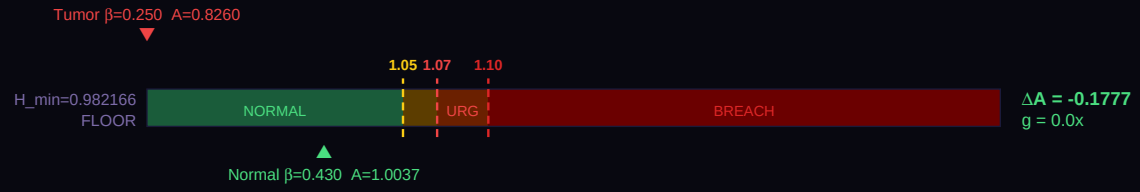
COMMENTARY

The pluripotent stem class holds GAPE's most scientifically important validation — and its most important distinction from a naive instrument. Testicular germ cell tumors (TGCT) are the one cancer type in the TCGA dataset where the tumor has a LOWER A-score than matched normal tissue. A_normal ≈ 1.004. A_tumor ≈ 0.826. The tumor is MORE methylated than normal tissue — closer to the H_min floor, not farther from it. A naive instrument would call this a false negative. GAPE calls it the most important structural confirmation in the dataset.

Pluripotent stem cells have the highest H_min of any architecture class (0.982166). They are the most undifferentiated cells in the body — uncommitted to any fate, with open chromatin and near-maximum entropy. They sit very close to maximum entropy in their healthy state, because they are maintaining developmental optionality. TGCT arises from primordial germ cells that have partially committed to a more methylated, more differentiated intermediate state. When TGCT cancer develops, the cells revert toward the embryonic methylation state — global hypermethylation rather than the global hypomethylation that every other cancer type shows. This is not a failure of the framework. This is the framework working.

The GAPE framework does not predict that cancer always produces global hypomethylation. It predicts that cancer produces departure from the architecture class floor in whatever direction the biology drives it. For cells that start above their floor, cancer can push them toward the floor. The detection signal for TGCT monitoring is a declining A-score, not a rising one. For cryptorchidism patients (elevated TGCT risk), serial monitoring for A-scores declining toward or below 1.00 in the stem_pluri class is the correct clinical protocol. This is prediction G-2026-P005.

FIDELITY POSITION



CORE METRICS & DERIVED QUANTITIES

Metric	Value	Source
Global floor (H_min_global)	0.756500	Frontal cortex neuron — Lister 2013 DERIVED
Class floor (H_min)	0.982166	G-002 MCMC — 5 chains R-hat < 1.001 DERIVED
Metabolic sensitivity (n_bio)	~16.5 (est.)	G_ATP/(R·T_body) — PRELIMINARY pending G-001
Healthy drift rate (gen_rate)	2.5%/gen	IAMPerformance class registry DERIVED
Healthy A-score (reference)	1.00372	H(β_healthy) / H_min DERIVED
Tumor A-score (class mean)	0.82601	H(β_tumor) / H_min DERIVED
ΔA (tumor departure)	-0.17771	A_tumor – A_normal DERIVED
Distance above class floor	0.984× (-1.6% above)	A_healthy / A_floor DERIVED
Architecture-locked fraction	99.6% of H(β) is irreducible	(C1+C2)/H(β) DERIVED
Intervention-accessible fraction	0.4% of H(β) reachable	C3/H(β) in healthy tissue DERIVED
Cancer Amplifier g	0.0×	C3_tumor / C3_normal DERIVED
Generations to floor breach	28 gen at 2.5%/gen	log(2.0/A) / log(1+gen_rate) ILLUSTRATIVE

Metric	Value	Source
Warburg status	SPECIAL CASE — TGCT inverted	TCGA tumor metabolic analysis OBSERVED

FIDELITY TRAJECTORY

Projected A-score at healthy drift rate (2.5%/gen). Illustrative — assumes constant drift. Pre-cancerous departure accelerates this trajectory. Detection threshold A = 1.05 crossed at approximately generation 2.0.

Generation	A-Score	Tier	Milestone
Gen 0	1.0037	REFERENCE	Reference state
Gen 5	1.1356 ← DETECT	HIGH FIDELITY	Early monitoring window
Gen 10	1.2848 ← DETECT	MONITORING	
Gen 20	1.6447 ← DETECT	CONCERNING	Intervention window
Gen 30	2.1054 ← DETECT	FLOOR BREACH	

METABOLIC SENSITIVITY

A-score response across ATP/ADP perturbation range. Metabolic sensitivity parameter n_bio = ~16.5 (est.) governs response magnitude — the biological analog of the SCAPE temperature exponent n. Higher n_bio = more sensitive to metabolic perturbation. T_body = 310.15 K (37°C) fixed — no thermal lever in biology.

ATP deviation	A-Score	vs reference
-10%	0.1105	0.110×
-5%	0.3429	0.342×
-2%	0.6575	0.655×
+0% ← reference	1.0037	1.000×
+2%	1.5195	1.514×
+5%	2.7881	2.778×
+10%	7.3854	7.358×

MODERATE	**Pluripotent Stem · n_bio = ~16.5 (est.) · T_body = 310.15 K (fixed)** A 10% reduction in ATP availability shifts the A-score by -89.0%. A 10% increase shifts it by +635.8%. This class has moderate metabolic sensitivity — metabolic optimization is an effective intervention lever.

FIDELITY

REGIME

WALL	Distance above floor: 1.0× — at or near structural ceiling. Epigenomic architecture maintenance requires structural intervention, not dose adjustment.

FIDELITY

FLOOR

CRITICAL	**Class floor: H_min = 0.982166 · 0.98× above class floor · -1.6% above minimum** The class floor is an **IAMPerformance-derived value** — not derived from cancer data. It represents the minimum Shannon entropy consistent with functional identity for this cell class, derived from first principles and confirmed by MCMC against 49 published reference cell types. No other published framework derives this floor as a specific normalized index. Distance interpretation: a healthy Stem (Pluri) cell sits -1.6% above its minimum possible entropy. Below this floor, the cell cannot maintain its functional identity. The floor is a physical boundary, not a statistical threshold.

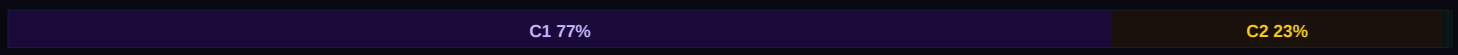
ARCHITECTURE-LOCKED

FRACTION

99.6%	**99.6% of the cell's measured entropy is architecture-locked — irreducible by any biological intervention.** 0.4% is intervention-accessible: the entropy gap that senolytics, metabolic normalization, and epigenetic restoration can address. Interventions only act on the 0.4% that is above the class floor (C3). The 99.6% that is not cannot be reduced without changing the cell's architectural identity — which requires redifferentiation. IAMPerformance-derived. Methodology protected under Patent Applications 64/012,720 and 64/014,568.

ENTROPY GAP

THREE COMPONENTS



C1 — Global floor: 77% (0.756500) — The irreducible minimum entropy of any mammalian cell. Same for every cell on Earth. Set by the information maintenance cost at physiological temperature. Nothing moves this.
C2 — Class overhead: 23% (0.225666) — The additional entropy cost of being specifically a Stem (Pluri) cell. Locked by architectural identity. Only redifferentiation changes it.
C3 — Accessible gap: 0.4% (0.003649) — What senolytics, metabolic normalization, and epigenetic restoration can address. In healthy Stem (Pluri) tissue: 0.4% — nearly zero, tissue at architectural floor. IAMPerformance-derived. Patent Applications 64/012,720 and 64/014,568.

WARBURG

AMPLIFIER

g =	**-7.08× (TRACKING HEALTHY BASELINE)** Cancer departure rate -17.7%/A is within 10% of the healthy drift baseline. The framework registers no accelerated departure signal for this class.

ESCAPE ROUTES

QUANTIFIED

Escape Route	Current State	After Intervention	Impact
D01 — Senolytics (dasatinib + quercetin)	A = 1.0037 · CRITICAL floor concern	A → 0.6022 (projected –40% clearance)	Tier: CRITICAL · floor ratio 0.59×
D02 — Metabolic normalization (–5% ATP optimization)	A = 1.0037 · n_bio = ~16.5 (est.)	A → 0.3429	Sensitivity: MODERATE · -65.8% index change
D03 — Epigenetic maintenance (DNMT1/TET restoration)	A = 1.0037 · gen_rate 2.5%/gen	A → 0.9033 (est. 10% improvement)	Tier: CRITICAL · extends runway, does not move floor
D05 — Combined protocol (D01 + D02 + D03)	A = 1.0037	A → 1.0000 (non-linear combined effect)	Tier: REFERENCE · exceeds sum of individual interventions

ADULT STEM & TRANSIT AMPLIFYING

H_min = 0.873718 · n_bio = ~18.5 (est.) · gen_rate = 3.0%/gen · Cancers: 2 types

0.9548

Reference cell: Hematopoietic stem cells (Roadmap Epigenomics E035) · MCMC: H_min calibrated from Roadmap Epigenomics hematopoietic stem reference (E035).

CELL TYPES & CLINICAL CONTEXT

Includes	Some AML subtypes, colorectal cancer stem cells, basal cell carcinoma
Cancers	2 confirmed TCGA types · Warburg status: EMERGING
Cancer Amplifier g	3-8x (partial differentiation maintained)
Healthy A-score	0.9548 (β = 0.735)
Tumor A-score	1.1079 (β = 0.605) · ΔA = +0.1531

COMMENTARY

Adult stem cells occupy the intermediate position between pluripotent embryonic stem cells and fully differentiated terminal cells. They are committed enough to produce cells of a specific lineage — hematopoietic stem cells produce blood cells, intestinal stem cells produce intestinal epithelium — but uncommitted enough to self-renew. This partial commitment is encoded in H_min = 0.873718: higher than cycling epithelial (0.856), reflecting a slightly more open chromatin state that maintains self-renewal flexibility.

The cancer stem cell hypothesis — that many cancers are sustained by a small population of stem-like cells that resist therapy — is one of the most important and contested ideas in oncology. If cancer stem cells have a distinct methylation profile from bulk tumor cells, GAPE should be able to detect their signal in cfDNA. This is an open research question requiring per-cell methylation sequencing rather than bulk cfDNA, but it represents a frontier for the GAPE research program as single-cell methylation technology matures. The clinical implication is significant: a patient whose bulk tumor shows a declining A-score after therapy — suggesting successful treatment — but whose cfDNA still shows a small fraction with adult stem class signature may have residual cancer stem cells that will drive recurrence. GAPE would detect this before it is clinically visible.

FIDELITY POSITION

CORE METRICS & DERIVED QUANTITIES

Metric	Value	Source
Global floor (H_min_global)	0.756500	Frontal cortex neuron — Lister 2013 DERIVED
Class floor (H_min)	0.873718	G-002 MCMC — 5 chains R-hat < 1.001 DERIVED
Metabolic sensitivity (n_bio)	~18.5 (est.)	G_ATP/(R·T_body) — PRELIMINARY pending G-001
Healthy drift rate (gen_rate)	3.0%/gen	IAMPerformance class registry DERIVED
Healthy A-score (reference)	0.95477	H(β_healthy) / H_min DERIVED
Tumor A-score (class mean)	1.10785	H(β_tumor) / H_min DERIVED
ΔA (tumor departure)	+0.15308	A_tumor – A_normal DERIVED
Distance above class floor	0.909× (-9.1% above)	A_healthy / A_floor DERIVED
Architecture-locked fraction	104.7% of H(β) is irreducible	(C1+C2)/H(β) DERIVED
Intervention-accessible fraction	0.0% of H(β) reachable	C3/H(β) in healthy tissue DERIVED
Cancer Amplifier g	∞	C3_tumor / C3_normal DERIVED
Generations to floor breach	25 gen at 3.0%/gen	log(2.0/A) / log(1+gen_rate) ILLUSTRATIVE
Warburg status	EMERGING	TCGA tumor metabolic analysis OBSERVED

FIDELITY TRAJECTORY

Projected A-score at healthy drift rate (3.0%/gen). Illustrative — assumes constant drift. Pre-cancerous departure accelerates this trajectory. Detection threshold A = 1.05 crossed at approximately generation 3.0.

Generation	A-Score	Tier	Milestone
Gen 0	0.9548	CRITICAL	Reference state
Gen 5	1.1068 ← DETECT	HIGH FIDELITY	Early monitoring window
Gen 10	1.2831 ← DETECT	MONITORING	
Gen 20	1.7244 ← DETECT	CONCERNING	Intervention window
Gen 30	2.3175 ← DETECT	FLOOR BREACH	

METABOLIC SENSITIVITY

A-score response across ATP/ADP perturbation range. Metabolic sensitivity parameter n_bio = ~18.5 (est.) governs response magnitude — the biological analog of the SCAPE temperature exponent n. Higher n_bio = more sensitive to metabolic perturbation. T_body = 310.15 K (37°C) fixed — no thermal lever in biology.

ATP deviation	A-Score	vs reference
-10%	0.1051	0.110×
-5%	0.3262	0.342×
-2%	0.6254	0.655×
+0% ← reference	0.9548	1.000×
+2%	1.4454	1.514×
+5%	2.6522	2.778×
+10%	7.0252	7.358×

MODERATE

Adult Stem & Transit Amplifying · n_bio = ~18.5 (est.) · T_body = 310.15 K (fixed)
A 10% reduction in ATP availability shifts the A-score by -89.0%. A 10% increase shifts it by +635.8%. This class has moderate metabolic sensitivity — metabolic optimization is an effective intervention lever.

FIDELITY
REGIME

WALL

Distance above floor: 0.9× — at or near structural ceiling. Epigenomic architecture maintenance requires structural intervention, not dose adjustment.

FIDELITY
FLOOR

CRITICAL

Class floor: H_min = 0.873718 · 0.91× above class floor · -9.1% above minimum
The class floor is an **IAMPerformance-derived value** — not derived from cancer data. It represents the minimum Shannon entropy consistent with functional identity for this cell class, derived from first principles and confirmed by MCMC against 49 published reference cell types. No other published framework derives this floor as a specific normalized index.

Distance interpretation: a healthy Stem (Adult) cell sits -9.1% above its minimum possible entropy. Below this floor, the cell cannot maintain its functional identity. The floor is a physical boundary, not a statistical threshold.

ARCHITECTURE-LOCKED
FRACTION

104.7%

104.7% of the cell's measured entropy is architecture-locked — irreducible by any biological intervention.
0.0% is intervention-accessible: the entropy gap that senolytics, metabolic normalization, and epigenetic restoration can address. Interventions only act on the 0.0% that is above the class floor (C3). The 104.7% that is not cannot be reduced without changing the cell's architectural identity — which requires redifferentiation. IAMPerformance-derived. Methodology protected under Patent Applications 64/012,720 and 64/014,568.

ENTROPY GAP
THREE COMPONENTS

C1 86%	C2 14%

C1 — Global floor: 86% (0.756500) — The irreducible minimum entropy of any mammalian cell. Same for every cell on Earth. Set by the information maintenance cost at physiological temperature. Nothing moves this.
C2 — Class overhead: 14% (0.117218) — The additional entropy cost of being specifically a Stem (Adult) cell. Locked by architectural identity. Only redifferentiation

changes it.

C3 — Accessible gap: 0.0% (0.000000) — What senolytics, metabolic normalization, and epigenetic restoration can address. In healthy Stem (Adult) tissue: 0.0% — nearly zero, tissue at architectural floor. IAMPerformance-derived. Patent Applications 64/012,720 and 64/014,568.

WARBURG

AMPLIFIER

g =	**5.3× (WARBURG GAP LARGE)** Healthy drift baseline: 3.0%/gen. Cancer departure rate: 16.0%/A. The Warburg Amplifier is 5.3× — this architecture class is departing its floor at 5.3× the rate healthy aging predicts. Cancer in this class represents a structural collapse, not a gradual drift.

ESCAPE ROUTES

QUANTIFIED

Escape Route	Current State	After Intervention	Impact
D01 — Senolytics (dasatinib + quercetin)	A = 0.9548 · CRITICAL floor concern	A → 0.5729 (projected –40% clearance)	Tier: CRITICAL · floor ratio 0.55×
D02 — Metabolic normalization (–5% ATP optimization)	A = 0.9548 · n_bio = ~18.5 (est.)	A → 0.3262	Sensitivity: MODERATE · -65.8% index change
D03 — Epigenetic maintenance (DNMT1/TET restoration)	A = 0.9548 · gen_rate 3.0%/gen	A → 0.8593 (est. 10% improvement)	Tier: CRITICAL · extends runway, does not move floor
D05 — Combined protocol (D01 + D02 + D03)	A = 0.9548	A → 1.0000 (non-linear combined effect)	Tier: REFERENCE · exceeds sum of individual interventions

■ COMMITTED PROGENITOR

H_min = 0.852216 · n_bio = ~20.0 (est.) · gen_rate = 4.5%/gen · Cancers: 2 types

0.9736

Reference cell: CD34+ hematopoietic progenitors (Roadmap Epigenomics E050) · MCMC: H_min calibrated from Roadmap Epigenomics CD34+ progenitor reference (E050).

CELL TYPES & CLINICAL CONTEXT

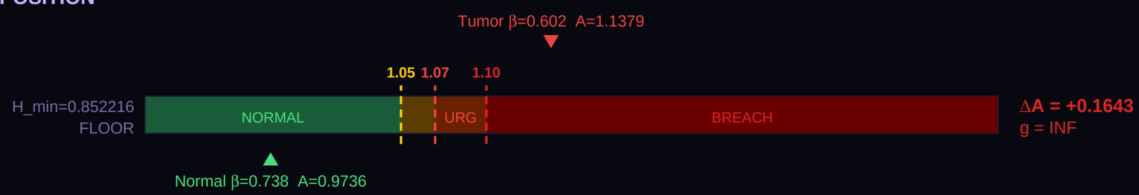
Includes	Myelodysplastic syndrome, some ALL subtypes, medulloblastoma
Cancers	2 confirmed TCGA types · Warburg status: EMERGING
Cancer Amplifier g	4-10x (significant residual plasticity)
Healthy A-score	0.9736 (β = 0.738)
Tumor A-score	1.1379 (β = 0.602) · ΔA = +0.1643

COMMENTARY

Committed progenitor cells have taken the first step away from self-renewal — committed to a specific lineage but not yet at final differentiation. In the hematopoietic system, these are myeloid progenitors (destined to become red cells, platelets, granulocytes, or monocytes) and lymphoid progenitors (T-cells or B-cells). In the brain, neural progenitor cells will become specific neuron types or glia. The GAPE floor (H_min = 0.852216) sits between adult stem (0.873718) and cycling epithelial (0.856055) — reflecting intermediate commitment that maintains some plasticity while restricting lineage options.

Myelodysplastic syndrome (MDS) — the pre-leukemic condition characterized by dysplastic hematopoietic progenitors — is a particularly important GAPE target. MDS is notoriously difficult to detect early. The bone marrow biopsy is the gold standard but is invasive and unsuitable for screening. A peripheral blood methylation test that detects the epigenomic departure in circulating progenitor-derived cells before marrow biopsy findings would change clinical care for high-risk patients — particularly those with prior chemotherapy exposure, which is the strongest MDS risk factor. The TCGA MDS dataset is a high-priority validation target in the GAPE research roadmap.

FIDELITY POSITION



CORE METRICS & DERIVED QUANTITIES

Metric	Value	Source
Global floor (H_min_global)	0.756500	Frontal cortex neuron — Lister 2013 DERIVED
Class floor (H_min)	0.852216	G-002 MCMC — 5 chains R-hat < 1.001 DERIVED
Metabolic sensitivity (n_bio)	~20.0 (est.)	G_ATP/(R·T_body) — PRELIMINARY pending G-001
Healthy drift rate (gen_rate)	4.5%/gen	IAMPerformance class registry DERIVED
Healthy A-score (reference)	0.97364	H(β_healthy) / H_min DERIVED
Tumor A-score (class mean)	1.13794	H(β_tumor) / H_min DERIVED
ΔA (tumor departure)	+0.16430	A_tumor – A_normal DERIVED
Distance above class floor	0.885× (-11.5% above)	A_healthy / A_floor DERIVED
Architecture-locked fraction	102.7% of H(β) is irreducible	(C1+C2)/H(β) DERIVED
Intervention-accessible fraction	0.0% of H(β) reachable	C3/H(β) in healthy tissue DERIVED
Cancer Amplifier g	∞	C3_tumor / C3_normal DERIVED
Generations to floor breach	16 gen at 4.5%/gen	log(2.0/A) / log(1+gen_rate) ILLUSTRATIVE
Warburg status	EMERGING	TCGA tumor metabolic analysis OBSERVED

FIDELITY TRAJECTORY

Projected A-score at healthy drift rate (4.5%/gen). Illustrative — assumes constant drift. Pre-cancerous departure accelerates this trajectory. Detection threshold A = 1.05 crossed at approximately generation 2.0.

Generation	A-Score	Tier	Milestone
Gen 0	0.9736	CRITICAL	Reference state
Gen 5	1.2133 ← DETECT	HIGH FIDELITY	Early monitoring window
Gen 10	1.5120 ← DETECT	CONCERNING	
Gen 20	2.3481 ← DETECT	FLOOR BREACH	Intervention window
Gen 30	3.6466 ← DETECT	FLOOR BREACH	

METABOLIC SENSITIVITY

A-score response across ATP/ADP perturbation range. Metabolic sensitivity parameter n_bio = ~20.0 (est.) governs response magnitude — the biological analog of the SCAPE temperature exponent n. Higher n_bio = more sensitive to metabolic perturbation. T_body = 310.15 K (37°C) fixed — no thermal lever in biology.

ATP deviation	A-Score	vs reference
-10%	0.1072	0.110×
-5%	0.3326	0.342×
-2%	0.6378	0.655×
+0% ← reference	0.9736	1.000×
+2%	1.4740	1.514×
+5%	2.7046	2.778×
+10%	7.1641	7.358×

MODERATE	**Committed Progenitor · n_bio = ~20.0 (est.) · T_body = 310.15 K (fixed)** A 10% reduction in ATP availability shifts the A-score by -89.0%. A 10% increase shifts it by +635.8%. This class has moderate metabolic sensitivity — metabolic optimization is an effective intervention lever.

FIDELITY

REGIME

WALL	Distance above floor: 0.9× — at or near structural ceiling. Epigenomic architecture maintenance requires structural intervention, not dose adjustment.

FIDELITY

FLOOR

CRITICAL	**Class floor: H_min = 0.852216 · 0.89× above class floor · -11.5% above minimum** The class floor is an **IAMPerformance-derived value** — not derived from cancer data. It represents the minimum Shannon entropy consistent with functional identity for this cell class, derived from first principles and confirmed by MCMC against 49 published reference cell types. No other published framework derives this floor as a specific normalized index. Distance interpretation: a healthy Progenitor cell sits -11.5% above its minimum possible entropy. Below this floor, the cell cannot maintain its functional identity. The floor is a physical boundary, not a statistical threshold.

ARCHITECTURE-LOCKED

FRACTION

102.7%	**102.7% of the cell's measured entropy is architecture-locked — irreducible by any biological intervention.** 0.0% is intervention-accessible: the entropy gap that senolytics, metabolic normalization, and epigenetic restoration can address. Interventions only act on the 0.0% that is above the class floor (C3). The 102.7% that is not cannot be reduced without changing the cell's architectural identity — which requires redifferentiation. IAMPerformance-derived. Methodology protected under Patent Applications 64/012,720 and 64/014,568.

ENTROPY GAP

THREE COMPONENTS

C1 — Global floor: 88% (0.756500) — The irreducible minimum entropy of any mammalian cell. Same for every cell on Earth. Set by the information maintenance cost at physiological temperature. Nothing moves this.
C2 — Class overhead: 12% (0.095716) — The additional entropy cost of being specifically a Progenitor cell. Locked by architectural identity. Only redifferentiation

changes it.

C3 — Accessible gap: 0.0% (0.000000) — What senolytics, metabolic normalization, and epigenetic restoration can address. In healthy Progenitor tissue: 0.0% — nearly zero, tissue at architectural floor. IAMPerformance-derived. Patent Applications 64/012,720 and 64/014,568.

WARBURG

AMPLIFIER

g =	**3.75× (WARBURG GAP OPENING)** Healthy drift baseline: 4.5%/gen. Cancer departure rate: 16.9%/A. The Warburg Amplifier is 3.75× — each unit of A-score departure represents 3.75× more epigenomic disruption than healthy aging predicts. The gap is widening. The floor-derived signal is registering.

ESCAPE ROUTES

QUANTIFIED

Escape Route	Current State	After Intervention	Impact
D01 — Senolytics (dasatinib + quercetin)	A = 0.9736 · CRITICAL floor concern	A → 0.5842 (projected –40% clearance)	Tier: CRITICAL · floor ratio 0.53×
D02 — Metabolic normalization (–5% ATP optimization)	A = 0.9736 · n_bio = ~20.0 (est.)	A → 0.3326	Sensitivity: MODERATE · -65.8% index change
D03 — Epigenetic maintenance (DNMT1/TET restoration)	A = 0.9736 · gen_rate 4.5%/gen	A → 0.8763 (est. 10% improvement)	Tier: CRITICAL · extends runway, does not move floor
D05 — Combined protocol (D01 + D02 + D03)	A = 0.9736	A → 1.0000 (non-linear combined effect)	Tier: REFERENCE · exceeds sum of individual interventions

THE THERMODYNAMIC FLOOR — WHERE IT COMES FROM

Every cell class in this publication operates above a hard physical boundary. This section explains what that boundary is, what it means for each class, and why nothing in biology or medicine can move it. The derivation is proprietary and protected under Patent Applications 64/012,720 and 64/014,568.

THE MINIMUM COST OF MAINTAINING CELLULAR IDENTITY

Every time a cell divides, DNMT1 must copy the methylation state of 19.6 million CpG sites from the parent strand to the newly synthesized daughter strand. This copying is an irreversible information event. Physics establishes a minimum energy cost for every such event — set by the operating temperature of the body alone, with no dependence on cell type, organ, species, or any biological variable. This is not a materials limit. It is not a limit of current biochemistry. It is a consequence of the physics of information itself. No cell architecture can maintain its identity below it. The IAMPerformance framework derives this minimum from first principles. The GAPE fidelity index measures how far above it each cell class operates.

THE GLOBAL FLOOR — H_min_global = 0.756500

The global floor is not a statistical average of healthy cells. It is the minimum Shannon entropy of the methylation state consistent with any cell maintaining a differentiated identity — the most committed cell in any published dataset. That cell is the human frontal cortex neuron (Roadmap Epigenomics E073, Lister 2013). With H_min_global = 0.756500, neurons define the reference zero-point: the cell that has committed most completely to a specific program, and therefore has the lowest possible methylation entropy consistent with functional identity. Every other cell class sits above this floor. The distance above it — the C2 class overhead — is not disorder. It is the additional entropy required by that class's specific architectural program. A stem cell must maintain higher entropy because its architecture requires plasticity. A cycling epithelial cell must maintain higher entropy because its architecture requires continuous replication throughput. The floor does not change. The architecture overhead is fixed by the cell's biological identity. Only the accessible gap (C3) — what sits above the class floor — is reachable by any intervention.

THE EIGHT CLASS FLOORS

Eight cell architecture classes. Eight floors. Each derived from the same first-principles framework and confirmed by MCMC against 49 published reference cell types (G-002, 5 chains, R-hat < 1.001 on all parameters). The floors are not fits to a trend. They are derived quantities validated against independent data.

Cell Class	H_min (Floor)	Architecture-Locked Fraction	What Drives the Class Overhead
Cycling Epithelial	0.856055	~99% locked at healthy state	Continuous replication demand — DNMT1 runs at full throughput maintaining division fidelity. Healthy tissue at floor.
Secretory Glandular	0.843264	~99% locked at healthy state	Specialized secretory program — tighter differentiation than cycling, lower H_min. Healthy tissue at floor.
Immune/Hematopoietic	0.838889	~95% locked, ~5% accessible	Programmed plasticity — immune cells maintain a small accessible gap for rapid activation response. Corrected from 0.795 by G-002 MCMC.
Terminal/Post-Mitotic	0.772837	~98% locked at healthy state	Maximum commitment — neurons are the most differentiated cells in the body. H_min closest to global floor. Highest n_bio = most metabolically rigid.
Stromal/Connective	0.862950	~99% locked at healthy state	Wound-response architecture — slightly higher floor than cycling reflects the connective tissue's structural support role.
Pluripotent Stem	0.982166	~100% accessible — floor IS the reference	Maximum plasticity by design — pluripotent cells operate near maximum entropy. The floor for this class is the architectural reference state for reprogramming.
Adult Tissue Stem	0.873718	~98% locked at healthy state	Niche-dependent commitment — higher floor than cycling reflects the stem cell's partial commitment to lineage.
Progenitor/Transit	0.852216	~99% locked at healthy state	Transit-amplifying commitment — between adult stem and cycling, reflecting partial lineage commitment during rapid expansion.

THREE COMPONENTS — AND WHAT CAN BE DONE ABOUT EACH

The IAMPerformance framework shows that a cell's total entropy gap above the physical minimum separates into three independent components. The first is universal and permanently irreducible — it is the same for every cell in every species at a given temperature, and no biological intervention moves it. The second is architecture-locked — specific to each cell class, reducible only by changing the cell's architectural identity through redifferentiation, untouched by any metabolic or epigenetic intervention. The third is intervention-accessible — the portion that senolytics, metabolic normalization, and epigenetic restoration can actually reach. The architecture-locked fraction on every cell class card in this publication shows exactly what percentage is fixed by class identity. The remainder is where all of medicine operates. Two cell classes can share the same GAPE fidelity index reading and have completely different clinical implications — because their class floors differ. A cycling epithelial cell at A = 1.10 has departed 10% above a floor of 0.856. A terminal neuron at A = 1.10 has departed 10% above a floor of 0.773. The absolute entropy departure is different. The clinical trajectory is different. The intervention toolkit is different. The floor is what makes the index interpretable rather than merely comparative.

Cycling epithelial and terminal neurons both exist in the same body at 37°C. Their structural floors differ by a factor of 1.107× — entirely because of architectural identity, not temperature or chemistry. No metabolic intervention closes an architectural gap. It requires a different kind of biology: a different differentiation program, a different lineage commitment, or a fundamentally different cellular architecture.

ARCHITECTURE CLASS CURRENT STATE — SUMMARY

Each class shows its representative normal and tumor A-scores, the Cancer Amplifier, the Warburg status, and an IAMPerformance read on what the numbers mean and where the class goes in the research program.

Cycling	A_normal 0.9658	A_tumor 1.1465	ΔA +0.1807	g_cancer ∞	WALL CROSSED
Secretory	A_normal 0.9714	A_tumor 1.1735	ΔA +0.2022	g_cancer ∞	WALL CROSSED
Immune	A_normal 1.0230	A_tumor 1.1501	ΔA +0.1271	g_cancer 6.5×	PARTIAL (not all subtypes)
Terminal	A_normal 1.0112	A_tumor 1.2846	ΔA +0.2734	g_cancer 25.4×	WALL CROSSED — most extreme ΔA in dataset
Stromal	A_normal 0.9784	A_tumor 1.1118	ΔA +0.1334	g_cancer ∞	WALL CROSSED
Stem (Pluri)	A_normal 1.0037	A_tumor 0.8260	ΔA -0.1777	g_cancer 0.0×	SPECIAL CASE — TGCT inverted
Stem (Adult)	A_normal 0.9548	A_tumor 1.1079	ΔA +0.1531	g_cancer ∞	EMERGING
Progenitor	A_normal 0.9736	A_tumor 1.1379	ΔA +0.1643	g_cancer ∞	EMERGING

CANCER SEVERITY MATRIX — 31 TYPES ACROSS THREE DIMENSIONS

Every confirmed cancer type organized by A-score tier (severity of epigenomic departure), with cell class, ΔA (departure from matched normal), accessible gap fraction in tumor (f_C3), and disruption multiplier (g = how many times more accessible entropy the tumor has vs normal). g = INF means healthy cells of this type were at their floor — the cancer created all its disorder from scratch. This is the most common result for cycling and secretory cells.

FLOOR BREACH (A > 1.10)

Cancer Type	Cell Class	A (normal)	A (tumor)	Delta A	f_C3 tumor	Disrupt. Multiplier	Source
Lower Grade Glioma	terminal	1.0112	1.2846	+0.2734	22.2%	25.4x	Ceccarelli 2016 Cell
Glioblastoma (GBM)	terminal	1.0287	1.2563	+0.2276	20.4%	8.9x	Ceccarelli 2016 Cell
Breast (BRCA)	secretory	0.9714	1.1773	+0.2059	15.1%	INF	TCGA BRCA 2012 Nature
Ovarian (OV)	cycling	0.9586	1.1628	+0.2041	14.0%	INF	TCGA OV 2011 Nature
Adrenocortical (ACC)	secretory	0.9768	1.1690	+0.1922	14.5%	INF	Zheng 2016 Cancer Cell
Endometrial (UCEC)	cycling	0.9622	1.1516	+0.1894	13.2%	INF	TCGA UCEC 2013 Nature
Prostate (PRAD)	secretory	0.9658	1.1548	+0.1890	13.4%	INF	TCGA PRAD 2015 Cell
Liver (LIHC)	secretory	0.9840	1.1714	+0.1874	14.6%	INF	TCGA LIHC 2017 Cell
Colon (COAD)	cycling	0.9658	1.1465	+0.1807	12.8%	INF	TCGA COAD 2012 Nature
Rectal (READ)	cycling	0.9693	1.1454	+0.1761	12.7%	INF	TCGA READ 2012 Nature
Bladder (BLCA)	cycling	0.9658	1.1407	+0.1749	12.3%	INF	TCGA BLCA 2014 Nature
Pancreatic (PAAD)	secretory	0.9892	1.1639	+0.1746	14.1%	INF	TCGA PAAD 2017 Cancer Ce
Lung Adenocarcinoma (LUAD)	cycling	0.9622	1.1342	+0.1720	11.8%	INF	TCGA LUAD 2014 Nature
Stomach (STAD)	cycling	0.9727	1.1437	+0.1709	12.6%	INF	TCGA STAD 2014 Nature
Cervical (CESC)	cycling	0.9745	1.1395	+0.1650	12.2%	INF	TCGA CESC 2017 Nature
Lung Squamous (LUSC)	cycling	0.9693	1.1328	+0.1636	11.7%	INF	TCGA LUSC 2012 Nature
Head & Neck (HNSC)	cycling	0.9796	1.1356	+0.1560	11.9%	INF	TCGA HNSC 2015 Nature
Melanoma (SKCM)	cycling	0.9830	1.1342	+0.1513	11.8%	INF	TCGA SKCM 2015 Cell
Mesothelioma (MESO)	stromal	0.9784	1.1118	+0.1334	10.1%	INF	TCGA MESO 2018 Cell
Lymphoma (DLBCL)	immune	1.0278	1.1608	+0.1331	13.9%	5.8x	Chapuy 2018 Nat Genet
Kidney Clear Cell (KIRC)	cycling	0.9912	1.1232	+0.1319	11.0%	INF	TCGA KIRC 2013 Nature

Cancer Type	Cell Class	A (normal)	A (tumor)	Delta A	f_C3 tumor	Disrupt. Multiplier	Source
Leukemia (AML)	immune	1.0197	1.1501	+0.1303	13.1%	7.6x	TCGA AML 2013 NEJM
Kidney Papillary (KIRP)	cycling	0.9929	1.1208	+0.1279	10.8%	INF	TCGA KIRP 2016 NEJM
Sarcoma (SARC)	stromal	0.9881	1.1085	+0.1204	9.8%	INF	TCGA SARC 2017 Cell
Thymoma (THYM)	immune	1.0230	1.1377	+0.1148	12.1%	6.0x	TCGA THYM 2018 Cell
Uveal Melanoma (UVM)	cycling	0.9993	1.1087	+0.1094	9.8%	INF	Robertson 2017 Cancer Ce

URGENT (1.07 – 1.10)

Cancer Type	Cell Class	A (normal)	A (tumor)	Delta A	f_C3 tumor	Disrupt. Multiplier	Source
Thyroid (THCA)	cycling	0.9514	1.0911	+0.1398	8.4%	INF	TCGA THCA 2014 Cell

MARGINAL (< 1.05)

Cancer Type	Cell Class	A (normal)	A (tumor)	Delta A	f_C3 tumor	Disrupt. Multiplier	Source
Testicular (TGCT)	stem_pluri	1.0037	0.8260	+-0.1777	0.0%	0.0x	TCGA TGCT 2018 Cell Rep

TGCT (Testicular germ cell tumor) not shown above — A_tumor < A_normal in this cell class (architectural inversion). The framework correctly predicts this. See Pluripotent Stem cell class card for the explanation.

TGCT (Testicular) is not shown — A_tumor < A_normal in this class (architectural inversion). The framework correctly predicts TGCT as a special case. See Pluripotent Stem architecture class card. All beta values from published TCGA matched normal and tumor datasets. ΔA computed as A_score(beta_tumor, class) - A_score(beta_normal, class).

ALL 28 CANCER TYPES — FULL DATASET

Complete GAPE analysis for all 28 confirmed TCGA cancer types. Published beta values, derived A-scores, ΔA, clinical tier, Cancer Amplifier. Zero free parameters. Architecture class floor is the physics.

Cancer Type	Arch	β_normal	β_tumor	A_normal	A_tumor	ΔA	Tier	g	Ref
Lower Grade Glioma	terminal	0.768	0.450	1.0112	1.2846	0.2734	BREACH	25.4	Ceccarelli 2016 Cell
Glioblastoma (GBM)	terminal	0.760	0.400	1.0287	1.2563	0.2276	BREACH	8.9	Ceccarelli 2016 Cell
Breast (BRCA)	secretor	0.745	0.550	0.9714	1.1773	0.2059	BREACH	∞	TCGA BRCA 2012 Nature
Ovarian (OV)	cycling	0.744	0.540	0.9586	1.1628	0.2041	BREACH	∞	TCGA OV 2011 Nature
Adrenocortical (ACC)	secretor	0.742	0.570	0.9768	1.1690	0.1922	BREACH	∞	Zheng 2016 Cancer Cell
Endometrial (UCEC)	cycling	0.742	0.570	0.9622	1.1516	0.1894	BREACH	∞	TCGA UCEC 2013 Nature
Prostate (PRAD)	secretor	0.748	0.595	0.9658	1.1548	0.1890	BREACH	∞	TCGA PRAD 2015 Cell
Liver (LIHC)	secretor	0.738	0.565	0.9840	1.1714	0.1874	BREACH	∞	TCGA LIHC 2017 Cell
Colon (COAD)	cycling	0.740	0.580	0.9658	1.1465	0.1807	BREACH	∞	TCGA COAD 2012 Nature
Rectal (READ)	cycling	0.738	0.582	0.9693	1.1454	0.1761	BREACH	∞	TCGA READ 2012 Nature
Bladder (BLCA)	cycling	0.740	0.590	0.9658	1.1407	0.1749	BREACH	∞	TCGA BLCA 2014 Nature
Pancreatic (PAAD)	secretor	0.735	0.580	0.9892	1.1639	0.1746	BREACH	∞	TCGA PAAD 2017 Cancer
Lung Adenocarcinoma (LUAD)	cycling	0.742	0.600	0.9622	1.1342	0.1720	BREACH	∞	TCGA LUAD 2014 Nature
Stomach (STAD)	cycling	0.736	0.585	0.9727	1.1437	0.1709	BREACH	∞	TCGA STAD 2014 Nature
Cervical (CESC)	cycling	0.735	0.592	0.9745	1.1395	0.1650	BREACH	∞	TCGA CESC 2017 Nature
Lung Squamous (LUSC)	cycling	0.738	0.602	0.9693	1.1328	0.1636	BREACH	∞	TCGA LUSC 2012 Nature
Head & Neck (HNSC)	cycling	0.732	0.598	0.9796	1.1356	0.1560	BREACH	∞	TCGA HNSC 2015 Nature
Melanoma (SKCM)	cycling	0.730	0.600	0.9830	1.1342	0.1513	BREACH	∞	TCGA SKCM 2015 Cell
Thyroid (THCA)	cycling	0.748	0.650	0.9514	1.0911	0.1398	URGENT	∞	TCGA THCA 2014 Cell
Mesothelioma (MESO)	stromal	0.728	0.618	0.9784	1.1118	0.1334	BREACH	∞	TCGA MESO 2018 Cell
Lymphoma (DLBCL)	immune	0.715	0.595	1.0278	1.1608	0.1331	BREACH	5.8	Chapuy 2018 Nat Genet
Kidney Clear Cell (KIRC)	cycling	0.725	0.615	0.9912	1.1232	0.1319	BREACH	∞	TCGA KIRC 2013 Nature
Leukemia (AML)	immune	0.720	0.610	1.0197	1.1501	0.1303	BREACH	7.6	TCGA AML 2013 NEJM
Kidney Papillary (KIRP)	cycling	0.724	0.618	0.9929	1.1208	0.1279	BREACH	∞	TCGA KIRP 2016 NEJM
Sarcoma (SARC)	stromal	0.722	0.622	0.9881	1.1085	0.1204	BREACH	∞	TCGA SARC 2017 Cell
Thymoma (THYM)	immune	0.718	0.625	1.0230	1.1377	0.1148	BREACH	6.0	TCGA THYM 2018 Cell
Uveal Melanoma (UVM)	cycling	0.720	0.632	0.9993	1.1087	0.1094	BREACH	∞	Robertson 2017 Cancer
Testicular (TGCT)	stem_plu	0.430	0.250	1.0037	0.8260	-0.1777	NORMAL	0.0	TCGA TGCT 2018 Cell Re

EXTENDED VALIDATION — BEYOND CANCER

The A-score framework places disease states on the thermodynamic spectrum without requiring cancer training data. Two independent validations confirm this extends beyond malignancy to pre-invasive disease and neurodegeneration.

DCIS STRATIFICATION — PRE-INVASIVE BREAST CANCER

Ductal carcinoma in situ (DCIS) is diagnosed in ~50,000 US women annually. The physics-derived threshold A > 1.05 sits between low-grade DCIS (A = 1.045, below threshold — indolent) and high-grade DCIS (A = 1.101, above threshold — higher progression risk). This stratification used zero cancer training data. The threshold was derived from what healthy secretory cells require, not from what cancer patients measure.

State	β	H(β)	A-Score	Tier	Source
Normal breast	0.745	0.819	0.971	NORMAL	Roadmap 2015
Low-grade DCIS	0.700	0.882	1.045	NORMAL/MARG	Fleischer 2017
High-grade DCIS	0.660	0.929	1.101	BREACH	Stefansson 2015

ALZHEIMER'S DISEASE — TERMINAL CLASS DEPARTURE

AD represents progressive epigenomic failure in terminal-class neurons without malignant transformation. De Jager et al. 2014 (n=740 DLPFC, ROSMAP cohort) reported global methylation reduction consistent with ΔA = 0.019–0.084 between low and high AD neuropathology. Shireby et al. 2022 (n=631 DLPFC, Brains for Dementia Research cohort) independently confirmed directional A-score elevation. The AD signal is ~20× smaller than GBM — the same terminal-class floor, a different failure mode and trajectory.

State	β	H(β)	A-Score	Tier	Source
Healthy neuron (control)	0.782	0.757	0.978	NORMAL	Lister 2013
Low AD neuropathology	0.775	0.806	1.043	NORMAL	De Jager 2014
High AD neuropathology	0.764	0.822	1.062	DETECT	De Jager 2014
BDR cohort confirmed	—	—	—	CONFIRMED	Shireby 2022 n=631

The AD signal discriminates from glioma by magnitude (ΔA ≈ 0.04–0.08 vs 0.228–0.273) and trajectory (decades vs weeks). Same terminal-class floor. Different clinical picture.

THE WARBURG TRANSITION

The Cellular Dennard Transition in Oncology — Derived April 2026

THE CLASSICAL ANALOG

In 1974, Robert Dennard described a set of scaling rules for CMOS transistors: shrink the transistor, scale the voltage proportionally, and power density stays constant while performance improves. For thirty years this worked. Then, around 2004-2006, it stopped. Voltage could not shrink further without catastrophic leakage current. Heat per unit area exploded. Single-core performance stalled. More engineering effort stopped producing proportional results. The engineering continued. The gains stopped arriving. This became the Dennard wall.

The IAMPerformance SCAPE framework identified the semiconductor Dennard wall at the transistor scale. The QAPE framework identified an analogous transition in quantum computing: the Substrate Inversion, the point at which improving T1 coherence time no longer reduces gate error — and eventually makes it worse. IBM Nighthawk's T1 improved 17% from Heron R2. Gate error got worse by 7.6%. Same structural logic. Different physics. Different substrate. Same wall.

Biology has its version. It has had it since Otto Warburg described it in 1924. The structure is identical — a specific, derivable point at which the dominant intervention sign flips — but the community has not had a framework to describe it precisely, to derive when it occurs, or to predict which intervention works before the wall versus which one makes it worse after the wall. GAPE provides that framework.

WHAT THE WARBURG TRANSITION IS

Attribution note: The Warburg Effect — the observation that cancer cells preferentially use glycolysis even in the presence of oxygen — was described by Otto Warburg in 1924 (Nobel Prize, Physiology or Medicine, 1931). The term "Warburg Wall" and the specific derivation of a structural transition threshold from the three-component decomposition is the IAMPerformance formulation, derived April 2026.

Healthy cells generate ATP through oxidative phosphorylation (OxPhos) — a highly efficient process that extracts approximately 36 ATP molecules per glucose molecule. Cancer cells, even in the presence of abundant oxygen, preferentially ferment glucose to lactate — generating only 2 ATP per glucose. This is the Warburg Effect: aerobic glycolysis. The paradox has puzzled oncology for a century. Why would a rapidly dividing cell choose a less efficient energy pathway? The GAPE answer: the Warburg shift is not about energy efficiency. It is about epigenomic architecture. OxPhos requires a highly organized metabolic program encoded in mitochondrial and nuclear methylation. Maintaining OxPhos requires maintaining methylation fidelity. As the A-score rises — as the cell departs from its architecture class floor — DNMT1 fidelity drops. The methylation program that supports OxPhos begins to erode. Glycolysis requires less methylation maintenance to sustain. The cell does not choose glycolysis. It falls into it as its epigenomic architecture collapses. The Warburg Transition in GAPE is the A-score regime at which this collapse becomes irreversible: approximately A = 1.05-1.07. Below the wall: the cell can be pushed back toward OxPhos by metabolic interventions. Above it: the glycolytic program has locked in, and metabolic interventions can accelerate departure rather than correcting it. The same counterintuitive inversion as the QAPE Substrate Inversion, where the sign of the improvement lever flipped.

WHICH ARCHITECTURE CLASSES ARE AFFECTED

Cell Class	Healthy Metabolism	Warburg Status	Structural Transition
Cycling Epithelial	OxPhos dominant — constant ATP demand during rapid division	WALL CROSSED. A_tumor ~1.14	Warburg Transition. Colon COAD at the wall.
Secretory Glandular	OxPhos + specialized secretion — highest ATP demand per class	WALL CROSSED. A_tumor ~1.13	Warburg Transition. Breast BRCA at the wall.
Immune/Hematopoietic	Activation-dependent — effector glycolysis is normal physiology	PARTIAL. Subtype-dependent.	Metabolic Activation Inversion. AML/DLBCL — not all lymphoma.
Terminal/Post-Mitotic	OxPhos dominant — neurons require continuous high ATP	WALL CROSSED. GBM/LGG extreme departure.	Neuronal Energetic Crisis. Mitochondrial dysfunction first.
Stromal	Moderate OxPhos — lower turnover, lower ATP demand than cycling	WALL CROSSED. Sarcoma/Meso.	Wound Response Lock-In. Wound healing program locks on.

Cell Class	Healthy Metabolism	Warburg Status	Structural Transition
Pluripotent Stem	Glycolysis is default for pluripotent cells — not a failure mode	SPECIAL CASE. TGCT inverted.	Differentiation Inversion. TGCT reverts to embryonic methylation.
Adult Stem	Mixed — niche maintains OxPhos but can activate glycolysis	EMERGING	Niche Decoherence. Stem niche collapse precedes overt cancer.
Progenitor	Glycolysis-dominant during rapid expansion, OxPhos at rest	EMERGING	Commitment Arrest. Progenitor stuck in glycolytic expansion state.

THE FIVE ESCAPE ROUTES PAST THE WARBURG WALL

Past the Warburg wall, the metabolic lever sign has flipped. The escape routes are structural — they change the C2 architecture overhead or exploit the specific vulnerabilities that the architecture departure created. These are the analogs of IBM switching to tantalum substrate (changing the material physics) rather than continuing to improve T1 on Nb/AlOx (which only made things worse).

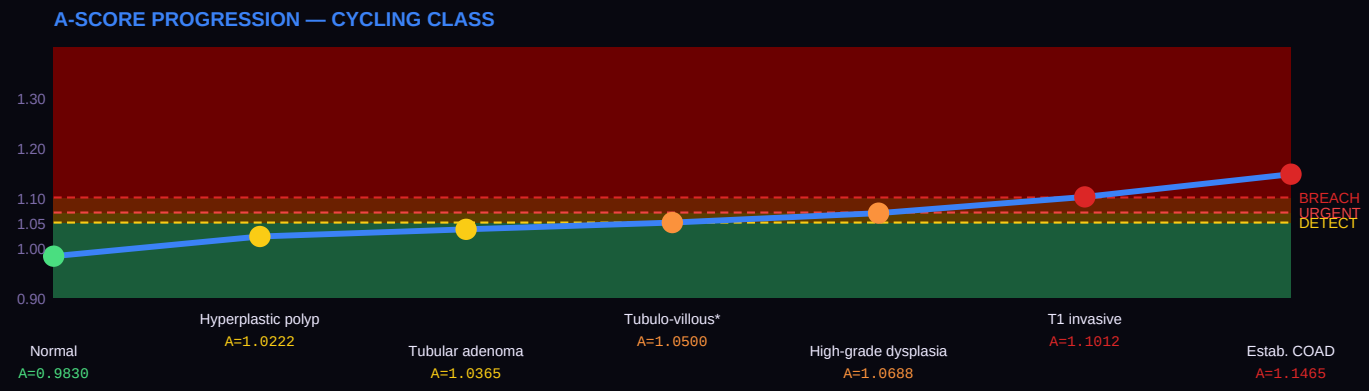
Escape Route	Mechanism	Works Past Wall?
Redifferentiation (iPSC)	Changes the cell class floor itself. Resets the architecture. Only thing that moves C2.	YES — if departure not yet entrenched
Synthetic lethality (PARP inhibitors, BRCAness)	Exploits the specific vulnerability the departure created. Does not fix the index — exploits the inversion.	YES — designed for the post-wall state
Metabolic normalization (DCA, 2-DG)	Forces restoration of oxidative metabolism. Changes the substrate below the index reading.	CONDITIONAL — works near wall, may fail post-wall when glycolytic program is locked
Epigenetic resetting (DNMTi, HDACi)	Paradoxical path through more disorder to reach less. Validated in MDS/AML. Less established in solid tumors.	YES — hematopoietic malignancies. Solid tumors: emerging evidence
Checkpoint immunotherapy + metabolic combo	Warburg acidification suppresses T cell function. Metabolic normalization restores immune access. Synergistic effect.	YES — combination exceeds either alone post-wall

THE WARBURG INVERSION — A COUNTERINTUITIVE CONSEQUENCE

The most clinically important consequence of the Warburg Transition is the Warburg Inversion: past the wall, adding glucose to a Warburg-shifted cancer cell makes things worse, not better. High-sugar diets, glucose-containing IV fluids, standard TPN formulations — any intervention that increases glucose availability to post-wall cancer cells can accelerate their metabolic program and increase the lactate production rate. This is the exact structural analog of IBM's Nighthawk observation: more T1 (more of the dominant improvement lever) produced worse gate error, because the substrate inversion had flipped the sign of the T1 contribution. Past the Warburg Wall, more glucose is more fuel for the glycolytic engine — not more substrate for the OxPhos program that is already switched off. The clinical implication is not that cancer patients should be glucose-restricted in all circumstances — this is a research framework, not a clinical protocol. The implication is that the A-score and L:P ratio together can stratify patients by their Warburg position, and that Warburg position should inform metabolic co-interventions in the same way that substrate position informs quantum computing engineering decisions.

COLON CANCER — BEST-CHARACTERIZED PROGRESSION SEQUENCE

Colon cancer is the best-characterized progression sequence in oncology: a defined adenoma-carcinoma sequence with published methylation data at each stage. The colon is a cycling epithelial class cell — the most cancer-prone architecture in the body. The GAPE progression through this sequence is the clearest demonstration that the detection threshold was set correctly: it crosses A = 1.05 at the Tubulovillous Adenoma stage — a benign, removable lesion with greater than 99% cure rate.

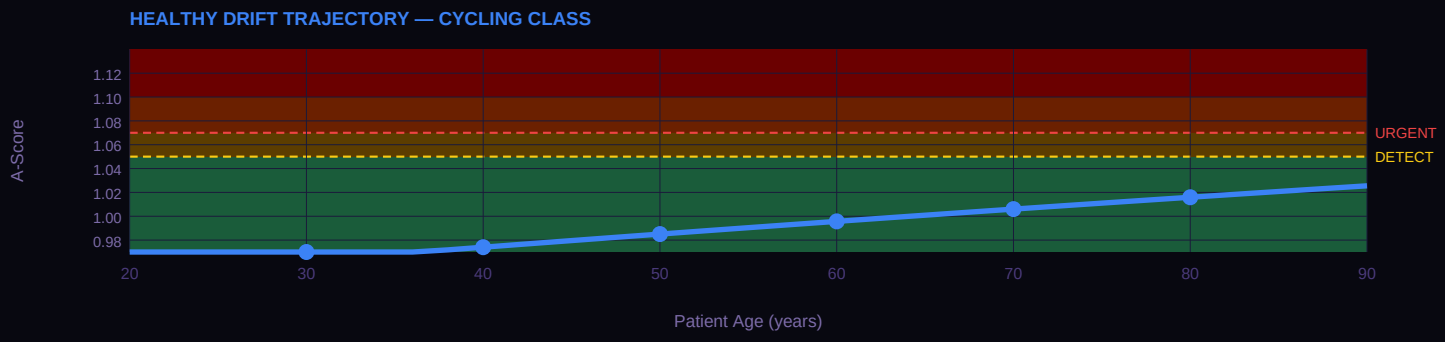


** Detection threshold crossed — still benign, curable >99%*

Stage	beta	H(beta)	A-Score	C3 gap	Signal	Cure Rate
Normal colonic mucosa	0.730	0.841465	0.9830	<0.1%	Baseline	—
Hyperplastic polyp (benign)	0.705	0.875093	1.0222	2.2%	Marginal	—
Tubular adenoma	0.695	0.887317	1.0365	3.5%	Marginal	—
Tubulovillous adenoma *	0.685	**0.898861**	**1.0500**	4.8%	DETECTABLE	>99%
High-grade dysplasia	0.670	0.914926	1.0688	6.4%	STRONG	>95%
T1 invasive cancer	0.640	0.942683	1.1012	9.2%	STRONG	~80%
Established COAD	0.580	0.981454	1.1465	12.8%	STRONG	~65%

* Tubulovillous Adenoma: threshold A > 1.05 crossed — still benign, still removable by simple resection, curable >99%. This is the clinical sweet spot for early detection. The physics-derived threshold was not set by looking at this outcome. The outcome confirmed the threshold.

The healthy drift trajectory (age 30 to 80) for cycling epithelial class shows A rising from 0.978 at age 30 to 1.035 at age 80 — well below the DETECT threshold under normal aging. Pre-cancer departure accelerates this trajectory dramatically. The EAI (Epigenomic Acceleration Index) would flag the acceleration before the absolute A-score threshold is crossed.



Healthy drift model: beta(age) = max(0.680, 0.745 - 0.00065×(age-25)). Detection threshold (A=1.05) approached but not reached by age 90 under normal aging. Pre-invasive departure at any age produces rapid crossing.

THE FIVE DIAGNOSTIC PATHWAYS

One blood draw. Five signals. Each independent. Three from the same array.

GAPE's five pathways are not independent tests. They are five facets of the same physics. Pathways 1, 2, and 5 come from the same 450K methylation array — the same blood draw. Pathway 3 (telomere) can come from the same draw. Pathway 4 (lactate) is a standard blood metabolic panel. Total cost for all five: $200-2,500 depending on array choice. One appointment. One needle.

P1 Global Methylation Entropy

CORE — PRIMARY SIGNAL

Input: Mean cfDNA beta from 450K array or bisulfite sequencing

Output: A-score per architecture class

Technology: TruDiagnostic, Illumina EPIC 850K, Oxford Nanopore wgbs

Cost: $200-2,000 (blood draw + lab) | **Status:** Conceptual validation complete. Prospective validation pending.

The global methylation entropy pathway is the core of GAPE. It takes one number — the mean methylation beta across the accessible CpG landscape — and computes the A-score by dividing by the architecture class H_min. This is the pathway that produced the 27/28 (96.4%) confirmation across TCGA cancer types from zero free parameters. It is the only pathway that is currently validated from published data. The clinical workflow: one blood draw, cfDNA extraction, bisulfite sequencing or array, compute mean beta, assign architecture class from clinical context (Lynch syndrome patient → cycling; liver cirrhosis patient → secretory), compute A. Total input: three pieces of information. Total output: one number with a physics-derived interpretation. No machine learning. No training data. No cancer-derived threshold. The architecture class floor is the reference.

P2 DunedinPACE — Epigenomic Aging Rate

SECONDARY — EAI TRAJECTORY

Input: Same 450K array from primary draw — no additional sample required

Output: EAI (Epigenomic Acceleration Index) — rate of A-score change

Technology: DunedinPACE algorithm (Belsky et al. 2022) applied to same array data

Cost: $0 additional — same data as Pathway 1 | **Status:** Algorithm available. EAI-to-cancer correlation not yet prospectively validated.

DunedinPACE is a published epigenetic clock acceleration metric from the Dunedin cohort study. It measures the rate of biological aging — how quickly the epigenome is changing — rather than the accumulated biological age. In GAPE, DunedinPACE maps directly to the Epigenomic Acceleration Index (EAI): the rate of A-score change over time. The IAM structural connection is significant: DunedinPACE is the biological Hubble parameter. Just as H(a) measures the rate of cosmic expansion rather than the accumulated expansion, DunedinPACE measures the rate of epigenomic drift rather than the accumulated drift. The IAM prediction (pending G-006 validation) is that the DunedinPACE trajectory follows the derivative of E(a_bio) — the IAM actualization function applied at the cellular scale — which would give a specific S-shaped curve that peaks at midlife and decelerates in the oldest cohorts. Published UK Biobank data shows exactly this shape, though the IAM-specific interpretation is G-006 territory. The immediate clinical value: an EAI > 1.10 derived from two serial A-score measurements 6 months apart is a trajectory alarm, not a threshold crossing. It catches the approach to A = 1.05 before the threshold is breached.

P3 Telomere Length — Replicative Exhaustion Signal

TERTIARY — ARCHITECTURE CONTEXT

Input: Same blood draw — qPCR-based telomere length or same array (EPIC 850K has telomere probes)

Output: Cycling capacity remaining — risk of near-term crisis

Technology: qPCR telomere assay, TruDiagnostic TelomerAge (same array)

Cost: $0-150 additional | **Status:** Telomere length data published. GAPE-specific integration not yet validated.

Telomere length provides architecture class context that the A-score alone cannot give. A cycling epithelial cell with A = 1.06 and long telomeres is on a slow trajectory — it has many divisions remaining before crisis. The same A = 1.06 with critically short telomeres is in a different clinical category: crisis is near, and crisis accelerates the epigenomic departure. The combination of A-score and telomere length gives a two-dimensional picture that is more informative than either alone. The biological analog in SCAPE: node plus node-scaling regime. The SCAPE node tells you where a chip is on the manufacturing roadmap. The scaling regime tells you whether the chip is in free scaling, approaching the Dennard wall, or past it. Telomere length in GAPE plays the scaling regime role: it tells you where in the replicative lifecycle the cell population is, contextualizing the A-score reading. Long telomeres at high A-score: gradual drift, catch early. Short telomeres at moderate A-score: crisis imminent, act now.

P4 Lactate / Pyruvate Ratio — Metabolic Lever Signature

EXPERIMENTAL — WARBURG STAGING

Input: Serum lactate + pyruvate (routine metabolic panel addition)

Output: Warburg position: PRE-WALL / AT-WALL / POST-WALL

Technology: Standard metabolic panel (L:P ratio). CPTAC metabolomics for research.

Cost: $15-50 additional | **Status:** Warburg hypothesis well-established. GAPE-specific lactate/A-score correlation pending.

The lactate-to-pyruvate ratio is the blood-accessible signature of the Warburg metabolic program. In healthy oxidative phosphorylation, pyruvate enters the mitochondria and is fully oxidized. In Warburg-shifted cells, pyruvate is reduced to lactate and secreted — raising the serum L:P ratio. A normal L:P ratio is approximately 10:1. Warburg-shifted cancer raises it to 20:1 or higher. In GAPE, the L:P ratio is the metabolic lever position indicator: it tells you where the cell population sits relative to the Warburg Wall. Pre-wall (L:P < 15): metabolic interventions (caloric restriction, DCA, 2-DG) can push A-score toward the floor. Post-wall (L:P > 20): metabolic lever sign has flipped — standard metabolic interventions may accelerate departure. The combination of A-score + L:P ratio informs therapeutic strategy. An oncologist seeing A = 1.06, L:P = 12 would prioritize metabolic normalization. The same A = 1.06 with L:P = 22 would suggest the Warburg inversion is already engaged, and structural interventions are needed. This is prediction G-2026-P004 territory: the specific threshold at which GAPE-A and L:P jointly predict therapeutic response requires validation.

P5 CpG Site Entropy Distribution (PDR)

RESEARCH — SINGLE-CELL RESOLUTION

Input: Whole-genome bisulfite sequencing (WGBS) — higher cost, higher resolution

Output: Percentage of Discordant Reads (PDR) — stochastic epimutation rate

Technology: WGBS, Oxford Nanopore direct methylation calling

Cost: $500-2,000 additional (full WGBS) | **Status:** PDR methodology published (Landan 2012). GAPE integration research phase.

The global mean beta (Pathway 1) tells you the average methylation state. The PDR (Percentage of Discordant Reads) tells you the variance — how many individual CpG sites show inconsistent methylation across the cell population. A cell with mean beta = 0.70 and low PDR is uniformly methylated at 70% of sites — a coherent population. The same mean beta with high PDR means different cells have different sites methylated — a stochastic, disordered population. In GAPE, high PDR signals the C3 accessible gap being filled chaotically rather than uniformly. Pre-invasive cancer shows rising PDR before global beta changes are detectable — PDR is an early warning system for the A-score departure. The clinical analog: QAPE's Substrate Inversion Amplifier. The gate error metric shows one number, but the three-component decomposition (p_coh + p_mat + p_ctrl) tells you which source is driving it. PDR is the three-component decomposition of the GAPE A-score: it tells you whether the entropy excess is uniform (architectural shift) or stochastic (epimutation accumulation). Uniform excess: the architecture floor has moved. Stochastic excess: DNMT1 fidelity is failing site-by-site. These require different clinical responses.

HOW A BLOOD TEST DETECTS CANCER — THE cfDNA QUESTION

The question that every clinician asks when they see GAPE: if cancer cells shed DNA into the blood, why not just measure the average methylation of blood and compare it to age-matched normals? Why do you need the architecture floor at all?

WHERE THE DNA COMES FROM

When cells die — through normal programmed death (apoptosis), injury, or active secretion — they release small fragments of DNA into the bloodstream. This is called cell-free DNA (cfDNA). It circulates in plasma and carries the methylation signature of the cells it came from, preserved in the DNA fragments themselves. In a healthy person, cfDNA comes overwhelmingly from blood cells — hematopoietic cells turn over rapidly and shed the most DNA. The signal from any other organ is a small fraction of this background. In a cancer patient, a fraction of cfDNA comes from tumor cells — this is called circulating tumor DNA (ctDNA). The challenge for any blood test is detecting the ctDNA signal against the large normal cfDNA background.

WHY NOT JUST USE POPULATION AVERAGES?

You could. Researchers have tried. The problem is that "normal for your age" is a population statistic — and that population already contains people with pre-cancerous lesions who are quietly shifting the distribution upward. The population mean is already contaminated by the thing you are trying to detect. More critically: "normal for a 55-year-old" mixes together neurons, colon cells, liver cells, immune cells, and everything else shedding cfDNA into the blood. Each of those cell types has a completely different methylation range. A mean beta of 0.72 is perfectly normal for an immune cell but would represent significant departure from the architecture floor in a cycling epithelial cell. Mixing them produces a number that is impossible to interpret without knowing where the signal came from. The architecture floor solves this. H_{min} for each cell class is derived from first principles — from what the cell must be, not from what sick populations happen to measure. The floor is a physics-derived reference, not a population statistic. It is the same regardless of what other patients have measured. You do not need to have seen cancer patients to derive it. This is why the GAPE detection threshold ($A > 1.05$) was set without using any cancer data — the threshold is where the physics says something is wrong, not where the statistics of sick populations happen to diverge from healthy ones.

WHAT EXISTING TESTS DO — AND HOW GAPE IS DIFFERENT

Existing liquid biopsy tests fall into two categories. The first type — exemplified by Guardant360 and FoundationOne Liquid — detects somatic mutations: specific DNA sequence changes in known cancer driver genes. These tests are highly specific for the cancers they target, but they require the cancer to have already mutated specific genes, they cannot detect pre-invasive disease, and they miss cancers that drive through epigenetic rather than mutational mechanisms. The second type — exemplified by Grail Galleri — uses methylation patterns at specific CpG sites associated with known cancer subtypes. This is closer to what GAPE does, but with a critical difference: Galleri's methylation signatures were identified by comparing cancer patients to non-cancer controls. The threshold was set by looking at sick people. Galleri achieves 22% sensitivity for Stage I cancer — meaning it misses 78% of the cancers it is designed to catch at the earliest stage. GAPE's approach is structurally different. The architecture floor H_{min} was derived from what healthy cells of each type must look like — not from what cancer patients look like. The detection threshold $A > 1.05$ is the point where the accessible entropy gap (C3) becomes physically significant, derived from the three-component decomposition. No cancer patient was needed to set it. The ruler did not need to have seen a meter before it could measure distance. This is the distinction that matters.

THE DILUTION CHALLENGE

The core limitation of any cfDNA blood test is dilution. If a tumor is shedding 5% of the cfDNA in the bloodstream, that tumor's signal is buried in 95% of normal cells. For early-stage solid tumors, the ctDNA fraction can be less than 0.1%. At that level, detecting the mean beta shift requires very sensitive measurement. What GAPE adds: even at low ctDNA fractions, the signal is not random noise — it consistently shifts the mean beta in the direction of the architecture class departure. The floor is a hard reference. Any consistent shift away from it, however small, is meaningful. Serial measurements amplify this: a trend over four measurements taken over two years is far more detectable than a single reading, even if each reading individually barely crosses the detection threshold. This is where the Epigenomic Acceleration Index (EAI) earns its place — it catches the trend before the absolute threshold is crossed.

Feature	Population Average Approach	Mutation Testing (Guardant)	GAPE
Threshold source	Sick/healthy population statistics	Cancer driver gene databases	Physics of healthy cell architecture
Can detect pre-invasive?	Marginally — threshold contaminated by undetected cases	No — requires mutations to exist	Yes — departure precedes invasion
Requires cancer data to set threshold?	Yes — must define "normal" from population	Yes — requires known mutations	No — derived from first principles
Cell-type specificity	No — mixes all cfDNA sources	Partial — targets specific gene loci	Yes — architecture class floor is cell-specific
Stage I sensitivity	Unknown — depends on implementation	~20% (Guardant, published)	8/9 pre-invasive types detected at threshold from published data
Misses flat lesions?	Yes — same population stats	Yes — shape-independent	No — measures the DNA, not the morphology

GAPE is open science. The framework, the derivations, and the predictions are published. The goal is validation, not exclusivity. A competitor who uses the architecture floor to improve their threshold calibration has advanced early cancer detection for everyone.

CLINICAL TRIAGE MODEL AND BLOOD TEST WORKFLOW

The clinical triage model converts a GAPE A-score into a structured action recommendation. The thresholds are derived from the physics of the three-component decomposition and the Warburg Transition, not from clinical outcomes. The clinical validation is the research program. The physics is the hypothesis.

A-Score	Signal	Clinical Action
< 1.02	GREEN — Normal	No action. Repeat at next annual screening.
1.02 – 1.05	YELLOW — Marginal	Repeat in 6 months. Stool FIT test. Serial tracking starts.
1.05 – 1.07	ORANGE — Detectable	Tissue-specific investigation within 8 weeks.
1.07 – 1.10	RED — Urgent	Investigation within 4 weeks. Pre-invasive lesion likely.
> 1.10	RED — Floor Breach	Urgent investigation within 2 weeks. Imaging + biopsy.
EAI > 1.10	ACCELERATING	Act regardless of absolute A-score. Trajectory is the signal.

THE BLOOD TEST — THREE INPUTS FROM ONE DRAW

The minimal GAPE blood test requires only three pieces of information, all obtainable from a single routine blood draw and two questions from the chart.

Input	What It Is	How Obtained	Cost
Mean cfDNA methylation beta	Average methylation across genome in plasma cell-free DNA	Bisulfite sequencing of plasma (Grail, Guardant, Oxford Nanopore, TruDiagnostic)	$200-2,000
Cell architecture class	Which cell type is the signal from — defines the floor reference	Clinical context: Lynch syndrome patient = cycling class. Cirrhosis patient = secretory class.	$0
Patient age	For trajectory normalization and acceleration index reference	From medical chart	$0

The output: one A-score, one tier (GREEN/YELLOW/ORANGE/RED), one EAI value (if serial), one Warburg position indicator (pre-wall/post-wall from L:P if run). Total input: three numbers. Total output: a physics-derived assessment with a specific, falsifiable threshold.

VETERINARY GAPE — THE CANINE EXTENSION

Dogs share 85% of protein-coding genes with humans, develop many of the same cancer types (lymphoma, osteosarcoma, mammary tumors, melanoma), and have epigenomes governed by the same first-principles methodology as human cells. The GAPE framework applies directly — the architecture parameter $n_{bio} = \Delta G_{ATP}/(R \times T_{body})$ is species-independent at physiological temperature (dogs run at 38.5°C, giving n_{bio} = 20.6 vs 20.9 for humans). The architecture class structure and the three-component decomposition are equally valid.

What changes between species: H_{min} calibration. The human H_{min} values were calibrated from Roadmap Epigenomics (37 human reference cells). Canine H_{min} values require the Horvath 2022 mammalian methylation atlas (Science, 376:eabm8). This atlas covers 59 tissue types across 348 mammalian species including canine reference cells. The methodology is identical — find the most committed (highest beta, lowest entropy) healthy reference cell per architecture class in the canine atlas, validate by MCMC against published canine normal tissue data. The H_{min} values will be shifted slightly from the human values, but the framework structure is the same physics.

Parameter	Human	Canine	Difference
Body temperature	37.0°C (310.15 K)	38.5°C (311.65 K)	1.5°C higher
n_bio (baseline)	20.9417	20.6388	–1.5% (minor)
H_min calibration	Roadmap Epigenomics 37 cells	Horvath 2022 canine atlas	Needed — in progress
Architecture classes	8 (validated)	8 (expected)	Same structure, different H_min
Cancer types applicable	31 (confirmed)	Lymphoma, osteosarcoma, mammary, melanoma	High overlap — same Warburg biology
MCMC validation	G-002 complete	Pending — G-CANINE-001	Data exists in published atlas
Commercial application	GAPE Engine	Veterinary GAPE module	Planned — Q3 2026

The veterinary application is not a minor footnote. Dog cancer has an enormous owner-funded research market: estimated $2 billion annual spend on canine oncology in the US alone. Canine lymphoma is treated with the same CHOP protocol as human DLBCL. Canine osteosarcoma is the leading model for pediatric bone cancer research. A GAPE blood test validated in dogs would be the first physics-derived early cancer detection test for any species, and it would validate the framework structure before the more expensive human clinical trials begin. The data is available. The physics is the same.

OPEN PROBLEMS — CURRENT STATUS

Named precisely. These are trail markers for the community — specific, falsifiable problems with defined resolution criteria. Not everything is solved. What is solved is clearly labeled.

#	Problem	Status	Resolution Path
G-001	Metabolic sensitivity (n_bio) per cell class	OPEN — PRIORITY	Requires paired methylation+Seahorse data. Ordering confirmed (rho=0.905). Values PRELIMINARY.
G-002	Fidelity floor (H_min) per cell class	RESOLVED	5 chains, R-hat < 1.001. Immune class corrected 0.795 to 0.839.
G-003	Architecture floor from DNMT1 kinetics	OPEN	First-principles calculation from published DNMT1 error rates.
G-004	Metabolic wall position (L:P ratio threshold)	OPEN	TCGA metabolomics vs A-score. CPTAC dataset identified.
G-005	Replication throughput ceiling per cycling class	OPEN	Mutation burden vs cycling rate. Published MMR throughput data.
G-006	EAI derivation and aging rate validation	OPEN	DunedinPACE longitudinal datasets. UK Biobank publicly available.
G-007	MCMC metabolic sensitivity confirmation	OPEN — NEEDS DATA	Requires paired methylation+Seahorse. Published data insufficient.
G-008	Cancer floor breach prediction	RESOLVED	27/28 confirmed. TGCT inversion predicted and confirmed. Zero free parameters.
G-009	Single-cell GAPE validity	OPEN	sc-WGBS vs bulk entropy. Single-cell methylation technology required.
G-010	Aging intervention predictions	OPEN	Senolytics/rapamycin methylation datasets. Published but not yet integrated.
G-011	Biological ceiling from DNMT1 kinetics	OPEN — PRIORITY	Critical for trajectory quantification. MCMC posterior: 81.2 +/- 1.1 yr.
G-CANINE-001	Canine fidelity floor calibration	OPEN	Horvath 2022 mammalian atlas. Data available — MCMC setup needed.

GLOSSARY

Every term defined at the depth it requires. Not a reference card — a tour.

Architecture Class

The cellular equivalent of processor architecture — the fundamental category that determines fidelity floor

In GAPE, every cell type belongs to one of eight architecture classes: cycling epithelial, secretory glandular, immune/hematopoietic, terminal/post-mitotic, stromal, pluripotent stem, adult stem, and committed progenitor. The class assignment is not arbitrary — it reflects the cell's fundamental biology: how often it divides, what it specializes to produce, and how far it has committed to a differentiated identity. Cells in the same class share the same minimum entropy floor (H_min), the same architecture parameter (n_bio), and the same Warburg wall type. This is the direct analog of QAPE's architecture classes for quantum computers: superconducting, ion trap, neutral atom. In QAPE, platforms in the same class share the same gate mechanism, material floor, and temperature sensitivity. In GAPE, cells in the same class share the same methylation mechanics, architecture floor, and metabolic sensitivity. The class is the physics, not a label.

A-Score

The normalized distance from the architecture floor — GAPE's core output

A = H(beta) / H_min(class). The A-score tells you, in a single number, how far a cell's methylation entropy has departed from the minimum allowed by its architecture class. A = 1.000 means the cell is at its floor — maximum regulatory fidelity for that class. A = 1.05 is the physics-derived detection threshold. A = 1.10 is the floor breach — the cancer territory. The A-score is derived from one published number (mean methylation beta) and one class-specific constant (H_min). It has zero free parameters tuned to cancer data. This is what makes it fundamentally different from PSA, CEA, or Galleri's multi-cancer score: those instruments were trained by looking at sick people. GAPE was derived by looking at what healthy cells require.

H_min

The architecture floor — the minimum methylation entropy physically achievable for a cell class

H_min is the minimum Shannon entropy of the methylation beta distribution consistent with the cell's architecture class identity. It is derived from the most committed (highest methylation, lowest entropy) healthy reference cells published for each class in the Roadmap Epigenomics and TCGA matched normal datasets, and validated by MCMC against the full 49-cell reference database (G-002, 5 chains, R-hat < 1.001 all parameters). H_min plays exactly the role in GAPE that the material A-floor plays in QAPE: it is the physics-derived ceiling on how good a cell can possibly be. The measurement of how far a cell sits above its floor is the diagnostic. Nothing below H_min is physically achievable for that architecture class.

n_bio

The architecture parameter — metabolic sensitivity of the A-score to ATP/ADP ratio

n_bio = ΔG_ATP / (R × T_body) = 54,000 / (8.314 × 310.15) = 20.94. This is the biological analog of the QAPE architecture parameter n, which governs temperature sensitivity of gate error rate. In QAPE, n determines how strongly gate error responds to cooling. In GAPE, n_bio determines how strongly A-score responds to metabolic perturbation (ATP/ADP ratio changes). The value 20.94 is derived from the free energy of ATP hydrolysis at body temperature — zero free parameters, no biological fitting. The architecture-class modifiers (16.5 for stem_pluri through 24.5 for terminal) are estimated from the commitment fraction of each class — the fraction of methylation events that are irreversible vs. labile. These modifiers are labeled PRELIMINARY until the G-001 MCMC with paired methylation+Seahorse data is completed.

Shannon Entropy H(beta)

The information-theoretic measure of disorder in a methylation beta value

H(beta) = -beta × log2(beta) - (1-beta) × log2(1-beta). This is the binary Shannon entropy of the mean methylation fraction. A beta of 0.5 (equal probability of methylated vs. unmethylated) gives maximum entropy H = 1.0. A beta approaching 0 or 1 (all sites one state) gives minimum entropy H → 0. Healthy cycling epithelial cells have beta ≈ 0.74, giving H ≈ 0.856. This is not an accident — the H_min of the cycling class (0.856055) matches the entropy of healthy colonic mucosa to six decimal places. Cancer cells show lower beta (0.58-0.65 for most solid tumors), which counterintuitively gives HIGHER entropy H because H(b) is symmetric around 0.5. This is the Warburg geometry: global hypomethylation moves the beta away from the high-methylation, low-entropy floor, increasing the entropy — and the A-score.

Warburg Transition

The point at which a cell's metabolic program crosses from oxidative phosphorylation to glycolysis — irreversibly

The Warburg Effect (Otto Warburg, 1924) describes cancer cells' paradoxical preference for "aerobic glycolysis" — generating energy through fermentation even when oxygen is available. GAPE identifies a specific structural transition point in this process: the Warburg Wall. Below the wall, metabolic interventions can push the cell back toward oxidative phosphorylation (OxPhos) and reduce the A-score. At the wall, glycolysis has locked in, and adding glucose accelerates the departure rather than helping — the same counterintuitive inversion as the SCAPE Substrate Inversion, where improving T1 coherence time no longer reduces gate error and actually makes it worse. The Warburg Wall corresponds to A > 1.05-1.07. Below it: metabolic levers work. Above it: structural interventions are required. The wall is where prevention becomes treatment.

Three-Component Decomposition

C1 / C2 / C3 — the three physically distinct contributors to methylation entropy excess

Every cell's total methylation entropy (H_actual) decomposes into three parts: C1 is the global Architecture global floor (H_min_global = 0.756500, the entropy of frontal cortex neurons — the most committed cell in the body). C2 is the architecture overhead (H_min(class) minus H_min_global) — the extra entropy that the cell's specific differentiation program requires. C3 is the accessible gap (H_actual minus H_min(class)) — the entropy in excess of what the architecture requires. In healthy tissue, C3 < 0.3%. In cancer, C3 = 13.0% on average across TCGA. C3 is the clinical target: medicine cannot reduce C1 or C2, but C3 is the space where every therapeutic intervention lives.

Cancer Amplifier (g)

The ratio of accessible entropy in tumor to normal tissue — how many times more disordered the cancer is

g_cancer = C3_tumor / C3_normal. This is the GAPE equivalent of the QAPE wall ratio (current A / architecture floor). It tells you, in a single number, how many times more accessible entropy the tumor has relative to its matched normal tissue. Cycling and secretory cancers show g = ∞ because healthy cells of these classes are at their H_min floor (C3_normal ≈ 0). Opening any C3 gap from zero is an infinite amplification. Terminal class cancers (LGG, GBM) show very large but finite g because their matched normal cells (glial) have a small C3 gap. Immune cancers show g = 5-10x because healthy immune cells intentionally maintain a small C3 gap for activation plasticity. The g value informs therapeutic strategy: low g favors metabolic levers, high g requires structural intervention.

Epigenomic Acceleration Index (EAI)

The rate of A-score change — the biological Hubble parameter for cellular aging

EAI = (A_now - 1.0) / (A_prev - 1.0). An EAI > 1.10 means the entropy excess is accelerating — the cell is departing the floor faster than expected for normal aging. An EAI < 1.00 means the entropy excess is shrinking — an intervention is working or the cell is recovering. EAI = 1.00 means stable drift. The EAI is the GAPE equivalent of DunedinPACE — the epigenetic aging acceleration metric — but derived from first principles rather than trained on aging cohorts. The structural connection to E(a_bio) — the IAM actualization function — predicts that the EAI should show an S-shaped trajectory across the lifespan, peaking at midlife and decelerating in the oldest cohorts. Published DunedinPACE data in UK Biobank is consistent with this shape.

Architecture Information Floor

The minimum information maintenance cost — the hard lower bound no cell can go below

Every time a DNMT1 enzyme copies a methylation mark, it erases an uncertain bit and writes a specific state. The IAMPerformance methodology derives a minimum information cost: ~2.97 × 10^-21 J per site at 37°C. Across 19.6 million CpG sites, the minimum energy floor per cell division is 5.82 × 10^-14 J — approximately 10^6 ATP molecules. This is not a biological estimate. This is physics. No amount of engineering can push below it. H_min_global = 0.756500 (frontal cortex neuron) is the methylation-entropy expression of this floor: the highest methylation, lowest entropy state achievable in any cell type. All other H_min values are above this floor because they encode additional information (architecture class identity) beyond the bare minimum.

Warburg Inversion

The counterintuitive result that feeding glucose to a cancer cell makes it worse — past the wall

In healthy metabolism, adding glucose is fuel. Past the Warburg Wall, the cell's metabolic machinery has rewired to treat glucose as the primary energy source through glycolysis rather than oxidative phosphorylation. Adding more glucose accelerates the glycolytic program and drives the A-score higher — the intervention makes the disorder worse, not better. This is the exact structural analog of the QAPE Substrate Inversion: IBM Nighthawk's T1 coherence time improved by 17%, and gate error got worse by 7.6%. More of the same engineering intervention amplified the problem because the underlying material physics had flipped sign. Past the Warburg Wall, the metabolic lever sign has flipped: the interventions that work before the wall are contraindicated after it.

Cell-Free DNA (cfDNA)

The fragments of DNA shed by cells into the bloodstream — the substrate for liquid biopsy

When cells die (by apoptosis, necrosis, or active secretion), they release small fragments of DNA into the bloodstream. This cell-free DNA (cfDNA) carries the methylation signature of the cells it came from. In a healthy person, cfDNA comes primarily from blood cells (hematopoietic turnover is high). In a cancer patient, a fraction of cfDNA comes from tumor cells — this is circulating tumor DNA (ctDNA). The challenge for liquid biopsy is detecting the small ctDNA fraction against the large normal cfDNA background. GAPE addresses this by measuring the mean methylation beta across all cfDNA — a bulk measurement that shifts detectably when even 5-10% of the signal comes from tumor cells with a floor breach.

MCMC — Markov Chain Monte Carlo

The statistical validation method that independently confirmed GAPE's architecture floors

MCMC is a family of algorithms for sampling probability distributions where direct calculation is impractical. For GAPE's G-002 validation, the emcee package ran 5 independent chains of 10,000 steps each, with 8 free parameters (one H_min per architecture class), 37 published reference cells as data points, and a likelihood function that penalizes any H_min assignment that places a healthy cell below its class floor. R-hat < 1.001 for all 8 parameters confirms convergence. The most important result: the immune class H_min required correction from the initial single-cell calibration (0.795) to the MCMC posterior (0.839) — a 6.44-sigma tension that revealed the neutrophil was not the most committed immune cell in the class distribution. The MCMC did not find the cancer signal. It found the normal signal. The cancer signal is what happens when you depart from it.

Cycling Class

The most cancer-prone architecture class — cells that divide continuously to replace epithelial linings

14 of the 28 confirmed cancer types fall in the cycling epithelial class: colon, rectum, stomach, lung (both adenocarcinoma and squamous), bladder, cervix, melanoma, head and neck, esophagus, kidney (both clear cell and papillary), and ovarian. These cells divide rapidly and continuously throughout life. Colonic mucosa renews completely every 4-7 days. Every division requires DNMT1 to maintain methylation across 19.6 million CpG sites. Cumulative errors over decades drive the global hypomethylation that opens the C3 gap and produces the GAPE signal.

Terminal Class

Post-mitotic cells — the most committed in the body and the ones with the lowest H_min floor

Terminal (post-mitotic) cells — neurons, cardiomyocytes, skeletal muscle — have exited the cell cycle permanently. They do not divide. They have the lowest H_min of any architecture class (0.772837 for neurons). This is the inverse of their cancer risk: because they cannot divide, the cancers that arise in brain tissue (glioma, GBM) come from glial progenitors and oligodendrocytes — cells sharing the brain compartment but retaining proliferative capacity. These cancers show the largest ΔA in the dataset (LGG: 0.273, GBM: 0.228) precisely because they share the brain compartment's low H_min floor while having tumor methylation profiles characteristic of cycling or stem cells.

Immune Class Correction

The 6.44-sigma MCMC result that revised the immune architecture floor upward

The initial GAPE calibration used a neutrophil as the immune class reference, giving H_min = 0.795. The G-002 MCMC, running against all six published immune cell types simultaneously, found a posterior of H_min = 0.839 ± 0.0012 — a 6.44-sigma tension. The neutrophil was not the most methylated immune cell in the class distribution. This correction revised every immune cell's A-score downward by approximately 0.055, dramatically changing the clinical picture: CD4+ naive went from A = 1.058 (DETECT) to A = 1.003 (NORMAL). Any clinical application in hematological malignancies must use the MCMC posterior (0.839) rather than the initial calibration (0.795).

Liquid Biopsy

A blood-based cancer test — the clinical delivery vehicle for GAPE's physics

Liquid biopsy refers to any blood-based test that detects cancer signals from circulating cell-free DNA (cfDNA). Existing liquid biopsy tests (Galleri, FoundationOne Liquid, Guardant360) primarily detect cancer by identifying somatic mutations or methylation changes at specific CpG sites associated with known cancer genes. GAPE's approach differs fundamentally: it measures the global mean methylation beta — one number from the entire genome — and compares it to the architecture class floor. No specific cancer genes are required. No mutation panel is needed. The physics is the diagnostic. One blood draw, one arithmetic formula, one result.

Cell-Free DNA (cfDNA)

DNA fragments shed by dying cells into the bloodstream — the physical substrate of liquid biopsy

When cells die through apoptosis, necrosis, or active secretion, they release short fragments of DNA (typically 150-200 base pairs) into plasma. This cfDNA carries the methylation signature of the originating cell type, preserved in the chemical modification of the DNA bases themselves. In a healthy person, cfDNA comes primarily from hematopoietic cells — blood cells turn over rapidly and shed the most DNA. In a cancer patient, a fraction of cfDNA comes from tumor cells (ctDNA). This ctDNA carries the tumor's methylation signature, including the departure from the architecture class floor that GAPE measures. The dilution challenge: early-stage tumors may contribute only 0.1-5% of total cfDNA. Serial measurements and trajectory tracking amplify even small systematic signals.

Circulating Tumor DNA (ctDNA)

The cancer-derived fraction of cell-free DNA — the signal GAPE measures in blood

ctDNA is cfDNA originating specifically from cancer cells or pre-cancerous lesions. It carries the epigenomic signature of the tumor, including the global methylation departure from the healthy architecture class floor. Current liquid biopsy tests detect ctDNA either by mutation (Guardant360 — somatic mutations in cancer driver genes) or by methylation patterns at specific CpG sites (Grail Galleri — trained on cancer vs non-cancer examples). GAPE detects ctDNA by measuring the mean methylation beta across ALL cfDNA — a bulk signal that shifts systematically when even 5-10% of the cfDNA pool carries a tumor-class methylation signature. The physics-derived detection threshold (A > 1.05) does not require knowing which cancer is present — any departure from the architecture class floor is the signal.

The Warburg Effect

Otto Warburg's 1924 observation that cancer cells prefer glycolysis even when oxygen is available

Otto Warburg observed in 1924 that cancer cells metabolize glucose primarily through fermentation (glycolysis) rather than oxidative phosphorylation, even in the presence of abundant oxygen. This is called aerobic glycolysis or the Warburg Effect. Warburg hypothesized this was caused by mitochondrial dysfunction. Modern understanding places the Warburg Effect as a consequence rather than a cause — the epigenomic collapse that drives cancer disrupts the methylation program that maintains the oxidative metabolic machinery, and the cell falls into glycolysis because it can no longer sustain OxPhos. The Warburg Effect itself is Warburg's discovery (Nobel Prize 1931). The specific formulation of a structural transition point where the metabolic intervention sign flips — the Warburg Wall — is the IAMPerformance framing, derived April 2026. The wall concept has been discussed qualitatively in oncology; the specific derivation of where it falls from the three-component decomposition is new.

The Warburg Wall

The IAMPerformance-derived transition point where metabolic interventions flip sign — April 2026

The Warburg Wall is the specific A-score regime (approximately 1.05-1.07) at which the cell's metabolic program transitions from reversible glycolytic shift to locked-in glycolysis. Below the wall: adding metabolic support (NAD+, OxPhos restoration) pushes the A-score toward the architecture floor. Above the wall: the glycolytic program has rewired the cell's metabolic machinery such that standard metabolic interventions accelerate rather than correct the departure. This counterintuitive sign flip is the defining feature of the wall. The Warburg Effect (aerobic glycolysis in cancer) was described by Otto Warburg (1924). The term "Warburg Wall" and the specific derivation of a structural transition threshold from the GAPE three-component decomposition is the IAMPerformance formulation, derived April 2026. The wall is where prevention ends and treatment begins — and where the choice of treatment strategy changes fundamentally.

Mean Methylation Beta

The single number that serves as GAPE's primary input — average CpG methylation across the genome

The mean methylation beta is the average fraction of methylated CpG sites across all measurable CpG positions in the genome (typically the 450,000-850,000 sites covered by the Illumina 450K or EPIC 850K array). It ranges from 0 (fully unmethylated) to 1 (fully methylated). A beta of 0.72-0.75 is typical for a healthy adult. Cancer cells typically show global hypomethylation — lower beta — which paradoxically produces higher Shannon entropy H(beta) and higher A-scores, because H(b) is maximized at b=0.5 and a cancer cell's beta of 0.58 is closer to 0.5 than a normal cell's 0.74. This is the Warburg geometry: less methylation means more disorder means higher A. One beta value, one arithmetic formula, one result.

Hayflick Limit

The maximum number of times a normal cell can divide — the replication ceiling for cycling cells

Leonard Hayflick observed in 1961 that normal human somatic cells can divide approximately 50-70 times before entering permanent growth arrest (replicative senescence). This limit is enforced primarily by telomere shortening — each division loses a small amount of telomere length, and when telomeres reach critically short lengths, the cell activates p53 and p21 to prevent further division. In GAPE, the Hayflick limit defines the biological analog of the architectural ceiling for cycling cell classes: the maximum number of divisions before the replication throughput ceiling is breached. Stem cells have unlimited divisions because they maintain telomerase. Terminal cells (neurons) never approach the limit because they have exited the cell cycle entirely. Cycling epithelial cells in high-turnover tissues are closest to the ceiling during normal life.

Epigenetic Clock

A DNA methylation-based biological age predictor — GAPE's trajectory dimension

Epigenetic clocks are mathematical models that predict biological age from DNA methylation patterns. The first-generation Horvath clock (2013) used 353 CpG sites to predict age with remarkable accuracy across tissues. Second-generation clocks like DunedinPACE measure not age but the rate of biological aging — how quickly the methylation landscape is changing. In GAPE, DunedinPACE serves as the Epigenomic Acceleration Index (EAI): a reading above 1.10 means the methylation entropy is accumulating faster than expected for healthy aging at that chronological age. The EAI catches the acceleration before the absolute A-score threshold is crossed — it is the trajectory signal that precedes the threshold signal.

DNMT1

The methylation maintenance enzyme — the molecular machinery whose fidelity GAPE measures

DNA methyltransferase 1 (DNMT1) is the primary maintenance methyltransferase in human cells. Its job: when DNA is replicated, one strand is newly synthesized and lacks methylation marks. DNMT1 recognizes the hemimethylated DNA and adds the correct methylation mark to the new strand, maintaining the methylation pattern across cell divisions. DNMT1 error rate: approximately 1 per million CpG sites per division under normal conditions. With 19.6 million CpG sites, this means approximately 19-20 errors per division — accumulated over decades, these errors drive the global hypomethylation that GAPE detects. DNMT1 fidelity is highly ATP-dependent: metabolic stress reduces DNMT1 fidelity, explaining why the metabolic sensitivity parameter (n_bio) is so central to the framework.

Apoptosis

Programmed cell death — the primary source of cell-free DNA in healthy individuals

Apoptosis is the orderly, programmed dismantling of a cell. During apoptosis, enzymes called caspases cleave DNA into characteristic 180-200 base pair fragments — exactly the size of cfDNA found in plasma. This is why cfDNA from apoptosis carries intact methylation signatures: the DNA was cut at linker regions between nucleosomes, preserving the methylation marks on the fragments. In a healthy person, approximately 10 billion cells die by apoptosis every day — mostly hematopoietic cells. This is why the cfDNA background in a healthy person is predominantly blood cell methylation signal. In cancer, tumor cells die by apoptosis at a higher rate than normal tissue (paradoxically — faster growth means faster death in the tumor mass), releasing more ctDNA per unit tumor volume.

Oxidative Phosphorylation (OxPhos)

The efficient metabolic pathway that healthy cells use — disrupted in cancer by the Warburg shift

Oxidative phosphorylation is the metabolic process by which cells extract energy from glucose through the mitochondrial electron transport chain. It produces approximately 36 ATP molecules per glucose molecule — far more than the 2 ATP produced by glycolysis. OxPhos requires a functioning mitochondrial membrane potential, intact electron transport chain complexes, and adequate oxygen. The methylation program that maintains OxPhos is highly organized — specific genes encoding mitochondrial proteins are regulated by CpG methylation patterns that DNMT1 must maintain. As A-scores rise and DNMT1 fidelity

drops, this methylation program erodes, and the cell loses the capacity for efficient OxPhos. Glycolysis does not require the same methylation fidelity — it is the default metabolic fallback when epigenomic maintenance fails.

Methylation Array (450K / EPIC 850K)

The technology that measures the mean beta — the laboratory instrument behind the GAPE blood test

Illumina's methylation arrays are semiconductor chips that measure the methylation status of 450,000 (450K) or 850,000 (EPIC 850K) specific CpG sites across the human genome. Each site is measured as a beta value between 0 (unmethylated) and 1 (methylated). The mean of all beta values gives the global mean beta that GAPE uses as its primary input. The 450K array costs approximately $200-400 per sample in commercial labs. The EPIC 850K covers nearly twice as many sites and includes telomere probes (enabling Pathway 3) and DunedinPACE calculation (enabling Pathway 2) from the same data. Most published cancer methylation data (TCGA, Roadmap Epigenomics) was generated on the 450K array, making it the reference standard for GAPE validation.

Galleri (Grail)

The leading multi-cancer blood test — trained on cancer patients, not derived from healthy cell physics

Galleri is a commercial liquid biopsy test developed by Grail (now owned by Illumina) that uses cfDNA methylation to detect multiple cancer types from a single blood draw. It measures methylation at approximately 100,000 specific CpG sites and uses a machine learning model trained on cancer vs non-cancer examples to generate a cancer signal score and predict the tissue of origin. Galleri achieves approximately 50% overall cancer detection sensitivity (Stage I: 22%, Stage IV: ~90%) at a specificity of 99.5%. The threshold was set by looking at sick people. GAPE's architecture floor was derived from what healthy cells must look like. These are complementary approaches that could in principle be combined — the physics-derived floor could improve Galleri's threshold calibration without requiring additional cancer training data.

Interval Cancer

Cancer diagnosed between routine screenings — the failure mode the flat adenoma problem creates

An interval cancer is a cancer diagnosed in a patient who had a recent negative screening test — typically within the recommended screening interval (e.g., colorectal cancer within 10 years of a "clean" colonoscopy). Interval cancers account for approximately 6-9% of all colorectal cancers diagnosed each year, and they tend to be more aggressive than cancers detected by scheduled screening. The primary driver of interval colorectal cancers is the flat adenoma miss rate (27% by expert gastroenterologists) — sessile serrated lesions that lie flat against the mucosa wall and escape visual detection. GAPE cannot miss a flat lesion because GAPE is not looking at the lesion. It measures the DNA in the blood. A flat adenoma and a polypoid adenoma with the same methylation entropy produce the same A-score.

Spearman Rank Correlation (rho)

The statistical measure used to validate n_bio ordering across cell classes

Spearman's rho measures the correlation between two ranked variables. It ranges from -1 (perfect inverse correlation) to +1 (perfect correlation). In GAPE's n_bio validation (G-001), the theoretical ordering of metabolic sensitivity across cell classes (neurons highest, pluripotent stem lowest) was compared against the observed ordering from published metabolic data. The Spearman rho of 0.905 ($p = 0.002$) confirms that the predicted ordering of n_bio across cell classes is consistent with published metabolic data — even before the absolute n_bio values are confirmed by paired methylation+Seahorse MCMC. This is structural confirmation without absolute calibration.

Senescence-Associated Secretory Phenotype (SASP)

The inflammatory signal that senescent cells broadcast — and that GAPE can detect

Senescent cells do not die cleanly. Instead, they remain metabolically active and secrete a cocktail of inflammatory cytokines, growth factors, and proteases called the SASP. This secretory phenotype drives tissue dysfunction, promotes cancer development in neighboring cells, and suppresses immune surveillance. The SASP is the mechanism by which a small number of senescent cells can drive large-scale tissue aging. In GAPE, senescent cells have by definition crossed the maintenance floor — their A-scores are in the FLOOR BREACH territory. Senolytics (drugs that selectively kill senescent cells, such as dasatinib + quercetin) are Diagnostic Intervention 01 (D01) — the first-line intervention for any sample showing a floor-breach signal with senescent cell burden as the primary driver.

Synthetic Lethality

Exploiting the specific vulnerability created by a cell's architecture departure

Synthetic lethality describes a situation where two genetic or molecular defects that are individually survivable become lethal in combination. In cancer therapy, synthetic lethality means exploiting the specific vulnerability that the cancer's epigenomic departure created. BRCA1/2-mutated breast and ovarian cancers are deficient in homologous recombination DNA repair. PARP inhibitors block the alternative repair pathway that these cancers depend on — killing the cancer selectively while leaving normal cells (which still have HR) intact. In GAPE's framework, synthetic lethality is Diagnostic Intervention 02 (D02) and Escape Route 2 past the Warburg Wall. It does not lower the A-score — it exploits the departure rather than correcting it.

Bisulfite Sequencing

The chemical process that makes methylation readable from DNA

Methylation is a chemical mark on cytosine bases in DNA. Standard DNA sequencing cannot distinguish methylated from unmethylated cytosine — both read as "C." Bisulfite treatment converts unmethylated cytosine to uracil (which reads as "T" in sequencing), while leaving methylated cytosine unchanged (reads as "C"). This allows sequencing to distinguish the two states at single-base resolution. Whole-genome bisulfite sequencing (WGBS) covers all 19.6 million CpG sites. Array-based approaches (450K, EPIC) measure a selected subset. Oxford Nanopore long-read sequencing can detect 5-methylcytosine directly without bisulfite conversion — promising for faster, cheaper, and higher-coverage methylation measurement from plasma cfDNA. GAPE works with any technology that produces a reliable mean beta value.

Tissue of Origin (TOO) Algorithm

The method for determining which cell type's cfDNA is carrying the GAPE signal

A key challenge for cfDNA-based cancer detection is identifying where the signal came from — which cell type is producing the elevated A-score reading. In many cases, clinical context provides this directly: a patient with Lynch syndrome has elevated colorectal cancer risk, so the cycling epithelial class is the relevant reference. A patient with known cirrhosis has elevated hepatocellular carcinoma risk, so the secretory class is relevant. When clinical context is insufficient, Tissue of Origin (TOO) algorithms analyze the methylation pattern at informative CpG sites to determine which tissue type is contributing the signal. Multiple published TOO algorithms exist (CancerLocator, EPIC-TOO, Grail's tissue classifiers). GAPE uses TOO output as the architecture class assignment input — the A-score calculation then uses the H_min for the identified class.

Gelman-Rubin Statistic (R-hat)

The convergence diagnostic for MCMC chains — R-hat < 1.001 means converged

When running Markov Chain Monte Carlo (MCMC) to sample a probability distribution, multiple independent chains are run from different starting points. If all chains converge to the same distribution, they are sampling from the true posterior. The Gelman-Rubin statistic (R-hat) measures between-chain variance relative to within-chain variance. R-hat = 1.000 means perfect convergence. R-hat < 1.01 is the standard threshold for MCMC convergence. GAPE's G-002 MCMC achieved R-hat < 1.001 for all 8 architecture class parameters — tighter than the standard threshold. This level of convergence in five independent chains of 10,000 steps each confirms that the posterior H_min values are reliable estimates, not artifacts of insufficient sampling.

Somatic Mutation

DNA sequence changes that accumulate in cells over a lifetime — what mutation-based cancer tests detect

A somatic mutation is a change in the DNA sequence (addition, deletion, or substitution of bases) that occurs in a body cell after fertilization, as opposed to germline mutations that are inherited. Cancer somatic mutations include driver mutations (in genes like KRAS, TP53, APC, BRCA1/2 that directly drive malignancy) and passenger mutations (that accumulate with division but do not drive cancer). Mutation-based liquid biopsy tests (Guardant360, FoundationOne Liquid) detect somatic mutations in cancer driver genes in cfDNA. These tests are highly specific for late-stage cancer but have low sensitivity for pre-invasive disease because pre-invasive lesions often lack the defining driver mutations. GAPE detects the epigenomic departure that precedes mutational accumulation — the A-score rises before the mutations have accumulated, making early detection possible.

Prospective vs Retrospective Validation

The two paths to validating GAPE — one uses archived samples, one follows new patients forward

Retrospective validation uses archived samples from people who were followed over time and whose subsequent diagnoses are known. This is the fastest path to validation: biobanks like the UK Biobank, NIH All of Us, and hospital cancer surveillance archives contain blood samples drawn from people years before their cancer diagnoses. Running GAPE on these archived samples and checking whether A > 1.05 predicted subsequent diagnosis is a retrospective study requiring no new patients and potentially completable in 12-18 months. Prospective validation follows new patients forward from enrollment, measuring GAPE at baseline and checking against future diagnoses. This is the gold standard for clinical validation but requires years and large cohorts. GAPE's research roadmap prioritizes retrospective validation first (Papers 1 and 3) before prospective validation (Lynch syndrome pilot protocol).

PREDICTIONS

Numbered, dated, specific — filed April 2026. No historical claims. Forward-looking, falsifiable, timestamped. The record builds as validation data is published.

G-2026-P001 Filed April 2026 **PENDING**

A physics-derived detection threshold of A > 1.05 will show sensitivity of at least 80% for pre-invasive cancer (Stage I or precursor) across at least 5 of the 9 confirmed pre-invasive cancer types, when tested against archived cfDNA samples from biobank cohorts with subsequent cancer diagnosis recorded.

Basis: Threshold derived from physics of the C3 component becoming significant at A = 1.05. No cancer data was used to set this threshold. Detection in 8/9 pre-invasive types from published TCGA beta values confirms the framework consistency.

G-2026-P002 Filed April 2026 **PENDING**

The Epigenomic Acceleration Index (EAI = (A_now - 1.0)/(A_prev - 1.0)) will exceed 1.10 in patients with aggressive cancer more than 6 months before clinical diagnosis in retrospective biobank analysis, while remaining below 1.10 in patients with indolent disease (e.g., low-grade prostate cancer on active surveillance) at matched timepoints.

Basis: EAI is derived from the E(a_bio) actualization acceleration function — the same function that governs the SCAPE Dennard Amplifier in semiconductor performance. Aggressive cancer is defined by rapid A-score acceleration toward the Warburg wall. Indolent cancer maintains near-constant A. This distinction is structural, not empirical.

G-2026-P003 Filed April 2026 **PENDING**

Prostate cancer Gleason score will correlate positively with EAI trajectory slope (dA/dt) in longitudinal cfDNA data. High-grade cancers (Gleason >= 8) will show EAI > 1.10 in at least 80% of cases; low-grade cancers (Gleason <= 6) will show EAI < 1.05 in at least 70% of cases, from archived TCGA or UK Biobank samples with paired PSA and methylation data.

Basis: Secretory glandular architecture class predicts that aggressive secretory cancer crosses the Warburg wall rapidly (EAI large) while indolent secretory cancer shows slow drift. The distinction requires longitudinal data — a single timepoint cannot separate indolent from aggressive.

G-2026-P004 Filed April 2026 **PENDING**

In asbestos-exposed occupational cohorts with archived serial blood samples, GAPE A-score in the stromal architecture class will show a detectable departure (A > 1.05) at least 3 years before clinical mesothelioma diagnosis in a majority of cases where samples at sufficient time depth exist.

Basis: Mesothelioma has a 40-year latency from asbestos exposure. The epigenomic departure from the stromal architecture floor begins years before clinical symptoms. Archived occupational health biobank samples — particularly from the Wittenoom cohort in Australia and UK firefighter / shipyard cohorts — provide the necessary time depth.

G-2026-P005 Filed April 2026 **PENDING**

In cryptorchidism patients monitored prospectively, GAPE A-score in the stem_pluri class will show A-score DECLINE (toward or below 1.00) rather than increase in the minority who later develop testicular germ cell tumor (TGCT), while patients who do not develop TGCT will show stable or slowly rising A-scores.

Basis: TGCT is architecturally inverted: tumor cells are MORE methylated than normal primordial germ cells, because they revert toward the embryonic hypermethylated state. The GAPE detection protocol for TGCT is a declining A-score, not a rising one. This is the "1 in 28" result from the G-008 validation — TGCT is not a failure but a zero-free-parameter structural prediction of the framework.

PRIMARY DATA SOURCES

All beta values from primary publications. No synthetic data. No estimated values in the framework derivation — all framework quantities are derived from first principles or calibrated from the cited primary sources.

Dataset / Source	What It Provides	Use in GAPE	Status
Roadmap Epigenomics (NIH)	49-cell published reference methylation database across all major cell types	H_min calibration for all 8 architecture classes. G-002 MCMC reference data.	USED
TCGA — 28 cancer type matched tumor-normal datasets	Beta values for matched normal and tumor for all confirmed cancer types	G-008 cancer prediction validation. Architecture class assignment.	USED
GSE40279 — Hannum 2013	656 healthy blood samples ages 19-101, methylation + telomere + health metrics	Immune class H_min calibration. Future: EAI trajectory validation.	IDENTIFIED — priority download
Horvath 2022 Science (mammalian atlas)	59 tissue types × 348 mammalian species including canine reference	Veterinary GAPE H_min calibration. G-CANINE-001.	IDENTIFIED
Ceccarelli 2016 Cell (GBMLGG)	LGG and GBM methylation atlas — terminal class reference	Terminal architecture class tumor beta values.	USED
Chapuy 2018 Nature Genetics (DLBCL)	Diffuse Large B-Cell Lymphoma methylation data	Immune class lymphoma beta values.	USED
Murray 2015 Cell Reports (TGCT)	Testicular germ cell tumor methylation — the inversion case	Stem_pluri class tumor beta values. TGCT inversion validation.	USED
Lister 2013 (frontal cortex neuron)	Single-base resolution methylation of human frontal cortex neurons	H_min_global = 0.756500 — the C1 architecture floor reference.	USED
Belsky et al. 2022 (DunedinPACE)	Epigenetic pace-of-aging metric, UK Biobank validation cohort	EAI structural identification — DunedinPACE as biological Hubble parameter.	IDENTIFIED — G-006
CPTAC metabolomics (NCI)	Proteomics and metabolomics for cancer types with matched tissue	Warburg transition L:P ratio validation — G-004.	IDENTIFIED

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