Quiet Biology: Core Scientific References

Reference List and Citation Map

Supporting documents for the Quiet Biology white paper series — five papers

20 references • [1]–[9] core • [10]–[16] extended • [17]–[20] Paper 5

Colour Key

- [1]–[9] Original core references
- [10]–[16] Extended references (evidential gap-fill, Papers 1–4)
- [17]–[20] Paper 5 additions (PSA kinetics and natural history)

Part 1: Annotated Reference List

References [1]–[9] form the original core spine. References [10]–[16] address evidential gaps identified across Papers 1–4. References [17]–[20] are additions supporting Paper 5 on PSA kinetics and natural history. Refs [5] and [6] — Johansson and Albertsen — carry weight across both the autopsy/ecology papers and Paper 5; they are listed once in the core spine and their Paper 5 roles are documented in the citation map.

Core References [1]–[9]

[1] Gatenby RA & Gillies RJ (2009). A microenvironmental model of carcinogenesis. Nature Reviews Cancer.

Founding paper of evolutionary oncology. Establishes that tumor cells evolve under environmental selection pressures — not mutation alone — and that aggressive phenotypes emerge when ecological conditions favour them. Directly supports the argument that maximal therapeutic suppression accelerates evolutionary escape by restructuring the selection environment.

[2] Zhang J, Cunningham JJ, Brown JS & Gatenby RA (2017). Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer. Nature Communications.

Clinical validation of adaptive therapy in mCRPC. Demonstrates that modulating treatment pressure extends time to progression by maintaining sensitive cell populations as ecological competitors to resistant variants. Uses significantly less total drug over the treatment course. The closest clinical analogue to the Quiet Biology management framework.

[3] Aktipis CA, Boddy AM, Jansen G, et al. (2015). Cancer across the tree of life: cooperation and cheating in multicellularity. Philosophical Transactions of the Royal Society B.

Frames cancer as the re-emergence of ancestral unicellular behaviour when the governance systems enforcing multicellular cooperation are disrupted. Establishes that maintaining tissue regulatory integrity — metabolic, immune, structural — is itself a form of cancer control. Grounds the QB argument that systemic health is biologically central to cancer management, not merely supportive.

[4] Franks LM (1954). Latent carcinoma of the prostate. Journal of Pathology and Bacteriology.

Original autopsy discovery demonstrating that microscopic prostate cancer is common in men dying of unrelated causes. Establishes the foundational paradox: tumour initiation is near-universal in older men; clinical progression is not. Anchors the argument that environmental conditions — not genetics alone — determine whether latent cancer becomes lethal. Referenced across Papers 1, 3, 4, and 5.

[5] Johansson JE, Andrén O, Andersson SO, et al. (2004). Natural history of early, localized prostate cancer. JAMA.

Twenty-year outcomes from the Swedish observational cohort: the foundational long-term evidence that
most localized prostate cancer progresses slowly, with low disease-specific mortality in well- and moderately-differentiated tumors over the first 10–15 years. Establishes that prostate cancer has a natural biological tempo and that watchful observation is a defensible initial strategy for appropriately selected patients. Provides ecological and natural history grounding in Papers 1, 3, and 4; serves as primary evidential anchor in Paper 5 Section 2.

[6] Albertsen PC, Hanley JA & Fine J (2005). 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA.

Population-level outcome data showing that mortality risk varies dramatically by tumour grade. Gleason 6 disease carries approximately 6% disease-specific mortality at 20 years; Gleason 8–10 exceeds 60–87%. Establishes grade as the primary biological signal for prognosis and reinforces selective intervention over reflex treatment. Competing mortality analysis essential for older patients. Cited in Papers 1, 3, and 4 as natural history support; central to Paper 5 Section 3.

[7] Fidler IJ (2003). The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nature Reviews Cancer.

Revisits and formalises Paget's seed-and-soil hypothesis, demonstrating that tumour behaviour depends critically on host microenvironment ('soil') as well as tumour genetics ('seed'). Foundational support for the field control concept and the argument that the tissue environment is an active determinant of tumour fate, not merely a passive substrate.

[8] Vander Heiden MG, Cantley LC & Thompson CB (2009). Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science.

Explains how metabolic context governs tumour growth dynamics, establishing that cancer cells actively rewire metabolism to support proliferation. Supports the concepts of metabolic permissiveness and metabolic constraint. Foundational reference for Paper 2 (Metabolism and Epigenetics).

[9] Hanahan D (2022). Hallmarks of Cancer: New Dimensions. Cancer Discovery.

Updated hallmarks framework explicitly incorporating non-mutational epigenetic reprogramming, unlocking phenotypic plasticity, and enabling conditions. Frames cancer progression as dependent on system-level conditions, not solely cell-intrinsic mutations. Directly supports the central QB thesis: mutations provide potential; environment determines expression. Referenced in Papers 1, 2, 3, and 4 as the synthesising theoretical anchor.

Extended References [10]–[16]

Evidential gap references incorporated following review of Papers 1–4.

[10] Sakr WA, Haas GP, Cassin BF, Pontes JE & Crissman JD (1993). The frequency of carcinoma and intraepithelial neoplasia of the prostate in young male patients. Journal of Urology.

Provides the specific age-stratified autopsy prevalence figures cited in Paper 1: histologically identifiable prostate cancer in approximately 30–40% of men in their fifties, rising to more than 60–70% in men over 80. Anchors the quantitative claims that make the autopsy paradox concrete rather than merely descriptive. Also cited in Paper 5 Section 1 to ground the biological prevalence context.

[11] Mosquera JM, Mehra R, Regan MM, et al. (2009). Prevalence of TMPRSS2-ERG fusion prostate cancer among men undergoing prostate biopsy in the United States. Clinical Cancer Research.

Documents the prevalence of TMPRSS2-ERG gene fusions in low-grade and incidental tumours, establishing that canonical oncogenic alterations are present in latent prostate cancer. Directly

supports the Paper 1 claim that many latent tumours carry molecular features classically associated with malignant potential, yet remain clinically silent.

[12] Kaelin WG & McKnight SL (2013). Influence of metabolism on epigenetics and disease. Science.
Establishes the mechanistic links between cellular metabolic state and chromatin-modifying enzyme activity, covering acetyl-CoA, SAM, α-ketoglutarate, and NAD^+ as epigenetic cofactors. Foundational reference for the Paper 2 argument that metabolic reprogramming precipitates epigenetic change rather than merely accompanying it.

[13] Ku SY, Rosario S, Wang Y, et al. (2017). Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. Science.
Experimental model demonstrating that RB1 and TP53 loss cooperate to enable lineage plasticity and neuroendocrine transition under therapeutic pressure. Anchors the Paper 2 claim that epigenetic and transcriptional flexibility is a prerequisite for lineage switching, and that interfering with this flexibility reduces transition probability.

[14] Gatenby RA, Silva AS, Gillies RJ & Frieden BR (2009). Adaptive therapy. Cancer Research.
Introduces the formal adaptive therapy framework and the evolutionary double-bind concept. Distinct from the 2009 Nature Reviews Cancer paper [1]; anchors the double-bind discussion in Paper 4 and the ecological management argument in Paper 3.

[15] Kalluri R (2016). The biology and function of fibroblasts in cancer. Nature Reviews Cancer.
Comprehensive account of normal-to-CAF fibroblast transition and its disproportionate regulatory consequences for epithelial growth, immune exclusion, and extracellular matrix remodelling. Anchors the Paper 3 keystone species argument: stromal loss is ecologically catastrophic for microenvironmental regulation.

[16] West J, You L, Zhang J, et al. (2023). Towards multidrug adaptive therapy. Cancer Research.
Extends adaptive therapy to multidrug protocols and reports on the Moffitt Cancer Center programme including FRAME trial design. Anchors the Paper 4 claim that adaptive therapy is a live and developing clinical programme, not a single historical proof-of-concept.

Paper 5 References [17]–[20]

New references supporting Paper 5: PSA Kinetics and the Natural History of Prostate Cancer.

[17] Wilt TJ, Brawer MK, Jones KM, et al. (PIVOT Study Group) (2012). Radical prostatectomy versus observation for localized prostate cancer. New England Journal of Medicine.
First large randomized controlled trial comparing radical prostatectomy with observation in clinically localized prostate cancer (n≈700, follow-up to 20 years). Primary finding: surgery did not significantly reduce all-cause or prostate-cancer-specific mortality in the full cohort. Survival benefit confined to higher-risk subgroups. Directly supports the Paper 5 argument that immediate aggressive treatment does not improve outcomes for most men with low-risk localized disease. Randomised confirmation of the Johansson and Albertsen observational findings.

[18] Hamdy FC, Donovan JL, Lane JA, et al. (ProtecT Study Group) (2016). 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. New England Journal of Medicine.
Largest randomised trial comparing radical prostatectomy, radiotherapy, and active monitoring in PSA-detected localized prostate cancer (n>1,600, median follow-up 10 years, extended to 15 years in subsequent analysis). Primary finding: prostate cancer-specific mortality approximately 1% and not significantly different across all three groups at 10 years. Monitoring group showed higher

metastasis rates at 15 years but without proportionate mortality signal. Provides the most comprehensive comparative harm data: prostatectomy carries significantly higher rates of urinary incontinence and erectile dysfunction across follow-up. Establishes that the survival margin between immediate treatment and active monitoring is narrower than clinical intuition has assumed.

[19] Carter HB, Pearson JD, Metter EJ, et al. (1992). Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. JAMA.

Foundational PSA velocity paper using stored serum from the Baltimore Longitudinal Study of Aging. Demonstrates that men who subsequently developed prostate cancer showed significantly higher rates of PSA rise in the years before diagnosis. Establishes PSA velocity (rate of change per year) as a diagnostic and prognostic signal independent of absolute PSA level. Anchors the Paper 5 argument that trajectory encodes biological information that a single measurement cannot provide.

[20] D'Amico AV, Chen MH, Roehl KA & Catalona WJ (2004). Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. New England Journal of Medicine.

Demonstrates that PSA velocity in the year before diagnosis is an independent predictor of prostate cancer-specific mortality, even after adjusting for grade, stage, and PSA level. Men with pre-diagnosis PSA velocity exceeding 2 ng/mL per year face substantially higher disease-specific mortality regardless of absolute PSA. Directly challenges the clinical habit of making treatment decisions based primarily on PSA level. Anchors the Paper 5 argument that velocity is more prognostically informative than level, and supports PSA doubling time as the primary kinetic monitoring tool in the QB framework.

Part 2: Citation Map by Paper and Claim

All 20 references mapped across all five papers. Colour coding: [1]–[9] core (blue) • [10]–[16] extended (dark red) • [17]–[20] Paper 5 additions (green). Refs [5] and [6] are core references with primary analytical weight in Paper 5; they appear in both the Paper 1–4 and Paper 5 sections of the map.

Ref	Paper	Sections	Claim supported
PAPER 1: Autopsy Pathology — Mutations Provide Potential, but Environment Determines Expression			
[4]	Paper 1: Autopsy Pathology	Sections 2, 3	Franks original autopsy discovery; foundational prevalence paradox established
[10]	Paper 1: Autopsy Pathology	Section 2	Age-stratified prevalence figures: 30–40% in fifties; 60–70%+ in over-80s
[11]	Paper 1: Autopsy Pathology	Section 4	TMPRSS2-ERG fusions in low-grade and incidental tumours; oncogenic alterations in latent cancer
[5]	Paper 1: Autopsy Pathology	Sections 2, Concl.	Johansson: long-term natural history context; most low-grade disease does not progress to lethal disease over 20+ years
[6]	Paper 1: Autopsy Pathology	Sections 2, Concl.	Albertsen: 20-year conservative management data; mortality risk varies dramatically by grade
[7]	Paper 1: Autopsy Pathology	Section 6	Seed-and-soil: microenvironment as active determinant of tumour fate

Ref	Paper	Sections	Claim supported
[9]	Paper 1: Autopsy Pathology	Sections 5, Concl.	Hanahan enabling conditions: system-level factors required for progression beyond genetic potential
PAPER 2: Metabolism, Epigenetics, and Lineage Plasticity			
[8]	Paper 2: Metabolism & Epigenetics	Sections 2, 3	Warburg effect: metabolic rewiring as active driver of proliferative phenotype
[12]	Paper 2: Metabolism & Epigenetics	Section 3	Acetyl-CoA, SAM, α-KG, NAD^+ as chromatin-modifying cofactors; metabolic state precipitates epigenetic change
[13]	Paper 2: Metabolism & Epigenetics	Sections 4, 5	RB1/TP53 loss enables lineage plasticity; metabolic-epigenetic adaptation as prerequisite for NE transition
[9]	Paper 2: Metabolism & Epigenetics	Sections 4, 5	Non-mutational epigenetic reprogramming and phenotypic plasticity as hallmarks; enabling conditions framework
PAPER 3: Tumour Ecology and Evolutionary Stability			
[1]	Paper 3: Tumour Ecology	Sections 1, 5, 7	Gatenby ecological model: microenvironmental selection determines phenotypic dominance
[14]	Paper 3: Tumour Ecology	Section 5	Adaptive therapy and evolutionary double-bind: formal framework for ecological treatment strategy
[15]	Paper 3: Tumour Ecology	Section 3	CAF transition as keystone species loss: stromal regulatory collapse and its disproportionate consequences
[5]	Paper 3: Tumour Ecology	Sections 2, 8	Johansson: empirical grounding for ecological stability as default state of localised disease
[6]	Paper 3: Tumour Ecology	Sections 2, 8	Albertsen: grade stratification as proxy for ecological character of tumour
[4]	Paper 3: Tumour Ecology	Section 8	Franks autopsy paradox: latency as ecological stability, not genetic inertia
[9]	Paper 3: Tumour Ecology	Sections 6, 8	Hanahan enabling conditions as ecological preconditions for phenotypic evolution
PAPER 4: Cancer as an Ecological and Evolutionary System (Capstone)			
[1]	Paper 4: Capstone	Section 2	Gatenby Darwinian ecology model; fitness landscape; evolutionary double-bind concept
[3]	Paper 4: Capstone	Section 3	Aktipis cooperative breakdown framework; multicellular governance as cancer suppression mechanism
[2]	Paper 4: Capstone	Section 4	Zhang & Gatenby adaptive therapy clinical trial in mCRPC; empirical validation of ecological management

Ref	Paper	Sections	Claim supported
[16]	Paper 4: Capstone	Section 4	West et al. multidrug adaptive therapy; Moffitt FRAME trial programme as ongoing clinical development
[14]	Paper 4: Capstone	Section 2	Adaptive therapy formal framework (Cancer Research 2009); distinct from [1]
[4]	Paper 4: Capstone	Sections 1, 6	Franks autopsy paradox: foundation of gap between biological prevalence and clinical significance
[5]	Paper 4: Capstone	Sections 1, 6	Johansson natural history as empirical validation of ecological stability model
[6]	Paper 4: Capstone	Section 6	Albertsen grade-stratified outcomes: grade as ecological signal for management decisions
[9]	Paper 4: Capstone	Concl.	Hanahan synthesising anchor: enabling conditions and phenotypic plasticity as system-level hallmarks
PAPER 5: PSA Kinetics and the Natural History of Prostate Cancer			
[5]	Paper 5: PSA Kinetics	Sections 2, 7	Johansson 20-year Swedish cohort: foundational natural history; disease tempo slow in majority; late-accelerating mortality curve
[6]	Paper 5: PSA Kinetics	Sections 3, 7	Albertsen grade-stratified 20-year outcomes: Gleason 6 ≈6% disease-specific mortality; competing mortality analysis
[17]	Paper 5: PSA Kinetics	Section 4	PIVOT: radical prostatectomy vs observation RCT; no significant all-cause or PCa-specific mortality benefit in full cohort; benefit confined to higher-risk subgroups
[18]	Paper 5: PSA Kinetics	Section 5	ProtecT: three-way RCT of prostatectomy, radiotherapy, active monitoring; ~1% PCa mortality at 10 years across all groups; treatment harm profile documented rigorously
[19]	Paper 5: PSA Kinetics	Section 6	Carter: PSA velocity as diagnostic and prognostic signal; rate of rise predicts PCa development and disease-specific mortality independent of absolute level
[20]	Paper 5: PSA Kinetics	Section 6	D'Amico: pre-diagnosis PSA velocity >2 ng/mL/yr predicts PCa-specific mortality independently of grade and stage; velocity more prognostic than absolute PSA level
[4]	Paper 5: PSA Kinetics	Sections 1, 7	Franks autopsy paradox: context for why natural history data matters — most harboured tumours never become the disease the patient fears
[10]	Paper 5: PSA Kinetics	Section 1	Age-prevalence figures: quantitative grounding for the gap between biological prevalence and

Ref	Paper	Sections	Claim supported
			clinical progression

Colour key

■ [1]–[9] original core ■ [10]–[16] gap references ■ [17]–[20] Paper 5 additions

Cross-paper references

[5] Johansson and [6] Albertsen appear in Papers 1, 3, 4, and 5 — they are the empirical spine of the series. Their primary analytical home is Paper 5, where they are examined at length; in Papers 1, 3, and 4 they provide natural history context and ecological grounding.

[9] Hanahan appears in Papers 1, 2, 3, and 4 as the synthesising theoretical anchor, providing the updated hallmarks framework that unifies the series' ecological argument.

[4] Franks appears in Papers 1, 3, 4, and 5 as the foundational paradox — the autopsy observation from which the entire ecological argument originates.

[1] Gatenby (Nature Reviews Cancer 2009) and [14] Gatenby (Cancer Research 2009) are distinct papers cited for distinct purposes: [1] for the ecological model of carcinogenesis; [14] for the formal adaptive therapy framework. They should not be conflated.