The Valley of Death in the Translational Research Pipeline

James E. Coleman

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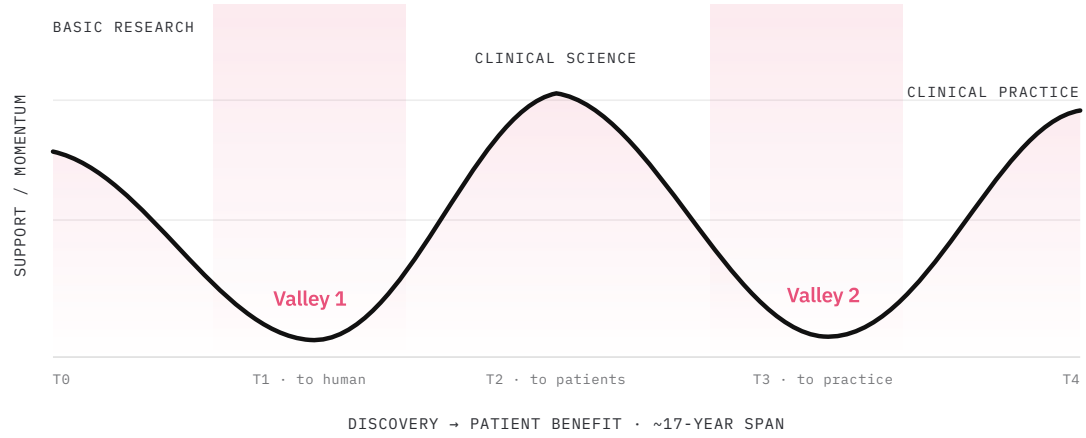
ABSTRACT *Promising discoveries are lost not because they lack scientific merit, but because the infrastructure to move them from discovery to application does not exist — or exists in a form structurally hostile to translation.*

FIG. — THE JOURNEY ACROSS THE VALLEY

0 OF 100 REACH PATIENTS



WHAT IT TAKES TO CROSS — AND WHO DOESN'T

86

~86%

About 86% of research findings never reach clinical practice at all.[1]

14

14%

Only 14% make it all the way to **patient benefit**.[1]

17 yr

The few that do take about seventeen years to travel from discovery to adoption.[1][2]

$2.6B

— at roughly $2.6B to approve a single new drug.[3]

§ 01 Anatomy of the Valley

A structural chasm, *not a metaphor.*

The "Valley of Death" is the structural chasm between basic research outputs and their applied use[6] — a term popularized in the biomedical-research context to describe discoveries that stall between the laboratory and the clinic. It is not a metaphor for difficulty — it is a precise description of a funding, incentive, and infrastructure desert that swallows the majority of scientifically valid discoveries before they can be tested in the real-world contexts that would determine their utility. In one landmark analysis, of 101 basic-science findings published with explicit clinical promise, only five were licensed for clinical use roughly two decades later.[7]

The work the valley strands is rarely dramatic. Consider a 2022 preclinical stroke study — co-authored by Dr. Jeffrey Moorhead, MD, DPT — that set out to resolve what it framed as a "translational issue": whether adding physical rehabilitation would help or hinder a neural stem-cell therapy implanted into injured brain tissue. The intuitive assumption was that two beneficial interventions would compound. They did not. The combination "exerted sub-additive therapeutic effects," and on

some measures the exercise actively suppressed the cell therapy's benefit[10] — a result whose entire value lies in redirecting how the therapy is carried toward human trials. This is the texture of translation: painstaking, expensive, frequently counterintuitive work that establishes not whether a discovery is promising but whether it survives contact with a realistic treatment context. It is exactly this work that the funding and incentive structures below leave underfunded.

The valley exists between two well-funded regions: upstream basic science, supported by government and academic funding structures optimized for discovery; and downstream commercialization, supported by private capital optimized for late-stage risk-reduction. The space between — where discoveries require translation, safety testing, proof-of-concept at scale, and regulatory pathway development — is systematically underfunded and organizationally unsupported.

T0	T1	T2	T3	T4	T5
Basic Science	**Discovery Translation**	Clinical Validation	Effectiveness Research	Practice Integration	**Scale & Impact**
Funded	~60%	~14%	~9%	~5%	Funded

T2–T4 COMPLETION RATES ARE A MODELED SCHEMATIC; THE ~14% T1→PRACTICE ANCHOR IS SOURCED TO BALAS & BOREN 2000.[1] OTHER STAGE RATES ARE ILLUSTRATIVE. THE STAGE LABELS FOLLOW THIS MODEL; THEY MAP ONTO THE NIH TRANSLATIONAL SPECTRUM, CONVENTIONALLY DEFINED T0–T4 (BASIC → TRANSLATION TO HUMANS → TO PATIENTS → TO PRACTICE → TO POPULATION HEALTH).

The stages shaded red — T2 through T4 — represent the valley. Funding for this zone is a fraction of the adjacent regions: of the NIH funding tied to drugs approved between 2010 and 2019, roughly 83% supported basic research on biological targets versus about 17% for applied, translational work on the drugs themselves,[8] and NIH's dedicated translational-science center (NCATS) receives only about 2% of the NIH budget.[9] The shortfall persists despite the fact that these stages are precisely where scientific merit is converted into evidence of applied impact.



The floor of Death Valley — the gap where research that survives the lab still dies before it reaches use.

Photo: Paxson Woelber · CC BY-SA 3.0

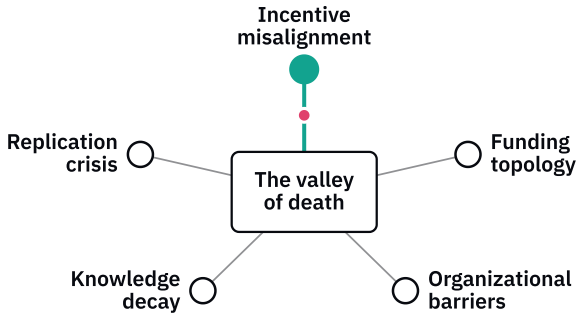
> *"The valley is not a gap in ambition. It is a gap in architecture — the organizational, funding, and institutional infrastructure required to carry a discovery from the bench to the bedside, the classroom, or the field."*
>
> — TRANSLATIONAL RESEARCH FRAMEWORK

§ 02 Root Causes of Failure

Five systemic failures *that compound.*

The valley is not an accident. It is the predictable product of incentive structures that optimize for different outcomes at each stage of the pipeline. Basic science rewards discovery novelty; clinical research rewards safety demonstration; commercial development rewards return on investment. Translation — the work of moving between these reward logics — is valued by none of them sufficiently.

FIG. 2.1 — STRUCTURAL CAUSES OF TRANSLATIONAL FAILURE STATE 1 OF 5



CAUSE 1

Incentive misalignment

Academic reward structures (publication, grant success, citation) do not value the iterative, non-publishable work of translation. Researchers who pursue translation sacrifice career advancement under conventional metrics.

CAUSE 2

Funding topology

Government funding instruments are designed for either basic research or large-scale efficacy trials — not the middle work. Application requirements, timelines, and deliverable expectations of available mechanisms do not match translational work realities.

CAUSE 3

Organizational barriers

Translation requires collaboration across institutional types — academic, clinical, regulatory, commercial — that have incompatible cultures, IP frameworks, timelines, and decision criteria. The transaction costs of multi-institutional translation are prohibitive without specialized infrastructure.

CAUSE 4

Knowledge decay

Research findings lose operational validity as conditions change. Translation pipelines that operate on 10–15 year timescales routinely arrive with findings superseded by context changes — rendering the translational work moot at arrival.

CAUSE 5

Replication crisis

Systematic overestimation of effect sizes in small-sample discovery research means many findings entering the translational pipeline have a negative expected value for translation.[4][5] Without better T1 gatekeeping, the valley fills with discoveries that should never have entered.

A diagram of the relation, not a chart of data. Five structural causes feed the same gap. Choose a cause to hold it.

These failures do not fall evenly. The valley strands most reliably the discoveries with the weakest commercial pull — rare and pediatric diseases, conditions concentrated in low-income and underserved populations, and behavioral, rehabilitative, and preventive interventions that no product can monetize. Because the middle stages are financed largely by expected private return, translation becomes a function of market size rather than clinical need — and the populations already least served are the ones whose discoveries are least likely to cross. A serious bridge strategy has to treat health equity as a design parameter, not a byproduct.

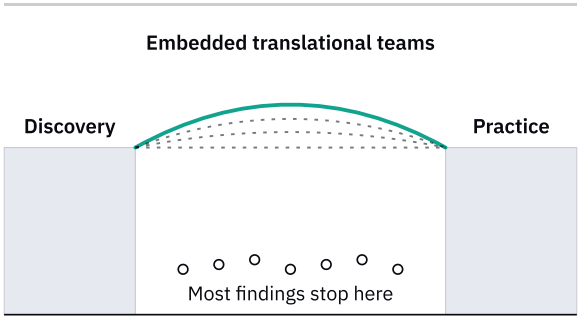
§ 03 Bridge Strategies

Compress the middle, *don't fill the valley.*

Effective strategies for crossing the valley share a common architectural feature: they compress the time and cost of the middle stages rather than attempting to fill the funding gap with more capital. Capital-filling strategies have been tried repeatedly and fail consistently because the barrier is not financial — it is structural.

> *"You cannot build a bridge across the Valley of Death by pouring money into the valley. You build it by building infrastructure that lets translation happen faster, cheaper, and with higher fidelity to both the upstream science and the downstream application context."*
>
> — TRANSLATIONAL RESEARCH FRAMEWORK

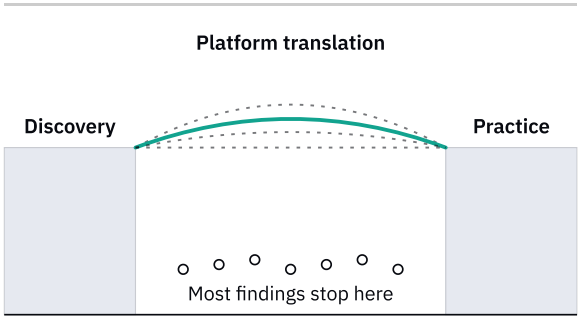
FIG. 2.2 — BRIDGE STRATEGY TAXONOMY STATE 1 OF 4



BRIDGE 1

Embedded translational teams

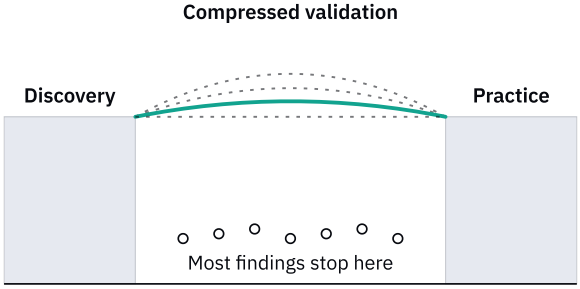
Dedicated organizations whose sole function is managing the T2–T4 transition, with institutional arrangements that align their incentives with successful crossing rather than grant acquisition or publication output.



BRIDGE 2

Platform translation

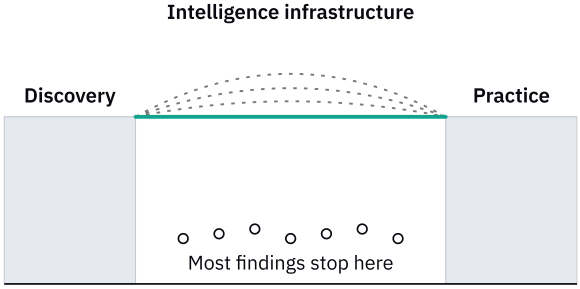
Models that reduce per-finding translation costs by standardizing protocols, regulatory pathways, and deployment infrastructure across categories of findings. The fixed cost of translation is amortized across many discoveries rather than paid fresh each time.



BRIDGE 3

Compressed validation

Adaptive trial designs, real-world evidence frameworks, and regulatory pathway engineering that compress the T2–T3 timeline without sacrificing scientific validity. Speed and rigor are not irreconcilable when the process is architecturally redesigned.



BRIDGE 4

Intelligence infrastructure

Building the decision-quality information systems that allow translational gatekeepers to identify which discoveries merit the investment of crossing — rather than defaulting to academic prestige or funder preference as proxies for translational potential.

A diagram of the relation, not a chart of data. Four ways to carry a finding from discovery to practice. Each state draws one bridge, and the dot crosses it.

§ 04 Design Intelligence Applied

The intelligence gap *inside the pipeline.*

The design intelligence frameworks established in WP 1.0 have direct application here. The intelligence gap that afflicts organizations generally manifests acutely in translational pipelines, where decision-relevant information about which discoveries merit translation resources is systematically unavailable to the organizations making those decisions.

The most consequential design intervention in a translational pipeline is not clinical trial design or regulatory strategy — it is the decision architecture that determines which discoveries enter the pipeline at all. A translation pipeline with excellent execution and poor intake selection will fail. A pipeline

with rigorous selection, well-designed validation processes, and feedback loops that improve intake criteria over time will compound its success rate.

This is where the organizational intelligence infrastructure described in the previous paper intersects directly with translational research practice: the organizations that cross the valley most reliably are those that have built the greatest capacity to assess translational potential early, with high accuracy, at low cost. That capacity is not scientific — it is informational, architectural, and designed.

That sentence is the thruline of this series. Whether the gap runs from data to decision, discovery to treatment, or transaction to trust, the barrier is the same shape: not a shortage of raw material, but the absence of designed infrastructure to carry it across — built around the people who do the crossing. The clinical instance is the sharpest. In a translational-research collaboration this author conducted with practicing clinician-scientists — led by Dr. Jeffrey Moorhead (MD, DPT), with Moore, Brooks, Ghuman, Tramontini, Mayo, and Coleman — the clinician-scientist is treated as the pipeline's scarce, decisive resource: the human bridge who "bridge[s] the gap between medical care and scientific research." That work proposes precisely the infrastructure this paper argues for — a cloud-hosted, API-integrated, human-centered software platform that operationalizes the unglamorous middle of translation: organizing the research program, managing the grant, integrating data across siloed systems, and coordinating multi-disciplinary teams.[11] The valley is crossed, in other words, by building the system the bridge-builders currently lack.

↳ The series thruline

The gap between knowledge and action is an infrastructure problem, not a resource problem — crossed by systems designed around the people who do the crossing. Here the gap runs from discovery to treatment — the clinical instance, developed with practicing clinician-scientists. The same move recurs across the series: build the system the people who do the crossing currently lack.

§ R References — Primary Sources

Sources *& notes.*

Externally sourced figures are cited to their primary source below. The only remaining modeled element is the T0–T5 funnel's intermediate completion rates (apart from the ~14% anchor, which is sourced), labeled as such in the figure; the translational funding shortfall is now quantified against NIH portfolio data.

1. [1]Balas EA, Boren SA. "Managing Clinical Knowledge for Health Care Improvement." *Yearbook of Medical Informatics* 2000; 9: 65–70. Origin of the "17 years / 14% of original research reaches patient benefit" estimate (hence ~86% does not). doi:10.1055/s-0038-1637943.

2. [2]Morris ZS, Wooding S, Grant J. "The answer is 17 years, what is the question: understanding time lags in translational research." *Journal of the Royal Society of Medicine* 2011; 104(12): 510–520. Corroborates the ~17-year translation lag. doi:10.1258/jrsm.2011.110180.

3. [3]DiMasi JA, Grabowski HG, Hansen RW. “Innovation in the pharmaceutical industry: New estimates of R&D costs.” *Journal of Health Economics* 2016; 47: 20–33 (Tufts CSDD, announced 2014). The ~$2.6B figure is the cost to develop and win approval for a new drug. doi:10.1016/j.jhealeco.2016.01.012.

   Applied here as a proxy for translational cost; the original study measures pharmaceutical R&D specifically, and the estimate is debated.

4. [4]Ioannidis JPA. “Why Most Published Research Findings Are False.” *PLoS Medicine* 2005; 2(8): e124. doi:10.1371/journal.pmed.0020124.

5. [5]Open Science Collaboration. “Estimating the reproducibility of psychological science.” *Science* 2015; 349(6251): aac4716. doi:10.1126/science.aac4716.

6. [6]Butler D. “Translational research: crossing the valley of death.” *Nature* 2008; 453(7197): 840–842. doi:10.1038/453840a.

7. [7]Contopoulos-Ioannidis DG, Ntzani EE, Ioannidis JPA. “Translation of highly promising basic science research into clinical applications.” *The American Journal of Medicine* 2003; 114(6): 477–484. Of 101 basic-science findings claiming clinical promise, 5 were licensed for clinical use ~20 years later. PMID 12731504.

8. [8]Galkina Cleary E, Jackson MJ, Ledley FD. “Government as the First Investor in Biopharmaceutical Innovation: Evidence from New Drug Approvals 2010–2019.” Institute for New Economic Thinking, Working Paper No. 133 (2021). ~83% of NIH funding went to basic research on targets vs. ~17% to applied research on the drugs. ineteconomics.org.

9. [9]National Center for Advancing Translational Sciences (NCATS), FY2021 Congressional Justification; NIH Office of Budget. NCATS FY2020 enacted funding was $832.9M of NIH's ~$40B total (≈2%). NIH Office of Budget.

   The ~2% share is computed from NCATS’s enacted appropriation against NIH’s total budget authority.

10. [10]Ghuman H, Perry N, Grice L, Gerwig M, Moorhead J Jr, Nitzsche F, Poplawsky AJ, Ambrosio F, Modo M. “Physical therapy exerts sub-additive and suppressive effects on intracerebral neural stem cell implantation in a rat model of stroke.” *Journal of Cerebral Blood Flow & Metabolism* 2022; 42(5): 826–843. PMID 34826373 · doi:10.1177/0271678X211062955.

    A collectively authored study (Dr. Jeffrey Moorhead, MD, DPT, is a co-author), cited as a translational-research example, not an individual statement.

11. [11]Dr. Jeffrey Moorhead (MD, DPT), Moore J, Brooks R, Ghuman H, Tramontini F, Mayo E, Coleman JE. “Transforming Translational Research: Leveraging Cloud Infrastructure for Enhanced Collaboration and Efficiency to Sustain Innovations through the Valley of Death.” Working manuscript, University of Arizona / HumanData.

    Unpublished working manuscript co-authored by the author of this series; quotations are from the manuscript's introduction.