Metabolism as Platform Medicine

Why the next strategic frontier is not discovery alone, but evidence architecture across organs, endpoints, and markets.

Strategy Report · Current as of June 2026

Executive Summary

For much of its history, metabolic medicine advanced one organ at a time — and that discipline is exactly what made the present moment possible. Decades of specialized work mapped the signals, receptors, pathways, and feedback loops governing glucose, adiposity, appetite, liver fat, filtration, and cardiovascular risk, each at a resolution only a dedicated field can reach. But the closer each specialty looked, the more clearly the same biology reappeared across domains. Metabolism was never confined to the organ that named the disease. The task ahead is not to abandon specialization, but to connect what it made visible.

The leading therapeutic classes have made that recognition unavoidable. SGLT2 inhibitors grew from a diabetes treatment into foundational heart-failure and chronic-kidney-disease medicine across a decade of dedicated outcomes trials.[1][2] GLP-1 and incretin therapies expanded further and faster, gathering evidence across cardiovascular risk, kidney disease, MASH, obesity, and sleep apnea.[3][4][5] Commercial activity reflects the same shift. Integrated biology is increasingly acquired as well as built, and analysts estimate the GLP-1/incretin market at roughly $53–63 billion for 2025.[8]

Yet every one of those crossings was won through its own trial, label, and payer pathway. That is the defining tension of metabolic medicine in 2026: the biology is integrated, but the proof is not. Evidence is still generated through structures built one organ at a time — an architecture that was rational for the questions it was designed to answer, now being asked to evaluate therapies that act across heart, kidney, liver, adipose tissue, brain, and pancreatic islet. The real translational gap is no longer only bench-to-bedside. It is the gap between system-level biology and the organ-specific machinery still used to prove, label, reimburse, and defend it.

No single medical specialty currently “practices metabolism” as an integrated field. We call our reading of this moment *metabolism as platform medicine* — a strategic lens, not a regulatory category. The term comes from oncology, which spent a decade organizing evidence around shared mechanisms and

biomarker-defined populations, backed by dedicated infrastructure.[6] Metabolism has the cross-organ biology for that kind of organization. It does not yet have the architecture, though master protocols are beginning to emerge.[7]

The next advantage will not come from the molecule alone. It will come from the evidence architecture around it: the endpoints, trials, labels, payer logic, and durability data that convert a cross-organ signal into integrated proof. That is where development strategy, diligence, and translational planning now need to move earlier.

What not to overclaim is part of the same discipline. Benefit on therapy is not automatically durable disease modification. Analyst estimates are not facts. A signal across organs is not integrated evidence until a trial is built to capture it. And platform medicine in metabolism is an interpretation we argue for — not a designation that already exists.

Key takeaways - Metabolic biology is integrated; the proof that validates it remains compartmentalized. - SGLT2 and GLP-1/incretin therapies show how one mechanism can expand across organs, but each crossing still had to be won by its own trial. - Metabolism is beginning to build platform infrastructure; oncology remains more mature. - The next advantage is evidence architecture, not the molecule alone. - Credibility depends on knowing what the evidence does not yet support.

---

1. The Thesis

Three facts now sit together that did not a decade ago. The mechanisms are validated. The cross-organ effects are reproducible in large trials. And the institutions that generate and reward evidence are still organized by organ.

That third fact is the thesis of this report. The translational gap in metabolic disease is no longer only the familiar one between a mechanism and its first approval. The harder gap is structural: integrated biology on one side, and on the other an evidence system still partitioned by specialty, organ, endpoint, indication, and label. The body runs the disease as one connected system; the proof is still generated one compartment at a time.

We call our reading of this moment **metabolism as platform medicine**. In a structured scan of academic, consulting, venture, trade, and patent sources conducted in June 2026, we did not identify prior field-level use of this framing.[9] We offer it as an interpretation, not a discovery and not an established regulatory category, and it builds on the cross-organ clinical frameworks already emerging rather than replacing them.[10][11]

The logic is straightforward. The biology is integrated, and the case studies show it. The evidence architecture is not, and the oncology comparison shows what mature architecture looks like and what

metabolism still lacks. Because architecture rather than biology is now the binding constraint, the most valuable questions in the field have become questions of evidence design rather than discovery.

The implication is direct: the next advantage in metabolic disease will go to organizations that design evidence for biology that already behaves as a platform, instead of re-proving it one organ at a time.

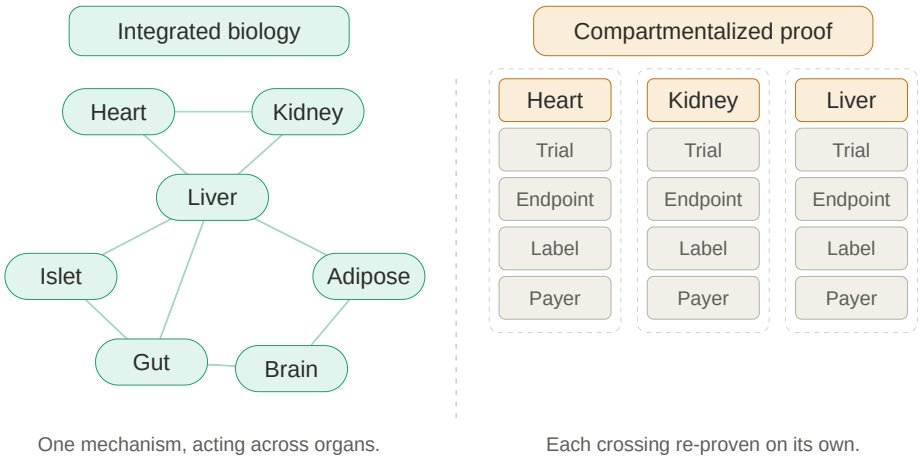

Figure 1 · The evidence-architecture gap. Metabolic biology crosses organs faster than the evidence system recognizes it. Conceptual framework, Integral BioStrategy.

2. Why Metabolism Is Becoming Platform Medicine

The case for treating metabolism as a platform is not that the disease burden is large. It is that scale, biology, assets, and budgets are now converging across boundaries that were built to keep them apart.

Start with the scale of the disease, because it is what raises the stakes. An estimated 589 million adults were living with diabetes in 2024, over 90% of it type 2.[12] Chronic kidney disease affected roughly 788 million adults globally in 2023.[13] Cardiovascular disease caused approximately 19.2 million deaths in 2023 and remains the leading cause of death worldwide.[14] An estimated 890 million adults were living with obesity in 2022.[15] An estimated 1.3 billion adults may have metabolic dysfunction-associated steatotic liver disease, though that figure varies by diagnostic criteria: modeled estimates fall near 16%, while some meta-analyses run closer to 38%.[16]

The overlap is the real point. These are not six separate epidemics. To a large degree they are the same patients, counted in different clinics: the person with type 2 diabetes who also carries obesity, kidney decline, heart-failure risk, and liver fat. Yet that patient is studied, regulated, and reimbursed as if each

condition stood alone. Scale creates the opportunity. The overlap creates the strategic complexity, because a single mechanism can now touch several of those conditions at once.

Cross-organ drugs are what brought the mismatch into focus. When one molecule earns benefit in cardiology, nephrology, and hepatology, a single specialty's frame no longer captures everything the medicine does. Clinical medicine has recognized this. In 2023, the American Heart Association defined cardiovascular-kidney-metabolic, or CKM, syndrome, recognizing that these conditions share pathophysiology and progress together.[10] The emerging cardio-renal-hepatic-metabolic (CRHM) framing extends the same logic to the liver.[11]

These frameworks matter, and it is worth being exact about what they settle. CKM and CRHM validate the biology: they describe how to stage and manage a patient whose disease crosses organs. They do not prescribe how a company should generate evidence for a cross-organ asset, how a regulator should review one, or how a payer should value benefit that lands in more than one specialty's budget. Adjacent commercial work has the same boundary. McKinsey's Metabolic Health Initiative (2025) frames the opportunity through a wellness and health-economics lens, not a drug-development one.[17]

There is a deeper question underneath these frameworks, and it is worth naming precisely. Nosology — the discipline that decides how diseases are defined and grouped — has long treated these conditions as a cluster: "metabolic syndrome," and now CKM, are names for the observation that they keep company. But a cluster, or a syndrome, still counts its members as separate entities that co-occur. The reading the cross-organ evidence increasingly supports is stronger: that these are, in substantial part, one connected biology expressed in different tissues rather than several diseases that happen to coincide. The strategic argument does not require that stronger reading to be formally adopted — reclassifying disease is slow, contested, and beside the commercial point. What matters is the asymmetry it exposes. The biology is already being described as more unified than the evidence system that tests and approves drugs against it, and that gap widens as cross-organ data accumulate. Whether the field ultimately settles on syndrome, cluster, or single disease, the architecture for generating proof should track the biology, not the inherited label.

The silos are not an accident, and they will not dissolve on their own. Regulatory review is organized into divisions defined by organ and indication. Reimbursement is negotiated through specialty-specific budgets. Trial endpoints were standardized within specialties long before a single molecule routinely spanned all three. Each made sense in isolation; together they now lag the biology. That unfinished translation, from integrated biology to integrated evidence, is what the rest of this report examines.

---

3. The Evidence-Architecture Gap

The gap here is not biological. It is architectural, and oncology shows what closing it can look like.

Over roughly a decade, oncology organized itself around one premise: that cancers are often best understood by shared mechanism and biomarker, not only by organ of origin. The FDA established an Oncology Center of Excellence in 2017.[6] FDA guidance on biomarker-driven master protocols lets multiple therapies and sub-studies share infrastructure, control arms, and patient-assignment logic.[18] A companion-diagnostic infrastructure grew alongside, and a strategic vocabulary developed in which "platform" companies were a recognized category with their own valuation logic.

The clearest embodiment came in the tissue-agnostic approval. On May 23, 2017, the FDA cleared pembrolizumab for any unresectable or metastatic solid tumor that is microsatellite-instability-high or mismatch-repair-deficient — the agency's first approval defined by a molecular feature rather than the organ of origin.[35] Larotrectinib followed on November 26, 2018, for NTRK-fusion-positive solid tumors, the first tissue-agnostic targeted therapy.[36] In both, a mechanism was proven once, against the biology, and licensed across organ sites at once — the regulatory system certifying mechanism over location.

The analogy to oncology is useful, but it is not exact. Oncology's platform logic often rests on biomarker-defined populations, where a shared molecular alteration can guide therapy across tumor types. Metabolism's current platform logic is more often revealed through mechanism pleiotropy and cross-organ outcomes: one mechanism acting across several disease domains. That difference matters. It is why patient selection, decision-grade biomarkers, and companion-diagnostic infrastructure remain open questions in metabolic disease rather than solved infrastructure. The comparison to oncology is not a claim that metabolism should copy oncology directly. It is a way to show what mature evidence architecture can look like once a field begins to organize around mechanisms that cut across inherited categories.

Metabolism does not have to look outside itself for the pattern; it has already lived a smaller version of it. For most of its modern history, diabetes was organized around a single number. Glucose was the definition, the diagnostic threshold, and the treatment target — the metabolic counterpart to the organ of origin, the inherited surface label the field built itself around. But glucose was never the whole disease. The United Kingdom Prospective Diabetes Study showed that intensively lowering it reduced microvascular complications yet produced no significant reduction during the trial in the macrovascular events that kill most patients; the cardiovascular and mortality benefit emerged only years later, in long-term post-trial follow-up — the so-called legacy effect.[37][38] And the disease beneath the number is not one thing: type 2 diabetes spans lean and obese, insulin-deficient and insulin-resistant phenotypes, and data-driven analyses now resolve adult-onset diabetes into several distinct subgroups with different complication trajectories.[39] The modern cross-organ drugs closed the loop on the lesson — SGLT2 inhibitors and GLP-1 receptor agonists deliver cardiovascular and renal benefit through pathways only partly about glucose at all. Targeting the number, like classifying a tumor by its site, captured something real and missed the biology underneath. It is the same move oncology made, already run once inside metabolism's own borders.

Metabolism has the integrated biology but not, yet, that architecture. The central claim of this report is deliberately calibrated:

Metabolism is beginning to develop platform infrastructure, but it still lacks the institutional depth, regulatory guidance, and scale that oncology has built.

The qualification matters. The clearest counter-example to any claim of outright absence is SYNERGY-OUTCOMES: an early master protocol in metabolic disease, a single large trial of roughly 4,500 participants studying both retatrutide and tirzepatide in patients with MASLD at risk of major adverse liver outcomes, now enrolling.[7] It does not contradict the thesis. It confirms the direction of it. The field is already beginning to build the architecture it lacks, which is why the strategic window is open now rather than hypothetical.

A single trial, though, is not yet a system. A mature platform architecture rests on roughly four pillars:

- a disease-spanning regulatory home that reviews across organ divisions;
- a library of master protocols that let assets share controls and infrastructure;
- a companion-diagnostic infrastructure that assigns patients by biomarker rather than by organ;
- a shared strategic vocabulary in which platform assets are understood, valued, and funded as a category.

Metabolism is early on each. There is, as yet, no disease-specific Center of Excellence, no established library of master protocols beyond early entrants, no mature companion-diagnostic infrastructure, and no settled cross-organ regulatory guidance.

The effect of that immaturity shows up in how indications are won. To date, each approved GLP-1 and SGLT2 indication has required its own organ-specific Phase 3 program[19] — pipeline logic applied to platform-like biology. This is not a failure of regulation. Organ-specific outcomes trials are how a system built on prospective, compartmentalized proof confirms benefit responsibly, and that bar has protected patients. The strategic question is not whether that evidence should be required, but how early cross-organ benefit can be anticipated within it — because integrated biology has had to be demonstrated one trial at a time even when the mechanism was already understood.

[Table 1: Cross-organ trial evidence by therapeutic class]

Class / Trial	Domain	Primary result
SGLT2 — EMPA-REG OUTCOME	Diabetes + CVD	HR 0.86 for MACE [1]
SGLT2 — CREDENCE	Diabetes + CKD	HR 0.70 renal composite [20]
SGLT2 — DAPA-HF	Heart failure (reduced EF)	HR 0.74 [2]
SGLT2 — EMPEROR / DELIVER	Heart failure (reduced/preserved EF)	Composite reductions [22]; DELIVER HR 0.82 [21]
GLP-1 — SELECT	Cardiovascular (obesity, no diabetes)	HR 0.80 for MACE [3]
GLP-1 — FLOW	Kidney (diabetes + CKD)	HR 0.76 [4]
GLP-1 — ESSENCE	MASH	62.9% resolution vs 34.3%; 36.8% fibrosis improvement [5]
GLP-1 — SURMOUNT-OSA	Obstructive sleep apnea	FDA-approved indication, Dec 2024 [23]

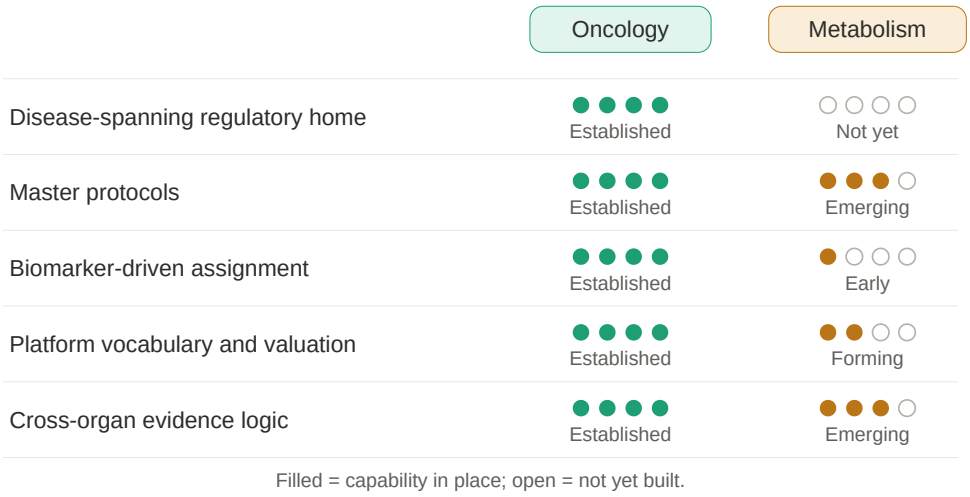

Figure 3 · Oncology vs metabolism — platform-infrastructure maturity. Metabolism is beginning to build this infrastructure; SYNERGY-OUTCOMES is an early example, not a mature system.

The binding constraint, in other words, is now architectural. The biology rewards a platform approach; the evidence system still rewards a pipeline approach. A company that recognizes this early, and designs evidence to capture cross-organ benefit on purpose, is positioned differently from one that treats each indication in isolation.

Evidence note: The oncology-infrastructure claims (FDA Oncology Center of Excellence, 2017; FDA master-protocols guidance, 2022) draw on FDA and regulatory sources.[6][18] The metabolic counter-example, SYNERGY-OUTCOMES, is a registered, enrolling trial (NCT07165028);[7] we describe it as an early example, not a mature system.

4. Case Study: SGLT2 Inhibitors

SGLT2 inhibitors show what integrated biology costs when its evidence is built sequentially.

The class was designed to lower blood glucose by blocking renal glucose reabsorption, with modest expected effects on HbA1c, weight, and blood pressure. The original commercial expectation was a niche diabetes therapy.

What followed was not anticipated. A cardiovascular safety trial mandated under post-2008 diabetes-drug guidance returned more than safety: a marked reduction in cardiovascular death and heart-failure hospitalization, with event curves separating far earlier than any glucose effect could explain.[1] The benefit was real, but it could not be claimed for the patients who would most benefit without dedicated trials in each population.

So the evidence was built indication by indication, across roughly a decade (see Table 1). SGLT2 inhibitors show a consistent class effect across heart failure and chronic kidney disease, each established by its own outcomes trial. By the mid-2020s, guidelines positioned the class as foundational therapy for combined cardiovascular and renal risk, well beyond diabetes.

For development teams, the lesson is that a cross-organ mechanism can create substantial value, but a sequential evidence path pays for it in time, capital, and delayed recognition: roughly a decade and tens of thousands of randomized patients to convert one mechanism into cross-specialty standard of care. The companies that anticipated the cross-organ effects early were positioned to act on them sooner. For any asset with plausible cross-organ biology today, the planning lesson is to design for those effects during early development rather than characterize them after approval.

Evidence note: Each SGLT2 outcome is drawn from its peer-reviewed pivotal trial (NEJM, 2015–2022). [1][20][2][22][21] The hazard ratios reflect each trial's primary composite endpoint; population, follow-up, and confidence intervals should be read from the source trials.

---

5. Case Study: GLP-1 / Incretin Therapies

If SGLT2 inhibitors are the historical parable, GLP-1 receptor agonists are the contemporary case: the clearest live example of platform-like biology, and of the evidence lag that still surrounds it.

GLP-1 receptor agonists have shown cross-organ benefit in dedicated Phase 3 trials spanning cardiovascular risk, kidney disease, MASH, and obstructive sleep apnea (see Table 1). The pattern matches SGLT2, one mechanism proven through sequential organ-specific trials, but compressed in time and increasingly designed rather than discovered. The commercial scale that followed is real: Eli Lilly's tirzepatide alone generated $36.5 billion in fiscal 2025.[24]

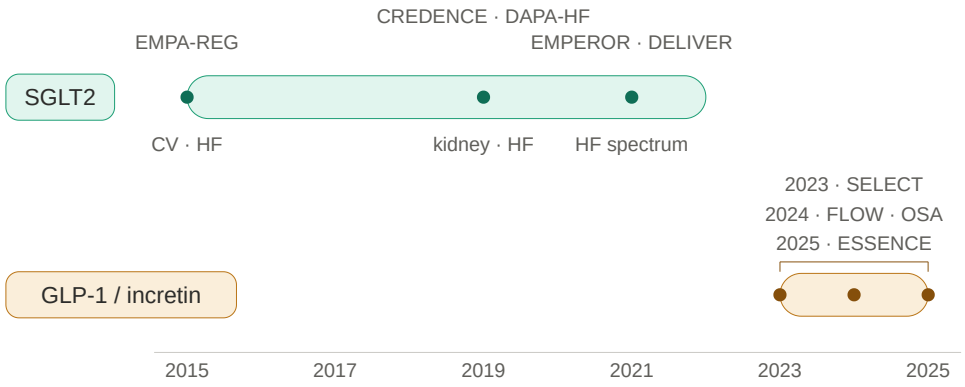

Figure 2 · Indication-expansion timeline. SGLT2 evidence accrued across roughly a decade; GLP-1/incretin evidence compressed into three years. Chronology of indication expansion, not a head-to-head efficacy comparison.

This is exactly where restraint matters, because the GLP-1 story is the easiest in medicine to overstate. Three caveats belong in any rigorous reading.

First, persistence. Real-world GLP-1 persistence has been low, with some analyses finding roughly 14% of patients still on therapy at three years in earlier cohorts, though persistence appears to be improving among more recent initiators.[25] Benefit on therapy and benefit over a population's lifetime are not the same thing.

Second, weight regain after discontinuation, where the evidence conflicts and should be read as unresolved. Some analyses show substantial regain toward baseline after stopping. A large company-commissioned real-world analysis of more than 135,000 records found roughly 68% of patients maintaining or continuing to lose weight at six months post-discontinuation.[26] The findings are not reconciled, and the honest position is to say so.

Third, body composition. Weight lost is not uniformly fat. Lean-mass preservation is moving from footnote to differentiator: in the BELIEVE phase 2 trial, combining bimagrumab with semaglutide limited lean-mass loss to about 2.9% versus about 7.4% with semaglutide alone, with roughly 92% of weight loss coming from fat in the combination group.[27]

The implication for asset strategy is that durability, persistence, and body composition belong in the evidence plan from the start, not as later additions. A narrative that leads with peak efficacy and treats those three as footnotes understates its own risk; a credible one holds the breadth and the open questions together.

Evidence note: SELECT, FLOW, and ESSENCE are peer-reviewed (NEJM, 2023–2025);[3][4][5] SURMOUNT-OSA underlies an FDA-approved indication (December 2024).[23] Persistence and weight-regain figures come from real-world analyses whose findings conflict and are presented here as

unresolved;[25][26] the BELIEVE lean-mass data are from a peer-reviewed phase 2 trial (Nature Medicine, 2026).[27]

---

6. Market Map: What Is Moving and Why It Matters

Market data should support the thesis, not replace it. The figures below appear sparingly, as context for where capital is concentrating, not as forecasts and not as valuation commentary. All market-size figures are analyst estimates that vary by scope and methodology, stated as of 2026.

[Table 2: Market estimates and caveats]

Segment	Estimate (analyst, 2026)	Caveat
GLP-1 / incretin	~$53–63B in 2025 (consensus ~$60–63B); analysts project roughly $130–255B by the mid-2030s [8]	Wide variance by inclusion criteria and scope; long-range figures highly uncertain
SGLT2 inhibitors	Estimates range ~$13–20B in 2025, clustering near $17–18B [29]	Generic erosion underway; range reflects scope/definition differences
MASH pharmacotherapy	Roughly $8–34B by the early 2030s [30]	Highly dependent on diagnosis rates and access

The numbers matter less than the shift they describe. The cardiometabolic market is consolidating from a set of siloed franchises into one space where the same mechanism competes across several budgets at once. Three patterns stand out.

Capital is concentrating around validated cross-organ biology. Revenue sits heavily in a small number of incretin and SGLT2 assets, while the first approved MASH therapy, Madrigal's resmetirom, generated roughly $958 million in its first full year (2025), early evidence that payers will fund metabolic-liver therapy when benefit is clear.[28]

New modalities and geographies are entering the same space. Oral incretins arrived in this window: oral semaglutide 25 mg was FDA-approved on December 22, 2025 and launched in January 2026,[31] with orforglipron (Foundayo) following on April 1, 2026.[32] China, meanwhile, has become a significant source of metabolic out-licensing, reversing the traditional direction of deal flow: mazdutide (Innovent) became the first dual GCG/GLP-1 agonist approved anywhere, cleared by China's NMPA on June 27, 2025,[33] and AstraZeneca's January 2026 agreement with CSPC reached $1.2 billion upfront, up to $3.5 billion in development and regulatory milestones, and up to $13.8 billion in commercial milestones — roughly $18.5 billion in total if all are met.[34]

And integrated biology is now acquired as often as it is built. When large players choose to buy cross-organ mechanisms rather than develop them, much of what they are paying for is the validated, organ-spanning evidence behind the molecule, not the molecule alone.

The practical consequence is that capital is already moving toward cross-organ biology, but the value any program captures still depends on evidence quality, differentiation, durability, and access. Securing the mechanism is only part of the problem; the durable advantage sits in the evidence. None of this is a recommendation about any company or security; it maps where attention and capital are concentrating, and the direction is consistent.

Evidence note: All market-size figures are analyst estimates that vary by scope and methodology and are stated as of 2026; they are directional, not forecasts.[8][29][30] Revenue and approval figures draw on company filings/earnings and regulatory sources, date-stamped to fiscal 2025 or the stated approval date.[24][28][31][32][33][34]

---

7. Strategic White Space

The open questions in metabolic disease are now largely about evidence design, and the useful form of each one names the decision it would change.

[Table 3: Strategic white-space questions]

Question	What it would change	Status
What durability evidence would change payer behavior on a cross-organ asset?	Asset positioning and reimbursement	Underdeveloped
What endpoint would raise regulatory confidence in integrated cross-organ benefit?	Trial design and approval pathway	Becoming feasible (SYNERGY-OUTCOMES)
What biomarker would change patient selection rather than describe it?	Population definition and label	No mature infrastructure
What maintenance evidence would close the gap between trial efficacy and real-world persistence?	Long-term value and access	Open; oral options now exist
What trial design would reduce the need to re-prove the same biology organ by organ?	Capital efficiency and time-to-recognition	Early (master protocols emerging)
In MASH, which evidence (fibrosis, hard outcomes, body composition) actually moves prescribing and access?	Differentiation in a crowding class	Early commercial

The throughline is that each question is answered with evidence, not assertion. The cross-organ endpoint question carries the most leverage: SYNERGY-OUTCOMES suggests the regulatory and operational path is becoming feasible,[7] and whoever generalizes that design beyond a single trial will shape how the next decade of cross-organ assets is evaluated.

A note of restraint applies to the higher-hype items. Precision metabolic medicine, biomarker-guided therapy, and continuous-glucose monitoring outside diabetes are scientifically interesting but, on current

evidence, premature as near-term certainties. They belong here as open questions, not settled opportunities.

Evidence note: This section poses strategic questions, not predictions. The durability, endpoint, and maintenance items extend directly from the trial evidence above; the higher-hype items are flagged as emerging and not yet supported by mature outcome evidence.

---

8. What Different Stakeholders Need to Decide

The architecture framing turns into a specific diligence question for each actor. These are questions a serious team should be able to answer before it commits.

Founders and CEOs. Does the evidence plan match the biology? An asset with cross-organ potential, run as a single-indication program, may be underbuilding the very evidence that would make it valuable, and that gap rarely shows up in the pitch.

Pharma strategy and business development. Is this asset being valued on single-indication terms or on cross-organ platform terms? The difference is usually evidence that has not been designed yet, which makes it a diligence finding rather than a line in the data room.

Investors. Does diligence test the evidence architecture, or only the mechanism and the headline data? A validated mechanism with a thin plan for proving cross-organ benefit and defending durability is a more fragile asset than its top-line trial reads.

Translational teams. Are biomarker and endpoint choices being made as core strategy or as downstream execution? In a platform-style field, endpoint design is itself a strategic choice, and deferring it forecloses options later.

Payer and market-access teams. Can the value framework recognize benefit that lands in more than one budget, or does it carry forward a specialty-silo logic that will undervalue an integrated mechanism and slow its access?

Across these roles, the underlying question is the same: how integrated biology will be proven and paid for. None of them has a single right answer, and the answer for a single-asset company differs from the answer for a diversified developer. The platform lens does not settle the decision; it makes the question sharper, and a decision made with the cross-organ structure in view is easier to defend than one reached by default.

---

9. What Not to Overstate

These cautions are not formalities. They are where the report's credibility comes from, and in a crowded field that credibility is itself an advantage.

Benefit on therapy is not the same as benefit after it. A drug that works while taken has demonstrated exactly that, and no more. Durability after discontinuation is a separate question, and in metabolic disease that evidence is genuinely unsettled.

A positive trial is not a label. It demonstrates an effect in a studied population. It does not, by itself, create an approved indication, a reimbursed use, or proof that the result generalizes.

Treat market estimates as estimates. The figures here are ranged and dated because analysts disagree depending on definitions. They indicate scale and direction, not settled value.

A signal across organs is not yet integrated evidence. Observing that a mechanism helps several organs is not the same as proving, in a study built for it, that it should be developed, reviewed, and reimbursed as one platform. Closing that distance is the work, not the conclusion.

Platform medicine here is an interpretation, not a designation. It is the lens we propose, not a guidance document or an agreed-upon term. We argue for it. We do not present it as settled.

A report that respects these lines is more useful in a diligence room than one that does not, because it tells a decision-maker where the evidence actually stands.

---

10. How Integral BioStrategy Thinks

Our approach is deliberately narrow and explicit.

We read biology across systems rather than within a single specialty, because the mechanisms that matter in metabolic disease rarely respect organ boundaries.

We organize evidence by decision relevance, by what a founder, a board, a diligence team, or a development group actually needs to decide, rather than by academic completeness.

And we grade every claim: proven, plausible, emerging, or unsupported. That grading is the discipline that lets a team build a position it can defend and avoid the overclaiming that quietly erodes credibility in front of regulators, partners, and investors.

Our role is to design evidence architecture. We do not run trials, negotiate payer contracts, or execute transactions.

This report is scientific and strategic analysis. It is not medical, investment, legal, tax, regulatory, or securities advice. Nothing in it guarantees regulatory approval, payer coverage, or commercial outcome, and nothing in it should be read as a recommendation regarding any company or security.

Related reading: The Translational Gap in Metabolic Disease — a narrative companion to this report, written for a general strategic audience.

Sources and Evidence Notes

Numbered endnotes, grouped by category. Markers [n] appear at first mention and on reuse in the report above. URLs were verified on 2026-06-04; market figures are analyst estimates, dated, and directional. Source-tier labels: Peer-reviewed · Regulatory · Registry · Company filing · Public-health authority · Analyst estimate · Internal scan · Secondary. Current as of June 2026.

1. Clinical-trial evidence

- **[1] EMPA-REG OUTCOME** — Peer-reviewed. Zinman et al., NEJM, 2015. https://www.nejm.org/doi/full/10.1056/NEJMoa1504720 — SGLT2 CV/HF benefit (HR 0.86 MACE).
- **[2] DAPA-HF** — Peer-reviewed. McMurray et al., NEJM, 2019. https://www.nejm.org/doi/full/10.1056/NEJMoa1911303 — HFrEF (HR 0.74).
- **[3] SELECT** — Peer-reviewed. Lincoff et al., NEJM, 2023. https://www.nejm.org/doi/full/10.1056/NEJMoa2307563 — CV MACE (HR 0.80) in obesity without diabetes.
- **[4] FLOW** — Peer-reviewed. Perkovic et al., NEJM, 2024. https://www.nejm.org/doi/10.1056/NEJMoa2403347 — kidney outcomes (HR 0.76).
- **[5] ESSENCE** — Peer-reviewed. Phase 3 semaglutide in MASH, NEJM, 2025. https://www.nejm.org/doi/full/10.1056/NEJMoa2413258 — 62.9% resolution vs 34.3%; 36.8% fibrosis improvement (FDA MASH approval Aug 15 2025).
- **[20] CREDENCE** — Peer-reviewed. NEJM, 2019. https://www.nejm.org/doi/full/10.1056/NEJMoa1811744 — renal composite (HR 0.70).
- **[21] DELIVER** — Peer-reviewed. NEJM, 2022. https://www.nejm.org/doi/full/10.1056/NEJMoa2206286 — HFpEF/mrEF (HR 0.82).
- **[22] EMPEROR-Reduced / EMPEROR-Preserved** — Peer-reviewed. Packer et al., NEJM, 2020 (Reduced): https://www.nejm.org/doi/full/10.1056/NEJMoa2022190 · Anker et al., NEJM, 2021 (Preserved): https://www.nejm.org/doi/full/10.1056/NEJMoa2107038 — HF composite reductions.
- **[23] SURMOUNT-OSA** — Regulatory/company. FDA approval of tirzepatide (Zepbound) for OSA, December 2024. https://investor.lilly.com/news-releases/news-release-details/fda-approves-zepboundr-

tirzepatide-first-and-only-prescription

- **[27] BELIEVE** — Peer-reviewed (phase 2; n=507). Bimagrumab plus semaglutide in obesity, Nature Medicine, 32:869–882, March 2026. https://www.nature.com/articles/s41591-026-04204-0 — combination limited lean-mass loss to ~2.9% vs ~7.4% with semaglutide alone; ~92% of weight loss from fat in the combination group.
- **[37] UKPDS 33** — Peer-reviewed. UK Prospective Diabetes Study Group, *Lancet*, 1998 — intensive glucose control reduced microvascular complications; macrovascular reduction non-significant in-trial. https://pubmed.ncbi.nlm.nih.gov/9742976/
- **[38] UKPDS 10-year post-trial follow-up** — Peer-reviewed. Holman et al., *NEJM*, 2008 — emergent reductions in myocardial infarction and all-cause mortality (the "legacy effect"). https://www.nejm.org/doi/full/10.1056/NEJMoa0806470
- **[39] Diabetes subgroups** — Peer-reviewed. Ahlqvist et al., *Lancet Diabetes & Endocrinology*, 2018 — data-driven cluster analysis (n=8,980) resolving adult-onset diabetes into five subgroups with distinct outcome trajectories. https://www.thelancet.com/article/S2213-8587(18)30051-2/fulltext

2. Public-health burden

- **[12] IDF Diabetes Atlas, 11th ed.** — Public-health authority. IDF / Lancet Diabetes & Endocrinology, 2024/2025. https://diabetesatlas.org/ — diabetes 589M (2024); 853M by 2050; >$1T spend.
- **[13] GBD 2023 CKD** — Peer-reviewed. The Lancet, 2025-11-07. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(25)01853-7/fulltext — CKD ~788M (2023).
- **[14] GBD 2023 CVD** — Peer-reviewed. JACC, 2025-09. https://www.jacc.org/doi/10.1016/j.jacc.2025.08.015 — CVD ~19.2M deaths (2023); leading cause.
- **[15] Obesity ~890M (2022)** — Public-health authority. WHO, "Obesity and overweight" fact sheet (2022 data). https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight — over 890 million adults living with obesity in 2022 (~16% of adults).
- **[16] MASLD ~1.3B; 16% vs 38%** — Peer-reviewed. GBD 2023 MASLD (~1.3B; 16.1% age-standardized): https://pubmed.ncbi.nlm.nih.gov/41990758/ · Meta-analysis trend (~38.2%, 2016–2019): https://pmc.ncbi.nlm.nih.gov/articles/PMC12130103/ — figures presented as definition-dependent.

3. Regulatory architecture

- **[6] FDA Oncology Center of Excellence** — Regulatory. Authorized by the 21st Century Cures Act (2016); established Jan 2017. https://www.fda.gov/about-fda/fda-organization/oncology-center-excellence

- **[7] SYNERGY-OUTCOMES (NCT07165028)** — Registry. "A Master Protocol of Multiple Agents in Adults With MASLD." https://clinicaltrials.gov/study/NCT07165028 — ~4,500 participants; retatrutide + tirzepatide; MASLD/MALO; ~224 weeks; enrolling.
- **[18] FDA master-protocols guidance** — Regulatory. "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics," FDA final guidance, March 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and
- **[19] Representative FDA label histories** — Regulatory (pointer). Drugs@FDA: https://www.accessdata.fda.gov/scripts/cder/daf/ — supports "each indication required its own Phase 3." Cite 2–3 representative labels at finalization.
- **[35] Pembrolizumab — first tissue/site-agnostic approval** — Regulatory. FDA accelerated approval, May 23 2017, for MSI-H/dMMR unresectable or metastatic solid tumors; the FDA's first tissue/site-agnostic indication. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-first-tissuesite-agnostic-indication
- **[36] Larotrectinib — second tissue-agnostic approval (first targeted)** — Regulatory. FDA accelerated approval, Nov 26 2018, for NTRK-fusion-positive solid tumors; the first tissue-agnostic targeted therapy. https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions-0

4. Company financials and approvals

- **[24] Eli Lilly FY2025 results** — Company filing. "Lilly reports fourth-quarter 2025 financial results," Feb 2026. https://investor.lilly.com/news-releases/news-release-details/lilly-reports-fourth-quarter-2025-financial-results-and-provides — tirzepatide $36.5B (Mounjaro $22.965B + Zepbound $13.542B).
- **[28] Madrigal FY2025 results** — Company filing. GlobeNewswire, 2026-02-19. https://www.globenewswire.com/news-release/2026/02/19/3240955/0/en/Madrigal-Pharmaceuticals-Reports-Fourth-Quarter-and-Full-Year-2025-Financial-Results.html — resmetirom ~$958M (first full year).
- **[31] Oral semaglutide 25 mg approval** — Regulatory/company. FDA approval Dec 22 2025; Novo Nordisk. https://www.biospace.com/press-releases/novo-nordisk-a-s-wegovy-pill-approved-in-the-us-as-first-oral-glp-1-for-weight-management
- **[32] Orforglipron (Foundayo) approval** — Regulatory. FDA approval Apr 1 2026 (CNPV program); Eli Lilly. https://investor.lilly.com/news-releases/news-release-details/fda-approves-lillys-foundayotm-orforglipron-only-glp-1-pill
- **[33] Mazdutide approval** — Regulatory. NMPA approval Jun 27 2025; Innovent. https://www.prnewswire.com/news-releases/innovent-announces-mazdutide-first-dual-gcgglp-1-

receptor-agonist-received-approval-from-chinas-nmpa-for-chronic-weight-management-302493152.html — first dual GCG/GLP-1.

- **[34] AstraZeneca–CSPC collaboration** — Company press + reporting. AstraZeneca press release, 2026-01-30: https://www.astrazeneca.com/media-centre/press-releases/2026/astrazeneca-agrees-obesity-and-t2d-deal-with-cspc.html · Reuters: https://ca.finance.yahoo.com/news/astrazeneca-strikes-deal-18-5-131516815.html — $1.2B upfront; up to $3.5B development/regulatory milestones; up to $13.8B commercial milestones; up to ~$18.5B total if all milestones met (CSPC, HKEX: 01093). Deal terms only; no company financial-risk or impairment characterization is stated or implied.

5. Market estimates

- **[8] GLP-1 / incretin market** — Analyst estimate. Polaris Market Research (~$52.8B, 2025); Fortune Business Insights (~$62.8B, 2025; ~$254B by 2034); Morgan Stanley (~$190B by 2035). https://www.polarismarketresearch.com/industry-analysis/glp-1-market · https://www.fortunebusinessinsights.com/glp-1-receptor-agonist-market-112827 · https://www.morganstanley.com/insights/articles/glp1-weight-loss-market-may-double-190-billion-2035 — ~$53–63B (2025; consensus ~$60–63B); roughly $130–255B by the mid-2030s.
- **[29] SGLT2 market** — Analyst estimate. Future Market Insights (~$17.8B, 2025); Straits Research (~$13.4B); Global Market Insights (~$20.4B). https://www.futuremarketinsights.com/reports/sglt2-inhibitors-market · https://straitsresearch.com/report/sglt2-inhibitors-market · https://www.gminsights.com/industry-analysis/sglt2-inhibitors-market — estimates range ~$13–20B in 2025, clustering near $17–18B.
- **[30] MASH market** — Analyst estimate. DataM Intelligence (~$8.1B 2025 → ~$31.8B by 2033); Grand View Research (~$7.7B 2024 → ~$33.8B by 2030); The Business Research Company (~$8.6B by 2030). https://www.datamintelligence.com/research-report/nash-or-mash-treatment-market · https://www.grandviewresearch.com/industry-analysis/non-alcoholic-steatohepatitis-nash-treatment-market-report — roughly $8–34B by the early 2030s.

6. Originality and adjacent frameworks

- **[9] Originality scan** — Internal scan. Integral BioStrategy structured scan, June 2026. No external URL. A documented scan result: in our June 2026 scan we did not identify prior field-level use of this framing. Not an absolute novelty claim.
- **[10] CKM syndrome** — Peer-reviewed. AHA Presidential Advisory, Circulation, 2023-10-09. https://www.ahajournals.org/doi/10.1161/cir.0000000000001184 — cited as parallel precedent for the biology.
- **[11] CRHM concept (emerging)** — Peer-reviewed. Theodorakis & Nikolaou, "From CKM to Cardiovascular-Renal-Hepatic-Metabolic Syndrome," Biomolecules, 2025. https://www.mdpi.com/2218-273X/15/2/213 — labeled emerging concept, not consensus.

- **[17] McKinsey Metabolic Health Initiative** — Secondary (consulting). "The path toward a metabolic health revolution," McKinsey Health Institute, 2025-05-20. https://www.mckinsey.com/mhi/our-insights/the-path-toward-a-metabolic-health-revolution — wellness/health-economics lens; characterization is Integral BioStrategy's interpretation, not a competitive claim.

7. Evidence caveats (real-world)

- **[25] Real-world persistence** — Secondary/RWE. Prime Therapeutics (3-year persistence study); HealthVerity (GLP-1 trends 2025). https://blog.healthverity.com/glp-1-trends-2025-real-world-data-patient-outcomes-future-therapies — ~14% persistence at 3 yr in earlier cohorts; improving in recent initiators.
- **[26] nference real-world analysis (company-commissioned)** — Secondary. nference (135k+ records); AJMC coverage (Gasoyan). https://nference.com/publications/aWZ1vBEAAB8AP7-A/What-happens-to-weight-after-we-stop-prescribing-GLP-1-therapies · https://www.ajmc.com/view/weight-regain-after-glp-1-discontinuation-is-less-rapid-in-real-world-hamlet-gasoyan-phd — ~68% maintaining/losing at 6 mo; presented as one side of an unresolved conflict. The conflicting BMJ meta-analysis was not located; draft keeps the generic "some analyses show regain."

Integral BioStrategy — Strategy Report, Draft 08 (publication-source-final), current as of June 2026. Figure/table placeholders are intentional and pending build. Time-sensitive claims (approvals, revenues, deal terms, market estimates) are date-stamped and subject to change.