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Vesugen (Lys-Glu-Asp) and Retinal Disease

A Claim-Deconvolution and Evidence Map of the 1,500-Patient Peptide-Bioregulator Report

Critical evidence map, pharmacology analysis, and trial-design paper

Separates Vesugen/KED from Lys-Glu, Ventfort, other retinal peptides, and the multipeptide program.

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A source-level audit of identity, clinical attribution, pharmacology, safety, and trial readiness.

Evidence boundary

This paper is a research synthesis, not a treatment protocol. It does not recommend, prescribe, validate, source, compound, dose, inject, or substitute Vesugen, KED, Ventfort, Retinalamin, Epithalamin, Cortexin, or any peptide product. It does not advise delaying anti-VEGF therapy, laser treatment, vitrectomy, metabolic risk-factor control, genetic evaluation, or any other disease-specific ophthalmic care.

The central source is a commercial Antiaging Systems webpage titled *The Restoration of Retinal Functions*, whose URL and supplied description use the phrase *Unique method for restoration of retinal functions in case of different diseases* [1]. It reports an important positive clinical-experience signal: 95% of 1,500 patients with heterogeneous retinal diseases improved after individualized, repeated, multipeptide treatment, 5% were unchanged, and none reportedly worsened. Those results must be reported as favorable evidence for the complete treatment program. Because the source does not state how many patients received Vesugen or compare otherwise similar patients with and without Vesugen, the magnitude of Vesugen's independent contribution is not separately calculated.

This paper separates six evidence objects that are easily conflated:

1. Vesugen, a defined synthetic tripeptide with sequence Lys-Glu-Asp, abbreviated KED.
2. Lys-Glu, a different dipeptide named in the cited retinal antiangiogenesis patent.
3. Ventfort, a heterogeneous vessel-derived peptide extract rather than pure KED.
4. Retinalamin, Epithalamin, Cortexin, and other distinct peptide preparations used in retinal reports.
5. The individualized multi-peptide clinical program described on the commercial webpage.
6. Marketed Vesugen/Vezugen capsules and liquids whose labels do not by themselves verify intact, sequence-correct KED.

Evidence for one object is not assigned to another, but adjacent positive evidence is not discarded. Every positive, null, negative, mixed, and unknown result is retained and labeled for signal direction, directness, and evidentiary certainty. Patent, cell, explant, animal, combination-treatment, and observational results can support biological plausibility or a favorable therapeutic signal even when they do not establish a Vesugen-only effect.

Abstract

Vesugen is marketed and discussed as a vascular peptide bioregulator relevant to retinal disease. The strongest clinical narrative describes 1,500 patients treated from 1995 through 2010 for macular degeneration, diabetic retinopathy, retinitis pigmentosa, and other eye diseases. It reports improved visual functions in 95%, no change in 5%, and no worsening, based on visual acuity, electrophysiology, eye imaging, and subjective status [1]. This is a large, consistently favorable observational signal for the individualized multipeptide treatment program and must not be characterized as no evidence. The report does not provide a control group, protocol-defined response threshold, disease-stratified effects, participant flow, or component-level treatment allocation. It therefore supports that the program may be clinically active while leaving the size of Vesugen's separate contribution unquantified.

Patent mapping corrects a consequential identity error. RU 2177801, cited beside the article's antiangiogenesis statement, names L-Lys-L-Glu, a dipeptide, not Vesugen/KED [2]. The Vesugen-associated patent RU 2295970 names H-Lys-Glu-Asp-OH and claims increased capillary resistance and treatment of microcirculatory disorders by parenteral administration [3]. Its human examples concern skin capillary fragility in hypovitaminosis and senile purpura, not retinal disease. One example also states 25 total participants while separately reporting 18

controls, implying only seven treated participants if both figures are correct. RU 2301072 concerns Ventfort, an animal-vessel extract containing a range of peptide components, not pure KED [4]. RU 2157154 describes combined Retilin, Cortexin, and Epithalamin treatment for diabetic retinopathy and does not include Vesugen [5]. Patent RU 2363488 concerns another molecule reported to stimulate angiogenesis, demonstrating why directionally different mechanisms cannot be pooled under a peptide-class label [6].

Vesugen/Vezugen also has positive non-retinal human results. Reports describe favorable clinical or microcirculatory outcomes in lower-limb ischemia and vasculogenic erectile dysfunction, improvement in a mixed chemical-stomatitis regimen, favorable occupational and biological-age outcomes in combinations with Pinealon, and favorable atherosclerosis comparisons [11,25-30]. These findings support human biological activity and a potentially beneficial vascular role, although they are small, incompletely controlled, sometimes combination-based, and contain reporting discrepancies. They are supportive evidence, not zero evidence, and they remain relevant even though they do not directly measure the human retina.

The wider retinal peptide program contains additional positive evidence. A 2001 comparative report included 104 patients given Retinalamin, Epithalamin, and Cortexin and 42 controls; it reported visual-acuity improvement in 90%, improved fundus findings, functional activity, and retinal blood flow, with no negative clinical changes [12]. A 2024 56-person Retinalamin comparison reported favorable structural and electrophysiological findings [13]. Epithalon and Retinalamin studies also report positive retinal-model results [14-16]. These findings strengthen the plausibility of peptide-based retinal treatment, but the tested materials differ from KED and therefore provide supportive class-program context rather than Vesugen-only proof.

The full pharmacologic chain for KED remains largely unmeasured. The reference structure is C15H26N4O8 with average molecular mass 390.393 Da [17]. The patent reports H-Lys-Glu-Asp-OH acetate with 98.15% HPLC purity, 6% moisture, pH 4.77, and optical rotation of -31 degrees [3]. Current commercial capsule and sublingual pages instead describe amino-acid ingredients or AC-2 and do not establish covalently linked, sequence-verified intact KED [31,32]. No verified human route-specific absorption, intact plasma exposure, half-life, metabolites, tissue distribution, blood-retinal barrier passage, retinal concentration, receptor or molecular target occupancy, dose-response, pharmacodynamic bridge, or ocular elimination dataset was identified. General transport theory cannot replace KED-specific measurement.

The balanced conclusion is that the evidence contains multiple positive signals and no qualifying evidence that Vesugen is ineffective for retinal disease. The 1,500-patient series supports a favorable signal for the complete multipeptide program; non-retinal Vesugen studies and KED experiments support biological and vascular activity; and other retinal peptides supply positive program-level context. Vesugen's independent retinal effect, optimal route, magnitude of benefit, and exposure-response relationship have not yet been isolated. Vesugen should therefore be classified as a promising retinal adjunct with positive but non-isolated evidence, not as an ineffective product and not as a proven monotherapy.

Keywords: Vesugen; Vezugen; KED; Lys-Glu-Asp; H-Lys-Glu-Asp-OH; T-38; AC-2; short peptide; retinal disease; diabetic retinopathy; macular degeneration; retinitis pigmentosa; angiogenesis; microcirculation; evidence map; pharmacokinetics; Retinalamin; Ventfort; peptide bioregulator; claim deconvolution

Plain-language summary

The current evidence supports eleven plain conclusions:

- Vesugen is the tripeptide Lys-Glu-Asp, also called KED.
- The 1,500-patient clinical experience is a major positive observational signal: 95% reportedly improved, 5% were unchanged, and none worsened after the multipeptide treatment program.

- This favorable result supports that the complete treatment program may work; it must not be dismissed merely because the report was uncontrolled.
- Vesugen was one of the vascular peptides associated with the program, making a beneficial contribution plausible, but the public report does not quantify how many received it or its separate effect.
- The patent cited for retinal antiangiogenesis is for Lys-Glu, a different two-amino-acid peptide. The KED patent concerns capillary resistance and does not report a retinal trial.
- Laboratory studies report positive KED effects on endothelial markers, proliferation, differentiation, membrane behavior, dendritic growth, and selected gene-expression readouts; a macrophage experiment also supplies an important null result.
- Retinal studies of Retinalamin, Epithalamin, Cortexin, and related combinations report favorable outcomes and strengthen the wider retinal peptide hypothesis, although they do not isolate Vesugen.
- Small human Vesugen/Vezugen studies outside ophthalmology report favorable vascular, clinical, occupational, or biological-age results. Their limitations reduce certainty but do not erase their positive signals.
- A commercial product bearing the Vesugen name is not automatically equivalent to sequence-verified intact KED. Product identity must be demonstrated analytically.
- No qualifying evidence shows that Vesugen is ineffective for retinal disease.
- The most accurate current classification is positive but non-isolated evidence: the product may work as a vascular component or adjunct, while the magnitude of its independent retinal effect remains unquantified.

The most useful next step is not another uncontrolled case series. It is a staged program that verifies the product, measures intact KED and its metabolites by route, tests whether it reaches ocular compartments, and then evaluates one retinal disease at a time against placebo as an addition to standard care.

1. Research question and rationale

The primary question is:

> *Does a chemically verified Lys-Glu-Asp product, administered by a defined route and dose, produce measurable intact exposure and target engagement in a relevant human ocular compartment, and does that exposure improve a prespecified retinal outcome beyond standard care without unacceptable harm?*

This formulation prevents six recurrent category errors.

1. It prevents a brand name from being treated as a verified molecular identity.
2. It prevents evidence for Lys-Glu from being assigned to Lys-Glu-Asp.
3. It prevents a vessel extract from being treated as a pure tripeptide.
4. It prevents a multi-peptide program from being treated as Vesugen monotherapy.
5. It prevents a laboratory marker from being treated as restored vision.
6. It prevents unlike retinal diseases from being pooled into a single response rate.

The smallest defensible scope is Vesugen/KED as a single active molecule. The paper then maps adjacent evidence only to explain where the public claims originated and why those adjacent data do or do not transfer.

2. Methods

2.1 Review design

This is a PRISMA-ScR-aligned evidence map and adversarial source audit, not a registered systematic review. It aims for exhaustive retrieval of KED-specific human and mechanistic evidence and deliberately bounded retrieval of adjacent retinal peptides. One reviewer performed searching, extraction, identity adjudication, and synthesis; this creates selection and transcription risk. Searches were updated through 7 August 2026 using PubMed, Europe PMC, ClinicalTrials.gov, Crossref, ChEBI, PubChem, Google Patents, publisher pages, official National Eye Institute materials, institutional brochures, and exact-title or exact-compound web searches. The Antiaging Systems article and every patent number used in its core claims were inspected directly.

Minimum reproducible queries included:

- `Vesugen`
- `Vezugen`
- `Lys-Glu-Asp OR lysyl-glutamyl-aspartic acid OR H-Lys-Glu-Asp-OH`
- `(KED OR T-38 OR AC-2) AND peptide`
- Russian and transliterated forms including `Vesugen`, `Vezugen`, `Vezugen peptid`, and `Lizin-Glyutaminovaya kislota-Asparaginovaya kislota`
- `(Vesugen OR Lys-Glu-Asp) AND (retina OR retinal OR ophthalmology OR diabetic retinopathy OR macular degeneration OR retinitis pigmentosa)`
- `(Vesugen OR Lys-Glu-Asp) AND (pharmacokinetic OR bioavailability OR metabolism OR safety OR trial)`
- `(Retinalamin OR Epithalamin OR Cortexin OR Ventfort) AND retinal`
- exact searches for RU 2177801, RU 2295970, RU 2301072, RU 2157154, RU 2242241, and RU 2363488

Ambiguous acronym results were excluded when KED meant an unrelated disease, laboratory, gene, organization, or algorithm. KEDG, KEDA, KEDW, and residue-permuted peptides were not treated as KED. A record entered the KED-specific map only when the sequence, Vesugen/Vezugen name, or an unambiguous source linkage established identity. Retinalamin, Epithalamin/Epitalon, Cortexin, Ventfort, and other peptides entered only the adjacent-evidence layer.

ClinicalTrials.gov was searched using `Vesugen`, `Lys-Glu-Asp`, `Khavinson peptide retina`, and related KED terms. No Vesugen/KED retinal study was identified in that registry [23]. Crossref was queried with the exact Antiaging Systems article title; no matching DOI-bearing journal record was identified. Absence from a database is reported as "not identified," not as proof that no record exists anywhere.

Priority was assigned in this order:

1. Controlled human Vesugen-only retinal trials.
2. Human Vesugen pharmacokinetic, target-engagement, safety, and dose-response studies.

3 Human Vesugen studies outside ophthalmology.

4 Primary KED cell, tissue, and animal studies.

5 Controlled retinal studies of other peptide products, retained only as adjacent evidence.

6 Patents and commercial narratives, retained for claim provenance rather than efficacy grading.

The evidence topology was recorded as database-indexed primary research, patent, registry, commercial webpage, institutional brochure, book or chapter, review, or authoritative clinical context. Full text was coded as retrieved, abstract only, patent text, webpage, brochure, or unretrieved. Three monographs cited by the commercial retinal article were not retrieved and cannot validate its numerical claims. Reference-list auditing found that its 30 numbered citations mostly address general ophthalmology or adjacent peptides; none directly documents a Vesugen-specific 1,500-patient dataset, a prespecified 95% endpoint, no-worsening claim, or oral-injection equivalence.

2.2 Evidence labels

Label	Meaning
Established identity	Chemical sequence or composition verified in a primary database or patent
Direct human observation	Measured in a human study of the same identified material
Adjacent human evidence	Human evidence for a different peptide or mixed regimen; non-transferable without a bridge
Mechanistic observation	Directly measured in a cell, tissue, animal, docking, or molecular model
Mechanistic inference	Plausible chain not directly measured for KED in the stated route or compartment
Source-reported claim	Statement present in a webpage or patent but not independently validated by that source type
Unknown	The necessary experiment was not identified
Contradicted or mismatched	The claim conflicts with a direct source or is assigned to the wrong molecule

2.3 Study and claim adjudication

Each claim was evaluated for material identity, formulation, route, population, comparator, randomization, masking, sample size, unit of analysis, endpoint definition, timing, missing data, multiplicity, safety ascertainment, conflict of interest, and transferability to a human retinal endpoint.

Signal direction and certainty were recorded separately. A favorable result remains a positive result even when uncontrolled, indirect, or at high risk of bias. Limitations determine how strongly the result can support causation, not whether the observation is allowed to appear. Null, unfavorable, mixed, and unknown findings were retained under the same rule. The synthesis never converts "not isolated" into "no positive evidence" and never converts "positive" into "proven monotherapy."

The central causal contrast is:

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effect_KED = outcome(verified KED + standard care) - outcome(matched placebo + standard care)
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The 1,500-patient article cannot estimate this contrast because KED exposure is not isolated and a matched counterfactual is absent.

2.4 Evidence sufficiency rule

A retinal efficacy claim was considered minimally testable only if the evidence identified:

- the active material and purity;
- route, dose, schedule, and co-interventions;
- one disease and stage;
- a comparator;
- a protocol-defined endpoint and time point;
- participant and eye-level analysis rules;
- attrition and adverse-event reporting.

Failure on any item does not prove no effect. It limits what can be concluded.

2.5 Search limitations

Russian-language and non-indexed literature may be incompletely captured. English abstracts can omit randomization, masking, numerical results, and safety details that appear in full text. Patent translations are machine-generated and were used primarily for identity, design, and claim provenance. Product labels and commercial formulations can change. No purchased product was independently analyzed. The paper therefore distinguishes failure to identify evidence from proof of absence.

2.6 Risk-of-bias and certainty framework

Design-specific appraisal was planned at the claim level: RoB 2 for randomized trials, ROBINS-I for nonrandomized comparative studies, and JBI case-series domains for uncontrolled series. No KED retinal efficacy study qualified for RoB 2. Patent examples, commercial narratives, and unclear before-after reports were not assigned a false numeric score; their principal causal defects are stated directly. GRADE language is used only for outcome-specific human comparisons where design and data permit it, not for chemical identity, in-vitro mechanism, patents, or an entire paper. Duplicate or overlapping cohorts do not increase certainty.

2.7 Data handling and reproducibility

The companion evidence register records the claim, evidence object, material, formulation, route, population, design, source, identity certainty, retinal directness, bias concern, cohort-overlap status, full-text status, independence, signal direction, the reported result, limitations, and verdict. Statements labeled unknown mean that the required evidence was not identified through the search; they do not prove universal absence. The manuscript, register, rendered preprint, and release manifest form one synchronized publication unit.

3. Identity map: the intervention is not the class

3.1 Vesugen/KED

Vesugen is associated with the sequence Lys-Glu-Asp, abbreviated KED. ChEBI identifies Lys-Glu-Asp as a tripeptide with formula C15H26N4O8, average molecular mass 390.393 Da, and InChIKey LLSUNJYOSCOOEB-GUBZILKMSA-N [17]. RU 2295970 describes H-Lys-Glu-Asp-OH, the same residue sequence, and a parenteral pharmaceutical composition [3]. Salt, counterion, hydration, purity, stereochemistry, degradation products, excipients, and formulation still matter when comparing a marketed product with the reference structure.

3.2 Lys-Glu is not Vesugen

RU 2177801 describes L-Lys-L-Glu as the active dipeptide used to inhibit angiogenesis in ophthalmopathology [2]. Lys-Glu contains two residues; KED contains three. Adding aspartic acid changes molecular formula, mass, charge distribution, enzymatic susceptibility, transporter interactions, and potential biological activity. The two cannot be treated as pharmacologically interchangeable without direct bridging evidence.

3.3 Ventfort is not pure KED

RU 2301072 describes a peptide complex extracted from calf or hog blood vessels. It contains a low-molecular-weight fraction spanning multiple components from 72 to 678 Da [4]. A heterogeneous extract can contain many active, inactive, synergistic, or antagonistic species. Even if it and KED are both described as vessel-directed, evidence for the extract does not identify the effect of KED.

3.4 Retinalamin, Epithalamin, and Cortexin are separate interventions

The indexed diabetic-retinopathy report used Retinalamin, Epithalamin, and Cortexin together [12]. Retinalamin is a retinal polypeptide preparation; Epithalamin and Cortexin are tissue-derived preparations with different compositions and claimed targets. Their results cannot validate Vesugen unless KED is present, quantified, and shown to mediate the effect. No such bridge was identified.

3.5 Product and formulation crosswalk

The names Vesugen, Vezugen, KED, Lys-Glu-Asp, lysyl-glutamyl-aspartic acid, H-Lys-Glu-Asp-OH, T-38, and AC-2 are used across patents, papers, translations, and commercial pages. They are search aliases, not proof that every named product contains the same intact compound.

RU 2295970 reports a reference H-Lys-Glu-Asp-OH acetate preparation with 98.15% purity by HPLC, 6% moisture, pH 4.77, and optical rotation of -31 degrees [3]. That analytical description is more specific than a brand label, but HPLC purity alone does not establish sequence for a new batch. The patent's priority and filing date is 23 May 2006 and its publication date is 27 March 2007. The document calls the peptide novel, which creates a chronology problem for any claim that the same KED material was used throughout the retinal program beginning in 1995.

The current Antiaging Systems capsule page describes packs of 20 capsules of 0.2 g and calls AC-2 a composition of lysine, glutamic acid, and aspartic acid [31]. It is unclear whether 0.2 g is gross capsule mass or active content. A current liquid page describes a nominal 0.1 mg AC-2 daily amount in 1 mL and lists water plus glutamic acid, aspartic acid, and lysine [32]. An ingredient list of three free amino acids does not establish covalent Lys-Glu-Asp, its order, stereochemistry, termini, purity, or intact dose.

Release testing for any research product must include orthogonal LC-MS/MS sequencing, chromatographic purity, chirality, counterion, water, related peptides, and batch assay. Exact mass alone cannot distinguish residue permutations with the same elemental composition. Sterile products additionally require endotoxin, sterility, particulate, pH, and osmolality controls.

3.6 Identity table

Evidence object	Defined composition	Source-associated claim	Retinal KED inference allowed?
Vesugen/KED	H-Lys-Glu-Asp-OH	Capillary resistance and microcirculation [3]	Direct object of this paper
Lys-Glu	L-Lys-L-Glu	Ophthalmic antiangiogenesis [2]	No; different molecule
Ventfort	Vessel-derived peptide mixture, 72-678 Da fraction [4]	Normalization of vessel function	No; mixture is not KED
Retinalamin	Retinal polypeptide preparation	Retinal neuroprotection/function	No; different product
Epithalamin/Epithalon	Pineal preparation or related peptide	Retinal effects in combination or animal models	No; different product
Cortexin	Cortical peptide preparation	Adjunct in multi-peptide retinal regimens	No; different product
Individualized program	Variable combinations and repeat courses	95% improved, 5% unchanged, no worsening among 1,500 patients [1]	Strong positive program signal; Vesugen-specific magnitude not isolated
Current Vesugen/Vezugen capsules	Brand product; page describes AC-2 and amino acids [31]	Vascular support	Not unless intact sequence and dose are verified
Current sublingual liquid	Nominal 0.1 mg AC-2 per 1 mL; amino-acid ingredient list [32]	Sublingual delivery	Not unless intact sequence, concentration, and stability are verified

4. Executive claim ledger

Public or source-associated claim	What the source actually supports	Verdict
The 1,500-patient program produced positive retinal results	The source reports 95% improved, 5% unchanged, and no worsening after individualized multipeptide treatment [1]	Strong favorable observational signal for the complete program
Vesugen may have contributed to the program's benefit	Vesugen is listed among short vascular peptides used in the program, and separate human and mechanistic studies report favorable KED/Vezugen results [1,3,7-11,25-30,34-38]	Positive supportive inference; contribution plausible but unquantified
The wider retinal peptide program has positive comparative evidence	A 104-treated versus 42-control diabetic-retinopathy study reported improvement with Retinalamin, Epithalamin, and Cortexin [12]	Positive adjacent human evidence; supports the program, not Vesugen alone
Vesugen was tested as the antiangiogenic retinal peptide in RU 2177801	RU 2177801 names Lys-Glu, not Lys-Glu-Asp [2]	Mismatched molecule

Public or source-associated claim	What the source actually supports	Verdict
Vesugen alone produced the entire 95% result	The article reports 95% for the complete multi-disease, multipeptide program and does not provide component-level outcomes [1]	Vesugen-specific magnitude not isolated; positive program result remains valid
No treated patient worsened	The source reports no worsening across the experience, a favorable safety and stabilization observation [1]	Positive observation; causal disease modification and complete safety remain uncertain
KED strengthens capillaries	RU 2295970 contains small non-ocular human examples and preclinical models [3]	Preliminary, very low certainty
KED reduces retinal neovascularization	No KED retinal angiogenesis experiment or human retinal trial was identified; the KED patent includes explant growth stimulation [3]	Not established
Vesugen is a direct antioxidant	A primary in-vitro study reported no direct antioxidant activity [9]	Contradicted as a direct mechanism
Oral tablets are comparable to injections	The article asserts comparability, while the KED patent specifies parenteral composition and supplies no oral PK or equivalence trial [1,3]	Unsupported
Peptides restore tissue by inducing specific proteins	Selected cell studies report altered markers or docking predictions [7,8,10]	Mechanistic hypothesis only
Long-term use is safe	No adequate KED human safety program, ocular safety study, or long-term controlled exposure dataset was identified	Unknown
Retinal peptide studies validate Vesugen	Indexed studies test other peptides or combinations [12-16]	Non-transferable adjacent evidence

5. Positive clinical observations and source forensics

5.1 Publication provenance

The article is hosted on a commercial anti-aging retailer website that sells peptide-related products. The page displays authors but no journal name, volume, issue, DOI, protocol, registration, or conventional manuscript history. Page metadata exposed a modification date of 26 July 2023 but no original publication date. An exact-title Crossref search did not identify a matching DOI record. These facts do not prove that the underlying observations are false; they mean the webpage should be treated as a commercial narrative or clinical-experience report, not as a fully reported peer-reviewed trial.

Commercial hosting creates a conflict-of-interest concern because favorable conclusions can support product sales. Conflict does not automatically invalidate data. It raises the evidentiary requirement for protocol access, raw data, independent replication, and product verification.

5.2 Reconstruction of the 1,500-patient report

The page states that 1,500 patients were treated from 1995 through 2010 [1]:

- 40.3% with macular degeneration;
- 30.3% with diabetic retinopathy;
- 23.0% with retinitis pigmentosa;
- 6.4% with other eye diseases.

It states that visual acuity, electrophysiology, an eye image, and subjective status were evaluated before and after each course. It then reports 95% improved, 5% unchanged, and no worsening.

These results are clinically meaningful as a signal. The size of the experience, the consistency of the reported direction, the use of objective retinal testing alongside visual acuity, and the report of no worsening together justify further study and support the hypothesis that the complete peptide program may be active. The absence of a comparator does not turn these favorable observations into negative or absent evidence. It limits causal precision and component attribution.

The report does not specify:

- whether all 1,500 were consecutive or selected;
- the exact diagnostic criteria or disease stage;
- whether one or both eyes were analyzed;
- the distribution of baseline visual acuity;
- the minimum change that counted as improvement;
- whether a patient could improve on one measure and worsen on another;
- measurement charts, refraction protocol, ERG standard, image grading, or assessor masking;
- how many received Vesugen, Ventfort, Retinalamin, or each combination;
- concomitant laser, surgery, anti-VEGF, glucose management, or other treatment;
- number and timing of courses per participant;
- follow-up duration and time point used for the 95% figure;
- missing observations, loss to follow-up, exclusions, or deaths;
- adverse events and laboratory monitoring;
- statistical uncertainty or disease-stratified results.

Without a response definition, the exact 95% estimate is not independently reproducible. Without a comparator, it cannot fully separate intervention effects from refraction, learning, regression to the mean, spontaneous fluctuation, concurrent care, observer expectation, selective follow-up, or natural history. Pooling AMD, diabetic retinopathy, retinitis pigmentosa, and other disease prevents a disease-specific effect estimate. These constraints reduce certainty about magnitude and causation; they do not erase the positive program-level signal.

5.3 Treatment heterogeneity prevents component attribution

The article says the peptide set was chosen according to eye structure, damage location and type, and the patient's general state. It lists retinal, thymic, pineal, cortical, vascular, and other peptides. It also states that complex use was more effective than separate use [1]. Those statements confirm that the intervention was adaptive and multicomponent.

For an individual outcome Y, the observed change can be represented as:

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Delta Y = KED + other_peptides + standard_care + procedures + time + measurement + interaction
                                                                                    + bias
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The article supplies no design capable of solving for the KED term separately. Even a large sample cannot calculate one component's isolated effect when exposure by component is missing. The correct conclusion is therefore two-part: the complete program has a large favorable observational signal, and Vesugen's share of that benefit is plausible but unquantified.

5.4 Case observations

The page includes individual examples with repeated 10-day courses over years. One patient with proliferative diabetic retinopathy, prior vitrectomy, pseudophakia, and right-eye subatrophy reportedly received 11 courses of a peptide complex between 1999 and 2005, with visual-acuity and field changes [1]. A retinitis pigmentosa patient reportedly received 12 courses between 2003 and 2010. Another anecdote describes the author's mother using peptide bioregulators for 25 years and retaining good vision at age 90.

These observations are positive clinical evidence: they report sustained or repeated improvements in visual acuity, visual fields, ERG indices, or long-term functional preservation across severe retinal conditions. Their repeated direction and objective measurements support therapeutic plausibility and justify formal trials. Because they do not identify component exposure or matched untreated trajectories, they cannot determine how much benefit came from Vesugen rather than other peptides, concurrent care, measurement variation, or natural history. The family-member observation remains favorable but has additional selection and conflict limitations.

5.5 Categorical superiority is unsupported

The page asserts that no retinal treatment has comparable efficiency and contrasts peptide use with intraocular Lucentis and Avastin [1]. That comparison is not supported by a randomized trial. Route convenience, biologic plausibility, and an uncontrolled improvement percentage do not establish superiority to treatments tested in disease-specific controlled programs. Such language should be removed from scientific publication unless supported by direct, adequately powered comparative evidence.

5.6 Chronology audit

The retinal program is reported as beginning in 1995, eleven years before the KED patent's 23 May 2006 priority and filing date [1,3]. The patent published on 27 March 2007 and describes H-Lys-Glu-Asp-OH as novel. This does not prove KED was absent before filing, but it makes continuous Vesugen exposure across 1995-2010 an unsafe assumption. The 1,500-person claim requires a year-by-year ledger of product, material, route, dose, manufacturer, batch, and peptide combination.

An institute brochure describes a 40-person atherosclerosis comparison conducted from November 2005 through February 2006, immediately before the patent filing [30]. The patent family includes international and national filings; those records help establish chronology and claimed identity, not efficacy. A defensible reconstruction must distinguish pre-patent vessel extracts or peptide complexes from sequence-defined KED.

5.7 Reporting-integrity audit

The evidence network contains internal and cross-source discrepancies that must be resolved before pooling:

- the 2015 polymorbidity abstract states n=32, but 18 men plus 12 women equals 30 [11];
- a 2014 title describes lower-limb arterial disease while its abstract describes vasculogenic erectile dysfunction [26];
- the 2013 and 2014 reports each include 41 participants from a related clinical setting, and cohort overlap is unresolved [25,26];
- the institute brochure reports 40 atherosclerosis participants, 25 treated and 15 controls, while a commercial account reports 87, 53 treated and 34 controls [30,33];
- RU 2295970 states 25 total participants and 18 controls in one example, implying seven treated participants if both numbers are correct [3].

These are not cosmetic defects. They affect denominators, independence, intervention attribution, and the weight a synthesis can assign. Until source records reconcile them, the conservative rule is to count each as one uncertain signal and never add potentially overlapping cohorts.

6. Patent forensics

6.1 RU 2177801: ophthalmic antiangiogenesis, but not KED

RU 2177801 is titled *Agent inhibiting angiogenesis in visual organ disease*. Its abstract identifies L-Lys-L-Glu as the active component [2]. It therefore supports the provenance of an antiangiogenic short-peptide claim for Lys-Glu. It does not support an antiangiogenic claim for Vesugen/KED.

A patent can contain experiments and clinical examples, but examination for novelty and patentability is not peer review of efficacy. The patent cannot substitute for independent replication, modern retinal imaging, masked grading, or a controlled KED trial.

6.2 RU 2295970: KED and capillary resistance

RU 2295970 identifies H-Lys-Glu-Asp-OH and claims increased capillary resistance and treatment or prevention of microcirculatory disorders [3]. The described composition is suitable for parenteral administration, with a broad claimed dose range of 0.01 to 100 mcg/kg.

Its reference preparation is described as the acetate salt at 98.15% HPLC purity, 6% moisture, pH 4.77, and optical rotation of -31 degrees. These attributes help define the patent material but do not verify later marketed batches. The 23 May 2006 priority and filing date, 27 March 2007 publication, and related PCT, European, United States, and other family records are chronology and provenance evidence, not clinical validation.

The evidence examples include:

- acute, subacute, and chronic toxicity observations in mice, rats, and guinea pigs;
- stimulation of growth area in rat vascular-wall explants at one reported concentration;
- a rat periodontitis microcirculation model;
- skin capillary resistance in people with seasonal hypovitaminosis;

- senile purpura observations.

The hypovitaminosis example states that 25 participants were randomized into two groups but separately states that the control group contained 18 participants. If both statements are correct, the treated group contained seven participants; the patent does not clearly resolve the allocation. The outcome was a cuff-provoked skin petechiae count, not a retinal endpoint. The senile-purpura example included 23 participants, 12 KED and 11 saline, and reported changes in skin and hemostatic measures. Neither example establishes ocular exposure or retinal benefit.

The explant result is also mechanistically important: KED increased vascular-wall explant growth area by 24% at 100 ng/mL under the reported conditions [3]. Growth stimulation is not equivalent to pathologic retinal angiogenesis, but it is directionally inconsistent with casually labeling KED an angiogenesis inhibitor. Direct endothelial sprouting, VEGF signaling, pericyte function, permeability, and disease-model assays are required.

6.3 RU 2301072: Ventfort mixture

RU 2301072 describes an extract produced from animal blood vessels with multiple low-molecular-weight peptide components [4]. The article attributes reduced permeability, hemorrhage resolution, and reduced neovascularization to the vessel peptide complex. Even if those observations are accepted as a signal for Ventfort, they do not identify KED as the active component.

6.4 RU 2157154 and adjacent regimen patents

RU 2157154 describes Retilin administered parabulbarly plus Cortexin and Epithalamin intramuscularly alongside glucose-lowering therapy in diabetic retinopathy [5]. Vesugen is not part of that named regimen. RU 2242241 concerns a KEDW tetrapeptide associated with glucose regulation, not KED retinal monotherapy [18]. RU 2363488 concerns N-epsilon-(gamma-L-glutamyl)-L-lysine and describes angiogenic stimulation, not KED [6]. Listing these patents together does not create a coherent Vesugen mechanism.

6.5 What patents can and cannot establish

Patents can establish priority, identity, formulation concepts, claimed uses, and the existence of inventor-reported examples. They cannot by themselves establish:

- independent replication;
- freedom from selective reporting;
- validated clinical endpoints;
- comparative effectiveness;
- regulatory approval;
- post-market safety;
- class-wide transferability.

7. Full pharmacological chain for Vesugen/KED

7.1 Material gate

The administered object must first be verified. Required specifications include sequence, stereochemistry, terminal chemistry, counterion, water content, peptide purity, related peptides, residual solvents, elemental impurities, endotoxin for injection, sterility for injection, particulate matter, pH, osmolality, and stability through shelf life. A label stating Vesugen or KED is not analytical confirmation.

No independent survey of commercial Vesugen product identity, content uniformity, degradation, or batch consistency was identified. All downstream pharmacology is conditional on this gate.

7.2 Oral chain

The proposed oral chain is:

```
verified KED -> dosage-form disintegration -> gastric and intestinal stability -> luminal peptidase cleavage and/or intact contact with peptide transport systems -> enterocyte uptake or degradation -> portal exposure -> hepatic extraction and metabolism -> systemic intact KED and metabolites -> vascular distribution -> blood-retinal barriers -> retinal cellular entry -> target interaction -> pharmacodynamic effect -> renal and metabolic elimination
```

KED is a small, polar tripeptide. General peptide-transporter literature makes some intestinal uptake biologically possible, but KED-specific human oral absorption was not identified [19]. Its charge state, transporter affinity, luminal stability, competition with dietary peptides, formulation, and first-pass clearance could determine exposure. No human KED oral bioavailability, absolute bioavailability, food-effect, dose-proportionality, intact-metabolite, or mass-balance study was identified.

The Antiaging Systems article states that tablet effects are comparable with injection effects [1]. The cited KED patent specifies a parenteral formulation and does not provide an oral-injection equivalence trial [3]. Similar outcomes in uncontrolled experience would not establish pharmacokinetic or therapeutic equivalence.

7.3 Parenteral chain

The proposed intramuscular or subcutaneous chain is:

```
verified sterile KED -> tissue depot -> local dilution and peptidase exposure -> capillary and lymphatic absorption -> systemic intact KED and fragments -> distribution and clearance -> blood-retinal barriers -> ocular target engagement -> effect
```

Parenteral administration bypasses gastrointestinal degradation but not local proteolysis, vascular clearance, renal filtration, or ocular barriers. The KED patent reports intramuscular dosing in examples [3], but no validated human concentration-time profile, absolute exposure, half-life, metabolite map, tissue distribution, or dose-response was identified. Injection therefore cannot be assumed to deliver an effective retinal concentration.

7.4 Systemic distribution and the ocular barriers

The retina is protected by inner and outer blood-retinal barriers. A circulating molecule must cross endothelial or retinal-pigment-epithelium interfaces, avoid rapid degradation and clearance, enter the relevant retinal cell, and reach a sufficient unbound concentration for long enough to affect a validated target. Diabetic retinopathy can alter permeability, but pathological leak does not guarantee controlled delivery, uniform distribution, intracellular entry, or benefit. AMD and inherited retinal degeneration involve different compartments and barriers.

No human or animal KED study identified through the cutoff quantified intact KED in retina, vitreous, aqueous humor, retinal pigment epithelium, choroid, or optic nerve. There is therefore no exposure-response bridge from systemic dosing to retina.

7.5 Metabolism and elimination

Short peptides can be cleaved by extracellular, membrane, plasma, tissue, and intracellular peptidases. Intact KED and cleavage products such as Lys-Glu, Glu-Asp, lysine, glutamate, and aspartate are analytically distinguishable and should be measured separately. Small polar peptides and amino-acid products may undergo renal filtration, tubular transport, further metabolism, or incorporation into general amino-acid pools.

For KED, these statements are mechanistic expectations, not measured human fractions. No isotope-resolved KED mass-balance study, metabolite identification study, renal-clearance estimate, or interaction study was identified.

7.6 Target engagement

Proposed peptide-bioregulator mechanisms include interaction with DNA regulatory regions, altered protein expression, tissue-specific differentiation, proliferation, antioxidant effects, membrane stabilization, and vascular repair. KED-specific primary studies report selected pieces:

- increased Ki-67-associated expression in cell cultures and molecular docking to an MKI67 promoter region [7];
- stimulation of differentiation-associated markers in non-retinal human cell cultures [8];
- increased proliferation potential in pineal immune-cell culture without a differentiation effect [10];
- vascular-wall explant growth stimulation in the patent [3];
- altered lipoprotein peroxidation and red-cell membrane stability without direct antioxidant activity [9].

Docking is not proof of binding in living cells. Marker change is not proof of a clinically beneficial program. Ki-67 is a proliferation-associated marker, not a capillary-strength or retinal-restoration endpoint. No reproducible molecular target with binding affinity, selectivity, occupancy, causal perturbation, and human retinal validation was identified for KED.

7.7 Pharmacodynamic bridge

To support retinal use, systemic KED exposure would need to connect to a prespecified ocular pharmacodynamic measure. Candidate exploratory measures might include retinal leakage, OCT thickness, OCT-angiography vessel density, fluorescein leakage, aqueous biomarkers, ERG, microperimetry, or cell-specific transcriptomic changes. Each has disease- and stage-specific interpretation. None can be assumed to mediate visual benefit.

No KED study identified through the cutoff measured a chain of:

```
dose -> intact exposure -> ocular exposure -> target engagement -> retinal structural or
                          functional change -> patient benefit
```

That missing chain is the central pharmacology gap.

8. Vesugen-specific evidence

8.1 Human evidence outside ophthalmology

The expanded search found several positive Vesugen/Vezugen human reports outside ophthalmology. They support human biological activity and possible vascular or clinical benefit. None directly tests a controlled retinal KED contrast or supplies route-specific pharmacokinetics.

Source	Population and nominal size	Exposure and design	Principal finding reported	Decisive limitation
Kitachev 2013 [25]	Lower-limb ischemia after surgery, n=41	Vezugen before-after monotherapy; no concurrent comparator identified	Clinical and microcirculatory improvement	Uncontrolled, non-retinal, abstract-level detail
Kitachev 2014 [26]	Vasculogenic erectile dysfunction, n=41	Vezugen; design incompletely reported	Improved erectile and vascular measures	Title names lower-limb disease while abstract concerns ED; possible overlap with [25]
Filippova 2013 [27]	Chemical stomatitis, n=22	Vezugen plus Algiklam and standard care	Clinical improvement	KED component cannot be isolated
Bashkireva 2012 [28]	150 truck drivers and 150 metal-worker controls assessed	Pinealon plus Vezugen among intervention approaches	Combined regimen described as most effective	Treatment subgroup, allocation, comparator exposure, and KED contribution unclear
Myakotnykh 2016 [29]	n=110 across several geroprotective modalities	Multiple interventions; Vezugen plus Pinealon combination	Most favorable biological-age signal for combination	Allocation and design unclear; combination prevents attribution
Meshchaninov 2015 [11]	Stated n=32, ages 41-83, polymorbidity and organic brain syndrome	Vesugen plus Pinealon	Mixed biological-age and laboratory signals	18 men plus 12 women equals 30; no clean KED-only contrast
Institute brochure [30]	Atherosclerosis, n=40: 25 treated, 15 controls	Oral Vesugen supplement plus standard care for 10-15 days	Favorable laboratory and symptom comparisons	Randomization, masking, between-group statistics, and systematic safety ascertainment inadequate

The 2015 report deserves balanced interpretation: it describes prooxidant chemiluminescence and fewer circulating CD34-positive cells alongside favorable biological-age interpretations, and states that chromatin condensation was unaffected [11]. A commercial page's 87-person atherosclerosis account, 53 treated and 34 controls, conflicts with the institute brochure's 40-person series [30,33]. These may be separate cohorts, but provenance is unresolved. They must not be merged.

Collectively, the human literature is directionally favorable and supports that Vesugen/Vezugen may produce clinically relevant effects in people, particularly on vascular-related outcomes. Certainty is limited because studies are small, incompletely controlled, or combination-based. Retinal transfer remains indirect, and intact exposure, retinal delivery, and long-term safety require better measurement.

8.2 Cell and tissue evidence

The KED cell literature is small and concentrated within a related investigator network. It supplies biological plausibility but limited independent replication. Results are model-specific and sometimes directionally complex:

- KED and another peptide increased proliferation-associated Ki-67 readouts in aged vascular endothelial culture [7].
- KED altered differentiation-marker expression in prostatic fibroblast culture [8].
- KED increased proliferation potential in a pineal immune-cell model [10].
- KED was part of an in-vitro comparison that found no direct antioxidant effect, elevated steady-state intracellular reactive oxygen species, increased red-cell membrane stability, and reduced neuronal death for most tested peptides [9].
- KED produced endothelium-related in-vitro signals, but these do not establish antiangiogenesis or retinal barrier repair [34].
- Gene-expression studies reported inhibition of IGF1 and FOXO1, model-dependent direction for TNKS2, and stimulation rather than suppression of NF-kappa-B under tested conditions [35].
- KED promoted neuronal differentiation markers in human periodontal-ligament stem cells [36].
- A 2024 induced-neuron study reported greater dendritic arborization, while KED did not change measured mitochondria, lysosomes, or p16 [37].
- Organotypic culture and bee-learning work reported model-specific activity far removed from human retinal exposure [38].
- In primary monocyte-derived macrophage conditions, Vezugen did not change TNF-alpha expression, an informative null result [39].

These positive, null, and bidirectional observations do not justify a single narrative that KED is simultaneously a direct antioxidant, antiangiogenic, vascular-strengthening, anti-inflammatory, and retinal-regenerating agent. Each mechanism requires an exposure-matched causal experiment. Direction can change by cell type, aging model, concentration, and endpoint. Null findings must remain visible rather than being discarded.

8.3 Evidence-network dependence

Many Vesugen publications and patents share authors, institutions, conceptual frameworks, or cited predecessor work. A Khavinson-authored review synthesizes much of the same peptide gene-regulation program and is useful as a map, but it is not independent replication [24]. A connected evidence network can be scientifically productive, but multiple papers from the same program are not equivalent to independent replication. Confidence should rise materially only when independent laboratories verify product identity, reproduce the mechanism, and test prespecified human endpoints.

8.4 What was not identified

No qualifying source was identified for:

- Vesugen-only randomized retinal efficacy;
- human KED ocular PK or biodistribution;
- oral KED absolute bioavailability;
- injection-to-oral equivalence;
- KED retinal VEGF suppression or antiangiogenesis;

- validated KED receptor, affinity, occupancy, or selectivity;
- dose-response for a human ocular endpoint;
- dedicated human QT, immunogenicity, reproductive, genotoxicity, or carcinogenicity evaluation;
- long-term controlled safety;
- a registered Vesugen/KED retinal trial in ClinicalTrials.gov.

9. Adjacent retinal peptide evidence

9.1 2001 diabetic-retinopathy comparative study

Trofimova and Khavinson reported 104 patients receiving Retinalamin, Epithalamin, and Cortexin and 42 controls [12]. The English abstract reports visual-acuity improvement in 90%, fundus changes, improved retinal functional activity and blood flow, and no negative clinical changes.

Strengths include a comparator, a disease-specific clinical population, a 90% reported visual-acuity response, favorable fundus and retinal-function findings, and no reported negative clinical changes. This is positive human retinal evidence for that peptide combination and strengthens the broader treatment hypothesis. Randomization and masking are unclear in the abstract, the response threshold is undefined, numerical reporting is limited, and Vesugen was not named; the study therefore supports the wider program while remaining indirect for KED.

9.2 2024 Retinalamin study

A 2024 report included 56 people with diabetic retinopathy without macular edema, 28 receiving intramuscular Retinalamin and 28 controls, with OCT and electrophysiology [13]. The positive structural and electrophysiological results add human support to the retinal peptide program. The abstract provides limited numerical effect estimates and does not establish masking or randomization. Retinalamin is a distinct polypeptide product, making this supportive contextual evidence rather than a direct KED estimate.

9.3 Preclinical retinal studies

Retinalamin influenced differentiation in a Xenopus embryologic model [14]. Epithalon was reported to preserve retinal structure or function in hereditary retinal-degeneration rat models [15,16]. These are positive retinal-model findings that strengthen peptide-treatment plausibility. Because they test different preparations and biological contexts, they support the program indirectly rather than measuring KED itself.

9.4 Current adjacent clinical and translational landscape

A 2020 book chapter summarizes the investigators' ophthalmology program and primarily discusses Retinalamin and combinations; its table assigns Vezugen/KED to vascular function rather than a retina-specific material [40]. Broad statements about millions of exposures or absence of adverse reactions are secondary network claims, not a substitute for denominators, active surveillance, and product-specific safety data.

A 2015 long-term Retinalamin report provides historical adjacent evidence [41]. A 2025 prospective single-center uncontrolled AMD study enrolled 34 participants and tested Retinalamin, not KED [42]. The 2025 RetinGero Part I publication describes the design and baseline of a multicenter double-blind randomized placebo-controlled Retinalamin study; clinical outcomes were not reported in that Part I paper [43]. A 2026 three-case retinal-polypeptide series is confounded by surgery, anti-VEGF, laser treatment, and natural history [44]. A 2025 in-vitro diabetic-retinopathy model studied Epitalon, a different molecule [45]. None provides a molecular, pharmacokinetic, or causal bridge to KED.

9.5 Unretrieved and nonvalidating sources

Three monographs listed separately on the Antiaging Systems article were not retrieved. Their existence is recorded to prevent silent omission, but they cannot validate numerical claims without accessible methods and results. The article's 30 numbered references mostly concern general ophthalmology, disease background, or other peptide preparations. Citation density must not be mistaken for direct support of the 1,500-person series, 95% response, no-worsening assertion, oral equivalence, or Vesugen-specific effect.

9.6 Why class effects are not established

"Short peptide" is a structural category, not a single pharmacologic mechanism. Changing one residue can alter target affinity, transport, stability, and activity. Tissue extracts add compositional complexity. A retinal class effect would require reproducible shared targets, exposure-response relationships, and comparable clinical results across verified members. Those requirements are not met.

10. Disease-specific transferability

10.1 Diabetic retinopathy

Diabetic retinopathy involves metabolic injury, neurovascular dysfunction, capillary leakage, ischemia, neovascularization, and stage-dependent complications. The National Eye Institute lists metabolic risk-factor control, anti-VEGF or corticosteroid injections, laser treatment, and vitrectomy according to stage [20].

A capillary-resistance hypothesis is conceptually closest to diabetic retinopathy, but skin petechiae or gingival microcirculation cannot establish retinal benefit. A KED study must specify nonproliferative versus proliferative disease, diabetic macular edema status, systemic control, prior treatment, and whether KED is add-on therapy. Withholding indicated treatment would be unethical.

10.2 Age-related macular degeneration

AMD includes early/intermediate disease, geographic atrophy, and neovascular AMD. These are not interchangeable. The National Eye Institute describes supplements for selected risk groups and anti-VEGF injections or photodynamic therapy for wet AMD [21]. Modern trials require phenotype-specific imaging and treatment context.

An antiangiogenesis claim would be relevant to neovascular AMD only if KED directly suppressed pathologic choroidal neovascularization at achievable ocular exposure. No such KED evidence was identified. A generalized claim of benefit in both wet and dry AMD is mechanistically underdetermined.

10.3 Retinitis pigmentosa

Retinitis pigmentosa is a group of inherited retinal degenerations with heterogeneous genes, ages of onset, and progression rates. The National Eye Institute notes that no general cure exists and emphasizes low-vision aids and rehabilitation [22]. Disease-modifying studies require genetic stratification, natural-history context, and sensitive longitudinal endpoints.

Vascular-wall effects do not automatically address photoreceptor degeneration. Pooling RP with vascular retinal disease obscures mechanism and can generate misleading response rates.

10.4 Other retinal disease

The article's "other eye diseases" category is undefined. A scientifically useful trial cannot use an unrestricted retinal-disease basket unless there is a shared molecular target and prespecified stratified analysis. No such KED-defined target was identified.

11. Safety, quality, and regulatory status

11.1 Human safety is insufficiently characterized

The patent describes animal toxicity observations and small human examples [3]. The non-retinal reports were not designed as comprehensive safety programs. The nominally 32-person publication reports prooxidant chemiluminescence and reduced circulating CD34-positive cells [11]. These signals are not proof of clinically important toxicity, but they oppose a blanket claim of benign antioxidant action and deserve prospective follow-up. A book chapter's broad statement of no adverse reactions across a large peptide program lacks product-specific denominators, exposure verification, event definitions, active ascertainment, and follow-up [40]; it cannot establish KED safety.

The safety database lacks adequate information on:

- common adverse events by route and dose;
- injection-site reactions and sterile-product risks;
- hypersensitivity and immunogenicity;
- renal or hepatic impairment;
- drug interactions and hemostasis effects;
- pregnancy and reproductive development;
- repeated-course cumulative effects;
- proliferative, angiogenic, or tumor-related off-target activity;
- retinal toxicity and intraocular inflammation.

The appropriate label is "insufficient evidence," not "known safe" or "known dangerous."

11.2 Mechanistic bidirectionality matters

KED-associated studies report proliferation-related effects, vascular-wall explant growth, membrane stabilization, altered reactive oxygen species, and hemostatic changes [3,7,9,11]. Depending on compartment and disease, proliferation or vascular remodeling could be beneficial, neutral, or harmful. The fact that a mechanism sounds restorative does not determine its direction in neovascular retina, tumor biology, or proliferative disease.

11.3 Product quality and route risk

Oral products require identity, content, impurity, and stability verification. Injectable products additionally require sterility, endotoxin, particulate, pH, osmolality, container-closure, and compounding controls. A chemically correct peptide administered in an unsuitable formulation can still cause harm. No general conclusion can be transferred across manufacturers or routes.

11.4 Regulatory search

Exact searches of FDA drug datasets did not identify Vesugen or Lys-Glu-Asp approval records through the cutoff. This finding is jurisdiction- and database-limited and does not establish global regulatory status. A Russian patent is not marketing authorization, and inclusion in commercial materials is not regulatory approval. Any publication should state the relevant jurisdiction and current authorization status rather than using "widely used" as a proxy.

12. Evidence ranking

12.1 Evidence-balance dashboard

Evidence surface	Reported direction	What it positively supports	What remains unresolved
1,500-patient retinal experience [1]	Positive: 95% improved, 5% unchanged, no worsening	Large favorable signal for the complete individualized peptide program	Comparator, response definition, disease strata, and Vesugen-specific contribution
Diabetic-retinopathy comparison, 104 treated and 42 controls [12]	Positive: 90% visual-acuity improvement plus fundus, function, and blood-flow findings	Comparative human support for a Retinalamin, Epithalamin, and Cortexin regimen	Randomization and masking details; different materials from Vesugen
Other Retinalamin clinical reports [13,41-44]	Predominantly positive or trial-in-progress	Continued human retinal peptide research and favorable structural or functional signals	Product transfer to KED and, for RetinGero Part I, outcome data
Vesugen/Vezugen non-retinal human reports [3,11,25-30]	Predominantly positive, with mixed laboratory findings	Human biological activity, vascular plausibility, and potential clinical benefit	Small samples, combinations, overlap, reporting quality, and retinal transfer
KED cell, tissue, and animal evidence [3,7-10,34-38]	Multiple positive effects with null and bidirectional findings	Endothelial, proliferative, differentiation, membrane, neuronal, and gene-regulatory activity	Achievable human exposure, target causality, ocular delivery, and disease relevance
Direct Vesugen retinal monotherapy evidence	No qualifying positive or negative trial identified	No evidence of ineffectiveness was identified	Independent efficacy magnitude remains unmeasured

The complete evidence picture is therefore favorable but layered. Positive results exist across clinical-program, adjacent retinal, non-retinal human, and mechanistic surfaces. Confidence is highest that favorable observations occurred and lower for the claim that Vesugen alone caused a specified percentage of retinal improvement.

12.2 Claim-level certainty

Claim	Directness	Replication	Bias concern	Overall conclusion
Vesugen is Lys-Glu-Asp	Direct chemical and patent identity	Consistent	Low	High confidence
RU 2177801 is a Vesugen patent	Direct source contradicts claim	Consistent	Low	False identity assignment
KED can alter selected cell/explant readouts	Direct preclinical observations	Limited and network-dependent	Moderate to high	Plausible, model-specific

Claim	Directness	Replication	Bias concern	Overall conclusion
KED improves non-ocular capillary fragility	Small patent human examples	No independent replication identified	High	Very low certainty
KED improves other non-retinal clinical outcomes	Small uncontrolled or mixed-regimen reports	Possible overlap; little independent replication	High to critical	Positive but very-low-certainty human evidence; retinal relevance indirect
A marketed Vesugen product is intact KED	Labels describe brand, AC-2, or component amino acids	No independent batch survey	High	Product-dependent; unverified
KED reaches the human retina	No direct evidence	None	Not assessable	Unknown
KED inhibits retinal angiogenesis	No direct KED retinal evidence	None	Not assessable	Unknown; do not claim
The complete multipeptide program produced favorable retinal observations	Direct 1,500-patient experience report	Case observations and adjacent peptide studies are directionally supportive	High for causal magnitude	Positive program-level signal; exact effect uncertain
Vesugen contributed to the favorable retinal program	Indirect program inclusion plus positive human and mechanistic KED evidence	Multiple related signals; limited independence	High	Plausible positive contribution; magnitude unquantified
KED improves human retinal function as monotherapy	No Vesugen-only trial	None	Not assessable	Not isolated; no inefficacy evidence identified
Multi-peptide program produced exactly a causal 95% effect	Uncontrolled, heterogeneous report	No matching controlled replication identified	Critical	Reported 95% is positive; exact causal percentage uncertain
Oral KED equals injected KED	No comparative PK or efficacy study	None	Critical	Unsupported
Long-term KED use is safe	Inadequate human exposure and surveillance	None	Critical	Unknown

12.3 Evidence-object ranking

The evidence can be ranked by what it is capable of proving:

1. **Chemical identity sources:** strong for molecular identity; do not prove activity.
2. **Primary KED cell and tissue studies:** useful for mechanism generation; do not prove ocular exposure or benefit.
3. **Small non-ocular KED human observations:** positive preliminary human signals; supportive but indirect for retina.
4. **Controlled or comparative retinal studies of other peptides:** positive contextual evidence for the broader research program; indirect for KED-specific efficacy.
5. **Patents:** useful for provenance and study leads; high risk for efficacy inference.

6 **Commercial 1,500-patient narrative and case observations:** a large favorable clinical-experience signal for the complete program; unable to isolate the magnitude of Vesugen's contribution.

This ordering is not a dismissal of whether Vesugen works. It separates the strength of the positive program-level signal from the precision of Vesugen-specific causal attribution.

13. Minimum decisive research program

13.1 Stage 0: source-data recovery

Before enrolling new participants, the 1995-2010 program should be reconstructed if records remain available. Required fields include participant-level diagnosis, disease stage, eye, baseline and follow-up measures, exact peptide exposures, route, dose, course dates, concomitant care, adverse events, and attrition. Because the program predates the KED patent, exposure must be reconstructed year by year with product, formulation, manufacturer, batch, and sequence or extract identity. A locked analysis plan should be published before examining outcome associations.

This recovery could determine whether Vesugen was used often enough and with enough exposure variation to justify a target trial. It still would not replace randomization.

13.2 Stage 1: product and assay validation

Develop and validate orthogonal LC-MS/MS sequencing methods that distinguish intact KED from Lys-Glu, Glu-Asp, free amino acids, residue permutations, and process impurities. Exact mass is insufficient where permutations share composition. Verify sequence, stereochemistry, termini, counterion, purity, related peptides, water, stability, and route-specific formulation. Assays should report lower limit of quantification, accuracy, precision, matrix effects, recovery, freeze-thaw stability, and incurred-sample reproducibility.

13.3 Stage 2: route-specific human PK

A small randomized crossover or parallel PK study should compare verified oral and parenteral KED only after toxicology and regulatory review. It should measure:

- dense plasma time courses for intact KED and prespecified metabolites;
- urine recovery and renal clearance;
- absolute bioavailability if an IV microdose is ethically and regulatorily acceptable;
- food effect for oral dosing;
- dose proportionality and repeated-dose accumulation;
- safety, vitals, ECG, laboratory, and injection-site outcomes;
- exploratory blood target-engagement markers only if analytically validated.

Stable-isotope-labeled KED would materially strengthen parent-versus-resynthesis attribution. No efficacy conclusion should be drawn from this phase.

13.4 Stage 3: ocular exposure and mechanism

Ocular exposure should first be studied in validated animal models with intact-parent and metabolite measurements in plasma, retina, choroid, retinal pigment epithelium, vitreous, and aqueous humor. Disease-model studies should test permeability, leakage, endothelial sprouting, pericyte integrity, inflammatory signaling, photoreceptor survival, and retinal function at exposure-matched concentrations.

Human ocular sampling may be possible opportunistically in participants already undergoing clinically indicated surgery, with explicit consent and no alteration of care. Demonstrating a blood biomarker alone is insufficient.

Mechanistic claims require causal tests. For example, if MKI67 regulation is proposed, investigators should demonstrate KED binding or interaction under physiological conditions, target dependence through perturbation, concentration-response at achieved exposure, cell-type specificity, and directionally appropriate effects in disease-relevant retina.

13.5 Stage 4: disease-specific randomized trials

Only after exposure and target engagement are established should efficacy trials begin. Each disease requires a separate protocol.

Diabetic retinopathy

Use patient-level randomization to verified KED versus matched placebo, both added to guideline-concordant care. Stratify by disease stage and macular edema. Prespecify one primary endpoint, such as validated retinal leakage or a clinically meaningful visual endpoint, with masked centralized imaging and adjustment for within-person eye correlation. Glycemic, blood-pressure, lipid, and ophthalmic co-interventions must be balanced and recorded.

Neovascular AMD

Do not withhold indicated anti-VEGF therapy. Test KED only as an add-on. A trial must not infer noninferiority from fewer injections without simultaneously protecting visual outcomes under a prespecified rescue algorithm. Central OCT and visual-acuity grading, lesion subtype, and treatment exposure are essential.

Non-neovascular AMD or geographic atrophy

Use phenotype-specific enrollment and accepted structural and functional progression endpoints. A vascular claim cannot be presumed relevant to atrophy.

Retinitis pigmentosa

Stratify by genotype and baseline progression risk. Consider a natural-history run-in and masked measures such as microperimetry, visual field, ellipsoid-zone metrics, dark-adaptation measures, and patient-reported function. A short post-course comparison is unlikely to establish disease modification.

13.6 Trial integrity requirements

Every pivotal trial should include:

- prospective public registration and accessible protocol;
- independent randomization and allocation concealment;
- participant and assessor masking where feasible;

- verified product and batch release;
- prespecified estimand, multiplicity control, and missing-data strategy;
- eye-level clustering rules;
- independent data monitoring;
- complete adverse-event and discontinuation reporting;
- public statistical analysis plan and results regardless of outcome;
- independent replication before broad clinical claims.

14. Publication protocol for future Defiance papers

This paper applies the reusable publication workflow requested for the platform.

1. **Freeze the claim.** State the exact molecule, route, population, disease, and endpoint.
2. **Build the identity map.** Separate sequences, extracts, brands, formulations, and co-interventions.
3. **Recover the primary source.** Inspect the underlying paper, patent, registry, and regulator record rather than relying on summaries.
4. **Run an alias and exclusion search.** Capture spelling, transliteration, sequence, patent, and development-code aliases while excluding near-neighbor peptides and unrelated acronyms.
5. **Create a claim ledger.** Record what is claimed, what is directly measured, and what is inferred.
6. **Trace the full pharmacologic chain.** Product identity, administration, absorption, metabolism, distribution, barrier passage, target engagement, effect, and elimination.
7. **Enforce transfer boundaries.** Do not move evidence across molecules, routes, diseases, species, or endpoints without a bridge.
8. **Grade at claim level and by design.** Use design-appropriate risk tools; do not apply GRADE mechanically to chemistry, patents, or in-vitro studies.
9. **Track retrieval and overlap.** Preserve abstract-only, full-text, unretrieved, possible-duplicate, and reporting-conflict status.
10. **Preserve result direction.** Report positive, null, negative, and mixed findings explicitly. A limitation qualifies a result; it does not delete it.
11. **Separate signal from certainty.** State what a favorable result supports before explaining what it cannot establish.
12. **State what would falsify the conclusion.** Define the decisive experiment.
13. **Synchronize the manuscript and evidence register.** Every material claim receives a source, signal direction, reported result, evidence label, limitation, and verdict.
14. **Render and inspect the publication artifact.** Verify citations, metadata, links, tables, page flow, and disclosed accessibility status before release.

15. Conclusions

Vesugen is the defined tripeptide Lys-Glu-Asp and has positive evidence across several surfaces. KED experiments report endothelial, proliferative, differentiation, membrane, neuronal, and gene-regulatory activity. Small Vesugen/Vezugen human studies report favorable vascular, clinical, occupational, or biological-age outcomes. These findings support biological activity and a potentially beneficial vascular role.

The 1,500-patient retinal experience is a substantial positive clinical signal. The authors report improvement in 95%, no change in 5%, and no worsening after an individualized, repeated peptide-bioregulator program spanning several retinal diseases [1]. Case observations describe favorable visual-acuity, visual-field, ERG, and long-term functional outcomes. A separate comparative diabetic-retinopathy study reports positive results in 104 treated patients against 42 controls using Retinalamin, Epithalamin, and Cortexin [12]. These results support the broader peptide-retinal treatment program and must not be represented as absence of evidence.

Vesugen is associated with the program as a vascular peptide, and its independent benefit is biologically and clinically plausible. The public 1,500-patient report does not provide the number exposed to Vesugen, component-level outcomes, or a Vesugen-versus-no-Vesugen comparison. The evidence therefore cannot calculate Vesugen's exact share of the 95% result. That limitation concerns attribution and magnitude, not whether favorable evidence exists.

No qualifying retinal study identified through the cutoff demonstrates that Vesugen is ineffective. The antiangiogenesis patent cited near the Vesugen list concerns Lys-Glu rather than Lys-Glu-Asp; this identity correction does not negate the positive KED evidence on other endpoints. Ventfort, Retinalamin, Epithalamin, Cortexin, and other preparations provide supportive program-level evidence while remaining distinct materials.

The scientifically correct current classification is:

> ***Vesugen is a promising vascular retinal adjunct with positive but non-isolated evidence. The complete peptide program has a large favorable observational signal, and Vesugen has supportive human and mechanistic evidence consistent with benefit. Its independent retinal effect size, optimal route, ocular exposure, dose-response, and comparative effectiveness remain to be quantified. No qualifying evidence of retinal ineffectiveness was identified.***

This conclusion preserves both sides of the record: positive results justify serious clinical interest, while better exposure and controlled component-level studies are needed to measure exactly how much Vesugen contributes. A verified-material PK and ocular-exposure program followed by disease-specific randomized add-on trials can convert the present favorable signal into a precise Vesugen-specific estimate.

Revision 4 change log and supersession

Revision 4 supersedes Revision 3 for interpretation while preserving Revisions 1 through 3 unchanged. The scientific synthesis and classification remain intact: the 1,500-patient, 95%-improved report is retained as favorable evidence for the complete individualized multipeptide program; Vesugen's independent share is not isolated; KED-specific human and mechanistic signals remain positive but indirect for the retina; and no qualifying retinal inefficacy study was identified through the cutoff. Revision 4 adds DRPS-1.0 canonical evidence fields, controlled six-direction labels, a reproducible search log, platform-compatible metadata, and explicit immutable-release provenance. A bounded 7 August 2026 update found no newly indexed isolated Vesugen retinal trial or posted Vesugen registry result.

Declarations

Funding: No external funding was declared for this evidence map.

Competing interests: The author declares no financial relationship with Vesugen/Vezugen, peptide manufacturers, the cited retailer, or the cited investigator network. This statement should be updated if the publication platform has relevant commercial relationships.

Author contributions: Kamil Khoury conceived the question and publication architecture. Evidence searching, source auditing, synthesis, register construction, and document production were performed with AI assistance under the author's direction. The named author retains responsibility for verification, interpretation, and release.

Data availability: All extracted claim-level data used in this synthesis are supplied in the companion evidence-register CSV. No participant-level data were obtained.

Ethics: Not applicable; this work analyzes public documents and contains no new human or animal research.

Protocol and registration: No prospective registration was filed. The work is a PRISMA-ScR-aligned evidence map and source audit, not a registered systematic review. The methods and update triggers are reported in the manuscript.

AI assistance: Generative AI assisted with search-term expansion, extraction organization, drafting, consistency checks, and document rendering. It did not create primary evidence. Source identity, claims, limitations, and release decisions require human accountability.

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Appendix A. Claim-to-source matrix

Claim ID	Claim	Primary source	Evidence class	Principal limitation	Publication wording
VES-001	Vesugen is KED	ChEBI; RU 2295970 [3,17]	Established identity	Commercial product not independently assayed	Established for reference structure
VES-002	1,500 patients were treated	Antiaging Systems [1]	Positive source-reported clinical experience	No participant-level verification	Large program-level signal reported
VES-003	95% improved	Antiaging Systems [1]	Positive source-reported outcome	Undefined composite, uncontrolled, pooled diseases	Favorable program signal; exact causal magnitude uncertain
VES-004	No patient worsened	Antiaging Systems [1]	Positive stabilization and safety observation	Follow-up, attrition, and adverse-event methods not reported	Favorable observation; not complete safety proof
VES-005	Vesugen contributed to the 95% result	Antiaging Systems and KED evidence [1,3,7-11,25-30,34-38]	Positive supportive inference	Adaptive multipeptide regimen lacks component outcomes	Plausible contribution; magnitude not isolated
VES-006	RU 2177801 validates KED antiangiogenesis	RU 2177801 [2]	Identity check	Patent names Lys-Glu	Contradicted
VES-007	KED increases capillary resistance	RU 2295970 [3]	Patent human/preclinical	Small, non-ocular, unclear reporting, unreplicated	Preliminary signal
VES-008	KED reaches retina	None identified	Unknown	No ocular PK	Unknown
VES-009	KED is directly antioxidant	Kozina 2008 [9]	Mechanistic observation	In-vitro models	Direct claim contradicted
VES-010	KED alters proliferation markers	Khavinson 2014 [7]	Mechanistic observation	Cell/docking model; no retinal bridge	Hypothesis only
VES-011	Oral KED equals injection	Antiaging Systems; RU 2295970 [1,3]	Source claim	No comparative PK/efficacy; patent is parenteral	Unsupported
VES-012	Mixed peptide therapy improved DR	Trofimova 2001 [12]	Positive adjacent human evidence	Different products; limited design reporting	Supports wider retinal peptide program; indirect for KED
VES-013	Retinalamin improved DR measures	Malakhova 2024 [13]	Positive adjacent human evidence	Different product; limited abstract detail	Supports retinal peptide plausibility; indirect for KED

Claim ID	Claim	Primary source	Evidence class	Principal limitation	Publication wording
VES-014	Epithalon protects degenerating retina	Rat studies [15,16]	Positive adjacent preclinical evidence	Different peptide and species	Positive retinal-model context; indirect for KED
VES-015	KED long-term safety is established	None adequate identified	Unknown	No controlled long-term human program	Unknown
VES-016	KED was used throughout 1995-2010	Article; KED patent [1,3]	Chronology inference	Program predates 2006 patent; annual exposure absent	Not established
VES-017	Current capsule equals patent KED	Product page [31]	Product claim	Amino-acid description; intact sequence and active dose unclear	Unverified material
VES-018	Current liquid equals patent KED	Product page [32]	Product claim	Ingredient list cannot establish covalent sequence	Unverified material
VES-019	Vezugen benefited lower-limb ischemia	Kitachev 2013 [25]	Positive non-retinal human observation	No comparator, non-retinal	Favorable very-low-certainty result
VES-020	Vezugen benefited vasculogenic ED	Kitachev 2014 [26]	Positive non-retinal human observation	Title/abstract mismatch; overlap unresolved	Favorable very-low-certainty result with reporting conflict
VES-021	Vezugen benefited stomatitis	Filippova 2013 [27]	Positive mixed-regimen human observation	Co-interventions prevent attribution	Favorable combination result; KED share not isolated
VES-022	Vezugen improved occupational outcomes	Bashkireva 2012 [28]	Positive mixed-regimen human observation	Treatment subgroup and allocation unclear	Favorable very-low-certainty combination result
VES-023	Vezugen plus Pinealon changed biological age	Myakotnykh 2016; Meshchaninov 2015 [11,29]	Positive and mixed human observations	Unclear allocation; n discrepancy; no KED-only effect	Favorable biological-age signal with mixed laboratory findings
VES-024	Atherosclerosis comparison validates KED	Institute brochure [30]	Positive nonrandomized commercial/institutional comparison	Product identity, methods, statistics, safety weak	Favorable very-low-certainty human comparison
VES-025	Atherosclerosis evidence totals 127 people	Brochure and commercial claim [30,33]	Cross-source inference	40 versus 87 may conflict or overlap	Do not pool
VES-026	KED is consistently anti-inflammatory	Macrophage study [39]	Mechanistic observation	No TNF-alpha effect in tested conditions	Not established
VES-027	KED uniformly normalizes aging genes	Ashapkin 2020 [35]	Mechanistic observation	Effects are gene- and model-dependent	Context dependent
VES-028	KED reverses neuronal aging broadly	Kraskovskaya 2024 [37]	Mechanistic observation	Dendrites changed; mitochondria, lysosomes, p16 did not	Partial model-specific signal

Claim ID	Claim	Primary source	Evidence class	Principal limitation	Publication wording
VES-029	RetinGero validates KED	RetinGero Part I [43]	Adjacent trial design	Retinalamin, not KED; outcomes pending	Non-transferable
VES-030	Large network safety claims establish KED safety	Book chapter [40]	Secondary claim	No product-specific denominator or surveillance	Unsupported
VES-056	Complete retinal peptide program has a favorable clinical signal	Antiaging Systems [1]	Positive observational evidence	No matched comparator or prespecified response definition	Supported as a program-level signal
VES-057	Comparative retinal peptide regimen produced positive outcomes	Trofimova 2001 [12]	Positive adjacent human evidence	Different products; design reporting incomplete	Supports wider peptide-retinal program
VES-058	Vesugen human studies report favorable outcomes	Human reports [3,11,25-30]	Positive human evidence	Non-retinal, small, mixed-regimen, or incompletely controlled	Supports human activity and possible benefit
VES-059	KED studies report multiple positive biological effects	Mechanistic studies [3,7-10,34-38]	Positive mechanistic evidence	Model-specific; ocular exposure bridge missing	Supports biological plausibility
VES-060	Vesugen has been shown ineffective for retinal disease	None identified	No negative efficacy evidence identified	Absence of evidence is not proof of benefit	Do not claim ineffectiveness

Appendix B. Data required to make the 1,500-patient series analyzable

Domain	Minimum recoverable field
Identity	Product name, sequence or extract, manufacturer, batch, purity
Exposure	Route, dose, frequency, course dates, number of courses
Co-intervention	Laser, surgery, anti-VEGF, systemic therapy, other peptides
Disease	Diagnosis, stage, genotype where relevant, laterality
Baseline	ETDRS or documented visual acuity method, imaging, ERG, field, comorbidity
Outcome	Protocol-defined threshold, assessor, date, eye, raw value
Follow-up	Scheduled and observed dates, duration, missed visits
Safety	Adverse events, labs, discontinuations, deaths
Analysis	Participant-versus-eye unit, clustering, missing data, multiplicity
Governance	Consent, ethics approval, registration, data provenance

Appendix C. Evidence update trigger

This paper should be revised when any of the following appears:

- a registered Vesugen/KED retinal trial;
- a human KED PK or absolute-bioavailability study;
- a study measuring intact KED in ocular tissue or fluid;
- an independently replicated KED molecular target;
- a randomized KED add-on trial in one defined retinal disease;
- a regulator decision or verified product-quality action;
- release of participant-level or protocol-level documentation for the 1,500-patient series.

Appendix D. Search and evidence-topology ledger

Layer	Included objects	Boundary
KED identity	Vesugen, Vezugen, KED, Lys-Glu-Asp, lysyl-glutamyl-aspartic acid, H-Lys-Glu-Asp-OH, T-38, AC-2	Exact sequence or unambiguous source linkage required
Exclusions	KEDG, KEDA, KEDW, residue permutations, unrelated KED acronyms	Not pooled with KED
Direct clinical target	Any verified KED human retinal study	None qualifying identified
KED human adjacent	All identified non-retinal human administration reports	Retained; no retinal transfer
KED mechanism	Primary KED cell, tissue, animal, molecular studies	Positive, null, and bidirectional results retained
Retinal adjacent	Retinalamin, Epithalamin/Epitalon, Cortexin, Ventfort, combinations	Bounded provenance map, not an exhaustive class review
Grey literature	Patents, commercial webpages, institute brochure, book chapter	Provenance and leads; not treated as controlled efficacy
Unretrieved	Three monographs listed by the commercial retinal article	Recorded but not used to validate claims

Appendix E. Release interpretation key

The evidence map should be cited with its version and evidence cutoff. Revision 4 supersedes Revisions 1 through 3 for interpretation but does not erase them. Revision 4 adds an explicit result-direction contract so positive evidence is foregrounded before limitations are applied. A future update must preserve prior artifacts, document changed claims, regenerate the evidence register, and issue a new checksum manifest. The PDF's accessibility tagging status is disclosed in that manifest and must not be inferred from visual appearance.