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Strategic context:

Standardized Medical Name: Diabetic Macular Edema (DME)

Target Patient Profile:

- **Temporality:** Prevalent
- **Disease Stage/State:** Active DME requiring intervention. This encompasses both treatment-naïve patients and previously treated patients, including those with persistent or recurrent edema despite standard-of-care anti-VEGF therapy (suboptimal responders) or those experiencing high treatment burden.

Strategic Rationale: Pharmaceutical Relevance (2025-2026):

Diabetic Macular Edema (DME) is a central focus of the pharmaceutical industry in 2025-2026, driven by the urgent need to overcome the significant limitations of current anti-VEGF therapies. While effective, these treatments require frequent intravitreal injections, imposing a substantial burden that leads to poor adherence and reduced real-world outcomes. Furthermore, approximately 40-60% of patients exhibit suboptimal response or persistent edema.

The strategic agenda for 2025-2026 is focused on disrupting the current paradigm through enhanced durability, novel delivery modalities, and new mechanisms of action, even as the standard of care evolves with the adoption of longer-acting agents like faricimab (Vabysmo) and high-dose aflibercept (Eylea HD).

1. **The Shift Towards Non-Invasive Delivery (Topical and Oral):** A major potential disruption is the advancement of treatments that eliminate the need for injections.

    - **Topical:** Oculis is advancing OCS-01 (high-concentration dexamethasone eye drop). The pivotal Phase 3 DIAMOND trials are ongoing, with topline data expected in Q2 2026 and an NDA submission planned for 2H 2026. This could introduce the first topical treatment for DME.
    - **Oral:** Boehringer Ingelheim initiated the Phase II THULITE study in July 2025 for BI 1815368, investigating an oral therapy to reduce vascular permeability. Additionally, Rezolute Bio is advancing RZ402, an oral Plasma Kallikrein Inhibitor (PKI) targeting VEGF-independent pathways.

2. **The Race for Extreme Durability and Sustained Release:** Efforts to develop long-acting implants (6+ months) are maturing, particularly Tyrosine Kinase Inhibitors (TKIs).

- EyePoint Pharmaceuticals' DURAVYU (vorolanib sustained-release TKI implant) demonstrated positive Phase 2 VERONA results in early 2025. Initiation of Phase 3 trials in DME is anticipated by the end of 2025 or early 2026.

3. **Targeting Novel Pathways for Persistent Edema:** To address suboptimal responders, the industry is investigating mechanisms beyond VEGF-A/Ang-2.

    - Merck/EyeBio initiated the Phase 2b/3 BRUNELLO trial in September 2025 for MK-3000 (Restoret), a Wnt signaling pathway agonist, targeting vascular instability in patients with persistent edema.
    - Recognizing the role of inflammation, Roche is developing Vamikibart (anti-IL-6) in Phase II, and Kodiak Sciences is developing KSI-501 (anti-IL-6/anti-VEGF bispecific), with Phase 3 data expected in 2026.

4. **Transformative Potential of Gene Therapy:** Gene therapies aiming for sustained, endogenous anti-VEGF production are progressing. 4D Molecular Therapeutics (4DMT) presented positive Phase 2 SPECTRA data for 4D-150 in 2025 (receiving RMAT designation), demonstrating durable activity and supporting advancement toward Phase 3.

Intended Clinical Application Research Utility:

Epidemiological research on this prevalent DME cohort is essential to support the commercialization, market access, and strategic positioning of the diverse therapies entering the market post-2026. This research will facilitate comparative effectiveness analysis by characterizing the contemporary (2025-2026) real-world treatment burden, injection frequencies, adherence rates, and visual outcomes associated with the uptake of new long-acting agents (e.g., Eylea HD, Vabysmo). By quantifying the prevalence and characteristics of patients who remain suboptimal responders despite these advancements, the data will substantiate the value proposition of novel mechanism therapies (e.g., MK-3000, RZ402) and alternative delivery systems (e.g., OCS-01, DURAVYU, 4D-150).

Phenotype Description: Diabetic Macular Edema (DME), Active Disease

1. Clinical Condition

Recommended Phenotype: Diabetic Macular Edema (DME) **Synonyms:** Clinically Significant Macular Edema (CSME) (Historical term); Diabetic Maculopathy (Often used interchangeably when edema is the primary feature).

2. Detailed Presentation

Diabetic Macular Edema (DME) is a primary sight-threatening complication of diabetes mellitus (Type 1 and Type 2) and the leading cause of moderate vision loss in the working-age population. It results from chronic hyperglycemia inducing microvascular changes and the breakdown of the inner blood-retinal barrier. This process is mediated by increased vascular permeability driven by Vascular Endothelial Growth Factor (VEGF), inflammatory mediators (e.g., IL-6), and dysfunction in other pathways (e.g., Angiopoietin-Tie2, Wnt signaling). This leads to the accumulation of extracellular fluid and lipoprotein exudates within the macula, the retinal area responsible for central, high-acuity vision.

Clinical Presentation and Assessment: Patients may be asymptomatic early on, but typically present with gradual, painless blurring or distortion of central vision (metamorphopsia) as the edema involves the fovea (center-involved DME). Assessment involves:

- **Visual Acuity Testing:** Measured using standardized charts (e.g., ETDRS); Best Corrected Visual Acuity (BCVA) is the primary functional measure.
- **Dilated Fundus Examination:** Slit-lamp biomicroscopy reveals retinal thickening, microaneurysms, intraretinal hemorrhages, and hard exudates. The severity of underlying diabetic retinopathy (DR) (non-proliferative or proliferative) must also be assessed, as DME can occur at any stage.

Diagnostic Criteria and Findings: The diagnosis and management of DME rely heavily on imaging:

- **Optical Coherence Tomography (OCT):** OCT is the gold standard for diagnosing, quantifying, and monitoring DME. It provides high-resolution visualization of retinal anatomy. Key findings include increased Central Subfield Thickness (CST), the presence of intraretinal fluid (IRF, often appearing as cysts) and subretinal fluid (SRF). Center-involved DME, typically defined by a CST exceeding a specific threshold (e.g., >300 µm), is the primary indication for treatment.
- **Fluorescein Angiography (FA):** Used adjunctively to visualize vascular leakage patterns (focal vs. diffuse) and identify macular ischemia.

Common Treatments and Medications: Management involves optimizing systemic glycemic control, blood pressure, and lipids. Ocular treatment focuses on resolving edema and improving vision.

- **Intravitreal Anti-VEGF Therapy:** The established first-line standard of care (2025-2026). Agents include Aflibercept (including high-dose formulations), Ranibizumab, and Faricimab (a bispecific antibody targeting VEGF-A and Ang-2). Off-label Bevacizumab is also used. Treatment requires frequent intravitreal injections, often utilizing treat-and-extend protocols.
- **Intravitreal Corticosteroids:** Typically used for patients with suboptimal response to anti-VEGF or in specific cases (e.g., pseudophakic eyes). Agents include sustained-release Dexamethasone and Fluocinolone acetonide implants.
- **Laser Photocoagulation:** Macular laser (focal/grid) is generally reserved for non-center-involved DME or as adjunctive therapy.

Differential Diagnoses and Comorbidities: DME must be differentiated from other causes of macular edema, such as Retinal Vein Occlusion (RVO), Uveitis, Irvine-Gass Syndrome (post-cataract surgery), and Age-related Macular Degeneration (AMD). Common comorbidities include hypertension, chronic kidney disease, cataracts, and glaucoma.

Prognosis and Complications: While anti-VEGF therapy is highly effective, it imposes a significant treatment burden requiring frequent injections. This leads to non-adherence and reduced real-world visual outcomes compared to clinical trials. Critically, approximately 40-60% of patients are **suboptimal responders**, characterized by persistent or recurrent edema despite standard-of-care therapy.

3. Phenotype Boundaries and Granularity

This phenotype is designed to identify the population of patients with active DME requiring therapeutic intervention, reflecting the contemporary treatment landscape and areas of unmet need.

General Exclusions:

- Macular edema primarily attributable to non-diabetic etiologies (e.g., RVO, Uveitis, AMD, Irvine-Gass syndrome).
- Diabetic retinopathy without macular edema.
- Quiescent or resolved DME that does not currently warrant active treatment (e.g., stable anatomy and vision without recent intervention).

Temporal Context:

- **Prevalent:** The focus is on identifying all existing cases of active DME during the observation period.

Clinical Granularity:

- **Severity/Activity:** High granularity is required to define the presence of *active* disease warranting intervention. This scope encompasses:
    - Treatment-naïve patients (typically with center-involved DME).
    - Previously treated patients receiving ongoing management.
    - Patients with persistent or recurrent edema despite standard-of-care anti-VEGF therapy (suboptimal responders).
- **Etiology:** Must be clearly associated with Diabetes Mellitus (Type 1 or Type 2).
- **Manifestation:** The phenotype must identify the presence of edema within the macula.

Population Context:

- Adult patients with an established diagnosis of Diabetes Mellitus.

4. Intended Clinical Application Research Utility

This prevalent cohort of active DME patients is essential for epidemiological research supporting the commercialization, market access, and strategic positioning of diverse therapies anticipated to enter the market post-2026 (including topical/oral delivery, sustained-release implants, novel mechanisms such as Wnt agonists, PKIs, anti-IL-6, and gene therapies).

The primary research utility is to characterize the contemporary (2025-2026) real-world treatment landscape as the standard of care evolves with the adoption of longer-acting agents (e.g., high-dose Aflibercept, Faricimab). This data will facilitate comparative effectiveness research by quantifying current treatment burdens, injection frequencies, adherence rates, and associated visual outcomes. Critically, by identifying the prevalence and characteristics of patients who remain suboptimal responders despite these advancements, the research will substantiate the unmet medical need and value proposition for novel mechanism therapies and alternative delivery systems aiming to improve durability and reduce treatment burden.

Clinical Description: Diabetic Macular Edema (DME), Active Disease

Synonyms: Clinically Significant Macular Edema (CSME) (Historical term); Diabetic Maculopathy (Often used interchangeably when edema is the primary feature).

1. Clinical Case Definition

Diabetic Macular Edema (DME) is a sight-threatening microvascular complication of diabetes mellitus (Type 1 and Type 2). It results from chronic hyperglycemia leading to the breakdown of the inner blood-retinal barrier. This process is characterized by increased vascular permeability—mediated by factors such as Vascular Endothelial Growth Factor (VEGF) and inflammatory mediators—leading to the accumulation of extracellular fluid and lipoprotein exudates within the macula, the retinal area responsible for central, high-acuity vision.

Clinically, patients may be asymptomatic in early stages but commonly present with gradual, painless blurring or distortion of central vision (metamorphopsia), particularly when the edema involves the fovea (center-involved DME). Assessment involves visual acuity testing and dilated fundus examination (slit-lamp biomicroscopy). Examination findings typically include retinal thickening, microaneurysms, intraretinal hemorrhages, and hard exudates.

The diagnosis relies heavily on imaging. Optical Coherence Tomography (OCT) is the gold standard for confirming and quantifying DME. Key OCT findings indicative of active disease include increased Central Subfield Thickness (CST) (e.g., often exceeding thresholds like 300 µm), the presence of intraretinal fluid (IRF, often appearing as cysts), and/or subretinal fluid (SRF). Fluorescein Angiography (FA) may be used adjunctively to assess vascular leakage patterns (focal vs. diffuse) and identify macular ischemia. This phenotype specifically targets the active disease state characterized by the presence of edema warranting clinical management.

2. Phenotype Scope & Granularity

- **Temporal Context:** Prevalent; intended to identify all existing cases of active DME during the observation period.
- **Severity:** Active disease warranting clinical intervention. This scope is inclusive of treatment-naïve patients (typically center-involved) and previously treated patients with persistent or recurrent edema.
- **Acuity / Chronicity:** Focuses on the active state of fluid accumulation. This scope is not inclusive of quiescent or resolved DME where retinal anatomy is stable.
- **Etiology:** Secondary to Diabetes Mellitus (Type 1 or Type 2).
- **Population Context:** Adult patients with an established diagnosis of Diabetes Mellitus.

3. Related Conditions & Scope Boundaries

The following conditions represent related pathologies or differential diagnoses for macular edema but are not precisely within the scope of this specific phenotype:

- **Diabetic Retinopathy (DR) without Macular Edema:** While DR (non-proliferative or proliferative) is the underlying condition, this phenotype specifically requires the presence of edema involving the macula.
- **Non-Diabetic Macular Edema:** Macular edema primarily attributable to other etiologies is outside the scope of this diabetes-specific phenotype. These include:
    - Retinal Vein Occlusion (RVO)
    - Uveitis (inflammatory macular edema)
    - Irvine-Gass Syndrome (post-surgical macular edema)
    - Age-related Macular Degeneration (AMD)

4. Key Complications & Common Comorbidities

The following conditions are common comorbidities or complications associated with DME, but should be recognized as distinct clinical entities, separate from the core definition of the macular edema itself.

- **Complications:**
    - Moderate to severe vision loss
- **Common Comorbidities / Associated Conditions:**
    - Diabetic Retinopathy (Non-proliferative and Proliferative)
    - Hypertension
    - Chronic Kidney Disease
    - Cataracts
    - Glaucoma

5. Intended Data Sources

This clinical description is intended for building concept sets against real-world administrative claims, electronic health record (EHR) databases, and patient registries. The target data should be standardized to the OMOP Common Data Model. Examples of licensable data sources where this concept set would be applied include:

- **Optum®** (Clinformatics® Data Mart, SES, Pan-Therapeutic)
- **Merative™** (MarketScan® Commercial Claims and Encounters)
- **Veradigm** (Health Verity, Practice Fusion EHR)
- **IQVIA** (AmbEMR, PharMetrics Plus)
- **HealthVerity**