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Strategic context:

Standardized Medical Name: Active Non-Infectious Uveitis (NIU) Requiring Systemic Immunomodulatory Therapy

Target Patient Profile:

- **Temporality:** Prevalent patients with chronic or recurrent disease experiencing active inflammation (incident flare or persistent activity).
- **Disease Stage/State:** Active Non-Infectious Uveitis (primarily intermediate, posterior, or panuveitis) where local therapy (e.g., topical or injected corticosteroids) is insufficient or inappropriate. The disease state necessitates the initiation or escalation of systemic immunomodulatory therapy (IMT) for disease control and/or explicit steroid-sparing purposes.

Strategic Rationale: Pharmaceutical Relevance (2025-2026):

The management of Active Non-Infectious Uveitis (NIU) requiring systemic therapy is defined by a critical unmet need for effective, steroid-sparing treatments. While systemic corticosteroids are the mainstay for inducing acute remission, their long-term use is severely limited by significant ocular (e.g., glaucoma, cataracts) and systemic toxicities. The current standard of care relies on conventional DMARDs (e.g., methotrexate, mycophenolate) and the only approved systemic biologic, the anti-TNF agent Adalimumab. However, many patients experience inadequate response, intolerance, or seek more convenient administration routes.

The strategic imperative for the 2025-2026 horizon is the introduction of novel, targeted systemic therapies—particularly oral small molecules—that can induce durable, steroid-free remission.

The industry's focus has been significantly shaped by recent pipeline dynamics. The failure of IL-17A inhibition in NIU, highlighted by the discontinuation of Acelyrin's Izokibep in late 2024/early 2025 following unsuccessful Phase 2b/3 results, has underscored the difficulty of treating this condition and intensified investment in alternative pathways.

This has elevated the strategic relevance of the Janus Kinase (JAK) and Tyrosine Kinase 2 (TYK2) pathways, which offer the potential for potent immunosuppression via oral administration. The most significant late-stage asset defining the 2025-2026 landscape for systemic NIU treatment is:

- **Brepocitinib (Priovant Therapeutics):** This oral, dual TYK2/JAK1 inhibitor is the leading candidate in late-stage development. Following positive Phase II (NEPTUNE) results demonstrating dose-dependent steroid-sparing efficacy, Brepocitinib is currently

being evaluated in the global, pivotal Phase III CLARITY program (NCT06431373). This large-scale program is actively enrolling patients with active intermediate, posterior, and panuveitis. The progression of CLARITY positions Brepocitinib as a potential paradigm-shifting oral alternative to Adalimumab and conventional DMARDs in the near term.

The phenotype of Active NIU requiring systemic immunomodulatory therapy is therefore central to the 2025-2026 agenda, as it defines the exact population where emerging oral therapies aim to demonstrate superiority or significant differentiation over the current standard of care.

Intended Clinical Application Research Utility:

Epidemiological research on this phenotype is critical to support the market access and strategic positioning of emerging oral systemic therapies, notably TYK2/JAK1 inhibitors, in the 2025-2026 timeframe. Research utility includes characterizing the real-world effectiveness, failure rates, and switching patterns associated with the current standard of care (cDMARDs and Adalimumab), and quantifying the clinical and economic burden associated with long-term corticosteroid dependence. This data is essential for comparative effectiveness analysis, Health Technology Assessments (HTA), and demonstrating the unmet need addressable by novel, high-efficacy steroid-sparing agents.

Phenotype Description: Active Non-Infectious Uveitis (NIU) Requiring Systemic Immunomodulatory Therapy

1. Clinical Condition

Recommended Phenotype: Active Non-Infectious Uveitis (NIU) Requiring Systemic Immunomodulatory Therapy

Synonyms and Related Terms:

- Systemic NIU
- Sight-threatening Non-Infectious Uveitis
- Steroid-dependent Uveitis
- Non-infectious intermediate uveitis, posterior uveitis, or panuveitis

2. Detailed Presentation

Non-Infectious Uveitis (NIU) encompasses a heterogeneous group of intraocular inflammatory disorders arising from autoimmune or autoinflammatory processes. NIU may be purely ocular or associated with systemic diseases (e.g., sarcoidosis, Behçet's disease, spondyloarthritis). This phenotype specifically addresses patients with active inflammation involving the intermediate, posterior, or all segments of the uveal tract (panuveitis), where the severity, chronicity, or sight-threatening nature of the disease necessitates the use of systemic immunomodulatory therapy (IMT).

Clinical Presentation and Assessment: The clinical presentation varies by anatomical location.

- **Intermediate Uveitis:** Characterized primarily by inflammation of the vitreous (vitritis). Patients often present with floaters and blurred vision. Key signs include vitreous cells, "snowballs" (inflammatory aggregates), and "snowbanking" (exudate over the pars plana).
- **Posterior Uveitis:** Involves the retina and/or choroid. Symptoms include significant vision loss, scotomas (blind spots), and floaters. Findings may include retinal vasculitis (sheathing, leakage), chorioretinitis, retinitis, and optic disc edema.
- **Panuveitis:** Inflammation involving the anterior chamber, vitreous, and retina/choroid concurrently. Presentation is often severe, combining symptoms of anterior (pain, redness, photophobia) and posterior segment inflammation.

Clinical assessment relies on comprehensive ophthalmologic examination, including slit-lamp biomicroscopy and dilated fundus examination. Disease activity is graded based on standardized criteria (e.g., Standardization of Uveitis Nomenclature (SUN) criteria) assessing anterior chamber cells/flare and vitreous haze. The defining characteristic of this phenotype is *active* inflammation—either a new flare or persistent activity—that is not adequately controlled by local therapies alone.

Diagnostic Criteria and Investigations: The diagnosis of NIU is contingent upon the rigorous exclusion of infectious etiologies (e.g., syphilis, tuberculosis, viral retinitis) and masquerade syndromes (e.g., intraocular lymphoma). Investigations are tailored to the clinical presentation:

- **Laboratory Tests:** Serological testing for infectious agents, inflammatory markers (ESR, CRP), and screening for systemic autoimmune associations (e.g., HLA-B27, ANA, ACE levels).
- **Ocular Imaging:** Essential for monitoring disease activity and complications. Optical Coherence Tomography (OCT) is crucial for detecting and quantifying cystoid macular edema (CME), a common cause of vision loss. Fundus Fluorescein Angiography (FFA) identifies retinal vasculitis and leakage in the posterior segment.

Treatment Paradigm: The therapeutic goal is to rapidly control inflammation, prevent structural damage, and achieve durable, steroid-free remission.

- **Corticosteroids:** The mainstay for acute management. They may be administered locally (periocular or intravitreal injections/implants) or systemically. Oral corticosteroids (e.g., prednisone) are used for inducing remission but are unsuitable for long-term maintenance due to significant ocular and systemic toxicity.
- **Systemic Immunomodulatory Therapy (IMT):** The necessity for IMT defines this phenotype. IMT is initiated when local therapy is insufficient, when steroids cannot be tapered to a safe maintenance dose (steroid dependence), or explicitly to avoid steroid toxicity (steroid-sparing).
    - *Conventional DMARDs (cDMARDs):* Antimetabolites (e.g., methotrexate, mycophenolate mofetil) are common first-line agents. Calcineurin inhibitors (e.g., cyclosporine) may also be used.
    - *Biologic Therapies:* The TNF-alpha inhibitor Adalimumab is the established systemic biologic therapy for NIU.

Prognosis and Complications: NIU is often chronic and recurrent. Inadequately controlled inflammation leads to cumulative ocular damage. Common complications include CME, cataracts, glaucoma/ocular hypertension (often exacerbated by corticosteroid use), and optic atrophy. Furthermore, long-term systemic corticosteroid use carries significant systemic morbidity, including osteoporosis, diabetes mellitus, hypertension, and increased infection risk.

3. Phenotype Boundaries and Granularity

This phenotype is defined by the intersection of active, non-infectious inflammation in specific anatomical locations and the clinical requirement for systemic immunomodulatory treatment.

General Exclusions:

- Uveitis confirmed or strongly suspected to be of infectious etiology (bacterial, viral, fungal, parasitic).

- Masquerade syndromes (e.g., intraocular lymphoma).
- Isolated anterior uveitis that is typically managed with topical therapy alone and carries a different therapeutic pathway.
- Uveitis fully controlled by local therapies (topical, periocular, or intravitreal injections/implants) alone, without the need for systemic IMT.
- Inactive (quiescent) disease not requiring active treatment escalation.

Temporal Context:

- **Target State:** Prevalent. The phenotype captures patients with established chronic or recurrent disease who are experiencing active inflammation (either an incident flare or persistent activity) requiring initiation or escalation of systemic therapy.

Clinical Granularity:

- **Etiology:** Must be specified as Non-Infectious. Associated systemic autoimmune diseases (e.g., sarcoidosis) and idiopathic NIU are included.
- **Anatomical Location:** Must include involvement of the intermediate, posterior segment, or panuveitis.
- **Acuity:** Active disease (current flare or persistent inflammation).
- **Severity:** High severity, defined by inflammation that is sight-threatening, refractory to local treatment, or characterized by corticosteroid dependence.

Population Context:

- The population is restricted to patients for whom the treating clinician has determined that systemic immunomodulatory therapy is necessary for disease control and/or explicit steroid-sparing purposes.

4. Intended Clinical Application Research Utility

This phenotype is strategically designed to support market access, Health Technology Assessments (HTA), and the strategic positioning of novel, targeted systemic therapies entering the NIU landscape in the 2025-2026 timeframe, particularly oral small molecules targeting the TYK2/JAK1 pathways.

The primary research utility is to generate real-world evidence regarding the current standard of care (conventional DMARDs and Adalimumab) within this specific population, where a critical unmet need exists for effective, durable, steroid-sparing options. Key applications include:

1. **Comparative Effectiveness Research:** Characterizing the real-world effectiveness, failure rates, intolerance, and switching patterns associated with existing systemic therapies.

2. **Burden of Illness Quantification:** Quantifying the clinical and economic burden associated with long-term systemic corticosteroid dependence, including the incidence of steroid-related ocular and systemic toxicities.
3. **Unmet Need Demonstration:** Establishing the proportion of patients who remain steroid-dependent or experience inadequate disease control despite current therapies, thereby highlighting the unmet need addressable by emerging high-efficacy, oral agents aiming to achieve steroid-free remission.

Clinical Description: Active, Severe Non-Infectious Uveitis (Intermediate, Posterior, or Panuveitis)

Synonyms: Systemic NIU, Sight-threatening Non-Infectious Uveitis, Steroid-dependent Uveitis, Non-infectious intermediate uveitis, posterior uveitis, or panuveitis.

1. Clinical Case Definition

Non-Infectious Uveitis (NIU) is a heterogeneous group of intraocular inflammatory disorders arising from autoimmune or autoinflammatory processes. It may manifest as a purely ocular condition (idiopathic) or be associated with systemic diseases (e.g., sarcoidosis, Behçet's disease, spondyloarthritis). This phenotype specifically defines active, severe inflammation involving the intermediate, posterior, or all segments of the uveal tract (panuveitis). The severity is characterized by inflammation that is sight-threatening, chronic, recurrent, or refractory to management with local therapies alone (often characterized as steroid-dependent).

The diagnosis of NIU is contingent upon the rigorous exclusion of infectious etiologies (e.g., syphilis, tuberculosis, viral retinitis) and masquerade syndromes (e.g., intraocular lymphoma). Clinical assessment relies on comprehensive ophthalmologic examination, including slit-lamp biomicroscopy and dilated fundus examination. Disease activity is confirmed and graded using standardized criteria (e.g., Standardization of Uveitis Nomenclature (SUN) criteria), assessing anterior chamber cells/flare and vitreous haze.

The clinical presentation varies by anatomical location:

- **Intermediate Uveitis:** Characterized primarily by inflammation of the vitreous (vitritis), often presenting with floaters and blurred vision. Key signs include vitreous cells, "snowballs" (inflammatory aggregates), and "snowbanking" (exudate over the pars plana).
- **Posterior Uveitis:** Involves the retina and/or choroid, often causing significant vision loss or scotomas. Findings may include retinal vasculitis (sheathing, leakage), chorioretinitis, retinitis, and optic disc edema.
- **Panuveitis:** Concurrent inflammation involving the anterior chamber, vitreous, and retina/choroid, often presenting with severe symptoms combining features of anterior (pain, redness, photophobia) and posterior inflammation.

Supporting investigations include laboratory tests for inflammatory markers (ESR, CRP) and screening for systemic autoimmune associations (e.g., HLA-B27, ANA, ACE levels). Ocular imaging is essential; Optical Coherence Tomography (OCT) is used to detect and quantify cystoid macular edema (CME), and Fundus Fluorescein Angiography (FFA) identifies retinal vasculitis and posterior segment leakage.

2. Phenotype Scope & Granularity

- **Temporal Context:** Prevalent. Intended to identify patients with established chronic or recurrent disease experiencing active inflammation (either an incident flare or persistent activity).
- **Severity:** High severity. This scope is defined by inflammation that is sight-threatening, steroid-dependent, or refractory to local treatment. It excludes mild cases managed solely with local therapies.
- **Acuity / Chronicity:** Active disease (current flare or persistent inflammation) within a chronic or recurrent context.
- **Etiology:** Non-Infectious (autoimmune or autoinflammatory). Includes both idiopathic NIU and NIU associated with systemic autoimmune diseases.
- **Population Context:** Patients with confirmed anatomical involvement of the intermediate segment, posterior segment, or panuveitis meeting the severity criteria.

3. Related Conditions & Scope Boundaries

The following conditions represent distinct clinical entities or different states of the disease and are not within the scope of this phenotype:

- **Infectious Uveitis:** Uveitis caused by bacterial, viral, fungal, or parasitic agents is a distinct etiology and is not within the scope of this non-infectious phenotype.
- **Masquerade Syndromes:** Conditions mimicking uveitis, such as intraocular lymphoma, are distinct pathological entities and are not within scope.
- **Isolated Anterior Uveitis:** Inflammation confined solely to the anterior chamber represents a different anatomical scope and typically a different severity profile; it is not within the scope of this phenotype.
- **Inactive (Quiescent) NIU:** Disease states without active inflammation are not within the scope of this active phenotype.
- **Mild or Locally Controlled NIU:** Uveitis that is fully controlled by local therapies (topical, periocular, or intravitreal) represents a lower severity and is not within the scope of this severe phenotype.

4. Key Complications & Common Comorbidities

The following conditions are frequent complications of the disease, associated systemic conditions, or consequences of common treatments (e.g., corticosteroids). They must be differentiated from the core definition of active severe NIU itself.

- **Ocular Complications:**
    - Cystoid Macular Edema (CME)
    - Cataracts
    - Glaucoma / Ocular Hypertension
    - Optic Atrophy

- **Associated Systemic Diseases (Comorbidities):**
    - Sarcoidosis
    - Behçet's disease
    - Spondyloarthritis
- **Common Iatrogenic/Treatment-Related Conditions:**
    - Osteoporosis
    - Diabetes Mellitus
    - Systemic Hypertension

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**

Clinical Description: Active, Severe Non-Infectious Uveitis (Intermediate, Posterior, or Panuveitis)

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The diagnosis of NIU is contingent upon the rigorous exclusion of infectious etiologies (e.g., syphilis, tuberculosis, viral retinitis) and masquerade syndromes (e.g., intraocular lymphoma). Clinical assessment relies on comprehensive ophthalmologic examination, including slit-lamp biomicroscopy and dilated fundus examination. Disease activity is confirmed and graded using standardized criteria (e.g., Standardization of Uveitis Nomenclature (SUN) criteria), assessing anterior chamber cells/flare and vitreous haze.

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