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Strategic context:

Standardized Medical Name: Severe Immune Checkpoint Inhibitor (ICI)-induced Hepatotoxicity (Grade 3/4)

Target Patient Profile:

- **Temporality:** Incident (Patients experiencing a new, acute episode of hepatotoxicity secondary to ICI exposure).
- **Disease Stage/State:** Severe (Grade 3 or Grade 4 hepatotoxicity according to CTCAE criteria). This critically includes the subset of patients who are steroid-refractory or steroid-dependent, requiring second-line immunosuppression.

Strategic Rationale: Pharmaceutical Relevance (2025-2026):

Severe Immune Checkpoint Inhibitor (ICI)-induced hepatotoxicity is a critical, dose-limiting toxicity in oncology. As ICIs (e.g., anti-PD-1/L1 and anti-CTLA-4) increasingly serve as the backbone of treatment across numerous malignancies—often used in combination regimens which confer higher toxicity rates—the management of severe immune-related adverse events (irAEs) is a major strategic priority. Severe hepatotoxicity frequently mandates the cessation of life-saving cancer therapy and carries a risk of acute liver failure.

The primary unmet clinical need, and the focus of the 2025-2026 industry agenda, is the management of steroid-refractory cases. The current standard of care (SoC), high-dose corticosteroids, is ineffective in a significant subset of patients (estimates range widely, up to 20-37%). Furthermore, prolonged steroid use is associated with substantial morbidity and may potentially blunt the anti-tumor efficacy of ICIs. While second-line agents like mycophenolate mofetil (MMF) are used empirically, there are no standardized, prospectively validated protocols for steroid-refractory ICI-hepatotoxicity.

This gap has catalyzed significant R&D investment in targeted, steroid-sparing therapies that can rapidly resolve severe irAEs while minimizing broad immunosuppression—often termed "decoupling" toxicity from efficacy. Key pipeline activities demonstrating this focus for the 2025-2026 horizon include:

- **JAK Inhibition:** Targeting the JAK-STAT pathway to dampen inflammatory cytokine signaling is a leading strategy. Notably, **Itacitinib** (a selective JAK1 inhibitor) is in an active Phase II trial (NCT05660421) specifically evaluating its use in patients with various steroid-refractory irAEs, explicitly including hepatitis. The estimated primary completion is September 2026.
- **IL-6 Pathway Modulation:** Interleukin-6 is recognized as a key driver of the inflammatory cascade in severe irAEs. While agents like tocilizumab are sometimes

used off-label based on retrospective evidence, the industry is actively exploring IL-6 blockade in prospective trials both for the management of refractory irAEs and for mitigating toxicity in combination with ICIs (e.g., NCT04940299), underscoring the strategic importance of this pathway.

The advancement of these programs demonstrates a high industry commitment to establishing new, targeted standards of care for steroid-refractory ICI-hepatotoxicity within the immediate strategic horizon.

Intended Clinical Application Research Utility:

Epidemiological research characterizing the contemporary management of incident severe ICI-induced hepatotoxicity is critical to support the development, regulatory submission, and commercialization of novel therapies targeting steroid-refractory irAEs (e.g., JAK inhibitors) in 2025-2026. This research utility includes quantifying the precise unmet need (e.g., real-world failure rates of corticosteroids and MMF), defining clinical outcomes (time to resolution, mortality, rates of successful ICI rechallenge), and establishing the burden of illness. This data is essential for market access planning, providing vital real-world comparator data for late-stage clinical trials, and contextualizing the efficacy of emerging treatments against the current, non-standardized SoC.

Phenotype Definition: Severe Immune Checkpoint Inhibitor (ICI)-induced Hepatotoxicity (Grade 3/4)

1. Clinical Condition

Recommended Phenotype: Severe Immune Checkpoint Inhibitor (ICI)-induced Hepatotoxicity (Grade 3/4)

Common Synonyms:

- Severe ICI-Hepatitis
- Grade 3 or 4 Immune-related Adverse Event (irAE) Hepatitis
- Severe immune-mediated hepatitis secondary to checkpoint inhibition
- Checkpoint inhibitor-associated liver injury

2. Detailed Presentation

Clinical Overview and Assessment Immune Checkpoint Inhibitors (ICIs)—including anti-PD-1, anti-PD-L1, and anti-CTLA-4 agents—are foundational therapies in oncology. By non-specifically activating the immune system, they can induce immune-related adverse events (irAEs). ICI-induced hepatotoxicity is a significant, potentially life-threatening inflammatory condition of the liver parenchyma.

The presentation is highly variable. Most patients are identified through asymptomatic elevations in liver function tests (LFTs) during routine monitoring. When symptoms occur, they are typically non-specific, including fatigue, anorexia, nausea, and right upper quadrant discomfort. Fever may be present. Jaundice or scleral icterus indicates significant hyperbilirubinemia. In the most severe cases (Grade 4), signs of acute liver failure, such as encephalopathy or coagulopathy, may develop. A thorough history must establish a temporal link between ICI administration (monotherapy or combination regimens) and the onset of liver injury, and critically exclude alternative etiologies.

Diagnostic Criteria and Investigations The diagnosis relies on identifying characteristic patterns of liver injury in the context of ICI exposure and excluding other causes. Severity is graded according to the Common Terminology Criteria for Adverse Events (CTCAE). This phenotype specifically focuses on **Severe (Grade 3 and Grade 4)** toxicity, defined by the following laboratory parameters based on the Upper Limit of Normal (ULN):

- **Grade 3 (Severe):** Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) >5.0–20.0 × ULN; OR Total Bilirubin (TBil) >3.0–10.0 × ULN.
- **Grade 4 (Life-threatening):** AST or ALT >20.0 × ULN; OR TBil >10.0 × ULN; OR signs of acute liver failure (e.g., new-onset significant coagulopathy or encephalopathy).

The pattern of injury is most commonly hepatocellular, but can also be cholestatic or mixed.

Essential diagnostic workup includes:

- **Laboratory Tests:** Comprehensive metabolic panel (AST, ALT, Alkaline Phosphatase, TBil, albumin) and synthetic function markers (PT/INR).
- **Serologies:** Testing for viral hepatitis (Hepatitis A, B, C; potentially CMV, EBV, HSV) and autoimmune hepatitis markers (e.g., ANA, anti-smooth muscle antibodies).
- **Imaging:** Abdominal imaging (ultrasound, CT, or MRI) is critical to rule out biliary obstruction, vascular thrombosis, or metastatic disease progression in the liver.
- **Liver Biopsy:** Often recommended for Grade 3/4 toxicity, especially if the diagnosis is uncertain or the patient is not responding to initial management, to confirm the immune-mediated etiology.

Treatment and Management Management of Grade 3/4 hepatotoxicity requires immediate intervention and typically hospitalization.

1. **ICI Discontinuation:** The offending ICI therapy is immediately held; permanent discontinuation is often necessary.
2. **Corticosteroids (First-Line):** High-dose systemic corticosteroids (e.g., methylprednisolone or prednisone, 1-2 mg/kg/day) are the standard of care (SoC).
3. **Steroid-Refractory/Dependent Management (Second-Line):** A critical subset of patients fails to improve within 48-72 hours of high-dose steroids (steroid-refractory) or cannot be tapered off steroids without recurrent hepatitis (steroid-dependent). These cases require escalation to second-line immunosuppression. The most common agent is Mycophenolate Mofetil (MMF). Other agents used empirically include tacrolimus or anti-thymocyte globulin (ATG).

Differential Diagnoses and Prognosis Key differential diagnoses include malignant infiltration of the liver, acute viral hepatitis, drug-induced liver injury (DILI) from non-ICI medications, biliary obstruction, and vascular events. Severe ICI-hepatotoxicity mandates cessation of potentially life-saving cancer treatment. Steroid-refractory cases have higher morbidity and mortality. Complications include acute liver failure and significant morbidity from prolonged high-dose steroid exposure (e.g., opportunistic infections, hyperglycemia).

3. Phenotype Boundaries and Granularity

This phenotype is defined to capture acute, severe liver injury directly attributable to ICI therapy, with a focus on the population requiring significant immunosuppressive intervention.

General Exclusions

- Mild or moderate (Grade 1 or 2) hepatotoxicity.
- Liver injury determined to be caused by etiologies other than ICI therapy (e.g., viral hepatitis, tumor progression, other DILI, obstruction).
- Autoimmune hepatitis unrelated to ICI exposure.

- Exacerbation of underlying chronic liver disease (e.g., NASH/MASH) without evidence of acute ICI-induced injury.

Temporal Context

- **Incident:** The focus is exclusively on identifying the new onset of an acute episode of severe hepatotoxicity occurring during or shortly after exposure to an Immune Checkpoint Inhibitor.

Clinical Granularity

- **Severity (Required):** Restricted to Severe (Grade 3 or Grade 4), defined by laboratory parameters consistent with CTCAE criteria.
- **Acuity (Required):** The event must be acute.
- **Etiology (Required):** The hepatotoxicity must be attributed to exposure to an immune checkpoint inhibitor.
- **Clinical State (Required):** Identification of the treatment response is critical. Stratification into steroid-responsive vs. steroid-refractory or steroid-dependent (i.e., requiring escalation to second-line immunosuppression such as MMF) is a key characteristic of this population.

Population Context

- Patients with a confirmed diagnosis of malignancy who are actively receiving, or have recently received, Immune Checkpoint Inhibitor therapy (monotherapy or combination).

4. Intended Clinical Application Research Utility

The primary research utility of this phenotype is to support the development, regulatory strategy, and commercialization of novel, targeted, steroid-sparing therapies (e.g., JAK inhibitors, IL-6 pathway modulators) for the management of severe and steroid-refractory ICI-induced hepatotoxicity, aligned with industry pipelines active in the 2025-2026 horizon.

This phenotype enables epidemiological research to characterize the contemporary standard of care and quantify the precise unmet clinical need. Key research objectives include:

1. **Quantifying Unmet Need:** Determining the real-world incidence of steroid failure (refractory or dependent cases) among patients treated with high-dose corticosteroids and/or MMF.
2. **RWE Comparator Data:** Establishing robust real-world comparator data for late-stage clinical trials (e.g., Phase II/III) evaluating new targeted treatments against the current, non-standardized SoC.
3. **Outcomes and Burden of Illness:** Defining critical clinical outcomes (time to resolution of hepatitis, mortality, rates of opportunistic infection secondary to immunosuppression, success rates of ICI rechallenge) to support market access planning.

Clinical Description: Severe Hepatotoxicity (Grade 3/4)

Synonyms: Severe Acute Liver Injury, Grade 3 or 4 Liver Toxicity, Severe Hepatitis (when meeting severity criteria).

1. Clinical Case Definition

Severe Hepatotoxicity is an acute, potentially life-threatening condition characterized by significant injury and inflammation of the liver parenchyma. This phenotype defines a state of severe liver impairment based on standardized laboratory parameters, irrespective of the underlying etiology (e.g., drug-induced, viral, autoimmune, ischemic).

The clinical presentation is highly variable. Patients may be asymptomatic, identified solely through routine laboratory monitoring. When symptoms occur, they are often non-specific, including fatigue, malaise, anorexia, nausea, and right upper quadrant discomfort. The development of jaundice or scleral icterus indicates significant hyperbilirubinemia. The pattern of liver injury identified through laboratory assessment (including AST, ALT, Alkaline Phosphatase, TBil) can be hepatocellular, cholestatic, or mixed.

This phenotype is strictly defined by the severity of the biochemical abnormalities, corresponding to **Severe (Grade 3) or Life-threatening (Grade 4)** toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) standards, based on the Upper Limit of Normal (ULN):

- **Grade 3 (Severe):** Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) >5.0–20.0 × ULN; OR Total Bilirubin (TBil) >3.0–10.0 × ULN.
- **Grade 4 (Life-threatening):** AST or ALT >20.0 × ULN; OR TBil >10.0 × ULN. Grade 4 may also be defined by clinical signs of acute liver failure, such as new-onset significant coagulopathy (e.g., elevated PT/INR) or hepatic encephalopathy, irrespective of the degree of LFT elevation.

2. Phenotype Scope & Granularity

- **Temporal Context:** Incident. Focuses on identifying the new onset of an acute episode of severe hepatotoxicity.
- **Severity:** Restricted to Severe (Grade 3) or Life-threatening (Grade 4) based on CTCAE laboratory or clinical criteria. This scope is not inclusive of mild (Grade 1) or moderate (Grade 2) toxicity.

- **Acuity / Chronicity:** Acute event. This scope is not inclusive of stable chronic liver disease or cirrhosis unless an acute, severe exacerbation meeting the laboratory criteria occurs.
- **Etiology:** Etiology-agnostic. This definition captures the state of severe liver injury regardless of the underlying cause.
- **Population Context:** General population, although the CTCAE criteria are most commonly applied in oncology, clinical trials, and severe adverse drug reaction monitoring.

3. Related Conditions & Scope Boundaries

This phenotype defines the severity of liver injury, not the cause. The following conditions are related but distinct in scope:

- **Mild or Moderate Hepatotoxicity (Grade 1/2):** Liver enzyme elevations that do not meet the criteria for Grade 3 or higher are not within the scope of this phenotype.
- **Chronic Liver Disease / Cirrhosis:** The stable, chronic state of liver disease is not within the scope of this acute phenotype. However, an acute-on-chronic event that meets Grade 3/4 criteria *is* within scope.
- **Isolated Hyperbilirubinemia (e.g., Gilbert's Syndrome):** Benign conditions causing elevated bilirubin without evidence of significant parenchymal injury or cholestasis are not within scope.

4. Key Complications & Common Comorbidities

This section differentiates the core phenotype from its common clinical consequences or associations.

- **Acute Liver Failure (ALF):** The primary and most severe complication, characterized by encephalopathy and coagulopathy, representing the extreme end of the Grade 4 spectrum.
- **Coagulopathy:** Impaired synthetic function of the liver leading to bleeding risk.
- **Hepatic Encephalopathy:** Neuropsychiatric abnormalities due to the liver's inability to detoxify blood.
- **Hepatorenal Syndrome:** Kidney failure developing secondary to severe liver disease.

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**