Hepatocellular Carcinoma: A Comprehensive Disease Characteristics Report

Disease: Hepatocellular Carcinoma (HCC) **Suggested MONDO ID:** MONDO:0007256 (hepatocellular carcinoma) **Category:** Malignant epithelial neoplasm of the liver (primary liver cancer) **Report scope:** 15-section disease knowledge-base template **Evidence base:** 15 confirmed findings; 92 papers reviewed

Summary

Hepatocellular carcinoma (HCC) is the dominant form of primary liver cancer, accounting for approximately 80% of primary liver tumors, and ranks as the **third leading cause of cancer-related mortality worldwide** (PMID: 35782375). It arises overwhelmingly (~80–90% of cases) on a background of chronic liver disease and cirrhosis, driven by a well-defined set of etiologies: chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcohol-associated liver disease, non-alcoholic fatty liver disease/steatohepatitis (NAFLD/NASH, now often termed MASLD/MASH), and dietary aflatoxin B1 exposure (PMID: 31347138). Globally the etiologic landscape is shifting: viral HCC is declining because of HBV vaccination and effective antivirals, while metabolic (NASH/obesity/diabetes-related) HCC is rising and may become the dominant cause (PMID: 32319693).

At the molecular level, HCC is characterized by a small set of recurrent somatic driver events — **TERT promoter, TP53, and CTNNB1 (Wnt/β-catenin)** mutations serve as the core initiating drivers, with AXIN1 and other alterations converging on a defined group of oncogenic pathways (Wnt/β-catenin, PI3K/AKT/mTOR, RAS/MAPK/ERK, HGF/c-MET, Hippo-YAP/TAZ, TGF-β) (PMID: 33958712; PMID: 41476776). Epigenetic dysregulation (DNA methylation imbalance, histone modification, chromatin reorganization, non-coding RNAs) and metabolic reprogramming (a Warburg-like aerobic glycolysis and altered lipid metabolism) are additional hallmarks, and the tumor develops within an immunosuppressive

microenvironment enriched for regulatory T cells and M0/M2 macrophages that both drives aggressive recurrence and provides the rationale for anti-VEGF plus checkpoint-inhibitor therapy.

Clinically, HCC is remarkable among solid tumors in that it can be diagnosed **noninvasively** in at-risk cirrhotic patients using dynamic contrast imaging (LI-RADS: arterial-phase hyperenhancement + washout ± capsule) supported by serum AFP and PIVKA-II. It shows a strong **male predominance (~2–4:1)** with a sex-hormone mechanistic basis. Management is stage-based following the BCLC framework — curative resection/ablation/transplantation for early disease, TACE/radioembolization for intermediate disease, and now immunotherapy-based systemic combinations (atezolizumab+bevacizumab or durvalumab+tremelimumab) for advanced disease. Prevention is anchored by HBV vaccination (proven primary prevention) and semiannual ultrasound ± AFP surveillance, with coffee consumption a robust dose-dependent protective factor. This report details all of these dimensions across the 15-section template.

Section 1: Disease Information

Overview. Hepatocellular carcinoma is a malignant epithelial tumor arising from hepatocytes. It is the dominant primary liver cancer and represents a major global oncologic burden. "Hepatocellular carcinoma (HCC) accounts for some 80% of primary liver tumors... HCC is the sixth most common type of cancer and the third leading cause of cancer-related mortality worldwide" (PMID: 35782375).

Key identifiers (suggested):

Resource	Identifier
MONDO	MONDO:0007256
MeSH	D006528 (Carcinoma, Hepatocellular)
ICD-10	C22.0
ICD-11	2C12.0
DOID	DOID:684
NCI Thesaurus	C3099

Synonyms / alternative names: hepatocellular carcinoma; HCC; hepatoma; malignant hepatoma; primary liver cell carcinoma; liver cell carcinoma; hepatocarcinoma. (Note: HCC is distinct from intrahepatic cholangiocarcinoma and from combined hepatocellular-cholangiocarcinoma [cHCC-CCA], a rare 2–5% mixed entity — PMID: 42272781.)

Information source type: The content in this report is derived predominantly from aggregated disease-level resources (systematic reviews, meta-analyses, cohort studies, genomic consortia such as TCGA/ICGC, GWAS meta-analyses), rather than from individual EHR patient records. Some cited studies use EHR/registry data (e.g., TriNetX cohorts).

Section 2: Etiology

Primary causal factors. HCC is a multifactorial disease caused by chronic hepatocellular injury from infectious, toxic, and metabolic insults, on which somatic genetic/epigenetic drivers accumulate. The principal causes: "the major risk factors for HCC development are chronic liver disease and cirrhosis due to hepatitis B virus (HBV) and/or hepatitis C virus (HCV), alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), steatohepatitis, intake of aflatoxin-contaminated food, diabetes, and obesity" (PMID: 31347138). Approximately 80–90% of HCC arises on established cirrhosis.

Environmental / lifestyle risk factors: chronic viral hepatitis (HBV, HCV), heavy alcohol use, aflatoxin B1 dietary exposure, tobacco smoking, obesity, type 2 diabetes, metabolic syndrome, older age, and male sex. Metabolic risk factors are increasing: "the prevalence of metabolic risk factors for HCC, including metabolic syndrome, obesity, type II diabetes and non-alcoholic fatty liver disease (NAFLD) are increasing and may jointly become the major cause of HCC globally" (PMID: 32319693).

Genetic risk factors (germline susceptibility). A multi-ancestry GWAS meta-analysis of 17,697 cases identified **15 genome-wide significant risk loci**, including MAP3K9, DHRS1, MTTP, and 8q24.21 (PMID: 42357869). Established susceptibility genes influencing lipid/metabolic handling include **PNPLA3, TM6SF2, MBOAT7, and TERT** (PMID: 41699549). The PNPLA3 I148M (rs738409) variant is a particularly important, fibrosis-independent risk allele (see Section 4/10).

Protective factors. *Environmental:* **coffee consumption** is a robust, dose-dependent protective factor (~35% risk reduction per 2 extra cups/day; see Finding F011). HBV vaccination and antiviral therapy prevent virally driven HCC. *Pharmacologic:* metformin use in diabetics

may lower risk — cumulative metformin exposure after HCV cure was associated with lower HCC risk (HR 0.46 per year; 95% CI 0.27–0.77) (PMID: 42499017). *Genetic protective:* rare loss-of-function/protective alleles at metabolic loci are under investigation but not firmly established.

Gene–environment interactions. The clearest example is PNPLA3 I148M acting on a background of fatty liver disease to raise HCC risk independent of fibrosis (PMID: 25278690). Diabetes/hyperinsulinemia interacts with hepatic oncogenic signaling (insulin/IGF-1 → PI3K/AKT/mTOR and RAS/MAPK), amplifying the Warburg effect and chronic inflammation (PMID: 42364319). CHB–MAFLD comorbidity has dual, dose-dependent effects on hepatocarcinogenesis (PMID: 42367770).

Section 3: Phenotypes

HCC is frequently asymptomatic in early stages (detected on surveillance imaging) and produces nonspecific symptoms as it advances. Clinical presentation "extends from right upper abdominal quadrant pain and weight loss to obstructive jaundice and lethargy" (PMID: 28839428).

Phenotype	Type	HPO suggestion	Notes / frequency
Right upper quadrant / abdominal pain	Symptom	HP:0002027 (abdominal pain)	Common in symptomatic disease
Weight loss / cachexia	Constitutional	HP:0001824	Advanced disease
Fatigue / lethargy	Symptom	HP:0012378	Common
Hepatomegaly / abdominal mass	Clinical sign	HP:0002240	Palpable in large tumors
Jaundice	Sign	HP:0000952	Obstructive/advanced
Ascites	Sign	HP:0001541	Cirrhosis/portal hypertension
Elevated alpha-fetoprotein	Lab abnormality	HP:0006254 (abnormal AFP)	Diagnostic/prognostic biomarker
Portal vein thrombosis	Complication	HP:0030242	Marker of macrovascular invasion

Paraneoplastic phenotypes. Paraneoplastic syndromes (PNS) occur in **20–40% of HCC patients** and portend poor prognosis (Finding F014): "a significant proportion (20-40%) of patients with HCC develop paraneoplastic syndromes" (PMID: 35649187). In a 534-patient cohort, 22.3% were PNS-positive, with hypercalcemia (~6.3%), hypoglycemia (~5.8%), erythrocytosis (~3.9%), thrombocytosis (~3.9%), and hypercholesterolemia (~2.4%) (PMID: 34974464). PNS-positivity is an independent prognostic factor (PMID: 24480222).

Age of onset / severity / progression: adult- to late-onset (typically >50 years); severity variable but often severe given the cirrhotic background; progression typically progressive without treatment. **Quality of life** is affected by the underlying cirrhosis (ascites, fatigue, portal hypertensive symptoms — including lower urinary tract symptoms, PMID: 24798455) as well as tumor burden.

Section 4: Genetic / Molecular Information

Core somatic drivers (Finding F002). Large-scale genome sequencing has defined a compact set of initiating drivers: "Large-scale HCC genome sequencing analyses have identified core drivers (TERT, TP53, and CTNNB1/AXIN1) as initial molecular events" (PMID: 33958712). Nearly half of HCC patients carry oncogenic driver mutations such as TP53, CTNNB1, or TERT (PMID: 41699549).

Gene (HGNC)	Alteration	Pathway / consequence	Origin
TERT	Promoter mutation (earliest/most frequent)	Telomerase reactivation, cellular immortalization	Somatic
TP53	Missense/nonsense/ deletion	Loss of tumor-suppressor / p53 pathway	Somatic (aflatoxin → R249S hotspot)
CTNNB1	Activating missense	Wnt/β-catenin hyperactivation	Somatic
AXIN1	Loss of function	Wnt/β-catenin (negative regulator loss)	Somatic
ARID1A	Loss of function	Chromatin remodeling	Somatic
PNPLA3 (I148M)	Germline risk variant	Hepatic lipid metabolism	Germline
TERT, TM6SF2, MBOAT7	Germline susceptibility loci	Senescence / lipid metabolism	Germline

Variant types/classes: missense, nonsense, frameshift, splice-site, and structural/chromosomal alterations; the TERT lesion is a non-coding promoter point mutation. Somatic drivers are documented in COSMIC/TCGA/ICGC; germline risk variants in GWAS Catalog/gnomAD. In liquid biopsy, CTNNB1 and ARID1A were the most frequently mutated genes in baseline ctDNA (25%), followed by SF3B1 (20%) and TERT (18%) (PMID: 40596669). Concomitant TERT+TP53+CTNNB1 co-mutation within a single clone can occur (PMID: 37968991); single-gene mutations serve as diagnostic/prognostic/predictive biomarkers (PMID: 40765562).

Functional consequences: TERT = gain of telomerase function; CTNNB1 = gain-of-function/ constitutive Wnt signaling; TP53/AXIN1/ARID1A = loss of function.

Epigenetic information (Finding F015). Four interconnected epigenetic layers operate in HCC: (1) "global DNA hypomethylation of oncogenes and hypermethylation of tumor suppressors" (PMID: 40057667); (2) aberrant histone modifications; (3) genome-wide chromatin loop rearrangement; (4) non-coding RNA regulation. Specific examples: **SFRP5** promoter hypermethylation silences a Wnt antagonist and constitutively activates Wnt/β-catenin (reversible by the demethylating agent 5-Aza) (PMID: 40814770); **PAX6** promoter

hypermethylation promotes growth/metastasis via CDH1/THBS1 (PMID: 39614377); methylation-silencing of the **C14MC (miR-379/miR-656) cluster** removes tumor-suppressor miRNAs (PMID: 42286554).

Chromosomal abnormalities: recurrent copy-number alterations and chromosomal instability accompany the point-mutation drivers; 8q24.21 (near MYC) is a germline risk locus (PMID: 42357869).

Section 5: Environmental Information

Environmental factors / toxins: Aflatoxin B1 (a mycotoxin contaminating stored grains/nuts, CHEBI:2504) is a classic hepatocarcinogen causing the TP53 R249S signature. Tobacco smoke is an established risk factor (PMID: 28839428).

Lifestyle factors: heavy **alcohol** (ethanol, CHEBI:16236) consumption (alcoholic liver disease → cirrhosis → HCC); diet/obesity driving NAFLD/NASH; physical inactivity and diabetes. Coffee is protective (Section 2, F011).

Infectious agents: the two dominant infectious causes are **hepatitis B virus (HBV; NCBI:txid10407)** and **hepatitis C virus (HCV; NCBI:txid11103)**. Chronic HBV/HCV cause a majority of HCC globally through chronic inflammation, fibrosis, and (for HBV) direct integration/HBx oncogenic effects. Perinatal HBV transmission causes >85% chronic carriage if untreated (PMID: 28870397); transfusion-associated HCV remains a concern in vulnerable groups (PMID: 42488322).

Section 6: Mechanism / Pathophysiology

Molecular pathways (Finding F002). HCC converges on a defined set of oncogenic signaling cascades: "the Wnt/β-catenin, TGF-β, PI3K/AKT/mTOR, MAPK/ERK, HGF/c-MET, Notch and Hippo-YAP/TAZ pathways are known to contribute to promoting aggressive HCC behaviour" (PMID: 41476776). c-MYC is a central oncogenic transcription factor integrating these pathways and metabolic reprogramming (PMID: 40473083); miRNAs shape these same pathways (PMID: 40943288). Suggested GO terms: GO:0016055 (Wnt signaling pathway), GO:0038083 (PI3K signaling), GO:0007179 (TGF-β receptor signaling).

Cellular processes: dysregulated proliferation, evasion of apoptosis, replicative immortality (TERT), chronic inflammation, and impaired autophagy/senescence. GO suggestions: GO:0008283 (cell population proliferation), GO:0006915 (apoptotic process), GO:0006954 (inflammatory response).

Metabolic reprogramming (Finding F012). A Warburg-like aerobic glycolysis and altered lipid metabolism are hallmarks. The fatty-acid receptor **CD36** is overexpressed in HCC and drives growth via "mTOR-mediated oncogenic glycolysis via activation of Src/PI3K/AKT signaling axis" (PMID: 33771982). HBV infection dysregulates aerobic glycolysis/lipid metabolism (Glut1 upregulation, glucose influx, lactate secretion — "a classic metabolic signature also observed in cancer cells") (PMID: 28768434).

Immune involvement (Finding F008). HCC harbors an immunosuppressive tumor microenvironment (TME) enriched for **regulatory T cells and M0/M2 macrophages** with upregulated checkpoints (PD-1, CTLA-4, PD-L1) (PMID: 42470438). Early/polyclonal intrahepatic recurrence is "associated with early recurrence, high phenotypic plasticity and a regulatory T cell enriched immunosuppressive microenvironment" (PMID: 42481381). AID–OSMR–STAT3 signaling remodels the immune microenvironment (PMID: 42462445). CL suggestions: CL:0000815 (regulatory T cell), CL:0000235 (macrophage), CL:0000182 (hepatocyte).

Tissue damage mechanisms: chronic inflammation → oxidative stress → fibrosis/cirrhosis → dysplasia → carcinoma. HBx transgenic models show carcinogenesis "accompanied by the activation of β-catenin and Jun N-terminal kinase (JNK) signaling pathways as well as the production of reactive oxygen species" (PMID: 28874700). NF-κB signaling links hepatitis to HCC (PMID: 30723284).

Sex dimorphism (Finding F013). HCC is strongly male-predominant. Mechanistically, "the androgen/androgen receptor (AR) accelerate cell proliferation and virus infection, especially during the initial stage of HCC, while estrogen/estrogen receptor (ER) function in an opposite way to induce cell apoptosis and immune responses" (PMID: 36563929). Murine models link male predisposition to cytokine-mediated "liver-gender disruption" (PMID: 18089782).

Causal chain (upstream → downstream)

```
Chronic insult (HBV/HCV/alcohol/NASH/aflatoxin)
        |
        ▼
Chronic inflammation + oxidative stress
        |
        ▼
Fibrosis ──► Cirrhosis (present in 80–90%)
        |
        ▼
Somatic drivers accumulate: TERT (immortalization)
   + TP53 (loss of checkpoint) + CTNNB1/AXIN1 (Wnt ON)
        |
        ▼
Pathway hyperactivation: Wnt/β-catenin, PI3K/AKT/mTOR,
   MAPK/ERK, c-MET, Hippo-YAP; metabolic reprogramming (CD36→glycolysis)
        |
        ▼
Immunosuppressive TME (Tregs, M2 macrophages, PD-L1)
        |
        ▼
Dysplastic nodule ──► Hepatocellular carcinoma ──► vascular invasion / metastasis
```

Section 7: Anatomical Structures Affected

Organ level: Primary organ = **liver** (UBERON:0002107); tumor arises from hepatocytes. Secondary involvement: **portal vein** (macrovascular invasion, UBERON:0002017), regional lymph nodes, lungs (most common extrahepatic metastatic site), bone, and adrenal glands. Body system: **digestive/hepatobiliary system** (UBERON:0002423, hepatobiliary system).

Tissue / cell level: malignant transformation of **hepatocytes** (CL:0000182) — parenchymal epithelial cells of the liver. The cholangiocyte-phenotype (CK19+) subtype carries poorer prognosis (PMID: 42400611). Non-parenchymal cells (Kupffer cells/macrophages, hepatic stellate cells driving fibrosis, endothelial cells) participate in the TME.

Subcellular level: nucleus (TERT/TP53/CTNNB1 nuclear signaling; GO:0005634), mitochondria (metabolic reprogramming; GO:0005739), and plasma membrane receptors (CD36, c-MET; GO:0005886).

Localization / lateralization: HCC occurs within the liver parenchyma (often the larger right lobe); may be unifocal, multifocal, or infiltrative. Multifocality can reflect intrahepatic metastasis or multicentric occurrence.

Section 8: Temporal Development

Onset: Typically **adult-to-geriatric onset** (usually >50 years), developing insidiously over years-to-decades of chronic liver disease. Onset is chronic/insidious; the tumor is often clinically silent until advanced. Early-onset HCC (<50 y) is part of the broader rise in early-onset GI cancers (PMID: 42295754).

Progression / staging (Finding F009). Staged by the **Barcelona Clinic Liver Cancer (BCLC)** system integrating tumor burden, liver function, and performance status (PMID: 28839428): very early/early (0/A), intermediate (B), advanced (C, with macrovascular invasion/ extrahepatic spread), and terminal (D). Progression rate is variable; disease course is progressive without treatment. After curative treatment, **recurrence is common** and follows distinct clonal modes (early polyclonal vs late) (PMID: 42481381).

Patterns: Remission is treatment-induced (curative resection/ablation/transplant, or sustained response to systemic therapy — durable complete responses are now reported with SIRT + targeted + immunotherapy, PMID: 42022453). Critical intervention window: detecting HCC at early BCLC 0/A stage enables curative therapy — the rationale for surveillance.

Section 9: Inheritance and Population

Epidemiology. HCC is the sixth most common cancer and third leading cause of cancer mortality worldwide (PMID: 35782375). Incidence is highest in East Asia and sub-Saharan Africa (HBV- and aflatoxin-endemic regions); in Western countries NASH-related HCC is rising while viral HCC declines (PMID: 31347138; PMID: 36139633).

Inheritance. HCC is **not a Mendelian disease**; it is a somatically driven cancer with **polygenic/multifactorial germline susceptibility**. GWAS identified 15 risk loci (PMID: 42357869); PNPLA3/TM6SF2/MBOAT7/TERT contribute inherited risk (PMID: 41699549). Classical Mendelian concepts (penetrance, anticipation, carrier frequency) do not directly apply.

Demographics. Strong **male predominance (~2–4:1)** with a sex-hormone mechanistic basis (Section 6, F013). Ethnicity affects prevalence and outcomes: non-Caucasian patients often have poorer survival (PMID: 37344125). Age distribution skews to older adults, with a rising early-onset segment.

Section 10: Diagnostics

Noninvasive imaging diagnosis (Finding F007). Uniquely among solid tumors, HCC can be diagnosed **without biopsy** in at-risk cirrhotic patients using LI-RADS criteria on multiphase CT or gadoxetic-acid MRI: arterial-phase hyperenhancement, non-peripheral "washout," and enhancing capsule. "For LR-5 in identifying HCC, sensitivity was 79-83%, specificity was 91-97%, and accuracy was 89-92%" (PMID: 38951191). MRI outperforms CT in sensitivity (89.3% vs 78.9% for APASL criteria) (PMID: 40487794). Contrast-enhanced ultrasound (CEUS) adds high specificity (100%) for inconclusive small nodules (PMID: 40055232).

Serum biomarkers. Alpha-fetoprotein (AFP) and **PIVKA-II (DCP)** aid diagnosis and risk stratification (PMID: 40293522). LOINC: AFP 1834-1. Emerging biomarkers: **methylated SEPT9** outperformed AFP (AUROC 0.79 vs 0.71; P=0.002) and, combined with AFP, recovered 78% of AFP-missed cases (PMID: 42390849); the **GAAD algorithm** (gender/age/AFP/PIVKA-II) and liquid-biopsy ctDNA/cfDNA fragmentomics are advancing (PMID: 42312979; PMID: 42353299).

Pathology / IHC. When biopsy is needed, diagnosis integrates morphology with immunohistochemistry (glypican-3, HSP70, glutamine synthetase; β-catenin/GS for Wnt-activated tumors) and can be supported by driver-mutation detection (TERT/CTNNB1/TP53) (PMID: 40276913). **Differential diagnosis:** dysplastic nodule, hepatocellular adenoma, intrahepatic cholangiocarcinoma, cHCC-CCA (PMID: 42272781), histiocytic sarcoma (PMID: 42405293), and benign inflammatory mimics (e.g., xanthogranulomatous inflammation) (PMID: 41909198).

Diagnostic pitfalls: LR-M lesions require biopsy (only ~46% are HCC) (PMID: 40293522); benign mimics can simulate LR-5 kinetics in fibrotic livers (PMID: 41909198).

Section 11: Outcome / Prognosis

Survival. Prognosis is stage- and liver-function-dependent (Finding F005). Advanced disease with best current systemic therapy achieves median OS approaching ~19–24 months (IMbrave150 5-year OS 19%) (PMID: 42022453). Early-stage disease treated curatively achieves substantially better long-term survival, though recurrence is frequent.

Prognostic factors (Finding F005). AFP is an independent prognostic factor after hepatectomy — DFS HR 1.391 (95% CI 1.193–1.623) and OS HR 1.267 (95% CI 1.080–1.486); the combined AFP–FIB-4 score improves prediction (DFS HR 1.404; OS HR 1.378) (PMID: 42323530). **Microvascular invasion (MVI)** is "a critical prognostic risk factor" (PMID: 42480815). **BCLC stage** and **ALBI grade** (liver function) are key (PMID: 42449617). Molecular/liquid-biopsy prognostics: ctDNA CTNNB1/TP53/ARID1A/KEAP1 mutations predict poor OS pre-TACE (PMID: 40596669); 5mC gene signatures (PMID: 42304060); radiomics/machine-learning models (PMID: 42413246; PMID: 42344442).

Complications: hepatic decompensation, portal vein thrombosis, variceal bleeding, and paraneoplastic syndromes (20–40%, poor prognosis; F014) (PMID: 35649187). Within PNS, erythrocytosis and thrombocytosis were independent predictors of *better* prognosis while hypoglycemia/hypercalcemia predicted worse outcome (PMID: 34974464).

Section 12: Treatment

Stage-based (BCLC) framework (Finding F009).

BCLC stage	Standard treatment	MAXO suggestion
Very early / early (0/A)	Resection, local ablation (RFA/MWA/PEI/cryo), liver transplantation (Milan criteria)	MAXO:0001175 (surgical procedure), MAXO:0000004 (radiofrequency ablation)
Intermediate (B)	TACE, radioembolization (TARE/SIRT)	MAXO:0000527 (chemoembolization)
Advanced (C)	Systemic immunotherapy-based combinations	MAXO:0000765 (immunotherapy)
Terminal (D)	Best supportive care	MAXO:0000922 (palliative care)

Curative options. Liver resection, ablation, and transplantation; transplant is restricted to **Milan criteria** ("one tumor ≤ 5 cm, or up to three tumors no larger than 3 cm, along with the absence of gross vascular invasion or extrahepatic spread") (PMID: 34696292). Downstaging into Milan criteria enables acceptable post-transplant outcomes (PMID: 36813012). For recurrence within Milan criteria after resection, RR/RFA and TACE achieve comparable outcomes except for late recurrence, where RR/RFA is preferred (PMID: 25933127; PMID: 32355732).

First-line systemic therapy is now immunotherapy-based (Finding F003). "Current international guidelines recommend atezolizumab plus bevacizumab (A+T) or durvalumab plus tremelimumab (Dur/Tre) as first-line regimens for unresectable HCC. In the 5-year update of IMbrave150, A+T achieved an objective response rate (ORR) of 30% and a 5-year overall survival (OS) rate of 19%" (PMID: 42022453). This superseded single-agent TKIs (sorafenib/lenvatinib, median OS ~10–14 months) (PMID: 36497349). Network meta-analyses support atezolizumab+bevacizumab superiority over lenvatinib (HR 0.59) (PMID: 34239810; PMID: 33638735).

Mechanistic rationale for anti-VEGF + ICI (Finding F008): "anti-VEGF therapy induces vascular normalization, enhances immune cell infiltration, and reduces immunosuppression within the TME, thereby converting immunologically 'cold' tumors into 'hot' tumors that are more responsive to checkpoint blockade" (PMID: 42467392).

Second-line / other options: regorafenib, cabozantinib, ramucirumab, nivolumab+ipilimumab, pembrolizumab (PMID: 40704000; PMID: 34953051). **Emerging/experimental:** c-MYC-targeted approaches (PMID: 40473083); RNA therapeutics such as MTL-CEBPA saRNA (PMID: 29511346); miRNA-based strategies (PMID: 40943288); demethylating agents (5-Aza) targeting epigenetic silencing (PMID: 40814770); plant-derived/curcumin adjuncts under preclinical study (PMID: 41044771; PMID: 41751435).

Section 13: Prevention

Primary prevention (Finding F004). HBV vaccination is proven primary prevention: "hepatitis B vaccination can protect them from HCC, as has been demonstrated in Taiwan and other countries" (PMID: 26651252). Perinatal prevention: "This risk is reduced by 90% with HBV vaccine given along with hepatitis B immune globulin (HBIG) starting at birth" (PMID: 28870397). (Note: age-period-cohort analyses caution that secular time-trends also contributed to observed pediatric HCC declines in Taiwan — PMID: 25660961.) Antiviral therapy

(nucleos(t)ide analogues for HBV; direct-acting antivirals achieving SVR for HCV) reduces HCC incidence (PMID: 25241970). Other primary prevention: aflatoxin reduction, alcohol moderation, metabolic risk-factor control; coffee consumption and (in diabetics) metformin are protective.

Secondary prevention / surveillance (Finding F004). "Current guidelines recommend semiannual surveillance with ultrasound and α-fetoprotein, but this strategy has suboptimal sensitivity" (PMID: 42017860); fewer than 1 in 4 cirrhotic patients receive adequate surveillance. Risk-stratified surveillance and emerging biomarkers (methylated SEPT9, GAAD, liver stiffness) aim to improve early detection (PMID: 41921193; PMID: 42390849; PMID: 42394831).

Tertiary prevention: management of cirrhosis complications and post-treatment recurrence surveillance. **Genetic counseling** is limited given the polygenic nature but PNPLA3 genotyping may inform metabolic-HCC risk stratification.

Section 14: Other Species / Natural Disease

- **Taxonomy:** HCC occurs naturally across mammals. *Homo sapiens* (NCBI:txid9606); animal models include *Mus musculus* (NCBI:txid10090), *Rattus norvegicus* (NCBI:txid10116), and the **woodchuck** *Marmota monax*.
- **Natural disease model:** The **woodchuck hepatitis virus (WHV)** produces an HBV-like chronic hepatitis and near-universal HCC, serving as a key natural model of virally driven hepatocarcinogenesis.
- **Orthologous genes:** Tp53, Ctnnb1, Tert are conserved across mouse/rat/human, enabling cross-species mechanistic study.
- **Comparative biology:** HCC develops in companion animals (dogs) and other species; core inflammation → fibrosis → carcinoma mechanisms and oncogenic pathway conservation permit translational study (Alliance of Genome Resources for orthology). *Not zoonotic* — HCC itself is non-transmissible, though its causal viruses have species-specific counterparts.

Section 15: Model Organisms

Model systems (Finding F006). Rodent models dominate HCC research:

Model	Type	Mechanism / use
DEN (diethylnitrosamine)-treated mice/rats	Chemical carcinogenesis	Genotoxic HCC induction; C57BL/6 background
c-Myc transgenic	Oncogene-driven	Proliferation-driven tumorigenesis
HBx transgenic (e.g., C1485T)	Viral oncogene	β-catenin/JNK/ROS-driven; enhanced DEN susceptibility (PMID: 28874700)
HCV-transgenic + PML deficiency	Viral + tumor-suppressor loss	Spontaneous liver tumors (PMID: 31144474)
TAK1 knockout; Vps33b conditional KO	Tumor-suppressor loss	Inflammation-driven HCC (PMID: 29729199)
NASH/diet-induced models	Metabolic etiology	Recapitulate MASLD-HCC
Woodchuck (WHV)	Natural viral model	HBV-like chronic infection → HCC

Genetic model types: knockout, conditional, transgenic, and humanized models. Etiology-oriented subtyping compares murine tumors to TCGA etiologic subsets (PMID: 30967480).

Limitations: "Murine liver tumors often fail to recapitulate the complexity of human hepatocellular carcinoma (HCC), which might explain the difficulty to translate preclinical mouse studies into clinical science" (PMID: 30967480). Human cell lines (HepG2, Huh7, Hep3B), patient-derived organoids, and iPSC systems complement in vivo models. Resources: MGI, RGD, Cellosaurus.

Mechanistic Model / Interpretation

HCC is best understood as the endpoint of a **chronic-injury → inflammation → fibrosis/cirrhosis → dysplasia → carcinoma** sequence, on which a compact set of somatic drivers act. The upstream trigger is etiology-specific (HBV, HCV, alcohol, NASH, aflatoxin) but converges on a shared downstream program: sustained hepatocyte injury and regeneration create a mutagenic, inflammatory, and immunosuppressive niche in which **TERT-promoter mutation (immortalization)**, **TP53 loss (checkpoint failure)**, and **CTNNB1/AXIN1 alterations (Wnt/β-catenin activation)** initiate malignancy. These drivers hyperactivate a defined pathway network (Wnt, PI3K/AKT/mTOR, MAPK/ERK, c-MET, Hippo-YAP), which — reinforced by

epigenetic dysregulation and metabolic reprogramming (CD36→Warburg glycolysis) — produces a proliferative, invasive tumor embedded in a Treg/M2-macrophage-rich, checkpoint-high microenvironment.

This model explains the therapeutic landscape: because the tumor is immunosuppressed and highly vascular, **anti-VEGF vascular normalization + checkpoint blockade** is synergistic and now first-line; because early tumors are curable, **surveillance + noninvasive imaging diagnosis** is the central strategy; and because HBV is a dominant upstream cause, **vaccination is the most effective primary prevention**. Sex-hormone signaling (AR pro-tumor, ER protective) accounts for the male predominance, and germline modifiers (PNPLA3, and 15 GWAS loci) tune individual risk on the environmental background.

Evidence Base

Finding	Key PMIDs	Evidence type	Support
F001 Burden & etiology	35782375, 31347138, 32319693	Human review/epi	Strong
F002 Core drivers & pathways	33958712, 41699549, 42357869, 41476776	Genomics/GWAS	Strong
F003 Immunotherapy first-line	42022453, 40704000, 34239810, 33638735	RCT/meta-analysis	Strong
F004 HBV vaccine & surveillance	26651252, 42017860, 28870397	Human/guidelines	Strong
F005 Prognostic factors	42323530, 42480815, 42449617	Cohort	Strong
F006 Animal models	30967480, 28874700, 31144474	Model organism	Moderate
F007 Noninvasive imaging dx	38951191, 40487794, 40055232	Diagnostic accuracy	Strong
F008 Immunosuppressive TME	42467392, 42481381, 42470438	Human/multi-omics	Strong
F009 Stage-based treatment	34696292, 36813012, 33780876	Guidelines	Strong
F010 PNPLA3 / non-cirrhotic NAFLD-HCC	25278690	Human review	Moderate
F011 Coffee protective	28490552, 28846640, 32830818	Dose-response meta-analysis	Strong
F012 Metabolic reprogramming	33771982, 28768434	In vitro/mechanistic	Moderate
F013 Sex dimorphism	36563929, 18089782	Human/mouse	Moderate
F014 Paraneoplastic syndromes	35649187, 24480222, 34974464	Cohort/review	Moderate
F015 Epigenetic dysregulation	40057667, 40814770, 42286554, 39614377	Mechanistic	Strong

Selected landmark evidence. The genomic landscape defining TERT/TP53/CTNNB1 as initiating events (PMID: 33958712) and the multi-ancestry GWAS of 15 risk loci (PMID: 42357869) anchor the genetics sections. The IMbrave150-based practice change (PMID: 42022453) and the TME/anti-VEGF+ICI mechanism (PMID: 42467392) together explain modern treatment. Coffee dose-response meta-analyses (PMID: 28490552; PMID: 28846640) provide the strongest protective-factor evidence.

Limitations and Knowledge Gaps

1. **Etiologic drift not fully quantified.** The transition from viral to metabolic (MASLD/MASH) HCC is documented directionally but exact future incidence projections remain uncertain (PMID: 32319693).
2. **Non-cirrhotic HCC.** NAFLD-HCC arising in non-cirrhotic livers challenges surveillance strategies keyed to cirrhosis (PMID: 25278690); no validated surveillance protocol exists for this population.
3. **Surveillance sensitivity.** Ultrasound ± AFP has suboptimal sensitivity and poor real-world uptake; emerging biomarkers (SEPT9, GAAD, ctDNA) need prospective validation and survival-benefit confirmation (PMID: 42017860; PMID: 42390849).
4. **Model fidelity.** Murine models incompletely recapitulate human tumor complexity, limiting translation (PMID: 30967480).
5. **Predictive biomarkers for immunotherapy.** No robust biomarker reliably predicts response to atezolizumab+bevacizumab / durvalumab+tremelimumab; ~70% do not achieve objective response.
6. **No dedicated experimental data.** This report is a literature synthesis; no primary dataset was analyzed. Findings F001–F015 rest on published human, model-organism, and in vitro evidence, and some ontology IDs (MONDO/HPO/GO/CL/UBERON/CHEBI/MAXO) are suggested and should be verified against current ontology releases.

Proposed Follow-up Experiments / Actions

1. **Validate multi-analyte early-detection panels** (methylated SEPT9 + AFP + PIVKA-II/GAAD + cfDNA fragmentomics) prospectively for survival benefit, especially in non-cirrhotic MASLD-HCC.
2. **Develop and validate risk-stratified surveillance models** incorporating PNPLA3 genotype, FIB-4/liver stiffness, and etiology to tailor surveillance intensity (PMID: 41921193).
3. **Immunotherapy response biomarkers:** correlate TME composition (Treg/M2 density, PD-L1, Wnt/β-catenin activation status) with response to anti-VEGF+ICI to enable patient selection.
4. **Test epigenetic combination therapy:** demethylating agents (5-Aza) restoring SFRP5/C14MC + checkpoint blockade in preclinical models.
5. **Chemoprevention trials:** prospective evaluation of metformin (in diabetics) and coffee/caffeine as adjunct prevention in high-risk cirrhosis.
6. **Sex-hormone axis intervention:** explore AR-targeting strategies given the androgen-driven early carcinogenesis mechanism.
7. **Improve models:** develop humanized/organoid systems that better capture the immunosuppressive TME for translational immunotherapy testing.

Report compiled from 15 confirmed findings and 92 reviewed papers. Evidence types span human clinical/epidemiological, model-organism, in vitro, and computational sources as annotated. Ontology suggestions (MONDO, HPO, GO, CL, UBERON, CHEBI, MAXO) are provided for knowledge-base curation and should be verified against current ontology releases.
