Supplementary Table 1 | Demographic and clinicopathological characteristics of individuals in training cohort.

Disease type	Age (years)	Gender (n, %)		Stage (n, %)	
	(Median [MIN, MAX])	Male	Female	Early stage	Late stage
Malignant tumor	56.5 [36, 84]	93 (46.5%)	107 (53.5%)	101 (50.5%)	99 (49.5%)
Non-small cell lung cancer	63.0 [37, 77]	28 (56.0%)	22 (44.0%)	22 (44.0%)	28 (56.0%)
Hepatocellular carcinoma	56.5 [36, 71]	39 (78.0%)	11 (22.0%)	34 (68.0%)	16 (32.0%)
Ovarian cancer	56.5 [36, 74]	0	40 (100%)	15 (37.5%)	25 (62.5%)
Colorectal cancer	62.5 [36, 84]	18 (60.0%)	12 (40.0%)	10 (33.3%)	20 (66.7%)
Breast cancer	50.5 [36, 73]	0	20 (100%)	12 (60.0%)	8 (40.0%)
Renal cell carcinoma	56.5 [42, 71]	8 (80.0%)	2 (20.0%)	8 (80.0%)	2 (20.0%)
Benign tumor	47.0 [33, 78]	11 (27.5%)	29 (72.5%)	NA	NA
Benign lung tumor	59.0 [42, 69]	5 (71.4%)	2 (28.6%)		
Benign colonic neoplasm	52.5 [45, 63]	6 (75.0%)	2 (25.0%)		
Benign ovarian tumor	54.0 [33, 78]	0	25 (100%)		
Inflammatory diseases	49.0 [25, 92]	55 (71.4%)	22 (28.5%)	NA	NA
Pneumonia	59.5 [34, 92]	12 (60.0%)	8 (40.0%)		
Inflammatory bowel disease	50.0 [30, 79]	5 (71.4%)	2 (28.6%)		
Hepatitis B	48.5 [25, 76]	38 (76.0%)	12 (24.0%)		
Healthy control	54.0 [25, 78]	51 (66.2%)	26 (33.8%)	NA	NA

Abbreviations: NA, not applicable.

Supplementary Table 2 | Demographic and clinicopathological characteristics of individuals in validation cohort.

	Age (years)	Gender (n, %)		Stage (n, %)	
	(Median [MIN, MAX])	**Male**	**Female**	**Early stage**	**Late stage**
Malignant tumor	56.5 [38, 84]	98 (49.0%)	102 (51.0%)	115 (57.5%)	85 (42.5%)
Non-small cell lung cancer	63.0 [40, 68]	30 (60.0%)	20 (40.0%)	28 (56.0%)	22 (44.0%)
Hepatocellular carcinoma	56.5 [38, 74]	41 (82.0%)	9 (18.0%)	32 (64.0%)	18 (36.0%)
Ovarian cancer	56.5 [31, 80]	0	40 (100%)	17 (42.5%)	23 (57.5%)
Colorectal cancer	63.5 [45, 77]	19 (63.3%)	11 (36.7%)	15 (50.0%)	15 (50.0%)
Breast cancer	52.5 [38, 84]	0	20 (100%)	18 (90.0%)	2 (10.0%)
Renal cell carcinoma	58.5 [46, 71]	8 (80.0%)	2 (20.0%)	5 (50.0%)	5 (50.0%)
Benign tumor	46.5 [30, 74]	11 (27.5%)	29 (72.5%)	NA	NA
Benign lung tumor	56.5 [38, 71]	4 (57.1%)	3 (42.9%)		
Benign colonic neoplasm	56.5 [41, 74]	7 (87.5%)	1 (12.5%)		
Benign ovarian tumor	56.5 [30, 70]	0	25 (100%)		
Inflammation	50.0 [22, 84]	54 (70.1%)	23 (29.9%)	NA	NA
Pneumonia	61.5 [22, 76]	14 (70.0%)	6 (30.0%)		
Inflammatory bowel disease	50.0 [38, 84]	5 (71.4%)	2 (28.6%)		
Hepatitis B	49.0 [29, 72]	35 (70.0%)	15 (30.0%)		
Healthy control	54.5 [26, 80]	47 (61.0%)	30 (39.0%)	NA	NA

Abbreviations: NA, not applicable.

Supplementary Table 3 | Demographic and clinicopathological characteristics of 12 HCC patients undergoing treatment with TACE.

Case	Age (years)	Gender	BCLC stage	No. of treatment sessions	Response
HCC 1	57	Male	B	2	CR
HCC 2	64	Male	B	3	PR
HCC 3	66	Female	A	2	PR
HCC 4	53	Male	A	2	SD
HCC 5	68	Male	A	1	SD
HCC 6	68	Female	A	2	SD
HCC 7	44	Male	B	1	SD
HCC 8	50	Male	A	2	SD
HCC 9	46	Male	C	2	SD
HCC 10	57	Male	B	1	PD
HCC 11	54	Female	B	1	PD
HCC 12	59	Male	B	1	PD

Abbreviations: TACE, transcatheter arterial chemoembolization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Supplementary Table 4 | Summary of capture-based mtDNA sequencing data.

Subjects	No. of patients	Specimen types	No. of samples	Average number of total reads	Average mtDNA depth	Average Q30	Average mtDNA mapping rate
HCC	100*	Plasma	100	14,494,509	3,549	94.07%	27.05%
		Fresh tumor tissue	40	9,701,715	5,938	93.23%	63.70%
		Adjacent non-tumor	40	8,962,550	5,324	93.08%	61.03%
		PBMC	40	9,264,812	4,234	92.16%	52.55%
HCC with TACE	12**	Plasma	24	14,253,905	5,306	94.01%	29.71%
NSCLC	100	Plasma	100	11,259,595	3,729	93.19%	33.73%
CRC	60	Plasma	60	11,241,468	3,660	94.37%	34.36%
OV	80	Plasma	80	13,274,750	4,213	93.32%	27.13%
BC	40	Plasma	40	11,701,715	3,745	92.93%	30.04%
RCC	20	Plasma	20	12,246,006	4,063	92.82%	31.06%
BLT	14	Plasma	14	13,500,546	4,639	92.48%	32.90%
BCN	16	Plasma	16	14,471,723	5,379	92.85%	31.56%
BOT	50	Plasma	50	13,274,750	4,218	93.45%	32.67%
HB	100	Plasma	100	13,962,550	4,489	92.11%	29.35%
PN	40	Plasma	40	11,264,812	3,900	93.78%	31.01%
IBD	14	Plasma	14	11,241,468	3,800	92.56%	29.82%
HC	154	Plasma	154	12,488,021	4,121	93.84%	29.34%

Abbreviations: HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; OV, ovarian cancer; BC, breast cancer; RCC, renal cell carcinoma; BLT, benign lung tumors; BCN, benign colonic neoplasm; BOT, benign ovarian tumor; HB, hepatitis B; PN, pneumonia; IBD, inflammatory bowel disease. HC, healthy control. *Fresh tumor tissue, adjacent non-tumor and PBMC were collected from 40 of 100 patients with HCC. **Blood was collected 1 day before and 6 to 9 weeks after first TACE treatment in 12 patients with HCC.

Supplementary Table 5 | Summary of whole genome sequencing data.

Subjects	No. of patients	Specimen types	No. of samples	Average number of total reads	Average nDNA (mtDNA) depth	Average mtDNA coverage	Average Q30
HCC	30	Plasma	30	152,987,154	15 (78.91)	100%	93.25%
HCC with TACE	12*	Plasma	24	141,166,884	15 (65.25)	100%	92.42%
BOT	30	Plasma	30	124,186,415	15 (59.84)	100%	92.74%
HB	30	Plasma	30	132,178,567	15 (61.19)	100%	92.98%
HC	30	Plasma	30	101,357,859	15 (71.91)	100%	92.41%

Abbreviations: HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; BOT, benign ovarian tumor; HB, hepatitis B; HC, healthy control. *Blood was collected 1 day before and 6 to 9 weeks after the first TACE treatment in 12 patients with HCC.

Supplementary Table 6 | Summary of tumor-derived somatic mutations and germline variants in 40 patients with hepatocellular carcinoma.

	Tumor-derived somatic mutations (n = 138)	**Germline variants (n = 1192)**
Substitution types (n, %)		
$T_H > C_H$	24 (17.39%)	390 (32.72%)
$T_L > C_L$	30 (21.74%)	284 (23.82%)
$C_H > T_H$	46 (33.33%)	192 (16.11%)
$C_L > T_L$	21 (15.22%)	262 (21.98%)
Other	17 (12.32%)	64 (5.37%)
Heteroplasmy level in plasma (Median [MIN, MAX])	0.02465 (0.0104-0.3035)	0.98250 (0.9607-1.0000)
Heteroplasmy level in tumor tissue (Median [MIN, MAX])	0.02430 (0.0108-0.3029)	0.99030 (0.9896-1.0000)

Supplementary Table 7 | MEFI performance for cancer detection in validation cohort.

Cohort	**No. of Cancer**	**No. of Control**	**AUC (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
MT *vs*. HC	200	77	0.9735 (0.9562-0.9908)	91.00% (86.22%-94.23%)	91.94% (82.47%-96.51%)
MT *vs*. BT	200	40	0.9423 (0.9092-0.9754)	78.33% (70.15%-84.76%)	97.50% (87.15%-99.87%)
MT *vs*. INF	200	77	0.9498 (0.9200-0.9796)	88.46% (81.83%-92.88%)	93.51% (85.68%-97.19%)

Abbreviations: MT, malignant tumor; HC, healthy control; BT, benign tumors; INF, inflammation; AUC, area under the curve.