**Supplementary Table 3.** Clinical performance of Elecsys assays, AFP, AFP-L3, and PIVKA-II, and algorithmic scores GAAD (Cobas) and GALAD (Cobas), with or without ultrasound, for the detection of early-stage HCC

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Sensitivity** | **Specificity** | **PPV, 1% prevalence** | **PPV, 2% prevalence** | **PPV, 3% prevalence** | **PPV, 4% prevalence** | **PPV, 5% prevalence** | **NPV, 1% prevalence** | **NPV, 2% prevalence** | **NPV, 3% prevalence** | **NPV, 4% prevalence** | **NPV, 5% prevalence** |
| **Early-stage HCC (overall)** |
| AFP | 0.30 | 0.94 | 0.05 | 0.10 | 0.14 | 0.18 | 0.22 | 0.99 | 0.99 | 0.98 | 0.97 | 0.96 |
| AFP-L3 | 0.27 | 0.95 | 0.05 | 0.10 | 0.15 | 0.19 | 0.23 | 0.99 | 0.98 | 0.98 | 0.97 | 0.96 |
| PIVKA-II | 0.52 | 0.90 | 0.05 | 0.10 | 0.14 | 0.18 | 0.22 | 0.99 | 0.99 | 0.98 | 0.98 | 0.97 |
| GAAD | 0.58 | 0.90 | 0.06 | 0.11 | 0.16 | 0.20 | 0.24 | 1.00 | 0.99 | 0.99 | 0.98 | 0.98 |
| GALAD | 0.58 | 0.90 | 0.05 | 0.10 | 0.15 | 0.19 | 0.23 | 1.00 | 0.99 | 0.99 | 0.98 | 0.98 |
| AFP+US | 0.55 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.98 | 0.98 |
| AFP-L3+US | 0.55 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.98 | 0.98 |
| PIVKA-II+US | 0.67 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 | 0.98 |
| GAAD+US | 0.70 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 | 0.98 |
| GALAD+US | 0.70 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 | 0.98 |
| US alone | 0.42 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.98 | 0.98 | 0.97 |
| **Early-stage cirrhotic HCC** |
| AFP | 0.36 | 0.92 | 0.04 | 0.08 | 0.12 | 0.15 | 0.19 | 0.99 | 0.99 | 0.98 | 0.97 | 0.96 |
| AFP-L3 | 0.32 | 0.92 | 0.04 | 0.07 | 0.11 | 0.14 | 0.17 | 0.99 | 0.99 | 0.98 | 0.97 | 0.96 |
| PIVKA-II | 0.59 | 0.80 | 0.03 | 0.06 | 0.08 | 0.11 | 0.13 | 0.99 | 0.99 | 0.98 | 0.98 | 0.97 |
| GAAD | 0.59 | 0.83 | 0.03 | 0.07 | 0.10 | 0.13 | 0.16 | 1.00 | 0.99 | 0.99 | 0.98 | 0.97 |
| GALAD | 0.59 | 0.83 | 0.03 | 0.07 | 0.10 | 0.13 | 0.16 | 1.00 | 0.99 | 0.99 | 0.98 | 0.97 |
| AFP+US | 0.41 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.98 | 0.98 | 0.97 |
| AFP-L3+US | 0.41 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.98 | 0.98 | 0.97 |
| PIVKA-II+US | 0.64 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 | 0.98 |
| GAAD+US | 0.64 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 | 0.98 |
| GALAD+US | 0.64 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 | 0.98 |
| US alone | 0.27 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.98 | 0.97 | 0.96 |
| **Early-stage non-cirrhotic HCC** |
| AFP | 0.18 | 0.96 | 0.04 | 0.08 | 0.12 | 0.15 | 0.18 | 0.99 | 0.98 | 0.97 | 0.97 | 0.96 |
| AFP-L3 | 0.18 | 0.97 | 0.06 | 0.11 | 0.16 | 0.21 | 0.25 | 0.99 | 0.98 | 0.97 | 0.97 | 0.96 |
| PIVKA-II | 0.36 | 0.96 | 0.08 | 0.15 | 0.21 | 0.26 | 0.31 | 0.99 | 0.99 | 0.98 | 0.97 | 0.97 |
| GAAD | 0.55 | 0.94 | 0.08 | 0.16 | 0.22 | 0.28 | 0.32 | 1.00 | 0.99 | 0.99 | 0.98 | 0.98 |
| GALAD | 0.55 | 0.93 | 0.08 | 0.14 | 0.20 | 0.25 | 0.30 | 1.00 | 0.99 | 0.99 | 0.98 | 0.98 |
| AFP+US | 0.82 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 |
| AFP-L3+US | 0.82 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 |
| PIVKA-II+US | 0.73 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 | 0.99 |
| GAAD+US | 0.82 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 |
| GALAD+US | 0.82 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 |
| US alone | 0.73 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 | 0.99 |
| **Early-stage HCC with HBV etiology** |
| AFP | 0.27 | 0.91 | 0.03 | 0.06 | 0.09 | 0.11 | 0.14 | 0.99 | 0.98 | 0.98 | 0.97 | 0.96 |
| AFP-L3 | 0.27 | 0.92 | 0.03 | 0.07 | 0.10 | 0.12 | 0.15 | 0.99 | 0.98 | 0.98 | 0.97 | 0.96 |
| PIVKA-II | 0.41 | 0.94 | 0.06 | 0.12 | 0.16 | 0.21 | 0.25 | 0.99 | 0.99 | 0.98 | 0.97 | 0.97 |
| GAAD | 0.50 | 0.88 | 0.04 | 0.08 | 0.12 | 0.15 | 0.19 | 0.99 | 0.99 | 0.98 | 0.98 | 0.97 |
| GALAD | 0.50 | 0.88 | 0.04 | 0.08 | 0.11 | 0.15 | 0.18 | 0.99 | 0.99 | 0.98 | 0.98 | 0.97 |
| AFP+US | 0.45 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.98 | 0.98 | 0.97 |
| AFP-L3+US | 0.45 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.98 | 0.98 | 0.97 |
| PIVKA-II+US | 0.59 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.98 | 0.98 |
| GAAD+US | 0.64 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 | 0.98 |
| GALAD+US | 0.64 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 | 0.98 |
| US alone | 0.32 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.98 | 0.97 | 0.97 |
| **Early-stage HCC with HCV etiology** |
| AFP | 0.44 | 0.97 | 0.13 | 0.23 | 0.31 | 0.38 | 0.44 | 0.99 | 0.99 | 0.98 | 0.98 | 0.97 |
| AFP-L3 | 0.33 | 0.98 | 0.13 | 0.23 | 0.32 | 0.38 | 0.44 | 0.99 | 0.99 | 0.98 | 0.97 | 0.97 |
| PIVKA-II | 0.78 | 0.88 | 0.06 | 0.12 | 0.17 | 0.21 | 0.25 | 1.00 | 0.99 | 0.99 | 0.99 | 0.99 |
| GAAD | 0.78 | 0.92 | 0.09 | 0.16 | 0.23 | 0.29 | 0.34 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 |
| GALAD | 0.78 | 0.91 | 0.08 | 0.15 | 0.21 | 0.27 | 0.32 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 |
| AFP+US | 0.78 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 |
| AFP-L3+US | 0.78 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 |
| PIVKA-II+US | 0.89 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 |
| GAAD+US | 0.89 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 |
| GALAD+US | 0.89 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 |
| US alone | 0.67 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.99 | 0.99 | 0.99 | 0.98 |

AFP, α-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive fraction of α-fetoprotein; GAAD, gender (biological sex), age, AFP, PIVKA-II; GALAD, gender (biological sex), age, AFP-L3, AFP, PIVKA-II; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NPV, negative predictive value; PIVKA-II, protein induced by vitamin K absence or antagonist II; PPV, positive predictive value; US, ultrasound.