LEAD 2024
APAC HCC Expert Meeting
25-26 Oct | Hong Kong

Addressing Funding Challenges through HECON Study of Biomarker-based Screening for HCC in Thai patients with Compensated Cirrhosis

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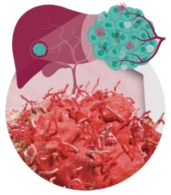
OUTline of the PRESENTATION



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Economic evaluation of biomarker-based Screening for HCC in Thai Patients with Compensated Cirrhosis

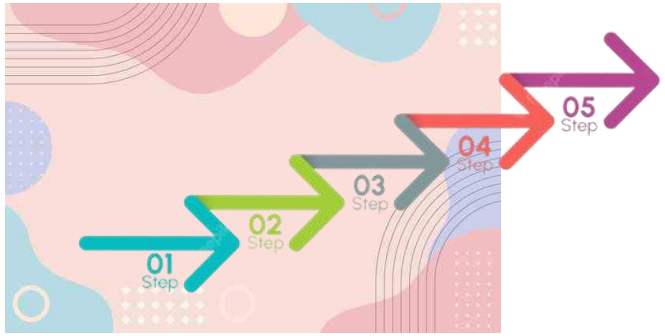
√ Current status of HCC surveillance in Thailand

Unmet needs for early detection and tools for surveillance

√ HECON study using biomarkers for HCC surveillance

√ Summary and perspective

QA



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Current Status in THAILAND

HEPATOCELLULAR CARCINOMA

Conventional and emerging tools for HCC surveillance

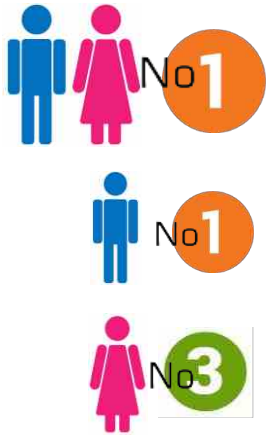
Current Situation
HCC in THAILAND

Statistics at a glance, 2022

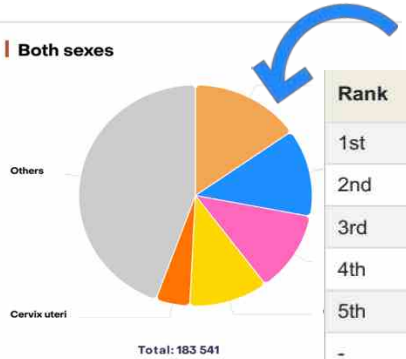
GLOBAL CANCER OBSERVATORY

Number of new cases
183 541

Number of deaths
118 829



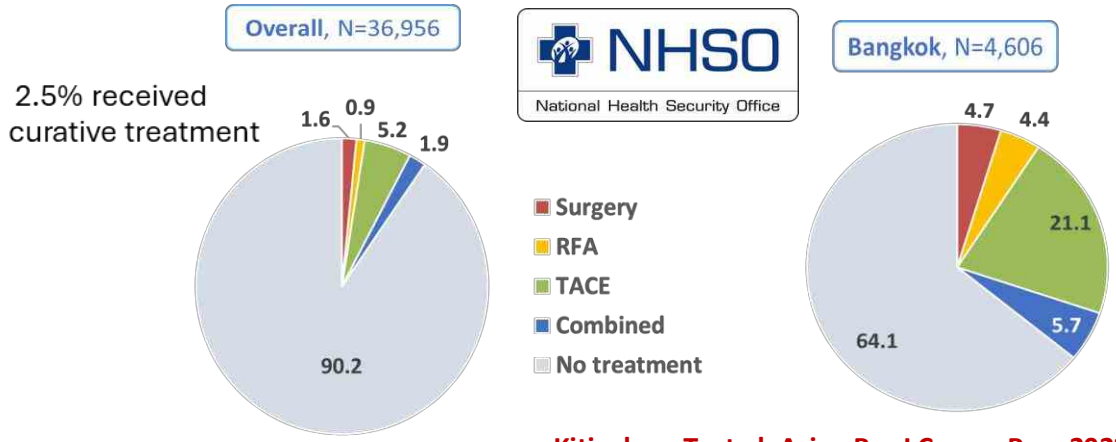
LIVER CANCERS 15.2%



Rank	Cancer site	Number of cases	Percent
1st	Liver	27 936	15.2%
2nd	Lung	23 494	12.8%
3rd	Breast	21 628	11.8%
4th	Colorectum	20 173	11.0%
5th	Cervix uteri	8 662	4.7%
-	Others	81 648	44.5%

Number of new cases in 2022, both sexes, all ages

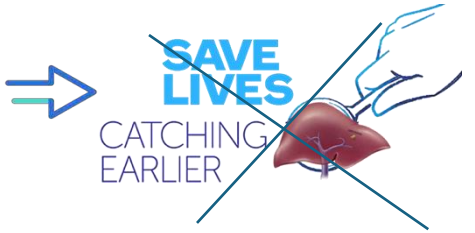
Proportion of HCC undergoing different treatments in Thailand



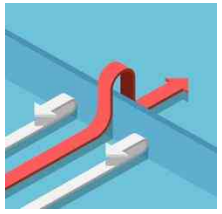
Kitiyakara T, et al. Asian Pac J Cancer Prev 2022

The surveillance programme for HCC is not well-implemented

Lack of EARLY DETECTION In resource limitations



Several BARRIERS



Inadequate HCC AWARENESS & KNOWLEDGE

REIMBURSED POLICY

Surveillance tools ?

International Guidelines

Current Recommendation

- HCC surveillance using **ultrasound (US) and alpha-fetoprotein (AFP) every 6 months is the standard of care** in high-risk populations, particularly cirrhosis

Data from Meta-analysis

- 32 studies (1990–2016, including 13,367 patients) studied the sensitivity of US ± AFP for the detection of HCC in patients with cirrhosis

Conclusions: Using US + AFP increases the sensitivity of early HCC detection in clinical practice

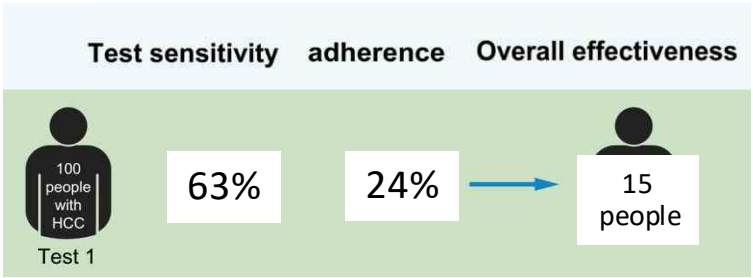
Tzartzeva K, et al. *Gastroenterology* 2018

Limitations of ultrasound-based screening

- Ultrasound has low sensitivity in early HCC, especially in obese patients with fatty liver
- Ultrasound is dependent on operator experience
- Ultrasound screening has poor adherence (e.g., barriers including the need for separate radiology appointments, cost, travel time)
- A meta-analysis showed adherence rates were 24%

Wolf E, et al. *Hepatology* 2021

Low sensitivity in MASLD



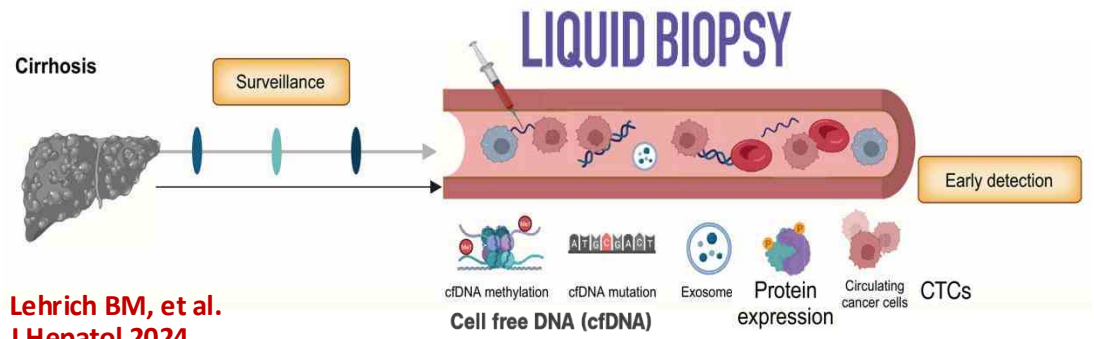
US + AFP ARE NOT ADEQUATE

Improving HCC surveillance

Moving beyond ultrasound-based screening ?

New Blood-based Biomarkers

Moving beyond ultrasound-based screening



Lehrich BM, et al.
J Hepatol 2024

NEW Tumor Markers

PIVKA-II (DCP)

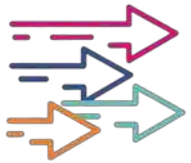
± AFP L3

protein induced by vitamin K absence-II

des-gamma carboxy-prothrombin

+ AFP

Combination Assays



Algorithm

GALAD Score

Protein markers: AFP, AFP-L3, DCP; gender; age

GAAD score

gender age AFP DCP

Development and clinical validation of a novel algorithmic score (GAAD) for detecting HCC in prospective cohort studies

Teerha Piratvisuth[1] | Jinlin Hou[2] | Tawesak Tanwandee[3] |
Thomas Berg[4] | Arndt Vogel[5] | Jörg Trojan[6] | Enrico N. De Toni[7]
Masatoshi Kudo[8] | Anja Eiblmaier[9] | Hanns-Georg Klein[10] |
Johannes Kolja Hegel[11] | Kairat Madin[12] | Konstantin Kroeniger[12] |
Ashish Sharma[13] | Henry L.Y. Chan[14]

Hepatology Communications. 2023;7:e0317.

AFP

PIVKA-II (DCP)

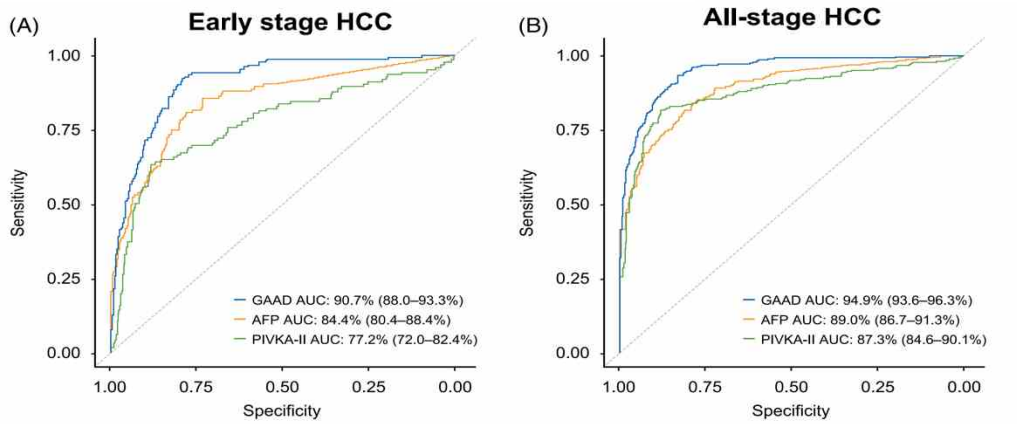
DIGITAL
Algorithm

GAAD
SCORE

GAAD = **G**ender, **A**ge, **A**FP, **D**CP (PIVKA-II)

Aid in diagnosis for **early-stage** HCC

GAAD cut-off score 2.57 (Range 0-10)



algorithm development
≈ validation study

AUC for differentiation between early-stage HCC and CLD was 91.4% with 70.1% sensitivity and 93.7% specificity.

GAAD also showed strong specificity, with a lower rate of false positives regardless of disease stage, etiology, or region.

GAAD
is better than
AFP or
PIVKA-II (DCP)

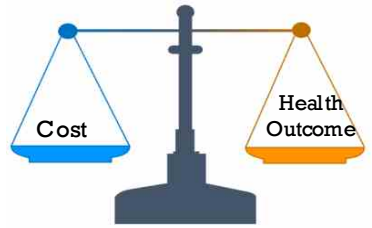
Conclusions: The GAAD algorithm significantly improves early-stage HCC detection for patients with CLD undergoing HCC surveillance.

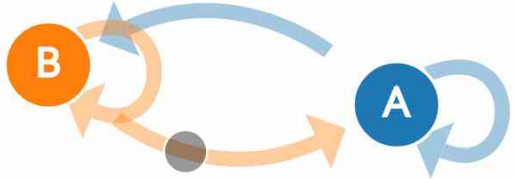
MATHEMATICAL MODELING

Economic Model

2

Cost–utility analysis (CUA)

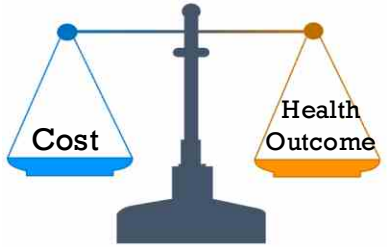




CUA has become an essential method for decision-making and reimbursement of new technologies in healthcare

Cost–utility analysis (CUA)

- Defined as **the balance of costs and health outcomes** to determine whether an intervention justifies its cost.



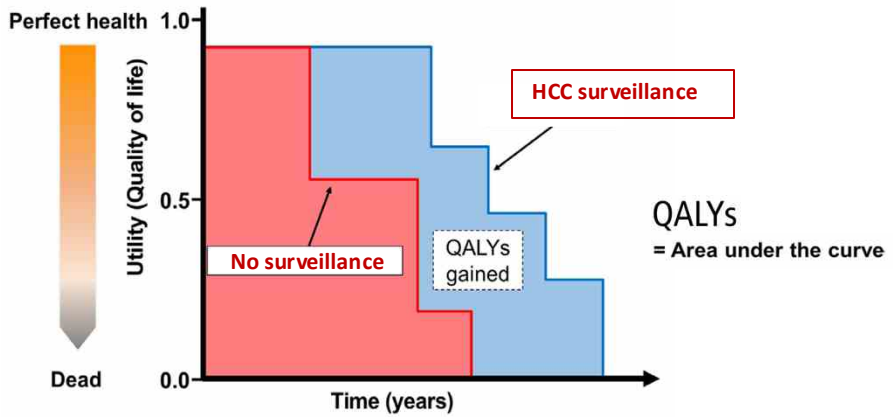
- **Societal perspective (payers and patients)**
- Followed the Thai Health Technology Assessment (HTA) guidelines
- Estimated lifetime costs and health outcomes

HEALTH Outcome

QALYs

quality-adjusted life years

A metric combining two-dimensional health outcomes:
- Quantity (length of life) and
- Quality of life (QOL)



Costs

Medical costs
(e.g., interventions, medication, hospitalisation)
Non-medical costs
(e.g., travel for patients and caregivers)
Other costs

Incremental cost-effectiveness ratio (ICER)

$$ICER = \frac{(\text{Cost of A}) - (\text{Cost of B})}{(\text{QALY of A}) - (\text{QALY of B})}$$

$$\text{Ratio} = \frac{\text{Cost}}{\text{Outcome}}$$

Willingness-to-pay (WTP) threshold

Thailand:
160,000 THB
=5000 USD

Target population and scope of the model

PICO Scenario

Population

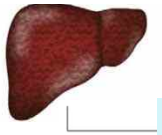
Intervention

Comparison

Outcome

Patients at high-risk of HCC

Compensated Cirrhosis (all causes)



40-60 years

3% incidence rate

HCC surveillance every 6 months

No surveillance

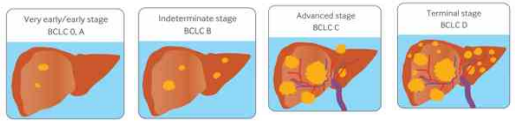
US US+AFP GAAD GALAD

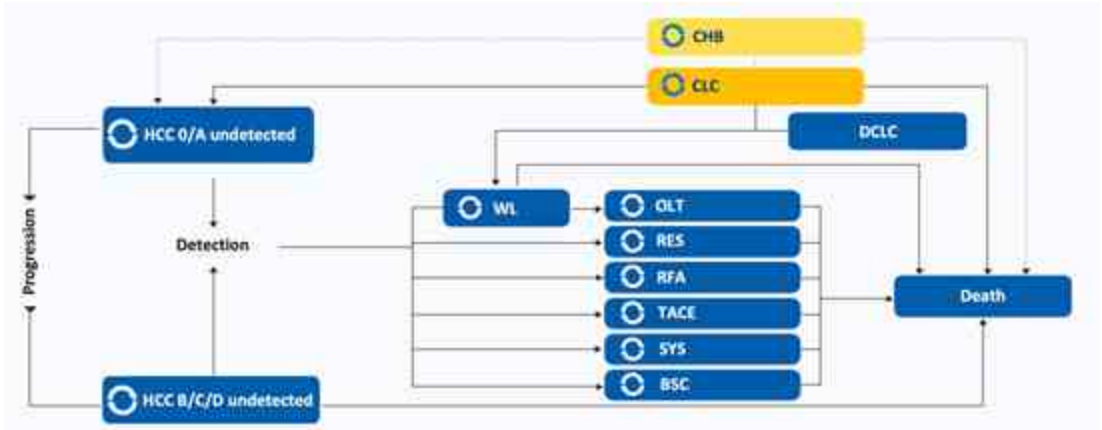
PIVKA-II + AFP

Markov model

Micro-simulation model reflecting the disease progression in cirrhosis

Detecting HCC → Rx BCLC OUTCOME

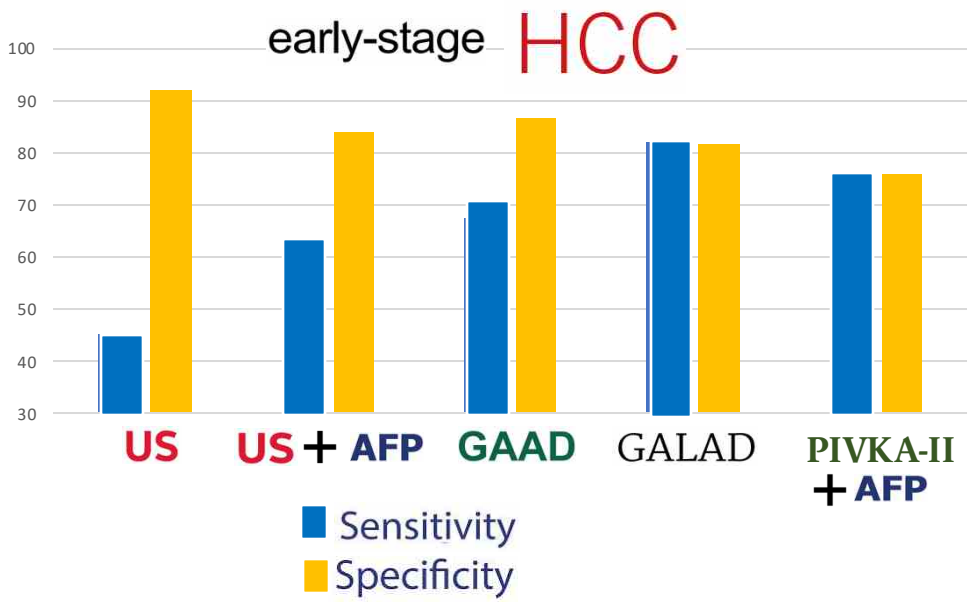




Data input: Diagnostic performance

Type of HCC surveillance

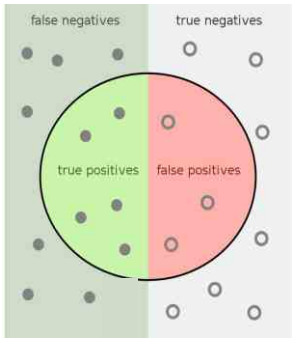
- 5 different screening methods plus 'no routine surveillance' were compared



Tzartzeva K, et al. *Gastroenterology* 2018;
Roche Diagnostics, Data on file;
Berhane S, et al. *Clin Gastroenterol Hepatol* 2016

Sensitivity & Specificity

- **Higher sensitivity** is associated with a **higher early-detection** rate (higher true-positive rate) **and better survival**
- **Higher specificity** is associated with a **lower false-positive rate and lower unnecessary procedures & costs** (e.g., CT, MRI)



Sensitivity = True positive / True positive + false negative

True positive rate

Specificity = True negative / True negative + false positive

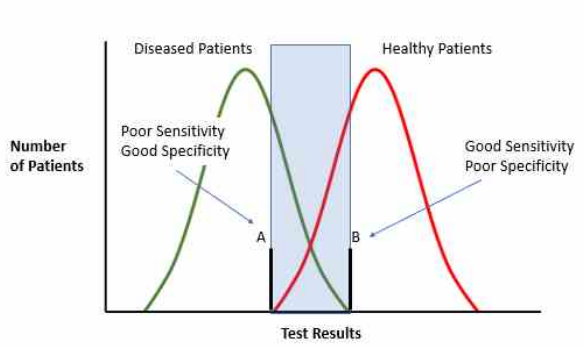
True negative rate

Health Outcome

COST

BALANCING

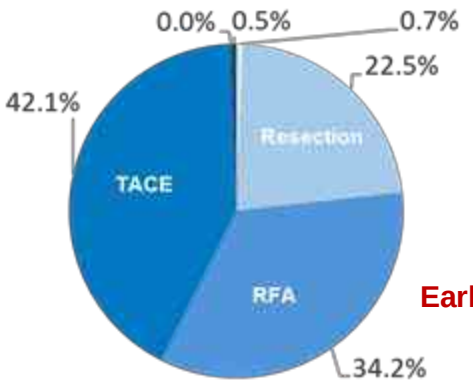
& Sensitivity
Specificity



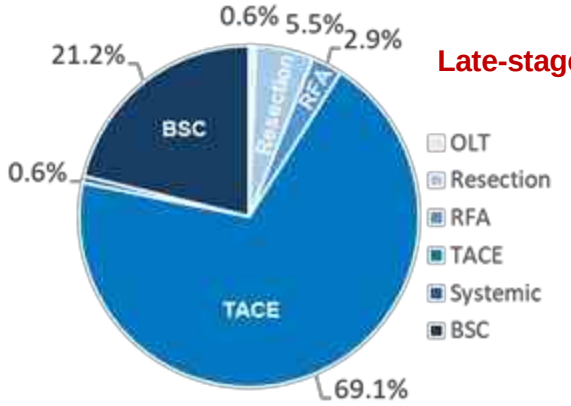
Data input: Treatment and survival data used in the model

The analysis used new real-world data from Chulalongkorn Hospital to estimate health outcomes.

Current treatment of HCC

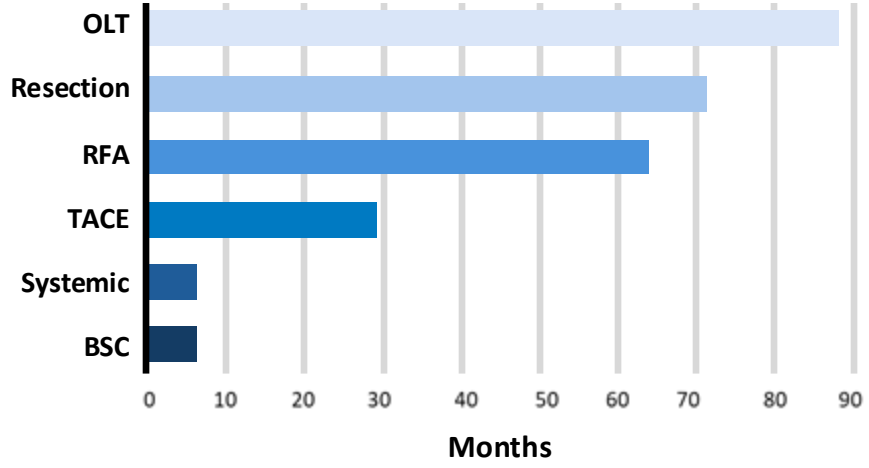


Early-stage HCC



Late-stage HCC

Treatments: *The data were sourced to identify treatment type by early-stage HCC (BCLC stage 0-A) and late-stage HCC (B/C/D)*



Treatment-related survival: *Median survival was obtained for each treatment option*

Data Input: Considered Costs & Utilities

Limitation in the Use of Cost-effectiveness Analysis

- Available data were drawn from heterogeneous populations
- Data on essential outcomes may not be available and needed extrapolation

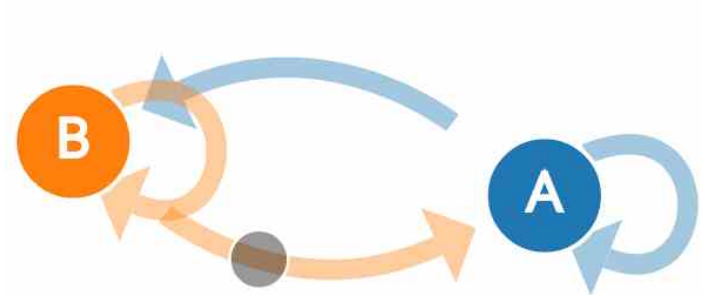
Costs for key parameters

	Cost type	Cost (฿)	Source
Surveillance Methods	US surveillance	800	King Chulalongkorn Memorial Hospital
	US + AFP surveillance	1,070	King Chulalongkorn Memorial Hospital
	GAAD surveillance	1,150	King Chulalongkorn Memorial Hospital
	GALAD surveillance	2,251	King Chulalongkorn Memorial Hospital
	PIVKA + AFP surveillance	850	King Chulalongkorn Memorial Hospital
Confirmation of HCC	Confirmatory HCC (True positive)	11,493	Sangmala (2014), assuming cost of 1 MRI
	Confirmatory HCC (False positive)	11,493	Sangmala (2014), assuming cost of 1 MRI
HCC Treatments	Transplantation	513,914	Chanree et al., DRG Chulabhorn Hospital
	Resection	62,227	Chanree et al., DRG Chulabhorn Hospital
	RFA	80,717	Chanree et al., DRG Chulabhorn Hospital
	TACE	62,676	Chanree et al., DRG Chulabhorn Hospital
	BSC, per month	2,672	Chanree et al., DRG Chulabhorn Hospital
	Systemic treatment, annual	33,654	Chanree et al., DRG Chulabhorn Hospital

MANAGEMENT COST
LIVER DISEASE

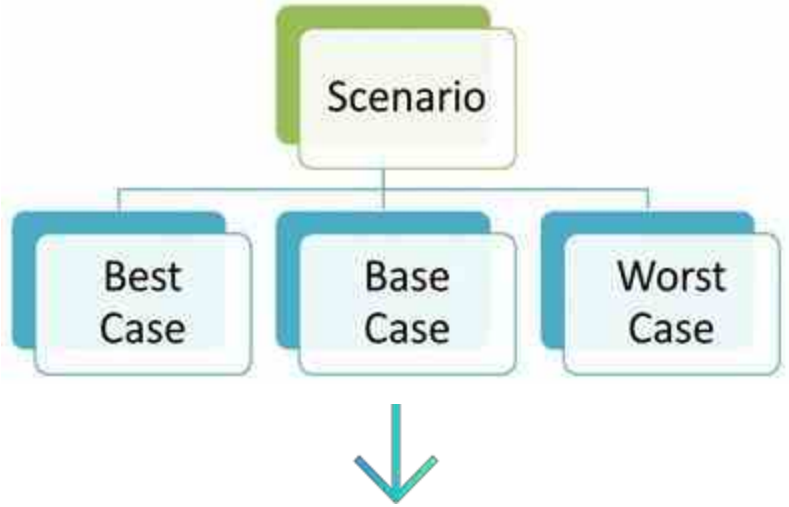
Health state	Utilities	Source
CLC	0.75	Zhang et al (2021)
Non-Cirrhotic Chronic Hepatitis B	0.73	Zhang et al (2021)
Fibrosis 3	0.73	Assumed same as for NC.CHB
DCLC	0.68	Zhang et al (2021)
HCC undetected	0.64	Zhang et al (2021)
WL	0.64	Assumed same as HCC
OLT & Post	0.64	Assumed same as HCC
Resection and Post	0.64	Assumed same as HCC
RFA & Post	0.64	Assumed same as HCC
TACE & Post	0.64	Assumed same as HCC
BSC & Post	0.4	Cucchetti, 2014
Systemic treatment	0.62	Zhang et al (2021), terminal stage
Palliative care	0.4	Cucchetti, 2014

Base-case scenario 1:
Surveillance strategies vs 'No surveillance' as the standard of care in compensated cirrhosis



Markov Modelling Analysis

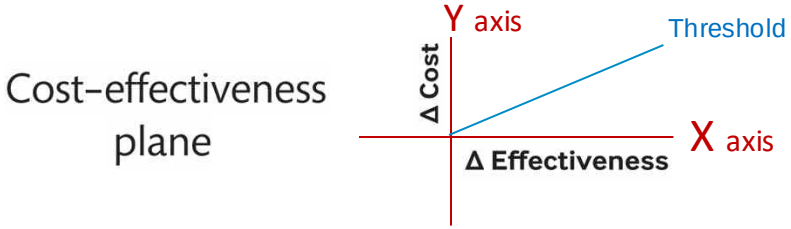
10,000 micro-simulations to maintain optimal efficiency

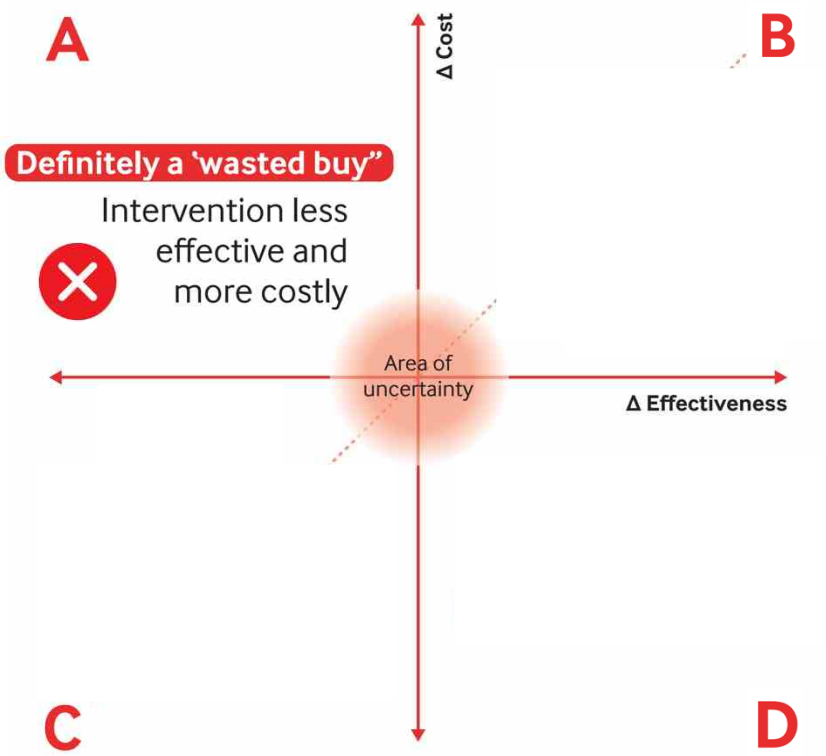


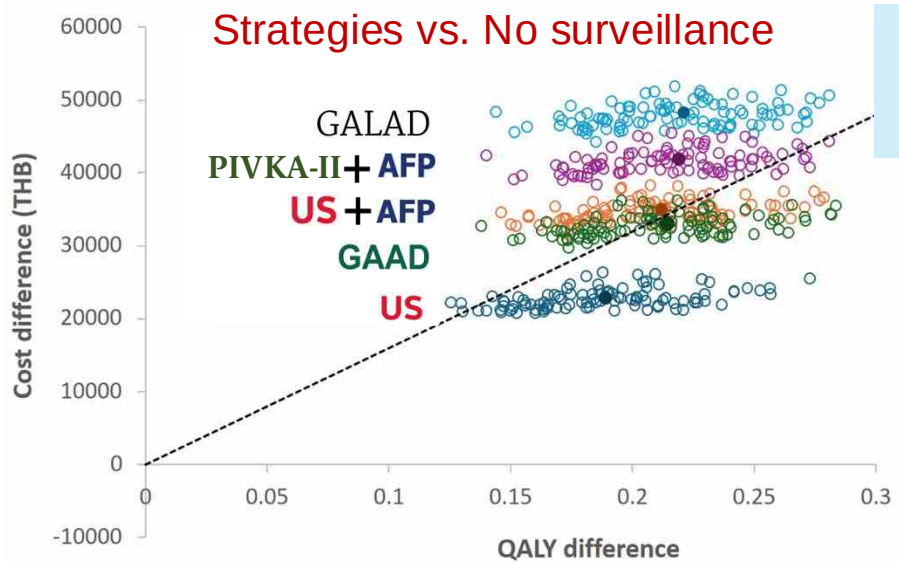
AVERAGE point of reference

"Base-case" means the case that is the most likely to occur in the scenario

Result comparison for surveillance options







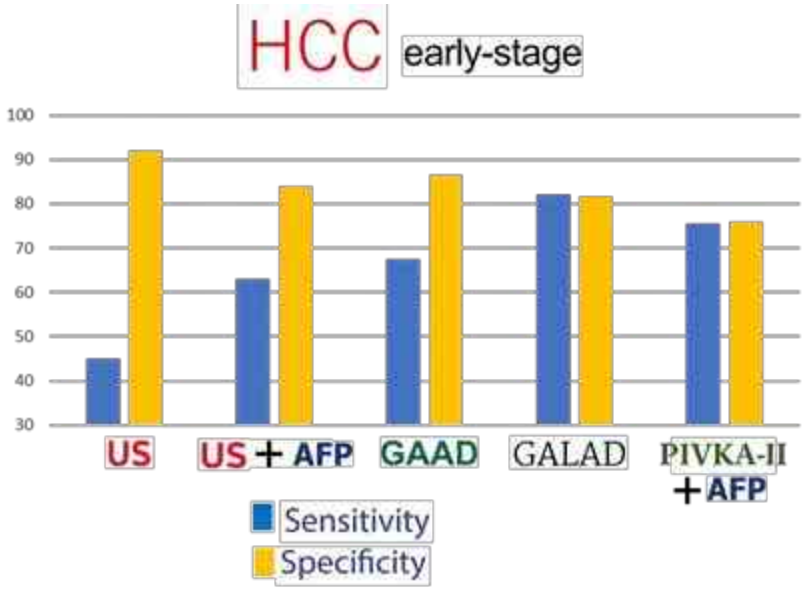
Willingness-to-pay Threshold: THB 160,000/QALY

Base-case results

GALAD	ICER: THB218,529/QALY
PIVKA-II + AFP	ICER: THB191,388/QALY
US + AFP	ICER: THB164,943/QALY
Threshold	
GAAD	ICER: THB154,275/QALY
US	ICER: THB120,894/QALY

Ultrasound (alone) and **GAAD** appear to be cost-effective options in the base-case scenario

The role of sensitivity and specificity in true- and false-positive detection and associated cost-effectiveness



Tzartzeva K, et al. Gastroenterology 2018;
Roche Diagnostics, Data on file;
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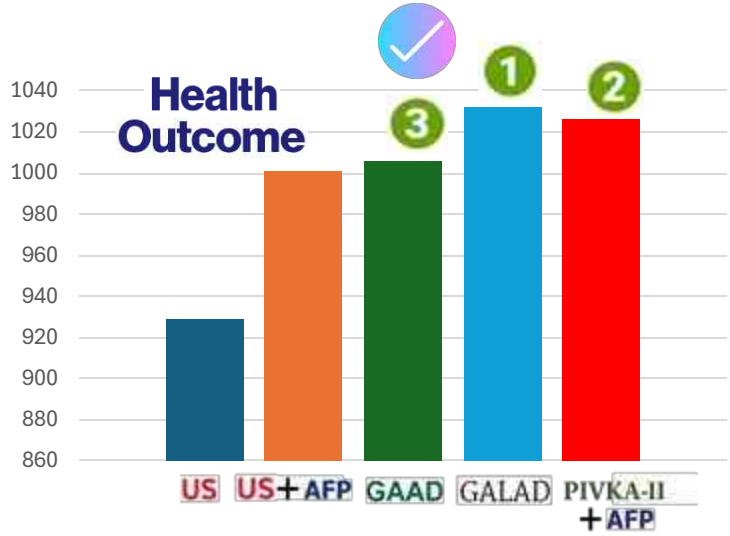
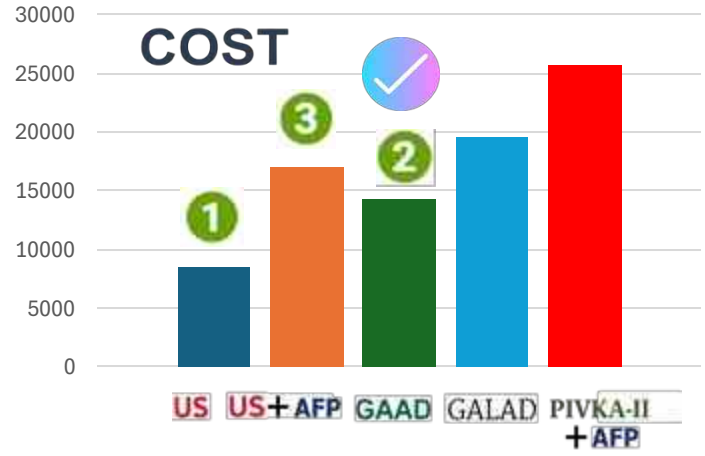


Sensitivity

Number of early-stage HCC cases detected

** Calculations based on bi-annual surveillance of 10,000 simulated patients over a 20-year time horizon*



Specificity

Number of lower false positive HCC diagnosis

$$\text{Specificity} = \frac{\text{True negative}}{\text{True negative} + \text{false positive}}$$

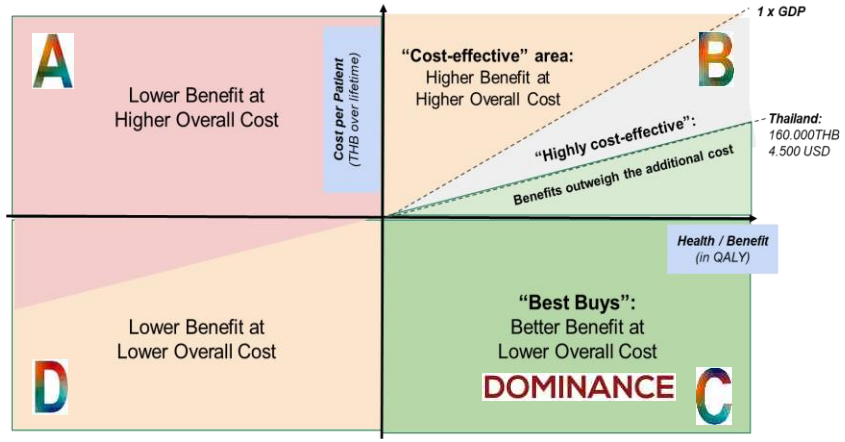
- **Higher false positive rates were costly in the model since these required unnecessary confirmatory testing (e.g., CT or MRI)**

COST <25% surveillance tests, >40% treatment-related, 35% cost for follow up on false positive results

Base-case scenario 2:

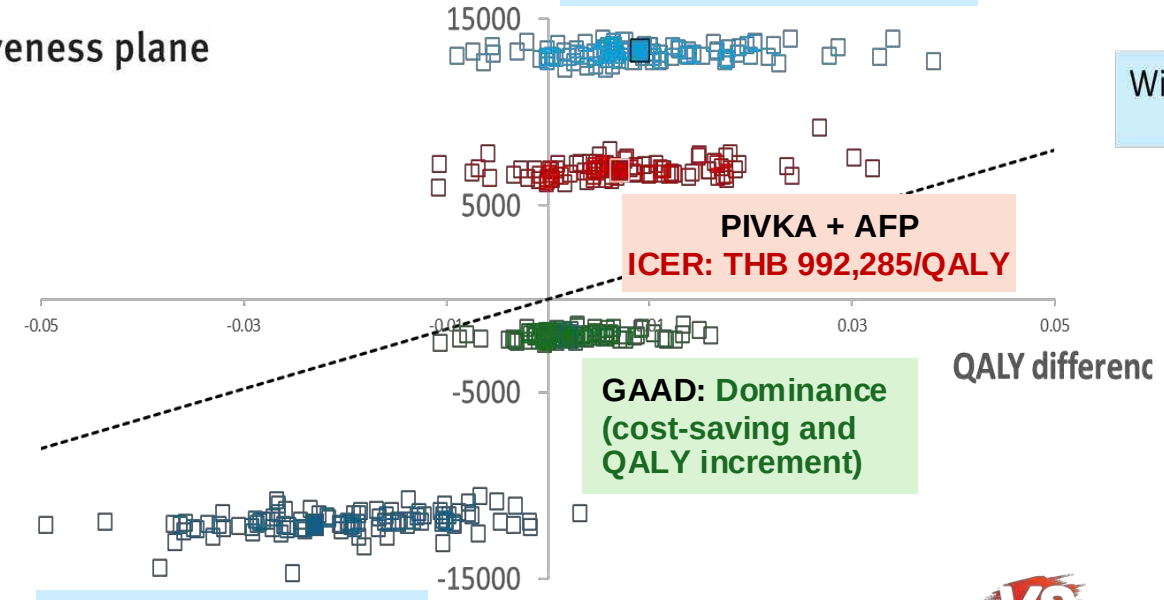
Surveillance strategies vs ‘US + AFP’ as the standard of care in compensated cirrhotis

Cost-effectiveness analysis by surveillance strategies vs AFP+US as the standard of care



Cost effectiveness plane

GALAD
ICER: THB 1,480,777/QALY



Willingness-to-pay Threshold:
THB160,000/QALY

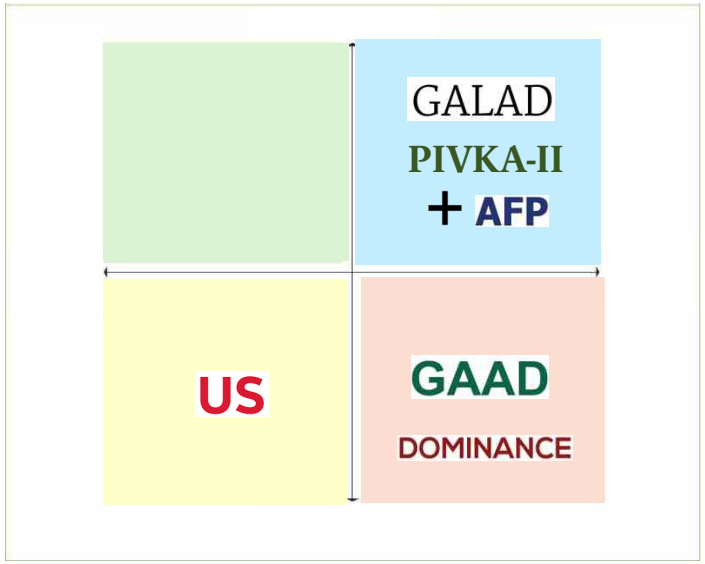
PIVKA + AFP
ICER: THB 992,285/QALY

GAAD: Dominance (cost-saving and QALY increment)

US alone: Loss of QALYs

VS

US + AFP

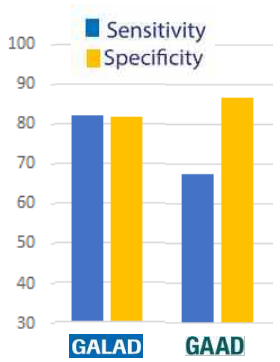


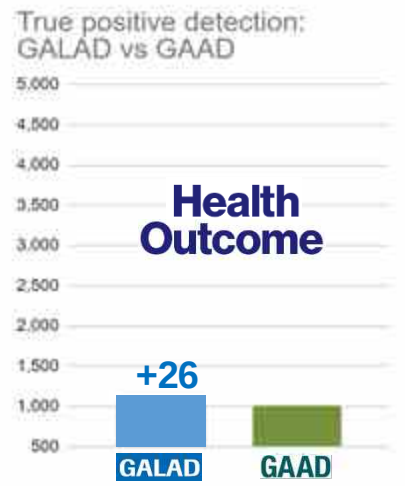
Further scenario analysis:
GAAD vs GALAD in compensated cirrhosis

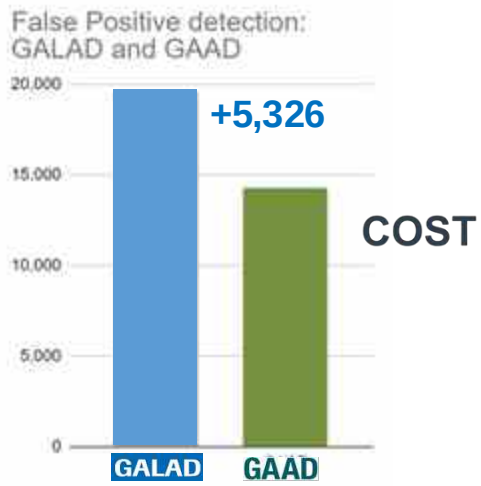
=> How do different algorithms compare?

The comparison of GALAD vs GAAD

GALAD is associated with increased **true positives** (2.5%), but also increased **false positives** and **overall costs** (>25%)







Diagnostic Outcomes	GALAD	GAAD	DIFFERENCE
True positive (TP)*	1,032	1,006	+26
False Positive (FP)*	19,590	14,264	+5,326

Cost-effectiveness	GALAD	GAAD
ICERs vs. No surveillance	218,586	154,372
ICERs vs. US+AFP	1,429,553	Dominant (-868,301)

Costs associated with **false positive rates** (extra CT/MRI) are suggested to outweigh the impact of True Positive detections and associated better health, even adjusting the lower price of GALAD

Outcomes	GALAD	GAAD
Total cost (THB)	77,650	62,597
Total QALYs	6.63	6.62
Life years	9.28	9.28
Cost-effectiveness		
ICERs vs. No surveillance	223,816	154,372
ICERs vs. US+AFP	5,006,009	Dominant

Diagnostic outcomes	GALAD	GAAD
TP	969	948
TN	87,103	92,359
FN	223	452
FP	19,299	14,043
Early detection		
% of HCC early detected	92%	86%

- **GAAD** is still suggested to **remain the dominant strategy** in the majority of simulations
  - This is **mainly due to its lower associated costs for false positive** detection.

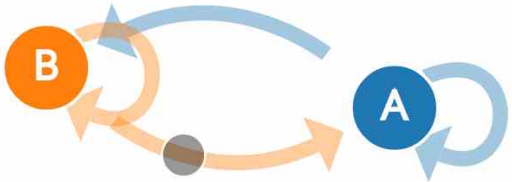
MATHEMATICAL MODELING

Economic Model

2

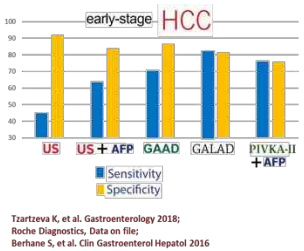
Cost–utility analysis (CUA)

Limitations of the Study



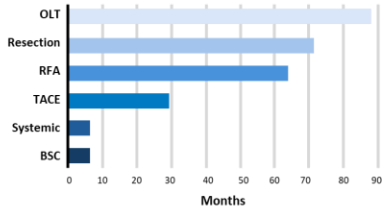
Limitations of the study

1. The diagnostic accuracy of all alternative surveillance methods cannot be directly compared.



Tzartzeva K, et al. Gastroenterology 2018;
Roche Diagnostics, Data on file;
Berhane S, et al. Clin Gastroenterol Hepatol 2016

2. Survival outcomes were based on treatment modalities, not HCC stages.



Treatment-related survival:
Median survival was obtained for each treatment option

BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update ☆

Key point

Staging is linked to the first option to be considered according to scientific evidence.

Personalised treatment indications are established according to an expert clinical decision-making process where all dimensions of a patient's profile are taken into account.

3. Real-world compliance and performance may differ, especially in rural areas.

Lack of ADEQUATE MEDICAL FACILITIES for TREATMENT

4. Patient burden from false positive results could not be completely evaluated.

Weighing the benefits of Hepatocellular Carcinoma surveillance against potential harms

False-positive results commit patients to undergo further, potentially invasive and ultimately unnecessary diagnostic testing

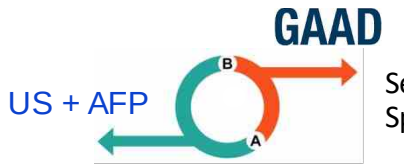
The Cost of EMOTIONAL & FINANCIAL aspects

CONCLUSION

HCC surveillance in high-risk group esp., cirrhosis is very important regarding clinical and economic perspective

CLINICAL

GAAD VS US + AFP



Sensitivity 70%
Specificity 90%

Sensitivity 63%
Specificity 84%

GAAD has higher sensitivity for detecting early HCC and could have better adherence than US+AFP

ECONOMIC

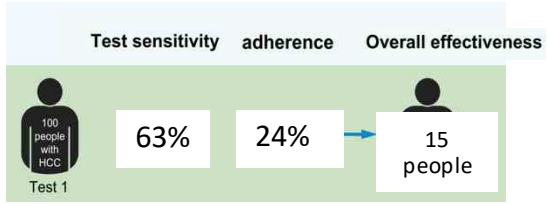
GAAD VS US + AFP

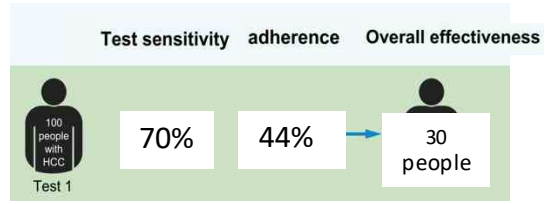
HEALTH ECONOMICS DATA

GAAD is suggested to be the dominant strategy (Cost-saving and QALY increment)

Future Perspectives

Implementation





MORE Feasible option ⇨ Increasing Acceptance & UPTAKE

GAAD is a suitable option for HCC surveillance in Thailand, considering its clinical and economic benefits, as well as the feasibility (one-stop service) and potential availability of the test

REIMBURSED POLICY HCC surveillance

GAAD SCORE

CAPITATION → FEE-FOR-SERVICE

LIMITED BUDGET

Optimize TESTING TREATMENT

THANK YOU *for* YOUR ATTENTION