Cost-Effectiveness Analysis: Ultrasound with Alpha-Fetoprotein versus Ultrasound Alone for At-Risk Hepatocellular Carcinoma Patients with and without Cirrhosis Progression: A Systematic Review

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Abstract

This investigation assesses the cost-effectiveness of employing ultrasound in conjunction with Alpha-Fetoprotein (AFP) screening versus using ultrasound alone for early detection of Hepatocellular Carcinoma (HCC) among at-risk individuals. The urgency for effective early detection strategies is underscored by HCC's significant global and national impact, particularly in the Philippines. HCC primarily arises from chronic liver diseases, notably cirrhosis due to hepatitis infections, emphasizing the need for accurate surveillance methods. This research aims to compare the effectiveness and economic viability of combined versus single-modality screening approaches, highlighting the potential for enhanced sensitivity and specificity when utilizing both ultrasound and AFP in HCC surveillance.

A rigorous methodological framework supports the study's objectives, involving a comprehensive review and analysis of relevant studies and economic evaluations to determine the most cost-effective screening strategy for high-risk populations. The process includes a detailed search strategy across multiple databases (i.e., PUBMED, CINAHL,

Cochrane, Web of Science, OVID, Science Direct, MedNar, Google Scholar, ProQuest) to identify pertinent evaluations. Importantly, the study employs a robust screening and appraisal methodology involving multiple independent reviewers at various stages. Initially, two independent reviewers will screen studies for eligibility based on titles and abstracts. Subsequently, another pair of independent reviewers will evaluate the studies based on full-text articles. Additionally, two other independent reviewers will undertake a critical appraisal of the papers. Finally, two researchers will extract data from the studies included in the analysis.

Methodological quality assessment will utilize Drummond's Checklist, and data synthesis will be conducted using the JBI Dominance Ranking Matrix to classify the cost-effectiveness outcomes of the included studies. This structured approach ensures a comprehensive and unbiased evaluation of the data, aiming to provide clear insights into the economic evaluations, design features, implementation contexts, and optimal screening methods for early-stage HCC detection. By elucidating the cost-effectiveness of combining ultrasound with AFP screening compared to ultrasound alone, this study seeks to inform healthcare policy and practice, enhancing surveillance strategies for individuals at heightened risk for HCC and facilitating early intervention to improve health outcomes.

Background

Hepatocellular carcinoma (HCC) is the primary form of liver cancer, originating from hepatocytes, the main liver cells (Rawla et al., 2018). Holding the rank as the most prevalent type of liver cancer, HCC also stands as the second most common cause of global cancer-related deaths (Y. Liu et al., 2019; Shiani et al., 2017; Sung et al., 2021). Each year, approximately 900,000 people worldwide receive a diagnosis of HCC. Interestingly, it is the fifth most common cancer among men and the ninth among women (Serraino et al., 2023). In 2020, global statistics recorded an approximate death toll of 830,180 from liver cancer (Cancer.Net Editorial Board, 2023).

When zooming in to the Philippines, the data indicate that the incidence rate of HCC is 11.4 per 100,000 of the population (Ornos et al., 2023). The predominant cause of HCC in the country remains chronic hepatitis B infection (Ashtari, 2015). Liver cancer is the nation's fourth most widespread cancer type, with a 5-year prevalence rate across all age groups marked at 10.01 per 100,000 population (Ornos et al., 2023). Recent figures from the Philippine Statistics Authority shed light on the gravity of liver diseases, accounting for 27.3 cases per 1,000 deaths in 2020 (Ornos et al., 2023). However, it is crucial to note that the actual scope of liver disease in the Philippines might be greater than documented, given the scarcity of comprehensive epidemiological studies (Ornos et al., 2023).

The development and progression of HCC are closely linked to conditions of fibrosis and cirrhosis, mainly resulting from chronic liver injury and inflammation (Dara et al., 2016; Rawla et al., 2018). HCC originates primarily from hepatocytes, in contrast to benign lesions originating from liver progenitor cells (Division of Signal Transduction and Growth Control, DKFZ-ZMBH Alliance, German Cancer Research Center (DKFZ), Heidelberg, Germany et al., 2019).Chronic liver diseases, particularly cirrhosis induced by hepatitis B or hepatitis C infections, stand out as the leading risk factors for HCC (Mayo Clinic, 2023). The cirrhotic liver is marked by inflammation, necrosis, fibrosis, and consistent regeneration, all

of which collectively drive the development of HCC (Fabregat & Caballero-Díaz, 2018). Interestingly, while HCC can manifest in noncirrhotic livers, there's typically an underlying presence of fibrosis hinting at regeneration (Desai et al., 2019). Furthermore, infections such as hepatitis B or C not only increase the risk of HCC, but certain conditions, including hemochromatosis and alpha-1 antitrypsin deficiency, also contribute (Schaefer et al., 2015).

Ultrasound (U/S) is the primary screening method for HCC recommended by regional liver societies (Fateen & Ryder, 2017). The American Association for the Study of Liver Diseases (AASLD) recommends HCC surveillance for all adults with cirrhosis, noting its role in improving survival and early detection (Heimbach et al., 2018). However, AASLD does not provide guidance for those with advanced fibrosis without cirrhosis (Heimbach et al., 2018). The European Organization for Research and Treatment of Cancer suggests HCC surveillance for both cirrhotic patients and those with advanced liver fibrosis (European Association for the Study of the Liver & European Organization for Research and Treatment of Cancer, 2012). While a blood test is available to identify those most likely to develop HCC, it is not yet widely adopted (J. Liu et al., 2020).

Ultrasound is widely recognized as an effective screening tool for HCC, reporting a sensitivity of over 60% and a specificity exceeding 90%, along with a positive predictive value of 70% (Daniele et al., 2004). However, its efficacy can be improved when combined with alpha-fetoprotein (AFP). Together, they achieve an improved sensitivity of 90.2% and specificity of 83.3% (Giannini et al., 2012). This enhanced sensitivity is invaluable for early detection of HCC, especially among those with cirrhosis or advanced fibrosis. A steadily increasing AFP level of 7 ng / mL / month is indicative of HCC even if the absolute AFP level does not exceed 200 ng/mL (Arrieta et al., 2007). Specific measurements such as serum fractions of alpha-fetoprotein L3 and alpha-fetoprotein P4 + P5 help distinguish HCC from mere cirrhosis and even predict the onset of HCC in cirrhotic patients (Sato et al., 1993). The combined use of ultrasound and AFP every 6 months is recommended for the surveillance of HCC in high-risk populations (Danila, 2014). Recent advances such as the longitudinal AFP screening algorithm have further improved the sensitivity and facilitate earlier detection of HCC among patients, especially those with advanced fibrosis or cirrhosis (Tayob et al., 2016).

Given the increasing global incidence of HCC and the imperative need for timely detection to improve patient outcomes, this study aims to identify and summarize the best available evidence on the use and costs of combining ultrasound with AFP compared to the use of ultrasound alone in the screening of people at risk of developing HCC, both with and without progression to cirrhosis.

1. Assess the cost-effectiveness of combining ultrasound with AFP compared to using ultrasound alone in screening patients at risk of developing HCC, considering the direct and indirect costs associated with each screening method.
2. Assess health economic evaluations in relation to the benefits of both screening methods from the public payer perspectives.
3. Analyze the available evidence to determine the specific design features of the screening programs that contribute to their effectiveness.
4. Identify the implementation contexts under which these screening programs / models produce lower costs and greater effectiveness for detecting HCC in its early stages, especially in patients with progression to cirrhosis.

5. Synthesize the review findings to draw inferences regarding:
    1. Optimal design characteristics conducive to the success of screening programs;
    2. Implementation strategies that promote both cost efficiency and effectiveness in the early detection of HCC.

We will recommend optimal design and implementation strategies for screening programs to ensure cost-effective and timely detection of HCC in at-risk populations.

Research Questions

Does the combination of ultrasound with AFP offer a cost-effective strategy to reduce mortality and morbidity from HCC in adults at risk of developing HCC, both with and without progression to liver cirrhosis, throughout their lifetime?

What are the budget and resource implications of introducing AFP to ultrasound for the screening of individuals with at-risk HCC?

Method

Inclusion Criteria

Population

The primary population of interest for the systematic review includes individuals who are at risk of developing HCC. This group includes patients with chronic infections of hepatitis B or C, those with a familial history of HCC, patients diagnosed with alcoholic liver disease, and individuals affected by nonalcoholic steatohepatitis (NASH) or fatty liver disease. Furthermore, those with conditions such as hemochromatosis, exposure to aflatoxins, or other recognized risk factors for HCC also fall into this primary group. Within this principal population, there are two vital subgroups to consider. The first consists of patients who have progressed to cirrhosis, a condition known to considerably increase the risk of HCC. Distinguishing this subgroup is essential, as it can shed light on the varying utility of screening methods for individuals at increased risk. The second subgroup includes patients who have not yet shown progression to cirrhosis. Assessing this group will elucidate the cost-effectiveness and resource utilization of screening techniques for those potentially at a lower risk compared to their cirrhotic counterparts.

Intervention

Combining ultrasound with AFP (Alpha-fetoprotein) offers a comprehensive approach for the early detection of HCC. While ultrasound visualizes liver abnormalities, AFP acts as a tumor marker, often elevated in patients with HCC. This dual screening is vital for those with cirrhosis due to their increased risk but remains crucial for noncirrhotic individuals to

ensure early intervention and improved outcomes.

Comparator

Ultrasound is a key non-invasive tool for detecting HCC. It is vital to identify liver abnormalities, especially in people with cirrhosis, given their increased risk of HCC. Even for those without cirrhosis, ultrasound remains essential for early detection and better treatment outcomes.

Outcome

This review will use several key metrics to comprehensively assess the cost-effectiveness of health interventions. The incremental cost-effectiveness ratio (ICER) compares the additional costs and benefits of interventions with alternatives, offering a clear cost perspective. We aim to ensure that our findings are both clinically potent and economically sustainable. The cost-effectiveness acceptability curve visually represents the probability of an intervention's cost-effectiveness, shedding light on uncertainties inherent in economic evaluations. Cost-Effectiveness Analysis (CEA) evaluates costs versus health outcomes. Cost-Utility Analysis (CUA) weighs costs against quality-adjusted life-years (QALYs), ensuring a holistic view of patient impacts. Lastly, the net benefit ratio will guide us in discerning the interventions that offer optimal value, aiming for both cost efficiency and maximal health outcomes.

Types of Studies

Full economic evaluation studies (i.e., CEA, CUA, CBA, and CMA) and partial economic evaluations (i.e., cost analysis, cost-description studies, and cost-outcome descriptions) of ultrasound with AFP compared to ultrasound alone will be considered for inclusion in the review. Modeling studies will be considered in addition to those that rely only on empirical data.

Studies without cost analysis will also be omitted. We will exclude studies centered on populations with a preexisting diagnosis of HCC, as our objective is distinctly geared towards screening. Additionally, studies that focus solely on pediatric populations will not be considered.

Search Strategy

The search strategy aims to find both published and unpublished studies. In this review, a three-step search strategy will be utilized. An initial limited search of MEDLINE and CINAHL will be carried out, followed by an analysis of the text words contained in the title and abstract and of the index terms used to describe articles. A second search using all identified keywords and index terms will then be carried out across all included databases. Third, the reference list of all identified reports and articles will be searched for additional studies. Studies published in 1995 will be considered for inclusion in this review.

For a comprehensive literature search, we will explore a wide variety of databases. Our primary search will be initiated on

platforms like PubMed, CINAHL, Cochrane (CENTRAL), and Web of Science. We will further delve into specialized economic evaluation repositories such as the NHS Economic Evaluation Database and the Health Economic Evaluations Database. Our inquiry will be anchored on the MEDLINE (OVID) platform, and the search strategy formulated there will be adapted and executed on other notable scientific databases. These include the Cochrane Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), EMBASE (OVID), National Health Service Economic Evaluation Database (NHS EED), HERDIN, and Science Direct. We will extend our search to platforms such as MedNar and Google Scholar. Additionally, we will delve into ProQuest dissertations to capture academic theses and dissertations relevant to our topic. Furthermore, the online clinical trials registers will be scoured to identify any pertinent trials or studies that may not have made their way into mainstream publications. This approach ensures that our review remains both exhaustive and inclusive of all available literature, published or otherwise.

These search terms will be used in combination using Boolean operators.

1. HCC concept: ((((((((((((Carcinoma, Hepatocellular[Mesh]) OR Liver Neoplasms[Mesh:noexp]) OR Hepatocellular carcinoma[Title/Abstract]) OR Hepatocarcinoma[Title/Abstract]) OR HCC[Title/Abstract]) OR Hepatoma[Title/Abstract]) OR Liver cell carcinoma[Title/Abstract]) OR liver cancer[Title/Abstract]) OR primary liver cancer[Title/Abstract])))) AND
2. Economic concept: ((((((Costs and Cost Analysis[Mesh])) OR Economics, Medical[Mesh]) OR (Fees and Charges[Mesh]))) OR ((((((((((((((((economic evaluation[Title/Abstract]) OR cost[Title/Abstract]) OR effectiveness[Title/Abstract]) OR cost effectiveness[Title/Abstract]) OR cost-effectiveness[Title/Abstract]) OR cost benefit[Title/Abstract]) OR cost utility[Title/Abstract]) OR cost analysis[Title/Abstract]) OR CUA[Title/Abstract]) OR CEA[Title/Abstract]) OR CBA[Title/Abstract]) OR health economic*[Title/Abstract]) OR economic*[Title/Abstract]) OR direct cost[Title/Abstract]) OR indirect cost[Title/Abstract]) OR intangible cost[Title/Abstract]) OR health care cost[Title/Abstract])))) AND
3. Screening concept: ((((((((((diagnostic imaging[Mesh]) OR alpha-Fetoproteins[Mesh]) OR Liver Function Tests[Mesh]) OR screening[Title/Abstract]) OR surveillance[Title/Abstract]) OR alpha-fetoprotein*[Title/Abstract]) OR ultrasound[Title/Abstract]) OR ultrasonography[Title/Abstract])

Assessment of Methodological Quality

Drummond's Checklist is an esteemed evaluative instrument tailored for the critical assessment of economic evaluations (Appendix I). Formulated by Michael Drummond et al., it has solidified its relevance within the domain of health technology assessment (HTA). The checklist is structured with ten salient queries, encapsulating elements from the study's methodology and data procurement to its analytical approaches and dissemination. It is envisaged for use by HTA scholars and decision-makers, facilitating a rigorous examination of economic evaluations and identifying avenues for methodological refinement.

Search Results

The study will present the results of the search and study selection. This includes a flowchart that presents the search results (see Figure 1). Appendix II will report the search strategies used to search each electronic database. Appendix III will list all the studies excluded at full text examination or critical appraisal with reasons for their exclusion.

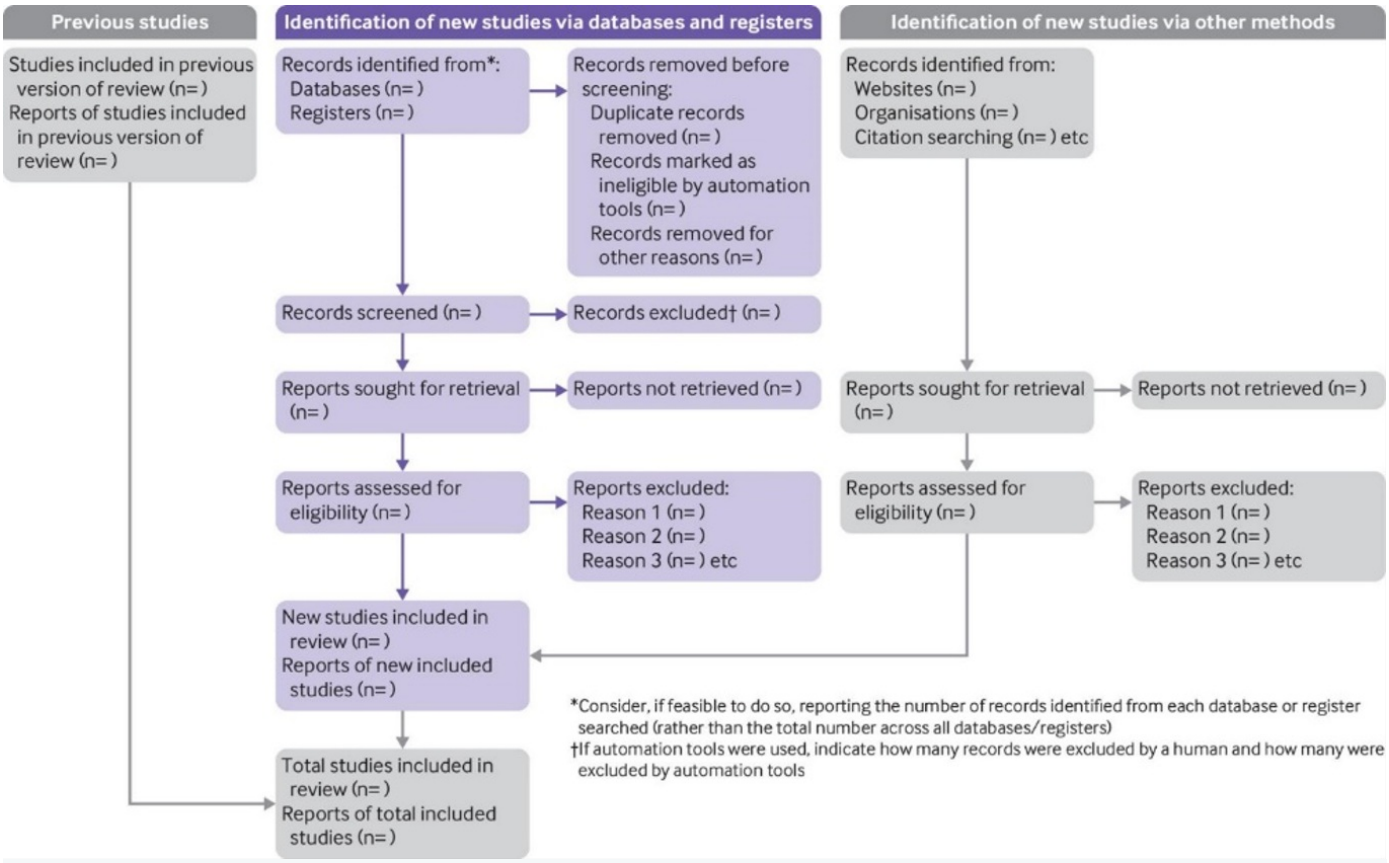

Figure 1. PRISMA Flow Diagram (Page et al., 2021)

Data Extraction

Two independent reviewers will extract information from the research papers. Disagreements will be resolved through discussion. If disagreement persists, a third reviewer will be consulted. First, there will be descriptive details, which include data about the study's participants or population, the specific intervention being analyzed, the comparator(s) used, and the expected outcomes. Additionally, insights into the study methodology will be provided. This involves the type of evaluation design implemented, the analytical perspectives adopted, the source of the effectiveness data, and the currencies and prices chosen for cost assessments. The time span of the analysis, the sensitivity examinations, and metrics concerning resource use, cost, and health/clinical effectiveness will also be considered. Furthermore, the contextual background of the study will be detailed, highlighting the geographical location, the health care framework, the broader environment of service delivery, and the cultural context. Finally, results related to resource consumption, costs, or cost-effectiveness will be presented. Whenever available, conclusions from the authors regarding the factors that influence the intervention's cost-effectiveness will also be included (Gomersall et al., 2014). Table 1 reports the characteristics of the included studies.

Table 1. Table of characteristics of included studies

Author, design type (CMA, CEA, CBA, CUA) and date	Population, Intervention Comparator and Outcomes	Methods (incl. perspective, measure of costs and health effects, time horizon, discounting, sensitivity testing, data sources, modeling if used)	Context (geographical location, health care and broader service delivery setting including human resource availability and capacity, technology and culture)	Author conclusion and reviewer reflection

In the JBI Dominance Ranking Matrix (DRM) (Figure 2), there are nine unique classifications, denoted A through I. These classifications categorize the cost-effectiveness results of studies based on both the direction and the magnitude of the ICER. For example:

- If an intervention is more expensive but also more effective, it is classified as 'A'.
- If an intervention is more effective and less costly, it receives the G classification.

This matrix is crucial for reviewers, helping them systematically categorize the cost-effectiveness of interventions (Gomersall et al., 2014).

Regarding the final phase, the 3x3 matrix directs reviewers to assign one of the nine categories (A-I) to each study's cost-effectiveness outcome. This decision is based on the cost and effectiveness relative to a comparator. The options from A to I guide reviewers in their classification process (Gomersall et al., 2014).

		Clinical Effectiveness		
		+	0	-
Cost	+	A	B	C
	0	D	E	F
	-	G	H	I

Key

	Effectiveness	Cost
+	Better	Lower
0	Equal	Equal
-	Poorer	Higher

Figure 2. The nine options for classifying cost-effectiveness findings of included studies (select one)

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Data analysis and synthesis method

For this review, we will employ a systematic approach to analyze and encapsulate data from the selected studies, specifically utilizing the JBI DRM along with narrative summaries and tabular representations to address the study's objectives. Our presentation of findings, rooted in the JBI methodology, will be organized into three distinct sections.

1. Dominance Ranking Framework Classification: Here, we will visually and descriptively detail the dominance classification of each study, guiding our audience through the synthesis process. An example extraction table can be seen in Figure 3.
2. Incremental Cost-Effectiveness Measures Analysis: This segment will emphasize the varied incremental cost-effectiveness results of our chosen studies. We will employ narrative descriptions and tables to juxtapose and elucidate these findings.
3. Inferring Factors for Intervention Efficiency: In our concluding section, we will offer a comprehensive narrative that amalgamates the results of the included studies. This will highlight the defining characteristics and conditions that make an intervention not only more effective but also more cost-effective compared to other alternatives (Gomersall et al., 2014).

Cost	# of studies	Health benefit	Implication for decision-makers
+	0	-	Reject intervention
0	0	-	Reject intervention
+	0	0	Reject intervention
-	0	-	Unclear – Judgment required on whether intervention preferable considering incremental cost-effectiveness measures and priorities/willingness-to-pay
0	0	0	Unclear - Judgment required on whether

			intervention preferable considering incremental cost-effectiveness measures and priorities/willingness-to-pay
+	2	+	Unclear - Judgment required on whether intervention preferable considering incremental cost-effectiveness measures and priorities/willingness-to-pay
-	3	0	Favor intervention
0	3	+	Favor intervention
-	2	+	Favor intervention

Figure 3. Three-by-three matrix dominance classification for cost-effectiveness outcomes/findings of economic evaluations

Appendices

Appendix I. Drummond's Checklist

1. Was a well-defined question presented in answerable form?

1.1. Did the study examine both costs and effects of the service(s) or the program (s)?

1.2. Did the study involve a comparison of alternatives?

1.3. Was a point of view for the analysis stated and was the study placed in any particular decision-making context?

2. Was a comprehensive description of the competing alternatives given (i.e., can you tell who did what to whom, where, and how often)?

2.1. Were there any important alternatives omitted?

2.2. Was (should) a do-nothing alternative considered?

3. Was the effectiveness of the program or services established?

3.1. Was this done through a randomized controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?
3.2. Was the effectiveness established through an overview of clinical studies?
3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in the results?

4. Were all the important and relevant costs and consequences for each alternative identified?

4.1. Was the range wide enough for the research question at hand?
4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)
4.3. Were capital costs as well as operating costs included?

5. Were costs and consequences measured accurately in appropriate physical units (e.g., hours of nursing time, number of physician visits, lost work days, gained life-years)?

5.1. Were any of the identified items omitted from the measurement? If so, does this mean that they did not carry weight in the subsequent analysis?
5.2. Were there special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. Were the costs and consequences properly valued?

6.1. Were the sources of all the values clearly identified? (Possible sources include market values, patient or client preferences and views, policy makers' views, and health professionals' judgments)6.2. Were market values used for changes involving resources gained or depleted?
6.3. Where market values were absent (e.g., volunteer labor) or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?
6.4. Was the valuation of consequences appropriate for the question posed (i.e., has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?

7. Were costs and consequences adjusted for differential timing?

7.1. Were the costs and consequences that occur in the future 'discounted' to their current values?
7.2. Was any justification given for the discount rate used?

8. Was an incremental analysis of the costs and consequences of alternatives performed?

8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?

9. Was allowance made for uncertainty in the estimates of costs and consequences?

9.1. If the data on costs and consequences were stochastic (a randomly determined sequence of observations), were appropriate statistical analyses performed?
9.2. If a sensitivity analysis was used, was justification provided for the range of values (or for key study parameters)?
9.3. Were the study results sensitive to changes in the values (within the assumed range for the sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?

10. Did the presentation and discussion of the study results include all issues of interest to users?

10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g., cost-effectiveness ratio)? If so, was the index interpreted intelligently or mechanistically?
10.2. Were the results compared with those of others who have investigated the same question? If so, were there allowances for potential differences in the study methodology?
10.3. Did the study discuss the generalizability of the results to other settings and patient/client groups?
10.4. Did the study allude to or take account of other important factors in the choice or decision under consideration (e.g., distribution of costs and consequences, or relevant ethical issues)?
10.5. Did the study discuss implementation issues, such as the feasibility of adopting the 'preferred' program given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?

Appendix II. Search Strategy

1. HCC concept: ((((((((((((Carcinoma, Hepatocellular[Mesh]) OR Liver Neoplasms[Mesh:noexp]) OR Hepatocellular carcinoma[Title/Abstract]) OR Hepatocarcinoma[Title/Abstract]) OR HCC[Title/Abstract]) OR Hepatoma[Title/Abstract]) OR Liver cell carcinoma[Title/Abstract]) OR liver cancer[Title/Abstract]) OR primary liver cancer[Title/Abstract])))) AND
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3. Screening concept: ((((((((((diagnostic imaging[Mesh]) OR alpha-Fetoproteins[Mesh]) OR Liver Function Tests[Mesh]) OR screening[Title/Abstract]) OR surveillance[Title/Abstract]) OR alpha-fetoprotein*[Title/Abstract]) OR ultrasound[Title/Abstract]) OR ultrasonography[Title/Abstract])

Appendix III. List of studies excluded in full text and critical appraisal with reasons

Title of Excluded Articles	Reasons for Exclusion

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