

## Supplementary material

Table S1. Supplementary methods- search strategy.

Table S2. Risk of Bias within Studies- Newcastle-Ottawa Quality Assessment Scale (NOS) score of the included studies

Table S3. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2020 checklist

Figure S1. *Accuracy Metrics (sensitivity and specificity) Comparison for cutaneous squamous cell carcinoma per 40-GEP class and AJCC8/ BWH T stage.*

**Supplementary Table S1: search strategy.**

Search strategy for EMBASE:	
('squamous cell skin carcinoma'/exp OR 'cutaneous squamous cell carcinoma' OR 'skin squamous cell carcinoma' OR 'squamous carcinoma, skin' OR 'squamous cell carcinoma of the skin' OR 'squamous cell skin carcinoma' OR 'squamous skin carcinoma') AND ('gene expression profiling'/exp OR 'gene expression analysis' OR 'gene expression profile' OR 'gene expression profiling' OR 'gene product profiling')	
Search strategy for Cochrane Library	
#1	squamous cell skin carcinoma
#2	cutaneous squamous cell carcinoma
#3	gene expression profile
#4	gene expression analysis
#5	#1 OR #2
#6	#3 OR #4
#7	#5 AND #6
Search strategy for PubMed/Medline	
("squamous cell skin carcinoma"[Title/Abstract] OR "cutaneous squamous cell carcinoma"[Title/Abstract]) AND ("gene expression profile"[Title/Abstract] OR "gene expression analysis"[All Fields]) Translations gene expression profile: "transcriptome"[MeSH Terms] OR "transcriptome"[All Fields] OR ("gene"[All Fields] AND "expression"[All Fields] AND "profile"[All Fields]) OR "gene expression profile"[All Fields] gene expression analysis: "gene expression profiling"[MeSH Terms] OR ("gene"[All Fields] AND "expression"[All Fields] AND "profiling"[All Fields]) OR "gene expression profiling"[All Fields] OR ("gene"[All Fields] AND "expression"[All Fields] AND "analysis"[All Fields]) OR "gene expression analysis"[All Fields] squamous cell: "epithelial cells"[MeSH Terms] OR ("epithelial"[All Fields] AND "cells"[All Fields]) OR "epithelial cells"[All Fields] OR ("squamous"[All Fields] AND "cell"[All Fields]) OR "squamous cell"[All Fields] skin: "skin"[MeSH Terms] OR "skin"[All Fields] carcinoma: "carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR "carcinomas"[All Fields] OR "carcinoma's"[All Fields] cutaneous: "cutaneous"[All Fields] OR "cutaneously"[All Fields] OR "cutanous"[All Fields] squamous cell carcinoma: "carcinoma, squamous cell"[MeSH Terms] OR ("carcinoma"[All Fields] AND "squamous"[All Fields] AND "cell"[All Fields]) OR "squamous cell carcinoma"[All Fields] OR ("squamous"[All Fields] AND "cell"[All Fields] AND "carcinoma"[All Fields])	
Search strategy for Google Scholar	

((Gene expression profile) OR (40-GEP) AND (Cutaneous squamous cell carcinoma)) AND metastatic risk)

Table S2. *Risk of Bias within Studies* - Newcastle-Ottawa Quality Assessment Scale (NOS) score of the included studies

Study, first author, year (reference)	Selection				Comparability	Outcome			Aggregate score
	Representativeness of the exposed cohort (maximum: *)	Selection of the non-exposed cohort (maximum: *)	Ascertainment of exposure (maximum: *)	Demonstration that outcome of interest was not present at start of study (maximum: *)	Comparability of cohorts on the basis of the design or analysis (maximum: **)	Assessment of outcome (maximum: *)	Whether follow-up was long enough to occur (maximum: *)	Adequacy of follow-up of cohorts (maximum: *)	
Wysong et al. (2020) [12]	B	?	A	A	A+B	B	A	A	8
Ibrahim et al. (2021) [13]	B	?	A	A	A+B	B	A	A	8
Arron et al. (2022) [14]	B	?	A	A	A+B	B	A	A	8

Table S3. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2020 checklist: recommended items to address in a systematic review protocol\*

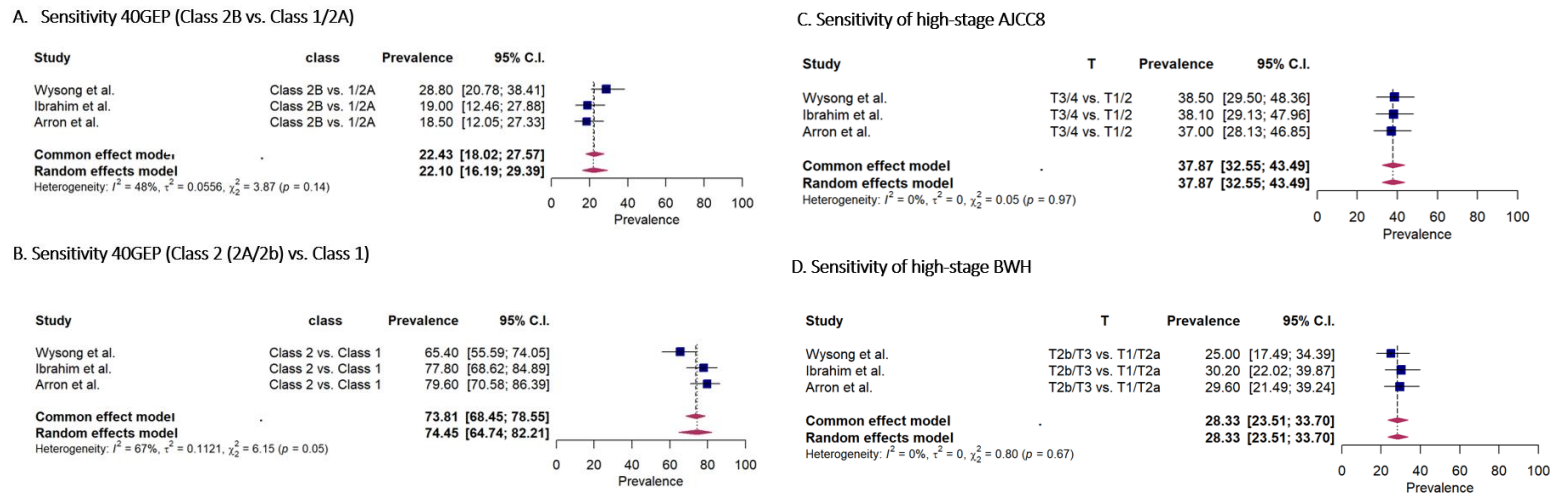
Section and Topic	Item #	Checklist item
<b>TITLE</b>		
Title	1	Identify the report as a systematic review.
<b>ABSTRACT</b>		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
<b>INTRODUCTION</b>		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
<b>METHODS</b>		
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.

Section and Topic	Item #	Checklist item
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
<b>RESULTS</b>		
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study characteristics	17	Cite each included study and present its characteristics.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.

Section and Topic	Item #	Checklist item
<b>DISCUSSION</b>		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
<b>OTHER INFORMATION</b>		
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing interests	26	Declare any competing interests of review authors.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

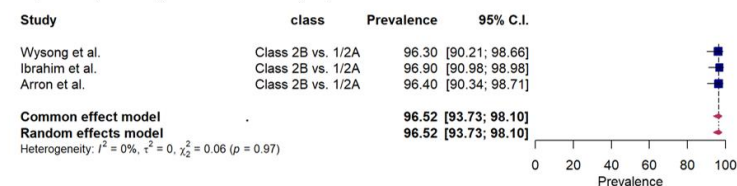
Accuracy Metrics (sensitivity and specificity) Comparison for cutaneous squamous cell carcinoma per 40-GEP class and AJCC8/ BWH T stage.

**Figure S1.** Accuracy of risk prediction of the 40-gene expression profile class and Brigham and Women’s Hospital or American Joint Committee on Cancer Cancer Staging Manual, Eighth Edition binary T stage.

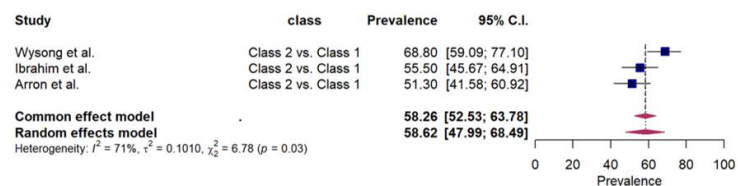




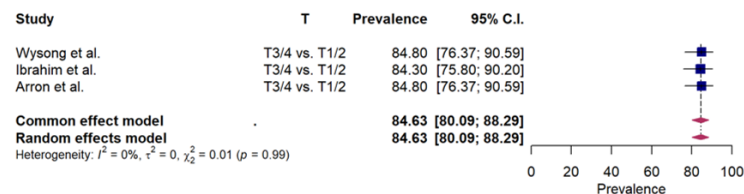
#### E. Specificity 40GEP (Class 2B vs. Class 1/2A)



#### F. Specificity 40GEP (Class 2 (Class 2A/2B) vs. Class 1)



#### G. Specificity of high-stage AJCC8



#### H. Specificity of high-stage BWH

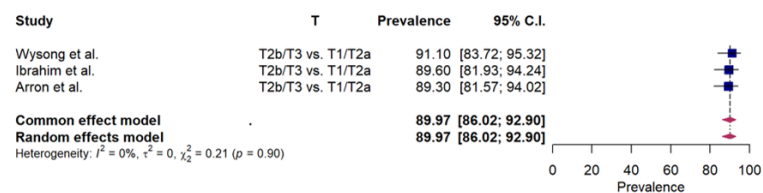


Figure S1. Forest plot of the accuracy metrics; rates of sensitivity (figures A-D) and specificity (figures E-H). (A) sensitivity for 40-GEP (class 2B vs. class 1/2A), (B) sensitivity for 40-GEP (class 2 (2A/2B) vs. class 1), (C) sensitivity for AJCC8 (T3/T4 vs. T1/T2), (D) sensitivity for BWH (T2b/T3 vs. T1/T2a), (E) specificity for 40-GEP (class 2B vs. class 1/2A), (F) specificity for 40-GEP (class 2 (2A/2B) vs. class 1), (G) specificity for AJCC8 (T3/T4 vs. T1/T2) and (H) specificity for BWH (T2b/T3 vs. T1/T2a). AJCC8, American Joint Committee on Cancer Cancer Staging Manual, eighth edition; BWH, Brigham and Women's Hospital; GEP, gene expression profile [12,13,15].