NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Health Technology Assessment for early detection of oral cancer

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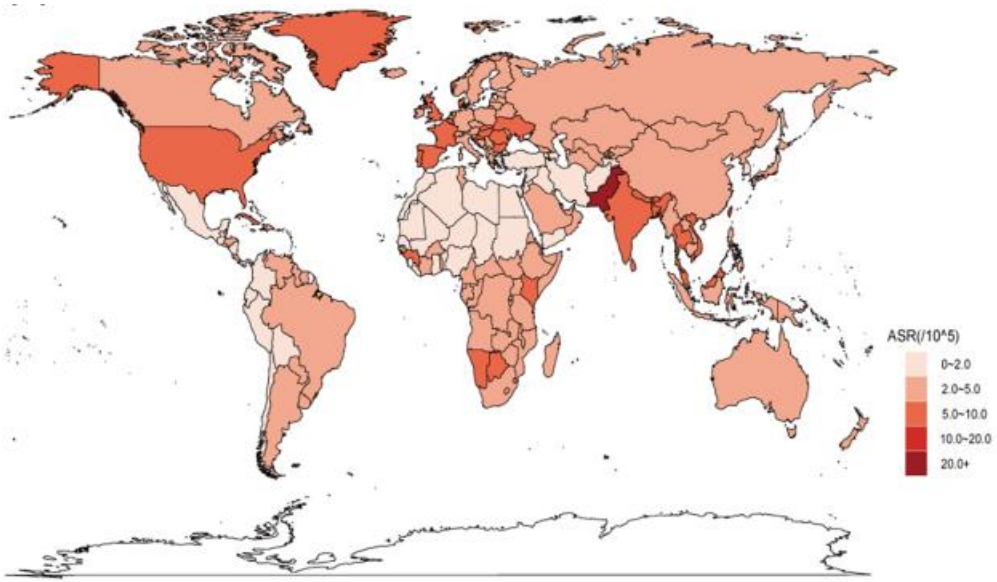
OECI Helsinki, 12 June 2024

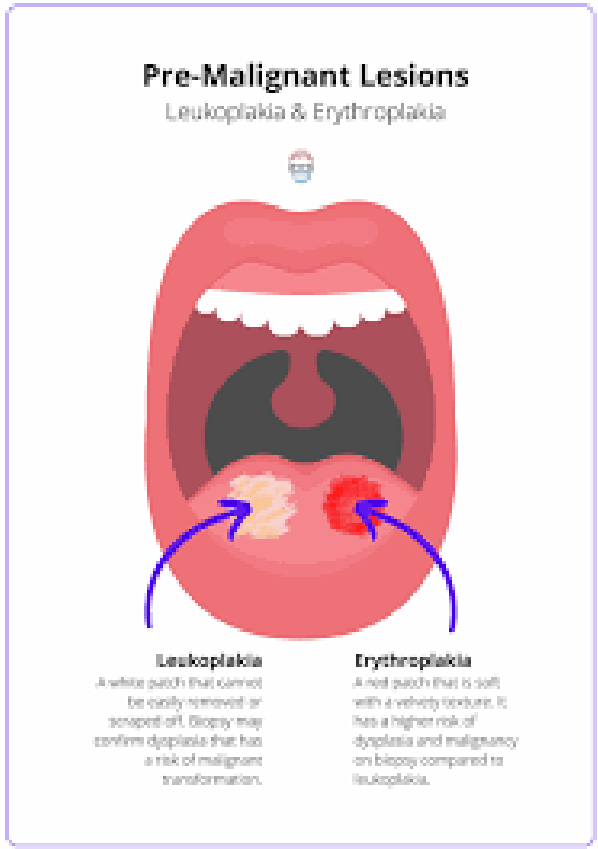
Context of oral cancer

- Incidence oral cancer over 650,000 patients worldwide
- Patient-, care giver-, societal- and economical burden is high:
  -> complex surgeries, radiotherapy, immunotherapy, extensive rehabilitation
- Prevention/early detection can support reduction of societal burden
- Instruments to evaluate prevention programs: Health Technology Assessment (HTA)



Background OPMD, precancerous lesions of oral cancer

OPMD: Oral Potential Malignant Disorder - group of oral mucosal lesions with an increased risk of malignant transformation



Current landscape – clinical management

OPMD

- Under researched field, unmet medical need
- Heterogeneous evidence, definitions
- Heterogeneous management of OPMD

→ rationale COST action! Network of expertise

Table 3. Definitions of the Most Common Oral Potentially Malignant Disorders.*

Disorder	Definition
Oral potentially malignant disorder	Any oral mucosal abnormality that is associated with a significantly increased risk of oral cancer
Leukoplakia	A predominantly white plaque of questionable risk after the exclusion of other known diseases or disorders that carry no increased risk of cancer
Erythroplakia	A predominantly fiery red patch that cannot be characterized clinically or pathologically as any other definable disease
Submucous fibrosis	A chronic disease affecting the oral mucosa that initially results in loss of fibroelasticity of the lamina propria and can result in fibrosis of the lamina propria and the submucosa of the oral cavity, along with epithelial atrophy
Lichen planus	A chronic inflammatory disorder of unknown cause (with characteristic relapses and remissions) that is manifested as white reticular lesions, accompanied or not by atrophic, erosive, or ulcerative plaque-type areas; frequent bilaterally symmetric lesions in which desquamative gingivitis may be a feature
Lichenoid lesions	Oral lesions with lichenoid features but lacking the typical clinical or histopathological appearances of oral lichen planus (i.e., may show asymmetry or are reactions to dental restorations or certain drugs)

* Data are from Warnakulasuriya et al.[15]

INTERCEPTOR – COST Action

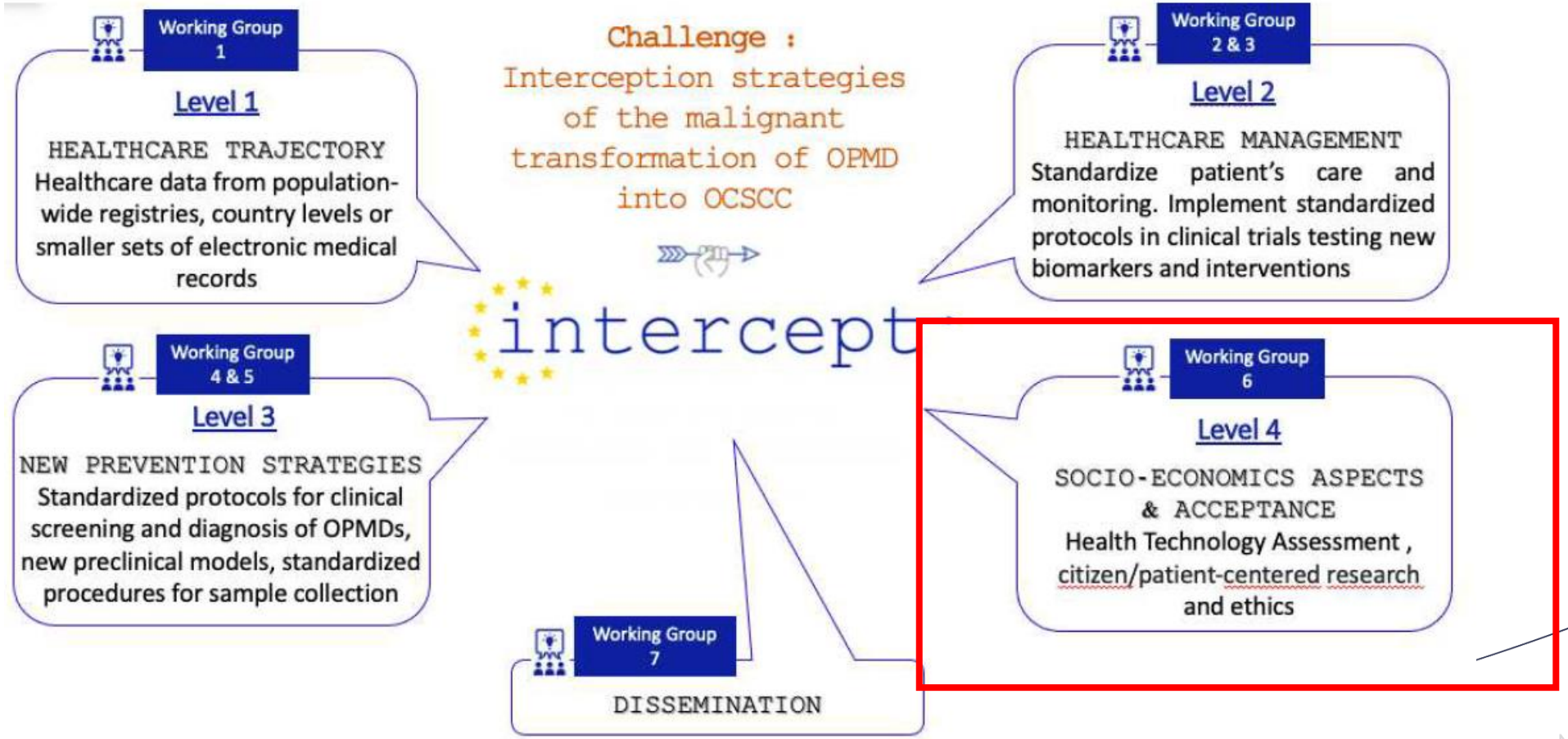
PI: Pierre Saintigny, Centre Léon Bérard, Lyon, France

AIM:

INTercEption of oRal CancEr develoPmenT (INTERCEPT) COST Action aims to develop a new multidisciplinary approach and to reorganize disease care management by establishing support for people affected by OPMD, which will result in prevention of malignant transformation. An innovative approach to address the prevention challenges beyond weaning programs and antismoking/drinking advertising campaigns is foreseen.

Funded by the European Union

COST-Action = network building, learning from each other



Aim WP6: socio-economics, ethics and acceptance

To build a network of Expertise to gather cost- and patient related data, to perform generalizable Health Technology Assessments (HTA), including cost-effectiveness analysis, patient related aspects, organizational aspects and ethical implications, to ultimately decrease the economic burden of HNC.

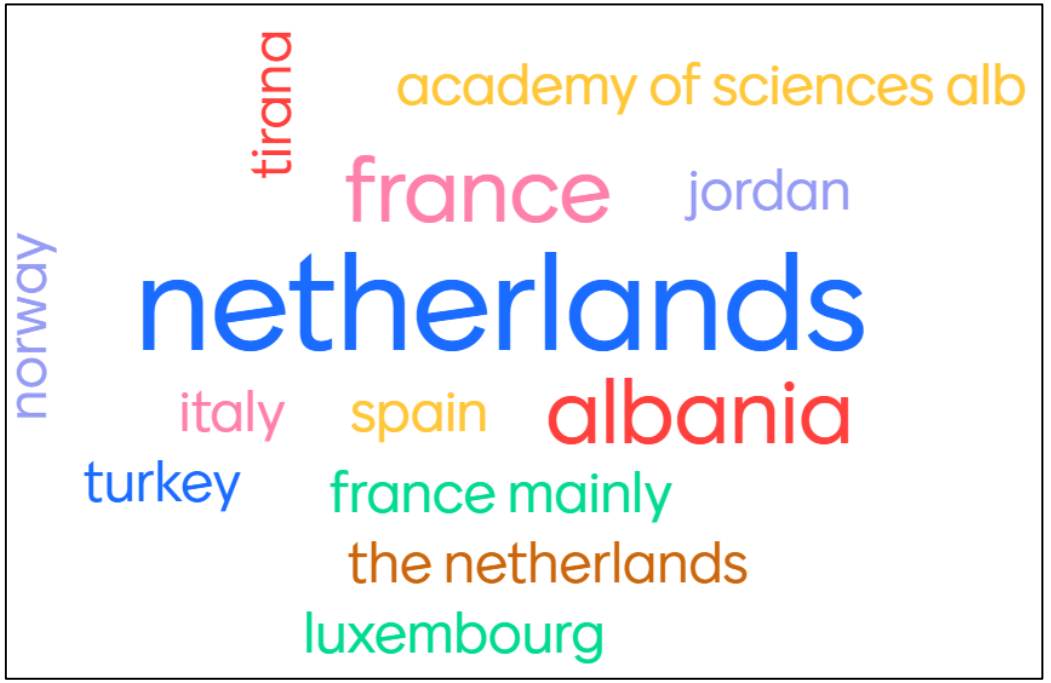
Components:

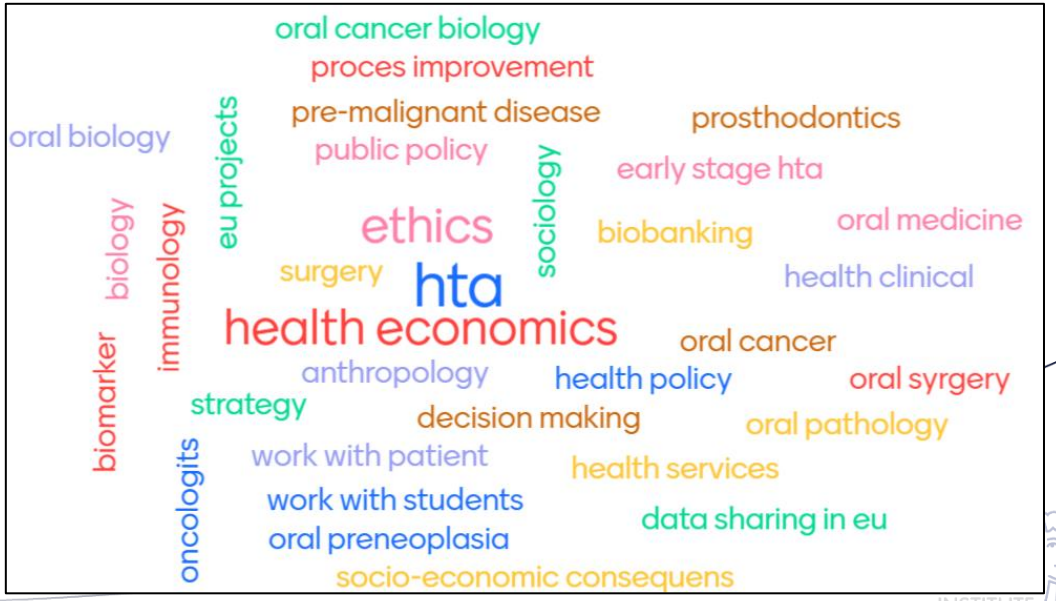
1. Workshop 21-22 September 2023 with stakeholders
2. Framework HTA for OPMD (cost-effectiveness, organizational, ELSI aspects)
3. National campaigns

If you want to join, please register at: www.e-services.cost.eu

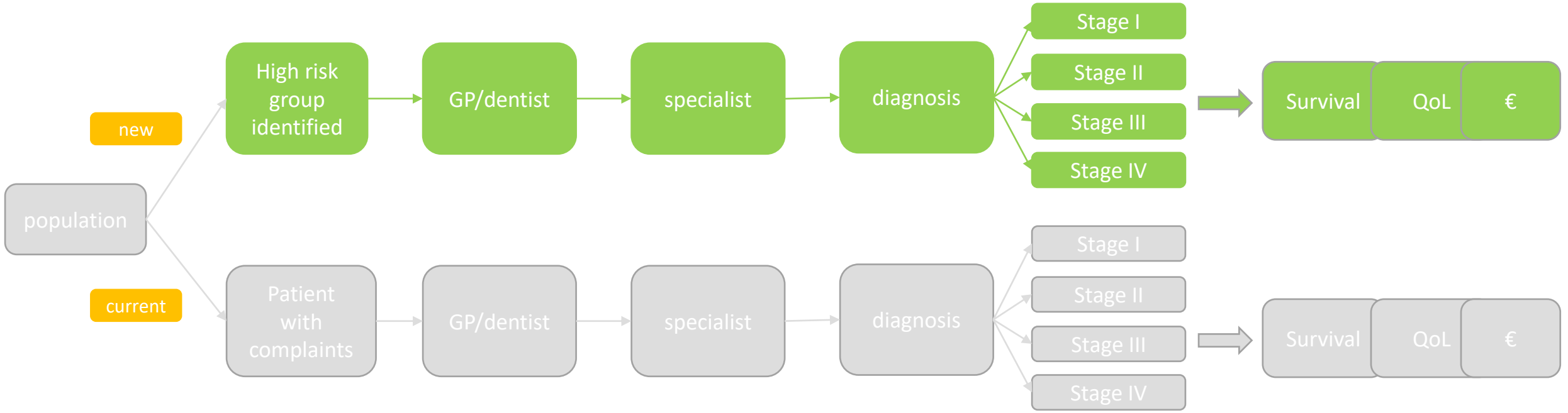
What was done the first year:

- First online meeting WP6
- 12 countries, many different expertises
- = building capacity
- Workshop with stakeholders
- Every 2 months WG-meeting with guest speaker





HTA framework



Review of literature

Cost-effectiveness analysis

Ethical- aspects

Part of 1 HTA framework = review

Cost of oral potentially malignant disorders (OPMD): Review of the Literature

Objective

- To review cost assessment of OPMD screening & management

Method

- Databases included Medline, Gale Academic OneFile, and Academic Search Index

- Articles (English language) published between January 1, 2000 and May 31, 2024

Review HTA in early detection of OPMD

- The search process consisted of combinations of three keywords using Boolean operators ‘AND’/‘OR’: *[oral potential malignant disorder OR leukoplakia] AND [cost]*

- Studies were considered eligible if an economic evaluation was included. Studies were excluded if they did not clearly comprise a cost assessment *(including CEA, CUA, cost consequence, and cost benefit),* as well as reviews, systematic reviews, clinical effectiveness studies, study protocols

- We further hand-searched the citations of the retrieved eligible papers to identify additional publications that might have been missed during the initial search

Review HTA in early detection of OPMD

Results: Of the initial 4,120 records identified, twelve studies published between 2000 and 2024 were selected for inclusion

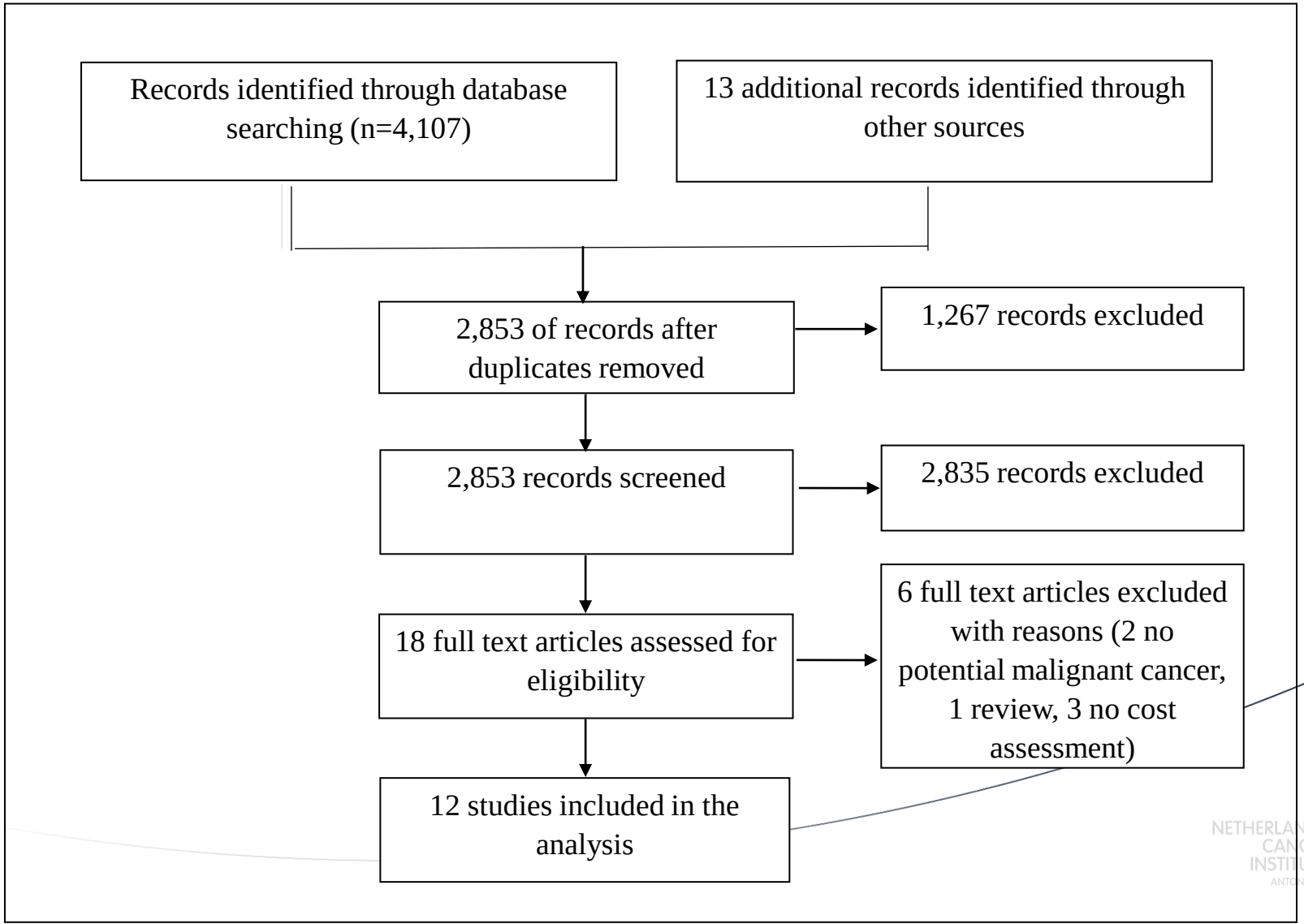


Fig. 1 PRISMA flow diagram

Figure 1: Prisma flow diagram

Review HTA in early detection of OPMD (screening)

Table 1: Study characteristics

Reference	Type of evaluation	Method	Country	Results
[12] van der Meij et al. 2002	CEA of screening for oral cancer in oral lichen planus patients	Decision-analytic model	Netherlands	The marginal cost-effectiveness was calculated as $53 430 per life saved.
[2] Dedhia et al. 2011	CEA for yearly screening of high-risk men	Markov modeling	USA	No-Screen arm dominated (i.e. is more expensive and less effective than screening)
[10] Speight et al. 2006	Alternative oral cancer screening programs in primary care environment	Markov	UK	the ICER of opportunistic high-risk screening by a GDP was £22,850 per additional QALY compared with no screening
[4] Huang et al. 2019	CEA OC screening program	Retrospective study	Taiwan	US$ 5579 per LYS (cancer detected before stage I)
[11] Subramanian et al. 2008	CEA comparing oral cancer screening vs.no screening	RCT	India	The incremental cost per life-year saved was US$ 835 for all individuals eligible for screening and US$ 156 for high-risk individuals
[6] Kumdee et al. 2018	CUA of oral precancer screening program, compared to the no-screening	Markov modeling	Thailand	THB 311,030 per QALYs gained (threshold is THB 160,000 per QALY gained)

Figure 1: Prisma flow diagram

Review HTA in early detection of OPMD (management)

Table 1: Study characteristics

Reference	Type of evaluation	Method	Country	Results
[3] Dwivedi et al. 2023	CEA for screening of high-risk population vs. no screening; mass-screening vs. no screening	Markov modeling	India	High-risk screening was dominant over no-screening; high-risk screening was cost-effective compared to the mass-screening.
[8] Raman et al. 2021	cost of treating OPMD	Retrospective study	Malaysia	OPMD 4,583 MYR (USD 4,139) potential economic benefit of investing in preventive medicine and early detection
[9] Raman et al. 2021	household out-of-pocket (OOP) family expenditure for treatment of OPMD	cross-sectional survey	Malaysia	OPMD 2.320 MYR
[7] Patel et al. 2021	Costs incurred by patients for the care of OPMD	prospective study	India	costs of OPMD INR 500
[5] Idrees et al. 2022	CUA of oral liquid-based brush cytology (OLBC) in the diagnosis of OC and OPMD (screening technique)	prospective study	Australia	Cost of OLBC was less than 26% of the cost of surgical biopsy (no CUA)
[1] Amarasinghe et al. 2021	Cost description (management of patient with an OPMD)	hospital-based costing	Sri Lanka	US$ 140 for OPMD management per patient/year (including healthcare and societal costs)

Figure 1: Prisma flow diagram

Review HTA in early detection of OPMD

Strength: This literature review complements existing reviews on the economic burden of oral cancers *(e.g. Ribeiro-Rotta et al. 2022)* and economic evaluations of oral cancer screening *(Raman et al. 2023) -> both screening and OPMD disease management*

Limitation: Some studies may be missed considering that the abstracts were screened by one reviewer (LP) only

Ribeiro-Rotta RF, Rosa EA, Milani V, Dias NR, Masterson D, da Silva EN, Zara ALSA. The cost of oral cancer: A systematic review. PLoS One. 2022 Apr 21;17(4):e0266346. doi: 10.1371/journal.pone.0266346. PMID: 35446870; PMCID: PMC9022815.

Raman S, Shafie AA, Tan BY, Abraham MT, Chen Kiong S, Cheong SC. Economic Evaluation of Oral Cancer Screening Programs: Review of Outcomes and Study Designs. Healthcare (Basel). 2023 Apr 21;11(8):1198. doi: 10.3390/healthcare11081198. PMID: 37108032; PMCID: PMC10138408.

Next steps

- To add a full text second reviewer
- To provide a general interpretation of the results in the context of other evidence (cf. part of 2 HTA framework = Early Cost-effectiveness Analysis)
- to perform a critical appraisal using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) instrument checklist in order to assess the methods employed and the quality of the reporting of the published cost evaluations

References

1. Amarasinghe H, Jayasinghe RD, Dharmagunawardene D, Attygalla M, Kumara DR, Kularatna S, Johnson NW. Economic cost of managing patients with oral potentially malignant disorders in Sri Lanka. Community Dent Oral Epidemiol. 2022 Apr;50(2):124-129. doi: 10.1111/cdoe.12639. Epub 2021 Apr 25. PMID: 33899256.

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3. Dwivedi P, Lohiya A, Bahuguna P, Singh A, Sulaiman D, Singh MK, Rajsekar K, Rizwan SA. Cost-effectiveness of population-based screening for oral cancer in India: an economic modelling study. Lancet Reg Health Southeast Asia. 2023 Jun 2;16:100224. doi: 10.1016/j.lansea.2023.100224. PMID: 37694179; PMCID: PMC10485781.

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5. Idrees M, Farah CS, Sloan P, Kujan O. Oral brush biopsy using liquid-based cytology is a reliable tool for oral cancer screening: A cost-utility analysis: Oral brush biopsy for oral cancer screening. Cancer Cytopathol. 2022 Sep;130(9):740-748. doi: 10.1002/cncy.22599. Epub 2022 Jun 15. PMID: 35704619; PMCID: PMC9544877.

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7. Patel JR, Rupani MP. Costs incurred by patients with oral potentially malignant disorders: is there a public health need for financial protection in India? BMC Res Notes. 2021 Oct 24;14(1):396. doi: 10.1186/s13104-021-05814-2. PMID: 34689827; PMCID: PMC8543918.*

8. Raman S, Shafie AA, Abraham MT, Shim CK, Maling TH, Rajendran S, Cheong SC. Provider cost of treating oral potentially malignant disorders and oral cancer in Malaysian public hospitals. PLoS One. 2021 May 13;16(5):e0251760. doi: 10.1371/journal.pone.0251760. PMID: 33984051; PMCID: PMC8118562.

9. Raman S, Shafie AA, Abraham MT, Shim CK, Maling TH, Rajendran S, Cheong SC. Household Catastrophic Health Expenditure from Oral Potentially Malignant Disorders and Oral Cancer in Public Healthcare of Malaysia. Asian Pac J Cancer Prev. 2022 May 1;23(5):1611-1618. doi: 10.31557/APJCP.2022.23.5.1611. PMID: 35633545; PMCID: PMC9587868.

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11 Subramanian S, Sankaranarayanan R, Bapat B, Somanathan T, Thomas G, Mathew B, Vinoda J, Ramadas K. Cost-effectiveness of oral cancer screening: results from a cluster randomized controlled trial in India. Bull World Health Organ. 2009 Mar;87(3):200-6. doi: 10.2471/blt.08.053231. PMID: 19377716; PMCID: PMC2654641.

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Part of 2 HTA framework = Early Cost-effectiveness Analysis

Objective

- To explore the potential cost-effectiveness of a hypothetical biomarker to stratify patients with Oral Potentially Malignant Disorders (OPMD) based on their risk of developing Oral Squamous Cell Carcinoma (OSCC).

Performed by Master Student NKI: Alessandro Catanzaro

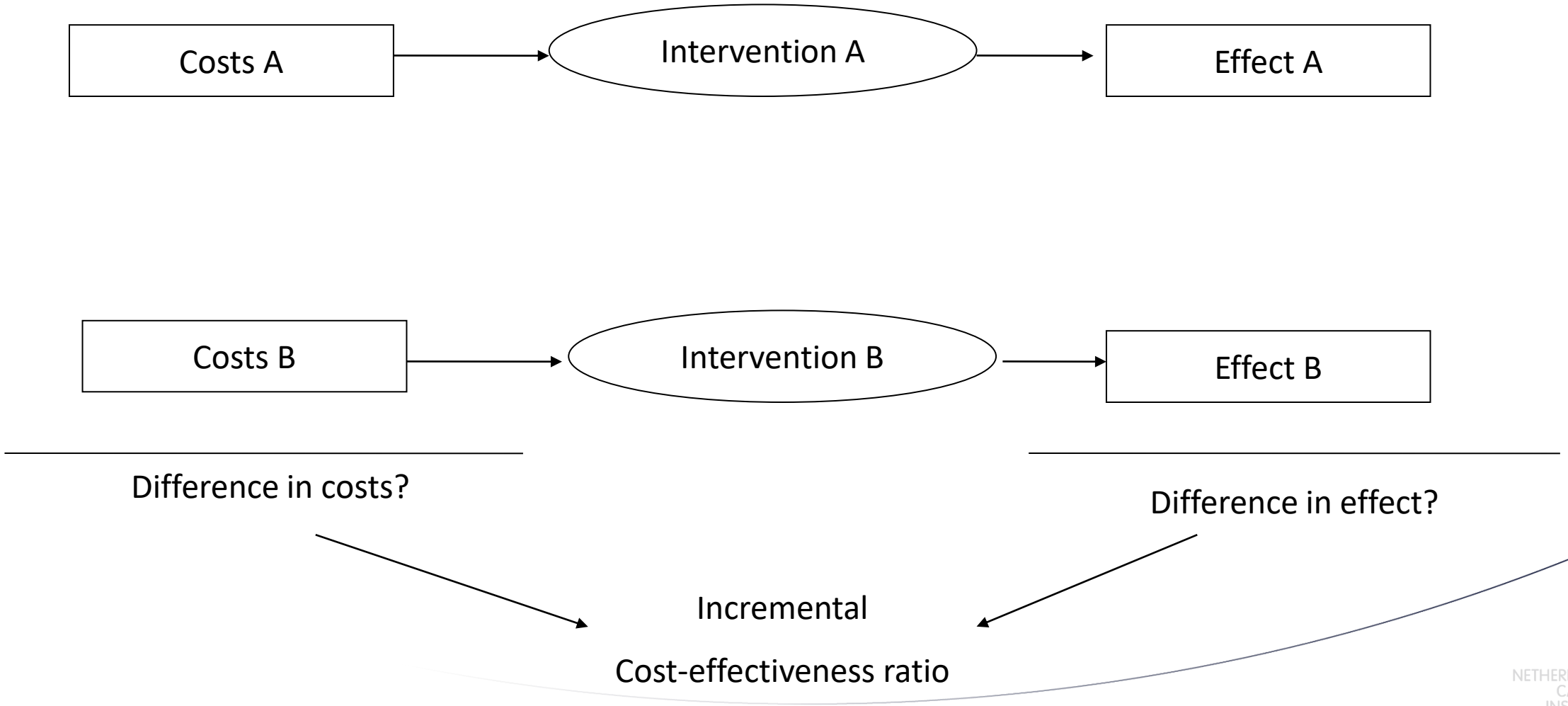
Design cost-effectiveness analysis

- Population: OPMD patients
- Intervention: LOH: low, high risk*
- Comparator: WHO 2017 classification: mild, moderate, severe dysplasia
- Outcome: incremental cost-effectiveness ratio (ICER)

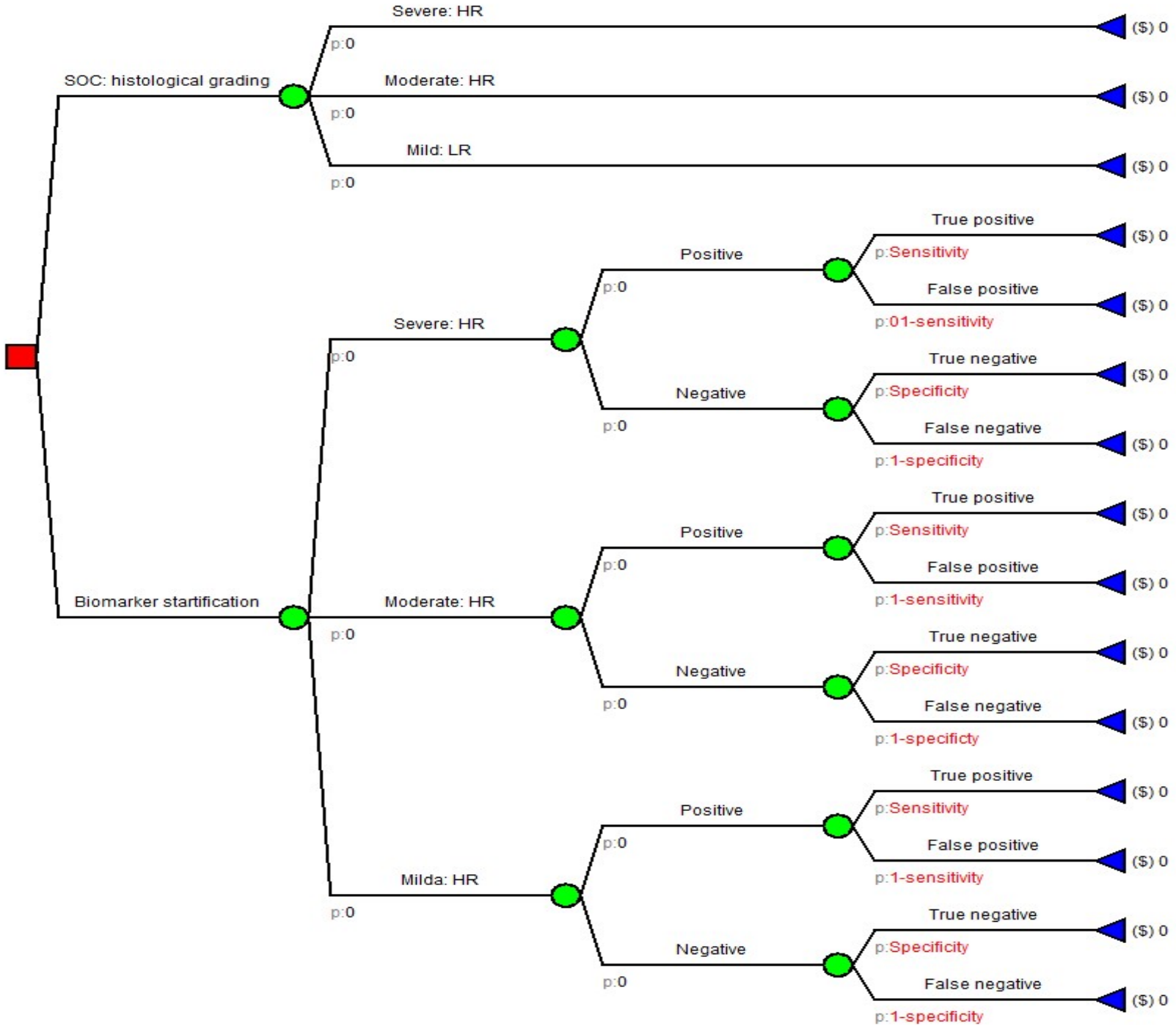
- Setting: Dutch
- Perspective: healthcare
- Time horizon: Lifetime
- Willingness to pay threshold €20,000/QALY

*William ea, JAMA oncology, 2015

Cost-Effectiveness Analysis

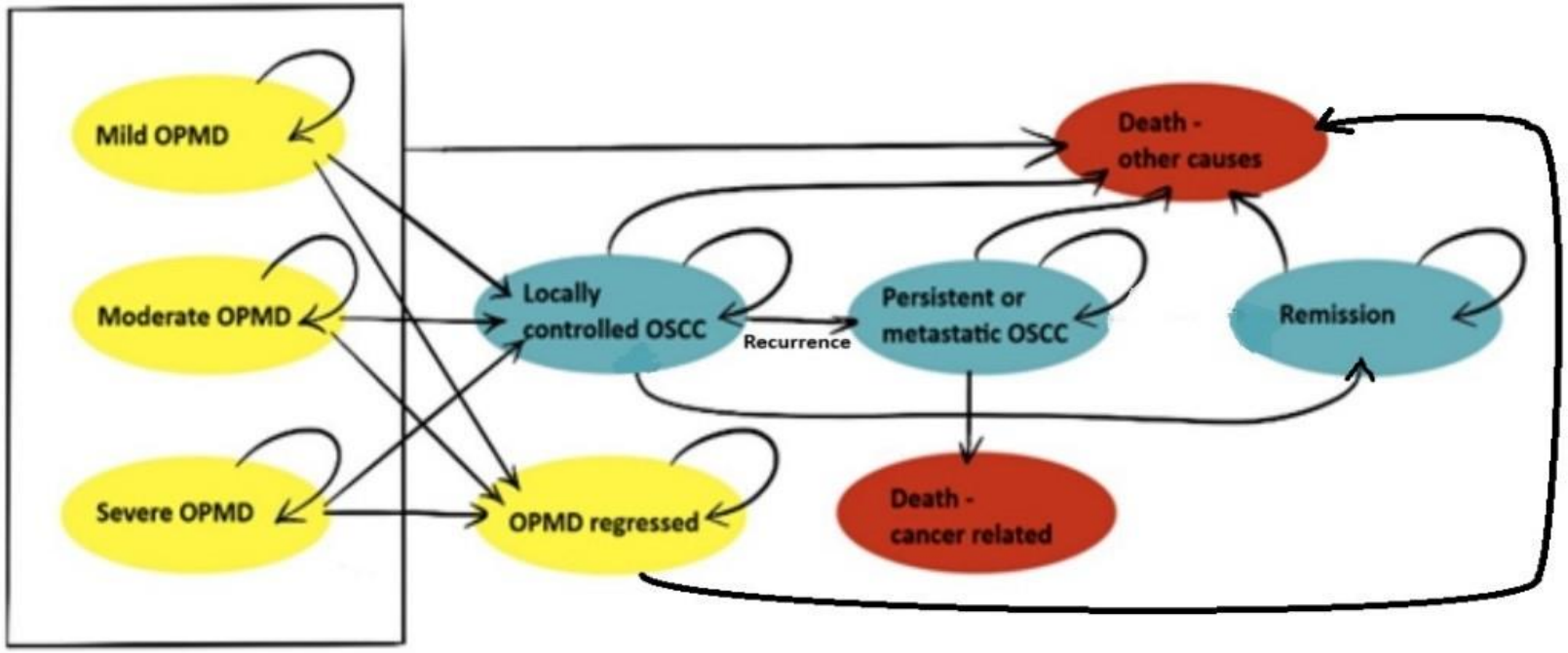


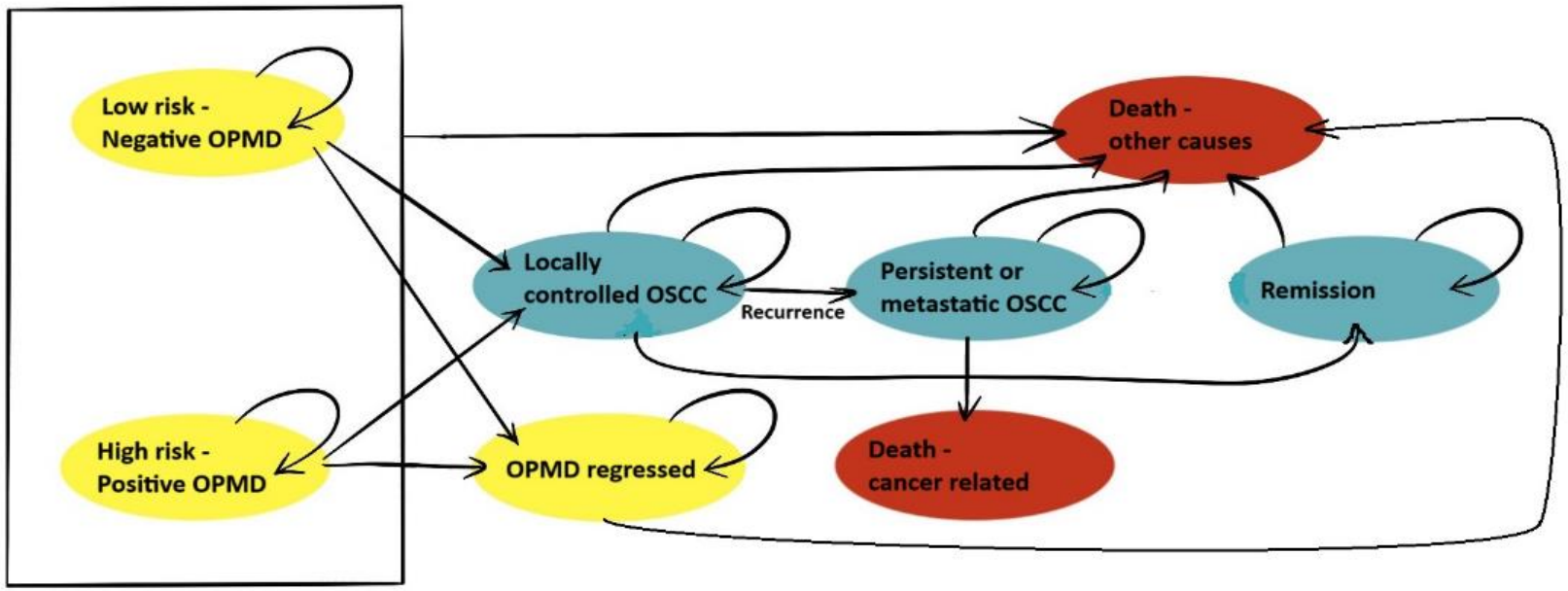
Decision tree



Model:

Time dependent
State transition model

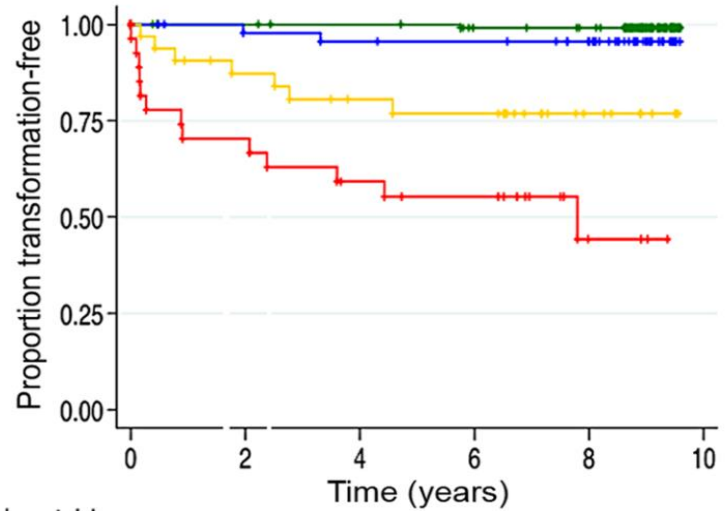


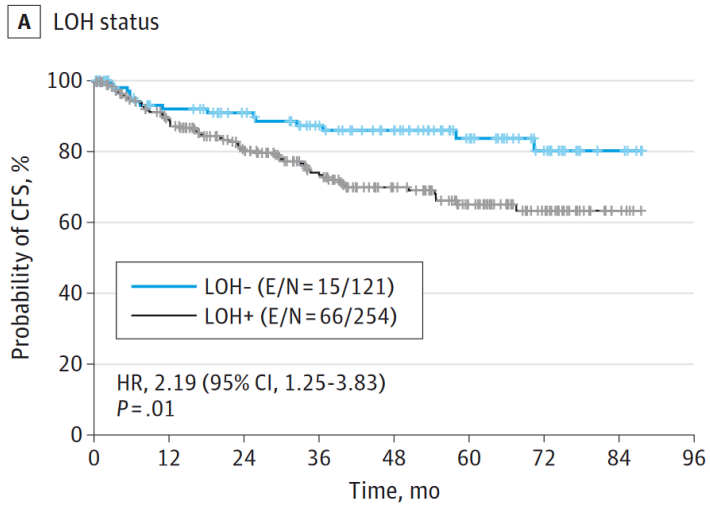


Input – transition probabilities

Table 1. Summary model inputs

Description	Value	Source
Probabilities		
Proportion of Mild OPMD	0.482	William et al. (2016)
Proportion of Moderate OPMD	0.388	William et al. (2016)
Proportion of Severe OPMD	0.129	William et al. (2016)
Mild OPMD		
Proportion of Positive	0.57	Assumption from EPOC
Proportion of Negative	0.43	Assumption from EPOC
Moderate OPMD		
Proportion of Positive	0.72	Assumption from EPOC
Proportion of Negative	0.28	Assumption from EPOC
Severe OPMD		
Proportion of Positive	0.71	Assumption from EPOC
Proportion of Negative	0.29	Assumption from EPOC
Base case Sensitivity	0.94	Mao et al. (1996)
Base case Specificity	0.37	Mao et al. (1996)
Oral cancer mortality rate (Over 5 years)	0.681	Mucke et al. (2009)
Relative rate of cancer death		
Age 55 - 64	1.5	Rogers et al. (2009)
Age 65 -74	1.6	Rogers et al. (2009)
Age >75	3.4	Rogers et al. (2009)
Rate of OSCC recurrence	0.2	Ganly et al. (2013)
RR of developing cancer after excision	0.51	Khoudigian-Sinani et al. (2017)





Input – Costs, Quality-of-Life

Costs (2023, €)		
Cost of visit	€ 127.50	2024 Dutch cost manual
Cost of biopsy	€ 120.23	NZA DBC, product 234084
Cost of biomarker assay	€ 165.30	Estimation, average FISH/PCR
Cost of OPMD excision	€ 2,535.00	NZA DBC, product 029299017
Cost of OSCC surgery	€ 8,660.00	NZA DBC, product 029299018
Number of courses of RT	35	
Cost of one course of RT	€ 940.00	NZA DBC, product 990061030
Number of courses of chemotherapy	3	
Cost of one course of chemotherapy	€ 3,910.00	NZA DBC, product 029299028
Costs metastatic OSCC (per cycle)	€ 32,160.00	Linden et al. (2015)
Utilities		
Utility OPMD health state	0.92	Downer et al. (1997)
Utility locally controlled OSCC	0.88	Downer et al. (1997)
Utility persistent/metastatic OSCC	0.68	Downer et al. (1997)
Utility remission from OSCC	1	Assumption
Utility loss for excision	0.05	Assumption

Preliminary Results

Base case

Table. Base case: 94% sensitivity, 37% specificity

	Cost	QALYs	NMB	ICER
SOC	€ 16,227.00	14.26805	€ 269,134.00	NA
BI	€ 17,307.82	14.28851	€ 266,795.00	€ 52,828.67

Table. Base case: 95% sensitivity, 50% specificity

	Cost	QALYs	NMB	ICER
SOC	€ 16,227.00	14.26805	€ 269,134.00	NA
BI	€ 17,360.27	14.31874	€ 269,014.50	€ 22,358.73

Results – scenario analyses

Table. ICER values threshold analysis considering a price of €165.3 and base case visit and follow-up intervals

Sensitivity	Specificity				
	30%	50%	75%	90%	100%
30%	(D) -69662.48	(D) -133110	€ 2,312,825.00	€ 203,654.70	€ 127,937.40
50%	(D) -76160.62	(D) -251762.8	€ 155,894.60	€ 82,270.46	€ 63,140.62
75%	(D) -107352.3	€ 152,021.20	€ 42,762.00	€ 31,088.26	€ 26,580.09
90%	(D) -1000396	€ 36,585.63	€ 18,709.26	€ 15,204.60	€ 13,695.10
100%	€ 32,657.67	€ 11,618.83	€ 8,304.78	€ 7,511.88	€ 7,152.44

Alternative scenarios

Table. Alternative scenario 1: biomarker assay only for Moderate and Severe dysplasia

	Cost	QALYs	NMB	ICER
SOC	€ 16,227.00	14.26805	€ 269,134.00	NA
BI	€ 10,367.65	14.51201	€ 279,872.60	-24017.51

Table. Alternative scenario 2: biomarker assay only for Moderate dysplasia

	Cost	QALYs	NMB	ICER
SOC	€ 16,227.00	14.26805	€ 269,134.00	NA
BI	€ 10,921.31	14.42558	€ 277,590.30	-33681.18

Table. Alternative scenario 3. limited follow ups based on O&M surgeon elicitation

	Cost	QALYs	NMB	ICER
SOC	€ 13,344.48	14.26805	€ 272,016.50	NA
BI	€ 16,167.80	14.28851	€ 269,602.40	137998.1

Preliminary Conclusion

- A hypothetical biomarker for OPMD should at least have a sensitivity of 90% and specificity of 75%.
- The cost-effectiveness becomes more favorable when tailor follow-up schemes

Discussion & next steps

HTA framework

- This is an early analysis with a hypothetical biomarker: information for further research
- Base case for incorporating RWD from database and biobank COST-action
- -> Include potential new biomarkers
- -> Include QoL data from COST-action
- -> Include cost data from different countries

- Future: Build cost-effectiveness model with screening part (link with review results)

Funded by
the European Union

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COST-action core group & members

OECI Helsinki, 12 June 2024

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