KCE REPORT 242S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

ONCOGENETIC TESTING FOR PERSONS WITH HEREDITARY ENDOCRINE CANCER SYNDROMES

APPENDIX

KCE REPORT 242S
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

ONCOGENETIC TESTING FOR PERSONS WITH HEREDITARY ENDOCRINE CANCER SYNDROMES

APPENDIX

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COLOPHON

Title:	Oncogenetic testing for persons with hereditary endocrine cancer syndromes – Appendix
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APPENDIX REPORT

TABLE OF CONTENTS

LIST OF TABLES

1. COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

1.1. Composition of the Guideline Development Group

Clinicians	Field of expertise, affiliations
Bruce Poppe, President of the GDG	Clinical geneticist, UZ Gent
Marie Bex	Endocrinologist, UZ Leuven
Bert Bravenboer	Endocrinologist, UZ Brussel
Kathleen Claes	Molecular geneticist, UZ Gent
Bruno Lapauw	Endocrinologist, UZ Gent
Alexandre Persu	Nephrologist, UCL
Kris Poppe	Endocrinologist, CHU – St. Pierre
Urielle Ullman	Clinical geneticist, Institut de Pathologie de Gosselies
Tom Van Maerken	Clinical geneticist, UZ Gent
Laurent Vroonen	Endocrinologist, Université de Liège

1.2. Composition of the KCE expert team

KCE member	Specific role
Kristel De Gauquier	Program Director
Sabine Stordeur	Principal Coordinator
Joan Vlayen	Principal Investigator
Frank Hulstaert	Methodological support

1.3. Acknowledgements

The Belgian Cancer Registry is acknowledged for the provision of epidemiologic data.

2. SEARCH STRATEGIES

2.1. Search strategy for guidelines

Guidelines were identified through the search for systematic reviews and primary studies, and through a search of the websites of the following organisations: STOET (www.stoet.nl), American Thyroid Association (ATA, www.thyroid.org), American Association of Clinical Endocrinologists (AACE, www.aace.com), Endocrine Society (www.endocrine.org), and the European Thyroid Association (ETA, www.eurothyroid.com).

Six guidelines were included and appraised using the AGREE II instrument.

2.2. Search strategies for other publications (systematic reviews, meta-analyses, individual studies)

2.2.1. Systematic reviews

Date	**09-05-2014**
Database	OVID Medline
Search Strategy	1 men1.mp. (1366) 2 men2$.mp. (578) 3 RET.mp. (5356) 4 VHL.mp. (2877) 5 SDH$.mp. (4115) 6 or/1-5 (13415) 7 meta-analysis.mp,pt. or review.pt. or search:.tw. (2031107) 8 6 and 7 (2000) 9 limit 8 to yr="2008 - 2014" (779)

Date	**09-05-2014**
Database	OVID PreMedline
Search Strategy	1 men1.mp. (67) 2 men2$.mp. (43) 3 RET.mp. (383) 4 VHL.mp. (201) 5 SDH$.mp. (356) 6 or/1-5 (979)

	7 meta-analysis.mp,pt. or review.pt. or search:.tw. (32466) 8 6 and 7 (28) 9 limit 8 to yr="2008 - 2014" (25)

Date	**09-05-2014**
Database	Embase
Search Strategy	#1. men1 OR ret OR vhl OR sdh* OR men2* (18782) #2. men1 OR ret OR vhl OR sdh* OR men2* AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2008-2014]/py (46)

Date	**09-05-2014**
Database	Cochrane Library
Search Strategy	#1 men1:ti,ab #2 SDH*:ti,ab #3 RET:ti,ab #4 VHL:ti,ab #5 men2:ti,ab #6 #1 OR #2 OR #3 OR #4 OR #5
Note	CDSR: N=54 DARE: N=2 HTA: N=11

2.2.2. Primary studies

Date	**12-05-2014**
Database	OVID Medline
Search Strategy	1 men1.mp. (1366) 2 exp Paraganglioma/ (19511) 3 PGL.mp. (1167) 4 2 or 3 (20503)

	5	exp Succinate Dehydrogenase/ (11913)
	6	SDH$.mp. (4115)
	7	5 or 6 (14297)
	8	4 and 7 (534)
	9	exp Pheochromocytoma/ (13779)
	10	exp Succinate Dehydrogenase/ (11913)
	11	SDH$.mp. (4115)
	12	exp Proto-Oncogene Proteins c-ret/an, ge, ph [Analysis, Genetics, Physiology] (1014)
	13	RET.mp. (5356)
	14	(VHL and (gene* or mutat*)).mp. (2388)
	15	10 or 11 or 12 or 13 or 14 (21690)
	16	9 and 15 (680)
	17	1 or 8 or 16 (2272)

Date	**09-05-2014**	
Database	OVID PreMedline	
Search Strategy	1	men1.mp. (67)
	2	paraganglioma$.mp. (344)
	3	PGL.mp. (80)
	4	2 or 3 (388)
	5	SDH$.mp. (360)
	6	4 and 5 (57)
	7	pheochromocytoma$.mp. (567)
	8	SDH$.mp. (360)
	9	RET.mp. (391)
	10	(VHL and (gene* or mutat*)).mp. (161)
	11	8 or 9 or 10 (878)
	12	7 and 11 (65)
	13	1 or 6 or 12 (158)

Date	09-05-2014
Database	Embase
Search Strategy	#1. men1:ab,ti (1415) #2. 'paraganglioma'/exp (5504) #3. pgl:ab,ti (1432) #4. 'succinate dehydrogenase'/exp (13147) #5. sdh*:ab,ti (5192) #6. 'succinate dehydrogenase'/exp OR sdh*:ab,ti (14555) #7. 'paraganglioma'/exp OR pgl:ab,ti (5880) #8. 'succinate dehydrogenase'/exp OR sdh*:ab,ti AND ('paraganglioma'/exp OR pgl:ab,ti) (653) #9. 'pheochromocytoma'/exp (18278) #10. sdh*:ab,ti (5192) #11. 'succinate dehydrogenase'/exp (13147) #12. 'protein ret'/exp (2587) #13. ret:ab,ti (6677) #14. vhl:ab,ti AND (gene*:ab,ti OR mutat*:ab,ti) (2798) #15. sdh*:ab,ti OR 'succinate dehydrogenase'/exp OR 'protein ret'/exp OR ret:ab,ti OR (vhl:ab,ti AND (gene*:ab,ti OR mutat*:ab,ti)) (25867) #16. 'pheochromocytoma'/exp AND (sdh*:ab,ti OR 'succinate dehydrogenase'/exp OR 'protein ret'/exp OR ret:ab,ti OR (vhl:ab,ti AND (gene*:ab,ti OR mutat*:ab,ti))) (1327) #17. men1:ab,ti OR ('succinate dehydrogenase'/exp OR sdh*:ab,ti AND ('paraganglioma'/exp OR pgl:ab,ti)) OR ('pheochromocytoma'/exp AND (sdh*:ab,ti OR 'succinate dehydrogenase'/exp OR 'protein ret'/exp OR ret:ab,ti OR (vhl:ab,ti AND (gene*:ab,ti OR mutat*:ab,ti)))) (2998) #18. men1:ab,ti OR ('succinate dehydrogenase'/exp OR sdh*:ab,ti AND ('paraganglioma'/exp OR pgl:ab,ti)) OR ('pheochromocytoma'/exp AND (sdh*:ab,ti OR 'succinate dehydrogenase'/exp OR 'protein ret'/exp OR ret:ab,ti OR (vhl:ab,ti AND (gene*:ab,ti OR mutat*:ab,ti)))) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2008-2014]/py (1082)

Date	12-05-2014	
Database	Cochrane Library	
Search Strategy	#1	men1:ti,ab
	#2	MeSH descriptor: [Paraganglioma] 1 tree(s) exploded
	#3	PGL:ti,ab
	#4	#2 or #3
	#5	MeSH descriptor: [Succinate Dehydrogenase] 1 tree(s) exploded
	#6	SDH*:ti,ab
	#7	#5 or #6
	#8	#4 and #7
	#9	MeSH descriptor: [Pheochromocytoma] 1 tree(s) exploded
	#10	MeSH descriptor: [Proto-Oncogene Proteins c-ret] 1 tree(s) exploded
	#11	RET:ti,ab
	#12	(VHL and (gene* or mutat*)):ti,ab
	#13	#5 or #6 or #10 or #11 or #12
	#14	#9 and #13
	#15	#1 or #8 or #14
Note	CENTRAL: N=5	

3. QUALITY APPRAISAL

3.1. Quality appraisal tools

3.1.1. Guidelines

The AGREE II evaluation score was used to critically appraise guidelines retrieved (Table 1).

Table 1 – AGREE II instrument

Critical appraisal of clinical practice guidelines - AGREE II
Domain 1. Scope and Purpose
1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
Domain 2. Stakeholder Involvement
4. The guideline development group includes individuals from all the relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.
Domain 3. Rigour of Development
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
Domain 4. Clarity of Presentation
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.

Critical appraisal of clinical practice guidelines - AGREE II
Domain 5. Applicability
18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/ or auditing criteria.
Domain 6. Editorial Independence
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

3.1.2. Systematic reviews

AMSTAR criteria were used to assess systematic reviews (Table 2).

Table 2 – AMSTAR checklist

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	□ Yes □ No □ Can't answer □ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	□ Yes □ No □ Can't answer □ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	□ Yes □ No □ Can't answer □ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	□ Yes □ No □ Can't answer □ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	□ Yes □ No □ Can't answer □ Not applicable

10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

3.1.3. Diagnostic accuracy studies

The quality assessment tool used for the quality assessment of diagnostic accuracy studies was QUADAS 2 Tool (Table 3).

Table 3 – The QUADAS 2 tool

Item	Label	Yes	No	Unclear
Domain 1: Patient selection				
1.1	Was a consecutive or random sample of patients enrolled?			
1.2	Was a case-control design avoided?			
1.3	Did the study avoid inappropriate exclusions?			
Could the selection of patients have introduced bias? Risk: LOW/HIGH/UNCLEAR				
Is there concern that the included patients do not match the review question? Concern: LOW/HIGH/UNCLEAR				
Domain 2: Index test(s)				
2.1	Were the index test results interpreted without knowledge of the results of the reference standard?			
2.2	If a threshold was used, was it pre-specified?			
Could the conduct or interpretation of the index test have introduced bias? Risk: LOW/HIGH/UNCLEAR				
Is there concern that the index test, its conduct, or interpretation differ from the review question? Concern: LOW/HIGH/UNCLEAR				
Domain 3: Reference standard				

Item	Label	Yes	No	Unclear
3.1	Is the reference standard likely to correctly classify the target condition?			
3.2	Were the reference standard results interpreted without knowledge of the results of the index test?			
Could the reference standard, its conduct, or its interpretation have introduced bias? Risk: LOW/HIGH/UNCLEAR				
Is there concern that the target condition as defined by the reference standard does not match the review question? Concern: LOW/HIGH/UNCLEAR				
Domain 4: Flow and timing				
4.1	Was there an appropriate interval between index test(s) and reference standard?			
4.2	Did all patients receive a reference standard?			
4.3	Did patients receive the same reference standard?			
4.4	Were all patients included in the analysis?			
Could the patient flow have introduced bias? Risk: LOW/HIGH/UNCLEAR				

3.1.4. Primary studies for therapeutic interventions

To assess risk of bias of randomised controlled trials, we used Cochrane Collaboration's tool (Table 4).

Table 4 – Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		

Domain	Support for judgement	Review authors' judgement
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

3.2. Guidelines quality appraisal

Six guidelines were included and appraised by one researcher (JV) using the AGREE II instrument (Table 5).

Table 5 – AGREE scores of identified guidelines

Source	Title	Standardised Score						Final Appraisal
		Scope	Stakeholder involvement	Rigour of development	Clarity	Applicability	Editorial Independence	
AACE 2009	American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Medical Guidelines for the Management of Adrenal Incidentalomas	50.0%	5.6%	16.7%	72.2%	12.5%	50.0%	Not recommended
ATA 2009	Medullary Thyroid Cancer: Management Guidelines of the American Thyroid Association	72.2%	38.9%	25.0%	77.8%	16.7%	75.0%	Not recommended
Binderup et al. 2013	Von Hippel-Lindau disease (vHL). National clinical guideline for diagnosis and surveillance in Denmark. 3rd Edition.	38.9%	50.0%	0.0%	5.6%	20.8%	0.0%	Not recommended
Endocrine Society 2014	Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline	44.4%	38.9%	29.2%	88.9%	25.0%	83.3%	Not recommended
STOET 2010	Erfelijke tumoren. Richtlijnen voor diagnostiek en preventive, 2010.	50.0%	11.1%	6.3%	72.2%	12.5%	0.0%	Not recommended
Thakker 2012	Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1)	44.4%	16.7%	22.9%	83.3%	16.7%	75.0%	Not recommended

3.3. Systematic reviews

3.3.1. Selection process

In total, 917 references were identified through the search in Medline, PreMedline, Embase and the Cochrane Library. After de-duplication (N=65) and removal of reviews published before 2008 (N=8) or in a language other than English, Dutch or French (N=63), 781 references remained. Based on title and abstract 755 reviews were excluded. Twenty-six reviews were included for full-text evaluation. Of these, two were finally included (Table 6). One additional review was identified though hand-searching of the MSAC website.[1]

Table 6 – Included SRs

Reference	Disease / Genetic test(s)
van Hulsteijn LT 2012 [2]	Malignant paraganglioma / SDHB, SDHD
MSAC 2011 [3]	von Hippel-Lindau syndrome / VHL
MSAC 2013 [1]	RET

3.3.2. Quality appraisal

Table 7 shows the results of the AMSTAR risk of bias assessment for the three included systematic reviews.

Table 7 – Methodological quality of the included systematic review (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assessed and docu-mented	Quality assess-ment used in conclus-ions	Appro-priate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
van Hulsteijn LT 2012	Can't answer	Can't answer	Y	Can't answer	Y	Y	Y	Y	Y	N	N
MSAC 2011	Y	Can't answer	Y	Y	Y	Y	Y	Y	Not applicable	N	N
MSAC 2013	Y	Can't answer	Y	Can't answer	Y	Y	Y	Y	Not applicable	N	N

3.4. Primary studies

3.4.1. Selection process

In total, 3517 references were identified through the search in Medline, PreMedline, Embase and the Cochrane Library. After de-duplication (N=846) and removal of studies published before 1990 (N=6) or in a language other than English, Dutch or French (N=131), 2534 references remained. Based on title and abstract 2373 references were excluded. One-hundred and sixty-one studies were included for full-text evaluation. Of these, 59 were finally included.

3.4.2. Quality appraisal

Table 8 shows the results of the QUADAS 2 risk of bias assessment for the 59 included primary studies.

Table 8 – Methodological quality of the included primary studies for diagnosis

Author, year	Items (QUADAS 2)																	
	Patient selection					Index test(s)				Reference standard				Flow and timing				
	1.1	1.2	1.3	Risk	Concern	2.1	2.2	Risk	Concern	3.1	3.2	Risk	Concern	4.1	4.2	4.3	4.4	Risk
MEN1																		
Balogh K 2007	?	Y	?	?	?	?	NA	?	Low	?	?	?	Low	?	Y	?	Y	?
Bassett JH 1998	?	Y	?	?	?	?	NA	?	Low	?	?	?	Low	?	Y	?	Y	?
Burgess JR 2000	N	Y	?	High	?	?	NA	?	Low	?	?	?	Low	?	Y	N	Y	?
Cardinal JW 2005	?	Y	?	?	?	?	NA	?	Low	?	?	?	Low	?	Y	?	Y	?
Ellard S 2005	?	Y	N	High	?	?	NA	?	Low	?	?	?	Low	?	?	?	Y	?
Hai N 2000	N	Y	N	High	?	N	NA	?	Low	?	?	?	Low	?	Y	?	Y	?
Lairmore TC 2004	?	Y	?	?	?	?	NA	?	Low	?	?	?	Low	?	Y	?	Y	?
Lourenco DM 2007	?	Y	?	?	?	?	NA	?	Low	?	?	?	Low	?	Y	?	Y	?
Pieterman CR 2009	N	Y	?	High	?	?	NA	?	Low	?	?	?	Low	?	Y	?	Y	?
Poncin J 1999	?	Y	?	?	?	?	NA	?	Low	?	?	?	Low	?	Y	?	Y	?
Schaaf L 2007	?	Y	?	?	?	?	NA	?	Low	?	?	?	Low	?	?	?	N	High
Tham E 2007	?	Y	N	High	?	?	NA	?	Low	N	?	High	Low	?	?	N	Y	?
Tso AW 2003	?	Y	?	?	?	?	NA	?	Low	N	?	High	Low	?	Y	N	Y	?
Waterlot C 1999	N	Y	?	High	?	?	NA	?	Low	?	?	?	Low	?	Y	?	Y	?
Paraganglioma																		
Bacca A 2013	Y	Y	Y	Low	Low	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low

Boedeker CC 2007	?	Y	?	?	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Brouwers FM 2006	Y	Y	Y	Low	Low	Y	NA	Low	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Burnichon N 2009	?	Y	Y	?	?	Y	NA	Low	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Dannenberg H 2002	?	Y	?	?	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Fakhry N 2008	?	Y	?	?	?	Y	NA	Low	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Hensen EF 2011	Y	Y	N	High	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Hensen EF 2010	?	Y	?	?	?	Y	NA	Low	Low	?	N	?	Low	?	Y	?	Y	?
Hes FJ 2010	?	Y	?	?	?	Y	NA	Low	Low	?	N	?	Low	?	Y	?	Y	?
Klein RD 2008	?	Y	?	High	?	?	NA	?	Low	Y	N	Low	Low	?	Y	Y	Y	Low
Lima J 2007	?	Y	?	?	?	?	NA	?	Low	Y	N	?	Low	?	Y	Y	Y	Low
Neumann HP 2009	?	Y	N	High	?	Y	NA	Low	Low	Y	N	?	Low	?	Y	Y	Y	Low
Papaspyrou K 2012	?	Y	N	High	?	?	NA	?	Low	Y	?	Low	Low	?	N	?	N	High
Persu A 2012	?	Y	Y	?	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Persu A 2008	?	Y	Y	?	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Piccini V 2012	Y	Y	Y	Low	Low	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Sevilla MA 2009	?	Y	?	?	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Sridhara SK 2013	?	Y	?	?	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Phaeochromocytoma																		
Erlic Z 2009	?	Y	?	?	?	Y	NA	Low	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Gimenez-Roqueplo 2006	?	?	?	?	?	?	NA	?	Low	?	?	?	Low	?	?	?	?	?
Gimenez-Roqueplo 2003	?	Y	Y	?	?	Y	NA	Low	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Mysliwiec J 2013	Y	Y	Y	Low	Low	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Neumann HP 2002	Y	Y	Y	Low	Low	Y	NA	Low	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Pigny P 2009	?	Y	Y	?	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
SDHB IHC																		
Castelblanco E 2013	?	Y	N	High	?	Y	NA	Low	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Gill AJ 2010	?	Y	N	High	?	Y	NA	Low	Low	Y	?	Low	Low	?	Y	N	Y	Low
Pai R 2014	?	Y	N	High	?	Y	NA	Low	Low	Y	?	Low	Low	?	Y	N	Y	Low
van Nederveen FH 2009	?	Y	?	?	?	Y	NA	Low	Low	Y	?	Low	Low	?	Y	Y	Y	Low
van Nederveen FH 2009	Y	Y	Y	Low	Low	Y	NA	Low	Low	Y	?	Low	Low	?	Y	Y	Y	Low

Phaeochromocytoma / paraganglioma																		
Amar L 2005	?	Y	?	?	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Amar L 2007	?	Y	N	High	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Buffet A 2012	?	Y	?	?	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Cascon A 2013	Y	Y	Y	Low	Low	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Cascon A 2009	Y	Y	Y	Low	Low	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Castellano M 2006	?	Y	?	?	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Fishbein L 2013	Y	Y	N	High	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Iacobone M 2011	Y	Y	N	High	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Jafri M 2013	Y	Y	Y	Low	Low	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Kim J 2013	?	Y	?	?	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Krawczyk A 2010	?	Y	?	?	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Lefebvre S 2012	Y	Y	Y	Low	Low	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low
Mannelli M 2009	?	Y	?	?	?	?	NA	?	Low	Y	?	Low	Low	?	Y	Y	Y	Low

4. EVIDENCE TABLES

4.1. Systematic reviews

MSAC 2013	
Methods	
• **Design**	HTA
• **Source of funding and competing interest**	Commissioned by the Department of Health and Ageing on behalf of MSAC No conflicts of interest
• **Search date**	July-August 2012
• **Searched databases**	PubMed, EMBASE, Web of Science, Cocrane Library, Current Contents, Cinahl, EconLit; expert clinicians
• **Included study designs**	All
• **Number of included studies**	N=135
• **Statistical analysis**	No statistical analysis performed on clinical data
Patient characteristics	
• **Eligibility criteria**	• Patients presenting with medullary thyroid carcinoma (MTC); • Patients presenting with adrenal phaeochromocytoma (under 50 years of age); • Patients presenting with hyperparathyroidism plus a diagnosis of MTC or phaeochromoctyoma in a close relative; • First-degree relatives of patients with a diagnosis of MEN2 or a known pathogenic RET mutation.
Interventions	
• **Index test(s)**	Strategy with RET mutation testing
• **Reference standard**	Long-term clinical assessment (ideally over the life-time of the patient)
Results	**Narrative presentation of results, see scientific report**
Limitations and other comments	
• **Limitations**	• Language restriction (English) • Partly duplicate study selection

MSAC 2011	
Methods	
• **Design**	HTA
• **Source of funding and competing interest**	Commissioned by the Department of Health and Ageing on behalf of MSAC No conflicts of interest
• **Search date**	May 2011
• **Searched databases**	PubMed, EMBASE, Web of Science, Cocrane Library, Current Contents, Cinahl, EconLit, PsycINFO; trial registers, Google Scholar; hand searching; expert clinicians; references
• **Included study designs**	All
• **Number of included studies**	N=109
• **Statistical analysis**	No statistical analysis performed on clinical data
Patient characteristics	
• **Eligibility criteria**	• Patients presenting with symptoms suggestive of VHL syndrome • Family members of patients who are positive for a VHL mutation
Interventions	
• **Index test(s)**	Strategy with VHL mutation testing
• **Reference standard**	Long-term clinical assessment (ideally over the life-time of the patient)
Results	**Narrative presentation of results, see scientific report**
Limitations and other comments	
• **Limitations**	• Language restriction (English) • Partly duplicate study selection

van Hulsteijn LT 2012	
Methods	
• **Design**	SR + MA
• **Source of funding and competing interest**	Not commissioned No conflicts of interest

• **Search date**	2000 - August 2011
• **Searched databases**	PubMed, EMBASE, Web of Science, Cochrane Library and Academic Search Premier; references
• **Included study designs**	Follow-up studies or cross-sectional studies
• **Number of included studies**	N=12
• **Statistical analysis**	Meta-analysis using an exact likelihood approach: logistic regression with a random effect at the study level
Patient characteristics	
• **Eligibility criteria**	• SDHB-mutation or SDHD-mutation carriers
• **Patient characteristics**	• Mean age at first diagnosis of paraganglioma: 28.7 – 47.1y for SDHB, 26.5 – 39.7y for SDHD
• **Prevalence of disease**	• SDHB: 0-54% • SDHD: 0-23%
Interventions	**Prevalence study**
• **Index test(s)**	Not applicable
• **Reference standard**	Not applicable
Results	
• **Pooled risk of malignant paraganglioma**	Incidence studies: • SDHB: 17% (95%CI 10-28%) • SDHD: 8% (95%CI 2-26%) Prevalence studies: • SDHB: 13% (95%CI 4-34%) • SDHD: 4% (95%CI 2-7%)
Limitations and other comments	
• **Limitations**	• Unclear if language restriction was used • Unclear if duplicate selection

4.2. Primary studies

Amar 2005	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• Supported by the Cortico et Medullosurrenale: les Tumeurs Endocrines network, with the support of Projet Hospitalier de Recherche Clinique Grant No. AOM02068 and Grants from L'Institut National de la Santé et de la Recherche Médicale (INSERM) and the Ministère Délégué à la Recherche et aux Nouvelles Technologies; the Paraglioma network, with the support of Groupement d'Intèrêt Scientifique Institut des Maladies Rares; and Groupe des Tumeurs Endocrines, with the support of Ministère de la Santé et de la Protection Sociale • No competing interests
• **Setting**	Multicentre study, France
• **Sample size**	N=314
• **Statistical analysis**	Fisher's exact test for small samples X^2 test for larger groups Analysis of variance test to compare more than two variables
Patient characteristics	
• **Eligibility criteria**	• Patients with a phaeochromocytoma or functional paraganglioma
• **Patient characteristics**	• Females: 55% • Mean age: 41.3y • Malignant tumours: 17% • Familial/syndromic cases: 18%
• **Prevalence of disease**	Mutation: 27.4% • VHL: N=25 • SDHB: N=21 • SDHD: N=11 • RET: N=16 • NF1: N=13

Interventions								
• **Index test(s): disease characteristics**	Extra-adrenal tumours, bilateral tumours, malignant disease, familial/syndromic presentation							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD, VHL and RET mutations (no details)							
• **Time interval between tests**	Unclear							
Results								
• **Extra-adrenal tumours**	Se	65%	Sp	100%	PPV	100%	NPV	88%
• **Bilateral tumours**	Se	33%	Sp	87%	PPV	48%	NPV	77%
• **Malignant disease**	Se	42%	Sp	98%	PPV	88%	NPV	82%
• **Familial/syndromic presentation**	Se	21%	Sp	85%	PPV	35%	NPV	74%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients • Unclear blinding							

Amar 2007	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• Supported by Grant AOM 02068 from the Assistance Publique-Hôpitaux de Paris, Délégation à la Recherche Clinique, for the Cortico and Medullo-surrenale: les Tumeurs Endocrines network • No competing interests
• **Setting**	3 tertiary referral centres, France
• **Sample size**	N=54
• **Statistical analysis**	Unpaired Student's t test or Mann-Whitney U test for quantitative variables X^2 test or Fisher's exact test for qualitative variables
Patient characteristics	
• **Eligibility criteria**	• Patients with metastatic phaeochromoctyoma or (thoracoabdominal) paraganglioma • Presence of metastases either at presentation or during a recurrence

• **Patient characteristics**	• Females: 46% • Mean age at diagnosis of malignancy: 42.0y • Familial/syndromic cases: 9%							
• **Prevalence of disease**	SDHB mutation: 42.6%							
Interventions								
• **Index test(s): disease characteristics**	Familial/syndromic presentation, extra-adrenal disease, hypersecreting tumour							
• **Reference standard**	Mutational analysis for SDHB (no details)							
• **Time interval between tests**	Unclear							
Results								
• **Familial/syndromic presentation**	Se	9%	Sp	90%	PPV	40%	NPV	57%
• **Extra-adrenal tumour**	Se	70%	Sp	71%	PPV	64%	NPV	76%
• **Hypersecreting tumour**	Se	83%	Sp	6%	PPV	40%	NPV	33%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients • Exclusion of 18 eligible patients because of various reasons • Unclear blinding							

Bacca 2013	
Methods	
• **Design**	Prospective cohort study, consecutive enrolment of patients
• **Source of funding and competing interest**	Not reported
• **Setting**	University centre, Italy
• **Sample size**	N=17 (and 17 relatives)
• **Statistical analysis**	Unpaired t test for quantitative variables, X^2 test or Fisher exact test for qualitative variables
Patient characteristics	

• **Eligibility criteria**	• Patients with head and neck paraganglioma • Patients with syndromic features of well-known inherited syndromes, such as Von Hippel-Lindau, multiple endocrine neoplasia and neurofibromatosis type 1 were excluded							
• **Patient characteristics**	• Females: 82% • Mean age: 48.2y • Multiple tumours: 47% • Familial cases: 18%							
• **Prevalence of disease**	Mutation: 41.2%							
Interventions								
• **Index test(s)**	• Disease characteristics (affected patients): multiple tumours, functioning paraganglioma, malignant disease, family history • Mutational analysis for SDHB, SDHC, SDHD, SDHAF2, VHL and RET mutations (PCR) (relatives)							
• **Reference standard**	• Mutational analysis for SDHB, SDHC, SDHD, SDHAF2, VHL and RET mutations (PCR) (affected patients) • Follow-up (relatives): clinical observation, urinary metanephrine evaluation, and ultrasound scan and/or MRI at 1-year intervals							
• **Time interval between tests**	Unclear							
Results								
Affected patients								
• **Multiple tumours**	Se	86%	Sp	80%	PPV	75%	NPV	89%
• **Functioning paragangliomas**	Se	29%	Sp	100%	PPV	100%	NPV	67%
• **Malignant disease**	Se	0%	Sp	100%	PPV	Not calculable	NPV	59%
• **Family history**	Se	43%	Sp	100%	PPV	100%	NPV	71%
Relatives								
• 17 relatives screened: 10 positive (SDHD), 4 clinically affected • PPV: 40%; follow-up duration not reported								
Limitations and other comments								
• **Limitations**	• Blinding unclear							

Balogh 2007	
Methods	
• **Design**	Cohort study, unclear design
• **Source of funding and competing interest**	Not reported
• **Setting**	Single university centre, Hungary
• **Sample size**	N=32 index patients; N=21 first degree relatives
• **Statistical analysis**	Not reported
Patient characteristics	
• **Eligibility criteria**	• Patients with familial and sporadic MEN1 or with a MEN1-related state consisting of familial occurrence of one main MEN1 tumour, sporadic primary hyperparathyroidism at a young age, or one major plus one minor MEN1 lesion • Or, first degree relatives of index patients
• **Definitions**	• MEN1: at least two of the three major lesions (anterior pituitary gland, parathyroid glands and endocrine pancreas) • Familial MEN1: at least one first degree relative in whom at least one of the three main target organs was affected • MEN1-related state: one of the three main lesions plus at least one other lesion or multiple parathyroid tumours with onset before the age of 30 years, recurrent primary hyperparathyroidism or familial isolated primary hyperparathyroidism
• **Patient characteristics**	• Females: 78% • Mean age: 41.9y • Familial MEN1: N=6; sporadic MEN1: N=13; MEN-related state: N=13 • Symptomatic first degree relatives: N=6
• **Prevalence of disease**	Mutation: 47.4% in MEN1 patients, 7.7% in MEN1-related state
Interventions	
• **Index test(s)**	• Disease characteristics (index patients): familial vs. sporadic, three vs. two main lesions, hyperparathyroidism, pancreatic tumour, pituitary tumour, presence of minor lesions
• **Reference standard**	• Mutational analysis for MEN1 (PCR amplification) • Follow-up (relatives): unclear
• **Time interval between tests**	Unclear
Results	

Affected MEN1 patients								
• **Familial disease**	Se	67%	Sp	100%	PPV	100%	NPV	77%
• **Three main MEN1 lesions**	Se	11%	Sp	90%	PPV	50%	NPV	53%
• **Hyperparathyroidism**	Se	89%	Sp	20%	PPV	50%	NPV	67%
• **Pancreatic tumour**	Se	44%	Sp	60%	PPV	50%	NPV	55%
• **Pituitary tumour**	Se	89%	Sp	10%	PPV	47%	NPV	50%
• **Presence of minor lesions**	Se	22%	Sp	80%	PPV	50%	NPV	53%
MEN1-related state								
• **Familial disease**	Se	0%	Sp	83%	PPV	0%	NPV	91%
• **Hyperparathyroidism**	Se	100%	Sp	42%	PPV	13%	NPV	100%
• **Pancreatic tumour**	Se	0%	Sp	83%	PPV	0%	NPV	91%
• **Pituitary tumour**	Se	0%	Sp	75%	PPV	0%	NPV	90%
• **Presence of minor lesions**	Se	0%	Sp	25%	PPV	0%	NPV	75%
Relatives								
• 6 symptomatic 1st-degree relatives: all positive for mutation								
• 15 asymptomatic relatives: 1 positive, 14 negative								
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients							
	• Blinding unclear							

Bassett 1998	
Methods	
• **Design**	Cohort study, unclear design
• **Source of funding and competing interest**	Not reported
• **Setting**	UK; unclear how many centres
• **Sample size**	N=63 unrelated probands; total of 947 family members
• **Statistical analysis**	X^2 test Mann-Whitney U-test
Patient characteristics	
• **Eligibility criteria**	• Unrelated MEN1 probands and their family members
• **Definitions**	• MEN1: at least two of the three major lesions (anterior pituitary gland, parathyroid glands and endocrine pancreas) - Familial MEN1: at least one first degree relative in whom at least one of the three main target organs was affected
• **Patient characteristics**	Unclear for total population
• **Prevalence of disease**	Unclear
Interventions	
• **Index test(s)**	• Mutational analysis for MEN1 (PCR amplification)
• **Reference standard**	• Follow-up (relatives): unclear
• **Time interval between tests**	Unclear
Results	
Relatives	
• Age-related penetrance (calculated from 201 mutant-gene carriers): 0% <5y, 52% at 20y, 100% at 60y	
Limitations and other comments	
• **Limitations**	• Unclear if consecutive patients • Blinding unclear

Boedeker 2007									
Methods									
• **Design**	Retrospective cohort study								
• **Source of funding and competing interest**	No competing interests								
• **Setting**	International study								
• **Sample size**	N=195								
• **Statistical analysis**	Not reported								
Patient characteristics									
• **Eligibility criteria**	Patients with head and neck paragangliomas								
• **Patient characteristics**	• Females: 66%								
• **Prevalence of disease**	SDH mutation: 32.3%								
Interventions									
• **Index test(s): disease characteristics**	Distant metastases								
• **Reference standard**	Mutational analysis for SDHB, SDHC and SDHD (not further specified)								
• **Time interval between tests**	Not reported								
Results									
• **Distant metastases**	Se	11%	Sp	100%	PPV	100%	NPV	70%	
Limitations and other comments									
• **Limitations**	• Unclear if consecutive patients • Unclear blinding								

Brouwers 2006								
Methods								
• **Design**	Prospective cohort study, consecutive inclusion							
• **Source of funding and competing interest**	• Supported by the intramural program of the National Institute of Child Health and Human Development, the National Institute of Neurological Disorders and Stroke, and the National Cancer Institute, National Institutes of Health • No competing interests							
• **Setting**	Single centre, US							
• **Sample size**	N=44							
• **Statistical analysis**	X^2, Student t test, or ANOVA with Scheffe´´s post hoc test							
Patient characteristics								
• **Eligibility criteria**	• Patients with malignant paraganglioma • No previous mutation testing • Not related, not referred because of suspicion of hereditary disease							
• **Patient characteristics**	• Females: 39% • Mean age: 35.1y (own calculation) • Familial cases: 2%							
• **Prevalence of disease**	SDHB mutation: 40.9%							
Interventions								
• **Index test(s): disease characteristics**	Metastases at initial diagnosis, bone metastases							
• **Reference standard**	Mutational analysis for SDHB (PCR-based bidirectional sequencing)							
• **Time interval between tests**	Not reported							
Results								
• **Metastases at initial diagnosis**	Se	33%	Sp	69%	PPV	43%	NPV	60%
• **Bone metastases**	Se	83%	Sp	31%	PPV	45%	NPV	73%
Limitations and other comments								
• **Limitations**	• Unclear blinding of reference standard							

Buffet 2012								
Methods								
• **Design**	Retrospective cohort study							
• **Source of funding and competing interest**	• Supported by the Institut National de la Santé et de la Recherche Médicale and by the Programme Hospitalier National de Recherche Clinique grants COMETE 1, COMETE 2 and COMETE 3 (AOM 06 179) for the COMETE Network, and by the GIS-Institut des Maladies Rares for the PGL.NET network, as well as by grants from Assistance Publique-Hôpitaux de Paris, Ministère Délégué à la Recherche et des Nouvelles Technologies, the Institut National du Cancer, la Ligue contre le Cancer, and the Agence Nationale de la Recherche (ANR 08 GENOPATH 029 MitOxy) • Competing interests not reported							
• **Setting**	Multicentre study, France							
• **Sample size**	N=1620 index cases							
• **Statistical analysis**	Not reported							
Patient characteristics								
• **Eligibility criteria**	• Patients with phaeochromocytoma and/or paraganglioma							
• **Patient characteristics**	• Mean age: 45y • Malignant disease: 10.3%							
• **Prevalence of disease**	Mutation: 22.4%							
Interventions								
• **Index test(s): disease characteristics**	Familial/syndromic presentation							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD, RET and VHL (direct sequencing, multiplex PCR, multiplex ligation-dependent probe amplification)							
• **Time interval between tests**	Not reported							
Results								
• **Familial syndromic presentation**	Se	78%	Sp	72%	PPV	45%	NPV	92%
Limitations and other comments								
• **Limitations**	• Probably overlap with Burnichon 2009, Gimenez-Roqueplo 2003, Amar 2005 • Unclear if consecutive patients							

	• Unclear blinding

Burgess 2000								
Methods								
• **Design**	Cohort study, unclear design							
• **Source of funding and competing interest**	• Supported by a research grant from the Cancer Council of Tasmania • Competing interests not reported							
• **Setting**	Tasmania, unclear how many centres							
• **Sample size**	N=152 family members							
• **Statistical analysis**	t-test for normally distributed variables X^2 test for non-parametric data							
Patient characteristics								
• **Eligibility criteria**	• Consenting members from MEN1 family							
• **Definitions**	• MEN1: not clearly provided • Familial MEN1: individuals with an established family history of MEN1 occurring in conjunction with uni-glandular endocrine neoplasia (primary hyperparathyroidism, pituitary neoplasia, or enteropancreatic neoplasia)							
• **Patient characteristics**	• Not reported							
• **Prevalence of disease**	Mutation: 90.1% in clinically affected member, 0% in unaffected members							
Interventions								
• **Index test(s)**	Disease characteristics (see below)							
• **Reference standard**	• Mutational analysis for MEN1 (PCR amplification) • Follow-up (relatives): biochemical and radiological screening							
• **Time interval between tests**	Unclear							
Results								
• **Any endocrinopathy**	Se	98%	Sp	94%	PPV	93%	NPV	99%
• **Parathyroid tumour**	Se	98%	Sp	94%	PPV	93%	NPV	99%
• **Gastrinoma**	Se	31%	Sp	100%	PPV	100%	NPV	67%
• **Prolactinoma**	Se	23%	Sp	99%	PPV	94%	NPV	64%

• **Parathyroid tumour + gastrinoma**	Se	31%	Sp	100%	PPV	100%	NPV	67%
• **Parathyroid tumour + prolactinoma**	Se	23%	Sp	99%	PPV	94%	NPV	64%
• **Gastrinoma + prolactinoma**	Se	14%	Sp	100%	PPV	100%	NPV	62%
• **Parathyroid tumour + gastrinoma + prolactinoma**	Se	14%	Sp	100%	PPV	100%	NPV	62%

Limitations and other comments	
• **Limitations**	• No consecutive patients • Blinding unclear

Burnichon 2009	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interest**	• Supported by the Institut National de la Santé et de la Recherche Médicale and by Programme Hospitalier de Recherche Clinique Grant COMETE 2 for the COMETE Network (AOM 06 179); by the GIS-Institut des Maladies Rares for the PGL.NET network; by the Program Hospitalier National de Recherche Clinique 2004 (PCR05007); and by the Groupe des Tumeurs Endocrines • No competing interests
• **Setting**	Multicentre study, France (PGL.NET)
• **Sample size**	N=445
• **Statistical analysis**	Unpaired Student's t test, X^2 test or Fisher's exact test; logistic regression and two-way ANOVA
Patient characteristics	
• **Eligibility criteria**	• Patients with head and neck and/or thoracic-abdominal or pelvic paraganglioma • Patients who presented only a single pheochromocytoma (unique adrenal catecholamine-secreting tumor) without another head and neck or thoracic-abdominal or pelvic paraganglioma and/or a family history of hereditary paraganglioma as well as patients suffering from a von Hippel Lindau disease were not included
• **Patient characteristics**	• Females: 55% • Mean age at first diagnosis: 42.7y

	• Familial cases: 23% • Multiple tumours: 27%							
• **Prevalence of disease**	SDH mutation: 54.4%							
Interventions								
• **Index test(s): disease characteristics**	Age ≤35y, multiple tumours, familial disease, head and neck paraganglioma							
• **Reference standard**	Mutational analysis for SDHB, SDHC and SDHD (PCR amplification, quantitative multiplex PCR of short fluorescent fragments method, or multiplex ligation-dependent probe amplification)							
• **Time interval between tests**	Not reported							
Results								
• **Age ≤35y**	Se	55%	Sp	83%	PPV	80%	NPV	61%
• **Multiple tumours**	Se	46%	Sp	95%	PPV	92%	NPV	60%
• **Familial disease**	Se	42%	Sp	100%	PPV	99%	NPV	59%
• **Head and neck location**	Se	75%	Sp	27%	PPV	55%	NPV	48%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive inclusion • Unclear blinding of reference test							

Cardinal 2005	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• No competing interests • Funding not reported
• **Setting**	Single referral centre, Australia and New Zealand
• **Sample size**	N=150
• **Statistical analysis**	Not reported
Patient characteristics	

• **Eligibility criteria**	• Patients with persistently elevated hormone levels and tumours of the parathyroid, pituitary, endocrine pancreas, gastrin cells, thymic or bronchial carcinoids, or other miscellaneous tumours of adrenal, adipose, or thyroid origin
• **Definitions**	• Not provided
• **Patient characteristics**	• Not provided
• **Prevalence of disease**	Mutation: 36.7%
Interventions	
• **Index test(s)**	Familial history of MEN1-related disease
• **Reference standard**	• Mutational analysis for MEN1 (PCR amplification)
• **Time interval between tests**	Unclear
Results	
• **Family history**	Se 84% Sp 59% PPV 54% NPV 86%
Limitations and other comments	
• **Limitations**	• Unclear if consecutive patients • Heterogeneous population • Blinding unclear

Cascon 2013	
Methods	
• **Design**	Retrospective cohort study, consecutive patients
• **Source of funding and competing interest**	• Supported in part by the Fondo de Investigaciones Sanitarias (projects PS09/00942 and PI11/01359), Fundación Mutua Madrileña, and a grant from the Seventh Framework Programme • No competing interests
• **Setting**	Multicentre study, Spain
• **Sample size**	N=447
• **Statistical analysis**	X^2 or Fisher's exact test
Patient characteristics	
• **Eligibility criteria**	• Patients with clinical diagnosis of phaeochromocytoma and/or paraganglioma
• **Patient characteristics**	• Mean age: 41.3y (own calculation)

• **Prevalence of disease**	Mutation: 38.7%							
Interventions								
• **Index test(s): disease characteristics**	Familial disease (paediatric population only), bilateral phaeochromocytoma, head and neck paraganglioma, combined phaeochromocytoma and paraganglioma							
• **Reference standard**	Mutational analysis for SDHA, SDHB, SDHC, SDHD, SDHAF2, VHL and RET (multiplex PCR or multiplex ligation-dependent probe amplification)							
• **Time interval between tests**	Not reported							
Results								
• **Familial disease (paediatric population only)**	Se	40%	Sp	91%	PPV	91%	NPV	40%
• **Bilateral phaeochromocytoma**	Se	25%	Sp	95%	PPV	75%	NPV	67%
• **Head and neck paraganglioma**	Se	29%	Sp	81%	PPV	49%	NPV	64%
• **Combined phaeochromocytoma and paraganglioma**	Se	8%	Sp	97%	PPV	62%	NPV	62%
Limitations and other comments								
• **Limitations**	• Potential overlap with Cascon 2009 • Unclear blinding							

Cascon 2009	
Methods	
• **Design**	Retrospective cohort study, consecutive patients
• **Source of funding and competing interest**	• Supported in part by the Fondo de Investigaciones Sanitarias (projects PS09/00942 and PI11/01359), Fundación Mutua Madrileña, and a grant from the Seventh Framework Programme • No competing interests
• **Setting**	Multicentre study (public hospitals), Spain
• **Sample size**	N=237, of which 192 were non-syndromic

• **Statistical analysis**	Fisher's exact test for small samples ANOVA test to compare more than two variables							
Patient characteristics								
• **Eligibility criteria**	• Patients with clinical diagnosis of phaeochromocytoma and/or paraganglioma							
• **Patient characteristics**	Not reported							
• **Prevalence of disease**	Mutation: 25%							
Interventions								
• **Index test(s): disease characteristics**	Familial disease, bilateral phaeochromocytoma, head and neck paraganglioma, multiple tumours, malignant disease							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD, VHL and RET (multiplex PCR or multiplex ligation-dependent probe amplification)							
• **Time interval between tests**	Not reported							
Results	**Non-syndromic patients only**							
• **Familial disease**	Se	40%	Sp	97%	PPV	79%	NPV	83%
• **Bilateral phaeochromocytoma**	Se	38%	Sp	22%	PPV	14%	NPV	52%
• **Head and neck paraganglioma**	Se	38%	Sp	89%	PPV	53%	NPV	81%
• **Multiple tumours**	Se	13%	Sp	87%	PPV	24%	NPV	75%
• **Malignant disease**	Se	8%	Sp	91%	PPV	24%	NPV	75%
Limitations and other comments								
• **Limitations**	• Potential overlap with Cascon 2013 • Unclear blinding							

Castellano 2006								
Methods								
• **Design**	Retrospective cohort study							
• **Source of funding and competing interest**	• Supported by research grants funded by the Italian MIUR, under PRIN No. 2004069534—002 and by the Fondazione della Comunità Bresciana • Competing interests not reported							
• **Setting**	Two university centres, Italy							
• **Sample size**	N=45							
• **Statistical analysis**	Not reported							
Patient characteristics								
• **Eligibility criteria**	• Patients with non-syndromic phaeochromocytoma and/or paraganglioma							
• **Patient characteristics**	Not reported							
• **Prevalence of disease**	Mutation: 35.6%							
Interventions								
• **Index test(s): disease characteristics**	Family history (no 2x2 tables possible for other characteristics)							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD, VHL and RET (PCR)							
• **Time interval between tests**	Not stated							
Results								
• **Family history**	Se	19%	Sp	100%	PPV	100%	NPV	69%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients • Unclear blinding							

Castelblanco 2013	
Methods	
• **Design**	Cohort study, unclear if prospective
• **Source of funding and competing interest**	• Supported by grants, 2009SGR794, RD12/0036/0013, and Programa de Intensificación de la Investigación ISCIII • E.C. holds a predoctoral fellowship from AGAUR 2012FI-B2 00125; AdC is predoctoral fellows from La Caixa Fundation • Tumour samples were obtained with the support of Xarxa Catalana de Bancs de Tumours, the Tumour Banc Platform of RTICC and RD09/0076/00059, as well as the Spanish Tumour Bank Network coordinated by CNIO
• **Setting**	Single university centre, Spain
• **Sample size**	N=64
• **Statistical analysis**	Not reported
Patient characteristics	
• **Eligibility criteria**	• Patients with phaeochromocytoma and/or paraganglioma
• **Patient characteristics**	• Females: 44% • Malignant disease: 8%
• **Prevalence of disease**	Mutation: 70.3% • SDHB: N=9 • SDHD: N=5 • RET: N=23 • VHL: N=8
Interventions	
• **Index test(s): disease characteristics**	Immunohistochemistry for SDHB (blinded evaluation)
• **Reference standard**	Mutational analysis for SDH, VHL and RET (direct sequencing)
• **Time interval between tests**	Not stated
Results	
• **Detection of SDH mutation**	Se 100% Sp 94% PPV 82% NPV 100%
Limitations and other comments	
• **Limitations**	• Unclear if consecutive patients • Unclear if blinded evaluation of reference test

Dannenberg 2002								
Methods								
• **Design**	Retrospective cohort study							
• **Source of funding and competing interest**	Not reported							
• **Setting**	Single centre, the Netherlands							
• **Sample size**	N=57							
• **Statistical analysis**	X^2 or unpaired t test							
Patient characteristics								
• **Eligibility criteria**	Patients with parasympathetic paraganglioma and available specimens and constitutional DNA							
• **Patient characteristics**	• Females: 63% • Mean age at first diagnosis: 42.4y • Family history: 33% • Multiple tumours: 30%							
• **Prevalence of disease**	SDHD mutation: 56.1%							
Interventions								
• **Index test(s): disease characteristics**	Familial disease, multiple tumours, recurrent disease							
• **Reference standard**	Mutational analysis for SDHD (PCR amplification)							
• **Time interval between tests**	Not reported							
Results								
• **Familial disease**	Se	59%	Sp	100%	PPV	100%	NPV	66%
• **Multiple tumours**	Se	47%	Sp	92%	PPV	88%	NPV	58%
• **Recurrent disease**	Se	13%	Sp	88%	PPV	57%	NPV	44%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients • Unclear blinding							

Ellard 2005								
Methods								
• **Design**	Retrospective cohort study							
• **Source of funding and competing interest**	• Competing interests not reported • Support by the Royal Devon & Exeter NHS Foundation Trust and the Research & Development Directorate							
• **Setting**	Single referral centre, UK; patients referred by endocrinologists and clinical geneticists throughout the UK							
• **Sample size**	N=292							
• **Statistical analysis**	Not reported							
Patient characteristics								
• **Eligibility criteria**	• Patients referred for MEN1 testing							
• **Definitions**	• MEN1: at least two of the three major lesions (anterior pituitary gland, parathyroid glands and endocrine pancreas) • Familial MEN1: at least one first degree relative in whom at least one of the three main target organs was affected • Suspicious /atypical of MEN1: two or more MEN1-related tumours, multiple parathyroid tumours before age of 30, recurrent hyperparathyroidism, gastrinoma or multiple islet cell tumours, familial isolated hyperparathyroidism							
• **Patient characteristics**	• Females: 64% • Mean age: index cases 50y, symptomatic relatives 48y, unaffected relatives 28y							
• **Prevalence of disease**	Mutation: 34.5% in all patients, 46.7% in MEN1 patients							
Interventions								
• **Index test(s)**	Disease characteristics, see below							
• **Reference standard**	• Mutational analysis for MEN1 (PCR amplification)							
• **Time interval between tests**	Unclear							
Results	**All patients**							
• **Familial disease**	Se	63%	Sp	72%	PPV	54%	NPV	79%
Results	**MEN1 patients**							
• **Familial disease**	Se	56%	Sp	84%	PPV	76%	NPV	69%
• **Three major lesions**	Se	38%	Sp	91%	PPV	79%	NPV	63%
• **Parathyroid disease**	Se	100%	Sp	5%	PPV	48%	NPV	100%
• **Pancreatic disease**	Se	82%	Sp	72%	PPV	72%	NPV	82%

• **Pituitary disease**	Se	56%	Sp	14%	PPV	36%	NPV	27%
• **Minor lesions**	Se	18%	Sp	95%	PPV	75%	NPV	57%

Limitations and other comments	
• **Limitations**	• Unclear if consecutive patients • Heterogeneous population • For 15 index cases no clinical information available: excluded from analysis • For 6 unaffected relatives no mutation testing done • Blinding unclear

Erlic 2009	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• German Cancer Foundation (Deutsche Krebshilfe) Grant 107995 (H.P.H. Neumann), the Deutsche Forschungsgemeinschaft (NE 571/5-3; H.P.H. Neumann), and the European Union (LSHC-CT-2005-518200; H.P.H. Neumann) • No competing interests
• **Setting**	International study (European-American Pheochromocytoma Registry)
• **Sample size**	N=989
• **Statistical analysis**	Multiple logistic regression analysis
Patient characteristics	
• **Eligibility criteria**	• Patients who presented clinically with apparently non-syndromic phaeochromocytoma at the time of registration • In the situation where several subjects from one family were affected, only the index case of the family was used for purposes of this study • Patients who developed phaeochromocytoma after molecular-genetic testing was done were excluded • Exclusion of families in the Blackforest region in Germany, who mostly are unaware of being related to each other, but who carry an identical VHL mutation
• **Patient characteristics**	• Females: 57% • Mean age at first diagnosis: 42.3y • Multiple tumours: 21%

	• Malignant disease: 8%							
• **Prevalence of disease**	Mutation (SDHB, SDHD, RET): 18.9%							
Interventions								
• **Index test(s): disease characteristics**	Age ≤ 45y, malignant disease, multiple tumours, adrenal location, previous head and neck paraganglioma, family history							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD, RET and VHL (PCR-based mutation scanning, multiplex genomic qPCR, multiplex ligation-dependent probe amplification)							
• **Time interval between tests**	Not reported							
Results								
• **Age ≤ 45y**	Se	84%	Sp	55%	PPV	30%	NPV	94%
• **Malignant disease**	Se	13%	Sp	92%	PPV	28%	NPV	82%
• **Multiple tumours**	Se	50%	Sp	90%	PPV	54%	NPV	89%
• **Adrenal location**	Se	59%	Sp	12%	PPV	14%	NPV	56%
• **Previous HNP**	Se	12%	Sp	100%	PPV	88%	NPV	83%
• **Family history**	Se	9%	Sp	97%	PPV	40%	NPV	82%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients • Unclear blinding of reference standard							

Fakhry 2008	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	Not reported
• **Setting**	Single university centre, France
• **Sample size**	N=23
• **Statistical analysis**	Fisher's exact test for nominal variables and with Mann-Whitney test for ordinal variables

Patient characteristics								
• **Eligibility criteria**	Patients that have been operated on cervical paragangliomas							
• **Patient characteristics**	• Females: 65% • Mean age at first diagnosis: 45.4y (own calculation) • Family history: 17% • Multiple tumours: 30%							
• **Prevalence of disease**	SDH mutation: 35%							
Interventions								
• **Index test(s): disease characteristics**	Family history, multiple tumours, malignant disease							
• **Reference standard**	Mutational analysis for SDHB, SDHC and SDHD (PCR amplification)							
• **Time interval between tests**	Not reported							
Results								
• **Familial disease**	Se	50%	Sp	100%	PPV	100%	NPV	79%
• **Multiple tumours**	Se	88%	Sp	100%	PPV	100%	NPV	94%
• **Malignant disease**	Se	13%	Sp	87%	PPV	33%	NPV	65%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients • 29 eligible patients, but only 23 patients with full work-up available (6 lost to follow-up) • Unclear blinding of reference standard							

Fishbein 2013	
Methods	
• **Design**	Retrospective cohort study, consecutive patients
• **Source of funding and competing interest**	• Supported in part by the PheoPara Alliance and 2-T32-DK007314-31 • No competing interests
• **Setting**	Single university centre, US
• **Sample size**	N=139

• **Statistical analysis**	Two-tailed t-test for comparison of two groups One way ANOVA for independent samples along with a Bonferroni test for comparison between multiple groups							
Patient characteristics								
• **Eligibility criteria**	• Patients with phaeochromoytoma and/or paraganglioma							
• **Patient characteristics**	• Females: 50% • Mean age at first diagnosis: 38.98y • Familial: 26% • Metastatic disease: 22%							
• **Prevalence of disease**	Mutation: 41% • SDHB: N=19 • SDHD: N=10 • VHL: N=6 • RET: N=3 • NF1: N=7							
Interventions								
• **Index test(s): disease characteristics**	Extra-adrenal disease only, head-and-neck location only, multiple tumours, family history, malignant disease							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD, VHL and RET (direct sequencing)							
• **Time interval between tests**	Not stated							
Results								
• **Extra-adrenal disease only**	Se	27%	Sp	80%	PPV	48%	NPV	61%
• **Head-and-neck location only**	Se	22%	Sp	82%	PPV	45%	NPV	60%
• **Multiple tumours**	Se	44%	Sp	94%	PPV	83%	NPV	71%
• **Family history**	Se	58%	Sp	95%	PPV	90%	NPV	77%
• **Malignant disease**	Se	22%	Sp	78%	PPV	42%	NPV	59%
Limitations and other comments								
• **Limitations**	• Exclusion of 29 patients: reasons provided • Unclear blinding							

Gill 2010									
Methods									
• **Design**	Cohort study, unclear if prospective or retrospective								
• **Source of funding and competing interest**	Not reported								
• **Setting**	Single centre, Australia								
• **Sample size**	N=58								
• **Statistical analysis**	Not reported								
Patient characteristics									
• **Eligibility criteria**	• Patients with phaeochromoytoma and/or paraganglioma								
• **Patient characteristics**	• Females: 53% • Mean age: 50y								
• **Prevalence of disease**	Mutation: 37.9% • SDHB: N=6 • SDHD: N=5 • SDHC: N=1 • VHL: N=6 • RET: N=2 • NF1: N=2								
Interventions									
• **Index test(s): disease characteristics**	Immunohistochemistry for SDHB (blinded evaluation)								
• **Reference standard**	Mutational analysis for SDH, VHL and RET (PCR and direct sequencing)								
• **Time interval between tests**	Not stated								
Results									
• **Detection of SDH mutation**	Se	100%	Sp	93%	PPV	80%	NPV	100%	
Limitations and other comments									
• **Limitations**	• Unclear if consecutive patients								

	• Unclear blinding of reference test

Gimenez-Roqueplo 2006								
Methods								
• **Design**	Retrospective cohort study							
• **Source of funding and competing interest**	• INSERM, GIS-Institut des Maladies Rares for the PGL.NET network and the Association pour la Recherche pour le Cancer • No other competing interests							
• **Setting**	Unclear							
• **Sample size**	N=57 (only Italian data presented here)							
• **Statistical analysis**	Not reported							
Patient characteristics								
• **Eligibility criteria**	• Patients with phaeochromocytoma or functional paraganglioma							
• **Patient characteristics**	Not reported							
• **Prevalence of disease**	Mutation (VHL, SDHB, SDHD, RET, NF1): 24.6%							
Interventions								
• **Index test(s): disease characteristics**	Malignant disease, extra-adrenal location							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD, RET and VHL (no details)							
• **Time interval between tests**	Not reported							
Results								
• **Malignant disease**	Se	7%	Sp	98%	PPV	50%	NPV	76%
• **Extra-adrenal location**	Se	36%	Sp	77%	PPV	33%	NPV	79%
Limitations and other comments								
• **Limitations**	• Limited information on study design and methods							

Gimenez-Roqueplo 2003								
Methods								
• **Design**	Retrospective cohort study							
• **Source of funding and competing interest**	• Supported by the Institut National de la Santé et de la Recherche Médicale and by PHRC Grant AOM 95201 for the COMETE Network • No competing interests							
• **Setting**	Multicentre study, France							
• **Sample size**	N=84							
• **Statistical analysis**	Student's t test or ANOVA for phenotypic differences; X^2 and Fisher's exact test for differences in distributions							
Patient characteristics								
• **Eligibility criteria**	• Patients with apparently sporadic phaeochromocytoma • Exclusion of patients with a personal or family history of HNP, MEN2A and 2B, VHL disease, or NF1 • Exclusion of patients with phenotypic clues for MEN2, VHL, or NF1							
• **Patient characteristics**	• Females: 57% • Mean age at first diagnosis: 44y (own calculation)							
• **Prevalence of disease**	SDHB mutation: 9.5%							
Interventions								
• **Index test(s): disease characteristics**	Extra-adrenal location, malignant disease							
• **Reference standard**	Mutational analysis for SDHB, SDHD, RET and VHL (PCR amplification)							
• **Time interval between tests**	Not reported							
Results (only 2x2 tables possible for SDHB)								
• **Extra-adrenal location**	Se	63%	Sp	87%	PPV	33%	NPV	96%
• **Malignant disease**	Se	83%	Sp	79%	PPV	24%	NPV	98%
Limitations and other comments								
• **Limitations**	- Unclear if consecutive patients - Unclear blinding of reference standard - Series also included in Amar 2005							

Hai 2000								
Methods								
• **Design**	Retrospective cohort study							
• **Source of funding and competing interest**	• Competing interests not reported • Supported in part by grants-in-aid for Scientific Research from the Japanese Ministry of Education, Science and Culture (No. 0644128, no. 06671024, no. 07671129, no. 07557353, no. 08671152, no. 09671051 and no. 09257225), Mochida Foundation for Medical and Pharmaceutical Research, Kowa Foundation for Life Science, Shimizu Foundation for Immunology Research, Kyoto University Foundation, Kurozumi Foundation, Inamori Foundation, Clinical Pathology Research Foundation of Japan, Fujiwara Memorial Foundation, The Mother and Child Health Foundation, Sagawa Foundation for Cancer Research, Kanehara Foundation and SRF for Biomedical Research							
• **Setting**	Japan							
• **Sample size**	N=20							
• **Statistical analysis**	X^2 test							
Patient characteristics								
• **Eligibility criteria**	• Case reports of Japanese sporadic MEN1 patients published within 10 years							
• **Definitions**	• MEN1: at least two of the three major lesions (anterior pituitary gland, parathyroid glands and endocrine pancreas) • Familial MEN1: at least one first degree relative in whom at least one of the three main target organs was affected							
• **Patient characteristics**	• Females: 70% • Mean age: 52.5y (own calculation)							
• **Prevalence of disease**	Mutation: 40%							
Interventions								
• **Index test(s)**	Disease characteristics, see below							
• **Reference standard**	• Mutational analysis for MEN1 (PCR amplification)							
• **Time interval between tests**	Unclear							
Results								
• **Parathyroid disease**	Se	100%	Sp	8%	PPV	42%	NPV	100%
• **Pancreatic disease**	Se	88%	Sp	67%	PPV	64%	NPV	89%
• **Pituitary disease**	Se	63%	Sp	17%	PPV	33%	NPV	40%

Limitations and other comments	
• **Limitations**	• No consecutive sample • Unclear blinding

Hensen 2011								
Methods								
• **Design**	Retrospective cohort study							
• **Source of funding and competing interest**	• Supported by the European Union 6th Framework Programme (Project No: 518200) • No competing interests							
• **Setting**	Single university centre, the Netherlands							
• **Sample size**	N=236							
• **Statistical analysis**	Not reported							
Patient characteristics								
• **Eligibility criteria**	Patients with head and neck paraganglioma							
• **Patient characteristics**	• Females: 49% • Mean age at first diagnosis: 39.3y (own calculation) • Family history: 80% • Multiple tumours: 68%							
• **Prevalence of disease**	SDH mutation: 90.6%							
Interventions								
• **Index test(s): disease characteristics**	Familial history, malignant disease, multiple tumours, adrenal phaeochromocytoma, extra-adrenal phaeochromocytoma							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD and SDHAF2 (PCR amplification)							
• **Time interval between tests**	Not reported							
Results								
• **Familial disease**	Se	88%	Sp	95%	PPV	99%	NPV	45%
• **Malignant disease**	Se	2%	Sp	100%	PPV	100%	NPV	10%
• **Multiple tumours**	Se	73%	Sp	68%	PPV	96%	NPV	21%

• **Adrenal phaeochromocytoma**	Se	12%	Sp	100%	PPV	100%	NPV	12%	
• **Extra-adrenal phaeochromocytoma**	Se	7%	Sp	100%	PPV	100%	NPV	12%	
Limitations and other comments									
• **Limitations**	• Out of 366 consecutive patients, 130 were excluded (of which 25 with an uncertain diagnosis) • 1 patients with SDHC mutation excluded from analysis • Unclear blinding								

Hensen 2010	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• No funding reported • No competing interests
• **Setting**	Single university centre, the Netherlands
• **Sample size**	N=243
• **Statistical analysis**	Penetrance calculation; expressed as Kaplan-Meier curve
Patient characteristics	
• **Eligibility criteria**	Relatives of seven-generation family with head and neck paragangliomas; D92Y missense mutation in the SDHD gene
• **Patient characteristics**	Not reported
• **Prevalence of disease**	See below
Interventions	
• **Index test(s)**	Mutational analysis for SDHD
• **Reference standard**	Clinical evaluation and MRI screening
• **Time interval between tests**	Not reported
Results: generation VI and VII (N=211 family members that were alive; N=189 accepted testing)	
• **Mutation positive**	N=64: 63 that tested positive, one obligate carrier 53 paternal and 11 maternal mutation carriers

• **Penetrance**	138 children of male mutation carriers, at 50% risk of inheritance: • 30 symptomatic paragangliomas: estimated overall clinical penetrance = 43% (30/69) • 6 paragangliomas detected with MRI screening: estimated overall penetrance = 52% (36/69)
• **Kaplan-Meier analysis**	• Overall clinical penetrance = 57% (30/53); maximum reached at 47y • Overall penetrance = 68% (36/53); increasing to 87% at 70y
Limitations and other comments	
• **Limitations**	• Potential selection bias • Unclear blinding of reference standard (probably not) • Unclear if reference standard was always identical

Hes 2010	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• No funding reported • No competing interests
• **Setting**	Single university centre, the Netherlands
• **Sample size**	N=19
• **Statistical analysis**	Penetrance calculation; expressed as Kaplan-Meier curve
Patient characteristics	
• **Eligibility criteria**	Relatives of index-patient with an extra-adrenal paraganglioma and SDHB mutation
• **Patient characteristics**	Not reported
• **Prevalence of disease**	See below
Interventions	
• **Index test(s)**	Presymptomatic mutation screening (SDHB)
• **Reference standard**	Yearly clinical evaluation (including catecholamine screening) and MRI/CT screening (at least every two years or if excessive catecholamine secretion)
• **Time interval between tests**	Not reported
Results	

• **Mutation positive**	• 14/19 carriers • 11 underwent clinical screening: two were identified with subclinical vagal paragangliomas
• **Kaplan-Meier analysis**	• Penetrance = 26% at 48y
Limitations and other comments	
• **Limitations**	• Potential selection bias • Unclear blinding of reference standard (probably not) • Unclear if reference standard was always identical

Iacobone 2011	
Methods	
• **Design**	Retrospective cohort study, consecutive patients
• **Source of funding and competing interest**	Not reported
• **Setting**	Single university centre, Italy
• **Sample size**	N=71
• **Statistical analysis**	Fisher exact or X^2 test, Mann-Whitney test, Student t test, Spearman correlation, and linear regression test
Patient characteristics	
• **Eligibility criteria**	• Patients with phaeochromocytoma and/or secreting sympathetic thoraco-abdominal paraganglioma
• **Patient characteristics**	• Females: 52% • Mean age: 44.8y
• **Prevalence of disease**	Mutation: 22.5%
Interventions	
• **Index test(s): disease characteristics**	Familial/syndromic presentation (no reliable 2x2 tables possible for other characteristics)
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD, VHL and RET (multiplex genomic qPCR, multiplex ligation-dependent probe amplification)
• **Time interval between tests**	Not stated
Results	

• **Familial/syndromic presentation**	Se	50%	Sp	93%	PPV	67%	NPV	86%	
Limitations and other comments									
• **Limitations**	• 109 eligible consecutive patients, but only 71 with complete follow-up • Unclear blinding								

Jafri 2013	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interest**	• MJ was supported by the Birmingham Women's Hospital Springboard Fellowship and MRC Clinical Training Fellowship; ER was supported by the NIHR Clinical Training Fellowship; DGE and FL were supported by the Manchester BRC • No other competing interests reported
• **Setting**	Single genetic centre, UK; referral from across the UK
• **Sample size**	N=501
• **Statistical analysis**	Logistic regression to determine the predictive power of models explored ROC curves to determine the accuracy of models using different age cut-offs Student's t-tests to compare the ages in different subgroups
Patient characteristics	
• **Eligibility criteria**	• Patients (probands) with non-syndromic presentation of phaeochromocytoma/paraganglioma or head and neck paraganglioma • If more than one member of a family was referred, only the proband case was included in this study
• **Patient characteristics**	• Females: 53% • Median age: 36y for patients with phaeochromocytoma/paraganglioma, 39y for patients with head and neck paraganglioma
• **Prevalence of disease**	Mutation: 36.7%
Interventions	
• **Index test(s): disease characteristics**	See below

• **Reference standard**	Mutational analysis for SDHB, SDHD and VHL mutations (PCR amplification, multiplex ligation-dependent probe amplification)							
• **Time interval between tests**	Not reported							
Results	**Complete population (N=501)**							
• **Head and neck location**	Se	30%	Sp	90%	PPV	63%	NPV	69%
Results	**Location other than head and neck (N=413)**							
• **Familial disease**	Se	47%	Sp	87%	PPV	62%	NPV	78%
• **Malignant disease**	Se	23%	Sp	90%	PPV	53%	NPV	72%
• **Extra-adrenal phaeochromocytoma**	Se	45%	Sp	74%	PPV	44%	NPV	75%
Results	**Head and neck location (N=88)**							
• **Familial disease**	Se	60%	Sp	91%	PPV	92%	NPV	58%
• **Malignant disease**	Se	4%	Sp	97%	PPV	67%	NPV	38%
Limitations and other comments								
• **Limitations**	• Unclear blinding							

Kim 2013	
Methods	
• **Design**	Prospective (?) cohort study
• **Source of funding and competing interest**	• Funded by a Seoul National University Hospital grant (Grant No. 04-2012-0340) • No competing interests
• **Setting**	3 referral centres, South-Korea
• **Sample size**	N=53
• **Statistical analysis**	t-test or Wilcoxon rank sum test for continuous variables Fisher's exact or X^2 test for nominal variables
Patient characteristics	
• **Eligibility criteria**	Patients with apparently sporadic pheochromocytoma/paraganglioma
• **Patient characteristics**	• Females: 51%

	• Mean age: 50.1y • Family history: 0%							
• **Prevalence of disease**	Mutation: 13.2%							
Interventions								
• **Index test(s): disease characteristics**	Extra-abdominal paraganglioma, multiple tumours, bilateral phaeochromocytoma, malignant disease, recurrence							
• **Reference standard**	Mutational analysis for SDHB, SDHD, VHL and RET mutations (multiplex ligation-dependent probe amplification)							
• **Time interval between tests**	Not reported							
Results								
• **Extra-abdominal paraganglioma**	Se	0%	Sp	93%	PPV	0%	NPV	86%
• **Multiple tumours**	Se	14%	Sp	96%	PPV	33%	NPV	88%
• **Bilateral phaeochromocytoma**	Se	14%	Sp	96%	PPV	33%	NPV	88%
• **Malignant disease**	Se	14%	Sp	93%	PPV	25%	NPV	88%
• **Recurrence**	Se	14%	Sp	98%	PPV	50%	NPV	88%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients • Unclear blinding							

Klein 2008								
Methods								
• **Design**	Retrospective cohort study							
• **Source of funding and competing interest**	• No funding reported • No competing interests							
• **Setting**	Single centre, US							
• **Sample size**	N=39 (27 with paraganglioma)							
• **Statistical analysis**	X^2 test or Fisher exact test							
Patient characteristics								
• **Eligibility criteria**	Patients with malignant sympathetic paraganglioma or phaeochromocytoma; control group = patients with benign sympathetic paraganglioma							
• **Patient characteristics**	• Females: 48% • Mean age at first diagnosis: 34.2y (own calculation) • Family history: 8%							
• **Prevalence of disease**	SDH mutation: 40.7%							
Interventions								
• **Index test(s): disease characteristics**	Malignancy							
• **Reference standard**	Mutational analysis for SDHB and SDHD mutations (PCR amplification)							
• **Time interval between tests**	Not reported							
Results								
• **Malignancy**	Se	55%	Sp	38%	PPV	38%	NPV	55%
Limitations and other comments								
• **Limitations**	• Case-control design • Unclear blinding of index test							

Krawczyk 2010								
Methods								
• **Design**	Cohort study, unclear design							
• **Source of funding and competing interest**	• Not reported							
• **Setting**	Multicentre study, Poland							
• **Sample size**	N=60							
• **Statistical analysis**	Not reported							
Patient characteristics								
• **Eligibility criteria**	• Patients with apparently sporadic phaeochromocytoma and/or paraganglioma							
• **Patient characteristics**	• Mean age at diagnosis: 35.6y • Malignant disease: 20.7%							
• **Prevalence of disease**	Mutation: 30%							
Interventions								
• **Index test(s): disease characteristics**	Multiple tumours							
• **Reference standard**	Mutational analysis for SDHB, SDHD, RET and VHL mutations (PCR amplification)							
• **Time interval between tests**	Not reported							
Results								
• **Multiple tumours**	Se	44%	Sp	88%	PPV	62%	NPV	79%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients • Unclear blinding							

Lairmore 2004	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interest**	• Competing interests not reported • Supported by American Cancer Society Grant RPG-99-183-01-CCE, Washington University GCRC grant M01 RR00036, and a Washington University Cancer Center Research Development Award
• **Setting**	Single university centre, US
• **Sample size**	N=56
• **Statistical analysis**	Not reported
Patient characteristics	
• **Eligibility criteria**	• At risk members of 9 MEN1 kindreds
• **Definitions**	• MEN1: at least two of the three major lesions (anterior pituitary gland, parathyroid glands and endocrine pancreas) • Familial MEN1: at least one first degree relative in whom at least one of the three main target organs was affected
• **Patient characteristics**	• Mean age: 30.1y
• **Prevalence of disease**	Mutation: 12.5%
Interventions	
• **Index test(s)**	• Mutational analysis for MEN1 (PCR amplification)
• **Reference standard**	• At least annual biochemical screening, including measurement of total or ionized serum calcium, intact parathyroid hormone, prolactin, and fasting gastrin and pancreatic polypeptide; selected imaging tests
• **Time interval between tests**	Unclear
Results	
• 7 mutation positive patients	
• Hypercalcemia was either present at the time of genetic diagnosis or developed during the period of follow-up in 6 patients	
• One patient has not yet developed hyperparathyroidism (mean follow-up 35.8 months)	
Limitations and other comments	
• **Limitations**	• No consecutive sample • Unclear blinding

Lefebvre 2012								
Methods								
• **Design**	Retrospective cohort study							
• **Source of funding and competing interest**	• Not reported							
• **Setting**	Single centre, France							
• **Sample size**	N=269							
• **Statistical analysis**	Not reported							
Patient characteristics								
• **Eligibility criteria**	• Unrelated patients with paraganglioma and/or phaeochromocytoma • Absence of NF1, RET or VHL mutation							
• **Patient characteristics**	• Mean age at diagnosis: 44y							
• **Prevalence of disease**	Mutation: 14.5%							
Interventions								
• **Index test(s): disease characteristics**	Family history, multiple tumours, head and neck paraganglioma, metastatic disease							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD and SDHAF2 mutations (Denaturing High Pressure Liquid Chromatography or Multiplex PCR/liquid chromatography)							
• **Time interval between tests**	Not reported							
Results								
• **Family history**	Se	26%	Sp	98%	PPV	71%	NPV	89%
• **Multiple tumours**	Se	44%	Sp	91%	PPV	45%	NPV	90%
• **Head and neck paraganglioma**	Se	21%	Sp	95%	PPV	42%	NPV	88%
• **Metastatic disease**	Se	13%	Sp	93%	PPV	25%	NPV	86%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients • Unclear blinding							

Lima J 2007								
Methods								
• **Design**	Retrospective cohort study							
• **Source of funding and competing interest**	• Funded by the Fundação para a Ciência e a Tecnologia, Portugal • No competing interests							
• **Setting**	Single centre: Hospital Central de Asturias, Spain							
• **Sample size**	N=48							
• **Statistical analysis**	Fisher's exact test, ANOVA test, and X^2 test with the Yates correction							
Patient characteristics								
• **Eligibility criteria**	• Patients diagnosed with cervical paraganglioma between 1981 and 2005 • Availability of DNA from peripheral blood leukocytes, tumour tissue, and clinical data • Patients displaying syndromic features associated with VHL, MEN2, or NF1 were excluded							
• **Patient characteristics**	• Females: 60% • Mean age at diagnosis: 49y • Multiple tumours: 15% • Local and/or distant metastases: 0% • Familial cases: 25%							
• **Prevalence of disease**	Mutation: 41.7%							
Interventions								
• **Index test(s): disease characteristics**	Tumour location, recurrent disease, familial disease, multiple tumours							
• **Reference standard**	Mutational analysis for SDHB, SDHC and SDHD mutations (PCR-single-strand conformation polymorphism analysis)							
• **Time interval between tests**	Not reported							
Results								
• **Familial disease**	Se	60%	Sp	100%	PPV	100%	NPV	78%
• **Head & neck location**	Se	90%	Sp	0%	PPV	39%	NPV	0%
• **Recurrent disease**	Se	35%	Sp	86%	PPV	64%	NPV	65%
• **Multiple tumours**	Se	35%	Sp	100%	PPV	100%	NPV	68%

Limitations and other comments	
• **Limitations**	• Unclear if consecutive patients • No blinded interpretation of reference test

Lourenco 2007	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• Not reported
• **Setting**	Single university centre, Brasil
• **Sample size**	N=154
• **Statistical analysis**	ANOVA, Kruskall Wallis, and Mann-Whitney tests
Patient characteristics	
• **Eligibility criteria**	• MEN1 index cases (group I), clinically diagnosed MEN1 cases (group II), and genetically diagnosed MEN1 cases (group III)
• **Definitions**	• MEN1: at least two of the three major lesions (anterior pituitary gland, parathyroid glands and endocrine pancreas) • Familial MEN1: at least one first degree relative in whom at least one of the three main target organs was affected
• **Patient characteristics**	• Mean age: 30.1y
• **Prevalence of disease**	Mutation: 12.5%
Interventions	
• **Index test(s)**	• Mutational analysis for MEN1 (PCR amplification)
• **Reference standard**	• Annual biochemical exams and a tri-annual imaging investigation
• **Time interval between tests**	Unclear
Results	
• 13 index cases • 141 relatives at risk: 39 mutation positive: o 28 symptomatic cases (detected through clinical screening) o 11 asymptomatic cases (detected through genetic screening)	

• 101/102 MEN1 negative patients: no MEN1-related disease • 1/102 MEN1 negative patient: sporadic primary hyperparathyroidism (MEN1 phenocopy)	
Limitations and other comments	
• **Limitations**	• No consecutive sample • Unclear blinding

Mannelli 2009								
Methods								
• **Design**	Prospective (?) cohort study, consecutive patients							
• **Source of funding and competing interest**	• Supported by funds from the Italian University and Research Ministry (MIUR) (Grant 2006060473_01), by an unrestricted grant from Villa Gisella (Florence, Italy), and by the Fondazione della Comunità Bresciana (Brescia, Italy) • No competing interests							
• **Setting**	Multicentre study, Italy (N=17, Italian Pheochromocytoma/Paraganglioma Network)							
• **Sample size**	N=501							
• **Statistical analysis**	X^2 test							
Patient characteristics								
• **Eligibility criteria**	• Patients with phaeochromocytoma and/or paraganglioma							
• **Patient characteristics**	• Females: 57% • Mean age: 44.7y							
• **Prevalence of disease**	Mutation: 32.1%							
Interventions								
• **Index test(s): disease characteristics**	Familial disease, secretory tumour(s), multiple tumours, malignant disease							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD, VHL and RET mutations (PCR amplification)							
• **Time interval between tests**	Not reported							
Results								
• **Familial disease**	Se	32%	Sp	99%	PPV	91%	NPV	75%
• **Secretory tumour(s)**	Se	77%	Sp	20%	PPV	31%	NPV	65%

• **Multiple tumours**	Se	37%	Sp	91%	PPV	65%	NPV	75%
• **Malignant disease**	Se	6%	Sp	95%	PPV	36%	NPV	68%
Limitations and other comments								
• **Limitations**	• Unclear blinding							

Mysliwiec 2013								
Methods								
• **Design**	Retrospective cohort study; consecutive patients							
• **Source of funding and competing interest**	Not reported							
• **Setting**	Single university centre, Poland							
• **Sample size**	N=15							
• **Statistical analysis**	Mann-Whitney test							
Patient characteristics								
• **Eligibility criteria**	Patients with phaeochromocytoma							
• **Patient characteristics**	• Females: 53% • Mean age: women 46y, men 65.3y							
• **Prevalence of disease**	Mutation: 20% (RET, VHL)							
Interventions								
• **Index test(s): disease characteristics**	Age ≤ 45y, extra-adrenal location, malignant disease							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD, VHL and RET mutations (no details)							
• **Time interval between tests**	Not reported							
Results								
• **Age ≤ 45y**	Se	33%	Sp	83%	PPV	33%	NPV	83%
• **Extra-adrenal location**	Se	0%	Sp	83%	PPV	0%	NPV	77%
• **Malignant disease**	Se	0%	Sp	92%	PPV	0%	NPV	79%
Limitations and other comments								

• **Limitations**	• Unclear blinding of reference standard (probably not)

Neumann 2002	
Methods	
• **Design**	Retrospective cohort study, consecutive patients
• **Source of funding and competing interest**	• Supported by grants from the Center of Clinical Research (3000 1257 C5) of the Albert Ludwigs University, the Deutsche Forschungsgemeinschaft (NE 571/4-1), the Polish Committee of Scientific Research (4PO5B813), and the National Institutes of Health (R01HD39058 and P30CA16058) • Competing interests not reported
• **Setting**	Multicentre study, Germany and Poland
• **Sample size**	N=271
• **Statistical analysis**	Fisher's (two-tailed) unpaired exact test, two-sided X^2 test
Patient characteristics	
• **Eligibility criteria**	• Unrelated patients with non-syndromic phaeochromocytoma • Exclusion of cases discovered by clinical or genetic screening of persons without symptoms of illness • Exclusion of patients with neurofibromatosis type 1 or a family history
• **Patient characteristics**	• Females: 57% • Mean age: 40y
• **Prevalence of disease**	Mutation: N=66 (24%) • RET: N=13 • VHL: N=30 • SDHD: N=11 • SDHB: N=12
Interventions	
• **Index test(s): disease characteristics**	Age at onset ≤18y, multifocal disease, extra-adrenal phaeochromocytoma
• **Reference standard**	Mutational analysis for SDHB, SDHD, VHL and RET mutations (analysis of single-strand conformation polymorphisms and direct sequencing)
• **Time interval between tests**	Not reported

Results								
• **Age at onset ≤18y**	Se	41%	Sp	90%	PPV	56%	NPV	83%
• **Multifocal disease**	Se	32%	Sp	98%	PPV	81%	NPV	82%
• **Extra-adrenal phaeochromocytoma**	Se	21%	Sp	92%	PPV	47%	NPV	78%
Limitations and other comments								
• **Limitations**	• Unclear blinding of reference standard (probably not)							

Neumann 2009	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• H.P.H. Neumann is supported by grants from the German Cancer Foundation (Deutsche Krebshilfe) Grant 107995 (H.P.H. Neumann), the Deutsche Forschungsgemeinschaft (NE 571/5-3; H.P.H. Neumann), and the European Union (LSHC-CT-2005-518200; H.P.H. Neumann). C. Eng is the recipient of a Doris Duke Distinguished Clinical Scientist Award, and is the Sondra J. and Stephen R. Hardis Endowed Chair of Cancer Genomic Medicine at the Cleveland Clinic. C. Suarez is supported by a grant from the Fondo de Investigaciones Sanitarias (FIS; PI052071) and Red Tematica de Investigacio´n Cooperativa en Ca´ncer (RD06/0020/0034). M. Robledo is supported by a grant from FIS (PI042154) and Centro de Investigación Biomédica En Red de Enfermedades Raras • No competing interests
• **Setting**	International study (European-American Paraganglioma Registry)
• **Sample size**	N=598
• **Statistical analysis**	Univariate + multivariate analysis
Patient characteristics	
• **Eligibility criteria**	• Patients presenting with head and neck paraganglioma before molecular diagnosis • Individuals with known germline mutation at presentation and families where germline mutation was present in one member were excluded • From each family, only the first registered member was included
• **Patient characteristics**	Females: 71% Mean age at diagnosis: 49y Multiple tumours: 86%

	Familial cases: 11%							
• **Prevalence of disease**	Mutation: 30.6%							
Interventions								
• **Index test(s): disease characteristics**	Age ≤ 40y, familial disease, multiple tumours, previous phaeochromocytoma, malignant disease							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD, VHL and RET mutations (multiplex PCR)							
• **Time interval between tests**	Not reported							
Results								
• **Familial disease**	Se	35%	Sp	99%	PPV	94%	NPV	78%
• **Age ≤ 40y**	Se	59%	Sp	79%	PPV	55%	NPV	81%
• **Malignant disease**	Se	12%	Sp	97%	PPV	67%	NPV	72%
• **Multiple tumours**	Se	37%	Sp	97%	PPV	83%	NPV	78%
• **Previous phaeochromocytoma**	Se	14%	Sp	100%	PPV	93%	NPV	72%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients • No blinded interpretation of reference test • Exclusion of one case with RET mutation and one case with VHL mutation							

Pai 2014	
Methods	
• **Design**	Cohort study, unclear if prospective of retrospective
• **Source of funding and competing interest**	• Council for Scientific and Industrial Research, India • No competing interests
• **Setting**	Single centre, India
• **Sample size**	N=44
• **Statistical analysis**	Done with STATA 10.0
Patient characteristics	

• **Eligibility criteria**	• Patients with phaeochromocytoma and/or paraganglioma
• **Patient characteristics**	• Age: range 16-66y
• **Prevalence of disease**	Mutation: 29.5% • SDHB: N=3 • SDHD: N=3 • RET: N=3 • VHL: N=4
Interventions	
• **Index test(s): disease characteristics**	Immunohistochemistry for SDHB (blinded evaluation)
• **Reference standard**	Mutational analysis for SDH, VHL and RET (PCR sequencing)
• **Time interval between tests**	Not reported
Results	
• **Detection of SDH mutation**	Se 100% Sp 92% PPV 67% NPV 100%
Limitations and other comments	
• **Limitations**	• Unclear if consecutive patients • Unclear blinding of reference test

Papaspyrou 2012	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	Not reported
• **Setting**	Single university centre, Germany
• **Sample size**	N=175; 86 patients underwent genetic analysis
• **Statistical analysis**	Not reported
Patient characteristics	
• **Eligibility criteria**	Patients with craniocervical paragangliomas

• **Patient characteristics**	• Females: 66% • Bilateral tumours: 13%
• **Prevalence of disease**	SDH mutation: 39.5%
Interventions	
• **Index test(s): disease characteristics**	Tumour location, multiple tumours, malignant disease
• **Reference standard**	Mutational analysis for SDHB, SDHC and SDHD (not further specified)
• **Time interval between tests**	Not reported
Results: discordant data in text and tables	
Limitations and other comments	
• **Limitations**	• 8 patients excluded from analysis (5 had already described polymorphisms that did not predispose to development of PGL, and 1 had an already described SDHB polymorphism of unclear importance; rest unclear) • Unclear blinding

Persu 2012 (update of Persu 2008)	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interest**	• Supported by the F.R.S.M. convention No. 3.4510.11 (to A.P.); Interuniversity Attraction Poles initiated by the Belgian Federal Science Policy, network 5/25 and 6/5; Concerted Research Actions (A.R.C.) – Convention No. 02/07/276 and 07/12-005 of the Belgian French Community Ministry; the F.N.R.S. (Fonds national de la recherche scientifique) • Competing interests not reported
• **Setting**	22 centres, Belgium
• **Sample size**	N=112
• **Statistical analysis**	Not reported
Patient characteristics	
• **Eligibility criteria**	• Patients with either sporadic or familial phaeochromocytoma and/or paraganglioma • Patients diagnosed with or suspected of having Multiple Endocrine Neoplasia type 2, von Hippel-Lindau syndrome, or neurofibromatosis type 1 were excluded
• **Patient characteristics**	Females: 71%

	Mean age at diagnosis: 49.2y (own calculation) Multiple tumours: 10% Local and/or distant metastases: 3% Familial cases: 14%							
• **Prevalence of disease**	SDH mutation: 37.3% (for the 51 sporadic paragangliomas)							
Interventions								
• **Index test(s): disease characteristics**	Bilateral tumours, multiple tumours, recurrence							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD and VHL (quantitative multiplex PCR of short fluorescent fragments or Multiplex Ligation-dependent Probe Amplification)							
• **Time interval between tests**	Not reported							
Results: only for the 51 sporadic paragangliomas								
• **Bilateral tumours**	Se	26%	Sp	97%	PPV	83%	NPV	69%
• **Multiple tumours**	Se	21%	Sp	100%	PPV	100%	NPV	68%
• **Recurrence**	Se	0%	Sp	78%	PPV	0%	NPV	57%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients • Unclear blinding							

Piccini 2012 (overlap with Mannelli 2009)								
Methods								
• **Design**	Prospective cohort study, consecutive inclusion							
• **Source of funding and competing interest**	• Supported by Fondazione Cassa di Risparmio di Pistoia e Pescia (Prot. 2010.0278), Istituto Toscano Tumori (Prot. AOOGRT/325462/Q.80.110), and by funds from the Italian University and Research Ministry (MIUR) (Grant 2006060473_01) • No competing interests							
• **Setting**	Multicentre study, Italy							
• **Sample size**	N=79							
• **Statistical analysis**	X^2 and t-tests							
Patient characteristics								
• **Eligibility criteria**	Patients with head and neck paragangliomas							
• **Patient characteristics**	Females: 66% Mean age: 45.7y Multiple tumours: 29% Familial cases: 13%							
• **Prevalence of disease**	SDH or VHL mutation: 45.6%							
Interventions								
• **Index test(s): disease characteristics**	Familial disease, multiple/recurrent tumours							
• **Reference standard**	Mutational analysis for SDHA, SDHB, SDHC, SDHD, SDHAF2 and VHL (Multiplex Ligation-dependent Probe Amplification)							
• **Time interval between tests**	Not reported							
Results								
• **Familial disease**	Se	28%	Sp	100%	PPV	100%	NPV	62%
• **Multiple/recurrent**	Se	39%	Sp	100%	PPV	100%	NPV	66%
Limitations and other comments								
• **Limitations**	• Unclear blinding							

Pieterman 2009	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• Not reported
• **Setting**	Single university centre, the Netherlands
• **Sample size**	N=74 (43 clinical diagnosis, 30 genetic diagnosis, 1 undetermined diagnostic method)
• **Statistical analysis**	X^2 test, student's *t*-test or the Mann–Whitney *U*-test
Patient characteristics	
• **Eligibility criteria**	• Patients aged 16+ with clinical or genetic diagnosis of MEN1
• **Definitions**	• MEN1: at least two of the three major lesions (anterior pituitary gland, parathyroid glands and endocrine pancreas) • Familial MEN1: at least one first degree relative in whom at least one of the three main target organs was affected
• **Patient characteristics**	• Females: 53% • Mean age at diagnosis: 32y
• **Prevalence of disease**	NA
Interventions	
• **Index test(s)**	Disease characteristics, see below
• **Reference standard**	• Mutational analysis for MEN1 (PCR amplification)
• **Time interval between tests**	Unclear
Results	**Clinical vs. genetic diagnosis**
• **Number of manifestations at time of MEN1 diagnosis**	• None: 0 vs. 19 • One: 17 vs. 6 • Two: 11 vs. 5 • Three: 3 vs. 0
• **Number of manifestations at end of follow-up**	• None: 0 vs. 13 • One: 2 vs. 8 • Two: 5 vs. 5

	• Three: 6 vs. 4
• **Malignancy (metastases)**	• 10 vs. 0
• **Deaths**	• 10 vs. 0: 5 MEN1-related deaths
Limitations and other comments	
• **Limitations**	• No consecutive sample: exclusion of 22 patients with uncertain diagnosis of MEN1 (negative clinical screening or no mutation analysis performed) and 4 patients with insufficient information • Unclear blinding • Median follow-up: 11y (clinical diagnosis) vs. 3y (genetic diagnosis)

Pigny 2009	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• No funding • No competing interests
• **Setting**	Single university centre, France
• **Sample size**	N=100
• **Statistical analysis**	Not reported
Patient characteristics	
• **Eligibility criteria**	• Patients with an apparently sporadic phaeochromocytoma or paraganglioma that signed informed consent for genetic testing, no familial history • Exclusion of patients with extra-abdominal paraganglioma, patients with phaeochromocytoma and paraganglioma
• **Patient characteristics**	• Females: 45% • Age: range 13-95y
• **Prevalence of disease**	Mutation: N=8 (8%) • RET: N=3 • VHL: N=2 • SDHD: N=2 • SDHB: N=1

Interventions								
• **Index test(s): disease characteristics**	Age at onset ≤20y, age at onset ≤40y							
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD, RET and VHL (PCR-sequencing)							
• **Time interval between tests**	Not reported							
Results								
• **Age at onset ≤20y**	Se	13%	Sp	98%	PPV	33%	NPV	93%
• **Age at onset ≤40y**	Se	50%	Sp	63%	PPV	11%	NPV	94%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients • Unclear blinding of reference standard (probably not)							

Poncin 1999	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• Competing interests not reported • Supported by The Fonds National de la Recherche Scientifique (Grant numbers: FRSM 3.4566.89 and 3.4628.93); The Fonds de Recherche de la Faculté de Médecine de l' Université de Liège
• **Setting**	Multicentre study, Belgium
• **Sample size**	N=57 (25 probands)
• **Statistical analysis**	X^2 test
Patient characteristics	
• **Eligibility criteria**	• Patients with MEN1 and their relatives; patients with MEN1-related disease
• **Definitions**	• MEN1: at least two of the three major lesions (anterior pituitary gland, parathyroid glands and endocrine pancreas) • Familial MEN1: at least one first degree relative in whom at least one of the three main target organs was affected
• **Patient characteristics**	• Unclear
• **Prevalence of disease**	Mutation: 79.2%
Interventions	

• **Index test(s)**	Disease characteristics, see below								
• **Reference standard**	• Mutational analysis for MEN1 (PCR amplification)								
• **Time interval between tests**	Unclear								
Results	**53 MEN1 patients only**								
• **Familial disease**	Se	86%	Sp	82%	PPV	95%	NPV	60%	
Limitations and other comments									
• **Limitations**	• Unclear if consecutive sample • Unclear blinding								

Schaaf 2007	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• Not reported
• **Setting**	Multicentre study, Germany (German MEN1 database, 72 centres)
• **Sample size**	N=419, including 306 MEN1 patients
• **Statistical analysis**	See article
Patient characteristics	
• **Eligibility criteria**	• Patients with MEN1
• **Definitions**	• MEN1: at least two of the three major lesions (anterior pituitary gland, parathyroid glands and endocrine pancreas) • Familial MEN1: at least one first degree relative in whom at least one of the three main target organs was affected
• **Patient characteristics**	• Females: 59% • Mean age: 51y
• **Prevalence of disease**	Mutation: %
Interventions	
• **Index test(s)**	No 2x2 tables possible for disease characteristics
• **Reference standard**	• Mutational analysis for MEN1 (PCR and direct DNA sequencing)
• **Time interval between tests**	Unclear

Results	**Age-related penetrance**
• **Age-related penetrance**	10%, 35%, 67%, 81% and 100% at 20, 30, 40, 50 and 65y, respectively
Limitations and other comments	
• **Limitations**	• Unclear if consecutive sample • Only 199 patients underwent genetic testing • Unclear blinding

Sevilla 2009	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• Supported by grant PI05-2071 of Fondos de Investigación Sanitaria (FIS), Spain and by RTICC grant RD06/0020/0034 • Competing interests not reported
• **Setting**	Single centre (?), Spain
• **Sample size**	N=24
• **Statistical analysis**	X^2 test
Patient characteristics	
• **Eligibility criteria**	Patients with parasympathetic paragangliomas
• **Patient characteristics**	Females: 58% Mean age at diagnosis: 42y Local and/or distant metastases: 4% Familial cases: 33%
• **Prevalence of disease**	SDH mutation: 62.5%
Interventions	
• **Index test(s): disease characteristics**	Age ≤ 40y, familial disease, multiple tumours, previous phaeochromocytoma, malignant disease, recurrence, functional paraganglioma
• **Reference standard**	Mutational analysis for SDHB, SDHC, SDHD and VHL (Multiplex Ligation-dependent Probe Amplification)
• **Time interval between tests**	Not reported

Results								
• **Familial disease**	Se	53%	Sp	100%	PPV	10%	NPV	56%
• **Age ≤ 40y**	Se	67%	Sp	11%	PPV	56%	NPV	17%
• **Malignant disease**	Se	0%	Sp	89%	PPV	0%	NPV	35%
• **Multiple tumours**	Se	33%	Sp	100%	PPV	100%	NPV	47%
• **Previous phaeochromocytoma**	Se	7%	Sp	100%	PPV	100%	NPV	39%
• **Recurrence**	Se	13%	Sp	100%	PPV	100%	NPV	41%
• **Functional paraganglioma**	Se	7%	Sp	89%	PPV	50%	NPV	36%

Limitations and other comments	
• **Limitations**	• Overlap with Neumann 2009 • Unclear if consecutive patients • Unclear blinding

Sridhara 2013	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	No grant support or competing interests
• **Setting**	Single centre, US
• **Sample size**	N=26
• **Statistical analysis**	X^2 analysis, Fisher's exact test, Welch t-test
Patient characteristics	
• **Eligibility criteria**	Patients with head and neck paraganglioma
• **Patient characteristics**	Females: 61.6% Mean age: 43.5y Distant metastases: 27% Familial cases: 31%

• **Prevalence of disease**	SDH mutation: 61.5%							
Interventions								
• **Index test(s): disease characteristics**	Family history, bilateral disease, secretory paranganglioma and/or phaeochromocytcoma, distant metastases							
• **Reference standard**	Mutational analysis for SDH (not further specified)							
• **Time interval between tests**	Not reported							
Results								
• **Familial disease**	Se	38%	Sp	80%	PPV	75%	NPV	44%
• **Bilateral disease**	Se	81%	Sp	80%	PPV	87%	NPV	73%
• **Secretory paranganglioma and/or phaeochromocytcoma**	Se	13%	Sp	80%	PPV	50%	NPV	36%
• **Distant metastases**	Se	31%	Sp	80%	PPV	71%	NPV	42%
Limitations and other comments								
• **Limitations**	• Unclear if consecutive patients • Unclear blinding							

Tham 2007	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• Supported by the Swedish Cancer Society and King Gustaf V's Jubilee Foundation • No competing interests
• **Setting**	Single university centre, Sweden
• **Sample size**	N=200 probands, 169 relatives
• **Statistical analysis**	Not reported
Patient characteristics	
• **Eligibility criteria**	• Non-related probands (i.e. first family member referred to the clinic) referred for MEN1 mutation testing
• **Definitions**	• MEN1: at least two of the three major lesions (anterior pituitary gland, parathyroid glands and endocrine pancreas)

	• Familial MEN1: at least one first degree relative in whom at least one of the three main target organs was affected							
• **Patient characteristics**	• Females: 62% • Median age: 44y							
• **Prevalence of disease**	Mutation: 24%							
Interventions								
• **Index test(s)**	Disease characteristics, see below							
• **Reference standard**	• Mutational analysis for MEN1 (PCR and multiplex ligation-dependent probe amplification)							
• **Time interval between tests**	Unclear							
Results	**All patients**							
• **Familial disease**	Se	83%	Sp	88%	PPV	68%	NPV	94%
Results	**MEN1 patients**							
• **Three major lesions**	Se	62%	Sp	84%	PPV	64%	NPV	83%
Results	**Relatives**							
• **Prevalence of MEN1 mutation**	• Presymptomatic relatives: 18% • Symptomatic relatives: 94%							
Limitations and other comments								
• **Limitations**	• Unclear if consecutive sample • Clinical information was missing for 2 patients • Unclear blinding							

Tso 2003	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• Supported by a CRCG grant from the University of Hong Kong • Competing interests not reported
• **Setting**	Single centre, China
• **Sample size**	N=12 index patients, 47 relatives

• **Statistical analysis**	Fisher's exact test							
Patient characteristics								
• **Eligibility criteria**	• Patients with MEN1, and their relatives							
• **Definitions**	• MEN1: at least two of the three major lesions (anterior pituitary gland, parathyroid glands and endocrine pancreas) • Familial MEN1: at least one first degree relative in whom at least one of the three main target organs was affected							
• **Patient characteristics**	• Females: 75% • Median age: 32y							
• **Prevalence of disease**	Mutation: 75%							
Interventions								
• **Index test(s)**	Disease characteristics, see below							
• **Reference standard**	• Mutational analysis for MEN1 (PCR)							
• **Time interval between tests**	Unclear							
Results	**MEN1 patients**							
• **Familial disease**	Se	67%	Sp	100%	PPV	100%	NPV	50%
• **Three major lesions**	Se	33%	Sp	100%	PPV	100%	NPV	33%
Results	**First-degree relatives**							
• **Prevalence**	19% with MEN1 mutation							
Limitations and other comments								
• **Limitations**	• Unclear if consecutive sample • Unclear blinding							

van Nederveen 2009								
Methods								
• **Design**	Retrospective and prospective cohort study							
• **Source of funding and competing interest**	• The Netherlands Organisation for Scientific Research, Dutch Cancer Society, Vanderes Foundation, Association pour la Recherche contre le Cancer, Institut National de la Santé et de la Recherche Médicale, and a PHRC grant COMETE 3 for the COMETE network • No competing interests							
• **Setting**	Multicentre study (mainly the Netherlands and France)							
• **Sample size**	Retrospective part: N=175; prospective part: N=45							
• **Statistical analysis**	Fisher's exact test							
Patient characteristics								
• **Eligibility criteria**	• Patients with phaeochromocytoma and/or paraganglioma							
• **Patient characteristics**	• Females: 60% • Mean age at first diagnosis: 39.2y (own calculation)							
• **Prevalence of disease**								
Interventions								
• **Index test(s): disease characteristics**	Immunohistochemistry for SDHB (blinded evaluation)							
• **Reference standard**	Mutational analysis for SDH, VHL and RET (PCR sequencing)							
• **Time interval between tests**	Not reported							
Results								
• **Detection of SDH mutation: prospective study**	Se	100%	Sp	84%	PPV	90%	NPV	100%
• **Detection of SDH mutation: retrospective study**	Se	100%	Sp	97%	PPV	96%	NPV	100%
Limitations and other comments								
• **Limitations**	• Unclear blinding of reference test • Unclear if consecutive patients in retrospective part							

Waterlot 1999	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	• Supported by grants from the Comité du Nord de la Ligue Contre le Cancer and the contract PHRC N° 97-048. • Competing interests not reported
• **Setting**	Single university centre, France
• **Sample size**	N=91 members from a MEN1 family
• **Statistical analysis**	Not reported
Patient characteristics	
• **Eligibility criteria**	• MEN1 pedigree
• **Definitions**	• MEN1: at least two of the three major lesions (anterior pituitary gland, parathyroid glands and endocrine pancreas) • Familial MEN1: at least one first degree relative in whom at least one of the three main target organs was affected
• **Patient characteristics**	• Females: 56%
• **Prevalence of disease**	Mutation: 41.6%
Interventions	
• **Index test(s)**	Clinical screening (medical history, clinical examination, imaging, lab tests)
• **Reference standard**	• Mutational analysis for MEN1 (PCR)
• **Time interval between tests**	Unclear
Results	
• **Phenotypic screening ('92-'95)**	14/54 affected
• **Genetic screening ('95 onwards)**	• Clinically affected members (N=14): all positive • Asymptomatic members (N=34): o 6 positive o 28 negative (excluded from annual screening: before, 10 were tested annually)
Limitations and other comments	
• **Limitations**	• Unclear if consecutive sample, probably not • Unclear blinding

5. DIAGNOSTIC META-ANALYSES

5.1. MEN1

5.1.1. MEN1 phenotype – familial disease

Log likelihood = -14.950948 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	.8848012	.3715607			.1565557	1.613047
E(logitSp)	1.890302	.4106143			1.085513	2.695092
Var(logitSe)	.2771771	.3116191			.0306045	2.510321
Var(logitSp)	.0051751	.0599946			7.01e-13	3.82e+07
Corr(logits)	1	.			.	.
HSROC						
Lambda	5.440837	13.27946			-20.58642	31.4681
Theta	-2.393352	7.611756			-17.31212	12.52541
beta	-1.990401	5.824704	-0.34	0.733	-13.40661	9.42581
s2alpha	.1514947	.8820999			1.68e-06	13697.56
s2theta	0	.			.	.
Summary pt.						
Se	.7078162	.0768434			.5390592	.833834
Sp	.86879	.0468075			.7475359	.9367364
DOR	16.04029	9.655731			4.929656	52.19246
LR+	5.394529	2.111377			2.504954	11.61736
LR-	.3363112	.0934699			.1950607	.5798465
1/LR-	2.973436	.8263973			1.724594	5.12661

Covariance between estimates of E(logitSe) & E(logitSp) .0278516

5.1.2. MEN1 phenotype – three major lesions

Log likelihood = -21.805491 Number of studies = 5

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-.7929898	.4092145			-1.595036	.009056
E(logitSp)	3.052876	.6580767			1.763069	4.342682
Var(logitSe)	.5903428	.484756			.1180717	2.951635
Var(logitSp)	1.118958	1.118063			.1578677	7.931119
Corr(logits)	-1	.			.	.
HSROC						
Lambda	1.671393	.6883001			.3223494	3.020436
Theta	-1.766151	.4807288			-2.708362	-.8239395
beta	.319725	.4764962	0.67	0.502	-.6141903	1.25364
s2alpha	0	.			.	.
s2theta	.8127539	.6344115			.1760097	3.753027
Summary pt.						
Se	.3115271	.0877675			.1686766	.502264
Sp	.9549065	.0283368			.8535936	.9871653
DOR	9.581997	4.642623			3.707114	24.76715
LR+	6.908472	3.340426			2.677959	17.82215
LR-	.7209846	.0789598			.5817084	.8936073
1/LR-	1.386992	.1518986			1.11906	1.719074

Covariance between estimates of E(logitSe) & E(logitSp) -.1828832

5.1.3. MEN1 phenotype – parathyroid tumour

Log likelihood = -16.202377 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	4.286418	.8471755			2.625984	5.946851
E(logitSp)	-1.02406	1.239911			-3.454241	1.406122
Var(logitSe)	.0447938	.2699876			3.32e-07	6049.327
Var(logitSp)	5.545091	4.208211			1.252926	24.54098
Corr(logits)	-1	.			.	.
HSROC						
Lambda	13.99073	20.51522			-26.21836	54.19981
Theta	7.302374	9.814301			-11.9333	26.53805
beta	2.4093	2.994373	0.80	0.421	-3.459564	8.278163
s2alpha	0	.			.	.
s2theta	.4983828	1.535001			.001191	208.5607
Summary pt.						
Se	.9864325	.0113381			.9325153	.9973928
Sp	.2642374	.2410586			.0306426	.8031535
DOR	26.11104	37.04219			1.619105	421.0886
LR+	1.340694	.4377414			.7069836	2.542436
LR-	.0513459	.0597597			.0052459	.5025629
1/LR-	19.47577	22.66719			1.989801	190.6248

Covariance between estimates of E(logitSe) & E(logitSp) -.121272

5.1.4. MEN1 phenotype – pituitary tumour

Log likelihood = -20.916115 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	.1054909	.500006			-.8745028	1.085485
E(logitSp)	-.6058317	1.728836			-3.994288	2.782625
Var(logitSe)	.6127148	.5455166			.1070066	3.508376
Var(logitSp)	8.518776	6.886298			1.747004	41.53942
Corr(logits)	-1	.			.	.
HSROC						
Lambda	-.11004	.4207686			-.9347314	.7146513
Theta	.2587217	.9061287			-1.517258	2.034701
beta	1.316064	.2869854	4.59	0.000	.7535831	1.878545
s2alpha	2.20e-13	.			.	.
s2theta	2.28464	1.828724			.4758602	10.96873
Summary pt.						
Se	.5263483	.1246544			.2943182	.7475305
Sp	.3530106	.394856			.0180874	.9417296
DOR	.606324	.7888614			.0473417	7.765432
LR+	.8135347	.3354595			.362564	1.82544
LR-	1.341749	1.195489			.2340222	7.692821
1/LR-	.7452958	.664053			.1299913	4.273099

Covariance between estimates of E(logitSe) & E(logitSp) -.7730668

5.1.5. MEN1-related state – familial disease

Log likelihood = -24.103582 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	1.143343	.3201563			.5158482	1.770838
E(logitSp)	1.179457	.3490345			.495362	1.863552
Var(logitSe)	.1980821	.2557665			.0157674	2.488451
Var(logitSp)	.3663994	.3162841			.0674806	1.98944
Corr(logits)	.0475536	.7591901			-.8944537	.9119433
HSROC						
Lambda	2.344738	.5075799			1.349899	3.339576
Theta	.1610112	.5105949			-.8397365	1.161759
beta	.3075213	.7761113	0.40	0.692	-1.213629	1.828672
s2alpha	.564425	.5828719			.0745736	4.271961
s2theta	.1282952	.1467341			.0136355	1.207116
Summary pt.						
Se	.7582929	.0586798			.6261764	.8545618
Sp	.7648502	.0627754			.6213688	.8657104
DOR	10.20421	4.890957			3.988334	26.1076
LR+	3.224722	.9020913			1.863696	5.579682
LR-	.3160189	.0815792			.1905366	.5241405
1/LR-	3.164368	.8168702			1.907885	5.248335

Covariance between estimates of E(logitSe) & E(logitSp) .0027055

5.2. Paraganglioma / phaeochromocytoma

5.2.1. Familial disease

5.2.1.1. Familial disease – all tests, whole population

Log likelihood = -136.12075 Number of studies = 22

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-.2640085	.2178543			-.6909951	.1629781
E(logitSp)	3.560371	.3467189			2.880815	4.239928
Var(logitSe)	.8889804	.3024423			.4563548	1.731736
Var(logitSp)	1.605454	.7242408			.6631472	3.886742
Corr(logits)	-.2090636	.2608783			-.6332801	.3117564
HSROC						
Lambda	2.765225	.5258228			1.734631	3.795818
Theta	-1.688664	.262088			-2.202347	-1.174981
beta	.2955433	.2778765	1.06	0.288	-.2490846	.8401713
s2alpha	1.889803	.8317051			.79763	4.477459
s2theta	.7222111	.2577147			.3588561	1.453476
Summary pt.						
Se	.4343786	.0535255			.3338117	.5406546
Sp	.9723576	.0093192			.9468898	.985796
DOR	27.0142	10.25259			12.83923	56.83882
LR+	15.71419	5.348483			8.064489	30.62013
LR-	.5817011	.054454			.4841918	.6988472
1/LR-	1.719096	.1609274			1.430928	2.065297

Covariance between estimates of E(logitSe) & E(logitSp) -.0118173

5.2.1.2. Familial disease – SDH, whole population

Log likelihood = -47.405648 Number of studies = 9

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-.2843358	.391712			-1.052077	.4834057
E(logitSp)	4.063688	.5263959			3.031971	5.095405
Var(logitSe)	1.148742	.6299203			.3921572	3.364996
Var(logitSp)	1.009999	1.019818			.139587	7.30798
Corr(logits)	.409704	.5752826			-.7257651	.945785
HSROC						
Lambda	3.921249	1.406992			1.163595	6.678903
Theta	-2.235956	.6175352			-3.446303	-1.02561
beta	-.0643586	.5614527	-0.11	0.909	-1.164786	1.036068
s2alpha	3.036894	2.236849			.7169194	12.86438
s2theta	.3179154	.3512075			.0364731	2.771091
Summary pt.						
Se	.4293911	.0959751			.2588264	.6185518
Sp	.9831048	.0087433			.9539977	.9939125
DOR	43.78765	31.76378			10.56539	181.4753
LR+	25.41501	15.48944			7.696918	83.91967
LR-	.5804151	.0989496			.4155518	.8106851
1/LR-	1.722905	.2937221			1.233525	2.406439

Covariance between estimates of E(logitSe) & E(logitSp) .0478408

5.2.1.3. *Familial disease – SDH, paraganglioma only*

Log likelihood = -34.709976 Number of studies = 7

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	.1405483	.3664978			-.5777741	.8588707
E(logitSp)	4.239914	.6055647			3.053029	5.426799
Var(logitSe)	.7340817	.4376302			.2281876	2.361548
Var(logitSp)	.8435372	2.52325			.0023984	296.6743
Corr(logits)	-.3959153	1.27232			-.9976658	.987599
HSROC						
Lambda	4.240642	2.885615			-1.41506	9.896344
Theta	-1.974803	1.538908			-4.991007	1.0414
beta	.0694918	1.490492	0.05	0.963	-2.851818	2.990802
s2alpha	.950719	3.294039			.0010686	845.8322
s2theta	.5492289	.5592894			.074638	4.041539
Summary pt.						
Se	.5350793	.0911734			.3594449	.7024247
Sp	.9857958	.0084794			.9549131	.9956221
DOR	79.87494	49.74683			23.56539	270.7363
LR+	37.67059	21.75604			12.1452	116.8423
LR-	.4716196	.0915372			.3223896	.6899262
1/LR-	2.120353	.411542			1.44943	3.101837

Covariance between estimates of E(logitSe) & E(logitSp) -.0565691

5.2.1.4. Familial disease – SDHB, whole population

Log likelihood = -77.252524 Number of studies = 11

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-.7715041	.2637015			-1.288349	-.2546588
E(logitSp)	1.965589	.2595555			1.45687	2.474309
Var(logitSe)	.5842502	.3473168			.1822169	1.873308
Var(logitSp)	.6496848	.31018			.2548662	1.656125
Corr(logits)	-.611468	.2512409			-.9047402	.0750798
HSROC						
Lambda	1.121856	.5143275			.1137926	2.129919
Theta	-1.353182	.2452581			-1.833879	-.8724846
beta	.053079	.3311711	0.16	0.873	-.5960044	.7021625
s2alpha	.4787487	.3065713			.1364686	1.67951
s2theta	.4964122	.2486452			.1859897	1.32494
Summary pt.						
Se	.3161538	.0570124			.2161323	.4366771
Sp	.8771366	.0279718			.8110535	.922321
DOR	3.300537	.8530311			1.988793	5.477464
LR+	2.573213	.5292142			1.719552	3.85067
LR-	.7796348	.0564588			.6764718	.8985302
1/LR-	1.282652	.0928858			1.112929	1.478258

Covariance between estimates of E(logitSe) & E(logitSp) -.035055

5.2.1.5. *Familial disease – SDHB, paraganglioma only*

Log likelihood = -27.38146 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-.4927787	.4321044			-1.339688	.3541303
E(logitSp)	1.369937	.31774			.7471783	1.992696
Var(logitSe)	.5422122	.5075061			.0865868	3.395368
Var(logitSp)	.3142925	.254464			.0642934	1.53639
Corr(logits)	-.6077619	.4160802			-.9639235	.528311
HSROC						
Lambda	1.140061	.723908			-.278773	2.558894
Theta	-1.000005	.341888			-1.670093	-.3299171
beta	-.2726666	.5389953	-0.51	0.613	-1.329078	.7837446
s2alpha	.3238407	.3337163			.0429707	2.440567
s2theta	.3318512	.2723737			.0664205	1.658
Summary pt.						
Se	.3792392	.1017246			.2075614	.5876188
Sp	.79737	.0513376			.6785636	.8800281
DOR	2.404059	.9557065			1.10296	5.239993
LR+	1.871585	.5021011			1.106248	3.166404
LR-	.7785103	.1129163			.5858748	1.034484
1/LR-	1.284504	.1863064			.9666652	1.706849

Covariance between estimates of E(logitSe) & E(logitSp) -.0648179

5.2.1.6. *Familial disease – SDHD, whole population*

Log likelihood = -74.372467 Number of studies = 11

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	.085287	.2303147			-.3661215	.5366955
E(logitSp)	2.127959	.2830719			1.573148	2.682769
Var(logitSe)	.3507024	.2629251			.0806834	1.524379
Var(logitSp)	.7702347	.3876439			.2872303	2.065456
Corr(logits)	-.5132128	.3333539			-.8964933	.3094162
HSROC						
Lambda	1.851828	.4484411			.9728996	2.730757
Theta	-.8220886	.2877293			-1.386028	-.2581496
beta	.3933787	.4230905	0.93	0.352	-.4358634	1.222621
s2alpha	.5059995	.4074345			.1044134	2.452132
s2theta	.3932339	.2128744			.1361002	1.136169
Summary pt.						
Se	.5213088	.0574741			.4094785	.6310434
Sp	.8935911	.0269162			.8282319	.9360022
DOR	9.145351	2.64044			5.193284	16.10493
LR+	4.899108	1.147166			3.096002	7.75234
LR-	.5356938	.0600349			.430054	.6672833
1/LR-	1.866738	.2092042			1.498614	2.32529

Covariance between estimates of E(logitSe) & E(logitSp) -.0249079

5.2.1.7. *Familial disease – SDHD, paraganglioma only*

Log likelihood = -29.601537 Number of studies = 5

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	.2358828	.1397591			-.0380401	.5098057
E(logitSp)	2.159183	.5181535			1.14362	3.174745
Var(logitSe)	.0083566	.03211			4.48e-06	15.58663
Var(logitSp)	1.083139	.943233			.1965305	5.969506
Corr(logits)	-1	.			.	.
HSROC						
Lambda	1.435823	.4007642			.6503394	2.221306
Theta	.0779918	.6492558			-1.194526	1.35051
beta	2.432285	1.991709	1.22	0.222	-1.471394	6.335963
s2alpha	0	.			.	.
s2theta	.0951385	.185327			.0020905	4.329841
Summary pt.						
Se	.5586988	.0344582			.4904911	.6247609
Sp	.8965237	.0480685			.7583437	.9598727
DOR	10.96891	5.368904			4.202715	28.62842
LR+	5.399294	2.417256			2.245201	12.98431
LR-	.492236	.0386691			.4219924	.574172
1/LR-	2.031546	.1595942			1.741638	2.369711

Covariance between estimates of E(logitSe) & E(logitSp) -.0242196

5.2.1.8. *Familial disease – VHL, whole population*

Log likelihood = -33.873433 Number of studies = 5

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-.9601116	1.0039			-2.92772	1.007497
E(logitSp)	1.854644	.3152068			1.23685	2.472438
Var(logitSe)	4.301717	3.7225			.7889563	23.45475
Var(logitSp)	.4631648	.3105306			.1244641	1.723562
Corr(logits)	-.9066117	.1087548			-.9911017	-.3013711
HSROC						
Lambda	2.687726	.6746076			1.365519	4.009932
Theta	-1.893841	.6116421			-3.092637	-.6950442
beta	-1.114343	.3682912	-3.03	0.002	-1.836181	-.3925058
s2alpha	.2636399	.2804398			.032777	2.120576
s2theta	1.345615	.9519645			.3363046	5.38405
Summary pt.						
Se	.2768558	.2009875			.0508002	.7325299
Sp	.8646714	.0368839			.7750152	.9221869
DOR	2.446191	1.884735			.5403297	11.07444
LR+	2.045805	1.082931			.7249147	5.773529
LR-	.8363225	.2045615			.517813	1.350749
1/LR-	1.195711	.2924666			.7403301	1.931199

Covariance between estimates of E(logitSe) & E(logitSp) -.2567678

5.2.1.9. *Familial disease – RET, whole population*

Log likelihood = -23.08493 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	.081498	2.02081			-3.879217	4.042213
E(logitSp)	2.026533	.3508083			1.338962	2.714105
Var(logitSe)	12.62136	13.29276			1.601861	99.44605
Var(logitSp)	.4532134	.3464135			.1013181	2.027302
Corr(logits)	-.8576361	.2194588			-.9940916	.3293625
HSROC						
Lambda	4.690851	1.193107			2.352405	7.029297
Theta	-2.309949	1.006158			-4.281982	-.3379151
beta	-1.663391	.486772	-3.42	0.001	-2.617447	-.7093358
s2alpha	.6809797	1.078103			.0305874	15.16094
s2theta	2.221443	1.805389			.4517051	10.92484
Summary pt.						
Se	.5203632	.5043646			.0202485	.9827444
Sp	.8835549	.0360931			.7923191	.9378538
DOR	8.232018	14.67772			.2499257	271.145
LR+	4.468742	3.461562			.9791075	20.39577
LR-	.5428489	.5549734			.0731924	4.026169
1/LR-	1.842133	1.883277			.248375	13.66262

Covariance between estimates of E(logitSe) & E(logitSp) -.5138192

5.2.2. Multiple tumours

5.2.2.1. Multiple tumours – all tests, whole population

Log likelihood = -103.76961 Number of studies = 17

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-.3486881	.1805596			-.7025784	.0052021
E(logitSp)	2.73352	.2528794			2.237886	3.229155
Var(logitSe)	.406121	.2095148			.1477498	1.116308
Var(logitSp)	.6548532	.3871855			.2055258	2.086515
Corr(logits)	-.5235045	.274772			-.8675301	.1593289
HSROC						
Lambda	2.032848	.5264698			1.000987	3.06471
Theta	-1.409349	.2394653			-1.878692	-.9400054
beta	.2388799	.3690162	0.65	0.517	-.4843785	.9621384
s2alpha	.4914603	.3145937			.1401578	1.723295
s2theta	.392838	.1899338			.1522877	1.013356
Summary pt.						
Se	.4137006	.0437952			.3312408	.5013005
Sp	.9389759	.01449			.9036004	.9619168
DOR	10.85724	2.70583			6.66168	17.69518
LR+	6.779293	1.494959			4.400264	10.44456
LR-	.6244031	.0439236			.5439854	.7167089
1/LR-	1.60153	.1126596			1.395267	1.838284

Covariance between estimates of E(logitSe) & E(logitSp) -.0172198

5.2.2.2. *Multiple tumours – SDH, whole population*

Log likelihood = -40.600246 Number of studies = 7

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	.0977002	.2462245			-.3848909	.5802913
E(logitSp)	2.436721	.4007135			1.651336	3.222105
Var(logitSe)	.3201174	.2158434			.0853838	1.200171
Var(logitSp)	.858693	.6268895			.2053135	3.591354
Corr(logits)	-1	.			.	.
HSROC						
Lambda	2.029063	.3253778			1.391334	2.666792
Theta	-.8894976	.3217866			-1.520188	-.2588075
beta	.4933617	.2712121	1.82	0.069	-.0382042	1.024928
s2alpha	0	.			.	.
s2theta	.5242925	.3398801			.1471533	1.868001
Summary pt.						
Se	.5244056	.0614095			.4049478	.6411344
Sp	.9195849	.0296322			.8390716	.9616577
DOR	12.60912	2.890844			8.045135	19.76226
LR+	6.521234	1.79477			3.802443	11.18399
LR-	.5171837	.0532457			.4226793	.6328179
1/LR-	1.933549	.199065			1.580233	2.36586

Covariance between estimates of E(logitSe) & E(logitSp) -.0843175

5.2.2.3. *Multiple tumours – SDH, paraganglioma only*

Log likelihood = -33.723712 Number of studies = 6

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	.1282767	.2936749			-.4473155	.7038689
E(logitSp)	2.501951	.4793864			1.562371	3.441532
Var(logitSe)	.3996939	.2869792			.0978514	1.632631
Var(logitSp)	1.049481	.8110728			.2307481	4.773212
Corr(logits)	-1	.			.	.
HSROC						
Lambda	2.128763	.3657823			1.411843	2.845683
Theta	-.9010917	.3806397			-1.647132	-.1550515
beta	.4826758	.2846908	1.70	0.090	-.0753079	1.040659
s2alpha	0	.			.	.
s2theta	.6476658	.4465356			.1676822	2.501584
Summary pt.						
Se	.5320253	.0731175			.3899992	.669045
Sp	.9242785	.0335512			.8266933	.9689776
DOR	13.87693	3.701339			8.227274	23.40621
LR+	7.02608	2.322635			3.675603	13.43067
LR-	.5063135	.0637691			.3955602	.6480769
1/LR-	1.975061	.2487547			1.543027	2.52806

Covariance between estimates of E(logitSe) & E(logitSp) -.1224568

5.2.2.4. *Multiple tumours – SDHB, whole population*

Log likelihood = -81.046969 Number of studies = 12

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-1.327268	.2688172			-1.85414	-.8003961
E(logitSp)	1.528742	.2599617			1.019226	2.038257
Var(logitSe)	.4352112	.4252295			.0641241	2.953786
Var(logitSp)	.7279244	.3225713			.3054121	1.734948
Corr(logits)	-.5566494	.3402514			-.9208	.325986
HSROC						
Lambda	-.1651298	.6957612			-1.528797	1.198537
Theta	-1.426838	.2204299			-1.858873	-.9948036
beta	.2571829	.509703	0.50	0.614	-.7418167	1.256183
s2alpha	.4990803	.425059			.0940189	2.649266
s2theta	.4380806	.2820675			.1240194	1.547456
Summary pt.						
Se	.2096116	.0445362			.1353875	.3099408
Sp	.8218221	.0380663			.7348218	.8847557
DOR	1.223204	.3563174			.6911068	2.164973
LR+	1.176418	.2760664			.7426987	1.863419
LR-	.9617512	.0549697			.8598279	1.075756
1/LR-	1.03977	.059429			.9295786	1.163023

Covariance between estimates of E(logitSe) & E(logitSp) -.027494

5.2.2.5. *Multiple tumours – SDHB, paraganglioma only*

Log likelihood = -30.760276 Number of studies = 5

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-1.514345	.4424576			-2.381546	-.6471438
E(logitSp)	.9648051	.4674403			.048639	1.880971
Var(logitSe)	.726704	.7124359			.1063821	4.96417
Var(logitSp)	.9933967	.6624157			.2688595	3.670456
Corr(logits)	-1	.			.	.
HSROC						
Lambda	-.7451684	.52284			-1.769916	.2795793
Theta	-1.264858	.4437113			-2.134517	-.3952001
beta	.1563055	.3659683	0.43	0.669	-.5609792	.8735901
s2alpha	0	.			.	.
s2theta	.8496501	.6408806			.1937266	3.726412
Summary pt.						
Se	.1802958	.0653905			.0845908	.3436335
Sp	.7240828	.0933884			.5121574	.8677226
DOR	.5772155	.1318264			.3689247	.903105
LR+	.6534417	.1153731			.4622925	.9236276
LR-	1.132059	.0799243			.9857649	1.300063
1/LR-	.8833465	.062365			.7691934	1.014441

Covariance between estimates of E(logitSe) & E(logitSp) -.1810551

5.2.2.6. *Multiple tumours – SDHC, whole population*

Log likelihood = -26.87693 Number of studies = 5

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-1.554175	.4188606			-2.375127	-.7332236
E(logitSp)	1.590863	.1602122			1.276853	1.904873
Var(logitSe)	.1329549	.2475649			.0034574	5.112814
Var(logitSp)	.1058239	.0781669			.0248796	.4501159
Corr(logits)	-1	.			.	.
HSROC						
Lambda	.2162954	1.311529			-2.354254	2.786845
Theta	-1.576127	.2596565			-2.085044	-1.067209
beta	-.1141166	.8843498	-0.13	0.897	-1.84741	1.619177
s2alpha	0	.			.	.
s2theta	.1186162	.1312461			.0135616	1.037477
Summary pt.						
Se	.174484	.0603324			.0850891	.3244877
Sp	.8307375	.0225279			.7819136	.8704421
DOR	1.037369	.4024647			.4849482	2.219071
LR+	1.030849	.330159			.5502665	1.931153
LR-	.9937146	.0672687			.8702425	1.134705
1/LR-	1.006325	.0681224			.8812861	1.149105

Covariance between estimates of E(logitSe) & E(logitSp) -.025297

5.2.2.7. *Multiple tumours – SDHD, whole population*

Log likelihood = -79.694549 Number of studies = 13

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	.3344711	.1570335			.0266911	.642251
E(logitSp)	2.183757	.2484802			1.696744	2.670769
Var(logitSe)	.1225786	.0973497			.0258468	.5813306
Var(logitSp)	.6073247	.3465768			.19846	1.858527
Corr(logits)	-.6797166	.3068009			-.9600314	.2813395
HSROC						
Lambda	1.962713	.2446822			1.483145	2.442281
Theta	-.4823455	.2927737			-1.056171	.0914804
beta	.8001554	.446503	1.79	0.073	-.0749745	1.675285
s2alpha	.1747762	.1890859			.0209696	1.456718
s2theta	.2291521	.1290462			.0759928	.6909954
Summary pt.						
Se	.5828469	.0381806			.5066724	.6552621
Sp	.8987813	.0226051			.8451091	.9352796
DOR	12.40659	2.929436			7.810291	19.70777
LR+	5.758294	1.189555			3.841066	8.632488
LR-	.464132	.039387			.3930132	.5481202
1/LR-	2.15456	.1828394			1.824417	2.544444

Covariance between estimates of E(logitSe) & E(logitSp) -.0153248

5.2.2.8. *Multiple tumours – SDHD, paraganglioma only*

Log likelihood = -33.357449 Number of studies = 6

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	.4311712	.2024441			.034388	.8279545
E(logitSp)	2.738556	.6820092			1.401842	4.075269
Var(logitSe)	.1318356	.1225278			.0213269	.8149635
Var(logitSp)	2.036169	1.635			.4220051	9.824493
Corr(logits)	-1	.			.	.
HSROC						
Lambda	2.236183	.2213709			1.802304	2.670062
Theta	-.26333	.4218947			-1.090228	.5635685
beta	1.368635	.3567192	3.84	0.000	.669478	2.067792
s2alpha	0	.			.	.
s2theta	.5181116	.4102676			.1097484	2.445956
Summary pt.						
Se	.6061533	.0483298			.5085962	.6959222
Sp	.9392637	.0389068			.802476	.9832961
DOR	23.80098	12.96949			8.180185	69.25108
LR+	9.98009	5.813554			3.186373	31.2588
LR-	.4193143	.0399401			.347906	.5053792
1/LR-	2.384846	.2271587			1.978712	2.87434

Covariance between estimates of E(logitSe) & E(logitSp) -.1045944

5.2.2.9. *Multiple tumours – VHL, whole population*

Log likelihood = -34.662915 Number of studies = 6

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-.1418482	.2255159			-.5838512	.3001548
E(logitSp)	1.997873	.1925004			1.620579	2.375166
Var(logitSe)	.094891	.155626			.0038125	2.361774
Var(logitSp)	.1564009	.1382109			.0276717	.8839813
Corr(logits)	-.8273253	.4759662			-.9994891	.9443621
HSROC						
Lambda	1.602529	.7756285			.0823247	3.122732
Theta	-.961987	.4009096			-1.747755	-.1762186
beta	.2498469	.8433934	0.30	0.767	-1.403174	1.902868
s2alpha	.0420718	.1247039			.0001262	14.02865
s2theta	.1113058	.1154794			.014568	.8504255
Summary pt.						
Se	.4645973	.0560963			.3580469	.5744804
Sp	.8805735	.0202441			.8348749	.9149139
DOR	6.398249	1.416342			4.146061	9.873851
LR+	3.890237	.6146954			2.854157	5.302421
LR-	.6080159	.0587832			.5030607	.7348682
1/LR-	1.644694	.1590097			1.360788	1.987832

Covariance between estimates of E(logitSe) & E(logitSp) -.0194559

5.2.2.10. Multiple tumours – RET, whole population

Log likelihood = -32.927672 Number of studies = 6

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-.0063688	.3895829			-.7699372	.7571996
E(logitSp)	1.880144	.1650606			1.556631	2.203657
Var(logitSe)	.3699187	.4985979			.0263516	5.192844
Var(logitSp)	.1063427	.1060344			.0150651	.7506578
Corr(logits)	-.7188727	.4447959			-.9911744	.7157121
HSROC						
Lambda	2.563016	.9062205			.7868563	4.339175
Theta	-1.286171	.5200543			-2.305459	-.2668837
beta	-.6233083	.7260109	-0.86	0.391	-2.046264	.799647
s2alpha	.1115167	.1713521			.005488	2.266013
s2theta	.1704593	.1797737			.0215728	1.346897
Summary pt.						
Se	.4984078	.0973947			.3164927	.6807454
Sp	.8676277	.0189572			.8258694	.9005774
DOR	6.512837	2.273627			3.285612	12.90994
LR+	3.765196	.6924685			2.625672	5.399265
LR-	.5781192	.1072397			.4019032	.8315977
1/LR-	1.729747	.320864			1.202505	2.488161

Covariance between estimates of E(logitSe) & E(logitSp) -.0285747

5.2.3. Bilateral tumours

5.2.3.1. Bilateral tumours – all tests, whole population

Log likelihood = -40.047172 Number of studies = 6

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-.525633	.3345653			-1.181369	.1301029
E(logitSp)	2.266077	.7854777			.7265688	3.805585
Var(logitSe)	.4897225	.4758888			.072911	3.289325
Var(logitSp)	3.285739	2.025664			.9814442	11.0002
Corr(logits)	-.3005248	.4485818			-.8555736	.5759605
HSROC						
Lambda	.5620371	.8811155			-1.164918	2.288992
Theta	-1.126985	.4114027			-1.93332	-.3206511
beta	.951754	.5608665	1.70	0.090	-.1475241	2.051032
s2alpha	1.774573	1.373998			.3890756	8.093821
s2theta	.8248599	.6130233			.1922119	3.539812
Summary pt.						
Se	.371536	.07812			.2348062	.5324799
Sp	.9060283	.0668764			.6740519	.9782379
DOR	5.699873	4.416072			1.248483	26.02243
LR+	3.953701	2.731849			1.020605	15.31616
LR-	.6936472	.088852			.539641	.8916047
1/LR-	1.441655	.1846672			1.121573	1.853084

Covariance between estimates of E(logitSe) & E(logitSp) -.0643229

5.2.3.2. Bilateral tumours – SDHB, whole population

Log likelihood = -20.98373 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-5.998768	3.506449			-12.87128	.8737465
E(logitSp)	1.052827	.6434381			-.2082888	2.313942
Var(logitSe)	6.395353	10.7047			.2404933	170.0694
Var(logitSp)	1.58986	1.157152			.3817918	6.620506
Corr(logits)	-1	.			.	.
HSROC						
Lambda	-2.744783	.4693847			-3.66476	-1.824805
Theta	-2.863411	1.112772			-5.044403	-.6824178
beta	-.6959629	.7610497	-0.91	0.360	-2.187593	.7956672
s2alpha	0	.			.	.
s2theta	3.188686	3.323763			.4133826	24.59638
Summary pt.						
Se	.0024757	.0086593			2.57e-06	.7055247
Sp	.7413173	.1233895			.4481152	.9100251
DOR	.0071122	.0236775			.0000104	4.850313
LR+	.0095703	.0321132			.0000133	6.872927
LR-	1.34561	.2200325			.9766343	1.853987
1/LR-	.7431571	.1215201			.539378	1.023925

Covariance between estimates of E(logitSe) & E(logitSp) -.8130299

5.2.3.3. Bilateral tumours – SDHD, whole population

Log likelihood = -28.547137 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-1.584263	.9384629			-3.423617	.2550903
E(logitSp)	1.585198	.8270987			-.0358859	3.206282
Var(logitSe)	2.670214	2.940524			.308444	23.11617
Var(logitSp)	2.519484	2.024651			.5215408	12.17124
Corr(logits)	.1709081	.5560156			-.7397641	.8604725
HSROC						
Lambda	.0469764	1.572736			-3.035529	3.129481
Theta	-1.584904	.5781375			-2.718033	-.4517757
beta	-.0290523	.6797247	-0.04	0.966	-1.361288	1.303184
s2alpha	6.074097	5.256004			1.114101	33.11607
s2theta	1.07523	.9841631			.1788105	6.465618
Summary pt.						
Se	.1701926	.1325364			.0315655	.563429
Sp	.8299394	.1167367			.4910295	.96107
DOR	1.000935	1.339464			.0726636	13.78779
LR+	1.000776	1.111399			.113513	8.823242
LR-	.999841	.2276391			.6399313	1.562171
1/LR-	1.000159	.2277115			.6401349	1.562668

Covariance between estimates of E(logitSe) & E(logitSp) .1130045

5.2.4. Malignant tumours

5.2.4.1. Malignant tumours – all tests, whole population

Log likelihood = -82.33151 Number of studies = 16

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-2.111058	.2881707			-2.675862	-1.546254
E(logitSp)	2.689201	.3362229			2.030216	3.348186
Var(logitSe)	.9316525	.4586574			.3549792	2.445147
Var(logitSp)	1.322289	.6635958			.4944789	3.535942
Corr(logits)	-.9480184	.0662998			-.9959096	-.4842872
HSROC						
Lambda	.1596083	.5095703			-.8391312	1.158348
Theta	-2.383994	.2923251			-2.956941	-1.811047
beta	.17508	.2367289	0.74	0.460	-.2889002	.6390602
s2alpha	.1153905	.1390237			.0108801	1.223789
s2theta	1.081069	.4858826			.4480058	2.608692
Summary pt.						
Se	.1080267	.0277672			.0644128	.175628
Sp	.9363864	.0200278			.8839333	.9660454
DOR	1.782725	.3916659			1.158977	2.742167
LR+	1.69817	.3468878			1.137902	2.534296
LR-	.9525697	.0193053			.9154736	.9911689
1/LR-	1.049792	.0212757			1.00891	1.092331

Covariance between estimates of E(logitSe) & E(logitSp) -.0739099

5.2.4.2. Malignant tumours – SDHB, whole population

Log likelihood = -65.044242 Number of studies = 11

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-1.073924	.433933			-1.924417	-.2234305
E(logitSp)	2.714604	.2560145			2.212825	3.216383
Var(logitSe)	1.696296	1.077424			.4884835	5.890516
Var(logitSp)	.5967017	.3252392			.2050218	1.736659
Corr(logits)	-.9752983	.0501868			-.9995564	-.1730967
HSROC						
Lambda	2.697805	.5504399			1.618963	3.776648
Theta	-2.175963	.3692169			-2.899615	-1.452311
beta	-.5223925	.2650038	-1.97	0.049	-1.04179	-.0029946
s2alpha	.0497034	.1001736			.0009569	2.581787
s2theta	.9936471	.5304688			.3489871	2.829143
Summary pt.						
Se	.2546577	.0823636			.1273699	.4443736
Sp	.9378829	.014915			.9013953	.9614462
DOR	5.158679	1.284837			3.166179	8.405072
LR+	4.099639	.6881646			2.950279	5.696763
LR-	.7947072	.0771725			.6569747	.9613149
1/LR-	1.258325	.1221935			1.040242	1.522129

Covariance between estimates of E(logitSe) & E(logitSp) -.0959044

5.2.4.3. *Malignant tumours – SDHB, paraganglioma only*

Log likelihood = -13.738899 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-2.797419	1.008859			-4.774746	-.8200919
E(logitSp)	3.568571	.2900035			3.000174	4.136967
Var(logitSe)	1.116375	1.723748			.0541383	23.02051
Var(logitSp)	.0543309	.1114658			.0009743	3.029567
Corr(logits)	-1	.			.	.
HSROC						
Lambda	6.283839	4.527483			-2.589865	15.15754
Theta	-4.455833	1.762964			-7.91118	-1.000486
beta	-1.511375	1.121097	-1.35	0.178	-3.708685	.6859357
s2alpha	0	.			.	.
s2theta	.2462795	.3517361			.014988	4.046814
Summary pt.						
Se	.0574638	.0546415			.0083696	.3057441
Sp	.9725771	.0077347			.952582	.9842799
DOR	2.162256	2.099844			.3223107	14.50572
LR+	2.095468	1.918438			.3483301	12.60582
LR-	.969112	.054597			.8678002	1.082252
1/LR-	1.031872	.0581327			.9239996	1.152339

Covariance between estimates of E(logitSe) & E(logitSp) -.0793966

5.2.4.4. *Malignant tumours – SDHD, whole population*

Meta-analysis of diagnostic accuracy

Log likelihood = -56.617307 Number of studies = 10

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-2.880951	.5244063			-3.908769	-1.853134
E(logitSp)	2.443421	.2601587			1.933519	2.953323
Var(logitSe)	1.314569	1.059737			.2707629	6.38231
Var(logitSp)	.4802856	.3035175			.1391813	1.657365
Corr(logits)	.0290245	.5449337			-.7778558	.7997735
HSROC						
Lambda	.9029895	1.320658			-1.685452	3.491431
Theta	-2.691324	.2945433			-3.268618	-2.11403
beta	-.5034418	.5311427	-0.95	0.343	-1.544462	.5375787
s2alpha	1.635299	1.259917			.3612339	7.402971
s2theta	.3857623	.2679878			.0988537	1.505382
Summary pt.						
Se	.0531033	.0263689			.0196705	.1355054
Sp	.920079	.0191304			.8736385	.9504203
DOR	.6456291	.3899054			.1976648	2.108807
LR+	.6644474	.3776606			.2180982	2.024273
LR-	1.029147	.037125			.9588962	1.104545
1/LR-	.9716783	.0350519			.9053503	1.042866

Covariance between estimates of E(logitSe) & E(logitSp) .0110146

5.2.4.5. *Malignant tumours – SDHD, paraganglioma only*

Log likelihood = -13.79403 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-3.175337	.4917239			-4.139098	-2.211576
E(logitSp)	3.326589	.4023431			2.538011	4.115167
Var(logitSe)	.4100765	.4940496			.0386687	4.348811
Var(logitSp)	.0720632	.1872076			.000443	11.72154
Corr(logits)	-1	.			.	.
HSROC						
Lambda	3.082014	4.155946			-5.063491	11.22752
Theta	-3.596907	.8694078			-5.300915	-1.892899
beta	-.8693998	1.291032	-0.67	0.501	-3.399777	1.660977
s2alpha	0	.			.	.
s2theta	.1719053	.2681568			.0080815	3.656679
Summary pt.						
Se	.0401045	.0189295			.0156872	.0987158
Sp	.9653298	.0134657			.9267639	.9839389
DOR	1.16329	.6505685			.3887357	3.481139
LR+	1.156741	.6222747			.4030213	3.320048
LR-	.9943706	.0212588			.9535651	1.036922
1/LR-	1.005661	.0215001			.9643924	1.048696

Covariance between estimates of E(logitSe) & E(logitSp) -.0454566

5.2.4.6. *Malignant tumours – VHL, whole population*

Log likelihood = -34.034581 Number of studies = 7

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-2.698783	.3533539			-3.391343	-2.006222
E(logitSp)	2.026652	.2152872			1.604697	2.448608
Var(logitSe)	.0072847	.0586591			1.02e-09	52067.63
Var(logitSp)	.2564903	.1663356			.0719551	.9142828
Corr(logits)	-1	.			.	.
HSROC						
Lambda	-5.742055	15.22854			-35.58944	24.10533
Theta	-3.703011	5.944165			-15.35336	7.947338
beta	1.780655	4.020501	0.44	0.658	-6.099382	9.660692
s2alpha	0	.			.	.
s2theta	.0432257	.1754019			.0000152	122.9586
Summary pt.						
Se	.0630452	.0208728			.0325671	.1185512
Sp	.8835671	.0221479			.8326739	.9204596
DOR	.5106198	.2028999			.2343496	1.112579
LR+	.5414728	.1987837			.2636856	1.111903
LR-	1.060423	.0339813			.9958691	1.129161
1/LR-	.9430201	.0302191			.8856133	1.004148

Covariance between estimates of E(logitSe) & E(logitSp) -.0066563

5.2.5. Recurrent disease

5.2.5.1. Recurrent disease – all tests, whole population

Log likelihood = -16.236754 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-1.970106	.7481135			-3.436382	-.5038309
E(logitSp)	2.380651	.593786			1.216852	3.54445
Var(logitSe)	1.118443	1.560743			.0725765	17.23582
Var(logitSp)	.6378173	.9158739			.0382308	10.64092
Corr(logits)	.4019584	.754062			-.8708916	.9751967
HSROC						
Lambda	1.027499	2.070589			-3.030782	5.085779
Theta	-2.225775	.4889248			-3.18405	-1.2675
beta	-.2808206	.9996525	-0.28	0.779	-2.240104	1.678462
s2alpha	2.36821	2.718296			.2496825	22.46221
s2theta	.2525553	.4026269			.011101	5.745828
Summary pt.						
Se	.1223775	.0803483			.0311776	.3766408
Sp	.9153399	.0460141			.7715091	.9719264
DOR	1.507638	1.560398			.1982932	11.46269
LR+	1.445515	1.33597			.2362258	8.845408
LR-	.9587942	.1074353			.7697436	1.194276
1/LR-	1.042977	.1168682			.8373274	1.299134

Covariance between estimates of E(logitSe) & E(logitSp) .0794796

5.2.5.2. Recurrent disease – SDHD, whole population

Log likelihood = -16.236754 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-1.970106	.7481135			-3.436382	-.5038309
E(logitSp)	2.380651	.593786			1.216852	3.54445
Var(logitSe)	1.118443	1.560743			.0725765	17.23582
Var(logitSp)	.6378173	.9158739			.0382308	10.64092
Corr(logits)	.4019584	.754062			-.8708916	.9751967
HSROC						
Lambda	1.027499	2.070589			-3.030782	5.085779
Theta	-2.225775	.4889248			-3.18405	-1.2675
beta	-.2808206	.9996525	-0.28	0.779	-2.240104	1.678462
s2alpha	2.36821	2.718296			.2496825	22.46221
s2theta	.2525553	.4026269			.011101	5.745828
Summary pt.						
Se	.1223775	.0803483			.0311776	.3766408
Sp	.9153399	.0460141			.7715091	.9719264
DOR	1.507638	1.560398			.1982932	11.46269
LR+	1.445515	1.33597			.2362258	8.845408
LR-	.9587942	.1074353			.7697436	1.194276
1/LR-	1.042977	.1168682			.8373274	1.299134

Covariance between estimates of E(logitSe) & E(logitSp) .0794796

5.2.6. Extra-adrenal disease

5.2.6.1. Extra-adrenal disease – all tests, whole population

Log likelihood = -55.165165 Number of studies = 9

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-1.06394	.292771			-1.63776	-.4901189
E(logitSp)	2.044334	.2710176			1.51315	2.575519
Var(logitSe)	.5511328	.3345043			.1677368	1.810857
Var(logitSp)	.4474647	.3325132			.1042862	1.919954
Corr(logits)	-.9050183	.1187177			-.9924115	-.2101517
HSROC						
Lambda	1.143723	.4821378			.1987501	2.088695
Theta	-1.581794	.271979			-2.114863	-1.048725
beta	-.1041891	.3682974	-0.28	0.777	-.8260386	.6176605
s2alpha	.094336	.1032251			.0110476	.805538
s2theta	.4730169	.2849556			.1452428	1.54049
Summary pt.						
Se	.2565573	.0558419			.1627701	.3798656
Sp	.8853739	.0275048			.8195275	.9292693
DOR	2.665509	.6460536			1.657562	4.286377
LR+	2.23821	.4411799			1.520961	3.293697
LR-	.8396935	.0507568			.745879	.9453077
1/LR-	1.190911	.0719867			1.057857	1.3407

Covariance between estimates of E(logitSe) & E(logitSp) -.0502098

5.2.6.2. *Extra-adrenal disease – SDHB, whole population*

Log likelihood = -54.203492 Number of studies = 8

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	.2277651	.3443578			-.4471637	.9026939
E(logitSp)	1.776507	.1997538			1.384997	2.168017
Var(logitSe)	.654018	.5952061			.1098833	3.892672
Var(logitSp)	.2557732	.161427			.0742392	.8812043
Corr(logits)	-.3070027	.4173486			-.8397543	.5269214
HSROC						
Lambda	2.426586	.6080408			1.234848	3.618324
Theta	-1.033177	.3972401			-1.811753	-.2546004
beta	-.4694219	.5335662	-0.88	0.379	-1.515193	.5763487
s2alpha	.5668705	.3550003			.1661202	1.934396
s2theta	.2672815	.2051533			.0593779	1.203131
Summary pt.						
Se	.5566964	.0849825			.3900353	.7115028
Sp	.855265	.0247269			.7997923	.8973405
DOR	7.42069	2.637642			3.697342	14.89358
LR+	3.846315	.7721793			2.59513	5.700731
LR-	.5183231	.0969637			.3592234	.7478879
1/LR-	1.929299	.3609176			1.337099	2.783783

Covariance between estimates of E(logitSe) & E(logitSp) -.0160716

5.2.6.3. *Extra-adrenal disease – SDHD, whole population*

Log likelihood = -43.814978 Number of studies = 6

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-.8053447	.5604994			-1.903903	.293214
E(logitSp)	1.710088	.3246099			1.073864	2.346311
Var(logitSe)	1.465632	1.14086			.3187445	6.739184
Var(logitSp)	.4844111	.4597531			.0753948	3.112338
Corr(logits)	-.3869501	.479809			-.9076851	.6029719
HSROC						
Lambda	1.644756	.8694057			-.059248	3.34876
Theta	-1.433009	.4006409			-2.218251	-.6477675
beta	-.553554	.6228258	-0.89	0.374	-1.77427	.6671621
s2alpha	1.033107	.9054006			.1854233	5.756075
s2theta	.5843195	.4442042			.1316923	2.592629
Summary pt.						
Se	.3088834	.1196523			.1296673	.5727828
Sp	.8468477	.0421008			.745331	.9126406
DOR	2.471297	1.406045			.810277	7.537307
LR+	2.016837	.8304342			.8998872	4.520159
LR-	.816105	.1363457			.5882159	1.132284
1/LR-	1.225333	.2047149			.8831708	1.700056

Covariance between estimates of E(logitSe) & E(logitSp) -.0479134

5.2.6.4. *Extra-adrenal disease – VHL, whole population*

Log likelihood = -34.128512 Number of studies = 6

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-1.28479	.4365105			-2.140335	-.4292453
E(logitSp)	1.462745	.169265			1.130992	1.794498
Var(logitSe)	.7082061	.5915957			.137757	3.640874
Var(logitSp)	.1262754	.0908992			.0308022	.5176728
Corr(logits)	-1	.			.	.
HSROC						
Lambda	1.416141	.5181549			.4005763	2.431706
Theta	-1.542947	.2898957			-2.111132	-.9747615
beta	-.862135	.3397999	-2.54	0.011	-1.528131	-.1961393
s2alpha	0	.			.	.
s2theta	.2990468	.2098719			.0755725	1.183354
Summary pt.						
Se	.2167359	.0741027			.1052378	.3943066
Sp	.8119521	.0258444			.7560218	.8574779
DOR	1.194771	.3787323			.6418908	2.223865
LR+	1.152557	.2830008			.7122904	1.864953
LR-	.9646678	.0690634			.8383738	1.109987
1/LR-	1.036626	.0742152			.9009116	1.192785

Covariance between estimates of E(logitSe) & E(logitSp) -.0593543

5.2.7. Secretory tumours

5.2.7.1. Secretory tumours – all tests, whole population

Log likelihood = -20.332456 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-1.130545	.8179838			-2.733764	.472674
E(logitSp)	1.289264	.9593208			-.5909707	3.169498
Var(logitSe)	2.095112	1.677901			.436024	10.0671
Var(logitSp)	2.728831	2.228018			.5507987	13.51949
Corr(logits)	-1	.			.	.
HSROC						
Lambda	-.0009193	.3372789			-.6619738	.6601353
Theta	-1.207299	.8335292			-2.840986	.4263883
beta	.132133	.2533218	0.52	0.602	-.3643686	.6286346
s2alpha	0	.			.	.
s2theta	2.391068	1.836357			.5307174	10.7726
Summary pt.						
Se	.2440606	.1509139			.0610102	.6160165
Sp	.7840225	.162443			.3564122	.9596702
DOR	1.172008	.7227784			.3499404	3.92525
LR+	1.130028	.5436644			.440119	2.901404
LR-	.9641807	.1330826			.7356479	1.263709
1/LR-	1.03715	.1431543			.7913217	1.359346

Covariance between estimates of E(logitSe) & E(logitSp) -.6045371

5.2.8. Head-and-neck location

5.2.8.1. Head-and-neck location – all tests, whole population

Log likelihood = -54.263547 Number of studies = 7

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-.1879857	.5166015			-1.200506	.8245346
E(logitSp)	.8307574	.8062279			-.7494202	2.410935
Var(logitSe)	1.77186	1.080543			.5362122	5.854938
Var(logitSp)	4.387888	2.636318			1.351572	14.24531
Corr(logits)	-.9928465	.0162063			-.9999167	-.5275353
HSROC						
Lambda	.4264231	.1801369			.0733612	.7794851
Theta	-.4490319	.6410413			-1.70545	.8073859
beta	.453409	.1413999	3.21	0.001	.1762703	.7305478
s2alpha	.0398924	.0873448			.000546	2.914773
s2theta	2.778346	1.641275			.8728693	8.843487
Summary pt.						
Se	.4531415	.1280161			.2313852	.6951981
Sp	.6965151	.1704219			.3209476	.9176574
DOR	1.901745	.6264378			.9971605	3.626932
LR+	1.493127	.4410233			.8369089	2.663883
LR-	.7851352	.0464365			.6991985	.8816342
1/LR-	1.273666	.0753304			1.134257	1.430209

Covariance between estimates of E(logitSe) & E(logitSp) -.4041875

5.2.8.2. *Head-and-neck location – SDHC, whole population*

Log likelihood = -25.21826 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	1.108007	.6241936			-.1153902	2.331404
E(logitSp)	1.124445	.6886787			-.2253406	2.47423
Var(logitSe)	.4152784	.6130543			.0230014	7.497645
Var(logitSp)	1.865209	1.341			.4557769	7.633127
Corr(logits)	-1	.			.	.
HSROC						
Lambda	2.385417	.8620856			.6957602	4.075074
Theta	.4203105	.7491891			-1.048073	1.888694
beta	.7510896	.6502698	1.16	0.248	-.5234159	2.025595
s2alpha	0	.			.	.
s2theta	.8801027	.8465713			.1335864	5.798352
Summary pt.						
Se	.7517573	.1164859			.4711844	.9114447
Sp	.7548122	.1274543			.443902	.9223154
DOR	9.322694	6.079112			2.597124	33.46495
LR+	3.066048	1.411799			1.243463	7.560056
LR-	.32888	.1347365			.147338	.7341082
1/LR-	3.040623	1.245691			1.362197	6.787114

Covariance between estimates of E(logitSe) & E(logitSp) -.2193459

5.2.8.3. Head-and-neck location – SDHD, whole population

Log likelihood = -42.927254 Number of studies = 6

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	1.312449	.6269195			.0837091	2.541188
E(logitSp)	1.54141	.4319372			.6948289	2.387992
Var(logitSe)	2.07594	1.448899			.528591	8.152854
Var(logitSp)	1.080948	.6400749			.3386667	3.450143
Corr(logits)	-1	.			.	.
HSROC						
Lambda	2.929442	.2195026			2.499225	3.359659
Theta	-.3498365	.5260523			-1.38088	.681207
beta	-.3262877	.2024258	-1.61	0.107	-.7230351	.0704596
s2alpha	0	.			.	.
s2theta	1.497993	.9208772			.4489951	4.99779
Summary pt.						
Se	.7879226	.1047586			.5209151	.9269793
Sp	.8236696	.0627337			.6670403	.915907
DOR	17.35463	4.80312			10.08867	29.85358
LR+	4.468446	1.061076			2.80563	7.116764
LR-	.2574787	.1092138			.1121218	.591279
1/LR-	3.883817	1.647385			1.691249	8.918873

Covariance between estimates of E(logitSe) & E(logitSp) -.2515

5.2.8.4. Head-and-neck location – VHL, whole population

Log likelihood = -18.462225 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	-3.53003	.8545886			-5.204993	-1.855067
E(logitSp)	1.477631	.1613217			1.161446	1.793815
Var(logitSe)	.1810693	.6960499			.0000968	338.8097
Var(logitSp)	.0747408	.0662186			.0131648	.424328
Corr(logits)	-1	.			.	.
HSROC						
Lambda	-.986004	4.17063			-9.160289	7.188281
Theta	-2.336478	.4652561			-3.248363	-1.424593
beta	-.4424266	1.90687	-0.23	0.817	-4.179823	3.29497
s2alpha	0	.			.	.
s2theta	.1163326	.236842			.0021515	6.290231
Summary pt.						
Se	.0284698	.0236373			.0054591	.1352791
Sp	.8142144	.024403			.7615953	.8573944
DOR	.1284264	.1072412			.0249958	.6598446
LR+	.1532399	.1244803			.0311833	.7530473
LR-	1.193212	.0409511			1.115589	1.276236
1/LR-	.8380742	.0287628			.7835544	.8963874

Covariance between estimates of E(logitSe) & E(logitSp) -.0295272

5.2.9. IHC SDHB testing

5.2.9.1. SDHB – whole population

Log likelihood = -11.736315 Number of studies = 4

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	23.04746	28577.08			-55987.01	56033.1
E(logitSp)	1.381943	.2630957			.8662846	1.897601
Var(logitSe)	4.322923	47440.14			0	.
Var(logitSp)	.1475865	.1583252			.0180264	1.208324
Corr(logits)	-.0193875	43.27938			-1	1
HSROC						
Lambda	13.1219	6526.32			-12778.23	12804.47
Theta	3.34601	11974.94			-23467.11	23473.8
beta	-1.688636	5487.045	-0.00	1.000	-10756.1	10752.72
s2alpha	1.566533	8553.584			0	.
s2theta	.407119	2244.479			0	.
Summary pt.						
Se	1	2.80e-06			.	1
Sp	.7993028	.0422052			.703972	.8696197
DOR	4.07e+10	1.16e+15			0	.
LR+	4.982631	1.047813			3.299567	7.524204
LR-	1.22e-10	3.50e-06			0	.
1/LR-	8.17e+09	2.33e+14			0	.

Covariance between estimates of E(logitSe) & E(logitSp) .1575838

5.2.9.2. SDHD – whole population

Log likelihood = -11.012515 Number of studies = 4

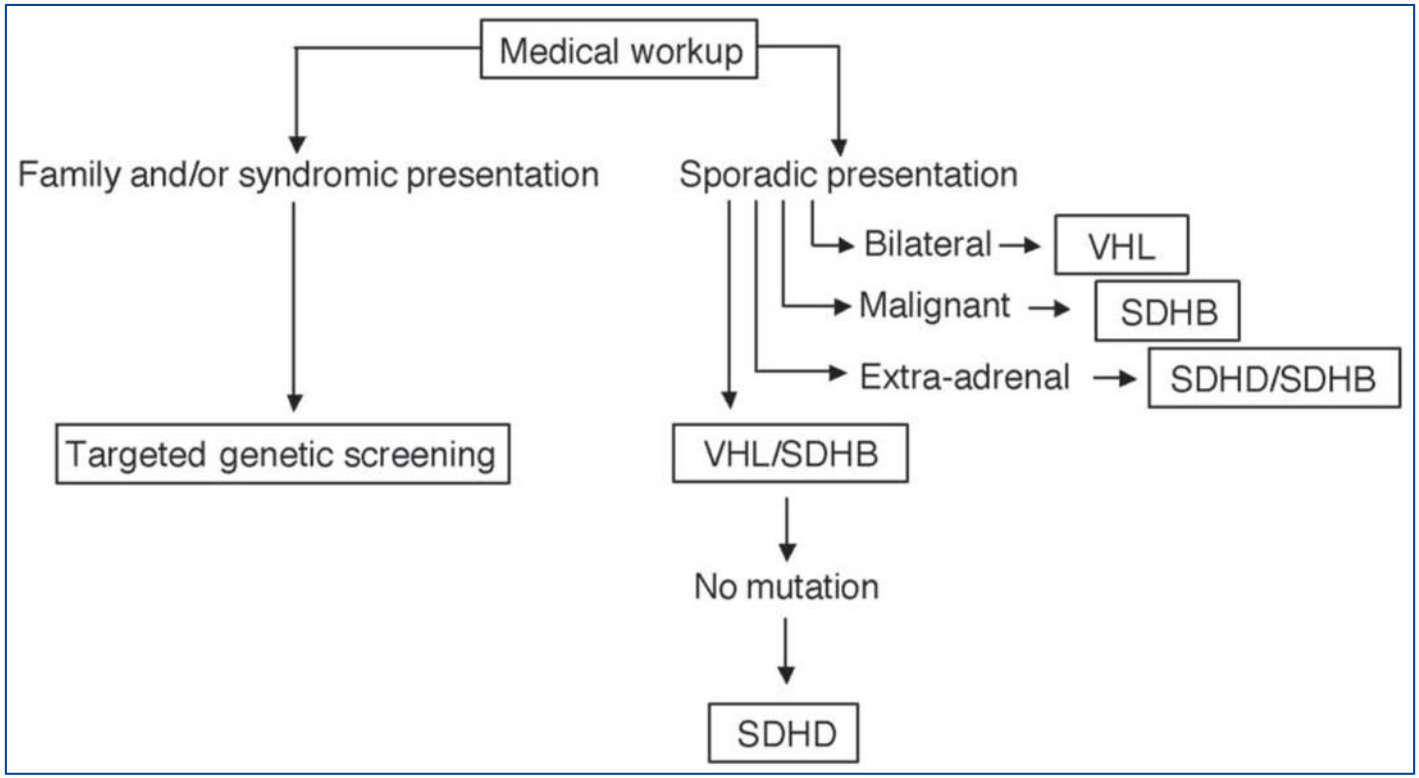
	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	19.2136	2514.611			-4909.334	4947.761
E(logitSp)	1.246534	.2045161			.84569	1.647379
Var(logitSe)	.1285633	1481.194			0	.
Var(logitSp)	.0490476	.0865769			.0015421	1.560005
Corr(logits)	-.1412143	1281.641			-1	1
HSROC						
Lambda	16.68633	37730.81			-73934.34	73967.71
Theta	6.75707	23430.7			-45916.56	45930.08
beta	-.4818156	5760.562	-0.00	1.000	-11290.98	11290.01
s2alpha	.1363898	582.1915			0	.
s2theta	.0453111	311.8953			0	.
Summary pt.						
Se	1	.0000114			.	1
Sp	.7766993	.0354708			.6996622	.8385364
DOR	7.69e+08	1.93e+12			0	.
LR+	4.478267	.7113618			3.280188	6.113942
LR-	5.83e-09	.0000147			0	.
1/LR-	1.72e+08	4.32e+11			0	.

Covariance between estimates of E(logitSe) & E(logitSp) .0510278

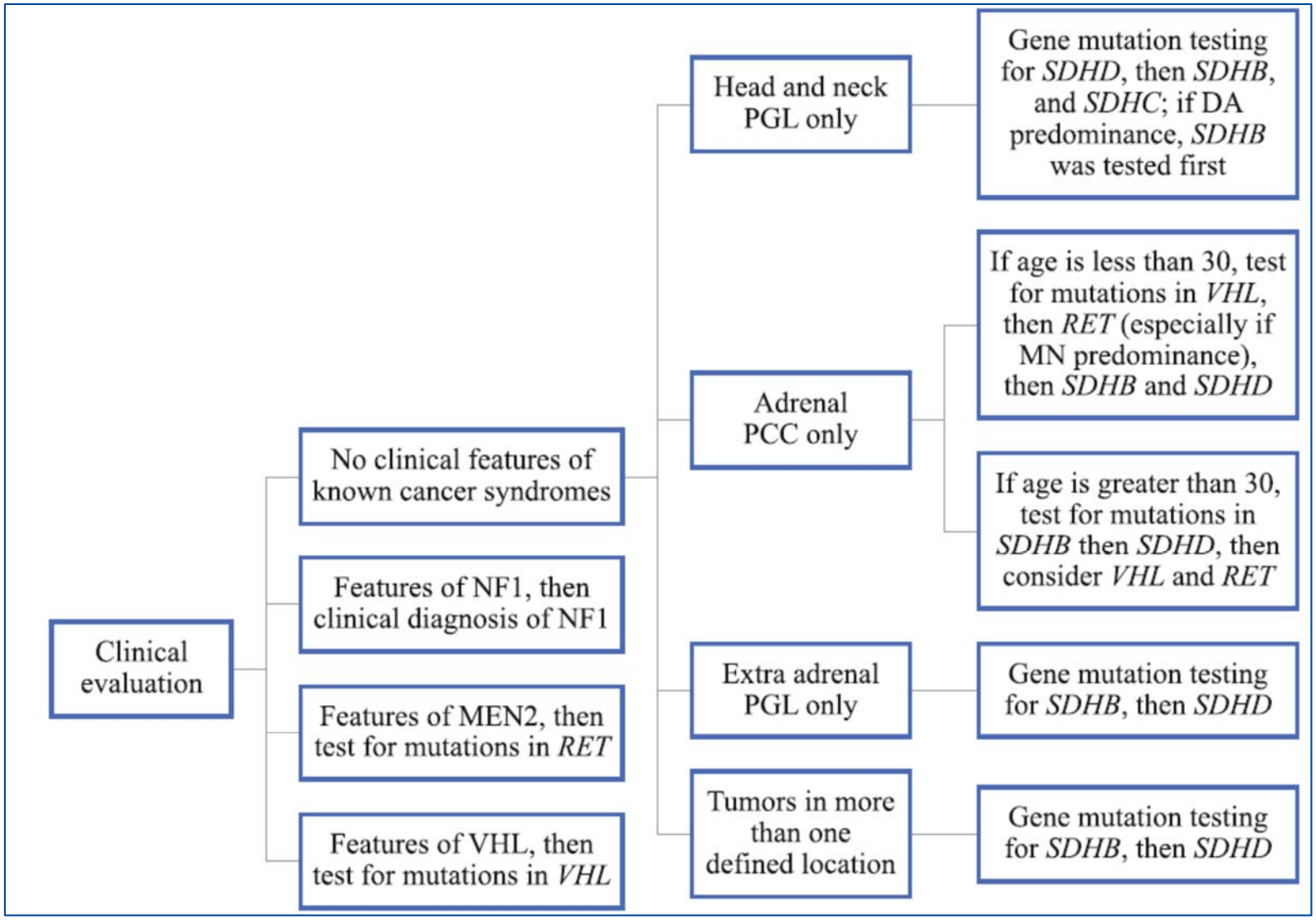
6. GENETIC TESTING ALGORITHMS FOR PHAEOCHROMOCYTOMA AND/OR PARAGANGLIOMA IDENTIFIED IN THE LITERATURE

6.1. Algorithms

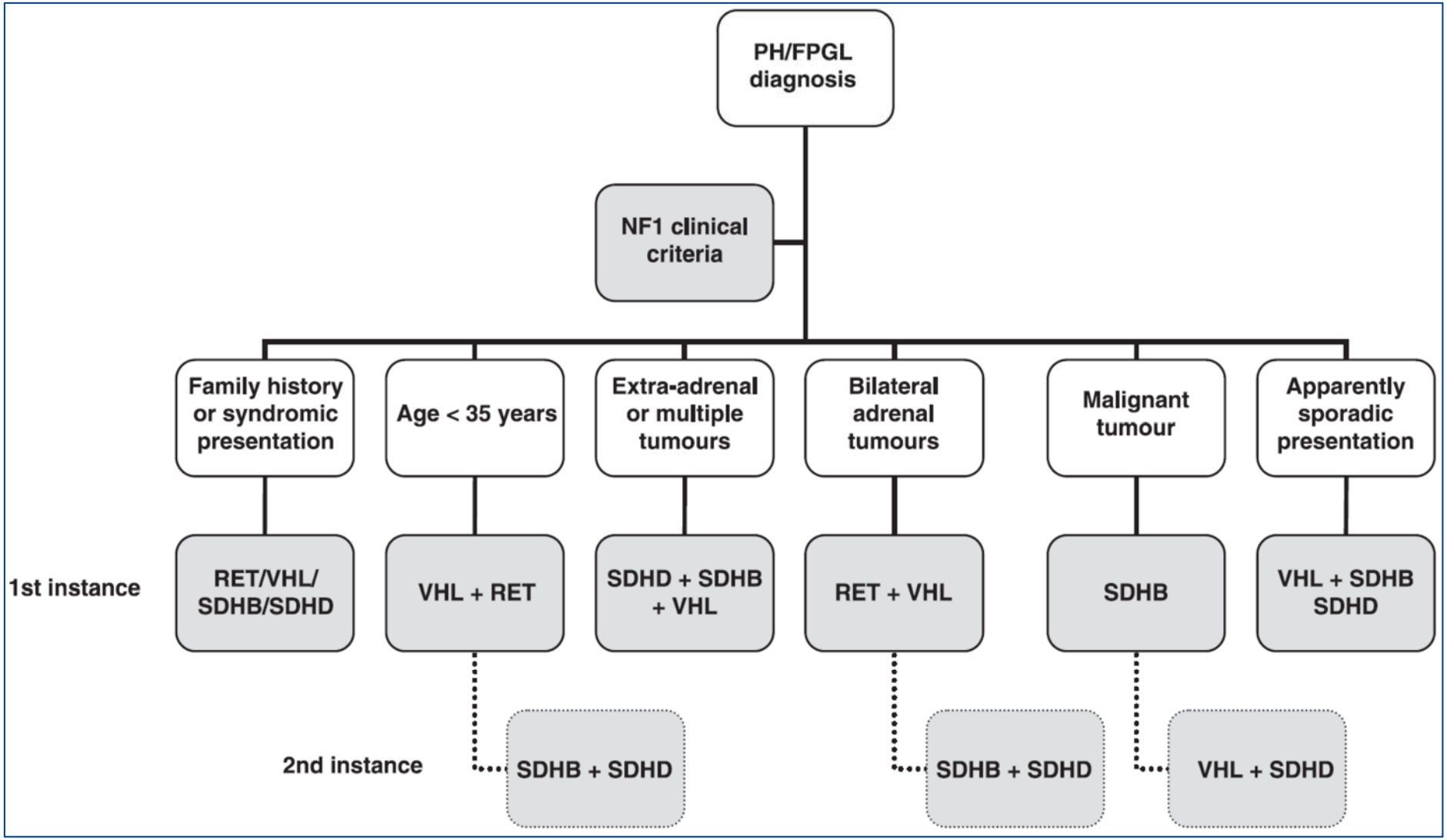
Amar 2005



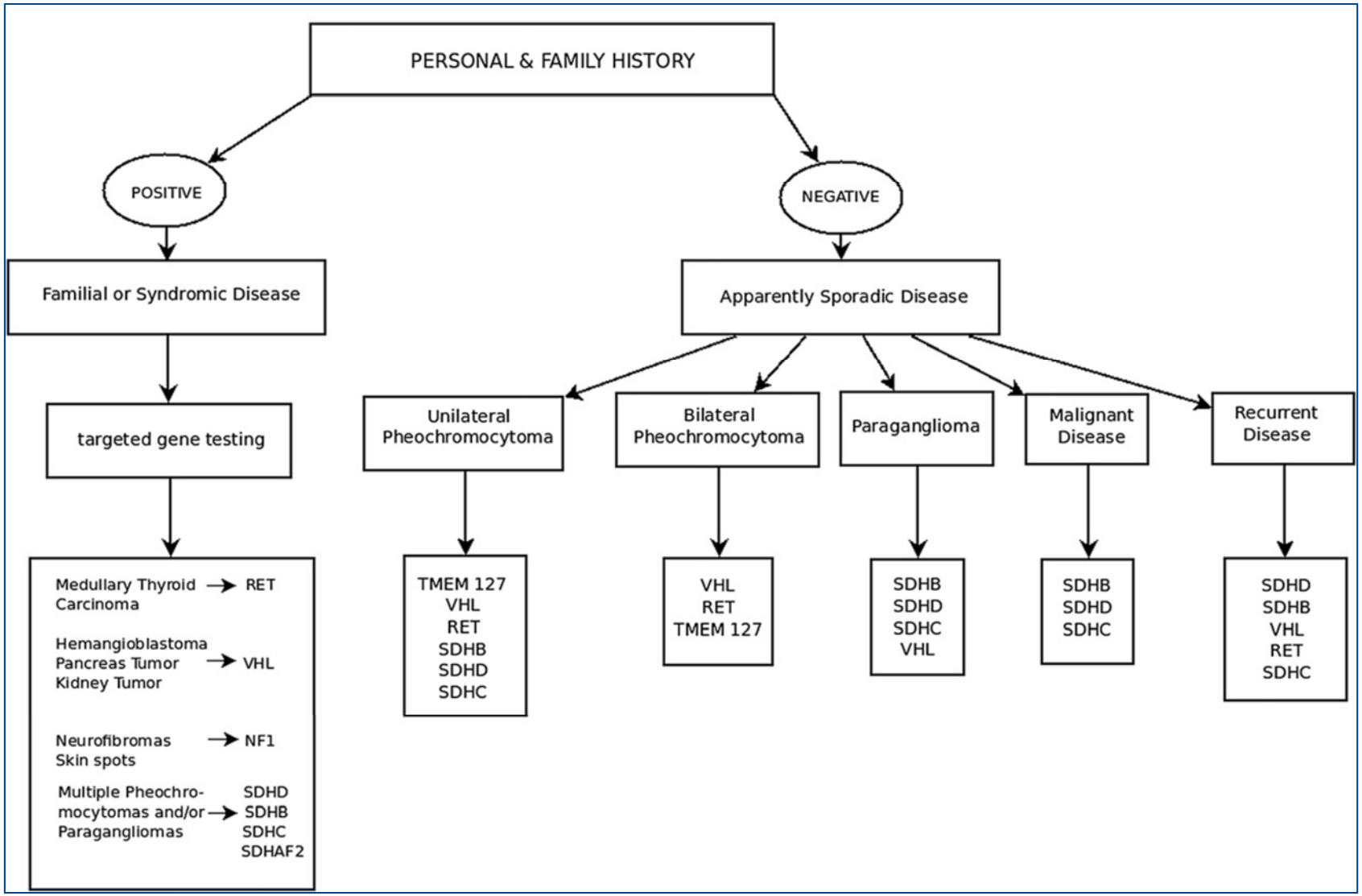
Fishbein 2013



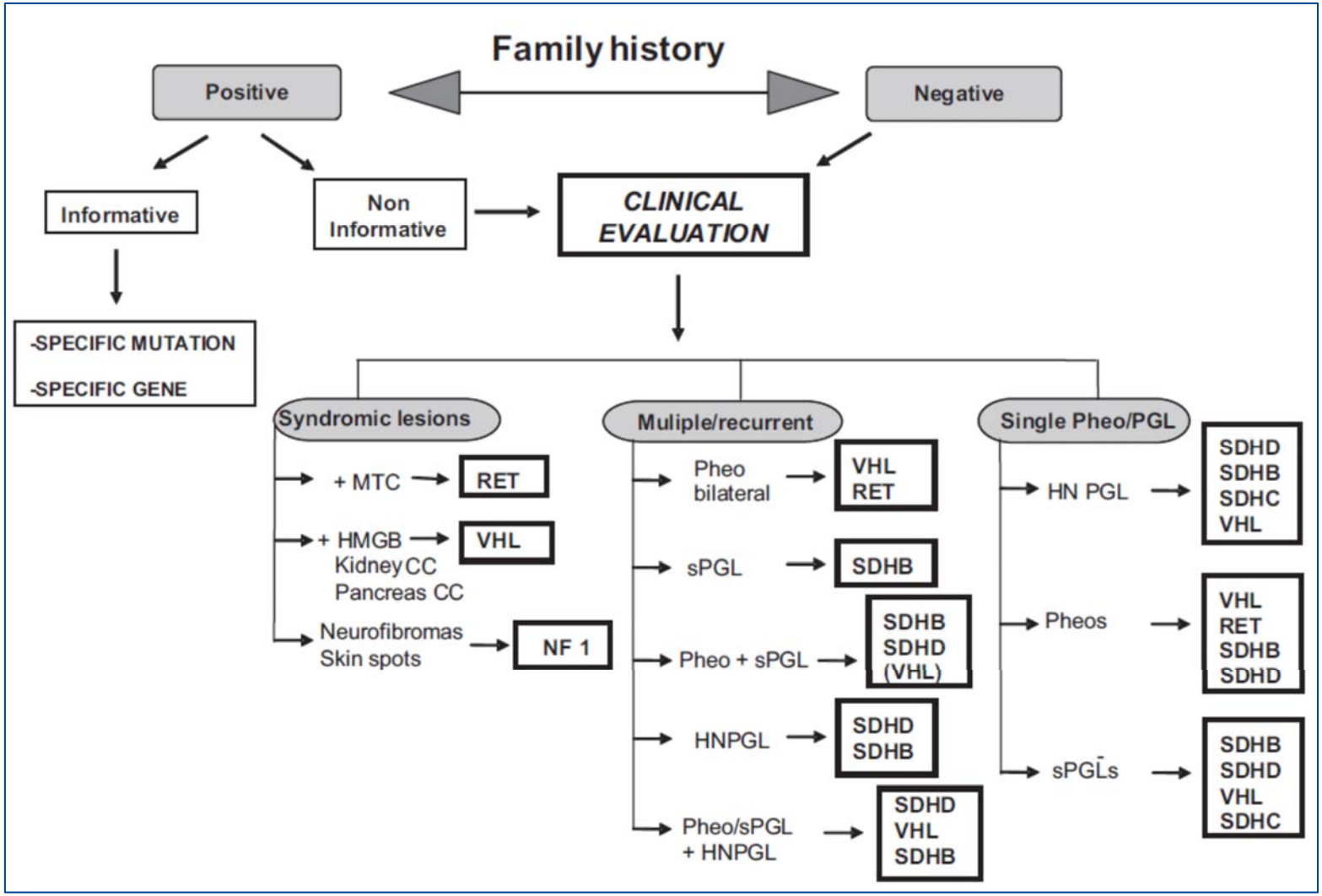
Gimenez-Roqueplo 2006



Iacobone 2011



Mannelli 2009



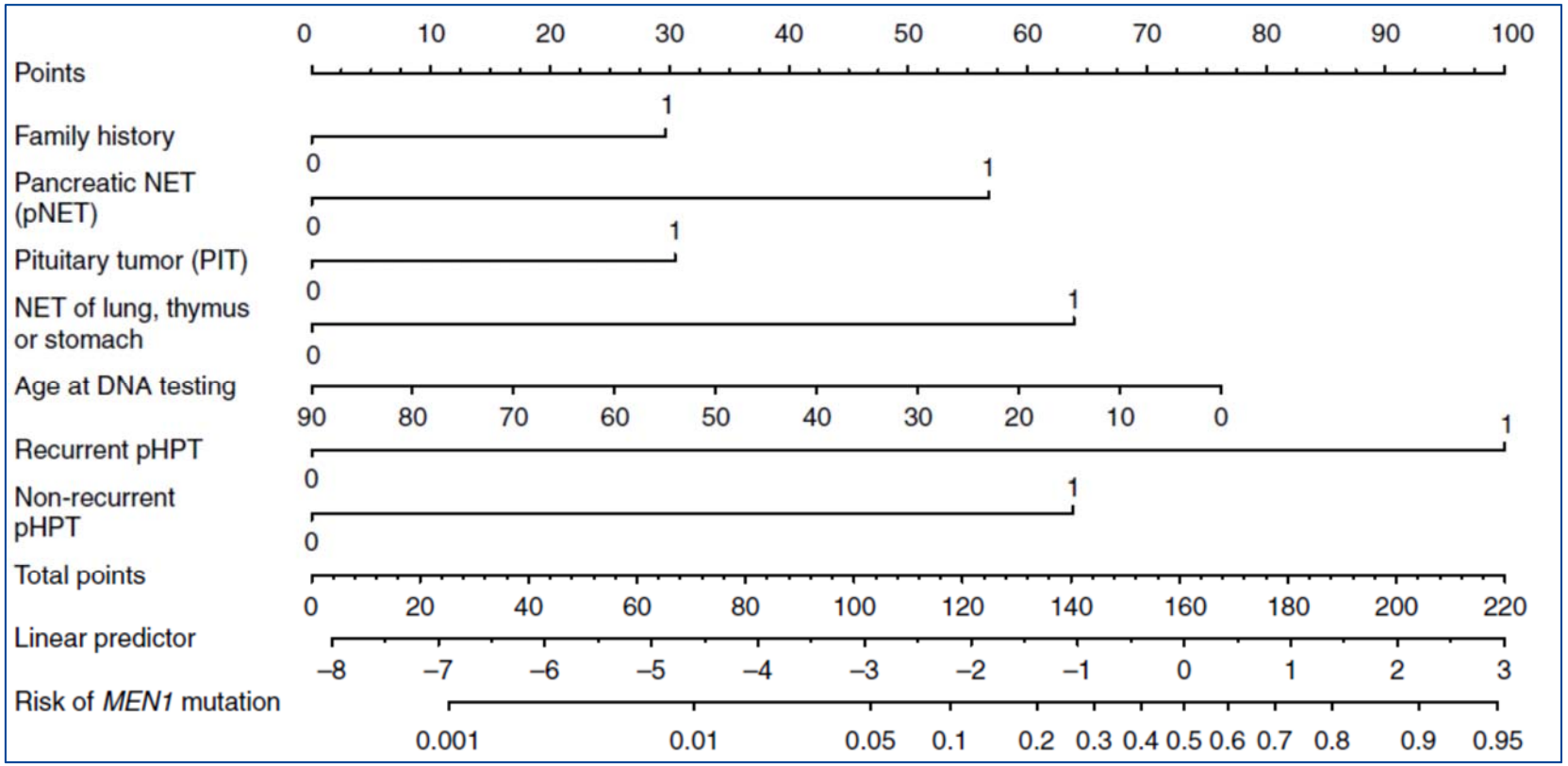
6.2. Nomogram of de Laat et al.

De Laat et al. proposed a momogram to predict MEN1 mutation in patients with sporadically occurring endocrine tumours (see figure below).[4] In the article they discuss three examples to explain the use of the nomogram:

- Example 1: A 54-year-old patient (score = 30 points) with the combination of a negative family history (score = 0 points), a non-recurrent and non-multiglandular primary hyperparathyroidism (score = 63 points), and a pancreatic neuro-endocrine tumour (score = 57 points) has a sum score of 150 points, corresponding with a linear predictor of -0.50 and a risk of 38% of having a MEN1 mutation.

- Example 2: A 41-year-old patient (score = 42 points) with a positive family history (score = 29 points) and recurrent primary hyperparathyroidism (score = 100 points) has a sum score of 171 points, corresponding with a linear predictor of 0.50 and a risk of 63% of having a MEN1 mutation.

- Example 3: A 51-year-old patient (score = 33 points) with a negative family history (score = 0 points) of pituitary tumor (score = 31 points) and a pancreatic neuro-endocrine tumour (score = 57 points) has a sum score of 121 points, corresponding with a linear predictor of -2.0 and a risk of 11% of having a MEN1 mutation.



NET: neuro-endocrine tumours; pHPT: primary hyperparathyroidism; PIT: pituitary tumour.

7. NOMENCLATURE CODES

AMB	HOS	Description NL	Description FR	Cost (01-01-2015)
565331	565342	Enkelvoudig moleculair onderzoek voor het opsporen van constitutionele aandoeningen, inclusief DNA isolatie, drie of minder mutaties per onderzocht gen (Diagnoseregel 10, 11, 18)	Analyse moléculaire simple pour la recherche d'affections constitutionnelles, incluant l'extraction de l'ADN, maximum trois mutations par gène analysé (Règle diagnostique 10, 11, 18)	€78.61
565390	565401	Moleculair onderzoek voor het opsporen van constitutionele aandoeningen of voor het bepalen van een individueel genetisch profiel met het oog op genetisch advies en/of voor diagnostische doeleinden, inclusief DNA isolatie (Diagnoseregel 10, 11, 18)	Analyse moléculaire pour la recherche d'affections constitutionnelles ou établissement d'un profil génétique individuel à des fins de conseil génétique et/ou à des fins diagnostiques, incluant l'extraction de l'ADN (Règle diagnostique 10, 11, 18)	€157.21
565434	565445	Predictief genetisch onderzoek naar een familiale mutatie in het kader van kanker of familiaal kankersyndroom, inclusief DNA isolatie (Diagnoseregel 12)	Examen génétique prédictif d'une mutation familiale dans le cadre de cancer ou d'un syndrome cancéreux familial, incluant l'extraction de l'ADN (Règle diagnostique 12)	€157.21
565456	565460	Complex moleculair genetisch onderzoek voor het opsporen van een constitutionele aandoening (niveau 1) (Diagnoseregel 6, 10, 18)	Analyse moléculaire complexe pour la recherche d'une affection constitutionnelle (niveau 1) (Règle diagnostique 6, 10, 18)	€362.00
565471	565482	Complex moleculair genetisch onderzoek voor het opsporen van een constitutionele aandoening (niveau 2) (Diagnoseregel 6, 10, 18)	Analyse moléculaire complexe pour la recherche d'une affection constitutionnelle (niveau 2) (Règle diagnostique 6, 10, 18)	€565.75
565493	565504	Complex moleculair genetisch onderzoek voor het opsporen van een constitutionele aandoening (niveau 3) (Diagnoseregel 6, 10, 18)	Analyse moléculaire complexe pour la recherche d'une affection constitutionnelle (niveau 3) (Règle diagnostique 6, 10, 18)	€1 396.28
565515	565526	Complex moleculair genetisch onderzoek voor het opsporen van mutaties in het kader van kanker of familiaal kankersyndroom (niveau 1) (Diagnoseregel 10, 18)	Analyse moléculaire complexe pour la recherche de mutations dans le cadre de cancer ou de syndrome cancéreux familial (niveau 1) (Règle diagnostique 10, 18)	€362.00

AMB	HOS	Description NL	Description FR	Cost (01-01-2015)
565530	565541	Complex moleculair genetisch onderzoek voor het opsporen van mutaties in het kader van kanker of familiaal kankersyndroom (niveau 2) (Diagnoseregel 10, 18)	Analyse moléculaire complexe pour la recherche de mutations dans le cadre de cancer ou de syndrome cancéreux familial (niveau 2) (Règle diagnostique 10, 18)	€565.75
565552	565563	Complex moleculair genetisch onderzoek voor het opsporen van mutaties in het kader van kanker of familiaal kankersyndroom (niveau 3) (Diagnoseregel 10, 18)	Analyse moléculaire complexe pour la recherche de mutations dans le cadre de cancer ou de syndrome cancéreux familial (niveau 3) (Règle diagnostique 10, 18)	€1 396.28

8. EXTERNAL REVIEW

Item	Recommendation(s)	SH1	SH2	SH3	SH4	SH5	SH6	Comments	GDG1	GDG2	GDG3	GDG4	GDG5	Comments	Action
MEN2	All patients with a clinical diagnosis of MEN2 (*see box in text*) or a sporadic MTC, and selected patients with a phaeochromocytoma (*see below*) should be offered germline RET testing.		5	5	4	NA	5		5	5	5	5	5	GDG5: For this recommendation (and the recommendations below) I would suggest to also add genetic counseling in addition to testing	Genetic counselling added as recommended for all 4 syndromes
	Once a germline RET mutation has been identified in a proband, RET mutation analysis should be offered to all first-degree relatives, preferentially before the age of 5 years if not yet reached.		5	5	5	NA	5	SH3: ideal situation ...but ethical problem: the child is not able to decide for disclosing or not disclosing genetic information	5	5	5	5	5	GDG4: Regarding the age criterion: possible exception for the unique 'Flemish' mutation (founder effect) in codon 666 (c.1998delGinsTTCT) with low clinical penetrance (well known by E. Legius) (no prophylactic thyroidectomy)	Was already added as comment
MEN1	All patients with a clinical diagnosis of MEN1(*see box in text*) should be offered MEN1genetic testing.		5	5	4	5	5	SH4: regarding the box, in men 1, HPT is due to parathyroid hyperlasia. You can exclude all HPT due to adenoma. Pancreatic tumors are also multiple and not isolated. You can reduce the field of screening	5	5	5	5	5		Was already done with in box
	In patients with a clinical suspicion of MEN1(*see box in text*) MEN1genetic testing may be considered.		3	4	4	4	5	SH4: same remark	5	5	5	5	5		
	MEN1mutation analysis should be offered to all first-degree relatives of MEN1mutation carriers (*or first-degree relatives of patients with clinical MEN1who died before genetic testing was carried out*).	5	5	5	5	5	5		5	5	5	5	5	GDG3: Comment on the second part of this recommendation: "or first-degree relatives of patients with clinical MEN1who died before genetic testing was carried out": This is correct, but the same is also true for families with MEN2 and for families with VHL disease. If you explicitly recommend this here, then it seems logical to recommend this for MEN2 and VHL disease as well (offer testing of MEN2/VHL in first-degree relatives of patients with clinical MEN2/clinical VHL disease who died before genetic testing was carried out). Alternatively, you can omit this second part of the recommendation (because this is a general principle in medical genetics: if there is a clinical diagnosis of a hereditary condition with incomplete penetrance in a family and all clinically affected relatives have died, presymptomatic genetic testing should be offered to the first-degree relatives of the affected patients)	Ok, added for all 4 syndromes
VHL	All patients with a clinical diagnosis of VHL (*see box in text*) should be offered VHL genetic testing.	5	5		5	5	5		5	5	5	5	5		
	In patients with a suspected phenotype of VHL (*see box in text*), VHL genetic testing may be considered.	5	4		5	3	5		5	5	5	5	5		
	Once a germline VHL mutation has been identified in a proband, VHL mutation analysis should be offered to all first-degree relatives as soon as possible.	5	5		5	4	5		5	5	5	5	5		
PHEO/PGL	In patients with phaeochromocytoma / paraganglioma and syndromic features, targeted genetic testing should be offered.	5	4	4	5	NA	5		5	5	5	5	5		
	All patients with phaeochromocytoma / paraganglioma that lack syndromic features should be offered genetic testing for SDHx genes (SDHD + SDHB + SDHC), VHL and RET (in this order).	5	3	4	5	NA	5		5	5	5	5	5		
	If tumour tissue is available, SDHB immunohistochemistry testing could be considered as a triage test before proceeding with genetic testing for SDHx genes.	4	4	5	5	NA	NA		4	5	5	5	5	GDG1: I would like to see more evidence in the literature	Is shown in fact that it is a weak recommendation
	In patients with phaeochromocytoma / paraganglioma and clinical features (i.e. age < 35 years, metastatic disease, recurrent disease, bilateral tumours and/or familial disease) suggestive of a mutation who test negative for SDHx, VHL and RET, further genetic testing may be considered.	5	3	4	3	NA	4	SH6: if possible	5	5	5	5	5		
	Genetic counselling should be offered to all patients with phaeochromocytoma / paraganglioma.	5	3	3	5	NA	5		5	5	5	4	5	GDG3: This is correct, but the same is true for patients with MEN2 / MEN1 / VHL disease: all these patients should be offered genetic counseling GDG4: Irrespective of age?? Is this sentence complete? Genetic counseling offered to pts with PheoPGL **who have a mutation**	See comment above
	Once a germline mutation has been identified in a proband, mutation analysis should be offered to all first-degree relatives irrespective of age.	5	5	5	5	NA	5		5	5	5	5	5		

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3. Morona JK, Newton S, Wang S, Tamblyn D, Ellery B, Merlin T. Genetic testing for hereditary mutations in the VHL gene that cause von Hippel-Lindau syndrome. Canberra, ACT: 2011 September 2011. MSAC application no 1153, Assessment report Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32011000604/frame.html
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