Original Article

Diagnostic reliability of mandibular second molar maturation in the identification of the mandibular growth peak: A longitudinal study

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ABSTRACT

Objective: To investigate the diagnostic reliability of mandibular second molar maturation in assessing the mandibular growth peak using a longitudinal design.

Materials and Methods: From the files of the Burlington and Oregon growth studies, 40 subjects (20 from each collection, 20 males and 20 females) with at least seven annual lateral cephalograms taken from 9 to 16 years were included. Mandibular second molar maturation was assessed according to Demirjian et al., and mandibular growth was defined as annual increments of Co-Gn distance. A full diagnostic reliability analysis (including positive likelihood ratio) was performed to establish the diagnostic reliability of dental stages E, F, and (pooled) GH in identifying the imminent mandibular growth peak.

Results: None of the dental maturation stages reliably identified the mandibular growth peak with greatest overall mean accuracy and positive likelihood ratio of 0.77 (stage F) and 2.7 (stage E), respectively.

Conclusions: Use of the mandibular second molar maturation is not recommended for planning treatment requiring identification of the mandibular growth peak. (*Angle Orthod.* 2017;87:665–671.)

KEY WORDS: Dental maturation; Mandibular growth; Diagnosis; Orthodontics

INTRODUCTION

Efficiency of functional treatment and growth modification, especially to correct skeletal Class II malocclusion, depends on assessing skeletal maturity. Skeletal effects are maximized if treatment is performed during the pubertal growth spurt, irrespective

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whether removable¹ or fixed² appliances are used. Therefore, efforts have been made to find reliable indicators for predicting skeletal maturity in individual subjects. These indicators have included radiographic hand-wrist maturational (HWM) methods,³ third finger middle phalanx (MPM) method,⁴.⁵ cervical vertebral maturational (CVM) method,⁴ dental maturation,⁻,² and dental emergence.⁴ In particular, dental maturity assessed through calcification stages,⁻ and it can be carried out on panoramic or intraoral radiographs, which are routinely used for different purposes. Therefore, dental maturation has been proposed as a useful method for assessing the pubertal growth spurt.⁴

Many studies have been performed, including a meta-analysis,¹¹ evaluating the correlation between mandibular second molar maturation and the HWM,¹²⁻¹⁴ MPM,¹⁵ and CVM^{16,17} methods. High correlations were reported between mandibular second molar maturation and the other maturation methods studied in all these investigations regardless of the ethnicity of the sample population. However, contrasting conclusions were drawn, with some studies recommending^{12,14,17} or discouraging^{15,16} the use of mandibular second molar maturation as a diagnostic tool for predicting the pubertal growth spurt. If second

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molar maturation is indeed a reliable indicator of growth timing, it would be especially useful for determining when functional appliance treatment should be performed to take advantage of the mandibular growth peak. However, confirming a high correlation between mandibular second molar maturation and the HWM, MPM, or CVM methods constitutes only indirect evidence that assessment of dental maturation is helpful in identifying the mandibular growth peak.

The purpose of this study was to assess the diagnostic reliability of using mandibular second molar maturation for predicting the mandibular growth peak. This was accomplished using longitudinal growth records from the files of the Burlington and Oregon growth studies, along with a dedicated diagnostic reliability analysis.

MATERIALS AND METHODS

Subjects were selected from the records of the Burlington and Oregon growth studies, extracted from the American Association of Orthodontists Foundation (AAOF) Craniofacial Growth Legacy Collection (www. aaoflegacycollection.org). Subjects were selected for inclusion if they had a consecutive series of annual lateral cephalograms from 9 to 16 years. However, although most of the Burlington Growth Study cases missed the 15-year record, this specific time point was used whenever present (see also below), for a total of at least seven records per subject. Cases in which the mandibular growth peak could not be precisely associated with any annual age interval were excluded. Therefore, even the inclusion of cases in which the 15-year record was missing did not impair the study.

Subjects were included if they had an ANB angle between 0° and 6° and facial divergence (SN-CoGn angle) between 25° and 42°. Exclusion criteria included incomplete records, radiographs of poor diagnostic quality, subjects with recognizable craniofacial (or other) conditions or syndromes, any history of orthodontic treatment, and loss of space or crowding in the posterior area that prevented normal eruption of the mandibular second molar.

From the original sample available in the AAOF Craniofacial Legacy Collection after selection, a total of 40 subjects (20 males, 20 females), equally divided between the Burlington and Oregon growth studies, were included. Specifically, all the cases from the Burlington Growth Study that were analyzed along with corresponding mandibular growth recordings constituted a subset of a larger sample used in a previous investigation⁵ on the diagnostic reliability of a different growth indicator in identifying the mandibular growth peak. Fixed magnification factors of 10% and 8% were

Table 1. Description of Circumpubertal Mandibular Second Molar Maturation Stages D to H According to Demirjian et al.⁷

Stage and Description

- D: (1) Crown formation is complete down to the cementoenamel junction, (2) pulp horns become visible, and (3) root formation begins in the form of a spicule.
- E: (1) Walls of the pulp chamber form straight lines, the continuity of which is broken by the presence of the pulp horn, which is larger than in the previous stage, (2) root length is less than crown height, and (3) root bifurcation begins to be visible
- F: (1) Walls of the pulp chamber form a more or less isosceles triangle, with the apex ending in a funnel shape and (2) root length is equal to or greater than crown height.
- G*: Walls of the root canal are parallel and its apex is slightly open.
- H*: (1) Apex is completely closed and (2) periodontal membrane has a uniform width around the root and apex. GH: Stages G and H pooled.

adopted for the Burlington and Oregon collections, respectively, as recommended by these growth studies.

Assessment of Mandibular Second Molar Maturity

Evaluation of mandibular second molar maturity was carried out by assessing the calcification stages according to the method of Demirjian et al.⁷ (stages D to H) on the lateral cephalograms that were available as part of these collections. These stages are defined as reported in Table 1. An orthodontist who was blinded to the subjects' skeletal maturation stages, age, and sex, assessed the dental maturity of the mandibular second molars. An attempt was made to consider the distal root in assigning the last stages (G and H) that were pooled in the present study as a unique GH stage. Gray scales were inverted as necessary to enhance visibility.

Total Mandibular Length Assessment and Identification of the Mandibular Growth Peak

A customized digitization regimen and analysis with cephalometric software (Viewbox, version 3.0, dHAL Software, Kifissia, Greece) were used for all cephalograms examined. Total mandibular length was measured using the distance between Condylion (Co) and Gnathion (Gn) for each recording. All cephalograms from the Oregon Growth Study were traced by an operator and checked for accuracy by a second investigator. Details of the tracing of the Burlington Growth Study sample are reported elsewhere.⁵

Increments in Co-Gn distance were calculated for each subject according to each annual age interval from 9–10 years to 15–16 years. Since annual intervals were not always equal to 12 months, annualized increments were derived. The individual dental stage

 $^{^{\}star}$ Whenever possible, stages G and H have been assigned according to the distal root. 7

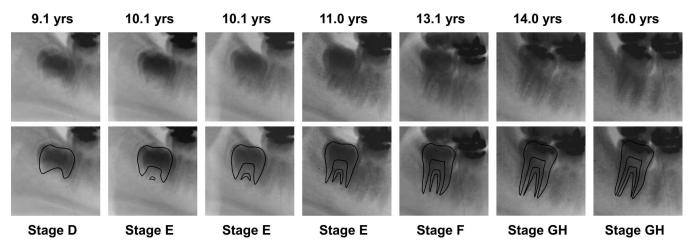


Figure 1. Annual mandibular second molar maturation with corresponding tracings of subject Burlington 1391 (female) with corresponding actual ages. Inverted grey scale.

at the beginning of each annual age interval was also recorded. Finally, the annual age interval of maximum individual increment for the Co-Gn distance was identified as the one displaying the greatest increment of the whole series, that is, mandibular growth peak, and subsequently was used for diagnostic reliability analysis.18 Moreover, in 15 Burlington Growth Study cases missing the 15-year annualized increment, the Co-Gn distances were calculated for the biannual 14-16-year interval, when the mandibular growth peak could be excluded from having occurred in this interval and the mandibular second molar had reached stage GH at the 14-year recording (12 cases). The 15-year records were available for the remaining five cases, and one of those showed a mandibular growth peak in the 15-16-year interval. Therefore, in 3 out of 20 cases, the maturational stage of the mandibular second molar could not be assigned reliably at the 15–16-year interval.

Method Error and Data Analysis

The method of moments variance estimator¹⁹ was used to evaluate the method error of the recordings for each cephalometric parameter. This analysis was performed on 20 paired recordings (10 for each growth study) randomly selected and expressed as a mean (95% confidence interval [CI]). Repeatability of the dental stage assignment in an additional 20 pairs of randomly selected cases (10 for each growth study) was evaluated using percentage of agreement and by both unweighted and linear-weighted kappa coefficients presented as means (95% CI).²⁰

Diagnostic Reliability Assessment

Diagnostic reliability assessment was calculated for each annual age interval, and it included sensitivity,

specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy,²¹ and positive likelihood ratio (LHR)²² and reported as a mean (95% CI). For each diagnostic parameter, an overall weighted mean was also calculated, taking into account the paired nature of the data. This analysis evaluated the capability of circumpubertal stages E, F, and GH in identifying the maximum individual increments of Co-Gn distance according to a previously reported procedure.^{5,18} A threshold of a positive LHR of ≥10²²² was considered for assessing satisfactory reliability. Since no relevant differences were seen between the Burlington and Oregon growth studies, results from the pooled sample were reported.

RESULTS

Method error for the Co-Gn distance was 0.68 mm (0.51–0.99 mm). Overall percentage of agreement for the DM stages was 85% (17 cases out of 20). The unweighted kappa coefficient was 0.80 (0.59–1), and the weighted kappa coefficient was 0.88 (0.76–1).

A clinical example of a subject (Burlington 1391, female) with full tracings of the mandibular second molar at each age is shown in Figure 1. In this case, stages E and F lasted for about 3 years and 1 year, respectively.

The full list of the individuals' mandibular second molar stages from 9 to 16 years and the corresponding annual increments in Co-Gn distance according to each annual age interval are summarized in Table 2. A total of 5 subjects out of 20 from the Burlington Growth Study also had records at 15 years, and none of the remaining 15 subjects showed a mandibular growth peak in this 14–16 year biannual interval. With few exceptions, all the subjects showed stages D and GH at the 9- and 16-year recordings, respectively. None of the subjects skipped any stage in the progression of

Table 2. Individual Mandibular Second Molar Stages and Corresponding Subsequent Annualized Increments in Co-Gn (Mm) According to Each Annual Age Interval

	9–10 y		10–11 y		11–12 y		12–13 y		13–14 y		14–15 y		15–16 yrs	
ID, Sex	DSª	Co-Gn	DS	Co-Gn	DS	Co-Gn	DS	Co-Gn	DS	Co-Gn	DS	Co-Gn	DS	Co-Gn
Burlington Growth Study														
135, M	D	1.7	Ε	2.7	F	3.0	F	0.3	F	6.1	GH	1.7*	GH*	1.7*
231, M	D	2.0	Ε	2.5	Ε	0.5	F	4.4	GH	2.9	GH	2.0*	GH*	2.0*
392, M	D	3.9	D	1.5	Ε	1.5	Е	0.7	F	4.5	F	2.1*	NA	2.1*
636, M	D	0.5	D	1.6	E	4.6	E	0.3	F	1.8	F	4.7	GH	6.3
706, M	D	3.1	D	1.5	Е	0.6	Е	1.2	F	3.9	F	3.2	GH	3.1
742, M	D	2.0	D	0.9	E	1.4	F	2.2	F	2.5	GH	-0.1	GH	1.7
763, M	D	0.4	D	1.8	Е	1.5	Е	3.1	F	6.0	GH	1.4*	GH*	1.4*
863, M	D	2.5	Е	1.9	Е	1.4	F	3.4	F	3.3	GH	7.5	GH	1.3
871, M	D	4.0	Е	0.4	Е	4.5	Е	1.5	F	3.3	GH	3.9	GH	1.9
163, F	D	1.0	Ε	1.5	Е	1.5	F	4.5	F	1.3	GH	0.7*	GH*	0.7*
188, F	D	3.3	Е	3.7	E	2.2	F	0.1	F	2.2	GH	0.9*	GH*	0.9*
198, F	D	2.2	Е	2.3	Е	2.9	F	1.6	GH	0.8	GH	0.6*	GH*	0.6*
208, F	D	1.2	E	3.5	F	3.2	GH	2.3	GH	3.0	GH	1.0*	GH*	1.0*
316, F	D	4.3	D	1.8	E	5.2	E	0.2	F	0.2	F	0.6*	NA	0.6*
321, F	D	2.2	E	3.5	E	2.1	F	1.4	F	0.7	GH	1.3*	GH*	1.3*
487, F	D	2.2	Ē	0.9	Ē	5.5	F	3.3	GH	1.6	GH	1.2*	GH*	1.2*
595, F	Ē	4.5	Ē	1.6	Ē	1.4	F	0.5	GH	2.9	GH	2.3*	GH*	2.3*
602, F	D	3.2	Ē	2.8	E	3.8	F	1.6	GH	0.5	GH	1.6*	GH*	1.6*
855, F	D	1.7	E	2.3	E	3.5	E	0.2	F	0.6	F	1.4*	NA	1.4*
1391, F	D	-0.1	Ē	0.8	Ē	1.5	Ē	0.7	F	4.6	GH	1.9*	GH*	1.9*
Oregon Growth Study	_	• • • • • • • • • • • • • • • • • • • •	_	0.0	_		_	0	•		O			
089-1, M	Е	2.1	Е	1.6	F	1.7	F	2.0	GH	2.3	GH	2.5	GH	5.3
105-1, M	D	1.6	D	2.3	E.	1.9	E.	3.2	F	4.9	GH	3.1	GH	0.9
105-2, M	D	1.9	Ē	2.5	Ē	2.2	Ē	3.1	F	3.6	GH	1.2	GH	4.0
121-3, M	D	2.5	Ē	2.8	F	3.3	F	3.1	GH	3.9	GH	5.5	GH	1.3
144, M	D	2.7	D	3.0	D	1.3	E.	3.2	E	3.1	F	5.6	F	2.3
153, M	D	2.0	Ē	2.1	Ē	1.8	Ē	1.8	F	8.1	F.	2.4	GH	0.1
179, M	Ē	2.4	Ē	3.3	F	2.5	F	4.1	GH	5.9	GH	1.9	GH	5.3
183-1, M	D	1.5	D	2.1	E.	2.1	E.	2.4	F	2.9	F	4.3	GH	1.4
240, M	D	2.3	Ē	1.7	Ē	2.0	F	2.0	F	7.2	GH	2.7	GH	2.1
295, M	Ē	1.9	Ē	2.2	F	2.0	F	2.0	F	2.8	GH	7.9	GH	1.8
317-2, M	D	2.3	D	2.2	D	2.1	Ē	2.6	E	7.6	F	2.4	GH	3.3
76, F	D	2.6	Ē	1.9	Ē	2.2	Ē	2.4	F	1.9	GH	3.0	GH	1.0
083-1, F	Ē	1.9	F	1.9	F	4.8	GH	0.6	GH	0.9	GH	0.9	GH	NA
100-1, F	D	3.0	E	3.0	E.	2.5	F	3.3	F	1.9	GH	2.1	GH	0.2
100-1, 1 100-2, F	D	2.2	Ē	3.1	Ē	2.5	F	1.9	F	4.8	GH	1.5	GH	2.2
132, F	D	1.7	D	2.0	D	2.7	E.	2.4	E.	4.2	E	0.7	F	2.5
248, F	D	1.9	E	1.0	E	2.3	Ē	2.5	F	3.8	F	1.1	GH	1.8
250-1, F	D	2.5	Ē	2.7	F	3.2	F	5.9	GH	1.0	GH	-0.3	GH	0.4
251, F	D	1.9	D	1.6	E.	2.0	E.	2.6	F	5.5	GH	0.8	GH	1.5
251, F 251-1, F	D	1.5	D	1.9	E	1.7	F	4.8	F	2.1	GH	2.5	GH	1.5
201-1, 1	D	1.5	D	1.5		1.7	'	4.0	1	۷.۱	GH	2.5	un	1.0

^a DS indicates dental maturation stage; M, male; F, female; *, film at 15 years not available with data derived from previous recording (dental stage) or biannual interval (mandibular length); **NA**, not available or not derivable from previous film. **Bold** indicates maximum individual annual increments in Co-Gn.

stages, and there was similar timing of dental maturation between sexes.

Values of the annualized mandibular growth peak in Co-Gn distance ranged from 2.5 mm (Burlington 742, 13–14 years) to 8.1 mm (Oregon 153, 13–14 years). Males showed generally later mandibular growth peaks compared with females, especially for the Burlington Growth Study.

Results of the overall diagnostic reliability assessment of the mandibular second molar stages E, F, and GH in identifying the mandibular growth peak are

summarized in Table 3. Low scores were generally observed, with few exceptions. Mean sensitivity ranged from 0.29 (stage GH) to 0.43 (stage E), mean specificity ranged from 0.69 (stage GH) to 0.43 (stage E), mean PPVs ranged from 0.10 (stage GH) to 0.22 (stage F), mean NPVs ranged from 0.64 (stage GH) to 0.90 (stage F), mean accuracy ranged from 0.64 (stage GH) to 0.77 (stage F), and mean positive LHRs ranged from 0.6 (stage GH) to 2.7 (stage E).

Detailed results for the diagnostic reliability of each of the mandibular second molar stages E, F, and GH,

Table 3. Overall Diagnostic Reliability of Dental Maturation in Identifying Mandibular Growth Peak

Dental Stage	Diagnostic Parameter	Mean (95% CI)
E	Sensitivity	0.43 (0.33–0.52)
	Specificity	0.71 (0.60-0.83)
	PPV ^a	0.21 (0-0.47)
	NPV	0.86 (0.75-0.98)
	Accuracy	0.65 (0.52-0.79)
	Positive LHR	2.7 (0.8–9.7)
F	Sensitivity	0.39 (0.19-0.60)
	Specificity	0.78 (0.66-0.91)
	PPV	0.22 (0.05-0.38)
	NPV	0.90 (0.79-1)
	Accuracy	0.77 (0.65-0.89)
	Positive LHR	1.4 (0.4–4.5)
GH	Sensitivity	0.29 (0.11-0.47)
	Specificity	0.69 (0.60-0.79)
	PPV	0.10 (0-0.22)
	NPV	0.85 (0.73-0.97)
	Accuracy	0.64 (0.52-0.75)
	Positive LHR	0.6 (0.3–1.5)

 $^{^{\}rm a}$ PPV indicates positive predictive value; NPV, negative predictive value; LHR, likelihood ratio.

and according to each annual age interval are summarized in the Appendix.

DISCUSSION

This study reported on the diagnostic reliability of the mandibular second molar stages E, F, and GH in identifying the mandibular growth peak. The longitudinal study design has been previously used to evaluate diagnostic reliability of other growth indicators, 5.18 but it has never been used to study their relationship to dental maturity. Moreover, while previous studies correlated dental maturation stages with other growth indicators such as CVM8.14.16.23-27 or HWM, 12.24.28 the present study focused, for the first time, on the mandibular growth peak itself. The present results showed that none of the maturational stages of the mandibular second molar reach satisfactory diagnostic reliability to consistently identify the mandibular growth peak, irrespective of the sample of origin.

The most common and widely accepted method used of scoring dental maturation is the one described by Demirjian et al.⁷ This method has the advantage of using relative values of root formation to crown height, rather than absolute lengths. Therefore, foreshortened or elongated projections of developing teeth do not affect the reliability of this assessment.⁷ Moreover, mandibular teeth are preferred to maxillary teeth because they are subjected to less superimposition with other skeletal structures. Mandibular second molar maturation was assessed on lateral cephalograms rather than on panoramic radiographs. Due to the inclusion of cephalograms of good quality, staging exhibited good repeatability. Moreover, to avoid errors

in determining the last stages (G and H), which may appear similar on a lateral cephalogram, pooling in a unique stage, GH, was accomplished. Only 8 cases of the 40 examined (Table 2) had a stage GH followed by a mandibular growth peak. Therefore, neither stage G nor H could have reached a level of diagnostic reliability in identifying the mandibular growth peak.

A recent study¹⁷ reported that mandibular second molar stages F and G correspond to the pubertal growth spurt for females and males, respectively. Other evidence¹⁸ indicated that none of the stages of the mandibular second molar are specifically associated with a given CVM stage, except for stages up to D and stage H, that would be indicative of a prepubertal and postpubertal growth phase, respectively. This conclusion has been confirmed by a meta-analysis¹¹ including subjects of different ethnicities. However, the capability of mandibular second molar maturation to identify a prepubertal growth phase would have minimal clinical relevance since the early mixed and intermediate mixed dentition can be used instead for the same purpose.⁹

The apparent inconsistency among previous investigations might be explained by study design characteristic. All the previous investigations^{8,12,13,15-17} exploring an association between dental and skeletal maturation (including those focused on the mandibular second molar) followed a cross-sectional design and did not include any data on the mandibular growth peak itself, which would have major clinical relevance. On the basis of correlation analyses only, most of the previous studies12-14,17 reported mandibular second molar maturation as a reliable indicator of the pubertal growth spurt. On the contrary, only a few investigators^{15,16} reported opposite conclusions by including a diagnostic reliability analysis. The lack of a specific diagnostic reliability analysis when investigating the capability of dental maturation analysis to identify the pubertal growth spurt has been criticized.29 One of the reasons underlying this noteworthy lack of relevant data on diagnostic reliability may be the difficulty of performing such analysis from longitudinal data in a subset of selected subjects, all with a predetermined condition (mandibular growth peak) or a diagnostic outcome (a given dental stage).5,18

Previous studies^{8,12,14,16,23–28} investigating the predictive reliability of dental maturation did not evaluate mandibular growth directly but instead used other growth indicators, thus reporting only indirect evidence of any correlation between dental maturation and the mandibular growth peak. This is of particular relevance considering that growth indicators such as CVM¹⁸ and others^{3,5} are not suitable for the correct identification of the mandibular growth peak in all subjects.

Future longitudinal studies may be warranted to fully elucidate the role of maturation of other teeth in identifying the mandibular growth peak in individual subjects.

CONCLUSIONS

- None of the dental maturation stages identified were found to be adequately reliable for predicting the mandibular growth peak.
- The use of maturation of the mandibular second molar is not recommended for planning the ideal time to begin functional appliance treatment for skeletal Class malocclusion.

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APPENDIX Diagnostic Reliability of Dental Maturation in Identifying the Mandibular Growth Peak as Annualized Increment in Co-Gn Distance According to Each Annual Age Interval From 9 to 16 Years

Stage Parameter 9-10 y 10-11 y 11-12 y 12-13 y 13-14 y 14-15 y 15-16 y E Sensitivity 1 1 0.86 0 0.13 0 0 Specificity 0.90 0.39 0.30 0.49 0.96 0.97 1 PPV 0.20 0.15 0.21 0 0.67 0 - PPV 0.20 0.15 0.21 0 0.67 0 - NPV 1 1 0.91 0.77 0.62 0.87 0.92 Accuracy 0.90 (0.50-20.99) (0.060-0.95) (0.13-1.20) 0.87 0.92 Accuracy 0.90 0.45 0.40 0.43 0.63 0.85 0.92 Positive LHR 9.7 1.6 1.2 - 3.0 - - - Specificity 1 0.97 0.79 0.57 0.44 0.77 0.95 PPV	Dental	Diagnostic Parameter	Age Intervals									
Specificity			9–10 y	10–11 y	11–12 y	12–13 y	13–14 y	14–15 y	15–16 y			
Specificity	E	Sensitivity	1	1		0		0	0			
PPV		Specificity	0.90	0.39	'	0.49	` ,	0.97	1			
PPV												
NPV		PPV	` ,	` ,	` ,	` ,	` ,	` ,	_			
NPV						-		-				
Accuracy 0.90		NPV	` ,	,	` ,	0.77	,	0.87	0.92			
Accuracy			•	•								
Positive LHR		Accuracy	0.90	0.45	, ,	` ,	,	` ,	` ,			
Fositive LHR 9.7 1.6 1.2 - 3.0		riodardoy										
F Sensitivity - 0 0 0.14 1 0.80 0.40 0 Specificity 1 0.97 0.79 0.57 0.44 0.77 0.95 Specificity 1 0.92 0.13 0.25 0.46 0.20 0 NPV 1 0.92 0.81 1 0.068-0.95 (0.67-1) (0.79-1) (0.68-1) Accuracy 1 0.90 0.68 0.63 0.58 0.73 0.88 0.73 0.88 Positivity - 0 0 0 0.13 0.25 0.46 0.20 0 Specificity 1 0.90 0.68 0.63 0.58 0.73 0.80 Positive LHR 0.7 2.3 1.4 1.7 Specificity 1 1 1 1 0.94 0.63 0.60 1 Specificity 1 1 1 0.94 0.66 0.69 (0.67-1) (0.69-2.2) (0.56-0.0) Specificity 1 1 1 1 0.94 0.63 0.20 0.70-0.89 Specificity 1 1 1 1 0.94 0.63 0.20 0.70-0.89 Specificity 1 1 1 1 0.94 0.63 0.20 0.60 0.60 Specificity 1 0.90 0.68 0.63 0.58 0.73 0.88 Specificity 1 1 1 0.94 0.63 0.60 1 Specificity 1 0.94 0.63 0.20 0.60 0.60 Specificity 1 0.94 0.63 0.26 0.60 Specificity 1 0.93 0.83 0.87 0.52 0.82 1 Specificity 1 0.93 0.83 0.87 0.52 0.82 1 Specificity 1 0.93 0.83 0.87 0.52 0.82 1 Specificity 1 0.93 0.83 0.83 0.83 0.83 0.83 0.83 0.80 0.30 0.14 Specificity 1 0.93 0.83 0.83 0.83 0.83 0.83 0.80 0.30 0.14 Specificity 1 0.93 0.83 0.83 0.83 0.83 0.80 0.30 0.14 Specificity 1 0.93 0.83 0.83 0.83 0.83 0.83 0.83 0.83 0.8		Positive LHR	,	` ,	` ,	(0.27 0.00)	,	(0.7 1 0.00)	(0.00 1)			
F Sensitivity - 0 0 0.14 1 0.80 0.40 0 0		r contro Ermi	• • • •									
Specificity 1 0.97 0.79 0.57 0.44 0.77 0.95 (0.92-1) (0.65-0.93) (0.41-0.74) (0.25-0.63) (0.63-0.91) (0.87-1) PPV - 0 0 0.13 0.25 0.46 0.20 0 NPV 1 0.92 0.81 1 0.79 0.90 0.92 (0.84-1) (0.68-0.95) (0.06-0.44) (0.27-0.65) (0-0.45) Accuracy 1 0.90 0.68 0.63 0.58 0.73 0.88 (0.81-0.99) (0.81-0.99) (0.53-0.82) (0.47-0.78) (0.42-0.73) (0.59-0.86) (0.77-0.98) Positive LHR - 0 0 0 0 0.13 0.60 1 Specificity 1 1 1 1 0.94 0.63 0.26 0.06 Specificity 1 1 1 1 0.94 0.63 0.26 0.06 Specificity 1 1 0.93 0.83 0.87 0.52 0.82 1 NPV 1 0.93 0.83 0.87 0.52 0.82 1 Accuracy 1 0.93 0.83 0.87 0.52 0.82 1 (0.84-1) (0.84-1) (0.71-0.94) (0.76-0.98) (0.34-0.70) (0.59-1) Accuracy 1 0.93 0.83 0.83 0.87 0.52 0.82 1 (0.84-1) 0.93 0.83 0.83 0.83 0.43 0.30 0.14 (0.84-1) (0.84-1) (0.71-0.94) (0.71-0.94) (0.27-0.58) (0.16-0.44) (0.02-0.25) Positive LHR 0 0.3 0.8 1.1	F	Sensitivity	(0.0 2 1.0)	` ,	` ,	1	,	0.40	0			
Specificity 1 0.97 0.79 0.57 0.44 0.77 0.95 PPV - 0 0.13 0.25 0.46 0.20 0 NPV 1 0.92 0.81 1 0.79 0.90 0.92 NPV 1 0.92 0.81 1 0.79 0.90 0.92 Accuracy 1 0.90 0.68 0.63 0.58 0.73 0.88 Positive LHR - - 0.7 2.3 1.4 1.7 - GH Sensitivity - 0 0 0 0.13 0.60 1 Feedificity 1 1 1 0.94 0.63 0.58 0.73 0.88 GH Sensitivity - 0 0 0.14 0.99-2.2) (0.59-0.86) (0.77-0.98) GH Sensitivity - 0 0 0.13 0.60 1 0.09 0.06 0.06		Conditivity		Ü		•			Ü			
PPV		Specificity	1	0.97	` ,	0.57	` ,	` ,	0.95			
PPV - 0 0 0.13 0.25 0.46 0.20 0 NPV 1 0.92 0.81 1 0.79 0.90 0.92 (0.84-1) (0.68-0.95) (0.57-1) (0.79-1) (0.84-1) Accuracy 1 0.90 0.68 0.63 0.58 0.73 0.88 (0.81-0.99) (0.53-0.82) (0.47-0.78) (0.42-0.73) (0.59-0.86) (0.77-0.98) Positive LHR 0 0 0 0 0.13 0.60 1 Specificity 1 1 1 1 0.94 0.63 0.26 0.06 Specificity 1 1 1 1 0.94 0.63 0.26 0.06 PPV 0 0 0.87-1) (0.43-0.82) (0.11-0.40) (0-0.14) PPV 0 0 0.18 0.10 0.09 NPV 1 0.93 0.83 0.87 0.52 0.82 1 Accuracy 1 0.93 0.83 0.83 0.87 0.52 0.82 1 Accuracy 1 0.94 0.63 0.30 0.14 PPV 0 0 0.18 0.10 0.09 NPV 1 0.93 0.83 0.87 0.52 0.82 1 Accuracy 1 0.93 0.83 0.83 0.87 0.52 0.82 1 Positive LHR 0 0.83 0.83 0.83 0.43 0.30 0.14 PPOSITIVE LHR 0.3 0.8 1.1		opcomony	•									
NPV 1 0.92 0.81 1 0.79 0.90 0.92 Accuracy 1 0.90 0.68 0.63 0.58 0.73 0.88 (0.77-0.98) Positive LHR - 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0		PPV	_	` ,	'	` ,	` ,	,	'			
NPV 1 0.92 0.81 1 0.79 0.90 0.90 0.92 (0.84-1) (0.68-0.95) (0.57-1) (0.79-1) (0.84-1) (0.84-1) (0.68-0.95) (0.57-1) (0.79-1) (0.84-1) (0.84-1) (0.84-1) (0.68-0.95) (0.57-1) (0.79-1) (0.84-1) (Ü					Ü			
Accuracy 1 0.84-1) (0.68-0.95) (0.57-1) (0.79-1) (0.84-1) Accuracy 1 0.90 0.68 0.63 0.58 0.73 0.88 Positive LHR 0.7 2.3 1.4 1.7 - (0.1-4.6) (1.6-3.4) (0.9-2.2) (0.5-6.0) GH Sensitivity - 0 0 0 0 0.13 0.60 1 Specificity 1 1 1 1 0.94 0.63 0.26 0.06 PPV 0 0.18 0.10 0.90 PPV 0 0.18 0.10 0.09 NPV 1 0.93 0.83 0.83 0.87 0.52 0.82 1 Accuracy 1 0.93 0.83 0.83 0.87 0.52 0.82 1 Accuracy 1 0.93 0.83 0.83 0.83 0.43 0.30 0.14 Positive LHR 0.3 0.8 1.1		NPV	1	0.92	` ,	,	` ,	` ,	0.92			
Accuracy 1 0.90 0.68 0.63 0.58 0.73 0.88 (0.81–0.99) (0.53–0.82) (0.47–0.78) (0.42–0.73) (0.59–0.86) (0.77–0.98) (0.77–0.98) (0.59–0.86) (0.77–0.98) (0.47–0.78) (0.42–0.73) (0.59–0.86) (0.77–0.98) (0.77–0.58) (0.77–0.94) (0.77–0.94) (0.77–0.94) (0.77–0.94) (0.77–0.98) (0.77–0.58) (0.16–0.44) (0.02–0.25) (0.98–1) (0.84–1) (0.71–0.94) (0.71–0.94) (0.77–0.94) (0.77–0.58) (0.16–0.44) (0.02–0.25) (0.98–1) (0.84–1) (0.71–0.94) (0.71–0.94) (0.77–0.58) (0.16–0.44) (0.02–0.25) (0.16–0.44)						•						
Continue LHR		Accuracy	1	` ,	,	0.63	` ,	` ,	` ,			
Positive LHR 0.7 2.3 1.4 1.7 (0.1-4.6) (1.6-3.4) (0.9-2.2) (0.5-6.0) (0.1-4.6) (1.6-3.4) (0.9-2.2) (0.5-6.0) - (0.		Hooditaby										
GH Sensitivity - 0 0 0 0 0.13 0.60 1 Specificity 1 1 1 1 0.94 0.63 0.26 0.06 PPV 0 0.84-1) (0.71-0.94) (0.76-0.98) (0.34-0.70) (0.59-1) Accuracy 1 0.93 0.83 0.83 0.83 0.43 0.30 0.14 Positive LHR 0.3 0.8 1.1		Positive I HR	_	(0.01 0.00)	,	` ,	` ,	,	(0.77 0.00)			
GH Sensitivity - 0 0 0 0 0.13 0.60 1 Specificity 1 1 1 1 0.94 0.63 0.26 0.06 PPV 0 0 0.18 0.10 0.09 NPV 1 0.93 0.83 0.87 0.52 0.82 1 NPV 1 0.93 0.83 0.87 0.52 0.82 1 Accuracy 1 0.93 0.83 0.83 0.83 0.43 0.30 0.14 Positive LHR 0 0.3 0.8 1.1		1 COMIVE ELIM										
Specificity 1 1 1 1 0.94 0.63 0.26 0.06 (0.87–1) (0.43–0.82) (0.11–0.40) (0–0.14) PPV 0 0.18 0.10 0.09 (0–0.41) (0–0.41) (0–0.18) NPV 1 0.93 0.83 0.87 0.52 0.82 1 (0.84–1) (0.84–1) (0.71–0.94) (0.76–0.98) (0.34–0.70) (0.59–1) Accuracy 1 0.93 0.83 0.83 0.83 0.43 0.30 0.14 (0.84–1) (0.84–1) (0.71–0.94) (0.71–0.94) (0.27–0.58) (0.16–0.44) (0.02–0.25) Positive LHR 0.3 0.8 1.1	GH	Sensitivity	_	0	,	,	` ,	` ,	1			
Specificity 1 1 1 0.94 (0.87-1) (0.43-0.82) (0.11-0.40) (0-0.14) PPV - - - 0 0.18 (0-0.41) (0-0.21) (0-0.18) NPV 1 0.93 (0.83 (0.87 (0.52 (0.34-0.70)) (0.59-1)) 0.82 (0.84-1) (0.71-0.94) (0.76-0.98) (0.34-0.70) (0.59-1) Accuracy 1 0.93 (0.83 (0.83 (0.83 (0.83 (0.83 (0.43 (0.30)) (0.16-0.44)) (0.02-0.25)) Positive LHR - - - 0.3 (0.71-0.94) (0.27-0.58) (0.16-0.44) (0.02-0.25)		Conditivity		Ü	Ü	Ü			·			
PPV 0 0.18 0.10 0.09 (0-0.14) NPV 1 0.93 0.83 0.87 0.52 0.82 1 (0.84-1) (0.84-1) (0.94-0.94) (0.71-0.94) (0.76-0.98) (0.34-0.70) (0.59-1) Accuracy 1 0.93 0.83 0.83 0.83 0.43 0.30 0.14 (0.84-1) (0.84-1) (0.71-0.94) (0.71-0.94) (0.27-0.58) (0.16-0.44) (0.02-0.25) Positive LHR 0.3 0.8 1.1		Specificity	1	1	1	0.94	` ,	` ,	0.06			
PPV 0 0.18 0.10 0.09 NPV 1 0.93 0.83 0.87 0.52 0.82 1 (0.84-1) (0.71-0.94) (0.76-0.98) (0.34-0.70) (0.59-1) Accuracy 1 0.93 0.83 0.83 0.83 0.43 0.30 0.14 (0.84-1) (0.71-0.94) (0.71-0.94) (0.27-0.58) (0.16-0.44) (0.02-0.25) Positive LHR 0.3 0.8 1.1		opcoorty	•	•	•							
NPV 1 0.93 0.83 0.87 0.52 0.82 1 (0.84-1) (0.71-0.94) (0.76-0.98) (0.34-0.70) (0.59-1) Accuracy 1 0.93 0.83 0.83 0.83 0.43 0.30 0.14 (0.84-1) (0.71-0.94) (0.71-0.94) (0.71-0.94) (0.27-0.58) (0.16-0.44) (0.02-0.25) Positive LHR 0.3 0.8 1.1		PPV	_	_	_	` ,	,	,	'			
NPV 1 0.93 0.83 0.87 0.52 0.82 1 (0.84-1) (0.71-0.94) (0.76-0.98) (0.34-0.70) (0.59-1) Accuracy 1 0.93 0.83 0.83 0.83 0.43 0.30 0.14 (0.84-1) (0.71-0.94) (0.71-0.94) (0.27-0.58) (0.16-0.44) (0.02-0.25) Positive LHR 0.3 0.8 1.1						· ·						
(0.84–1) (0.71–0.94) (0.76–0.98) (0.34–0.70) (0.59–1) Accuracy 1 0.93 0.83 0.83 0.43 0.30 0.14		NPV	1	0.93	0.83	0.87	` ,	` ,				
Accuracy 1 0.93 0.83 0.83 0.43 0.30 0.14 (0.84–1) (0.71–0.94) (0.71–0.94) (0.27–0.58) (0.16–0.44) (0.02–0.25) Positive LHR – – – 0.3 0.8 1.1			•						·			
(0.84–1) (0.71–0.94) (0.71–0.94) (0.27–0.58) (0.16–0.44) (0.02–0.25) Positive LHR – – – 0.3 0.8 1.1		Accuracy	1	` ,	,	` ,	` ,	` ,	0.14			
Positive LHR 0.3 0.8 1.1			•									
		Positive LHR	_	-	-	(3.7 : 3.54)	` ,	,				
							(0.1–1.3)	(0.4–1.7)	(1.0–1.2)			

Note: Data are presented as mean (95% CI) with n=40 in each age interval, except for the 15–16-year interval with n=37.

^a PPV indicates positive predictive value; NPV, negative predictive value; LHR, likelihood ratio; –, not derivable.