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Spectrum of Dental Phenotypes in Nonsyndromic Orofacial Clefting

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Appendix

Rules to Evaluation Agenesis

Maxillary Lateral Incisor (LI):

- If the subject is an adult with permanent canines erupted and the lateral incisor (LI) is not erupted: Mark Agenesis
  - Unless subject has multiple teeth with gross decay and/or multiple missing teeth likely due to extractions
- If the subject is an adult with poor dentition (gross decay): mark Other, make note in
- quadrant notes section = Not Present.
- If the permanent canine is erupted or ectopically erupted into LI space, and LI is not present: mark Agenesis
- If obvious cleft and LI not present:
  - If 1st permanent molar(s) erupted: mark Agenesis with low confidence
  - If permanent canines erupted: mark Agenesis with high confidence

Maxillary Central Incisor (CI):

- If obvious cleft and the central incisor (CI) not present:
  - If 1st permanent molar(s) is/are erupted: mark Agenesis with low confidence.
  - If permanent canines are erupted: mark Agenesis with high confidence.

Second Premolar:

- If the second permanent molar is erupted, have minimal restorations, no gross decay, no history of tooth extraction given: mark Agenesis with low confidence
  - Unless subject has a history of orthodontics: mark Other, make note in quadrant notes section: mark Not Present
- If the second permanent molar is erupted and the subject has multiple teeth with gross decay and 2nd premolar not present: mark Not Present

Rules for "Other"

- If permanent tooth is erupting and remnants of primary tooth are still present: mark the permanent tooth as present.
- If tooth is blurry or unable to clearly see the outline of the tooth: mark Other, make a note in quadrant notes section: Not Visible
- If teeth are not visible in photo: mark Other, make a note quadrant notes section: Not Visible
- If unable to determine the position of the tooth: mark Other, make a note in quadrant notes section: Not Visible, Unable to tell position
- If root tips are present and unable to tell position of the tooth: mark Other, make a note in quadrant notes section: Unable to tell position, root tips
- If primary teeth are present and permanent first molar and posterior have not erupted: mark Other, make a note in quadrant notes section: Not Visible
- If primary teeth present and permanent first molar erupted, but second permanent molar not erupted: mark Other, make a note quadrant notes section: Not Visible
- If permanent second molar is erupted and permanent canine not erupted: mark Other, make a note in quadrant notes section: Not Present, impacted
- If 3rd molars are not present, with no history of 3rd molar extractions: mark Other, make a note in quadrant notes section: Not Visible

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Appendix Table 1. Study Population (1,745 Males, 2,096 Females, 2 Unknown Sex).

Country	Site	Proband Case	Sibling Unaffected	Parent Unaffected	Proband Control	Sibling Control	Parent Control	Total	Rating
United States	Colorado	16	21	27	0	0	0	64	Exam
	Pittsburgh	38	39	57	85	5	10	234	Exam and photo
	Iowa	111	106	169	149	37	71	643	Photo
	Texas	83	133	142	0	0	0	358	Exam and photo
Guatemala		45	32	87	177	23	80	444	Exam
Argentina		117	64	155	33	5	11	385	Exam
Hungary		102	94	190	187	82	175	830	Photo
Nigeria[a]		1[a]	0	3	1[a]	0	0	5	Exam
Philippines		147	247	356	98	0	0	848	Photo
Total		660	736	1186	730	152	347	3811	
Male sex		398	332	494	332	75	115	1745	
Female sex		261	404	692	397	77	232	2063	
Age, mean (range), y		9.8 (<1–74)	12.0 (<1–52)	37.8 (15–73)	25.9 (<1–74)	12.3 (1–55)	37.4 (19–79)		

[a]Sex of probands in Nigeria unknown.

Appendix Table 2. Definition of Dental Anomalies.

Dental Anomaly	Definition
Hypoplasia	A defect involving the surface of the enamel associated with a reduced thickness of enamel. It can occur in the forms of pits, grooves, or large areas of missing enamel.
Microdontia	Any tooth in which the incisal mesiodistal width appears narrower than the cervical width (i.e., cone shape, peg shape) or that appears much smaller than its regular size compared with its contralateral homolog or that appears out of proportion compared with other teeth of the same group (i.e., incisors, canines, premolars, molars).
Impacted	A tooth that fails to erupt into the dental arch, regardless of adequate space. The determination of impactions was used only for canines that were still not erupted even though permanent second molars were fully erupted.
Rotated	Any turn of the long axis of a tooth either mesially or distally in relation to the line of occlusion.
Displaced	Any tilt of the long axis of the tooth either buccally or lingually from the normal anatomical position in the dental arch or in a way that it appears outside of the line of occlusion.
Agenesis	The failure of any tooth to develop during embryonic growth and development due to the absence of primordial tissue. Agenesis was determined based on the age of the subjects. For instance, agenesis of the permanent lateral was determined only after the eruption of the permanent canines. Agenesis of second premolars was determined only after eruption of the second permanent molars.
Supernumerary	Any tooth that appears in addition to the regular number of teeth. Only erupted supernumeraries were counted in this study.
Any anomaly	Counts of at least one occurrence of any of the anomalies evaluated in this study.
Any anomaly	Counts of at least one occurrence of any of the anomalies evaluated in this study except for dental malposition (rotated or displaced teeth).

The second and third permanent molars were excluded from the study.

Appendix Table 3. Recording of Anomalies in Primary Dentition (Maxilla, Mandible).

Country	Site	Hypoplasia	Microdontia	Impacted	Rotated	Displaced	Agenesis	Supernumerary
United States	Colorado	5, 2	0, 0	0, 0	7, 0	6, 0	0, 0	5, 0
	Pittsburgh	4, 10	4, 3	0, 2	18, 17	8, 0	6, 0	1, 0
	Iowa	7, 1	2, 0	0, 0	137, 152	53, 7	8, 0	8, 1
	Texas	12, 4	4, 4	0, 0	84, 94	31, 6	26, 0	2, 0
Guatemala		0, 0	0, 0	0, 0	0, 0	0, 0	4, 0	0, 1
Argentina		14, 7	0, 1	0, 0	1, 0	1, 0	11, 0	2, 0
Hungary		23, 1	3, 1	0, 2	112, 133	36, 12	5, 1	4, 0
Nigeria		0, 0	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0
Philippines		16, 13	1, 1	0, 0	69, 96	51, 19	13, 0	5, 3
Total		81, 38	14, 10	0, 4	428, 492	186, 44	73, 1	27, 5

Appendix Table 4. Recording of Anomalies in Permanent Dentition (Maxilla, Mandible).

Country	Site	Hypoplasia	Microdontia	Impacted	Rotated	Displaced	Agenesis	Supernumerary
United States	Colorado	22, 13	3, 0	0, 0	0, 6	4, 3	0, 0	1, 0
	Pittsburgh	59, 26	0, 0	1, 2	55, 71	21, 37	9, 7	1, 0
	Iowa	14, 18	5, 0	13, 4	1,095, 1,706	345, 283	59, 3	0, 1
	Texas	35, 19	36, 2	14, 7	712, 1,007	183, 159	77, 14	2, 3
Guatemala		0, 0	4, 0	6, 1	6, 10	7, 20	12, 9	1, 0
Argentina		62, 15	11, 0	3, 0	6, 7	15, 3	68, 12	5, 0
Hungary		38, 14	13, 0	15, 5	1,518, 2,071	383, 387	61, 15	4, 0
Nigeria		0, 0	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0
Philippines		129, 58	65, 3	16, 3	1,603, 2,584	496, 632	105, 23	18, 3
Total		359, 163	137, 5	68, 22	4,995, 7,462	1,454, 1,524	391, 83	32, 7

Appendix Table 5. Case Probands: Primary Dentition, Cleft Type, and Laterality.

	Cleft Type, *n* (%)				Laterality of Cleft (CL or CLP), *n* (%)			
	CL (*n* = 78, 17%)	CLP (*n* = 303, 65%)	CP (*n* = 85, 18%)	*P* Value	Left Cleft (*n* = 172)	Right Cleft (*n* = 85)	Both Sides (*n* = 107)	*P* Value
Right maxilla								
Hypoplasia	2 (3)	13 (4)	1 (1)	0.42	5 (3)	6 (7)	4 (4)	0.28
Microdontia	1 (1)	4 (1)	0	0.67	1 (<1)	2 (1)	2 (2)	0.44
Impacted	0	0	0	NA	0	0	0	NA
Rotated	16 (21)	63 (21)	17 (20)	1.00	31 (18)	25 (29)	21 (20)	0.11
Displaced	7 (9)	42 (14)	3 (4)	0.01	13 (8)	20 (24)	15 (14)	0.002
Agenesis	1 (1)	22 (7)	0	0.002	2 (1)	8 (9)	13 (12)	1E-04[a]
Supernumerary	8 (10)	5 (2)	0	5E-04	6 (3)	1 (1)	5 (5)	0.41
Any anomaly	26 (32)	101 (33)	19 (22)	0.15	47 (27)	35 (41)	41 (38)	0.04
Any anomaly[b]	11 (14)	41 (14)	1 (1)	8E-04	13 (8)	17 (20)	21 (20)	0.003
Left maxilla								
Hypoplasia	1 (1)	13 (4)	2 (2)	0.45	9 (5)	2 (1)	3 (2)	0.50
Microdontia	3 (4)	4 (1)	1 (1)	0.27	2 (1)	1 (1)	4 (4)	0.29
Impacted	0	0	0	NA	0	0	0	NA
Rotated	22 (28)	70 (23)	15 (18)	0.27	45 (26)	19 (22)	26 (24)	0.81
Displaced	3 (4)	59 (19)	5 (6)	4E-05[a]	26 (5)	9 (11)	26 (43)	0.03
Agenesis	2 (3)	37 (12)	0	3E-05[a]	25 (5)	2 (2)	11 (10)	0.006
Supernumerary	6 (8)	7 (2)	0	0.01	1 (<1)	8 (9)	3 (3)	9E-04
Any anomaly	27 (35)	117 (39)	19 (22)	0.02	70 (40)	28 (33)	43 (40)	0.47
Any anomaly[b]	11 (14)	52 (17)	3 (4)	0.002	30 (17)	12 (14)	19 (18)	0.76
Maxilla								
Hypoplasia	2 (2)	20 (7)	2 (2)	0.20	11 (6)	6 (7)	5 (5)	0.75
Microdontia	3 (4)	6 (2)	1 (1)	0.56	3 (2)	2 (2)	4 (4)	0.51
Impacted	0	0	0	NA	0	0	0	NA
Rotated	26 (33)	96 (32)	20 (23)	0.30	55 (32)	30 (35)	33 (31)	0.79
Displaced	10 (13)	81 (27)	6 (7)	3E-05[a]	35 (20)	23 (27)	31 (29)	0.21
Agenesis	3 (4)	52 (17)	0	1E-07[a]	27 (16)	9 (11)	18 (17)	0.47
Supernumerary	13 (17)	12 (4)	0	1E-05[a]	7 (4)	8 (9)	8 (7)	0.20
Any anomaly	35 (45)	151 (50)	23 (27)	8E-04[a]	86 (50)	43 (51)	52 (48)	0.97
Any anomaly[b]	17 (22)	76 (25)	3 (2)	7E-06[a]	39 (23)	23 (27)	27 (26)	0.68
Mandible								
Hypoplasia	0	4 (1)	0	0.61	2 (1)	0	2 (2)	0.69
Microdontia	0	2 (<1)	1 (1)	0.73	1 (<1)	0	1 (<1)	1.00
Impacted	0	3 (<1)	0	1.00	1 (<1)	0	1 (<1)	1.00
Rotated	15 (19)	68 (22)	25 (29)	0.27	37 (22)	21 (25)	22 (21)	0.77
Displaced	1 (1)	10 (3)	3 (4)	0.73	6 (3)	3 (4)	2 (2)	0.79
Agenesis	0	1 (<1)	0	1.00	0	0	1 (<1)	0.53
Supernumerary	0	2 (<1)	1 (1)	0.73	1 (<1)	0	0	1.00
Any anomaly	16 (20)	78 (26)	26 (31)	0.33	31 (18)	17 (20)	20 (19)	0.91
Any anomaly[b]	0	12 (4)	2 (2)	0.22	5 (3)	0	6 (6)	0.08

CL, cleft lip; CLP, cleft lip and palate; CP, cleft palate; NA, not applicable.
[a]Indicates significance ($P < 1.5E-04$).
[b]Any anomaly without malposition (displacement and rotation).

Appendix Table 6. Case Probands: Permanent Dentition, Cleft Type, and Laterality.

	Cleft Type, *n* (%)				Laterality of Cleft (CL or CLP), *n* (%)			
	CL (*n* = 95, 19%)	CLP (*n* = 336, 68%)	CP (*n* = 66, 13%)	*P* Value	Left Cleft (*n* = 178)	Right Cleft (*n* = 100)	Both Sides (*n* = 125)	*P* Value
Right maxilla								
Hypoplasia	2 (2)	32 (10)	0	0.004	6 (4)	11 (11)	16 (13)	0.004
Microdontia	4 (4)	18 (5)	1 (2)	0.52	3 (2)	9 (9)	8 (6)	0.01
Impacted	0	15 (4)	1 (2)	0.06	4 (2)	5 (5)	4 (3)	0.42
Rotated	51 (54)	151 (45)	27 (41)	0.21	78 (44)	48 (48)	54 (43)	0.76
Displaced	20 (21)	107 (32)	18 (27)	0.12	42 (23)	38 (38)	33 (26)	0.04
Agenesis	11 (12)	101 (30)	0	5E-11[a]	30 (17)	35 (35)	39 (31)	9E-04
Supernumerary	5 (5)	4 (1)	0	0.03	8 (4)	0	0	0.005
Any anomaly	58 (61)	218 (65)	32 (48)	0.04	105 (59)	67 (67)	80 (64)	0.38
Any anomaly[b]	20 (21)	142 (42)	2 (3)	1E-12[a]	46 (26)	50 (50)	55 (44)	6E-05[a]
Left maxilla								
Hypoplasia	6 (6)	36 (11)	1 (2)	0.03	21 (12)	4 (4)	16 (13)	0.05
Microdontia	10 (11)	24 (7)	2 (3)	0.20	16 (9)	3 (3)	10 (8)	0.16
Impacted	1 (1)	15 (4)	1 (2)	0.25	7 (4)	1 (1)	3 (2)	0.36
Rotated	57 (60)	158 (47)	29 (44)	0.06	93 (52)	50 (50)	51 (41)	0.13
Displaced	21 (22)	124 (37)	14 (21)	0.003	67 (38)	24 (24)	36 (29)	0.05
Agenesis	12 (13)	117 (35)	0	2E-13[a]	63 (35)	18 (18)	38 (30)	0.008
Supernumerary	1 (1)	6 (2)	0	0.85	1 (<1)	1 (1)	3 (2)	0.45
Any anomaly	65 (68)	228 (68)	31 (47)	0.005	133 (53)	57 (57)	77 (48)	0.004
Any anomaly[b]	26 (27)	161 (48)	4 (6)	2E-12[a]	89 (50)	25 (25)	56 (45)	2E-04
Maxilla								
Hypoplasia	8 (8)	54 (16)	1 (1)	7E-04	25 (4)	12 (12)	23 (18)	0.38
Microdontia	12 (13)	35 (10)	2 (3)	0.08	18 (10)	10 (10)	13 (10)	1.00
Impacted	1 (1)	26 (8)	2 (3)	0.02	10 (6)	6 (6)	5 (4)	0.78
Rotated	65 (68)	183 (54)	32 (48)	0.02	104 (58)	56 (56)	64 (40)	0.46
Displaced	31 (32)	152 (45)	23 (35)	0.04	75 (43)	42 (42)	45 (36)	0.48
Agenesis	20 (21)	160 (48)	0	6E-19[a]	73 (41)	41 (41)	53 (42)	0.97
Supernumerary	6 (6)	10 (3)	0	0.08	9 (5)	1 (1)	3 (2)	0.18
Any anomaly	73 (77)	258 (77)	35 (53)	5E-04	143 (80)	73 (73)	89 (71)	0.15
Any anomaly[b]	37 (40)	209 (62)	5 (8)	7E-18[a]	102 (57)	56 (56)	70 (56)	0.97
Mandible								
Hypoplasia	5 (5)	6 (2)	1 (2)	0.16	5 (3)	3 (3)	2 (1)	0.78
Microdontia	0	1 (<1)	0	1.00	0	1 (1)	0	0.25
Impacted	0	4 (1)	2 (3)	0.20	1 (<1)	1 (1)	1 (<1)	11.00
Rotated	68 (72)	198 (59)	39 (59)	0.07	115 (55)	60 (60)	68 (54)	0.21
Displaced	25 (26)	54 (16)	11 (17)	0.08	29 (16)	24 (24)	14 (11)	0.04
Agenesis	5 (5)	13 (4)	1 (2)	0.48	8 (4)	3 (3)	7 (6)	0.68
Supernumerary	0	2 (<1)	0	1.00	1 (<1)	0	1 (<1)	1.00
Any anomaly	73 (77)	210 (63)	41 (62)	0.03	121 (68)	67 (65)	72 (58)	0.15
Any anomaly[b]	10 (11)	24 (7)	4 (6)	0.48	15 (8)	8 (8)	9 (7)	0.97

CL, cleft lip; CLP, cleft lip and palate; CP, cleft palate.
[a]Indicates significance ($P < 1.5E-04$).
[b]Any anomaly without malposition (displacement and rotation).

OFC Dental Phenotype Part 2 Intra-Oral Photos

4106

Recorded by
Initials

Letters Numbers
Study ID

mm dd yyyy
Date / /

Number Number
Individual ID –

Overall Photo Quality

○ Poor
○ Good

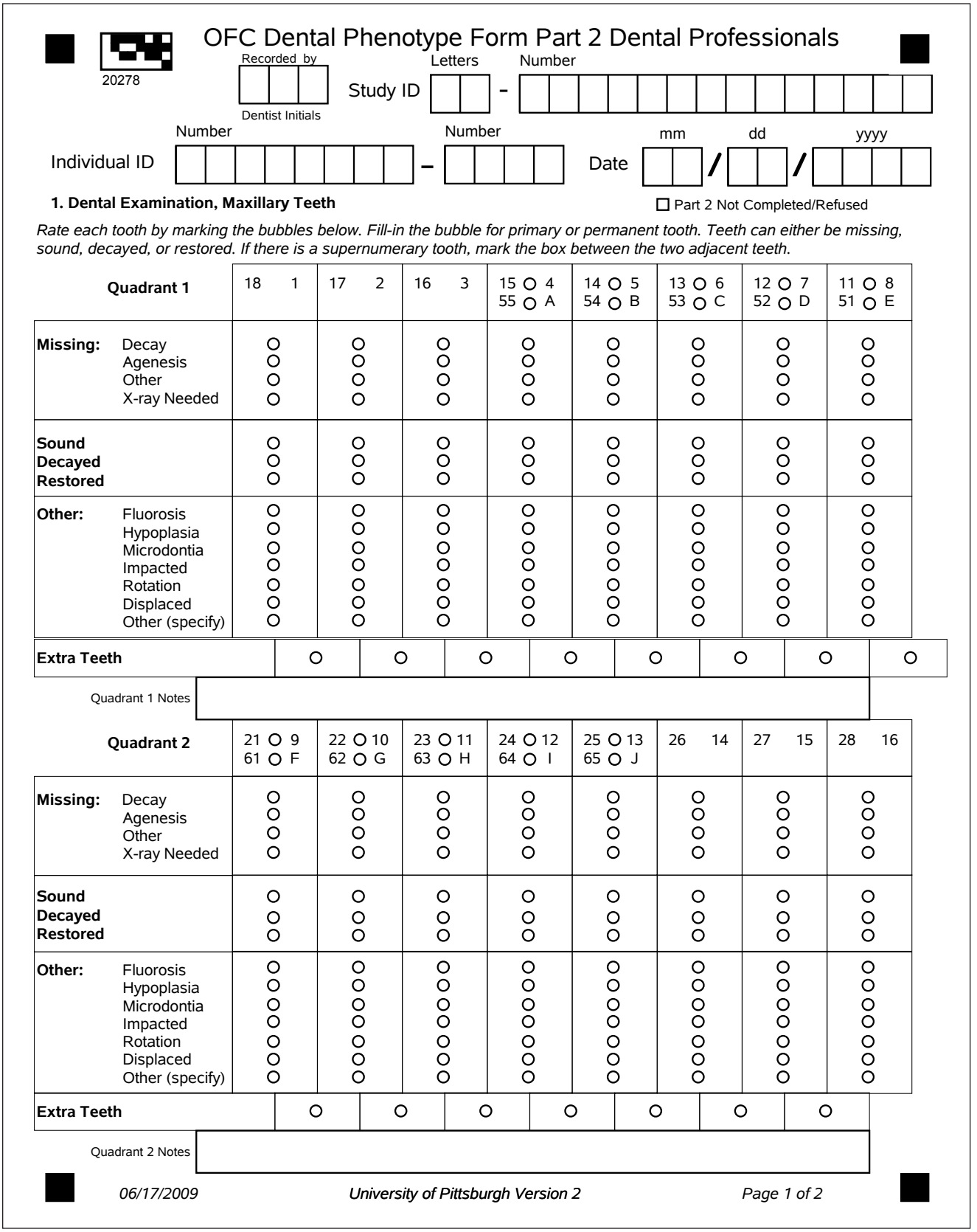
1. Dental Examination, Maxillary Teeth

Rate each tooth by marking the bubbles below. Each tooth should have an entry. Fill-in the bubble for primary or permanent tooth. Teeth can either be missing or present. If there is space or a supernumerary tooth, mark the box between the two adjacent teeth.

Quadrant 1	18 1	17 2	16 3	15 ○ 4 55 ○ A	14 ○ 5 54 ○ B	13 ○ 6 53 ○ C	12 ○ 7 52 ○ D	11 ○ 8 51 ○ E
Missing: Agenesis	○	○	○	○	○	○	○	○
Other	○	○	○	○	○	○	○	○
Present	○	○	○	○	○	○	○	○
Present Status:								
Full coverage (crown)	○	○	○	○	○	○	○	○
Partial coverage (onlay, cusp replacement, veneers)	○	○	○	○	○	○	○	○
Filling (amalgam, composite)	○	○	○	○	○	○	○	○
Gross decay	○	○	○	○	○	○	○	○
Attrition more than 2/3 of the clinical crown	○	○	○	○	○	○	○	○
If present:								
Fluorosis	○	○	○	○	○	○	○	○
Hypoplasia	○	○	○	○	○	○	○	○
Hypocalcification	○	○	○	○	○	○	○	○
Microdontia	○	○	○	○	○	○	○	○
Impacted	○	○	○	○	○	○	○	○
Rotation	○	○	○	○	○	○	○	○
Displaced	○	○	○	○	○	○	○	○
Mammalons	○	○	○	○	○	○	○	○
Incisal Fissures	○	○	○	○	○	○	○	○
Other (specify below)	○	○	○	○	○	○	○	○
Confidence: Low	○	○	○	○	○	○	○	○
High	○	○	○	○	○	○	○	○
Extra Teeth	○	○	○	○	○	○	○	○
Space Between Teeth	○	○	○	○	○	○	○	○

Quadrant 1 Notes

Appendix Figure 1. Intraoral photograph evaluation form.



OFC Dental Phenotype Form Part 2 Dental Professionals

20278

Recorded by
Dentist Initials

Study ID Letters – Number

Individual ID Number – Number

Date mm / dd / yyyy

1. Dental Examination, Maxillary Teeth

☐ Part 2 Not Completed/Refused

Rate each tooth by marking the bubbles below. Fill-in the bubble for primary or permanent tooth. Teeth can either be missing, sound, decayed, or restored. If there is a supernumerary tooth, mark the box between the two adjacent teeth.

		Quadrant 1							
		18 1	17 2	16 3	15 4 / 55 A	14 5 / 54 B	13 6 / 53 C	12 7 / 52 D	11 8 / 51 E
Missing:	Decay	○	○	○	○	○	○	○	○
	Agenesis	○	○	○	○	○	○	○	○
	Other	○	○	○	○	○	○	○	○
	X-ray Needed	○	○	○	○	○	○	○	○
Sound		○	○	○	○	○	○	○	○
Decayed		○	○	○	○	○	○	○	○
Restored		○	○	○	○	○	○	○	○
Other:	Fluorosis	○	○	○	○	○	○	○	○
	Hypoplasia	○	○	○	○	○	○	○	○
	Microdontia	○	○	○	○	○	○	○	○
	Impacted	○	○	○	○	○	○	○	○
	Rotation	○	○	○	○	○	○	○	○
	Displaced	○	○	○	○	○	○	○	○
	Other (specify)	○	○	○	○	○	○	○	○
Extra Teeth		○	○	○	○	○	○	○	○

Quadrant 1 Notes

		Quadrant 2							
		21 9 / 61 F	22 10 / 62 G	23 11 / 63 H	24 12 / 64 I	25 13 / 65 J	26 14	27 15	28 16
Missing:	Decay	○	○	○	○	○	○	○	○
	Agenesis	○	○	○	○	○	○	○	○
	Other	○	○	○	○	○	○	○	○
	X-ray Needed	○	○	○	○	○	○	○	○
Sound		○	○	○	○	○	○	○	○
Decayed		○	○	○	○	○	○	○	○
Restored		○	○	○	○	○	○	○	○
Other:	Fluorosis	○	○	○	○	○	○	○	○
	Hypoplasia	○	○	○	○	○	○	○	○
	Microdontia	○	○	○	○	○	○	○	○
	Impacted	○	○	○	○	○	○	○	○
	Rotation	○	○	○	○	○	○	○	○
	Displaced	○	○	○	○	○	○	○	○
	Other (specify)	○	○	○	○	○	○	○	○
Extra Teeth		○	○	○	○	○	○	○	

Quadrant 2 Notes

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Appendix Figure 2. In-person dental exam form.