Examining Diagnostic Trends and Establishing Diagnostic Criteria for Dental Eruption Disorders

Stephanie Golubic Rhoads, DMD, MBE

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Approved by:

Sylvia A. Frazier-Bowers, DDS, PhD

William R. Proffit, DDS, MS, PhD

Lucia H. Cevidanes, DDS, MS, PhD

J. Timothy Wright, DDS, MS

ABSTRACT

STEPHANIE GOLUBIC RHOADS: Examining Diagnostic Trends and Establishing Diagnostic Criteria for Dental Eruption Disorders
(Under the direction of Dr. Sylvia A. Frazier-Bowers)

Objectives: Eruption disorders are frequently misdiagnosed. Confidence and diagnostic accuracy of Mechanical Failure of Eruption (MFE), ankylosis, and Primary Failure of Eruption (PFE) were assessed and a diagnostic rubric was established based on genotype:phenotype correlations. **Methods:** In a nationwide survey AAO and AAPD members, participants diagnosed 15 cases of verified eruption disorders. **Results:** The diagnostic accuracies of MFE (61%), ankylosis (42%), and PFE (33%) were significantly different (P<.0001). The percentages of participants reporting confidence in diagnosing MFE, ankylosis, and PFE were 98%, 87%, and 75% respectively. Orthodontists were more accurate than pediatric dentists (P<.0001). In our genotype:phenotype study of 64 individuals, 100% with a mutation in *PTH1R*, and 93% of all PFE individuals exhibited ≥ one infraoccluded permanent first molar. **Conclusions:** Orthodontists and pediatric dentists over-estimate their diagnostic ability for eruption disorders. To improve diagnosis, we have established that an infraoccluded, supracrestal first molar is a hallmark feature of PFE.

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Establishing the Diagnostic Criteria for Eruption Disorders Based on Genetic and Clinical Data

1. INTRODUCTION

Eruption disorders pose a challenge for both pediatric dentists and orthodontists, in diagnosis, in treatment planning, and execution of treatment mechanics. While relatively rare, these alterations to normal eruption patterns can pose a significant burden to a practitioner seeking to best manage such a case and limit the resulting negative side effects.

There are three main categories of eruption disorders. Mechanical Failure of Eruption (MFE) is described as the failure of a tooth to erupt due to a physical obstruction of its eruption pathway, such as arch length discrepancy, pathology, or a supernumerary tooth.[1, 2] Ankylosis is defined as the fusion of the cementum on the root of the tooth to bone, eliminating the periodontal ligament space.[2, 3] Finally, Primary Failure or Eruption (PFE) is described as a failure of the eruption mechanism itself,[4] with a clear eruption pathway.[5] PFE presents as infra-occlusion of the affected teeth resulting in a posterior open bite malocclusion. While each type of eruption disorder, whether Mechanical Failure of Eruption (MFE), ankylosis, or Primary Failure of Eruption (PFE), requires careful treatment planning and treatment options that are both mechanically and technically difficult, the accurate diagnosis of these disorders is the first and most critical step in treating patients with these anomalies. These eruption disorders often appear clinically similar and misdiagnosis can lead to negative treatment outcomes and frustration by both the practitioner and patient.

In the first paper, *Accuracy and Confidence Level of Pediatric Dentists and Orthodontists in the Diagnosis of Eruption Disorders*, we sought to test the hypotheses that the diagnostic accuracy and the reported diagnostic confidence for MFE, ankylosis, and PFE are low and equal overall and that there is no demographic characteristic that is associated with improved accuracy or confidence. Our specific aims were to: 1) determine the accuracy of ED diagnosis with current records by orthodontists and pediatric dentists and 2) assess the confidence level of participants in diagnosing and treating eruption disorders and compare perceived confidence with actual accuracy.

The purpose of our second paper, *Establishing the Diagnostic Criteria for Eruption Disorders Based on Genetic and Clinical Data*, was to establish definitive criteria to differentiate and diagnose eruption disorders, specifically Primary Failure of Eruption (PFE) and ankylosis. The combination of objective genetic information and clinical data from affected individuals was utilized to establish a genotype:phenotype correlation for PFE and by extension, an objective diagnosis [ie determined by associating clinical (phenotypic) features with genetic (genotypic) analysis]. Therefore, our specific aims were to: 1) compare clinical features identified in a genetically characterized PFE sample set to a broader dataset of patients diagnosed with PFE based on clinical parameters only, 2) compare features of the PFE sample set to features identified in a small ankylosis sample, and 3) identify hallmark developmental and morphological features of PFE, providing clinicians with greater diagnostic certainty and subsequent improved clinical management.

Through these two investigations, we hoped to gain insight into the diagnostic patterns of practitioners when faced with eruption disorders, assess the significance of the

potential diagnostic deficiencies, and contribute to the improvement of the diagnostic rubric for eruption disorders.

Accuracy and Confidence Level of Pediatric Dentists and Orthodontists in the Diagnosis of Dental Eruption Disorders

2.1 ABSTRACT

Introduction: Eruption disorders are often misdiagnosed and clinically mismanaged. **Methods:** A nationwide survey was used to assess confidence and diagnostic accuracy for Mechanical Failure of Eruption (MFE), ankylosis, and Primary Failure of Eruption (PFE). AAO and AAPD members (11% response rate) diagnosed cases of eruption disorders previously verified via genetic analysis or treatment history. **Results:** The mean diagnostic accuracies were 61% for MFE, 42% for ankylosis, and 33% for PFE. Diagnostic accuracies were statistically different (P<.0001). Participants reporting to be "confident" or "very confident" in diagnosing PFE, ankylosis, and MFE were 98%, 87%, and 75% respectively. Orthodontists were more accurate than pediatric dentists (P<.0001). Residents and recent graduates were more accurate in diagnosing MFE and PFE than experienced clinicians. **Conclusions:** The low diagnostic accuracy of eruption disorders, particularly PFE, indicates a great need for improved diagnostic tools and updated education for practitioners. Accuracy may be a reflection of exposure to the disorder in practice, opportunity to observe treatment results, and up-to-date education on eruption disorder research. The development of enhanced diagnostic techniques for clinical distinctions among eruption disorders should be sought and emphasis must be placed on family history and history of orofacial trauma that may contribute to the presentation.

2.2 INTRODUCTION

A comprehensive understanding of normal dental development and tooth eruption are fundamental to pediatric dental and orthodontic practices. The dental practitioner must monitor the developing dentition for any deviations from the normal expected eruption sequence, timing, and pathway. Alterations in the molecular pathways underlying normal eruption can result in an eruption disorder;[1, 6] early detection and management of these situations provides the best chance at a successful treatment outcome. Misdiagnosis can lead to suboptimal treatment choices, which are often detrimental to the overall treatment outcome.

A critical step in diagnosing eruption disorders lies in initially determining its broad etiology. Eruption disorders may manifest as a part of a dental syndrome, such as Cleidocranial Dysplasia or present in the absence of obvious systemic disease.[1] It is critical that diagnosis of these distinct eruption disorders, which can be linked to a specific etiology, be differentiated since each commands a different treatment modality. Major examples of non-syndromic eruption disorders include three distinct, yet clinically similar entities: Mechanical Failure of Eruption (MFE), ankylosis, and Primary Failure of Eruption (PFE). MFE is described as the failure of a tooth to erupt due to a mechanical obstruction of its eruption pathway, such as a cyst, another tooth, or soft tissue pressure from a lateral tongue thrust or thumb habit.[1, 2] Once diagnosed, this can often be treated successfully with the removal of the mechanical blockage.

Ankylosis occurs when the cementum on the root of the tooth fuses to the bone, eliminating the periodontal ligament space.[2, 3] Ankylosis is most often diagnosed through radiographic examination based largely on the absence of a visible periodontal ligament

space but may also be based on lack of clinically-appreciable physiologic mobility and a sharp sound noted upon percussion of the affected tooth.[7] However, any one of these diagnostic criteria can easily be misinterpreted.[1] Particularly when evaluating a two dimensional radiograph, the appearance of PDL fusing to bone can be overstated or completely undetected. To date, there are no scientific studies evaluating the ability to diagnose ankylosis using a Cone Beam CT scan of any size or resolution. Large field of view CBCT scans, have an average resolution of 0.3-0.4 voxels [8] which appears inadequate to evaluate whether a fusion of cementum and bone exists. The important goal in distinguishing ankylosis from other eruption problems is that unlike PFE, the ankylosed tooth can be extracted and the remaining teeth will likely be responsive to orthodontic treatment.[3]

Finally, first described by Proffit and Vig, PFE is defined as a failure of the eruption mechanism itself,[4] which cannot be explained by a syndrome or a mechanical interference.[5] A hallmark of PFE is that these teeth do not respond favorably to orthodontic traction and, in fact, attempted orthodontic treatment often results in a worsened malocclusion and increased open bite due to intrusion of adjacent teeth.[1, 6, 9] PFE presents as infra-occlusion of the affected teeth resulting in a posterior open bite malocclusion. Typically, all teeth distal to the most mesially affected tooth also fail to erupt. A diagnosis of PFE is critical as it dictates that treatment with continuous archwires should be avoided. Some successful treatment has been reported by multiple individual tooth osteotomies or selective individual tooth extractions followed by implant restorations to restore a functional occlusion.[5]

Our current understanding of eruption disorders has been strengthened by human genetic studies which have highlighted mutations in parathyroid hormone receptor 1 (*PTH1R*) as a causative factor for familial cases of PFE.[1, 5, 6, 9] A study of nine family members revealed *PTH1R* as an autosomal dominant mutation associated with a PFE phenotype. All family members with PFE had a mutation in the *PTH1R* gene in this study, while those without PFE lacked this mutation.[5] The *PTH1R* mutation that is associated with PFE results in the formation of a nonfunctional, truncated protein. Haploinsufficiency appears to be the underlying cause of PFE, in which insufficient amounts of functional receptors are formed from the unaffected allele. Since non-syndromic PFE patients do not exhibit any peripheral signs of the disease, it may be hypothesized that this mutation causes a disruption confined to alveolar bone in the epithelial and mesenchymal signaling pathways that are necessary for normal bone resorption and apposition in tooth eruption.[5, 9] This information implicates genetic mutations in *PTH1R* as diagnostic of PFE and is important in the context that many patients diagnosed with PFE by the presence of a confirmed mutation in *PTH1R* were initially misdiagnosed with ankylosis.[1, 6] Additionally, PFE and ankylosis preferentially affect molars and posterior teeth, making them even more difficult to distinguish from one another.[6]

The treatment decisions and, therefore, the success of the chosen treatment, rely heavily on accurate diagnosis of eruption disorders. However, eruption disorders often exhibit similar radiographic and clinical presentations, resulting in frequent misdiagnosis. Due to the lack of distinct diagnostic criteria, many clinicians may be less confident or proficient in diagnosing and treating eruption disorders. We propose here to determine

the practitioner's level of confidence in eruption disorder diagnosis, as well as the actual accuracy of diagnosis in order to assess the significance of this problem in a typical practice. This logical first step is essential to determine the potential need to improve current diagnostic methods to distinguish these disorders and to reveal factors that may facilitate a more accurate diagnosis. Further, the establishment of distinct diagnostic criteria which can be obtained through appropriate records and tests will enable confident diagnoses and the subsequent implementation of more effective treatment options for each eruption disorder. Gaining any additional information about these eruption disorders, such as reported diagnostic prevalence, is helpful in characterizing the disorders and potentially offering insight into practitioner familiarity with each diagnosis.

Our study sought to test the hypotheses that the diagnostic accuracy and the reported diagnostic confidence for MFE, ankylosis, and PFE are low and equal overall and that improved accuracy or confidence is not explained by demographic characteristics.

2.3 MATERIALS AND METHODS

Survey Tool

This project has been reviewed and approved by the University of North Carolina Institutional Review Board (study number 11-1897). A nationwide cross-sectional electronic survey was developed and conducted utilizing a survey developed in Qualtrics software (Provo, UT). Questions were multiple choice or Likert-type scale. The participants were presented with unidentified cases of eruption disorders including PFE, MFE, and ankylosis (5 cases of each in random order). Intraoral photographs, a panoramic radiograph, and some pertinent patient information, such as age, gender, and history of orofacial trauma were provided. Those representative cases were selected as follows: for PFE prior verification was made through genetic analysis i.e. a mutation in the *PTH1R* gene; ankylosis was based on eruption disorders that were treated successfully with extraction of the affected tooth and orthodontic treatment of the remaining teeth; MFE was based on individuals successfully treated with the removal of the mechanical interference and orthodontic treatment of the entire dentition. The participant was asked to diagnose each case from a list of answer options based on his or her own clinical acumen. Participants were also asked to provide demographics, including their gender, specialty, number of years since graduating from the most recent specialty program, practice setting, and practice size. Confidence scales (5 point scales) were used to assess the participant's level of confidence in diagnosing and treating each type of eruption disorder with a variety of records. Finally, the participant was asked to estimate the number of cases that he or she diagnosed with PFE, MFE, and ankylosis in his or her practice during the past year.

A pilot study was completed first, in which ten residents and faculty in the orthodontic and pediatric dentistry departments of the University of North Carolina School of Dentistry completed the survey to evaluate the effectiveness of the survey tool. The survey was altered accordingly based on the feedback provided.

The electronic survey was sent via email to all active, affiliate, academic, student, and service members of the American Association of Orthodontists (AAO) (N=10,203) and all active members of the American Academy of Pediatric Dentists (AAPD) (N=5,639). Surveys were sent directly by the AAO and the investigators sent emails to members of AAPD directly. No identifying information was linked to the responses. This survey was re-sent with a reminder email to both AAO and AAPD members 3 weeks after the initial contact in hopes of increasing the response rate.

Inclusion criteria included active members of AAO or AAPD. Exclusion Criteria include respondent refusal and non-active members of AAO or AAPD. Student, resident, and retired members will be excluded from the questions seeking information about prevalence. Based upon number of respondents, all retired participants were excluded.

Statistical Analysis

Our statistical model makes the assumption that returned surveys are representative of a random sampling throughout the country. There were 1144 respondents included in the statistical analysis, after excluding those who did not answer all 15 case questions, as well as retired participants. Based upon the distribution of responses, practice settings of “hospital,” “subsidized healthcare plan,” and “other” were all grouped together as “other.” The purpose of the analysis is to assess whether the

respondent's accuracy or confidence is affected by the type of problem (MFE, Ankylosis, PFE) adjusting for specialty, practice setting, and years since graduation.

The outcome variables of accuracy and confidence were treated as continuous variables. Accuracy was calculated as the number of correct responses to 5 scenarios presented for each type of problem. Confidence was the Likert-like score associated with the confidence in diagnosing each type of problem given clinical exam + all necessary radiographs. Since scores for all three types of problem were available from each respondent, the dataset was viewed as a correlated dataset. Linear mixed models were used to analyze accuracy and confidence, separately. Unstructured covariance structure between MFE, Ankylosis, and PFE was assumed. Although confidence scores were skewed, mixed models are robust for non-normal data and a residual analysis supported the use of the linear mixed model. All analyses were conducted using SAS 9.3.

2.4 RESULTS

The survey was delivered by the AAO and AAPD to 10,203 and 5,639 individuals respectively. A total of 1,723 individuals participated in the survey, with 1,217 completing all 15 cases presented in the survey. This equates to an overall response rate of 10.8%, with 7.7% completing all case questions. According to unpublished data from the Loyalty Research Center, an AAO research partner, the average response rates for surveys sent by the AAO to all members is between 10-15%. Our response rate falls within this average range, although it is on the lower end possibly due to the length and to the level of engagement required to complete this survey. Of the total participants included in the statistical analyses (1144), 43% were orthodontists and 57% were pediatric dentists. The demographics of participants are displayed in Table 1.

Diagnostic Accuracy

We first analyzed the overall accuracy in diagnosis for MFE, PFE, and ankylosis with the given records to determine whether the overall accuracies were high or low and if there was a difference among the means based upon the type of eruption disorder. The unadjusted mean score for MFE was 3.04 out of 5 total cases (Lower CI 2.97, Upper CI 3.10). This equates to 61% correct. The mean score for ankylosis was 2.12 (Lower CI 2.05, Upper CI 2.18), or 42% correct. The mean score for PFE was 1.66 (Lower CI 1.59, Upper CI 1.74), or 33% correct Table 2). There is a statistically significant difference ($P<.0001$) in the accuracy of diagnosis between each pair of eruption disorders, even after adjusting for specialty, practice setting, and years since graduation (Table 3).

The results of a linear mixed model revealed that there is a statistically significant difference in the accuracy of eruption disorder diagnosis between orthodontists and pediatric dentists, with orthodontists being more accurate ($F=34.9$, $P<.0001$) (Table 4). Specifically, orthodontists are significantly more accurate in the diagnosis of PFE and MFE ($P=.0036$, $<.0001$), but no statistical difference exists in the diagnosis of ankylosis (Table 5). There is no overall statistical difference in the accuracy of eruption disorder diagnosis as a result of practice setting nor was the pattern of response for all three types of problems affected by practice setting ($P=0.77$). Additionally, the average accuracy was not significantly different among the three categories of practice setting ($P=0.49$). There was no statistical difference in overall accuracy as a result of years since graduation ($P=0.63$). However, the pattern of responses was not the same for the categories used to characterize years since graduation ($P<0.002$) when type of eruption disorder was considered as a variable. Those residents and clinicians in practice less than 10 years were more accurate than those in practice >20 years with respect to MFE and PFE ($P=.0036$, $.087$). More experienced clinicians who have been in practice >20 years were most accurate in ankylosis diagnosis ($P=.0027$). Table 6 lists all average accuracies for each category of participant and for each eruption disorder.

Participant Confidence

When asked to estimate their confidence level in diagnosing MFE, ankylosis, and PFE, the highest median confidence levels were reported when practitioners were given the option of a clinical exam plus all necessary radiographs. The reported mean confidence levels (out of 5) with clinical exam and all necessary radiographs were 4.33

(Lower CI 4.29, Upper CI 4.38) for MFE, 3.78 (Lower CI 3.72, Upper CI 3.85) for ankylosis, and 3.14 (Lower CI 3.08, Upper CI 3.21) for PFE (Table 2). There was a statistically significant difference between the average estimated confidence of each pair of eruption disorder s ($P<.0001$), even after adjusting for specialty, practice setting, and years since graduation. (Table 3, Fig 1)

There is also a statistically significant difference in the reported confidence in eruption disorder diagnosis based upon specialty ($F=16.6$, $P<.0001$ with pediatric dentists expressing greater confidence than orthodontists for ankylosis and PFE), practice setting ($F=2.73$, $P=.04$ with residents expressing significantly less confidence than both academic faculty and private practice + other in MFE diagnosis), and years since graduation ($F=10.65$, $P=.001$ with those in practice <10 years exhibiting less confidence than those in practice >20 years for MFE and less confidence than those in practice 11-20 years for both MFE and PFE). Overall confidence increased as years since graduation increased (Table 4).

The reported confidence levels in treating each eruption disorder were somewhat lower than the confidence of diagnosis. Participants reporting to be “confident” or “very confident” in the treatment of eruption disorders are as follows: 90% for MFE, 69% for ankylosis, and 39% for PFE.

Accuracy versus Confidence

There is a large disparity between the relative confidence in diagnosis and the actual diagnostic accuracy. Ninety-eight percent of participants reported that they were

"confident" or "very confident" in the diagnosis of MFE. However, only 35% of the participants diagnosed 4 or 5 of the cases correctly and only 8% of participants diagnosed all 5 cases correctly. When asked to estimate their confidence level in the diagnosis of ankylosis, 87% of participants responded "confident" or "very confident." This is in contrast to 11% of participants who correctly diagnosed 4 or 5 cases correctly and only 1.5% who were correct in all 5 diagnoses of ankylosis. Seventy-five percent of participants responded that they were "confident" or "very confident" in PFE diagnosis. A total of 10% of participants correctly diagnosed 4 or 5 cases, while 0.26% were correct in 100% of PFE diagnoses. (Figure 2)

Estimated Prevalence

The final aim of this study was to estimate the percentage of a clinician's practice that is composed of patients with each eruption disorder. This question was not answered by those in residency or those who were retired. This was calculated by dividing the estimated number of each disorder seen in the practice per year by the number of new patient exams per year. This evaluation revealed that 0.73% (SD 0.36) of the patients seen in a typical practice exhibit MFE, 0.63% (SD 0.37) exhibit ankylosis, and 0.37% (SD 0.28) exhibit PFE.

2.5 DISCUSSION

Previous studies have shown that PFE is frequently misdiagnosed as ankylosis,[1, 6] resulting in improper treatment plans for the patient. This can lead to great frustration for the treating orthodontist, referring pediatric dentist, and for the patient who is experiencing a worsened malocclusion and extended treatment time. It is important to improve the ability of clinicians to diagnose eruption disorders accurately. The first logical step in this regime is to determine the current diagnostic accuracy of practicing clinicians, as well as their perceived confidence level in the diagnosis of these disorders.

Our study revealed that diagnostic accuracy of eruption disorders is overall very low for MFE (61% correct), ankylosis (42% correct), and PFE (33% correct). Since the participant was given three diagnostic choices for each case, this indicates that diagnostic accuracy for PFE is no greater than chance. Therefore, clinicians are unlikely to reliably diagnose PFE accurately in practice. The percentage of cases accurately diagnosed in a busy practice setting is likely lower than 33% because the eruption disorder may go completely unidentified survey, whereas the participants were informed that an eruption disorder existed in this survey. For comparison purposes, the percentage of occlusal caries accurately diagnosed via visual inspection ranges from 46-92% correct[10-12]. Interestingly, in all three studies, dental students diagnosed occlusal caries with the highest sensitivity when compared to faculty, recent graduates, and more experienced practitioners.

The accuracies among the three eruption disorders are statistically different from one another. There may be many explanations for this outcome. The most intuitive rationale is that the difference in accuracy is related to familiarity with the disorders and

frequency that each disorder is seen in practice. Our estimates indicate that MFE is seen most often in practice (0.73%) followed by ankylosis (0.63%) and then PFE (0.37%). It must be noted that these numbers represent estimation within the population of patients who seek treatment at a pediatric dental office or orthodontic office only. There may be many cases of each eruption disorder in the general population who never seek treatment in either type of practice and, therefore, are not included in our estimate. Alternatively, more of these patients with severe malocclusions may seek treatment. This group who seeks treatment may represent a higher percentage of people with eruption disorders than exists in the general population. Additionally, these are estimates offered by the participating clinicians and are not numbers verified by chart reviews. Therefore, the percentages in this study provide a rough estimate of what one might expect to see as a percentage of the average practice and also to give an indication of which disorder is seen the most and least. Existing data reports that failure of eruption of first and second molars is seen about 1.5% of the time in a normal population.[13] Our estimates are similar to this report because they did not differentiate between ankylosis and PFE in their study. Any differences may also be a consequence of the factors noted above. We feel confident, however, that MFE is seen much more frequently than PFE, for example and that this mere aspect of frequency of exposure to each eruption disorder is reflected in the accuracy with which each is diagnosed.

Additionally, MFE often has an obstruction that is notable either clinically or radiographically that can be used to explain the failure of the tooth to erupt. This is more intuitive than diagnosing ankylosis or PFE, which, to date, are most definitively diagnosed via histological and genetic diagnoses, respectively.

The fact that orthodontists diagnose eruption disorders more accurately than pediatric dentists most likely stems from the fact that orthodontists are faced with treatment of each malocclusion, while pediatric dentists are taxed with the responsibility to refer aberrant eruption patterns accompanied by a suggested diagnosis. Orthodontists have the opportunity to see the results of their treatment decisions based upon that diagnosis. Orthodontists have successfully treated many cases of MFE and therefore understand the presentation to a greater extent. They may have also had more experiences where failed attempts at treatment of ankylosis or PFE resulted in frustration and obstacles, making such cases more memorable. Pediatric dentists often do not have the opportunity to verify their initial diagnosis with treatment results and therefore are less accurate in the diagnosis of eruption disorders.

Interestingly, the reported confidence of participants in the diagnosis of each eruption disorder was very high overall. The estimated confidence levels did decrease in the same order as the accuracy, indicating that practitioners are more confident diagnosing disorders that appear in their practice more frequently and with which they have greater diagnostic accuracy. However, the confidence levels were substantially higher than the actual accuracy for each disorder. (Figure 2) The majority of participants reported that they were “confident” or “very confident” in the diagnosis of each eruption disorder, revealing that they are poorly assessing their diagnostic abilities. This overestimation of diagnostic accuracy may lead practitioners to make confident, yet inaccurate, diagnoses without spending time to thoroughly study the case and exhaust all avenues that may improve the likelihood of making an accurate diagnosis. This can lead to increased possibility of improper treatment modalities and negative consequences to

the patient. Clinicians need to be aware that accuracy of eruption disorder diagnosis is low and extra caution and diligence should be paid to cases such as these.

As expected, confidence increased with years since graduation and residents exhibited the lowest confidence in every situation. However, this increased confidence did not translate to increased diagnostic accuracy. In fact, those in practice longer, exhibiting more confidence, did not diagnose eruption disorders with greater accuracy than current residents. Current residents were actually the most accurate in diagnosis of both PFE and MFE, with those in practice >30 years exhibiting the lowest accuracy. In the diagnosis of ankylosis, however, more experienced clinicians were, in fact, more accurate. This reflects the fact that clinicians do not accurately gage their ability to diagnose eruption disorders. Additionally, while residents and more recent graduates lack the clinical exposure of more experienced practitioners, they are likely receiving more education on eruption disorders, particular PFE, than those who graduated more than 10 years ago. As more information is gathered about eruption disorders, more time is allotted to this topic in residency programs. Therefore, the advantage of more recent education focused on highly researched topics, such as eruption disorders, appears to compensate for the lack of clinical expertise. As new resident classes graduate after receiving a more thorough education about eruption disorders, the hope is that the diagnostic accuracy of this group will improve further with experience and surpass the diagnostic abilities of those veteran clinicians today. With the combination of continually advancing education and research on the topic, and clinical experience, the diagnostic accuracy of eruption disorders should continue to improve over time.

After reviewing the participant responses to each individual case, some generalizations can be made. When studying the responses to the PFE cases, unilateral PFE was diagnosed accurately about 33% of the time, while bilateral cases had a higher percentage correct (about 43%). There was one very mild case PFE that was diagnosed incorrectly by 98% of participants, most of whom diagnosed it as MFE (Figure 3). Therefore, the more subtle and unilateral cases are more likely to be misdiagnosed. However, this mild case exhibited a mutation in *PTH1R* and therefore would result in much worsened occlusion if treated conventionally by orthodontic appliances. This patient underwent genetic analysis due to a confirmed family history of PFE, underscoring the importance of a thorough family history during the initial exam to enhance diagnostic accuracy. But since this genetic analysis was completed after treatment with a continuous archwire, the initial consequence was indeed a significantly worsened lateral open bite.[5] These observations highlight the need for extreme caution in eruption disorder diagnoses, even by those with the most attuned clinical acumen, as well as a need for the development of improved diagnostic techniques to avoid improper treatment.

There was no consistent pattern noted to describe the cases where ankylosis was diagnosed more accurately. However, ankylosis was misdiagnosed as PFE much more frequently than it was misdiagnosed as MFE (in all but one case). Ankylosis diagnosis appears to be inconsistent, and largely inaccurate.

There was also no obvious pattern to determine which MFE cases were diagnosed most inaccurately. However, in the case in which MFE was misdiagnosed 76% of the time (highest percentage of misdiagnosis for any MFE case), most participants diagnosed

the case as PFE. Of note is the observation that there is obvious alveolar bone coverage occlusal to the crown of the affected tooth (Figure 4). Based on recent findings by our team, a supracrestal presentation of affected teeth is a hallmark feature of PFE. Therefore, the tooth without a cleared eruption pathway will not be a tooth affected by PFE (Under review, *AJODO* 2013) (Figure 5).

A limitation of this study was the use of clinical photographs and radiographs alone, without a clinical exam and interview. A clinical exam and interview may help improve the diagnostic ability of many clinicians.

Based upon the low diagnostic accuracy of all eruption disorders, and particularly PFE, there is a great need for improved diagnostic tools and updated education for practitioners in practice. Clinical distinctions between each eruption disorder should be sought and emphasis must be placed on the patient interview to gain insight about family history of eruption disorders or history of dental or facial trauma that may contribute to the presentation of ankylosed teeth, for example. Additionally, as more information is gathered about the cause of each eruption disorder, there may be more opportunity to discern the proper diagnosis based upon patient exam and a greater availability for genetic testing to verify the eruption disorder diagnosis. Genetic analysis to verify PFE may one day become a chairside tool. In the meantime, simple diagnostic distinctions should be sought to prevent misdiagnosis and improper treatment decisions.

2.6 CONCLUSION

1. Diagnostic accuracy of eruption disorders is low with MFE accuracy higher than ankylosis, which is higher than PFE.
2. Diagnostic confidence is much higher than actual accuracy.
3. Diagnostic accuracy of MFE and PFE increased slightly with recent trainees (residents) as compared to seasoned practitioners. Experienced clinicians exhibited greater accuracy in ankylosis diagnosis.
4. Accuracy may be a reflection of the prevalence of the disorder in practice, opportunity to observe the results of attempted treatment of the disorders, and up-to-date education on the most recent advances in eruption disorder research.

Table 2.1: Participant Demographics

	Number (Percent)
Gender	
Male	718 (63%)
Female	420 (37%)
Specialty	
Orthodontist	493 (43%)
Pediatric Dentist	651 (57%)
Primary Practice Setting	
Academic Resident	129 (11%)
Academic Faculty	82 (7%)
Private Practice	861 (76%)
Other	69 (6%)
Years Since Graduation	
Current Resident	129 (11%)
<5 Years	213 (19%)
5-10 Years	146 (13%)
11-20 Years	233 (20%)
21-30 Years	237 (21%)
>30 Years	186 (16%)

Table 2.2: Least square mean and 95%. C.I for accuracy and confidence in the diagnosis of MFE, ankylosis, and PFE.

Outcome	**type**	**Estimate**	**95% C.I.**	
Accuracy	MFE	3.04	2.97	3.10
	Ankylosis	2.12	2.05	2.18
	PFE	1.66	1.59	1.74
Confidence	MFE	4.33	4.29	4.38
	Ankylosis	3.78	3.72	3.85
	PFE	3.14	3.08	3.21

Note: Specialty, practice setting, years since graduation were not adjusted for in this table.

Table 2.3: Pairwise comparison of type for accuracy and confidence based on the model that has four covariates of type, specialty, practice setting, and years since graduation

Outcome	Group 1	Group 2	Diff (Group 1 - Group 2)	SE	t Value	P[#]
Accuracy	Ankylosis	MFE	-0.92	0.05	-18.72	<.0001
		PFE	0.46	0.05	9.02	<.0001
	MFE	PFE	1.38	0.05	29.41	<.0001
Confidence	Ankylosis	MFE	-0.55	0.03	-16.29	<.0001
		PFE	0.64	0.03	19.03	<.0001
	MFE	PFE	1.19	0.04	33.25	<.0001

[#] P values were adjusted by Scheffe's method.

Table 2.4: The results from linear mixed models showing the effect of type of disorder, specialty, practice setting, and years since graduation on overall diagnostic accuracy and confidence

Outcome	Effect	Num DF	Den DF	F Value	P
Accuracy	type	2	1135	454.24	<.0001
	specialty	1	1135	34.9	<.0001
	practice setting	3	1135	0.39	0.7581
	years since graduation	1	1135	1.95	0.1627
Confidence	type	2	1131	554.16	<.0001
	specialty	1	1131	16.61	<.0001
	practice setting	3	1131	2.73	0.0425
	years since graduation	1	1131	10.65	0.0011

Table 2.5: Differences in Accuracy and Confidence based upon type of disorder and specialty, primary practice setting, and years since graduation

Variable	Group 1	Group 2	Type	Accuracy				Confidence			
				Diff (Gr1-Gr2)	SE	t	P	Diff (Gr1-Gr2)	SE	t	P
Specialty	Orthodontist	Pediatric Dentist	Ankylosis	0.01	0.07	0.20	0.8429	-0.58	0.06	-9.38	<.0001*
			MFE	0.19	0.07	2.92	0.0036*	0.43	0.04	10.01	<.0001*
			PFE	0.59	0.07	8.00	<.0001*	-0.32	0.07	-4.83	<.0001*
Practice Setting	Academic Faculty	Academic Resident	Ankylosis	0.09	0.17	0.54	0.5918	0.19	0.15	1.24	0.2161
			MFE	-0.05	0.16	-0.33	0.7388	0.29	0.11	2.72	0.0066*
			PFE	0.06	0.18	0.31	0.7589	0.07	0.16	0.40	0.6870
	Academic Faculty	Private+Other	Ankylosis	0.03	0.13	0.24	0.8136	0.03	0.12	0.26	0.7936
			MFE	0.03	0.13	0.25	0.8024	0.01	0.08	0.17	0.8620
			PFE	0.17	0.14	1.20	0.2303	-0.14	0.13	-1.13	0.2600
	Academic Resident	Private+Other	Ankylosis	-0.06	0.12	-0.51	0.6124	-0.16	0.11	-1.48	0.1379
			MFE	0.08	0.11	0.76	0.4478	-0.27	0.07	-3.71	0.0002*
			PFE	0.12	0.13	0.90	0.3673	-0.21	0.11	-1.84	0.0662
Years Since Graduation	11-20yrs	<10yrs	Ankylosis	0.15	0.09	1.57	0.1158	0.01	0.09	0.16	0.8722
			MFE	-0.11	0.09	-1.17	0.2435	0.15	0.06	2.40	0.0163*
			PFE	-0.12	0.10	-1.12	0.2609	0.26	0.09	2.79	0.0053*
	11-20yrs	>20yrs	Ankylosis	-0.10	0.09	-1.04	0.2990	0.09	0.08	1.02	0.3086
			MFE	0.12	0.09	1.37	0.1696	-0.06	0.06	-1.06	0.2913
			PFE	0.04	0.10	0.35	0.7262	0.12	0.09	1.32	0.1859
	<10yrs	>20yrs	Ankylosis	-0.24	0.08	-3.01	0.0027*	0.07	0.07	0.97	0.3338
			MFE	0.23	0.08	2.92	0.0036*	-0.21	0.05	-4.01	<.0001*
			PFE	0.15	0.09	1.71	0.0878	-0.14	0.08	-1.76	0.0790

* Statistically significant with P<.05

Table 2.6: Mean accuracy

	PFE (Mean/ SD)	Ankylosis(Mean/SD)	MFE (MEan/SD)
Ortho	1.99 / 1.35	2.14 / 1.17	3.14 / 1.11
Pedo	1.41 / 1.14	2.10 / 1.09	2.96 / 1.07
Academic Resident	1.84 / 1.36	1.95 / 0.99	3.22 / 1.11
Academic Faculty	1.78 / 1.31	2.18 / 1.19	3.02 / 1.15
Private Practice	1.63 / 1.26	2.14 / 1.14	3.01 / 1.08
Other	1.61 / 1.14	2.17 / 1.07	2.99 / 1.13
Resident	1.84 / 1.36	1.95 / 0.99	3.22 / 1.11
<5 years ago	1.77 / 1.25	2.04 / 1.08	3.18 / 1.09
5-10 years ago	1.58 / 1.24	1.95 / 1.05	3.02 / 1.10
11-20 years ago	1.61 / 1.26	2.15 / 1.09	3.03 / 1.11
21-30 years ago	1.65 / 1.25	2.23 / 1.18	3.02 / 1.04
>30 years ago	1.56 / 1.28	2.27 / 1.25	2.79 / 1.06

Table 2.7: Mean confidence

	PFE (Mean/ SD)	Ankylosis(Mean/SD)	MFE (MEan/SD)
Ortho	2.96 / 1.18	3.45 / 1.19	4.58 / 0.56
Pedo	3.28 / 1.06	4.04 / 0.89	4.14 / 0.84
Academic Resident	2.86 / 0.86	3.66 / 0.84	3.98 / 0.77
Academic Faculty	3.05 / 1.23	3.83 / 1.16	4.39 / 0.70
Private Practice	3.20 / 1.15	3.78 / 1.11	4.39 / 0.76
Other	3.09 / 1.02	3.94 / 0.82	4.16 / 0.68
Resident	2.86 / 0.86	3.66 / 0.84	3.98 / 0.77
<5 years ago	3.09 / 1.01	3.91 / 0.90	4.22 / 0.74
5-10 years ago	3.09 / 1.11	3.80 / 1.02	4.25 / 0.97
11-20 years ago	3.32 / 1.16	3.84 / 1.10	4.40 / 0.74
21-30 years ago	3.13 / 1.26	3.73 / 1.16	4.47 / 0.70
>30 years ago	3.24 / 1.14	3.72 / 1.25	4.51 / 0.57

Fig. 2.1: Average accuracy and confidence of participants in the diagnosis of PFE, ankylosis, and MFE.

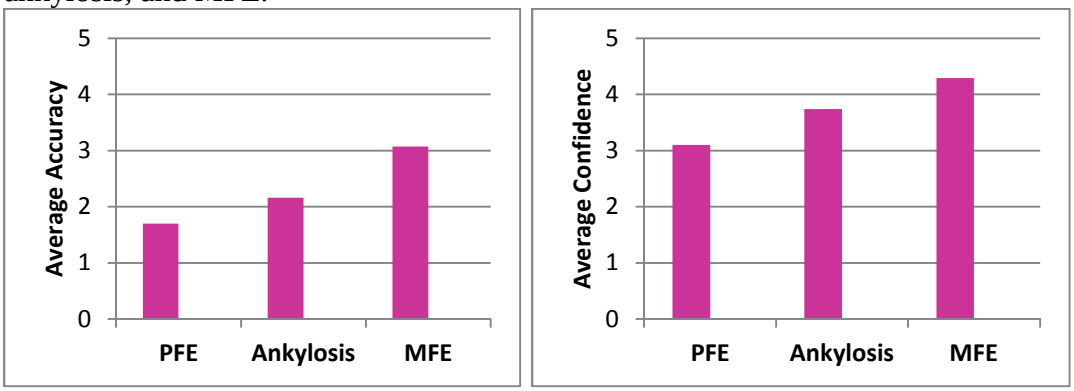


Figure 2.2: Comparison between accuracy and confidence level of participants

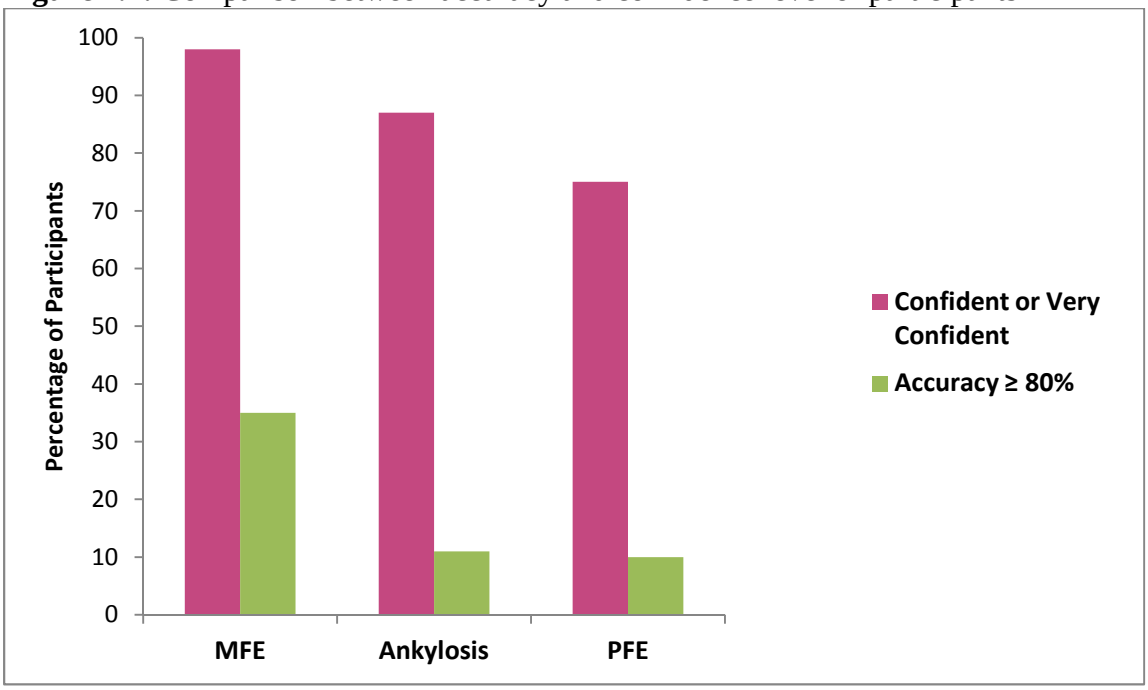


Figure 2.3: Patient exhibiting PFE that is confirmed via genetic analysis to reveal a mutation in *PTH1R*. This case was misdiagnosed by 98% of participants in the survey. **A,** Clinical Photographs

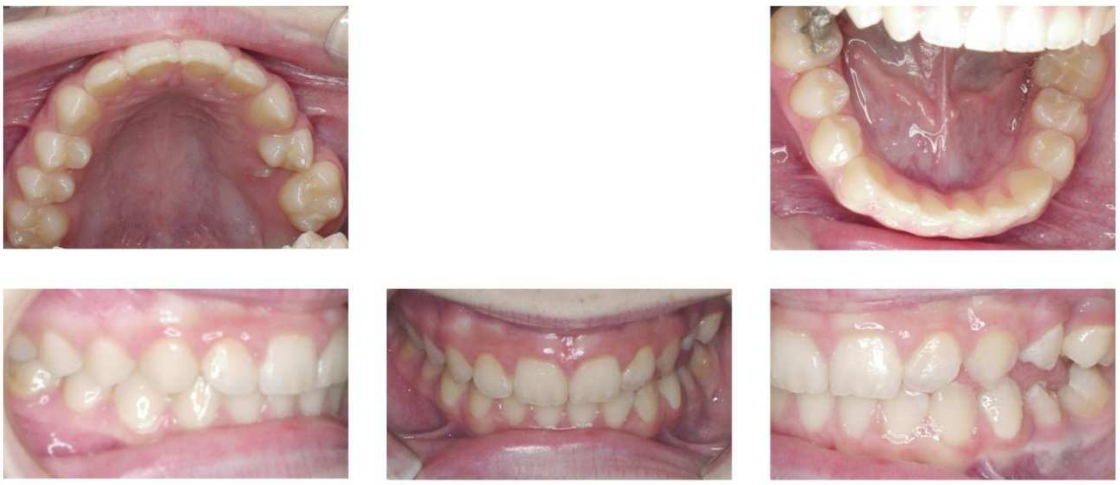


Figure 2.3: B, Panoramic film

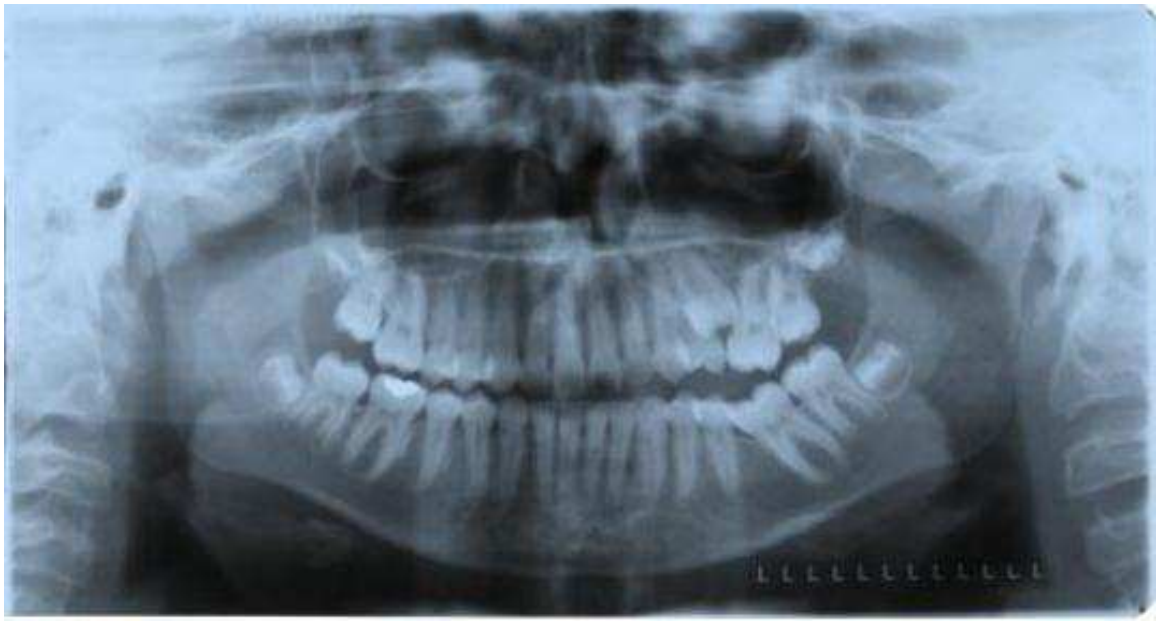


Figure 2.4: MFE case that was most frequently misdiagnosed (by 75% of participants). **A,** Clinical Photographs

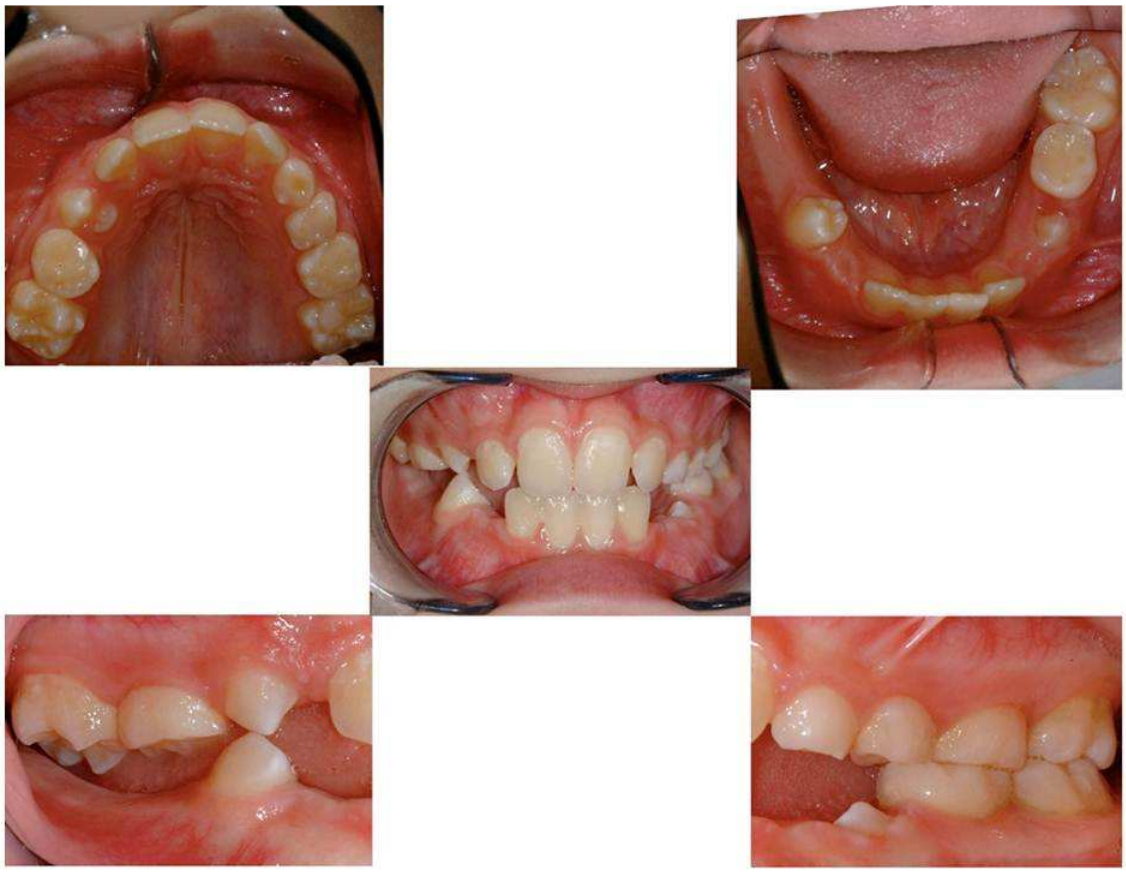


Figure 2.4: B, Panoramic film which illustrates the alveolar bone occlusal to the crown of the lower right first molar. This is paramount to excluding a diagnosis of PFE.

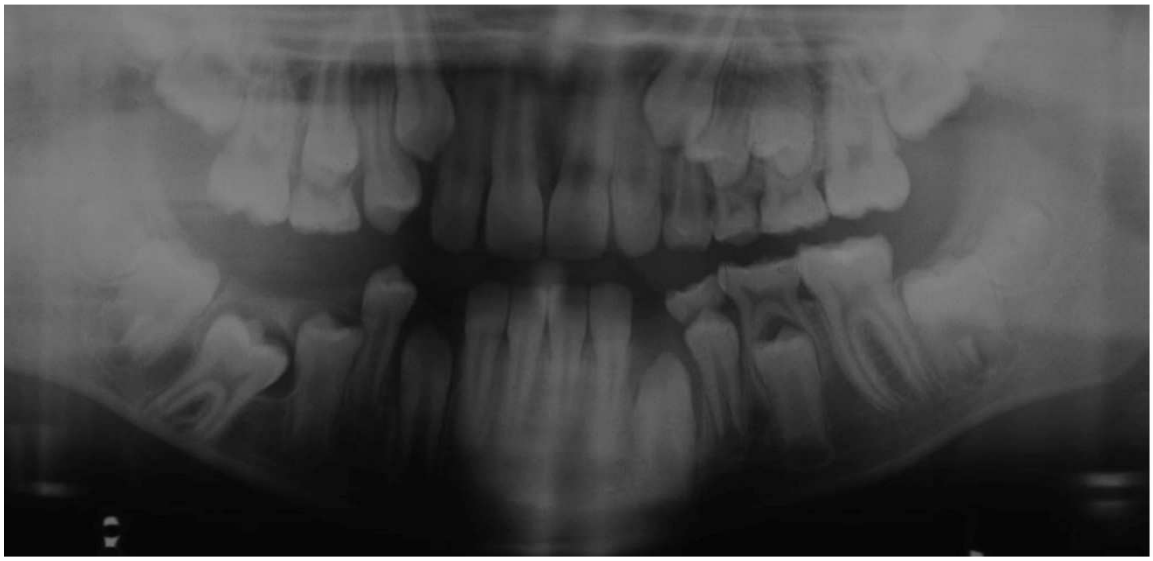
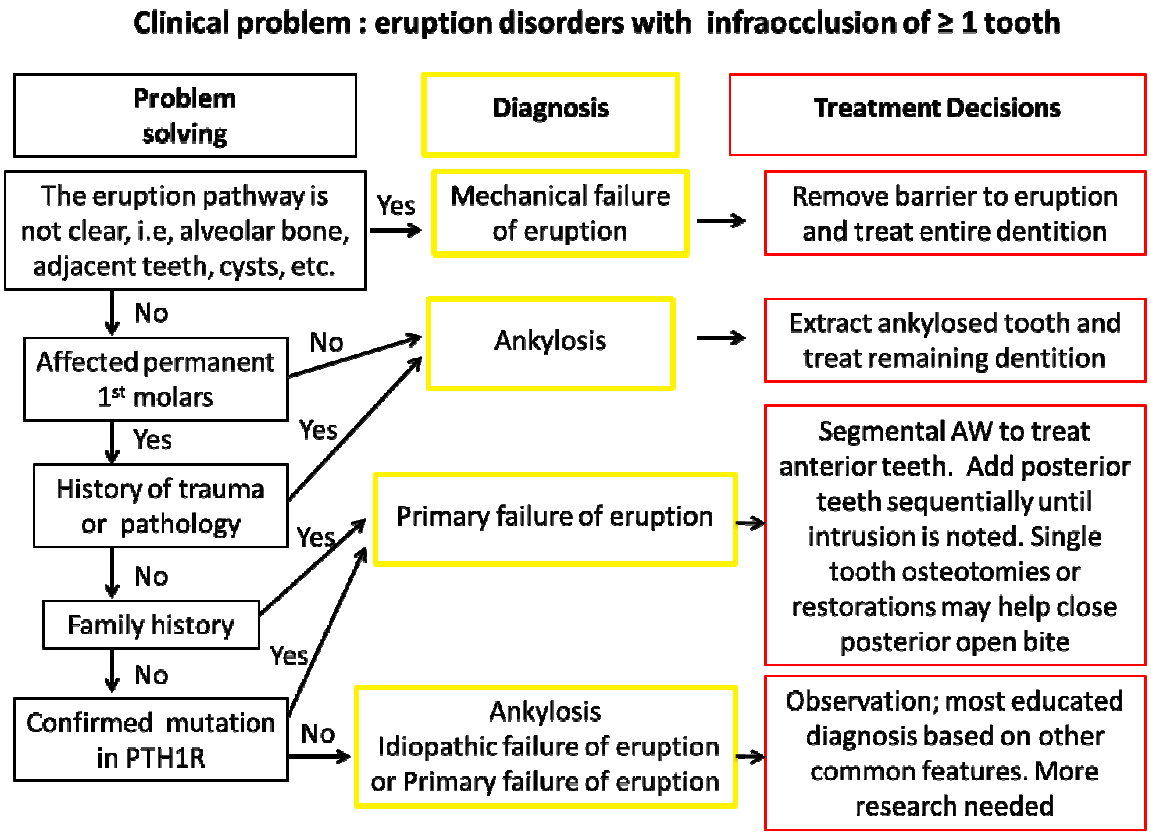


Figure 5: Decision tree for diagnosis and treatment of eruption disorders. Modified from *Rhoads et. al. AJODO 2013* to include treatment considerations.



Establishing the Diagnostic Criteria for Eruption Disorders Based on Genetic and Clinical Data

3.1 ABSTRACT

Introduction: Proper diagnosis and management of eruption disturbances remains challenging but is critical to a functional occlusion. The objective of this study is to establish definitive criteria to differentiate and diagnose eruption disorders, specifically Primary Failure of Eruption (PFE) and ankylosis. **Methods**: Sixty-four affected individuals were placed into 3 Cohorts: PFE diagnosed through confirmed presence of *PTH1R* mutation (N=11), PFE diagnosed based upon clinical criteria (N=47), and ankylosis diagnosed based upon clinical criteria (N=6). These groups were assessed to identify clinical features that differentiate PFE and ankylosis. **Results:** Ninety-three percent of individuals in the PFE Genetic and Clinical Cohorts (N=58) and 100% in the Genetic PFE Cohort present with at least one infraoccluded permanent first molar. Additionally, a novel functional *PTH1R* mutation, 1092delG, was identified and linked to PFE in the primary dentition. **Conclusion**: An infraocluded, supracrestal first molar is a hallmark feature of PFE, which often presents with involvement of both arches, permanent or primary dentition, uni- or bilateral affection, infraoccluded 2nd premolar and/or 2nd molar, and multiple affected adjacent teeth. Our results further suggest that PFE and ankylosis may be clinically indistinguishable without knowledge of prior trauma, treatment history, genetic information or obliteration of the PDL space.

3.2 INTRODUCTION

The process of eruption in the human dentition is complex and remains poorly understood. While advances in molecular biology have increased our understanding of the mechanisms underlying human dental eruption, the clinical correlations remain elusive. Consequently, our understanding of eruption is based on multiple, yet differing theories that are both controversial and ill-supported. Eruption disorders therefore create a rare and unique diagnostic challenge for general dentists seeking to monitor the dental development of their patients; but it is particularly complex for the orthodontist and pediatric dentist who are tasked with the management of these patients. The gestalt of this challenge is a lack of definitive clinical diagnostic criteria to distinguish between different types of eruption disorders and/or differentiate them from idiopathic delayed dental development.

Disturbances in dental eruption can occur for many reasons. Among these are two very different clinical problems that form the central basis of this report, Primary Failure of Eruption (PFE; OMIM: 125350) and ankylosis. Ankylosis is histologically defined as the fusion of cementum to bone in at least one area lacking a periodontal ligament space.[14,3] The resultant occlusion exhibits a tooth that ceases to erupt, drift, or move despite normal adolescent growth or orthodontic traction. In contrast to ankylosis, PFE does *not* include a fusion of the cementum to the bone, but is marked by a disturbance in the eruption mechanism itself causing a non-ankylosed tooth to fail to fully or partially erupt.[4] In fact, surgeons extracting teeth diagnosed as PFE note that the tooth is mobile within the socket, further differentiating these teeth from ankylosed teeth[4] (Tim Turvey, personal communication, 12/3/2012). PFE was initially described based upon its

clinical appearance. This description of PFE remains the most comprehensive diagnostic indicator to date and includes the following features: it primarily affects posterior teeth; affects all teeth posterior to the most anteriorly affected tooth; occlusion manifests as a lateral open bite; and teeth do not respond favorably to orthodontic forces.[4] A common clinical dilemma is distinguishing PFE from ankylosis – mainly because both disorders carry a similar clinical appearance and developmental fate. In fact, there is some evidence that PFE is often misdiagnosed as ankylosis.[1, 5] It is important, however to recognize that ankylosis and PFE dictate distinct treatment modalities and inaccurate diagnosis could significantly alter the treatment success. The misdiagnosis and mismanagement of either eruption disorder could result in inappropriate and extended treatment, significant financial burdens, patient frustration, and an inferior occlusal condition.

The fact remains that PFE is a rare, yet handicapping disorder in which the treatment options are unclear and unpredictable. The few treatment options that exist at this time to improve the occlusion of a patient exhibiting PFE include small segmental osteotomies and prosthetic restoration of the occlusion.[4,15] However, no treatment or very limited esthetic treatment is often the best option because treatment orthodontically with a continuous archwire, even after extracting the most severely affected tooth, results in exacerbation of the lateral open bite by intrusion of the adjacent teeth and frequent resultant ankylosis of the affected teeth.[5,1, 4] This is in contrast to ankylosis, which can be successfully treated by extraction of the ankylosed tooth and subsequent orthodontic movement of all other teeth. Thus, misdiagnosis of PFE and treatment with a continuous

archwire can actually lead to an inferior occlusal result, providing a significant disservice to the patient.

It is expected that the uncertainty surrounding eruption disorder diagnosis will diminish with the increasing application of genetic analysis in this field. Unlike the limited clinical indicators discussed above, genetic analysis of specific genes offers an objective measure of the presence of pathology. Recent studies revealed that a genetic mutation in the *PTH1R* gene (associated with bone homeostasis) is also associated with PFE. The mutation is present in multiple members of some families who exhibit PFE.[5, 6, 9,16] It has previously been reported that 10-40% of PFE cases are familial,[4, 15-17] and we anticipate that this estimate will increase as more is learned about the genetic makeup of those patients diagnosed with PFE. The potential for a genetic diagnosis of PFE or other dental disorders illustrates a huge step forward in establishing a definitive and objective diagnosis of PFE in patients who are exhibiting clinical characteristics of the disorder. Although genetic "testing" is not currently available for use in clinical practice for most dental disorders, it is in early phases of development for use in the diagnosis of PFE and will possibly act as a chairside diagnostic test in the future. Logical first steps in developing this diagnostic rubric are to document, and then associate the clinical features of PFE with the associated genetic mutations.

In this report we seek to take advantage of a unique dataset to establish clinical diagnostic criteria that distinguish PFE from other eruption disorders, particularly ankylosis. The combination of objective genetic information and clinical data from affected individuals can be utilized to establish a genotype-phenotype correlation for PFE and by extension, an objective diagnosis [ie determined by associating clinical

(phenotypic) features with genetic (genotypic) analysis]. We therefore compare clinical features identified in the genetically characterized sample set to a broader dataset of patients diagnosed with PFE based on clinical parameters only. The resultant developmental and morphological features identified in individuals exhibiting obvious clinical characteristics of PFE and harboring a genetic mutation in *PTH1R* will represent a hallmark of the condition, providing clinicians with greater diagnostic certainty and subsequent improved clinical management.

3.3 MATERIALS AND METHODS

A dataset of 64 patients with eruption disorders was collected at the University of North Carolina at Chapel Hill over several years. This dataset consists of patients of the University of North Carolina at Chapel Hill Graduate Orthodontic Clinic, Faculty Practice, and various private practices (sent for consultation and recommendations from faculty at the University of the University of North Carolina). After phenotypic review using radiographs and/or clinical photos, individuals were placed into 3 categories: patients definitively diagnosed with PFE through genetic analysis which revealed a mutation in *PTH1R* (N=11) [Genetic PFE Cohort], patients diagnosed with PFE based upon clinical records alone (N=47) [Clinical PFE Cohort], and patients diagnosed with ankylosis based upon clinical criteria (N=6) [Clinical Ankylosis Cohort]. All records were evaluated by 3 separate investigators and agreement in diagnosis and feature identification was confirmed for all cases. Those included in the ankylosis cohort had a confirmed history of trauma or were treated with extraction of the affected tooth/teeth and exhibited successful orthodontic treatment of the remaining teeth. All other cases were diagnosed as PFE based upon clinician acumen, history of unsuccessful orthodontic treatment, or genetic analysis.

Of the 58 individuals diagnosed with PFE, 27 underwent genetic (mutational) analysis (previously described); a mutation or polymorphism in *PTH1R* was identified in 11 individuals and an unclassified non-functional single nucleotide polymorphism (SNP) in *PTH1R* was identified in the remaining 16. These 11 individuals comprise the Genetic PFE Cohort, while patients with SNPs were grouped into the Clinical PFE Cohort. Mutational analysis was performed as follows: DNA was extracted and purified from

salivary samples (Oragene, DNA Genotek, Toronto, Ontario, Canada). All coding regions of *PTH1R* (exons 3-16) were amplified and sequenced using previously described primer sets.[9] Splice junctions were included in the sequencing results by using primer sets designed to delineate regions that the included a minimum amount of 25 bases on intron sequence, in addition to the exon sequences. The amplification of sequences was performed using HotStart polymerase chain reaction MasterMix (GE Healthcare Life Sciences, NH) under the following conditions: 10 minute at 95^{o}C activation/premelt, followed by 35 cycles of 30 seconds at 94 ^{o}C melt, 30 seconds at 60 ^{o}C anneal, and 3 minutes at 72 ^{o}C extension. The polymerase chain reaction products were purified with Exosapit (Affymetrix, CA) and sequenced at The University of ### Genome Analysis Core facility. All sequences were compared to a wild type *PTH1R* (accession NM_000316.2) from GenBank release GRCh37- using the BLAST algorithm.

Clinical (phenotypic) information was reviewed for all three cohorts to assess clinical features of the affected individuals. The records assessed included a minimum of a panoramic radiograph for every patient, and cephalometric radiographs, intraoral periapical radiographs, and clinical photographs were used when available. The following information was gathered for all three cohorts:

1) Unilateral or bilateral presentation of infraoccluded teeth
2) Arch involved (affected teeth present in the maxilla, mandible, or both)
3) Teeth presenting with infraocclusion (at least one premolar, first molar, second molar)
4) Location of affected teeth in alveolar ridge (supracrestal or infracrestal). 3rd molars were excluded from evaluation, as were second molars in young patients

who would not be expected to have second molars erupted according to normal dental eruption timing

5) Presence or absence of root anomalies, including description
6) Presence or absence of any other abnormal or noteworthy findings, including specific descriptions
7) Record types provided

Additionally, the following information was included when available and applicable:

1) PFE Type I or II (determined by the degree of eruption of the second molars, as discussed below)
2) Age
3) Presence of Class III dental or skeletal relationship (determined by high quality clinical photos and/or cephalometric radiograph that clearly demonstrates a skeletal Class III relationship were required. Those patients lacking these records were classified as indeterminable.)

For the Clinical PFE and Genetic PFE Cohorts, the classification of PFE was recorded as Type I or II as previously described in the literature.[6, 17] These types are distinguished based upon the timing of onset and therefore presentation. Briefly, Type 1 PFE is characterized by a progressive posterior open bite, in which all teeth distal to the most mesial infra-occluded tooth are affected and do not erupt into occlusion. Type 2 PFE exhibits greater eruption potential, although still inadequate, for the more distal teeth, such as second molars. Comparison of the eruption disorders based upon the three cohorts was completed in order to identify similar and distinguishing characteristics. The Genetic PFE Cohort provides an objective basis to classify the associated clinical

features. Therefore, the following comparisons were made: clinical features of the Genetic PFE Cohort with the Clinical PFE and Clinical Ankylosis Cohorts based upon the attributes listed above.

3.4 RESULTS

Twenty-four of the 58 total PFE patients had age information available. The average age of the patients in this dataset for which age was recorded was 12 years, 9 months with a range of 6 years, 2 months to 18 years, 4 months.

Previously identified mutations in the *PTH1R* gene in addition to a novel mutation in *PTH1R*, (1092 del G, which results in a frameshift and premature termination of the *PTH1R* protein) formed the basis of the Genetic Cohort. This novel mutation, associated with the clinical finding of infraoccluded primary teeth, was discovered in a small nuclear family (N=2). The index case was a 7 years, 9 months old male who exhibited PFE affection of the permanent and primary teeth in the form of a right lateral posterior open bite and mild Class lll skeletal malocclusion. (Figure 1)

Establishment of Genotype:Phenotype Correlation

We evaluated a subset of cases with eruption failure that included both clinical and genetic data in order to establish a genotype:phenotype correlation. Table I summarizes the number and percentage of patients in our entire sample (N=64) who exhibit various clinical features. Specifically, the Genetic Cohort (N=11) was examined for clinical characteristics of PFE. Since individuals in the Genetic Cohort exhibit a confirmed mutation in *PTH1R*, hallmark features consistent with PFE are outlined based upon this dataset. Our phenotypic analysis primarily using radiographs and clinical photographs reveals the following:

Six of 11 individuals present with affected teeth unilaterally, while 5 of 11 illustrate a bilateral presentation of infraoccluded teeth. A great majority of patients (10 of 11 or 90.2%) exhibit infraoccluded teeth in both the maxilla and mandible. One

patient has affected teeth in the mandible only. At least one premolar is affected in 8 of 11 (72.7%) of patients and at least one second molar is severely affected in 7 of 11 (63.6%) of the patients. This, however, may be an underestimation, due to the early dental age of some patients, prohibiting the second molar eruption potential from being truly evaluated. Of particular significance is the finding that 100% of patients have an affected permanent first molar. The one individual presenting in the mixed dentition is noted to have all primary molars on the right affected. The affected teeth in each dental quadrant are adjacent to one another.

In the Genetic PFE Cohort, 100% of patients have a supracrestal presentation of affected teeth. Supracrestal was defined by a completely cleared eruption pathway, with no alveolar bone noted occlusal to the affected tooth. There are no instances of individuals in this group with exclusively infracrestal affected teeth, although 2 patients have one ectopically placed second molar which remains infracrestal (excluding second and third molars when age and developmental status preclude their eruption). Further, 4 of 11 individuals exhibit characteristics of Type 1 PFE, in which the second molar is at least as severely affected as the first permanent molar. Six of 11 present as Type 2 PFE, in which the second molar retains more eruptive capability than the first molar, though still remaining infraoccluded. One individual is indeterminable due to an early dental developmental age without the eruption of the second molar at the time of records.

We also investigated the presence or absence of simultaneous notable dental features. Class III malocclusion and/or skeletal patterns are noted in 7 of 11 (64%) of patients. One patient did not have adequate records to judge the Angle classification or skeletal pattern. Dilacerated roots are observed in 1 of 11 patients. Finally, 4 of 11 (36%)

of these patients present with at least one other dental anomaly, including impacted teeth (N=3) and infraoccluded, over-retained primary teeth (N=2). Figure 2 presents an example of a patient in the Genetic Cohort illustrating many of the hallmark features of PFE.

Features of the Clinical PFE Cohort

In the Clinical PFE Cohort (N=47), the majority of the cases that we reviewed exhibit primary failure of eruption bilaterally (26 of 47 or 55%). Of the remaining cases with unilateral presentation, 10 present only on the left and 11 present only on the right. PFE most often presents as infraoccluded teeth in both the maxillary and mandibular arches (33 of 47 or 70%). In our sample, however, 5 patients exhibit features of PFE only in the mandibular arch and 9 illustrate affected teeth only in the maxillary arch. Essentially all affected teeth are supracrestal, despite being infraoccluded (40 of 47 or 85%). As previously noted, we excluded second and third molars when age and developmental status precluded their eruption. Importantly, the first molar is always supracrestal, demonstrating either a notable clear eruption pathway through the bone or presenting most often supragingivally yet below the plane of occlusion.

At least one first permanent molar is affected in 43 of 47 cases (91%) belonging to the Clinical PFE Cohort. Furthermore, a second permanent molar (31 or 66%) and at least one premolar (30 or 64%) are very frequently affected. In all 10 patients in the mixed dentition, at least one primary tooth is affected. Teeth as far anterior as the canine are affected in many patients and all affected teeth in each quadrant are adjacent to one another. Twenty-five of 47 or 53% of the Clinical PFE Cohort patients have PFE type I and 13 of 47 or 28% patients exhibit PFE type 2. For the remaining cases (N=9), the

classification of PFE is indeterminable, primarily due to inadequate dental development or dental age at the time of records.

Other dental features noted in the Clinical PFE Cohort include alterations in root morphology (ie notably blunted or dilacerated roots (N=10 or 21%) and a remarkable prevalence of co-segregating dental anomalies such as missing teeth (second premolars, N=3; maxillary laterals, N=1), delayed eruption of multiple teeth (N=6), impacted teeth (N=7), and transposition of 2 teeth (N=2). Finally, a high prevalence of Class III malocclusion is also noted within this Cohort with a total of 11 of 47 (23%) patients demonstrating a Class III dental, and often skeletal, relationship. The classification could not be determined for 21 of the patients due to inadequate records.

PFE versus Ankylosis

The Clinical Ankylosis Cohort (N=6) presents with a mean age of 10 years, 1 month. Most cases present unilaterally, with only 1 of 6 cases presenting with bilaterally affected teeth. Additionally, the affected teeth are confined to 1 arch in every case. The affected tooth or teeth are found in the maxilla in 2 of the cases and in the mandible in 4 of the cases. In all cases the affected tooth is a permanent first molar. With the exception of the one case that presents bilaterally (affecting both maxillary permanent first molars), all other cases present as a single affected tooth. Similarly to teeth affected by PFE, all but one tooth in this group of patients is supracrestal. Other dental features which are also prevalent in this patient Cohort include Class III malocclusion (N=3), missing second premolars (N=2), blunted roots (N=1), and ectopic canines (N=1).

3.5 DISCUSSION

The available information and technology that can be utilized for the accurate diagnosis of eruption disorders is severely lacking, hindering the ability of clinicians to make the best treatment decisions for their patients. While definitive and objective diagnosis through genetic analysis may one day represent the gold standard, the research on this front remains in the nascent stages of development. However, with rapid progress being made in "personalized medicine," the clinical applicability of genetic testing for the practicing orthodontist is likely in the near future. The establishment of definitive clinical criteria to aid in the diagnosis of eruption disorders is critical for the present day.

In this study, we evaluated the clinical phenotype of individuals in a Genetic PFE Cohort who present with a functional mutation in the *PTH1R* gene. Previous studies reveal that PFE presents as a progressive lateral open bite unable to be eliminated through orthodontic traction which often has an associated familial mutation in *PTH1R*.[1, 4-6, 9, 17, 18] The genotype:phenotype correlation presented here was based on the Genetic Cohort and revealed that specific phenotypic characteristics represent hallmark features of PFE since 100% of affected individuals possess these features. These include the involvement of the permanent first molar and supracrestal presentation of the affected teeth. Although the posterior lateral open bite is a diagnostic feature of PFE, it must be noted that there are alternative documented causes of a lateral open bite, such as manifestations of Mechanical Failure of Eruption (MFE) (ie an unleveled COS, lateral tongue thrust) or a skeletal discrepancy (particularly a progressive mandibular asymmetry).[19] These cases can typically be successfully treated with orthodontic mechanics and/or orthognathic surgery. Therefore, such causes of a lateral open bite must be ruled out prior to

consideration of a PFE diagnosis. After eliminating the likelihood of MFE or skeletal discrepancy, the presence of a lateral open bite remains a key diagnostic feature of PFE. Nonetheless, a comparison between individuals with a mutation in the *PTH1R* gene and those who have not yet been genetically assessed provides an additional objective measure (ie infraoccluded first molar) that can be applied to the clinical diagnostic regime.

Moreover, through our genetic analysis procedure, we found that the presence of a familial *1092delG* mutation in *PTH1R* is associated with affection of primary teeth. This novel, functional mutation has been found in two family members- one of which is currently in mixed dentition. This finding represents the first report of a *PTH1R* mutation and affection of primary teeth.

Since this was a retrospective study, investigators did not have the ability to complete genetic analysis on every individual included. This is a potential limitation of the study because it resulted in a smaller number (11) of patients with a confirmed mutation in *PTH1R*. However, when the Genetic and Clinical PFE Cohorts were compared, no striking variations were noted between the clinical features in the two groups. Thus, we contend that the Genetic and Clinical PFE Cohorts for practical purposes can be analyzed as one group since an absence of a mutation in *PTH1R* does not rule out PFE but the presence of a mutation confirms a diagnosis of PFE. For instance, of the patients who underwent genetic analysis, 16 individuals analyzed harbored non-functional single nucleotide polymorphisms (SNPs) whose role in the eruption disorder is uncertain at this time. This underscores the fact that at least one other gene is probably responsible for the presentation of PFE. We can conclude that PFE is a complex disorder

which is most likely the outcome of genetic alterations in multiple different genes and resultant disturbances in various molecular pathways.

The most striking feature of PFE noted in our Genetic Cohort is that the first permanent molar is always involved. This hallmark feature is also seen in the Clinical PFE Cohort in the majority of individuals. Collectively, when the Genetic and Clinical PFE cohorts are combined, the first permanent molar is affected 93% of the time. Other hallmark clinical features associated with individuals harboring a mutation in *PTH1R*, as well as those diagnosed clinically, are a frequent involvement of second premolar and second molar, multiple adjacent teeth affected, a supracrestal presentation of the infraoccluded teeth, bilateral presentation in most cases, involvement of teeth in both the maxilla and mandible, frequent Class III malocclusion, and a high prevalence of concurrent dental anomalies. This, therefore, provides the basis for a genotype:phenotype correlation that can be applied to the diagnosis of individuals with eruption disorders who do not have genetic data available. Our characterization of common PFE findings is consistent with previous reports.[1, 4-6, 15, 17, 18] Evidence of substantial variability in presentation among PFE patients, and particularly noted variability among quadrants within a single patient, suggest a combination of environmental and epigenetic factors influencing PFE presentation as well as a manifestation of a patterning effect whereby spatial and temporal control (ie combinatorial code)[20] of molecular pathways lead to a varied phenotype.

We also sought to identify clinical features that can be used to distinguish between PFE and ankylosis. It is likely that an ascertainment bias favoring PFE over ankylosis exists in our sample since a significant number of PFE cases are sent for our

consultation and because our database was initially established for the purpose of identifying probable PFE cases. Our analysis revealed that features common to PFE and ankylosis include supracrestal presentation of the affected teeth and the involvement of the permanent first molar. We speculate that the first molar involvement in both disorders is due to molecular timing of defects in the eruption mechanism (ie the temporal and spatial specificity favors the first erupting permanent tooth in a posterior quadrant). However, there are distinctions noted between the clinical appearance of PFE and ankylosis in these cohorts studied that can be used to distinguish the two disorders. For ankylosis, the affected tooth was confined to only 1 arch in every case, which is strikingly different than PFE, in which 74% of cases exhibit features in both arches. Bilateral presentation of affected teeth is apparent in 53% of PFE cases, in which multiple adjacent teeth are typically affected and infraoccluded; only one case of ankylosis (17%) exhibited bilateral presentation and a maximum of one affected tooth is noted per quadrant. Taken together, we have applied our phenotype:genotype analysis to a clinical decision tree (Figure 3) to provide the clinician a systematic tool to aid in the diagnosis of eruption disorders.

Of note is the high number of both PFE and anklyosis patients exhibiting other concurrent dental anomalies. This may support a hypothesis that ankylosis is also under intricate genetic control and may, in fact, result from a variation of the misdirected molecular pathway that leads to the presentation of PFE. Dental anomaly patterns have been studied by Shalish and Peck (2010), who concluded that patients with infraoccluded primary teeth (most of which continued on to normal eruption of the premolars) were 2 to 7 times more likely to exhibit another dental anomaly when compared to reference

samples. They noted a significant correlation between infraocclusion of at least one primary tooth and increased occurrence of tooth agenesis, microdontia of maxillary lateral incisors, palatally displaced canines, and a distal angulation of the mandibular second premolar.[21] Hypodontia in eruption disorders has been reported as a particularly common finding.[15, 21] These anomalies appear to be under genetic control and may result from disturbances in the same or intertwined genetic and molecular pathways. Studying them as a group may reveal information about other connected dental anomalies and may disclose that they are all, in fact, manifestations of the same spectrum of eruption disturbances.

Despite the fact that the numbers reported may underrepresent the prevalence of Class III patterns in the studied cohorts (many patients lacked adequate records to determine the skeletal pattern), 31% of the PFE individuals exhibit a Class III relationship, which is much higher than the reported prevalence of this malocclusions in American children (<1%) and in the Japanese population (at its highest at 3-5%).[22] As a result of the high association between PFE and Class III patterns, one may speculate that there is a generalized disturbance in bone metabolism and turnover that not only inhibits normal eruption of teeth and development of the alveolar bone, but also precludes the proper forward and downward growth of the entire maxilla. Since a strong genetic component to Class III skeletal relationships has been demonstrated in previous research, there appears to be an overlapping genetic component to dental and skeletal disturbances that remains to be elucidated.[23] This important connection could shed light on the normal eruption process, the genetic influence on eruption disturbances, and the interaction between molecular pathways that orchestrate the complex process of dental eruption.

3.6 CONCLUSION

Definitive diagnosis of PFE is currently made through the identification of a mutation in *PTH1R*, which has been shown in this study to be largely consistent with the diagnosis of PFE based upon clinical parameters. Hence, the use of our Genetic PFE Cohort establishes 2 clinical parameters that will guide our diagnosis of PFE: involvement of the first permanent molar and supracrestal presentation of affected teeth, in which the eruption pathway is completely clear of obstruction and clear of alveolar bone occlusal to the tooth. Other hallmark clinical features which, if present, can help support a diagnosis of PFE are involvement of second premolar and second molar, multiple adjacent teeth affected, bilateral presentation, involvement of teeth in the maxilla and mandible, Class III malocclusion, and concurrent dental anomalies. Although the only means of establishing a definitive PFE diagnosis at this time is the identification of a mutation in *PTH1R*, the identification of clinical diagnostic criteria is essential for many reasons. The lack of a mutation in *PTH1R* does not preclude a PFE diagnosis. There are most likely other mutations that are linked to variations of PFE which remain to be identified through ongoing research. Additionally, genetic analysis is not readily available to practicing clinicians who must make important treatment decisions based upon a clinical diagnosis. The hallmark features of PFE identified in this paper through the establishment of a genotype:phenotype correlation can provide clinicians with a means of making a confident and evidence-supported PFE diagnosis. However, it also raises speculation about how confidently PFE can be differentiated from ankylosis. The features present in 100% of PFE cases were also common in anklyosis cases. Pragmatically speaking our results suggest that the two may sometimes be clinically

indistinguishable without knowledge of prior trauma, ability to radiographically or otherwise identify an intact PDL space, evaluating treatment response, or obtaining genetic information for the patient. However, we attempted to highlight some features that can be helpful in clinically differentiating between PFE and ankylosis based upon the information available at this time. Referencing the hallmark features of PFE outlined in this paper, along with the characteristics specific to ankylosis, will aid the clinician in providing the most confident diagnosis to the patient and offering the most appropriate and comprehensive treatment plan options.

Table 3.1: Descriptive characteristics of the three cohorts studied

	PFE (genetic) (N=11)		PFE (clinical) (N=47)		Ankylosis (N=6)	
	N	%	N	%	N	%
Symmetry						
Unilateral	6	54.5	21	44.7	5	83.3
Bilateral	5	45.5	26	55.3	1	16.7
Arch Involved						
Maxilla	0	0.0	9	19.1	2	33.3
Mandible	1	9.1	5	10.6	4	66.7
Both	10	90.9	33	70.2	0	0.0
Teeth Involved						
At least one premolar	8	72.7	30	63.8	0	0.0
Permanent First Molar	11	100.0	43	91.5	6	100.0
Permanent Second Molar	7	63.6	31	66.0	0	0.0
Location in alveolar ridge						
Supracrestal	11	100.0	40	85.1	5	83.3
Infracrestal	0	0.0	2	4.3	1	16.7
Both	0	0.0	5	10.6	0	0.0
PFE Classification						
Type 1	4	36.4	25	53.2	N/A	N/A
Type 2	6	54.5	13	27.7	N/A	N/A
Indeterminable	1	9.1	9	19.1	N/A	N/A
Mutation Type						
Intronic- Substitution	4	36.3	N/A	N/A	N/A	N/A
Coding- Substitution	2	18.2	N/A	N/A	N/A	N/A
Coding- Insertion (Frameshift)	3	27.3	N/A	N/A	N/A	N/A
Coding- Deletion (Frameshift)	2	18.2	N/A	N/A	N/A	N/A
Coding- Non-Functional SNP	0	0.0	16	34.0	N/A	N/A
Angle Class III	7	63.6	11	23.4	3	50.0
Dilacerated or Blunted Roots	1	9.1	10	21.3	2	33.3
Other Dental Anomaly Present	4	36.4	16	34.0	2	33.3

Table 1: This chart compares the descriptive characteristics of the three cohorts studied. The first is a group of PFE patients who have undergone genetic analysis to confirm that they harbor a mutation in *PTH1R*. The second is a group of patients diagnosed with PFE through clinical assessment. The third is a small group of patients diagnosed with ankylosis through clinical assessment.

Fig 3.1 A Chromatogram demonstrates a familial 1092 G deletion in the *PTH1R* gene linked to infraocclusion of primary teeth in an affected child.

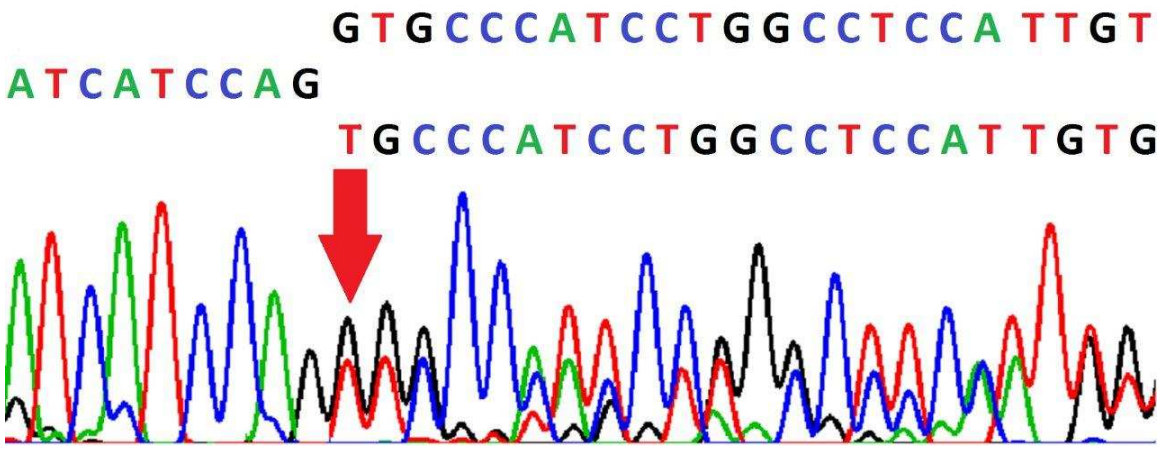


Fig 3.1 B Panoramic radiograph illustrating involvement of both primary and permanent teeth in the affected patient who carries a 1092 G deletion in *PTH1R*.

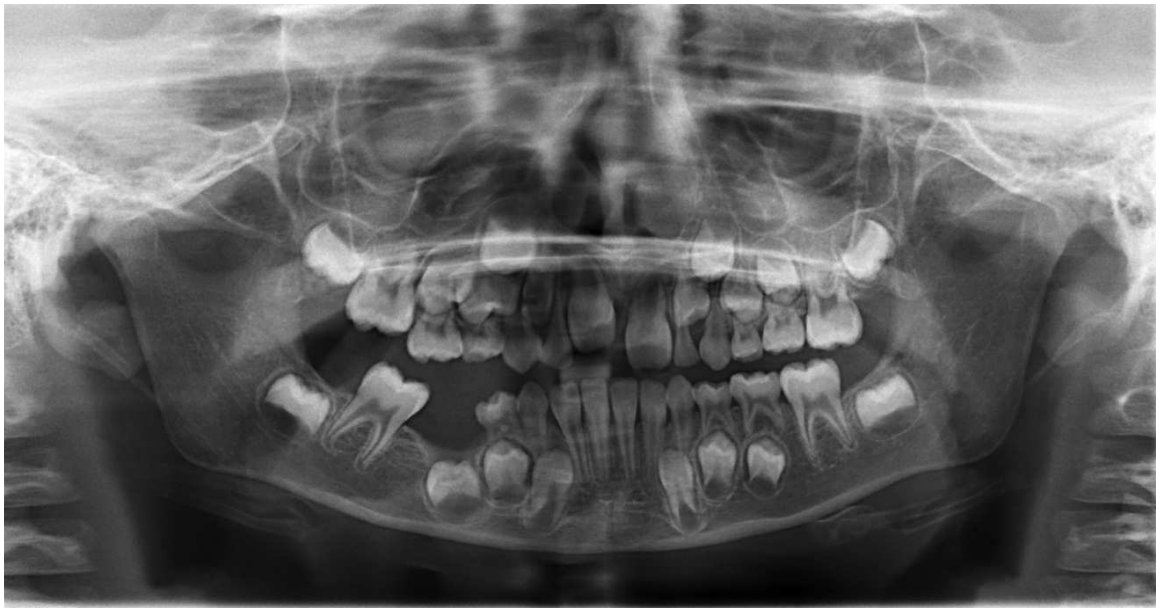


Fig 3.2 A, Clinical photos demonstrating Type ll PFE with posterior openbite on the left side in the affected individual in which the second molar has maintained more eruptive potential than the first molar. The lower right permanent first molar is also affected.

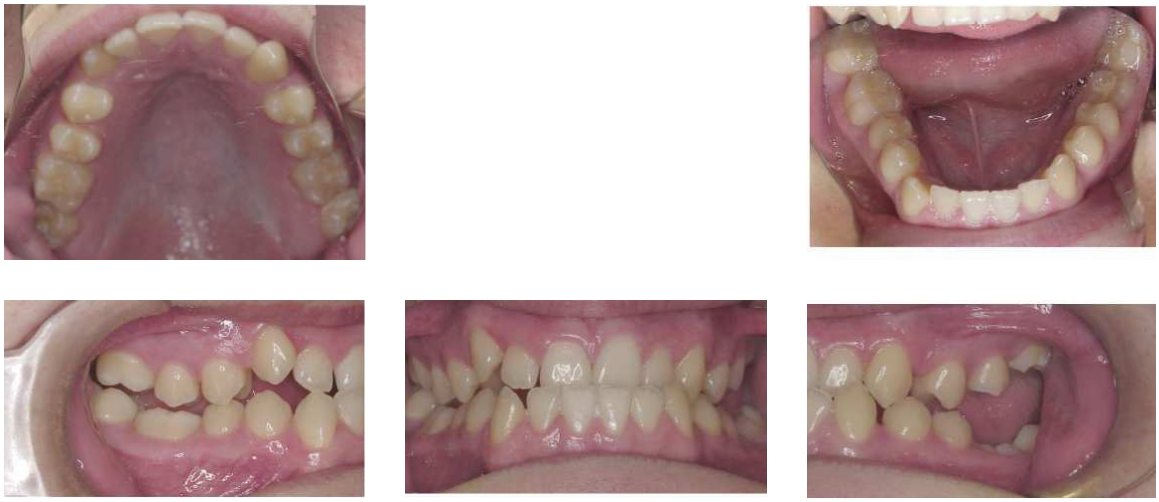


Fig 3.2 B Panoramic radiograph

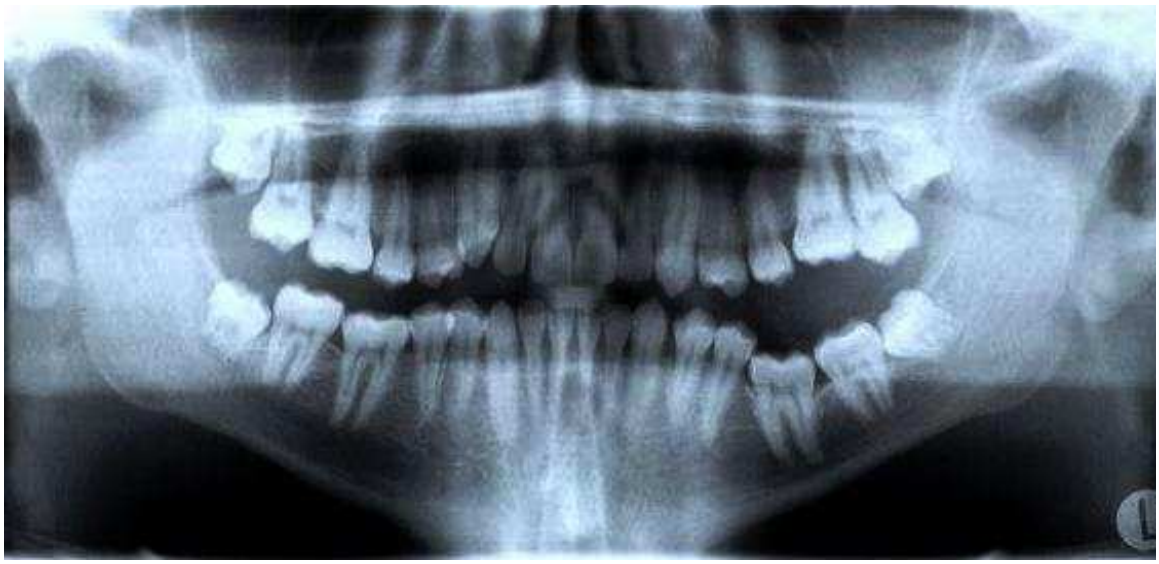


Fig 3.2 C Cephalometric radiograph demonstrating a Class III skeletal and dental pattern.

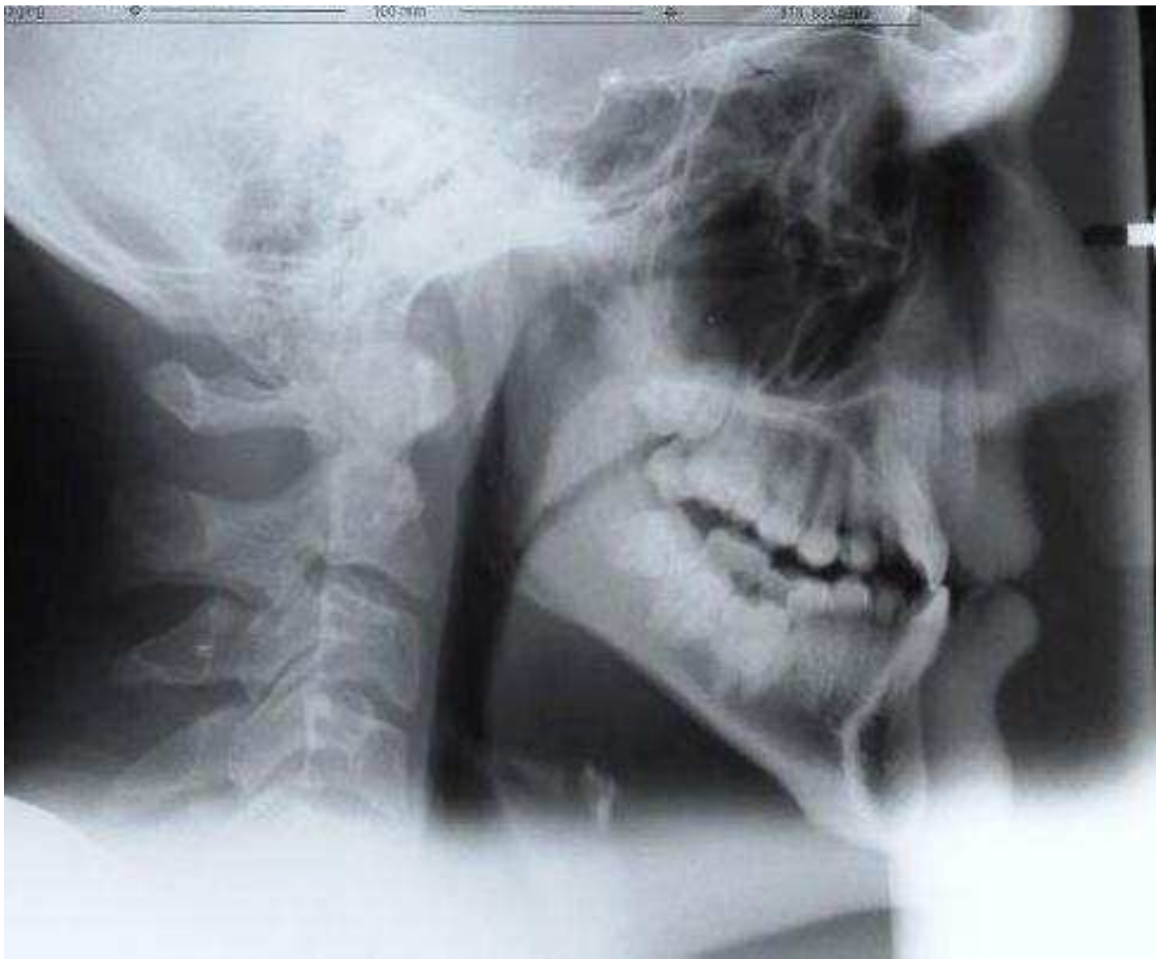
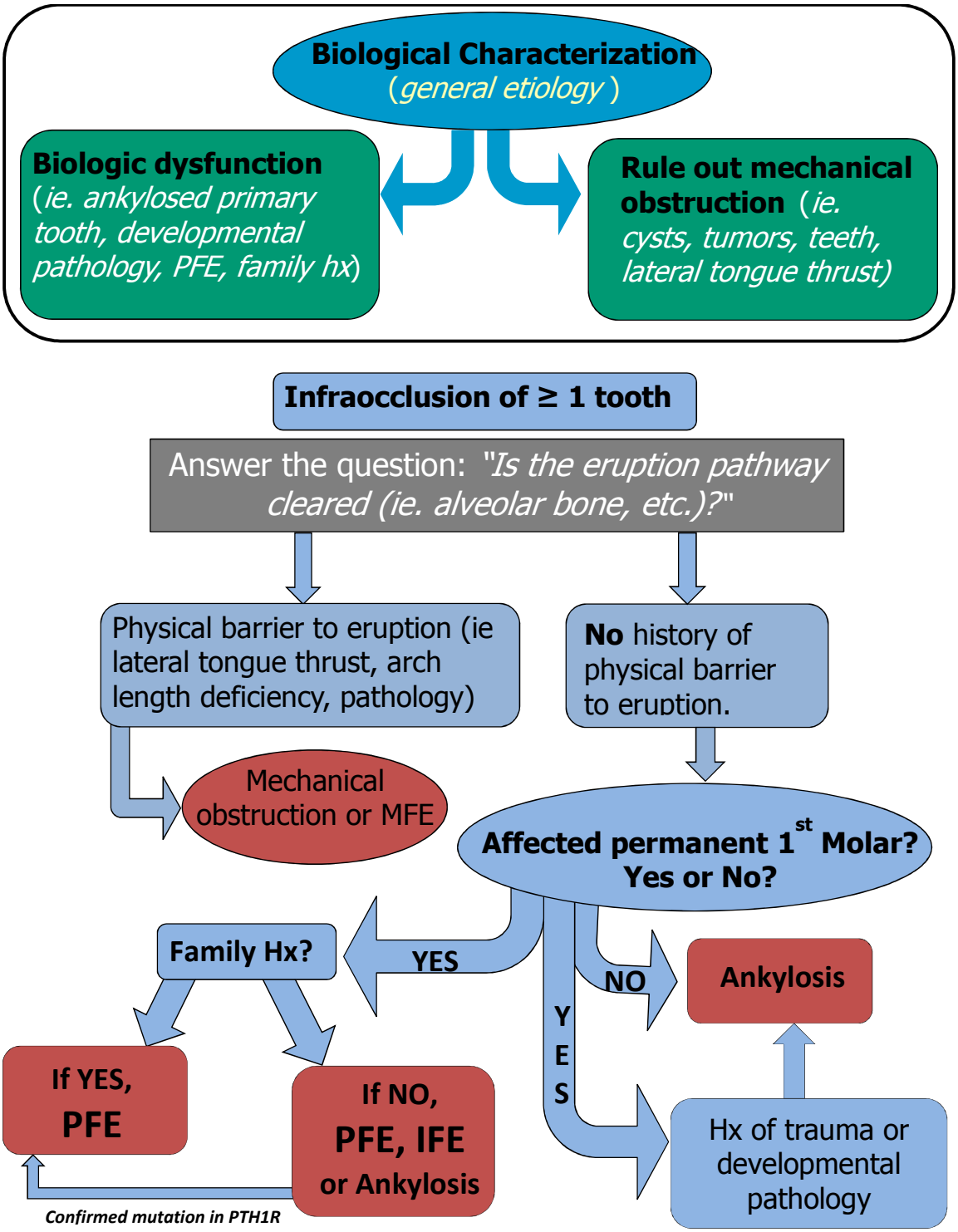


Figure 3.3 Decision tree provided as a tool for use by the clinician, to aid in the formation of an objective and systematic diagnosis of eruption disorders. This decision tree also assumes that dental development is sufficient to analyze the eruption potential of the permanent first molar. MFE (Mechanical Failure of Eruption), PFE (Primary Failure of Eruption), IFE (Idiopathic Failure of Eruption).



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