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Improvement in the risk assessment of oral leukoplakia through morphology-related copy number analysis

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Oral leukoplakia is the most common type of oral potentially malignant disorders and considered a precursor lesion to oral squamous cell carcinoma. However, a predictor of oral leukoplakia prognosis has not yet been identified. We investigated whether copy number alteration patterns may effectively predict the prognostic outcomes of oral leukoplakia using routinely processed paraffin sections. Comparison of copy number alteration patterns between oral leukoplakia with hyperplasia (HOL, *n*=22) and dysplasia (DOL, *n*=21) showed that oral leukoplakia with dysplasia had a higher copy number alteration rate (86%) than oral leukoplakia with hyperplasia (46%). Oral leukoplakia with dysplasia exhibited a wider range of genomic variations across all chromosomes compared with oral leukoplakia with hyperplasia. We also examined a retrospective cohort of 477 patients with oral leukoplakia with hyperplasia with detailed follow-up information. The malignant transformation (MT, *n*=19) and leukoplakia recurrence (LR, *n*=253) groups had higher frequencies of aneuploidy events and copy number loss rate than the free of disease (FD, *n*=205) group. Together, our results revealed the association between the degree of copy number alterations and the histological grade of oral leukoplakia and demonstrated that copy number alteration may be effective for prognosis prediction in oral leukoplakia patients with hyperplasia.

oral leukoplakia, copy number alteration, prognosis prediction

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INTRODUCTION

Oral squamous cell carcinoma (OSCC), a major pathological type of head and neck cancer, accounts for more than 90% of all oral malignancies (Ng et al., 2017; Jemal et al., 2010). While the diagnosis and treatment of many cancers have significantly improved over the last decades, the early detection and effective management of OSCC remain challenging (Jemal et al., 2004; Haddad and Shin, 2008; Goodson and Thomson, 2011; Almangush et al., 2021; Chai et al., 2020; Lindemann et al., 2018). Oral potentially malignant disorders are thought to be the precancerous lesions of OSCC, and research has been focused on identifying reliable indicators to identify patients with these lesions. The development of new strategies for disease prediction based on molecular pathology is considered to have promising potential for the improvement of patient survival.

Oral leukoplakia (OL) is the most common oral potentially malignant disorder and is defined by the World Health Organization as a white plaque of questionable risk after exclusion of other known diseases or disorders that carry no increased risk for cancer (Warnakulasuriya and Ariyawardana, 2016; Lee et al., 2000; EI-Nagger et al., 2017; Yanik et al., 2015). Currently, the standard diagnostic and prognostic assessments of OL are clinical examinations as well as biopsy, if necessary, to exclude other oral mucosal disorders and determine the presence or absence of epithelial dysplasia. Dysplasia-free OL is often designated as simple hyperplasia or hyperkeratosis. OL lesions with varying degrees of epithelial dysplasia are determined by histopathological examination based on architectural and cytological characteristics (Staines and Rogers, 2017). Importantly, OL with epithelial dysplasia shows a higher risk of malignant transformation (up to 13%) compared with dysplasia-free OL (2.1%) (Lee et al., 2000; Gao et al., 2012). Based on the presence and severity of epithelial dysplasia (i.e., mild, moderate, or severe) determined by pathological examinations, clinicians decide whether to monitor the lesion or to surgically intervene (Gomes et al., 2015; Monteiro et al., 2017). Lesions with a higher dysplasia grade show a higher risk of malignant transformation (Mehanna et al., 2009; Warnakulasuriya et al., 2011). Therefore, clinical therapy for these lesions tends to be surgical removal or even more radical approaches. However, histological grading of epithelial dysplasia is often subjective and displays low levels of intra- and inter-observer agreements (Holmstrup et al., 2007). Moreover, recent longitudinal studies have yielded contradictory results, suggesting that morphological assessment alone may not be a reliable predictor of OL prognosis (Saintigny et al., 2011; Bosman, 2001). Furthermore, no study has confirmed that surgical excision sufficiently prevents OL recurrence and/or malignant transformation (Lodi et al., 2016), indicating that both treated and untreated patients require close surveillance. Therefore, to better stratify patients and clarify individualized plans for clinical treatment and follow-up, the identification of prognostic indicators of OL is of great clinical significance.

In recent decades, substantial effort has been made to identify key molecular markers for the malignant transformation and prognosis of OL. Several genomic alterations have been identified in OL, including single nucleotide variations and mutation hotspots in genes related to the cell cycle and cancer regulatory pathways, such as *TP53*, *Ki-67*, and *NOTCH1* (Zhang et al., 2017; Ding et al., 2018; Yagyuu et al., 2017; Gissi et al., 2015). Loss of heterozygosity and changes in DNA methylation are also significantly associated with clinical outcomes in OL patients (Tsao et al., 2009; Zhou et al., 2011; Zhang et al., 2012; Türke et al., 2017). However, the frequencies of these mutations and altered biomarkers are low, and only a small number of OL cases harbor these genetic alterations (Mello et al., 2020). Thus, the intervention methods involving these markers have not yet proven to be practical (Dionne et al., 2014). Consequently, an effective marker to determine OL prognostic outcome has not yet been identified.

Copy number alterations (CNAs) include deletions, insertions, and duplications of DNA segments (Beroukhim et al., 2010). Unlike the analysis of single hotspot genes, whole genome scale CNA profiling can determine a full spectrum of large-scale genomic variation events, which allows for the identification of common genetic alterations. Recent research has reported that genomic copy number classification can be used in the early diagnosis of esophageal cancer (Killcoyne et al., 2020).

In the present study, we examined the potential of applying CNA analysis through low-depth whole-genome sequencing to predict prognosis and/or malignant potential in OL patients. Our approach integrated pathological findings with CNA profiling of OL tissues. We used laser capture microdissection (LCM) to acquire small-scale tissue samples (200−500 cells) from OL epithelium containing morphological information (foci taken from epithelial hyperplasia or dysplasia) using routinely processed paraffin sections. We applied this approach to elucidate an association between copy number instability and OL prognosis prediction by retrospectively analyzing OL patients with follow-up data. We identified high-risk CNA-harboring hyperplastic tissues, the molecular signature of which significantly improved the effectiveness of malignancy prediction in morphologically normal lesions.

RESULTS

Generation of spatial copy number maps

We combined LCM with a direct whole-genome library construction method to determine the correlation between pathological information and genomic alterations in OL. To improve the throughput while minimizing the amplification bias of the whole-genome sequencing of mini-bulk samples, we developed a scalable library construction method that used Tn5 transposase to tagment genomic DNA without pre-amplification (Figure 1).

The sections were 10 μm thick and stained with hematoxylin-eosin, which allowed for morphological analysis (Figure 1A). LCM was directly performed on the sections; we obtained cells with clearly defined morphology and high purity at the size of hundreds of micrometers. Each dissected sample contained 200−500 cells and was collected in tubes with lysis buffer to release the DNA from histones (Figure 1B). DNA fragments were amplified using PCR primers containing sample barcodes (Figure 1C). In each sequencing run, we commonly pooled 200–400 sample libraries.

Considering the number of cells and DNA degradation in formalin-fixed paraffin-embedded (FFPE) samples, the quality of constructed libraries was very similar to single-cell libraries. Therefore, an approximate sequencing depth of 0.3 Gb (0.1×) was obtained for each sample, which was similar to depths reported in single-cell CNA studies (Baslan et al., 2012; Mallory et al., 2020). A circular binary segmentation algorithm (Olshen et al., 2004) was used to determine the copy number profiles (resolution 2 Mb, alpha=0.0001, min.width=5, undo.SD=2). We mainly focused on arm- or chromosome-level copy number changes with high confidence to eliminate false identifications of small-sized CNAs. Median absolute pairwise difference (MAPD) and the number of mapping reads were the major parameters used to filter out low-quality samples. CNA profiles for qualified samples could be mapped to original spatial locations to infer the relationship between the molecular signatures of cells with distinct morphologies and phenotypes (Figure 1D).

CNA patterns of OL with hyperplasia or dysplasia

We collected biopsy samples from 529 OL patients. Among these patients, 52 OL patients, including 26 OL with dysplasia (DOL) and 26 OL with hyperplasia (HOL), were diagnosed during 2018−2019 and did not have prognosis information, while 477 HOL patients diagnosed during 2012−2015 had follow-up information. Among the 477 HOL patients with prognosis information, 205 (43.0%) were free of disease, while 253 (53.0%) had recurring symptoms, and 19 (4.0%) exhibited malignant transformation (Table S1 in Supporting Information).

We laser-captured 1,650 samples from the 529 OL patients and obtained valid sequencing data for 998 samples. We used an MAPD<0.25 and a number of mapping reads>100 k as the major criteria to further filter out unqualified sequencing data (Figure S1 in Supporting Information). Finally, 580 samples from 260 patients were found to be suitable for subsequent CNA analysis.

We analyzed the CNA ratio according to patient characteristics in the overall OL patient group (Table S2 in Supporting Information). We found that the CNA ratio varied according to patient age, with older patients showing a higher CNA ratio compared with younger patients (χ^2=12.043, P=0.017). Sex and site had no significant correlation with CNAs.

We then evaluated whether there were differences in copy number profiles between DOL and HOL patients by analyzing the data from the 26 HOL and 26 DOL patients diagnosed during 2018−2019. Overall, 43 samples from 22 HOL patients and 61 samples from 21 DOL patients passed the quality filtering. HOL is considered a benign proliferative lesion. We found that 18 samples (from 10 patients) of the 43 HOL samples harbored arm-level CNAs, most of which were aneuploidies (Figure 2A). Copy number gains (77.9%) were more frequent than losses (22.1%), with a preference for certain chromosomes (Figure S2A–C in Supporting Information). Chr 1, Chr 8, Chr 20, Chr 2, Chr 6, and Chr 5 tended to have a high frequency of copy number gain events, while copy number losses mainly occurred at a low frequency on Chr 5, Chr 8, Chr 13, and Chr 16.

DOL patients showed even higher rates of CNAs and aneuploidies than HOL patients (Figure 2B). Importantly, in DOL patients, the genomic variation events occurred on all chromosomes with a specific location preference (Figure S2A and B in Supporting Information). More than 25% of the samples harbored CNAs at Chr 20, Chr 8 and Chr 3. Notably, copy number breakpoints were found in Chr 3, Chr 5, Chr 7, Chr 9, and Chr 10 at a high frequency; in contrast, copy number breakpoints were not often detected in HOL samples. These breakpoints were repeated across patients, indicating a higher level of genome reorganization in DOL patients as compared with that in HOL patients. While HOL samples tended to display copy number gains, in DOL samples, the occurrence rate of copy number gains (66.2%) was closer to that of copy number loss (33.8%) (Figure S2C in Supporting Information).

Among the 22 HOL patients possessing qualified data, 10 patients (46%) were found to have CNAs, while 18 out of 21 (86%) DOL patients showed changes in copy number (χ^2=7.667, P=0.006) (Figure 2C). The rate of copy number changes was similar between male and female patients in both the HOL and DOL groups (Figure S2D in Supporting Information).

We further used two numerical indices, CNAscore and COUNTscore, to quantitatively depict the landscape of copy number changes in each sample and evaluate the CNA differences between the HOL and DOL groups. CNAscore is an empirical index that combines two major components that

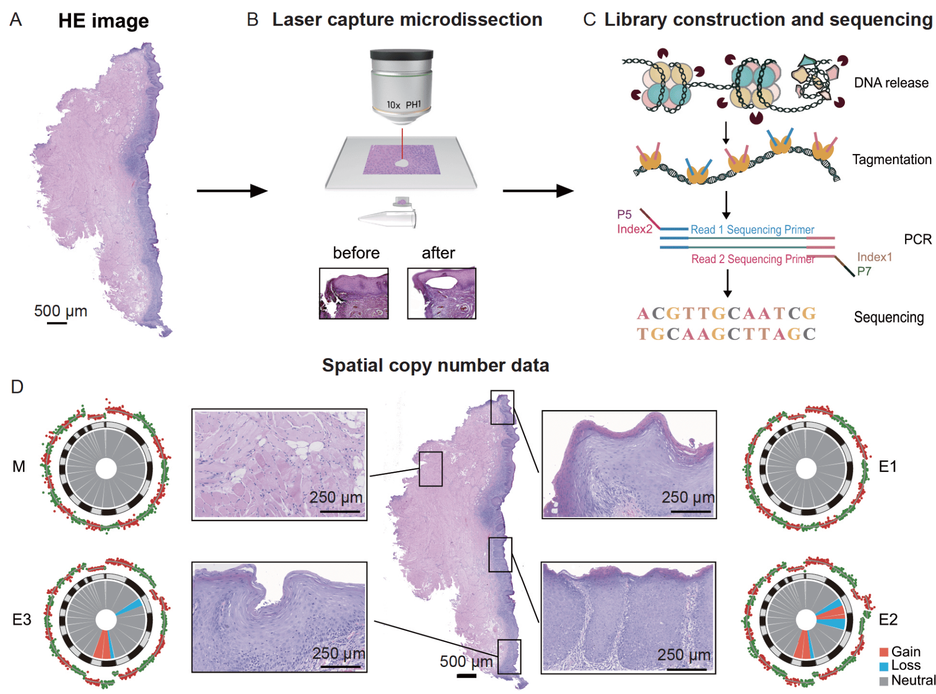

Figure 1 Overview of the copy number profiling method. A, Hematoxylin and eosin (H&E) stained images were used to scan whole tissues and identify cell morphologies. B, Mini-bulk samples were directly dissected by LCM. C, Work-flow of library construction. DNA molecules were released from histones and tagmented by the Tn5 enzyme. Each library was barcoded and amplified using PCR. Barcoded libraries were pooled and subjected to next-generation sequencing. D, Copy number profiles were mapped to their original coordinates in tissue sections. A representative example of three epithelial samples (E1, E2 and E3) and one muscle sample (M) is shown.

reflect the degree of copy number changes and the general copy number deviation from a neutral value (see MATERIALS AND METHODS). COUNTscore evaluates the number of CNA segments in each sample and also reflects the frequency of the structural variation in the genome (see MATERIALS AND METHODS). We calculated the frequency distributions of CNAscore and COUNTscore values in the HOL and DOL samples (Figure 2D). The DOL group showed a relatively uniform distribution, with more samples possessing a higher CNAscore and COUNTscore. Conversely, most HOL samples showed low a CNAscore and COUNTscore. Considering the limitations of CNAscore and COUNTscore (see MATERIALS AND METHODS), we believe it is necessary to consider the results of both scores to establish a comprehensive conclusion when estimating the severity of CNAs.

We further found that 18 out of 61 DOL samples (30%) displayed severe copy number changes (CNAscore>4.3 and COUNTscore>7) compared with only 1 out of 43 (2%) of HOL samples (Figure S3 in Supporting Information). These results are in accordance with previous observations that DOL cases have more structural genomic variations than HOL cases.

Taken together, these results showed that compared with HOL samples, DOL samples exhibited more serious genome rearrangements in terms of a higher CNA occurrence rate, a broader distribution of CNAs, and a higher frequency of copy number breakpoints. Such histologically associated CNA profiles suggested that genome instability may correlate with lesion severity.

Association between CNA events and disease progression of HOL

As one of the cancer hallmarks, CNA events in the HOL samples may have the potential to serve as molecular signatures to predict the risk of disease progression or even further malignant transformation in certain patients morphologically diagnosed as hyperplasia. Therefore, we next examined the possible correlation between the CNA events in the epithelial samples collected from HOL patients and disease progression. We conducted a retrospective analysis in HOL patients who had been diagnosed in our hospital from 2012 through 2015 and possessed a detailed follow-up. Of the 1,449 LCM samples from the 477 HOL patients, 433 LCM samples passed the quality filtering after sequencing, and 219 patients were thus further analyzed (Table S1 in Supporting Information). We divided these patients into three categories based on the phenotype and severity of their 5-year outcomes: free of disease (FD), leukoplakia recurrence (LR), and malignant transformation (MT). FD indicated a group of patients with no white plaque during the follow-up period after removal of the primary lesions; LR represented patients with recurrence of the white plaque in

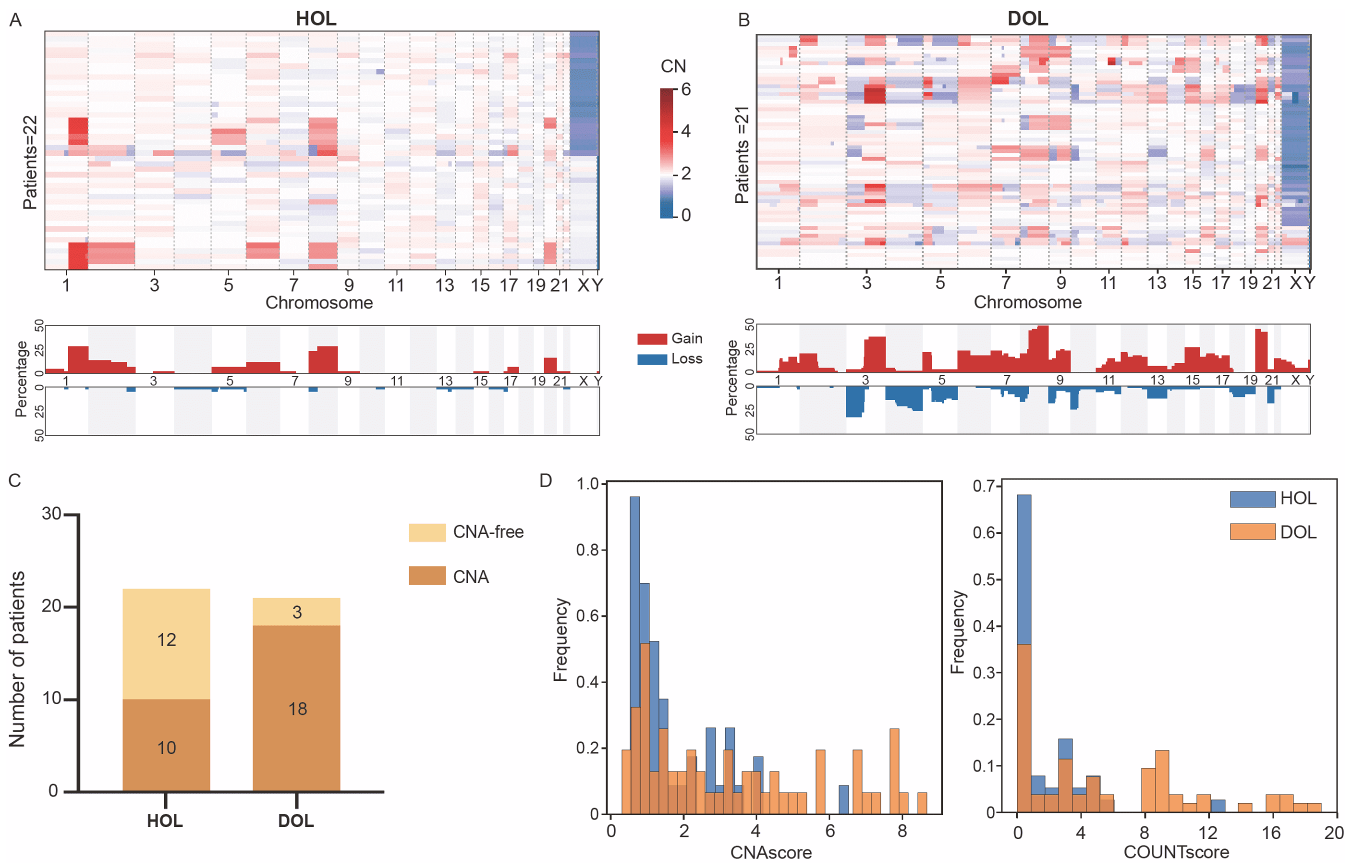

Figure 2 Comparison of copy number alteration between HOL and DOL. A and B, CNA profiles of 43 samples from 22 HOL patients (A) and 61 samples from 21 DOL patients (B) enrolled during 2018–2019. Heatmap (upper panel) and aggregation of CNAs (lower panel) showing the key CNA events in specific chromosomes. In the lower panel, the *y*-axis indicates the percentage of samples harboring CNAs. C, Proportions of HOL and DOL patients harboring CNAs. D, Normalized frequency distributions of CNAscore (left panel) and COUNTscore (right panel) for HOL and DOL samples.

the same site of the primary lesion; and MT included patients with lesions that showed malignant transformation to OSCC after removal of the primary leukoplakia.

One of the main genomic characteristics of HOL tissues was that most CNA events occurred at the whole-chromosome level. We found that such aneuploidies showed significantly high occurrence rates in Chr 1, Chr 2, Chr 7, Chr 8 and Chr 20 (Figure 3A and B). Notably, the hotspot aneuploidies did not occur at similar rates among the patient groups. Patients in the FD group had a significantly lower incidence than those in the groups with disease progression (LR and MT) (Figure S4A in Supporting Information).

We further observed four major differences in the CNA profiles among the FD, LR, and MT groups (Figure 3A and B). First, although aneuploidy events of Chr 1, Chr 2, Chr 7, Chr 8, and Chr 20 were observed in all groups, they were most frequent in the MT group followed by the LR group, and both were significantly more frequent than those in the FD group (Figure S4A and B in Supporting Information). For example, 50% of the Chr 8 gain events were identified in MT samples, followed by 36% in LR samples, and 11% in FD samples. Second, copy number losses were rare in the FD group (10.1%), but occurred at a relatively higher rate in the MT (18.2%) and LR (16.5%) groups (Figure S4C in Supporting Information). Third, in addition to the shared aneuploidy hotspots, the MT and LR groups contained more CNA events on many other chromosomes, while the FD group rarely showed CNA events outside of the hot spots (Figure S4B in Supporting Information). Fourth, compared with the LCM samples in the FD group, a number of LCM samples in the LR and MT groups contained breakpoints, similar to the observation in DOL samples. Moreover, we found that 5 out of 76 (7%) LR patients and 2 out of 10 (20%) MT patients harbored the signature Chr 3 breakpoints identical to those seen in DOL cases. Both LR and MT patients harbored Chr 5 breakpoints: 4% in the LR group and 30% in the MT group. Furthermore, three (4%) LR patients showed breakpoints in both Chr 4 and Chr6, while six (60%) MT patients showed breakpoints in Chr 1 and one (10%) MT patient showed breakpoints in Chr 7, Chr 11, and Chr 12.

Despite the small number of patients in the MT group, all 10 (100%) MT patients had CNAs, while 31 out of 130 (23.8%) FD patients and 43 out of 76 (56.6%) LR patients harbored CNAs (χ^2=41.157, P<0.0001). We also used

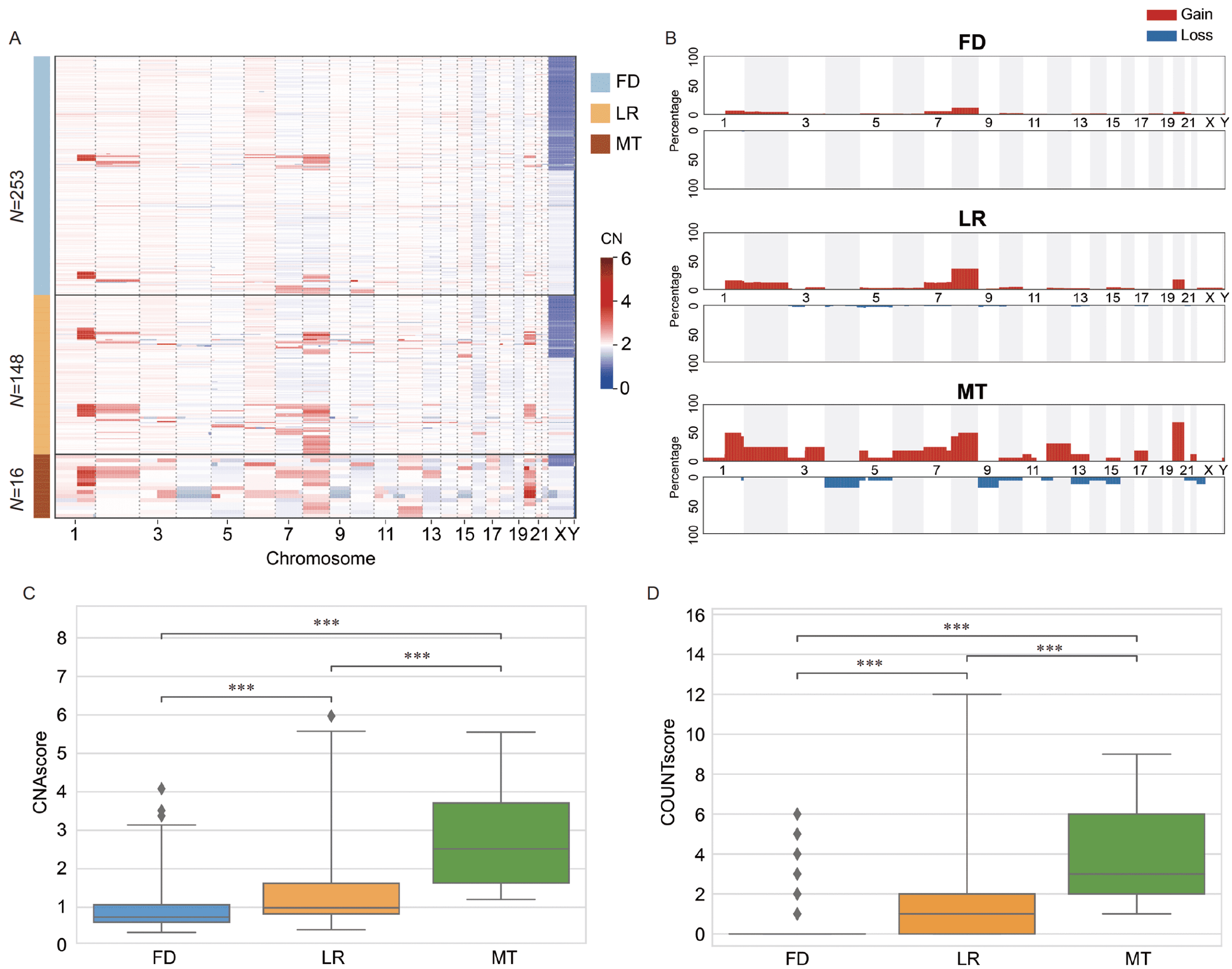

Figure 3 CNAs are associated with disease progression of HOL. A, Heatmap showing the epithelial CNA profiles of HOL patients categorized to three groups (FD, LR and MT) based on 5-year outcomes. B, Accumulation of copy number changes in samples from the three categories. *y*-axis indicates the percentage of samples harboring CNAs. C and D, Boxplots showing the distributions of CNAscore (C) and COUNTscore (D), indicating an association between the degree of CNAs and disease progression. (*t*-test , ***, $P<0.001$).

CNAscore and COUNTscore to quantitatively depict the degree of copy number changes of the three groups. Both scores could separate the FD, LR, and MT groups, with MT samples showing the highest CNAscore and COUNTscore followed by LR samples (Figure 3C and D). Notably, both scores of HOL tissue samples in the MT group were comparable with those obtained in the DOL samples (Figure S4D in Supporting Information), which displayed a strong tendency to develop into OSCC. This observation indicates an association between the severity of copy number changes and the development of leukoplakia.

CNA evolution during disease progression

We further examined the CNA profiles of the hyperplastic tissues obtained from the same individuals prior to and following the recurrence of leukoplakia (Figure 4A and B; Figure S5A in Supporting Information). There were four such patients, and 21 LCM samples passed quality filtering. For each individual, both the CNAscore and COUNTscore were similar for the primary and recurrent leukoplakia tissues (Figure S5B in Supporting Information); however, neither score was sensitive enough for small-sized variations. Such indices could not reveal the finer scale difference in CNA events. Newly occurring small variation features in the recurrent samples, such as Chr 8 gains in patient LR-P509 and Chr 6 breakpoints in patient LR-P258, did not cause a significant change in either score (Figure 4B).

Four of the enrolled HOL patients were later diagnosed with OSCC. We evaluated the CNA profiles of these MT group patients using 26 LCM samples (Figure 4C and D; Figure S5C in Supporting Information). As an intra-individual control, CNA profiling was performed on muscle cells captured from the same section that exhibited no evidence of aneuploidy (Figure S5C in Supporting Information). The hyperplastic epithelial samples collected from

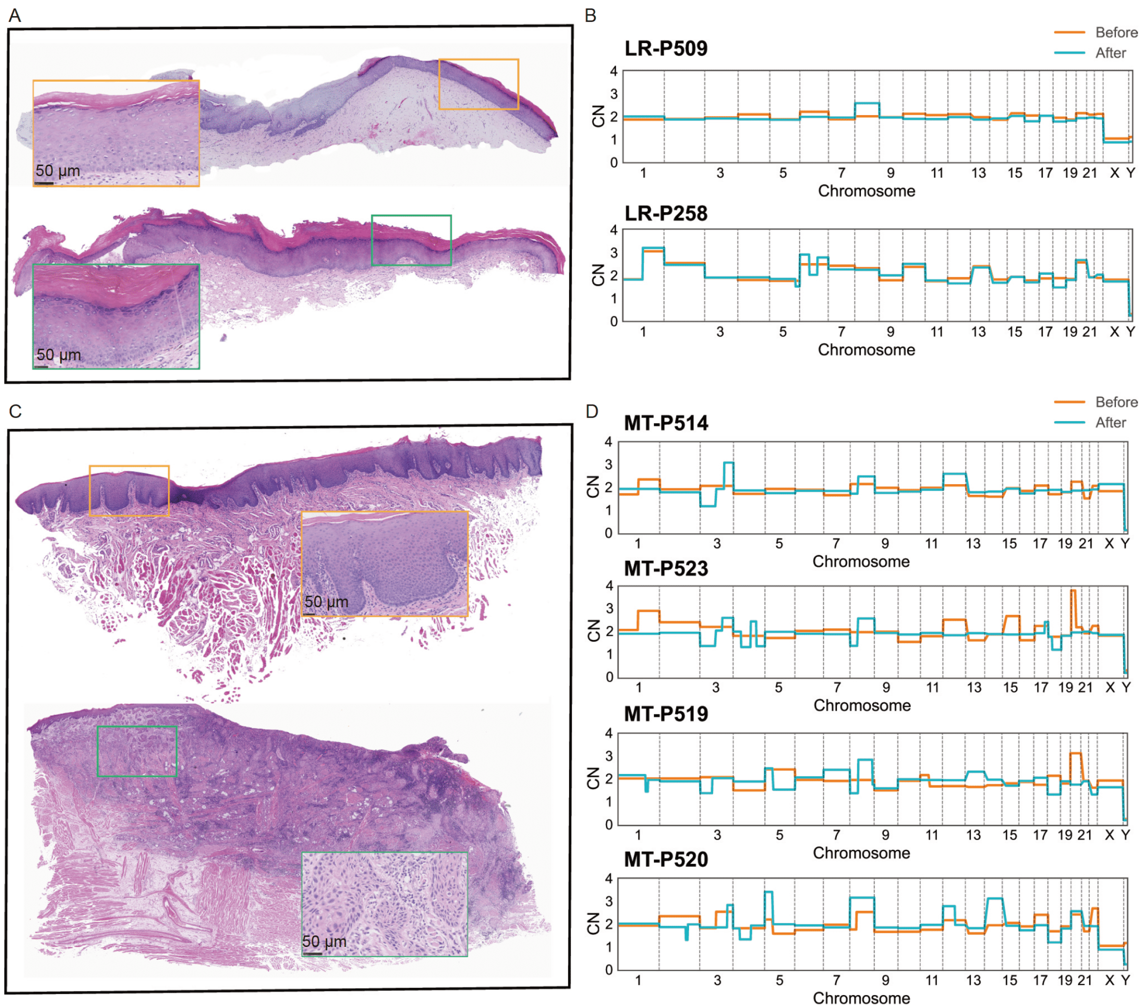

Figure 4 Copy number profiling during disease progression. A, H&E images showing primary epithelial tissues (upper panel) and recurrent epithelial tissues (lower panel) from patient LR-P509. Enlarged images indicate regions isolated by LCM. B, Copy number profiles of primary and recurrent tissues in patients LR-P509 and LR-P258. Copy number in each bin was calculated as the median value of all samples of the same cell type from each patient. C, H&E images showing primary epithelial tissues (upper panel) and tumor tissues following malignant transformation (lower panel) from patient MT-P520. Enlarged images indicate regions isolated by LCM. D, Copy number profiles of primary epithelial tissues and malignant tumor tissues in patients MT-P514, MT-P523, MT-P519 and MT-P520. Copy number in each bin was calculated as the median value of all the samples of the same cell type from each patient.

different locations of the tissue section showed a pattern of abnormal copy numbers (Figure 4D, Figure S5C in Supporting Information), indicating that genome structural variations had developed, and probably clonally expanded, for a period of time without noticeable morphological changes.

Certain location-specific CNA events, such as breakpoints in Chr 3, Chr 4, Chr 5, and Chr 8, were shared among the four OSCC patients. Interestingly, comparison of HOL and OSCC samples from the same individual showed that the CNA profiles were not identical (Figure 4D; Figure S5C in Supporting Information). For example, aneuploidy events of Chr 14 and Chr 18 were identified in tumor samples but absent in HOL samples, and several aneuploidy events in HOL samples were not found in tumor samples. This longitudinal inconsistency in CNA patterns suggests that there may be certain key events of genome reorganization that are tightly associated with tumorigenesis and reflects the possible selection of specific clones during this process.

Taken together, the association of the CNA profile and the risk of leukoplakia recurrence or malignant transformation provides an additional layer of quantitative information, via the CNAscore and COUNTscore, to the conventional pathological assessment based on morphological features. Such integration of genomic variation data with pathological identification may offer a unique tool to predict the potential outcome in HOL patients.

Delineating spatially clonal genotypes

Using LCM, we mapped the copy number profile of each sample to its original spatial coordinate and illustrated the high-resolution heterogeneity between histologically similar lesions. Mini-bulk sequencing, aided with pathological identification, offered high cellular purity of each sample and hence would allow for the identification of CNA that only occurred as small clones.

Spatially adjacent sampling of the DOL lesion can also generate different CNA patterns, and we found two such cases among all the DOL patients (Figures 1D and 5A). For example, in patient P36, the normal epithelial tissues showed no evidence of copy number changes (Figure 5A and B); however, four CNA clones were identified in the four adjacent DOL samples (D1, D2, D3, and D4). The four clones shared similar aneuploidy of Chr 8, Chr 9, Chr 10, Chr 16, Chr 19, and Chr 20 and exhibited different features of Chr 3, Chr 6, Chr 7, Chr 13, and Chr 22 (Figure 5B).

A similar phenomenon was also found in HOL patients. For example, two CNA clones were also identified in patient P22 (Figure 5C); one of the clones was formed by morphologically normal cells and the other contained three hyperplastic cell clusters. Two clones shared the same CNAs in Chr 1, Chr 2, and Chr 20, and yet the copy numbers in Chr 6 and Chr 8 were different (Figure 5D). Although we had dissected multiple hyperplastic cell clusters that were scattered throughout the HOL tissue, we observed no intra-tissue heterogeneity from CNA profiling.

These two examples unveil the possible clone expansion of leukoplakia cells. Furthermore, the existence of aneuploidy in morphologically normal cells also agrees with the recent reports on the various types of cancers. Together, our observations suggested that genomic variations may provide an additional facet to help predict the developmental fate of leukoplakia cells.

DISCUSSION

Recent research has demonstrated that genomic changes in many cancers may occur prior to other alterations that can be detected by conventional pathological techniques (Gerstung et al., 2020). Given that chromosome structural variations are considered a hallmark of cancer and were recently found in morphologically noncancerous tissues (Zhou et al., 2020), we believe that such CNAs in morphologically normal cells may provide new insights into the prognosis of OL, the most common premalignant lesion of OSCC.

Previous studies have reported that a variety of CNAs, such as aberrations in Chr 5q, 7p, 7q, and 8p, are involved in the development and malignant transformation of OL (Wood et al., 2017; Bhattacharya et al., 2011; Bhosale et al., 2011; de Boer et al., 2019). However, these studies have two major limitations. First, most of the studies focused on specific genomic chromosomes, and second, these studies used large bulk samples as input for sequencing, which resulted in unavoidable mixing of various cell types.

In the present study, the combination of LCM and mini-bulk sequencing allowed us to link histopathological information with genomic alterations in OL samples. The copy number profiling of 529 OL patients yielded comprehensive and detailed findings showing that HOL is chromosomally distinct from DOL. Moreover, we identified different CNA clones within relatively close epithelial regions, which are typically obscured by bulk tissue sequencing approaches. Although there is some evidence of possible correlations between DOL and OSCC through common genomic variations (Ho et al., 2013), it remains unclear which variations could serve as markers for diagnosis or prognosis monitoring. Furthermore, because HOL has been conventionally considered a benign lesion with negligible malignant potential, the majority of previously published OL studies have focused on DOL. Therefore, the prediction of outcomes for HOL is even more challenging.

From the perspective of pathology, hyperplasia has long been thought to be a harmless and mild lesion that mainly exhibits epithelial hyperkeratosis and disappearance of nuclei. However, hyperplasia may lead to completely different fates of disease progression, and its malignant potential remains one of the most challenging topics for clinical pathologists. Our study provides a new strategy to quantitatively evaluate the probability of transformation from HOL to OSCC through whole genome CNA landscape assessment using paired HOL and OSCC samples.

Examination of the frequencies of CNA events in hyperplasia and dysplasia samples showed a clear association between genomic changes and pathological grades. In our retrospective study of the correlation between CNA profiles and prognostic outcomes of HOL, we observed that patients with poor prognostic outcomes showed a higher degree of genomic variations. Intriguingly, some morphologically hyperplastic samples with abnormal copy number profiles transformed into OSCC. Importantly, we found that morphologically different HOL and DOL shared many common genomic variations, suggesting that these two types of lesions may share the same causes.

Currently, the prognostic assessment of OL still mainly depends on clinical features and histopathological diagnosis based on atypical epithelial performance (Warnakulasuriya et al., 2008; Karatayli-Ozgursoy et al., 2015). However, the grading systems based only on cytological changes are limited in providing reliable results to predict malignant potential and prognostic outcomes. Because morphological grading is relatively subjective and relies largely on the pathologists' experience, an objective and reliable prognostic indicator of OL is urgently needed (Pitiyage et al., 2009; Rivera et al., 2017). The correlation between CNA occurrence and malignant transformation that we observed through whole-genome shallow sequencing in the present study shows that CNA may be an effective auxiliary indicator for the disease outcome of precancerous lesions. We recommend a novel follow-up program for OL patients via a

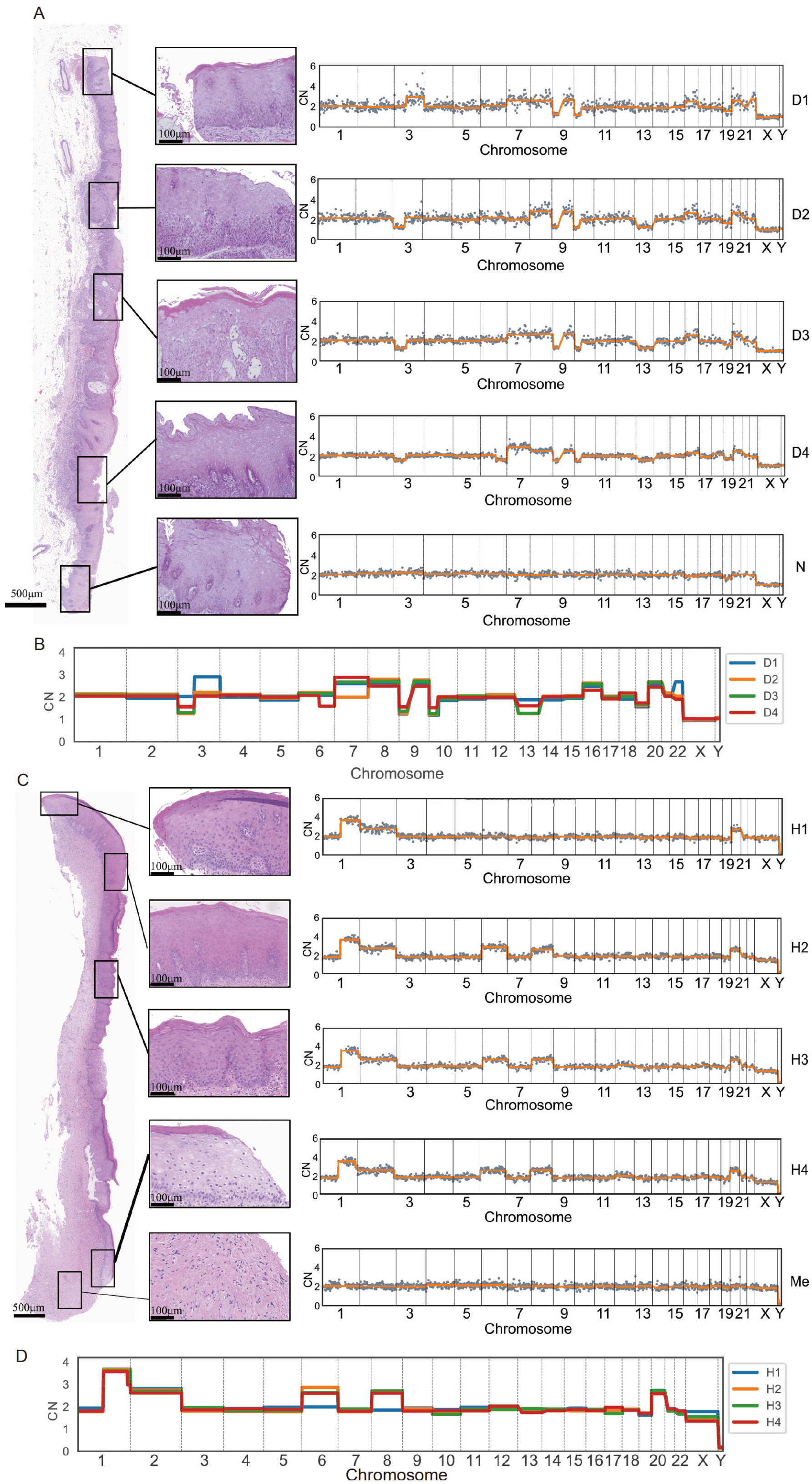

Figure 5 Identification of spatially clonal genotypes. A, CNA profiles (right panel) of four epithelial dysplasia samples (D1, D2, D3, and D4) and one normal epithelial sample (N) isolated from the same tissue slice from DOL patient P36. H&E images (left panel) showing regions isolated by LCM. B, Four CNA subclones were identified in D1, D2, D3, and D4. C, CNA profiles (right panel) of four epithelial samples (H1, H2, H3 and H4) and one mesenchymal sample (Me) isolated from the same tissue slice from HOL patient P22. H&E images (left panel) showing regions isolated by LCM. D, Two CNA subclones were identified in H1, H2, H3, and H4.

combination of morphological analysis and genomic copy number profiling. The morphological HOL patients lacking arm-level CNA tended to have a relatively better prognosis, and therefore regular re-examination is sufficient in these patients. However, HOL patients harboring arm-level CNAs are better treated as DOL patients, with intensive follow-up to monitor possible malignant transformation.

Our findings also have important implications for clinical surgery. One of the key factors of *in situ* recurrence after surgical resection is the incomplete removal of lesion tissues. During traditional surgery, safety margins are largely determined by the subjective judgment of pathologists. However, CNA examination may be a more sensitive method to identify safe margins and evaluate genome alterations as an additional assessment of future surgical risks. Our results indicated that arm-level CAN-containing cells can appear as morphologically normal, suggesting that submicroscopic-level molecular pathology investigation should be performed for many clinical cases. Complete removal of dysplastic regions as well as morphologically normal epithelia with genomic alterations is needed, using quantitative scores as guidelines for the arrangement of marginal resection.

Although all the samples in the present study were collected from a single hospital, we believe that CNA profiling of morphologically normal HOL tissues has general advantages over conventional approaches for risk evaluation. A multi-center study will further improve the reliability of risk assessment and optimize the quantitation of the degree of change in copy number. We conducted our investigation mainly using FFPE samples, which have limitations compared with fresh or frozen samples because of degraded DNA in FFPE samples. Approximately half of the samples did not pass the quality filter for inclusion data analysis. Further improvement should be planned to optimize sequencing library construction using low-quality FFPE samples.

MATERIALS AND METHODS

Sample collection, preparation, and staining

This research was approved by the Institutional Review Board of Peking University Hospital of Stomatology, and written informed consent was obtained from all patients (approval NO. PKUSSIRB-201949116). A total of 1,650 samples were collected from 529 OL cases; all samples were FFPE samples (Table S1 in Supporting Information) retrieved from the Department of Pathology, Peking University Hospital of Stomatology. Among the 529 OL patients, 52 had enrolled in the past two years and therefore did not have 5-year prognosis information. The remaining OL patients had been diagnosed as hyperplasia OL from 2012 to 2015 and possessed detailed follow-up information.

FFPE samples were sectioned into 10-μm tissue slices using a tissue microtome (REM710, Yamato, Japan), and placed on PEN-membrane glass slides (Leica, USA). Staining procedures were performed as previously described with slight modifications (Martelotto et al., 2017). Briefly, FFPE slides were soaked in xylene three times for 10 min each and subsequently rehydrated in a series of ethanol immersions for 1 min each (twice in 100% ethanol, followed by 95%, 70%, and 50% ethanol). After washing with DEPC-treated water, slides were subjected to hematoxylin and eosin (H&E) staining by standard protocol. Finally, sequential ethanol solutions were used to dehydrate the samples. Slides were scanned using a digital slice scanning device (NanoZoomer 2.0T).

LCM and cell lysis

Stained slides were micro-dissected using an LCM system (LMD7, Leica). The areas of interest, containing morphologically normal epithelia, hyperplasia, and dysplasia, were captured and reviewed by three independent experienced pathologists. Muscle or mesenchyme tissues distant from the lesion regions were also obtained as germline control. LCM was performed using a 10× objective, and the number of cells in each captured tissue sample was maintained at 200–500. Typically, FFPE samples less than two years old displayed better DNA preservation than those over 5 years old, indicating that a greater number of cells may be required for the preparation of sequencing libraries. Captured tissues were lysed in 8 μL lysis buffer (6.4 μL nuclease-free water, 0.24 μL 1 mol L^{-1} Tris- HCl, 0.16 μL 500 mmol L^{-1} NaCl, 0.08 μL 500 mmol L^{-1} EDTA, 0.32 μL 5% Triton and 0.8 μL Proteinase K) at 50°C for 12 h.

Whole-genome amplification and sequencing

DNA in lysis buffer was tagmented using Tn5-transposase (Vazyme, Nanjing, China), amplified by 20 cycles of PCR, and purified using VAHTS DNA clean beads (Vazyme). Approximately 2 μg final amplified product was obtained for each sample. The concentration of the samples was measured using the Qubit system (Invitrogen, USA) and the fragment size (ranging from 300 to 700 bp) was determined by the Fragment Analyzer (Agilent, USA). Samples that failed in library construction were excluded before sequencing. Libraries with low concentration or incorrect size distribution as determined by the Agilent Fragment Analyzer were identified as unqualified and excluded before sequencing. Libraries were then sequenced on an Illumina HiSeq 4000 sequencer with PE150.

Bioinformatics analysis

We filtered out unqualified samples in wet-lab quality control. Sequenced samples without sufficient sequencing data (<0.1 M paired-end reads) were excluded before performing bioinformatic analysis. In total, 652 unqualified samples were removed leaving 998 samples for bioinformatic analysis. Adapter trimming was first performed on 2×150 paired-end reads using Cutadapt (version 2.10) (Martin, 2011) under default setting, which were subsequently aligned to the human reference genome (hg19) by Bowtie2 aligner (version 2.2.9) (Langmead and Salzberg, 2012) using default setting. The hg19 genome was downloaded from the UCSC Genome Browser: http://hgdownload.cse.ucsc.edu/goldenPath/hg19/bigZips/. Approximately 1 M mapped reads were obtained for each sample. Reads were tabulated into non-overlapping dynamic bins (2 Mb resolution) across the genome. Lowess regression normalization was performed to reduce the GC bias of bin counts. Copy number was called by R package DNAcopy (version 1.44.0) (Seshan and Olshen, 2020) using circular binary segmentation algorithm (alpha=0.0001, min.width=5, undo.SD=2).

Statistical analysis

As widely used in in previous CNA studies (Kader et al., 2016; Ning et al., 2015), we calculated the MAPD (Affymetrix, 2008) of sampling bins to judge the dispersion of data points which reflects the quality of CNA profiles and filter out low-quality samples (MAPD≥0.25). If x_i is the copy number value of the *i*th bin, then

$$\text{MAPD}=\text{median}\left(\left|x_{i+1}-x_i\right|\right),$$

where *i* is ordered by genomic position. The determination of the MAPD threshold was based on the distribution of MAPD shown in Figure S1B in Supporting Information. Passing-filter samples were also examined manually. Unqualified examples either with low coverage (mapping reads<100 k) or noisy bins (MAPD>0.25) are shown in Figure S1C in Supporting Information.

Because copy number change events covering larger genome regions may influence more genes and different copy number gains or losses may have different dosage effects in the regulation of cell activities, we assume both factors should be considered when estimating CNA severity. We first developed CNAscore to calculate the level of sample genome rearrangement in samples. CNAscore of the *j*th chromosome was first calculated by

$$\text{CNAscore}_j=\text{mean}\left(\left|s_i-s_{i-1}\right|\right)+0.5*\left|\text{mean}(s_i)-\text{norm}\right|,$$

where *i* is ordered by the genomic position within a specific chromosome, s_i is the segment value at position *i*, and norm is the neutral copy number of each segment (norm=0, 1, or 2).

The CNAscore of each sample was calculated as the sum of the values of all 24 chromosomes:

$$\text{CNAscore}=\sum_{j=1}^{24}\text{CNAscore}_j.$$

The CNAscore comprises two parts. The first penalizes the variation between adjacent segments, which reflects the level of fluctuation among CNA segments. The second part penalizes deviation of the estimated average ploidy from the neutral state. As a result, longer CNA or CNA with higher copy number would have a bigger influence on ploidy estimation, thus increasing the value of CNAscore. The drawback of CNAscore is the fluctuation of segment values and that ploidy inferring may inevitably be influenced by library quality; that is, among samples sharing the same CNA profiles, those with noisier bins may have higher CNAscores.

COUNTscore calculates the sum of CNA segments in each sample, and it has been used in previous studies to quantify the severity of CNA changes (Davoli et al., 2017; Taylor et al., 2018). For diploid chromosomes, copy number gain is defined as a copy number>2.3, and copy number loss is defined as a copy number<1.6 based on the copy number distribution of all the bins (Figure S6A in Supporting Information). For haploid chromosomes, copy number gain is defined as copy number>1.5, and copy number loss is defined as copy number<0.5. In comparison with CNAscore, COUNTscore is less likely to be affected by sample quality; however, COUNTscore is limited by the copy number cut-offs, and therefore it may underestimate the copy number state of each sample, especially in bulk cases. Thus, we combined both CNAscore and COUNTscore to fully evaluate the genome complexity of each sample. The cut-offs of defining CNA events are shown in Figure S6 in Supporting Information and found the major conclusions were robust to the cut-off selection. A COUNTscore>0 was used to infer samples with CNAs to reduce false positive calling.

Statistical differences between HOL and DOL were determined using Chi-squared (χ^2) test. Other analyses were performed using independent *t*-test. *P*<0.05 was considered statically significant.

Compliance and ethics *The author(s) declare that they have no conflict of interest. This research was approved by Institutional Review Board of Peking University Hospital of Stomatology, and written informed consent was obtained from all patients (approval NO. PKUSSIRB-201949116).*

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References

Affymetrix. (2008). Median of the absolute values of all pairwise differences and quality control on affymetrix genome-wide human SNP array 6.0. Available from: URL: http://tools.thermofisher.com/content/sfs/brochures/mapd_snp6_whitepaper.pdf.

Almangush, A., Leivo, I., and Mäkitie, A.A. (2021). Biomarkers for immunotherapy of oral squamous cell carcinoma: current status and

challenges. Front Oncol 11, 616629.
Baslan, T., Kendall, J., Rodgers, L., Cox, H., Riggs, M., Stepansky, A., Troge, J., Ravi, K., Esposito, D., Lakshmi, B., et al. (2012). Genome-wide copy number analysis of single cells. Nat Protoc 7, 1024–1041.
Beroukhim, R., Mermel, C.H., Porter, D., Wei, G., Raychaudhuri, S., Donovan, J., Barretina, J., Boehm, J.S., Dobson, J., Urashima, M., et al. (2010). The landscape of somatic copy-number alteration across human cancers. Nature 463, 899–905.
Bosman, F.T. (2001). Dysplasia classification: pathology in disgrace? J Pathol 194, 143–144.
Bhattacharya, A., Roy, R., Snijders, A.M., Hamilton, G., Paquette, J., Tokuyasu, T., Bengtsson, H., Jordan, R.C.K., Olshen, A.B., Pinkel, D., et al. (2011). Two distinct routes to oral cancer differing in genome instability and risk for cervical node metastasis. Clin Cancer Res 17, 7024–7034.
Bhosale, P.G., Cristea, S., Ambatipudi, S., Desai, R.S., Kumar, R., Patil, A., Kane, S., Borges, A.M., Schäffer, A.A., Beerenwinkel, N., et al. (2011). Chromosomal alterations and gene expression changes associated with the progression of leukoplakia to advanced gingivobuccal cancer. Transl Oncol 10, 396–409.
Chai, A.W.Y., Lim, K.P., and Cheong, S.C. (2020). Translational genomics and recent advances in oral squamous cell carcinoma. Semin Cancer Biol 61, 71–83.
Davoli, T., Uno, H., Wooten, E.C., and Elledge, S.J. (2017). Tumor aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy. Science 355, eaaf8399.
de Boer, D.V., Brink, A., Buijze, M., Stigter-van Walsum, M., Hunter, K. D., Ylstra, B., Bloemena, E., Leemans, C.R., and Brakenhoff, R.H. (2019). Establishment and genetic landscape of precancer cell model systems from the head and neck mucosal lining. Mol Cancer Res 17, 120–130.
Ding, X., Zheng, Y., Wang, Z., Zhang, W., Dong, Y., Chen, W., Li, J., Chu, W., Zhang, W., Zhong, Y., et al. (2018). Expression and oncogenic properties of membranous Notch1 in oral leukoplakia and oral squamous cell carcinoma. Oncol Rep 39, 2584–2594.
Dionne, K.R., Warnakulasuriya, S., Binti Zain, R., and Cheong, S.C. (2014). Potentially malignant disorders of the oral cavity: Current practice and future directions in the clinic and laboratory. Int J Cancer 136, 503–515.
EI-Nagger, A.K., Chan, J.K.C., Grandis, J.R., Takata, T., and Slootweg, P.J. (2017). WHO Classification of Head and Neck Tumours. 4th ed. Geneva: World Health Organization.
Gao, Y., Guo, Z.L., Luo, H.Y., and Wang, J. (2012). Clinicopathological characteristics of malignant transformation in 85 cases of oral leukoplakia (in Chinese). Chin J Stomatol 47, 410–413.
Gerstung, M., Jolly, C., Leshchiner, I., Dentro, S.C., Gonzalez, S., Rosebrock, D., Mitchell, T.J., Rubanova, Y., Anur, P., Yu, K., et al. (2020). The evolutionary history of 2,658 cancers. Nature 578, 122–128.
Gissi, D.B., Gabusi, A., Servidio, D., Cervellati, F., and Montebugnoli, L. (2015). Predictive role of p53 protein as a single marker or associated with ki67 antigen in oral leukoplakia: a retrospective longitudinal study. Open Dent J 9, 41–45.
Gomes, C.C., Fonseca-Silva, T., Galvão, C.F., Friedman, E., De Marco, L., and Gomez, R.S. (2015). Inter- and intra-lesional molecular heterogeneity of oral leukoplakia. Oral Oncol 51, 178–181.
Goodson, M.L., and Thomson, P.J. (2011). Management of oral carcinoma: Benefits of early precancerous intervention. Br J Oral Max Surg 49, 88–91.
Haddad, R.I., and Shin, D.M. (2008). Recent advances in head and neck cancer. N Engl J Med 359, 1143–1154.
Holmstrup, P., Vedtofte, P., Reibel, J., and Stoltze, K. (2007). Oral premalignant lesions: is a biopsy reliable? J Oral Pathol Med 36, 262–266.
Ho, M.W., Field, E.A., Field, J.K., Risk, J.M., Rajlawat, B.P., Rogers, S.N., Steele, J.C., Triantafyllou, A., Woolgar, J.A., Lowe, D., et al. (2013). Outcomes of oral squamous cell carcinoma arising from oral epithelial dysplasia: rationale for monitoring premalignant oral lesions in a multidisciplinary clinic. Br J Oral Maxillofac Surg 51, 594–599.
Jemal, A., Clegg, L.X., Ward, E., Ries, L.A.G., Wu, X., Jamison, P.M., Wingo, P.A., Howe, H.L., Anderson, R.N., and Edwards, B.K. (2004). Annual report to the nation on the status of cancer, 1975-2001, with a special feature regarding survival. Cancer 101, 3–27.
Jemal, A., Siegel, R., Xu, J., and Ward, E. (2010). Cancer statistics, 2010. CA Cancer J Clin 60, 277–300.
Kader, T., Goode, D.L., Wong, S.Q., Connaughton, J., Rowley, S.M., Devereux, L., Byrne, D., Fox, S.B., Mir Arnau, G., Tothill, R.W., et al. (2016). Copy number analysis by low coverage whole genome sequencing using ultra low-input DNA from formalin-fixed paraffin embedded tumor tissue. Genome Med 8, 121.
Karatayli-Ozgursoy, S., Pacheco-Lopez, P., Hillel, A.T., Best, S.R., Bishop, J.A., and Akst, L.M. (2015). Laryngeal dysplasia, demographics, and treatment: a single-institution, 20-year review. JAMA Otolaryngol Head Neck Surg 141, 313.
Killcoyne, S., Gregson, E., Wedge, D.C., Woodcock, D.J., Eldridge, M.D., de la Rue, R., Miremadi, A., Abbas, S., Blasko, A., Kosmidou, C., et al. (2020). Genomic copy number predicts esophageal cancer years before transformation. Nat Med 26, 1726–1732.
Langmead, B., and Salzberg, S.L. (2012). Fast gapped-read alignment with Bowtie 2. Nat Methods 9, 357–359.
Lee, J.J., Hong, W.K., Hittelman, W.N., Mao, L., Lotan, R., Shin, D.M., Benner, S.E., Xu, X.C., Lee, J.S., Papadimitrakopoulou, V.M., et al. (2000). Predicting cancer development in oral leukoplakia: ten years of translational research. Clin Cancer Res 6, 1702–1710.
Lindemann, A., Takahashi, H., Patel, A.A., Osman, A.A., and Myers, J.N. (2018). Targeting the DNA damage response in OSCC with *TP*53 mutations. J Dent Res 97, 635–644.
Lodi, G., Franchini, R., Warnakulasuriya, S., Varoni, E.M., Sardella, A., Kerr, A.R., Carrassi, A., MacDonald, L.C.I., and Worthington, H.V. (2016). Interventions for treating oral leukoplakia to prevent oral cancer. Cochrane Database Syst Rev 7, 1–72.
Mallory, X.F., Edrisi, M., Navin, N., and Nakhleh, L. (2020). Methods for copy number aberration detection from single-cell DNA-sequencing data. Genome Biol 21, 208.
Martelotto, L.G., Baslan, T., Kendall, J., Geyer, F.C., Burke, K.A., Spraggon, L., Piscuoglio, S., Chadalavada, K., Nanjangud, G., Ng, C.K. Y., et al. (2017). Whole-genome single-cell copy number profiling from formalin-fixed paraffin-embedded samples. Nat Med 23, 376–385.
Martin, M. (2011). Cutadapt removes adapter sequences from high-throughput sequencing reads. EMBnet.journal 17, 10.
Mehanna, H.M., Rattay, T., Smith, J., and McConkey, C.C. (2009). Treatment and follow-up of oral dysplasia—A systematic review and meta-analysis. Head Neck 31, 1600–1609.
Mello, F.W., Melo, G., Guerra, E.N.S., Warnakulasuriya, S., Garnis, C., and Rivero, E.R.C. (2020). Oral potentially malignant disorders: A scoping review of prognostic biomarkers. Crit Rev Oncol/Hematol 153, 102986.
Monteiro, L., Barbieri, C., Warnakulasuriya, S., Martins, M., Salazar, F., Pacheco, J.J., Vescovi, P., and Meleti, M. (2017). Type of surgical treatment and recurrence of oral leukoplakia: a retrospective clinical study. Med Oral 22, 217–223.
Ng, J.H., Iyer, N.G., Tan, M.H., and Edgren, G. (2017). Changing epidemiology of oral squamous cell carcinoma of the tongue: a global study. Head Neck 39, 297–304.
Ning, L., Li, Z., Wang, G., Hu, W., Hou, Q., Tong, Y., Zhang, M., Chen, Y., Qin, L., Chen, X., et al. (2015). Quantitative assessment of single-cell whole genome amplification methods for detecting copy number variation using hippocampal neurons. Sci Rep 5, 11415.
Olshen, A.B., Venkatraman, E.S., Lucito, R., and Wigler, M. (2004). Circular binary segmentation for the analysis of array-based DNA copy number data. Biostatistics 5, 557–572.
Pitiyage, G., Tilakaratne, W.M., Tavassoli, M., and Warnakulasuriya, S. (2009). Molecular markers in oral epithelial dysplasia: review. J Oral Pathol Med 38, 737–752.
Rivera, C., Oliveira, A.K., Costa, R.A.P., De Rossi, T., and Paes Leme, A.F.

(2017). Prognostic biomarkers in oral squamous cell carcinoma: a systematic review. Oral Oncol 72, 38–47.

Saintigny, P., Zhang, L., Fan, Y.H., El-Naggar, A.K., Papadimitrakopoulou, V.A., Feng, L., Lee, J.J., Kim, E.S., Ki Hong, W., and Mao, L. (2011). Gene expression profiling predicts the development of oral cancer. Cancer Prev Res 4, 218–229.

Seshan, V.E., and Olshen, A.B. (2020). DNAcopy: DNA copy number data analysis R package Version 1.64.0..

Staines, K., and Rogers, H. (2017). Oral leukoplakia and proliferative verrucous leukoplakia: a review for dental practitioners. Br Dent J 223, 655–661.

Taylor, A.M., Shih, J., Ha, G., Gao, G.F., Zhang, X., Berger, A.C., Schumacher, S.E., Wang, C., Hu, H., Liu, J., et al. (2018). Genomic and functional approaches to understanding cancer aneuploidy. Cancer Cell 33, 676–689.e3.

Tsao, A.S., Liu, D., Martin, J., Tang, X., Lee, J.J., El-Naggar, A.K., Wistuba, I., Culotta, K.S., Mao, L., Gillenwater, A., et al. (2009). Phase II randomized, placebo-controlled trial of green tea extract in patients with high-risk oral premalignant lesions. Cancer Prev Res 2, 931–941.

Türke, C., Horn, S., Petto, C., Labudde, D., Lauer, G., and Wittenburg, G. (2017). Loss of heterozygosity in FANCG, FANCF and BRIP1 from head and neck squamous cell carcinoma of the oral cavity. Int J Oncol 50, 2207–2220.

Warnakulasuriya, S., and Ariyawardana, A. (2016). Malignant transformation of oral leukoplakia: a systematic review of observational studies. J Oral Pathol Med 45, 155–166.

Warnakulasuriya, S., Reibel, J., Bouquot, J., and Dabelsteen, E. (2008). Oral epithelial dysplasia classification systems: predictive value, utility, weaknesses and scope for improvement. J Oral Pathol Med 37, 127–133.

Warnakulasuriya, S., Kovacevic, T., Madden, P., Coupland, V.H., Sperandio, M., Odell, E., and Møller, H. (2011). Factors predicting malignant transformation in oral potentially malignant disorders among patients accrued over a 10-year period in South East England. J Oral Pathol Med 40, 677–683.

Wood, H.M., Daly, C., Chalkley, R., Senguven, B., Ross, L., Egan, P., Chengot, P., Graham, J., Sethi, N., Ong, T.K., et al. (2017). The genomic road to invasion—examining the similarities and differences in the genomes of associated oral pre-cancer and cancer samples. Genome Med 9, 53.

Yagyuu, T., Hatakeyama, K., Imada, M., Kurihara, M., Matsusue, Y., Yamamoto, K., Obayashi, C., and Kirita, T. (2017). Programmed death ligand 1 (PD-L1) expression and tumor microenvironment: Implications for patients with oral precancerous lesions. Oral Oncol 68, 36–43.

Yanik, E.L., Katki, H.A., Silverberg, M.J., Manos, M.M., Engels, E.A., and Chaturvedi, A.K. (2015). Leukoplakia, oral cavity cancer risk, and cancer survival in the U.S. elderly. Cancer Prev Res 8, 857–863.

Zhang, L., Poh, C.F., Williams, M., Laronde, D.M., Berean, K., Gardner, P. J., Jiang, H., Wu, L., Lee, J.J., and Rosin, M.P. (2012). Loss of heterozygosity (LOH) profiles—Validated risk predictors for progression to oral cancer. Cancer Prev Res 5, 1081–1089.

Zhang, X., Kim, K.Y., Zheng, Z., Bazarsad, S., and Kim, J. (2017). Nomogram for risk prediction of malignant transformation in oral leukoplakia patients using combined biomarkers. Oral Oncol 72, 132–139.

Zhou, J., Cao, J., Lu, Z., Liu, H., and Deng, D. (2011). A 115-bp MethyLight assay for detection of p16 (CDKN2A) methylation as a diagnostic biomarker in human tissues. BMC Med Genet 12, 67.

Zhou, Y., Bian, S., Zhou, X., Cui, Y., Wang, W., Wen, L., Guo, L., Fu, W., and Tang, F. (2020). Single-cell multiomics sequencing reveals prevalent genomic alterations in tumor stromal cells of human colorectal cancer. Cancer Cell 38, 818–828.e5.

SUPPORTING INFORMATION

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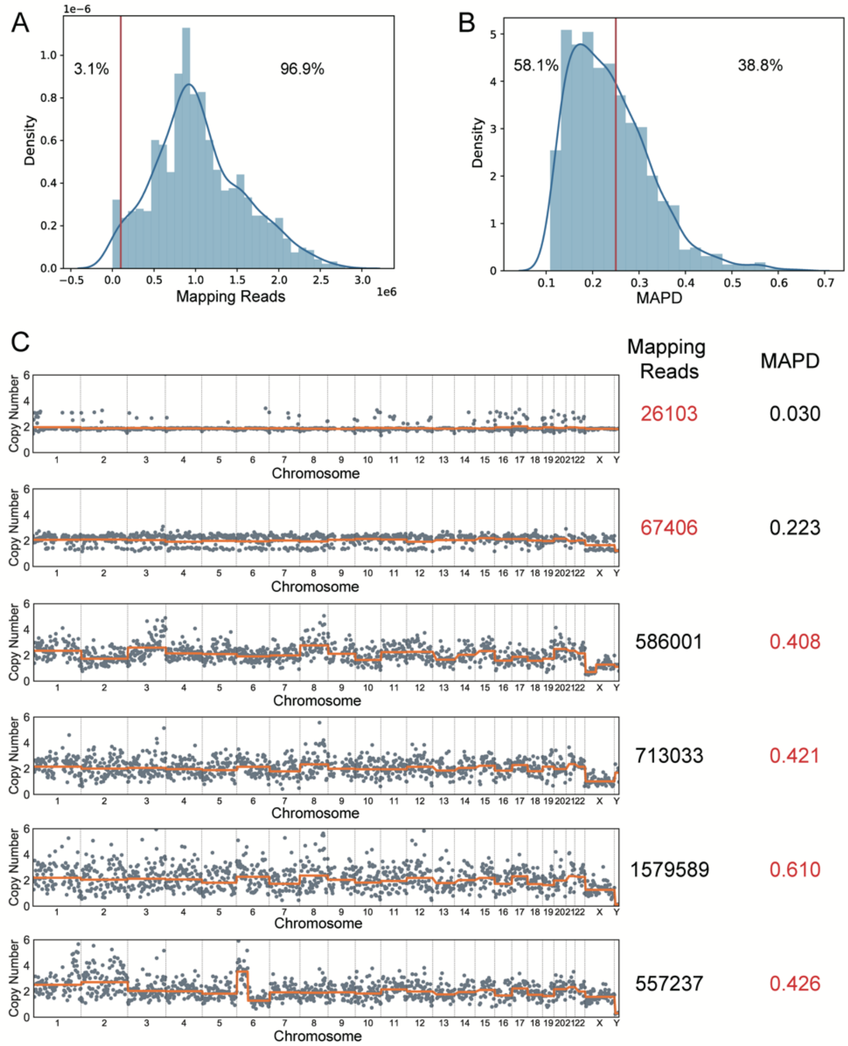
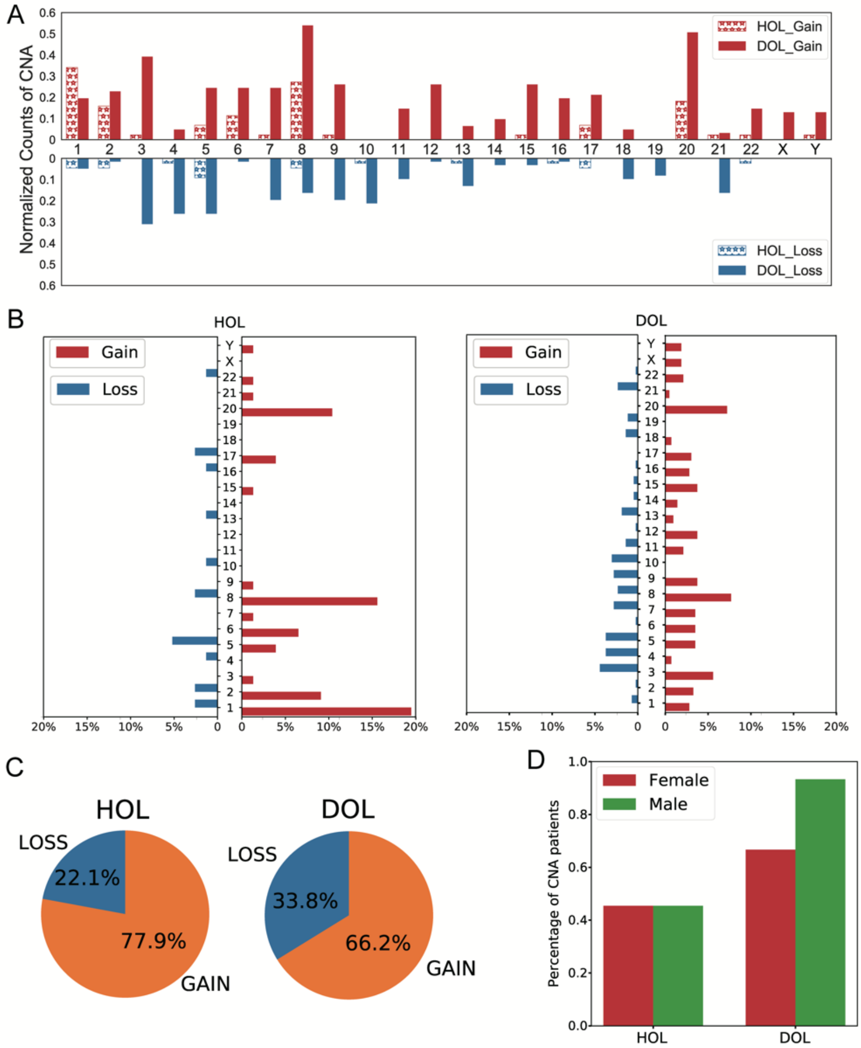
Supplementary information



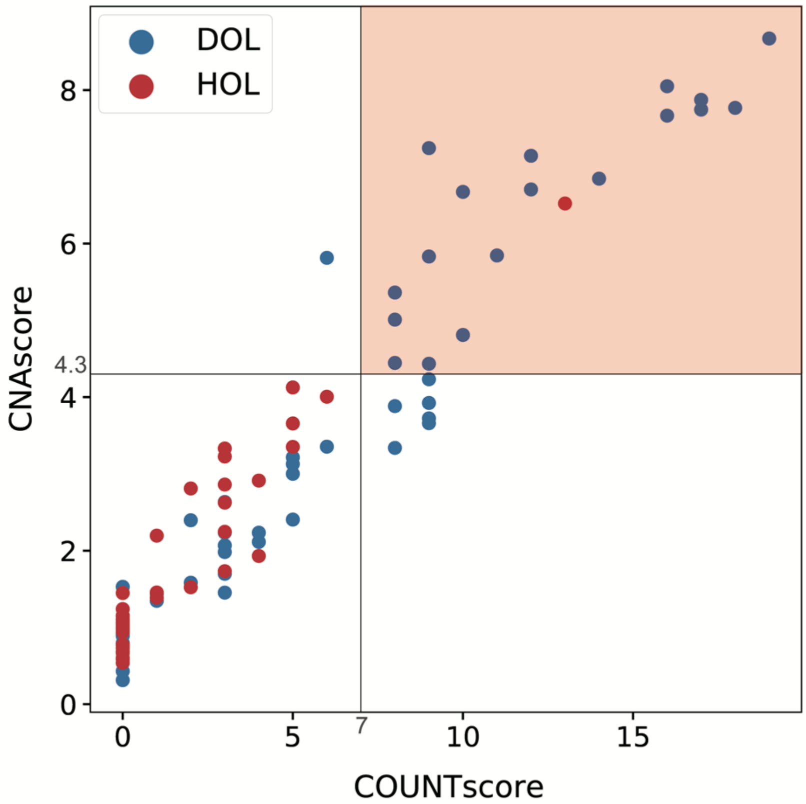
Supplementary Fig. 1 Quality control of sequencing data.

(**a**) Mapping reads distribution of 998 samples with valid sequencing data. A total of 31 samples (3.1%) with mapping reads <100k were filtered out. (**b**) MAPD distribution of 967 samples that passed the filter of mapping reads. A total of 387 samples (38.8%) with an MAPD ≥0.25 were filtered out, leaving 580 samples (58.1%) that qualified for downstream analysis. (**c**) Examples showing unqualified samples with either mapping reads <100k or an MAPD ≥0.25.

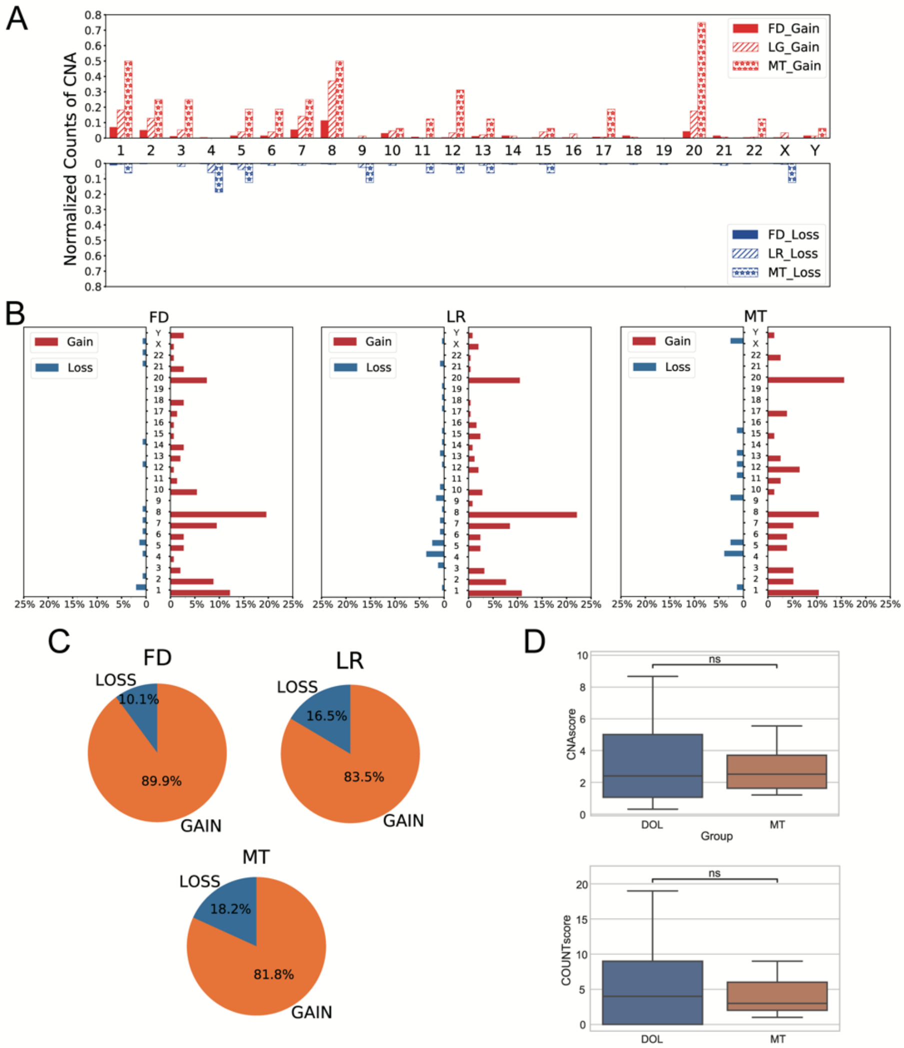


Supplementary Fig. 2 CNA differences between HOL and DOL.

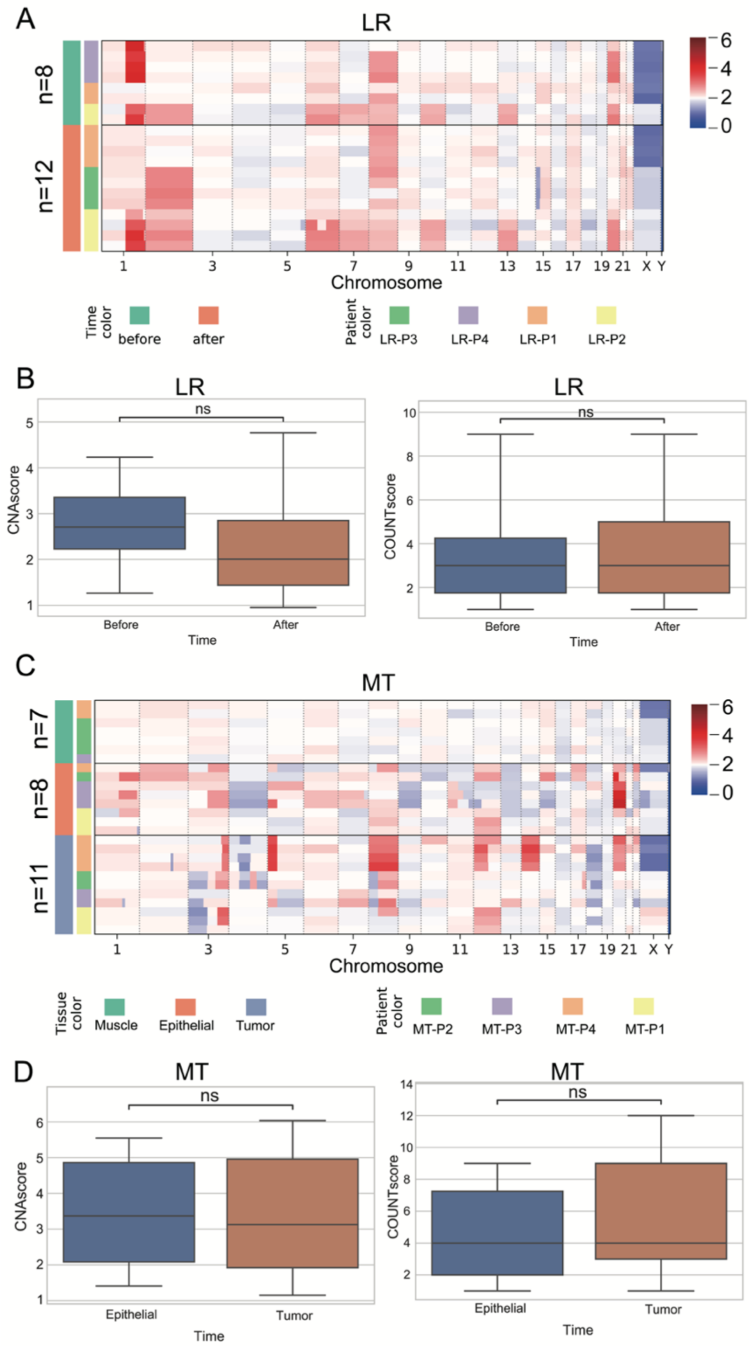
(**a**) Normalized CNA counts across the genome in HOL and DOL. Copy number gains and losses in each chromosome were counted and then divided by the number of HOL or DOL samples. (**b**) Distribution of the CNA ratio across the genome in HOL (left panel) and DOL (right panel). Copy number gains and losses for each chromosome were counted and then divided by the total CNA counts in HOL or DOL. (**c**) Copy number gain and loss ratio in HOL (left panel) and DOL (right panel). (**d**) Percentage of male and female CNA patients.



Supplementary Fig. 3 Correlation between CNAscore and COUNTscore.
The presence of a CNAscore >4.3 and a COUNTscore >7 was defined as a severe CNA region (red).

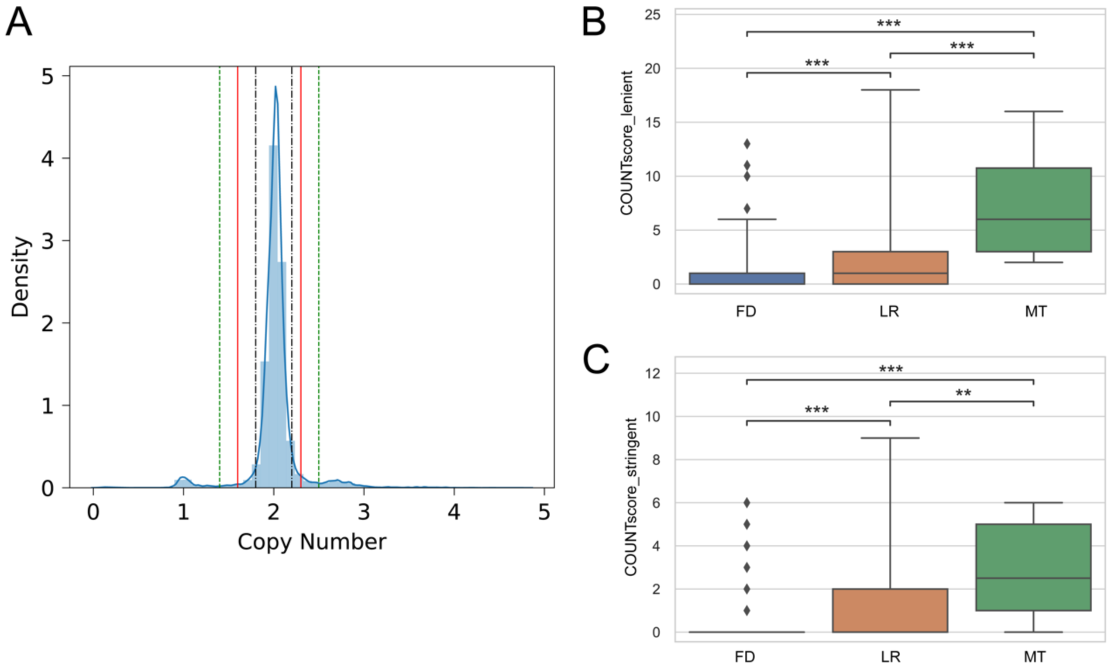


Supplementary Fig. 4 CNA differences among FD, LR, and MT.
(**a**) Normalized CNA counts across the genome in FD, LR, and MT. Copy number gains and losses in each chromosome were counted and then divided by the number of samples in FD, LR, or MT. (**b**) Distribution of CNA ratio across the genome in FD (left panel), LR (middle panel), and MT (right panel). Copy number gains and losses in each chromosome were counted and then divided by the total CNA counts in FD, LR, or MT. (**c**) Copy number gain and loss ratio in FD (upper left panel), LR (upper right panel), and MT (lower panel). (**d**) Boxplots showing the distributions of CNAscore (upper panel) and COUNTscore (lower panel) in DOL and MT.



Supplementary Fig. 5 CNA profiles of four LR patients and four MT patients with samples at two time points.

(**a**) CNA profiles of samples prior to and following leukoplakia recurrence in four LR patients. (**b**) Boxplots showing the distributions of CNAscore (left panel) and COUNTscore (right panel) for samples prior to and following leukoplakia recurrence. (**c**) CNA profiles of control muscle samples, epithelial samples, and tumor samples following malignant transformation in four MT patients. (**d**) Boxplots showing the distributions of CNAscore (left panel) and COUNTscore (right panel) for epithelial samples and tumor samples malignant transformation.



Supplementary Fig. 6 Discussion on the copy number cut-offs.

(a) Distribution of copy numbers of all the bins. Cut-off of copy numbers were showed in red solid line (<1.6;>2.3, used in the paper), black dash line (<1.8;>2.2, lenient cut-off) and green dash line (<1.4;>2.5, stringent cut-off) **(b)** COUNTscore_lenient distribution of FD, LR and MT groups. (*** p<0.001, t-test). **(c)** COUNTscore_stringent distribution of FD, LR and MT groups. (*** p<0.001, ** 0.001<p<0.01, t-test)

Supplementary Table 1 Summary of histopathological and clinical information of all OL patients.

See the attached file.

Supplementary Table 2 CNA ratio according to patient characteristics.

characteristics	Patient number (%)			*p*
	Total	CNA	CNA-free	
Sex				
Female	132	59 (44.6)	73 (55.4)	0.592
Male	128	53 (41.4)	75 (58.6)	
Age				
<40	46	13 (28.2)	33 (71.8)	0.017
40-49	53	20 (37.7)	33 (62.3)	
50-59	77	32 (41.6)	45 (58.4)	
60-69	65	34 (52.3)	31 (47.7)	
>70	19	13 (68.4)	6 (31.6)	
Site				
Tongue	100	45 (45.0)	55 (55.0)	0.239
Gingiva	34	16 (47.1)	18 (52.9)	
Cheek	106	43 (40.6)	63 (59.4)	
Floor of mouth	4	2 (50.0)	2 (50.0)	
Palate	7	5 (71.4)	2 (28.6)	
Lip	9	1 (11.1)	8 (88.9)	

Patient number	age	gender	site	sample time	sample type	ological clas	CNAscore	COUNTscore	MAPD	mapreads	IA qualificati	5-year prognosis
					E		1.92351819	3	0.11975	1761029	√	
					E		2.32552794	1	0.1575	2424457	√	
					E		1.1992624	0	0.129725	2528755	√	
					M		1.3873243	0	0.1217	2019050	√	
					M		1.89310033	2	0.1815	778396	√	
1	46	Female	Cheek	2019	M	hyperplasia	3.08273338	4	0.197	587379	√	non available
					E		0.7092452	0	0.1235	1298933	√	
					E		0.90676862	0	0.13075	891868	√	
					E		0.87440372	0	0.13875	913998	√	
					M		1.1329124	0	0.1385	1071863	√	
					M		1.11008379	0	0.1395	1087540	√	
2	63	Male	Tongue	2019	M	hyperplasia	1.42098719	0	0.2245	84461	×	non available
3	55	Male	Tongue	2019	E	hyperplasia	1.06009156	0	0.19425	797660	√	non available
					E		1.65791802	0	0.18	759885	√	
					E		1.53754971	0	0.33205	1116269	×	
4	53	Female	Cheek	2019	E	hyperplasia	1.41799483	0	0.2788	809118	×	non available
					E		1.90822581	0	0.29035	847883	×	
					E		1.10982637	0	0.2365	436802	√	
					E		1.31597778	0	0.22025	662224	√	
5	35	Female	Gingiva	2019	E	hyperplasia	1.16031733	0	0.16525	548293	√	non available
6	58	Female	Cheek	2019	E	hyperplasia	1.17358765	1	0.1798	931250	√	non available
					E		1.65367255	3	0.21275	890036	√	
					E		1.08973652	0	0.20325	774284	√	
7	59	Male	Gingiva	2019	E	hyperplasia	1.16081268	0	0.1975	919305	√	non available
					E		2.67001885	5	0.43975	1146075	×	
					E		2.06041905	4	0.280575	1099310	×	
					E		1.62887534	2	0.243875	959039	√	
8	69	Male	Gingiva	2019	E	hyperplasia	2.33373246	4	0.42015	1089597	×	non available
					E		1.86873856	3	0.479675	1210502	×	
					E		1.67774302	2	0.29925	887736	×	
					E		2.22769192	3	0.471175	870437	×	
9	66	Male	Palate	2019	E	hyperplasia	2.49342397	4	0.550675	1212955	×	non available
					E		2.14114437	4	0.40935	933208	×	
					E		1.31040797	0	0.303175	1153076	×	
					E		1.24448374	0	0.25	1099626	√	
10	28	Male	Tongue	2019	E	hyperplasia	2.14656746	3	0.433475	915219	×	non available
					E		0.85178591	0	0.16675	925060	√	
					E		0.85185295	0	0.142	872165	√	
					E		0.77685291	0	0.14875	856002	√	
11	23	Male	Tongue	2019	E	hyperplasia	0.78249523	0	0.16925	1001182	√	non available
					E		1.70726706	1	0.23425	488464	√	
					E		1	1	0	1560	×	
					E		1	1	0	5616	×	
12	83	Female	Gingiva	2019	E	hyperplasia	1.29494739	0	0.228025	1338455	√	non available
					E		5.77904767	6	0.47475	196793	×	

					E		0.99535967	0	0.209975	1334679	√	
					E		1.28250623	0	0.2351	1147761	√	
13	64	Female	Cheek	2019	E	hyperplasia	2.20192435	3	0.30445	903176	×	non available
					E		1.60955873	1	0.363675	1025776	×	
					E		1.22732629	0	0.26525	965981	×	
14	52	Male	Palate	2019	E	hyperplasia	1.3866542	2	0	34540	×	non available
					E		1.26935966	0	0.2355	562165	√	
					E		1.70851834	1	0.29045	1226001	×	
					E		1.49275501	0	0.2845	819032	×	
15	52	Female	Cheek	2019	E	hyperplasia	1.34170954	0	0.2455	660917	√	non available
					E		1.12445781	0	0.266875	1086381	×	
					E		1.07987119	0	0.216125	927563	√	
					E		0.80050209	0	0.21475	1035489	√	
16	37	Male	Gingiva	2019	E	hyperplasia	1.36553919	0	0.3095	856614	×	non available
					E		1.44578883	0	0.30825	1074428	×	
					E		1.20968625	0	0.23725	813978	√	
					E		1.16005144	0	0.28	993484	×	
17	45	Male	Cheek	2019	E	hyperplasia	1.4806945	1	0.37	722513	×	non available
					E		2.14618738	3	0.38145	910539	×	
					E		0.87003279	0	0.1754	1173735	√	
					E		1.11056705	0	0.2621	1142159	×	
18	46	Female	Cheek	2019	E	hyperplasia	1.67783436	1	0.346525	1203500	×	non available
					E		1.31052546	0	0.22405	1497155	√	
					E		1.87018622	0	0.29535	1096857	×	
					E		1.51398177	0	0.262275	1251987	×	
19	63	Female	Cheek	2019	E	hyperplasia	1.51672829	0	0.282	589028	×	non available
					E		2.11026683	3	0.34075	476260	×	
					E		2.40178317	2	0.287	263026	×	
					E		3.18508804	5	0.43925	510679	×	
					E		3.65890878	4	0.35375	590911	×	
					E		3.51597309	7	0.3665	321229	×	
					E		3.11678988	2	0.32125	315318	×	
					M		2.20077932	2	0.31225	220794	×	
20	59	Male	Palate	2018	M	hyperplasia	1.84603179	1	0.3485	274890	×	non available
					E		3.06681809	4	0.17385	1432681	√	
					E		1.00737453	2	0	4788	×	
					E		2.77733636	3	0.1635	464799	√	
					M		1.60112077	0	0.245325	1233030	√	
21	61	Male	Tongue	2018	M	hyperplasia	0.99303439	0	0.19525	1271175	√	non available
					E		4.44708353	5	0.143125	893434	√	
					E		4.39411219	5	0.146275	961625	√	
					E		4.07589175	7	0.141125	868336	√	
					Me		0.76630069	0	0.206	608705	√	
					Me		0.76321387	0	0.15015	1154210	√	
22	55	Female	Cheek	2019	Me	hyperplasia	2.69901989	5	0.19975	678965	√	non available
					E		2.98743236	3	0.119	1883931	√	

					E		2.1694423	3	0.12875	948062	√	
23	56	Male	Cheek	2019	E	hyperplasia	2.75492392	3	0.11625	1660965	√	non available
					E		3.75894588	5	0.273125	965849	×	
24	31	Male	Cheek	2019	E	hyperplasia	3.72260714	4	0.373225	903506	×	non available
					E		2.60884971	2	0.196125	1035246	√	
					E		3.21066707	4	0.33175	545623	×	
					E		3.428872	4	0.3086	900813	×	
25	58	Female	Cheek	2019	E	hyperplasia	3.39190827	3	0.32735	987210	×	non available
					E		3.41878301	5	0.235625	1314322	√	
					E		6.64644286	13	0.19325	1194408	√	
					E		4.55582604	6	0.329975	1296240	×	
26	36	Male	Cheek	2019	E	hyperplasia	3.47284803	10	0.3731	1157447	×	non available
					E		7.74540491	17	0.136	1842846	√	
					E		8.04967804	16	0.13925	2017469	√	
					E		6.70544845	12	0.1435	1972020	√	
					M		2.19356811	3	0.2285	1219034	√	
					M		1.62345177	1	0.18575	1120499	√	
27	32	Male	Tongue	2019	M	dysplasia	1.67016241	1	0.188	1746893	√	non available
					E		2.2115394	4	0.16975	1976927	√	
					E		1.63457009	3	0.132	1634433	√	
					E		2.17513806	3	0.1556	1337318	√	
					M		1.11388481	0	0.1615	973067	√	
					M		1.11862567	0	0.135	2116639	√	
28	58	Male	Tongue	2019	M	dysplasia	1.00493348	2	0	3285	×	non available
					E		5.70568547	8	0.2525	1155177	×	
					E		5.94177932	11	0.16425	1837861	√	
					E		7.02733392	14	0.18875	1228825	√	
					M		1.09926763	0	0.2095	780121	√	
					M		1.4069802	2	0.282	573418	×	
29	45	Male	Cheek	2019	M	dysplasia	2.0081829	3	0.2815	481549	×	non available
					E		4.17121471	8	0.14275	1021342	√	
					E		3.10796902	4	0.1455	699419	√	
					E		4.41843466	8	0.158	640905	√	
					M		1.84174763	1	0.1885	661999	√	
					M		1.4237293	1	0.16525	608996	√	
30	63	Female	Tongue	2019	M	dysplasia	0.97862861	0	0.146	756236	√	non available
					E		5.16023339	8	0.2205	154414	√	
					E		4.5196722	8	0.23275	93012	×	
					E		7.89426899	17	0.13255	2619130	√	
					M		2.52893201	3	0.147275	1589289	√	
					M		2.66951495	4	0.11925	2493984	√	
31	68	Female	Tongue	2019	M	dysplasia	1.22450003	0	0.111	1730690	√	non available
					E		2.49284044	5	0.129	896334	√	
					E		3.4410174	6	0.1252	1057553	√	
					E		1.26412085	1	0.14775	564067	√	
					M		1.27029657	0	0.15175	802743	√	

					M		1.10553747	0	0.14375	805247	√	
32	63	Male	Tongue	2019	M	dysplasia	1.32190408	2	0.216	808931	√	non available
					E		5.44115591	8	0.1445	1183041	√	
33	43	Male	Tongue	2019	E	dysplasia	6.77555993	10	0.154	1128234	√	non available
					E		7.76820785	18	0.2175	904194	√	
					E		8.01341693	15	0.2525	720547	×	
					E		7.24404316	9	0.2495	1023258	√	
					E		8.67175409	19	0.18225	1093300	√	
					E		8.19658986	14	0.29025	980540	×	
					E		7.87260208	17	0.24425	885219	√	
					E		7.14380603	12	0.246975	992531	√	
34	67	Male	Tongue	2018	M	dysplasia	2.17653716	3	0.418575	1057921	×	non available
					E		1.35379538	0	0.307	865591	×	
					E		1.26504576	2	0	31677	×	
					E		1.17227903	0	0.23175	841489	√	
					E		1.33390039	0	0.2635	901502	×	
					E		0.91802797	0	0.173	915646	√	
					E		0.70768112	0	0.16325	935125	√	
					E		2.36032408	4	0.169	867145	√	
					E		2.53738393	2	0.1785	675052	√	
					E		3.26781794	5	0.19975	533480	√	
					E		2.81436194	3	0.19125	665035	√	
					E		1.28130168	0	0.211	444584	√	
35	55	Male	Tongue	2018	M	dysplasia	1.30507421	0	0.20675	549513	√	non available
					E		1.46924663	2	0	27172	×	
					E		1.41090238	1	0.34675	468035	×	
					E		0.83783144	0	0.152	873822	√	
					E		1.1287536	0	0.24925	1002513	√	
					E		1.06884626	0	0.12975	964407	√	
					E		3.09570047	5	0.1305	1067952	√	
					E		3.84196094	9	0.18275	870028	√	
					E		4.01615253	8	0.217	1044937	√	
					E		4.07776695	9	0.2455	1365248	√	
36	69	Male	Palate	2018	M	dysplasia	1.03755495	0	0.1835	1215669	√	non available
					E		1.59552401	2	0.1875	994922	√	
					E		1.5977775	0	0.17875	1349440	√	
					E		1.18839705	0	0.1575	1145144	√	
					E		1.16011178	0	0.13575	1324834	√	
					E		1.12430102	1	0.19275	1254671	√	
					E		1.07966909	0	0.17925	1175789	√	
					M		1.25445801	0	0.21475	1190785	√	
37	38	Male	Cheek	2018	M	dysplasia	1.50891109	0	0.1429	1285274	√	non available
					E		6.17463183	12	0.46145	1262497	×	
					E		5.99409075	9	0.207025	1411753	√	
					E		4.38279411	9	0.17575	1043937	√	
					E		5.60666065	9	0.2612	857102	×	

					E		5.94690484	10	0.380575	902612	×	
38	60	Male	Tongue	2018	M	dysplasia	1.77568725	1	0.37875	875958	×	non available
					E		4.7590507	9	0.30125	107094	×	
39	62	Female	Tongue	2019	E	dysplasia	3.61348942	7	0.29725	144509	×	non available
					E		2.16305068	4	0.29825	125737	×	
					E		2.22762866	3	0.35375	115594	×	
					E		1.67820799	2	0.21325	91213	×	
40	64	Female	Tongue	2019	E	dysplasia	1.78318784	3	0.2445	131910	√	non available
					E		1.53316122	0	0.3045	64896	×	
					E		1.43286097	1	0.27175	73017	×	
					E		1.76628759	1	0.26475	112302	×	
41	54	Male	Cheek	2019	E	dysplasia	1.97696322	1	0.37725	137746	×	non available
					E		2.30061629	4	0.3655	130859	×	
					E		1.42641973	0	0.29825	101419	×	
					E		1.00556099	2	0	11396	×	
42	50	Male	Tongue	2019	E	dysplasia	1.66902179	1	0.22625	58160	×	non available
					E		3.36642849	8	0.24675	244114	√	
					E		1.04084909	2	0	12802	×	
					E		2.31030586	4	0.27625	204611	×	
43	31	Male	Tongue	2019	E	dysplasia	1.1353513	2	0	9590	×	non available
					E		4.35673651	6	0.318	186496	×	
					E		5.72357307	9	0.3665	285908	×	
					E		3.89099879	8	0.35725	318844	×	
44	78	Female	Tongue	2019	E	dysplasia	3.71910314	7	0.30725	250144	×	non available
					E		4.95886795	11	0.25775	292818	×	
					E		1.2901125	0	0.2645	234745	×	
					E		4.4547253	9	0.25625	252381	×	
45	35	Male	Tongue	2019	E	dysplasia	3.80556104	9	0.228425	988096	√	non available
					E		2.6532076	3	0.2675	53418	×	
					E		1.98488003	3	0.23975	125213	√	
					E		1.98530456	4	0.2735	133584	×	
46	62	Female	Tongue	2019	E	dysplasia	2.51848966	3	0.209	51468	×	non available
					E		2.17915009	3	0.14475	749800	√	
					E		6.00275594	6	0.14475	849870	√	
47	63	Male	Tongue	2019	E	dysplasia	4.71146163	10	0.139	1079714	√	non available
					E		1.42358513	1	0.198975	779990	√	
					E		1.98991776	0	0.17925	1156691	√	
48	57	Male	Tongue	2019	E	dysplasia	1.05841714	0	0.17525	622999	√	non available
					E		1	1	0	3496	×	
					E		0.8237	0	0.124575	963132	√	
49	63	Female	Tongue	2019	E	dysplasia	0.59742738	0	0.12335	969230	√	non available
					E		1.18888605	0	0.24	208920	√	
					E		1.17248458	0	0.19425	196613	√	
					E		1.88745093	2	0.27625	281253	×	
50	59	Male	Gingiva	2019	E	dysplasia	1.66650563	2	0.3265	113344	×	non available
					E		0.47599176	0	0.117775	952017	√	

					E		0.42876153	0	0.119675	1071795	√	
51	65	Female	loor of mout	2019	E	dysplasia	1.56764555	2	0.14725	1208999	√	non available
					E		1.41683856	0	0.2655	613097	×	
					E		1.24114581	2	0.01	21219	×	
					E		1.4030236	2	0.015	23481	×	
52	68	Male	Tongue	2019	E	dysplasia	2.00214589	2	0.03	26130	×	non available
					E		1.52446193	1	0.331	283514	×	
					E		1.28343365	1	0.3595	209943	×	
53	66	Male	Cheek	2012	E	hyperplasia	1.4066354	0	0.32	264225	×	free of disease
					E		2.04342087	3	0.21875	652428	√	
					E		2.48393166	6	0.28275	266547	×	
					E		4.1360697	5	0.385	425610	×	
54	63	Female	Cheek	2012	E	hyperplasia	3.47306573	5	0.31025	340194	×	free of disease
					E		1.77298445	2	0.23125	480515	√	
					E		1.71923697	1	0.319	185687	×	
55	49	Male	Tongue	2012	E	hyperplasia	1.46311092	0	0.2975	468980	×	free of disease
56	46	Female	Tongue	2012	E	hyperplasia	1.03714539	0	0.177	860774	√	free of disease
					E		0.87717816	0	0.20725	356316	√	
					E		0.85234872	0	0.2155	431759	√	
					E		1.31668586	1	0.25525	316598	×	
57	53	Female	Tongue	2012	E	hyperplasia	1.5250068	1	0.313	164335	×	free of disease
58	59	Male	Cheek	2012	E	hyperplasia	1.59993726	2	0.1725	575687	√	free of disease
					E		1.53826904	1	0.25575	141376	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
59	32	Male	Tongue	2012	E	hyperplasia	0.89281178	0	0.188	526011	√	free of disease
					E		0.61844046	0	0.123975	1104223	√	
					E		1.42098189	0	0.225	8461	×	
60	61	Female	Tongue	2012	E	hyperplasia	0.73165193	0	0.157575	1039308	√	free of disease
					E		2.08435199	2	0.20225	775707	√	
					E		2.00628561	2	0.24375	220516	√	
					E		1.77826375	2	0.1425	790901	√	
61	69	Male	Gingiva	2012	E	hyperplasia	1.75433594	2	0.22025	563718	√	free of disease
					E		1.79994445	3	0.201	900885	√	
					E		2.12337284	3	0.1735	617918	√	
					E		1.57436815	3	0.1593	931280	√	
62	55	Female	Cheek	2012	E	hyperplasia	2.33318689	3	0.20325	703092	√	free of disease
					E		0.91089307	0	0.184	688991	√	
63	44	Female	Gingiva	2012	E	hyperplasia	1.13062683	0	0.269	405995	×	free of disease
					E		0.74312774	0	0.17	835626	√	
					E		1.42098882	0	0.25	84161	×	
64	64	Female	Tongue	2012	E	hyperplasia	0.65421654	0	0.12325	836948	√	free of disease
					E		0.84000224	0	0.1846	676289	√	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
65	52	Male	Tongue	2012	E	hyperplasia	0.83825636	0	0.143	1003863	√	free of disease

					E		0.83249589	0	0.13175	866321	√	
					E		0.75567535	0	0.184	479425	√	
66	65	Female	Cheek	2012	E	hyperplasia	0.72205201	0	0.12155	1200968	√	free of disease
					E		0.72902273	0	0.1375	1037621	√	
					E		0.94198649	0	0.158975	999752	√	
67	43	Female	Cheek	2012	E	hyperplasia	0.84731272	0	0.1549	952742	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
68	64	Female	Cheek	2012	E	hyperplasia	×	×	×	×	×	free of disease
					E		1.72535086	3	0.19275	779929	√	
					E		3.22478139	4	0.26525	759720	×	
69	53	Female	Tongue	2012	E	hyperplasia	2.60365877	3	0.23025	338922	√	free of disease
					E		1.60085455	2	0.24125	255861	√	
					E		1.49257669	0	0.3676	913497	×	
70	58	Male	Tongue	2012	E	hyperplasia	1.18526727	0	0.27225	807744	×	free of disease
					E		0.96104942	0	0.192925	1083240	√	
					E		1.1535509	0	0.211	772575	√	
71	55	Female	Cheek	2012	E	hyperplasia	1.18342432	0	0.219	750501	√	free of disease
					E		3.88390481	5	0.31225	1427888	×	
					E		3.73722063	3	0.367675	1122478	×	
72	63	Female	Cheek	2012	E	hyperplasia	3.52465978	5	0.344	177623	×	free of disease
					E		2.93460631	3	0.331	538822	×	
					E		3.46538815	6	0.40875	586001	×	
73	54	Male	Tongue	2012	E	hyperplasia	4.20720205	3	0.252	904977	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
74	59	Male	Tongue	2012	E	hyperplasia	×	×	×	×	×	free of disease
75	39	Male	Gingiva	2012	E	hyperplasia	×	×	×	×	×	free of disease
76	47	Male	Tongue	2012	E	hyperplasia	×	×	×	×	×	free of disease
					E		0.75571351	0	0.1575	891360	√	
					E		3.47480279	10	0.331	115447	×	
					E		×	×	×	×	×	
77	39	Female	Tongue	2012	E	hyperplasia	0.77011259	0	0.159	871817	√	free of disease
					E		0.66048628	0	0.126	1029026	√	
					E		0.67465496	0	0.11975	1073920	√	
78	68	Male	Tongue	2012	E	hyperplasia	0.65565467	0	0.128	815962	√	free of disease
79	65	Male	Cheek	2012	E	hyperplasia	1.17736056	0	0.1255	1041371	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
80	48	Female	Cheek	2012	E	hyperplasia	×	×	×	×	×	free of disease
					E		1.46854857	2	0.1755	605613	√	
					E		3.83904811	5	0.3125	427888	×	
81	82	Male	Gingiva	2012	E	hyperplasia	1.37154189	2	0.17925	865291	√	free of disease

					E		0.74520528	0	0.14325	1072151	√	
					E		0.76750678	0	0.1805	1015453	√	
82	54	Male	Cheek	2012	E	hyperplasia	0.71018368	0	0.1265	1047251	√	free of disease
					E		0.73696835	0	0.1415	845977	√	
					E		0.58767627	0	0.122025	1109412	√	
83	64	Female	Cheek	2012	E	hyperplasia	0.82686989	0	0.13725	748611	√	free of disease
					E		0.79617396	0	0.1465	1050972	√	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
84	56	Male	Lip	2012	E	hyperplasia	1.33694533	1	0.1625	881205	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
85	65	Female	Lip	2012	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
86	56	Female	Tongue	2012	E	hyperplasia	×	×	×	×	×	free of disease
87	32	Male	Tongue	2012	E	hyperplasia	0.75134134	0	0.176	554594	√	free of disease
88	49	Male	Cheek	2012	E	hyperplasia	0.88726717	0	0.149	1480715	√	free of disease
89	53	Male	Lip	2012	E	hyperplasia	3.16281644	6	0.2115	516359	√	free of disease
					E		1.03153935	0	0.216	771275	√	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
90	39	Male	Cheek	2012	E	hyperplasia	1.00487676	0	0.198	639802	√	free of disease
					E		1.46653596	1	0.313825	1311178	×	
					E		1.0345476	0	0.248575	1244765	√	
					E		1.11011475	0	0.26225	1145402	×	
91	56	Male	Cheek	2012	E	hyperplasia	1.15161127	0	0.265	1082663	×	free of disease
					E		0.99619608	0	0.1315	971547	√	
					E		0.9949271	0	0.1328	1101402	√	
92	46	Female	Gingiva	2012	E	hyperplasia	1.15111269	0	0.25	108263	×	free of disease
					E		1.04661804	0	0.196	504486	√	
					E		1.05002359	0	0.211	524996	√	
93	53	Male	Tongue	2012	E	hyperplasia	0.95417053	0	0.2065	606930	√	free of disease
					E		0.8695119	0	0.21825	618040	√	
					E		1.00631362	0	0.23075	603223	√	
					E		1.51112685	0	0.125	8263	×	
94	16	Male	Cheek	2012	E	hyperplasia	0.96000051	0	0.18025	581341	√	free of disease
					E		1.45099738	1	0.134	1081804	√	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
95	27	Female	Gingiva	2012	E	hyperplasia	0.63033075	0	0.1435	870110	√	free of disease
					E		0.79142758	0	0.16975	563238	√	
					E		×	×	×	×	×	

					E		×	×	×	×	×	
96	60	Male	Cheek	2012	E	hyperplasia	0.89296055	0	0.1625	481969	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
97	60	Female	Tongue	2012	E	hyperplasia	×	×	×	×	×	free of disease
					E		0.82606658	0	0.14425	1199608	√	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
98	65	Male	Cheek	2012	E	hyperplasia	1.10313469	0	0.141	814493	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
99	81	Male	Palate	2012	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
100	47	Male	Gingiva	2012	E	hyperplasia	×	×	×	×	×	free of disease
					E		1.54072532	0	0.385275	771296	×	
					E		1.41296157	0	0.3215	744959	×	
101	74	Male	Cheek	2012	E	hyperplasia	1.99371397	3	0.37825	1244065	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
102	52	Female	Gingiva	2012	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
103	36	Male	Tongue	2012	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
104	58	Female	Gingiva	2012	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
105	36	Male	Lip	2012	E	hyperplasia	×	×	×	×	×	free of disease
106	71	Male	Lip	2012	E	hyperplasia	1.22578482	2	0.168675	1061444	√	free of disease
107	43	Male	Gingiva	2012	E	hyperplasia	1.53598499	2	0.1255	1183589	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
108	76	Female	Gingiva	2012	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
109	65	Female	Lip	2012	E	hyperplasia	×	×	×	×	×	free of disease
					E		1.87578672	3	0.421975	713033	×	
					E		×	×	×	×	×	

					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		2.98726815	5	0.341875	1037231	×	
110	58	Male	Palate	2012	E	hyperplasia	4.0808135	6	0.33175	897002	×	free of disease
					E		1.57712347	1	0.351425	1058408	×	
					E		1.49027161	0	0.301925	1191845	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
111	55	Female	Gingiva	2012	E	hyperplasia	3.77649399	7	0.28085	933118	×	free of disease
					E		1.82633111	0	0.396425	991584	×	
					E		2.09731814	2	0.385	270259	×	
112	75	Female	Gingiva	2012	E	hyperplasia	1.55572785	0	0.29645	1075912	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
113	60		Cheek	2012	E	hyperplasia	×	×	×	×	×	free of disease
					E		0.99111748	0	0.1734	1146872	√	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
114	35	Female	Tongue	2013	E	hyperplasia	0.99340048	0	0.142675	1253673	√	free of disease
					E		1.50549577	2	0.1561	1687107	√	
					E		1.41261572	0	0.315	74959	×	
					E		2.08666606	2	0.184775	1064693	√	
115	54	Female	Lip	2013	E	hyperplasia	3.47480794	10	0.431	125447	×	free of disease
					E		1.28732765	1	0.2605	236189	×	
					E		0.8731056	0	0.1585	502991	√	
116	49	Female	Cheek	2013	E	hyperplasia	1.56136686	1	0.22375	67406	×	free of disease
117	43	Female	Cheek	2013	E	hyperplasia	2.2308865	2	0.166025	1211451	√	free of disease
118	66	Male	Cheek	2013	E	hyperplasia	0.91098148	0	0.169	723712	√	free of disease
					E		0.94270378	0	0.17875	594820	√	
					E		0.99726207	0	0.19375	609983	√	
					E		1.22615724	0	0.515	1274959	×	
					E		0.94448869	0	0.1815	495171	√	
					E		1.18196635	0	0.20775	471732	√	
119	31	Female	Tongue	2013	E	hyperplasia	1.29098503	0	0.2205	530869	√	free of disease
					E		1.14312541	0	0.1485	1312462	√	
					E		0.67255068	0	0.12	1500660	√	
120	30	Male	Tongue	2013	E	hyperplasia	0.83754969	0	0.13425	1218069	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
121	63	Male	Tongue	2013	E	hyperplasia	×	×	×	×	×	free of disease

					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
122	84	Female	Cheek	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		1.04119508	0	0.233	465216	√	
					E		1.14137236	0	0.187	552010	√	
123	53	Female	Tongue	2013	E	hyperplasia	0.75356763	0	0.1545	589516	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
124	55	Female	Cheek	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		0.6941518	0	0.13225	975276	√	
					E		1.14727101	1	0.188	213066	√	
125	41	Female	Cheek	2013	E	hyperplasia	1.54072321	0	0.38275	71296	×	free of disease
					E		0.96803406	0	0.191625	1727903	√	
					E		1.86861521	1	0.21275	4639	×	
126	57	Female	Cheek	2013	E	hyperplasia	2.86861521	1	0.11275	48639	×	free of disease
					E		0.81821871	0	0.17825	2266683	√	
					E		0.60343194	0	0.1745	2187771	√	
127	49	Male	Cheek	2013	E	hyperplasia	0.75489265	0	0.1955	2083584	√	free of disease
					E		2.6755628	5	0.22725	543860	√	
					E		0.97076009	0	0.23465	995507	√	
128	67	Female	Cheek	2013	E	hyperplasia	0.92717265	0	0.21375	1002734	√	free of disease
129	77	Female	Palate	2013	E	hyperplasia	0.88861956	0	0.1869	2106079	√	free of disease
130	62	Female	Cheek	2013	E	hyperplasia	0.81659289	0	0.1695	835166	√	free of disease
131	61	Male	Palate	2013	E	hyperplasia	1.21379423	1	0.225	573714	√	free of disease
					E		0.58693498	0	0.1534	2101366	√	
					E		0.7182202	0	0.1615	2448553	√	
132	34	Male	Cheek	2013	E	hyperplasia	0.78520894	0	0.2025	2375479	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
133	40	Male	Cheek	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
134	54	Male	Gingiva	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
135	50	Female	Gingiva	2013	E	hyperplasia	×	×	×	×	×	free of disease

					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
136	49	Female	Cheek	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		2.3043273	2	0.217825	1557850	√	
					E		2.35693068	1	0.164525	1490437	√	
137	57	Female	Tongue	2013	E	hyperplasia	2.44665583	2	0.23105	1092708	√	free of disease
138	26	Male	Tongue	2013	E	hyperplasia	0.98651958	0	0.221	640442	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
139	42	Male	Palate	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
140	66	Female	Tongue	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
141	27	Male	Tongue	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		2.06092769	2	0.2537	2181401	×	
					E		1.85726449	2	0.21105	2126308	√	
142	54	Female	Tongue	2013	E	hyperplasia	1.84817284	2	0.2559	2447775	×	free of disease
					E		1.8499404	3	0.1545	615610	√	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		1.8232538	3	0.15575	678625	√	
					E		1.80487643	3	0.164	514381	√	
143	40	Male	Gingiva	2013	E	hyperplasia	1.8686151	1	0.521275	14639	×	free of disease
					E		1.215428	0	0.2913	1783299	×	
					E		1.10207736	0	0.24085	1375370	√	
144	40	Female	Gingiva	2013	E	hyperplasia	1.24909145	0	0.2975	1470896	×	free of disease
					E		0.87950594	0	0.182175	1548666	√	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		0.98528307	0	0.23085	1724955	√	
145	69	Female	Gingiva	2013	E	hyperplasia	1.11422747	0	0.26625	1534470	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	

					E		×	×	×	×	×	
146	63	Female	Lip	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
147	58	Female	Tongue	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		1.28103172	0	0.222675	1205534	√	
					E		2.65364125	2	0.544275	1677709	×	
148	70	Female	Gingiva	2013	E	hyperplasia	2.53704512	4	0.61015	1579589	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
149	55	Male	Cheek	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		0.76947507	0	0.146	1093169	√	
150	53	Male	Cheek	2013	E	hyperplasia	0.7284607	0	0.17485	1000357	√	free of disease
					E		0.70238522	0	0.18875	492870	√	
151	56	Female	Gingiva	2013	E	hyperplasia	1.08737713	0	0.25825	495822	×	free of disease
					E		1.03836292	0	0.23125	402357	√	
152	58	Male	Tongue	2013	E	hyperplasia	1.05883026	0	0.23675	378901	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
153	67	Female	Lip	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
154	68	Male	Cheek	2013	E	hyperplasia	×	×	×	×	×	free of disease
155	49	Female	Cheek	2013	E	hyperplasia	1.11493894	0	0.179	704286	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
156	24	Male	Lip	2013	E	hyperplasia	×	×	×	×	×	free of disease
157	53	Male	Tongue	2013	E	hyperplasia	0.77016324	0	0.21275	1310162	√	free of disease
					E		1.02240427	0	0.234625	1430631	√	
					E		1.84812843	2	0.259	2447765	×	
158	45	Female	Cheek	2013	E	hyperplasia	1.7045604	2	0.21475	1968567	√	free of disease
					E		0.50753707	0	0.1105	2246650	√	
					E		0.53279072	0	0.1095	1726763	√	
159	42	Male	Tongue	2013	E	hyperplasia	0.55679548	0	0.1158	1959619	√	free of disease
160	29	Male	Tongue	2013	E	hyperplasia	0.89162374	0	0.15775	600033	√	free of disease
					E		×	×	×	×	×	

					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
161	73	Male	Lip	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		1.60864563	1	0.354325	1277605	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
162	58	Female	Cheek	2013	E	hyperplasia	1.34257198	0	0.327175	1517287	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
163	56	Male	Cheek	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
164	69	Female	Cheek	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
165	50	Male	Lip	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
166	52	Female	Lip	2013	E	hyperplasia	×	×	×	×	×	free of disease
167	61	Male	Tongue	2013	E	hyperplasia	0.59486055	0	0.11585	2797840	√	free of disease
					E		1.90202399	3	0.25335	1668566	×	
					E		2.04684488	3	0.308675	1492701	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
168	67	Male	Gingiva	2013	E	hyperplasia	2.0899895	2	0.32695	1356398	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
169	34	Male	Cheek	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
170	56	Female	Cheek	2013	E	hyperplasia	×	×	×	×	×	free of disease

					E		0.73326519	0	0.1515	1630323	√	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
171	53	Male	Cheek	2013	E	hyperplasia	0.69812477	0	0.159	1781515	√	free of disease
					E		0.77184755	0	0.17735	1765803	√	
					E		0.54671198	0	0.1344	1949445	√	
172	22	Male	Tongue	2013	E	hyperplasia	1.69810145	3	0.12205	1392246	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
173	71	Female	Cheek	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		1.03880718	1	0.154375	1596993	√	
					E		1.7311134	2	0.17925	1550777	√	
174	39	Female	Gingiva	2013	E	hyperplasia	1.18178399	1	0.19425	605210	√	free of disease
175	72	Male	Gingiva	2013	E	hyperplasia	1.26095277	1	0.25575	1890354	×	free of disease
					E		3.17660813	4	0.12345	1964856	√	
					E		3.11046272	4	0.136425	1628954	√	
176	64	Female	Gingiva	2013	E	hyperplasia	2.80874196	4	0.177	512963	√	free of disease
177	39	Female	Palate	2013	E	hyperplasia	0.75950956	0	0.164525	1542581	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
178	52	Female	Gingiva	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
179	43	Male	Gingiva	2013	E	hyperplasia	×	×	×	×	×	free of disease
					E		0.83657411	0	0.127	1089120	√	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
180	47	Male	Tongue	2014	E	hyperplasia	0.93876153	0	0.19375	333287	√	free of disease
					E		0.93158139	0	0.2279	1105806	√	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
181	52	Female	Gingiva	2014	E	hyperplasia	1.13347232	0	0.236	285777	√	free of disease
					E		1.06456351	0	0.2205	513107	√	
					E		1.09495467	1	0.20575	510825	√	
					E		1.04757237	1	0.208	545935	√	
					E		1.31175914	1	0.266	572072	×	
					E		3.52363262	6	0.217	798138	√	

182	28	Male	Tongue	2014	E	hyperplasia	1.0166792	0	0.2155	335509	√	free of disease
					E		1.67666307	3	0.211	392277	√	
					E		2.27917156	5	0.218	413267	√	
					E		2.91704756	6	0.29375	484788	×	
183	47	Male	Cheek	2014	E	hyperplasia	2.115224	5	0.279	440597	×	free of disease
					E		0.76271048	0	0.153	860026	√	
					E		1.01064628	0	0.20675	597606	√	
					E		1.29356074	1	0.2575	524748	×	
					E		0.93261898	0	0.2255	477608	√	
					E		1.12753257	0	0.2205	641945	√	
184	51	Male	Cheek	2014	E	hyperplasia	1.05962682	0	0.21125	446156	√	free of disease
					E		2.63476133	2	0.17575	892099	√	
					E		2.53129777	2	0.229	1145700	√	
					E		2.30538881	2	0.182	693855	√	
185	52	Male	Tongue	2014	E	hyperplasia	2.46099776	2	0.29725	488712	×	free of disease
					E		1.88439222	2	0.215675	1612023	√	
					E		1.02628251	0	0.213025	2255087	√	
186	49	Female	Gingiva	2014	E	hyperplasia	2.40784651	2	0.175325	1834289	√	free of disease
					E		0.62479814	0	0.16295	1182678	√	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
187	65	Female	Cheek	2014	E	hyperplasia	0.70423616	0	0.11875	1858255	√	free of disease
					E		1.20318189	0	0.30605	1056965	×	
188	56	Male	Gingiva	2014	E	hyperplasia	1.00823227	0	0.188825	1986815	√	free of disease
					E		1.17708109	0	0.1745	583466	√	
					E		0.65198428	0	0.146625	987567	√	
189	49	Female	Tongue	2014	E	hyperplasia	0.61854794	0	0.1355	895261	√	free of disease
190	53	Male	Cheek	2014	E	hyperplasia	0.64207131	0	0.1305	1967091	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
191	42	Male	Lip	2014	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
192	38	Male	Tongue	2014	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
193	62	Male	Cheek	2014	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	

					E		×	×	×	×	×	
					E		×	×	×	×	×	
194	58	Female	Gingiva	2014	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
195	59	Male	Lip	2014	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
196	68	Female	Cheek	2014	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
197	46	Female	Cheek	2014	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
198	54	Male	Tongue	2014	E	hyperplasia	×	×	×	×	×	free of disease
					E		1.39765567	1	0.2235	760992	√	
					E		2.60527621	3	0.289125	2697515	×	
199	57	Female	Cheek	2014	E	hyperplasia	3.07602752	4	0.295225	2125668	×	free of disease
200	54	Male	Cheek	2014	E	hyperplasia	0.81032982	0	0.1981	2585543	√	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
201	58	Male	Palate	2014	E	hyperplasia	×	×	×	×	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
202	80	Female	Tongue	2014	E	hyperplasia	×	×	×	×	×	free of disease
					E		2.15544824	4	0.214325	1894561	√	
					E		1.69691426	1	0.18625	1469450	√	
203	65	Female	Gingiva	2014	E	hyperplasia	1.03658739	0	0.27925	563389	×	free of disease
					E		1.45410726	1	0.23605	1725372	√	
					E		1.47909289	0	0.306175	1226688	×	
204	68	Female	Gingiva	2014	E	hyperplasia	1.31055167	0	0.27295	1476959	×	free of disease
205	78	Male	Tongue	2014	E	hyperplasia	1.0875055	2	0.189	493126	√	free of disease
206	60	Male	Gingiva	2014	E	hyperplasia	2.09074712	2	0.248675	844533	√	free of disease
					E		1.29260427	0	0.282	329972	×	
					E		1.16402996	0	0.237	542080	√	
207	33	Male	Lip	2014	E	hyperplasia	1.09241951	0	0.2565	545761	×	free of disease
					E		1.32852945	0	0.313425	1718457	×	

					E		1.42589257	0	0.3277	1751579	×	
208	49	Female	Gingiva	2014	E	hyperplasia	1.92043928	2	0.3101	1427380	×	free of disease
209	52	Male	Tongue	2014	E	hyperplasia	1.21533585	0	0.234	347546	√	free of disease
210	54	Male	Cheek	2014	E	hyperplasia	1.85119867	2	0.1325	883052	√	free of disease
					E		4.65697646	6	0.392325	1059424	×	
					E		4.46449926	6	0.195	894515	√	
					E		4.32569015	5	0.341775	901028	×	
211	49	Male	Palate	2014	E	hyperplasia	2.41814667	3	0.199	1087738	√	free of disease
					E		1.59860665	1	0.317	495270	×	
					E		1.51027772	0	0.31475	444487	×	
212	13	Female	Cheek	2014	E	hyperplasia	1.31748936	0	0.24775	431394	√	free of disease
					E		1.77054259	0	0.29625	370885	×	
					E		1.30538708	1	0.243025	1457548	√	
213	52	Female	Tongue	2014	E	hyperplasia	1.53405039	2	0.321225	1146847	×	free of disease
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
214	62	Female	Tongue	2014	E	hyperplasia	×	×	×	×	×	free of disease
					E		0.89001316	0	0.16625	1817777	√	
					E		0.92367396	0	0.18725	1730456	√	
215	35	Male	Cheek	2014	E	hyperplasia	0.77748492	0	0.1765	1414357	√	free of disease
					E		1.2740204	0	0.298825	1791739	×	
					E		1.49958038	0	0.36115	1793967	×	
216	24	Male	Cheek	2014	E	hyperplasia	1.36215165	0	0.31515	1390216	×	free of disease
217	20	Male	Tongue	2014	E	hyperplasia	0.84342548	0	0.208	908057	√	free of disease
					E		2.15725616	2	0.26675	637092	×	
					E		2.66163211	3	0.480275	2119558	×	
218	70	Female	Cheek	2014	E	hyperplasia	2.59463428	3	0.46345	1130637	×	free of disease
					E		1.31738548	0	0.26875	2019839	×	
					E		1.59726971	2	0.245425	2024481	√	
219	54	Male	Tongue	2014	E	hyperplasia	1.2267924	0	0.293975	2342356	×	free of disease
					E		0.99619126	0	0.24025	832885	√	
					E		1.24830341	0	0.332475	2093838	×	
220	86	Male	Tongue	2014	E	hyperplasia	1.54391336	0	0.374575	1499053	×	free of disease
					E		1.60765812	0	0.14105	1901849	√	
221	58	Female	Cheek	2014	E	hyperplasia	3.65371773	4	0.23875	1949351	√	free of disease
222	35	Male	Lip	2014	E	hyperplasia	0.73672301	0	0.14275	1854077	√	free of disease
223	56	Female	Cheek	2014	E	hyperplasia	0.76278045	0	0.177975	1858978	√	free of disease
					E		1.62448173	2	0.216925	2121739	√	
					E		3.71419	5	0.160525	1731420	√	
224	72	Female	Cheek	2014	E	hyperplasia	3.87412646	5	0.140025	1772385	√	free of disease
225	67	Female	Cheek	2014	E	hyperplasia	0.78330462	0	0.1416	1590687	√	free of disease
					E		0.56958869	0	0.160725	1853661	√	
					E		0.81472304	0	0.17865	2004965	√	
226	45	Female	Tongue	2014	E	hyperplasia	0.81488468	0	0.19025	1873319	√	free of disease

					E		1.45150933	2	0.17465	2163348	√	
227	55	Female	Lip	2014	E	hyperplasia	1.45387553	2	0.14285	1929283	√	free of disease
228	40	Male	Cheek	2015	E	hyperplasia	0.82609385	0	0.1835	1560448	√	free of disease
					E		1.89423499	2	0.19325	1625290	√	
229	73	Male	Cheek	2015	E	hyperplasia	1.51400262	2	0.13895	1076551	√	free of disease
					E		0.79271594	0	0.1805	1610273	√	
230	77	Female	Cheek	2015	E	hyperplasia	0.86871713	0	0.164025	1418499	√	free of disease
					E		0.59583965	0	0.141425	1201155	√	
					E		0.54073799	0	0.138475	1147247	√	
231	56	Female	Tongue	2015	E	hyperplasia	0.61449478	0	0.144675	1697994	√	free of disease
232	38	Male	Tongue	2015	E	hyperplasia	0.83824831	0	0.2145	983898	√	free of disease
					E		0.69509225	0	0.12575	1584267	√	
					E		0.68380875	0	0.174025	1542506	√	
233	57	Female	Tongue	2015	E	hyperplasia	0.79831151	0	0.18795	1499965	√	free of disease
					E		0.86515954	0	0.134	2615275	√	
					E		0.76262182	0	0.138	1282732	√	
234	54	Male	Cheek	2015	E	hyperplasia	0.6821962	0	0.14675	1479347	√	free of disease
235	35	Male	Cheek	2015	E	hyperplasia	0.65803367	0	0.1325	951864	√	free of disease
					E		0.59134987	0	0.1355	1588825	√	
					E		0.79392484	0	0.138	1557348	√	
236	60	Male	Tongue	2015	E	hyperplasia	0.56946364	0	0.166925	1570727	√	free of disease
					E		0.61234784	0	0.14625	1507370	√	
237	43	Male	Cheek	2015	E	hyperplasia	0.75761732	0	0.18175	1570111	√	free of disease
					E		0.70980456	0	0.1557	1764050	√	
238	51	Male	Cheek	2015	E	hyperplasia	1.55365691	2	0.14275	1521684	√	free of disease
					E		0.89873269	0	0.2025	1579431	√	
239	68	Male	Lip	2015	E	hyperplasia	1.61158675	2	0.263	512452	×	free of disease
					E		1.32095069	0	0.293	277562	×	
					E		1.19328284	0	0.254	391969	×	
					E		1.15600243	0	0.28275	352231	×	
240	37	Male	Cheek	2015	E	hyperplasia	1.15409217	0	0.23575	527201	√	free of disease
					E		0.62824128	0	0.1293	1484229	√	
241	55	Female	Cheek	2015	E	hyperplasia	0.87825074	0	0.158975	1665889	√	free of disease
242	64	Female	Lip	2015	E	hyperplasia	1.41191126	2	0.18725	824986	√	free of disease
					E		0.73134027	0	0.15445	1638824	√	
					E		0.86362091	0	0.169425	1625072	√	
243	54	Female	Cheek	2015	E	hyperplasia	0.65682454	0	0.113675	1443250	√	free of disease
					E		1.45555651	0	0.30125	797127	×	
					E		1.95720339	2	0.4517	998982	×	
					E		1.60477522	0	0.36795	1022716	×	
244	37	Male	Cheek	2015	E	hyperplasia	1.83712581	1	0.3763	814379	×	free of disease
245	50	Male	Cheek	2015	E	hyperplasia	1.4469866	2	0.20425	567972	√	free of disease
					E		0.70655252	0	0.18195	1036795	√	
246	78	Female	Gingiva	2015	E	hyperplasia	1.10257878	0	0.267375	1263621	×	free of disease
247	77	Male	Cheek	2015	E	hyperplasia	1.58269828	2	0.180225	1118754	√	free of disease
248	52	Female	Cheek	2015	E	hyperplasia	0.98435847	0	0.222975	893425	√	free of disease

					E		3.73209032	5	0.150525	1073076	√	
					E		3.69409071	5	0.29525	990629	×	
					E		4.01138225	5	0.176	796407	√	
249	59	Male	Cheek	2015	E	hyperplasia	3.94751152	5	0.294	652668	×	free of disease
250	47	Male	Cheek	2015	E	hyperplasia	1.99939406	2	0.1225	1005898	√	free of disease
251	37	Female	Tongue	2015	E	hyperplasia	1.10818605	0	0.159	623124	√	free of disease
					E		1.00737453	2	0	7938	×	
					E		0.82585195	0	0.20225	993537	√	
					E		1.39228421	0	0.2935	926347	×	
252	33	Male	Gingiva	2015	E	hyperplasia	1.35167903	0	0.308325	1066051	×	free of disease
					E		1.41622731	0	0.175	784191	√	
					E		1.37664638	0	0.219	816449	√	
253	54	Female	Cheek	2015	E	hyperplasia	1.91899206	1	0.2405	664061	√	free of disease
					E		0.68643886	0	0.172	845333	√	
254	44	Male	Tongue	2015	E	hyperplasia	0.60204962	0	0.15325	969954	√	free of disease
255	49	Female	Gingiva	2015	E	hyperplasia	0.90786169	0	0.218	302301	√	free of disease
					E		0.80244815	0	0.14125	756539	√	
					E		0.67321397	0	0.1324	1016099	√	
256	60	Female	Cheek	2015	E	hyperplasia	0.40169868	0	0.1254	1001723	√	free of disease
					E		1.75859955	2	0.2895	371926	×	
257	54	Male	Cheek	2015	E	hyperplasia	1.56585699	1	0.2815	253816	×	free of disease
					E		4.14855826	7	0.2085	733676	√	
					E		3.42487052	7	0.379	146832	×	
					E		5.44210938	9	0.35225	380203	×	
					E		2.96976563	1	0.25825	55154	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		4.66978431	6	0.487625	826081	×	
					E		4.9060172	7	0.299725	1105681	×	
					E		4.55342324	7	0.2842	872516	×	
	63			2012	E	hyperplasia	4.47418389	8	0.3155	648480	×	Recurrence
					E		4.64134556	9	0.285975	972069	×	
					E		4.61697052	7	0.288375	1053443	×	
					E		4.95343664	8	0.240775	1031725	√	
258	71	Female	Cheek	2019	E	hyperplasia	1.86141746	1	0.19525	861598	√	Recurrence(after)
					E		3.79717025	7	0.139	900605	√	
					E		3.25249025	7	0.146	925207	√	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
259	59	Male	Cheek	2012	E	hyperplasia	1.47764868	2	0.19825	1026756	√	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	

260	35	Male	Lip	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		2.30256723	2	0.569625	811821	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		2.53548272	4	0.566225	750585	×	
261	65	Female	Palate	2012	E	hyperplasia	0.45479133	1	0.13675	920639	√	Recurrence
					E		3.87018043	2	0.13	78375	×	
					E		1.53501103	0	0.30775	821375	×	
262	41	Female	Tongue	2012	E	hyperplasia	1.47388361	0	0.3299	719217	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
263	31	Female	Tongue	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
264	60	Male	Palate	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.28288221	1	0.13925	953956	√	
					E		1.15589184	0	0.28025	1109225	×	
265	73	Male	Cheek	2012	E	hyperplasia	1.82313514	1	0.2365	510419	√	Recurrence
					E		0.79576575	0	0.169825	1026682	√	
					E		1.62421829	1	0.1425	824455	√	
266	46	Female	Tongue	2012	E	hyperplasia	0.97606842	1	0.13965	1214595	√	Recurrence
267	62	Female	Cheek	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.04764116	0	0.2435	628266	√	
					E		0.9100278	0	0.2025	1028458	√	
268	46	Male	Cheek	2012	E	hyperplasia	0.83407962	0	0.17725	559322	√	Recurrence
					E		1.4435638	0	0.2842	958441	×	
					E		1.26658712	0	0.248475	1047054	√	
269	56	Female	Cheek	2012	E	hyperplasia	1.38842024	0	0.248225	874792	√	Recurrence
					E		1.23989993	0	0.265	236233	×	
					E		5.50287755	5	0.17925	1180701	√	
270	55	Male	Cheek	2012	E	hyperplasia	1.31785387	0	0.35125	760002	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
271	62	Male	Cheek	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		0.76619327	0	0.1425	876887	√	
					E		0.87967557	0	0.19175	850064	√	
272	42	Male	Tongue	2012	E	hyperplasia	0.98351192	0	0.18075	790967	√	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	

					E		×	×	×	×	×	
273	69		Gingiva	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.79046822	2	0.2225	578342	√	
274	44	Male	Gingiva	2012	E	hyperplasia	1.36071682	0	0.377	412307	×	Recurrence
					E		1.1471023	0	0.2475	803354	√	
					E		1.49460535	0	0.41105	903446	×	
275	58	Female	Gingiva	2012	E	hyperplasia	1.40072262	0	0.3294	945058	×	Recurrence
					E		1.10198846	0	0.22755	923559	√	
					E		0.89783546	0	0.218725	929048	√	
276	42	Female	Tongue	2012	E	hyperplasia	0.98280956	0	0.214875	896571	√	Recurrence
277	39	Female	loor of mout	2012	E	hyperplasia	1.57375301	3	0.162525	979828	√	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
278	44	Female	Tongue	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
279	56	Male	Tongue	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
280	68	Female	Lip	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
281	30	Female	Tongue	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
282	28	Male	Tongue	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
283	58	Male	Tongue	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		0.69296702	0	0.1557	1128835	√	
					E		0.93240257	0	0.201475	1093810	√	
284	54	Female	Tongue	2012	E	hyperplasia	1.0078193	0	0.14075	881215	√	Recurrence
					E		4.82828578	7	0.285275	944303	×	
					E		2.81110679	3	0.29825	790824	×	
285	64	Female	Gingiva	2012	E	hyperplasia	4.21454135	7	0.30575	897779	×	Recurrence
					E		×	×	×	×	×	
286	35	Male	Tongue	2012	E	hyperplasia	×	×	×	×	×	Recurrence

					E		3.19243594	4	0.322	297554	×	
					E		4.10143823	5	0.2943	1134078	×	
287	79	Female	Cheek	2012	E	hyperplasia	3.92799335	5	0.302275	900528	×	Recurrence
					E		2.22987759	3	0.325	872586	×	
					E		2.17489719	3	0.34285	1006432	×	
288	65	Male	Tongue	2012	E	hyperplasia	2.54463454	3	0.2275	1118489	√	Recurrence
					E		1.20835726	1	0.136	696430	√	
					E		1.21584808	1	0.1445	732263	√	
289	74	Female	Cheek	2012	E	hyperplasia	1.18169779	0	0.20675	620381	√	Recurrence
					E		1.00967039	0	0.2537	856571	×	
					E		1.21876261	0	0.257175	1033631	×	
290	46	Female	Cheek	2012	E	hyperplasia	1.10347261	0	0.2245	244336	√	Recurrence
					E		×	×	×	×	×	
291	57	Male	Cheek	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
292	43	Female	Cheek	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.52622041	2	0.22225	565762	√	
					E		1.65500288	1	0.29605	802925	×	
293	59	Male	Cheek	2012	E	hyperplasia	1.72580901	1	0.326	774671	×	Recurrence
					E		2.94741979	4	0.31875	527012	×	
					E		3.45323825	5	0.42625	557237	×	
294	59	Female	Cheek	2012	E	hyperplasia	4.23008265	6	0.47125	563861	×	Recurrence
					E		×	×	×	×	×	
295	55	Female	Cheek	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.14430767	0	0.2255	827332	√	
					E		1.19714332	0	0.2705	402695	×	
296	36	Male	Cheek	2012	E	hyperplasia	0.98697388	0	0.27675	798356	×	Recurrence
					E		1.00049034	1	0.159425	961995	√	
					E		1.53804225	2	0.153	555596	√	
297	74	Female	Tongue	2012	E	hyperplasia	1.67665943	2	0.157	722158	√	Recurrence
					E		×	×	×	×	×	
298	50	Male	Cheek	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		2.13204269	4	0.1685	840754	√	
					E		1.54497522	3	0.175	781016	√	
299	63	Female	Gingiva	2012	E	hyperplasia	1.5424898	3	0.19975	809066	√	Recurrence
					E		×	×	×	×	×	
300	29	Female	Cheek	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.68021617	2	0.175	801409	√	
					E		2.04628436	2	0.229675	913624	√	
301	65	Female	Cheek	2012	E	hyperplasia	1.44712434	2	0.1835	825798	√	Recurrence
					E		1.33519292	0	0.316975	800986	×	
					E		1.17325842	0	0.27125	987349	×	
302	78	Male	Palate	2012	E	hyperplasia	1.40472192	1	0.323175	832164	×	Recurrence
					E		4.19245839	5	0.1525	915154	√	
					E		4.142368	4	0.278525	939367	×	
303	58	Female	Cheek	2012	E	hyperplasia	1.17641269	1	0.1966	969289	√	Recurrence

					E		×	×	×	×	×	
304	47	Male	Gingiva	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		0.7996493	0	0.20075	810465	√	
					E		2.05363855	2	0.19625	822283	√	
305	54	Male	Tongue	2012	E	hyperplasia	1.90138292	3	0.139	866010	√	Recurrence
					E		4.09633049	5	0.19125	756960	√	
					E		4.01548688	5	0.16275	760233	√	
306	65	Female	Cheek	2012	E	hyperplasia	3.89601069	5	0.16975	760679	√	Recurrence
					E		1.2251654	1	0.30925	1037665	×	
					E		1.13964176	0	0.3297	957073	×	
307	45	Male	Cheek	2012	E	hyperplasia	1.06188589	0	0.264175	737816	×	Recurrence
					E		1.17100392	0	0.26125	458952	×	
308	52	Female	Tongue	2012	E	hyperplasia	1.00582284	0	0.23725	1019594	√	Recurrence
					E		×	×	×	×	×	
309	49	Male	Gingiva	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
310	62	Male	Palate	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		0.97895604	0	0.231	658033	√	
					E		1.16653449	0	0.3168	1203322	×	
311	48	Female	Cheek	2012	E	hyperplasia	1.04259205	0	0.24775	1115553	√	Recurrence
					E		1.31559831	0	0.30575	1038432	×	
					E		1.50343013	0	0.3389	1051104	×	
312	39	Male	Cheek	2012	E	hyperplasia	4.45299679	8	0.51175	210920	×	Recurrence
					E		1.70070903	0	0.34575	1150918	×	
					E		1.27797696	0	0.28075	743347	×	
313	57	Female	Tongue	2012	E	hyperplasia	2.54681779	1	0.237275	1007110	√	Recurrence
					E		×	×	×	×	×	
314	47	Male	Tongue	2012	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.23740762	0	0.25075	768222	×	
					E		1.78317487	0	0.3405	688727	×	
315	49	Female	Cheek	2012	E	hyperplasia	0.9203274	0	0.18825	877822	√	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
316	71	Female	Tongue	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
317	52	Female	Cheek	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
318	67	Female	Tongue	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	

					E		×	×	×	×	×	
319	45	Male	Tongue	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		0.85258728	0	0.191325	839945	√	
320	36	Male	Tongue	2013	E	hyperplasia	0.81170768	0	0.191	1515163	√	Recurrence
321	61	Male	Tongue	2013	E	hyperplasia	3.66464522	4	0.15325	1130018	√	Recurrence
					E		0.78575644	0	0.19795	1555666	√	
					E		0.80112544	0	0.193475	1776087	√	
322	27	Male	Tongue	2013	E	hyperplasia	1.01045941	0	0.190325	1930552	√	Recurrence
					E		0.95219094	1	0.133575	1979399	√	
					E		0.89829868	1	0.11525	1953812	√	
323	42	Male	Tongue	2013	E	hyperplasia	1.72580008	1	0.3261	74671	×	Recurrence
					E		3.08359721	4	0.13125	1124908	√	
					E		2.20994974	2	0.2525	1647870	×	
324	60	Female	Cheek	2013	E	hyperplasia	4.22368568	5	0.3295	1216273	×	Recurrence
					E		3.10846511	3	0.2255	1775342	√	
					E		1.68430131	2	0.174125	1450184	√	
325	66	Male	Cheek	2013	E	hyperplasia	2.14969964	3	0.188025	1093590	√	Recurrence
					E		1.98230653	2	0.144725	1225126	√	
					E		2.33716255	0	0.26875	112480	×	
326	51	Female	Cheek	2013	E	hyperplasia	2.81841715	5	0.572425	1220339	×	Recurrence
					E		×	×	×	×	×	
327	73	Male	Cheek	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
328	63	Male	Lip	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
329	71	Female	Cheek	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
330	60	Female	Tongue	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
331	58	Female	Palate	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
332	68	Female	Cheek	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	

						E		×	×	×	×	×	
						E		×	×	×	×	×	
333	73	Male	Cheek	2013		E	hyperplasia	×	×	×	×	×	Recurrence
						E		×	×	×	×	×	
334	58	Female	Gingiva	2013		E	hyperplasia	×	×	×	×	×	Recurrence
335	52	Male	Cheek	2013		E	hyperplasia	2.38744792	3	0.19525	975509	√	Recurrence
						E		1.23570916	1	0.21655	1392326	√	
						E		×	×	×	×	×	
						E		×	×	×	×	×	
						E		×	×	×	×	×	
336	60	Male	Cheek	2013		E	hyperplasia	0.99005282	0	0.33155	1912030	×	Recurrence
						E		1.26281618	1	0.25685	1938288	×	
						E		1.41103219	1	0.31965	2026810	×	
337	62	Female	Tongue	2013		E	hyperplasia	1.71541712	1	0.33495	1986398	×	Recurrence
					E			×	×	×	×	×	
338	49	Female	Cheek	2013		E	hyperplasia	5.88275488	11	0.15075	1226928	√	Recurrence
339	77	Male	Cheek	2013		E	hyperplasia	5.64548936	8	0.17725	991817	√	Recurrence
						E		1.45788562	1	0.279925	2344132	×	
						E		1.02031201	1	0.185525	2194504	√	
340	65	Male	Tongue	2013		E	hyperplasia	0.79007977	0	0.17625	1900333	√	Recurrence
						E		×	×	×	×	×	
						E		×	×	×	×	×	
						E		×	×	×	×	×	
341	50	Female	Tongue	2013		E	hyperplasia	×	×	×	×	×	Recurrence
						E		1.30937988	0	0.316	303803	×	
						E		0.98564327	0	0.275075	845878	×	
342	59	Male	Tongue	2013		E	hyperplasia	0.79653984	0	0.1966	2013740	√	Recurrence
						E		1.06774181	0	0.2468	1587228	√	
						E		1.45603221	0	0.31525	2274329	×	
343	66	Female	Tongue	2013		E	hyperplasia	1.06193897	0	0.22825	488983	√	Recurrence
						E		×	×	×	×	×	
						E		×	×	×	×	×	
344	44	Female	Tongue	2013		E	hyperplasia	×	×	×	×	×	Recurrence
						E		1.15154652	0	0.2466	945979	√	
						E		0.94859442	0	0.2283	1455125	√	
345	28	Female	Cheek	2013		E	hyperplasia	1.01628125	0	0.23225	662785	√	Recurrence
						E		1.58707187	2	0.15525	1512483	√	
						E		1.41102192	2	0.41965	2021810	×	
346	42	Female	Cheek	2013		E	hyperplasia	1.94638746	2	0.40045	1149562	×	Recurrence
						E		×	×	×	×	×	
						E		×	×	×	×	×	
						E		×	×	×	×	×	
						E		×	×	×	×	×	
347	59	Male	Tongue	2013		E	hyperplasia	×	×	×	×	×	Recurrence
						E		×	×	×	×	×	
						E		×	×	×	×	×	

					E		×	×	×	×	×	
					E		×	×	×	×	×	
348	62	Female	Gingiva	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
349	62	Female	Cheek	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		2.49111263	3	0.508875	1620764	×	
					E		2.03826321	2	0.391425	1785898	×	
350	50	Male	Cheek	2013	E	hyperplasia	1.96215492	2	0.3112	1895314	×	Recurrence
					E		4.168866	5	0.15665	2484278	√	
					E		3.59188151	4	0.191675	1173934	√	
351	33	Female	Tongue	2013	E	hyperplasia	3.34220681	4	0.140425	2316960	√	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
352	28	Male	Lip	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		2.69717129	6	0.531325	1061834	×	
					E		3.81355419	6	0.11375	1308015	√	
353	58	Female	Palate	2013	E	hyperplasia	3.71358433	7	0.1138	1442886	√	Recurrence
					E		0.95066358	1	0.135825	1878916	√	
					E		2.69711286	6	0.53125	61834	×	
354	75	Female	Cheek	2013	E	hyperplasia	1.34649966	1	0.14185	1332900	√	Recurrence
355	34	Female	Tongue	2013	E	hyperplasia	3.85567166	6	0.11275	1220783	√	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
356	51	Female	Cheek	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
357	71	Male	Tongue	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.19016382	0	0.25855	1832843	×	
					E		1.83385301	2	0.1575	1359716	√	
358	57	Female	Tongue	2013	E	hyperplasia	1.92730603	2	0.22535	1526747	√	Recurrence
					E		0.96997432	0	0.26465	1524936	×	
					E		4.99541339	7	0.461775	1507302	×	
359	67	Female	Cheek	2013	E	hyperplasia	4.53366213	7	0.35195	1433517	×	Recurrence
					E		1.25040634	0	0.304825	2247976	×	
					E		1.86257022	1	0.406375	2198272	×	
360	58	Female	Tongue	2013	E	hyperplasia	2.01947277	1	0.4256	2411599	×	Recurrence
					E		×	×	×	×	×	

					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
361	72	Female	Tongue	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
362	49	Male	Cheek	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
363	55	Male	Cheek	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
364	15	Male	Tongue	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		0.97626989	0	0.223325	2372624	√	
					E		1.10762397	0	0.22135	1944571	√	
365	69	Female	Tongue	2013	E	hyperplasia	7.1748639	14	0.36225	448638	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
366	52	Female	Tongue	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.0337209	2	0	9495	×	
					E		2.09015145	1	0.432375	1299796	×	
367	56	Male	Gingiva	2013	E	hyperplasia	2.18008239	1	0.3627	1298552	×	Recurrence
					E		4.15357651	5	0.202475	1515104	√	
					E		5.02732128	6	0.1615	996752	√	
368	62	Male	Cheek	2013	E	hyperplasia	0.81957155	0	0.169	421910	√	Recurrence
					E		1.21044952	0	0.238525	1792715	√	
					E		1.21381231	0	0.276375	1819399	×	
369	48	Female	Gingiva	2013	E	hyperplasia	1.18913121	0	0.223125	2190688	√	Recurrence
					E		2.35246482	3	0.372575	1998282	×	
					E		2.05393165	2	0.269825	2321926	×	
370	74	Female	Tongue	2013	E	hyperplasia	2.29595903	2	0.360175	2140599	×	Recurrence
					E		1.66688228	2	0.19275	1498921	√	
					E		1.73068109	2	0.18625	1292082	√	
371	77	Female	Cheek	2013	E	hyperplasia	1.1114236	0	0.268675	1538302	×	Recurrence
					E		2.35696328	2	0.459025	1500926	×	
					E		1.14850285	0	0.25675	816232	×	
372	74	Female	Gingiva	2013	E	hyperplasia	1.91121054	2	0.21485	1365597	√	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	

373	34	Male	Cheek	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		0.81501076	0	0.20875	1826907	√	
					E		1.60431635	0	0.24905	1677838	√	
374	43	Male	Lip	2013	E	hyperplasia	0.99097452	0	0.239	1598008	√	Recurrence
					E		1.39969611	0	0.223	101449	√	
					E		1.70128319	4	0.1235	2038400	√	
375	68	Male	Cheek	2013	E	hyperplasia	0.98923033	0	0.23125	1514028	√	Recurrence
					E		2.3257347	2	0.33125	740641	×	
					E		1.0337209	2	0	94915	×	
376	52	Female	Cheek	2013	E	hyperplasia	1.03259508	1	0.128875	1381038	√	Recurrence
					E		1.12292352	1	0.159825	1121345	√	
					E		4.38902557	4	0.075	48708	×	
377	79	Female	Gingiva	2013	E	hyperplasia	3.96703011	8	0.253	348074	×	Recurrence
					E		×	×	×	×	×	
378	53	Male	Cheek	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
379	39	Female	Tongue	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.81091824	3	0.24515	1351791	√	
380	50	Male	Cheek	2013	E	hyperplasia	1.96649975	3	0.296375	1624353	×	Recurrence
					E		×	×	×	×	×	
381	57	Female	Cheek	2013	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.36255901	0	0.299225	1775316	×	
					E		1.4059055	0	0.26925	1744722	×	
382	59	Female	Tongue	2013	E	hyperplasia	1.44694883	0	0.36845	1926673	×	Recurrence
					E		1.25449677	1	0.1587	2133557	√	
					E		1.2218188	1	0.200225	2057674	√	
383	47	Female	Tongue	2013	E	hyperplasia	2.27253908	1	0.1354	1476715	√	Recurrence
					E		×	×	×	×	×	
384	41	Male	Tongue	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
385	62	Female	Gingiva	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
386	55	Female	Cheek	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
387	45	Female	Cheek	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
388	67	Male	Gingiva	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
389	48	Male	loor of mout	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
390	62	Male	Tongue	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	

					E		×	×	×	×	×	
					E		×	×	×	×	×	
391	55	Female	Tongue	2014	E	hyperplasia	×	×	×	×	×	Recurrence
392	47	Male	loor of mout	2014	E	hyperplasia	1.16215122	0	0.22175	1435115	√	Recurrence
					E		×	×	×	×	×	
393	67	Female	Lip	2014	E	hyperplasia	×	×	×	×	×	Recurrence
394	48	Female	Cheek	2014	E	hyperplasia	3.00977094	5	0.2397	1996893	√	Recurrence
395	41	Male	Palate	2014	E	hyperplasia	2.33673581	3	0.299625	1586544	×	Recurrence
396	46	Female	Cheek	2014	E	hyperplasia	1.7395916	2	0.1534	1452601	√	Recurrence
					E		1.49790424	0	0.26025	689016	×	
					E		1.33191252	0	0.28935	2345126	×	
397	56	Male	Tongue	2014	E	hyperplasia	1.97008166	4	0.28395	1083385	×	Recurrence
					E		1.05381361	0	0.24495	2277952	√	
					E		1.18917143	0	0.292875	2375937	×	
398	53	Male	Tongue	2014	E	hyperplasia	1.03279909	0	0.230775	2281457	√	Recurrence
					E		1.25435406	0	0.3025	1130557	×	
					E		1.36944738	1	0.294625	687142	×	
399	36	Male	Cheek	2014	E	hyperplasia	1.56459349	0	0.2745	799643	×	Recurrence
					E		1.06582674	0	0.2864	978331	×	
					E		1.01839694	0	0.2705	1021666	×	
400	44	Male	Tongue	2014	E	hyperplasia	1.0320853	0	0.30775	1061440	×	Recurrence
401	64	Female	Cheek	2014	E	hyperplasia	1.2514272	0	0.2981	2040039	×	Recurrence
					E		×	×	×	×	×	
402	59	Male	Cheek	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
403	56	Male	Tongue	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.10273069	0	0.2457	1232176	√	
					E		0.94355348	0	0.251925	1194594	×	
404	28	Female	Tongue	2014	E	hyperplasia	1.20015444	0	0.276125	833640	×	Recurrence
405	33	Male	Cheek	2014	E	hyperplasia	0.98638251	0	0.2625	1913911	×	Recurrence
					E		×	×	×	×	×	
406	50	Male	Gingiva	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
407	61	Female	Cheek	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
408	31	Female	Tongue	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
409	45	Male	Cheek	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
410	61	Male	Gingiva	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.4085842	1	0.272775	932159	×	
					E		3.39152062	1	0.091	98777	×	
411	44	Female	Cheek	2014	E	hyperplasia	2.9884304	4	0.357325	971125	×	Recurrence

					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
412	56	Male	Tongue	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
413	34	Male	Tongue	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.07792096	0	0.248825	867081	√	
					E		1.3033415	0	0.2735	628186	×	
414	62	Female	Tongue	2014	E	hyperplasia	1.31037317	1	0.284	634309	×	Recurrence
					E		×	×	×	×	×	
415	61	Male	Tongue	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
416	68	Female	Gingiva	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.3345176	1	0.28375	631690	×	
					E		4.32672298	11	0.4095	403982	×	
417	65	Male	Palate	2014	E	hyperplasia	1.56647658	0	0.341225	1243066	×	Recurrence
					E		1.83800194	1	0.4796	993331	×	
					E		1.16787171	1	0.231	1048390	√	
418	27	Male	Cheek	2014	E	hyperplasia	1.78785983	3	0.43945	1246925	×	Recurrence
					E		1.49345157	1	0.307425	1236884	×	
					E		1.60418203	1	0.320025	1204384	×	
419	46	Female	Tongue	2014	E	hyperplasia	1.79678173	1	0.3752	1255405	×	Recurrence
					E		0.96974632	0	0.25625	1373375	×	
					E		1.36169225	0	0.35395	1091584	×	
420	33	Male	Tongue	2014	E	hyperplasia	1.66075969	1	0.427025	1710660	×	Recurrence
					E		1.49298397	1	0.3395	1110376	×	
					E		1.5746851	1	0.372	654873	×	
421	42	Male	Tongue	2014	E	hyperplasia	2.21097606	3	0.563775	1380527	×	Recurrence
					E		×	×	×	×	×	
422	69	Female	Tongue	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
423	41	Male	Cheek	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
424	57	Male	Cheek	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		3.10622985	6	0.38635	634411	×	
					E		3.19583441	6	0.3598	832269	×	
					E		3.58939166	7	0.3835	784706	×	
	59			2014	E	hyperplasia	3.62067444	7	0.34975	958723	×	Recurrence
					E		2.60317215	5	0.20925	1213328	√	
					E		2.33112502	4	0.25225	931374	×	
					E		2.54674555	3	0.25875	810576	×	
425	64	Female	Gingiva	2019	E	hyperplasia	2.45021278	3	0.32175	858391	×	Recurrence(after)
					E		4.50651591	6	0.209925	1253328	√	
					E		3.84701496	6	0.2491	1135487	√	

426	72	Female	Gingiva	2014	E	hyperplasia	3.92019422	5	0.29325	964935	×	Recurrence
					E		×	×	×	×	×	
427	74	Male	Cheek	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
428	30	Male	Cheek	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.14641958	0	0.23175	713355	√	
429	27	Male	Cheek	2014	E	hyperplasia	1.44021815	0	0.374675	1692777	×	Recurrence
					E		1.18007354	0	0.267125	1261898	×	
					E		1.53741202	0	0.37775	659513	×	
430	58	Female	Tongue	2014	E	hyperplasia	1.83116553	1	0.389925	926908	×	Recurrence
					E		0.82797551	0	0.22625	1182873	√	
					E		3.7784431	7	0.33975	240508	×	
431	43	Male	Tongue	2014	E	hyperplasia	0.89386323	0	0.2355	953629	√	Recurrence
					E		1.58271057	2	0.23595	1769694	√	
432	47	Male	Tongue	2014	E	hyperplasia	1.67504134	2	0.2586	1672998	×	Recurrence
					E		×	×	×	×	×	
433	42	Male	Cheek	2014	E	hyperplasia	×	×	×	×	×	Recurrence
434	62	Female	Tongue	2014	E	hyperplasia	0.55255066	0	0.12785	1329948	√	Recurrence
					E		1.59853035	1	0.2416	1497246	√	
					E		1.86229369	1	0.29835	1557926	×	
435	62	Male	Cheek	2014	E	hyperplasia	1.66473806	1	0.2295	2016306	√	Recurrence
					E		1.52362499	0	0.1846	1467887	√	
					E		2.10119785	2	0.323425	1210808	×	
436	63	Female	Gingiva	2014	E	hyperplasia	1.19455872	0	0.1988	1661942	√	Recurrence
					E		×	×	×	×	×	
437	47	Female	Cheek	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		0.90644524	0	0.199	1627046	√	
					E		1.50504783	1	0.27315	1465421	×	
438	44	Female	Tongue	2014	E	hyperplasia	0.93229881	0	0.231575	1559416	√	Recurrence
439	73	Female	Tongue	2014	E	hyperplasia	5.86411974	12	0.2145	706997	√	Recurrence
					E		×	×	×	×	×	
440	57	Male	Lip	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		2.56461325	3	0.191	885548	√	
					E		2.90605941	3	0.1925	1104455	√	
					E		3.11751294	3	0.213	1047185	√	
	57			2014	E	hyperplasia	2.70450446	2	0.28875	101680	×	Recurrence
					E		2.69399242	7	0.35585	1268191	×	
					E		2.29519533	4	0.3906	1316537	×	
					E		3.50651371	3	0.5054	775278	×	
441	61	Male	Cheek	2018	E	hyperplasia	1.71365547	2	0.28875	1018680	×	Recurrence(after)
					E		×	×	×	×	×	
442	56	Male	Cheek	2014	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.27594277	0	0.2401	1416941	√	
					E		2.19975811	5	0.351	366077	×	
443	52	Female	Tongue	2015	E	hyperplasia	1.32502794	1	0.248875	1261997	√	Recurrence
					E		×	×	×	×	×	

444	46	Male	Gingiva	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
445	48	Male	Tongue	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
446	42	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
447	65	Female	loor of mout	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.33297766	0	0.254	1489877	×	
					E		1.46554482	0	0.2467	1459810	√	
448	65	Female	Tongue	2015	E	hyperplasia	1.15599956	0	0.190275	1594196	√	Recurrence
					E		1.61377027	2	0.217375	1392240	√	
					E		2.08561783	2	0.32735	1075604	×	
449	76	Male	Cheek	2015	E	hyperplasia	1.8020318	2	0.3225	445417	×	Recurrence
					E		2.30594393	4	0.27125	752122	×	
					E		3.50436052	4	0.27395	2002049	×	
450	64	Female	Cheek	2015	E	hyperplasia	1.75791122	1	0.3625	1585416	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
451	78	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
452	51	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.02535632	0	0.22105	1611561	√	
					E		1.19799487	0	0.249675	1747851	√	
453	53	Female	Cheek	2015	E	hyperplasia	1.09346445	0	0.195675	1781367	√	Recurrence
					E		0.82749764	0	0.162075	1903340	√	
					E		1.22818322	1	0.169	2073112	√	
454	42	Female	Tongue	2015	E	hyperplasia	1.65954905	1	0.2433	1767560	√	Recurrence
					E		×	×	×	×	×	
455	58	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
456	69	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
457	37	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
458	62	Female	Gingiva	2015	E	hyperplasia	1.35215116	0	0.31325	480950	×	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
459	62	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
460	72	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		2.10891354	3	0.3643	1613871	×	
					E		1.73328169	2	0.26915	1788615	×	
					E		×	×	×	×	×	
					E		1.49098847	2	0.24095	1577260	√	
					E		1.99602684	2	0.43525	1815916	×	
461	66	Male	Tongue	2015	E	hyperplasia	2.13044444	2	0.445325	1606753	×	Recurrence

462	70	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
463	52	Female	Tongue	2015	E	hyperplasia	×	×	×	×	×	Recurrence
464	45	Male	Gingiva	2015	E	hyperplasia	×	×	×	×	×	Recurrence
465	34	Male	Tongue	2015	E	hyperplasia	×	×	×	×	×	Recurrence
466	45	Female	Tongue	2015	E	hyperplasia	×	×	×	×	×	Recurrence
467	53	Female	Tongue	2015	E	hyperplasia	×	×	×	×	×	Recurrence
468	62	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
469	61	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
470	60	Female	Palate	2015	E	hyperplasia	×	×	×	×	×	Recurrence
471	82	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.43390952	1	0.2521	1313486	×	
					E		1.06034463	0	0.243675	1581584	√	
472	61	Female	Tongue	2015	E	hyperplasia	1.31031277	0	0.277775	1263568	×	Recurrence
473	49	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.39253376	0	0.2734	1330767	×	
					E		2.27940813	4	0.31335	1280215	×	
474	44	Female	Cheek	2015	E	hyperplasia	1.22584584	0	0.2906	1217775	×	Recurrence
					E		×	×	×	×	×	
475	55	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		×	×	×	×	×	
476	52	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		2.6765996	4	0.641975	1366096	×	
					E		3.4635227	6	0.211675	1395144	√	
477	44	Female	Tongue	2015	E	hyperplasia	2.87077673	6	0.10865	1349480	√	Recurrence
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
					E		×	×	×	×	×	
478	56	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		1.66911023	2	0.375425	1477701	×	
					E		1.20268571	0	0.2925	1179061	×	
479	62	Male	Cheek	2015	E	hyperplasia	1.09257147	0	0.2435	1433000	√	Recurrence
					E		1.40303871	0	0.301225	1483275	×	
					E		1.52198062	1	0.331275	1509689	×	
480	53	Female	Gingiva	2015	E	hyperplasia	1.45075684	0	0.335	1316033	×	Recurrence
					E		1.08812665	0	0.204	1360954	√	
					E		1.72963226	0	0.331825	1559040	×	
481	44	Male	Tongue	2015	E	hyperplasia	2.32705644	5	0.532875	1681132	×	Recurrence
482	75	Female	Lip	2015	E	hyperplasia	×	×	×	×	×	Recurrence
483	53	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
484	61	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
485	73	Female	Palate	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		0.8402697	0	0.213675	1483766	√	
					E		1.06455341	0	0.24025	554106	√	
486	76	Female	Tongue	2015	E	hyperplasia	1.2415157	1	0.2004	1907412	√	Recurrence
487	49	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence

488	72	Female	Cheek	2015	E	hyperplasia	2.26459734	1	0.284325	1013761	×	Recurrence
489	68	Female	Tongue	2015	E	hyperplasia	×	×	×	×	×	Recurrence
490	68	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
491	69	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
492	45	Female	Gingiva	2015	E	hyperplasia	×	×	×	×	×	Recurrence
493	59	Female	Tongue	2015	E	hyperplasia	×	×	×	×	×	Recurrence
494	70	Female	Gingiva	2015	E	hyperplasia	×	×	×	×	×	Recurrence
495	31	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
496	63	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
497	78	Female	Tongue	2015	E	hyperplasia	×	×	×	×	×	Recurrence
498	33	Male	Tongue	2015	E	hyperplasia	×	×	×	×	×	Recurrence
499	63	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
500	55	Male	Tongue	2015	E	hyperplasia	×	×	×	×	×	Recurrence
501	49	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
502	52	Male	Gingiva	2015	E	hyperplasia	×	×	×	×	×	Recurrence
503	67	Female	Gingiva	2015	E	hyperplasia	×	×	×	×	×	Recurrence
504	56	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
505	49	Male	Gingiva	2015	E	hyperplasia	×	×	×	×	×	Recurrence
506	56	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
507	42	Male	Cheek	2015	E	hyperplasia	×	×	×	×	×	Recurrence
508	21	Male	Tongue	2015	E	hyperplasia	×	×	×	×	×	Recurrence
					E		2.04494309	3	0.42075	936976	×	
					E		1.73744726	2	0.415725	1221795	×	
					E		1.3253462	1	0.2608	1109201	×	
					E		1.32254118	0	0.209	827621	√	
	63			2015	M	hyperplasia	0.77427834	0	0.195	877383	√	Recurrence
					E		1.16643819	1	0.2355	850930	√	
					E		1.03936565	1	0.232	766455	√	
					E		1.44128424	1	0.28275	670049	×	
509	64	Male	Cheek	2016	E	hyperplasia	1.47865498	2	0.27	814841	×	Recurrence(after)
510	65	Male	Tongue	2015	E	hyperplasia	×	×	×	×	×	Recurrence
511	55	Male	Tongue	2012	E	hyperplasia	×	×	×	×	×	nalignant transformation
512	62	Female	Tongue	2012	E	hyperplasia	1.59969315	2	0.1485	821223	√	nalignant transformation
513	67	Male	Tongue	2012	E	hyperplasia	×	×	×	×	×	nalignant transformation
					E		2.40740903	2	0.221325	986933	√	
					E		1.72876197	2	0.2615	357899	×	
					E		2.34560208	2	0.3523	862765	×	
	43			2012	E	hyperplasia	1.56080504	1	0.29105	883138	×	nalignant transformatior
					T		1.40590554	0	0.2625	144722	×	
					T		1.21177167	1	0.16	799374	√	
514	44	Female	Tongue	2013	T	tumor	1.92769827	2	0.192	866142	√	nalignant transformatior
515	59	Female	Cheek	2012	E	hyperplasia	×	×	×	×	×	nalignant transformation
516	62	Female	Tongue	2013	E	hyperplasia	×	×	×	×	×	nalignant transformation
517	49	Female	Gingiva	2013	E	hyperplasia	×	×	×	×	×	nalignant transformation
518	74	Female	Gingiva	2013	E	hyperplasia	×	×	×	×	×	nalignant transformation
					E		2.96517731	2	0.16975	523931	√	

					E		5.05219598	6	0.19075	856481	√	
					E		5.71183289	8	0.2125	676171	√	
					E		5.63228918	7	0.259475	881668	×	
					M		0.82832942	0	0.18525	605877	√	
	73			2014	M	hyperplasia	2.17943704	1	0.173	751699	√	nalignant transformatior
					T		3.94751559	4	0.22125	660330	√	
					T		1.26383171	0	0.1595	787394	√	
					T		1.71819888	1	0.29875	404607	×	
519	74	Female	Cheek	2014	T	tumor	1.49367036	1	0.2955	1035920	×	nalignant transformatior
					E		3.89323078	7	0.186	753289	√	
					E		1.01662663	2	0	9501	×	
					E		5.54749671	10	0.33425	781151	×	
					E		5.50516048	8	0.3305	860171	×	
					E		1.56541178	1	0.346475	864398	×	
	34			2014	E	hyperplasia	3.20518774	6	0.41755	801366	×	nalignant transformatior
					T		4.8846232	10	0.253975	1175646	×	
					T		5.28302496	10	0.228075	1148154	√	
					T		5.47015746	10	0.1343	1101128	√	
					T		5.31216046	8	0.297	934914	×	
					M		0.85971773	0	0.1365	1131291	√	
520	36	Male	Tongue	2016	M	tumor	1.1124582	0	0.2285	1078638	√	nalignant transformatior
521	69	Female	Cheek	2014	E	hyperplasia	×	×	×	×	×	nalignant transformation
522	50	Male	Tongue	2014	E	hyperplasia	×	×	×	×	×	nalignant transformation
					E		5.33618665	7	0.2595	649116	×	
					E		4.87441108	5	0.285	682003	×	
					M		1.29474266	0	0.27725	799075	×	
	40			2014	M	hyperplasia	0.81971323	0	0.2185	677403	√	nalignant transformatior
					T		3.20889235	5	0.1545	537073	√	
					T		2.13379084	4	0.1535	534177	√	
					M		0.8329149	0	0.15225	512313	√	
523	41	Female	Tongue	2015	M	tumor	0.78786759	0	0.16175	474479	√	nalignant transformatior
					E		×	×	×	×	×	
524	72	Female	Gingiva	2014	E	hyperplasia	×	×	×	×	×	nalignant transformatior
					E		2.00705911	3	0.1802	1542882	√	
525	47	Female	Cheek	2014	E	hyperplasia	2.87864918	3	0.171775	1587345	√	nalignant transformatior
					E		×	×	×	×	×	
526	64	Female	Cheek	2015	E	hyperplasia	×	×	×	×	×	nalignant transformatior
527	50	Female	loor of mout	2015	E	hyperplasia	1.36098145	2	0.23175	973369	√	nalignant transformation
528	62	Female	Gingiva	2015	E	hyperplasia	×	×	×	×	×	nalignant transformation
					E		×	×	×	×	×	
529	69	Female	Gingiva	2015	E	hyperplasia	×	×	×	×	×	nalignant transformatior