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Personalized Medicine-A treasured tailor for tomorrow

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ABSTRACT: Personalized medicine is about individualized treatment of a disease.The approach focuses on identifying genetic, epigenomic and clinical information that helps in understanding how a person's unique genetic profile makes them vulnerable to certain diseases.This is a complete extension of traditional approach[One Size Fits All] to prediction of treatments that will be safe and effective for individual patient.Knowledge of personalized medicine facilitates earlier disease detection through biomarkers, omics& identification of early genomic and epigenomic events in disease development particularly carcinogenesis. This review focuses on the application of personalized medicine in oral cancer.
Key words-Pharmacogenomics, Biomarkers, Theranostics

I. INTRODUCTION

Various drugs can have different kinds of response and toxic reactions in different patients. The variations in body's response to drug treatment may be due to several factors such as illness, differences in pharmacokinetics and pharmacodynamics of drugs, environmental and genetic factors. The study of variations of DNA and RNA characteristics as related to drug response is known as pharmacogenomics. The application of this pharmacogenomics to the clinical management of an individual is referred to as personalized medicine.[1]Oral cancer is one of the most common malignant lesions of head and neck. Although, remarkable developments have occurred in the development of new therapies of cancer, management is less satisfactory. Personalization of cancer therapies is based on a better understanding of the disease at the molecular level and this has enabled early detection of cancer, more effective and less toxic treatment increasing the chances of cure.[2]

WHAT IS PERSONALIZED MEDICINE?

The National Cancer Institute defined personalized medicine as a 'form of medicine that uses information about a person's genes, proteins and environment to prevent, diagnose and treat the disease.[1]Personalized medicine can be simply described as prescription of specific therapeutics best suited for an individual. Presently, personalized medicine is applied in the following areas:

- Prediction
- Diagnostics
- Therapeutics
- Drug development

Mechanism Of Personalized Medicine

Recognition of interindividual differences in drug response is an essential step towards optimizing therapy for a disease. The traditional standard approaches to drug development and clinical therapy, such as 'trial and error', 'one drug fits all' are highly limited, contributing to 25-50% of drug toxicity and treatment factors.[1] On the other hand, pharmacogenomics with advantage of genomic techniques such as DNA sequencing, gene mapping and bioinformatics to allow researchers to identify the actual genetic basis of inter individual and interracial variation in drug efficacy, metabolism and transport.Genetic polymorphisms and mutations in drug metabolizing enzymes, transporters, receptors and other drug targets are linked to inter individual differences in efficacy and toxicity of many medications as well as the risk of genetic diseases. [3]

Pharmacodiagnostics{Theranostics}is considered as the pathway to what has been termed as "personalized medicine"-i.e., the use of molecular analysis to achieve optimal medical outcome in the management of disease or a patient's predisposition to disease. [3] Thus personalized medicine promises to bring about a new standard of health care, with potential to accelerate clinical trials, achieve better diagnostic efficacy and treatment outcome.

- Single nucleotide polymorphisms[SNPs]

SNPs are the most frequently found DNA sequence variations in the human genome.Approximately 1 million SNPs are likely to occur in human genes.SNPs found in the coding and regulatory regions of genes are likely to be the

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most relevant variants.Many efforts are being made to identify all SNPs and their relevance to disease susceptibility and treatment outcomes and may take several more years. [4]

- Drug Metabolizing Enzymes

There are more than 30 families of drug metabolizing enzymes in humans and essentially all have genetic variants, many of which translate into the functional changes in the proteins encoded. Many genetic tests have been identified depending on the enzyme present:

- CYP 450 genotyping test:

A group of enzymes known as CYP450 is responsible for metabolizing more than 30 types of medications.The test can determine how quickly and effectively these agents are eliminated from the body.

- Thiopurinemethyltransferase test:

An enzyme called thiopurinemethyltransferase breaks down a chemotherapy drug called thiopurine,which is used to treat leukemias.Some people have genetic variations that prevent them from producing this enzyme. This results in the accumulation of thiopurine in the body resulting in toxic reactions. A blood test can be used to check for variation before treatment begins, resulting in better dosing guidelines for physicians. [5]

PERSONALIZED MEDICINE IN ORAL CANCER

Cancer is a major global health issue.Oral cancer is one of the most common malignant lesions of head and neck .It is a part of group of cancers named head and neck cancer, which enclose a wide set of diverse tumour types arising from various anatomic structures, such as oral cavity, oropharynx and nasopharynx.Globally, oral cancer is one of the leading cancers, accounting for 2% of all cancer cases, with a nearly 50% mortality rate. [2]Data from the World Health Organization demonstrated that there are an estimated 5, 29,000 new cases of oral cavity and pharynx cases and more than 3, 00,000 deaths are caused by oral cancer each year. [6]Two thirds of global cases of oral cancers are reported in low and middle income countries, where half of these cases occur in South Asia.One fifth of all oral cancer cases and one fourth of all oral cancer deaths occur in India. [7]

Multiple factors contribute to the initiation of oral cancer.The risk factors include environmental risk factors, genetic susceptibility and epigenetic risk factors.In addition to the well-established roles of tobacco, alcohol and areca nut as risk factors, high risk human papilloma virus infection [HPV-16 & HPV-18] has been identified as a significant risk factor for oropharyngeal cancer. [6] Incidence rates of oral cancer vary widely throughout the world due to oral cancer associated behaviours including alcohol consumption, tobacco smoking, betel quid chewingand smokeless tobacco usage.

The main histologic type of oral cancer is squamous cell carcinoma[SCC], which accounts for nearly 90% of all oral cancer cases.The most common sites for oral cancer are the tongue and floor of mouth, which account for more than 50% of all the cases followed by gingiva, palatal mucosa, buccaland labial mucosa.Oral squamous cell carcinoma usually progresses rapidly, and the prognosis is closely associated with tumour staging.

Most OSCC develop from an existing premalignant lesion, such as leukoplakia, erythroplakia, or proliferative verrucousleukoplakia.In addition, OSCC is notorious for its high recurrence rate and the frequent occurrence of synchronous andmetachronous primary tumours. [8]

Despite technological advances and improvements in OSCC diagnosis and treatment modalities, its 5 years survival rate stays low around 50-60%.This is mainly due to delay in the diagnosis and by the relatively high tumour recurrence rates detected in these patients. Generally, at the time of diagnosis, only one third of OSCC patients have the disease at early stages. The understanding about biology and pathology of oral carcinogenesis process is still slow.This understanding is crucial to search and establish molecular targets to help in the early diagnosis, to predict the prognosis and also to direct the development of new therapeutic strategies. Here precision medicine plays an important role.Precision medicine is a medical model which focuses on two parts:

1. Cancer genomic utility
2. Generating big data of health and disease based on national cohort studies.

Cancer genomic utility includes risk assessment, clinical screening, diagnosis, treatment and prognostic prediction. Molecular epidemiology is the study of gene-disease association as well as gene-gene and gene-environment interactions using conventional epidemiological study designs combined with biomarkers. Rapid advances in human genomics are making it possible to develop detailed profiles of genetic susceptibility based on genetic variants in multiple pathways. [6]

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BIOMARKERS IN ORAL CANCER

Carcinogenesis is a complex process that occurs at the phenotype and genotype levels. Cancer development is driven by the accumulation of genetic and epigenetic changes that disturb the homeostatic equilibrium between cell proliferation and cell death. Research on cancer tissues has revealed that there may be a link between molecular level and tissue level changes that drive malignant changes in the tissue and play a major role in disease progression.

The National Cancer Institute has defined "biomarker" as a biological molecule found in blood, other body fluids or tissues that is a sign of a normal or abnormal process or of a condition of disease such as cancer. [9] Biomarker can be used for patient assessment in multiple clinical settings. They can be used for estimating disease risk, screening for occult primary cancers, distinguishing benign from malignant findings, determining prognosis, acting as predictors/screening and monitoring disease states.They can also be used to either detect recurrence or determine progression/response to therapy.Biomarkers are identified by various molecular techniques such as DNA arrays,high throughput sequencing, polymerase chain reaction, gene expression arrays, restricted fragment length polymorphism, gene chip, liquid chromatography, nuclear magnetic resonance, mass spectroscopy, enzyme assays and immunohistochemistry.

Biomarkers can be classified based on the disease state as:

- Predictivebiomarker
- Diagnostic biomarker
- Prognostic biomarker

Oral cancer biomarkers may be molecular markers of:

- Genetic mutations
- Polymorphisms of genes
- DNA copy number variance
- Telomere instabilities
- Cell cycle signaling pathways.

Human genome epidemiology (HuGE) is denoted as "an emerging field of inquiry that uses systematic applications of epidemiologic methods and approaches in population-based studies of the impact of human genetic variation on health and disease. [10]A key characteristic of HuGE is the molecular biological techniques applied in studies, especially those using DNA microarray chips in genome-wide association studies (GWASs). These techniques can compare millions of single nucleotide polymorphisms (SNPs) between genome DNA from cases and controls.

A prognostic biomarker informs about a likely cancer outcome. Potential biomarkers include the growth signaling oncogenes, epidermal growth factor receptor (EGFR) and cyclin D1, the antigrowth signaling components p53 and p21, apoptotic effectors such as Bcl-2 and also components involved in angiogenesis, invasion, and metastasis processes.GWASs have been conducted as a powerful method to screening novel genetic markers related to increased susceptibility for diseases.rs3828805 (HLA-DQB1), rs201982221 (LHPP), and rs1453414 (OR52N2/TRIM5) have been shown to be associated with oral and pharyngeal cancers. rs6547741 (GPN1), rs928674 (LAMC3), rs8181047 (CDKN2B-AS1), and rs10462706 (CLPTM1L) have been shown to be associated with oral cancer.[11] GWASs were carried out to study the genetic susceptibility of salivary gland carcinomas (SGC), OSCC, tongue SCC cells, and laryngeal SCC. Further, genome-wide disease association studies in chewing tobacco-associated oral cancers have explored gene-environment interactions. [12]GSTM3 have been shown to be associated with the susceptibility to oral cancer. SNPs are one of the most used biomarkers indicating genetic variation, associated with susceptibility and prognoses of oral cancer. Polymorphisms in GSTT1, GSTM1, CYP2E1, CYP1A2, ADH1C, and MTHFR have been studied[13].Polymorphisms of DNA repair genes have been shown to be related with cancer susceptibility. The association between polymorphisms in DNA repair genes (XRCC1; XRCC3; XPC; XPD; and MGMT and OSCC) was discussed, and the variant genotypes with XRCC3 and possibly XRCC1 194Trp and XPD exon 6 were associated with OSCC.[14]

In general, these SNPs influence the repair of DNA damage that is caused by environmental risk factors for oral cancer. Aberrant DNA methylation is often observed in SCC tissue and plays an important role in the development of SCC.Polymorphisms of DNA repair genes and genetic susceptibility of OSCC are associated. SNPs in genes that encode proteins involved in inflammation and immunomodulation (IL1a, IL1b, IL8, and TNFα) have been shown to influence susceptibility of OSCC.Copy number alterations (CNAs) as candidate molecular biomarkers for OSCC were explored using high-resolution array comparative genomic hybridization (aCGH) technique. The MGAM and ADAM9 genes may be used as biological markers for OSCC. [15]

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MicroRNAs (miRNAs) have gained attention as potential valuable biomarkers for carcinogenesis. Several altered miRNAs seem to play critical roles in the initiation and progression of OSCC by functioning either as oncogenes or as tumor suppressors. HPV infection leads to expression of cellular oncogenic and tumor suppressive miRNAs.miRNAs in human saliva as biomarkers for OSCC diagnosis purposes have been discussed. CirculatingmiRNAs from blood, serum, and plasma had been investigated in patients with OSCC. Specific miRNAs identified from samples (tissues, serum, plasma, or saliva) might have a potential clinical utility in the diagnosis, prognosis, and therapeutic targets of OSCC. The identified miRNAs may pave the way for future clinical use in the diagnosis, prognosis, and treatment of OSCC. [16]

CLINICAL SIGNIFICANCE	ORAL CANCER BIOMARKER
Screening for oral squamous cell carcinoma	Salivary biomarkers such as L-phenylalanine, Sphinganine, Phytosphingosine
Differential diagnosis	Proteomic marker CLAC2
Recurrence potential marker	CD34 expression
Predicting prognosis and distant metastasis	ITGA3 & ITGB4 expression

Table 1.Biomarkers in oral cancer

The biomarkers that identify germ-line mutations are significantly important in predicting individuals at risk for developing cancer, and who may have an adverse reaction to specific cancer therapy. Gene polymorphism in p53/p73, CCND1, MDM2, and Harvey Ras(H-Ras) are related to cell cycle, apoptosis, and cancer risk.Tandle et al. in a 2001 report suggested that an association between p53 genotypes and oral cancer was not observed in Indian patients. [17]Misra et al. in 2009 studied the polymorphisms at p53, p73, and MDM2 and analyzed the risk of oral cancer development at the combined three loci. [18] Their study results suggested that the presence of at least one risk allele at all three loci increases the risk of tobacco-associated leukoplakia and the development of oral cancer. [18]

OMICS IN ORAL CANCER

Emerging OSCC omics data hold great promise for understanding of the oral carcinogenesis process, predicting prognosis and helping in the development of targeted therapies. Advances in the powerful omics technologies: genomics, epigenomics, transcriptomics, proteomics, metabolomics and lipidomics are opening new routes towards biomarker discovery in order to allow early diagnosis and to differently discriminate the behavior of each tumor.Inomics technology, bioinformatics tools are required to extract relevant information from the complex huge amount of data and identify players in cancer pathways. Indeed, in this post-genomic era several questions remain to be addressed. [19]

Genomic, epigenomic and transcriptomic profiling

Oral cancer development lies in stepwise accumulation of genomic and epigenomic changes, compromising cell division, differentiation, immune recognition, tissue invasion and metastasis. DNA alterations can lead to aberrant RNA and protein, with widespread deregulation of transcription duringoncogenesis. Genomic changes play a significant role in tumourigenesis as well as in inter- and intratumourheterogeneity. Tumor progression models have been constructed, being Califano and colleagues in 1996, the first to describe a progression model for OSCC, where losses at chromosomal regions 3p, 9p, and 17p are considered early events in the carcinogenesis process.[20] In OSCC, alterations in almost all chromosomes have been frequently reported. Identification of epigenomic biomarkers has so far focused mainly on DNA methylation, since this is a wellknown epigenetic phenomenon with an established role in cancer. Growing evidence supports promoter CpG island hypermethylation as a bonafide mechanism for gene inactivation. [21]

Proteomic, metabolomic and lipidomic profiling

Biochemical and biological techniques have been used to identify proteins, metabolites and lipids in OSCC. Studies regarding OSCC have shown alteration in proteins associated to cell metabolism and structure, cellular adhesion or cell motility, signal transduction and oncoproteins. [22]The proteomics tools currently available enable the analysis of a huge variety of cellular protein characteristics, namely relative protein quantities, protein cellular sub-localization and their post-

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translational modifications, allowing the identification of numerous candidate protein biomarkers.Potential salivary biomarker peptides with sensitivity up to 90% and specificity of 83% in detecting OSCC have also been proposed. Moreover, classification algorithms based on differently expressed serum proteins seems to be able to distinguish patients with HNC from healthy controls with a high degree of sensitivity (83.3%) and specificity (90%). [23]Metabolite profiling of tissue and bio fluid samples from HNC using mass spectrometry-based metabolomics analysis has been demonstrated to be capable of discovering potential biomarkers for disease detection and treatment monitoring. In serum, levels of numerous metabolites linked to the glycolytic pathway, such as glucose, were observed to be higher in oral cancer patients who had disease relapse. Similarly, the levels of some amino acids were shown to be lower in this bio fluid.

The alterations in lipid profile have also long been associated with cancer, since lipids play a key role in maintenance of cell integrity; however, few reports are available on plasma lipid profile in HNC. An inverse relationship was found between the lipid levels and occurrence of oral cancer, thus, lower plasma lipid status may be a useful indicator of neoplastic lesions.[24]

TARGETED THERAPY IN ORAL CANCER

Targeted therapy is the foundation of precision medicine. It is a type of cancer treatment that targets the changes in cancer cells that help them grow, divide, and spread. As researchers learn more about the cell changes that drive cancer, they are better able to design promising therapies that target these changes or block their effects.

- **Types of Targeted Therapy**

Most targeted therapies are either small-molecule drugs or monoclonal antibodies.

- **Small-molecule drugs** are small enough to enter cells easily, so they are used for targets that are inside cell
- **Monoclonal antibodies** are drugs that are not able to enter cells easily. Instead, they attach to specific targets on the outer surface of cancer cells.

The development of novel therapeutic approaches or modifications of current strategies is paramount to improve individual health outcomes and survival, while early tumour detection remains a priority and significant challenge. In recent years, drug delivery systems and chronotherapy have been developed as alternative methods aiming to enhance the benefits of the current anticancer therapies, while minimizing their undesirable toxic effects on the healthy non-cancerous cells. Recent next-generation sequencing studies have identified numerous mutated genes and dysregulated pathways in head and neck cancers.Many of these altered pathways are targetable with new agents in development or being used in other cancers.Immune escape is thought to play a pivotal step in carcinogenesis. This has been elucidated in head and squamous cell carcinoma where an immunosuppressive environment, including increased PD-1/PD-L1 expression, promotes immune escape and tumor proliferation. Based upon the recognition of this pattern of immune dysregulation, checkpoint inhibitors targeting CTLA-4 **(ipilimumab)** and PD-1 **(pembrolizumab, nivolumab)** have been approved for use in numerous other malignancies, including melanoma, lung cancer, and renal cell carcinoma.[25] As these drugs have demonstrated impressive and, in some cases durable, responses there has been much interest in evaluating their utility in head and neck squamous cell carcinoma.

Currently, **Cetuximab is the only FDA-approved targeted therapy in head and neck cancer.**Cetuximab is an IgG1 monoclonal antibody against the ligand binding domain of EGFR and it is currently the only US Food and Drug Administration approved EGFR inhibitor for the treatment of HNSCC. The EGFR, a member of the ErbB family of receptor tyrosine kinases, is overexpressed in up to 90% of HNSCC.Cetuximab is a promising chemotherapeutic agent for treating OSCC that specifically binds to the epidermal growth factor receptor (EGFR). Cetuximab has been demonstrated to be associated with radiation therapy to improve local disease control rates and patient survival rates in locally advanced squamous cell carcinoma of the head and neck. In addition, treatment with cetuximab in conjunction with platinum drugs and fluorouracil was found to improve the survival of patients with recurrent or metastatic squamous cell carcinoma of head and neck (SCCHN). However, there is no established predictor of treatment response in OSCC. Since the tumor response cannot be accurately predicted, patients are administered cetuximab regardless of tumor sensitivity.Cetuximab use is not dependent on any personalized analysis of EGFR expressionlevels or mutational status. Given the potential for resistance to cetuximab therapy, increased screening for genetic alterations that drive response to EGFR inhibition at the time of diagnosis may be of importance. [26]

In regards to **cell cycle control, inactivation of TP53**, either through direct genetic

mutation or increased expression of p53 regulatory proteins (e.g. MDM2 amplification or HPV E6), is identified almost universally in HNSCC cases.Additionally commonly mutated genes regulating cell cycle include CCND1, CDKN2A, and CD4K4/6. Currently, inhibitors against multiple agents in this pathway are in early clinical trials.In particular, **the CDK inhibitor Palbociclib** (Ibrance) has been demonstrated to be effective in breast cancer (Finn et al. 2015), and recently achieved FDA approval.[27]

Anti-apoptotic and anti-cell death mechanisms are a key trait common to cancers. Sequencing analysis of HNSCC has shown frequent mutations in cell death pathways, suggesting a role for targeted agents. **Bortezomib (Velcade)** is an inhibitor of NF-κB. It is a key regulator in cell death pathways, where it is a proteasome inhibitor, inhibiting antiapoptotic genes (BCL-2, BCL-XL, and STAT3), and up regulating pro-apoptotic genes. It has FDA approval for use in multiple myeloma and mantle cell lymphoma, and is being investigated in HNSCC and other cancers. [28]

Deregulated protein tyrosine kinase activity is central to the pathogenesis of human cancers. Targeted therapy in the form of selective tyrosine kinase inhibitors (TKIs) has transformed the approach to management of various cancers and represents a therapeutic breakthrough. **Imatinib** was one of the first cancer therapies to show the potential for such targeted action. Imatinib, an oral targeted therapy, inhibits tyrosine kinases specifically BCR-ABL, c-KIT, and PDGFRA. Apart from its remarkable success in CML and GIST, Imatinib benefits various other tumors caused by Imatinib-specific abnormalities of PDGFR and c-KIT. Imatinib has also been proven to be effective in steroid-refractory chronic graft-versus-host disease because of its anti-PDGFR action. [29]

Flavopiridol (HMR 1275) has been identified recently as a novel antineoplastic agent in the primary screen conducted by the Developmental Therapeutics Program, National Cancer Institute. Flavopiridol inhibits most cyclin-dependent kinases (cdks) and displays unique anticancer properties. Here, we investigated whether this compound was effective against head and neck squamous cell carcinomas (HNSCC). Exposure of HNSCC cells to flavopiridol diminished cdc2 and cdk2 activity and potently inhibited cell proliferation (IC50 43-83 NM), which was concomitant with the appearance of cells with a sub-G1 DNA content. Moreover, DNA fragmentation and TUNEL (terminal deoxynucleotidyltransferase-mediated nick end labeling) reaction confirmed that flavopiridol induces apoptosis in all cell lines, even on certain HNSCC cells that are insensitive to apoptosis to DNA-damaging agents (gamma-irradiation and bleomycin). A tumorigenic HNSCC cell line was used to assess the effect of flavopiridol in vivo. Treatment (5 mg/kg per day, intraperitoneally) for 5 days and 10 weeks led to the appearance of apoptotic cells in the tumor xenografts and caused a 60-70% reduction in tumor size, which was sustained over a period of 10 wk. Flavopiridol treatment also resulted in a remarkable reduction of cyclin D1 expression in HNSCC cells and tumor xenografts[30]

II. CONCLUSION

We have entered an exciting era in personalized medicine for cancer therapy and the development of targeted therapies and novel approaches for HNSCC will assuredly play an important role in the ongoing battle against this deadly disease. Already, we are introducing targeted therapy concepts into HNSCC through ongoing precision medicine trials, where we expect the greatest impact to come for patients with relatively few genetic drivers. In the future, as our understanding of the interplay of disruptive genomic events driving HNSCC pathogenesis and response to therapy increases, so too will our ability to design optimal therapeutic approaches for patients with genetically complex disease.

REFERENCES

[1]. Surbhi,Kumar A ,NagpalA,VohraP.Personalizedmedicine:A step forward in dental treatment.J Indian Acad Oral Med Radiol 2015;27:76-80
[2]. Li et al.OralCancer:Genetics and the Role of Precision Medicine.DentClin N Am 62(2018)29-46.
[3]. Jeelani S, Reddy RC, Maheswaran T, Asokan GS, Dany A, Anand B. Theranostics: A treasured tailor for tomorrow. J Pharm Bioallied Sci. 2014;6
[4]. Reddy MS, Shetty SR, Vannala V. Embracing Personalized Medicine in Dentistry. J Pharm Bioallied Sci. 2019;11
[5]. Katara, P. Single nucleotide polymorphism and its dynamics for pharmacogenomics. InterdiscipSciComput Life Sci 6, 85–92 (2014).
[6]. Ribero et al.Early detection and personalized treatment in oral cancer;the impact of omicsapproaches.Molecularcytogenetics (2016)9:85.

[7]. Zhu et al.Biomarkers in Molecular Epidemiology Study of Oral Squamous Cell Carcinoma in the Era of Precision Medicine.CancerTransl Med 2017:3(6):214-8
[8]. Polverini PJ, D'Silva NJ, Lei YL. Precision Therapy of Head and Neck Squamous Cell Carcinoma. J Dent Res. 2018; 97(6):614–621.
[9]. Mishra A, Verma M. Cancer biomarkers: are we ready for the prime time? Cancers (Basel). 2010;2(1):190–208.
[10]. . Khoury MJ, Dorman JS. The human genome epidemiology network.Am J Epidemiol 1998; 148 (1): 1–3.
[11]. Carlsonet al. Genome-wide association analysesidentify new susceptibility loci for oral cavity and pharyngeal cancer.Nat Genet 2016; 48 (12): 1544–50
[12]. Bhatnagar R, Dabholkar J, Saranath D. Genome-wide diseaseassociation study in chewing tobacco associated oral cancers. OralOncol 2012; 48 (9): 831–5
[13]. Olivieri EH, da Silva SD, Mendonça FF, Urata YN, Vidal DO,FariaMde A, Nishimoto IN, Rainho CA, Kowalski LP, Rogatto SR.CYP1A2*1C, CYP2E1*5B, and GSTM1 polymorphisms are predictorsof risk and poor outcome in head and neck squamous cell carcinomapatients. Oral Oncol 2009; 45 (9): e73–9.
[14]. Kietthubthew S, Sriplung H, Au WW, Ishida T. Polymorphism in DNArepair genes and oral squamous cell carcinoma in Thailand. Int J HygEnviron Health 2006; 209 (1): 21–9.
[15]. Vincent-Chong, Vui King et al. "Genome wide analysis of chromosomal alterations in oral squamous cell carcinomas revealed over expression of MGAM and ADAM9." PloS one vol. 8,2 (2013)
[16]. Nowickaetal.ExtracellularmiRNAs as Biomarkers of Head and Neck Cancer Progression and Metastasi. Int. J. Mol. Sci. 2019, 20
[17]. Tandle, A &Sanghvi, Vatsal&Saranath, Dhananjaya. (2001). Determination of p53 genotypes in oral cancer patients from India. British journal of cancer. 84. 739-42. 10.
[18]. Misra C1, Majumder M, Bajaj S,Ghosh S, Roy B, RoychoudhuryS..Polymorphisms at p53, p73, and MDM2 loci modulate the risk of tobacco associated leukoplakia and oral cancer.MolCarcinog. 2009 Sep;48(9):790-800
[19]. Ribeiro, I.P., Barroso, L., Marques, F. et al. Early detection and personalized treatment in oral cancer: the impact of omics approaches. MolCytogenet 9, 85 (2016).
[20]. Califano J, van der Riet P, Westra W, Nawroz H, Clayman G, Piantadosi S, Corio R, Lee D, Greenberg B, Koch W, Sidransky D. Genetic progression model for head and neck cancer: implications for field cancerization. Cancer Res. 1996;56(11):2488–92.
[21]. Esteller et al.CpG island hypermethylation and tumor suppressor genes: a booming
[22]. Present, a brighter future.Oncogene (2002) 21, 5427 – 5440
[23]. Lo WY, Tsai MH, Tsai Y, Hua CH, Tsai FJ, Huang SY, Tsai CH, Lai CC. Identification of over-expressed proteins in oral squamous cell carcinoma (OSCC) patients by clinical proteomic analysis. ClinChimActa. 2007;376(1–2):101–7
[24]. Wadsworth JT, Somers KD, Stack Jr BC, Cazares L, Malik G, Adam BL, Wright Jr GL, Semmes OJ. Identification of patients with head and neck cancer using serum protein profiles. Arch Otolaryngol Head Neck Surg. 2004; 130(1):98–104.
[25]. Chawda JG, Jain SS, Patel HR, Chaduvula N, Patel K. The relationship between serum lipid levels and the risk of oral cancer. Indian J Med PaediatrOncol. 2011; 32(1):34–7.
[26]. Schwab, Katjana S et al. "Successful Treatment of Refractory Squamous Cell Cancer of the Head and Neck with Nivolumab and Ipilimumab." Case reports in oncology vol. 11,1 17-20. 4 Jan. 2018.
[27]. Larizadeh M H. Cetuximab for Squamous Cell Carcinoma of the Head and Neck, Int J Cancer Manag. 2017 ; 10(11)
[28]. Finn et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study.LancetOncol. 2015 Jan; 16(1):25-35.
[29]. Boccadoro, Mario et al. "Preclinical evaluation of the proteasome inhibitor bortezomib in cancer therapy." Cancer cell international vol. 5,1 18. 1 Jun. 2005.
[30]. NidaIqbal.Imatinib: A Breakthrough of Targeted Therapy in Cancer.Vol 2014
[31]. Patel V, Senderowicz AM, Pinto D Jr, et al. Flavopiridol, a novel cyclin-dependent

kinase inhibitor, suppresses the growth of head and neck squamous cell carcinomas by inducing apoptosis. J Clin Invest. 1998;102(9):1674-1681