Chapter

Personalised Precision Medicine - A Novel Approach for Oral Cancer Management

Deepa Jatti Patil and Rakesh Nagaraju

Abstract

Oral Cancer is one of the most common malignancies of the head and neck region. Despite technological advancements and improvements in Oral cancer diagnosis and treatment modalities, the 5-year survival rate remains low and is associated with poor prognosis and high mortality rate especially when detected at a later stage. The empirical therapy followed for the treatment of oral cancer includes surgery, radiotherapy and chemotherapy. The treatments are not equally efficacious for all patients, are associated with side effects and poor prognosis. The need of the hour is early diagnosis and tailored treatment therapies for individual patients. With the advent of immunotherapy, the cancer treatment has moved toward personalised precision medicine which tailors' treatments to each individual. Personalised precision medicine incorporates, molecular profiling of tumours with OMICS technology, biomarkers and companion diagnostics to build databases of patients and devise tailor made treatment approaches for individual patients. This article discusses the role of precision medicine in OSCC prevention, detection, and management by reviewing our understanding of OC from both genetic and OMICS perspectives.

Keywords: Personalised precision medicine, OMICS, Genomics, Transcriptomics, Proteomics, Metabolomics, Big data, Targetted therapy, Immunotherapy

1. Introduction

Oral cancer is a type of head and neck cancer (HNC), which encompasses a wide range of tumour types that arise from a variety of anatomic structures, including the oral cavity, oropharynx, larynx, hypopharynx, and nasopharynx. Squamous cell carcinomas (OSCCs) account for over 90% of these malignancies histopathologically, with over 50% occurring in the oral cavity [1]. Tobacco usage (smoked or chewed), arecanut, excessive alcohol use, and/or human papillomavirus (HPV) infection are the most major and well-established risk factors associated with this neoplasm [2–4].

Cancer is a major public health concern around the world. According to the International Agency for Research on Cancer's GLOBOCAN project, there were approximately 14.1 million newly diagnosed cancer cases and 8.2 million deaths worldwide in 2012.Oral cancer is one of the most common cancers worldwide, accounting for 2% of all cancer cases and having a nearly 50% mortality rate [5].

Oral and pharyngeal tumours are the sixth most common cancer worldwide [6]. Internationally, South Asian countries such as Sri Lanka, India, and Taiwan have the highest rates of oral cancer, which can be attributed to high rates of cigarette smoking and areca nut use in these countries [7].

Despite technological advancements and improvements in OSCC diagnosis and treatment modalities, the 5-year survival rate remains low, hovering around 50–60%, ranging from 80% for stage I cancers to 40% for stage IV cancers. This disparity can be explained by the delay in diagnosis as well as the relatively high tumour recurrence rates found in these patients. In general, only one-third of OSCC patients have the disease in its early stages at the time of diagnosis (I and II) [8].

Treatment strategies for OSCC differ depending on the stage of the disease at the time of diagnosis. Patients with localised disease are typically treated with surgery and/or radiotherapy, which results in a high chance of long-term survival but significant morbidity. Chemotherapy and radiotherapy and recently immunotherapy are the mainstays of treatment for metastatic OSCC [9]. Despite advances in understanding the pathobiological mechanisms of OSCC, the prognosis has not improved over the last few decades. This is largely due to the high morbidity and mortality rates associated with local and regional OSCC recurrences. The clinical challenge remains in detecting regional metastasis accurately and efficiently treating second primary OSCC and recurrent tumours [10].

The practise of medicine is still primarily empirical today, with doctors relying on pattern matching to make diagnoses based on a patient's medical history, physical examination, and test data. As a result, a prescribed treatment is frequently dependent on a physician's previous experience with patients with comparable symptoms. As a result, the best drug may be given for a "typical patient" with a certain condition. The treatment decisions are made through trial and error, and patients may experience unforeseen adverse effects or poor or no efficacy for a medicine that theoretically works in some people with that disease [11].

Traditional therapeutic procedures have a poor prognosis and are associated with negative side effects. Immunotherapy adoption has moved the field of cancer treatment toward the concept of precision and personalised medicine (PPM), which tailors' treatments to each individual. For cancer treatment, there are two options: the traditional approach and the PPM model. The fundamental distinctions between the classic cancer treatment approach and the developing precision and personalised medicine (PPM) concept are compared. Traditionally, cancer has been treated with "one-size-fits-all" treatments including chemotherapy, radiation, and surgical tumour removal. These treatments have a wide range of efficacy in different people, and they frequently destroy healthy, noncancerous organs and tissues. Individualised therapy customised to specific tissues, gene alterations, and personal characteristics relevant to each unique case of cancer characterise the PPM approach [12].

This article discusses the role of precision medicine in OC prevention, detection, and management by reviewing our understanding of OC from both genetic and OMICS perspectives.

2. Why personalised precision medicine (PPM)

Traditionally Surgery, Radiotherapy and chemotherapy have been used in the treatment of OC. Some people will only need one treatment, but most people will need a combination of medicines to combat cancer's resistance. When there are solid tumours that have not metastasized and are in easily accessible places of the

body, surgery can be utilised; nevertheless, many cancers do metastasis, necessitating more harsh therapies such as radiotherapy and chemotherapy. High doses of radiation and medicines are used in these methods to kill cancer cells and shrink tumours, but they often inflict additional damage to healthy cells [13]. It is stated that the given class of cancer medications is projected to be useless in up to 75% of patients The success of these treatments is influenced by a variety of factors, including the type, stage, and location of the cancer, as well as the patient's age and overall condition. This shows that before choosing a cancer treatment, various personal aspects should be examined [14]. Over the last decade, it has been increasingly obvious that no two patients' malignancies are exactly the same, and therefore generic treatments like chemotherapy and radiation may have varying outcomes. This standard cancer treatment strategy is extremely simple, resulting in ineffective, expensive treatments and unwanted side effects for patients [15]. It is well understood that a treatment's response varies across the variability of a population, including good and poor responders. Variables such as genetic predisposition, cohort heterogeneity, ethnicity, slow vs. quick metabolizers, epigenetic factors, and early vs. late stage of disease affect patient and therapy response. These variables influence whether or not a person will respond well to a certain treatment [11].

Immunotherapy, which uses a patient's own immune system to combat cancer, is another type of cancer treatment that has cleared the way for more specific and successful treatments. Monoclonal antibodies (mAbs), checkpoint inhibitors, cytokines, vaccinations, and adoptive cell transfer, most notably in the form of haematopoietic stem cell transplants (HSCTs) and chimeric antigen receptor (CAR) T-cell therapies, are examples of immunotherapy treatments [16]. Targeted therapeutics, such as cetuximab (monoclonal epidermal growth factor receptor [EGFR] antibody), bevacizumab (monoclonal vascular endothelial growth factor [VEGF] antibody), and mechanistic target of rapamycin (mTOR) inhibitors, have recently been introduced into treatment regimens or ongoing clinical trials to improve survival rate and reduce toxicity. With the advancement of immunotherapy, the Food and Drug Administration (FDA) has approved monoclonal antibodies that target programmed cell death protein-1 (PD-1), a receptor of the immune escape pathway, such as nivolumab and pembrolizumab, for recurrent and/or metastatic head and neck SCC [9]. Immunotherapy adoption has moved the field of cancer treatment toward the concept of personalised precision medicine (PPM), which tailors' treatments to each individual.

The purpose of PPM is to allow doctors to forecast the best course of action for a patient promptly, effectively, and precisely. Clinicians will require tools that are both compatible with their clinical workflow and cost-effective in order to achieve this. These techniques can make managing the biological complexity that underpins human diseases a lot easier. A PPM ecosystem is under constant development to enable the creation and refining of such tools, and it is the solution to the problem. Precision medicine emphasises the need of combining established clinical indicators with molecular profiling to provide diagnostic, prognostic, and therapeutic techniques tailored to the individual needs of each patient group. For the optimal utilisation of the PM ecosystem, accurate data interpretation is required. The PM ecosystem brings together omics and clinical data to solve problems [11].

A move from empirical treatment to PPM is now possible thanks to increased usage of Biomarkers and companion diagnostics (CDX) (the right medicine, for the right patient, at the right dose, at the right time) [17]. PPM is a more effective model that is ready to disrupt the "one size fits all" approach. Based on the measurement and manipulation of essential patient genetic and omic data, this perspective

promotes the creation of customised treatments for each individual subtype of cancer (transcriptomics, metabolomics, proteomics, etc.) [12].

Based on the definition provided by the National Cancer Institute, Personalised Precision Medicine, (PPM) is "an approach to patient care that allows doctors to select treatments that are most likely to help patients based on a genetic understanding of their disease."

2.1 The PPM method and its use to cancer therapy

Patients with a cancer are enrolled randomly to prevent bias in traditional drug development, employing a "all comers" method with the assumption that the enrolled patients are nearly homogeneous. The purpose of random enrollment is to guarantee that the general population is well represented. In practise, we never conduct clinical trials on patients who are randomly chosen; instead, we apply various forms of enrichments to patients' enrolment by using particular inclusion and exclusion criteria. Despite all of the efforts to enrich the community, the population that is ultimately chosen for the study can be quite diverse in terms of drug-metabolising capacity, environmental factors (e.g., nutrition, smoking habits, lifestyle, etc.), prior medication(s) exposure, and an individual's genetic and epigenetic make-up are all factors to consider. BMs are being used to better define molecular, genetic, and environmental changes. Drug developers have been studying the epigenetic makeup of patients and attempting to take a more objective stance.

Patient stratification is used to distinguish between likely responders and non-responders. When compared to randomly selected individuals, prospective stratification can result in a smaller and shorter clinical study. At a bare minimum, stratification can expedite approval for medication candidates targeted at a subset of patients while providing room for additional testing and market development in the more heterogeneous patient group. In the best-case scenario, it can reveal an effective therapeutic agent that would otherwise be lost in the noise generated by non-responders, as was the case with trastuzumab and gefitinib. This will not only decrease the duration of the clinical trial but will also be cost effective [18].

Scientists were able to read and understand an individual's genetic code, as well as detect hereditary predispositions to particular diseases, when the Human Genome Project (HGP) was completed. This watershed moment shifted the focus of health care from reactive to proactive. Scientists are currently striving to gain a detailed understanding of the body's function at numerous omics levels, as well as characterise how environmental exposures alter genetic predispositions. When all of this data is combined, scientists and doctors will be able to better anticipate how patients will respond to a particular treatment. CDx assays patients for genetic features that determine whether or not they will respond to a specific medication. This technique has the potential to have a significant impact on the patient's care. The transformation from a clinician choosing a generic medicine that is more or less experimental for the patient to one that effectively addresses the disease with PPM is the revolution [12].

2.2 Steps in PPM

1. Acquiring PPM data

2. Developing a PPM therapy

2.3 Acquiring PPM data

2.3.1 Tools for PPM

2.3.1.1 Biomarkers

Predictive BM for immunotherapy differs from typical BM used for targeted therapies in the case of cancer immunotherapy. Because of the complexity of the tumour microenvironment (TME), immune response, and molecular profiling, a more holistic approach is required than using a single analyte BM [3]. To address this issue, researchers have developed a multiplexing strategy, in which numerous BMs are used to provide more precise patient stratification. Histological analysis now includes concomitant analysis of immuno-oncology BMs, such as PD-L1 and immune cell infiltrates (**Figure 1**), as well as more comprehensive immune and tumour-related pathways (**Figure 2**) (the "Cancer Immunogram"). Multiplexed immunoprofiling, which generates a comprehensive biomarker collection that may be associated with clinical parameters, is critical for the effectiveness of PM in cancer immunotherapy [21, 22].

A specific gene or mutation must be linked to a clinical result before a PPM treatment can be created and utilised in patients. This is a significant endeavour; discovering a therapeutically relevant phenotype or polymorphism might take years of research involving many scientists. Furthermore, determining which polymorphisms cause patients to have a good or negative therapy response necessitates additional research. Sequencing DNA from a large number of people is the first step in deciphering the genetic code. This phase is becoming easier with the improvement of sequencing technologies. The most difficult issues are in interpreting these massive data sets, which is where bioinformatics comes in.

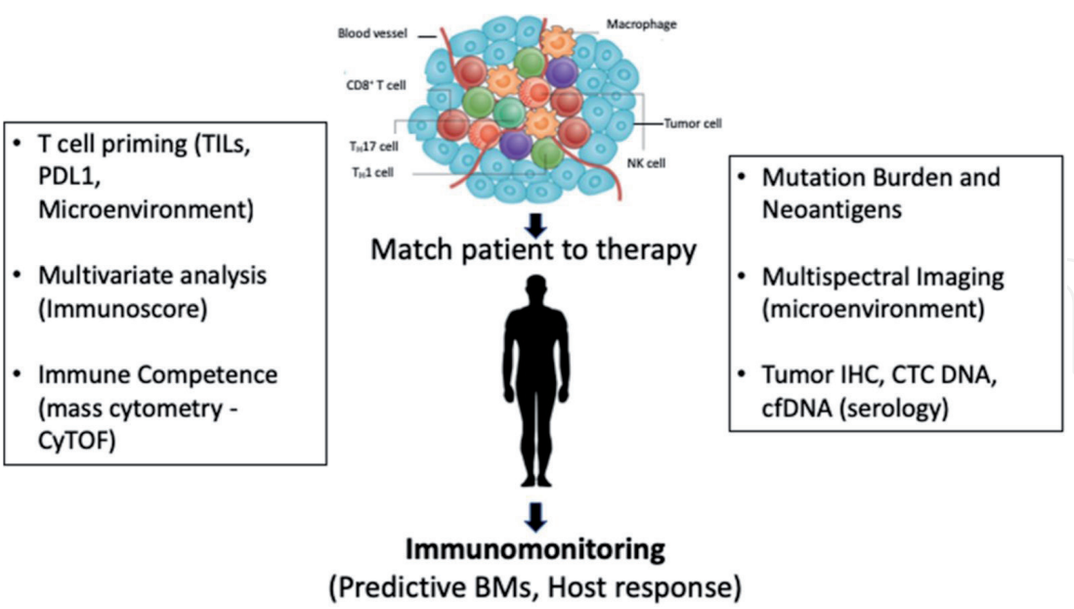

Figure 1.
Critical checkpoints for host and tumour profiling. A multiplexed biomarker approach is highly integrative and includes both tumour- and immune-related parameters assessed with both molecular and image-based methods for individualised prediction of immunotherapy response. Byassessing patient samples continuously one can collect a dynamic data on tissue-based parameters, such as immune cell infiltration and expressionof immune checkpoints, and pathology methods. These parameters are equally suited for data integration with molecular parameters. TILs: Tumour-infiltrating lymphocytes. PD-L1: Programmed cell death-ligand 1. Immunoscore: A prognostic tool for quantification of in situ immune cell infiltrates. Immunocompetence: body's ability to produce a normal immune response following exposure to an antigen (tumour drawing has been adapted from [19].

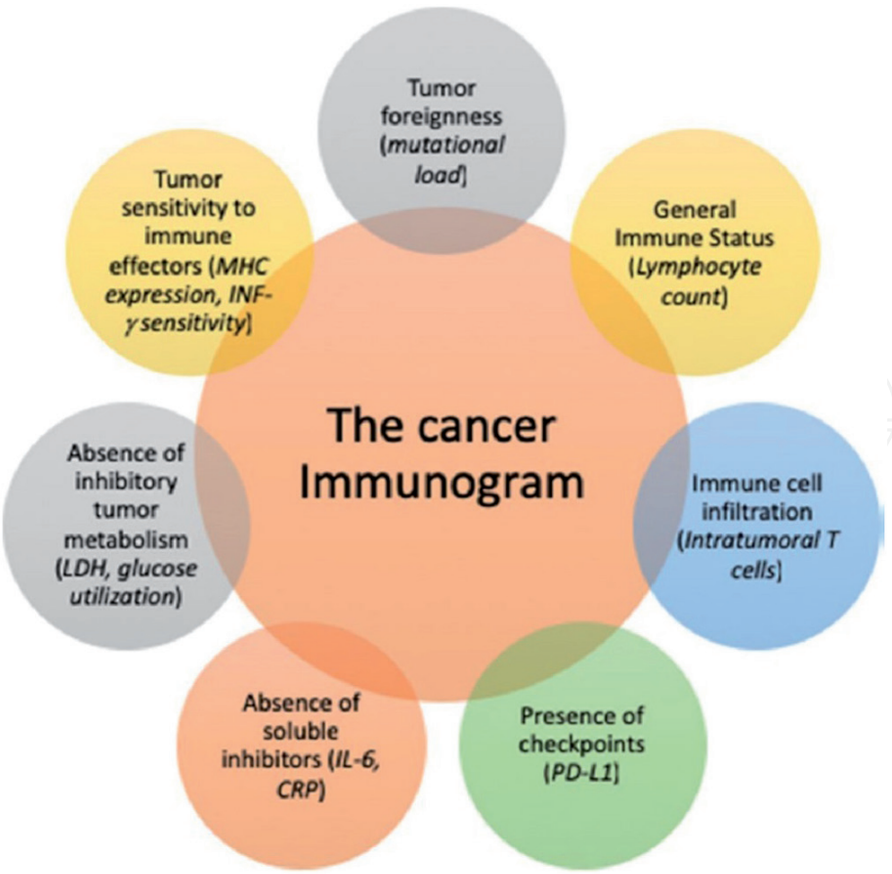

Figure 2.
The cancer immunogram. The schema depicts the seven parameters that characterise aspects of cancer-immune interactions for which biomarkers have been identified or are plausible. Italics represent those potential biomarkers for the different parameters (adapted from [20]).

Without the enormous achievement of sequencing the human genome, the discipline of PPM would not exist. From 1990 until 2003, the HGP took 13 years to complete. The International Human Genome Sequencing Consortium (IHGSC), which includes over 200 collaborators from 19 nations, was tasked with discovering new knowledge regarding the structure and organisation of the genome. The human genome has around 20,500 genes, and any two persons share 99.99 percent of their genome, implying that genetic individuality can be identified only in the remaining 0.01 percent. Long repeat sequences were also discovered in the genome, and single-base changes (single nucleotide polymorphisms [SNPs]) were found to have the potential to be distinct disease indicators. The use of bacterial artificial chromosomes (BAC) and Sanger sequencing aided in the early data collection. BAC vectors helped with the first stage of genome sequencing by determining the chromosomal location of DNA fragments recovered from a sample. Sanger sequencing, on the other hand, allowed for exact base-by-base identification of a DNA fragment. These approaches were expensive and inefficient, despite their importance in early sequencing attempts [23]. Next Generation Sequencing Technologies (NGSTs)23 have evolved as a result of years of research and development to solve these difficulties. NGSTs are a cost-effective addition to the BAC and Sanger sequencing technologies, allowing for high-dimensional and parallel sequencing [24].

Whole-genome sequencing and whole-exome sequencing are examples of genomics-related technology. There are a variety of commercial technologies for detecting gene mutations, SNPs, and copy number changes. The Cancer Genome Atlas (TCGA) is a joint project of the National Cancer Institute (NCI) and the National Human Genome Research Institute that began in 2005. In thirty-three

kinds of cancer, including head and neck SCC, the TCGA has created complete, multidimensional maps of important genetic alterations. Oral and oropharyngeal SCC has two different subgroups, according to thorough genetic profiling: HPV-negative cancers that commonly develop in the oral cavity and lips; and HPV negative cancers of the oral cavity and lips in particular. The molecular changes in these two subgroups of SCC correspond to their clinical behaviour and patient prognosis. The TCGA database demonstrated that the vast majority of HPV negative OSCCs have TP53 loss-of-function mutations and CDKN2A inactivation, which is consistent with previous findings. In addition, HPV negative OSCC showed a high amount of heterogeneity, according to integrated genomic analysis [25, 26]. Whole-exome sequencing, a transcriptomics approach for sequencing all of a genome's expressed genes, revealed new mutations that had been missed in prior studies (known as the exome. NOTCH1 mutations were found in around 15% of the patients, while mutations and focal copies of NOTCH1 were found in about 15% of the cases. NOTCH1 mutations were found in about 15% of cases, and NOTCH2/3 mutations and localised copy-number changes were found in another 11% of OSCC cases [27, 28].

OSCC's incredible diversity exemplifies how precision medicine may actually help patients and enhance medical care. The Pan Cancer Analysis of Whole Genomes project (PCAWG) is now steered to reveal noncoding driver mutations, such as alternative promoter usage, splicing, expression, editing, fusion, allele specific expression, and nonsynonymous variants, as it progresses from whole-exome sequencing to whole-genome sequencing [29]. MiRNAs and long noncoding RNAs (lncRNAs) are two types of noncoding transcripts. These noncoding transcripts, including miRNAs and long noncoding RNAs (lncRNAs), have a lot of potential for clinical research [30, 31].

2.3.1.2 Omics

While genomic data is crucial for establishing a full understanding of disease progression and therapeutic effects in physiological systems, intermediate omics levels such as the transcriptome, proteome, and metabolome are used to bridge the gap between genotypic effect and phenotypic event.

2.3.1.3 Transcriptomics

The transcriptome is the total mRNA within an individual or sample. Microarray and RNA sequencing (RNA-Seq) are two modern high-throughput sequencing approaches for collecting transcriptome data. Microarray analysis measures the amount of hybridization between a sample and corresponding probe to determine mRNA expression. The quantity of fluorescence seen within each well of the array corresponding to a given probe indicates the abundance of gene expression within a sample. Microarray analysis is constrained by the fact that designing probes requires prior knowledge of the gene's sequence. This approach is similar to Sanger sequencing in that it determines the mRNA sequence by adding fluorescently tagged nucleotide bases one by one. During each loop, fluorescent pictures are recorded, and their analysis shows the exact sequence as well as its expression level. Microarray analysis takes less time to prepare samples than RNA-Seq, although RNA-Seq does not require prior knowledge of gene sequences and may handle fewer samples. Both technologies have tremendous throughput capacities, but microarray has a higher cost-value at the moment [32, 33].

Genomic profiling enables modern medication development, which often includes either microarray analysis or RNA-Seq for transcriptome profiling. Both microarray and RNA-Seq analyses allow for the identification of disease phenotype

and medication effect within a system (single cell or bigger), which is crucial for the development of genome-specific therapeutics. Although RNA-Seq looks to be more advantageous for discovering novel genomic medication effects and disease characteristics, microarray analyses are less expensive and have more standardised techniques. In general, RNA-Seq results are better for clinical research since they have a lower signal-to-noise ratio than microarray results. Furthermore, as compared to microarray approaches, RNA-Seq results can be obtained from smaller sample quantities — nanogram versus microgram masses, respectively. As NGSTs become more widely used in clinical diagnostics, RNA-Seq methods are expected to become more standardised, eventually replacing microarray diagnostics [33, 34].

With transcriptomics technology, extensive attempts have been made to define OSCC at the molecular level. Reliable biomarkers are necessary to ease the prediction of clinical outcome and evaluate therapy efficacy in order to optimise therapeutic regimens for the management of OSCC. Dysregulation of several pathways (e.g., mRNA processing, cytoskeletal organisation, metabolic processes, cell cycle regulation, and apoptosis) was discovered when assessing a cohort of OSCC transcriptomes [35]. OSCC has also been recommended for molecular characterisation, similar to lung SCC [36]. Dysregulation of the KEAP1/ NFE2L2 oxidative stress pathway is one of the signalling pathways that has been impacted, SOX2 and TP63 lineage markers, as well as PIK3CA and EGFR mutations, were used differently. Different activation patterns of the EGFR pathway are linked to clinically diverse behaviours [37]. A molecular signature has also been proposed to help with OSCC treatment planning by predicting the existence of lymph node metastases using the primary tumour at the time of diagnosis [38]. Furthermore, microarray results demonstrated BGH3, MMP9, and PDIA3 upregulation in more than 80% of OSCC tumours, implying the relevance of ECM-cell receptor interactions in OSCC progression [39]. These transcriptional markers may be useful in the development of customised therapy regimens for the treatment of OSCC in the future.

2.3.1.4 Proteomics

The term "proteomics" refers to the process of identifying and cataloguing all proteins in a biological system, as well as their relationships. Protein structure, quantities, and cellular localizations, protein–protein interactions, and protein production and breakdown rates are all revealed by proteomic analysis. This data is utilised to figure out how the proteome changes throughout various biological activities and to spot disease patterns. Data on post-transcriptional alterations, or the quantity of proteins in a tissue, may be useful for illness diagnosis, progression, and treatment in the case of PPM. Mass spectrometry (MS) has been the primary instrument for gathering proteomic data for the past two decades, particularly to assess protein expression, identify protein modification sites, and analyse protein–protein interactions [40, 41].

The cellular abundance of proteins is primarily controlled by the quantity of translation, according to a landmark study published in 2011 that measured absolute mRNA and protein abundance and turnover using parallel metabolic pulse labelling [42]. Despite the fact that mRNA and protein levels are related to some extent, genome-wide protein abundance remains an important metric in determining cellular state and function. Intracellular and secreted proteins in body fluid specimens (e.g., serum, plasma, urine, and saliva) can be investigated using high-throughput total and phosphorylated protein analysis [43]. Alterations in protein expression in cell metabolism, adhesion, motility, and signal transduction have been discovered using proteomic analysis combined with in situ hybridization or immunohistochemistry [44, 45]. Promising results have been seen in studies.

Outcomes of salivary or serum proteomics in identifying OSCC and normal samples Analyses with a sensitivity and specificity of up to 90% [46, 47].

2.3.1.5 Metabolomics

The identification and analysis of metabolites, which are small-molecule intermediate products in metabolic reactions, is referred to as metabolomics. Because metabolites reflect both hereditary and environmental factors, a comprehensive metabolic examination is typically referred to as a "functional readout" of the current status of the organic system. The Human Metabolome Database (HMDB) is a freely accessible web resource that contains complete information on the human metabolome. The human metabolome is made up of peptides, lipids, amino acids, nucleic acids, carbohydrates, organic acids, biogenic amines, vitamins, minerals, and other tiny molecules found in the human body. The overall number of metabolites in HMDB 4.0 has increased dramatically from 40 153 in HMDB 3.0 to 114 100 in HMDB 4.0. This equates to approximately a fivefold increase [48].

In the context of PPM, metabolomic data could provide insight into an individual's unique physical reaction to a medicine, a technique known as metabolomics [49]. Currently, metabolomic studies of biofluids and tissues have aided in the development of PPM methods by discovering illness biomarkers that have the potential to aid doctors in diagnosis and early treatment. Because metabolites, unlike most proteins, travel throughout the body and appear in easily accessible biofluids like blood and urine one of the primary clinical advantages of metabolomics is that measurements may be conducted noninvasively [50]. Nuclear magnetic resonance (NMR) spectroscopy was commonly employed to identify metabolites in the early days of metabolomics research, but over the last decade, there has been a big movement toward MS, which offers superior resolution and sensitivity to small concentrations [51, 52].

Metabolite profiling of tissue and body fluid specimens with the purpose of biomarker discovery in OSCC research has revealed significant changes in energy metabolism pathways, according to mass spectrometry-based metabolomics analysis (eg, glycolysis and tricarboxylic acid cycle) [53]. Glycolytic metabolites (e.g., glucose) had higher amounts in OSCC patients' serum, while specific amino acids have lower levels (ie, valine, tyrosine, serine, and methionine) [54]. In OSCC tumour tissues, however, similar metabolite expression patterns are reversed, implying that this signature panel could be used as a screening tool. Early research, on the other hand, must be backed up with well-designed tests. Lipids have also been discovered as a significant class of metabolites, and abnormal cholesterol levels in the blood have been associated to a variety of cancers [55–57]. Total lipids, cholesterol, and high-density lipoprotein levels were shown to be considerably lower in OSCC patients compared to healthy controls [58, 59]. These lipidomic observations, albeit preliminary, may indicate greater usage of novel membrane synthesis by neoplastic cells and require further exploration.

These technologies will be collectively strong, with the potential to disclose molecular mechanisms and critical signalling pathways driving the disease, thanks to the rapid development of the omics tools outlined above. Furthermore, these tools have the potential to be utilised to identify new therapeutic targets as well as biomarkers that can be used to diagnose disease Cancer diagnosis, prognosis prediction, and treatment surveillance could all benefit from this technology.

2.3.1.6 Companion diagnostics (CDx)

The US FDA produced the first regulatory guideline document on CDx in 2014, and it was here that this type of assay was officially defined for the first time [60].

A CDx test is an in vitro diagnostic equipment that delivers information necessary for the safe and effective use of a related therapeutic product, according to this definition. This means that testing with this sort of assay is required and must be disclosed in both the medication and CDx assay labelling. CDx devices help clinicians provide the most effective, tailored medicines for their patients. In specific sections of DNA, relevant genetic information for defining malignancies can be identified (i.e., oncogenes). Some CDx are based on these specific oncogenes and can be used to evaluate whether or not a person will respond to a certain treatment in order to avoid sequencing the entire genome and obtaining superfluous information. Each CDx is linked to a certain medicinal treatment, which is linked to a particular genetic defect for which it is most effective [61]. Within the category of CDx products, there are a range of diagnostic procedures, each with its own role. Immunohistochemistry (IHC), fluorescent in situ hybridization (FISH), and real-time quantitative PCR (RT-qPCR) are examples of these techniques [62].

2.3.1.7 Data storage

After collecting the OMICS data, storage and analysis also poses a great challenge. The International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA; sponsored by the National Cancer Institute and the National Human Genome Research Institute) are two large databases for oncology data. The data gateway of the International Cancer Genome Centre (ICGC) focuses on 50 tumour types and defines them on genomic, transcriptomic, and epigenomic levels across genders, mutations, tumour stage, and other factors. The TCGA portal has thorough information on genetic alterations and gene expression in 11 different types of cancer tissues and 33 different cancer subtypes. On a large number of patients, analysis is performed on high-quality tumour samples and matched normal tissue samples [63, 64].

2.4 Single nucleotide polymorphisms (SNPs)

Despite the lifestyle habits of exposure to high risk factors for oral cancer with 80% attributable risk of tobacco per se, a small proportion of the tobacco habit develop persistent premalignant lesions, and 3–8% transform to the malignant phenotype. Genomic variants, somatic mutations and epigenetic regulation play a critical role in oral cancer. SNPs are the most common genomic variants. SNPs are single base changes in a gene's exonic coding region or non-coding intronic regions that affect gene expression and function directly or indirectly in more than 1% of an ethnic population. SNPs in intronic regions may modify the three-dimensional structure of DNA, causing changes in molecular attributes such as Gibbs free energy aectLnJ stability, as well as impacting DNA polymerase activity and transcription factor activity. Binding SNPs can be found in one or both alleles, giving rise to heterozygous or homozygous genotypes. The wild-type (WT) allele is the ancestral allele, while the SNP allele is the changed allele. In a cancer case–control group, the frequency of allelotypes and genotypes differed, indicating a link between SNPs and cancer [65].

The connection of SNPs with risk propensity or susceptibility to oral cancer has been studied in several populations. In a meta-analysis research, the authors analysed SNPs in oral cancer and identified 34 SNPs in 30 genes that are strongly linked with oral cancer [66]. SNP rs1800471 in TGF- gene, with GC genotype associated with increased risk and GG genotype with lower risk in numerous studies and populations; SNP rs1048943 in CYP1A1 gene, with AG + GG genotypes resulting in increased risk and WT AA genotype resulting in decreased risk. The GSTM1

null genotype was linked to an elevated risk, while the WT genotype was linked to a lower risk. Similarly, heterozygous genotypes of SNPs rs1800870-AG in the IL-10 gene, rs11549467-GA in the HIF gene, and rs861539-CT in the XRCC3 genes were linked to an increased risk of oral cancer, while WT genotypes were linked to a lower risk. The WT genotypes rs1801133-CC in MTHFR and rs20417-GG in COX-2, on the other hand, were related with an increased risk, while the corresponding SNP homozygous genotypes TT and CC were associated with a decreased risk [67].

SNP analysis using high-throughput genomic analysis, as reported in genome-wide association studies (GWAS), and next-generation sequencing has emerged as a strong tool for identifying susceptibility loci, allowing information on thousands of SNPs to be obtained at the same time. These platforms often work with smaller samples and are more expensive, thus they must be confirmed in larger samples using alternative technology such as nucleotide sequencing and real-time PCR.SNPs investigated in various studies contribute to increased susceptibility to oral cancer, and a panel of SNPs could be used as Predictive Biomarkers to screen high-risk individuals who are prone to oral cancer due to tobacco use, providing an objective, unbiased test assay to assess oral cancer risk in individuals [66].

2.5 Developing a PPM therapy

2.5.1 The application of omics data to treatment

Establishing the link between biological data, disease, and clinical translation is a fundamental difficulty in PPM: how can we understand the data collected to make meaningful medical decisions? In the medical field, "Big Data" refers to a larger collection of medical data encompassing the tracking of various medical indicators and biomarkers across thousands of individuals (primarily clinical and omics data). Researchers may test tissues for thousands of molecular targets using high-throughput data gathering, effectively recording the response of a complex system over time.

The reconciliation of various omics components allows for the generation of prediction models of human physiology that may be employed in experimental design and clinical trial development in the field of systems biology [68].

Systems biologists and bioinformatic scientists use statistically significant trend detection approaches to link observations to biological events and phenotypes. Multivariate decomposition techniques, predictive modelling and optimization strategies, and other statistics-based tools are examples of these. Statistically understanding Big Data trends is a separate field that is required for predictive modelling, clinical decision-making, and assistance [69].

Drug discovery techniques for a number of PPM cancer products have been developed thanks to advances in omics technologies. Circulating tumour cells (CTC) and DNA detection approaches have promise not just for early diagnosis, but also for personalised patient risk monitoring and the development of effective personalised therapy. Several other cancer medicines in development take advantage of the immune system's particular power and specialisation to fight cancer. This has been the focus of research for almost a century, and it has evolved into a distinct discipline known as immunoengineering. The ultimate goal of this profession is to tailor a more particular and potent immune response, which can lead to a powerful and effective personalised cancer treatment [70].

2.5.2 Early cancer detection using CTCs and DNA

CTCs and circulating tumour DNA (ctDNA), two forms of oncological biomarkers, have emerged as the face of non-invasive cancer diagnosis using

"liquid biopsy" procedures. Because research has shown that tumours release both types of biomarkers into the circulation early in cancer progression, there has been a lot of focus on their use in early detection and screening. CTCs and ctDNA are likely to become more effective in risk stratification, illness monitoring, and tailored treatment selection as research progresses and technology improves [71].

230 OSCC patients at various pathological stages of the disease and treatment modes were enrolled in a cross-sectional observational study. CTCs were obtained utilising the Onco Discover liquid biopsy method, which is based on immunomagnetic CTC enumeration and has been authorised by the Drug Controller General of India. The presence of CK18 and well-defined, DAPI-stained nuclei were found in CTCs. CTC were counted and then examined for stage, extracapsular spread (ECS), lymphovascular emboli (LVE), perineural invasion (PNI), and depth of invasion, among other clinicopathological criteria (DOI). To distinguish between early and advanced stages of dialysis, CTC cut off values were obtained. CTCs in OSCC patients were found to be associated with cancer stages (clinical and pathological) and aggressive pathological characteristics. We saw a 25–50 percent increase in CTC number when aggressive clinical characteristics were present, which frequently indicate a bad prognosis. Treatment-naive patients had a reduced number of CTCs in the early stages. The number of CTCs in advanced-stage OSCC patients was 50% greater than in early-stage OSCC patients. CTC might be considered a trustworthy measure to predict the disease outcome in oral cancer due to a positive connection of CTC number with numerous pathophysiological characteristics. The presence of CTC at all stages of the disease shows that OSCC is most likely a biologically systematic disease [72].

2.5.2.1 Organoids

Patient-derived tumour organoids, which serve as in vitro tumour models and predictors of medication responses, are one strategy now under investigation for customised cancer treatment. In vitro cancer cell lines, patient-derived xenografts, and 3D culture models are all used in traditional cancer research and therapy. Due to the diversity and variability of the tumour microenvironment, these are restricted in their ability to precisely correlate an individual tumour's response to a treatment. Organoids provide a more faithful depiction of this dynamic niche, and data suggests that the genetic and functional similarities between patient-derived tumour organoids and the real thing are striking [73].

2.5.3 Targetted mononclonal antibodies for cancer therapy

Because of their low cytotoxicity, high specificity, and scalability, mAbs have proven particularly promising for cancer therapies among the numerous molecular-based approaches (e.g., small compounds, mAbs, and vaccines). mAbs are Y-shaped proteins that can attach to a specific molecular target and are created either synthetically or by B lymphocytes. mAbs are one of the most rapidly expanding immunotherapies, with over 22 FDA-approved mAb-based oncology medicines. mAb-based therapies, in contrast to standard therapies (e.g., surgery, radiation, and/or chemotherapy), are targeted to specific molecular markers expressed by a specific tumour, and so are more likely to be effective [74]. Typically, monoclonal antibodies (e.g., cetuximab) or synthetic small molecules are used to target cancer-specific cell receptors or intracellular signalling pathways (eg, gefinitib) in OC [9]. The tested drugs include, Cetuximab (Erbitux), pembrolizumab (Keytruda) and nivolumab (Opdivo).

Anti-EGFR monoclonal antibodies (mAbs) possess an antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), and antitumor activity. Mice study has shown EMab-17(Anti-EGFR mAb) may be used as an antibody-based therapy for EGFR-expressing OSCC [75].

2.5.3.1 Immune check point inhibitors

The creation of antibodies capable of blocking coinhibitory immune cell receptors, or "immune checkpoints" — T-cell surface receptors that, when activated by specific ligands, limit the T-cytotoxic cell's immunological response — is a hopeful improvement in cancer treatment. Tumour cells tend to overexpress the ligands that activate these inhibitory receptors, allowing them to evade the immunological response of T cells and proliferate freely. Despite the fact that over two dozen individual costimulatory receptors have been identified, two of them — CTLA-4 and programmed cell death 1 (PD-1), have been the focus of antibody-based immune checkpoint blockade (ICB) treatments [76].

2.5.4 Non-invasive imaging for immunotherapy

Most of the patients do not respond to immunotherapy especially the immune check point inhibitors (ICI). The traditional imaging methods only provide anatomic information and do not define the concrete representation of response or progression, especially pseudo-progression due to tumour infiltrating lymphocytes (TILs); and third, toxicities are a potential concern for the widespread use of immunotherapy, which is associated with an increased risk of cancer progression. As a result, a reliable and repeatable imaging approach is critical for identifying the patient group most or least likely to react to immunotherapy [77].

Molecular imaging, in combination with disease-specific imaging probes, can provide non-invasive, early, and dynamic information about the effects of immune cells or other cells in the tumour microenvironment (TME), as well as target

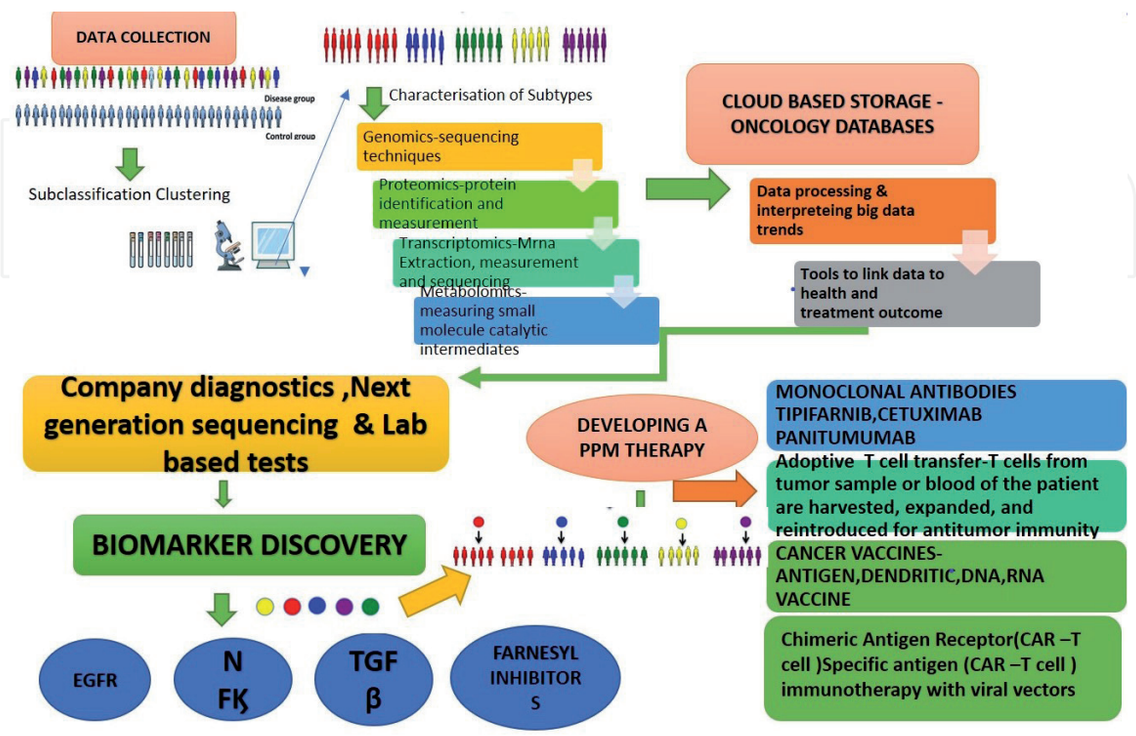

Figure 3.
Translation of PPM in to clinical practice.

expression and biodistribution of immunomodulatory drugs in the body, allowing clinicians to predict which patients will benefit most from immunotherapy. Furthermore, integrating immunotherapy with molecular imaging may improve cancer immunotherapy precision. Immunotherapies are classified into four major categories: Immune cell-based therapies, ICIs, tumour vaccines, and CAR-T cell therapy are all examples of this [78].

Figure 3 summarises the translation of PPM in to clinical practice.

3. Conclusion

This chapter has discussed the various aspects of PPM and the use of molecular and genetic profiling of tumours through omics technology for early diagnosis, formation of patient specific databases through next generation sequencing and tailored immunotherapy. Despite the advances in development technologies very few studies have been conducted in relation to OC and the research in this arena is in its budding stage. Future clinical trials on OC treatment should focus on translating the OMICs technology from bench to bedside with the use of biomarkers and CDx technologies. Tailored treatment therapies should be planned according to patients molecular and genetic profiling with consideration of individual factors. Pharma developers should create an effective medicine combining the traditional clinical data with a patient's biological profile, which includes a variety of omics-based statistics. The databases can be used to gather knowledge about disease and aid in its development more precise, safer, and better-targeted medicines for a variety of diseases in patient population.

Conflict of interest

"The authors declare no conflict of interest."

Author details

Deepa Jatti Patil[1*] and Rakesh Nagaraju[2]

1 Department of Oral Medicine and Radiology, K.M. Shah Dental College and Hospital, Sumandeep Vidyapeeth (Deemed University), Vadodara, Gujarat, India

2 Faculty of Dental Sciences, Department of Oral Medicine and Radiology, M.S. Ramaiah University of Applied Sciences, Bangalore, India

*Address all correspondence to: iafdeepa@gmail.com

References

[1] Forastiere A, Koch W, Trotti A, Sid D. Head and neck cancer. N Engl J Med. 2001;345(26):1890-900.

[2] Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet. 2008;371(9625):1695-1709.

[3] Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev. 2005;14(2):467-475.

[4] Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, Forastiere A, Gillison ML. Improved survival of patients with human papillomavirus positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008;100(4):261-269.

[5] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136: E359–E386.

[6] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.

[7] Warnakulasuriya S. Living with oral cancer: epidemiology with particular reference to prevalence and life-style changes that influence survival. Oral Oncol 2010; 46:407-410.

[8] Braakhuis BJ, Brakenhoff RH, Leemans CR. Second field tumors: a new opportunity for cancer prevention? Oncologist. 2005;10(7):493-500.

[9] Algazi AP, Grandis JR. Head and neck cancer in 2016: a watershed year for improvements in treatment? Nat Rev Clin Oncol 2017; 14:76-78.

[10] Schmitz S, Ang KK, Vermorken J, et al. Targeted therapies for squamous cell carcinoma of the head and neck: current knowledge and future directions. Cancer Treat Rev 2014; 40:390-404.

[11] Seyhan, A.A., Carini, C. Are innovation and new technologies in precision medicine paving a new era in patients centric care? J Transl Med 2019; 17:114.

[12] Krzyszczyk P et al The growing role of precision and personalized medicine for cancer treatment. Technology Singap World Sci 2018; 6(3-4): 79-100.

[13] Morgan G, Ward R & Barton M The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies. Clin. Oncol. (R. Coll. Radiol.) 16, 549-560 (2004). [PubMed: 15630849]

[14] Personalized Medicine Coalition. The personalized medicine report. Opportunity, challenges, and the future 2017, http://www.personalizedmedicine coalition.org/Userfiles/PMCCorporate/ file/The_PM_Report.pdf

[15] Burney IA & Lakhtakia R Precision medicine: Where have we reached and where are we headed? Sultan Qaboos Univ. Med. J 2917; 17: e255–e258.

[16] Maciejko L, Smalley M & Goldman A Cancer immunotherapy and personalized medicine: Emerging technologies and biomarker-based approaches. J. Mol. Biomark. Diagn 2017;8:

[17] Seyhan AA. Biomarkers in drug discovery and development. Eur Biopharm Rev. 2010; 1:19-25.

[18] Lee HJ, Seo AN, Kim EJ, Jang MH, Kim YJ, Kim JH et al. Prognostic and predictive values of EGFR overexpression and EGFR copy number alteration in HER2-positive breast cancer. Br J Cancer. 2014; 112:103.

[19] Nagarsheth N, Wicha MS, Zou WP. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. Nat Rev Immunol. 2017; 17:559-572.

[20] Blank CU, Haanen JB, Ribas A, Schumacher TN. The "cancer immunogram". Science. 2016; 352: 658-660.

[21] Blank CU, Haanen JB, Ribas A, Schumacher TN. The "cancer immunogram". Science. 2016; 352:658-660.

[22] Koelzer VH, Sirinukunwattana K, Rittscher J, Mertz KD. Precision immunoprofiling by image analysis and artificial intelligence. Virchows Arch. 2018. https ://doi.org/10.1007/s0042 8-018-2485-z.

[23] Chial H. DNA sequencing technologies key to the human genome project. Nat. Educ 2008;1:

[24] Goodwin S, McPherson JD & McCombie WR Coming of age: Ten years of next-generation sequencing technologies. Nat. Rev. Genet 2016; 17:333-351.

[25] Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature 2015; 517:576-582.

[26] Li CC, Shen Z, Bavarian R, Yang F, Bhattacharya A. Oral Cancer: Genetics and the Role of Precision Medicine. Dent Clin North Am. 2018;62(1):29-46. doi: 10.1016/j.cden.2017.08.002. PMID: 29126492.

[27] Agrawal N, Frederick MJ, Pickering CR, et al. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. Science 2011;333:1154-1157.

[28] Stransky N, Egloff AM, Tward AD, et al. The mutational landscape of head and neck squamous cell carcinoma. Science 2011; 333:1157-1160.

[29] Stein LD, Knoppers BM, Campbell P, et al. Data analysis: create a cloud commons. Nature 2015; 523:149-151.

[30] Wiklund ED, Gao S, Hulf T, et al. MicroRNA alterations and associated aberrant DNA methylation patterns across multiple sample types in oral squamous cell carcinoma. PLoS One 2011;6: e27840.

[31] Tang H, Wu Z, Zhang J, et al. Salivary lncRNA as a potential marker for oral squamous cell carcinoma diagnosis. Mol Med Rep 2013;7: 761-766.

[32] Lowe R, Shirley N, Bleackley M, Dolan S & Shafee T. Transcriptomics technologies. PLOS Comput. Biol 2017;13:e1005457.

[33] Kukurba KR & Montgomery SB. RNA sequencing and analysis. Cold Spring Harb. Protoc 2015, 951-969.

[34] Buguliskis JS Could RNA-Seq become the workhorse of precision medicine? Plowing through transcriptional variations by harnessing the powerful next-gen technique. Genet. Eng. Biotechnol. News 2015; 35:8-9.

[35] Severino P, Alvares AM, Michaluart P Jr, et al. Global gene expression profiling of oral cavity cancers suggests molecular heterogeneity within anatomic subsites. BMC Res Notes 2008; 1:113.

[36] Walter V, Yin X, Wilkerson MD, et al. Molecular subtypes in head and neck cancer exhibit distinct patterns of chromosomal gain and loss of canonical cancer genes. PLoS One 2013;8: e56823.

[37] Chung CH, Parker JS, Karaca G, et al. Molecular classification of head and neck squamous cell carcinomas using patterns of gene expression. Cancer Cell 2004; 5:489-500.

[38] van Hooff SR, Leusink FK, Roepman P, et al. Validation of a gene expression signature for assessment of lymph node metastasis in oral squamous cell carcinoma. J Clin Oncol 2012; 30:4104-4110.

[39] He Y, Shao F, Pi W, et al. Largescale transcriptomics analysis suggests overexpression of BGH3, MMP9 and PDIA3 in oral squamous cell carcinoma. PLoS One 2016;11: e0146530.

[40] Larance M & Lomond AI Multidimensional proteomics for cell biology. Nat. Rev. Mol. Cell. Biol 2015; 16:269-280.

[41] Han XM, Aslanian A & Yates JR Mass spectrometry for proteomics. Curr. Opin. Chem. Biol 2008;12: 483-490.

[42] Schwanhausser B, Busse D, Li N, et al. Global quantification of mammalian gene expression control. Nature 2011; 473:337-342.

[43] Malik UU, Zarina S, Pennington SR. Oral squamous cell carcinoma: key clinical questions, biomarker discovery, and the role of proteomics. Arch Oral Biol 2016; 63:53-65.

[44] Lo WY, Lai CC, Hua CH, et al. S100A8 is identified as a biomarker of HPV18- infected oral squamous cell carcinomas by suppression subtraction hybridization, clinical proteomics analysis, and immunohistochemistry staining. J Proteome Res 2007; 6:2143-2151.

[45] Hu S, Wong DT. Oral cancer proteomics. Curr Opin Mol Ther 2007; 9:467-476.

[46] Schaaij-Visser TB, Brakenhoff RH, Leemans CR, et al. Protein biomarker discovery for head and neck cancer. J Proteomics 2010; 73:1790-1803.

[47] Wadsworth JT, Somers KD, Stack BC Jr, et al. Identification of patients with head and neck cancer using serum protein profiles. Arch Otolaryngol Head Neck Surg 2004; 130:98-104.

[48] Wishart DS, Feunang YD, Marcu A, Guo AC, Liang K, Vázquez-Fresno R, *et al* HMDB 4.0: the human metabolome database for 2018. Nucleic Acids Res. 2018 4;46(D1):D608-D617.

[49] Monteiro MS, Carvalho M, Bastos ML & Guedes de Pinho P Metabolomics analysis for biomarker discovery: Advances and challenges. Curr. Med. Chem 2013;20:257-227.

[50] Roessner U & Bowne J What is metabolomics all about? Biotechniques 2009; 46:363.

[51] Everett JR, Loo RL & Pullen FS Pharmacometabonomics and personalized medicine. Ann. Clin. Biochem 2013; 50:523-545.

[52] Eckhart AD, Beebe K & Milburn M Metabolomics as a key integrator for "omic" advancement of personalized medicine and future therapies. Clin. Transl. Sci 2012; 5:285-288.

[53] Wang J, Christison TT, Misuno K, et al. Metabolomic profiling of anionic metabolites in head and neck cancer cells by capillary ion chromatography with orbitrap mass spectrometry. Anal Chem 2014; 86:5116-5124.

[54] Yonezawa K, Nishiumi S, Kitamoto-Matsuda J, et al. Serum and tissue metabolomics of head and neck cancer. Cancer Genomics Proteomics 2013;10: 233-238.

[55] Hu S, Wang J, Ji EH, et al. Targeted metabolomic analysis of head and neck cancer cells using high performance ion chromatography coupled with a Q exactive HF mass spectrometer. Anal Chem 2015; 87:6371-6379.

[56] Tie G, Yan J, Khair L, et al. Hypercholesterolemia increases

colorectal cancer incidence by reducing production of NKT and gamma delta T Cells from hematopoietic stem cells. Cancer Res 2017;77: 2351-2362.

[57] Codini M, Cataldi S, Lazzarini A, et al. Why high cholesterol levels help hematological malignancies: role of nuclear lipid microdomains. Lipids Health Dis 2016; 15:4.

[58] Acharya S, Rai P, Hallikeri K, et al. Serum lipid profile in oral squamous cell carcinoma: alterations and association with some clinicopathological parameters and tobacco use. Int J Oral Maxillofac Surg 2016; 45:713-720.

[59] Patel PS, Shah MH, Jha FP, et al. Alterations in plasma lipid profile patterns in head and neck cancer and oral precancerous conditions. Indian J Cancer 2004; 41:25-31.

[60] Papadopoulos N, Kinzler KW, Vogelstein B. The role of companion diagnostics in the development and use of mutation-targeted cancer therapies. Nat Biotechnol. 2006; 24: 985- 995.

[61] U.S. Food and Drug Administration. Mobile medical applications — Guidance for industry and food and drug administration staff (2015), https://www.fda.gov/downloads/MedicalDevices/.../UCM263366.pdf.

[62] U.S. Food and Drug Administration. List of cleared or approved companion diagnostic devices (in vitro and imaging tools) (2018), https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm.

[63] Pavlopoulou A, Spandidos DA & Michalopoulos I Human cancer databases (review). Oncol. Rep 2015;33:3-18.

[64] Kanehisa Laboratories. KEGG database (2017) http://www.genome.jp/kegg/kegg1.html.

[65] Damani Shah H, Saranath D, Pradhan S. Single nucleotide polymorphisms in transcription factor genes associated with susceptibility to oral cancer. J Cell Biochem. 2020 ;121(2):1050-1060.

[66] Multani S, Saranath D. Genotypic Distribution of Single Nucleotide Polymorphisms in Oral Cancer: Global Scene. Tumor Biol. 2016;37: 6169-6176.

[67] Multania S, Saranath D Single Nucleotide Polymorphisms and Risk of Oral Cancer: Indian Case-Control Study. J Clin Cell Immunol 2016;7: 448.

[68] Butcher EC, Berg EL & Kunkel EJ Systems biology in drug discovery. Nat. Biotechnol 2004; 22:1253-1259.

[69] McShane LM & Polley MY Development of omics-based clinical tests for prognosis and therapy selection: The challenge of achieving statistical robustness and clinical utility. Clin. Trials 2013; 10:653-665.

[70] Mackall CL Engineering a designer immunotherapy. Science 2018;359:990-991.

[71] Ried K, Eng P & Sali A. Screening for circulating tumour cells allows early detection of cancer and monitoring of treatment effectiveness: An observational study. Asian Pac. J. Cancer Prev 2017;18;2275-2285.

[72] Khandare J, Qayyumi B, Bharde A, Aland G, Jayant S, Tripathi S *et al* Correlation of CTCs with disease progression in Indian oral cancer patients. Journal of Clinical Oncology 2020 38:15 e15541-e15541.

[73] Aboulkheyr Es H, Montazeri L, Aref AR, Vosough M & Baharvand H Personalized cancer medicine: An organoid approach. Trends Biotechnol 2018;36: 358-371.

[74] Esteva FJ Monoclonal antibodies, small molecules, and vaccines in the

treatment of breast cancer. Oncologist 2004; 9:4-9.

[75] Takei J, Kaneko MK, Ohishi T, Kawada M, Harada H, Kato Y. A novel anti-EGFR monoclonal antibody (EMab-17) exerts antitumor activity against oral squamous cell carcinomas via antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. Oncol Lett. 2020;19(4):2809-2816.

[76] Hargadon KM, Johnson CE & Williams CJ Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors. Int. Immunopharmacol 2018; 62:29-39.

[77] Du Y, Qi Y, Jin Z, Tian J. Noninvasive imaging in cancer immunotherapy: The way to precision medicine. Cancer Lett. 2019; 466:13-22. doi: 10.1016/j.canlet.2019.08.009.

[78] R.A. Juergens, K.A. Zukotynski, A. Singnurkar, D.P. Snider, J.F. Valliant, K.Y. Gulenchyn, Imaging biomarkers in immunotherapy, Biomarkers Canc. 2016;8:1-13.