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EDITORIAL

Personalized targeted therapy for esophageal squamous cell carcinoma

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Abstract

Esophageal squamous cell carcinoma continues to heavily burden clinicians worldwide. Researchers have discovered the genomic landscape of esophageal squamous cell carcinoma, which holds promise for an era of personalized oncology care. One of the most pressing problems facing this issue is to improve the understanding of the newly available genomic data, and identify the driver-gene mutations, pathways, and networks. The emergence of a legion of novel targeted agents has generated much hope and hype regarding more potent treatment regimens, but the accuracy of drug selection is still arguable. Other problems, such as cancer heterogeneity, drug resistance, exceptional responders, and side effects, have to be surmounted. Evolving topics in personalized oncology, such as interpretation of genomics data, issues in targeted

therapy, research approaches for targeted therapy, and future perspectives, will be discussed in this editorial.

Key words: Cancer heterogeneity; Cultured tumor cells; Driver mutation; Drug side effects; Esophageal squamous cell carcinoma; Exceptional responder; High-throughput nucleotide sequencing; Neoplasm drug resistance; Personalized medicine; Xenograft model

Core tip: Esophageal squamous cell carcinoma represents a heavy burden on clinicians worldwide. Recently, researchers have discovered the genomic landscape of this cancer, which holds promise for an era of personalized oncology care. Evolving topics in personalized oncology, such as interpretation of genomics data, critical issues in targeted therapy, research approaches, and future perspectives, are discussed in this editorial.

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INTRODUCTION

Esophageal cancer is the eighth most common cause of cancer-related death worldwide[1]. Esophageal squamous cell carcinoma (ESCC) remains the predominant histology. Surgery is still the mainstay of treatment throughout the world, and an up to 50% five-year survival rate and < 5% surgical mortality rate can be achieved in select Asian centers[2]. Notwithstanding, multimodal treatment may achieve a better outcome, as overall survival improves modestly[3]. Most patients with localized disease will develop metastatic disease, with a minimal effects from combination chemotherapy[4]. After disease progression on first-line chemotherapy, there is no standard second-line treatment[5]. The unsatisfactory outcome in ESCC is mainly due to late diagnosis, the aggressiveness of this cancer, and lack of effective treatment strategies[6].

Recently, tremendous progress has been made in cancer genomics and epigenomics with the advent of high-throughput techniques, such as next-generation sequencing. Three groups have reported the genetic landscape of human ESCC with whole genome sequencing and whole exome sequencing[7-9]. Genomic alterations include: (1) single nucleotide variants of many genes with a relatively significant frequency (≥ 5%), such as *p53*, *KMT2D*, *Notch1/2/3*, *FAT1/3*, *Syne1*, *EP300*, *Rb1*, *Nfe2l2*, *Cdkn2a*, *Ajuba*, *Crebbp*, *Kdm6A*, *Fbxw7*, *MLL2/3*, *Pik3ca*, *Pten*, *Arid2*, *Pbrm1*, etc; (2) copy number alterations of many genes with a relatively significant frequency (≥ 5%), such as *CCND1*, *FGFs*, *CDKN2A*, *CDKN2B*, *Pik3ca*, *Dvl3*, *LRP5/6*, *KRas/MRas*, *EGFR*, *Akt1*, *Bcl2l1*, *Notch1/2/3*, *E2F1*, *SFRP4*, *SOS1/2*, *Birc5*, *Yap1*, *Sox2*, *Myc*, *IL7R*, etc; and (3) alterations in multiple signaling pathways, such as cell cycle regulation, apoptosis regulation, DNA damage control, histone modifications, as well as RTK-Ras-MAPK-PI3K-Akt, Hippo, Notch, Wnt, and Nfe2l2/Keap1 pathways. The overall mutation pattern appears similar to that of head and neck squamous cell carcinoma[10,11], but different from that of esophageal adenocarcinoma[12,13] and lung squamous cell carcinoma[14].

In addition to these descriptive data, smoking was not found to be related with signature mutations[7], but the lack of alcohol consumption was associated with a cluster of gene mutations[9]. Viral integration was not found in the genomes of 88 subjects[9]. Trinucleotide signature analysis suggested DNA cytidine deaminase (*APOBEC3B*)-induced deamination was mainly responsible for mutations[8,15]. Moreover, mutations of single genes or gene clusters were associated with patient survival, for example, *EP300* mutation[7,9]. Certain genes, for example, *XPO1*, were explored as a therapeutic target[8].

These landmark studies provided the research community with an enormous amount of information to better understand the molecular mechanisms of ESCC. This editorial is aimed to gain insights from such studies, and propose personalized and targeted therapy as a research direction in the future.

INTERPRETATION OF GENOMICS DATA

Driver genes and mutations

Currently available bioinformatics tools have been designed to prioritize gene mutations at the nucleotide, gene, pathway, and network levels. The number of nonsynonymous somatic mutations per ESCC averaged > 80. If a solid tumor ordinarily requires 5-8 hits (not necessarily 5-8 mutations) as suggested by classical epidemiologic studies, most of these mutations should be "passengers" instead of "drivers", which can offer selective growth advantage to the tumor cell[16]. Therefore, it is critical to identify which gene mutations are cancer drivers.

As driver mutations may occur at high or low frequencies[17], it may not be safe to prioritize driver mutations according to their frequencies. However, as a clinically relevant parameter, a high frequency of a mutation does support its potential significance in carcinogenesis. In addition to mutated drivers, Epi-drivers are a class of driver genes that are not frequently mutated but aberrantly expressed in tumors through epigenetic alterations in DNA methylation or chromatin modification. Although epigenetics in ESCC has been studied for many years[18,19], it is still

not clear how to differentiate epigenetic alterations that bring forth a selective growth advantage from those that do not[16]. According to Vogelstein *et al*[16]'s 20/20 rule, only 125 mutated-driver genes of human cancers have been discovered to date, and the number is nearing saturation. Tamborero *et al*[20] reported a list of 291 high-confidence cancer-driver genes and 144 candidate genes from 12 different types of cancer. Several databases have become available. For example, Network of Cancer Genes (NCG 4.0) contains 537 experimentally supported genes and 1463 candidate genes inferred using statistical methods[21]. The Candidate Cancer Gene Database contains cancer-driver genes from forward genetic screens in mice[22]. Considering tissue specificity of ESCC, there is a need to compile a cancer-driver gene list to support future research on ESCC therapy. However, it should be pointed out that cancer-driver genes may contain both driver mutations and passenger mutations in cancer. For example, APC mutations truncating the N-terminal amino acids are driver mutations, while those affecting other regions are passenger mutations. Even for the same driver gene (*e.g.*, *K-Ras*), different driver mutations (*e.g.*, mutations at codons 12, 13, and 61) have different impacts on carcinogenesis and clinical behaviors[23-25]. Because of these complexities, efforts need to be made in order to identify personalized driver genes in cancer[26].

Pathways and network

Increasing evidence suggests that dysregulation of cellular signaling pathways, rather than individual mutations, contributes to the pathogenesis of ESCC[27-29]. Driver genes usually do not work in isolation, but often function together to alter cellular processes[30]. There is a growing consensus that pathways rather than single genes are the primary target of mutations[31]. It is interesting that mutations in various components of a single pathway tend to be mutually exclusive[32]. Once driver genes or driver mutations are identified, the next step is to focus on driver pathways with genes grouped together according to the biochemical pathways that they play functional roles in. Pathway activity may be further validated by the downstream readouts, *e.g.*, mRNA and protein expression, morphology, and function. Incorporation of immunohistochemistry data, or even proteomics data, may help in evaluation of the pathway activity[33,34].

One major challenge in analyzing genomics data of ESCC is the lack of information of esophagus-specific pathways. Pathway databases, *e.g.*, KEGG, are fairly incomplete and lack tissue and cell specificities. Applying such pathway information in analyzing ESCC data may generate misleading outcomes. For example, using ChIP-seq analyses, Sox2-regulated genes in ESCC cells are different from those in embryonic stem cells because in ESCC, Sox2 tends to interact with p63 as opposed to Oct4 in embryonic stem cells[35]. Identifying bona fide target genes and using expression profiles of these genes to infer pathway activity in ESCC will be critical in the future[36].

Few bioinformatics methods involve a procedure for taking account of pathway interactions, i.e., pathways that are mutated in the same sample, and that are mutated together across a large subset of samples[8]. Similar to expression-based stratification, network-based stratification of tumor mutations can identify cancer subtypes to guide treatment and prognosis[37]. Categorizing ESCC into multiple subtypes according to its molecular alterations may be a practical step leading to final personalization of ESCC therapy. In fact, subtyping has been shown to be a successful approach in managing other cancers[38].

Drug selection

Selecting drugs according to genomics data has led to promising results in early studies on personalized and targeted therapy[39]. To date, most clinically approved targeted drugs are directed against kinases. Some of these have been utilized against ESCC (Table 1). Gefitinib, an epidermal growth factor receptor inhibitor, has been tested as a second-line treatment for esophageal cancer. In unselected patients it does not improve overall survival, but has palliative benefits in a subgroup of difficult-to-treat patients with a short-life expectancy[40]. Unfortunately, only a few cancer drivers have enzymatic activities that are targetable in this fashion, and whether a target is druggable becomes a research question[41]. Once a drug target is verified, drugs or experimental compounds may be developed. Several databases are available for search, including the Therapeutic Target Database[42] and DrugBank 4.0[43].

If the target is not druggable, its regulatory proteins or functional pathway may be targeted. For example, cyclin D1 amplification is commonly seen in human ESCC. As cyclin D1 mainly functions through CDK activation, CDK4 and CDK6 can be targeted instead of cyclin D1[44]. *TP53*, which encodes p53, is the most commonly mutated gene in human ESCC. Instead of targeting *TP53*, many strategies have been tested to restore the functions of p53 by delivering wildtype *TP53*, targeting the MDM2-p53 interaction, restoring the functions of mutant p53, targeting p53 family proteins, or eliminating the mutation in p53[45,46].

In addition to selecting drugs for targeted therapy, analysis of drug-metabolism genes in germ-line DNA can also optimize dosing and identify drug toxicity risk[47,48]. With the help of a database, such as Pharmacogenetics and Pharmacogenomics Knowledge Base, genetic variations can be associated with drug response[49].

ISSUES IN TARGETED THERAPY

Cancer heterogeneity

Various combinations of drivers and pathways result in intratumoral, intermetastatic, intrametastatic, or

Table 1 National clinical trials on targeted therapy of esophageal squamous cell carcinoma[1]

Target	Agent	NCT number (phase)
EGFR	Erlotinib	NCT00045526 (Ⅱ), NCT00030498 (Ⅰ), NCT00397384 (Ⅰ), NCT00524121 (Ⅱ), NCT01013831 (Ⅰ), NCT01561014 (Ⅰ), NCT01752205 (Ⅲ)
	Gefitinib	NCT00093652 (Ⅰ/Ⅱ), NCT00258297 (Ⅱ), NCT00258323 (Ⅱ), NCT00268346 (Ⅱ), NCT00290719 (Ⅰ)
	Icotinib	NCT01973725 (Ⅱ)
	Lapatinib	NCT00239200 (Ⅱ), NCT01666431 (Ⅱ)
	Nimotuzumab	NCT02272699 (Ⅱ/Ⅲ), NCT01232374 (Ⅱ), NCT01336049 (Ⅱ), NCT01402180 (Ⅱ/Ⅲ), NCT01486992 (Ⅱ), NCT01688700 (Ⅱ), NCT01993784 (Ⅰ/Ⅱ), NCT02011594 (Ⅱ), NCT02034968 (Ⅱ), NCT02041819 (Ⅱ)
	Panitumumab	NCT01077999 (Ⅱ), NCT01262183 (Ⅱ), NCT01627379 (Ⅲ)
	PF00299804	NCT01608022 (Ⅱ)
	Cetuximab	NCT02123381 (Ⅱ), NCT00109850 (Ⅱ), NCT00165490 (Ⅱ), NCT00381706 (Ⅱ), NCT00397384 (Ⅰ), NCT00397904 (Ⅱ), NCT00425425 (Ⅰ/Ⅱ), NCT00445861 (Ⅰ/Ⅱ), NCT00509561 (Ⅱ/Ⅲ), NCT00544362 (Ⅰ/Ⅱ), NCT00655876 (Ⅲ), NCT00757549 (0), NCT00815308 (Ⅱ), NCT01034189 (Ⅱ), NCT01107639 (Ⅲ)
IGF1R	Cixutumumab	NCT01142388 (Ⅱ)
PI3K	BKM120	NCT01626209 (Ⅰ), NCT01806649 (Ⅱ)
	BYL719	NCT01822613 (Ⅰ/Ⅱ)
	Rigosertib	NCT01807546 (Ⅱ)
HDAC	Entinostat	NCT00020579 (Ⅰ)
	Vorinostat	NCT00537121 (Ⅰ), NCT01249443 (Ⅰ)
HER3	LJM716	NCT01598077 (Ⅰ), NCT01822613 (Ⅰ/Ⅱ)
VEGFR	Vandetanib	NCT00732745 (Ⅰ)
	Sorafenib	NCT00917462 (Ⅱ)
VEGFA	Bevacizumab	NCT01212822 (Ⅱ)
PD-L1	MEDI4736	NCT01938612 (Ⅰ)
Bcl-2 mRNA	Oblimersen	NCT00003103 (Ⅰ/Ⅱ)
CDK9	Alvocidib	NCT00006245 (Ⅱ)
CRM1	Selinexor	NCT02213133 (Ⅱ)
FGFR	AZD4547	NCT01795768 (Ⅱ)
KIF11	Litronesib	NCT01059643 (Ⅱ)
TACSTD2	IMMU-132	NCT01631552 (Ⅰ/Ⅱ)

[1]"Esophageal squamous cell carcinoma" was searched at the website (www.clinicaltrials.gov). Targeted therapy has been or is being tried in 62/204 studies. Some of these agents target multiple molecules, for example, lapatinib (EGFR and Erbb2), rigosertib (PI3K and PLK), vandetanib (VEGFR, EGFR, and RET), and sorafenib (VEGFR, PDGFR and RAF).

interpatient heterogeneities. It may explain why the same treatment brings about either a favorable response or resistance in different patients, and why a patient that responds well initially can develop resistance over time. Intratumoral heterogeneity has been validated using single-cell RNA-seq of primary glioblastomas[50]. As the majority of cancer gene mutations appear in multiple regions of the same tumor, single-region sequencing may be adequate to identify the majority of cancer gene mutations[51]. It can be predicted that most cancer cells in the same tumor may share the major alterations. If this is proven true in ESCC, it will make treatment more predictable.

Intermetastatic and intrametastatic heterogeneity may not be a great concern. Despite many years of research, we have failed to identify a group of so-called metastasis genes. Metastasis is probably stochastic depending on the environment in the metastatic site[52]. Therefore, if we can understand genetic and epigenetic alterations in the primary tumor well, all cancer cells left at the primary site or metastatic sites would be expected to behave in the same way. Nevertheless, the prevalence of different patterns of tumor heterogeneity needs to be more robustly assessed in large patient cohorts, and new patterns will probably be identified as the wealth of genomic data of ESCC is analyzed[53].

Drug resistance

If carcinogenesis is regarded as an evolutionary process with successive new mutations driven by natural selection, chemotherapy, radiotherapy, and target therapy may all provide a potent source of artificial selection to alter clonal dynamics. Consequently, the antitumor therapy may lead to resistance[54]. Indeed, targeted therapy is associated with a high rate of resistance at the very beginning when vemurafenib, a *BRAF*^{V600E} inhibitor, was clinically used for melanoma. Combination of a BRAF^{V600E} inhibitor (dabrafenib) and a MEK inhibitor (trametinib) resulted in better response, yet did not prevent resistance from occurring. Distinct mechanisms include mutations in the target, reactivation of the targeted pathway, hyperactivation of alternative pathways, and cross-talk with the microenvironment[55]. Resistant cells may undergo a process called phenotype switching under the selection of targeted therapy[56]. Understanding these mechanisms has led to additional efforts in finding new therapies targeting the same target, the same pathway, or alternative pathways[57-59].

Three strategies are feasible measures in the handling of drug resistance. Before treatment, both bioinformatics and experimental modeling can provide information concerning heterogeneity[60-62]. There is a need to develop clinically useful measures of heterogeneity[63]. Secondly, during treatment, limited success can be achieved with a single agent. The combination strategy may be the best way to refrain from the inevitable development of resistance to single drug-targeted therapies[31]. Thirdly, longitudinal tumor sampling will be essential to decipher the impact of tumor heterogeneity on cancer evolution, and developing minimally invasive methods to profile heterogeneous tumor genomes will play a major part in following clonal dynamics in real time[61]. For ESCC, repeated biopsy, circulating tumor DNA analysis[64,65], and exfoliative cells[66,67] are all valid options for this purpose.

Exceptional responders

As opposed to drug resistance, exceptional responders

are patients who have a unique response to treatments that are not effective for most other patients. The National Cancer Institute has embarked on the Exceptional Responders Initiative to understand the molecular underpinnings of exceptional responses to treatment in cancer patients. In the past, exceptional responders led to clinical breakthroughs in treatments of certain types of cancer, and understanding of novel molecular mechanisms of carcinogenesis[68]. It is foreseeable that careful characterization and follow-up of these exceptional responders will be of great value in the future practice of personalized and targeted therapy of ESCC.

Side effects

As compared with traditional chemotherapy, targeted therapy is better tolerated. However, it does produce toxicities based on several major mechanisms, including on-target, off-target, hypersensitivity-related, and metabolite-induced toxicities. Vascular endothelial growth factor receptor inhibitors cause hypertension, and epidermal growth factor receptor inhibitors cause toxicities in tissues where they normally play an important functional role in tissue maintenance (*e.g.*, skin and gastrointestinal epithelia). Some of these on-target toxicities may serve as surrogate biomarkers for clinical response[69-73]. Considering these potential side effects, clinical oncologists should be prepared to educate the patients and undertake respective preventive and therapeutic measures.

RESEARCH APPROACHES FOR TARGETED THERAPY

For genomics-guided research, cell line-based platforms have become an indispensable tool[74,75]. Clarification of genetic and epigenetic alterations of established ESCC cell lines would be great tools for preclinical drug development[76,77], in particular, the KYSE series of ESCC cell lines that have been sequenced[7-9]. Patient-derived ESCC cells can be used for selection of potential individualized therapy[78,79]. These cells are particularly useful in identifying effective drug combinations for acquired resistance[57].

Several models have been put into preclinical research and even clinical applications. A patient-derived xenograft model of ESCC is created when cancerous tissue from a patient's primary tumor is implanted directly into immunodeficient mice. This model provides solutions to the translational challenges that researchers and clinicians face in cancer drug research and selection[80,81]. Carcinogen-induced models, for example, the N-nitrosomethylbenzylamine-induced model, represent classical models for ESCC research. They mimic human ESCC in not only etiology and histopathology, but also in molecular alterations (*e.g.*, *TP53* mutations[82,83]). However, exactly how well this model can mimic human ESCC at the genomics level has not been well studied. Whole exome sequencing has already shown that carcinogen-induced and genetically engineered models lead to carcinogenesis through different routes. A carcinogen-induced model is particularly important in understanding the complex mutation spectra seen in human cancers[84]. It is encouraging that genomic alterations in 4-nitroquinoline 1-oxide-induced mouse tongue cancer are well preserved[83].

Genetically engineered mouse models of human cancers have proven essential to dissect the molecular mechanisms behind carcinogenesis[85] and provide robust preclinical platforms for investigating drug efficacy[86] and resistance[87-89]. As an example, transgenic overexpression of *Sox2*, an amplified oncogene in ESCC[90], drives the complete process of carcinogenesis in mice[91]. This model can readily be used for preclinical drug development for *SOX2*-overexpressing ESCC. Although it may be difficult to target *SOX2* itself, its downstream genes or pathways, such as the Akt/mTOR pathway, can be targeted[79]. Biochemical outcomes may be used for assessment of the efficacy of a *Sox2*-targeting therapy even when it does not reduce tumor incidence or size in mice. Genome engineering with CRISPR-Cas9 *in vivo* is an extremely promising technique in identifying cancer-driver genes and testing drug targets[92]. It may ultimately be used for human gene therapy in the future[93].

As a hallmark of human cancer and a crucial determinant of variable response to treatment[75], genomic heterogeneity calls for revision of clinical trial design currently in use in order to implement personalized therapy[94]. The majority of traditional prospective clinical trials are disease or histopathology based. Genomics-driven trials, for example, mutation-, pathway-, and subtype-based trials, will be more widely used in drug development[95]. Two genomics-based study designs are currently being utilized to develop targeted therapies, and for exploratory and multi-agent sequential design[96]. ESCC fits both study designs very well because the esophagus can be biopsied before and after treatment.

FUTURE PERSPECTIVES

The biggest challenge in ESCC treatment is the translation of genomic discoveries into personalized therapies based on strategies sketched from patients' individual profiles[94]. The evasiveness of cancer cells has been a frustrating observation of clinical oncologists. Vogelstein *et al*[16] proposed that "there is order in cancer," pointing to the need to tackle ESCC as a disease status with its own homeostatic mechanisms. From the perspective of ten hallmarks of human cancer[97], Hanahan[98] proposed three strategically distinct "battlespace-guided plans" for cancer treatment: disruption of the enemy's many capabilities, defense against cancer's armed forces,

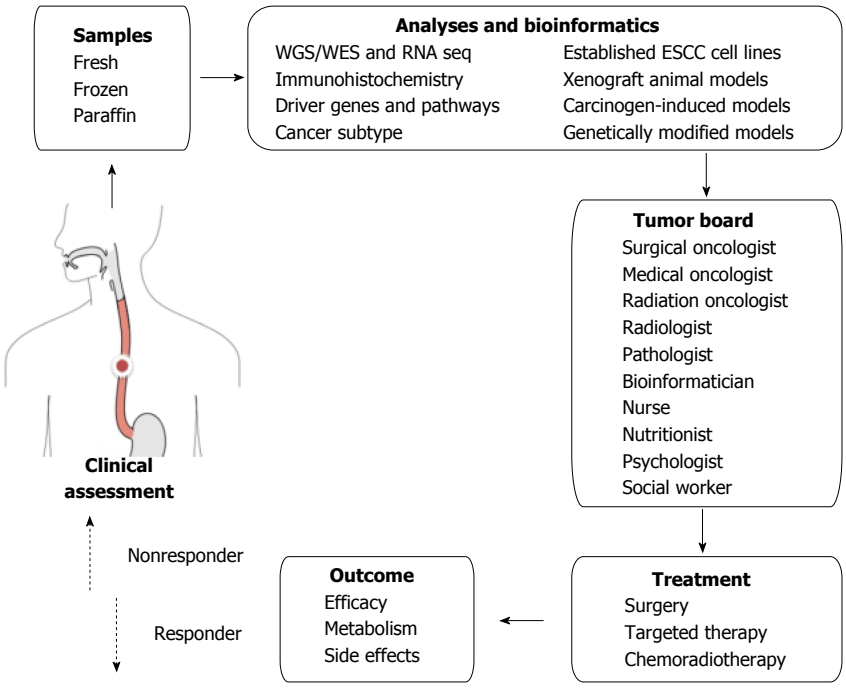

Figure 1 Personalized and targeted therapy for esophageal squamous cell carcinoma. The strategy is based on the concept that a patient's genetic makeup should guide his/her treatment. After a series of molecular analyses on tumor samples, bioinformatics is expected to identify driver genes, pathways, cancer subtype, and target drugs. A tumor board will synthesize all information and generate a personalized treatment plan. Nonresponders may be analyzed in a similar manner during subsequent surveillance and further treated. ESCC: Esophageal squamous cell carcinoma; WES: Whole exome sequencing; WGS: Whole genome sequencing.

and integration of the geographies of the battlefields. It is clear that combination therapy targeting multiple mechanisms would be the only option in the future. Using immunotherapy as an example, tremelimumab (anti-CTLA4) has been tested as a second-line therapy for esophageal cancer. Although the clinical response was not impressive, its biologic effect on T-cell activation seemed to be associated with clinical response[99]. Recent development of immunotherapy based on *ERBB2IP* mutation-specific $CD4^+$ T cells[100] and programmed-death ligand 1 (PD-L1) suppression is also quite promising. For patients in which pre-existing immunity is suppressed by PD-L1, blocking PD-L1 enhanced anti-cancer immunity (including one case of esophageal cancer)[101]. A realistic option in the near future can be a combination of target drugs and traditional chemoradiotherapy for ESCC. Target drugs are expected to kill cancer cells with specific genomic alterations, while traditional therapy acts in a much broader manner.

Technical issues continue to represent large hurdles for next-generation sequencing and bioinformatics, and they prevent us from gaining full insights into the mechanisms of carcinogenesis and metastasis of ESCC. Nonetheless, whole genome sequencing correlates with incomplete coverage of inherited disease genes, low reproducibility of genetic variation with the highest potential clinical effects, and uncertainty about clinically reportable sequencing findings[102]. Whole exome sequencing is particularly prone to errors, as only 61% of the mutated genes in ESCC are transcribed[8]. This is similar to what has been observed in pancreatic cancer: only 63% of the expected 251 driver-gene mutations were identified, suggesting a 37% false-negative rate. Marked discrepancies in the detection of missense mutations in identical cell lines (57.38%) have been reported due to inadequate sequencing of GC-rich areas of the exome[103]. The protein-coding genes account for only about 1.5% of the total genome. Although the vast majority of the alterations in noncoding regions are presumably passengers, some of these may be drivers, for example, mutations in the Tert promoter[104,105].

New computational and bioinformatics tools still need to be developed and improved due to low concordance of multiple variant-calling pipelines[106,107]. Directly comparing genome sequence reads may improve data quality as compared with initial alignment of reads to a reference genome[108].

Apart from the logistic challenges, financial, social and ethical challenges are also posed by personalized and targeted therapy[39]. In addition to viewing a patient's cancer as a biologic phenomenon waiting for medical attention alone, personalized therapy emphasizes biopsychosocial care by including communication and information giving, psychologic and emotional well-being, enhancement of function, addressing financial and spiritual concerns, and providing symptom control and social support[109]. If we look at one specific patient's ESCC from all these perspectives, a tumor board should involve not only medical staff but also supporting staff (Figure 1).

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