**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 16961**

**Columns: EDITORIAL**

**Personalized targeted therapy for esophageal squamous cell carcinoma**

Kang XZ *et al*. Therapy for esophageal squamous cell carcinoma

Xiao-Zheng Kang, Ke-Neng Chen, Yicheng Li, Jianying Li, Thomas A D’Amico, Xiaoxin Chen

**Xiao-Zheng Kang, Ke-Neng Chen**, Department of Thoracic Surgery I, Ministry of Education Key Laboratory of Carcinogenesis and Translational Research, Beijing Cancer Hospital, Peking University School of Oncology, Beijing 100142, China

**Thomas A D’Amico**, Division of Thoracic Surgery, Duke University Medical Center, Durham, NC 27707, United States

**Yicheng Li, Xiaoxin Chen**, Cancer Research Program, Julius L. Chambers Biomedical Biotechnology Research Institute, North Carolina Central University, Durham, NC 27707, United States

**Jianying Li**, Euclados Bioinformatics Solutions, LLC, Cary, NC 27519, United States

**Xiaoxin Chen**, Center for Esophageal Disease and Swallowing, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27519, United States

**Author contributions:** Kang XZ and Chen X contributed to the literature review, drafting and critical revision of the manuscript and formation of tables and figures; all authors commented and approved of the final draft.

**Supported by** grants fromBeijing Academic Leaders Program, NO. 2009-2-17; Beijing Natural Science Foundation, No. 7102029; Capital Medical Developed Research Fund, No. 2007-1023; New Scholar Star Program of Ministry of Education; National Basic Research Program of China, No. 2011CB504300; Specialized Research Fund for the Doctoral Program of Higher Education, No. 20130001110108; National Natural Science Foundation for Distinguished Young Scholars, No. 81301748; Science Fund for Creative Research Groups of the National Natural Science Foundation of China, No. IRT13003 and No. NIH/NCI U54 CA156735.

**Conflict-of-interest:** Dr. D'Amico serves as a consultant for Scanlan. Other authors have no potential conflict of interest relevant to this article to disclose.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** **Xiaoxin Chen, MD, PhD,** Cancer Research Program, Julius L. Chambers Biomedical Biotechnology Research Institute, North Carolina Central University, 700 George Street, Durham, NC 27707, United States. lchen@nccu.edu

**Telephone:** +1-919-5306425

**Fax:** +1-919-5307780

**Received:** February 4, 2015

**Peer-review started:** February 4, 2015

**First decision:** March 10, 2015

**Revised:** March 19, 2015

**Accepted:** April 28, 2015

**Article in press:**

**Published online:**

**Abstract**

Esophageal squamous cell carcinoma (ESCC) keeps causing a heavy burden on clinicians worldwide. Researchers have discovered the genomic landscape of ESCC, which holds promise for an era of personalized oncology care. One of the most pressing problems facing this issue is to improve understanding now available genomic data and identify the driver gene mutations, pathways, and networks. The emergence of a legion of new targeted agents has generated much hope and hype about more potent treatment regimens, but the accurate 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:** Esophageal squamous cell carcinoma; Personalized medicine; High-throughput nucleotide sequencing; Driver mutation; Cancer heterogeneity; Neoplasm drug resistance; Drug side effects; Exceptional responder; Cultured tumor cells; Xenograft model

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Esophageal squamous cell carcinoma creates 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.

Kang XZ, Chen KN, Li Y, Li J, D’Amico TA, Chen X. Personalized targeted therapy for esophageal squamous cell carcinoma. *World J Gastroenterol* 2015; In press

**INTRODUCTION**

Esophageal cancer accounts for the eighth most common cause of cancer-related death worldwide[1]{Ferlay, 2010 #12}{Ferlay, 2010 #12}. Esophageal squamous cell carcinoma (ESCC) remains the predominant histology. Surgery is still the mainstay of treatment throughout the world, and up to 50% of 5-year survival rate and lower than 5% of surgical mortality rate could be achieved in selected Asian centers[2]. Notwithstanding multimodality treatment may achieve a better outcome, overall survival improves modestly[3]. Most patients with localized disease will develop metastatic disease, the combination of chemotherapy actually many, effect actually really micro[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, 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 asnext-generation sequencing (NGS). Three groups have reported the genetic landscape of human ESCC with whole genome sequencing (WGS) and whole exome sequencing (WES)[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, RTK-Ras-MAPK-PI3K-Akt pathway, Hippo pathway, Notch pathway, Wnt pathway, Nfe2l2/Keap1 pathway, histone modifications, *etc*. The overall mutation pattern appears similar to that of head and neck SCC[10,11], but different from that of esophageal adenocarcinoma[12,13] and lung SCC[14].

In addition to these descriptive data, smoking was found to be not 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 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 driver mutations***

Currently available bioinformatics tools have been designed to prioritize gene mutations at the nucleotide level, gene level, pathway level, and network level.The number of non-synonymous somatic mutations per ESCC averaged more than 80. If a solid tumor ordinarily requires 5 to 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.

Since 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 Mut-drivers (mutated drivers), Epi-driver is 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’s 20/20 rule, only 125 ‘Mut-driver’ genes of human cancers have been discovered to date, and the number is nearing saturation[16]. 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]. Candidate Cancer Gene Database contains cancer driver genes from forward genetic screens in mice[22]. Considering tissue specificity of ESCC, there is a need of compiling 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 codon 12, 13 and 61) have different impact 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, function. Incorporation of immunohistochemistry data or even proteomics data may help 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 outcome. 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 profile 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 (EGFR) inhibitor, has been tested as a second-line treatment for esophageal cancer. In unselected patients it does not improve OS, but has palliative benefits in a subgroup of difficult-to-treat patients with short-life expectancy[40]. Unfortunately, only a few cancer drivers have enzymatic activities which 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, *e.g.*, Therapeutic Target Database[42], 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. Since cyclin D1 mainly functions through CDK activation, CDK4 and CDK6 can be targeted instead of cyclin D1[44]. *p53* is the most commonly mutated genes in human ESCC. Instead of targeting *p53*, many strategies have been tested to restore the functions of p53 by delivering wild-type *p53*, targeting MDM2-*p53* interaction, restoring the functions of mutant *p53*, targeting p53 family proteins, or eliminating mutation 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, *e.g.*, Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), 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 interpatient heterogeneities. It may explain why the same treatment brings about favorable response or resistance in different patients, and why a patient responds well initially and develops resistance over time. Intratumoral heterogeneity has been validated using single-cell RNA-seq of primary glioblastoma[50]. Since the majority of cancer gene mutations do 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 big 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 are 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 regard 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 anti-tumor therapy may lead to resistance[54]. Indeed, targeted therapy is associated with a high rate of resistance at the very beginning when Vermurafeni, a BRAFV600E inhibitor, was clinically used for melanoma. Combination of a BRAFV600E 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 therapy targeting the same target, the same pathway, or alternative pathways[57-59].

Three strategies are feasible measures in handling drug resistance. Before treatment, both bioinformatics and experimental modelling may inform 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 (NCI) 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 breakthrough in treatment of certain type 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, for example, on-target toxicity, off-target toxicity, hypersensitivity-related toxicities, metabolite-induced toxicities. Vascular endothelial growth factor (VEGF) receptor inhibitors cause hypertension and EGFR inhibitors cause toxicities in tissues where EGFR normally play an important functional role in tissue maintenance (*e.g.*, skin, 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, KYSE series of ESCC cell lines which 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, are a classical model for ESCC research. It mimics human ESCC in not only etiology and histopathology, but also in molecular alterations (*e.g.*, *p53* mutations[82,83]). However, exactly how well this model can mimic human ESCC at the genomics level has not been well studied. WES 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]. Using *Sox2*, an amplified oncogene in ESCC[90], as an example, transgenic *Sox2* overexpression 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, *e.g.*, 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-based or histopathology-based. Genomics-driven trials, for example, mutation-based trial, pathway-based trial, subtype-based trial, will be more widely used in drug development[95]. Two genomics-based study designs are currently being utilized to develop targeted therapies, exploratory design 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 from 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 tackling ESCC as a disease status with its own homeostatic mechanisms. From the perspective of ten hallmarks of human cancer[97], Hanahan proposed three strategically distinct “battlespace-guided plans” for cancer treatment, disruption of the enemy’s many capabilities, defense against cancer’s armed forces, and integration of the geographies of the battlefields[98]. 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 biological 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 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 of NGS and bioinformatics are still big hurdles and prevent us from gaining full insights into the mechanisms of carcinogenesis and metastasis of ESCC. WGS nonetheless correlates with incomplete coverage of inherited disease genes, low reproducibility of genetic variation with the highest potential clinical effects, and uncertainty about clinically reportable WGS findings[102]. WES 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 ~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 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 biological phenomenon waiting for medical attention alone, personalized therapy emphasizes biopsychosocial care by including communication and information giving, psychological and emotional well-being, enhancing function, addressing financial and spiritual concerns, 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).

**REFERENCES**

|  |
| --- |
| 1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]2 **Akiyama H**, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. *Ann Surg* 1994; **220**: 364-72; discussion 372-3 [PMID: 8092902]3 **Schweigert M**, Dubecz A, Stein HJ. Oesophageal cancer--an overview. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 230-244 [PMID: 23296250 DOI: 10.1038/nrgastro.2012.236]4 **Grünberger B**, Raderer M, Schmidinger M, Hejna M. Palliative chemotherapy for recurrent and metastatic esophageal cancer. *Anticancer Res* 2007; **27**: 2705-2714 [PMID: 17695436]5 **Rustgi AK**, El-Serag HB. Esophageal carcinoma. *N Engl J Med* 2014; **371**: 2499-2509 [PMID: 25539106 DOI: 10.1056/NEJMra1314530]6 **Ajani JA**, Barthel JS, Bentrem DJ, D'Amico TA, Das P, Denlinger CS, Fuchs CS, Gerdes H, Glasgow RE, Hayman JA, Hofstetter WL, Ilson DH, Keswani RN, Kleinberg LR, Korn WM, Lockhart AC, Mulcahy MF, Orringer MB, Osarogiagbon RU, Posey JA, Sasson AR, Scott WJ, Shibata S, Strong VE, Varghese TK, Warren G, Washington MK, Willett C, Wright CD. Esophageal and esophagogastric junction cancers. *J Natl Compr Canc Netw* 2011; **9**: 830-887 [PMID: 21900218]7 **Gao YB**, Chen ZL, Li JG, Hu XD, Shi XJ, Sun ZM, Zhang F, Zhao ZR, Li ZT, Liu ZY, Zhao YD, Sun J, Zhou CC, Yao R, Wang SY, Wang P, Sun N, Zhang BH, Dong JS, Yu Y, Luo M, Feng XL, Shi SS, Zhou F, Tan FW, Qiu B, Li N, Shao K, Zhang LJ, Zhang LJ, Xue Q, Gao SG, He J. Genetic landscape of esophageal squamous cell carcinoma. *Nat Genet* 2014; **46**: 1097-1102 [PMID: 25151357 DOI: 10.1038/ng.3076]8 **Lin DC**, Hao JJ, Nagata Y, Xu L, Shang L, Meng X, Sato Y, Okuno Y, Varela AM, Ding LW, Garg M, Liu LZ, Yang H, Yin D, Shi ZZ, Jiang YY, Gu WY, Gong T, Zhang Y, Xu X, Kalid O, Shacham S, Ogawa S, Wang MR, Koeffler HP. Genomic and molecular characterization of esophageal squamous cell carcinoma. *Nat Genet* 2014; **46**: 467-473 [PMID: 24686850 DOI: 10.1038/ng.2935]9 **Zeng H**, Zheng R, Guo Y, Zhang S, Zou X, Wang N, Zhang L, Tang J, Chen J, Wei K, Huang S, Wang J, Yu L, Zhao D, Song G, Chen J, Shen Y, Yang X, Gu X, Jin F, Li Q, Li Y, Ge H, Zhu F, Dong J, Guo G, Wu M, Du L, Sun X, He Y, Coleman MP, Baade P, Chen W, Yu XQ. Cancer survival in China, 2003-2005: a population-based study. *Int J Cancer* 2015; **136**: 1921-1930 [PMID: 25242378 DOI: 10.1002/ijc.29227]10 **Agrawal N**, Frederick MJ, Pickering CR, Bettegowda C, Chang K, Li RJ, Fakhry C, Xie TX, Zhang J, Wang J, Zhang N, El-Naggar AK, Jasser SA, Weinstein JN, Treviño L, Drummond JA, Muzny DM, Wu Y, Wood LD, Hruban RH, Westra WH, Koch WM, Califano JA, Gibbs RA, Sidransky D, Vogelstein B, Velculescu VE, Papadopoulos N, Wheeler DA, Kinzler KW, Myers JN. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. *Science* 2011; **333**: 1154-1157 [PMID: 21798897 DOI: 10.1126/science.1206923]11 **Stransky N**, Egloff AM, Tward AD, Kostic AD, Cibulskis K, Sivachenko A, Kryukov GV, Lawrence MS, Sougnez C, McKenna A, Shefler E, Ramos AH, Stojanov P, Carter SL, Voet D, Cortés ML, Auclair D, Berger MF, Saksena G, Guiducci C, Onofrio RC, Parkin M, Romkes M, Weissfeld JL, Seethala RR, Wang L, Rangel-Escareño C, Fernandez-Lopez JC, Hidalgo-Miranda A, Melendez-Zajgla J, Winckler W, Ardlie K, Gabriel SB, Meyerson M, Lander ES, Getz G, Golub TR, Garraway LA, Grandis JR. The mutational landscape of head and neck squamous cell carcinoma. *Science* 2011; **333**: 1157-1160 [PMID: 21798893 DOI: 10.1126/science.1208130]12 **Agrawal N**, Jiao Y, Bettegowda C, Hutfless SM, Wang Y, David S, Cheng Y, Twaddell WS, Latt NL, Shin EJ, Wang LD, Wang L, Yang W, Velculescu VE, Vogelstein B, Papadopoulos N, Kinzler KW, Meltzer SJ. Comparative genomic analysis of esophageal adenocarcinoma and squamous cell carcinoma. *Cancer Discov* 2012; **2**: 899-905 [PMID: 22877736 DOI: 10.1158/2159-8290.CD-12-0189]13 **Nones K**, Waddell N, Wayte N, Patch AM, Bailey P, Newell F, Holmes O, Fink JL, Quinn MC, Tang YH, Lampe G, Quek K, Loffler KA, Manning S, Idrisoglu S, Miller D, Xu Q, Waddell N, Wilson PJ, Bruxner TJ, Christ AN, Harliwong I, Nourse C, Nourbakhsh E, Anderson M, Kazakoff S, Leonard C, Wood S, Simpson PT, Reid LE, Krause L, Hussey DJ, Watson DI, Lord RV, Nancarrow D, Phillips WA, Gotley D, Smithers BM, Whiteman DC, Hayward NK, Campbell PJ, Pearson JV, Grimmond SM, Barbour AP. Genomic catastrophes frequently arise in esophageal adenocarcinoma and drive tumorigenesis. *Nat Commun* 2014; **5**: 5224 [PMID: 25351503 DOI: 10.1038/ncomms6224]14 **Cancer Genome Atlas Research N**. Comprehensive genomic characterization of squamous cell lung cancers. *Nature* 2012; **489**: 519-525 [PMID: 22960745 DOI: 10.1038/nature11404]15 **Helleday T**, Eshtad S, Nik-Zainal S. Mechanisms underlying mutational signatures in human cancers. *Nat Rev Genet* 2014; **15**: 585-598 [PMID: 24981601 DOI: 10.1038/nrg3729]16 **Vogelstein B**, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Kinzler KW. Cancer genome landscapes. *Science* 2013; **339**: 1546-1558 [PMID: 23539594 DOI: 10.1126/science.1235122]17 **Torkamani A**, Schork NJ. Identification of rare cancer driver mutations by network reconstruction. *Genome Res* 2009; **19**: 1570-1578 [PMID: 19574499 DOI: 10.1101/gr.092833.109]18 **Komatsu M**, Sasaki H. DNA methylation is a key factor in understanding differentiation phenotype in esophageal squamous cell carcinoma. *Epigenomics* 2014; **6**: 567-569 [PMID: 25531249 DOI: 10.2217/epi.14.56]19 **Cheng CP**, Kuo IY, Alakus H, Frazer KA, Harismendy O, Wang YC, Tseng VS. Network-based analysis identifies epigenetic biomarkers of esophageal squamous cell carcinoma progression. *Bioinformatics* 2014; **30**: 3054-3061 [PMID: 25015989 DOI: 10.1093/bioinformatics/btu433]20 **Tamborero D**, Gonzalez-Perez A, Perez-Llamas C, Deu-Pons J, Kandoth C, Reimand J, Lawrence MS, Getz G, Bader GD, Ding L, Lopez-Bigas N. Comprehensive identification of mutational cancer driver genes across 12 tumor types. *Sci Rep* 2013; **3**: 2650 [PMID: 24084849 DOI: 10.1038/srep02650]21 **An O**, Pendino V, D'Antonio M, Ratti E, Gentilini M, Ciccarelli FD. NCG 4.0: the network of cancer genes in the era of massive mutational screenings of cancer genomes. *Database (Oxford)* 2014; **2014**: bau015 [PMID: 24608173 DOI: 10.1093/database/bau015]22 **Abbott KL**, Nyre ET, Abrahante J, Ho YY, Isaksson Vogel R, Starr TK. The Candidate Cancer Gene Database: a database of cancer driver genes from forward genetic screens in mice. *Nucleic Acids Res* 2015; **43**: D844-D848 [PMID: 25190456 DOI: 10.1093/nar/gku770]23 **Alamo P**, Gallardo A, Di Nicolantonio F, Pavón MA, Casanova I, Trias M, Mangues MA, Lopez-PoUnited States A, Villaverde A, Vázquez E, Bardelli A, Céspedes MV, Mangues R. Higher metastatic efficiency of KRas G12V than KRas G13D in a colorectal cancer model. *FASEB J* 2015; **29**: 464-476 [PMID: 25359494 DOI: 10.1096/fj.14-262303]24 **Park JT**, Johnson N, Liu S, Levesque M, Wang YJ, Ho H, Huso D, Maitra A, Parsons MJ, Prescott JD, Leach SD. Differential in vivo tumorigenicity of diverse KRAS mutations in vertebrate pancreas: A comprehensive survey. *Oncogene* 2014 Jul; Epub ahead of print [PMID: 25065594 DOI: 10.1038/onc.2014.223]25 **Chen J**, Ye Y, Sun H, Shi G. Association between KRAS codon 13 mutations and clinical response to anti-EGFR treatment in patients with metastatic colorectal cancer: results from a meta-analysis. *Cancer Chemother Pharmacol* 2013; **71**: 265-272 [PMID: 23090619 DOI: 10.1007/s00280-012-2005-9]26 **Hou JP**, Ma J. DawnRank: discovering personalized driver genes in cancer. *Genome Med* 2014; **6**: 56 [PMID: 25177370 DOI: 10.1186/s13073-014-0056-8]27 **Nevins JR**. Pathway-based classification of lung cancer: a strategy to guide therapeutic selection. *Proc Am Thorac Soc* 2011; **8**: 180-182 [PMID: 21543798 DOI: 10.1513/pats.201006-040MS]28 **Gatza ML**, Lucas JE, Barry WT, Kim JW, Wang Q, Crawford MD, Datto MB, Kelley M, Mathey-Prevot B, Potti A, Nevins JR. A pathway-based classification of human breast cancer. *Proc Natl Acad Sci U S A* 2010; **107**: 6994-6999 [PMID: 20335537 DOI: 10.1073/pnas.0912708107]29 **Bild AH**, Yao G, Chang JT, Wang Q, Potti A, Chasse D, Joshi MB, Harpole D, Lancaster JM, Berchuck A, Olson JA, Marks JR, Dressman HK, West M, Nevins JR. Oncogenic pathway signatures in human cancers as a guide to targeted therapies. *Nature* 2006; **439**: 353-357 [PMID: 16273092 DOI: 10.1038/nature04296]30 **Gonzalez-Perez A**, Mustonen V, Reva B, Ritchie GR, Creixell P, Karchin R, Vazquez M, Fink JL, Kassahn KS, Pearson JV, Bader GD, Boutros PC, Muthuswamy L, Ouellette BF, Reimand J, Linding R, Shibata T, Valencia A, Butler A, Dronov S, Flicek P, Shannon NB, Carter H, Ding L, Sander C, Stuart JM, Stein LD, Lopez-Bigas N. Computational approaches to identify functional genetic variants in cancer genomes. *Nat Methods* 2013; **10**: 723-729 [PMID: 23900255 DOI: 10.1038/nmeth.2562]31 **Long GV**, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, Garbe C, Jouary T, Hauschild A, Grob JJ, Chiarion Sileni V, Lebbe C, Mandalà M, Millward M, Arance A, Bondarenko I, Haanen JB, Hansson J, Utikal J, Ferraresi V, Kovalenko N, Mohr P, Probachai V, Schadendorf D, Nathan P, Robert C, Ribas A, DeMarini DJ, Irani JG, Casey M, Ouellet D, Martin AM, Le N, Patel K, Flaherty K. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med* 2014; **371**: 1877-1888 [PMID: 25265492 DOI: 10.1056/NEJMoa1406037]32 **Ciriello G**, Cerami E, Sander C, Schultz N. Mutual exclusivity analysis identifies oncogenic network modules. *Genome Res* 2012; **22**: 398-406 [PMID: 21908773 DOI: 10.1101/gr.125567.111]33 **Shang L**, Liu HJ, Hao JJ, Jiang YY, Shi F, Zhang Y, Cai Y, Xu X, Jia XM, Zhan QM, Wang MR. A panel of overexpressed proteins for prognosis in esophageal squamous cell carcinoma. *PLoS One* 2014; **9**: e111045 [PMID: 25337715 DOI: 10.1371/journal.pone.0111045]34 **Zhang B**, Wang J, Wang X, Zhu J, Liu Q, Shi Z, Chambers MC, Zimmerman LJ, Shaddox KF, Kim S, Davies SR, Wang S, Wang P, Kinsinger CR, Rivers RC, Rodriguez H, Townsend RR, Ellis MJ, Carr SA, Tabb DL, Coffey RJ, Slebos RJ, Liebler DC. Proteogenomic characterization of human colon and rectal cancer. *Nature* 2014; **513**: 382-387 [PMID: 25043054 DOI: 10.1038/nature13438]35 **Watanabe H**, Ma Q, Peng S, Adelmant G, Swain D, Song W, Fox C, Francis JM, Pedamallu CS, DeLuca DS, Brooks AN, Wang S, Que J, Rustgi AK, Wong KK, Ligon KL, Liu XS, Marto JA, Meyerson M, Bass AJ. SOX2 and p63 colocalize at genetic loci in squamous cell carcinomas. *J Clin Invest* 2014; **124**: 1636-1645 [PMID: 24590290 DOI: 10.1172/JCI71545]36 **Verhaegh W**, van Ooijen H, Inda MA, Hatzis P, Versteeg R, Smid M, Martens J, Foekens J, van de Wiel P, Clevers H, van de Stolpe A. Selection of personalized patient therapy through the use of knowledge-based computational models that identify tumor-driving signal transduction pathways. *Cancer Res* 2014; **74**: 2936-2945 [PMID: 24695361 DOI: 10.1158/0008-5472.CAN-13-2515]37 **Hofree M**, Shen JP, Carter H, Gross A, Ideker T. Network-based stratification of tumor mutations. *Nat Methods* 2013; **10**: 1108-1115 [PMID: 24037242 DOI: 10.1038/nmeth.2651]38 **Sadanandam A**, Lyssiotis CA, Homicsko K, Collisson EA, Gibb WJ, Wullschleger S, Ostos LC, Lannon WA, Grotzinger C, Del Rio M, Lhermitte B, Olshen AB, Wiedenmann B, Cantley LC, Gray JW, Hanahan D. A colorectal cancer classification system that associates cellular phenotype and responses to therapy. *Nat Med* 2013; **19**: 619-625 [PMID: 23584089 DOI: 10.1038/nm.3175]39 **Roychowdhury S**, Iyer MK, Robinson DR, Lonigro RJ, Wu YM, Cao X, Kalyana-Sundaram S, Sam L, Balbin OA, Quist MJ, Barrette T, Everett J, Siddiqui J, Kunju LP, Navone N, Araujo JC, Troncoso P, Logothetis CJ, Innis JW, Smith DC, Lao CD, Kim SY, Roberts JS, Gruber SB, Pienta KJ, Talpaz M, Chinnaiyan AM. Personalized oncology through integrative high-throughput sequencing: a pilot study. *Sci Transl Med* 2011; **3**: 111ra121 [PMID: 22133722 DOI: 10.1126/scitranslmed.3003161]40 **Dutton SJ**, Ferry DR, Blazeby JM, Abbas H, Dahle-Smith A, Mansoor W, Thompson J, Harrison M, Chatterjee A, Falk S, Garcia-Alonso A, Fyfe DW, Hubner RA, Gamble T, Peachey L, Davoudianfar M, Pearson SR, Julier P, Jankowski J, Kerr R, Petty RD. Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial. *Lancet Oncol* 2014; **15**: 894-904 [PMID: 24950987 DOI: 10.1016/S1470-2045(14)70024-5]41 **Chen Y**, McGee J, Chen X, Doman TN, Gong X, Zhang Y, Hamm N, Ma X, Higgs RE, Bhagwat SV, Buchanan S, Peng SB, Staschke KA, Yadav V, Yue Y, Kouros-Mehr H. Identification of druggable cancer driver genes amplified across TCGA datasets. *PLoS One* 2014; **9**: e98293 [PMID: 24874471 DOI: 10.1371/journal.pone.0098293]42 **Qin C**, Zhang C, Zhu F, Xu F, Chen SY, Zhang P, Li YH, Yang SY, Wei YQ, Tao L, Chen YZ. Therapeutic target database update 2014: a resource for targeted therapeutics. *Nucleic Acids Res* 2014; **42**: D1118-D1123 [PMID: 24265219 DOI: 10.1093/nar/gkt1129]43 **Law V**, Knox C, Djoumbou Y, Jewison T, Guo AC, Liu Y, Maciejewski A, Arndt D, Wilson M, Neveu V, Tang A, Gabriel G, Ly C, Adamjee S, Dame ZT, Han B, Zhou Y, Wishart DS. DrugBank 4.0: shedding new light on drug metabolism. *Nucleic Acids Res* 2014; **42**: D1091-D1097 [PMID: 24203711 DOI: 10.1093/nar/gkt1068]44 **Musgrove EA**, Caldon CE, Barraclough J, Stone A, Sutherland RL. Cyclin D as a therapeutic target in cancer. *Nat Rev Cancer* 2011; **11**: 558-572 [PMID: 21734724 DOI: 10.1038/nrc3090]45 **Hong B**, van den Heuvel AP, Prabhu VV, Zhang S, El-Deiry WS. Targeting tumor suppressor p53 for cancer therapy: strategies, challenges and opportunities. *Curr Drug Targets* 2014; **15**: 80-89 [PMID: 24387333 DOI: CDT-EPUB-58493]46 **Khoo KH**, Verma CS, Lane DP. Drugging the p53 pathway: understanding the route to clinical efficacy. *Nat Rev Drug Discov* 2014; **13**: 217-236 [PMID: 24577402 DOI: 10.1038/nrd4236]47 **McLeod HL**. Cancer pharmacogenomics: early promise, but concerted effort needed. *Science* 2013; **339**: 1563-1566 [PMID: 23539596 DOI: 10.1126/science.1234139]48 **Harper AR**, Topol EJ. Pharmacogenomics in clinical practice and drug development. *Nat Biotechnol* 2012; **30**: 1117-1124 [PMID: 23138311 DOI: 10.1038/nbt.2424]49 **Thorn CF**, Klein TE, Altman RB. PharmGKB: the pharmacogenetics and pharmacogenomics knowledge base. *Methods Mol Biol* 2005; **311**: 179-191 [PMID: 16100408 DOI: 10.1385/1-59259-957-5: 179]50 **Patel AP**, Tirosh I, Trombetta JJ, Shalek AK, Gillespie SM, Wakimoto H, Cahill DP, Nahed BV, Curry WT, Martuza RL, Louis DN, Rozenblatt-Rosen O, Suvà ML, Regev A, Bernstein BE. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. *Science* 2014; **344**: 1396-1401 [PMID: 24925914 DOI: 10.1126/science.1254257]51 **Zhang J**, Fujimoto J, Zhang J, Wedge DC, Song X, Zhang J, Seth S, Chow CW, Cao Y, Gumbs C, Gold KA, Kalhor N, Little L, Mahadeshwar H, Moran C, Protopopov A, Sun H, Tang J, Wu X, Ye Y, William WN, Lee JJ, Heymach JV, Hong WK, Swisher S, Wistuba II, Futreal PA. Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing. *Science* 2014; **346**: 256-259 [PMID: 25301631 DOI: 10.1126/science.1256930]52 **Komori J**, Boone L, DeWard A, Hoppo T, Lagasse E. The mouse lymph node as an ectopic transplantation site for multiple tissues. *Nat Biotechnol* 2012; **30**: 976-983 [PMID: 23000933 DOI: 10.1038/nbt.2379]53 Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, B?rresen-Dale A-L. Signatures of mutational processes in human cancer. Nature 201354 **Greaves M**, Maley CC. Clonal evolution in cancer. *Nature* 2012; **481**: 306-313 [PMID: 22258609 DOI: 10.1038/nature10762]55 **Ramos P**, Bentires-Alj M. Mechanism-based cancer therapy: resistance to therapy, therapy for resistance. *Oncogene* 2014 Sep 29; Epub ahead of print [PMID: 25263438 DOI: 10.1038/onc.2014.314]56 **Kemper K**, de Goeje PL, Peeper DS, van Amerongen R. Phenotype switching: tumor cell plasticity as a resistance mechanism and target for therapy. *Cancer Res* 2014; **74**: 5937-5941 [PMID: 25320006 DOI: 10.1158/0008-5472.CAN-14-1174]57 **Crystal AS**, Shaw AT, Sequist LV, Friboulet L, Niederst MJ, Lockerman EL, Frias RL, Gainor JF, Amzallag A, Greninger P, Lee D, Kalsy A, Gomez-Caraballo M, Elamine L, Howe E, Hur W, Lifshits E, Robinson HE, Katayama R, Faber AC, Awad MM, Ramaswamy S, Mino-Kenudson M, Iafrate AJ, Benes CH, Engelman JA. Patient-derived models of acquired resistance can identify effective drug combinations for cancer. *Science* 2014; **346**: 1480-1486 [PMID: 25394791 DOI: 10.1126/science.1254721]58 **Juric D**, Castel P, Griffith M, Griffith OL, Won HH, Ellis H, Ebbesen SH, Ainscough BJ, Ramu A, Iyer G, Shah RH, Huynh T, Mino-Kenudson M, Sgroi D, Isakoff S, Thabet A, Elamine L, Solit DB, Lowe SW, Quadt C, Peters M, Derti A, Schegel R, Huang A, Mardis ER, Berger MF, Baselga J, Scaltriti M. Convergent loss of PTEN leads to clinical resistance to a PI(3)Kα inhibitor. *Nature* 2015; **518**: 240-244 [PMID: 25409150 DOI: 10.1038/nature13948]59 **Martz CA**, Ottina KA, Singleton KR, Jasper JS, Wardell SE, Peraza-Penton A, Anderson GR, Winter PS, Wang T, Alley HM, Kwong LN, Cooper ZA, Tetzlaff M, Chen PL, Rathmell JC, Flaherty KT, Wargo JA, McDonnell DP, Sabatini DM, Wood KC. Systematic identification of signaling pathways with potential to confer anticancer drug resistance. *Sci Signal* 2014; **7**: ra121 [PMID: 25538079 DOI: 10.1126/scisignal.aaa1877]60 **Ding L**, Ellis MJ, Li S, Larson DE, Chen K, Wallis JW, Harris CC, McLellan MD, Fulton RS, Fulton LL, Abbott RM, Hoog J, Dooling DJ, Koboldt DC, Schmidt H, Kalicki J, Zhang Q, Chen L, Lin L, Wendl MC, McMichael JF, Magrini VJ, Cook L, McGrath SD, Vickery TL, Appelbaum E, Deschryver K, Davies S, Guintoli T, Lin L, Crowder R, Tao Y, Snider JE, Smith SM, Dukes AF, Sanderson GE, Pohl CS, Delehaunty KD, Fronick CC, Pape KA, Reed JS, Robinson JS, Hodges JS, Schierding W, Dees ND, Shen D, Locke DP, Wiechert ME, Eldred JM, Peck JB, Oberkfell BJ, Lolofie JT, Du F, Hawkins AE, O'Laughlin MD, Bernard KE, Cunningham M, Elliott G, Mason MD, Thompson DM, Ivanovich JL, Goodfellow PJ, Perou CM, Weinstock GM, Aft R, Watson M, Ley TJ, Wilson RK, Mardis ER. Genome remodelling in a basal-like breast cancer metastasis and xenograft. *Nature* 2010; **464**: 999-1005 [PMID: 20393555 DOI: 10.1038/nature08989]61 **Diaz Jr LA,** Williams RT, Wu J, Kinde I, Hecht JR, Berlin J, Allen B, Bozic I, Reiter JG, Nowak MA. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. *Nature* 2012; **486**: 537-540 [PMID: 22722843 DOI: 10.1038/nature11219]62 **Kreso A**, O'Brien CA, van Galen P, Gan OI, Notta F, Brown AM, Ng K, Ma J, Wienholds E, Dunant C, Pollett A, Gallinger S, McPherson J, Mullighan CG, Shibata D, Dick JE. Variable clonal repopulation dynamics influence chemotherapy response in colorectal cancer. *Science* 2013; **339**: 543-548 [PMID: 23239622 DOI: 10.1126/science.1227670]63 **Marusyk A**, Almendro V, Polyak K. Intra-tumour heterogeneity: a looking glass for cancer? *Nat Rev Cancer* 2012; **12**: 323-334 [PMID: 22513401 DOI: 10.1038/nrc3261]64 **Spellman PT**, Gray JW. Detecting cancer by monitoring circulating tumor DNA. *Nat Med* 2014; **20**: 474-475 [PMID: 24804754 DOI: 10.1038/nm.3564]65 **Bettegowda C**, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, Bartlett BR, Wang H, Luber B, Alani RM, Antonarakis ES, Azad NS, Bardelli A, Brem H, Cameron JL, Lee CC, Fecher LA, Gallia GL, Gibbs P, Le D, Giuntoli RL, Goggins M, Hogarty MD, Holdhoff M, Hong SM, Jiao Y, Juhl HH, Kim JJ, Siravegna G, Laheru DA, Lauricella C, Lim M, Lipson EJ, Marie SK, Netto GJ, Oliner KS, Olivi A, Olsson L, Riggins GJ, Sartore-Bianchi A, Schmidt K, Shih lM, Oba-Shinjo SM, Siena S, Theodorescu D, Tie J, Harkins TT, Veronese S, Wang TL, Weingart JD, Wolfgang CL, Wood LD, Xing D, Hruban RH, Wu J, Allen PJ, Schmidt CM, Choti MA, Velculescu VE, Kinzler KW, Vogelstein B, Papadopoulos N, Diaz LA. Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci Transl Med* 2014; **6**: 224ra24 [PMID: 24553385 DOI: 10.1126/scitranslmed.3007094]66 **Kadri S**, Lao-Sirieix P, Fitzgerald RC. Developing a nonendoscopic screening test for Barrett's esophagus. *Biomark Med* 2011; **5**: 397-404 [PMID: 21657849 DOI: 10.2217/bmm.11.40]67 **Sepehr A**, Razavi P, Saidi F, Salehian P, Rahmani M, Shamshiri A. Esophageal exfoliative cytology samplers. A comparison of three types. *Acta Cytol* 2000; **44**: 797-804 [PMID: 11015982]68 **Subbiah IM**, Subbiah V. Exceptional responders: in search of the science behind the miracle cancer cures. *Future Oncol* 2015; **11**: 1-4 [PMID: 25572778 DOI: 10.2217/fon.14.204]69 **Liu S**, Kurzrock R. Toxicity of targeted therapy: Implications for response and impact of genetic polymorphisms. *Cancer Treat Rev* 2014; **40**: 883-891 [PMID: 24867380 DOI: 10.1016/j.ctrv.2014.05.003]70 **Pessi MA**, Zilembo N, Haspinger ER, Molino L, Di Cosimo S, Garassino M, Ripamonti CI. Targeted therapy-induced diarrhea: A review of the literature. *Crit Rev Oncol Hematol* 2014; **90**: 165-179 [PMID: 24373918 DOI: 10.1016/j.critrevonc.2013.11.008]71 **Jensen SB**, Peterson DE. Oral mucosal injury caused by cancer therapies: current management and new frontiers in research. *J Oral Pathol Med* 2014; **43**: 81-90 [PMID: 24261541 DOI: 10.1111/jop.12135]72 **Macdonald JB**, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part II: Inhibitors of intracellular molecular signaling pathways. *J Am Acad Dermatol* 2015; **72**: 221-36; quiz 237-8 [PMID: 25592339 DOI: 10.1016/j.jaad.2014.07.033]73 **Macdonald JB**, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part I: Inhibitors of the cellular membrane. *J Am Acad Dermatol* 2015; **72**: 203-18; quiz 219-20 [PMID: 25592338 DOI: 10.1016/j.jaad.2014.07.032]74 **Abaan OD**, Polley EC, Davis SR, Zhu YJ, Bilke S, Walker RL, Pineda M, Gindin Y, Jiang Y, Reinhold WC, Holbeck SL, Simon RM, Doroshow JH, Pommier Y, Meltzer PS. The exomes of the NCI-60 panel: a genomic resource for cancer biology and systems pharmacology. *Cancer Res* 2013; **73**: 4372-4382 [PMID: 23856246 DOI: 10.1158/0008-5472.CAN-12-3342]75 **Sharma SV**, Haber DA, Settleman J. Cell line-based platforms to evaluate the therapeutic efficacy of candidate anticancer agents. *Nat Rev Cancer* 2010; **10**: 241-253 [PMID: 20300105 DOI: 10.1038/nrc2820]76 **Ahmed D**, Eide PW, Eilertsen IA, Danielsen SA, Eknæs M, Hektoen M, Lind GE, Lothe RA. Epigenetic and genetic features of 24 colon cancer cell lines. *Oncogenesis* 2013; **2**: e71 [PMID: 24042735 DOI: 10.1038/oncsis.2013.35]77 **Martin D**, Abba MC, Molinolo AA, Vitale-Cross L, Wang Z, Zaida M, Delic NC, Samuels Y, Lyons JG, Gutkind JS. The head and neck cancer cell oncogenome: a platform for the development of precision molecular therapies. *Oncotarget* 2014; **5**: 8906-8923 [PMID: 25275298]78 **Shimada Y**, Maeda M, Watanabe G, Yamasaki S, Komoto I, Kaganoi J, Kan T, Hashimoto Y, Imoto I, Inazawa J, Imamura M. Cell culture in esophageal squamous cell carcinoma and the association with molecular markers. *Clin Cancer Res* 2003; **9**: 243-249 [PMID: 12538476]79 **Gen Y**, Yasui K, Nishikawa T, Yoshikawa T. SOX2 promotes tumor growth of esophageal squamous cell carcinoma through the AKT/mammalian target of rapamycin complex 1 signaling pathway. *Cancer Sci* 2013; **104**: 810-816 [PMID: 23510069 DOI: 10.1111/cas.12155]80 **Wu X**, Zhang J, Zhen R, Lv J, Zheng L, Su X, Zhu G, Gavine PR, Xu S, Lu S, Hou J, Liu Y, Xu C, Tan Y, Xie L, Yin X, He D, Ji Q, Hou Y, Ge D. Trastuzumab anti-tumor efficacy in patient-derived esophageal squamous cell carcinoma xenograft (PDECX) mouse models. *J Transl Med* 2012; **10**: 180 [PMID: 22935382 DOI: 10.1186/1479-5876-10-180]81 **Zhang J**, Jiang D, Li X, Lv J, Xie L, Zheng L, Gavine PR, Hu Q, Shi Y, Tan L, Ge D, Xu S, Li L, Zhu L, Hou Y, Wang Q. Establishment and characterization of esophageal squamous cell carcinoma patient-derived xenograft mouse models for preclinical drug discovery. *Lab Invest* 2014; **94**: 917-926 [PMID: 24999713 DOI: 10.1038/labinvest.2014.77]82 **Wang D**, Weghorst CM, Calvert RJ, Stoner GD. Mutation in the p53 tumor suppressor gene in rat esophageal papillomas induced by N-nitrosomethylbenzylamine. *Carcinogenesis* 1996; **17**: 625-630 [PMID: 8625469]83 **Onken MD**, Winkler AE, Kanchi KL, Chalivendra V, Law JH, Rickert CG, Kallogjeri D, Judd NP, Dunn GP, Piccirillo JF, Lewis JS, Mardis ER, Uppaluri R. A surprising cross-species conservation in the genomic landscape of mouse and human oral cancer identifies a transcriptional signature predicting metastatic disease. *Clin Cancer Res* 2014; **20**: 2873-2884 [PMID: 24668645 DOI: 10.1158/1078-0432.CCR-14-0205]84 **Westcott PM**, Halliwill KD, To MD, Rashid M, Rust AG, Keane TM, Delrosario R, Jen KY, Gurley KE, Kemp CJ, Fredlund E, Quigley DA, Adams DJ, Balmain A. The mutational landscapes of genetic and chemical models of Kras-driven lung cancer. *Nature* 2015; **517**: 489-492 [PMID: 25363767 DOI: 10.1038/nature13898]85 **Tuveson DA**, Jacks T. Technologically advanced cancer modeling in mice. *Curr Opin Genet Dev* 2002; **12**: 105-110 [PMID: 11790563]86 **Sharpless NE**, Depinho RA. The mighty mouse: genetically engineered mouse models in cancer drug development. *Nat Rev Drug Discov* 2006; **5**: 741-754 [PMID: 16915232 DOI: 10.1038/nrd2110]87 **Pirazzoli V**, Nebhan C, Song X, Wurtz A, Walther Z, Cai G, Zhao Z, Jia P, de Stanchina E, Shapiro EM, Gale M, Yin R, Horn L, Carbone DP, Stephens PJ, Miller V, Gettinger S, Pao W, Politi K. Acquired resistance of EGFR-mutant lung adenocarcinomas to afatinib plus cetuximab is associated with activation of mTORC1. *Cell Rep* 2014; **7**: 999-1008 [PMID: 24813888 DOI: 10.1016/j.celrep.2014.04.014]88 **Bergers G**, Hanahan D. Modes of resistance to anti-angiogenic therapy. *Nat Rev Cancer* 2008; **8**: 592-603 [PMID: 18650835 DOI: 10.1038/nrc2442]89 **Rottenberg S**, Nygren AO, Pajic M, van Leeuwen FW, van der Heijden I, van de Wetering K, Liu X, de Visser KE, Gilhuijs KG, van Tellingen O, Schouten JP, Jonkers J, Borst P. Selective induction of chemotherapy resistance of mammary tumors in a conditional mouse model for hereditary breast cancer. *Proc Natl Acad Sci U S A* 2007; **104**: 12117-12122 [PMID: 17626183 DOI: 10.1073/pnas.0702955104]90 **Bass AJ**, Watanabe H, Mermel CH, Yu S, Perner S, Verhaak RG, Kim SY, Wardwell L, Tamayo P, Gat-Viks I, Ramos AH, Woo MS, Weir BA, Getz G, Beroukhim R, O'Kelly M, Dutt A, Rozenblatt-Rosen O, Dziunycz P, Komisarof J, Chirieac LR, Lafargue CJ, Scheble V, Wilbertz T, Ma C, Rao S, Nakagawa H, Stairs DB, Lin L, Giordano TJ, Wagner P, Minna JD, Gazdar AF, Zhu CQ, Brose MS, Cecconello I, Jr UR, Marie SK, Dahl O, Shivdasani RA, Tsao MS, Rubin MA, Wong KK, Regev A, Hahn WC, Beer DG, Rustgi AK, Meyerson M. SOX2 is an amplified lineage-survival oncogene in lung and esophageal squamous cell carcinomas. *Nat Genet* 2009; **41**: 1238-1242 [PMID: 19801978 DOI: 10.1038/ng.465]91 **Liu K**, Jiang M, Lu Y, Chen H, Sun J, Wu S, Ku WY, Nakagawa H, Kita Y, Natsugoe S, Peters JH, Rustgi A, Onaitis MW, Kiernan A, Chen X, Que J. Sox2 cooperates with inflammation-mediated Stat3 activation in the malignant transformation of foregut basal progenitor cells. *Cell Stem Cell* 2013; **12**: 304-315 [PMID: 23472872 DOI: 10.1016/j.stem.2013.01.007]92 **Sánchez-Rivera FJ**, Papagiannakopoulos T, Romero R, Tammela T, Bauer MR, Bhutkar A, Joshi NS, Subbaraj L, Bronson RT, Xue W, Jacks T. Rapid modelling of cooperating genetic events in cancer through somatic genome editing. *Nature* 2014; **516**: 428-431 [PMID: 25337879 DOI: 10.1038/nature13906]93 **Doudna JA**, Charpentier E. Genome editing. The new frontier of genome engineering with CRISPR-Cas9. *Science* 2014; **346**: 1258096 [PMID: 25430774 DOI: 10.1126/science.1258096]94 **Wheeler DA**, Wang L. From human genome to cancer genome: the first decade. *Genome Res* 2013; **23**: 1054-1062 [PMID: 23817046 DOI: 10.1101/gr.157602.113]95 **Roychowdhury S**, Chinnaiyan AM. Translating genomics for precision cancer medicine. *Annu Rev Genomics Hum Genet* 2014; **15**: 395-415 [PMID: 25184532 DOI: 10.1146/annurev-genom-090413-025552]96 **Simon R**, Roychowdhury S. Implementing personalized cancer genomics in clinical trials. *Nat Rev Drug Discov* 2013; **12**: 358-369 [PMID: 23629504 DOI: 10.1038/nrd3979]97 **Hanahan D**, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]98 **Hanahan D**. Rethinking the war on cancer. *Lancet* 2014; **383**: 558-563 [PMID: 24351321 DOI: 10.1016/S0140-6736(13)62226-6]99 **Ralph C**, Elkord E, Burt DJ, O'Dwyer JF, Austin EB, Stern PL, Hawkins RE, Thistlethwaite FC. Modulation of lymphocyte regulation for cancer therapy: a phase II trial of tremelimumab in advanced gastric and esophageal adenocarcinoma. *Clin Cancer Res* 2010; **16**: 1662-1672 [PMID: 20179239 DOI: 10.1158/1078-0432.CCR-09-2870]100 **Tran E**, Turcotte S, Gros A, Robbins PF, Lu YC, Dudley ME, Wunderlich JR, Somerville RP, Hogan K, Hinrichs CS, Parkhurst MR, Yang JC, Rosenberg SA. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. *Science* 2014; **344**: 641-645 [PMID: 24812403 DOI: 10.1126/science.1251102]101 **Herbst RS**, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, Kohrt HE, Horn L, Lawrence DP, Rost S, Leabman M, Xiao Y, Mokatrin A, Koeppen H, Hegde PS, Mellman I, Chen DS, Hodi FS. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014; **515**: 563-567 [PMID: 25428504 DOI: 10.1038/nature14011]102 **Dewey FE**, Grove ME, Pan C, Goldstein BA, Bernstein JA, Chaib H, Merker JD, Goldfeder RL, Enns GM, David SP, Pakdaman N, Ormond KE, Caleshu C, Kingham K, Klein TE, Whirl-Carrillo M, Sakamoto K, Wheeler MT, Butte AJ, Ford JM, Boxer L, Ioannidis JP, Yeung AC, Altman RB, Assimes TL, Snyder M, Ashley EA, Quertermous T. Clinical interpretation and implications of whole-genome sequencing. *JAMA* 2014; **311**: 1035-1045 [PMID: 24618965 DOI: 10.1001/jama.2014.1717]103 **Hudson AM**, Yates T, Li Y, Trotter EW, Fawdar S, Chapman P, Lorigan P, Biankin A, Miller CJ, Brognard J. Discrepancies in cancer genomic sequencing highlight opportunities for driver mutation discovery. *Cancer Res* 2014; **74**: 6390-6396 [PMID: 25256751 DOI: 10.1158/0008-5472.CAN-14-1020]104 **Zhao Y**, Gao Y, Chen Z, Hu X, Zhou F, He J. Low frequency of TERT promoter somatic mutation in 313 sporadic esophageal squamous cell carcinomas. *Int J Cancer* 2014; **134**: 493-494 [PMID: 23818232 DOI: 10.1002/ijc.28360]105 **Killela PJ**, Reitman ZJ, Jiao Y, Bettegowda C, Agrawal N, Diaz LA, Friedman AH, Friedman H, Gallia GL, Giovanella BC, Grollman AP, He TC, He Y, Hruban RH, Jallo GI, Mandahl N, Meeker AK, Mertens F, Netto GJ, Rasheed BA, Riggins GJ, Rosenquist TA, Schiffman M, Shih IeM, Theodorescu D, Torbenson MS, Velculescu VE, Wang TL, Wentzensen N, Wood LD, Zhang M, McLendon RE, Bigner DD, Kinzler KW, Vogelstein B, Papadopoulos N, Yan H. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. *Proc Natl Acad Sci U S A* 2013; **110**: 6021-6026 [PMID: 23530248 DOI: 10.1073/pnas.1303607110]106 **Ding L**, Wendl MC, McMichael JF, Raphael BJ. Expanding the computational toolbox for mining cancer genomes. *Nat Rev Genet* 2014; **15**: 556-570 [PMID: 25001846 DOI: 10.1038/nrg3767]107 **O'Rawe J**, Jiang T, Sun G, Wu Y, Wang W, Hu J, Bodily P, Tian L, Hakonarson H, Johnson WE, Wei Z, Wang K, Lyon GJ. Low concordance of multiple variant-calling pipelines: practical implications for exome and genome sequencing. *Genome Med* 2013; **5**: 28 [PMID: 23537139 DOI: 10.1186/gm432]108 **Moncunill V**, Gonzalez S, Beà S, Andrieux LO, Salaverria I, Royo C, Martinez L, Puiggròs M, Segura-Wang M, Stütz AM, Navarro A, Royo R, Gelpí JL, Gut IG, López-Otín C, Orozco M, Korbel JO, Campo E, Puente XS, Torrents D. Comprehensive characterization of complex structural variations in cancer by directly comparing genome sequence reads. *Nat Biotechnol* 2014; **32**: 1106-1112 [PMID: 25344728 DOI: 10.1038/nbt.3027]109 **Cherny NI**, de Vries EG, Emanuel L, Fallowfield L, Francis PA, Gabizon A, Piccart MJ, Sidransky D, Soussan-Gutman L, Tziraki C. Words matter: distinguishing "personalized medicine" and "biologically personalized therapeutics". *J Natl Cancer Inst* 2014; **106**: [PMID: 25293984 DOI: 10.1093/jnci/dju321] |

**P-Reviewer:** Hsu PK, Sato Y **S-Editor:** Yu J **L-Editor:** **E-Editor:**

****

**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 or 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. Non-responders may be analyzed in a similar manner during subsequent surveillance and further treated.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 1 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](http://www.clinicaltrials.gov)). Targeted therapy has been or is being tried in 62 of 204 studies. Some of these agents target multiple molecules, for example, Lapatinib (EGFR and Erbb2), Rigosertib (PI3K and PLK), Vandetanib (VEGFR, EGFR and RET), Sorafenib (VEGFR, PDGFR and RAF).