Male patients with TERT mutation may be more likely to benefit from immunotherapy, especially for melanoma

Jia Li1*, Zhaoyan Li2*, Chenyue Zhang3, Chenxing Zhang4, Haiyong Wang5

1Department of Integrated Chinese and Western Medicine, Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou 450008, Henan, China
2Department of Oncology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (TCM), Shanghai 2000437, China
3Department of Integrated Therapy, Fudan University Shanghai Cancer Center, Shanghai Medical College, Shanghai 200032, China
4Department of Nephrology, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China
5Department of Internal Medicine-Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan 250117, China

*Equal contribution

Correspondence to: Haiyong Wang; email: wanghaiyong6688@126.com; https://orcid.org/0000-0002-0658-4479

Keywords: sex disparity, TERT mutation, immunotherapy, melanoma
Received: May 2, 2020    Accepted: June 28, 2020    Published: September 10, 2020

Copyright: Li et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

ABSTRACT

Genomic mutation may be key factors for sex-biased disparities in cancer diagnosis, prognosis and prediction of treatment response. Current study has revealed that sex-based dimorphism on the efficacy of immune checkpoint inhibitors (ICIs) in various cancers and confirmed that male patients can benefit more from immunotherapy. However, only a subset of male patients responds well to ICIs. Therefore, biomarkers are desperately needed to identify the group of patients who may be more likely to benefit from ICIs. With the availability of the cBioPortal database, we identified that TERT mutation may serve as a sex-specific cancer biomarker and TERT mutation frequency of melanoma was higher in male patients. Notably, we found that male patients with TERT mutation may be more likely to benefit from immunotherapy ($p = 0.006$), especially for melanoma ($p < 0.001$). Therefore, our research provides a possible direction for the exploration of immunotherapy prediction biomarkers based on sex difference.

INTRODUCTION

Sex is defined by biological differences in the chromosomes, reproductive organs, and sex steroid levels between men and women, while gender is determined by behaviors and activity differences in human society or culture between male and female [1]. In many cancer types, significant sex disparities in cancer incidence, survival, and prevalence and treatment responses have also been reported [2, 3]. Sex disparities in cancer are presumably induced by sex hormones, especially estrogen, which are known to modulate gene expression in many cancers [4, 5]. Genomic mutation, may be key factors for sex-biased disparities in mortality and incidence of cancers [6]. Most prior research on genomic determinants of sex differences have focused on TMB [7]. However, the mutant genes related to sex disparity have yet to be elucidated.

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment, showing higher efficacy than standard therapies in the management of several difficult-to-treat malignancies, including malignant melanoma, non-small-cell lung cancer, bladder cancer, and head and neck.

---

www.aging-us.com 17288 AGING
cancer, among many others [8]. Recently, sex-based ICI efficacy dimorphism has been found in various cancers, suggesting that male cancer patients benefit from ICIs more than female cancer patients [9, 10]. However, only a subset of patients responds well to ICIs. Recent studies suggested that TMB was an efficient pan-cancer biomarker for ICI response and was preferentially useful in female patients [11]. However, due to the non-uniform calculation, various sequencing approaches and exorbitant expenses, TMB is not an optimal indicator to ICIs responses in some types of cancer. Therefore, new biomarkers are desperately needed to identify the group of patients who may be more likely to benefit from ICIs.

Telomerase reverse transcriptase (TERT) mutations lead to aberrantly upregulate TERT expression, and ultimately enable telomere maintenance, which achieve unlimited proliferative capacity of tumor cells [12, 13]. Moreover, TERT mutations are identified as biomarkers of tumor aggressiveness and poor prognosis in several human cancer types [14–17]. Recently, a study on bladder cancer suggested that TERT promoter mutation has been identified as a potential predictive marker of Bacillus Calmette-Guérin (BCG) treatment which was regarded as one of the first and most successful of all oncological immunotherapies [18]. However, a comprehensive analysis of TERT mutation and their predictive value for ICIs has never been elucidated to date.

With the availability of the cBioPortal database, we firstly compared the mutant genes related to sex disparity, and then analyzed the frequency of TERT mutation between different sex groups in different cancer types. Finally, we explored the effect of TERT mutation and sex disparity on the efficacy of immunotherapy in pan cancer, especially melanoma.

**RESULTS**

**The differential mutant genes related to sex disparity**

Scatter plots all showed differences in genetic mutations between different sex groups (Figure 1A). The blue dots indicated that the p and q values were statistically significant, and the gray dots were not significant. We also showed the top 10 genes with the greatest difference of mutations in female and male. As shown in Figure 1B, the mutation frequency of PIK3CA, ATRX, CDH1, GATA3, MAP3K1, and ESR1 was higher in the female than in the male group (p <0.05). In TERT, ERG, VHL, and TMPRSS2, the mutation frequency was higher in the male than in the female group, and the difference was also statistically significant (p <0.05).

We further analyzed the frequency of TERT mutations between different sex groups in different cancer types. Figure 1C showed that Bladder Cancer, Glioma and Melanoma were the top three of TERT mutation frequency, while Esophagogastric cancer, Prostate cancer, and Pancreatic cancer were the last three. Notably, for Melanoma and Hepatobiliary cancer, TERT mutation frequency was higher in male patients than female patients.

![Figure 1. The differential mutant genes between female vs male group.](image)

(A) Scatter plots, the altered frequency of genetic mutations between female vs male group (%). The X axis represents altered frequency in female. The Y axis represents altered frequency in male. The blue dots indicate that the p and q values are statistically significant. (B) The top 10 genes with the greatest difference of mutations between female vs male group. The X axis represents genetic changes with the greatest difference. The Y axis represents differential mutant genes. The red histogram indicates female and the blue histogram indicates male. (C) The frequency of TERT mutations between female vs male group in different cancer types. X-axis represents common types of cancer. The Y axis represents percent of TERT mutation. The red histogram indicates female and the blue histogram indicates male.
Relationship between TERT mutation and sex disparity and immunotherapy

We first explored the association between sex and overall survival (OS) in the immunotherapy cohort. As shown in Figure 2A, male patients had significantly better median OS than female patients (19 months vs 15 months, \( p = 0.047 \)). From the above results, we found that TERT mutation was related to sex disparity. We also explored the predictive value of TERT mutation on the efficacy of immunotherapy. Surprisingly, patients in the TERT altered group showed a significantly longer median OS than unaltered group (Figure 2B, 24 months vs 17 months, \( p =0.002 \)).

In order to further understand whether male and female patients with TERT mutation can benefit from immunotherapy. We next conducted subgroup analysis in the TERT-male and TERT-female cohort. Notably, in TERT-male group, male patients in the TERT altered group had longer median OS than unaltered group (Figure 2C, 27 months vs 17 months, \( p =0.006 \)). Similar results were obtained in TERT-female cohort, female patients in the TERT altered group had longer median OS trend than unaltered group, but not statistically significant (Figure 2D, 19 months vs 14 months, \( p =0.193 \)).

Relationship between TERT mutation and immunotherapy in different sex groups of melanoma

To explore the predictive value of TERT mutation on the efficacy of immunotherapy in certain cancer types. The cancer types including non-small cell lung cancer, melanoma, bladder cancer, renal cell carcinoma, head and neck cancer, esophageogastric cancer, glioma and colorectal cancer were further analyzed. However, the result showed that only male melanoma patients in the TERT altered group had longer median OS than unaltered group (Figure 3A, 49 months vs 27 months, \( p<0.001 \)). Similar to pan cancer analysis, the statistically OS significant was not found for female

![Figure 2. The effect of TERT mutation and sex disparity on the efficacy of immunotherapy in cBioPortal database. (A) Kaplan-Meier survival analysis between female and male patients in ICI treatment cohort. The red curve represents female group, and the blue curve represents male group. (B) Kaplan-Meier survival analysis between TERT altered and unaltered group in ICI treatment cohort. The red curve represents TERT altered group, and the blue curve represents unaltered group. (C) Kaplan-Meier survival analysis between TERT altered and unaltered group in the TERT-male cohort. The red curve represents TERT altered group, and the blue curve represents unaltered group. (D) Kaplan-Meier survival analysis between TERT altered and unaltered group in the TERT-female cohort. The red curve represents TERT altered group, and the blue curve represents unaltered group.](image-url)
melanoma patients in the TERT altered group (Figure 3B, 60 months vs 44 months, \( p =0.511 \)). Other tumor types did not get a positive result, and the data were not given.

**DISCUSSION**

Sex disparities were biologically related to cancer diagnosis, prognosis, severity, and prediction of treatment response [2, 3]. Genomics studies showed a variation in the expression of autosomal genes between males and females [19, 20]. TMB, as a biomarker of response to ICIs, has been considered to be more predictive of the efficacy of immunotherapy in female patients [11]. However, due to the limitations of TMB application, we needed to explored new biomarkers related to sex disparity to better predict ICIs response.

In our study, we showed the top 10 genes with the greatest difference of mutations, which were related to sex disparity. This variation (genetic mutation) may help facilitate the identification of sex-specific cancer biomarkers. We found that PIK3CA and TERT were genes with the greatest differences between different sex groups. Strikingly, TERT mutation could be frequent in many malignancies and be identified as biomarkers of tumor aggressiveness and poor prognosis in several human cancer types [14–17]. We further analyzed the frequency of TERT mutations between different sex groups in different cancer types. The result showed that Bladder Cancer, Glioma and Melanoma were the top three of TERT mutation frequency, while Esophagogastric cancer, Prostate cancer, and Pancreatic cancer were the last three. Consistent results have also been confirmed the high prevalence of TERT mutation in bladder cancer, Glioma and Melanoma and a lower mutation frequency of breast cancer and prostate cancer, although they occurred with different frequencies [21–25]. Moreover, we also found that TERT mutation frequency of Melanoma and Hepatobiliary cancer was higher in male patients than female patients. Lee et al analyzed TERT promoter mutation in 162 tumor samples of the patients with HCC by sequencing and real-time PCR, respectively. The result showed that the TERT promoter mutation rate was 28.8% (46/160) in HCC and was associated with males (\( p =0.027 \)) [26]. Egberts et al also found highly recurrent TERT promoter mutations in malignant melanomas, and the prevalence of its TERT-promoter mutations was associated with the patient’s sex [23 (51.1%) men, 10 (21.3%) women; \( p = 0.004 \)] [27]. The above results suggested that TERT mutation might be closely related to sex, although efforts are still needed to evaluate the clinical utility of sex-biased TERT mutation in a larger patient cohort.

But for patients who received ICIs, what was the relationship between TERT mutation and OS? We evaluated the effect of TERT mutation and sex disparity on the efficacy of immunotherapy. Our results demonstrated that male patients and patients with TERT mutation all had significantly better median OS. More importantly, male patients with TERT mutation had longer median OS. Current study has revealed that sex-based dimorphism on the efficacy of ICIs in various cancers and confirmed that male patients can benefit more from immunotherapy [8, 28, 29]. As we all know, not all male patients can benefit from immunotherapy,

![Figure 3. The effect of TERT mutation on the efficacy of immunotherapy in melanoma database. (A) Kaplan-Meier survival analysis between TERT altered and unaltered group in the male cohort. The red curve represents TERT altered group, and the blue curve represents unaltered group. (B) Kaplan-Meier survival analysis between TERT altered and unaltered group in the female cohort. The red curve represents TERT altered group, and the blue curve represents unaltered group.](image-url)
and new biomarkers are still needed to predict the efficacy of immunotherapy. Our study reported that male patients with TERT mutation may be more likely to benefit from immunotherapy in a multitude of cancers.

Our study has not only found a high frequency of TERT mutations in melanoma, but also a higher frequency of mutations in male melanoma patients. In addition, effect of sex on immunotherapy may exist in specific cancer types rather than all cancer types [30, 31]. TERT mutation should also be like this. Our result showed that only male melanoma patients with TERT mutation had longer median OS. Therefore, male melanoma patients with TERT mutation may benefit from immunotherapy.

This study also has certain limitations. Firstly, our study was only a bioinformatic based on public databases. The next step is to confirm whether male patients with TERT mutation could benefit from immunotherapy through prospective or retrospective studies. Secondly, the immunotherapy data we collected for each cancer type was very limited. Although we did immunotherapy analyses in certain cancer types, the same conclusion was only obtained in melanoma. As for other tumor types, we need to determine whether male patients with TERT mutations benefit from immunotherapy.

In conclusion, using the cBioPortal database, we identified that TERT mutation may serve as a sex-specific cancer biomarker and TERT mutation frequency of melanoma was higher in male patients. Notably, we found that male patients with TERT mutation may be more likely to benefit from immunotherapy, especially for melanoma. However, the potential role of TERT mutation as biomarkers for immunotherapy are still needed to confirm by further clinical trials.

**MATERIALS AND METHODS**

All data in this study were selected from the cBioPortal database (https://www.cbioportal.org) [32]. To analyze the differences of gene mutation according to sex disparity, we used the MSK-IMPACT Clinical Sequencing Cohort [33], which contain 10336 patients/10945 samples with available mutation and sex status information.

For the relationship analysis between gender, TERT mutation and immunotherapy, we also selected TMB and Immunotherapy Cohort [34], which contains 1661 patients with various cancer types (including 320 cases of melanoma) with available survival, immunotherapy, TERT mutation and sex status information. Data between two groups were compared using unpaired t-test or Wilcoxon rank-sum test. Kaplan-Meier method was used to calculate the survival probability and log-rank test was used to compare the survival curves. All reported p values are two-tailed, and for all analyses, p <0.05 is considered statistically significant. This study was mainly based on the cBioPortal database and personal privacy information was not involved, so the informed consent was not needed.

**AUTHOR CONTRIBUTIONS**

Haiyong Wang designed the project and proposed the idea; Jia Li and Zhaoyan Li carried out data download and literature collection and wrote manuscript; Chenyue Zhang conducted bioinformatics analysis; Chenxing Zhang conducted chart and statistical processing. All authors read and approved the final manuscript.

**CONFLICTS OF INTEREST**

All authors declare that there is no conflicts of interest.

**FUNDING**

This study was supported jointly by Special funds for Taishan Scholars Project (Grant no. tsqn201812149), Academic promotion programme of Shandong First Medical University (2019RC004).

**REFERENCES**

1. Clayton JA, Tannenbaum C. Sex and gender reporting in research-reply. JAMA, 2017; 317:975. https://doi.org/10.1001/jama.2017.0151 PMID:28267852

2. Zhu Y, Shao X, Wang X, Liu L, Liang H. Sex disparities in cancer. Cancer Lett. 2019; 466:35–38. https://doi.org/10.1016/j.canlet.2019.08.017 PMID:31541696

3. Cook MB, McGlynn KA, Devesa SS, Freedman ND, Anderson WF. Sex disparities in cancer mortality and survival. Cancer Epidemiol Biomarkers Prev. 2011; 20:1629–37. https://doi.org/10.1158/1055-9965.EPI-11-0246 PMID:21750167

4. Özdemir BC, Dotto GP. Sex hormones and anticancer immunity. Clin Cancer Res. 2019; 25:4603–10. https://doi.org/10.1158/1078-0432.CCR-19-0137 PMID:30890551

5. Kim HI, Lim H, Moon A. Sex differences in cancer: epidemiology, genetics and therapy. Biomol Ther (Seoul). 2018; 26:335–42. https://doi.org/10.4062/biomolther.2018.103 PMID:29949843
6. Mostertz W, Stevenson M, Acharya C, Chan I, Walters K, Lamlerthton W, Barry W, Crawford J, Nevins J, Potti A. Age- and sex-specific genomic profiles in non-small cell lung cancer. JAMA. 2010; 303:535–43. https://doi.org/10.1001/jama.2010.80 PMID:20145230

7. Gupta S, Artomov M, Goggins W, Daly M, Tsao H. Gender disparity and mutation burden in metastatic melanoma. J Natl Cancer Inst. 2015; 107:dvj221. https://doi.org/10.1093/jnci/dvj221 PMID:26296643

8. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018; 359:1350–55. https://doi.org/10.1126/science.aar4060 PMID:29567705

9. Conforti F, Pala L, Bagnardi V, De Pas T, Martinetti M, Viale G, Gelber RD, Goldhirsch A. Cancer immunotherapy efficacy and patients’ sex: a systematic review and meta-analysis. Lancet Oncol. 2018; 19:737–46. https://doi.org/10.1016/S1470-2045(18)30261-4 PMID:29778737

10. Wang PF, Song HF, Zhang Q, Yan CX. Pan-cancer immunogenomics analyses reveal sex disparity in the efficacy of cancer immunotherapy. Eur J Cancer. 2020; 126:136–38. https://doi.org/10.1016/j.ejca.2019.12.008 PMID:31927214

11. Wang S, Zhang J, He Z, Wu K, Liu XS. The predictive power of tumor mutational burden in lung cancer immunotherapy response is influenced by patients’ sex. Int J Cancer. 2019; 145:2840–49. https://doi.org/10.1002/ijc.32327 PMID:30972745

12. Weinrich SL, Pruzan R, Ma L, Ouellette M, Tesmer VM, Holt SE, Bodnar AG, Lichtsteiner S, Kim NW, Trager JB, Taylor RD, Carlos R, Andrews WH, et al. Reconstitution of human telomerase with the template RNA component hTR and the catalytic protein subunit hTRT. Nat Genet. 1997; 17:498–502. https://doi.org/10.1038/ng1297-498 PMID:9398860

13. Lorber FK, Hockemeyer D. TERT promoter mutations and telomerases during tumorigenesis. Curr Opin Genet Dev. 2020; 60:56–62. https://doi.org/10.1016/j.gde.2020.02.001 PMID:32163830

14. Osella-Abate S, Bertero L, Senetta R, Mariani S, Lisa F, Coppola V, Metovic J, Pasini B, Puig SS, Fierro MT, Manrique-Silva E, Kumar R, Nagore E, et al. TERT promoter mutations are associated with visceral spreading in melanoma of the trunk. Cancers (Basel). 2019; 11:452. https://doi.org/10.3390/cancers11040452 PMID:30934988

15. Simon M, Hosen I, Gousias K, Rachakonda S, Heidenreich B, Gessi M, Schramm J, Hemminki K, Waha A, Kumar R. TERT promoter mutations: a novel independent prognostic factor in primary glioblastomas. Neuro Oncol. 2015; 17:45–52. https://doi.org/10.1093/neuonc/nou158 PMID:25140036

16. Melo M, da Rocha AG, Vinagre J, Batista R, Peixoto J, Tavares C, Celestino R, Almeida A, Salgado C, Eloy C, Castro P, Prazeres H, Lima J, et al. TERT promoter mutations are a major indicator of poor outcome in differentiated thyroid carcinomas. J Clin Endocrinol Metab. 2014; 99:E754–65. https://doi.org/10.1210/jc.2013-3734 PMID:24476079

17. Leão R, Lee D, Figueiredo A, Hermanns T, Wild P, Komosa M, Lau I, Mistry M, Nunes NM, Price AJ, Zhang C, Lipman T, Poyet C, et al. Combined genetic and epigenetic alterations of the TERT promoter affect clinical and biological behavior of bladder cancer. Int J Cancer. 2019; 144:1676–84. https://doi.org/10.1002/ijc.31935 PMID:30350309

18. Batista R, Lima L, Vinagre J, Pinto V, Lyra J, Máximo V, Santos L, Soares P. TERT promoter mutation as a potential predictive biomarker in BCG-treated bladder cancer patients. Int J Mol Sci. 2020; 21:947. https://doi.org/10.3390/ijms21030947 PMID:32023888

19. Shin JY, Jung HJ, Moon A. Molecular markers in sex differences in cancer. Toxicol Res. 2019; 35:331–41. https://doi.org/10.5487/TR.2019.35.4.331 PMID:31636844

20. van Nas A, Guhathakurta D, Wang SS, Yehya N, Horvath S, Zhang B, Ingram-Drake L, Chaudhuri G, Schadt EE, Drake TA, Arnold AP, Lusis AJ. Elucidating the role of gonadal hormones in sexually dimorphic gene coexpression networks. Endocrinology. 2009; 150:1235–49. https://doi.org/10.1210/jc.2013-0563 PMID:24476079

21. Vinagre J, Almeida A, Pópulo H, Batista R, Lyra J, Pinto V, Coelho R, Celestino R, Prazeres H, Lima L, Melo M, da Rocha AG, Preto A, et al. Frequency of TERT promoter mutations in primary melanoma. J Natl Cancer Inst. 2015; 107:djv221. https://doi.org/10.1093/jnci/djv221 PMID:26296643
bladder cancer and glioblastoma. Cell Cycle. 2013; 12:1637–38.  
https://doi.org/10.4161/cc.24662  
PMD: 23603989

23. Rachakonda PS, Hosen I, de Verdier PJ, Fallah M, Heidenreich B, Ryk C, Wiklund NP, Steineck G, Schadendorf D, Hemminki K, Kumar R. TERT promoter mutations in bladder cancer affect patient survival and disease recurrence through modification by a common polymorphism. Proc Natl Acad Sci USA. 2013; 110:17426–31.  
https://doi.org/10.1073/pnas.1310522110  
PMD: 24101484

24. Killela PJ, Reitman ZJ, Jiao Y, Bettegowda C, Agrawal N, Diaz LA Jr, Friedman AH, Friedman H, Gallia GL, Giovanella BC, Grollman AP, He TC, He Y, et al. 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 USA. 2013; 110:6021–26.  
https://doi.org/10.1073/pnas.1303607110  
PMD: 23530248

25. Bell RJ, Rube HT, Xavier-Magalhães A, Costa BM, Mancini A, Song JS, Costello JF. Understanding TERT promoter mutations: a common path to immortality. Mol Cancer Res. 2016; 14:315–23.  
https://doi.org/10.1158/MCR.16-0003  
PMD: 28151853

26. Lee HW, Park TJ, Jang SY, Park SY, Park WJ, Jung SJ, Lee JH. Clinicopathological characteristics of TERT promoter mutation and telomere length in hepatocellular carcinoma. Medicine (Baltimore). 2017; 96:e5766.  
https://doi.org/10.1097/MD.0000000000005766  
PMD: 28151853

27. Egebrys F, Krüger S, Behrens HM, Bergner I, Papaspyrou G, Werner JA, Alkatout I, Haag J, Hauschild A, Röcken C. Melanomas of unknown primary frequently harbor TERT-promoter mutations. Melanoma Res. 2014; 24:131–36.  
https://doi.org/10.1097/CMR.0000000000000048  
PMD: 24463461

28. Conforti F, Pala L, Bagnardi V, Viale G, De Pas T, Pagan E, Pennacchioli E, Cocorocchio E, Ferrucci PF, De Marinis F, Gelber RD, Goldhirsh A. Sex-based heterogeneity in response to lung cancer immunotherapy: a systematic review and meta-analysis. J Natl Cancer Inst. 2019; 111:772–81.  
https://doi.org/10.1093/jnci/djz094  
PMD: 31106827

29. Wang S, Cowley LA, Liu XS. Sex differences in cancer immunotherapy efficacy, biomarkers, and therapeutic strategy. Molecules. 2019; 24:3214.  
https://doi.org/10.3390/molecules24183214  
PMD: 31487832

30. Wu Y, Ju Q, Jia K, Yu J, Shi H, Wu H, Jiang M. Correlation between sex and efficacy of immune checkpoint inhibitors (PD-1 and CTLA-4 inhibitors). Int J Cancer. 2018; 143:45–51.  
https://doi.org/10.1002/ijc.31301  
PMD: 29424425

31. Grassadonia A, Sperduti I, Vici P, Iezzi L, Brocco D, Gamucci T, Pizzuti L, Mauger-Saccà M, Marchetti P, Cognetti G, De Tursi M, Natoli C, Barba M, Tinari N. Effect of gender on the outcome of patients receiving immune checkpoint inhibitors for advanced cancer: a systematic review and meta-analysis of phase III randomized clinical trials. J Clin Med. 2018; 7:542.  
https://doi.org/10.3390/jcm7120542  
PMD: 30545122

32. Gao J, Aksoy BA, Dogrusoz U, Dredner G, Gross B, Sumer SO, Sun Y, Jacobsen A, Sinha R, Larsson E, Cerami E, Sander C, Schultz N. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal. 2013; 6:p1.  
https://doi.org/10.1126/scisignal.2004088  
PMD: 23550210

33. Zehir A, Benayed R, Shah RH, Syed A, Middha S, Kim HR, Srinivasan P, Gao J, Chakravarty D, Devlin SM, Hellmann MD, Barron DA, Schram AM, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med. 2017; 23:703–13.  
https://doi.org/10.1038/nm.4333  
PMD: 28481359

34. Samstein RM, Lee CH, Shoushtari AN, Hellmann MD, Shen R, Janjigian YY, Barron DA, Zehir A, Jordan EJ, Omuro A, Kaley TJ, Kendall SM, Motzer RJ, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet. 2019; 51:202–06.  
https://doi.org/10.1038/s41588-018-0312-8  
PMD: 30643254