Prevalence of actionable mutations and copy number alterations and the price of a genomic testing panel

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ABSTRACT

Interest in genomic testing for the selection of cancer therapy is growing. However, the cost of genomic testing has not been well studied. We sought to determine the price of identifying mutations and copy number alterations (CNAs) in theoretically actionable genes across multiple tumor types. We reviewed data from The Cancer Genome Atlas to determine the frequency of alterations in nine tumor types. We used price information from a commonly used commercial genomic testing platform (FoundationOne) to determine the price of detecting mutations and CNAs in different types of tumors. Although there are large variations in the prevalence by tumor type, when the detection of both mutations and CNAs was considered overall, most patients had at least one alteration in a potentially actionable gene (84% overall, range 51%- 98% among tumor types assessed). The corresponding average price of identifying at least one alteration per patient ranges from $5,897 to $11,572. Although the frequency of mutations and CNAs in actionable genes differs by tumor type, most patients have an actionable genomic alteration detectable by a commercially available panel. Determining CNAs as well as mutations improves actionability and reduces the price of detecting an alteration.

INTRODUCTION

Genomic medicine is a rapidly growing field in oncology. In the past decade, we have seen growth in the number of new genomic tests available, and genomic testing is now often used to match patients to approved or investigational agents. However, genomic testing is expensive and may not be covered by insurance providers; thus, it can pose a significant financial burden on cancer patients. Currently, the literature on the cost of genomic testing in patients with cancer is limited. Although there are a few studies on the cost-effectiveness of genomic testing panel for specific cancer and subpopulation [1, 2], the comparison of prices of detection between different cancer types is largely unknown. Herein, we evaluate the prevalence of genomic alterations, the likelihood of detecting mutations and copy number alterations (CNAs) in actionable genes, and the relevant prices for detecting these alterations in several cancer types. This study aims to help researchers and practitioners understand the costs of identifying theoretically actionable alterations in multiple tumor types.

RESULTS

Table 1 shows the prevalence of testable mutations that were theoretically or pharmaceutically actionable and the average price for identifying one patient with
mutations in actionable genes by cancer type. Among 986 breast cancer patients in TCGA data, 586 (59%) had mutations in genes that were theoretically actionable and tested in the FoundationOne test. The frequency of mutations in theoretically actionable genes ranged from 25% in ovarian cancer to 93% in endometrial cancer. The price ranged from $22,907 in ovarian cancer to $6,254 in endometrial cancer. The prevalence of testable mutations in pharmaceutically actionable genes is relatively lower. The frequency of mutations in pharmaceutically actionable genes ranged from 10% in ovarian cancer to 72% in endometrial cancer, with corresponding price ranging from $55,556 in ovarian cancer to $8,035 in endometrial cancer.

Table 2 shows the prevalence of testable CNAs that were theoretically or pharmaceutically actionable and the price for identifying at least one actionable CNA. Notably, the rate of CNAs in theoretically actionable genes varied significantly by disease, from 475 (83%) of 571 glioblastoma multiforme patients to 15 (3%) of 504 clear cell renal cell carcinoma patients. Similarly, the prevalence of mutations in pharmaceutically actionable genes also varied substantially from 55% in glioblastoma multiforme patients to 1% in kidney clear cell carcinoma. Table 3 shows the prevalence of testable mutations and CNAs combined. In this table, we considered any patient who had at least one testable mutation or CNA as one actionable case. The table shows a higher prevalence and lower price than the first two tables. The prevalence of theoretically actionable mutations or CNAs was above 80% for all cancer types we studied except clear cell renal cell carcinoma where the prevalence was 50%. Endometrial cancer patients had the highest prevalence of 98%. Accordingly, the price ranged from $5,897 to $11,572 to identify one patient with theoretically actionable alterations. The prevalence of mutations or CNAs pharmaceutically actionable showed a similar pattern.

DISCUSSION

In this study we found significant variations in the prevalence of actionable gene mutations and CNAs among different types of tumors. This finding is in line with previous studies using hot-spot mutation testing platforms [7, 8]. However, for all the cancer types that we considered, the majority of patients had theoretically actionable gene mutations or CNAs that can be detected in one commercially available genomic test panel. In this paper, we focused on the next generation sequencing gene panels and did not consider routine tumor molecular profiling that may involve multiple assessments, each of which targets a single gene or type of mutation (e.g. HER2, BRCA1, BRCA2 in breast cancer, and EGFR, HER2, KRAS, and ALK in lung cancer). Although the price of a single gene test may be lower, it is likely that when traditional methods are used for multiple assessments, a larger quantity of DNA is needed and it leads to longer turnaround time. Given the rapidly growing number of genes tested in genomic test panels, we expect that the proportion of patients with testable and actionable gene mutations or CNAs will continue to grow. The number of targeted therapies has been growing rapidly in recent years. The targeted therapies in use today may cost 10,000
The genomic testing results can steer physicians and patients towards the experimental treatments that may be effective and away from the treatments that are unlikely to be effective for that patient. Combining the growing number of genes tested in panels with the growing number of expensive treatments can lead to significant cost savings. For example, the average cost for identifying one patient that has testable and actionable gene(s) based on FoundationOne test list price is approximately $8,049.

Cost/case* indicates the average cost for identifying one patient that has testable and actionable gene(s) based on FoundationOne test list price.

Table 2: Prevalence of Actionable Copy Number Alterations by Cancer Type

| Cancer Type                       | Total Number of Patients | Theoretically Actionable |Pharmaceutically Actionable |
|-----------------------------------|--------------------------|--------------------------|-----------------------------|
|                                   | Frequency | Percentage | Cost/case* | Frequency | Percentage | Cost/case* |
| Breast                            | 1033       | 535        | 51.8      | 11,199    | 281        | 27.2      | 21,324     |
| colon adenocarcinoma              | 427        | 144        | 33.7      | 17,200    | 66         | 15.5      | 37,516     |
| lung adenocarcinoma               | 493        | 175        | 35.5      | 16,338    | 67         | 13.6      | 42,678     |
| lung squamous cell carcinoma      | 489        | 326        | 66.7      | 8,700     | 228        | 46.6      | 12,438     |
| Ovarian                           | 569        | 410        | 72.1      | 8,049     | 224        | 39.4      | 14,732     |
| glioblastoma multiforme           | 571        | 475        | 83.2      | 6,972     | 316        | 55.3      | 10,481     |
| endometrial cancer                | 504        | 132        | 26.2      | 22,146    | 54         | 10.7      | 54,155     |
| kidney clear cell carcinoma       | 504        | 15         | 3.0       | 194,631   | 5          | 1.0       | 585,859    |
| head and neck cancer              | 388        | 204        | 52.6      | 11,031    | 90         | 23.2      | 25,000     |

Table 3: Prevalence of Either Actionable Mutations or Actionable CNAs by Cancer Type

| Cancer Type                       | Total Number of Patients | Theoretically Actionable | Pharmaceutically Actionable |
|-----------------------------------|--------------------------|--------------------------|-----------------------------|
|                                   | Frequency | Percentage | Cost/case* | Frequency | Percentage | Cost/case* |
| breast                            | 962       | 791        | 82.2      | 7,054     | 568        | 59.0      | 9,824      |
| colon adenocarcinoma              | 152       | 142        | 93.4      | 6,209     | 118        | 77.6      | 7,471      |
| lung adenocarcinoma               | 172       | 161        | 93.6      | 6,197     | 132        | 76.7      | 7,558      |
| lung squamous cell carcinoma      | 178       | 170        | 95.5      | 6,073     | 141        | 79.2      | 7,322      |
| ovarian                           | 311       | 254        | 81.7      | 7,102     | 140        | 45.0      | 12,883     |
| glioblastoma multiforme           | 273       | 266        | 97.4      | 5,952     | 211        | 77.3      | 7,504      |
| endometrial cancer                | 242       | 238        | 98.4      | 5,897     | 188        | 77.7      | 7,466      |
| kidney clear cell carcinoma       | 415       | 208        | 50.1      | 11,572    | 86         | 20.7      | 27,992     |
| head and neck cancer              | 302       | 278        | 92.1      | 6,301     | 171        | 56.6      | 10,244     |

Cost/case* indicates the average cost for identifying one patient that has testable and actionable gene(s) based on FoundationOne test list price.
targeted drug therapies and the trend of falling prices for genomic tests, genomic testing is poised to become more cost-effective when the entire course of treatment is taken into account.

This study has several limitations. First, the prevalence of gene mutations and CNAs was based on TCGA data, which may not reflect advanced/metastatic disease. Second, mutations may differ in their functional impact, and thus not all mutations in actionable genes are actionable. Third, not all theoretically actionable alterations are actionable in the context of the specific disease or genomic co-alterations. Fourth, KRAS was considered actionable in our analyses, which may inflate the prevalence of actionable genes. Fifth, we focused on mutations and CNAs only, without taking fusions into account; use of assays such as FoundationOne which provide not only mutation and CNA but also fusion information and common fusions, would increase the prevalence of actionable genomes. Finally it is important to recognize that the actual actionability for patients depends heavily on the trial availability [9]. Nevertheless, this is the first study that aims at understanding the costs of identifying actionable alterations using a genomic testing panel.

MATERIALS AND METHODS

We downloaded the most recent data from The Cancer Genome Atlas (TCGA) via the TCGA Data Portal [3]. TCGA provides data on clinical information, genomic characterization, and high-level sequence analysis of tumor genomes. In this study, we examined both somatic mutations and CNAs for nine cancer types: breast cancer, colon adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, ovarian cancer, glioblastoma multiforme, endometrial cancer, clear cell renal cell carcinoma, and head and neck cancer. For each cancer type, we determined the prevalence of specific somatic mutations and CNAs using TCGA data. Of note the TCGA data included a sample of patients with somatic mutation information, a sample of patients with CNA information and another subsample of patients with both somatic mutation and CNA information. We were not able to identify copy-neutral loss of heterozygosity (LOH) since this type of data was not provided by TCGA analysis group. Notice that we used curated TCGA somatic SNV mutation data instead of pipeline-generated SNV in this study. We only used focal copy number alterations, which were generated by GISTIC analysis. For the prevalence of CNAs, we used conservative thresholds to define copy number amplification and deletion. More specifically, if the copy number was above 6, the patient was considered to have copy number amplification, and if the copy number was below 1, the patient was considered to have copy number deletion; otherwise, the patient was considered to have non-significant CNAs. Such cutoffs are in line with reporting thresholds for next generation sequencing gene panels such as FoundationOne testing, on which we focus in our price calculation.

After establishing the prevalence of mutations and CNAs for the different cancer types that we studied, we matched it with the list of mutations that are testable in FoundationOne to obtain the prevalence of “testable” mutations and CNAs. We chose FoundationOne because it is a commonly used commercial genomic testing panel and because it is the only genomic testing panel currently available on the market with clear information on price and the list of genes that are covered in the test panel [4]. Starting from this testable list, we established the prevalence of “actionable” mutations and CNAs so as to arrive at a list that was both testable and actionable. Here, we distinguished between amplification and deletion for CNAs. Genes were determined as theoretically actionable if a FDA-approved or clinically available investigational drug either directly or indirectly targets the gene, as previously described [5]. For each gene under consideration, public Web sites (NCI Drug Dictionary, NCI Thesaurus, Selleckchem, Medkoo, DGIdb, PubMed, and ClinicalTrials.gov) were consulted to identify drugs that target the encoded protein at clinically relevant IC50 values, as determined experimentally. PubMed was used to search for relevant literature that demonstrated either preclinical or clinical sensitivity of the drug to genetic alterations in the gene of interest. Drugs targeting proteins downstream of the gene of interest (indirect targets) were also identified in this manner with corroborating published literature indicating their sensitivity to genetic alterations in the gene of interest. Potentially actionable genes are listed in Table 4. As the impact of genomic analysis on therapeutic decisions may differ depending on specific genes, we have also included a table (Table 5) that shows the five most frequently observed mutations for each tumor type to allow researchers to best assess the prevalence of actionable genes.

Further, we examined a smaller list of “pharmaceutically actionable” genes as this is important for the clinical implementation of biomarker-based therapy [5]. These included genes that have already been linked to FDA-approval of a drug (e.g. BRAF inhibitors), and gene variants known to affect drug effectiveness or toxicity, and that affect dosing guidelines and/or drug label information. This list is derived from genes that have well-known pharmacogenomics associations with drugs available on the market based on the Pharmacogenomics Knowledgebase [6]. We provided the list of pharmaceutically actionable genes with the corresponding drugs in the Supplementary Table S1.

Finally, we calculated the average price of identifying one patient with actionable alterations, using the list price of FoundationOne ($5,800) divided by the proportion of patients with at least one actionable
| Gene     | Potential therapeutic implications                                                                 | Mutations | Amplification | Deletion |
|----------|-----------------------------------------------------------------------------------------------------|------------|---------------|----------|
| ABL1     | Treatment with ABL or BCR-ABL inhibitors                                                           | Yes        | Yes           | No       |
| ABL2     | Treatment with ABL inhibitors                                                                     | Yes        | Yes           | No       |
| AKT1     | Treatment with AKT or mTOR inhibitors                                                              | Yes        | Yes           | No       |
| AKT2     | Treatment with AKT or mTOR inhibitors                                                              | Yes        | Yes           | No       |
| AKT3     | Treatment with AKT or mTOR inhibitors                                                              | Yes        | Yes           | No       |
| ALK      | Treatment with ALK inhibitors                                                                     | Yes        | Yes           | No       |
| AR*      | Resistance to anti-hormone therapy                                                                 | Yes        | Yes           | No       |
| ATM      | Treatment with PARP inhibitors                                                                    | Yes        | No            | Yes      |
| ATR      | Treatment with PARP inhibitors                                                                    | Yes        | No            | Yes      |
| AURKA    | Treatment with AURKA inhibitors                                                                    | Yes        | Yes           | No       |
| AURKB    | Treatment with AURKB inhibitors                                                                    | Yes        | Yes           | No       |
| BAP1     | Treatment with HDAC inhibitors                                                                     | Yes        | No            | Yes      |
| BCL2     | Treatment with BCL2 inhibitor and potential resistance to mTOR inhibitors                           | Yes        | Yes           | No       |
| BRAF     | Treatment with BRAF inhibitors                                                                     | Yes        | Yes           | No       |
| BRCA1    | Treatment with PARP inhibitors                                                                    | Yes        | No            | Yes      |
| BRCA2    | Treatment with PARP inhibitors                                                                    | Yes        | No            | Yes      |
| CCND1    | Treatment with CDK 4/6 inhibitors                                                                   | Yes        | Yes           | No       |
| CCND2    | Treatment with CDK 4/6 inhibitors                                                                   | Yes        | Yes           | No       |
| CCND3    | Treatment with CDK 4/6 inhibitors                                                                   | Yes        | Yes           | No       |
| CCNE1    | Treatment with CDK 2 Inhibitors                                                                    | Yes        | Yes           | No       |
| CDK4     | Treatment with CDK 4/6 inhibitors                                                                   | Yes        | Yes           | No       |
| CDK6     | Treatment with CDK 4/6 inhibitors                                                                   | Yes        | Yes           | No       |
| CDKN1B   | Treatment with CDK 2 Inhibitors                                                                    | Yes        | No            | Yes      |
| CDKN2A   | Treatment with CDK 4/6 inhibitors                                                                   | Yes        | No            | Yes      |
| CDKN2B   | Treatment with CDK 4/6 inhibitors                                                                   | Yes        | No            | Yes      |
| CDKN2C   | Treatment with CDK 4/6 inhibitors                                                                   | Yes        | No            | Yes      |
| CHEK2    | Treatment with Chk2 inhibitor                                                                     | Yes        | Yes           | No       |
| CSF1R    | Treatment with CSF1R monoclonal antibody and inhibitors                                            | Yes        | Yes           | No       |
| DDR2     | Treatment with DDR2 inhibitor                                                                      | Yes        | Yes           | No       |
| DNMT3A   | High risk” factor of myelodysplastic or myeloproliferative disorders required for trial enrollment. | Yes        | No            | No       |

(Continued)
| Gene             | Potential therapeutic implications                                                                 | Actionability | Mutations | CNAs       |
|------------------|--------------------------------------------------------------------------------------------------|---------------|-----------|------------|
| DOT1L            | Treatment with DOT1L inhibitor                                                                    |               | Yes       | Yes        | No         |
| EGFR             | Treatment with EGFR inhibitors                                                                   |               | Yes       | Yes        | No         |
| EPHA3*           | Treatment with Dasatinib                                                                        |               | Yes       | Yes        | No         |
| ERBB2 (HER2)     | Treatment with HER2 inhibitors, monoclonal antibodies, and targeted vaccines                     |               | Yes       | Yes        | No         |
| ERBB3 (HER3)     | Treatment with HER3 inhibitors                                                                   |               | Yes       | Yes        | No         |
| ERBB4 (HER4)     | Treatment with HER4 inhibitors                                                                   |               | Yes       | Yes        | No         |
| ESR1             | Anti-hormone resistance                                                                         |               | Yes       | No         | No         |
| FGF10            | Trial enrollment                                                                                |               | Yes       | Yes        | No         |
| FGF14            |                                                                                                 |               |           |            |            |
| FGF19            |                                                                                                 |               |           |            |            |
| FGF23            |                                                                                                 |               |           |            |            |
| FGF3             |                                                                                                 |               |           |            |            |
| FGF4             |                                                                                                 |               |           |            |            |
| FGF6             |                                                                                                 |               |           |            |            |
| FGFR1            | Treatment with FGFR1 inhibitors                                                                  |               | Yes       | Yes        | No         |
| FGFR2            | Treatment with FGFR2 inhibitors                                                                  |               | Yes       | Yes        | No         |
| FGFR3            | Treatment with FGFR3 inhibitors                                                                  |               | Yes       | Yes        | No         |
| FGFR4            | Treatment with FGFR4 inhibitors                                                                  |               | Yes       | Yes        | No         |
| FLT1             | Treatment with FLT1 inhibitors                                                                   |               | Yes       | Yes        | No         |
| FLT4             | Treatment with FLT4 inhibitors                                                                   |               | Yes       | Yes        | No         |
| GNA11            | Treatment with PKC and MEK inhibitors                                                             |               | Yes       | Yes        | No         |
| GNAQ             | Treatment with PKC and MEK inhibitors                                                             |               | Yes       | Yes        | No         |
| HGF              | Treatment HGF monoclonal antibody                                                                  |               | Yes       | No         | No         |
| HRAS             | Treatment with MEK Inhibitors                                                                    |               | Yes       | Yes        | No         |
| IGF1R            | Treatment with IGF1R monoclonal antibodies or inhibitors                                         |               | Yes       | Yes        | No         |
| IGF2             | Treatment with IGF1R monoclonal antibodies or inhibitors                                         |               | Yes       | Yes        | No         |
| JAK1             | Treatment with JAK inhibitors                                                                    |               | Yes       | Yes        | No         |
| JAK2             | Treatment with JAK inhibitors                                                                    |               | Yes       | Yes        | No         |
| JAK3             | Treatment with JAK inhibitors                                                                    |               | Yes       | Yes        | No         |
| KDR              | Treatment with KDR inhibitors                                                                    |               | Yes       | Yes        | No         |
| KIT              | Treatment with KIT inhibitors                                                                    |               | Yes       | Yes        | No         |
| KRAS             | Treatment with MEK Inhibitors                                                                    |               | Yes       | Yes        | No         |
| MAP2K1           | Treatment with MEK Inhibitors                                                                    |               | Yes       | Yes        | No         |

(Continued)
| Gene       | Potential therapeutic implications                                                                 | Actionability |
|------------|------------------------------------------------------------------------------------------------------|---------------|
|            |                                                                                                      | Mutations | Amplification | Deletion |
| MAP2K2     | Treatment with MEK Inhibitors                                                                       | Yes        | Yes          | No       |
| MAP2K4     | Treatment with JNK1 inhibitor                                                                       | Yes        | Yes          | No       |
| MAP3K1     | Treatment with JNK1 inhibitor                                                                       | Yes        | Yes          | No       |
| MDM2       | Treatment with MDM2 inhibitor or Nutlins that inhibit MDM2-p53 interaction.                          | Yes        | Yes          | No       |
| MET        | Treatment with MET inhibitors                                                                      | Yes        | Yes          | No       |
| MPL*       | Treatment with JAK2 inhibitors.                                                                     | Yes        | No           | No       |
| MTOR       | Treatment with mTOR inhibitors                                                                      | Yes        | Yes          | No       |
| MYCN       | Treatment with BET inhibitors                                                                      | Yes        | Yes          | No       |
| NF1        | Treatment with PI3K pathway inhibitors (PI3K/ALK/MTOR), MAPK pathway inhibitors (RAF/MEK/ERK), or HSP90 inhibitors | Yes        | No           | Yes      |
| NF2        | Treatment with PI3K pathway inhibitors (PI3K/ALK/MTOR), MAPK pathway inhibitors (RAF/MEK/ERK), or HSP90 inhibitors | Yes        | No           | Yes      |
| NOTCH1     | Treatment with Gamma Secretase inhibitors (GSIs)                                                    | Yes        | Yes          | No       |
| NOTCH2     | Treatment with GSIs                                                                                  | Yes        | Yes          | No       |
| NOTCH3     | Treatment with GSIs                                                                                  | Yes        | Yes          | No       |
| NPM1       | Correlate with positive response to all-trans retinoic acid therapy and chemotherapy in AML.        | Yes        | No           | No       |
| NRAS       | Treatment with MEK inhibitors                                                                       | Yes        | Yes          | No       |
| NTRK1      | Treatment with NTRK1 (TrkA) inhibitor                                                                | Yes        | Yes          | No       |
| NTRK2      | Treatment with NTRK2 (TrkB) inhibitor                                                                | Yes        | Yes          | No       |
| NTRK3      | Treatment with NTRK3 (TrkC) inhibitor                                                                | Yes        | Yes          | No       |
| PDGFRA     | Treatment with PDGFRA inhibitors                                                                     | Yes        | Yes          | No       |
| PDGFRB     | Treatment with PDGFRA inhibitors                                                                     | Yes        | Yes          | No       |
| PIK3CA     | Treatment with PI3K, AKT, or mTOR inhibitors                                                          | Yes        | Yes          | No       |
| PIK3CB     | Treatment with PIK3CB inhibitors                                                                     | Yes        | Yes          | No       |
| PIK3R1     | Treatment with PI3K, AKT or mTOR inhibitors                                                          | Yes        | No           | No       |
| PIK3R2     | Trial selecting for mutations                                                                        | Yes        | No           | No       |
| PTCH1      | Treatment with SMO inhibitors                                                                        | Yes        | No           | Yes      |

(Continued)
| Gene       | Potential therapeutic implications                                                                 | Actionability | Mutations | Amplification | Deletion |
|------------|--------------------------------------------------------------------------------------------------|---------------|-----------|---------------|----------|
| PTEN       | Treatment with p110beta, AKT, or mTOR inhibitors                                                 |               | Yes       | No            | Yes      |
| PTPN11     | Treatment with MEK Inhibitors                                                                    |               | Yes       | Yes           | No       |
| RAD50      | Treatment with PARP inhibitors                                                                   |               | Yes       | No            | Yes      |
| RAF1       | Potential resistance to RAF inhibitors                                                          |               | Yes       | Yes           | Yes      |
|            | Treatment with MEK inhibitors                                                                    |               |           |               |          |
| RET        | Treatment with Ret inhibitors                                                                    |               | Yes       | Yes           | No       |
| SMO        | Treatment with SMO inhibitors                                                                    |               | Yes       | Yes           | No       |
| SRC        | Treatment with SRC inhibitors                                                                    |               | Yes       | Yes           | No       |
| STK11      | Treatment with mTOR or AMPK inhibitors                                                           |               | Yes       | No            | Yes      |
| SYK        | Treatment with Syk inhibitors                                                                    |               | Yes       | Yes           | No       |
| TOP2A*     | Treatment with topoisomerase 2A inhibitors                                                       |               | Yes       | Yes           | Yes      |
| TSC1       | Treatment with mTOR inhibitors                                                                    |               | Yes       | No            | Yes      |
| TSC2       | Treatment with mTOR inhibitors                                                                    |               | Yes       | No            | Yes      |

Note. Genes were determined as theoretically actionable if there is an FDA-approved or clinically available investigational drug that either directly or indirectly targets the gene as previously described.
*Borderline classification as actionable.

Table 5: Top five most common mutations by cancer type

| Cancer type                  | Gene    | Percentage |
|------------------------------|---------|------------|
| breast                       | PIK3CA  | 32.05%     |
|                              | MAP3K1  | 7.10%      |
|                              | PTEN    | 3.55%      |
|                              | MAP2K4  | 3.25%      |
|                              | NF1     | 2.74%      |
| colon adenocarcinoma         | KRAS    | 37.66%     |
|                              | PIK3CA  | 16.88%     |
|                              | ATM     | 13.64%     |
|                              | BRAF    | 12.99%     |
|                              | NRAS    | 9.74%      |
| Lung adenocarcinoma          | KRAS    | 24.19%     |
|                              | NF1     | 11.29%     |
|                              | EGFR    | 10.89%     |
|                              | KDR     | 10.48%     |

(Continued)
alteration. Of note, we focused on the price of detecting “actionable patients”. If the patient had more than one mutation, he/she would still be counted as one. By doing this, we avoided the problem of overestimating the number of patients detected for actionable genes.

The Institutional Review Board at The University of Texas MD Anderson Cancer Center approved this study and waived the requirement for patient consent.

| Cancer type                          | Gene   | Percentage |
|--------------------------------------|--------|------------|
| Lung squamous cell carcinoma         | HGF    | 10.08%     |
|                                      | PIK3CA | 15.17%     |
|                                      | CDKN2A | 14.61%     |
|                                      | NF1    | 11.80%     |
|                                      | NOTCH1 | 7.87%      |
|                                      | PTEN   | 7.87%      |
| Ovarian                              | NF1    | 2.53%      |
|                                      | BRCA1  | 2.22%      |
|                                      | BRCA2  | 2.22%      |
|                                      | EGFR   | 1.90%      |
|                                      | KIT    | 1.58%      |
| Glioblastoma multiforme              | PTEN   | 30.74%     |
|                                      | EGFR   | 26.15%     |
|                                      | PIK3R1 | 11.31%     |
|                                      | PIK3CA | 10.60%     |
|                                      | NF1    | 10.25%     |
| Endometrial cancer                   | PTEN   | 64.92%     |
|                                      | PIK3CA | 53.23%     |
|                                      | PIK3R1 | 33.47%     |
|                                      | KRAS   | 21.37%     |
|                                      | FGFR2  | 12.50%     |
| Kidney clear cell carcinoma          | BAP1   | 8.55%      |
|                                      | MTOR   | 5.09%      |
|                                      | PTEN   | 3.67%      |
|                                      | ATM    | 2.44%      |
|                                      | PIK3CA | 2.44%      |
| Head and neck cancer                 | CDKN2A | 21.57%     |
|                                      | PIK3CA | 20.92%     |
|                                      | NOTCH1 | 19.28%     |
|                                      | ATR    | 5.88%      |
|                                      | NOTCH2 | 5.23%      |

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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