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Precision medicine of rare tumors: uncovering the potential actionable targets through genomic profiling

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Abstract

Rare tumors constitute a substantial portion of cancer diagnoses, however, research remains limited. To assess the utility of genomic testing for informing treatment decisions, we retrospectively evaluated the landscape of actionable genomic alterations and immune biomarkers in rare tumors. Genomic and clinical data from 42,569 patients with rare tumors, representing 137 cancer types and 15 classification systems, were obtained from public studies available on cBioPortal. Actionability was assessed using the CCBM knowledgebase. In this cohort, *TP53* (16.5%), *CDKN2A* (5.0%), *ATRX* (4.6%), *RB1* (4.2%), and *DNMT3A* (4.1%) were the most frequently mutated genes. At least one potential actionable biomarker was identified in 24.7% of patients with rare tumors, with considerable variation observed across cancer types (highest in Lung tumors [55.0%] and lowest in Thymic tumors [8.7%]). The actionable rates for approved/national guideline-recommended indications, clinical trial/biological evidence-supported indications, and off-label indications were 8.7% ($n = 3,713$), 5.4% ($n = 2,292$), and 10.6% ($n = 4,513$), respectively. High tumor mutation burden (4.3%, 1,046/24,354) and microsatellite instability (0.9%, 122/13,013) were infrequent in rare tumors, although the former was relatively common in Skin tumors (28.2%, 256/909). Additionally, copy number alterations that potentially indicating actionable proteomic biomarkers, such as *CD274* amplification, were detected in 277 patients. Complex cases involving multiple actionable biomarkers (3.8%, $n = 1,602$) and drug resistance mutations (24.2%, $n = 10,299$) were also identified. In conclusion, a significant proportion of patients with rare tumors harbor actionable biomarkers, supporting the potential clinical value of comprehensive genomic profiling. Prospective validation is still warranted. Further, molecular tumor board discussions are advised to interpretate complicated test results.

Keywords: Biomarker, personalized medicine, precision oncology, rare cancers, rare malignancies

INTRODUCTION

Rare tumors account for a large proportion of all cancer diagnoses. In Europe and the United States (US), rare cancers accounted for 20%-25% of diagnosed cancers^[1-3]. However, research on each cancer type is still severely lacking, leading to poor prognosis in rare tumor patients^[2-4]. The definition of rare tumors varies across regions, indicating differences in epidemiological backgrounds and healthcare priorities. In the US, the National Cancer Institute (NCI) defines rare cancers as those with an annual incidence of fewer than 15 cases per 100,000 individuals and those that affect fewer than 40,000 individuals^[5,6]. In Europe, RARECARENet sets the threshold at less than 6 cases per 100,000 per year^[7,8]. China has adopted a stricter definition: Rare tumors are defined as tumors with an annual incidence rate of fewer than 2.5 cases per 100,000^[9]. The regional heterogeneity of this definition not only complicates cross-border comparisons, but also emphasizes the necessity of adopting tailored approaches to rare tumor research and clinical management.

The clinical management of rare tumors is full of special challenges^[10]. Because of their low incidence, large-scale randomized controlled trials are often infeasible, leading to a lack of high-quality evidence to guide treatment decisions. Nearly 50% of rare tumors lack established clinical practice guidelines or standardized treatment recommendations^[9]. Therefore, rare tumor patients often receive treatments inferred from common cancer types, but the efficacy is limited^[11,12], indicating an urgent need for precise treatment strategies.

Precision oncology has become an encouraging approach to address these issues by tailoring treatment plans based on the molecular characteristics of individual tumors^[13]. The paradigm shift from organ- or histology-based therapy to molecular-guided therapy has a particular impact on rare cancers, which may be defined by unusual histology, anatomical sites, or uncommon molecular subtypes. Comprehensive genomic profiling (CGP) can identify actionable genomic alterations that may be targeted by drugs approved by

regulatory authorities such as the US Food and Drug Administration (FDA) and/or the National Medical Products Administration (NMPA), thereby providing therapeutic opportunities^[14,15]. Despite advances in detection technologies (e.g. next-generation sequencing) and the expansion of precision therapies (e.g. tumor-agnostic agents) that are changing the treatment landscape of common cancers, rare tumors remain a major challenge in modern oncology^[5,11]. The interpretation of genomic alterations requires a robust, up-to-date knowledgebase that accurately matches detected variations with approved or investigational therapies, while considering the evidence level and cancer type. In addition, complex situations, including co-occurring mutations, resistance-associated mutations, and even multi-omics biomarkers, can complicate clinical decision-making. In rare tumor environments where clinical experience is limited, these issues are magnified and off-label drug use may be the only available option.

To explore opportunities for biomarker-driven therapy, we conducted a systematic analysis of actionable genomic alterations and immune biomarkers in patients with rare tumors. In this study, we characterized the genomic landscape of rare tumors and estimated the proportion of patients who may benefit from targeted therapy or immunotherapy, aiming to inform clinical practice and support the inclusion of CGP in the routine management of rare tumors.

METHODS

Definition and classification of rare tumors

The definition of rare tumors is primarily based on Wang *et al.*^[9,16], who defined rare tumors in China as cancer types with an annual incidence rate of fewer than 2.5 per 100,000. To update the list of rare tumors, our expert group added several new entities, including Mesothelioma^[17-20], Thymic epithelial tumors^[21], and NUT carcinoma^[22], and additional cancer types from the Rare tumor list of China^[23]. The final list comprises 137 cancer types, which are classified into 15 tumor systems according to their primary anatomical sites and/or histopathological features [Supplementary Table 1].

Data source and patient selection

Genomic and clinical data were obtained from cBioPortal public studies, including The Cancer Genome Atlas (TCGA) cohorts [Supplementary Table 2]. Inclusion criteria were as follows: (1) the cancer type met the specified definition of rare tumors; (2) genomic testing of at least 50 genes required; and (3) molecular profiling data included at least one qualified genomic data type, i.e. somatic mutations, copy number alterations, structural variations/gene fusions, tumor mutation burden (TMB), or microsatellite instability (MSI). Patients diagnosed with multiple types of primary cancer were excluded. Studies focusing on specific gene mutations (such as basket trials) and non-real-world studies (including cell lines, patient-derived xenografts, and organoids) were also excluded.

For each eligible patient, demographic characteristics (including age and gender), cancer type and histology, specimen type, genomic alteration profile (including somatic mutations, copy number alterations, and gene fusions), TMB, and MSI status were extracted. TMB was calculated as the total number of somatic non-synonymous mutations per megabase (Mb) of sequenced genome. If multiple TMB values were recorded for a patient, the median value was used as the individual's TMB. High TMB was defined as ≥ 10 mutations/Mb. MSI status was determined using standard genomic instability metrics.

Definition of actionability and resistance

Actionability and resistance were queried using the CCBM knowledgebase (version 30 June, 2026). A case is considered "Actionable" if the patient's genomic alterations and/or immune biomarkers match any intervention(s) in the knowledgebase, and the drug targets are related to the signaling pathways of the

detected biomarkers. If matching interventions are found only for cancer types different from the patient's diagnosis, the case is classified as "Off label". If no matching interventions are found, the case is classified as "Non-actionable". Only oncogenic mutations listed in the COSMIC database were considered.

Evidence levels are allocated as follows: Level 1 includes biomarker-driven indications approved by regulatory authorities (i.e. NMPA and FDA); Level 2 includes biomarker-driven indications recommended by national guidelines (i.e. CSCO, CACA, and NCCN); Level 3 includes biomarker-guided interventions supported by clinical trials with more than 10 cases; and Level 4 includes biomarker-guided interventions supported by case reports or by preclinical studies.

In the actionability analysis, single and compound biomarker(s) were evaluated separately, as some compound biomarkers have distinct medical interpretations. For example, third- and fourth-generation EGFR-TKIs are recommended for non-small cell lung cancer patients with *EGFR* T790M and C797S mutations, respectively, but when *EGFR* T790M and C797S (trans) co-mutated, combination therapy with first- and third-generation EGFR-TKIs is recommended instead^[24-26]. The analysis also considered the hierarchical relationships between cancer types and genomic alterations. For instance, interventions matching broader categories such as "Solid tumors" are also defined as "Actionable". Similarly, interventions for broader genomic alterations, such as *EGFR* exon 20 oncogenic mutations and *EGFR* PACC mutations, are considered "Actionable" for specific mutations like *EGFR* C797S. This approach helps avoid gaps in interpretation due to tumor-agnostic agents or common biomarkers.

Statistical analysis

The genomic landscape was conducted at the sample level and the actionability analyses were conducted at the patient level. Descriptive statistics were used to summarize patient characteristics. Median values with ranges represented continuous variables, while frequencies with percentages represented categorical variables. Bioinformatics analysis comprised coordinating clinical annotations, integrating and aggregating genomic mutation profiles, classifying TMB and MSI status, and identifying genes with recurrent alterations in each tumor classification system. Heatmaps plotted by ComplexHeatmap (Version 2.26.1) presented genomic discoveries at the sample level. Bar charts displayed the top mutated genes for each classification system. All analyses were performed using R software (Version 4.5.1) and Python (Version 3.11.3). Visualization was performed using basic R functions.

RESULTS

Patient characteristics

The final analysis included 44,790 samples from 42,569 rare tumor patients. [Supplementary Table 3](#) summarizes the demographic characteristics of the study cohort. There was a total of 137 cancer types, spanning 15 classification systems [[Supplementary Table 1](#)]. The top five cancer types were glioblastoma ($n = 3,439$), cancer of unknown primary ($n = 2,927$), neuroblastoma ($n = 2,753$), leiomyosarcoma ($n = 2,520$), and angiosarcoma ($n = 1,798$).

Genomic landscape

The overall mutational profile of rare tumors and the mutational profiles of each tumor classification system are shown in [Supplementary Figures 1](#) and [2](#), respectively. In our cohort, the most frequently mutated genes among all rare cancer types were *TP53* (16.5%), *CDKN2A* (5.0%), *ATRX* (4.6%), *RB1* (4.2%), and *DNMT3A* (4.1%). Among them, *TP53*, *NF1*, *PTEN*, *IDH1*, and *PIK3CA* were the most common potential actionable targets.

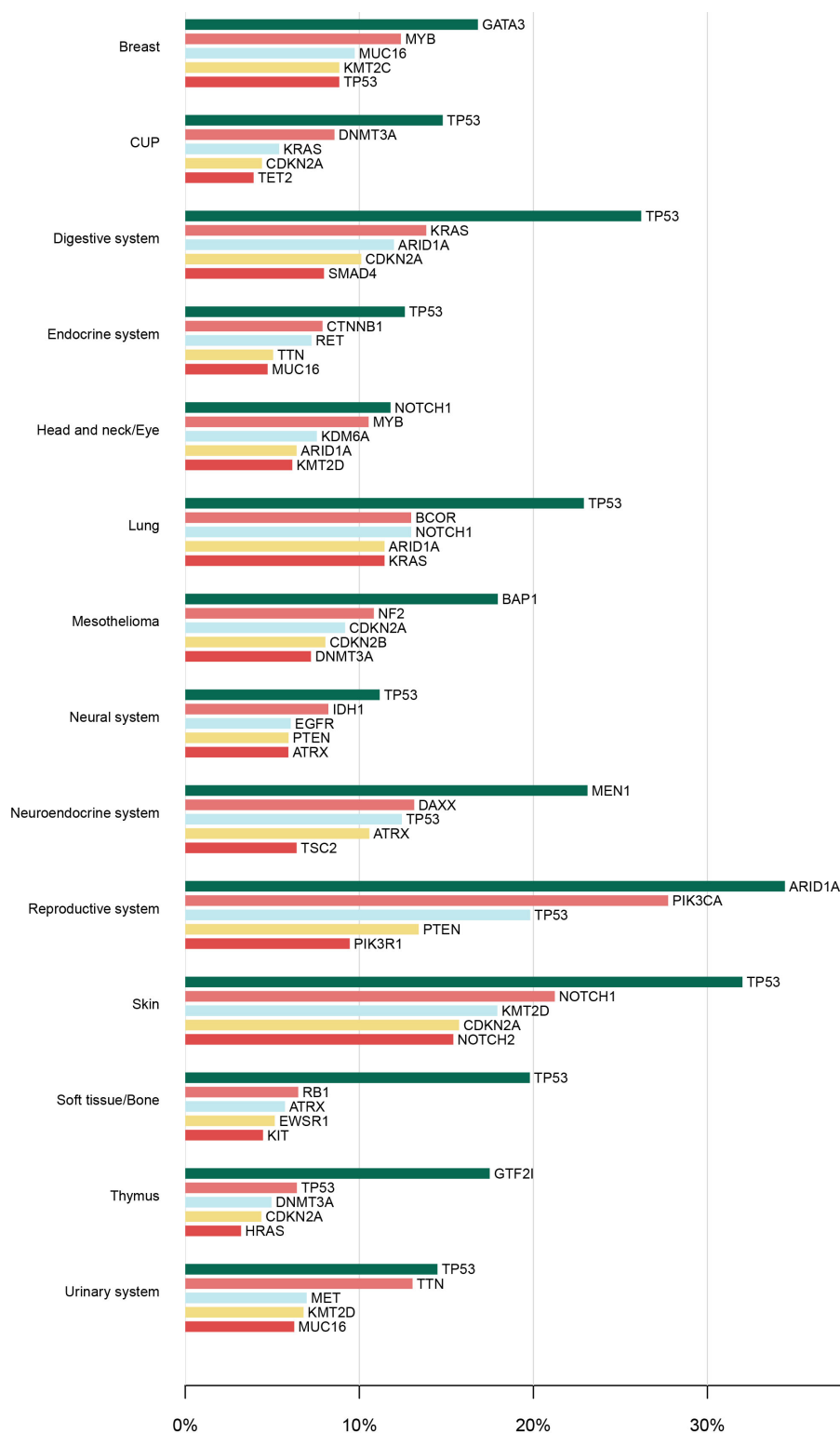


Figure 1. Top mutated genes by tumor classification system. NUT tumor was not shown as only one case was included. CUP: Cancer of unknown primary; NUT:

The top mutated genes in rare tumor patients stratified by tumor classification system were shown in [Figure 1](#). Tumors from different classification systems possessed unique mutational characteristics, with *GATA3*, *NOTCH1*, *BAP1*, *MEN1*, *ARID1A*, and *GTF2I* being the most prevalent mutated genes in Breast, Head and neck/Eye, Mesothelioma, Neuroendocrine system, Reproductive system, and Thymus tumors, respectively. *TP53* was the most prevalent mutated gene in the rest of the tumor classification systems.

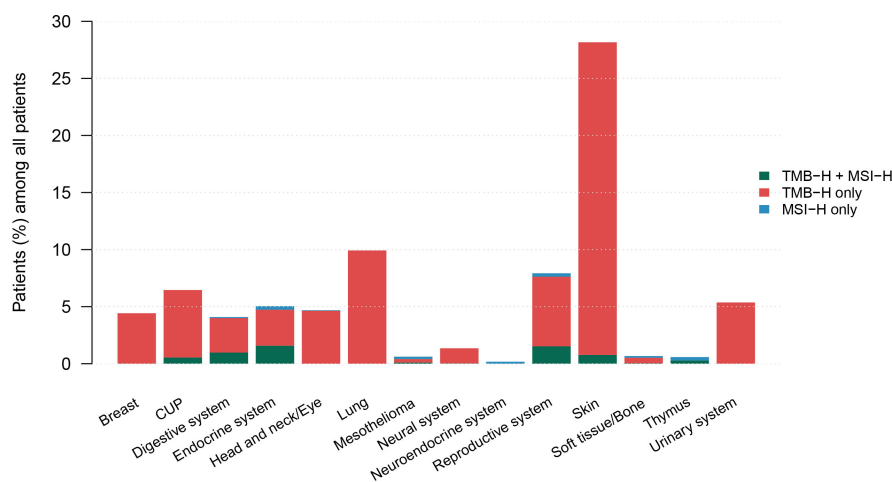


Figure 2. Immunotherapy biomarkers by tumor classification system. NUT tumor was not shown as only one case was included. Abbreviations: CUP: cancer of unknown primary; MSI-H: high microsatellite instability; TMB-H: high tumor mutation burden; NUT:

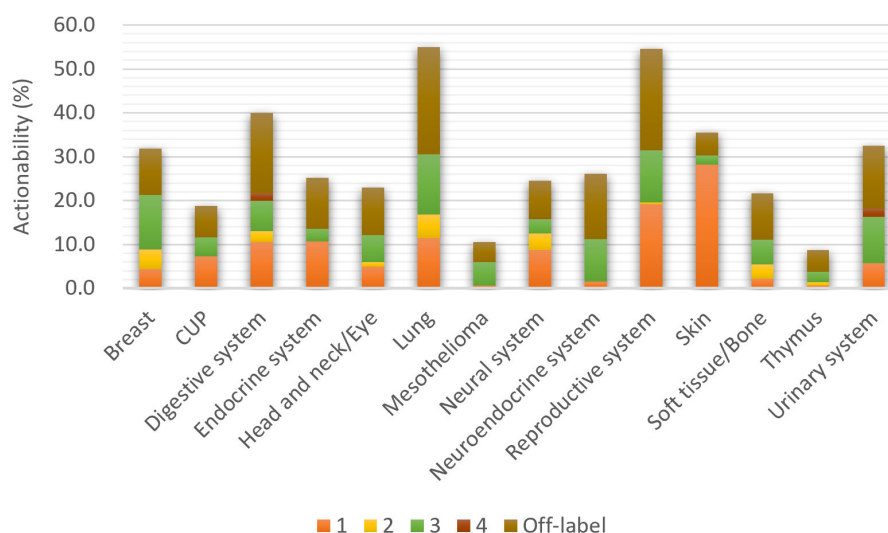


Figure 3. Proportion of actionable patients by evidence level. Evidence level 1 represents biomarker-driven indications approved by regulatory authorities; Level 2 represents biomarker-driven indications recommended by national guidelines; Level 3 represents biomarker-guiding interventions supported by clinical trials ($n > 10$); and Level 4 represents biomarker-guiding interventions supported by case reports ($n \leq 10$), or preclinical studies. NUT tumor was not shown as only one case was included. CUP: cancer of unknown primary; NUT:

The median TMB of rare tumors was 0.30 mutations/Mb (range: 0-510.47 mutations/Mb). Only 4.3% (1,046/24,354) and 0.9% (122/13,013) patients were classified as TMB-high and MSI-high, respectively. [Figure 2](#) shows the prevalence of actionable immune biomarkers (i.e., TMB-high and MSI-high) in rare tumor patients stratified by tumor classification system. The distribution of TMB and MSI status varied substantially across tumor classification systems, with Skin tumors (28.2%, 256/909) and Endocrine system tumors (1.9%, 6/317) exhibiting the highest rates of TMB-high and MSI-high, respectively.

Actionability analysis

[Figure 3](#) presents the proportion of rare tumor patients with actionable biomarkers identified, stratified by tumor classification system. In total, 24.7% (10,518/42,569) of patients harbored at least one potential actionable biomarker. When analysis was limited to biomarkers supported by high evidence levels (Level 1-2), the proportion decreased to 8.7% ($n = 3,713$). The actionable rates based on clinical trial/biological evidence and off-label indications were 5.4% ($n = 2,292$) and 10.6% ($n = 4,513$) for, respectively.

Among tumor classification systems, Lung tumors (55.0%, 72/131) exhibited the highest actionable rate, followed by Reproductive system (54.6%, 179/328), Digestive system (39.9%, 1,677/4,203), Skin (35.5%, 323/909), and Urinary system (32.6%, 182/559) tumors. With the exception of NUT carcinoma, which only included one case, Thymus tumors (8.7%, 30/343) demonstrated the lowest actionable rate. [Supplementary Table 4](#) provides a summary of the top mutated actionable genes and their corresponding possible therapeutic agents.

Additionally, several copy number alterations that may predict the expression of targetable proteins were identified. These alterations included: *CD274* amplification ($n = 50$, predicting PD-L1 overexpression), *KIT* amplification ($n = 24$, predicting CD117 overexpression), *ERBB2* amplification ($n = 127$, predicting HER2 overexpression), *PTEN* loss ($n = 7$, predicting PTEN deficiency), *BAP1* loss ($n = 38$, predicting BAP1 deficiency), *SMARCB1* loss ($n = 23$, predicting INI-1 deficiency), *CCND1* amplification ($n = 6$, predicting Cyclin D1 overexpression), *FGFR1* amplification ($n = 1$, predicting FGFR1 overexpression), and *HGF* amplification ($n = 1$, predicting HGF overexpression). It should be noted that these findings require validation through protein-based testing prior to informing treatment decisions.

Complex cases

Detailed case analyses revealed several complex situations that require special consideration. A total of 1,602 (3.8%) patients harbored two or more potential actionable biomarkers with the same evidence level. In such cases, it is important to consider combination therapy and prioritize treatment options. For example, two biliary tract cancer patients (Study ID: biliary_tract_msk_2026, Patient ID: P-0003289 & P-0011240) simultaneously detected *BRCA1/2* oncogenic mutation and *ERBB2* amplification, and one diffuse astrocytoma patient (Study ID: glioma_mskcc_2019, Patient ID: P-0019039) simultaneously detected *BARF* fusion and *IDH1* R132H mutation. To better interpretate these complicated results, molecular tumor board is recommended to tailor the treatment decision based on comprehensive information, including but not limited to multi-omics molecular test results, medical history, personal/family history, physical condition, and drug availability.

In addition, 10,299 (24.2%) patients harbored alterations related to targeted therapy resistance. The most frequently observed resistance-associated alterations included *TP53* (15.5%, $n = 6,590$, possibly resistant to ALK-TKI, Pemigatinib, and *etc.*), *PTEN* (3.0%, $n = 1,267$, possibly resistant to Adagrasib, Lorlatinib, and *etc.*), *KRAS* (2.6%, $n = 1,114$, possibly resistant to ALK-TKI, Cetuximab, and *etc.*), *NF1* (2.0%, $n = 854$, possibly resistant to Adagrasib, HER2-TKI, and *etc.*), and *MDM2* (1.5%, $n = 648$, possibly resistant to PD-(L)1 inhibitors). Notably, 59.5% (6,254/10,518) of patients with actionable biomarker(s) identified also exhibited co-occurring resistance alteration(s), which may limit the efficacy of targeted therapy. For example, an inflammatory myofibroblastic tumor patient (Study ID: sarcoma_mskcc_2022, Patient ID: P-0023268) had concurrent *ALK* fusion and *TP53* oncogenic mutation, indicating that ALK-TKI may be resistant; and a spindle cell carcinoma of lung patient (Study ID: msk_chord_2024, Patient ID: P-0011125) had concurrent *KRAS* G12C and *PTEN* oncogenic mutation, indicating that Adagrasib may be resistant.

DISCUSSION

In this study, the proportion of rare tumor patients with potential actionable biomarker identified was 24.7%, which was slightly higher than previously stated. Wang et al. analyzed the cBioPortal rare tumor cohort in 2020 and reported an actionable rate of 20.4%^[16]. This rising trend can be attributed to several factors. First, the number of approved indications and newly developed targeted therapies have increased in recent years. Since 2017, the FDA has approved nine pan-solid tumor indications^[27,28]. Novel targeted agents, such as Daraxonrasib (targeting *KRAS* G12X^[29]) and Rezatapopt (targeting *TP53* Y220C^[30,31]),

although still under clinical investigation, have made previously “undruggable” targets accessible. These advancements in drug development have expanded opportunities for precision medicine in rare tumor patients. Second, the updated knowledgebase enables a more extensive curation of actionable targets. The CCBM knowledgebase used in this study includes the hierarchical relationships of cancer types and genomic alterations, which helps to prevent omission of drug annotations related to tumor-agnostic agents and/or common biomarkers. Given the scarcity of rare tumors, it is not realistic to compare our results to real-world studies across all tumor classification systems. A recent study from Munich investigated the actionability of rare Endocrine and Neuroendocrine neoplasms^[32]. This study reported gene mutations similar to our results, including *KRAS* and *TP53*, partly confirming the reliability of these findings.

To enhance the identification of actionable targets in rare tumor patients, various strategies have been implemented to broaden matched interventions. The inclusion of investigational (evidence level 3-4) and off-label interventions has increased the proportion of patients with potential therapeutic options. A previous study indicated that approximately half of rare tumor patients do not meet the NCCN criteria for genetic testing^[33], suggesting that strict adherence to these guidelines may overlook numerous therapeutic opportunities. In our study, the actionable rates for investigational and off-label indications were 5.4% ($n = 2,292$), and 10.6% ($n = 4,513$), respectively. These patients may access novel drug treatments through participation in clinical trials. In fact, an Australian study reported that, with the assistance of molecular tests, nearly 80% of rare tumor patients were eligible for matching clinical trials^[34]. Additionally, immune biomarkers may be applicable to specific tumor types. According to our analysis, the incidence of TMB-high (4.3%) and MSI-high (0.9%) in rare tumor patients were lower compared to previously reported (15.5% and 7.4%, respectively^[35]). This discrepancy may result from differences in cancer type composition and racial backgrounds between cohorts. Although the overall detection rate was low, patients with Skin (28.2%, 256/909) and Lung (9.9%, 13/131) tumors exhibited a higher incidence of TMB-high and might benefit from immunotherapy. As research advances, the predictive value of immune biomarkers in rare tumors is becoming increasingly evident^[36,37]. Furthermore, copy number alterations predictive for actionable proteomic biomarkers, such as *CD274* amplification predicting for PD-L1 overexpression, may further expand the actionable rate. However, to avoid misinterpretation, the protein expression status of these patients should be confirmed through validation tests.

CGP has demonstrated significant benefits for rare tumor patients^[38]. Our findings further substantiate its role as a necessary tool in the management of rare tumors. Unlike common cancers, which have well-established treatment strategies, rare tumors usually lack standard-of-care options. Consequently, molecular testing becomes an essential step in guiding treatment decisions for these patients. The interpretation of genomic test report in rare tumors is particularly challenging due to limited clinical evidence and the presence of compound or resistance mutations. The establishment of a Molecular Tumor Board (MTB) specialized in rare tumors is strongly recommended. Such MTBs should comprise, at minimum, medical oncologists, pathologists, molecular biologists, clinical pharmacologists, and bioinformatics experts^[39]. MTB discussion offers multiple key advantages: (1) Genomic findings must be interpreted in the context of clinical factors such as patient characteristics, treatment history, and performance status, as isolated genomic alterations do not always translate into clinical benefit; (2) The use of cross-indication or off-label therapies, which may be the only available options for rare tumor patients, brings considerable uncertainties regarding efficacy and toxicity, MTB discussions can help assess these factors and prioritize treatment plans; (3) Many rare tumor patients may qualify for biomarker-driven clinical trials that are not widely publicized, and the MTB can facilitate the identification and enrollment in such trials; (4) Given the rarity of each tumor type, the MTB can serve as a central repository for real-world clinical experience, thereby generating evidence that may shape future treatment guidelines.

Several limitations of this study should be acknowledged. First, this was a retrospective analysis of existing genomic data, which introduced potential biases related to data quality, patient selection, and the absence of prospective clinical validation. Second, the study mainly relied on data from TCGA, which predominantly includes patients of North American and European ancestry. The generalizability of our findings to other populations, particularly Asian populations, where the mutational landscape of rare tumors may differ, warrants further investigation. Third, the genomic profiling panels used in the TCGA dataset varied in gene coverage. This variation may result in underestimation of actionable alterations in certain tumor types. Additionally, the differences in sequencing platforms, panel size, and analytical methods between studies may influence TMB estimates.

CONCLUSION

In conclusion, we demonstrated that a significant portion of rare tumors have potential actionable genomic alterations and immune biomarkers, indicating that genomic features can provide meaningful information for treatment selection in this underserved patient population. We suggest considering CGP as a standard component of the diagnostic workup for patients with rare tumors and reviewing molecular findings in the context of MTB to optimize precision treatment strategies. There is an urgent need for prospective studies and joint registration to validate these findings and generate the necessary evidence basis for developing treatment guidelines for rare tumors.

DECLARATIONS

Authors' contributions

Conception and design of the work: Lian B, Song Z, Xu, C.

Data acquisition and analysis: Lin G, Hao Y, Wang Q, Lu Y, Lv T, Zhu Y, Pan W, Zhang S, Guo Z, Pu X.

Main manuscript writing: Lin G, Hao Y, Wang Q.

All authors reviewed the manuscript.

Availability of data and materials

All authors declared that there are no conflicts of interest.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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