Quantifying the Expanding Landscape of Clinical Actionability for Patients with Cancer

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Conflicts of Interest

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Abstract

There is a continuing debate about the proportion of cancer patients that benefit from precision oncology, attributable in part to conflicting views as to which molecular alterations are clinically actionable. To quantify the expansion of clinical actionability since 2017, we annotated 47,271 solid tumors sequenced with the MSK-IMPACT clinical assay using two temporally distinct versions of the OncoKB knowledge base deployed 5 years apart. Between 2017 and 2022, we observed an increase from 8.9% to 31.6% in the fraction of tumors harboring a standard care (Level 1 or 2) predictive biomarker of therapy response and an almost halving of tumors carrying non-actionable drivers (44.2% to 22.8%). In tumors with limited or no clinical actionability, *TP53* (43.2%), *KRAS* (19.2%) and *CDKN2A* (12.2%) were the most frequently altered genes.

Statement of Significance

While clear progress has been made in expanding the availability of precision oncology-based treatment paradigms, our results suggest a continued unmet need for innovative therapeutic strategies, particularly for cancers with currently undruggable oncogenic drivers.

Introduction

The past 25 years have witnessed a dramatic expansion in the number of Food And Drug Administration (FDA)-approved cancer drugs, many of which are primarily or exclusively effective in biomarker defined populations (1). This expansion in precision-oncology cancer therapies has been driven by large-scale molecular profiling studies, advances in structure-based drug design and the development of next generation sequencing (NGS)-based diagnostic assays designed to simultaneously identify targetable genomic alterations in hundreds of cancer-associated genes (2–5). Equally important were innovations in clinical trial design such as basket studies that enabled the rapid testing of novel therapies in biomarker-selected patient cohorts across cancer types. The emergence of biomarker-centric trial design resulted in tumor agnostic drug (or drug combination) approvals for kinase inhibitors that target TRK/RET fusions and BRAF V600E, and pembrolizumab for microsatellite instability-high (MSI-H) or tumor mutation burden-high (TMB-H) tumors based on pan-cancer drug efficacies (6–13).

Despite the recent expansion in molecularly guided cancer therapies however, there remain conflicting views as to the fraction of patients with cancer that are eligible for these therapies, the clinical utility of universal tumor genomic profiling, and the impact of novel precision oncology drugs on patient outcomes. These conflicting views are in part the result of a lack of consensus as to what qualifies as a “clinically actionable” molecular alteration (14–16). To provide guidelines to rank molecular biomarkers by evidence-based clinical actionability, expert panels have been convened by the Association for Molecular Pathology (AMP), the American College of Medical Genetics and Genomics (ACMG), the American Society of Clinical Oncology (ASCO), and the College of American Pathologists (CAP) (3,17,18). Furthermore, to aid physicians in identifying the clinically relevant subset of genomic events, variant databases including MyCancerGenome, OncoKB, CIViC, JAX-CKB, PMKB, CGI and PCT have been developed (14,19–24). In some cases these knowledge bases have been integrated

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into clinical sequencing reporting workflows to allow clinicians to rapidly identify, in the point-of-care setting, genomic alterations which are predictive biomarkers of response to standard care therapies or eligibility criteria for trials of investigational therapies.

In this study, we reviewed all oncology drugs approved by the FDA since 1998 to determine whether each drug is most effective in a biomarker-defined population, targets a molecular alteration previously considered undruggable, or has a unique mechanism of action distinct from previously available therapies. We then quantified the recent expansion of clinical actionability through annotation of 47,271 clinically sequenced solid tumors using OncoKB versions from March 2017 and October 2022.

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Results

New precision oncology approvals (1998 to 2022)

To quantitate the impact of recent FDA drug approvals on the precision oncology landscape, we first reviewed the eligibility criteria for all FDA-approved oncology drugs beginning with the 1998 approval of trastuzumab up to 2022. Drug labels, consensus guidelines and the scientific literature were reviewed to determine whether molecular profiling was required to identify those patients most likely to benefit clinically. Since September 1998, 198 new oncology drugs were FDA-approved, of which 82.8% (n=164) were classified as molecularly targeted therapies based on the drug binding to or inhibiting a specific protein target. Non-targeted therapies (n=34, 17.2%) included cytotoxic chemotherapies, nucleoside metabolic inhibitors, and radiotherapies, among others. Fifty-two percent (n=86) of targeted therapies were classified as precision oncology drugs, as the use of these drugs is guided by pre-treatment biomarker testing. Among the 86 therapies classified as precision oncology drugs, 80.2% (n=69) had a genomic biomarker that could be detected by DNA-based next-generation sequencing (NGS) (**Figure 1a, Supplementary Table S1 and S2**). These therapies were most effective in tumors with alterations in 45 distinct genes, or in tumors exhibiting the MSI-H or TMB-H genomic signatures (**Table 1**).

We next determined whether each therapy could be considered first-in-class based on whether it targeted a molecular alteration previously not considered clinically actionable. For drugs targeting a previously actionable genomic alteration, we sub-classified each drug based on whether the drug-specific mechanisms of action were distinct from those used by prior drugs or whether these drugs targeted resistance mechanisms of a prior precision oncology therapy. Among precision oncology therapies, 47.8% (n=33) were classified as first-in-class, 10.1% (n=7) as mechanistically-distinct drugs targeting previously actionable genomic alterations, and 42.0% (n=29) as follow-on/resistance precision oncology therapies (**Figure 1a, Table 1, Supplementary Table S2**).

By plotting the number of first-in-class, mechanistically-distinct and follow-on/resistance precision oncology therapies FDA approved each year (**Figure 1b**), we observed a slow expansion in the landscape of clinical actionability from 1998 to 2012, corresponding to 1 or 2 first-in-class or follow-on drugs approved each year, if any. Nonetheless, this timeframe was notable for the FDA-approval of the first therapies targeting *BCR-ABL1*, *KIT*, *PDGFRA/B* and *PDGFB* (imatinib), *BRAF* (vemurafenib), and *EGFR* (erlotinib) (**Figure 1b**, **Table 1**). The years 2012 to 2017 were primarily notable for the approval

of drugs targeting alterations previously considered actionable based on prior FDA-approvals, with the notable exception of PARP inhibitors for *BRCA1/2*-mutant ovarian cancer, which represented the first drug approval based on a synthetic lethal mechanism of action.

Following 2017, a rapid increase in the rate of FDA approvals of precision oncology therapies was observed. Whereas the annualized median of precision oncology drug approvals over 20 years from 1998 through 2017 was 1, the annualized median rose to 8 per year in the 5-year period from 2017 to 2022. Between 2017 to 2022, 23 first-in-class drugs targeting 31 biomarker-defined patient populations and 18 follow-on drugs were FDA-approved, accounting for approximately 69.7% and 50.0% of all first-in-class and follow-on FDA drug approvals since 1998, respectively. In 2020, the greatest number of first-in-class precision oncology drugs was approved (n=8, 24.2%) along with the approval of four follow-on drugs (11.1%) (**Figure 1b**, **Table 1**). Notably, of the 33 first-in-class precision oncology therapies, 24.2% (n=8) have more than one genomic biomarker included as patient eligibility criteria in the corresponding FDA drug-labels (for example, imatinib is first-in-class for *BCR-ABL1*, *KIT*, *PDGFRA/B* and *PDGFB)* (**Figure 1b**, **Table 1**). Additionally, only seven biomarkers are targeted by 69.0% (20 of 29) of follow-on/resistance therapies, namely *ERBB2* amplification, *BCR-ABL1*, BRAF V600E, *ALK* fusions/mutations, *BRCA1/2* mutations and *FGFR2* fusions, highlighting the narrow scope of precision oncology drug development during this era (**Table 1**).

Expansion of clinical actionability from 2017 to 2022

To quantify the expansion in the landscape of clinical actionability since 2017, we used the precision oncology knowledge base OncoKB to annotate all mutations, focal copy number alterations and structural variants identified in 47,271 tumor samples sequenced using the MSK-IMPACT sequencing platform and available publicly as part of the AACR GENIE 11.0-public release (25) (see Methods) (**Supplementary Table S3**). Each tumor sample was analyzed using OncoKB releases from March 2017 (2017v1.8) and October 2022 (2022v3.17). To ensure adequate statistical power, we limited our tumor type-specific analyses to the 34 tumor types with ≥100 samples (**Figure 2a-b, Supplementary Figure S1a-b**).

From 2017 to 2022, there was an almost doubling (from 18.1 to 35.9%) of tumors with a somatic DNA mutation, fusion or copy number alteration that would make the corresponding patient eligible for treatment with a standard care targeted or immune-based therapy (Level 1 or 2), or enrollment onto a clinical trial of a cancer drug with promising clinical data (Level 3A) (**Figure 2a**). Consistent with the increase in clinical actionability from 2017 to 2022, there was a corresponding approximate 50% decrease in samples with oncogenic but not clinically actionable genomic alterations (from 44.2% to 22.8%). There was also an approximately 4-fold (from 7.7 to 30.2%) increase in the fraction of tumor samples with a Level 1 (FDA-recognized) biomarker of drug response. The largest single contribution to this increase (9.2 percentage points) was attributable to the FDA approval of pembrolizumab for solid tumors that are TMB-H (≥10 mut/MB) (**Figure 2a**). The fraction of tumors for which the highest level of actionability was a Level 2 biomarker remained consistent at ~1% in 2017 and 2022, whereas there was a 4.9 percentage point decrease (from 9.2% to 4.3%) in the fraction of samples in which the highest level of clinical actionability was a Level 3A investigational biomarker (**Figure 2a**). Finally, the number of samples for which the highest level of actionability was a Level 4 biomarker, defined as a genomic alteration predictive of drug response based on compelling preclinical data, increased >2-fold (from

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8.6% to 20.6%) (**Figure 2a**); this latter increase is likely indicative of increased annotation of Level 4 biomarkers following updates to the OncoKB curation protocol (OncoKB Standard Operating Procedure Version 2.2) for Level 4 alterations.

The number of tumor samples with at least one clinically actionable genomic alteration (OncoKB Levels 1-3A) varied widely as a function of cancer type, with gastrointestinal stromal tumors (GIST, 84.4%) having the highest proportion of samples with a clinically actionable genomic alteration versus mesothelioma (2.1%) with the lowest proportion. However, the fraction of patients with an actionable molecular alteration increased across all tumor types between 2017 and 2022 (**Figure 2b, Supplementary Figure S1a-b**). Across all tumor types, the median number of known or presumed driver mutations per sample was 4, and the median number of clinically actionable biomarkers of systemic therapy response per tumor sample was 1 (**Supplementary Figure S2a** shows the median mutation numbers for tumor types with samples ≥100). As previously noted (14), the number of clinically actionable genomic alterations in a tumor did not correlate with mutation burden. For example, while GISTs are characterized by a low tumor mutational burden (median of 3 non-synonymous mutations per sample detected by MSK-IMPACT) (**Supplementary Figure S2**), 82.9% of GISTs had a Level 1 biomarker predictive of drug response (**Figure 2b**). In contrast, although 85.5% of endometrial cancers, with a median of 9 mutations per sample, had at least 1 theoretically actionable mutation per sample, 38.2% of those were Level 3B alterations (**Figure 2b, Supplementary Figure S2**). Breast cancer, melanoma and non-small cell lung cancer (NSCLC) were found to have a large fraction of samples with two or more actionable genomic alterations (30.2%, 50.1%, and 39.1%, respectively), which is consistent with data demonstrating that these tumor types are driven by multiple targetable oncogenic mutations in non-redundant pathways (2) (**Supplementary Figure S2b**).

Notable expansions in clinical actionability during 2017 to 2022 resulted from first-in-class FDA approvals of alpelisib for *PIK3CA*-mutant breast cancer (28% of breast cancers), erdafitinib for *FGFR3*-mutant bladder cancer (24% of bladder cancers), pemigatinib, infigratinib and futibatinib for *FGFR2*-fusion-positive (5%), ivosidenib for *IDH1*-mutant cholangiocarcinomas (10%), and selpercatinib and pralsetinib for *RET*-fusion-positive lung and thyroid cancers (2% and 11%, respectively)(**Figure 2b**). KRAS G12C is the most prevalent KRAS mutant allele in NSCLC, and the FDA approval of the first KRAS-G12C targeted agent sotorasib increased the fraction of NSCLC samples with a Level 1 biomarker predictive of therapy response by 12 percentage points (**Figure 2b**).

There are now five tumor type-agnostic FDA approvals, all of which occurred in the past five years. These approvals substantially increased access to precision oncology-based therapies for patients with rare or unknown primary cancer subtypes. For example, among the 1,423 cancers of unknown primary (CUP) (**Figure 2b**), 21.4% (n=305) became eligible for the first time to receive an FDA-approved precision oncology-based therapy (Level 1) during this 5-year period. CUP with TMB-H or MSI-H status accounted for 18.8% (n=267), *BRAF* V600E mutation for 2.5% (n=35), and *RET* or *NTRK* fusions were identified in 3 CUP tumors. FDA approval of larotrectinib for *NTRK*-fusion-positive tumors had the greatest impact in salivary gland cancer (n=365) resulting in a 5.7 percentage point (n=21) increase in tumors classified as Level 1 in 2022 versus 2017. For gliomas (n=2,102), the tumor-agnostic approval of dabrafenib + trametinib for BRAF V600E-mutant tumors resulted in a 2.5 percentage point (n=52) increase in clinical actionability (**Figure 2b**). Collectively, after excluding cancer types in which

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pembrolizumab, combination dabrafenib/trametinib, or selpercatinib had already been approved, 5,321 of the 43,049 (12.4%) tumor samples without a standard care biomarker in 2017 (samples with Levels 3A, 3B, or 4 as the highest level of clinical actionability or no alteration with an OncoKB level) received Level 1 assignment by 2022 based on tumor type-agnostic FDA drug approvals.

Lastly, to assess the current limitations in precision oncology, we quantified the percent of non-actionable driver genes in samples with limited to no clinical actionability (Levels 3B or 4 as the highest level of clinical actionability, or no alteration with an OncoKB level). The most highly altered genes in these tumors included transcription regulators such as *TP53* (43.2%), *MYC* (5.0%) and *SMAD4* (4.6%), cell cycle regulators (*CDKN2A* [12.2%], *CDKN2B* [8.1%] and *CCND1* [4.3%]), kinases or kinase regulators (including *PIK3CA* [7.3%], *PIK3R1* [2.6%], *CDK4* [2.6%] and *STK11* [2.5%]), GTPases (predominantly *KRAS* [19.2%]) and the enzyme *TERT* (10.0%) (**Figure 2c-d**). Among non-actionable genes altered in >1% of samples, 51.5% (n=35) were tumor suppressor genes, 38.2% (n=26) were oncogenes, and the remaining 10.3% (n=7) were characterized as potentially both based on lineage context (for example, *NOTCH1*) or neither oncogenes or tumor suppressor genes (for example, *AGO2*) by OncoKB (**Supplementary Figure S3**). Overall, the most altered class of non-actionable genes was transcriptional regulators (55.8% of samples) followed by GTPases, kinases and cell cycle regulators (20.4%, 20.3% and 18.0% of samples, respectively) (**Figure 2d, Supplementary Table S4**).

Discussion

Our analysis of the landscape of precision oncology therapies and clinical actionability over the past 25 years revealed several findings reflective of the state of the field. Over one-third of oncology drugs FDA-approved since 1998 were classified as precision oncology drugs as they require the use of tumor or germline genomic profiling to determine patient eligibility. In March 2017, select alterations in 14 genes mutated within the context of 12 cancer types were Level 1 (standard care) biomarkers per OncoKB (**Supplementary Table S5**). By October 2022, 45 genes as well as MSI-H and TMB-H status are FDA-recognized biomarkers of treatment response and includes 5 tumor agnostic genomic biomarkers potentially relevant to all cancer types (**Table 1**). This increase in the number of clinically actionable biomarkers corresponds to an almost 4-fold increase (from 7.7% to 30.2%) in the fraction of solid tumor samples that now harbor an FDA-recognized genomic biomarker of response to an FDA-approved precision oncology therapy. It is important to note that not all targeted therapies require pre-treatment molecular testing for optimal clinical use. Therefore, not all targeted therapies were classified as precision oncology therapies in the analysis presented here. As examples, CD19-directed chimeric antigen receptor T cell (CAR-T) therapies such as axicabtagene ciloleucel (26) and tisagenlecleucel (27) as well as antibody drug conjugates such as enfortumab vedotin (28) and sacituzumab govitecan (29) do not require pretreatment molecular testing to guide their clinical use and were not classified as precision oncology therapies (30,31). It is, however, possible that future diagnostic platforms such as whole transcriptome RNA sequencing or functional assays that use fresh tumor tissue to interrogate biomarker profiling *in vitro* will allow for the biomarker-directed use of these novel cellular and immunotherapies prompting the future reclassification of these drugs to precision oncology therapies.

The basis for the surge in new precision oncology therapies since 2017 is multifactorial but we believe largely attributable to the development of multiplexed NGS-based clinical assays and innovations in

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clinical trial design such as basket trials (32,33). Cumulative technical advances have now enabled clinical sequencing panels to detect mutations and structural alterations in hundreds of cancer-associated genes at low cost using readily available archival tumor tissue or tumor-derived cell free DNA (34–37). By incorporating both standard care and investigational biomarkers into a single test, NGS-based diagnostic assays provide a platform for the identification of sufficient numbers of patients with cancer whose tumors harbor rare alterations to allow for the timely accrual of clinical trials in which study eligibility is restricted to only those patients with genomic profiles predictive of drug response.

Larotrectinib is an example of a precision oncology therapy whose development was facilitated by the widespread adoption of multigene NGS-based tumor genomic profiling and the basket trial design. *NTRK* fusions are common in several rare cancers such as infantile fibrosarcoma and mammary secretory carcinoma (>90%), but exceedingly rare in more common cancers such as lung and colorectal cancer (each <1%) (38). By employing a basket trial design, TRK kinase inhibitors were simultaneously tested in both common and rare cancers, an approach which is much more efficient than traditional disease-specific drug development paradigms (7). While the primary clinical use and billing indications for NGS-based diagnostic assays such as MSK-IMPACT have been for the detection of standard care biomarkers such as *EGFR* and *BRAF* mutations, inclusion of *NTRK1, NTRK2* and *NTRK3* and common *NTRK* fusion partners (e.g. *ETV6*) into the assay design had minimal impact on cost while enabling broad scale screening of patients with lung cancer, melanoma and other common cancers for clinically actionable but rare *NTRK* fusions (37). In the case of TRK inhibitors, the clinical activity observed across cancer types was sufficiently compelling to justify the first tumor-agnostic FDA approval of a kinase inhibitor. Had clinical multigene NGS-assays such as MSK-IMPACT been designed to detect mutations in only standard care biomarkers, a position strongly advocated for by some (15), it is likely that the development of TRK inhibitors would have been either infeasible or significantly delayed. Thus, the TRK-kinase inhibitor experience strongly supports the inclusion of all cancer genes in future NGS-based clinical assays, not just those with established clinical utility.

Despite the recent expansion in FDA-approved targeted therapies, the clinical impact of precision oncology has been an area of significant debate and controversy. Some have suggested that the rhetoric surrounding precision oncology exceeds the actual clinical benefit for patients (15), whereas others have advocated for an unduly broad definition of clinical actionability so as to create an overly-optimistic narrative of the field (39). To better quantitate the level of innovation in the precision oncology field, we determined which precision oncology drugs approved since 1998 were “first-in-class” in that the drug targeted a previously “undruggable” oncogenic alteration or were “mechanistically-distinct” in that the drug utilized a novel mechanism of action compared to previously approved agents. One goal was to determine the fraction of new drugs that were FDA-approved but mechanistically indistinguishable from previously available agents and therefore did not represent a clinically meaningful therapeutic advance in the field. We acknowledge that the assignment of drugs to categories was to a degree subjective. For example, we classified the EGFR selective kinase inhibitor osimertinib as a mechanistically-distinct precision oncology therapy targeting genomic alterations in the previously targetable *EGFR* gene rather than a first-in-class agent for the EGFR T790M gatekeeper resistance mutation. This assignment was based on the greater selectivity of osimertinib for most *EGFR* activating mutations including L858R and exon 19 deletions versus wildtype EGFR, as well as its improved central nervous system penetration and tolerability. The clinical activity of osimertinib in the

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progression setting is not due to its specificity for the EGFR T790M mutation *per se,* but rather the drug's retained potency against a broad range of mutations. This likely explains osimertinib's superior clinical activity in the first line setting compared to earlier generation EGFR tyrosine kinase inhibitors (40,41).

This current study had several limitations. First, not all patients whose tumors harbor an actionable alteration will or should receive a genomically matched therapeutic option, as non-molecularly guided standard care or investigational therapies may be more appropriate for some patients based on clinical factors such as disease state or prior treatment. As many precision oncology therapies are exceedingly expensive, drug access due to lack of insurance coverage or high co-pay requirements are also likely hurdles to the broader adoption of precision oncology. Additionally, the expanded actionability as defined in the current study was based on US FDA approvals, and access to newer agents may be more limited in other countries (42). Indeed, while the US, France and Canada have reported trials where 13 to 18% of patients enrolled were genomically matched to trials of precision oncology drugs (43–45), Singapore reported a match rate of only 5% (46). Second, not all patients with an actionable mutation respond equally to a genomically matched therapy, and the likelihood of response varies across cancer types. For example, the overall response rate (ORR) of adagrasib monotherapy in KRAS G12C mutant colorectal cancers is 23% (47), compared to 42.9% in KRAS G12C mutant NSCLC (48). These lineage-specific differences are consistent with adagrasib monotherapy being FDA-approved for patients with KRAS G12C mutant NSCLC, whereas combination therapy with an EGFR-targeted monoclonal antibody will likely be required in colorectal cancer for optimal clinical benefit. Third, as the AACR Project GENIE dataset included only somatic mutations, our analysis may have underestimated clinical actionability as it failed to capture potentially actionable germline alterations such as germline mutations in *BRCA1/2* that have been shown to be predictive of PARP inhibitor response (49). Finally, real-world datasets such as AACR GENIE are impacted by referral biases such as enrichment for patients with the financial means to pursue clinical trials at the tertiary referral centers that make up the consortium. Notably, only 6.5% of patients self-identified as African American or Black in our dataset highlighting the underrepresentation of some historically underserved populations. As the prevalence of targetable genomic alterations such as *EGFR* mutations vary as a function of race or ethnicity (50), different results may have been observed had we had analyzed a cohort with a more diverse patient population.

In sum, our data suggest significant expansion of the landscape of clinical actionability for patients with cancer. However, our data also raise concern that the recent acceleration in new first-in-class precision oncology agents may have peaked in 2020 and that novel strategies will be needed to further advance the field. Future progress will likely require the development of targeted therapies effective in patients whose tumors are driven by common tumor suppressor genes or transcriptions factors such as *TP53*, *CDKN2A/B*, *APC*, *PTEN*, *RB1*, *TERT* and *MYC* that, to date, have not been amenable to the small molecular inhibitors that have proven effective for gain-of-function kinase mutations. Additionally, as about a third of tumors analyzed in our study have more than one clinically actionable genomic alteration, more selective and less toxic targeted therapies that can be co-administered in combination will be required to achieve the full potential of precision oncology-based therapeutic strategies. Finally, novel diagnostic platforms such as whole genome and whole transcriptome sequencing, proteomics

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and secretome profiling and spatial -omics technologies will likely be needed to allow for the more targeted use of novel mechanistically-based precision oncology therapies (51).

Methods

Definitions used in this study

1. *Oncology Drug:* A drug approved by the US-Food and Drug Administration (FDA) for the treatment of cancer
2. *Targeted Therapy:* A cancer drug that binds to or inhibits a specific protein target
3. *Precision oncology therapy*: A drug that is most effective in a molecularly defined subset of patients and for which pre-treatment molecular profiling is required for optimal patient selection
4. *First-in-class precision oncology therapy*: A precision oncology therapy targeting an alteration previously classified as not actionable
5. *Mechanistically-distinct precision oncology therapy*: A precision oncology therapy targeting a previously actionable genomic alteration via a distinct mechanisms-of-action, or with significantly different selectivity versus older drugs
6. *Follow-on precision oncology therapy*: A precision oncology therapy with a mechanism of action largely similar to a previously FDA-approved first-in-class drug
7. *Resistance precision oncology therapy*: A precision oncology therapy with a mechanism of action largely similar to an FDA-approved first-in-class precision oncology drug, but with an expanded mutation profile that targets mutations that arise in the context of resistance to the first-in-class drug

Collection and sorting of FDA-approved anticancer drugs

Three sources were used to create a master list of all FDA-approved oncology drugs between September 1998 and November 2022:

1. FDA drug approval notifications posted to the Oncology (Cancer) / Hematologic Malignancies Approval Notifications page (drugs approved between June 14th, 2006 and November 4th, 2022 were collected and reviewed)
2. Sun J, Wei Q, Zhou Y, Wang J, Liu Q, Xu H. A systematic analysis of FDA-approved anticancer drugs. BMC Syst Biol. 2017;11:87 (Drugs listed in Table 1: Summary of FDA-approved anticancer drugs from 1949 to 2014, were collected and reviewed). Exact methods of FDA-approved anticancer drugs curation are provided in **Supplementary Note 1** in the **Supplementary Methods**.
3. Olivier T, Haslam A, Prasad V. Anticancer drugs approved by the US food and drug administration from 2009 to 2020 according to their mechanism of action. JAMA Netw. Open. 2021;4:e2138793 (FDA drug approvals between January 1st, 2017 and April 28th, 2017 were missing from the FDA.gov website, and this review was used to complete the drug list). Exact methods of FDA-approved anticancer drugs curation are provided in **Supplementary Note 2** in the **Supplementary Methods**.

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FDA drug approval notifications (from sources 1-3 above, if present) and FDA drug labels (from Drugs@FDA) for all drugs included in the three sources above were reviewed. Exclusion criteria for the master FDA-approved oncology drug list were the following:

1. Drugs FDA-approved for conditions related to cancer, although not the cancer itself (e.g., abatacept)
2. Oncology drugs first FDA-approved prior to 1998
3. Oncology drugs noted to be “biosimilars” in the FDA-approval notification

Additional criteria for counting FDA-approved oncology drugs included:

1. Oncology drugs FDA-approved for multiple indication were counted only once
2. Oncology drugs FDA-approved as a single agent and also in combination with a non-targeted agent(s)* were counted once
3. Oncology drugs FDA-approved only in combination(s) with a non-targeted agent(s)* were counted once
4. If two precision oncology therapies were FDA-approved as single agents, and also in combination with each other, we counted each single agent as well as the drug combination separately (ex. Dabrafenib, Trametinib, and Dabrafenib + Trametinib, count = 3.

*Note: The following drugs were considered non-targeted agents: chemotherapy, radiation, hormone/endocrine therapy, steroids, bevacizumab, axitinib, lenvatinib, cabozantinib, rituximab, ramucirumab, interferon alpha, proteasome inhibitor, anti-folate, hyaluronidase, pomalidomide

A master FDA oncology drug approval table was created with the following categories:

1. **Drug name:** Drug name extracted from one of the three sources listed above (source for Table 1, Column 3; Supplementary Table S1, Column 2; Supplementary Table S2, Column 2)
2. **Description**: A copy-pasted description of the FDA drug approval announcement (source for Table 1, Column 5)
3. **Date:** Date of FDA drug label publication - assigned drug approval date (source for Table 1, Column 1)
4. **Duplicate drug*:*** If a drug has already been counted once and is listed again, being it is FDA-approved for multiple indications Y/N
5. **Oncology drug**: Whether the drug is specifically indicated for the treatment of patients with cancer
6. **Targeted therapy**: (See definition above) Y/N (source for Supplementary Table S1, Column 5)
7. **Precision oncology therapy**: (See definition above) Y/N; Note: Targeted therapies were only considered precision oncology therapies if their use was guided by tumor somatic or germline molecular testing (source for Supplementary Table S1, Column 6)
8. **Biomarker specified in the FDA drug label**: Biomarker specified in the FDA label and/or used to select patients for treatment with the drug (if there is a corresponding FDA-approved companion diagnostic test for biomarker identification, this detection method is listed; if a DNA NGS-based detection method can be used to identify the biomarker, this is noted) (source for Table 1, Column 2 and Supplementary Table S2, Column 3)
9. **Method of biomarker detection**: DNA/NGS-based method of detection or IHC or Flow cytometry or FISH or CISH or PET-imaging or HLA-typing or Radionucleotide Scan. Note: if

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there is a corresponding FDA-approved companion diagnostic test for biomarker identification, this detection method is listed; if a DNA NGS-based detection method can be used to identify the biomarker, this is noted) (source for Supplementary Table S2, Column 4)

10. **Drug categorization:** First-in-class, Mechanistically-distinct, Follow-on, or Resistance precision oncology therapy (See definitions above) (source for Table 1, Columns 6-8; Supplementary Table S2, Column 5)

Note: Categories 8-10 above are applicable only to precision oncology therapies; category 10 is only applicable to drugs with an FDA-specified biomarker that can be detected by a DNA/NGS-based method.

Drug class and mechanism of action (Supplementary Table S1, Columns 3 and 4) were determined from the FDA drug label, Indications and Usage section, as well as from DrugBank Online (https://go.drugbank.com/)

OncoKB analysis of the MSK-IMPACT subset of the AACR Project GENIE dataset

Samples and patients

A total of 47,271 solid tumor samples from 42,154 patients sequenced at Memorial Sloan Kettering Cancer Center and included in the AACR Project Genomics Evidence Neoplasia Information Exchange (GENIE) version 11.0- public database (25) were considered for this analysis (dataset is referred to as the "MSK-IMPACT dataset" in this manuscript). This dataset included 66 main cancer types per the OncoTree Classification system (**Supplementary Table S3**) (52). The sample set was limited to the MSK-IMPACT analyzed tumors to ensure consistency in mutation, fusion, and copy number reporting across all samples.

Genomic Analysis. MSK samples selected for this study were sequenced on a custom, hybridization-based capture panel (MSK-IMPACT) to detect single nucleotide variants, small indels, copy number alterations, and structural variants from matched tumor-normal sequence data. Only somatic mutations were submitted by centers to AACR Project GENIE but an additional germline filter was added by AACR Project GENIE by using the gnomAD allele frequency threshold of 0.0005 or greater. Full details of AACR Project GENIE data processing is provided in their data guide (https://www.aacr.org/wp-content/uploads/2022/03/GENIE_data_guide_11.0-public.pdf). All files were downloaded from the AACR Project GENIE Synapse page. Tumor mutational burden (TMB) was calculated for each sample as the total number of nonsynonymous mutations, divided by the number of bases sequenced. TMB-H was defined as ≥10 mutations per Megabase, which is consistent with the FDA-approved companion diagnostic test for TMB-H tumors. MSI-H status was defined by an MSIsensor score > 10 (53).

***Tumor type-specific OncoKB Analysis*.** For all samples, mutations, copy number alterations, structural alterations and actionable mutational signatures (TMB-H, MSI-H) detected by MSK-IMPACT were annotated using OncoKB versions from March 2017 (2017v1.8) and October 2022 (2022v3.17). Details as to how OncoKB classifies the oncogenicity of variants and assigns levels of evidence are documented in detail in the OncoKB SOP Version 2.2. Rules for classifying oncogenicity and level of evidence assignment from OncoKB SOP Version 2.2 were applied to both the 2017 and 2022 OncoKB

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versions (**Supplementary Table S6**). Samples were classified by the alteration annotated with the highest level of evidence. The following ranking was employed: Samples were classified as either Level 1 (non-MSI-H and non-TMB-H) or Level 1 MSI-H before they were classified as Level 1 TMB-H (i.e., where the only genomic feature of the sample was that of TMB-H, considered Level 1) before they were classified as Level 2 before they were classified as Level 3A before they were classified as Level 3B before they were classified as Level 4.

Classification of driver genes with limited to no clinical actionability. The dataset included MSK-IMPACT samples (as described above) annotated with the OncoKB version from October 2022 (2022v3.17). Genes altered across samples that either harbored a variant of unknown significance, had no actionable driver, or for which the highest-level of actionability was Level 3B or 4, were quantified and characterized based on their mechanism of action (**Supplementary Table S4**).

Data Availability

The data generated in this study are publicly available in github at https://github.com/oncokb/oncokb-datahub/tree/main/PUBLICATION/2023/CANCER_DISCOVERY. Any additional information required to reanalyze the data reported in this article is available upon request from the corresponding author.

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Table Legend, Footnotes and Abbreviations

Table 1. FDA-recognized biomarkers and corresponding FDA-approved precision oncology therapies from 1998-2022.

[a] Includes MSI-H and TMB-H; Although some genes are listed >1x when different alterations within the same gene are indicated in separate FDA-drug labels, each gene is counted once (e.g. ERBB2 amplification and ERBB2 oncogenic mutations are listed separately, but the gene (*ERBB2*) is counted once)

[b] Drugs in italics are FDA approved for >1 genomically-defined patient population

[c] For combinations that include chemotherapy or other non-targeted agent(s), the chemotherapy or non-targeted agent(s) is not listed

[d] Cancer type as listed in the FDA drug label

[e] The first year the drug was FDA-approved for the indicated biomarker and tumor type-specific patient population (unless otherwise noted)

[f] FDA-specified genomic variant(s) listed only if different from variants listed in the label of the first-in-class drug

[g] While trastuzumab deruxtecan is FDA-approved for patients with HER2+ breast cancer (2019), HER2+ gastric or gastroesophageal junction adenocarcinoma (2021), HER2-low (IHC 1+ or IHC 2+/FISH-) breast cancer (2022), it is categorized as a first-in-class drug based on its approval in ERBB2-mutant NSCLC.

[h] The PML-RAR*α* fusion is the only biomarker in this analysis listed without a first-in-class drug. We consider arsenic trioxide to be a follow-on drug (FDA-approved for APL in 2000) and tretinoin (FDA-approved for APL in 1995) to be a first-in class drug for the treatment of patients with PML-RAR*α* fusion-positive APL. However, the FDA-approval of tretinoin is outside the scope of this analysis and not included here.

[i] In the FDA-drug label for dasatinib**,** BCR-ABL1 fusion was specified as patient eligibility criteria for BLL in 2006 and for CML in 2010.

[j] Erlotinib was initially FDA-approved in 2004 for the treatment of patients with NSCLC, irrespective of mutation status. In 2013, the FDA drug label was updated to specify patients with NSCLC with EGFR L858R or exon 19 deletion mutations

[k] In 2004, cetuximab was FDA-approved for the treatment of EGFR-expressing CRC, and in 2006 panitumumab was FDA-approved for the same indication. In 2009, FDA labels for both drugs were updated to include a recommendation that patients with *KRAS* mutant CRC does not receive the drug. In the current (9/2021) FDA drug label for cetuximab, the drug is indicated for “KRAS wild-type, EGFR-expressing, metastatic CRC”. In the current (9/2021) FDA drug label for panitumumab, the drug is indicated for “wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) metastatic colorectal cancer.” Although panitumumab is the first drug FDA-approved for patients with NRAS WT tumors (2015), it is considered a follow-on drug given its mechanism of action is comparable to that of cetuximab.

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[l] In 2014, olaparib was FDA-approved for the treatment of patients with ovarian cancer with germline *BRCA1/2* mutations; in 2018 the approval was expanded to include patients with somatic *BRCA1/2* mutant epithelial ovarian, fallopian tube or primary peritoneal cancer

[m] Olaparib is FDA-approved only in the germline setting in this indication

[n] Olaparib is FDA-approved in the germline and somatic setting in this indication

[o] Rucaparib is FDA-approved in the germline and somatic setting for both indications (OVC and mCRPC); in 2018 the approval for OVC was expanded to include patients with *BRCA* (germline and/or somatic)-associated epithelial ovarian, fallopian tube or primary peritoneal cancer

[p] Talazoparib is FDA-approved only in the germline setting in this indication

[q] In 2020, pemigatinib was FDA-approved for the treatment of patients with *FGFR2* fusion-positive cholangiocarcinoma. In 2022, pemigatinib was FDA-approved for patients with myeloid/lymphoid neoplasms with *FGFR1* rearrangements. Despite its association with a novel biomarker (FGFR1), pemigatinib is still considered a follow-on drug as its mechanism and survival benefit are comparable to that of erdafitinib and infigratinib.

[r] In 2020, capmatinib was FDA-approved for the treatment of patients with NSCLC with a *MET* exon 14 skipping mutation, and in early 2021 tepotinib was FDA-approved for the same indication. Since these drugs were developed together and received FDA-approval within months of one another, we consider both drugs as first-in-class.

[s] In 2020 both selpercatinib and pralsetinib were FDA-approved for the treatment of patients with *RET* fusion-positive NSCLC and thyroid cancer, as well as *RET*-mutant MTC. In 2022, the FDA-approval of selpercatinib was expanded to include the treatment of patients with *RET* fusion-positive solid tumors. Since these drugs were developed together and received FDA-approval within months of one another, we consider both as first-in-class.

BC, Breast Cancer; GEJ, Gastroesophageal Junction Adenocarcinoma; APL, Acute promyelocytic leukemia; CML, Chronic Myeloid Leukemia; ALL, Acute Lymphoblastic Leukemia; GIST, Gastrointestinal Stromal Tumor; NSCLC, Non-Small Cell Lung Cancer; MDS/MPD, Myelodysplastic Syndrome/ Myeloproliferative Disease; CEL, Chronic Eosinophilic Leukemia; CRC, Colorectal Cancer; IMT, Inflammatory Myofibroblastic Tumors; MEL, Melanoma; ECD, Erdheim Chester Disease; ATC, Anaplastic Thyroid Cancer; OVC, Ovarian Cancer; PAAD, Pancreatic Adenocarcinoma; mCRPC, metastatic castration-resistant Prostate Cancer; OVC/FT/PSEC, Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer; AML, Acute Myeloid Leukemia; CHOL, Cholangiocarcinoma; AdvSM, Advanced systemic mastocytosis; RCC, renal cell carcinoma; CNS central nervous system; pNET, pancreatic neuroendocrine tumors

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Figure Legends

Figure 1. Biomarker-driven FDA drug approvals between 1998 and 2022. A, Consort diagram detailing the categorization of oncology drugs FDA-approved between June 1998 and November 2022. Definitions for all categories are detailed in the methods. **B,** Number of first-in-class (black) and mechanistically distinct/follow-on/resistance (gray) precision oncology drugs FDA-approved between June 1998 and November 2022. Number of genomic biomarkers (genes and MSI-H and TMB-H) included in the “Indications and Usage” section of the FDA drug labels in drugs approved per year is shown with the blue line. *Arsenic trioxide, approved in 2000 is considered a follow-on drug after the first-in-class drug tretinoin approved in 1995 for PML-RARA fusion positive acute promyelocytic leukemia. **HRR (homologous recombination repair) genes include ATM, BARD1, BRIP1, CDK12, CHEK1/2, FANCL, PALB2, RAD51B/C/D, RAD54L. +Biomarkers specified as patient eligibility criteria in FDA drug labels of pre-existing FDA-approved drugs.

Figure 2. Analysis of the clinical actionability of solid tumor samples in 66 tumor types from the MSK-IMPACT cohort (n = 47,271). A, Frequency of actionable mutations pan-cancer in tumor samples annotated by OncoKB version March 2017 (2017v1.8) versus OncoKB version October 2022 (2022v3.17). **B,** Actionable mutations and associated gene prevalence per cancer types in 2017 versus 2022. For samples with Levels 3B, 4, or samples with non-actionable drivers, variants of unknown significance (VUS) or no alteration as highest actionability (n=30,320) **C,** Percent of samples with an oncogenic alteration in the indicated gene. Genes altered in >2% of samples are shown. **D,** Percent of samples with an oncogenic alteration in at least one gene in the indicated gene category. Genes in each category are shown in Supplementary Table S4 and include genes altered in >1% (n=68) of indicated samples.

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Table 1: FDA-recognized biomarkers and corresponding FDA-approved precision oncology therapies from 1998-2022

Year biomarker was first FDA-recognized	Gene and alteration Total number of genes[a] = 47	First-in-class precision oncology therapy(s)[b, c] N=33	Mechanism of action	FDA-approved cancer type[d] (year)[e]	Additional biomarker-specific FDA approved precision oncology therapy(s)[2, 3] N=36		
					Mechanistically-distinct drug (tumor type, year)[e, f] N=7	Follow-on drug (tumor type, year)[e, f] N=19	Resistance-targeting or follow-on drug (tumor type, year)[e, f] N=10
1998	*ERBB2* Amplification	Trastuzumab	HER2 -targeted agent	BC (1998) Gastric or GEJ (2010)	Lapatinib (BC, 2007) Pertuzumab + Trastuzumab (BC, 2012) Neratinib (BC, 2017) Trastuzumab Deruxtecan (BC, 2019; Gastric or GEJ, 2021)[g]	Ado-Trastuzumab Emtansine (BC, 2013) Tucatinib + Trastuzumab (BC, 2020) Margetuximab (BC, 2020)	NA
		Trastuzumab + Pembrolizumab	HER2-targeted agent + anti-PD-1 antibody	Gastric or GEJ (2021)	NA	NA	NA
2000	*PML-RARα* Fusion[h]	NA	NA	NA	NA	Arsenic Trioxide (APL, 2000)	NA
2001	*BCR-ABL1* Fusion	*Imatinib*	BCR-ABL1/PDGFR/ KIT inhibitor	CML (2001) ALL (2006)	Ponatinib (ALL with BCR-ABL1 and/or T315I, 2012; CML with ABL1 T315I, 2013)	NA	Dasatinib (ALL and CML, 2006)[i] Nilotinib (CML, 2007) Bosutinib (CML, 2012) Asciminib (CML with BCR-ABL1 and/or ABL1 T315I, 2021)
2002	*KIT* Oncogenic Mutations		BCR-ABL1/PDGFR/ KIT inhibitor	GIST (2002)	Ripretinib (GIST, 2020)	NA	Sunitinib (GIST, 2006) Regorafenib (GIST, 2013)
2004	*EGFR* L858R, Exon 19 deletions	Erlotinib	EGFR tyrosine kinase inhibitor for select sensitizing mutations	NSCLC (2004)[j]	Afatinib (NSCLC with EGFR exon 19 del or L858R, 2013; NSCLC with EGFR S768I, L861Q, or G719X, 2018) Osimertinib (NSCLC with EGFR T790M, 2015; NSCLC with EGFR Exon 19 del or L858R, 2018)	Gefitinib (NSCLC, 2015) Dacomitinib (NSCLC, 2018)	NA
2006	*PDGFRA* or *PDGFRB* Fusions	*Imatinib*	BCR-ABL1/PDGFR/ KIT inhibitor	MDS/MPN (2006)	NA	NA	NA
	FIP1L1-PDGFRA Fusion			CEL (2006)			
	PDGFB Fusions			Dermatofibrosarcoma Protuberans (2006)			
2009	*KRAS* Wildtype	Cetuximab[k]	Anti-EGFR antibody	CRC (2009)	NA	*Panitumumab* (CRC, 2009)[k]	NA
2010	*TSC1 or TSC2* Oncogenic Mutations	Everolimus	MTOR inhibitor	Tuberous sclerosis complex (TSC) (2010)	NA	NA	NA
2011	*ALK* Fusions	*Crizotinib*	ALK/ROS/MET inhibitor	NSCLC (2011) Anaplastic Large-Cell Lymphoma ALK Positive (2021) IMT (2022)	NA	NA	Ceritinib (NSCLC, 2014) Alectinib (NSCLC, 2015) Brigatinib (NSCLC, 2017) Lorlatinib (NSCLC, 2018)
	BRAF V600E (V600K,V60)	Vemurafenib	RAF inhibitor	MEL (V600E, 2011) ECD (V600, 2017)	NA	Dabrafenib (MEL with BRAF V600E, 2013)	NA
		Trametinib	MEK inhibitor	MEL (V600E/K, 2013)	NA	NA	NA

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		Dabrafenib +Trametinib	RAF inhibitor + MEK inhibitor	MEL (V600E/K, 2014) NSCLC (V600E, 2017) ATC (V600E, 2018) All Solid Tumors (V600E, 2022)	NA	Vemurafenib + Cobimetinib (MEL with BRAF V600E/K, 2015) Encorafenib + Binimetinib (MEL with BRAF V600E/K, 2018)	NA
		Encorafenib + Cetuximab	RAF inhibitor + anti-EGFR inhibitor	CRC (V600E, 2020)	NA	NA	NA
		Atezolizumab + Vemurafenib + Cobimetinib	Anti-PD-L1 antibody + RAF inhibitor + MEK inhibitor	MEL (V600, 2020)	NA	NA	NA
2014	*BRCA1* or *BRCA2* Oncogenic Mutations	*Olaparib*	PARP inhibitor	OVC (2014)[l] BC (2018)[m] PAAD (2019)[m] mCRPC (2020)[n]	NA	Rucaparib (OVC, 2016; mCRPC, 2020)[o] Talazoparib (BC, 2018)[p] Niraparib (OVC/FT/PSEC, 2019)	NA
2015	*NRAS* Wildtype	*Panitumumab*[k]	Anti-EGFR antibody	CRC (2015)	NA	NA	NA
2016	*ROS1* Fusions	*Crizotinib*	ALK/ROS1/MET inhibitor	NSCLC (2016)	NA	*Entrectinib* (NSCLC, 2019)	NA
2017	FLT3 Internal Tandem Duplication, D835, I836	Midostaurin	FLT3 inhibitor	AML (2017)	NA	Gilteritinib (AML, 2018)	NA
	MSI-H	*Pembrolizumab*	Anti-PD-1 antibody	All Solid Tumors (2017)	NA	Nivolumab (CRC, 2017)	NA
		Ipilimumab + Nivolumab	Anti-CTLA-4 antibody + anti-PD-1 antibody	CRC (2018)	NA	NA	NA
	IDH2 R140, R172	Enasidenib	IDH2 inhibitor	AML (2017)	NA	NA	NA
2018	*IDH1* R132	Ivosidenib	IDH1 inhibitor	AML (2018) CHOL (2021)	NA	NA	NA
	NTRK1, NTRK2 or NTRK3 Fusions	Larotrectinib	NTRK inhibitor	All Solid Tumors (2018)	NA	*Entrectinib* (All Solid Tumors, 2019)	NA
2019	*FGFR2* Fusions	Erdafitinib	FGFR inhibitor	Urothelial Carcinoma (2019)	NA	*Pemigatinib* (CHOL, 2020)[q] Infigratinib (CHOL, 2021) Futibatinib (CHOL, 2022)	NA
	FGFR3 Fusions, S249C, R248C, G370C, Y373C				NA	NA	NA
	PIK3CA E542K, E545D, E545K, E545G, E545A, H1047R, H1047L, H1047Y, C420R, Q546E, Q546R	Alpelisib	PI3Kα inhibitor	BC (2019)	NA	NA	NA
2020	*PDGFRA* Exon 18 Mutations	*Avapritinib*	PDGFRA/KIT inhibitor	GIST (2020)	NA	NA	NA
	SMARCB1 Deletion	*Tazemetostat*	EZH2 inhibitor	Epithelioid Sarcoma (2020)	NA	NA	NA

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	NF1 Oncogenic Mutations	Selumetinib	MEK1/2 inhibitor	Plexiform Neurofibroma (2020)	NA	NA	NA
	MET Exon 14 skipping mutations	Capmatinib, Tepotinib[r]	MET inhibitor	NSCLC (2020 [Capmatinib], 2021 [Tepotinib])	NA	NA	NA
	RET Fusions	Selpercatinib, Pralsetinib[s]	RET inhibitor	NSCLC (2020) Thyroid Cancer (2020) All Solid Tumors (2022; Selpercatinib only)	NA	NA	NA
	RET Oncogenic Mutations			MTC (2020)			
	ATM, BARD1, BRIP1, CDK12, CHEK1/2, FANCL, PALB2, RAD51B RAD51C, RAD51D, RAD54L Oncogenic Mutations	*Olaparib*	PARP inhibitor	mCRPC (2020)	NA	NA	NA
	TMB-H	*Pembrolizumab*	Anti-PD-1 antibody	All Solid Tumors (2020)	NA	NA	NA
	EZH2 *A692V, Y646F, Y646C, Y646S, Y646N, Y646H, A682G*	*Tazemetostat*	EZH2 inhibitor	Follicular Lymphoma (2020)	NA	NA	NA
2021	*EGFR* Exon 20 insertions	Amivantamab	EGFR and MET-directed bi-specifc antibody	NSCLC (2021)	NA	NA	NA
		Mobocertinib	EGFR-targeted kinase inhibitor				
	KRAS G12C	Sotorasib	KRAS G12C inhibitor	NSCLC (2021)	NA	NA	NA
	KIT D816	*Avapritinib*	PDGFRA/KIT inhibitor	AdvSM (2021)	NA	NA	NA
	VHL Oncogenic Mutations	Belzutifan	HIF-2α inhibitor	VHL-associated RCC, CNS hemangioblastomas, or pNET (2021)	NA	NA	NA
2022	*FGFR1* Fusions	*Pemigatinib*[q]	FGFR-inhibitor	Myeloid/Lymphoid Neoplasms with FGFR1 Rearrangement (2022)	NA	NA	NA
	ERBB2 Oncogenic Mutations	*Trastuzumab Deruxtecan*[g]	HER2 -targeted agent	NSCLC (2022)	NA	NA	NA

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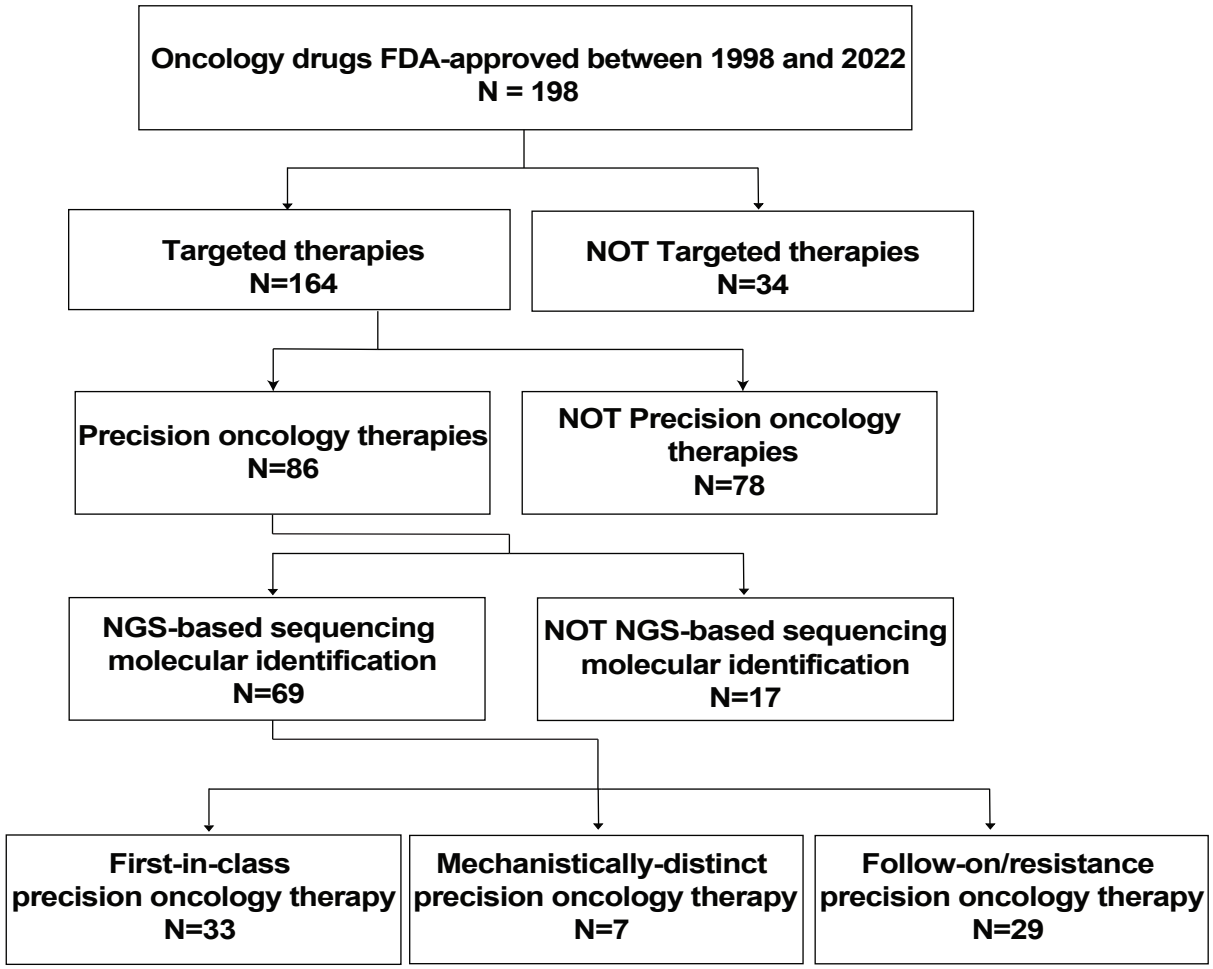

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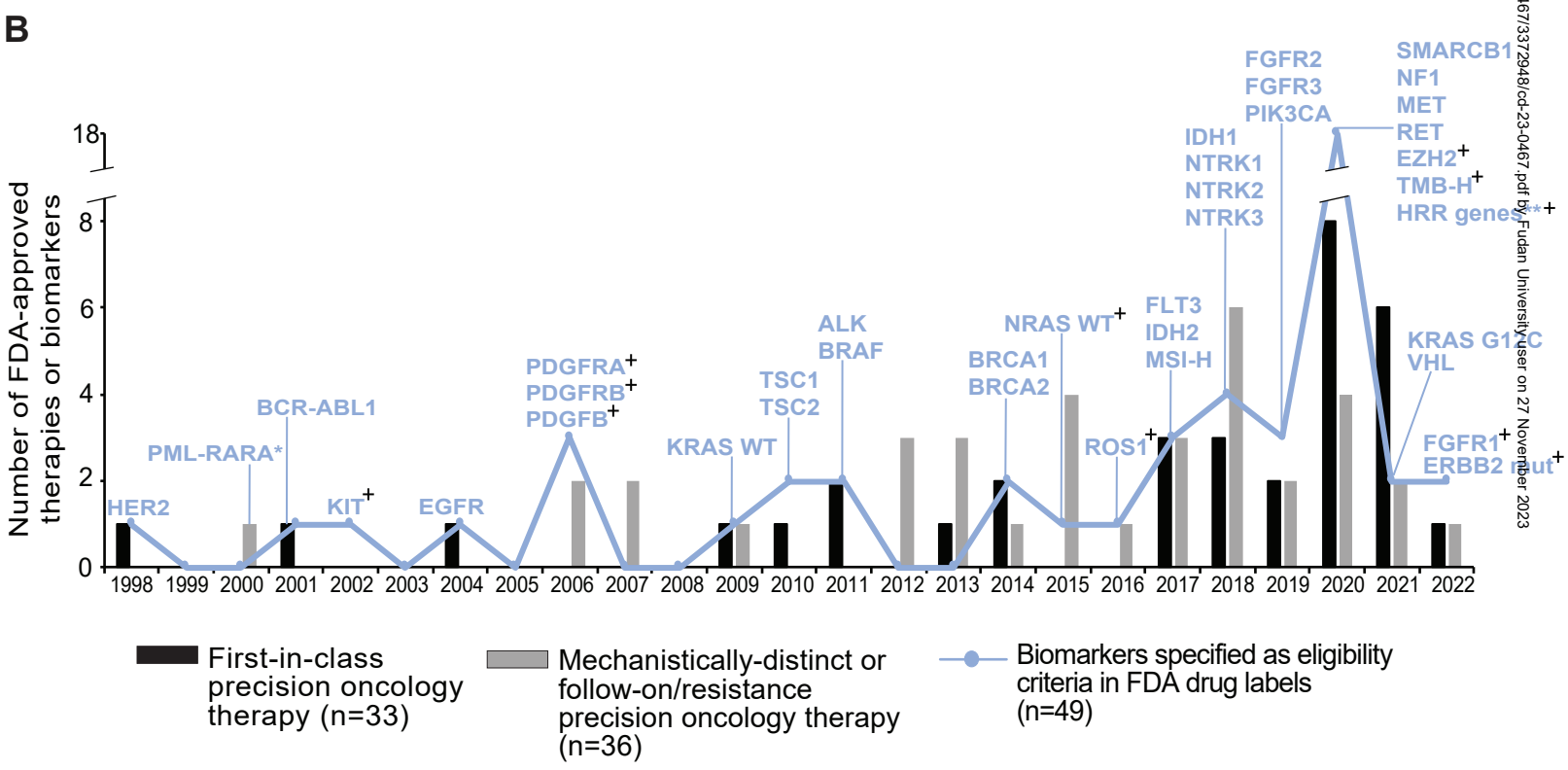

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Figure 1

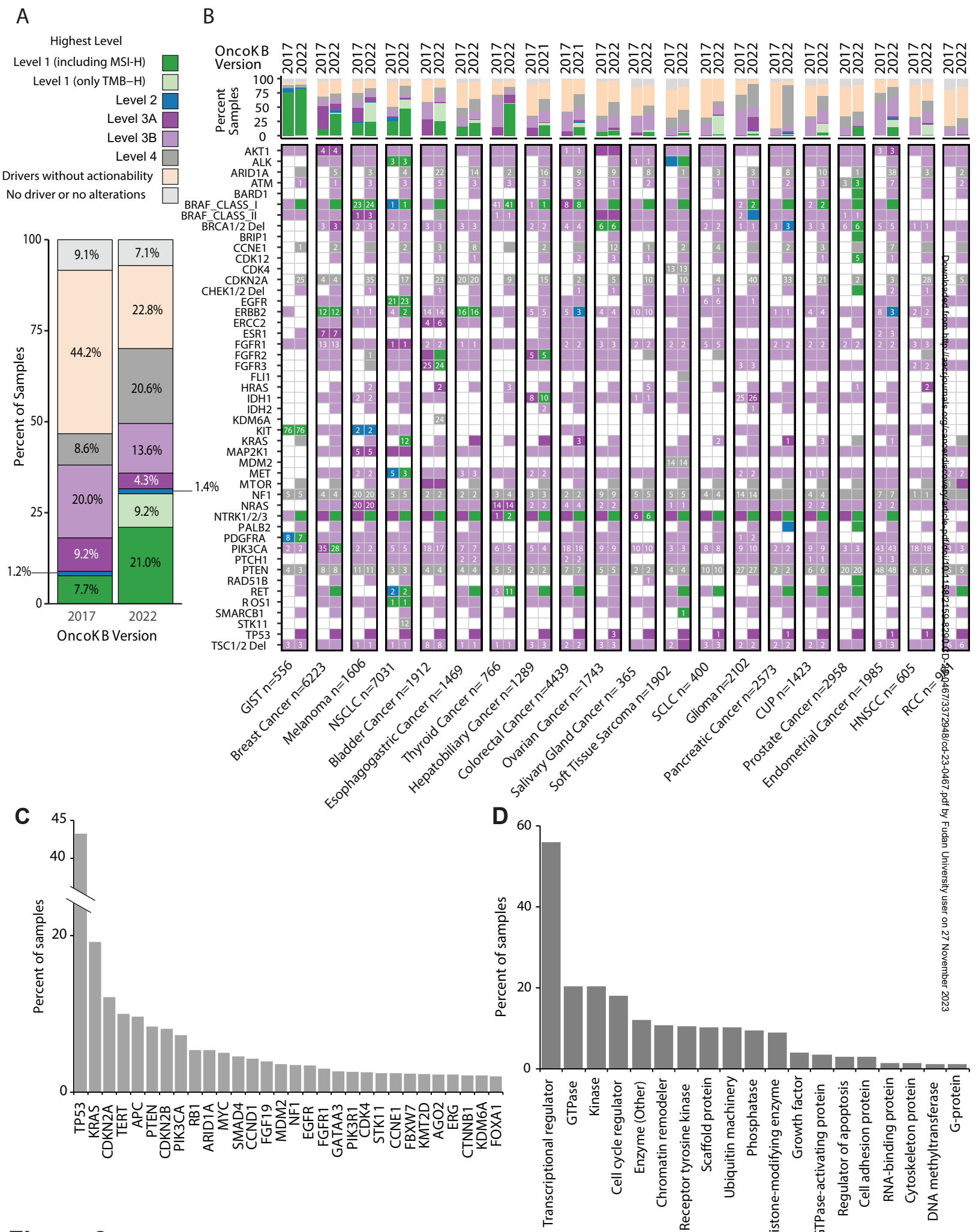

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Figure 2