Widespread Adoption of Precision Anticancer Therapies After Implementation of Pathologist-Directed Comprehensive Genomic Profiling Across a Large US Health System

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ABSTRACT

PURPOSE Precision therapies and immunotherapies have revolutionized cancer care, with novel genomic biomarker-associated therapies being introduced into clinical practice rapidly, resulting in notable gains in patient survival. Despite this, there is significant variability in the utilization of tumor molecular profiling that spans the timing of test ordering, comprehensiveness of gene panels, and clinical decision support through therapy and trial recommendations.

METHODS To standardize testing, we designed a pathologist-directed test ordering system at the time of diagnosis using a 523-gene DNA/RNA hybrid comprehensive genomic profiling (CGP) panel and extensive clinical decision support tools. To comprehensively characterize the clinical impact of this protocol, we developed a novel natural language processing (NLP)–based approach to extract clinical features from physician chart notes. We assessed test actionability rates, therapy choice, and outcomes across a set of 3,216 patients with advanced cancer.

RESULTS We observed 49% of patients had at least one actionable genomic biomarker-driven–approved and/or guideline-recommended targeted or immunotherapy (IO) and 53% of patients would have been eligible for a precision therapy clinical trial from three large basket trials. When assessing CGP versus an in silico 50-gene panel, 67% of tumors compared with 33% harbored actionable alterations including clinical trials. Among patients with 6 months or more of follow-up, over 52% received a targeted therapy (TT) or IO, versus 32% who received conventional chemotherapy alone. Furthermore, patients receiving TT had significantly improved overall survival compared with patients receiving chemotherapy alone ($P < .001$).

CONCLUSION Overall, these data represent a major shift in standard clinical practice toward molecularly guided treatments (targeted and immunotherapies) over conventional systemic chemotherapy. As guidelines continue to evolve and more precision therapeutics gain approval, we expect this gap to continue to widen.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

Genomic biomarker-driven precision therapy represents an evolution in cancer treatment over the past decade or more. Mutation-targeting therapies (eg, epidermal growth factor receptor [EGFR] tyrosine kinase inhibitors, tyrosine receptor kinase [TRK] kinase inhibitors, etc) have been associated with improved outcomes for patients with tumors harboring specific gene alterations.[1] In parallel, immune checkpoint inhibitor (ICI)–based immunotherapies have emerged as a major treatment modality resulting in remarkably durable responses.[2,3] Of note, key biomarkers for ICIs include PD-L1 immunohistochemistry (IHC)[4-7]; similar associations have been seen using genome-guided biomarkers including tumor mutational burden (TMB) and microsatellite instability (MSI) assessment.[8,9] The field continues to evolve and now common driver genes, such as *KRAS*, are targetable with precision and/or immunotherapeutic approaches.[10-12]

A key challenge in this landscape is enabling universal access to genomic testing that comprehensively covers all currently relevant genomic biomarkers. Barriers to CGP access include

CONTEXT

Key Objective
Does the routine implementation of in-house comprehensive genomic profiling (CGP) for patients with advanced-stage solid tumor improve patient actionability, treatment, and outcomes?

Knowledge Generated
In 52% of CGP-tested advanced-stage cancer patients with follow-up, the patient received a matched targeted therapy or immunotherapy as opposed to 32% of patients who received conventional systemic chemotherapy alone. Patients who received a TT had significant overall survival (OS) as opposed to patients who received only chemotherapy ($P < .001$).

Relevance
Removing barriers to routine CGP testing can broaden treatment opportunities to patients with cancer and improve OS relative to conventional chemotherapy alone.

preference for older tumor profiling tools such as single-gene or small panel testing, cost of CGP, variable coverage of CGP by insurers, and physician hesitancy, in part triggered by the complexity of the interpretation of CGP reports.[13-15] Despite this, emerging studies show a clear benefit in identification of a broader spectrum of actionable targets and survival gains for precision medicine–treated patient populations.[16-23] Additional CGP benefits include proper diagnostic tissue management, enabled by the assessment of all actionable markers in a single assay as well as potentially improved turnaround times versus traditional workflows where single biomarkers are often tested sequentially in a reflexive manner. CGP used as a pathologist-directed test after diagnosis also has the potential to aid the diagnostic process, as landmark tumor alterations or mutational signatures may resolve a differential diagnosis or help resolve a carcinoma of unknown primary.[24-28] To systematically assess the impact of pathologist-directed CGP testing, we developed a novel programmatic approach where testing was initiated at the time of diagnosis and performed at no cost to patients. From this, we evaluated the actionability of the CGP results and analyzed the systemic therapies and outcomes of the CGP-tested patient cohort.

METHODS

Study Design and Patient Population

For the current study, two novel changes were introduced to standard clinical workflows. First, we instituted a pathologist-directed protocol system-wide, where somatic testing was performed immediately at the time of diagnosis for all patients with advanced solid tumor, and second, we standardized all testing to a single 523-gene DNA/RNA CGP assay (ProvSeq). ProvSeq (Providence, Portland, OR) is an in-house laboratory-developed protocol (LDP) using hybrid capture–based DNA and RNA reagents on the basis of TruSight Oncology 500 High-Throughput kits and sequenced on a NovaSeq 6000 sequencer (Illumina, Inc, San Diego, CA). The assay involves the capture and sequencing of coding regions and intron-exon junctions of 523 genes (Appendix Table A1, online only), hybrid capture and RNA-seq of 23 genes for identification of fusions, and TMB and MSI assessment. Analysis for the assay is performed using the TruSight Oncology 500 local app (Illumina, Inc) along with STAR-Fusion. Interpretation for all cases was performed by an internal team of experts as per AMP/College of American Pathologists (CAP)/ASCO guidelines in conjunction with using the OncoKB knowledge base as well as ClinVar, gnomAD, and COSMIC public databases.[29-33] The ProvSeq LDP assay was validated according to standards set by the CAP. Analysis for this study included all patients with advanced cancer tested with CGP under the pathologist-directed protocol between September 2019 and November 2021. As an in silico comparator cohort, we also evaluated genomic profiles from this cohort by subsetting to the space of a 50-gene small panel (evaluating full coding regions for these genes), on the basis of a previous LDP used at Providence (ProvSeq Focus; Appendix Table A2 for the gene list). Note that this panel does not include TMB or MSI because of the smaller size of the genome interrogated. Additionally, 1,192 patients who underwent commercial sendout testing between October 2018 and October 2023 were analyzed to assess the impact pathologist-driven testing had on the time between genomic report date and first oncologist visit within the health system.

Institutional Review Board Approval

All research was performed under protocol 201900048 approved by Providence institutional review board. All CGP results and associated clinical metadata were deidentified and aggregated for these analyses.

Clinicogenomic Data Set Construction

Biomarker data included variant call files, annotations, designations of pathogenicity by pathologists/geneticists, clinical

interpretations, sequencing quality metrics, and PD-L1 IHC results. Biomarker results were linked to clinical data extracted from electronic medical records (EMRs). Cancer staging, histology, and vital status data were sourced from the systemwide Cancer Registry. Missing data points (eg, histology and treatment status) were manually curated. Patients who received testing between September 2019 and November 2021 were selected for further analysis (N = 3,216 patients; see Appendix Fig A1 for a schematic). These patients had a median follow-up time of 11 months (IQR, 3-19 months). Of those 3,216 patients, 2,028 patients (63%) had reported follow-up or treatment information. The 1,482 stage IV patients who had reported follow-up information and were not enrolled in a clinical trial or received a standard-of-care treatment were assessed for treatment selection after testing. These 1,482 stage IV patients had a median follow-up time of 15 months (IQR, 8-21 months).

Machine Learning–Based Chart Mining

As PD-L1 results were typically reported in free-text pathology reports in our data set, we developed a machine learning–based information extraction system, which uses a customized version of spaCy[34] for sentence segmentation and Python's Natural Language Toolkit (NLTK)[35] for tokenization. Each extracted result contains the PD-L1 gene mentions, assay types (22C3, 28–8, SP263, and SP142), staining intensity, analysis methods (tumor proportional score or combined positive score), and expression values (eg, <1%, 10, high). We developed our rules using notes before a certain date and constructed a randomly selected and expert annotated test set from pathology reports and progress notes after that date. Comparison with the test set shows that our pipeline achieved high performance: precision 97.5, recall 89.6, and F1 93.4.

Actionability Assessment

Actionability was assessed on the basis of criteria compiled in the OncoKB database.[30] Tumor types were translated to OncoTree codes, assessed for stage, and variants were matched to actionable biomarker categories (OncoKB levels 1 and 2). Patients were assigned to the level of most significant alteration on the basis of levels of evidence: actionable biomarkers predictive of response to US Food and Drug Administration (FDA)–approved therapies (level 1), or predict response to guideline-recommended or standard-of-care therapies (level 2) that are not FDA-approved. In instances where a biomarker became actionable within the window of our study (eg, *KRAS* G12C in 2021), patients who received genetic testing before the FDA approval date of the specific treatment were not considered actionable, even if they harbored the actionable alteration.

To assess clinical trial matching eligibility, the patients were compared to the enrollment criteria for three major basket trials (ASCO-TAPUR, NCI-MATCH, and MyPathway). Note that this limited list will likely lead to an underestimation of available trials matching to a patient's genomic profile; however, variability in biomarker eligibility descriptions across ClinicalTrials.gov created challenges with broader trial matching analyses. For this analysis, patients were counted as matched if they met the trial's genomic and cancer type enrollment criteria, and testing date fell within the trial's eligibility time frame. The ASCO-TAPUR clinical trial arm for treatment with cetuximab in patients with wild-type *KRAS*, *NRAS*, and *BRAF* was left out of the analysis to prevent a scenario where all patients would be eligible for a clinical trial regardless of whether they possessed wild-type or mutated *KRAS*/*NRAS*.

We also assessed actionability in the cohort on the basis of the original set of 523 genes in the CGP assay versus the subset of actionable mutations that would have been detected using a legacy 50-gene panel that was previously deployed at Providence (Appendix Tables A1 and A2) by in silico subsetting to the original 50 genes.

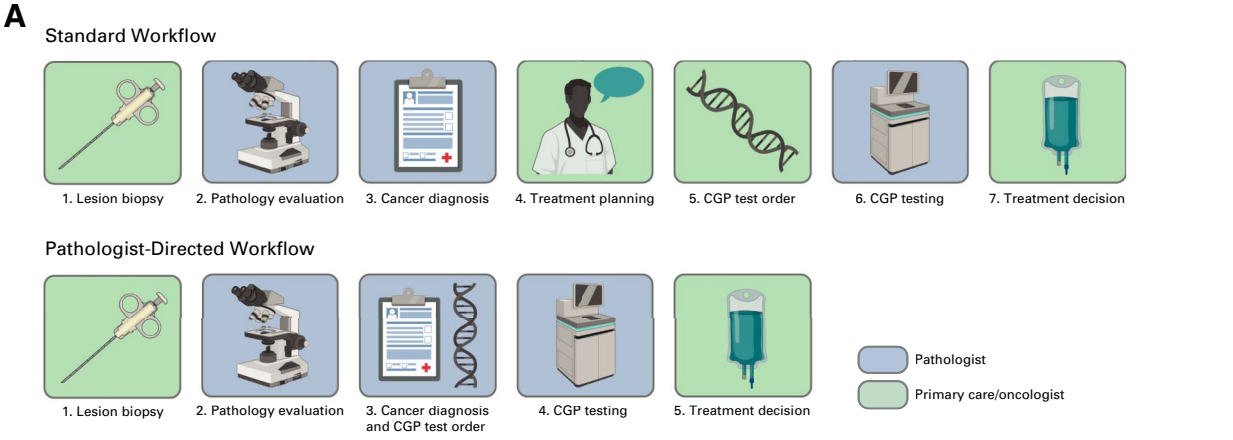
Treatment Selection and Outcomes

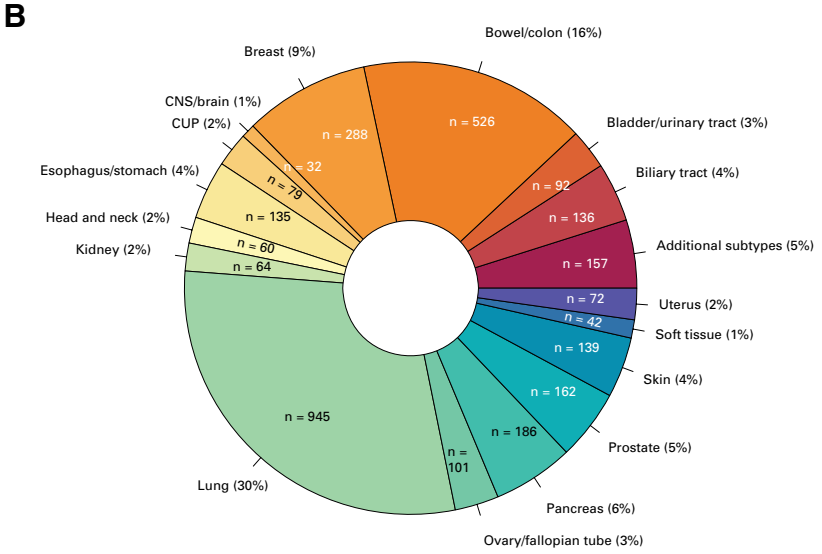
Treatments were classified by type of therapy: (1) matched targeted therapy (TT) defined as FDA approved and/or National Comprehensive Cancer Network guideline-based therapies requiring OncoKB level 1 and 2 biomarkers; (2) non–CGP biomarker–associated TTs are precision therapies that do not require actionable OncoKB level 1 and 2 biomarkers (eg, sorafenib in kidney cancer or everolimus in breast cancer); (3) off-label TTs are therapies that were administered to patients who lacked the matched OncoKB level 1 or 2 biomarker for the TT; (4) immunotherapy (IO) including ICI; (5) chemotherapy and IO (chemo + IO) combination therapy of ICI and traditional antineoplastics; and (6) chemotherapy only includes use of traditional antineoplastics.

Overall survival (OS) was documented for all tumor types (N = 1,463 patients) for patients with sufficient follow-up information and separately for a subset of patients with non–small cell lung cancer (NSCLC; N = 316 patients). OS was classified as months after report for the most recent CGP or first treatment to the date of last follow-up or death from any cause. OS by treatment type is presented in unadjusted Kaplan-Meier plots as well as a Cox proportional-hazards model adjusted for patient age and tumor type. All survival analyses were carried out in R v.4.2.2 using the survival package.

RESULTS

The goal of the study was to assess the impact of in-house CGP testing using a protocol where CGP testing was initiated by a pathologist immediately upon a histopathologic advanced cancer diagnosis (Fig 1A). This workflow replaced a previous methodology largely using oncologist-directed small panel testing (5-50 genes). By shifting next generation sequencing (NGS) upstream, we could facilitate (1)





Additional Subtypes	No. (%)
Liver	29 (0.9)
Thyroid	27 (0.8)
Missing/not reported	24 (0.7)
Cervix	17 (0.5)
Peritoneum	11 (0.3)
Adrenal gland	8 (0.2)
Ampulla of Vater	8 (0.2)
Pleura	6 (0.2)
Thymus	5 (0.2)
Vulva/vagina	5 (0.2)
Bone	4 (0.1)
Eye	4 (0.1)
Lymphoid	4 (0.1)
Other	3 (0.1)
Peripheral nervous system	1 (<0.1)
Testis	1 (<0.1)

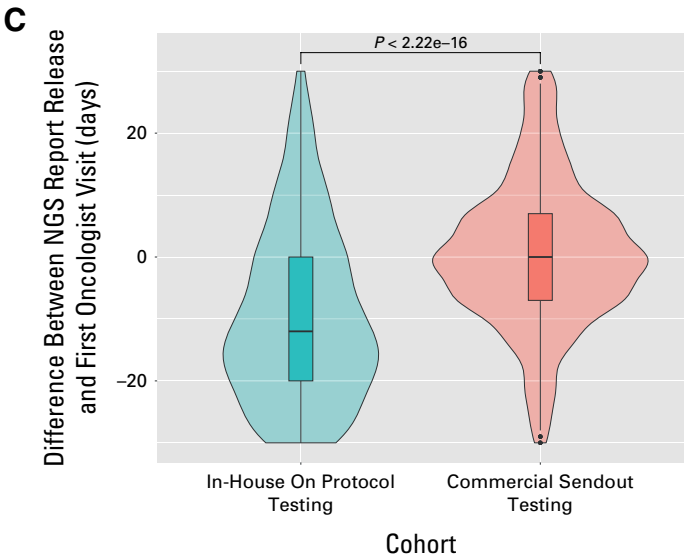


FIG 1. Overview of testing protocol and cancer subtypes. (A) Pathologist-directed testing versus previous standard genomic testing workflows in oncology. Created with BioRender.com. (B) Tumor type breakdown of the patients tested in this cohort. (C) Time difference between NGS report release date and first oncologist visit, in days, between pathologist-directed testing (N = 432 patients) and non–pathologist-directed testing (N = 1,192 patients). CGP, comprehensive genomic profiling; CUP, carcinoma of unknown primary; NGS, next generation sequencing.

TABLE 1. Patient Characteristics

Characteristic	All Patients	Stage IV Treated Patients	Stage IV Treated NSCLC Patients
Patients with advanced cancer tested using CGP	3,216	1,482	319
Age at the time of testing, years, median (IQR)	67.0 (60.0-75.0)	66.0 (58.0-74.0)	68.0 (62.0, 77.0)
Sex, No. (%)			
Female	1,684 (52.4)	779 (52.6)	163 (51.1)
Male	1,532 (47.6)	703 (47.4)	156 (48.9)
Race, No. (%)			
White	2,592 (80.6)	1,215 (82.0)	254 (79.6)
Black	76 (2.4)	33 (2.2)	6 (1.9)
Asian	149 (4.6)	87 (5.9)	23 (7.2)
American Indian or Alaska Native	35 (1.1)	15 (1.0)	5 (1.6)
Native Hawaiian or Other Pacific Islander	21 (0.7)	6 (0.4)	2 (0.6)
Unknown	343 (10.7)	126 (8.5)	29 (9.1)
Stage, No. (%)			
Stage III	401 (12.5)	· (—)	· (-)
Stage IV	2,815 (87.5)	· (—)	· (-)
Year of test ordered, No. (%)			
2019	85 (2.6)	45 (3.0)	13 (4.1)
2020	1,359 (42.3)	664 (44.8)	145 (45.4)
2021	1,772 (55.1)	773 (52.2)	161 (50.5)
Turnaround time in days,[a] median (IQR)	14.0 (12.0-15.0)	14.0 (12.0-15.0)	13.0 (11.0, 14.0)
Follow-up in months since testing ordered,[b] median (IQR)	11.0 (3.0-19.0)	15.0 (8.0-21.0)	15.0 (6.0, 21.0)
Deceased, No. (%)	1,508 (47.1)	693 (46.8)	159 (49.8)
Progression, No. (%)[c]	495 (15.4)	384 (25.9)	71 (22.3)

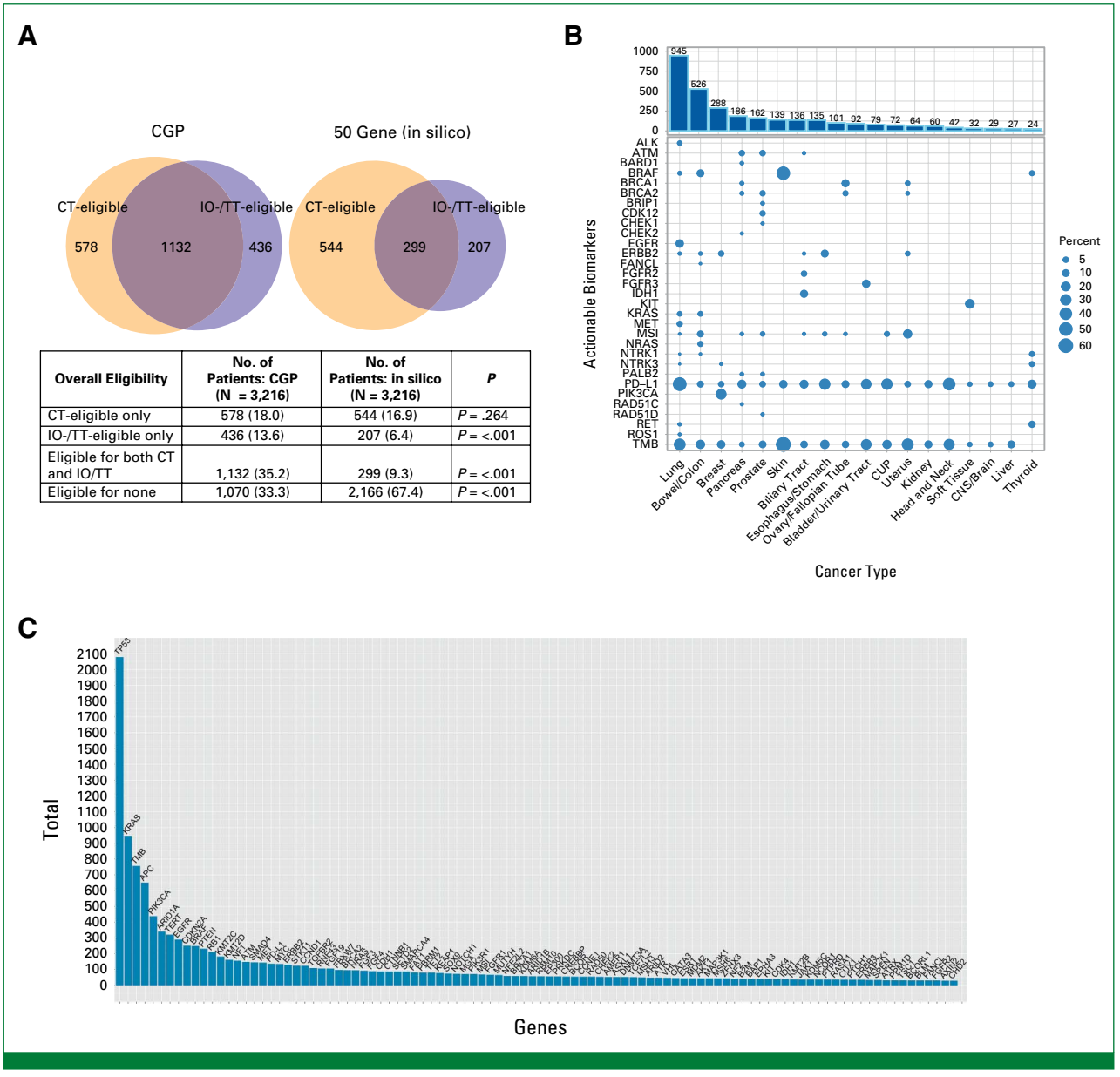
NOTE. Patient demographics for the cohort of 3,216 advanced-stage (III/IV) patients with CGP testing as well as the subset of 1,482 stage IV patients with at least 6 months of follow-up time who were evaluated for treatment and OS. Furthermore, the subset of 319 stage IV treated NSCLC patients highlighted as a most frequent tumor type evaluated for treatment and OS. CGP testing occurred between 2019 and 2021.
Abbreviations: CGP, comprehensive genomic profiling; EMR, electronic medical record; MSFT, Microsoft; NSCLC, non–small cell lung cancer; OS, overall survival.
[a]n = 24 missing values removed from average turnaround time calculation.
[b]n = 20 missing values were excluded from average follow-up time since testing ordered calculation.
[c]Progression derived from MSFT HealthNext Progression Model, Cancer Registry Data, and EMR treatment discontinuation documentation.

use of test results in the diagnostic process and (2) make results available earlier to the treating physician. Testing was also performed under the research protocol at no cost, to remove potential reimbursement-related barriers to CGP testing. The most frequent tumor types tested were lung (30%), bowel/colon (16%), breast (9%), pancreas (6%), and prostate (5%; Fig 1B) cancers. We observed a turnaround time of 14 days (IQR, 12-15 days, Table 1), which was similar to previous small panel testing at the same institution. Pathologist-directed testing made results available earlier in the clinical decision-making process; NGS results were available more frequently at the time of the initial medical oncologist visit (median −12 days) compared with non–pathologist-directed commercial sendout testing (median 0 days, $P < .005$; Fig 1C).

The study included 3,216 patients with advanced solid cancer whose tumors were subject to CGP between September 2019 and November 2021 (Table 1). The median age of patients was 67 years, 52% were female, and 80% were White. Most patients had metastatic disease (88%), 40% entered hospice, and 33% died during follow-up. Most of the 3,216 patients were tested in 2020 (42%) and 2021 (55%).

Results of Actionability Assessment

Overall, 49% (1,568/3,216) of CGP-tested patients had at least one guideline-based actionable biomarker (Fig 2A). Figure 2B shows the breakdown of mutations identified for genes that are actionable on the basis of FDA or standard-of-care biomarkers (OncoKB 1 and 2) without FDA approval. High TMB was the most frequent biomarker detected (22%) and was detected across almost all the main tumor types tested, followed by *BRAF* (11%), and *EGFR* (4%). Figure 2C shows the distribution of all detected pathogenic alterations (ie, not filtered by current actionability). As expected, we observed high mutational rates for common tumor suppressor genes such as *TP53*. Additionally, we identified a long



Overall Eligibility	No. of Patients: CGP (N = 3,216)	No. of Patients: in silico (N = 3,216)	P
CT-eligible only	578 (18.0)	544 (16.9)	P = .264
IO-/TT-eligible only	436 (13.6)	207 (6.4)	P = <.001
Eligible for both CT and IO/TT	1,132 (35.2)	299 (9.3)	P = <.001
Eligible for none	1,070 (33.3)	2,166 (67.4)	P = <.001

FIG 2. Mutational actionability/pathogenicity in the cohort. (A) Comparison of the proportion of guidelines-based IO/TT or clinical trial–based IO/TT eligibility for CGP-tested patients versus 50-gene in silico subset panels. (B) Frequency map showing the number of cases per tumor type with actionable mutations in the top evidence categories (OncoKB levels 1/2/R1). (C) Long-tail histogram plot for the top 100 pathogenic mutations across all cases. CGP, comprehensive genomic profiling; IO, immunotherapy; TT, targeted therapy.

tail of other clinically significant genes that may be targetable in the future.

53% (1,710/3,216) of patients tested with CGP matched to one or more arms across the three assessed basket clinical trials (ASCO-TAPUR, NCI-MATCH, and MyPathway), compared with 26% (843/3,216; $P < .001$) if patients were tested using only a 50-gene panel (in silico cohort). Matched cases included patients matching to IO trial arms on the basis of TMB-high but also cases matching on the basis of rare biomarkers (*NTRK*, *PTCH1* etc). Overall, 67% (2,146/3,216) of tumors from CGP-tested patients compared with 33% (1,050/3,216) for in silico 50-gene panel patients ($P < .001$) harbored actionable mutations on the basis of either guideline-based or clinical trial matching.

Treatment Utilization Across CGP-Tested Patients

We next assessed the frequency of utilization of precision/IO therapies for patients with actionable mutations compared with traditional anticancer therapies (eg, chemotherapy). From the original 3,216 patients in the cohort, 1,482 patients with documented clinical follow-up and treatment in our EMR were evaluated. Figure 3 shows treatment type utilization across the cohort, grouped by the type of biomarkers

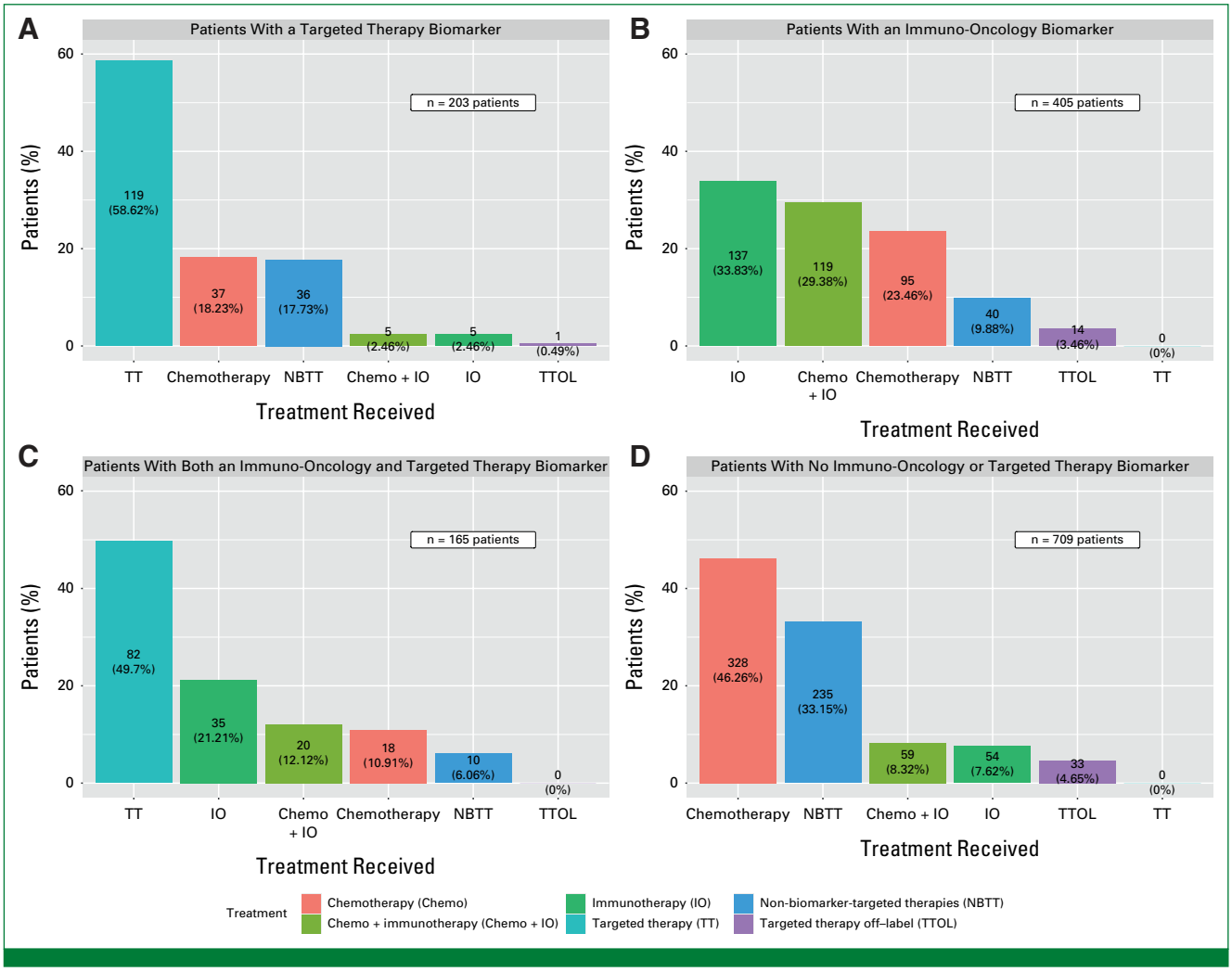


FIG 3. Distribution of types of therapy post-testing. Chemotherapy (Chemo), IO, chemo + IO, TT, NBTT, and TTOL use for patients with documented follow-up, grouped by the presence or absence of TT or IO biomarkers: (A) patients with a targeted therapy biomarker, (B) patients with an immuno-oncology biomarker, (C) patients with both an immuno-oncology and targeted therapy biomarker, and (D) patients with no immuno-oncology or targeted therapy biomarker. CT, computed tomography; IO, immunotherapy; NBTT, non–biomarker-targeted therapies; TT, targeted therapy; TTOL, targeted therapy off-label.

detected in their CGP profile. Of note, precision/IO therapy utilization was high, with 54% (311/570) of patients with an appropriate IO biomarker receiving either IO or IO plus chemotherapy. This far exceeded the percentage of tested patients who received chemotherapy alone (32%; 478/1,482). In patients with only an actionable TT biomarker, use of a TT was indeed the most widely used single modality, with 59% (119/203) of TT-positive patients receiving a TT. Similarly, for patients with only IO-positive biomarkers (TMB-high, MSI-high, or PD-L1–positive), IO was the dominant treatment modality, with 63% (256/405) of patients receiving an IO with or without chemotherapy. As expected, we detected little (TT) use in patients with no actionable mutations in their CGP profile (33 patients, 2.0% of cohort). An additional 74 stage IV patients were enrolled in a clinical trial for treatment. 59% (44/74) of those patients would have been eligible for a precision therapy clinical trial on the basis of the three basket trials we assessed with 14% (6/44) of those patients enrolling in the exact clinical trial that they were deemed eligible for. Off-label TT use was very rare in patients without an actionable TT biomarker (15 patients, 1% of cohort). IO use in patients without an IO-positive biomarker was more common, with 13% (123/912) receiving IO without a matched biomarker, indicative of newer IO treatment guidelines in advanced cancer.

Clinical Outcomes for CGP-Tested Patients

Across all tumor types, patients treated with biomarker-guided TT or IO show significant improvements in overall survival versus chemotherapy (Figs 4A and 4B). Median OS was 25 months (95% CI, 21 to Inf; TT) versus 17 months (95% CI, 15-22; chemotherapy only). Patients receiving TT had better survival outcomes compared with chemotherapy only (hazard ratio [HR], 0.66, [95% CI, 0.52 to 0.84], $P < .001$), even after controlling for age and tumor

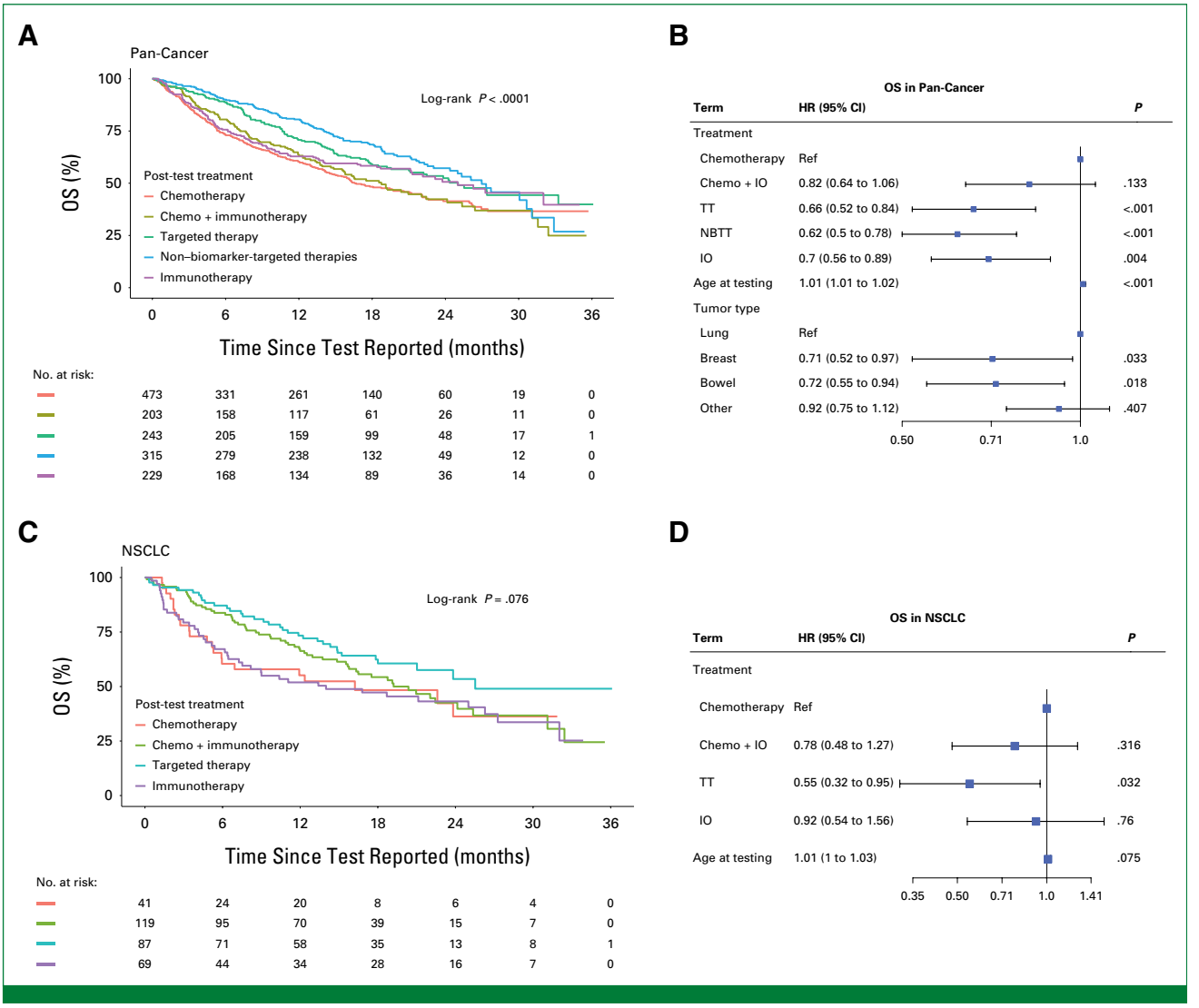


FIG 4. Overall survival in the CGP cohort. (A) Pan-cancer Kaplan-Meier curve showing survival after CGP testing for patients treated with different modalities. (B) Pan-cancer hazard model for treated patients. (C) NSCLC Kaplan-Meier survival curves for different treatment modalities. (D) NSCLC hazard model for treated patients. CGP, comprehensive genomic profiling; IO, immunotherapy; NSCLC, non–small cell lung cancer; OS, overall survival; TT, targeted therapy.

type. For the subset of patients diagnosed with NSCLC, the median OS was 26 months (95% CI, 21 to Inf; TT) versus 16 months (95% CI, 6 to Inf; chemotherapy only). Patients with NSCLC receiving TT had better survival outcomes compared with chemotherapy only (HR, 0.55 [95% CI, 0.32 to 0.95], $P = .032$) after controlling for age. We did not observe differences between chemotherapy and IO (or chemo-IO) survival, which may be due in part to cohort sizes.

DISCUSSION

Our study represents a unique look at the impact of a programmatic deployment of pathologist-directed CGP testing across a diverse community health system. Among CGP-tested patients, 49% had one or more actionable biomarkers for a TT or IO, a result that significantly exceeded the actionable fraction when we evaluated the same patients in silico using a legacy 50-gene panel, suggesting that many patients receiving small panel testing would likely benefit from being retested with a CGP. Although our study evaluated impact by removing testing cost barriers, in a real-world scenario, payers would need to consistently reimburse CGP testing to improve overall population outcomes and to accelerate utilization of CGP in a clinical setting. Moreover, given that a subset of patients will likely be uninsured or have significant copays, reducing the cost burden of testing remains an important goal for the community. Indeed, de Moor and colleagues have shown that cost burden was a major factor in oncologist consideration of precision medicine pathways.[36,37] Additionally, current payer prior authorization processes can add to testing turnaround times, potentially affecting whether test results are made available in the initial treatment window.

In the CGP-tested cohort, 36% (537/1,482) of patients received some type of TT or IO on the basis of the direct impact of a biomarker finding on a CGP report. Moreover, if we add in patients who received a non–biomarker-associated molecularly targeted therapy (eg, vascular endothelial growth factor inhibitors, cyclin-dependent kinase [CDK] inhibitors etc), we see that 68% (1,004/1,482) of patients received some type of TT or IO. This represents a fascinating paradigm shift in the treatment of advanced cancer and is indicative of the wide spectrum of targetable biomarkers that have made oncology the standard-bearer for precision approaches in medicine. Moreover, we found inherent value in making tumor genomic profiles available to researchers to aid in the development of the next generation of precision oncologic approaches. This is clear in the profound impact that The Cancer Genome Atlas has had on the field, and by newer data sharing consortia such as Project Genomics Evidence Neoplasia Information Exchange (GENIE), which has already aggregated over 100,000 tumor genomics cases and is rapidly growing in scale.[44-47]

Despite these successes, there are still significant gaps in providing precision medicine for all patients with advanced cancer. Many tested cases still do not yield an actionable marker, and that number is particularly high across some tumor types. Although some frequent targets have recently become actionable (*KRAS*, *IDH1* etc), more developments are needed, especially given that relevancy and utility have previously been cited as key rationales for oncologists' lack of utilization of genomic testing.[38] For the subset of patients with actionable markers who did not receive a precision therapy, significant effort needs to be invested to close these gaps including education and increased access to treatment. Moreover, socioeconomically disadvantaged communities may lack access to critical support systems related to precision medicine, such as clinical decision support, integration and alerts in electronic medical record systems, and access to precision medicine trials and molecular tumor boards.[38-40] Indeed, despite high matching rates to precision clinical trials, our data show that enrollment in these trials was low, consistent with other studies, and may be reflective of these factors.[41-43] As data complexity increases as well as integration of other modalities such as liquid biopsies, novel support strategies are needed to ensure that precision medicine is truly available to all who need it.

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EQUAL CONTRIBUTION

A.K.D., R.C.M., and A.V. contributed equally to this work.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

Genomic data analyzed in this study are available through cBioPortal from AACR Project GENIE under submitting institution Providence.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Widespread Adoption of Precision Anticancer Therapies After Implementation of Pathologist-Directed Comprehensive Genomic Profiling Across a Large US Health System

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APPENDIX

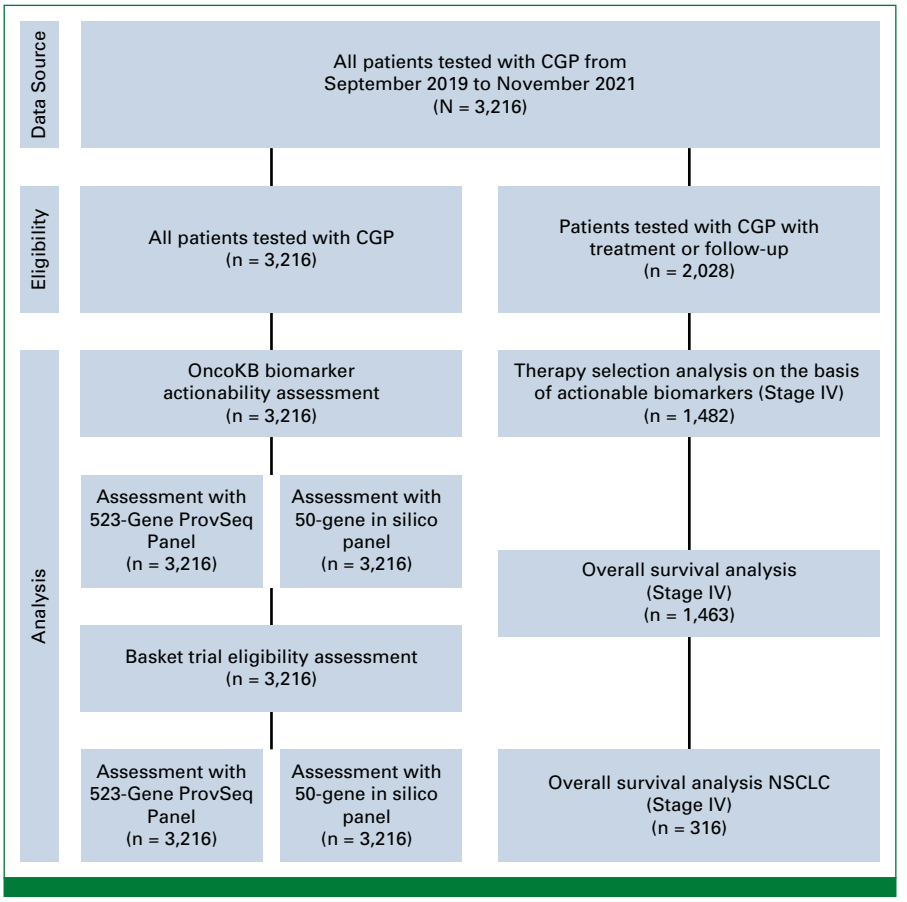

FIG A1. Flow diagram indicating scope of cohort throughout analyses. Flow diagram depicting the number of patients analyzed for overall actionability and clinical trial eligibility with the 523 Gene ProvSeq CGP panel and the 50-gene previous-generation in silico panel, in addition to the number of patients analyzed for therapy selection after testing and overall survival. CGP, comprehensive genomic profiling; NSCLC, non–small cell lung cancer.

TABLE A1. ProvSeq Gene List

Gene Symbol	Small Variants	Copy-Number Variants	Fusions (from RNA)
ABL1	✓	✓	✓
ABL2	✓	✓	–
ACVR1	✓	✓	–
ACVR1B	✓	✓	–
AKT1	✓	✓	–
AKT2	✓	✓	–
AKT3	✓	✓	✓
ALK	✓	✓	✓
ALOX12B	✓	✓	–
ANKRD11	✓	✓	–
ANKRD26	✓	✓	–
APC	✓	✓	–
AR	✓	✓	✓
ARAF	✓	✓	–
ARFRP1	✓	✓	–
ARID1A	✓	✓	–
ARID1B	✓	✓	–
ARID2	✓	✓	–
ARID5B	✓	✓	–
ASXL1	✓	✓	–
ASXL2	✓	✓	–
ATM	✓	✓	–
ATR	✓	✓	–
ATRX	✓	✓	–
AURKA	✓	✓	–
AURKB	✓	✓	–
AXIN1	✓	✓	–
AXIN2	✓	✓	–
AXL	✓	✓	✓
B2M	✓	✓	–
BAP1	✓	✓	–
BARD1	✓	✓	–
BBC3	✓	✓	–
BCL10	✓	✓	–
BCL2	✓	✓	✓
BCL2L1	✓	✓	–
BCL2L11	✓	✓	–
BCL2L2	✓	✓	–
BCL6	✓	✓	–
BCOR	✓	✓	–
BCORL1	✓	✓	–
BCR	✓	✓	–
BIRC3	✓	✓	–
BLM	✓	✓	–
BMPR1A	✓	✓	–
BRAF	✓	✓	✓
BRCA1	✓	✓	✓
BRCA2	✓	✓	✓
BRD4	✓	✓	–

(continued in next column)

TABLE A1. ProvSeq Gene List (continued)

Gene Symbol	Small Variants	Copy-Number Variants	Fusions (from RNA)
BRIP1	✓	✓	–
BTG1	✓	✓	–
BTK	✓	✓	–
C11orf30	✓	✓	–
CALR	✓	✓	–
CARD11	✓	✓	–
CASP8	✓	✓	–
CBFB	✓	✓	–
CBL	✓	✓	–
CCND1	✓	✓	–
CCND2	✓	✓	–
CCND3	✓	✓	–
CCNE1	✓	✓	–
CD274	✓	✓	–
CD276	✓	✓	–
CD74	✓	✓	–
CD79A	✓	✓	–
CD79B	✓	✓	–
CDC73	✓	✓	–
CDH1	✓	✓	–
CDK12	✓	✓	–
CDK4	✓	✓	✓
CDK6	✓	✓	–
CDK8	✓	✓	–
CDKN1A	✓	✓	–
CDKN1B	✓	✓	–
CDKN2A	✓	✓	–
CDKN2B	✓	✓	–
CDKN2C	✓	✓	–
CEBPA	✓	✓	–
CENPA	✓	✓	–
CHD2	✓	✓	–
CHD4	✓	✓	–
CHEK1	✓	✓	–
CHEK2	✓	✓	–
CIC	✓	✓	–
CREBBP	✓	✓	–
CRKL	✓	✓	–
CRLF2	✓	✓	–
CSF1R	✓	✓	✓
CSF3R	✓	✓	–
CSNK1A1	✓	✓	–
CTCF	✓	✓	–
CTLA4	✓	✓	–
CTNNA1	✓	✓	–
CTNNB1	✓	✓	–
CUL3	✓	✓	–
CUX1	✓	✓	–
CXCR4	✓	✓	–

(continued on following page)

TABLE A1. ProvSeq Gene List (continued)

Gene Symbol	Small Variants	Copy-Number Variants	Fusions (from RNA)
CYLD	✓	✓	–
DAXX	✓	✓	–
DCUN1D1	✓	✓	–
DDR2	✓	✓	–
DDX41	✓	✓	–
DHX15	✓	✓	–
DICER1	✓	✓	–
DIS3	✓	✓	–
DNAJB1	✓	✓	–
DNMT1	✓	✓	–
DNMT3A	✓	✓	–
DNMT3B	✓	✓	–
DOT1L	✓	✓	–
E2F3	✓	✓	–
EED	✓	✓	–
EGFL7	✓	✓	–
EGFR	✓	✓	✓
EIF1AX	✓	✓	–
EIF4A2	✓	✓	–
EIF4E	✓	✓	–
EML4	✓	✓	✓
EP300	✓	✓	–
EPCAM	✓	✓	–
EPHA3	✓	✓	–
EPHA5	✓	✓	–
EPHA7	✓	✓	–
EPHB1	✓	✓	–
ERBB2	✓	✓	✓
ERBB3	✓	✓	–
ERBB4	✓	✓	–
ERCC1	✓	✓	–
ERCC2	✓	✓	–
ERCC3	✓	✓	–
ERCC4	✓	✓	–
ERCC5	✓	✓	–
ERG	✓	✓	✓
ERRFI1	✓	✓	–
ESR1	✓	✓	✓
ETS1	✓	✓	✓
ETV1	✓	✓	✓
ETV4	✓	✓	✓
ETV5	✓	✓	✓
ETV6	✓	✓	–
EWSR1	✓	✓	✓
EZH2	✓	✓	–
FAM123B	✓	✓	–
FAM175A	✓	✓	–
FAM46C	✓	✓	–
FANCA	✓	✓	–

(continued in next column)

TABLE A1. ProvSeq Gene List (continued)

Gene Symbol	Small Variants	Copy-Number Variants	Fusions (from RNA)
FANCC	✓	✓	–
FANCD2	✓	✓	–
FANCE	✓	✓	–
FANCF	✓	✓	–
FANCG	✓	✓	–
FANCI	✓	✓	–
FANCL	✓	✓	–
FAS	✓	✓	–
FAT1	✓	✓	–
FBXW7	✓	✓	–
FGF1	✓	✓	–
FGF10	✓	✓	–
FGF14	✓	✓	–
FGF19	✓	✓	–
FGF2	✓	✓	–
FGF23	✓	✓	–
FGF3	✓	✓	–
FGF4	✓	✓	–
FGF5	✓	✓	–
FGF6	✓	✓	–
FGF7	✓	✓	–
FGF8	✓	✓	–
FGF9	✓	✓	–
FGFR1	✓	✓	✓
FGFR2	✓	✓	✓
FGFR3	✓	✓	✓
FGFR4	✓	✓	✓
FH	✓	✓	–
FLCN	✓	✓	–
FLI1	✓	✓	✓
FLT1	✓	✓	✓
FLT3	✓	✓	✓
FLT4	✓	✓	–
FOXA1	✓	✓	–
FOXL2	✓	✓	–
FOXO1	✓	✓	–
FOXP1	✓	✓	–
FRS2	✓	✓	–
FUBP1	✓	✓	–
FYN	✓	✓	–
GABRA6	✓	✓	–
GATA1	✓	✓	–
GATA2	✓	✓	–
GATA3	✓	✓	–
GATA4	✓	✓	–
GATA6	✓	✓	–
GEN1	✓	✓	–
GID4	✓	✓	–
GLI1	✓	✓	–

(continued on following page)

TABLE A1. ProvSeq Gene List (continued)

Gene Symbol	Small Variants	Copy-Number Variants	Fusions (from RNA)
GNA11	✓	✓	–
GNA13	✓	✓	–
GNAQ	✓	✓	–
GNAS	✓	✓	–
GPR124	✓	✓	–
GPS2	✓	✓	–
GREM1	✓	✓	–
GRIN2A	✓	✓	–
GRM3	✓	✓	–
GSK3B	✓	✓	–
H3F3A	✓	✓	–
H3F3B	✓	✓	–
H3F3C	✓	✓	–
HGF	✓	✓	–
HIST1H1C	✓	✓	–
HIST1H2BD	✓	✓	–
HIST1H3A	✓	✓	–
HIST1H3B	✓	✓	–
HIST1H3C	✓	✓	–
HIST1H3D	✓	✓	–
HIST1H3E	✓	✓	–
HIST1H3F	✓	✓	–
HIST1H3G	✓	✓	–
HIST1H3H	✓	✓	–
HIST1H3I	✓	✓	–
HIST1H3J	✓	✓	–
HIST2H3A	✓	–	–
HIST2H3C	✓	–	–
HIST2H3D	✓	✓	–
HIST3H3	✓	✓	–
HLA-A	*	–	–
HLA-B	*	–	–
HLA-C	*	–	–
HNF1A	✓	✓	–
HNRNPK	✓	✓	–
HOXB13	✓	✓	–
HRAS	✓	✓	–
HSD3B1	✓	✓	–
HSP90AA1	✓	✓	–
ICOSLG	✓	✓	–
ID3	✓	✓	–
IDH1	✓	✓	–
IDH2	✓	✓	–
IFNGR1	✓	✓	–
IGF1	✓	✓	–
IGF1R	✓	✓	–
IGF2	✓	✓	–
IKBKE	✓	✓	–
IKZF1	✓	✓	–

(continued in next column)

TABLE A1. ProvSeq Gene List (continued)

Gene Symbol	Small Variants	Copy-Number Variants	Fusions (from RNA)
IL10	✓	✓	–
IL7R	✓	✓	–
INHA	✓	✓	–
INHBA	✓	✓	–
INPP4A	✓	✓	–
INPP4B	✓	✓	–
INSR	✓	✓	–
IRF2	✓	✓	–
IRF4	✓	✓	–
IRS1	✓	✓	–
IRS2	✓	✓	–
JAK1	✓	✓	–
JAK2	✓	✓	✓
JAK3	✓	✓	–
JUN	✓	✓	–
KAT6A	✓	✓	–
KDM5A	✓	✓	–
KDM5C	✓	✓	–
KDM6A	✓	✓	–
KDR	✓	✓	✓
KEAP1	✓	✓	–
KEL	✓	✓	–
KIF5B	✓	✓	✓
KIT	✓	✓	✓
KLF4	✓	✓	–
KLHL6	✓	✓	–
KMT2B	*	–	–
KMT2C	*	–	–
KMT2D	*	–	–
KRAS	✓	✓	–
LAMP1	✓	✓	–
LATS1	✓	✓	–
LATS2	✓	✓	–
LMO1	✓	✓	–
LRP1B	✓	✓	–
LYN	✓	✓	–
LZTR1	✓	✓	–
MAGI2	✓	✓	–
MALT1	✓	✓	–
MAP2K1	✓	✓	–
MAP2K2	✓	✓	–
MAP2K4	✓	✓	–
MAP3K1	✓	✓	–
MAP3K13	✓	✓	–
MAP3K14	✓	✓	–
MAP3K4	✓	✓	–
MAPK1	✓	✓	–
MAPK3	✓	✓	–
MAX	✓	✓	–

(continued on following page)

TABLE A1. ProvSeq Gene List (continued)

Gene Symbol	Small Variants	Copy-Number Variants	Fusions (from RNA)
MCL1	✓	✓	–
MDC1	✓	✓	–
MDM2	✓	✓	–
MDM4	✓	✓	–
MED12	✓	✓	–
MEF2B	✓	✓	–
MEN1	✓	✓	–
MET	✓	✓	✓
MGA	✓	✓	–
MITF	✓	✓	–
MLH1	✓	✓	–
MLL	✓	✓	✓
MLLT3	✓	✓	✓
MPL	✓	✓	–
MRE11A	✓	✓	–
MSH2	✓	✓	✓
MSH3	✓	✓	–
MSH6	✓	✓	–
MST1	✓	✓	–
MST1R	✓	✓	–
MTOR	✓	✓	–
MUTYH	✓	✓	–
MYB	✓	✓	–
MYC	✓	✓	✓
MYCL1	✓	✓	–
MYCN	✓	✓	–
MYD88	✓	✓	–
MYOD1	✓	✓	–
NAB2	✓	✓	–
NBN	✓	✓	–
NCOA3	✓	✓	–
NCOR1	✓	✓	–
NEGR1	✓	✓	–
NF1	✓	✓	–
NF2	✓	✓	–
NFE2L2	✓	✓	–
NFKBIA	✓	✓	–
NKX2-1	✓	✓	–
NKX3-1	✓	✓	–
NOTCH1	✓	✓	✓
NOTCH2	✓	✓	✓
NOTCH3	✓	✓	✓
NOTCH4	✓	✓	–
NPM1	✓	✓	–
NRAS	✓	✓	–
NRG1	✓	✓	✓
NSD1	✓	✓	–
NTRK1	✓	✓	✓
NTRK2	✓	✓	✓

(continued in next column)

TABLE A1. ProvSeq Gene List (continued)

Gene Symbol	Small Variants	Copy-Number Variants	Fusions (from RNA)
NTRK3	✓	✓	✓
NUP93	✓	✓	–
NUTM1	✓	✓	–
PAK1	✓	✓	–
PAK3	✓	✓	–
PAK7	✓	✓	–
PALB2	✓	✓	–
PARK2	✓	✓	–
PARP1	✓	✓	–
PAX3	✓	✓	✓
PAX5	✓	✓	–
PAX7	✓	✓	✓
PAX8	✓	✓	–
PBRM1	✓	✓	–
PDCD1	✓	✓	–
PDCD1LG2	✓	✓	–
PDGFRA	✓	✓	✓
PDGFRB	✓	✓	✓
PDK1	✓	✓	–
PDPK1	✓	✓	–
PGR	✓	✓	–
PHF6	✓	✓	–
PHOX2B	✓	✓	–
PIK3C2B	✓	✓	–
PIK3C2G	✓	✓	–
PIK3C3	✓	✓	–
PIK3CA	✓	✓	✓
PIK3CB	✓	✓	–
PIK3CD	✓	✓	–
PIK3CG	✓	✓	–
PIK3R1	✓	✓	–
PIK3R2	✓	✓	–
PIK3R3	✓	✓	–
PIM1	✓	✓	–
PLCG2	✓	✓	–
PLK2	✓	✓	–
PMAIP1	✓	✓	–
PMS1	✓	✓	–
PMS2	✓	✓	–
PNRC1	✓	✓	–
POLD1	✓	✓	–
POLE	✓	✓	–
PPARG	✓	✓	✓
PPM1D	✓	✓	–
PPP2R1A	✓	✓	–
PPP2R2A	✓	✓	–
PPP6C	✓	✓	–
PRDM1	✓	✓	–
PREX2	✓	✓	–

(continued on following page)

TABLE A1. ProvSeq Gene List (continued)

Gene Symbol	Small Variants	Copy-Number Variants	Fusions (from RNA)
PRKAR1A	✓	✓	–
PRKCI	✓	✓	–
PRKDC	✓	✓	–
PRSS8	✓	✓	–
PTCH1	✓	✓	–
PTEN	✓	✓	–
PTPN11	✓	✓	–
PTPRD	✓	✓	–
PTPRS	✓	✓	–
PTPRT	✓	✓	–
QKI	✓	✓	–
RAB35	✓	✓	–
RAC1	✓	✓	–
RAD21	✓	✓	–
RAD50	✓	✓	–
RAD51	✓	✓	–
RAD51B	✓	✓	–
RAD51C	✓	✓	–
RAD51D	✓	✓	–
RAD52	✓	✓	–
RAD54L	✓	✓	–
RAF1	✓	✓	✓
RANBP2	✓	✓	–
RARA	✓	✓	–
RASA1	✓	✓	–
RB1	✓	✓	–
RBM10	✓	✓	–
RECQL4	✓	✓	–
REL	✓	✓	–
RET	✓	✓	✓
RFWD2	✓	✓	–
RHEB	✓	✓	–
RHOA	✓	✓	–
RICTOR	✓	✓	–
RIT1	✓	✓	–
RNF43	✓	✓	–
ROS1	✓	✓	✓
RPS6KA4	✓	✓	–
RPS6KB1	✓	✓	✓
RPS6KB2	✓	✓	–
RPTOR	✓	✓	–
RUNX1	✓	✓	–
RUNX1T1	✓	✓	–
RYBP	✓	✓	–
SDHA	✓	✓	–
SDHAF2	✓	✓	–
SDHB	✓	✓	–
SDHC	✓	✓	–
SDHD	✓	✓	–

(continued in next column)

TABLE A1. ProvSeq Gene List (continued)

Gene Symbol	Small Variants	Copy-Number Variants	Fusions (from RNA)
SETBP1	✓	✓	–
SETD2	✓	✓	–
SF3B1	✓	✓	–
SH2B3	✓	✓	–
SH2D1A	✓	✓	–
SHQ1	✓	✓	–
SLIT2	✓	✓	–
SLX4	✓	✓	–
SMAD2	✓	✓	–
SMAD3	✓	✓	–
SMAD4	✓	✓	–
SMARCA4	✓	✓	–
SMARCB1	✓	✓	–
SMARCD1	✓	✓	–
SMC1A	✓	✓	–
SMC3	✓	✓	–
SMO	✓	✓	–
SNCAIP	✓	✓	–
SOCS1	✓	✓	–
SOX10	✓	✓	–
SOX17	✓	✓	–
SOX2	✓	✓	–
SOX9	✓	✓	–
SPEN	✓	✓	–
SPOP	✓	✓	–
SPTA1	✓	✓	–
SRC	✓	✓	–
SRSF2	✓	✓	–
STAG1	✓	✓	–
STAG2	✓	✓	–
STAT3	✓	✓	–
STAT4	✓	✓	–
STAT5A	✓	✓	–
STAT5B	✓	✓	–
STK11	✓	✓	–
STK40	✓	✓	–
SUFU	✓	✓	–
SUZ12	✓	✓	–
SYK	✓	✓	–
TAF1	✓	✓	–
TBX3	✓	✓	–
TCEB1	✓	✓	–
TCF3	✓	✓	–
TCF7L2	✓	✓	–
TERC	✓	✓	–
TERT	✓	–	–
TET1	✓	✓	–
TET2	✓	✓	–
TFE3	✓	✓	–

(continued on following page)

TABLE A1. ProvSeq Gene List (continued)

Gene Symbol	Small Variants	Copy-Number Variants	Fusions (from RNA)
TFRC	✓	✓	–
TGFBR1	✓	✓	–
TGFBR2	✓	✓	–
TMEM127	✓	✓	–
TMPRSS2	✓	✓	✓
TNFAIP3	✓	✓	–
TNFRSF14	✓	✓	–
TOP1	✓	✓	–
TOP2A	✓	✓	–
TP53	✓	✓	–
TP63	✓	✓	–
TRAF2	✓	✓	–
TRAF7	✓	✓	–
TSC1	✓	✓	–
TSC2	✓	✓	–
TSHR	✓	✓	–
U2AF1	✓	✓	–
VEGFA	✓	✓	–
VHL	✓	✓	–
VTCN1	✓	✓	–
WISP3	✓	✓	–
WT1	✓	✓	–
XIAP	✓	✓	–
XPO1	✓	✓	–
XRCC2	✓	✓	–
YAP1	✓	✓	–
YES1	✓	✓	–
ZBTB2	✓	✓	–
ZBTB7A	✓	✓	–
ZFHX3	✓	✓	–
ZNF217	✓	✓	–
ZNF703	✓	✓	–
ZRSR2	✓	✓	–

NOTE. 523-DNA/RNA CGP for small variants, copy-number variants, and fusions implemented via pathologist-directed workflow. Check mark indicates gene is covered under the context of the column. Dashes indicate not covered. Asterisk indicates the small variant for the gene is only found in the gVCF file.
Abbreviations: CGP, comprehensive genomic profiling; gVCF, genomic variant call format.

TABLE A2. Small 50-Gene Panel

Gene Symbol	Small Variants	Copy Number Variants	DNA Fusions
ABL1	–	–	✓
AKT1	✓	–	–
AKT3		–	✓
ALK	✓	✓	✓
AR	✓	✓	–
AXL	–	–	✓
BRAF	✓	✓	✓
CCND1	–	✓	–
CDK4	✓	✓	–
CDK6	–	✓	–
CTNNB1	✓	–	–
DDR2	✓	–	–
EGFR	✓	✓	✓
ERBB2	✓	✓	✓
ERBB3	✓	–	–
ERBB4	✓	–	–
ERG	–	–	✓
ESR1	✓	–	–
ETV1	–	–	✓
FGFR1	–	✓	✓
FGFR2	✓	✓	✓
FGFR3	✓	✓	✓
FGFR4	–	✓	–
GNA11	✓	–	–
GNAQ	✓	–	–
HRAS	✓	–	–
IDH1	✓	–	–
IDH2	✓	–	–
JAK1	✓	–	–
JAK2	✓	–	–
JAK3	✓	–	–
KIT	✓	✓	–
KRAS	✓	✓	–
MAP2K1	✓	–	–
MAP2K2	✓	–	–
MET	✓	✓	✓
MTOR	✓	–	–
MYC	–	✓	–
MYCN	–	✓	–
NRAS	✓	–	–
NTRK1	–	–	✓
NTRK2	–	–	✓
NTRK3	–	–	✓
PDGFRA	✓	✓	✓
PIK3CA	✓	✓	–
PPARG	–	–	✓
RAF1	✓	–	✓
RET	✓	–	✓
ROS1	✓	–	✓
SMO	✓	–	–

NOTE. Fifty-gene legacy panel of small variants, copy-number variants, and fusions used before adoption of comprehensive genomic profiling. Check mark indicates gene is covered under the context of the column. Dashes indicate not covered.