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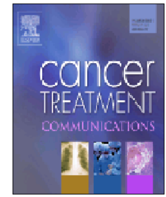

Experience with targeted next generation sequencing for the care of lung cancer: Insights into promises and limitations of genomic oncology in day-to-day practice

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ABSTRACT

Introduction: Tumor genotyping using single gene assays (SGAs) is standard practice in advanced non-small-cell lung cancer (NSCLC). We evaluated how the introduction of next generation sequencing (NGS) into day-to-day clinical practice altered therapeutic decision-making.
Methods: Clinicopathologic data, tumor genotype, and clinical decisions were retrospectively compiled over 6 months following introduction of NGS assay use at our institution in 82 patient-tumor samples (7 by primary NGS, 22 by sequential SGAs followed by NGS, and 53 by SGAs).
Results: SGAs identified abnormalities in 34 samples, and all patients with advanced *EGFR*-mutated or *ALK*-rearranged tumors received approved tyrosine kinase inhibitors (TKIs) or were consented for clinical trials. NGS was more commonly requested for *EGFR*, *ALK*, and *KRAS*-negative tumors ($p < 0.0001$). NGS was successful in 24/29 (82.7%) tumors. Of 17 adenocarcinomas (ACs), 11 (7 from patients with ≤ 15 pack-years of smoking) had abnormalities in a known driver oncogene. This led to a change in decision-making in 8 patients, trial consideration in 6, and off-label TKI use in 2. Of 7 squamous cell (SC) carcinomas, 1 had a driver aberration (*FGFR1*); 6 had other genomic events (all with *TP53* mutations). In no cases were clinical decisions altered ($p = 0.0538$ when compared to ACs).
Conclusions: Targeted NGS can identify a significant number of therapeutically-relevant driver events in lung ACs; particularly in never or light smokers. For SC lung cancers, NGS is less likely to alter current practice. Further research into the cost effectiveness and optimal use of NGS and improved provider training in genomic oncology are warranted.

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1. Introduction

The management of advanced non-small-cell lung cancer (NSCLC) is increasingly directed by knowledge of tumor genotype. Expert groups like the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), the Association for Molecular Pathology (AMP), and the American Society of Clinical Oncology (ASCO) now endorse routine testing for epidermal growth factor receptor (*EGFR*) mutations or anaplastic lymphoma kinase (*ALK*) rearrangements using rapid single gene assays (SGAs) [1–3]. Knowledge of these predictive biomarkers has permitted selective application of tyrosine kinase inhibitors (TKIs) [1–3], with *EGFR* and *ALK* TKIs having gained approval from the U.S. Food and Drug Administration (FDA) on the basis of these genomic features [4–9].

The genetic landscape of NSCLC is complex. Oncogenic and/or therapeutically-relevant genomic aberrations include: mutations, amplifications, deletions, and rearrangements/fusions. It is now well established that a significant proportion of lung adenocarcinomas (ACs) harbor mutations in driver oncogenes that can augment "sustained proliferative signaling"-a hallmark feature of tumorigenesis. These include mutations in: v-ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*), Raf murine sarcoma viral oncogene homolog B1 (*BRAF*), V-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (*ERBB2*), rearranged during transfection (*RET*), c-ros oncogene 1 (*ROS1*), and neurotrophic tyrosine kinase

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receptor type 1 (*NTRK1*), among others [10]. Squamous cell (SC) lung cancers may instead harbor genomic changes involving: fibroblast growth factor receptor (*FGFR*) 1/2/3/4, phosphatidylinositol-3-kinase catalytic subunit alpha1 (*PIK3CA*), and discoidin domain-containing receptor 2 (*DDR2*), among others [10,11].

Technological advances have led to the introduction of next generation sequencing (NGS) platforms into the thoracic oncology clinic [10]. As opposed to SGAs, NGS permits massive parallel sequencing that affords maximal tumor genomic assessment while using precious tumor samples sparingly [12]. These NGS assays offered by Clinical Laboratory Improvement Amendments (CLIA)-certified commercial or academic vendors are usually only feasible when based on a targeted panel of genes (i.e. targeted NGS) that select for the most readily targetable alterations. Many of these NGS assays, especially whole genome and whole exome, require substantial nucleic acid input (250ng-1ug), though some have been optimized to allow results from lower concentrations of deoxyribonucleic acid (DNA) and more recently ribonucleic acid (RNA) from formalin-fixed paraffin-embedded (FFPE) specimens or cytology specimens [12–14].

The feasibility and applicability of NGS in day-to-day clinical practice—as opposed to use in research settings alone—has not been well vetted in the literature to date. We therefore evaluated how the introduction of NGS assays into daily practice altered therapeutic decision-making for a cohort of NSCLCs treated by a multidisciplinary Thoracic Oncology team at this National Cancer Institute (NCI)-affiliated cancer center. In this cohort, NGS was applied as part of routine practice and not in parallel with other academic/commercial efforts, such as assay development or clinical trial screening.

2. Methods

2.1. Cohort selection and data collection

Patients seen at Beth Israel Deaconess Medical Center (BIDMC, a member of the Dana-Farber/Harvard Cancer Center) with a diagnosis of NSCLC and whose tumors were submitted for either SGA or NGS were identified through an ongoing Institutional Review Board-approved study [15,16]. Patient inclusion was restricted from May 1st to October 31st, 2014 (the 6-month interval since introduction of NGS in clinical NSCLC specimens). Clinical, pathologic, radiographic, and tumor genotyping parameters were collected by retrospective chart extraction and managed using REDCap electronic data capture tools hosted at BIDMC. A review of clinical documentation, clinical trial screening/consent, and anti-cancer therapies administered allowed for determination of clinical decision-making.

2.2. Tumor genotyping

Following routine pathologic diagnosis of NSCLC, tumor material (from surgical specimens, core needle biopsies or cell aspirates/concentrates) in FFPE tissue blocks was submitted for genomic analysis. SGAs (*EGFR* exon 18-21 mutation analysis, *KRAS* codon 12 and 13 mutation analysis, *ALK* fluorescence in situ hybridization [FISH], *ROS1* FISH) and NGS were performed as previously described [13–17]. Three different NGS assays were used. The first two were performed by an academic medical center (Massachusetts General Hospital; Boston, MA) using an anchored multiplex polymerase chain reaction (AMP) assay that employs a targeted sequencing strategy [13]. The first AMP assay (SNaPshot-NGS-V1) evaluates single nucleotide variants (SNV) and insertions/deletions (indels) in genomic DNA using NGS targeting 39 putative oncogenes and tumor suppressor genes [13]; this assay was used in 22 of the study cases. The second AMP assay (ALK, RET, ROS1 NGS Gene Fusion Assay) evaluates fusion transcript detection for *ALK*, *ROS1* and *RET* using genomic RNA [13]; this assay was used in 6 of the study cases. The third NGS assay (FoundationOne, Foundation Medicine; Cambridge, MA) interrogates 315 genes as well as introns of 28 genes involved in rearrangements using massively parallel DNA sequencing to characterize base substitutions, short indels, copy number alterations, and selected fusions [14]; this assay was used in 2 of the study cases. A CLIA-certified single gene *FGFR1* FISH test (Massachusetts General Hospital; Boston, MA) to evaluate copy number of *FGFR1* [17] was used in addition to NGS in SC carcinomas; this assay was used in 5 of the study cases.

2.3. Statistical methods

Fisher's exact test was used to compare categorical variables. All *p*-values reported were two-sided.

3. Results

3.1. Patient and tumor characteristics

Table 1 illustrates baseline patient and tumor characteristics. The cohort comprised 82 patients, most of whom had stage IV/recurrent disease (72.0%) and AC histology (90.2%).

3.2. SGAs for EGFR/ALK/KRAS/ROS1 and clinical decisions

Fig. 1 depicts the clinical use and outcomes of genomic analyses in the 82 patient-tumor samples. SGAs were ordered in 75 tumors. Analyses for abnormalities in *EGFR, ALK, KRAS*, and *ROS1* were successful in: 94.6% (71/75), 96% (72/75), 94.4% (68/72), and 79.7% (55/69), respectively. The increased failure rate of *ROS1* testing is

Table 1
Baseline characteristics of patients and tumors genotyped over a 6-month period.

Characteristic	Value
Age at time of tissue acquisition	
Median (range)	67 (34–92)
Women *n* (%)	49 (59.7)
Men *n* (%)	33 (40.3)
Race *n* (%)	
White	66 (80.5)
Asian	8 (9.8)
Black	5 (6.1)
Other	3 (3.6)
Smoking status *n* (%)	
Current smoker	27 (32.9)
Former smoker	41 (50.0)
Never smoker	14 (17.1)
Stage *n* (%)	
I–III	23 (28.0)
IV/recurrent	59 (72.0)
Histology *n* (%)	
Adenocarcinoma	74 (90.2)
Squamous cell carcinoma	7 (8.5)
NSCLC (NOS)	1 (1.2)
Type of tissue *n* (%)	
Surgical specimen	22 (26.8)
Small biopsy	17 (20.7)
Cytology cell block from aspirate/fluid	43 (52.4)
Anatomic site of tissue acquisition n (%)	
Bone	4 (4.9)
Brain	3 (3.6)
Extra-thoracic lymph node	5 (6.1)
Lung	27 (32.9)
Mediastinal/hilar lymph node	24 (29.3)
Pleura	12 (14.6)
Other	7 (8.5)

NSCLC, non-small-cell lung cancer; NOS, not otherwise specified.

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