Published OnlineFirst July 28, 2017; DOI: 10.1158/1078-0432.CCR-17-0899

Personalized Medicine and Imaging

Clinical Cancer Research

Real-Time Genomic Profiling of Pancreatic Ductal Adenocarcinoma: Potential Actionability and Correlation with Clinical Phenotype

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Abstract

Purpose: Molecular profiling in cancer has identified potential actionable drug targets that have prompted attempts to discover clinically validated biomarkers to guide therapeutic decision-making and enrollment to clinical trials. We evaluated whether comprehensive genetic analysis of patients with pancreatic adenocarcinoma is feasible within a clinically relevant timeframe and whether such analyses provide predictive and/or prognostic information along with identification of potential targets for therapy.

Experimental Design: Archival or prospectively acquired FFPE samples and matched normal DNA from $N = 336$ patients with pancreatic cancer were analyzed using a hybridization capture–based, next-generation sequencing assay designed to perform targeted deep sequencing of all exons and selected introns of 410 key cancer-associated genes. Demographic and treatment data were prospectively collected with the goal of correlating treatment outcomes and drug response with molecular profiles.

Results: The median time from protocol consent to reporting of the genomic results was 45 days with a median time from tissue delivery of 20 days. All genetic alterations identified were stratified based upon prior evidence that the mutation is a predictive biomarker of drug response using the MSKCC OncoKB classification. Three of 225 patients (1%) received a matched therapy based upon the sequencing results.

Conclusions: The practical application of molecular results to guide individual patient treatment is currently limited in patients with pancreatic adenocarcinoma. Future prospective molecular profiling efforts should seek to incorporate routine germline genetic analysis and the identification of DNA profiles that predict for clinical benefit from agents that target DNA damage repair and or immunotherapy. *Clin Cancer Res; 23(20); 6094–100. ©2017 AACR.*

Introduction

Pancreatic adenocarcinoma is characterized by poor clinical outcomes, aggressive tumor biology and early metastatic spread. The incidence of pancreatic adenocarcinoma is rising and it is projected to become the second most common cause of cancer-related death in the United States by 2020 (1). In contrast with other solid tumors, success in identifying molecular targets for therapeutic intervention in pancreatic cancer has been limited, in part due to significant inter- and intratumoral genetic heterogeneity, and the near ubiquity of activating mutations in KRAS, which to date remains an elusive therapeutic target. Initial studies evaluating the genomic landscape of pancreatic adenocarcinoma have identified mutations in KRAS, SMAD4, TP53, and CDKN2A (2) as the four most frequently altered genes.

More recent studies using next-generation sequencing techniques with whole-genome or exome sequencing have identified additional genetic alterations, including chromosomal rearrangements, focal amplifications, and multiple genes altered at low-level frequencies (<5%) that converge on several key pathways offering potential for therapeutic targeting. In addition, genetic alterations with prognostic or predictive value have been identified, including alterations in genes that play a central role in DNA repair whose loss is

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

This report evaluates the potential and actual therapeutic implications of comprehensive genetic analysis of patients with pancreatic cancer. In this single-institution study, a next-generation sequencing assay targeting all exons and selected introns of 410 key cancer-associated genes was performed on tumor samples from 336 patients and identified potentially actionable findings in 26% of cases. Three patients received matched systemic therapy based on the molecular-profiling results. These findings indicate that the practical application of molecular results to guide individual patient treatment is currently limited in patients with pancreatic adenocarcinoma; we anticipate that integration of genomic, epigenomic and transcriptomic analyses of tumor tissue and germline genetic testing may facilitate the future development of molecularly targeted and/or individualized therapy for patients with pancreatic cancer.

associated with a "BRCA-like" signature and response to platinum therapy (3). However, the practical utility of these studies has been limited in patients with advanced pancreatic adenocarcinoma as turn-around times for whole-exome and/or whole-genome sequencing are typically lengthy (approximately 6–12 weeks), these methods remain relatively costly and are as yet rarely available in a CLIA-certified setting, and the depth of coverage for these methods is inadequate to assure detection of relevant alterations in paucicellular neoplasms. Thus, the feasibility of whole-genome or exome sequencing for large numbers of patients in a clinically useful timeframe or cost-effective manner has not been demonstrated, although several studies are prospectively addressing this question.

The purpose of this study was to assess the feasibility of comprehensive next-generation sequencing in patients with pancreatic cancer in a clinically relevant manner and timeframe, and to identify potential novel therapeutic targets.

Materials and Methods

Patients

Patients were identified between March 2014 and March 2016, in medical and surgical oncology clinics, and were eligible for the study if they had a confirmed diagnosis of pancreatic cancer, and were receiving or planning to receive treatment for their disease at MSKCC. Written informed consent for tumor profiling was obtained under the IRB approved protocol NCT 01775072 "Tumor Genomic Profiling in Patients Evaluated for Targeted Cancer Therapy." The studies were conducted in accordance with the Declaration of Helsinki. Results from $N = 336$ patients with pancreatic cancer who had consented to this protocol were available on April 1, 2016. Clinical data were collected, including therapeutic response assessed by treating physician.

Sample preparation

A pathologist reviewed all tumor samples and microdissection was performed as needed to ensure adequate cellularity. Matched germline DNA from prospectively collected blood samples was analyzed in all patients. Although paired germline sequencing was employed for somatic mutation calling, regulatory restrictions during the initial study period precluded the reporting of germline mutations. Previously collected samples (e.g., tissue from prior resection or biopsy) were used in $N = 288$ cases (85%); while $N = 50$ samples (15%) were from patients who underwent prospective biopsy collection, including $N = 12$ patients who had prospective EUS guided FNA/FNB of a primary pancreatic tumor (Fig. 1A). All pathology specimens analyzed were derived from formalin-fixed paraffin-embedded tissue. On review of silent mutation frequency, 14 cases in which no somatic mutations were identified were deemed to have low tumor purity and were thus removed from the final analysis.

Genetic analysis

Tumors were profiled for genomic alterations using MSK-IMPACT, an in-house, CLIA-approved, deep sequencing assay. Custom DNA probes were designed for targeted sequencing of all exons and selected introns of 341 ($n = 20$) or 410 ($n = 318$) oncogenes, tumor-suppressor genes, and members of pathways deemed potentially actionable by targeted therapies. Fisher's exact tests were performed to look for significant difference in gene alterations (mutations and cna) between patient groups sharing a particular clinical feature.

Results

Three hundred and thirty-eight samples from 336 patients were included in the analysis (see Table 1 for patient demographics). Of 338 samples, 156 were surgical resection specimens, 52 were from EUS guided fine needle aspiration ($n = 32$) or EUS guided fine needle biopsy of the primary tumor ($n = 20$) and 129 were from a biopsy of metastatic sites; one patient had a CT-guided biopsy of the primary tumor. Fifty (14.8%) samples were prospectively obtained after patient consent to facilitate molecular profiling; including 12 cases (3.6%) obtained through EUS-guided biopsy of the primary tumor (Fig. 1A).

Frequently altered genes in pancreatic adenocarcinoma

All sequencing results were submitted to the patient's medical record, with a median turn-around time of 20 days following either prospective specimen acquisition or delivery of previously collected material. The median time from protocol consent to reporting of the genomic results was 45 days. One thousand three hundred and ninety-four mutations in 256 genes were identified from 324 samples with a median of 4 mutations per sample. Consistent with prior molecular

Table 1. Patient Demographics

Median age	**64 years (range, 34–89)**
Sex	
Male	54%
Stage at diagnosis	
Stage I/II	62%
Stage III/borderline resectable	18.5%
Stage IV	37.5%
Current/former smokers	50.5%
Primary tumor location	
Head	59%
Body	23%
Tail	17%

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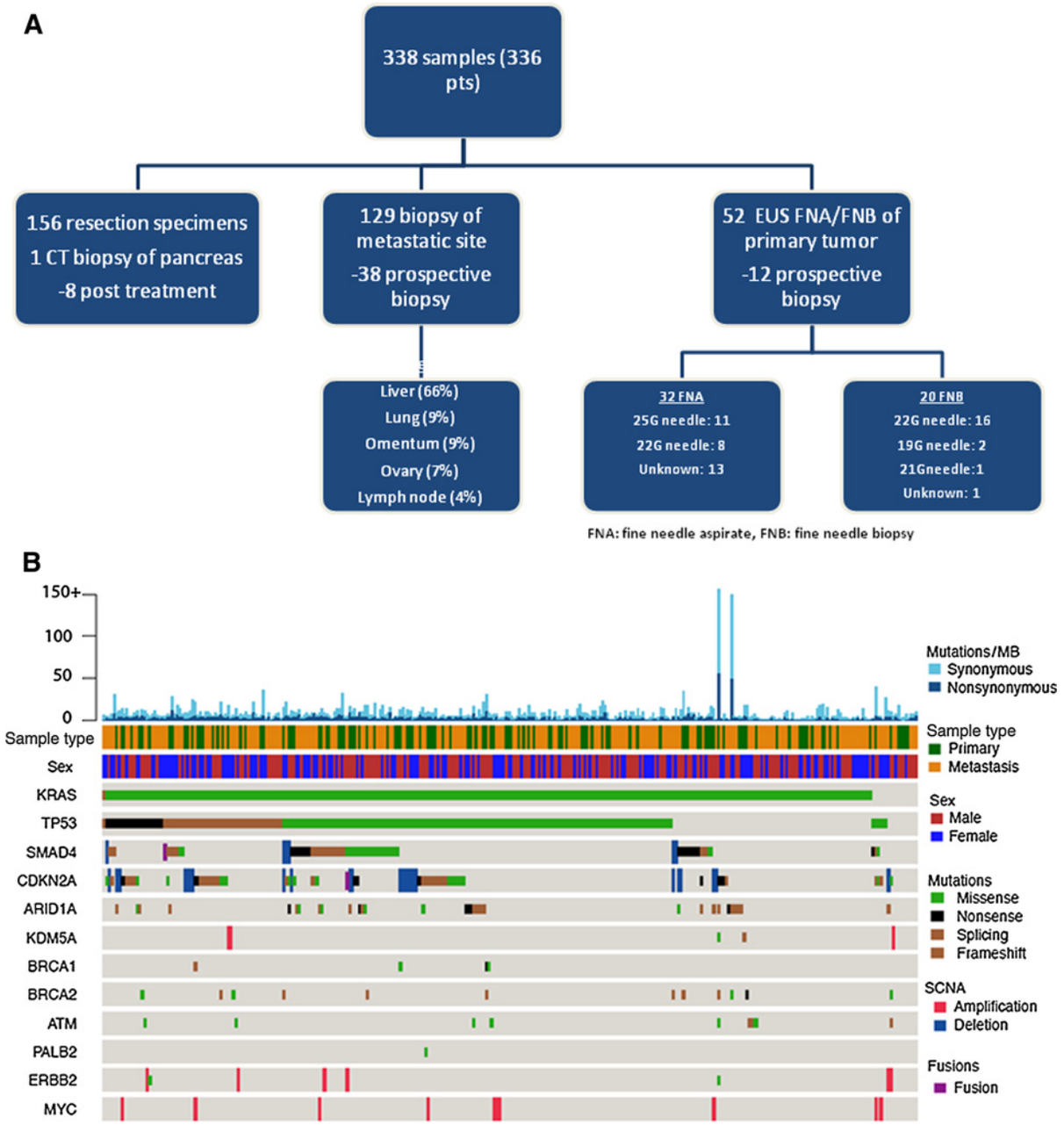

Figure 1.
A, Patient sample acquisition. **B,** Genetic alterations in all patients ($n = 336$).

studies of pancreatic cancers, KRAS mutations were most prevalent, occurring in 95% of samples, followed by TP53 (72%), SMAD4 (22%), and CDKN2A (18%). Additional genes mutated at > 3% frequency included ARID1A (11%), RNF43 (8%), BRCA2 (4%), KDM6A (4%), MLL2 (4%), PTPRT (4%), and TGFBR2 (4%). Multiple additional genes were mutated with low frequency (Fig. 1B). Three hundred and three copy-number alterations in 128 genes were identified; most commonly deletions at 9p21 involving CDKN2A and/or CDKN2B (14%) and amplifications of AKT2 (4%), MYC (4%), and ERBB2 (2%). Forty-three structural variants were identified in 36 samples, including fusions involving NTRK3-ETV6, SMARCA4-LDLR, MAPK4-SMAD4, PPM1D-MAFG, FGFR2-CEP55, BRAF-LUC7L2, and ALK-ASAP (Supplementary Table S2).

Eighteen samples (5.4%) were KRAS wild-type. Thirteen (3.9%) KRAS wild-type cases were typical conventional ductal pancreatic adenocarcinoma, with varying genetic drivers identified, some of which are potentially actionable, including a BRAF activating mutation, ERBB2 amplification, gene fusion events involving ROS-1 among others, and SMARCB1 loss (Table 2).

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Table 2. KRAS wild-type cases by MSK-IMPACT (19 cases)

	Samples	Alteration
1	Intraductal tubulopapillary neoplasm	FGFR2–MYOF fusion
2	EBV poorly differentiated carcinoma	FAT1 nonsense
3	Adenocarcinoma with mucinous features	NTRK3–ETV fusion
4	Colloid carcinoma arising from IPMN	GNAS R201C
5	Colloid carcinoma	GNAS R201H
6	Pancreas adenocarcinoma	MGA nonsense
7	Pancreas adenocarcinoma	BRCA2 loss (also germline)
8	Pancreas adenocarcinoma	TP53 mutant, RB1 loss
9	Pancreas adenocarcinoma	TP53 mutant, CDKN2A, MYC AMP
10	Pancreas adenocarcinoma	TP53 mutant, CDKN2A, SMAD4 loss, MYC AMP
11	Pancreas adenocarcinoma	ERBB2 AMP, CDKN2A loss
12	Pancreas adenocarcinoma	APC Missense
13	Pancreas adenocarcinoma	TP53 mutant, APC missense, NCOR1 amp
14	Pancreas adenocarcinoma	CCNE1 AMP
15	Pancreas adenocarcinoma	BRAF V600E, SMAD4 Loss
16	Pancreas adenocarcinoma	SMARCB1 loss
17	Pancreas adenocarcinoma	BCOR loss
18	Pancreas adenocarcinoma	ROS1-SLC4A4 Fusion, ATM loss, ERBB2 AMP
19	Pancreas adenocarcinoma	TP53 mutant, SMAD4 loss, BRAF-JHDM1Dfusion

Correlation of genetic alterations with clinical characteristics/outcomes

TGFBR2, CDKN2B, CSFR1, EPHA5, JAK2, and NF1 mutations were more often identified in samples from metastatic sites as compared with primary tumors (Table 3). Mutations in GNAS and RB1 were associated with any disease recurrence post-operatively. SMAD3 alterations were found only in samples from current or former smokers, while alterations in RECQI4 were more commonly identified in samples from patients diagnosed at age less than 50 years.

Potentially actionable genetic alterations

Genetic alterations were classified on an actionability scale of 1 to 4, where levels 1–2a alterations indicate standard therapeutic interventions, likely to be covered by insurance, whereas levels 2b–4 include investigational therapeutic alterations, which may direct a patient towards a clinical trial relevant to that biomarker. Two hundred and twenty-five patients were alive with metastatic or unresectable pancreatic cancer at the time when MSK-IMPACT results became available to the physician. Of the additional patients, five had died of metastatic disease before results were finalized and the remainder were alive without evidence of disease.

As there are no standard-of-care targeted agents for patients with pancreatic cancer, no patients had level 1 or 2A alterations. Eighteen patients (5.5%) had at least one somatic alteration that was classified as level 2b, defined as an FDA-approved biomarker in another cancer indication, but not FDA or NCCN-compendium listed for pancreatic adenocarcinoma. These included ERBB2 amplification (6 pts), CDK4 amplification (2 pts), BRCA1/2 mutations (8 pts), BRAF V600E mutation (1 pt), and fusion events involving ROS-1 and ALK1 (1 pt each). Fifteen of the 18 tumors with level 2B alterations had co-altered KRAS. One tumor had both level 2B and 3B alterations; containing mutations in IDH1 and BRCA2.

Table 3. Clinical characteristics assoicated with genetic alterations

	Gene	*P*	Sample (*n*)
Metastatic vs. primary	TGFBR2	0.009	10 vs. 4
	CDKN2B	0.02	15 vs. 10
	CSFR1	0.048	3 vs. 0
	EPHA5	0.048	3 vs. 0
	JAK2	0.048	3 vs. 0
	NF1	0.048	3 vs. 0
Disease recurrence y vs. n	GNAS	0.02	7 vs. 0
	RB1	0.03	6 vs. 0
Diagnosis <50 years	RECQI4	0.0003	5 vs. 1
Smoking	SMAD3	0.03	5 vs. 0

Fifteen patients (4.6%) had a level 3B alteration as their highest level actionable gene. Level 3B includes alterations for which clinical evidence links the biomarker to drug response in patients but use of the biomarker is not currently a standard-of-care in any cancer type. Level 3B genetic alterations co-occurring with KRAS mutations included mutations in AKT1 (1), ERBB2 (1) and PIK3CA (5 pts), and FGFR1 amplification (5 pts). Two patients had a tumor harboring a level 3B genetic alteration in the absence of KRAS mutation; activating gene fusions involving FGFR2 and NTRK3 were identified in these samples (Fig. 2).

Level 4 genetic alterations were classified as those which were not FDA-approved or NCCN compendium-listed biomarkers for a drug, but preclinical evidence potentially links the biomarker to response to a drug. Using this very broad and inclusive classification, 222 patients (68%) had alterations in one or more of these genes.

Three patients received matched systemic therapy based on the molecular profiling results. Clinical trial enrollment based on molecular profiling was limited to two of the 225 (1%) patients with advanced disease at time of MSK-IMPACT results. One patient with a KRAS wild-type ERBB2 amplified (level 2B) tumor received TDM-1 (trastuzumab emtansine) on a clinical trial in the fifth line setting but had no clinical benefit and progressed within 1 month. An additional patient with a KRAS mutant tumor (level 4) received combination therapy with a PI3 Kinase inhibitor and MEK inhibitor but had no clinical benefit and progressed within 2 months. One patient who harbored an activating ERBB2 V842I mutation (level 3), which is located at the kinase domain at exon 21, received trastuzumab at an outside institution with an unknown response. This tumor sample also had a co-occurring KRAS G12V mutation.

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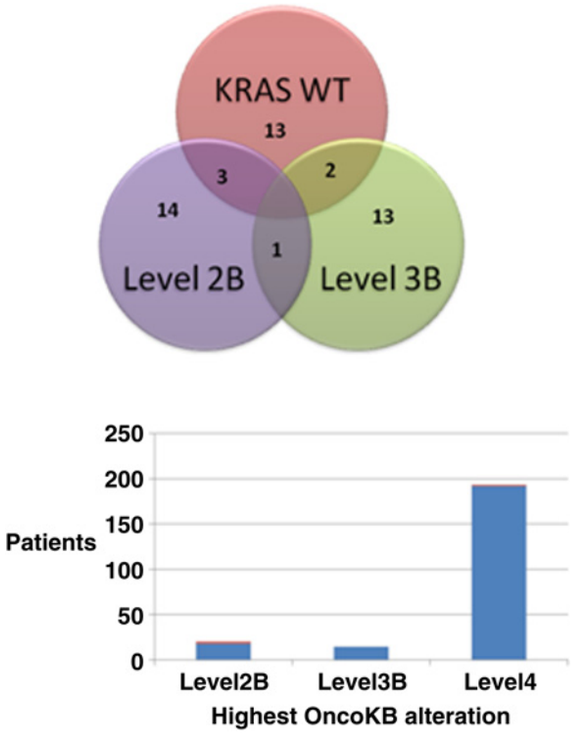

Figure 2.
Potentially actionable genetic alterations.

Six patients known to harbor a germline BRCA 1/2 mutation received cisplatin/gemcitabine in combination with a PARP inhibitor, but therapy selection in these cases was not based on the somatic profiling results.

Alterations in genes associated with DNA damage response

Two hundred and eight patients received platinum-based chemotherapy as first line treatment for locally advanced or metastatic disease, of whom radiographic response data were available on 166 at the time of analysis. 58 patients had partial or complete response to therapy (34%), 35 had progressive disease (21%), and 73 had stable disease (44%). Fifty of these patients had a somatic alteration in one or more genes associated with DNA damage response (DDR), including BRCA2, FANCA, ATM, and ATR, of whom 17 had a partial response to therapy (34%). In this dataset, somatic mutations in DDR genes failed to enrich for patients responding to platinum-based chemotherapy.

Fourteen (4.2%) patients had known germline BRCA2 mutations based on other testing whereas 2 patients had germline BRCA1 variants of unknown significance. In tumors from the 14 BRCA2 germline carriers, loss of heterozygosity resulting from missense/truncating mutations was identified in 50%. As anticipated, significant and prolonged responses to platinum-based chemotherapy were observed in this cohort (Supplementary Table S3). KRAS (74%), TP53 (49%), SMAD4, and CDKN2A/B alterations were common in these patients, although present at a lower frequency than in patients for whom germline BRCA 1/2 mutation status was unknown or negative. An additional 13 (3.9%) patients had somatic BRCA 1/2 mutations identified with unknown germline BRCA mutation status, whereas one patient with Lynch syndrome also had a somatic BRCA2 mutation. Clinical outcomes and response to platinum based chemotherapy was varied among this group of patients, potentially reflecting the unknown presence of germline genetic alterations and the unknown predictive effect of somatic BRCA mutations.

Two patients (0.6%) in the dataset were known carriers of Lynch Syndrome. Only one of these tumors had a hypermutated phenotype and significant response to treatment with an anti-PDL1 agent

Discussion

The successful development of molecularly targeted therapies in a variety of solid tumors over the last decade, coupled with increasing availability of next-generation sequencing techniques, has invigorated efforts to perform comprehensive molecular profiling of pancreatic tumors. Through large scale studies incorporating whole exome, genome and transcriptome sequencing, key insights have been gained into the molecular pathogenesis of pancreatic adenocarcinoma, with consistent identification of a complex and heterogenous mutational profile but with convergent effects on core molecular pathways including DNA repair, cell-cycle regulation, chromatin regulation, and axonal guidance (4–7). Through analysis of whole-genome sequencing, variations in chromosomal structure have allowed subclassification of pancreatic adenocarcinomas into subtypes with potential clinical relevance, including identification of a genetically unstable subgroup frequently defective in DNA repair that may be optimally treated with agents targeting a defective DDR, including PARP inhibitors or DNA-damaging–based chemotherapy (3, 8). The integration of RNA expression analysis with whole-genome sequencing has allowed alternative subclassification of pancreatic adenocarcinomas which provide rationale for several putative therapeutic strategies (8). These data provide strong rationale for the integration of molecular profiling into clinical practice in the management of patients with pancreatic adenocarcinoma, to optimally plan a personalized therapeutic strategy through referral to basket studies of investigational targeted therapies or immunotherapies or to guide the optimal selection of standard cytotoxic chemotherapies (9, 10).

At MSKCC, through a large-scale strategy to incorporate precision medicine into the clinical management strategy for all patients, we elected to offer molecular profiling to all patients with pancreatic adenocarcinoma treated at our institution. This effort demonstrated that comprehensive molecular profiling of patients using archival or newly collected FFPE tissue is feasible; with results available in the clinical chart with a median of 45 days from patient consent and with a median of 20 days from acquisition of the tumor specimen. The MSK-IMPACT platform has several advantages, including the concurrent sequencing of germline DNA to allow definitive calling of somatic mutations, deep coverage (mean 765X) to overcome the high stromal content characteristic of pancreatic tumors, and the ability to evaluate a large number of genes simultaneously while identifying all major classes of actionable genomic alterations (point mutations, small insertions and deletions, copy-number alterations and structural rearrangements). Concurrent sequencing of germline DNA is not currently

performed by many commercially available platforms, and increases the accuracy of somatic variant calling.

In this prospective sequencing initiative, we found previously identified driver alterations typical of PDAC, and as anticipated identified at low frequency additional genetic alterations in a wide variety of genes, some of which are targetable with current agents. Consistent with prior retrospective studies, our results again demonstrate frequent genetic alterations in key signaling pathways, including Notch signaling, chromatin remodeling, DNA repair, cell cycle, RNA processing, WNT and TGF beta signaling, and KRAS activation. However, the practical application of these results to the clinical management of patients was challenging and relatively limited during the study period due to a combination of factors. Activating mutations in KRAS are a key driver genetic alteration in almost every pancreatic adenocarcinoma, potentially limiting the value of targeting upstream mutations in genes such as FGFR, EGFR, ERBB2. In addition, many of the genetic alterations that have previously been classified in the broadest sense as targetable were defined as such based on only *in vitro* and/or limited *in vivo* preclinical data and their utility as predictive biomarkers in the setting of the complex co-mutation patterns and unique tumor microenvironment of pancreatic carcinomas remain theoretical. Novel therapeutic strategies using targeted therapies in combination, ideally directed against both KRAS-mediated signaling and simultaneously against compensatory or parallel-activated pathways may offer more potential for clinical efficacy. Overall, the results from this prospective sequencing effort were consistent with those of Chantrill and colleagues (11), who reported the interim data from a pilot phase of the IMPaCT trial; a molecularly guided clinical trial using NGS technologies for patients with recurrent or metastatic pancreatic ductal adenocarcinoma. Notably, we did observed significant radiographic and pathologic responses to platinum-based chemotherapy both known germline BRCA1/2 mutation carriers, and in a patient who had a somatic BRCA2 mutation. Additional common driver genetic alterations in KRAS, TP53, SMAD4 were seen at similar to slightly lower frequency in this population, indicating that these co-incident mutations did not preclude sensitivity to DNA damaging agents in patients with a defective DDR. In addition, both patients with germline BRCA1/2 mutations who underwent resection followed by adjuvant platinum-based therapy remain without disease recurrence, consistent with previously described prognostic benefit to platinum use in this setting (12–15). Although beyond BRCA 1/2, FANCA, and PALB2, the clinical significance of low frequency somatic mutations in genes such as MDC1, ATR, ATM and other DNA damage repair genes remains unclear, it is likely that germline alterations in these genes may represent a more robust biomarker to define patients in whom treatment with agents targeting a defective DDR may confer significant benefit in the metastatic or adjuvant setting (16–19). The profound and durable responses to platinum-based combinations in patients with somatic and germline alterations in DDR genes suggest that future prospective molecular profiling efforts should seek to incorporate routine germline genetic analysis in all patients. Analysis of tumors for genomic signatures of DDR deficiency may also more precisely identify those patients most likely to respond to cisplatin or PARP inhibitors than analysis of somatic and germline alterations in DDR genes alone. Finally, such signature analysis may also identify the rare hypermutated pancreatic adenocarcinoma, likely to respond to immune checkpoint blockade.

In conclusion, comprehensive molecular profiling of pancreatic tissue samples using archival tissue is feasible and can be performed within a clinically relevant timeframe. The pattern of genetic alterations identified from prospective targeted next-generation sequencing was consistent with reports from large scale retrospective whole-exome/genome studies using frozen pancreatic primary tissue samples. The practical utility of such analyses remains limited at this time; in a minority of patients we did identify mutations, copy number alterations and chromosomal rearrangements in genes strongly associated with clinical response to a targeted therapy including an NTRK fusion, inactivating alterations in BRCA1/2, ERBB2, and BRAF V600E. Given the low prevalence of these events, rapid, readily available and clinically feasible NGS of pancreatic tumors may best facilitate patient enrollment on non-disease specific early-phase studies to evaluate drug efficacy in molecularly enriched populations. Our data also support the hypothesis that the identification of germline mutations beyond BRCA1/2 in patients with pancreatic adenocarcinoma may assist with selection of patients for therapy, possible to a greater extent than that afforded by somatic mutation profiling alone. Looking forward, we anticipate that integration of genomic, epigenomic and transcriptomic analyses, as well as enhanced availability of relevant clinical trials, will enable the development of rational patient-specific therapeutic combinations for patients with pancreatic cancer.

Disclosure of Potential Conflicts of Interest

M.A. Lowery is a consultant/advisory board member for Agios Pharmaceuticals and Celgene. J.J. Harding is a consultant/advisory board member for Bristol-Myers Squibb. D.M. Hyman is a consultant/advisory board member for Atara, Boehringer Ingelheim, Chugai and CytomX, and reports receiving commercial research grants from AstraZeneca, Loxo Oncology and PUMA. D.B. Solit is a consultant/advisory board member for Loxo Oncology and Pfizer. E.M. O'Reilly is a consultant/advisor for Halozyme, Celgene, Merrimack, and BMS, and reports receiving research funding from MabVax, AstraZenica, Pfizer, and BMS. No potential conflicts of interest were disclosed by the other authors.

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Published OnlineFirst July 28, 2017; DOI: 10.1158/1078-0432.CCR-17-0899

Grant Support

This work was funded in part by the Marie-Josée and Henry R. Kravis Center for Molecular Oncology, the National Cancer Institute Cancer Center Core Grant No. P30-CA008748, the Suzanne Cohn Simon Pancreatic Cancer Research Fund, and the David M. Rubenstein Center for Pancreatic Cancer Research.

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Received March 27, 2017; revised April 25, 2017; accepted July 18, 2017; published OnlineFirst July 28, 2017.

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Published OnlineFirst July 28, 2017; DOI: 10.1158/1078-0432.CCR-17-0899

Clinical Cancer Research

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Clin Cancer Res 2017;23:6094-6100. Published OnlineFirst July 28, 2017.