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# Has Personalized Medicine for Pancreatic Cancer Arrived?

Ashley Krepline, MD, Susan Tsai, MD, MHS*

Department of Surgery, Medical College of Wisconsin, 8701 West Watertown Plank Road, Milwaukee, WI 53226-3596, USA

**Keywords**

• Pancreatic cancer • Precision medicine • Personalized medicine
• Next-generation sequencing • Clinical trial

**Key points**

- Next-generation DNA and RNA sequencing methodologies have enabled scientists to discriminate several molecular subtypes of pancreatic cancer.
- Up to a quarter of all pancreatic cancers may have a highly actionable mutation for which targeted therapies may be available.
- The translation of sequencing methodologies into clinical practice in a clinically relevant time frame remains challenging and requires a dedicated clinical infrastructure.
- Early studies utilizing molecular profiling to guide treatment have been associated with encouraging results.

## INTRODUCTION

In 1990, when the Human Genome Project was initiated, the objective was to sequence the entire human genome, and, although the project was met with initial skepticism, it ushered in a new era of clinical medicine whereby the genetic basis of disease could be leveraged to inform clinical care [1]. At the core of this revolution is a belief that a deeper understanding of the genetic basis of disease will result in the development of better targeted therapies, as highlighted by President Barack Obama in his 2015 State of the Union Address, when he laid out a vision for a national Precision Medicine Initiative in the United States [2]. The combination of rapidly declining costs for genomic

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*Corresponding author. *E-mail address:* stsai@mcw.edu

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technologies and the explosion of direct-to-consumer companies has made the promise of precision medicine accessible to the public and has irrevocably changed the landscape of oncology for patients and their families.

The terms, *precision medicine* and *personalized medicine*, although closely related, are subtly distinct. The US National Research Council has championed the development of a new taxonomy of human disease based on molecular biology and has defined precision medicine as a population-based approach of classifying individuals through genomic, environmental, or social characteristics, with the goal of identifying effective therapeutics based on a combination of these factors [3]. The report envisioned a comprehensive disease classification that combines information from biomedical research, public health, and health care–delivery communities to advance understanding of disease pathogenesis and improve health. In contrast, personalized medicine implies the development of therapeutics for specific individuals. Ideally, all patients receive personalized medicine, while precision medicine would serve as the foundation for the application of population-based observations at an individual level. Ultimately, the promise of precision medicine is captured in the ubiquitous phrase, "The right treatment for the right patient at the right time."

Coincident with the rapid advances in genomic sequencing technology, significant gains have been achieved in the development of effective therapeutics for pancreatic cancer. As one of the most challenging human malignancies to treat, pancreatic cancer currently is the third leading cause of cancer-related deaths in the United States [4]. Over the past decade, the chemotherapeutic options for patients with pancreatic cancer have evolved from single-agent gemcitabine to multiagent regimens, such as 5-fluorouracil, irinotecan, & oxaliplatin (FOLFIRINOX) and gemcitabine/nab-paclitaxel, which have produced significant gains in overall survival [5,6]. In addition, with the multiagent regimens, exceptional responders have been reported, notably among patients with genetic defects in the homologous recombination DNA repair pathway [7]. The molecular basis for these exceptional responders was uncovered when these patients received poly(ADP-ribose) polymerase (PARP) inhibitor–based and/or platinum-based therapies. Platinum-based agents cause DNA cross-linking and induce DNA strand breaks, which are unable to be repaired in cells with deficient DNA repair mechanisms, such as BRCA1 and BRCA2. In addition to platinum-based therapy, tumors with deficient DNA repair mechanisms also have increased sensitivity to PARP inhibitors, which target the ribosylation of ADP necessary for DNA repair pathways and apoptosis. In a study by O'Reilly and colleagues [8], 9 patients with BRCA mutations received PARP inhibitor in combination with gemcitabine and cisplatinum; 5 of 9 patients demonstrated a partial response and the remaining 4 patients demonstrated stable disease. These early observations reinforced the hypothesis that histopathologic similarities among pancreatic cancers belied an underlying genomic diversity, which, if fully understood, could be used to better stratify subgroups of patients for specific targeted agents.

## EVOLUTION OF THE MOLECULAR CLASSIFICATION OF PANCREATIC CANCER

Over the past 10 years, important advances in large sequencing efforts have culminated in a series of comprehensive integrated genomic analyses, summarized in Table 1. For several decades, it has been well established that pancreatic cancer was the product of the accumulation of successive genetic mutations. The progression from dysplasia to invasive carcinoma is paralleled by a series of genetic mutations that include the activation of the KRAS oncogene and the inactivation of the tumor suppressors genes, CDKN2A, TP53, and SMAD4 [9]. These 4 genetic alterations were confirmed in a seminal report by Jones and colleagues [10] in 2008, which sequenced a total of 114 metastatic pancreatic cancers. In addition, the sequencing revealed a diverse genetic mutations. Given that most cellular pathways and processes involve multiple proteins that function in a concerted manner, the investigators identified 12 core signaling pathways, which were altered in most pancreatic cancer specimens. Unfortunately, many of the pathways were not targetable, and no tumors carried mutations in homologous recombination deficiency. This study laid the framework, however, for future studies categorizing pancreatic cancer into subtypes and ignited the search for new therapeutic options for pancreatic cancer.

In 2011, Collisson and colleagues [11] performed a combined analysis of the transcriptional profiles of 27 resected tumor specimens, as well as those of human and mouse pancreatic cancer cell lines. By applying global gene expression analysis, they identified a 62-gene signature that could classify pancreatic cancers into 3 specific subtypes, which they defined as classical, quasimesenchymal, and exocrine-like. The classical subtype had genes that expressed high levels of epithelial and cell adhesion molecules and were phenotypically more well-differentiated. In contrast, the quasimesenchymal subtype demonstrated high levels of mesenchymal-associated genes and correlated with a more poorly-differentiated phenotype. The exocrine-like subtype had relatively high expression of tumor cell-derived digestive enzyme genes. Importantly, the genetic subtypes had prognostic significance, with patients with classical tumors having the most favorable survival. In the analysis of murine pancreatic cancer cell lines, the classical subtype was observed to be KRAS-dependent and, therefore, more susceptible to KRAS-targeted therapies. Similarly, knockdown of GATA6 expression reduced the growth of classical cell lines but not quasimesenchymal cell lines. Finally, the 62-gene signature has been validated in other published expression data sets, demonstrating the robust nature of the subtype classification [12].

In 2012, Biankin and colleagues [13] utilized whole-exome sequencing and copy number analysis of resected pancreatic cancer. A total of 99 samples were sequenced and, similar to other studies, common mutations were identified in: KRAS, TP53, CDKN2A, SMAD4, MLL3, TGFBR2, ARID1A, and SF3B1.

**Table 1**
Comparison of recent large-scale genomic studies in pancreatic cancer

| Study | Type of Tissue Utilized | Methodology | Classification |
|---|---|---|---|
| Jones et al [10], 2008 | 114 pancreatic cancers—metastatic patients | Sequencing of protein-coding exons with polymerase chain reaction | Identification of 12 core signaling pathways |
| Collison et al [11], 2011 | 27 microdissected tumors from surgical specimens + human and murine pancreatic cancer cell lines | Gene expression microarrays | Three subtypes identified<br>Classical: associated with adhesion and epithelial genes<br>Quasimesenchymal: mesenchyme-associated genes<br>Exocrine-like: associated with digestive enzyme genes |
| Biankin et al [13], 2012 | 142 primary resected pancreatic cancers | Exon sequencing and copy number analysis | Multiple core signaling pathways, including new subgroups involving: G1/S checkpoint, apoptosis, angiogenesis, transforming growth factor β signaling, and axon guidance |
| Waddell et al [14], 2015 | 142 primary resected pancreatic cancers | Whole-genome sequencing and copy number analysis | Subtypes<br>Stable: ≤50 structural variation events<br>Locally rearranged: significant focal event on 1 or 2 chromosomes<br>Scattered: moderate nonrandom chromosomal damage and <200 structural variations<br>Unstable: >200 structural variation events; defects in DNA maintenance. |

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**Table 1**
continued

| Study | Type of Tissue Utilized | Methodology | Classification |
|---|---|---|---|
| Moffitt et al [15], 2015 | 357 primary and metastatic pancreatic cancers, normal tissue, pancreatic cancer cell lines. | Virtual microdissection with microarrays and RNA sequencing | Two subtypes of tumors<br>Classical: high adhesion associated, ribosomal, and epithelial gene expression, elevated GATA-6<br>Basal-like: laminin and keratins<br>Two subtypes of stroma<br>Normal: markers for pancreatic stellate cells<br>Activated: genes associated with macrophages and tumor promotion |
| Bailey et al [16], 2016 | 456 primary resected pancreatic cancers | Integrated genomic analysis | Four subtypes<br>Squamous: enriched for integrin signaling and activated EGF signaling.<br>ADEX: transcriptional networks in later stages of pancreatic development and differentiation; genes associated with endocrine differentiation<br>Pancreatic progenitor: genes regulated pancreatic development, fatty acid oxidation, steroid hormone biosynthesis, pancreatitis and regeneration<br>Immunogenic: immune infiltrate; B-cell signaling pathways, antigen presentation, T-cell and Toll-like receptor signaling pathways |

In addition, they identified novel mutations in chromatin modification (EPC1 and ARID2) and DNA repair (ATM), which represent additional targetable mutations. The investigators also identified mutations in tumor cell invasion and metastases (SLIT2, ROBO2, SEMA3A, SEMA3E, and PLXNA1).

In 2015, 2 large-scale genomic studies were reported. Waddell and colleagues [14] utilized whole-genome sequencing in 100 patients with resected pancreatic cancer and identified 4 distinct subtypes: (1) stable subtype, which contained fewer than 50 structural variations and represented 20% of the samples, (2) locally rearranged subtype, in which the genetic abnormality was limited to one or two chromosomes, and represented 30% of the sample, (3) scattered subtype, which harbored a moderate number (<200) of structural variation events and represented 36% of the sample, and (4) unstable subtype which had a large number of structural variations, suggesting a defect in DNA maintenance.

The unstable subtypes were more likely to have mutations in BRCA1, BRCA2, PALB2, ATM, FANCM, XRCC4, and XRCC6 and were more likely to be responsive to platinum-based therapies. This was the first report to demonstrate that variation in chromosomal structure as an important mechanism of DNA damage in pancreatic carcinogenesis. Moffitt and colleagues [15] extended the work from Collison and colleagues by defining 2 tumor subtypes and 2 stromal subtypes, using a wide range of pancreatic cancer samples, including 145 primary tumors and 61 metastatic samples with adjacent normal controls. Unique to this analysis, the investigators performed a digital separation of gene expression between tumor, stroma, and adjacent normal tissue. Two tumor-specific subtypes were identified (classical and basal-like) and 2 stroma subtypes (normal and activated). An activated stroma was associated with significantly worse prognosis, and specific combinations of tumor and stroma subtypes had a cumulative effect on prognosis, with those patients with classical tumors and normal stroma having the best outcome. Overall, the Moffitt classical subtype overlapped with the Collison classical subtype and was characterized by high adhesion-associated proteins, ribosomal and epithelial gene expression, and elevated GATA6 expression.

Finally, in 2016, Bailey and colleagues [16] reported on 456 resected pancreatic cancers that underwent whole-exome sequencing and copy number analysis. Analysis included differential expression of transcription factors and downstream targets. The RNA analysis revealed clustering into 4 distinct subtypes: squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine (ADEX). The squamous subtype harbored the greatest number of mutations in TP53 and KDM6A and had the poorest prognosis. The pancreatic progenitor subtype expressed genes involved in pancreatic development, with an enrichment in inactivating mutation of TGFBR2. The immunogenic subtype was characterized by pathway-mediated acquired immune suppression. These tumors had significant immune infiltration and

up-regulation of inhibitory immune checkpoint pathways. The ADEX subtype was characterized by expression of genes involved in later stages of both pancreatic exocrine and endocrine cell development. When this transcriptome classification is compared with the Collison classification, there is significant overlap except for the addition of the immunogenic subtype. The Collison quasimesenchymal corresponds to the squamous subtype, classical corresponds to the pancreatic progenitor, and the exocrine-like to the ADEX. There was less similarity between the Moffitt and Bailey subtypes, likely due to the reduced stromal content in the latter study.

Overall, these studies demonstrate that reproducible biologic subgroups exist in pancreatic cancer. There are strong biologic similarities between the Collison, Moffitt, and Bailey classifications. In general, the prognosis of quasimesenchymal/squamous/basal-like subtypes is worse than that of the classical/pancreatic progenitor subtypes and may be more responsive to chemotherapy. The clinical utility of molecular subtyping is only realized if the information provided has an impact on treatment selection. The Know Your Tumor Initiative was developed as a joint collaboration between the Pancreatic Cancer Action Network and Perthera, with the goal of offering patients with pancreatic cancer multi-omic molecular profiling [17]. The study recruited patients from 44 states, including academic and community practices. Next-generation sequencing and immunohistochemical (IHC) profiling were performed in commercial laboratories (Foundation Medicine [Cambridge, MA], PGDX [Baltimore, MD], Caris Life Sciences [Dallas, TX], and NeoGenomics [Fort Myers, FL]). An online tumor board reviewed the molecular profiling results, and a report with treatment options was created for the treating oncologists. In total, 640 tumor specimens were sent for next-generation sequencing and IHC, 591 of which were pancreatic adenocarcinoma. After obtaining tissue from a local pathologist, the median time to report delivery was 30 days. Of 640 patients, 458 (72%) had metastatic disease, 137 (21%) had locally advanced disease, and 45 (7%) had resectable disease or borderline resectable disease. Of 640 patients, at least 1 mutation was identified in 616 samples (median 4 mutations per sample). The tumor board identified actionable genomic alterations in 50% of patients (with 27% highly actionable) and actionable proteomic alterations (excluding chemopredictive markers) in 5%. Highly actionable mutations were identified as those in the homologous recombinant DNA repair pathway (15%), cell cycle genes (11%), and AKT/mTOR (19%) pathways. As a result of the molecular profiling, 156 (24%) of 640 patients were transitioned to a new treatment regimen, 173 (27%) remained on their treatment started prior to sequencing, 111 (17%) passed away prior to transitioning to a new treatment based on tumor sequencing, and 200 (31%) patients were lost to follow-up. A subset analysis of patients with highly actionable biomarkers who received profile-directed therapy ($n = 17$) demonstrated a significantly longer median progression-free survival than those with unmatched therapy ($n = 18$) (hazard ratio 0.47; $P = .003$).

## TRANSLATING MOLECULAR PROFILING INTO CLINICAL RELEVANCE

Although the ability to characterize pancreatic cancers into molecular subtypes has evolved substantially over the past decade, its translation into clinical practice has been markedly slower. One of the first reported precision medicine trials for patients with pancreatic cancer was the individualized molecular pancreatic cancer therapy (IMPaCT) trial [18]. This was a pilot study of 76 patients with metastatic or recurrent pancreatic cancer who underwent targeted sequencing of BRCA1, BRCA2, PALB2, ATM, or KRAS genes as well as an assessment of HER2 amplification from formalin-fixed paraffin-embedded samples. Patients then were randomized to single-agent gemcitabine or target-specific therapy (patients deficient in the homologous recombinant DNA repair pathway received 5-fluorouracil and mitomycin C, patients with HER2 amplification received gemcitabine and trastuzumab, patients with wild-type KRAS received gemcitabine and erlotinib). A genetic target was identified in 22 (28%) patients (14 wild-type KRAS, 5 HER2 amplification, 2 BRCA2, and 1 ATM). The median time from enrollment to relay of test results was 21.5 days, but no patient was successfully treated on trial. The investigators recognized that rapid disease progression made the return of genomic results in a meaningful time frame challenging.

Another clinical trial designed to provide comprehensive real-time genomic analysis for patients with advanced pancreatic cancer was the comprehensive molecular characterization of advanced pancreatic ductal adenocarcinoma for better treatment selection (COMPASS) trial [19]. In this trial, 63 patients underwent tumor biopsy and whole-genome sequencing, and RNA sequencing was performed from the fresh tumor tissue. The primary endpoint of the trial was the feasibility of reporting the sequencing results prior to 8 weeks. Overall, 18 (28%) patients were identified with actionable mutations: 5, ARID1A; 1, BRAF; 4, CDK4/6; 4, PIK3CA; 3, PTEN; and 2, FNG43. Genomic results were reported at a median of 35 days from biopsy. In 5 patients, the second-line therapy was based on the COMPASS results. The investigators categorized the tumors based on the Moffitt classical and basal-like subtypes and compared responses to first-line chemotherapy based on molecular subtype. They observed improved progression-free survival among patients with the classical subtype who were treated with FOLFIRINOX. Importantly, GATA6 protein expression was found a robust surrogate biomarker for differentiating classical and basal-like subtypes, suggesting that simple proteomic correlates may be identified as surrogates of genomic subtyping.

Although the clinical value of genetic sequencing from these early experiences is mixed, the necessity of a robust clinical infrastructure to support the acquisition and analysis of biospecimens for next-generation sequencing within a reasonable timeframe was unquestionable. The investigators of the IMPaCT trial summarized the need for programmatic infrastructure including: (1) a

sufficient volume of patients, (2) the ability to acquire suitable tumor specimens for the testing platform, (3) a clinically acceptable turnaround time, and (4) an attractive clinical trial design for patients. [18]

Implicit in these requirements is a cooperative and integrated relationship between the molecular laboratories, clinical staff, and a variety of clinical disciplines, with dedicated resources to expedite the molecular profiling services. As previous studies have suggested, higher levels of physician engagement in multidisciplinary teams are associated with more rapid initiation of treatment and increased enrollment of patients in clinical trials [20,21].

An alternative approach to molecular profiling is the use of IHC protein expression rather than next-generation sequencing. This approach has several advantages over next-generation sequencing in that IHC profiling already is performed ubiquitously in pathologic laboratories, has a rapid turnaround time, and is relatively cost-effective. One of the first studies to utilize molecular profiling of tumors to guide treatment regimens was the Bisgrove study [22]. This study enrolled patients with a variety of refractory metastatic cancers and utilized IHC and flourescence in situ hybridization assays to assess 11 proteins and performed oligonucleotide microarray gene expression of an additional 51 genes. The goal of the study was to compare the progression-free survival for each patient using a treatment regimen selected by molecular profiling as compared with the prior progression-free survival on the most recent regimen prior to enrollment on the trial. In this study design, each patient served as his/her own control. In total, 86 patients enrolled in the study, and a molecular target was identified in 84 (98%). Of the 84 patients, 66 (79%) received profile-directed therapy, and 18 (27%) of the 66 patients had a progression-free survival, which exceeded the most recent regimen on which the patient had experienced progression (progression-free survival ratio $\geq$1.3).

The first molecular profiling trial in patients with localized pancreatic cancer recently was reported [23]. The trial utilized 6 putative biomarkers of chemotherapeutic responsiveness, including nucleoside transporter hENT1 and ribonucleotide reductase M1 for gemcitabine responsiveness, secreted protein acidic and rich in cysteine for nab-paclitaxel responsiveness, thymidylate synthase for 5-fluorouracil responsiveness, excision repair cross-complementing protein for platinum sensitivity, and topoisomerase 1 for irinotecan resistance. Biopsies from endoscopic ultrasound–guided fine-needle aspirates and surgical specimens underwent molecular profiling to guide neoadjuvant therapy and adjuvant therapy, respectively. The primary endpoint of the trial was to improve the rate of surgical resection after neoadjuvant therapy from 80% to 90% in patients with resectable pancreatic cancer and from 50% to 70% in patients with borderline resectable pancreatic cancer. In total, 130 patients were enrolled at 2 institutions, 61 (47%) with resectable disease and 69 (53%) with borderline resectable disease. Adequate cellularity for molecular profiling of the endoscopic ultrasound–guided fine-needle aspirate specimens was present in 95 (73%) patients, and the median time

to reporting of the molecular profiling was 5 days. Of the 130 patents, 107 (82%) completed all intended neoadjuvant therapy and surgery–56 (92%) patients with resectable disease and 51 (74%) patients with borderline resectable disease. The median overall survival of all patients was 38 months, 45 months among patients who completed all neoadjuvant therapy and surgery and 11 months for patients who were not resected. As alluded to from the IMPaCT study, the investigators noted that the inclusion of advanced gastroenterologists and integrated molecular pathology services was essential to developing a comprehensive pipeline to screen and enrolling patients with localized pancreatic ductal adenocarcinoma. The presence of on-site cytopathologists expedited the pathologic evaluation of the biopsy specimen and increased the yield of available tissue for molecular profiling [24]. In contrast to clinical trials utilizing next-generation sequencing, the rapid turnaround time utilizing IHC greatly improved the ability to place patients on molecular profiled therapy as the first line of therapy. Furthermore, close communication with the trial coordinators and the molecular pathology laboratory allowed for rapid reporting of results in a median of 5 days. In contrast, with next-generation sequencing the sample preparation, sequencing, and bioinformatic analysis can take up to 21 days. This study demonstrated the feasibility of utilizing molecular profiling to guide treatment selection and emphasized the need to identify rapid molecular assays to reduce patient attrition during molecular profiling [18].

## MOVING FROM PRECISION MEDICINE TO PERSONALIZED MEDICINE

With the exception of a small subset of patients with microsatellite instability, homologous recombinant DNA repair pathways, or potentially targetable KRAS mutations, the therapeutic implications of pancreatic cancer subtypes remain largely unknown. To better understand the biologic consequences of these subtypes, both patient-derived xenografts and patient-derived organoids offer an opportunity to test potential biomarkers and refine therapeutic interventions.

Patient-derived xenografts are generated directly from engraftment of individual human tumor tissue into severely immunocompromised mice to allow for the efficient engraftment of the tumor. These have been shown to faithfully recreate the genomic and histopathologic characteristics of the human tumor, including tumor heterogeneity, at least in early passages [25]. Generation of patient-derived xenografts may provide a renewable and valuable resource with which multiple treatments may be studied with the ultimate goal of determining the best therapeutic option for the patient. Clinical studies have demonstrated remarkable correlations between drug activity in the xenograft model and patient outcome [26]. Although patient-derived xenografts have yielded important insights into pancreatic cancer, their generation often requires a large amount of tissue, multiple months to establish, and serial passaging results in

replacement of human stroma with murine components. An alternative to patient-derived xenografts is the creation of 3-D cell cultures of dissociated tumors, also termed organoids. Patient-derived organoids have been established from surgical resection specimens, as well as fine-needle biopsy [27]. In a recent report, 66 patient-derived organoid cultures underwent molecular characterization using whole-genome and RNA sequencing, which recapitulated the molecular characteristics of the primary tumor [27]. The organoids were then subjected to the 5 chemotherapeutic agents most commonly used to treat patients with pancreatic cancer, with marked variability in response to therapy. Furthermore, the drug sensitivity of the organoid cultures reflected the clinical outcomes of the patients. These results suggest a broad range of intrinsic drug sensitivity to conventional chemotherapeutic agents and interpatient diversity to chemotherapeutic drug responses. The biologic basis of drug responsiveness currently is under investigation and may involve drug transport, metabolism, and/or response to cell damage. Importantly, such responses currently are not reflected in the models of pancreatic cancer subtyping and reveal the opportunity to further develop a complementary pharmacogenomic classification of drug response.

## SUMMARY

The era of next-generation sequencing has shepherded a new molecular taxonomy of pancreatic cancer, which may better inform our understanding disease pathogenesis. It will become important for surgeons to become familiar with these subtypes, especially how molecular genotypes are related to therapeutic vulnerabilities. Although the clinical impact of these advances is yet to be fully realized, there is a powerful momentum toward precision medicine for pancreatic cancer. In the future, streamlining clinical infrastructure and reducing turnaround time for genomic sequencing will be paramount, and these obstacles may be overcome with technological advancements or through the development of surrogate proteomic markers. Although advances in genomic classification have opened the door to precision medicine for pancreatic cancer, additional models, such as patient-derived organoids, may be necessary to fully realize a personalized approach for individual patients.

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