Lessons Learned From a Complete Remission of Advanced Metastatic Pancreatic Ductal Adenocarcinoma

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Background

The overall case fatality rate for ductal adenocarcinoma of the pancreas approaches 96%. Even patients who undergo successful surgical resection of early stage IA tumors will have a 5-year survival rate that is less than 40%.[1] Less than 1% of patients with metastatic pancreatic cancer will survive for 5 years. One-year survival of stage IV patients was approximately 2% in the pre-gemcitabine (Gemzar, Eli Lilly) era, 18% with gemcitabine treatment, and 24% with a combination regimen of gemcitabine and erlotinib (Tarceva, Genentech).[2] The limited benefit of these treatments is in part the result of intrinsic tumor resistance. Objective response rates with single-agent gemcitabine or the combination of gemcitabine and erlotinib are less than 10%. We present the case of a 44-year-old man with stage IV pancreatic cancer with omental metastasis, who achieved a complete remission after 3 years of gemcitabine-based therapy. We examined this case in detail in an attempt to identify molecular and histopathologic features of this patient's tumor that may have contributed to its unusual chemosensitivity. We found that the tumor had the usual activating mutation in *KRAS*, but that the patient was *BRCA2*-mutant. We believe that this finding is of interest because there have been other reports of increased sensitivity of pancreatic cancer cells carrying *BRCA2* mutations to treatments, including capecitabine (Xeloda, Genentech), mitomycin-C, gemcitabine, and cisplatin. These reports, when combined with this case, allow hypothesis-generating observations, which suggest that targeting DNA repair systems may be an important key to improving the efficacy of current treatments for pancreatic cancer. Physicians seeing patients with this molecular profile should approach them with a nonfatalistic view, since aggressive treatment may lead to favorable outcomes.

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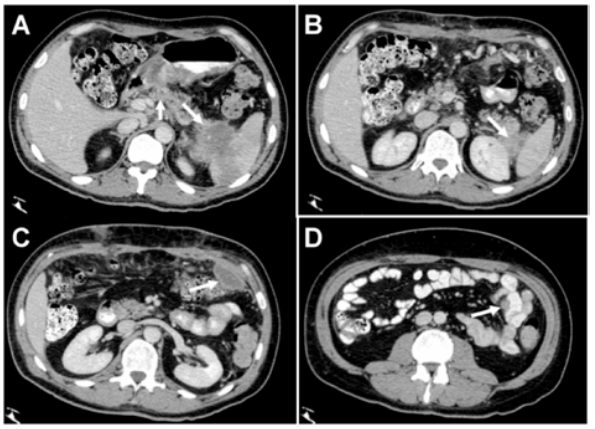


Figure 1. Pretreatment axial computed tomography (CT) scan images. A) Primary pancreatic mass involving the body and tail of the pancreas and invading the spleen and stomach. B) Involvement of the left perinephric fat. C) Large omental tumor implant. D) Mesenteric tumor implant.

Case Report

In the fall of 2005, a 44-year-old man with obesity and a 10-pack year history of cigarette smoking presented with left upper quadrant abdominal pain that radiated to the back. A computed tomography (CT) scan of the abdomen that was obtained in January 2006 revealed a 5-cm mass in the tail of the pancreas (Figure 1A). This mass invaded the spleen and extended to the perinephric fat (Figure 1B). There were perisplenic lymph nodes, the largest of which was 1.2 cm. There were multiple omental implants, with the largest in the left upper quadrant that

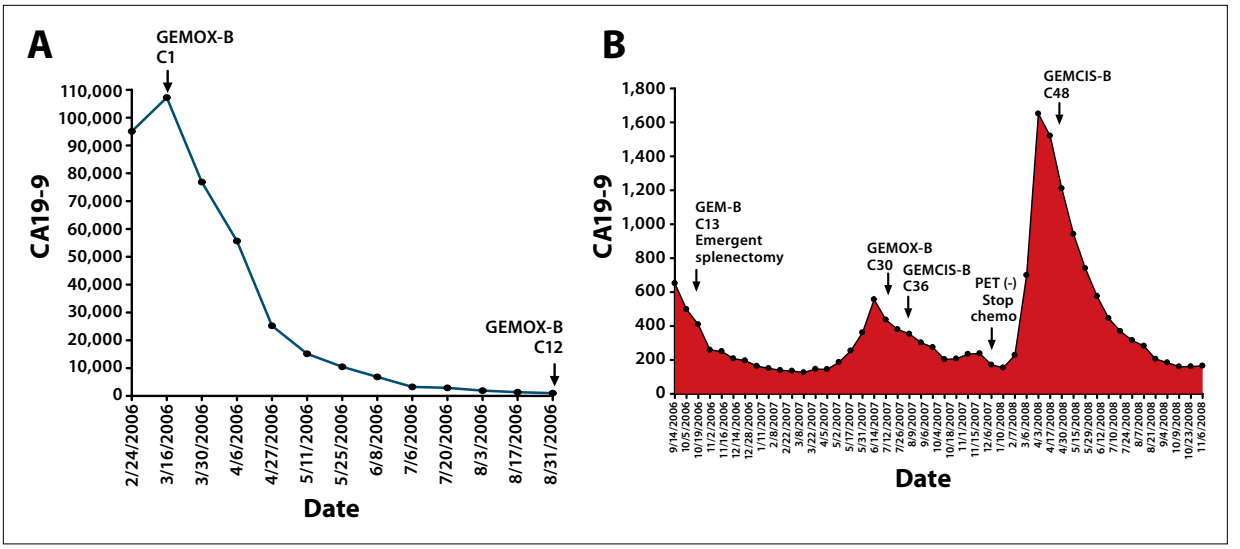


Figure 2. Response to therapy as monitored by serum CA19-9. A) CA19-9 during the initial 6 months of therapy with gemcitabine, oxaliplatin, and bevacizumab (GEMOX-B); cycles 1–12. B) CA19-9 during cycles 13–61. Cycles 13–29 are without platinum. From cycle 30 onward, platinum drugs are reintroduced.

measured 4.1 cm (Figure 1C). Tumor implants were also noted in the mesentery, medial to the descending colon (Figure 1D), and in the pelvis near the rectum. There was periportal lymphadenopathy and a small quantity of pelvic ascites. A CT scan of the thorax identified filling defects in the right pulmonary artery consistent with pulmonary emboli, so the patient was started on dalteparin. He subsequently underwent an exploratory laparotomy at an outside center. Surgical findings included generalized peritoneal carcinomatosis involving almost the entire omentum, a large mass located in the omentum anterior to the transverse colon, and a large exophytic tumor arising in the superior aspect of the head of the pancreas that appeared to be invading the stomach. A biopsy of the largest omental nodule showed metastatic adenocarcinoma consistent with a pancreatic primary. Any further attempt at surgical resection was abandoned, and the patient was given a prognosis of 3 months. The patient elected to proceed with systemic therapy in March 2006. A treatment regimen consisting of gemcitabine 1,000 mg/m^2, oxaliplatin 85 mg/m^2, and bevacizumab (Avastin, Genentech/Roche) 10 mg/kg every 14 days was initiated in March 2006. By this time, the CA19-9 level exceeded the upper limit of normal (which is 37 U/mL) and reached a value of 107,224 U/mL. After 6 months of chemotherapy, there was a 99% decline in the CA19-9 to 1,015 U/mL (Figure 2A). Restaging CT scans revealed that the tail of the pancreas mass had decreased from 5 cm to 3.9 cm, and the omental mass decreased from 4.1 cm to 2.5 cm. In September 2006, the patient developed persistent anemia that did not respond to darbepoetin and ferrous gluconate infusion, so he underwent further evaluation

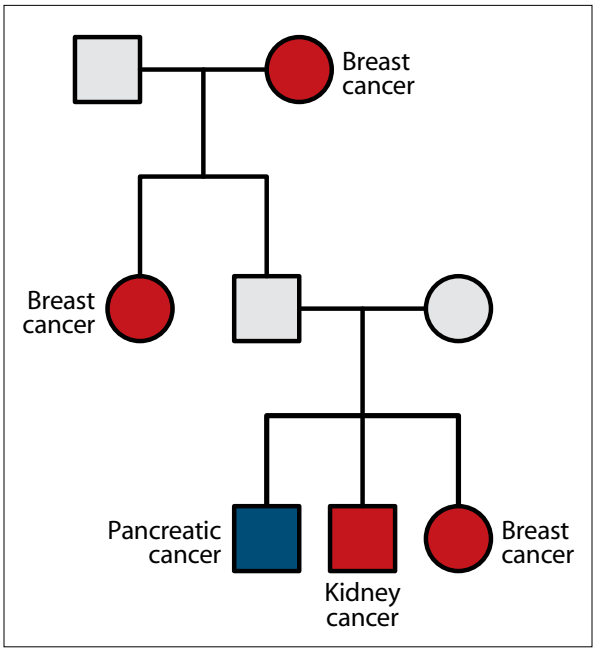
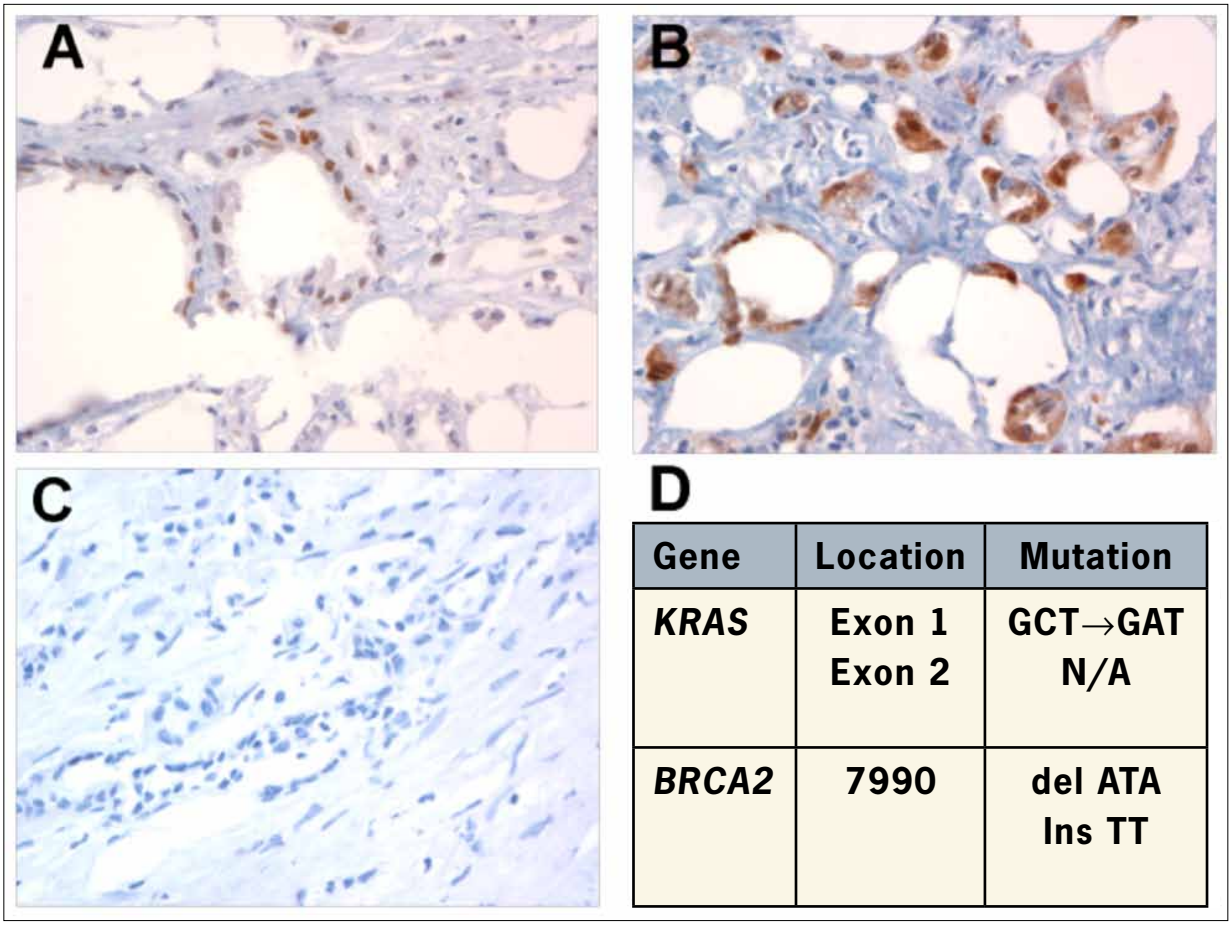


Figure 3. Pedigree of the patient's family.

with esophagogastroduodenoscopy (EGD). This revealed the presence of large gastric varicies with active bleeding that were likely due to splenic vein occlusion. Endoscopic banding initially arrested bleeding, but 72 hours later, the patient developed hemoptysis and bright red blood per rectum. Upon presentation, he was hypotensive, with a hemoglobin of 6.0 g/dL. After transfusion of 9 units of packed red blood cells and emergent attempts at endoscopic ligation, hemorrhage was still uncontrollable. It



Gene	Location	Mutation
KRAS	Exon 1 Exon 2	GCT→GAT N/A
BRCA2	7990	del ATA Ins TT

Figure 4. Characterization of the patient's tumor. Immunohistochemical staining for A) p53, B) p16, and C) human epidermal growth factor receptor 2 (HER2). D) Mutational analysis of *KRAS* in the tumor and *BRCA2* in the germline.

was initially proposed that since the patient had "end stage" pancreatic cancer, he should be enrolled in hospice and allowed to expire. Due to his excellent response to chemotherapy, we recommended aggressive intervention instead. The patient was taken to the operating room by the surgeon who originally examined him at presentation. An emergent splenectomy was performed, and hemostasis was achieved. During surgery, it was noted that most of the omental implants had regressed, and both masses in the pancreas were indeed much smaller when compared to the exploratory laparotomy done in January 2006. The patient resumed chemotherapy, and his CA19-9 continued to decline to a low of 126 U/mL (Figure 2B). Since we had confirmation of a dramatic response to chemotherapy at surgical exploration, we reviewed the patient's history and studied his tumor biopsy for clues that might explain this clinical behavior. We noted that he had a sister, a paternal aunt, and a paternal grandmother who were diagnosed with breast cancer (Figure 3). Another sister was diagnosed with a renal cell cancer. This pedigree raised the possibility that the patient was a carrier of a *BRCA* gene mutation. DNA sequencing revealed that the patient had an uncommon frame-shift mutation in exon 16, 7990del3ins2. Tumor cells deficient in *BRCA2* function would be expected to be more sensitive to chemotherapy-induced DNA damage. Loss of *BRCA2* has been reported to be a late event in the evolution of pancreatic cancer.[3] It is unknown if the genetic features of pancreatic adenocarcinoma arising in the context of pre-existing *BRCA2* mutation are the same as those arising in the absence of this mutation. Therefore, we examined this patient's tumor for the presence of *KRAS* mutation, p53, p16, and human epidermal growth factor receptor 2 (HER2) overexpression by standard immunohistochemical techniques. We found that the tumor harbored a typical activating mutation in *KRAS* exon 1 that is present in the majority of patients (Figure 4). This finding is consistent with the central pathogenetic role of *KRAS*, and implies that *BRCA2* loss may not bypass the requirement for *KRAS* activation in pancreatic cancer. It also indicates that major regression of pancreatic adenocarcinomas can occur despite unrestrained *KRAS* activity. We found p53

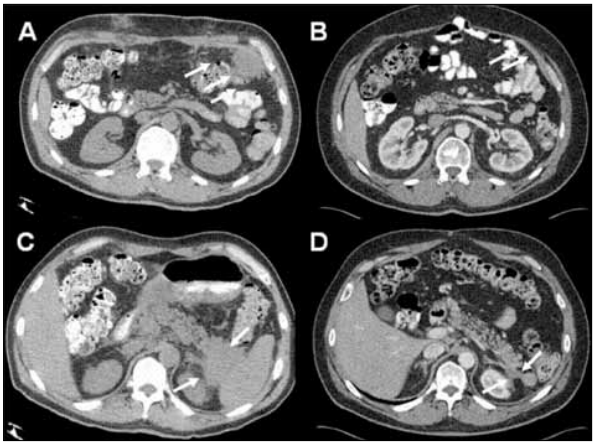


Figure 5. Axial computed tomography (CT) scan images demonstrating response to chemotherapy. Panels A and C are at baseline, and panels B and D are after chemotherapy. The upper panel shows regression of a large omental mass. The lower panel shows regression of the mass in the tail of the pancreas.

and p16 expression, indicating mutation of these genes, as is expected in pancreatic ductal adenocarcinoma.

We were also able to investigate the contribution of platinum drugs to the efficacy of this patient's regimen. To date, the patient has received greater than 80 courses of gemcitabine-based therapy, given every 14 days. Cycles 1–12 were given with oxaliplatin, and were associated with a dramatic response. During cycles 13–29, oxaliplatin was omitted, due to neuropathy. At first, gemcitabine and bevacizumab alone were associated with continued decline of the CA19-9. Then, the cancer evidently became resistant, and the CA19-9 began to rise rapidly. With cycle 34, oxaliplatin was reintroduced, and the CA19-9 again started to decline. Later, oxaliplatin was changed to cisplatin. Nevertheless, the tumor continued to respond. Therefore, it appears that the inclusion of a platinum drug was critical for the tumor response, and oxaliplatin and cisplatin were equally effective for this patient (Figure 5).

Discussion

Several important and intriguing lessons can be extracted from this case. First, advanced metastatic pancreatic cancer is not uniformly fatal, as there appears to be rare patients who can have dramatic responses to standard therapeutic agents. Second, even in such patients, radiographic responses may be slow to manifest. The journey from diagnosis to remission in this patient took 4 years of persistent chemotherapy treatment. Third, life-threatening complications of pancreatic cancer, such as thromboembolism and gastrointestinal bleeding, should be treated aggressively in patients who are responding to chemotherapy. Such interventions should not be viewed as futile, but rather as allowing for the maximum benefit of the chemotherapy to be realized. Finally, despite the presence of an activating mutation in *KRAS*, this patient's tumor was quite sensitive to chemotherapy-induced apoptosis. It is likely that the patient's germline *BRCA2* mutation was the molecular basis for this response. That the inclusion of the DNA-crosslinking agents oxaliplatin and cisplatin was obligatory in the treatment regimen is consistent with this hypothesis. It has been observed that pancreatic cells having defects in the Fanconi anemia/*BRCA2* pathway are remarkably sensitive to DNA-interstrand cross-linking agents, both in culture and in mouse xenografts.[4] Similar to this case, a patient with metastatic pancreatic cancer responded to third-line therapy with a combination of mitomycin-C and capecitabine.[5] In a study by Ferdinandos and associates, findings led to the conjecture that biallelic *BRCA2* inactivation promotes a distinct tumor type that might be more susceptible to targeted therapies.[6] Our patient's remarkable response to DNA-crosslinking agents suggests that he may have loss of heterozygosity in *BRCA2*. These observations suggest a translational research hypothesis that undermining DNA repair systems may be an effective therapeutic strategy. ATM, PARP, and Chk1/2 inhibitors are under investigation and may be used in clinical trials to test this hypothesis.

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Review

Is There a Case for Personalized Therapy of Pancreatic Cancer?

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This interesting case report by Mathew and colleagues[1] provides an opportunity to review the significance of the personalized therapy approach for patients with pancreatic cancer. Pancreatic cancer is one of the most fatal and chemotherapy-resistant cancers. Despite considerable improvement in overall cancer mortality in the past decade, statistics for pancreatic cancer have not changed significantly. Based on data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program, median survival time for pancreatic cancer is less than 1 year for all stages, and the relative mortality rate has remained unchanged over the past decade.[2] The efficacy of gemcitabine (Gemzar, Eli Lilly), the first pancreatic cancer drug approved by the US Food and Drug Administration (FDA), is modest at best.[3] Numerous cytotoxic and biologic agents were tested in combination with gemcitabine without success, and pancreatic cancer has become known as a "graveyard" for cancer drug development. It is important to recognize that it was the empiric approach that dominated the field of cancer drug development in the past 2 decades. New advances in gene sequencing technology are providing potentially valuable prognostic and predictive tools for oncologists.

Current Status of Systemic Therapy for Pancreatic Cancer

The majority of pancreatic cancer patients present with advanced and unresectable disease. Currently, the goal of therapy for these patients is to prolong survival without compromising quality of life. Gemcitabine has been the mainstay of therapy since its approval by the FDA in 1997.[3] It is one of the most well-tolerated chemotherapy drugs, and although response rates and survival improvements are modest, for many patients, it does appear to improve quality of life and clinical benefit response.

During the past 2 decades, the only drug that has shown some benefit when added to gemcitabine over gemcitabine alone in phase III trials is erlotinib (Tarceva, Genentech). The magnitude of clinical benefit was 6.24 months versus 5.91 months, favoring the gemcitabine plus erlotinib combination. Combinations of gemcitabine with platinum drugs and capecitabine (Xeloda, Genentech) did not demonstrate significant improvement in overall survival, but some post-hoc analyses suggested possible benefit for patients with better Eastern Cooperative Oncology Group (ECOG) performance status scores (0–1), as reviewed by Campen and colleagues.[4]

The use of gemcitabine as a backbone for systemic therapy of pancreatic cancer was recently challenged by the results from the PRODIGE 4/ACCORD 11 trial.[5] In this trial, patients with metastatic pancreatic cancer and good ECOG performance status scores (0–1) were randomized to receive either gemcitabine or the 4-drug combination 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX). There was a considerable and significant improvement in overall survival for patients in the FOLFIRINOX arm (11.1 months vs 6.8 months). This very intense and toxic regimen is an option for those few patients with unresectable pancreatic cancer who are of younger age and have excellent performance status scores.

Therapeutic Implications of Genetic and Molecular Complexity

Recent advances in the genetic and molecular fingerprinting of pancreatic cancer have been achieved via gene sequencing and cataloguing. A paper by Jones and coauthors[6] confirms that there is tremendous heterogeneity in specific mutations across pancreatic adenocarcinomas. Most genes are mutated in a small subset of tumors, but there is a multiplicity of affected signaling pathways. Thus, it is very unlikely that a single molecular target would be sufficient enough to derail pancreatic cancer cell growth and its propensity to metastasize. In terms of effective therapeutic approaches, it is likely more effective to target not specific genes, but pathways that are commonly deranged in pancreatic cancer, such as metabolic pathways, neoangiogenesis, cell cycle regulation, and DNA repair pathways.

Dysregulation of *Fanconi/BRCA2* Pathway

Proteins that are encoded by *BRCA1*, *BRCA2*, *FANNC*, and *FANCG* genes have a role in cellular DNA repair. This is a key mechanism that is involved in repairing damage caused by some of the DNA-intercalating chemotherapy drugs. A small number of pancreatic cancer cases are con-

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sidered familial, and *BRCA2* mutation is likely the most common and best-characterized gene mutation associated with familial pancreatic cancer. Although carriers of these mutations are at very high risk for breast and ovarian cancer, they also have an increased risk for pancreatic cancer (3–4 times greater than the general population).[7] *PALB2*, another gene involved in *BRCA1* and *BRCA2* interactions, was recently found to be mutated in some patients with hereditary pancreatic cancer.[8] Pancreatic cancer cell lines and xenografts carrying *BRCA*2 mutations have been shown to be more selective in vitro and in vivo to chemotherapy drugs, such as mytomicin C, platinum drugs, and poly ADP-ribose polymerase (PARP) inhibitors.[9,10] In addition, a number of clinical case reports suggest that some of these agents, which are not considered the standard of care for pancreatic cancer, can provide remarkable benefit in patients with suspected dysregulation of the *Fanconi/BRCA2* pathway.[10,11]

Conclusion

The case reported by Mathew and colleagues is of interest because the authors performed a retrospective genomic analysis of a very unusual clinical presentation of pancreatic cancer, and proposed a physiologically-driven hypothesis that can be applied to a subset of patients with pancreatic cancer. It is a strong example of reversing the traditional "bench to bedside" approach to problems in clinical medicine. It also emphasizes a new and emerging paradigm in drug development for epithelial malignancies. Because of the genetic complexity of epithelial malignancies, and the lack of dominant driving pathways (unlike those of some hematologic malignancies), it is likely that a more personalized approach would be a more successful strategy. A recent example of this concept is the successful clinical development of the non–small cell lung cancer drug crizotinib (Xalkori, Pfizer), which targets the *ALK* fusion gene. The *ALK* fusion gene is present in only 3–5% of patients with non–small cell lung cancer.[12] Rapid advances in gene sequencing technology will allow for much more affordable and faster prospective cancer genotyping. Based on this outcome, personalized cancer therapy may become more of a mainstream concept for some tumor types, including pancreatic cancer.

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