ORIGINAL ARTICLE

The Dutch Pancreas Biobank Within the Parelsnoer Institute
A Nationwide Biobank of Pancreatic and Periampullary Diseases

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Objectives: Large biobanks with uniform collection of biomaterials and associated clinical data are essential for translational research. The Netherlands has traditionally been well organized in multicenter clinical research on pancreatic diseases, including the nationwide multidisciplinary Dutch Pancreatic Cancer Group and Dutch Pancreatitis Study Group. To enable high-quality translational research on pancreatic and periampullary diseases, these groups established the Dutch Pancreas Biobank.

Methods: The Dutch Pancreas Biobank is part of the Parelsnoer Institute and involves all 8 Dutch university medical centers and 5 nonacademic hospitals. Adult patients undergoing pancreatic surgery (all indications) are eligible for inclusion. Preoperative blood samples, tumor tissue from resected specimens, pancreatic cyst fluid, and follow-up blood samples are collected. Clinical parameters are collected in conjunction with the mandatory Dutch Pancreatic Cancer Audit.

Results: Between January 2015 and May 2017, 488 patients were included in the first 5 participating centers: 4 university medical centers and 1 nonacademic hospital. Over 2500 samples were collected: 1308 preoperative blood samples, 864 tissue samples, and 366 follow-up blood samples.

Conclusions: Prospective collection of biomaterials and associated clinical data has started in the Dutch Pancreas Biobank. Subsequent translational research will aim to improve treatment decisions based on disease characteristics.

Pancreatic cancer is one of the most lethal cancers, with a 5-year survival rate of 6%.[1] Surgical resection combined with adjuvant chemotherapy shows the best outcomes with 5-year survival rates of 20%.[2,3] However, only 15% to 20% of patients present with a (potentially) resectable cancer.[4] Currently available

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chemotherapy strategies have only a limited effect on survival and quality of life, both in adjuvant and palliative setting.[5,6]

In various types of cancers, the development of new genetic and molecular tools has led to a more tailored treatment of patients based on selective tumor features.[7–9] Despite the increasing knowledge of tumor biology in pancreatic cancer, no translation into effective targeted treatment strategies has been achieved so far.[10] Several targeted agents for pancreatic cancer have been evaluated in clinical trials, but only the HER1/EGFR tyrosine kinase inhibitor erlotinib (in combination with gemcitabine) for locally advanced or metastatic pancreatic cancer has been approved by the Food and Drug Administration.[11] Improved selection of patients who may benefit from targeted therapies might lead to better outcomes. Currently, no validated biomarkers to guide personalized treatment decisions are available for erlotinib or other targeted therapies in pancreatic cancer.[10,12]

Pancreatic cancer shares biological characteristics with the 3 other periampullary tumors (ie, distal cholangiocarcinoma, duodenal carcinoma, and ampulla of Vater carcinoma), but important differences exist between their mutational profiles, biological behavior, and response to chemotherapy.[13] Research initiatives on molecular characterization and tailored treatment of periampullary tumors are currently limited, but urgently needed given the limited survival. Moreover, differentiation between these tumor types may be difficult, even on final pathology. This, while the correct diagnosis of the tumor type is extremely important for treatment decisions, as adjuvant chemotherapy is only indicated in case of pancreatic cancer and, based on recent evidence, distal cholangiocarcinoma.[14] Also in palliative setting, chemotherapy regimens differ between pancreatic cancer and other periampullary cancers.[15,16]

Chronic pancreatitis (CP) is a benign but debilitating disease associated with severe chronic abdominal pain and complications such as pseudocysts and bile duct or duodenal obstruction. Treatment is focused on pain management and exo- and endocrine insufficiency.[17] In severe cases, surgery is effective in relieving pain or to treat complications.[18] To further improve risk management and treatment strategies, a better understanding of the molecular mechanisms and genetic factors in CP is essential.[17,19,20]

In conclusion, more research should focus on genetics and biomarkers if care for these pancreatic diseases is to be improved. An important problem is the lack of high-quality biomaterials.[2] Biomaterials collected without a well-established biobank protocol often vary in the execution of collection, processing, and storage.[2,21,22] Moreover, clinical data are often not available or not properly associated with the samples. This is less of a problem within clinical trials, but materials collected during clinical trials often are not usable for other projects because of the narrow informed consent or the selected subset of patients included in the trial.[2,22] For these reasons, large-scale biobanks with a broad informed consent, which are linked to clinical data, and in which samples are uniformly collected, processed, and stored, are essential for future molecular and genetic research in pancreatic diseases.[2,21]

In the Netherlands, a strong nationwide platform for multicenter multidisciplinary research on pancreatic diseases has been established over a period of decades within the pancreatic cancer and pancreatitis research groups [Dutch Pancreatic Cancer Group (DPCG) and Dutch Pancreatitis Study Group (DPSG)]. Moreover, a nationwide collaboration for the establishment, expansion, and optimization of clinical biobanks for scientific research is provided by the Parelsnoer Institute (PSI). To facilitate future translational research on pancreatic diseases, the DPCG and DPSG established the Dutch Pancreas Biobank within the Parelsnoer collaboration.

The aim of the current study was not only to inform other researchers about the research opportunities of our biobank but also to provide a framework to those interested in biobanking or launching a similar initiative.

MATERIALS AND METHODS

Biobank Design

The Dutch Pancreas Biobank is incorporated in the PSI (www.parelsnoer.org).[23] The PSI is a nationwide network founded by the Dutch Federation of University Medical Centers (NFU) in 2007. During the past decade, biobanks have been established for several diseases (eg, gastroesophageal cancer, kidney failure, and cerebral stroke).[24–26] The PSI framework is designed to consider all relevant legal and ethical standards, including privacy and informed consent procedures. All PSI biobanks share the same central infrastructure (including IT system), striving for optimal harmonization of data collection. The PSI standard operating procedures are used by all participating centers to ensure high-quality biomaterials and harmonized collecting, processing, and storing processes.[27]

The Dutch Pancreas Biobank is part of the Dutch Pancreatic Cancer Project (PACAP), coordinated by the DPCG, which aims to improve outcomes of patients with pancreatic cancer. The PACAP includes a mandatory nationwide prospective registration of clinical data and patient-reported outcomes and the collection of biomaterials.

Funding

The Dutch government, NFU, and all 8 university medical centers financed the formation of PSI. Because all biobanking facilities have been established, costs for collection and storage of all PSI biobanks are covered by the individual participating hospitals. Moreover, PACAP receives funding from the Dutch Cancer Society (KWF Kankerbestrijding; grant no. UVA 2013–5842).

Eligibility and Informed Consent

All patients with an indication for pancreatic surgery are eligible for inclusion. This includes both patients with CP and patients with pancreatic or periampullary tumors [pancreatic cancer, distal cholangiocarcinoma, duodenal carcinoma, ampullary carcinoma, neuroendocrine tumors, metastases of other tumors to the pancreas, and cystic lesions (intraductal papillary mucinous neoplasm, mucinous cystic neoplasms, and serous cystic neoplasms)].

The biobank protocol and regulations were approved by the PSI, the Biobank Ethics Committee of the Academic Medical Center, Amsterdam, and by the institutional review boards (IRBs) of all the participating centers. Only patients able and willing to provide informed consent are included. Informed consent covers collection and use of encoded clinical data; collection, storage, and use of biomaterials; permission to obtain data from the municipal register, the general practitioner, and Statistics Netherlands (CBS); and permission to be approached in the future to provide extra data or biomaterials.

Data Collection

Clinical data of patients with pancreatic and periampullary disease are collected in conjunction with the Dutch Pancreatic Cancer Audit for patients with pancreatic and periampullary tumors and the Dutch Chronic Pancreatitis Registry (CARE) for patients with CP.

Clinical data registered in the Dutch Pancreas Biobank include medical history, intoxications, family history, physical examination, diagnostics, surgical procedures, pathology, and follow-up. For patients with CP, additional specific items on pain, complications, and interventions are collected.

Clinical data and biomaterial information are stored in Project Manager Internet Server (ProMISEe), the central database of PSI (Fig. 1). Data are pseudonymized via a Trusted Third Party. Biomaterial data include collection date, type of material, standard operating procedure deviations, DNA quality, and availability of the samples.

Collection of Biomaterials

Before surgery, venous blood samples are collected: a 10-mL serum clot tube and one or two 10-mL EDTA plasma tubes (Table 1). One of the EDTA plasma tubes and the serum tube are centrifuged, and serum and plasma are stored in 0.5-mL aliquots at −80°C. The other 10-mL ETDA plasma tube or the pellet from the first EDTA plasma tube is used for genomic DNA isolation from whole blood. DNA is isolated within 4 weeks and stored at 4°C or −20°C or less. DNA is stored as stock solutions, which will be diluted for actual use. DNA concentration and the quality of the stock solution (using, respectively, OD 260 nm and OD ratio 260–280 or fluorimetry) are measured. In the case of a DNA concentration less than 50 μg/mL, blood for DNA isolation will be collected again during follow-up.

In the Netherlands, pancreatic resections are currently performed in 18 centers, of which 13 centers currently participate in the Dutch Pancreas Biobank. In case of pancreatic or periampullary tumors, the resected specimen is immediately transported to the pathology department in an unfixed state. First, the pathologist takes the routine samples from the specimen required for diagnosis. Subsequently, samples (0.5 cm^3) for storage in the biobank are collected, without interfering with standard tissue processing for diagnostic purposes. Two samples of the tumor, one of the normal pancreatic tissue and one of the duodenum (in the case of pancreatoduodenectomy) or spleen (in the case of distal pancreatectomy with splenectomy), are collected. In addition, if possible, a macroscopically involved lymph node or metastasis is sampled. In the case of a pancreatic cyst, cyst fluid is collected. For patients with CP, samples (0.5 cm^3) from the pancreatic head, body, and tail are collected during surgery. All samples are snap frozen, usually within 1.5 hours after resection, and the samples are stored at −80°C. Follow-up is carried out according to the local standard of the participating hospitals. Biomaterials are collected at several time points during follow-up (Table 1).

Research Proposals and Use of Samples

To ensure that the collected biomaterials are used for high-quality research projects, a workflow for the review process has been established. Research proposals are submitted to the coordinator of the Dutch Pancreas Biobank and subsequently evaluated by a dedicated scientific committee. When approved by the scientific committee, the Dutch Pancreas Biobank scientific board has to approve the proposal as well. This scientific board consists of one member from all specialties involved in the treatment of patients with pancreatic diseases (surgery, medical oncology, gastroenterology, pathology, radiology, radiotherapy, and translational research) from each participating center. Hereafter, approval of the IRB from the centers of which samples are used will be acquired. Subsequently, the samples will be provided to the researcher within 4 weeks from the official request to the biobank.

RESULTS

Currently, 13 centers collaborate in the Dutch Pancreas Biobank. Four university medical centers and 1 nonacademic hospital have started with the collection of biomaterials. In 5 more centers, IRB approval has been obtained. Between February 2015 and May 2017, 488 patients have been included from the 5 centers, with over
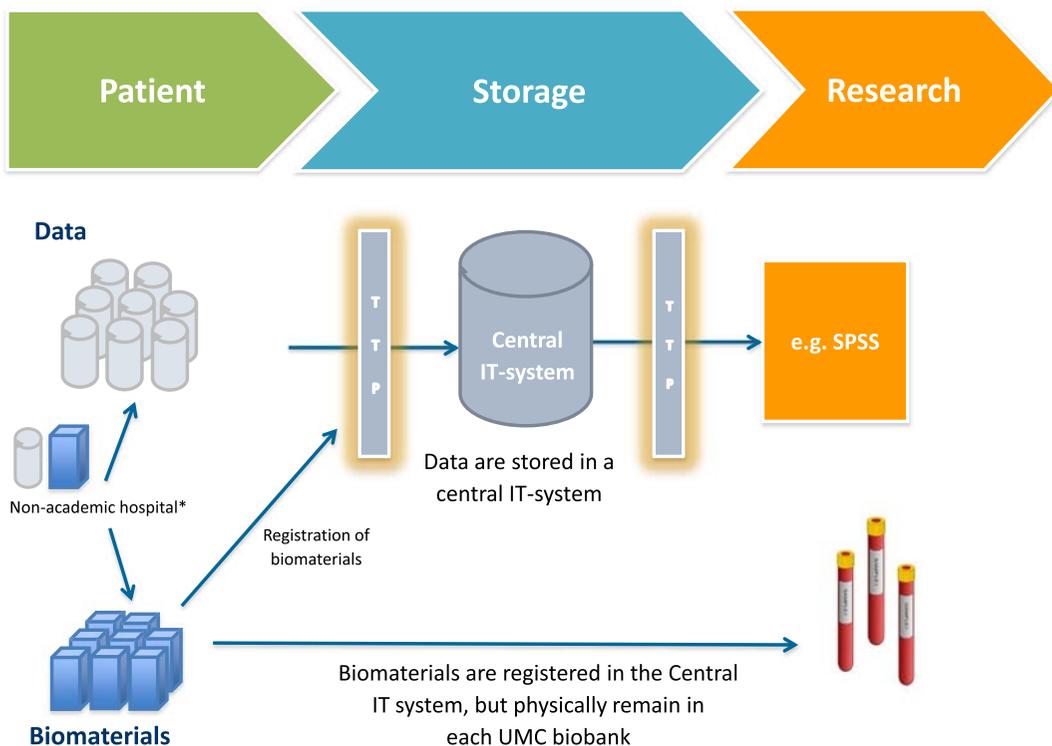
FIGURE 1. Workflow of data and biomaterial collection in the Dutch Pancreas Biobank. *Data and biomaterials collected in nonacademic hospitals are coded and transferred to one of the 8 UMCs. **Editor's note:** A color image accompanies the online version of this article.

TABLE 1. Overview of Collection Protocol of the Dutch Pancreas Biobank

Material	Quantity	Preoperative	At Time of Surgery	First Postoperative Visit	6 Mo	12 Mo	24 Mo	Recurrence
Blood								
Plasma	10 mL	X		X*	X*	X	X[†]	X*
Serum	10 mL	X		X*	X*	X	X[†]	X*
EDTA tube for DNA	10 mL	X						
Tissue								
Chronic pancreatitis	2 samples of the head		X					
Intraoperative samples	2 samples of the body		X					
	2 samples of the tail		X					
Pancreatic tumor or cyst	2 samples of the tumor		X					
Samples of resected specimen	1 sample normal pancreatic tissue		X					
	1 sample duodenum or spleen		X					
	Optional; 1 involved lymph node		X					
	Optional; 1 sample of metastasis		X					
Pancreatic (cyst) fluid	If available		X					
Clinical data	N/A	X	X	X	X	X	X	X

*Only in patients with pancreatic/periampullary tumor or cyst.

[†]Only in patients with chronic pancreatitis.

N/A indicates not available.

2500 samples collected: 1308 preoperative blood samples, 864 tumor tissue samples, 11 cyst fluid samples, and 366 follow-up blood samples.

Baseline Characteristics

Baseline characteristic of the patients who underwent resection in 2015 and 2016 are shown in Table 2. The majority of the included patients underwent a resection with curative intent because of suspected (pre) malignant disease (n = 275, 82.8%). The most frequent histopathological diagnosis in this group were pancreatic cancer (n = 119, 43.3%), pancreatic neuroendocrine tumor (NET) (n = 27, 9.8%), distal cholangiocarcinoma (n = 26, 9.5%), and carcinoma of the ampulla of Vater (n = 25, 9.1%). At the time of preoperative blood collection and during tumor tissue collection, 90.6% (n = 301) of the patients were systemic treatment naive. Adjuvant chemotherapy was discussed in the majority (n = 97, 81.5%) of patients with pancreatic cancer. In patients undergoing a pancreatic resection because of CP, the etiology was alcoholic in 57.7% (n = 15) of the patients. The indication for surgery was pain in 84.6% (n = 22) of patients, and the most frequently performed procedure was a Frey procedure (n = 11, 42.3%).

DISCUSSION

A nationwide biobank has been established in the Netherlands that aims to facilitate translational research toward more personalized medicine for patients with pancreatic disease. More than 2500 samples from 488 patients have been collected between February 2015 and May 2017, and the biobank is rapidly expanding.

In the last decade, several research groups acknowledged the importance of large-scale multicenter biobanks. The PANcreatic Disease ReseArch (PANDoRA) consortium retrospectively included clinical data and DNA samples from 2220 patients with pancreatic cancer from 15 research groups across 6 countries.[28] The consortium studied single nucleotide polymorphisms in patients with pancreatic cancer and was able to identify new pancreatic cancer susceptibility loci.[28] The Australian Pancreatic Cancer Genome Initiative BioResources (APGI; Australian contribution to the International Cancer Genome Consortium) is another example of such effort[29]; the APGI Bioresource supported the genomic analyses to identify molecular subtypes of pancreatic cancer and to describe the genome landscape of pancreatic NETs.[30–33] The Pancreatic Cancer Research Fund Tissue Bank established in the UK is a multicenter project similar to the Dutch Pancreas Biobank. In the Pancreatic Cancer Research Fund Tissue Bank, tissue, blood, saliva, and urine are collected in 6 centers.[22] Other large biobanking projects on pancreatic cancer include the biobank of the Liverpool Pancreas Biomedical Research Unit (now stored as part of Liverpool Good Clinical Practice Laboratory facility) and the Johns Hopkins Tissue Resource (Gastrointestinal Cancer Specialized Program of Research Excellence).[34,35] The Dutch Pancreas Biobank seems to stand out because of its long-term follow-up along with biomaterials and its coverage of the majority of the country.

While establishing and running this large and logistically complex nationwide project, we faced several challenges. First is the logistics; the infrastructure for processing, storing, and labeling of biomaterials is provided by the PSI, but each center has to set up their own clinical workflows. This includes obtaining informed consent, collection of blood samples, transportation of pathology specimens immediately after resection, collection of tissue samples, proper storage of all biomaterial, and registration of/association with clinical parameters. This is a very time-consuming process and may be challenging to implement in daily practice. We have found that sharing experiences between centers help to establish

TABLE 2. Baseline Characteristics of 358 Patients Included in the Dutch Pancreas Biobank in 2015–2016

Characteristics	(Pre-)Malignant Disease (n = 332)	CP (n = 26)
Age at inclusion, median (IQR)	67 (58–73)	50 (43–60)
Sex, male, n (%)	186 (56.0)	14 (53.8)
Comorbidity, n (%)*	251 (76.3)	25 (96.2)
Vascular	111 (33.7)	7 (26.9)
Malignancy	67 (20.4)	6 (23.1)
Cardiac	66 (20.1)	6 (23.1)
Diabetes mellitus	61 (18.5)	5 (19.2)
Gastrointestinal	49 (14.9)	6 (23.1)
Pulmonary	39 (11.9)	3 (11.5)
Neurologic/psychiatric	29 (8.8)	14 (53.8)
Endocrine	19 (5.8)	2 (7.7)
Other	78 (23.7)	11 (42.3)
Etiology of CP, n (%)	N/A	
Alcoholic		15 (57.7)
Idiopathic		8 (30.8)
Hereditary		2 (7.7)
Metabolic		1 (3.8)
ECOG score, n (%)*		N/A
ECOG 0	166 (52.5)	
ECOG 1	116 (36.7)	
ECOG 2	29 (9.2)	
ECOG 3	5 (1.6)	
Intoxications at baseline in CP, n (%)	N/A	
Smoking, yes		22 (84.6)
Alcohol consumption, yes		2 (7.7)
Indication for surgery, n (%) (>1 possible)		
Suspected (pre)malignant disease	332 (100)	0
Pain	0	22 (84.6)
Complications	0	6 (23.1)
Other	0	4 (15.4)
Resection, n (%)		N/A
Yes	275 (82.8)	
No	57 (17.2)	
Type of surgery (N$_{tot}$ = 300[†]), n (%)		
PPPD	123 (44.7)	0
Classical Whipple	86 (31.3)	2 (8.0)
Distal pancreatectomy	55 (20.0)	4 (16.0)
Frey procedure	N/A	11 (44.0)
Pancreatojejunostomy	N/A	7 (28.0)
Other	11 (4.0)	1 (4.0)
Histological diagnosis (N$_{tot}$ = 300[†]), n (%)*		
Pancreatic ductal adenocarcinoma	119 (43.9)	0
Pancreatic NET	27 (10.0)	0
Cholangiocarcinoma	26 (9.6)	0
Carcinoma of papilla of Vater	25 (9.2)	0
IPMN	22 (8.1)	0
Duodenal carcinoma	8 (3.0)	0
Chronic pancreatitis	6 (2.2)	23 (92.0)
Other	43 (15.9)	2 (8.0)

TABLE 2. *(Continued)*

Characteristics	(Pre-)Malignant Disease (n = 332)	CP (n = 26)
Positive lymph nodes in patients undergoing resection, n (%)		N/A
Pancreatic ductal adenocarcinoma (N$_{tot}$ = 119)	85 (71.4)	
Cholangiocarcinoma (N$_{tot}$ = 26)	17 (65.4)	
Carcinoma of papilla of Vater (N$_{tot}$ = 25)	14 (56.0)	
Duodenal carcinoma (N$_{tot}$ = 8)	6 (75.0)	
Distant metastases, n (%)*		N/A
Yes	36 (11.3)	
No	284 (88.8)	
Neoadjuvant treatment, n (%)		N/A
No	301 (90.6)	
Chemotherapy	12 (3.6)	
Chemoradiotherapy	18 (5.4)	
Radiotherapy	1 (0.3)	
Adjuvant treatment recommended, in patients undergoing resection, n (%)		N/A
Pancreatic ductal adenocarcinoma (N$_{tot}$ = 119)*	97 (82.2)	
Cholangiocarcinoma (N$_{tot}$ = 26)	1 (3.8)	
Carcinoma of papilla of Vater (N$_{tot}$ = 25)	1 (4.0)	
Duodenal carcinoma (N$_{tot}$ = 8)	2 (25.0)	

*Unknown in less than 5% of the patients.

[†]A total of 275 patients with (pre-)malignant disease and 25 patients with CP (in 1 patient with CP, the exploratory laparotomy was aborted, as there were no signs of CP during surgery).

ECOG indicates Eastern Cooperative Oncology Group; IPMN, intraductal papillary mucinous neoplasm; IQR, interquartile range; N/A, not applicable; PPPD, pylorus preserving pancreatoduodenectomy.

optimal workflows. A second challenge is gaining and maintaining the trust and commitment of all participating centers. Fortunately, the Netherlands has a strong infrastructure for multicenter collaboration, in part due to the establishment of the DPCG and DPSG. However, each center puts a lot of effort in the collection of the biomaterials and data and wants to ensure that samples are used for the most relevant projects. To at least partially overcome this challenge, a nationwide multidisciplinary scientific board was established within the working groups to assess each research proposal in a plenary meeting. A third difficulty is to combine ongoing institutional research projects and local biobanks with the Dutch Pancreas Biobank. Multidisciplinary collaboration and discussing the distribution of tumor tissue samples over different projects were helpful. The last challenge is costs associated with the project, not only for the materials for sample collection and storage but also for manpower to manage the processes. Because of the grant provided by the Dutch Cancer Society, we are able to cover part of the costs, but the remainder needs to be covered by the participating hospitals. A future aim is to obtain structural (governmental) funding.

Strengths of the Dutch Pancreas Biobank include the rigorous sampling protocol and the systematic collection of follow-up blood.[2] In addition, the harmonized biomaterial collection across centers is rather unique. This is possible because of the infrastructure and expertise of the PSI.[23] Moreover, the strong intention of multidisciplinary and multicenter collaboration in the Netherlands

will ensure long-term fruitful cooperation between the participating centers. Moreover, because of this collaboration, not only the university centers participate in the project but also several nonacademic hospitals. This not only makes it possible to collect a larger amount of samples but also ensures that the subset of patients included in the biobank is representative of the total population. Last, not only patients with pancreatic cancer but also patients with periampullary tumors, NETs, and CP are included, which is not the case in many other biobanks.

A limitation of this project is that we will be unable to collect follow-up samples of the subset of patients who return to their referring hospital for follow-up after surgery. In addition, only patients who planned to undergo resection and hence with earlier stage of disease are included. Therefore, we plan to expand the biobank to patients with locally advanced and metastatic disease. Blood collection will be feasible in these patients, but obtaining high-quality tumor tissue samples from these patients will be more difficult; tumor biopsies from the primary tumor or metastatic sites usually contain a limited amount of tumor tissue material, which is mostly reserved for diagnostic purposes. However, in the Netherlands, we have already gained experience with the collection and biobanking of tumor material during endoscopic procedures.[36] A known issue in pancreatic cancer tissue samples is the often low percentage of tumor cells in the samples. Microscopically, pancreatic cancer is characterized by an irregular pattern of tumor cells in abundant desmoplastic stroma.[37,38] This hampers genomic analyses, especially mutation calling, copy number alteration, and methylation analyses. Another problem is intratumor heterogeneity on both the morphological and genomic levels.[39] Sampling from multiple regions of the tumor may be a strategy to at least partially overcome this problem, but this is not always feasible because of tumor size and location.

A near future goal of the Dutch Pancreas Biobank is to collect samples in all 13 participating centers, which will lead to a fast growth of the number of samples. In the Netherlands, around 1000 patients per year undergo pancreatic surgery (all types of procedures and indications), and 75% is performed in the 13 centers participating in the biobank. As the great majority of the patients agree to participate in the project, it will be possible to collect samples of hundreds of patients per year. The desired next step would be to include patients with locally advanced and metastatic disease to make it possible to perform future studies with materials of patients with more advanced stages of the disease. The ultimate goal is to use this experience to embed high-quality biobanking into daily routine clinical practice to facilitate "real-time" molecular profiling to achieve personalized care for patients with pancreatic and periampullary diseases. Examples of such projects are the Precision-Panc initiative in the UK and the Precision Promise initiative in the United States.

In conclusion, large-scale biobanks are essential in an era focused on development of personalized treatment based on biomarkers and genomic signatures. Going forward, we would like the Dutch Pancreas Biobank within the PSI to support high-quality research projects, both nationally and internationally.

ACKNOWLEDGMENT

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