# Supplemental Digital Content 1

## SCREENING IN FAMILIAL PANCREATIC CANCER (FPC)

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### A. Definition of FPC

A number of genetic syndromes (e.g., BRCA1/2, HNPCC, FAMMM, Peutz Jeghers syndrome) predispose kindreds to a variable but higher-than-average risk of developing PC (Table 1). The term familial PC (FPC) has been used for families with 2 or more first-degree relatives (FDR) with PC not associated with another described familial hereditary cancer syndrome. In this paper the term FPC will be used to include both hereditary cancer syndromes as well as true FPC, as they share a number of common features, including approach to early detection of PC. Both intraductal papillary mucinous neoplasms (IPMN) and PanIN are precursor lesions for FPC; these lesions are higher grade, more common, and multifocal in individuals with FPC compared with patients with sporadic adenocarcinoma. Screening in FPC kindreds has been done, at least in the research setting, for over 20 years in over 1,500 individuals. It poses unique challenges because of the diffuse nature of the lesions and inability to readily distinguish low-grade from high-grade noninvasive lesions. There is much to be learned from the experience in this cohort of subjects.

#### *1. Establishment of Consortia*

While initial studies were reported from individual centers, the rarity of the disease led to formation of large multi-center and multi-national consortia for study of FPC. These consortia have carried out an extensive study of FPC kindreds throughout Europe and North America with development of national and international tumor registries including the North American National Familial Pancreatic Tumor Registry (NFPTR), the German National Case Collection of Familial Pancreatic Cancer (FaPaCa), and the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC).[1-3] The International CAPS Consortium is an open collaborative group that consists of centers from 12 countries and 4 continents (North America, Europe, Asia, and Australia). This Consortium includes nearly all established clinical screening and surveillance programs in the world and also serves as a resource to other sites initiating screening. Recently, Japan (via the Japanese Familial Pancreas Registry care of Kyoichi Takaori) joined the Consortium.[4] Two other key papers by the Hopkins group in 2014[5] and Seattle group in 2013[6] summarize the state of the field. In addition, the International Cancer of the Pancreas Screening (CAPS) summit paper (white paper from the CAPS Summit, Baltimore 2011) published in Gut[7] summarizes the current state of the field.

#### *2. Defining the High-risk FPC Cohort*

The high-risk group of FPC is defined as the presence of two or more relatives with PC and with at least one family member being a first degree relative (sibling, parent, or child). Klein and colleagues performed the largest prospective analysis of 5,179 individuals from 838 kindreds with FPC.[8] They found patients with one first-degree relative (FDR) affected with pancreatic cancer had a 4.5 fold increased risk of developing pancreatic cancer.[8] Two FDRs increased the risk to 6.4 fold, and 3 FDRs by 32 fold. These estimated risks have been found to be consistent in other population analyses.[2, 9]

Both IPMN and PanIN are found with greater frequency and at higher grade in patients with FPC when compared with controls.[10-12] In a comparison study of 51 resected pancreatic tissues from patients with a strong family history of pancreatic cancer versus pancreatic tissue from patients with sporadic pancreatic cancer, there is a 2.75-fold increased relative rate of PanIN per square centimeter, and an increase in the number of PanIN-3. Notably, high-grade IPMN were only found in familial cases and not in the sporadic cases.[10] Both IPMN and PanIN lesions are noted for their multifocality within resected pancreata of FPC patients.[11, 13] Incidence of PC in genetically predisposed kindreds is harder to estimate due to the heterogeneous risk of the

subgroups being followed. However, in all published studies, eight of 20 (40%) of the PCs diagnosed in screened high-risk individuals (HRIs) were not detected at baseline screening tests.[11]

***3. Stratifying Risk in FPC***

Attempts have been made to identify demographic, clinical, and lifestyle factors that can allow further stratification of the FPC at-risk individual (Table 2). Such risk stratification can insure that the highest risk individuals undergo cost-effective screening. PancPRO is a risk assessment tool available at no cost that can aid in screening decision making for management of FPC individuals.[14] The following risk factors enhance risk in FPC kindreds.

*a. Age:* Increasing age increases risk for FPC. Young age of onset of PC in a family member also independently increases risk in FPC kindreds but not in relatives of sporadic PC (hazard ratio 1.55 per year).[15]

*b. Number of Affected Relatives*: The risk in FPC kindreds is elevated among individuals with three affected FDR (odds ratio [OR] 32.0; 95% CI, 10.2-74.7), two FDR (6.4; CI, 1.8-16.4), or one FDR (4.6; CI, 0.5-16.4) with PC.[8]

*c. Smoking:* Smoking increases risk in FPC kindreds[8] and lowers the age of onset.[8, 16] Smoking is an independent risk factor (odds ratio [OR] 3.7; 95% CI, 1.8-7.6), with smokers developing cancer one decade earlier than nonsmokers (59 versus 69 years of age; *P*=.01).[17]

*d. Serologic Testing:* Serologic testing for early detection of PC remains elusive. Several biomarkers have been evaluated, most notably CA 19-9. However, no test has had adequate sensitivity or specificity for screening average risk populations. CA19-9 has been used as an initial screening test in one feasibility study of 546 individuals with at least one family member with pancreatic cancer.[18] If CA 19-9 returned greater than 37 U/mL, patients subsequently underwent evaluation with EUS. In this study, one pancreatic adenocarcinoma (T2N0M0) and 4 pancreatic neoplasias (neuroendocrine tumor, PanIN-1, mucinous cystic neoplasm [MCN], IPMN) were identified, resulting in a reported diagnostic yield of 0.9% (5/546) for pancreatic neoplasia and 0.2% yield for pancreatic adenocarcinoma.[18] The diagnostic yield for pancreatic neoplasia of this screening test is considerably lower than other reported screening trials; however, the diagnostic yield of detecting an asymptomatic high-risk lesion is on par with several trials (Table 3). Other studies have not found CA19-9 to be useful in the early detection of pancreatic neoplasia in FPC kindreds.[19-21]

*e. Glucose Tolerance Test, elevated HgbA1c and adult onset diabetes*: Testing high-risk patients for glucose intolerance may help identify genetically susceptible patients who are at additional risk for PC.[22] Diabetes and glucose intolerance are risk factors for pancreatic neoplastic progression including development of advanced PanIN lesions and cancer in FPC kindreds (OR 5.8; 95% CL, 1.3-25.2). In the Seattle group's experience, 50% of patients with an abnormal EUS had glucose intolerance, while only 17% of normal EUS patients had glucose intolerance, and of individuals with histologically proven PanIN-2/3 or cancer, 60% have glucose intolerance (Brentnall, unpublished data).[6] This finding awaits further validation.

***4. Who should be screened?***

Since an initial international consensus conference in 2003, general expert agreement exists that high-risk individuals with at least 5%-10% relative risk of developing PC and who would be suitable candidates for pancreatic surgery should undergo screening at specialty centers.[23] A utility analysis suggested that high-risk individuals with a lifetime pancreatic cancer risk >16% provides the most cost-effective cohort for screening.[24]

Many experts agree that screening should initiate at age 50 or 10 years prior to the earliest age of cancer onset in the family. Overall, the prevalence of high-grade neoplasia or cancer in patients younger than age 50 varies in published literature; however, when neoplasia does occur in young individuals (<age 50), it usually does so in the setting where other family members from that kindred have had early onset of cancer as well.[11, 14, 25] In summary, it may

be most cost-effective to start screening in high-risk individuals at age 50 or 10 years prior to the earliest age of pancreatic cancer onset in the family.[26] Mitigating factors that could additionally affect the timing for commencement of screening include smoking, new-onset diabetes, and patients who are symptomatic (Table 3).[17]

**B. Imaging in High-risk FPC Kindreds**
**Modality, Findings and Management**

*a. Imaging Modality:* When imaging the precursor lesions of pancreatic cancer, it is important to understand the limitations of the imaging modality and the pathology underlying the neoplastic progression of pancreatic cancer. The precursor lesions are mainly PanIN and IPMN-branch duct (mucinous cystic lesions). These changes occur in the small to medium size ducts. PanIN-3 lesions are quite small, by definition, and appear as parenchymal abnormalities, not cystic lesions. While MRI and MRCP are excellent at detecting small cystic lesions, these modalities have less to offer in terms of identifying parenchymal abnormalities. EUS is perhaps the best modality to identify both cystic and parenchymal lesions of the pancreas. To date, four studies have reported the use of MRI ± MRCP,[13, 19, 25, 27] and five studies have reported EUS as an initial screening test.[11, 14, 21, 28, 29] Canto et al recently published their prospective work comparing imaging modalities in 216 high-risk individuals.[22] MRI/MRCP and EUS vastly outperformed CT in the ability to detect any cystic or solid lesions, picking up 77% (MRI/MRCP) and 79% (EUS) of detected lesions as compared to only 13.8% (CT). The study reported a high prevalence of asymptomatic pancreatic lesions (61%), predominantly small cysts, increasing in frequency with age.[22] Given the need for frequent surveillance, and the risk of radiation, and lack of sensitivity, CT is not used in current screening protocols. However, EUS is more invasive compared to CT and MRI, and there is interobserver variability for interpretation of EUS findings even amongst experts.[30] The concordance between EUS and MRI/MRCP in detecting cystic lesions or masses was 91%. Notably in this published trial, MRI and EUS detected subcentimeter cysts in 33% and 36% of FPC patients, respectively.[22] In a review of all FPC screening programs, the prevalence of PanINs and cysts has been reported from 8.3% to 76% (Table 4). This is in comparison to the finding of incidental cysts in approximately 2.6% of the general population.[20, 31] MRI/MRCP has been used as the dominant strategy for screening in a few programs, but interval cancers and advanced cancers have been detected suggesting detection of preinvasive high-grade lesions is less than optimal. This may reflect the pathology of the disease and the limitations of the imaging test as noted above, whereby MRI/MRCP may be problematic in detecting the parenchymal PanIN lesions. One study in p16 mutation carriers reported a high (9%) rate of invasive PC over median of 4 years (4 of 7 detected after initial negative examination.[25] Another study reported advanced disease in 2 of 3 incident PC detected by MRI-based screening.[27]

Usually when one imaging test is abnormal in high-risk individuals, a second confirmatory test is performed. Two of the larger US cohorts studied to date,[6, 7] (e.g., the CAPS protocol led by M. Canto and the Seattle studies led by T. Brentnall) use EUS as the initial imaging test, followed by pancreatogram for validation. To better evaluate the ductal extent of worrisome EUS findings, the Seattle protocol often uses endoscopic retrograde pancreatography (ERP) to better detail the abnormalities in the secondary pancreatic ducts such as saccular dilations, which are associated with high-grade PanIN lesions (also Brentnall, unpublished data).[29] In this protocol, ERP has resulted in less than 3% risk of pancreatitis from the procedure. In contrast, the CAPS protocol and the International CAPS Consortium utilizes MRCP and EUS out of concerns for ERP-related pancreatitis.[7]

*b. Imaging Findings:*

***i. Cystic Changes*.** There is a high prevalence of pancreatic abnormalities detected by screening patients with genetic susceptibility to pancreatic cancer (about 2/3 of HRI some abnormality however mild)[7]; most are cystic lesions (39% in screening-naïve HRI with mean age of 56).[22] The majority of these lesions detected by EUS are branch duct intraductal papillary mucinous

neoplasms (BD-IPMN).[22, 32] Some of the detected small cysts are larger PanINs and incipient IPMNs.[6, 14, 22, 32] Pancreatic cystic lesions increase with age.[22] The prevalence of these cysts, adjusted for age, is 10 times that of what has been reported for sporadic cysts in the general population. These cysts can be found in 34% of high-risk subjects 50–59 years old, 53% of subjects 60–69 years old,[22] and can be multifocal in 61% overall.[12, 16, 22, 32] This multifocality of precursors reflects a field defect and impacts directly on surgical treatment strategy (partial versus total pancreas resection).[14, 22] An analogous phenotype is colonic polyposis. Not much data has been published on rate of metachronous pancreatic tumors, including invasive PC, in the remnant pancreas, but the CAPS and other formal surveillance programs have noted these "remote" cancer neoplasms. Pathological mapping of the entire pancreata in HRI from FPC families shows multifocal distribution of PanIN-3 (also Canto et al, unpublished data, Johns Hopkins).[22]

***ii. Chronic Pancreatitis-like Changes.*** High-risk patients are also disproportionately found to have chronic pancreatitis-type changes on EUS and pathology. Between 14%-60% of high-risk patients have been described to have parenchymal changes, including hyperechoic stranding, hypoechoic lobules, and echogenic duct-walls.[11, 22, 29] On resection these pancreata typically demonstrate lobular atrophy, exuberant fibroblast growth, and cystic changes in the tertiary ducts in the setting of PanIN and IPMN; these histologic pathology changes are likely the cause of the EUS findings. Unfortunately, despite a consensus-working group, EUS endoscopic impression of these changes is considerably operator dependent.[30]

***iii. Solid Lesions.*** Solid lesions are uncommon and are seen in 1.4% of those screened.[22] These lesions are problematic because invasive PC cannot always be ruled out by imaging and cytologic sampling during FNA. When resected, these solid lesions can be early invasive PC,[7] pancreatic neuroendocrine tumor,[7] or PanIN-1/2 lesions (false positive)[11, 12, 14, 28, 32] with associated lobulocentric parenchymal atrophy.

***iv. Incipient Precursors of PC.*** Currently the diagnosis of PanIN lesions is made solely through histology. No currently available clinical imaging study can identify PanIN lesions. Parenchymal abnormalities and side-branch irregularities can be suggestive, but ultimately a piece of tissue must be obtained for pathologic diagnosis. The pathologic precursors of pancreatic cancer have been well characterized. To understand the cancer risk of an individual with PanIN-3, it is important to be familiar with the epidemiology of pancreatic neoplasia pathology. Autopsy studies reveal that PanIN-1 is common, PanIN-2 is uncommon, and PanIN-3 are extremely rare in the general population; moreover PanIN-3 is almost always found in the setting of pancreatic cancer.[7, 33, 34] The commonality of PanIN-1 (also known as hyperplasia) in the pancreas suggests that the lesion is benign. In contrast, PanIN-3 appears to be a more ominous lesion; if it was an indolent lesion it would be seen more commonly at autopsy and it would be seen in settings other than pancreatic cancer.

The timeframe for neoplastic progression from PanIN-3 to cancer is unknown as there are few natural history studies. In mouse models, PanIN-3 is usually followed by development of invasive cancer. Additionally, there are case reports of non-familial patients with sporadic PanIN-3 lesions subsequently developing pancreatic cancer months to years later.[35] The time to pancreatic neoplastic progression may be accelerated in genetically susceptible individuals, just as it is in familial forms of colon cancer. Lastly, the genetic and environmental heterogeneity of FPC may be associated with variable rates of neoplastic progression.

Molecular characterization of multifocal familial PanIN lesions and multifocal IPMs (in both sporadic and familial resected pancreata) shows that multifocal neoplastic lesions arise independently.[36] Hence, any given duct within an affected pancreas from an FPC patient has its own risk for cancer development. In light of this, it is not surprising that higher grades (more PanIN-3) and larger numbers of PanIN lesions (density of PanIN per

square centimeter) are seen in the pancreas of FPC patients than those with sporadic PC. Similarly, high-grade (including incipient) BD-IPMNs are found only in familial cases compared to asymptomatic population controls.[10, 36] A critical part of improving early detection and prevention of PC is the development of 1) risk stratification algorithms, 2) imaging that can directly identify PanIN-3 and 3) non-invasive biomarkers that can identify PanIN-3.

***v. Extra-pancreatic Malignancy.*** Due to increased extra-pancreatic cancer related mortality,[1, 37, 38] cross-sectional imaging such as MRI may find additional primary malignancies. However, in reported screening on 1,054 genetically susceptible HRI, 17 non-pancreatic neoplasms were found (1.6% yield) of which 6 were benign neoplasms. This low yield may be due to the limited nature of abdominal MRI in diagnosing breast, skin, lung, or colorectal cancer. These extra-pancreatic cancers in FPC kindreds highlight the need to be comprehensive in screening for colon, skin, and breast cancer using standard methods such as colonoscopy, mammography, and physical exam.

***2. Management of Suspect Lesions***

Overall, the clinical management of imaging abnormalities in these high risk individuals is difficult and PC surveillance programs use a variety of approaches. However, the only current method of diagnosing the grade of PanIN lesions and IPMN with high-grade dysplasia is through histology. As such, many programs recommend targeted surgical removal of distinct masses/cysts for diagnostic and treatment purposes, with planned extension of total pancreatectomy if PanIN-3 lesions or IPMN with high-grade dysplasia are found. The CAPS group has proposed surgical management of solitary masses, suspected main duct or mixed IPMN, branch-duct IPMN >2cm and/or with concerning features such as mural nodules, and abnormal cytology.[22]

Three issues are central to the management of such neoplastic lesions in the setting of FPC: 1) IPMN and PanIN lesions can be multifocal and, in the latter case, usually involve the entire pancreas in FPC; 2) waiting for masses or confirmed cancer to form can be associated with metastatic disease; and 3) Stage 1 pancreatic cancer has a 40%-60% survival rate at 5-years, thus nearly half of the patients with early stage cancer still die of the disease. For these reasons, many investigators currently target PanIN-3 and/or IPMN with high-grade dysplasia as diagnostic criteria that would merit surgery. Finding those high-risk individuals who have high-grade PanIN-3 is more challenging than those with cystic IMPN, as the imaging changes in PanIN-3 can be subtler and there may not be a specific lesion to target with surgical sampling for pathology.

Thus, in the absence of masses or cystic lesions, the diagnosis of PanIN-3 must be made through removal of a distinctly abnormal, but untargeted tissue, to obtain a tissue diagnosis. At the University of Washington, high-risk individuals with changes consistent with chronic pancreatitis on EUS and abnormal ductal changes on ERP/MRP are offered a surgical sampling to obtain a tissue diagnosis. Usually a sample is obtained of the pancreatic tail by laparoscopy for full pathologic evaluation. Given the multifocal nature of the PanIN-3 disease in FPC, the histology found in the tail is usually representative of the pathology in the rest of the pancreas (unpublished data).[10, 13] If PanIN-3 is documented, total pancreatectomy is considered in FPC patients who are good surgical candidates, have sound psychiatric health, and who undergo extensive counseling regarding diabetes and the risk and benefits of surgery. The patient is always advised that the natural history of PanIN-3 lesions remains unknown. Weighing the risks and benefits of surgery is obviously complex, and is done on a case by case basis. Careful clinical assessment and informed patient decision-making are the central keys to management of PanIN-3. None of the patients who have undergone pancreatectomy for PanIN-3 in the Seattle program have developed pancreatic cancer in an average of 10 years of follow-up (data unpublished). Those who have PanIN-1/2 or other benign disease usually continue annual surveillance. If high-risk individuals have multifocal PanIN-2, insulin-dependent diabetes, and a strong family history of

PC, they might be considered for total pancreatectomy if they have a strong preference, as they are already diabetic. Other institutions have advocated for partial pancreatectomy of all high-risk lesions, with continued surveillance for progression.[14, 19, 21, 22, 25, 27] An additional concern, which may be addressed with future study, is how post-surgical changes complicate further surveillance of high-risk individuals.

Accepting the large amount of heterogeneity in studies, in a review of 1,545 individuals screened by EUS and/or MRI, approximately one-fifth of HRI (n=323) were found to have a clinically-relevant lesions as defined by their research protocol (Table 4).[6] Of these individuals, 62 surgeries were performed, and pancreatic cancer was found in 30% of the operated patients (n=19/62). Notably, the majority of the 19 discovered cancers were Stage II or more advanced; 5 had metastatic disease, and only 3 had T1N0M0 disease. When looking specifically at detecting and removing high-risk lesions (early stage PC, PanIN-3, IPMN with high-grade dysplasia), 29% of the operated patients (n=18/62) had "successful" resection. The programs that had the most success in detecting early stage cancer, PanIN-3, and IMPN with high-grade dysplasia were those that use a combination of EUS and MRI/MRCP/or ERP. Programs that relied on only MRI or MRCP had more individuals diagnosed with later-stage cancers. These findings suggest that a combination of imaging studies that include EUS may be more sensitive in detecting curable disease; however, further analysis using uniform imaging protocols would need to be performed to validate this conjecture.

As noted above, the natural history of neoplastic progression and timing of surgery are topics that need further evidenced-based research; nonetheless, the studies to-date do provide valuable information suggesting that waiting for masses/cancer to form can lead to metastatic and incurable disease. The fact that only 3 of 19 discovered cancers were T1N0M0 underscores the need to identify incipient disease (PanIN-3 or IMPN with high-grade dysplasia) at its highest grade of pre-cancer. Strategies that help identify these advanced neoplastic lesions are warranted; surgical or medical management at this earlier stage of disease may help prevent later-stage, incurable adenocarcinoma. In addition, further risk-stratification of FPC patients to identify those that require closest surveillance would be useful to appropriate health care resources in the most cost-effective manner.

***3. Gaps in the Field of Screening for FPC***

Among the various participants in the CAPS Consortium and the Seattle paper,[5-7] there was agreement on the following gaps in the field of screening and early detection of high-risk individuals that need further investigation.

*a. Who Should Be Screened? What Is the Appropriate Threshold for Screening?* Many experts make the recommendation for screening based on the number of family members affected: e.g., some recommend screening in kindreds with 2 affected family members with PC, including one first degree relative; alternatively other programs recommend screening for HRI in kindreds with 3 affected family members, one of whom is a first degree relative. When lifetime risk estimates can be calculated incorporating the number of affected family members in combination with environmental risk factors. The CAPS consensus suggested HRI with an overall lifetime risk of $\geq$5% or relative risk of at least 5-fold might warrant screening. General expert agreement for HRI and screening usually sets a level of 5%-10% lifetime risk. Cost-effectiveness analysis suggests that screening should be reserved for individuals with a lifetime risk of PC that is $\geq$16%.[24] It is unclear if FDRs of individuals with young onset of PC or both parents with PC should be screened. Data collected as part of large Hopkins CAPS 4 study will be imminently available. The estimated lifetime risk for PC for individuals with 1 first degree relative, but with a known genetic mutation (BRCA1, BRCA2, PALB2, HNPCC) should be better quantified with more recent studies specifically stratifying for these subgroups.

*b. How Should High-risk Individuals Be Screened? Which Approach Leads to the Highest Diagnostic Yield for Significant Neoplasia (Defined by Consensus to be PanIN-3, IPMN with High-grade*

*Dysplasia, and Early Resectable PC)?* This was one of the most controversial areas in the CAPS Summit – what imaging modalities should be used and how frequently should surveillance be performed? Some consensus was achieved, but this issue must be revisited based on accumulated and newer data and biomarkers. Data from groups using MRI as the primary screening modality have shown high rates of cancer development in HRI suggesting that this modality may be problematic.

*c. What Is the Most Cost-effective Approach to Screening?* A cost utility analysis was conducted by the Seattle group in 2003.[24] However, this needs to be updated given the accumulated data on performance characteristics and yield of various approaches using imaging, not included in this study, as well a large body of prospectively collected quality of life data from the Hopkins CAPS and other studies.

*d. When Should Surgery Be Performed? What Type Of Surgery Should Be Performed?* The indications for surgery are perhaps the most controversial aspect of the field. The decision to treat asymptomatic high risk individuals is a difficult one to make and should be performed in a multidisciplinary fashion in high volume centers with expertise in pancreatic surgery. [39]

The goal of screening and surveillance is to detect early PC and/or prevent it by resection of incipient precursors. Hence, the operative approach greatly impacts the outcomes of screening. At this time there is no consensus on these two questions.

Although imaging-detected cystic lesions are typically small and have no concerning features (such as those described in sporadic pancreatic cysts), recent data suggest these trivial multiple small IPMNs that do not fulfill Sendai[40] or Fukuoka criteria[41] for cyst resection are potentially markers of microscopic, high-grade PanIN precursor lesions elsewhere.[32] Hence, this greatly impacts on the surveillance and imaging strategies and selection of patients for treatment. Resected BD-IPMNs with high-grade dysplasia or early invasive cancer have almost been uniformly small and have not met standard international consensus criteria for management of pancreatic cysts. The Fukuoka 2012 revised guidelines for management of pancreatic cysts[41] have a sub-section on familial cysts, but these recommendations are based on expert opinion and need to be validated.

The clinical management of PanIN-3 and/or IMPN with high-grade dysplasia is complicated by the fact that precursor lesions are multifocal involving the entire pancreas and total pancreatectomy is associated with brittle diabetes and can be potentially life-threatening. The risks and benefits of surgical treatment have to be carefully weighed for each patient. Incorporated into that treatment assessment is the general health of the patient, the psychological profile, the cancer-risk assessment, the experience of the multi-specialty pancreatic cancer surveillance team, and, importantly, the wishes of the patient. Data from the CAPS Registry project and other large surveillance programs may help, as a randomized controlled trial is not feasible. In particular, the extent of surgery (total versus partial pancreatectomy) based upon preoperative imaging is difficult and to date has been addressed mainly by individualized multidisciplinary tumor board-type decision-making.

***4. Opportunities for Innovation***

*a. Collaboration:* Multicenter, prospective, IRB-approved, worldwide collaborative studies (registry approach most feasible) may collect and allow data sharing for answering key questions. One feasible option is the registry approach, such as the one that is already in process for the International CAPS Consortium Registry, which is hosted by the International CAPS Consortium.

This is an electronic comprehensive database in development since 2009, now hosted and launched by the Dutch group. The initial focus of this international collaboration, formalized at the International CAPS Summit, is the outcomes of screening and surveillance in high-risk individuals with a genetic predisposition (FPC and genetic syndromes) to answer the questions: 1) what are the goals of screening? And 2) what outcome(s) would be considered a success? It will also provide a

large set of pathologically-proven familial lesions detected by screening to understand what imaging-detected lesions are associated with high-grade neoplasia and early cancer, particularly those seen by EUS and not by CT or MRI. This project is already in progress and welcomes interested participants.

Suggestions for other collaborative projects are encouraged and under consideration, including those that address the other identified gaps in the field listed above, such as the natural history of precursor lesions, the optimal surveillance approach, and surgical outcomes in screened/surveyed high-risk individuals.

*b. Other Opportunities:*

***i. Registry-based natural history of precursor lesions*** detected by screening and surveillance imaging studies, such as MRI and EUS, will help with better characterization of high-risk lesions, or concerning features similar to the work in pancreatic cysts. In turn, the correlation of imaging findings with prevalence and types of neoplasia in resection specimens will impact the selection of patients for surveillance versus surgery and the type of surgery to be performed.

***ii. Virtual collaborative tissue banks***. The high cost and difficulty in setting up tissue banks can be challenging, especially given the regulatory and logistical issues that must be addressed. If international sharing is desired, such as in GWAS studies, these challenges may increase further, however smaller group collaborations might be quite feasible within funded projects.

***iii. Collaborative image repository of familial pancreatic neoplastic lesions.*** An imaging repository that included pedigreed lesions that have been evaluated by histology through resection and correlated with imaging could be a valuable resource for clinicians and researchers.

***iv. Risk stratification***. A better understanding of the diagnostic yield of screening and surveillance could be obtained if risk groups have standardized definitions and defined protocol imaging test(s) are used; other published papers have heterogeneous groups of high-risk individuals is common in FPC, where the genetic cause of the disease is unknown in approximately 80% of the kindreds. Additionally, better assessment of environmental and clinical risks stratification based on diabetes, smoking, plus genetic factors and age, could aid in risk stratification modeling. To this end, worldwide standardized criteria for glucose tolerance testing and/or definition of diabetes using HgbA1c would be valuable and could be incorporated into prospective cohort studies of high-risk FPC individuals, whereby diabetes is tested at baseline and re-tested over time.

***v. Worldwide, standardized criteria*** for glucose tolerance testing and definition of diabetes followed by prospective cohort study of high-risk individuals screened for diabetes at baseline and re-tested over time.

***vi. Surveillance strategies.*** Retrospective registry-based or prospective validation of the surveillance approaches is recommended in the Fukuoka 2012 paper[41] or CAPS[7] is needed.

***vii. Treatment strategies***. Pilot trials of chemoprevention may be one avenue for assessing clinical management for PanIN-3 and IMPN with high-grade dysplasia. The idea of preventive prophylactic pancreatectomy for the highest risk group of genetically predisposed individuals is usually not recommended because of the risks of pancreatectomy and the treatment of ensuing diabetes. However, the use of pancreatectomy for treatment of PanIN-3 lesions and SB-IPMN with high-grade dysplasia is another issue. This is not a prophylactic surgery, it is a treatment for carcinoma *in situ*, similar to treatment for multifocal carcinoma *in situ* in the stomach or colon. Treatment trials that included surgical resection of histologically proven carcinoma *in situ* in appropriate candidates, who are interested in surgery, would be helpful with abnormal pancreas by imaging tests, and predefined independently associated factors for PDA: number of affected individuals in family, age, diabetes, and smoking.

*c. Future Advances:* Assays that identify any PanIN lesion, independent of grade, are likely to lead to gross overtreatment and/or emotional turmoil, since low-grade PanIN-1 lesions are common and are likely of insufficient clinical significance even to justify follow-up. Similarly, multiple series have shown that individuals with branch duct IPMNs that do not harbor delineated criteria for resection (revised Sendai criteria) can, for the most part, be followed by conservative management and serial imaging except in FPC patients where they might be ominous. Ideally, a test that could specifically identify the demarcation is likely to be separating patients who have PanIN-1 and 2 from PanIN-3, and cystic lesions with at least high-grade dysplasia, from those with intermediate/ low-grade dysplastic lesions. Thus, the ideal strategy stage for early curable neoplasia detection would be the late stage precursor (PanIN-3 or high-grade dysplasia) – a point in the progression when surgical intervention is generally agreed to be indicated and when complete cure remains possible.

Because the preoperative detection of PanIN is difficult, if not impossible, macroscopic precursor lesions (MCN and IPMN) have been targeted as potential models to develop preoperative biomarkers predictive of high-grade dysplasia. To the extent that certain mutations (KRAS, CDKN2A/p16, TP53) may be shared between PanIN and these macroscopic precursors, it may be possible to use genetic analysis of cyst fluid (or even blood) to identify mutations that characterize pancreatic carcinoma *in situ* but are not found in the earlier stages of neoplastic progression. Some such mutations have been evaluated for their value to predict high-grade dysplasia, however, none of the mutation-based assays tried thus far has achieved wide acceptance as a marker of high-grade dysplasia. Furthermore, macroscopic precursor lesions, such as IMPN, exhibit mutations not typical of PanIN (e.g., GNAS, RNF43 mutations versus KRAS, CDKN2A/p16, TP53 mutations, respectively). This finding, suggests that there are significant differences in molecular carcinogenesis between these two categories of precursors that may limit the generalized applicability of biomarkers for all detection scenarios.

An important goal remains the identification of molecular biomarkers that are specific for high grades (i.e., not expressed in lower-grade PanIN), sensitive enough to be detected in most cases of PanIN-3 or early invasive carcinoma, and can be detected in practically-obtained biospecimens such as blood or stool. Future studies should assess the alternative strategies of 1) imaging alone versus 2) biomarkers alone versus 3) biomarkers, which if positive, are followed by imaging, and biomarkers given the anticipated variability in performance characteristics. The comparative studies will be difficult to conduct because PC is such an aggressive and rare disease. Hence, collaborative efforts that assess targeted screening of genetically predisposed individuals and focused, population-based screening will be critical to success.

***Summary***

Despite a lack of a universally accepted screening protocol, surveillance using EUS and/or MRI is well tolerated and for individuals at high-risk for pancreatic cancer, screening can find precancerous and early stage disease. Longer term data will hopefully clarify the best imaging modality, or combination of imaging modalities, for first-time screening and the timing of surveillance. Further research is also needed to clarify the natural history of PanIN (time to progression, risk factors, and imaging characteristics) to insure the successful management of high-risk individuals.
High-risk individuals who are genetically susceptible to PC, have abnormal findings on EUS and MRI including cysts, chronic inflammatory changes, and solid lesions that can be suggestive of pancreatic neoplasia; ultimately, tissue is correctly required for a pathologic diagnosis. Screening of high-risk individuals, histologic identification of incipient pancreas cancers, combined with surgical management can be curative and remove precursor lesions and early PC.

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**Table 1. Syndromes Associated with Familial Pancreatic Cancer (PFC)**

| | Relative Risk of Pancreatic Cancer | Cumulative lifetime risk by age 70 | Gene(s) identified | Extra-pancreatic malignancy |
|---|---|---|---|---|
| **Familial Pancreatic Cancer** | | | | |
| 1 first degree relative with PC | 2 to 3-fold | | Linkage 1p32, 5p15 and 13q22,<br>PALLD | Lung, colon, breast |
| 2 first degree relatives with PC | 6-fold | ~40% | | |
| ≥3 first degree relatives with PC | 14 to 32-fold | | | |
| **Hereditary Cancer Syndrome** | | | | |
| FAP | 2-3 fold | 5% | APC | Colon, duodenum, stomach |
| Hereditary<br>Breast<br>Ovarian<br>Cancer | 3.5 to 10-fold | 5% | BRCA1<br>BRCA2<br>PALB2 | Breast, ovarian, prostate |
| Lynch Syndrome (HNPCC) | 8.6 fold | 8<5% | MLH1, MLH2, MSH6 | Uterine, bladder, skin, ovary, bile duct, kidney, ureter |
| FAMMM | 13 to 47-fold | 17% | P16/<br>CDKN2A | Melanoma |
| Peutz-Jeghers | 132-fold | 36% | STK11 | breast, small Intestine, lung, esophagus, stomach, uterus, ovary |
| | | | | |
| Hereditary Pancreatitis | 50 to 80-fold | 40% | PRSSI, SPINK1 | |
| Cystic fibrosis | 5-fold | <5% | CFTR | Bile duct cancer |

Abbreviations: FAMMM, familial atypical multiple mole melanoma; FAP, familial adenomatous polyposis; HNPCC, hereditary non-polyposis colorectal carcinoma, PC, pancreatic cancer.

***Table 2. Factors Associated with Pancreatic Cancer Risk Among Members of FPC Kindreds***

| Factor | PC cases only OR *(95% CI) | PC or PanIN/IPMN cases OR * (95% CI) |
|---|---|---|
| Ever smoking | 3.7 (1.8-7.6) | 4.1 (2.0-8.2) |
| No. of affected FDR | 1.4 (1.1-1.9) | 1.4 (1.1-2.0) |
| History of diabetes | 2.1 (0.4-10.9) | 5.8 (1.3-25.2) |
| Male gender | 1.0 (05-2.1) | 0.9 (0.5-1.9) |

Abbreviations: FDR, first degree relatives; IPMN, intraductal papillary mucinous neoplasms; PanIN, pancreatic intraepithelial neoplasia; PC, pancreatic cancer.
*OR= individual odds ratios adjusted for each of the other variables in the table and for age, number of affected second-degree relatives, prior diagnosis of non-pancreatic cancer and relationship to other affected relatives (parent vs sibling).

***Table 3. Factors that influence selection of high-risk individuals for pancreatic cancer screening***

| | Genetic predisposition | Environmental | Family history | Symptomatic |
|---|---|---|---|---|
| Surveillance if any one factor is present | Peutz-Jegher,P16 gene (FAMM), palladin | _ | 2 or more family members, one of whom is a FDR | _ |
| Surveillance considered if a genetic predisposition is present (column 1) combined with other factors | BRCA1 or 2<br>HNPCC<br>FAP<br>PALB2 | Smoking, Exposure to benzenes or other carcinogens | 1 or more FDR with PC | New adult-onset diabetes, unexplained weight loss, epigastric or interscapular pain, malabsorption |

***Table 4. Diagnostic yield of reported pancreatic cancer screening programs***

| Study | N | Screening modality | Follow up reported | Diagnostic yield (%) | Surgical resection (%) | Pancreatic cancer | High grade neoplasm: Dysplasia or IPMN | Low grade neoplasm: Dysplasia or IPMN | Other pancreatic neoplasm | Successful yield[a] (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Kimmy et al, 2002 | 46 | EUS±ERP /MRCP | Mean 5y | 13/46 (28) | 12/46 (26) | - | 8 PanIN-3 | 4 PanIN-2 | _ | 8/46 (17) |
| Canto et al,2004 | 38 | EUS | Mean 22 mo | 29/38 (76) | 7/38 (18.4) | 1 stage IIb | PanIN-1 to PanIN-3 | 1 IPMN, 6 PanIN-1 to PanIN-2 | 3 SCA | 1/38 (2.6) |
| Canto et al,2006 | 78 | EUS | 12 mo | 17/78 (22) | 7/78 (10.2) | 1 stage IV | 2 PanIN-3, 1 HG IPMN | 5 LG IPMN, 2 PanIN-1 to PanIN-2 | _ | 3/78 (3.8) |
| Poley et al,2009 | 44 | EUS | First time screen | 10/44 (23) | 3/44 (6.8) | 2 stage IIb, 1 stage I | _ | _ | _ | 1/44 (2.3) |
| Langer et al, 2009 | 76 | EUS+MRI + MRCP | Median 2 examination | 28/76 (36) | 7/76 (9.2) | - | _ | 1 LG IPMN, 1 PanIN-1, 1 PanIN-2 | 3 SCA | 0/76 (0) |
| Verna et al, 2010 | 51 | EUS±MRI /MRCP | First time screen | 20/51 (39) | 6/51 (11.8) | 1 stage IV, 1 stage Ib | _ | 4 PanIN-2, 3 LG IPMN | _ | 0/51 (0) |
| Ludwig et al, 2011 | 109 | MRCP+EUS(+FNA) | 12 mo | 9/109 (8.3) | 6/109 (6.4) | 1 stage IIa | 1 PanIN-3 | 3 PanIN-1 to PanIN-2, LG IPMN | _ | 1/109 (0.9) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Vasen et al, 2011 | 79 | MRI+MRCP | 4 y | 16/79 (20) | 7/79 (10) | 7 PC (2 Stage Ia) | _ | 2 PanIN-2 | _ | 2/79 (2.5) |
| Zubarik et al, 2011 | 546 | CA 19-9 | First time screen | 5/546 (0.9) | 3/546 (0.5) | 1 stage IIb | _ | 1 PanIN-1 | 1 NET | 0/546 (0) |
| Al Sukhni et al, 2012 | 262 | MRI | Mean 4.2 y | 84/262 (32) | 4/262 (32) | 2 stage IV, 1 stage IIb | _ | 1 PanIN-1 to PanIN-2, 1 LG IPMN | _ | 0/262 (0) |
| Canto et al, 2012 | 216 | MRI, EUS, CT | 12 mo | 92/216 (42.6) | 5/216 (2.3) | - | 1 MD-IPMN with HGD and multiple PanIN-1-3,1 MD-IPMN, 1 PanIN-3 | 2 PanIN-1 to PanIN-2 | 1 NET | 3/216 (1.4) |
| Totals | | | | 323/1545 (21) | 67/1545 (4) | 19 | | | | 19/1545 (1.2) |

Diagnostic yield: percentage of patients with a pancreatic lesion found using screening modality.

Abbreviations: HG, high grade; HGD, High grade dysplasia; IPMN, intraductal pancreatic mucinous neoplasm; LG, Low grade; NET, neuroendocrine tumor; PC, pancreatic cancer; SCA, serous cystadenoma.

[a] Successful yield is surgical resection of PanIN-3, high grade IPMN, or T1N0M0 disease