National consensus and clinical guidance for diagnosis and management of Hereditary Pancreatic Cancer Syndrome

fapa

Belgian Polyposis Project
Hereditary Colorectal Cancer Project

CONTENTS

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Introduction

The life time risk of Pancreatic ductal adenocarcinoma (PDAC) in the general population is 1.5% with a 5-year survival rate of 8%. Most patients with pancreatic cancer are diagnosed with advanced-stage disease.

Improving early detection is likely to be the most effective way to reduce pancreatic cancer mortality. At present there are several pancreatic cancer screening programmes ongoing, some of them related to international registries. These guidelines are based on the results of the Cancer of the Pancreas Screening Study consortium (CAPS) and the CAPS registry.

About 5% to 10% of persons diagnosed with PDAC have a positive family history *(2 or more relatives affected with pancreatic cancer) (High Risk Group)* and 3% to 5% of the cases are due to known inherited tumor syndromes *(USPSTF 2019* [1]*, Goggins et al 2020* [2]*)*.

Detection of germline pathogenic variants has nowadays therapeutic implications for the patients e.g., BRCA1/BRCA2 germline pathogenic variants are an indication for poly ADP ribose polymerase (PARP) inhibitors. There is also an increased evidence that the detection of these germline pathogenic variants has cancer risk-reduction implications for healthy relatives who can follow established syndrome-specific surveillance guidelines.

The National Comprehensive Cancer Network (NCCN) and several Oncology societies recommend consideration of germline testing cancer predisposition genes for all newly diagnosed PDAC (*Stoffel et al 2019* [3]*, Tempero et al 2021* [4]*)*.

This document describes the guidelines for genetic testing in Belgium that have been agreed by a working group of professionals from different specialties (see list of participants) organized by FAPA.

Familial pancreatic cancer syndromes

Table 1: Genes associated with increased risk for pancreatic cancer. Extracted from Stoffel et al 2019 [3]

Genre	Syndrome	Pancreatic Cancer Risk (%)	Other Associated Cancers*
APC	Familial adenomatous polyposis	1-5	Colorectal, upper GI, thyroid, brain
ATM	Ataxia telangiectasia (biallectic) †	1-5	Breast, prostate, gastric
BRCA2	Hereditary breast ovarian cancer syndrome	5-10	Breast, ovary, prostate, melanoma
BRCA1	Hereditary breast ovarian cancer syndrome	2	Breast, ovary, prostate, melanoma
CDKN2A	Familial atypical multiple mole melanoma (FAMMM)	10-30	Melanoma
MLH1, MSH2, MSH6, PMS2, EPCAM	Lynch syndrome	5-10	Colorectal,uterine, upper GI, ovary, urinary tract, brain, sebaceous neoplasms
PALB2		5-10	Breast, prostate
STK11	Peutz Jeghers syndrome	10-30	Breast, Colorectal, upper GI, lung, reproductive tract
TP53	Li Fraumeni syndrome	Not defined	Breast, brain, sarcoma, adrenocortical carcinoma

* *Most commonly associated cancers.*

† *Biallelic ATM mutation carriers have ataxia telangiectasia. but a single ATM mutation is associated with increased risk for pancreatic cancer.*

Who can request a genetic test?

A genetic test for patients with exocrine pancreatic cancer in a care or specific screening program can be requested by gastroenterologists, surgeons, oncologists and geneticists.

Who should be tested for PDAC susceptibility genes?

Germline testing should be performed on:

1. All individuals diagnosed with exocrine pancreatic cancer
2. First degree relatives if it is impossible to test the individual who developed PDAC
3. Exclusion of pancreatic neuroendocrine tumor (PNET)
    - Approximatively 5-10% of the PNET are due to inherited syndromes which include MEN1, MEN4, VHL, NF1 and TSC.

Criteria for pre-test genetic counseling and genetic counseling in patient with PDAC

A familial anamnesis should be performed in all individuals with PDAC and the patient must have **pre-test counseling** and **genetic risk evaluation**. The pre-test genetic counseling can be performed by the gastroenterologist, the oncologist, surgeon or a clinical geneticist. The genetic risk evaluation should be performed by a geneticist if there is a specific germline mutation found in the individual with PDAC.

Families with clinical suspicion of hereditary pancreatic syndrome

Pre-test counseling should be offered to the following cancer-unaffected individuals and (preferably) after written consent. The pre-test counseling and genetic counseling of these relatives should be performed by a geneticist.

1. Members of families with an identified pathogenic cancer susceptibility gene variant
2. Pancreatic cancer–unaffected individuals from families that meet at least one of the criteria for pre-test counseling:

⩾ 3 affected individuals within the same parental branch, of whom at least one is a first degree relative	OR	⩾ 2 affected individuals who are first degree relative	OR	A strong clinical suspicion of one of the following syndromes: hereditary melanoma, hereditary breast- and ovarian cancer, Peutz-Jeghers syndrome, Li-Fraumeni syndrome, and Lynch syndrome	OR	Chronic pancreatitis. Predisposition to chronic pancreatitis due to either a PRSS1 or PRSS2 mutation leads to an estimated lifetime risk for pancreatic cancer of 40%. These genes should be tested if there is a strong clinical suspicion of chronic pancreatitis.

Which genes are eligible for hereditary PDAC risk evaluation?

The minimal set of genes, which are required for pancreatic cancer risk testing includes:

- (Goggins et al 2020 [2], Stoffel et al 2019 [3], Tempero et al 2021 [4])
- ATM
- BRCA1 BRCA2
- CDKN2A
- PALB2 STK11 TP53
- Lynch syndrome genes (MLH1 MSH2 MSH6 EPCAM)

Who is eligible for surveillance?

Since the incidence of PDAC in the general population is low *(lifetime risk 1.3%)*, surveillance is not recommended for the general population. It is although recommended for individuals considered to be at high risk of developing the disease *(ie, >5% lifetime risk)*.

The surveillance is currently divided in formal multidisciplinary pancreatic cancer screening programs according the estimated lifetime risk of PDAC. *(Goggins et al 2020 [2], Tempero et al 2021 [4])*

Individuals at high risk (HRI) for PDAC include:

- Unaffected relatives from familial pancreatic cancer (FPC) kindred with at least one affected first-degree relative and one affected second-degree relative
- All patients with Peutz-Jeghers syndrome (carriers of a germline STK11 mutation or fulfilling clinical criteria without germline STK11 mutation*) – independent of family history *(McGarrity et al 202112)*
- All carriers of a germline CDKN2A *(Overbeek KA 202111)*
- Carriers of a germline BRCA2, BRCA1, PALB2, ATM, MLH1, MSH2, or MSH6 gene mutation with at least one affected first-degree blood relative
- Carriers of a mutation in a pancreatitis predisposition genes (*PRSS1, PRSS2 and SPINK1)*

*Individuals with at least 2 of the following characteristics may be considered to have PJS:
- At least 2 Peutz-Jeghers type hamartomatous polyps in the small intestine
- Characteristic freckling of the mouth, lips, fingers, or toes
- At least 1 relative diagnosed with PJS

Who should be registered in the CAPS registry?

All High Risk Individuals (HRI) included in a surveillance program (with or without known mutations).

When should surveillance start in HRI?

Surveillance should take place in an expert center where pancreatic surgery is performed.

Table 2: Starting age of surveillance of High Risk Individuals

Peutz-Jeghers syndrome or CDKN2A mutation carriers	40 years or 10 years younger than the youngest affected blood relative[+]
Carriers of mutation BRCA1, BRCA2, ATM, PALB2, MLH1 or MSH2	45 or 50 years[*] or 10 years younger than the youngest affected blood relative
At the onset of diabetes in high risk individuals	Any age
HRI without known mutation	50 or 55 years[*] or 10 years younger than the youngest affected blood relative
Carriers of pancreatitis predisposition genes PRSS1, PRSS2 and SPINK 1	40 years

When should surveillance end?

There is no consensus on when surveillance should end.

It is recommended to continue surveillance as long as the patient is physically fit to undergo treatment and/or surgery.

Each "target" lesion should be included and discussed in a multidisciplinary board discussion because surgery might be an option

[+] on request of Belgian gastroenterologists

[*] no consensus for CAPS guidelines (Goggins et al 2020,2, Tempero et al 2021 4)

Surveillance tests, intervals and surgery.

Pancreatic cancer surveillance programs utilize a combination of endoscopic ultrasound and magnetic resonance imaging (Goggins et al 2020,2, Tempero et al 2021 4).

These programs may lead to the detection of asymptomatic pancreatic lesions, mostly cystic, that represent the major associated precursor lesions (pancreatic intraepithelial neoplasia; intraductal papillary mucinous neoplasms), in HRI (Canto et al 20185).

Most of the pancreatic cysts identified in HRI are small (<1 cm) and often multiple; their prevalence is much more common than in the general population and increases with patient age (Canto et al 20185).

Harboring a cystic lesion may also increase the risk of developing pancreatic cancer after 10 years of follow up (Chernyak et al 201513).

Biological evaluation

There are **no approved biomarkers** for screening and surveillance. Some programs include annual monitoring in HRI of

- Glucose testing *(fasting glucose or HbA1C)* to detect new- onset diabetes
- Serum Carbohydrate antigen 19-9 *(CA19-9)*. Around 10% of individuals do not have detectable CA19-9.

Screening methods *(Goggins et al 2020* [2]*, Stoffel et al 2019* [3]*, Tempero et al 2021* [4]*)*

- Dedicated high quality Endoscopic Ultrasonography (EUS) and Magnetic Resonance Imaging (MRI) pancreatic protocol with cholangiopancreatography (MRCP) are used for baseline screening

Gastroenterologist experience

- Careful EUS imaging under sedation using an electronic linear echoendoscope by an experienced echoendoscopist with additional use of contrast enhanced EUS and/or elastography if deemed necessary by the operator
- Fine-needle aspiration/biopsy must be performed during the same sedation procedure if detection of a pancreatic mass or mural nodule in a cyst
- Imaging is by preference performed every time in the same center. If this is not the case, the images of the former examinations should be available for comparison.

Radiologist experience

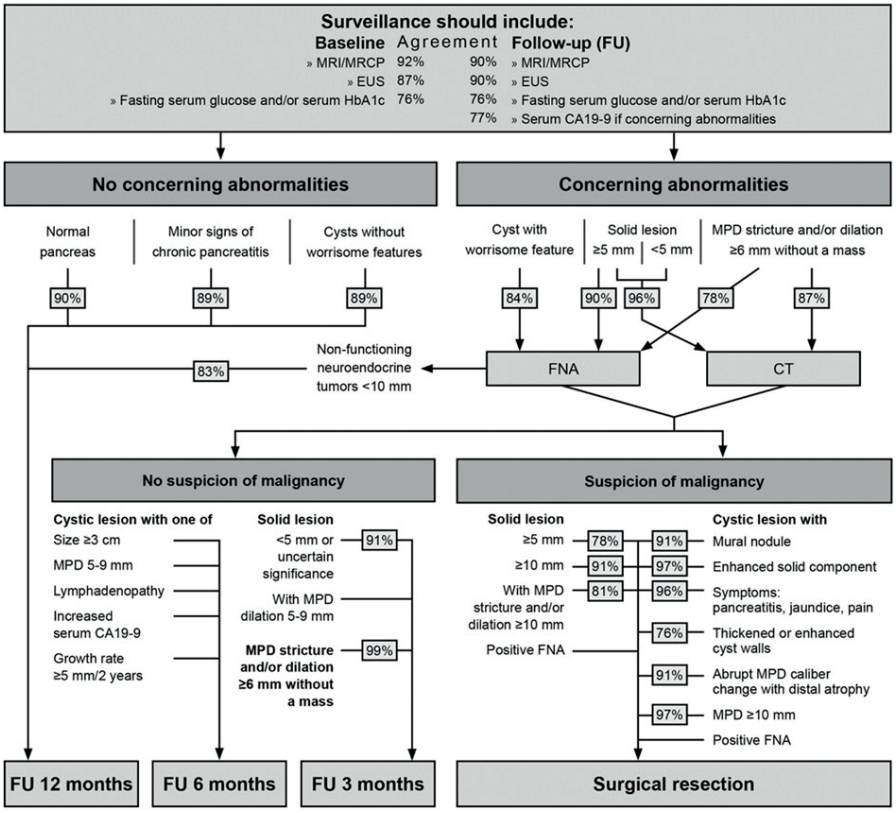
- State-of-the-art MR/MRCP including high resolution MRI of the pancreas with DWI, T2 and T1 weighted imaging with Gadolinium (in case of chronic pancreatitis depending on the results of the first examinations).
- Sequences must be obtained with state-of-the-art imaging depending on the device that you are using and according to the vendors directives.
- Axial breath-hold unenhanced and dynamic contrast-enhanced (0.1 mmol/kg of body weight), T1-weighted, 3-dimensional, fat-suppressed, spoiled gradient-echo imaging must be acquired in the arterial, portal venous, and delayed phases preferentially with the bolus tracking technique or at 20 seconds, 70 seconds, and 3 min, respectively

Surveillance policy

(Goggins et al 2020 [2], Stoffel et al 2019 [3], Tempero et al 2021 [4], Canto et al 2018 [5], Sagami et al 2021 6, KCE Report 105 [7])

We suggest to use the guidelines from Goggins et al 2020 [2] as a reference and to discuss every case in a multidisciplinary discussion in a center where pancreatic surgery is performed.

Figure 1 : Surveillance policy from Goggins et al 2020 [2]



- In the case of HRI without pancreatic abnormalities at baseline : perform EUS and/or MRI every 12 months.
- Neoplastic progression is more common in HRI older than age 60, and those with multiple cysts, and/or a mildly dilated MPD at baseline *(KCE Report 105* [7]*)*
- Surveillance intervals should be adjusted depending upon the stability of the indeterminate lesion and absence of radiologic features of neoplastic progression. Stable or improved appearance of pancreatic lesions may result in a decreased surveillance imaging frequency to every 12 months

Multidisciplinary discussion *(KCE Report 105* [7]*, Canto et al 2020* [8]*)*

- Patients with indeterminate lesions, masses, or cysts with worrisome features have to be discussed at regularly scheduled multidisciplinary conference involving surgeons, radiologists, gastroenterologists, and pathologists
- The screening programs are recommended to be done in experienced high-volume centers, ideally under research conditions

Surgical management

The possibility of surgery must be discussed during a multidisciplinary meeting in a referral center where pancreatic surgery is performed.

Surgical indications are theoretically:

- multiple cystic lesions > 10 mm *(growth or solid component)*
- solitary cystic lesion > 30 mm
- solid lesions/nodules >5 mm *(growing at MRI/EUS)*
- a dilated main pancreatic duct *(>10 mm)*
- positive cytology or biopsy *(HGD or adenocarcinoma)*

Life style

Although there is evidence that the expression of Hereditary Pancreatic Cancer is influenced by environmental factors, no sufficient data are available regarding which environmental factors play a significant role, but certain risk factors have been identified, such as smoking, obesity, diabetes, diet and inactivity *(Maisonneuve et al 2015* [10]*)*.

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Working group

These guidelines were prepared by an ad hoc working group of FAPA constituted by the specialists mention below. The meetings took place between June 2020 and September 2021. The guidelines were approved by the board of FAPA in November 2021.

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