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Position Paper

Italian registry of families at risk of pancreatic cancer: AISP Familial Pancreatic Cancer Study Group

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ABSTRACT

Pancreatic cancer is one of the main causes of cancer-related death worldwide, with a survival rate around 9%. In Italy 13,500 new cases of pancreatic cancer occurred in 2019. It is estimated that at least 5% have a hereditary background. Surveillance is advisable for healthy individuals with specific genetic syndromes with or without family history of pancreatic cancer or members of families with multiple cases of pancreatic cancer, irrespective of genetic syndromes. In 2010 the Italian Association for the Study of the Pancreas (AISP) defined criteria to include individuals in such surveillance programs with the first-round results published in 2019. In order to include other categories at high-risk and increase the diagnostic yield of surveillance, these criteria have recently been modified. The present position paper presents the updated criteria of the Italian Registry of Families at Risk of Pancreatic Cancer (IRFARPC) with their diagnostic yield calculation. Also, AISP priority projects concerning: (a) increasing awareness of citizens and primary care physicians through a dedicated App; (b) increasing access to germline testing to personalize surveillance; (c) measuring psychological impact of surveillance; (d) investigating the role of risk-modifiers and (e) evaluating the cost-effectiveness and ability to save lives of the program are briefly presented.

1. Background: prevention of pancreatic ductal adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is currently one of the main causes of cancer-related death worldwide, with a survival rate around 9% at 5 years [1].

This dismal prognosis has only slightly improved with progress in medical treatments [2]. Unfortunately, early clinical recognition of the disease is difficult and has little clinical impact on the disease course [3], and only a minority of patients are diagnosed at a stage allowing surgical cure. Therefore, prevention of PDAC is considered a priority [4]. Primary prevention is based on lifestyle measures, such as not smoking, avoiding excess of alcohol, red meat and sugar, keeping a normal body weight, and being physically active [5]. A drop of PDAC incidence of at least 30% would be obtained by such measures [6,7]. Secondary prevention (i.e. screening) is not advisable for the general population, given the relatively low lifetime risk of developing the disease.

Surveillance is advisable, instead, in subgroups of individuals at increased risk of developing the disease. These are represented by individuals with specific genetic syndromes with or without family history of PDAC and by members of families with multiple cases of PDAC, irrespective of the presence of an established diagnosis of genetic syndrome (cases of “familial pancreatic cancer”).

There is, indeed, a significant familial aggregation for PDAC. The rate of PDAC patients with a first-degree family member who had the same disease ranges from 5% to 10% and the lifetime risk of dying of PDAC has been estimated to be 4.1% for relatives of

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PDAC cases, increasing to 7.2% for the relatives of patients who developed disease aged <60 years [8]. Also, this risk increases substantially when more than one family member has been diagnosed with PDAC. International consensus has been reached for surveillance of subjects that are at substantially increased risk (usually >10%) of developing PDAC, based on their family history and/or of specific germline mutations [9]. A computerized tool named PancPRO, able to estimate the risk of developing PDAC based on a genetic model of susceptibility and family history of cancer has been proposed [10]. When tested in the families of 570 PDAC patients in Italy, it would have led to surveillance for some 3% of all families [11].

2. Development of AISP position statements and modifications over time

In 2010, the Italian Association of Pancreatology (Associazione Italiana Studio Pancreas – AISP) developed a first document with recommendations for individuals who should receive surveillance for the high-risk of developing PDAC [12]. This proposal was based on initial results of pivotal surveillance protocols initiated in the USA [13,14] and in Europe [15,16].

Criteria for surveillance according to the 2010 AISP Expert Consensus Statement on Familial Pancreatic Cancer were: (a) having ≥3 first, second or third degree relatives with PDAC on the same lineage or two relatives if at least one is a first degree; (b) having a mutation of BRCA1, BRCA2 or p16 with at least one first or second degree relative with PDAC; (c) being part of a PJS kindred (irrespective of family history); (d) having genetically verified hereditary pancreatitis; (e) having at least a 10-fold greater PancPRO risk of developing PDAC with respect to the general population.

In 2013 the International Cancer of the Pancreas Screening (CAPS) Consortium released its recommendations, that did not differ from the AISP ones, although being more restrictive in terms of enrollment of high-risk individuals [9].

In 2015, the need to offer an active surveillance program to the Italian population led to the creation of the Italian Registry of Families at Risk of Pancreatic Cancer (IRFARPC). IRFARPC aims to prospectively enroll individuals with familial and/or genetic predispositions to PDAC, with a multicentric structure. All participating units are high- or very high-volume centers for pancreatic disorders, according to validated criteria [17], and each center chose the diagnostic approach (e.g., MRCP or EUS) independently according to the treating physician's preference and to local facilities, in accordance with international guidelines [18]. Adults of ages up to 80 years were enrolled in the program. The enrollment criteria for predisposition to PDAC were rather broad, and they would include third-grade relatives and cases without any first-grade kinship. IRFARPC collected longitudinal demographic, clinical, anamnestic, and other medical data of enrolled individuals. The enrollment process was relatively fast, signing up 187 individuals over a 30 month period. In 2019, based on the results of the first round of surveillance [19], the scientific committee modified the protocol, dividing the structure of the registry into two hierarchical levels prospectively maintained (ClinicalTrials #NCT04095195). The first level is called "eligibility level" and defines criteria of predisposition (see below) without any age restrictions on entry. The second level is called "active surveillance level" and does have age restrictions that were set based on the type of predisposition, either familial or genetic. Once in the second level, an individual will undergo surveillance annually.

This flexible and liquid structure allows to collect longitudinally demographic, anamnestic (also pharmacological), and epidemiological data of a large population of subjects at risk of PDAC, including those who were not admitted to the second level due to age restrictions.

This would make an investigation into the geographic distribution of individuals at risk across the entire Italian national territory easier, thus including up to a thousand individuals at risk of PDAC [20]. The second level is reserved for subjects who have a familial and/or genetic predisposition and certain age, and therefore carry a considerable risk to develop PDAC throughout their lifetime, as these individuals are bound to benefit most from an ongoing imaging-based surveillance.

3. Updated 2020 criteria for surveillance according with AISP

Based on a consensus of the scientific committee, IRFARPC is now able to enroll individuals who will be at substantially increased risk of PDAC during their lifetime, based on family history or germline mutations in its registry, irrespective of their age. The groups at risk have been modified according with available evidence. As an example, while Lynch Syndrome was not among the conditions included in the previous statements, it is now.

Active surveillance, however, is only advised at a certain age, depending on the genetic background and on the age of affected family member(s). The process of selection of subjects for inclusion in the registry and in the active surveillance protocol and related criteria is summarized in Table 1. In the absence of pancreatic abnormalities, surveillance can then be performed by annual EUS or MRI with MRCP based on investigator's and patient's preference. EUS is at any rate indicated in those patients in whom MRI reports of ambiguous findings such as enlargement of a portion of the pancreas without a clear lesion, or in cases in which a mass is suspected because of indirect signs such as dilation of main pancreatic duct or of secondary ducts, without the evidence of a mass [21].

The protocol does not include specific indications for surgery, these being the same as for sporadic pancreatic disorders. Thus, indication for surgical or medical treatment or for additional investigations or changes in follow-up intervals for diagnosed PDAC, intraductal papillary mucinous neoplasms (IPMNs), or pancreatic neuroendocrine tumors (panNENs), are those developed from national and international guidelines according with institutional decision [22-28]. In this view, the indication for surgery is in some instance less aggressive compared to that of the new CAPS guidelines [18] that advise surgery in this setting even for small, non-functioning panNENs.

4. Retrospective application of updated criteria to the first AISP Cohort

In order to test whether the new enrolment criteria outlined in Section 3 might lead to an increased diagnostic yield, they have been applied retrospectively to the previously investigated population of individuals at high-risk of PDAC [19], resulting in a cohort of 134 individuals. One-hundred twenty-one subjects (90.3%) met criteria for FPC without known germline mutations, and thirteen (9.7%) had confirmed mutations (genetic predisposition). As expected, the mean age of the new cohort was higher than the previous one (57 ± 9 and 51 ± 12 years, respectively, $p<0.001$). Table 2 summarizes the demographic characteristics of the cohort. The new diagnostic yield for malignancies was 3.7% (vs. 2.6%), and the overall prevalence of premalignant/malignant lesions was 21.6%. The genetic predisposition group contained more individuals with a history of malignancy compared to the familial group (38.5% vs. 14.9%, $p=0.048$). When comparing the MRCP ($n=124$) and EUS ($n=10$) findings for premalignant/malignant lesions there were no statistically significant differences between the groups (22.3% vs. 15.4%, $p>0.05$). The previously identified risk factors associated with a diagnosis of premalignant or malignant lesions (smoking,

Table 1
Updated inclusion criteria for Registry accrual and Active Surveillance by means of annual Magnetic Resonance Imaging with Magnetic Resonance CholangioPancreatography (MRCP) or Endosocpic Ultrasound (EUS).

Group	Definition and Inclusion Criteria	Registry Accrual	Active Surveillance
Familiar Pancreatic Cancer	≥ two family members with PDAC in the same lineage, of whom at least one 1st degree. No germline mutations of those needed for inclusion in other groups.	At any age	Aged 45 or 10 years less than age of the youngest affected family member
Hereditary Pancreatitis	Recurrent Acute or Chronic Pancreatitis associated with confirmed pathogenic germline mutations of *SPINK1*, *PRSS1*, *CTRF* or *CTRC*.	At any age	Aged 40 or 5 years less than age of the youngest affected family member
Familial atypical multiple mole melanoma syndrome (FAMMM syndrome)	Confirmed pathogenic germline mutations of *CDKN2A* (p16-Leiden) regardless of PDAC family history.	At any age	Aged 30
Peutz-Jeghers Syndrome	Confirmed pathogenic germline mutations of *LKB1/STK11* regardless of PDAC family history.	At any age	Aged 30
BRCA1/BRCA2 mutation carriers	Confirmed pathogenic germline mutations of *BRCA1/BRCA2* with at least one 1st or 2nd degree family member with PDAC	At any age	Aged 40 or 5 years less than age of the youngest affected family member
Lynch Syndrome (HNPCC)	Confirmed pathogenic germline mutations of *MLH1/MSH2/MSH6* with at least one 1st or 2nd degree family member with PDAC	At any age	Aged 40 or 5 years less than age of the youngest affected family member
PALB2 mutation carriers	Confirmed pathogenic germline mutations of *PALB2* with at least one 1st or 2nd degree family member with PDAC	At any age	Aged 40 or 5 years less than age of the youngest affected family member

PDAC, pancreatic ductal adenocarcinoma; SPINK1, serine protease inhibitor Kazal-type 1; PRSS1, Cationic Trypsinogen; CTRF, Cystic fibrosis transmembrane conductance regulator; CTRC, Chymotrypsin C; FAMMM, familial atypical multiple mole melanoma; CDKN2A, cyclin-dependent kinase inhibitor 2A; LKB1/STK11, liver kinase B1/serine/threonine kinase 11;BRCA1, breast cancer 1; BRCA2, breast cancer 2; MLH1, mutL homolog 1; MSH2, mutS homolog 2; MSH6, mutS homolog 6; PALB2, partner and localizer of BRCA2.

Table 2
Demographic features of 134 subjects who received the first round of surveillance who would have been enrolled according with the 2020 AISP updated inclusion criteria for Active Surveillance.

Characteristics of asymptomatic HRI who were enrolled in the registry	n
Familial Pancreatic Cancer (FPC)	121 (90.3)
Genetic Syndrome (GS)	13 (9.7)
	3 (23.1)
13- HBOC (BRCA1)	
	3 (23.1)
13- HBOC (BRCA2)	
	3 (23.1)
13- FAMMM (p16/CDKN2A)	
	3 (23.1)
13- Peutz-Jegher syndrome (STK11/LKB1)	
	1 (7.7)
13- Hereditary pancreatitis (PRSS1)	

Variable	**All patients (*n* = 134)**	**FPC (*n* = 121)**	**GS (*n* = 13)**	**p-value**
Age, mean (SD)	57±9	57±9	54±9	n.s.
Female, gender	74 (55.2)	67 (55.4)	7 (53.8)	n.s.
Ever smokers[§]/current smokers	23 (17.2)	20 (16.5)	3 (23.1)	n.s.
Any regular alcohol intake	14 (10.4)	11 (9.1)	3 (23.1)	n.s.
Youngest relative with PDAC (median, IQR)	64±13	64±11	59±23	n.s.
Personal history of malignancies, n (%)	23 (17.2)	18 (14.9)	5 (38.5)	0.048*
HRI with 1 FDR affected	131 (97.7)	121 (100)°	10 (76.9)	0.003*
HRI with ≥ 2 FDR affected	45 (33.5)	45 (37.2)	–	n.s.
HRI with family history of malignancies	84 (62.7)	73 (60.3)	11 (84.6)	n.s

§ = ever smoker is a person who has smoked 100 cigarettes or more in his/her lifetime.
* = statistically significant. HBOC, hereditary breast-ovarian cancer; BRCA1, breast cancer 1; BRCA2, breast cancer 2; FAMMM, familial atypical multiple mole melanoma; CDKN2A, cyclin-dependent kinase inhibitor 2A; LKB1/STK11, liver kinase B1/serine/threonine kinase 11; PRSS1, Cationic Trypsinogen; PDAC, pancreatic ductal adenocarcinoma; IQR, interquartile range; HRI, high-risk individual; FDR, first-degree relative.

age > 50 years, and having had more than two relatives affected by PDAC) were all confirmed (OR 3.7, 95%CI [1.4–9.7]), $p = 0.007$; OR 4.6, 95%CI [1.3–16.4]), $p = 0.017$; OR 3.9, 95%CI [1.5–9.8],$p = 0.003$, respectively). However, only the last two were independently associated as confirmed by a multivariate analysis (OR 3.8, 95%CI [1.1–13.7], $p = 0.042$, and OR 3, 95%CI [1.1–8.2], $p = 0.028$, respectively).

As expected, the adoption of the new eligibility criteria in combination with the introduction of age restrictions significantly increased the diagnostic yield of PDAC to 3.7%, one the highest rates ever reported to date if considering those manuscripts dealing mostly with familial predisposition [29-36]. However, those studies were rather heterogeneous in terms of inclusion criteria and imaging tests which may affect any direct comparison. Nevertheless, when considering the Italian national territory and the low incidence of PDAC in Italy (12/100.000 inhabitants [20]), a diagnostic yield of 3.7% is considerable.

5. AISP priority projects within the surveillance registry

5.1. (a) increase awareness and dissemination

It has been estimated that 13,500 new cases of PDAC occurred in 2019 in Italy [20]. This estimate, considering the Country 60 million inhabitants, suggests an incidence of about 22 per 100,000 inhabitants. If only 5% of these cases are based on genetic susceptibility, it would mean that 675 cases per year belong to high-risk kindreds, being either familial or genetic ones. With a prudent estimate, this would suggest that there are at least 1350 (if there are two high-risk family members to be enrolled for each PDAC case) persons that should enter the Italian Registry and undergo surveillance each year. These raw data underline the importance to widen the Italian Registry to more Centres in the Country, with a more diffuse awareness of citizens and physicians, including primary care ones. AISP has developed specific grants for young investigators with this aim, and it has recently launched a free and user-friendly mobile App [37] that may be useful to spread the Italian Registry among relatives, caregivers, and family doctors dealing with PDAC or PDAC risk. Collaterally, it may help in increasing PDAC predisposition awareness. AISP is gathering detailed information on Centers that wish to take part to the Registry. Participating Centers will need to fulfill criteria set by AISP in terms of availability of resources (dedicated MDs and or Research Nurse or Data Manager) and facilities (pancreatic surgery, EUS, MRCP, genetics) or declare whether they will network with other Centers that have these characteristics. Ethic Committee approval will be necessary to join the study.

5.2. (b) Germline testing to personalize surveillance

Although the risk of developing lesions is different in subjects who are enrolled in surveillance programs based on family history alone, in the absence of the above mentioned germline mutations, or in those with pathogenic mutations, germline genetic testing is not a standard of care in patients with PDAC in Italy. AISP aims at widening this indication to ideally provide genetic germline analysis at least for all subjects in the Registry, in order to better define their surveillance strategy. Of note, the AISP registry includes BRCA1/BRCA2 mutation carriers with one 2nd degree family member affected by PDAC, while, conversely, the CAPS consortium does not advise surveillance in these subjects. Similarly, there was insufficient evidence at this time to include ATM mutation carriers in the program. Further studies with germline testing of families at high-risk are likely to widen the current criteria in the future.

5.3. (c) Psychological impact of PDAC surveillance

The feasibility of a surveillance program should be evaluated also addressing its psychological burden. Indeed, two combined and dangerous factors may cause permanently high levels of distress, cancer-related worry and screening-related worry. This distress may be further intensified by the family and personal history of the subjects enrolled, since usually they have been caregivers of parents or close relatives until the end of the disease, or they do have experienced personally a cancer history. The results so far indicate that high-risk individuals benefit from the enrollment in a surveillance program, with a reduction of cancer fear and anxiety over time [38]. The overall psychological status seems to be good [39], and a psychological intervention obtains benefits over time, especially in young individuals [40]. Recently, a single-center sub-cohort analysis of the IRFARPC reported that an MRCP-based annual surveillance program does not increase the levels of stress of individuals enrolled [41]. A dedicated prospective multicenter study will be designed and developed within IRFARPC to investigate the emotional impact of PDAC surveillance. This project will hopefully enrich literature on the psychological impact of an MRCP/EUS-based annual surveillance program in individuals at higher risk for PDAC.

5.4. (d) Analysis of risk modifiers

Sporadic PDAC risk is highly determined by risk factors such as smoking, overweigh, diabetes, diet and excessive alcohol intake [42]. However, there is also increasing evidence for a (chemo)preventive role of the use of commonly prescribed drugs, such as aspirin or statins, in affecting PDAC risk [43]. The IRFARPC will prospectively investigate the role of these factors and their dynamic changes over time in determining the risk of developing preneoplastic lesions or PDAC.

5.5. (e) Evaluation of efficacy of the program in terms of cost-effectiveness and ability to save lives

Although surveillance of high-risk individuals is currently performed as a part of research protocols in many Countries worldwide, the evidence supporting the view that this actually saves lives is limited. There is growing evidence that diagnosis of PDAC at early stage is increasing and that this results in improved survival [44]. Long-term surveillance of high-risk individuals allows early diagnosis in the majority of them with 3-years survival rates exceeding 85% [45]. The IRFARPC will record data to investigate further the actual cost-effectiveness of surveillance and to optimize promptly strategies to improve their efficacy.

In conclusion, familial PDAC is an underestimated entity and it deserves increased efforts from the Italian Health Community in order to identify earlier pre-malignant lesions or PDAC at an early stage, with higher chances to be cured. AISP aims at investigating a relatively large and consistent subgroup of Italian citizens by means of non-invasive or minimally invasive screening tools such as MRCP and EUS performed yearly, and at sharing the current program with all interested stakeholders (such as other Scientific Societies of the field, patients' associations and with decision makers and payers), in order to increase the awareness on the topic and the enrolment of high-risk individuals in the Italian Registry.

Declaration of Competing Interest

None.

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