



Screening for pancreatic cancer – a compelling challenge

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Efficacy of pancreatic cancer surveillance programs

The publication of the American Gastroenterology Association (AGA) Clinical Practice Update on Pancreas Cancer Screening in High-Risk Individuals (HRIs) underlines the increasing attention for this topic (1). Secondary prevention (surveillance) for pancreatic ductal adenocarcinoma (PDAC), however, remains a challenge with many unsolved questions (*Table 1*).

Revisiting the ten Wilson-Jungner criteria (2) for appraising a screening program's validity, when it comes to PDAC most have not been satisfied. Particularly, the fundamental principle that “treatment at an early stage should be of more benefit than at a later stage” has been scarcely investigated. The Johns Hopkins single-center experience reported promising efficacy results in terms of survival, with a median survival of 5.3 years [interquartile range (IQR), 1.2–11.1 years] and an outstanding 85% 3-year survival rate (3). Notably, several studies and some meta-analyses have shown that the diagnostic yield of pre-malignant or malignant lesions in HRIs undergoing screening/surveillance is much higher than the 1.6% lifetime risk of PDAC in unselected individuals. The lifetime risk of PDAC is as high as 40–60% in Peutz-Jeghers syndrome (PJS) or hereditary pancreatitis (HP) patients, or in the presence of ≥ 3 first-degree relatives (4–6). However, these reports' results do not provide evidence of survival benefits over time, leaving the issue of whether a screening/surveillance program for PDAC is effective still unsolved.

Who should be screened?

Selecting the population to be screened is crucial, and the stricter are the inclusion criteria, the higher is the diagnostic yield (7). The AGA document advises surveillance for all patients with PJS, HP and cyclin-dependent kinase inhibitor 2 (*CDKN2A*) gene mutation, irrespective of family history and for patients with ≥ 1 first degree relatives with PDAC with Lynch syndrome, or with mutations in Breast CAncer gene 1/2 (*BRCA1*, *BRCA2*), partner and localizer of *BRCA2* (*PALB2*), and ataxia telangiectasia mutated (*ATM*) genes. Individuals with ≥ 2 family members with PDAC of whom one first degree should also be screened. The main difference with the Cancer of the Pancreas Screening (CAPS) consortium guidelines regards the inclusion of HP, at least when associated with *PRSS1* mutations. CAPS does not include these subjects. Whether patients with chronic pancreatitis (CP), especially with early onset, associated with pathogenic mutations of serine peptidase inhibitor Kazal type 1 (*SPINK1*), cystic fibrosis transmembrane regulator (*CFTR*), chymotrypsin C (*CTRC*), carboxypeptidase A1 (*CPA1*) and carboxypeptidase B1 (*CPB1*) would benefit from surveillance is uncertain. As more patients with such mutations are likely to be diagnosed in the future, thanks to a more detailed investigation of causes of acute recurrent and CP, this is an important area for future research. The Italian Registry criteria for Surveillance of HRIs (7) are less rigid and allow to include all patients with a genetic cause of CP.

Also, while the AGA document underlines the importance of starting surveillance earlier in subjects with *CDKN2A* and *PRSS1* mutations and PJS, whether an annual

Table 1 Areas of uncertainty for pancreatic cancer surveillance

Question	Needs	Problems
Do surveillance protocols for PDAC save lives?	Studies on large populations of HRIs under active surveillance compared to other HRIs who do not undergo surveillance	Difficult in recruiting and having statistical power
Should surveillance be personalized?	Studies developing algorithms integrating genetics with environmental factors	Costs of genetics, need of validation
Is a widespread diffusion of surveillance for PDAC sustainable?	Studies on simulation of health resources and costs	Different health systems and reimbursement regulations across countries
Is the psychological burden of surveillance acceptable?	Studies on large cohorts of HRIs undergoing surveillance to measure its impact on quality of life	Development of <i>ad-hoc</i> PREMs and PROMs tools is needed possibly in collaboration with patients' associations

PDAC, pancreatic ductal adenocarcinoma; HRI, high-risk individual; PREMs, patient-reported experience measure; PROMs, patient-reported outcome measure.

examination is sufficient in these cases is also uncertain. Interval cancers have been reported in *CDKN2A* mutation carriers (8), and in such cases a 6-month interval may be more appropriate. Finally, while it is plausible that other factors such as smoking (9), overweight, diabetes or diet may modify the risk of developing cancer in HRIs, this must further be ascertained.

Is pancreatic cancer screening “sustainable”?

As we head toward a personalized medicine era, more PDAC patients will receive germline testing to choose the most appropriate treatment. However, this will also lead to an enormous increase in family members considered HRIs and eligible for surveillance.

At the very least, some 5% of sporadic PDAC patients, indeed, carry germline mutations of *BRCA1/2*, *ATM*, *PALB2*, *CDKN2A*, or of mismatch repair genes (10).

Thus, in the US, where almost 60,000 individuals are diagnosed with PDAC annually, at least 3,000 families would need surveillance, possibly some 10,000 new individuals per year. This estimate does not consider additional individuals meeting criteria based on family history in the absence of mutations and those with HP. As PDAC surveillance should only be performed in tertiary Centers with adequate facilities and high-volumes, we wonder whether this is a sustainable burden as part of research protocols.

Psychological burden

The need to ascertain a screening program's psychological

sustainability was recognized as a relevant issue already in 1968 (1). This aspect, however, has only been marginally investigated in PDAC screening/surveillance programs. A systematic review and other studies reported low-to-moderate levels of PDAC-related distress, acceptable rates of anxiety and distress, low-to-moderate levels of PDAC perceived risk, with an acceptable psychological status (11,12). However, it has been repeatedly found that subjects at a younger age may experience higher distress rates, which cannot be neglected (12,13). It must be considered that the psychological burden of HRIs undergoing screening/surveillance for PDAC may be heavily burdened by the oncological family history that had often seen the individual having played the role of caregiver of a strict relative before being a proband. Also, for some individuals (e.g., those suffering from Peutz-Jeghers or familial atypical multiple mole melanoma (FAMMM) syndromes or harboring a *BRCA1/2* mutation), this experience is exacerbated by the personal oncological history (of breast, ovarium or bowel cancers, or melanoma). The AGA guidelines do not recommend any psychological support to individuals undergoing screening/surveillance for PDAC. Instead, we believe it is advisable to include a psycho-oncologist in the team of clinicians dealing with screening/surveillance for PDAC so that any psychological distress would be promptly diagnosed and treated to obtain gains over time.

Conclusions

Prevention is likely the key issue to tackle PDAC mortality. Surveillance programs need to be refined and personalized, applying algorithms that consider genetics and other factors

that may increase or decrease the risk of developing lesions or modify their growth rate.

The development of well-structured and widespread surveillance programs with the capability to enroll all subjects at high risk and take care of all aspects of care, including psychology, is a challenge that researchers must face worldwide and that cannot be lost.

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