eGastroenterology

Pancreatic incidentaloma: incidental findings from history towards the era of liquid biopsy

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To cite: Löhr J-M, Vujasinovic M, Kartalis N, *et al*. Pancreatic incidentaloma: incidental findings from history towards the era of liquid biopsy. *eGastroenterology* 2024;**2**:e100082. doi:10.1136/egastro-2024-100082

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/egastro-2024-100082).

Received 16 April 2024
Accepted 15 August 2024

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ABSTRACT

This report provides an overview of the most common diagnostic methods that bring to light incidental findings of pancreatic cancer. It reviews the impact of medical imaging and genetic assessment on the definitions of incidental findings and incidentaloma of the pancreas. For different diagnostic approaches (eg, MRI and CT) and for different affections (cysts/intraductal papillary mucinous neoplasia, solid lesions), specific guidelines have been proposed and some are established. Based on this, we summarise the differences between the traditional methods with those applied in the PANCAID project. Biomarkers, genetic predispositions, mutations and circulating tumour cells give rise to different levels of concern. The final part of the report discusses the risks and the opportunities associated with further diagnostic procedures and surgical interventions. From the ethical perspective, the most urging question is, can a screening based on liquid biopsy and blood samples open a gateway for the prevention of pancreatic cancer—even if morbidity and lethality of today's surgical interventions is still very high?

INTRODUCTION

In analogy to the original description of incidental findings in the adrenal gland where from the term 'incidentaloma' was coined,[1] pancreatic lesions found by chance are referred to as 'pancreatic incidentalomas'.[2] Two types of incidental findings can be distinguished: (1) findings that come to light during a routine or preventive examination while the patient is free of any symptoms and (2) incidental findings that emerge during diagnostic procedures undertaken to clarify a disease while investigating different symptoms.

Within the last two decades, the meaning of the term incidentaloma has profoundly changed.[3] Just 15 years ago, incidentaloma could still be defined as 'incidental findings when using modern, high-resolution imaging'.[4] Today, the focus for incidental findings has shifted to mutations and genetic predispositions. From a legislative standpoint, incidental findings are defined as 'a result of medical examinations in context of diagnostics and research, that do not relate to the original question and that may have an impact on the health of an individual or its relatives'.[5] In its guidelines, the *American College of Genetics and Genomics* also included terms like 'serendipitous and iatrogenic' findings, 'non-incidental secondary findings', 'unanticipated findings' and 'off-target results'.[6] All the terms are framed from the diagnostician's perspective, which indeed gives them a serendipitous touch. Patients seem to prefer the more neutral term 'additional findings'.[7] As a conclusion, there is not a single common definition of pancreatic incidentalomas at present. As the lowest common denominator, an incidental finding, made on the occasion of an investigation not directed towards the pancreas, can be named.

Therefore, the true prevalence of pancreatic incidentalomas cannot be determined exactly and is influenced by the detection method, that is, imaging modality (ultrasound, CT, MRI) versus postmortem. For all studies, the reference size, the denominator, is the problem. While autopsy studies at time where virtually everybody was investigated would suggest a true denominator, this would primarily be true for those patients dying in the hospital with easily detectable lesions.[8] Nevertheless, as detailed below, the prevalence varies between 0.12% and up till 50% (table 1). As with adrenal incidentalomas, the clinical implications vary. While a cystic 'tumour' may require surveillance, solid lesion would trigger further investigations and eventually surgery.

We here include an exemplified case of a patient receiving abdominal CT series due to kidney stones. The patient suffered from typical colic-like attacks and blood in urine, pain in the left flank radiating towards the groin. There was no weight loss or upper abdominal pain, nausea, vomiting or loss of appetite. The native CT revealed

Table 1 Prevalence of incidental findings by time and method

Year	Method/reference	Prevalence	Findings	Reference
1882	Postmortem/all deceased	0.12 %	Not specified	8
1899	Postmortem/all deceased	1.15 %	Not specified	11
2018	Postmortem CT/deceased	28.10%	All possible lesions	16
2018	MRI/general healthy population	50 %	Cystic lesions	18

a very discrete abnormality around the pancreatic head (figure 1). Further four-phase CT for the pancreas and MRI confirmed the diagnosis of a pancreatic cancer (figure 1).

With the rise of liquid biopsy, blood samples are destined to identify genetic dispositions and mutations that may lead to pancreatic cancer, to detect circulating tumour cells, and to find specific biomarkers (figure 2). However, the question arises how a positive blood test in the absence of visible pathology is to be interpreted—and handled. There is a historical template for this process: CA 19–9, the only tumour marker for gastrointestinal

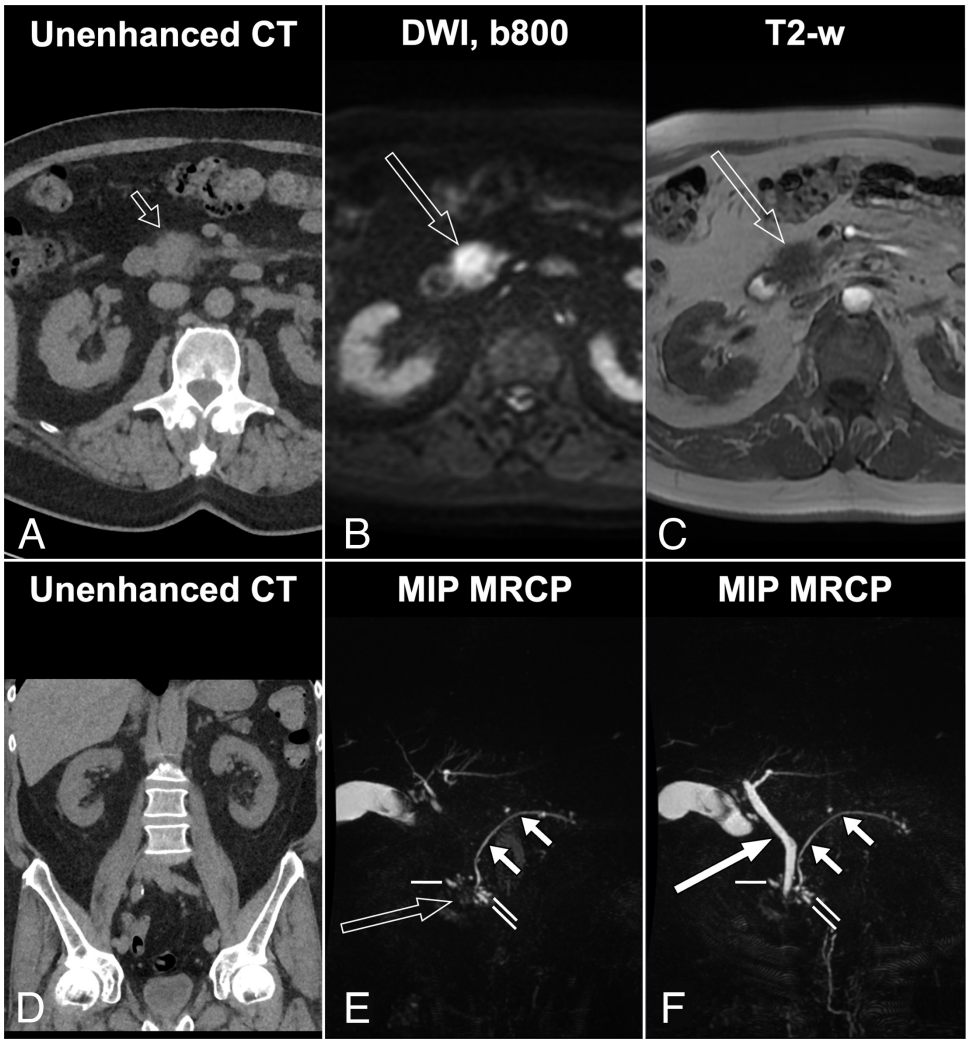


Figure 1 Axial (A, B, C) and coronal (D, E, F) images of a patient presenting with left renal colic. On the unenhanced CT of the abdomen and pelvis (A, D), no kidney or ureteral stones are identified. As an incidental finding, discrete peripancreatic fat stranding is present around the pancreatic head which leads to an effacing of the normal parenchymal contour (short open arrow in (A)). The finding was suspicious of a pancreatic head tumour. The presence of a tumour (long open arrow) is confirmed on diffusion-weighted (DWI) (B) and T2-weighted (C) MR imaging performed a few days later. On maximum intensity projection magnetic resonance cholangiopancreatography (MIP MRCP), there is no dilation of the main pancreatic duct [short arrows in (E) and (F)] or the extrahepatic bile ducts (long arrow in (F)). The tumour (long open arrow in (E)) causes slight dilation of some surrounding side branches (thin lines in (E) and (F)). Amylase and CA 19–9 were normal. After pancreaticoduodenectomy (pT2N0L0V1Pn1R1), the histopathological analysis showed pancreatic ductal adenocarcinoma, positive for MUC1, MUC5A, $p53^{mut}$ and loss of SMAD4.

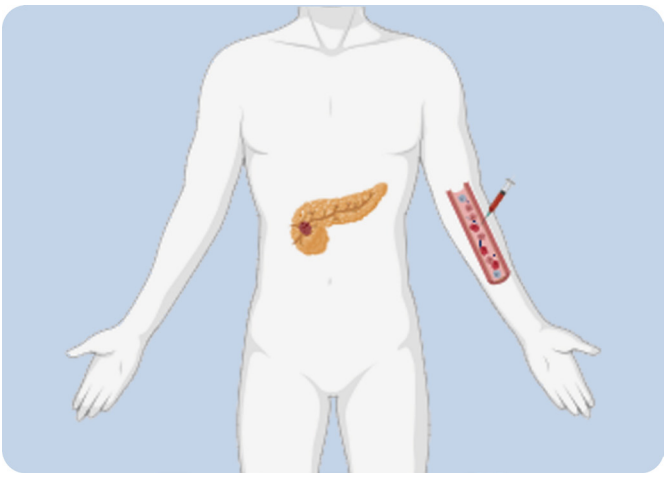


Figure 2 Graphical representation of pancreatic incidentaloma and liquid biopsy. Created with BioRender.com.

tumours, especially pancreatic cancer, has been found 'elevated' in healthy individuals.[9 10]

HISTORICAL INCIDENTAL FINDINGS

We first recap the problems that emerged from diagnostic methods. As radiography and other forms of medical imaging led to a sharp decline in postmortem examinations during the second half of the 20th century, they to some extend obscured older knowledge about the epidemiology of pancreatic cancer. In times when almost every patient who died in a hospital has usually been dissected, statistical reports about the cause of death regularly included more than ten thousand patients. In Vienna, Alios Biach reported on two patients who had died under his custody in 1882 with symptoms of biliary obstruction. Only their dissection revealed they had suffered from pancreatic cancer. Biach consulted the postmortem files of two decades in three Viennese Hospitals. Among 23 855 autopsies, he found 29 cases (0.12 %) where pancreatic cancer had been noted as the cause of death.[8] In his most influential textbook of internal medicine, William Osler quoted much higher figures from Milano: 132 tumours of the pancreas had been found in 11 472 dissections, that is, 1.15%.[11] Such data from the fin de siècle, although correct at the time, would not have included cystic structures within the organ. However, at least one syphilitic gumma had been counted in the cases from Milano. Notably, dissections were mostly reduced to macroscopically visible defects; broader epidemiological aspects have also to be taken into account when reading old statistics: in Austria, infant mortality oscillated around 20.9% at the turn of the century.[12] With one-fifth of the population having died before reaching the age of one, and infectious diseases (diphtheria, tuberculosis) taking their toll in childhood and young adulthood, the average life expectancy in Europe is estimated having been 40 years of age in 1900.[13] Although those who survived the scrooges of childhood had a good chance to reach the senium, the average central European would have missed the median age today considered for a pancreatic cancer diagnosis by decades. Recent data indicate that nearly 90% of the patients being diagnosed with pancreatic cancer are over 55 years of age and the median age of diagnosis is 70[14]; however, both the elder as well as the younger age groups are increasing.[15]

Histological postmortem assessments are rarely performed nowadays. Postmortem CT can give a hint. In a recent study looking into 356 deceased patients with diagnoses not related to the pancreas, postmortem CT revealed 100 individuals with pancreatic morphological abnormalities (28.1 %), including calcifications, enlargement, atrophy, cysts and dilatations of the main pancreatic duct.[16] Admittedly, although being incidental findings, they are no longer of any concern to the (already deceased) patient.

There are very few studies undertaken to screen an entire population for pancreatic cancer. Large cohort studies with MRI and CT have replaced the postmortem charts of the past. On the basis of MRI, a study suggests that cystic lesions might be found in up to between 15% and 30% of the population.[17] Within the Screening Health in Pomerania (SHIP) study, 1077 healthy individuals were subjected to whole-body MRI and followed over a 5-year period revealing no pancreatic cancer but cystic lesions (intraductal papillary mucinous neoplasia, IPMN) in about 50% of those individuals.[18] A long-term follow-up of 67 patients with cysts below 2 cm diameter did not reveal a single case leading to further problems[19]—something even confirmed for very small IPMN. A general screening has since been restricted to defined individuals at risk.[20 21] For pancreatic cancer, a screening of the entire healthy population, as done for breast, colorectal, cervix and prostate cancer, cannot be recommended due to a lack of evidence, biomarkers and health economical viability.[22]

SCREENING AND SURVEILLANCE

While screening cannot account for incidental findings, it adds some figures to what can be expected in terms of pancreatic incidentalomas. The first cancer screening method proposed for a general population started 100 years ago with the introduction of colposcopy and the Papanikolaou test.[23] The early diagnosis of cervical cancer is still the most successful field of cancer prevention.[24] Bearing in mind that every individual would only be screened once, the validity (sensitivity) of the tests had to be as high as possible, whereas the highest reliability could be secured in a second step. The vow 'validity first' remains to be of importance today. Genetic tests do impress with analytic sensitivities, while clinical or scientific validity remains a challenge.[25] Relatives suffering from pancreatic cancer, turning them into 'individuals at risk' (IAR), are easily detected with an old and conventional tool, family history, a forgotten art.[26]

At first sight the identification of IAR may seem to be the opposite of an incidental finding, as it is the result

of carefully planned policies. Studies as well as attentive general practitioners (GPs) might detect IAR by family anamneses. Once detected, the management of patients with increased risk for familial pancreatic cancer is assessed through further diagnostics.[21] Surveillance also implies to patients with a history of chronic pancreatitis.[27]

Having been identified as an IAR can justify invasive methods. Endoscopic ultrasound (EUS) and even more so endocsopic retrograde cholangio-pancreatography bear severe risks. However, they can detect IPMN, pancreatic intraepithelial neoplasia and early-stage pancreatic ductal adenocarcinoma in case the non-invasive cross-sectional imaging methods (ie, MRI, CT) are equivocal, ambiguous or demonstrate growth or worrisome features.[28]

INCIDENTAL FINDINGS IN LIQUID BIOPSY

Liquid biopsy is capable of determining early cancer in general.[29 30] Next-generation sequencing (NGS) can safely be done in liquid biopsy,[31 32] even in pancreatic cancer.[33–35]

Like NGS, liquid biopsy is becoming a commodity and a commercial market opening to the public: several companies aggressively advertise liquid biopsy to the general consumer market.[36] This will lead inevitably to incidental findings. Two liquid biopsy tests are already approved by Federal Drug Administration (FDA) and hence receive reimbursement. However, as with tumour tissue NGS, interpretation of data remains the major challenge,[37] even in liquid biopsy.[38]

Monitoring a patient with cancer with liquid biopsy can be misleading, for example, when a patient with lung cancer also suffer from leukaemia.[39] As described above, here a patient with symptoms was subjected to diagnostic procedures and something else was unintentionally detected—still an incidental finding. The psychological burden associated with a 'positive' finding is barely investigated so far and research in its infancy.[40] Patients found to be 'positive' with circulating tumour DNA (ctDNA) in a colorectal cancer study were reported to be more anxious about recurrence compared with those with a negative liquid biopsy/ctDNA test.[41] In a Canadian pilot study, participants were enthusiastic about ctDNA's potential to be comprehensive (detect multiple cancers), predictive (detect cancers early) and tailored (lead to personalised clinical management). Participants also acknowledged ctDNA's potential limitations, including false positive/negative risks and experiencing additional anxiety. However, they saw ctDNA's potential benefits outweighing its limitations. In conclusion, participants' belief in ctDNA's potential to improve their care overshadowed its limitations, indicating patients' support for using ctDNA in hereditary cancer syndromes care.[42] The consumer access to liquid biopsy tests will inevitably produce incidental findings and, in turn, trigger further investigations of which a significant number will be leading to normal findings rather than a tumour.

THE ETHICS OF INCIDENTAL FINDINGS IN LIQUID BIOPSY

Quite a few new biomarkers have changed the medical profession's understanding of diseases, some have emerged as key criteria for a diagnosis, and many had a profound impact on patients' lives. GPs as well as oncologists have learnt to deal with the most common biomarker of our time, the C reactive protein. It alerts to a broad variety of risks[43] and may trigger diagnostic procedures, prophylactic treatment or just attentive monitoring. For those organs not under the scheme of conventional cancer biomarkers or screening programmes, pan-cancer tests are advocated.[44] The more specific a biomarker, the more exact its statistically verified predictive value, the higher the efforts in diagnosis to clarify the suspicion it has brought up. At least that was the case until debates about long-term outcomes have changed the attitude towards a general screening for prostate cancer with prostate-specific antigen (PSA).[45] Since then, PSA has been used as an example for the potential dangers of overdiagnosis and overtreatment. In the case of pancreatic cancer, the facts and circumstances are dramatically different: overtherapy of an early tumour of the pancreas cannot be considered a risk under the same aspect as in the doctrine taught about PSA and prostate cancer. Pancreatic cancer is a life-threatening diagnosis. Yet another problem comes to the fore: the high morbidity and mortality related to pancreas surgery. Surgery for primary prostate tumour does not pose by far the risk of a pancreatoduodenectomy[46] or a pancreatectomy,[47] but pancreatic cancer turns out to be the common cancer with the lowest survival rate[48] and one of the top three causes of cancer death in the EU.[49–51] It has been declared a medical emergency 10 years ago.[52] The Bratislava statement and the United European Gastroenterology have, therefore, put the call for action on their banners.[51 53]

With next-generation sequencing becoming a commodity, the search for free DNA (ctDNA) will emerge as the most promising biomarker for the detection of pancreatic cancer in potential screening programmes. It will also be used as a marker to test patients in remission. The search for germline mutations might bring up further possibilities for the identification of individuals at risk.[54] For genome wide sequencing and other genetic testing, European and national laws codify limitations.[55] Guidelines have been published for different groups of patients.[56] Informed consent and the sovereignty of patients over their data are key issues.[57]

As early diagnosis with subsequent surgery is the best and often only option to save patients with pancreatic cancer, new biomarkers for an early detection will be greeted with great hope. It is promising as well as tempting to use them in big studies as soon as possible. With 1.5% of the population at risk, screening will be the next prospect. This might well also be the case with biomarkers with different levels of reliability and

Box 1 Points to consider for further studies in biomarkers (liquid biopsy) for pancreatic cancer

- ⇒ New biomarkers can create confusion.
- ⇒ New biomarkers can force new diagnostic procedures to be implemented and they can challenge old certainties.
- ⇒ The emergency situation (rising case numbers, high mortality rate, good outcome of surgery after early diagnosis) can justify the broad use of biomarkers with high sensitivity.
- ⇒ Biomarkers with low reliability might have to be accepted.
- ⇒ Informed consent does imply the information about the risks of pancreatic surgery.
- ⇒ Stakeholders and patient's organisations are to be involved.
- ⇒ Patients with suspicious biomarkers will need long-term professional care and surveillance even if no tumour can be found.
- ⇒ Despite the low survival rates and the benefit of most patients from early diagnosis, overdiagnosis and overtreatment could result in a small fraction of patients.
- ⇒ The value of biomarkers has to be monitored contagiously. Certified centres are to coordinate the development of procedures and the dissemination of knowledge.

specificity.[58] Potential pitfalls are as obvious as the reward.

How should we proceed with a biomarker that will detect pancreatic cancer correctly in 90% of the cases, while with 10% of the patients tested positive for the marker, no tumour can be detected? Ethical considerations are the opposite of straightforward resolutions. Ethics is only the theory of best practice; it does not provide decision-making schemes. There are remarkable approaches to similar cases, as biomarkers are on the advance in many fields. One is the involvement of stakeholders.[50] This has been tried in a most remarkable project in anticipation of the development of a test for Alzheimer's disease (AD). The increasingly early and highly sensitive prediction of AD with the help of biomarkers triggers discussions on many levels: about the right to know and not to know about employment and social law, about data security and about the legitimacy of a predictive diagnosis without the prospect of therapeutic options. Very soon commercial hands-on tests can predict AD and they are on the brink of being launched. In predictive governance, a publicly funded research group was founded in Germany to identify stakeholders and to issue a statement that defines the framework conditions under which such tests could be implemented. Some are also relevant for pancreatic cancer: the certification and monitoring of laboratories in close connection with research and guidelines and the implementation of guidelines for patient counselling.[59]

Biomarkers might emerge as the most frequent method soon, with which findings of (early) pancreatic cancer come to light. With its rising incidence and high mortality, this leads to an urge to use tests with a high sensitivity, even if their reliability and specificity might be low. In the light of the lives saved by early detection, this risk of overdiagnosis may be acceptable for a wide range of patients. Usually, it takes time and thorough discussions before an agreeable and scientifically evaluated code of conduct for the interpretation of new biomarkers is established. Biomarkers will broaden the gap between a worrying finding and a diagnosis requiring treatment. Insecurity and concern on the side of patients and their relatives must be taken seriously and resources to meet them professionally should be added to the costs of further studies. Investigating individuals at risk partaking in a surveillance programme for pancreatic cancer, we learnt that there is a high level of anxiety.[60 61] Patients with susceptible markers but without further evidence for pancreatic cancer should stay under surveillance. Long-term supervision by one and the same person should be ensured. Transmitting findings to the patient will become increasingly difficult, depending on the reliability of biomarkers and individual schemes of diagnostics. Training of professionals is required. Test evaluation, patient information and diagnostics will have to take place under certified conditions. Therefore, several aspects must be taken into consideration with biomarkers for pancreatic cancer (box 1).

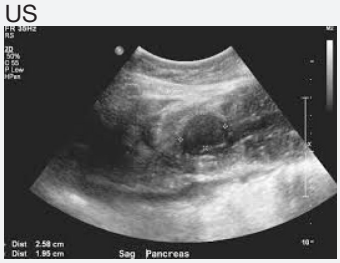
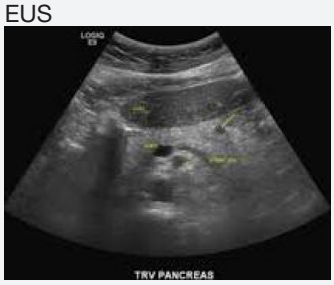
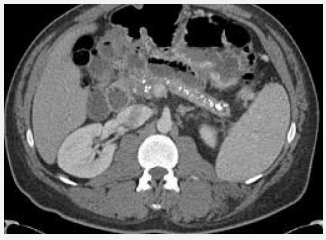
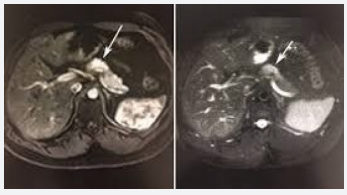
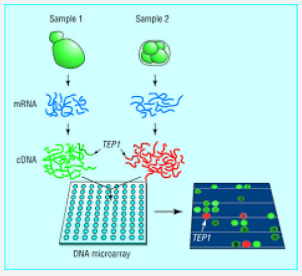
EXISTING GUIDELINES

The absence of guidelines for the management of incidentalomas in the pancreas and duct had been criticised frequently in the past,[4] which has profoundly changed within the last decade. Though it must be noted that guidelines have not been imposed in general. They react to the methods on which the findings rely. The high number of pancreatic cysts diagnosed in MRI and CT imaging found a clear response. The white paper by the American College of Radiology Incidental Findings Committee[62] can be summarised as follows: What grows is biopsied, and what measures over 2.5 cm is also biopsied. All findings below 2.5 cm are checked once for possible growth and then followed up at long intervals of up to 10 years depending on size. This paper has been discussed very controversially and European radiologists consider it wrong. In the aftermath clinicians called for further evaluations of the suspected structures with a variety of methods.[63] These recommendations are similar to guidelines for pancreatic cystic neoplasms (IPMN)[28]—the most found incidental finding in the pancreas.

CONCLUSION

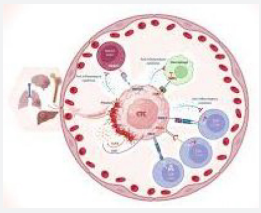
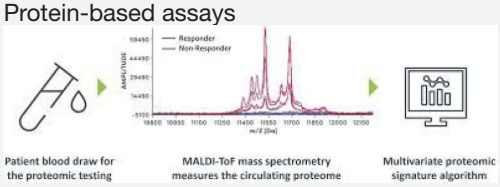
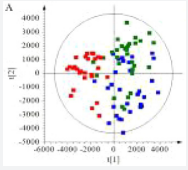
Incidental findings of pancreatic cancer experience an epistemological turn. By definition, incidentalomas or additional findings were closely related to the diagnostic process that brings them to light. The existing literature is dominated by the question on how to deal with medical images susceptible to pancreatic cancer. The diagnostic systems technically channel most of the further steps, for example, measuring a cyst, observing its growth, etc.

Table 2 Comparison of traditional, imaging-based findings of pancreatic incidentalomas with the liquid-biopsy-based detection assays

Method	Advantage	Disadvantage	Costs
Postmortem	'Ground truth' of a pancreatic lesion	Not population-based, small denominator No longer used/not of use to the patient	$
US 	Simple, non-invasive	Visualisation of the entire gland difficult Not population-based, small denominator	$
EUS 	Highest resolution closest to the gland	Invasive Not population-based, small denominator	$$
CT 	Good visualisation of the entire gland With proper protocol sensitive for lesions≥1 cm	Radiation Not population-based, small denominator	$$
MRI 	Good visualisation of the entire gland With proper protocol sensitive for lesions≤1 cm	Expensive Not population-based, small denominator	$$$
ctDNA 	Small blood sample needed	Tumour-agnostic testing may miss PDAC but is likely the test to be offered to healthy individuals Tumour-specific testing not suitable for searching any tumour—private mutations needed	$

Continued

Table 2 Continued

Method	Advantage	Disadvantage	Costs
CTC 	FDA-approved tests are available Captured CTC can be further analysed (NGS)	Especially PDAC is known to have the lowest number of CTCs of all solid tumours Special tubes/equipment needed or sent for service	$$
Protein-based assays 	Small blood sample needed	Tumour-agnostic testing may miss PDAC but is likely the test to be offered to healthy individuals	$$
Metabolomics 	Small blood sample needed Takes into account the host reaction to the tumour	Tumour-agnostic testing may miss PDAC but is likely the test to be offered to healthy individuals	$$

All images from bmj.com.
CTC, circulating tumour cells; EUS, endoscopic ultrasound; FDA, Federal Drug Administration; NGS, next-generation sequencing; PDAC, pancreatic ductal adenocarcinoma.

The shift comes from the patient's side. Medical imaging and more invasive diagnostic procedures such as EUS are used to diagnose individuals at risk. However, liquid biopsy adds a new dimension if used in a consumer-driven attitude and will inevitably produce also incidental findings triggering follow-up. However, at the same time, non-invasive liquid biopsy tests (or panels as developed within PANCAID) also hold the potential to further validate incidental findings derived from medical imaging. Both imaging-based (CT, MRI) and blood-based (liquid biopsy) tests have pros and cons when hitting an incidental finding (table 2).

In the future, artificial intelligence-triggered image analysis will help to identify incidental pancreatic lesions, even on native and/or venous phase scans[64] or on prediagnostic scans preceding the clinically overt diagnosis.[65] Indeed, another EU project (PANCAIM) is precisely thriving for this very important task.[66]

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Contributors J-ML and PO designed this work, MV and NK contributed and edited the manuscript.

Funding Funded by the European Union, PANCAIM (101016851) on the early detection of pancreatic cancer and PANCAID (101096309) on the use of liquid biopsy. Views and opinions expressed are however those of the authors only and do not necessarily reflect those of the European Union or European Health and Digital Executive Agency (HADEA). Neither the European Union nor the granting authority can be held responsible for them.

Competing interests J-ML is an Editorial Board Member for eGastroenterology.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

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