

## Imaging Symptoms in Other Cancers Which Can Be Used for Early Detection of Pancreatic Cancer

Atanas Hilendarov\*, Georgiev A and Chervenkov L

Department of Diagnostic Imaging, MU Plovdiv, Bulgaria.

### \*Correspondence:

Atanas D Hilendarov, Associate Professor, Department of Imaging Diagnostics, Medical University- Plovdiv, Bulgaria, Mobile: +359 888332642.

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### ABSTRACT

*The implementation of effective early detection programs has significantly improved treatment, prognosis, and life expectancy in breast, prostate, and colorectal cancers. Early-detection methods need to be developed for pancreatic ductal adenocarcinoma (PDAC), where progress during the past decades has remained slow.*

**Aim:** *The aim is to find and implement effective programs for early detection and significant improvement of treatment, prognosis and life expectancy in pancreatic cancer.*

**Material and Methods:** *We traing to use the experience from breast cancer, prostate cancer, and colorectal cancer to develop methods for early detection of pancreatic ductal adenocarcinoma (PDAC). A major breakthrough in early detection of PDAC will occur only through an interdisciplinary collaborative effort involving a critical mass of committed academic research institutions.*

**Results and Discussions:** *Pancreatic ductal adenocarcinoma (PDAC) has a devastating prognosis. Individuals and families face a bleak future and struggle with the lack of understanding of the disease, its etiology, and the dearth of treatment options. The 5-year survival rate of PDAC is only 8%, making it one of the deadliest human cancers [1,2]. Major breakthroughs are urgently needed in early diagnosis, treatment, and the eventual prevention of PDAC.*

**Conclusion:** *It is clear that in other cancers, the implementation of effective early detection programs has significantly improved treatment, prognosis, and life expectancy. It is imperative that effective early detection methods be developed for PDAC.*

### Keywords

Atanas Hilendarov, PDAC, Breast cancer.

### The Aim

#### Historical Trends in Cancer

When considering all cancer sites (all races, both sexes, ages older than 50), the 5-year death rate from 2008–2012 fell by 1.5% in the United States [3]; every state reported a falling cancer death rate [3]. Downward trends in mortality were reported in breast (women, -1.8%), colon and rectum (-3.1%), lung and bronchus (-2.1%), ovarian (-2.3%), and prostate cancers (-3.6%).

Tipping points for downward trends in these cancers a rebelieved to reflect both advances in early-detection procedures and more effective treatment. As an example, the prostate-specific antigen (PSA) test for prostate cancer received Foodland Drug Administration approval in 1986 as a monitor for treatment response and disease recurrence. In 1994, it was approved as a screening aid for diagnosis. Subsequently, the mortality rate for prostate cancer began to fall. Pancreatic ductal adenocarcinoma remains the sole major cancer whose mortality rate is rising; the 5-year death rate for PDAC in the United States rose by 0.4% during the 2008–2012 period [4-6]. Furthermore, the annual death rate attributed to PDAC is rising in 16 US states [6].

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## Material and Methods

### Challenges to Early Detection of PDAC

The hallmarks of PDAC are late onset of symptoms and subsequent rapid progression to death and are the principal reasons for its high mortality and low survival rate [7]. The primary challenges to developing early-detection methods for PDAC are clearly evident. Typically, PDAC presents in an advanced stage of the disease process making successful treatment challenging [8]. Traditional imaging has not been an effective tool for early-stage diagnosis of PDAC, and only invasive measures such as endoscopic ultrasound (EUS) are currently available to locate early disease. No validated biomarkers exist that can be used to diagnose early-stage PDAC. Thus, the death rate for patients with PDAC continues to rise.

## Results and Discussions

### Lessons Learned from Breast, Prostate and Colorectal Cancers

Mammography, PSA, and colonoscopy tests have had a major impact on the reduction in mortality rates in breast, prostate, and colorectal cancers, respectively. It is generally agreed that early diagnosis is the standard for these cancers and thus results in improved efficacy of available treatment strategies. This was not always the case. Before the 1990s in the United States, mortality rates for these cancers were high. Survival rates were notably impacted after the introduction of early-screening tests and protocols in all 3 cancers. Whether there is a direct cause and effect between screening tests and mortality remain controversial in prostate cancer; however, the downward trend lines for incidence and mortality are significant [9-17].

The correlation between the stage at which these cancers are detected and cancer-specific survival rates is notable. When colorectal cancer is diagnosed in Stages I or II, the 5-year survival rate is 90%; if diagnosed in Stage IV, the 5-year survival is only 13% [18]. Yet, only 58% of the eligible population is screened today with colonoscopy because of factors such as medical need, preparation, cost, and time [19]. A recent program instituted with a home-collection stool-based test shows improvement in the frequency of screening, with 73% of individuals complying.

The subsequent implementation of PSA screening changed the demographics of the newly diagnosed prostate cancer patient and together with the introduction of more effective treatments, resulted in a dramatic shift in statistics.

Although the PSA test is somewhat controversial today because of potential for over diagnosis of nonlethal prostate cancer, it is generally considered to be a “very good marker, although not perfect. There is indication that it is best to screen smarter by testing most men less often and focusing more on those identified as being at high risk. From 1975 through the 1980s, breast cancer mortality rates in the United States increased. Then, after the improvement’s in early detection and subsequent earlier treatment, breast cancer mortality decreased by 36% [20-23]. Mammography screening rates have increased in the past 3 decades and, thus, more cases of breast cancer have been detected at earlier stages. There is a consensus that mammography detects breast cancer at

a point where treatment strategies make a difference. Currently, the 5-year survival rate for breast cancer is 90%, with 95% of patients undergoing surgery [1]. However, the biology of breast cancer is varied, and there are clearly subtypes of breast cancer where progress has not been significant. During the past decade or more, it has become increasingly apparent that the density of breast tissue on mammography is variable, ranging from fatty to extremely dense. Women with dense breasts are at a disadvantage in mammographic screening because significant lesions are obscured by dense breast tissue. The phenomenon of dense breasts has led to the development and use of advanced imaging techniques such as magnetic resonance imaging and mammographic tomosynthesis because mammography is not as effective with this type of tissue. Aggressive subtypes often escape detection because of density tissues that mask cancer. Newer imaging approaches that are more sensitive, such as tomosynthesis, decrease recall rate and increase earlier detection. Yet, imaging tests are confounded by multiple variables including tumor characteristics, available equipment, interpretation by the readers, and cost. These problems apply particularly to the more aggressive biologic sub-types of breast cancer, which are more frequently diagnosed in younger women. Research is underway to identify circulating markers that may serve as a first filter to compensate for limitations of mammographic imaging, and select these women for screening with more advanced imaging technologies [24,25]. Lessons from these more aggressive breast cancer subtypes may be more applicable to the pancreatic cancer field; namely, the use of a first filter test, and the strategies of applying advanced imaging technologies.

Improvements in technologies and clinical advancements continue to progress in breast, prostate, and colorectal cancers. A primary message from the forum experts is that collaboration among all stakeholders is critical to the development of an early-detection strategy for PDAC. Academic researchers, government, industry, and philanthropy need to engage together to move forward. Simultaneous initiatives are occurring that, if folded into an intentional collaborative system, will lead to significant impact on early detection for PDAC. Efforts to identify high-risk subgroups that may be defined by ethnic and genetic background are garnering attention throughout the field. Similarly, there is continued progress in understanding the biology of the disease and to identify at-risk conditions such as smoking, obesity, chronic pancreatitis, and long-standing diabetes, as well as the link between weight loss, new-onset diabetes, fatigue, and depression preceding diagnosis of PDAC [26].

To initiate a screening trial for PDAC, high-risk groups (HRGs) need to be identified, potential biomarkers selected, and blood and plasma samples collected. Early engagement with government agencies is a priority in determining the path that must be followed throughout the regulatory process for an off-the-shelf cancer screening assay. Such a trial will not provide all the answers; however, it is a starting point that will serve as a vehicle for future studies.

Acceptance is increasing that a pan-cancer approach and looking

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across multiple cancer genomes is beneficial [27]. It is conjectured that there are shared molecular patterns among cancers, which may eventually result in analyzing cancers according to their genomic profiles rather than by their organ of origin or their stage. Minimally invasive liquid biopsies and tumor-activable mini circles are other potential pan-cancer diagnostic approaches [28]. Although continually evolving, screening tests in breast, prostate, and colorectal cancers have changed disease outcome. Applying these lessons to PDAC is critical to improve survival for individuals diagnosed with this disease

## **Conclusion**

### **Strategic Approach for the Future**

#### **Leadership**

A visionary group should provide leadership of a global collaborative effort involving intentional representation of key stake-holders, an open approach to new ideas within the field of early detection, and credibility in leading individuals with diverse expertise. The strategic facilitation of invested representatives from academic research, government, industry, and philanthropy will result in foundational and organizational support for a multidimensional approach to early detection of PDAC. The ultimate goal is to develop an evidence-based strategy for early detection that is broadly applicable.

#### **Organizational Structure and Business Planning**

Strategic collaboration, communication, and identification of resources are critical components of the organizational structure necessary to accomplish the underlying research to establish an early-detection protocol. Commitments from academia, Government, industry, and philanthropy are essential to the design of a research and development plan, with an early cost/benefit analysis as a factor. Both short-term and long-term business goals must be articulated. Although biotechnology companies engaged in biomarker development are intuitively part of such an effort, it is important to emphasize that companies that are active in the treatment space should be engaged as well because they are most likely to benefit from the increased survival of PDAC patients and their requirements for ongoing pharmaceutical support. The involvement of government agencies will be beneficial through their advisement regarding mandatory processes and procedures in developing a new early-detection method. In addition, attention to legal and finance elements, risk management, marketing and communication, and the development of partnership and alliance relationships are necessary to further the work of collaborative research teams and the translation to clinical practice.

#### **Funding and Partnerships**

Long-term sustainable funding is possible through committed partnerships and alliances to support global efforts, garner resources, and enhance visibility within and for the field of early detection. Purposeful cooperation and collaboration are developing within the philanthropic community supporting PDAC initiatives. A further deliberate collaborative investment approach involving Industry, government, and philanthropic entities is an essential next step.

## **Research Operations and Initiatives**

Multiple research priorities are currently being supported, with expectations of impact in the development of effective methods for early detection. It is estimated that more than 2000 studies of research-grade biomarkers in PDAC have been published, involving more than 2600 different gene and protein expression studies [29,30]. Serum carbohydrate antigen 19-9 (CA-19-9) is the only Food and Drug Administration–approved blood test for PDAC [30]. The CA 19-9 provides valuable information with regard to prognosis, overall survival, and response to treatments well as predicting postoperative recurrence [31]. However, it has been limited as a screening tool by its poor sensitivity, false-negative results, and increased false positivity when obstructive jaundice is present. Currently, none of the biomarkers have proven accurate enough to use as a diagnostic tool on the population level. It is anticipated that in the complicated field of early detection of sporadic PDAC, the partnering of research institutions specializing in PDAC studies with industry will afford the opportunity to share expertise and resources. The committed collaboration of various scientific and clinical disciplines must be championed to move the field from traditional silos of research.

## **Emerging Opportunities for Scientific Advancement**

Progress has been achieved in each of the 4 components of the Strategic Map for Innovation during the past year. Current priorities focus on identifying emerging opportunities for scientific advancement that hold the greatest promise for the future of early detection in PDAC. A roadmap of action items for the next 10 years includes 1: Identifying existing and novel biomarkers of early Practicelike: 1 to 10 years. 2: Validating promising existing and new biomarkers in retro-spectate samples: Timeline: 1 to 3 years. 3: Assembling a prospective high-risk cohort for sporadic Practicelike: 1 to 10 years. 4: Initiating a prospective screening study: Timeline: 1 to 10 years.

**Identifying Existing and Novel Biomarkers of Early PDAC: Timeline: 1 to 10 Years**  
**In Silico Purge of Existing Biomarkers**  
Numerous biomarkers have already been identified with widely varying levels of rigor in testing and validation. A thorough investigation of biomarkers that have been studied in early-stage PDAC needs to be initiated. This will involve a group of biostatisticians and independent researchers using predetermined levels of evidence to curate a panel of biomarkers that meet threshold for validation studies. Researchers will then participate in a think tank organized by philanthropy and governmental agencies to determine the final selection of biomarkers that are targeted for further validation. This in silico purge of existing biomarkers will identify those that are ready for validation in pre-symptomatic samples identified in action item no. 2. This is required because the retrospective sample resource is limited in number and sample volumes.

**Identifying Novel Biomarkers of PDAC**  
Emerging novel technologies promise to provide previously untested approaches to early detection. Some are in nascent stages of development and others are yet to be discovered. The National Institutes of Health has reviewed the first round of applicants for its recently launched

“Pancreatic Cancer Detection Consortium (U01)”. The goal of the request for application is to establish multidisciplinary teams of researchers and clinicians to establish the Pancreatic Cancer Detection Consortium to conduct research to improve the detection of early-stage PDAC and characterization of its precursor lesions. Concomitantly, in an unprecedented effort, the National Institute for Diabetes and Digestive and Kidney Diseases and National Cancer Institute (NCI) have collaborated to support another U01 consortium to study the relationship among diabetes, PDAC, and chronic pancreatitis. These 2 consortia have complementary strengths and address 2 critical areas as identified by the NCI as priorities for PDAC research, namely, (1) Understanding the biological relationship between PDAC and diabetes mellitus (DM) and (2) Evaluating longitudinal screening protocols for biomarkers for early detection of PDAC (<http://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/PDACframework.pdf>). It is critical to align and support these efforts to leverage their strengths for maximal benefit to the field of early detection. Validating Promising Existing and Novel Biomarkers in Retrospective Samples: Timeline: 1 to 3 Years Promising biomarkers identified in action item #1 and any novel markers that meet the predetermined criteria should be tested in pre symptomatic samples from various cohorts (from no. 2a).

A “bakeoff” in the pre symptomatic cohort will help identify a panel of 3 to 5 biomarkers that consistently demonstrate the ability to accurately identify PDAC in pre diagnostic cohorts. Assembling a Prospective High-Risk Cohort for Sporadic PDAC it is well recognized that it is not cost-effective to screen for PDAC in the general population; thus, screening will initially have to be confined to HRGs with significantly higher-than-average risk of PDAC. An HRG for PDAC could be defined as a cohort in which subjects are at 6 to 8 times higher risk of having PDAC compared with age-matched controls. This is similar to the risk of PDAC in subjects with 2 first-degree relatives with PDAC, which is currently the cohort that is screened for familial PDAC. Currently, new-onset diabetes in subjects older than 50 years (NoD cohort) is the only established HRG for sporadic PDAC. Although there are a number of lifestyle factors (eg, smoking), demographic features (eg, age >50 years), and comorbidities (eg, obesity, long-standing diabetes) that modestly (1.5-fold to 2-fold) increase the risk of developing PDAC, only NoD reaches the risk threshold for the HRG noted above.<sup>32</sup>In contrast to long-standing DM, which is a modest risk factor for PDAC, NoD is actually a biomarker for an occult asymptomatic cancer that has not yet manifested clinically. Compared with the age-matched general population, subjects older than 50 years who newly develop diabetes have 6-fold to 8-fold higher probability of being diagnosed with PDAC within 3 years of meeting criteria for diabetes [32,33]. This group is estimated to be approximately 1 million people per year [34] and accounts for approximately 25% of those diagnosed with PDAC. Assembling a cohort of 10,000 subjects with NoD will identify approximately 100 subjects with PDAC. This is an important and urgent initiative that requires immediate implementation. A consortium of approximately 10 to 15 centers, including large Health Maintenance Organization and community networks is required to assemble a HR cohort in which samples from pre-

symptomatic early-stage PDAC can be collected. The current NCI-National Institute for Diabetes and Digestive and Kidney Diseases consortium to study chronic pancreatitis, diabetes, and pancreatic cancer (<http://cscpdpc.mdanderson.org/>) is an ideal opportunity to assemble such a cohort and collect prospective samples from a cohort at high risk for sporadic PDAC.

**Initiating a Prospective Screening Study** Initiating a Prospective Screening Study Using Existing Tools it is important to start a longitudinal screening study for PDAC even with existing tools. Because it is an uncommon cancer, the screening strategy for PDAC will differ significantly from that of other major cancers. There are many lessons to be learned regarding the logistics of identifying high-risk subjects for PDAC, and these efforts should run parallel to efforts to identify clinically validated biomarkers and imaging approaches to early detection. A recommended conceptual framework for screening for PDAC is a prospective 2-sieve approach that includes 3 corephases: define, enrich, and find (Figure 2) [29]. Specifically, the paradigm recommends that investigators define HRGs for PDAC (first sieve), enrich these cohorts further for PDAC (second sieve), and find the actionable lesion(s). The NoD cohort could be used to test this conceptual framework. This will require enriching the NoD cohort for PDAC using a second sieve.

A biomarker or a panel of biomarkers specific for PDAC will further enrich the new-onset diabetes cohort 2-fold to 3-fold. The utility of an elevated CA 19-9 in the screening setting needs validation. It is also unclear if a rising CA 19-9, albeit within normal limits, could signal the presence of PDAC. It has been shown that whereas late onset of type 2 diabetes is associated with weight gain, diabetes in PDAC is paradoxically associated with weight loss that precedes onset of diabetes, suggesting that weight loss before onset of diabetes may be a predictor of PDAC. Thus, weight loss, elevated CA 19-9, or a yet-to-be-defined biomarker alone or in combination could act as a second sieve. In prospective screening studies using such a 2-sieve approach, the PDAC prevalence has been 3% to 7%. This compares favorably with the yield of screening colonoscopy for colon cancer. In a study of 13,992 asymptomatic patients who had screening with colonoscopy, 135 (0.9%) had invasive cancer or high-grade dysplasia and 7.3% had advanced neoplasia (tubular adenoma  $\geq 10$  mm, adenoma with villous histology, high-grade dysplasia, or invasive cancer).

Because the actionable lesion will require surgery for removal, its presence will, in all likelihood, need biopsy confirmation. The use of more invasive technology to histologically confirm the diagnosis, such as EUS with biopsy, would be needed in the third phase of finding the high-risk lesion. This assumes that the actionable lesion will be visible or obvious on EUS. However, in the familial pancreatic cancer setting, significant background noise due to chronic pancreatitis-like changes has proven to be a major hurdle to finding the high-risk lesion. The recent description of exocrine pancreatopathy (chronic pancreatitis-like changes) in diabetes [36] suggests that similar difficulties may plague EUS identification of high-risk lesions in patients with NoD. Overcoming this will likely

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require an imaging test that can localize the lesion to allow EUS-directed biopsy. Additional investments and support for developing imaging biomarkers and novel imaging techniques is essential to localize small high-risk lesions in presymptomatic patients, which cannot be currently identified using conventional imaging

Testing Biomarkers Validated in Retrospective Presymptomatic Samples and Novel Imaging Techniques in the Prospective Screening Study Prospective validation of biomarkers in HRGs is critical but will need to be linked to imaging studies that can calibrate risk. Patients with abnormal biomarker results will require imaging studies. The prospective NoD cohort can be used to test novel biomarkers, biochemical, molecular, and imaging in a prospective study.

### Summary

A major discovery in the study of early detection in PDAC will occur only when an interdisciplinary collaborative effort is used. The urgency of this need must drive a renewed commitment by key stakeholders for subsequent innovation. Notable progress in other cancer fields, particularly the strides made in early detection of breast, prostate, and colorectal cancers, provide benchmarks for the necessary breakthrough progress that will impact the PDAC field. It is time to apply this knowledge to achieve large-scale change. Bold steps must be taken to move the field forward from an epidemiologic perspective, through an advanced understanding of the biologic etiology of the disease, by the use of new models of identified HRGs for screening studies, and with the application of knowledge developed in other scientific fields. Patients diagnosed with PDAC and their families are desperate for progress in early detection. The pace of scientific and clinical innovation must increase. In addition to identifying the disease in its preliminary stages, these advancements will then impact the development of more effective treatment modalities to be administered during earlier stages of tumor development. This progressive influence on the field will have long-lasting effects on the quality of life and survival of the diagnosed individuals. Building on the knowledge that cancer is fundamentally a genomic disease, similarities and differences among genomic and cellular alterations in tumors are being investigated. Data suggest that cancers of disparate organs may actually have common cellular features as well as shared molecular patterns across tumor types. Congruently, cancers in the same organ may have molecular differences. The findings from genomic research will inform early detection in PDAC efforts as well as all cancer diagnosis and treatment. An HRG and numerous biomarker candidates related to PDAC have been identified for ongoing study.

Assembling the HRG for bio sample collection and identifying existing clinically annotated cohorts must be initiated rapidly. Large-scale validation studies are then necessary to determine which minimal biomarker panel would be most appropriate for screening. Using the prospective 2-sieve approach as a conceptual model for screening research will enrich the HRG and move toward cost-effective screening. Parallel research needs to further consider such factors as geographic location, smoking, obesity,

demo-graphic features, age, diabetes, and elevated levels of depression before diagnosis. A critical mass of committed research institutions, industry leaders, academic partners, government agencies, and key philanthropies must join together to accelerate advancements in early detection. For far too long, siloed efforts have stagnated progress and limited the creation of essential new knowledge. Recognition of the economic factors of research and development, treatment, and ongoing patient care is also critical in the large-scale planning for screening and early detection. The collective and ultimate outcomes of determining and implementing early-detection methods are focused on a better future for patients, their families, science, and medicine. The impact of improving quality of life, treatment options, and survival for those individuals diagnosed with PDAC will be immense. When this disease is classified as a chronic disease rather than a devastating deadly diagnosis, it will be said that success has been achieved.

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