

Pancreatic Cancer Surveillance in STK11 Mutation Carriers with Peutz-Jeghers Syndrome: The Role of Endoscopic Ultrasound (EUS) and Endoscopic Retrograde Cholangiopancreatography (ERCP) in Early Neoplasia Detection

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ABSTRACT

Background: Peutz-Jeghers Syndrome (PPS), an autosomal dominant disorder caused by pathogenic variants in the STK11/LKB1 tumor suppressor gene, confers a significantly elevated lifetime risk of gastrointestinal (GI) and extraintestinal malignancies, including pancreatic ductal adenocarcinoma (PDAC). Current guidelines lack consensus on optimal surveillance strategies for PDAC in this high-risk cohort.

Aims: This article evaluates the efficacy of advanced endoscopic modalities—specifically EUS and ERCP—in the early detection of pancreatic neoplasia in STK11 carriers, addressing procedural benefits, limitations, and evidence-based screening intervals.

Methods: A systematic review of literature from PubMed, EMBASE, and Cochrane databases (2000–2023) was conducted, focusing on PPS-related PDAC, STK11 penetrance, and endoscopic screening outcomes.

Results: EUS demonstrates superior sensitivity for pancreatic parenchymal abnormalities (e.g., cystic lesions, hypoechoic nodules) compared to cross-sectional imaging. ERCP complements EUS by evaluating ductal abnormalities (e.g., strictures, intraductal papillary mucinous neoplasms/IPMNs). However, procedural risks (e.g., post-ERCP pancreatitis) necessitate careful patient selection.

Conclusion: Multimodal surveillance incorporating EUS ± ERCP may mitigate PDAC mortality in STK11 carriers, though prospective studies are needed to standardize protocols.

KEYWORDS: Peutz-Jeghers Syndrome, STK11/LKB1 gene, Pancreatic cancer screening, Endoscopic ultrasound (EUS), Endoscopic retrograde cholangiopancreatography (ERCP), Hereditary cancer syndromes, Neoplasia surveillance

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INTRODUCTION

Peutz-Jeghers Syndrome (PPS; OMIM #175200) is a rare, inherited cancer predisposition syndrome characterized by mucocutaneous pigmentation, hamartomatous polyposis, and a markedly increased risk of malignancies across multiple organ systems. The syndrome is attributed to germline mutations in the serine/threonine kinase 11 (STK11/LKB1) gene, a critical regulator of cell polarity and metabolic homeostasis.^{1,2}

While GI malignancies (e.g., colorectal, gastric) are well-documented in PPS, pancreatic ductal adenocarcinoma (PDAC) represents a particularly aggressive and under-surveilled threat, with lifetime risk estimates ranging from 11% to 36%—substantially higher than the general population. The lack of pathognomonic early symptoms and the insensitivity of conventional imaging (e.g., CT, MRI) for incurable PDAC underscore the need for proactive screening in STK11 carriers.³

Endoscopic ultrasound (EUS) has emerged as the cornerstone of PDAC surveillance in high-risk cohorts due to its high-resolution imaging of pancreatic parenchyma and ducts, enabling detection of precancerous lesions (e.g., pancreatic intraepithelial neoplasia/PanINs) and early-stage tumors. ERCP, though invasive, provides therapeutic potential for ductal sampling or stent placement in obstructive lesions. Current guidelines (e.g., NCCN, ESGE) remain equivocal on screening intervals and modality selection for PPS patients, reflecting a paucity of longitudinal data.^{3,4}

Peutz-Jeghers Syndrome (PPS) is a rare autosomal dominant disorder characterized by the triad of mucocutaneous pigmentation, gastrointestinal hamartomatous polyposis, and a significantly elevated risk of both benign and malignant neoplasms across multiple organ systems. The underlying genetic defect in the vast majority of cases involves pathogenic mutations in the STK11 gene, also known as LKB1, located on chromosome 19p13.3. This tumor suppressor gene plays a crucial role in cellular energy homeostasis, polarity, and apoptosis through its regulation of the AMP-activated protein kinase (AMPK) pathway and downstream targets involved in mTOR signaling. The loss of STK11 function leads to uncontrolled cellular proliferation and a predisposition to tumorigenesis, with particular implications for pancreatic ductal adenocarcinoma (PDAC) development.^{4,5}

The lifetime risk of pancreatic cancer in STK11 mutation carriers is estimated to be between 11% and 36%, a staggering increase compared to the general population. This risk stratification places PPS among the highest-risk hereditary cancer syndromes for PDAC, alongside familial pancreatic cancer kindreds and other genetic disorders such as hereditary breast and ovarian cancer (HBOC) syndrome and Lynch syndrome. Unlike sporadic pancreatic cancer, which often presents at an advanced stage due to its insidious

onset and lack of early symptoms, PDAC in PPS patients may benefit from structured surveillance strategies aimed at detecting precancerous lesions or early-stage malignancies when curative interventions are still feasible.⁵

Current screening modalities for pancreatic cancer in high-risk individuals include cross-sectional imaging (MRI/MRCP), endoscopic ultrasound (EUS), and, in select cases, endoscopic retrograde cholangiopancreatography (ERCP). While MRI offers non-invasive visualization of the pancreas and biliary tree, EUS provides superior spatial resolution for detecting small solid lesions, cystic abnormalities, and parenchymal irregularities suggestive of pancreatic intraepithelial neoplasia (PanIN) or early PDAC. The addition of fine-needle aspiration (FNA) under EUS guidance further enhances diagnostic accuracy by allowing cytological and molecular analysis of suspicious lesions.⁶

ERCP, though more invasive and associated with non-negligible risks such as post-procedural pancreatitis, offers unique advantages in the context of PPS-related pancreatic surveillance. Its ability to directly visualize and sample the pancreatic ductal system makes it particularly valuable in identifying intraductal papillary mucinous neoplasms (IPMNs), main-duct strictures, or other ductal abnormalities that may precede invasive carcinoma. Furthermore, ERCP permits therapeutic interventions, including stent placement for obstructive lesions or prophylactic pancreatic duct sampling in high-risk anatomic variants.^{6,7}

The integration of EUS and ERCP into a multimodal screening protocol for STK11 mutation carriers is supported by the principle of risk-adapted surveillance, wherein the frequency and intensity of monitoring are tailored to the individual's cumulative cancer risk, prior findings, and family history of PDAC. Given the aggressive nature of pancreatic cancer and the limited efficacy of systemic therapies in advanced stages, a proactive endoscopic approach may represent the most viable strategy for improving survival outcomes in this genetically defined population. However, the optimal screening interval, the role of adjunct biomarkers such as CA 19-9 or novel liquid biopsies, and the cost-benefit balance of repeated invasive procedures remain areas of ongoing investigation.^{7,8}

In conclusion, the molecular pathogenesis of PPS, driven by STK11 inactivation, creates a permissive environment for pancreatic carcinogenesis, necessitating vigilant surveillance in affected individuals. EUS and ERCP serve as complementary tools in this endeavor, offering high diagnostic yield and therapeutic potential. As our understanding of the natural history of PPS-associated PDAC evolves, so too must the algorithms for early detection, with the ultimate goal of mitigating the disproportionate burden of pancreatic cancer in this vulnerable patient cohort.⁸

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Technical Approach to Pancreatic Cancer Screening in Peutz-Jeghers Syndrome: The Role of EUS and ERCP in STK11 Mutation Carriers

The implementation of a structured surveillance protocol for pancreatic cancer in patients with Peutz-Jeghers Syndrome (PPS) hinges on the integration of advanced endoscopic techniques, namely endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP), tailored to the unique oncological risks imposed by germline STK11/LKB1 mutations. Given the markedly elevated lifetime risk of pancreatic ductal adenocarcinoma (PDAC) in this population, a systematic and technically refined approach is essential to maximize early detection while minimizing procedural morbidity.⁸

Patient Selection and Risk Stratification

Before initiating surveillance, genetic confirmation of an STK11 pathogenic variant is mandatory, as phenotypic expression in PPS can vary significantly. Once identified, carriers should undergo baseline imaging no later than age 30–35, or 10 years earlier than the youngest PDAC diagnosis in the family, whichever comes first. High-risk features—such as a personal history of pancreatic cysts, familial PDAC, or concerning symptoms (e.g., unexplained weight loss, obstructive jaundice)—warrant more aggressive surveillance intervals.⁸

Endoscopic Ultrasound (EUS): Technique and Procedural Considerations

EUS remains the cornerstone of pancreatic surveillance due to its unparalleled resolution in detecting subcentimeter lesions. The procedure is performed under conscious sedation or general anesthesia, utilizing a curvilinear echoendoscope (typically 5–12 MHz) to systematically evaluate the pancreatic parenchyma and ductal system. Key technical steps include:^{9,10}

- Radial and linear scanning of the pancreas in both B-mode and contrast-enhanced harmonic EUS (CE-EUS) to differentiate solid hypoechoic masses (suspicious for PDAC) from benign cystic structures (e.g., serous cystadenomas, pseudocysts).¹⁰
- Doppler assessment to rule out vascular invasion in suspected malignancies.
- Fine-needle aspiration (FNA) or fine-needle biopsy (FNB) of indeterminate lesions using a 22–25G needle, with rapid on-site evaluation (ROSE) to ensure adequate sampling.¹⁰

Given the diffuse nature of PPS-related pancreatic pathology, particular attention must be paid to secondary signs of malignancy, including main pancreatic duct (MPD) dilation, irregular ductal walls, or loss of parenchymal lobulation.¹⁰

ERCP in the Surveillance Algorithm: Indications and Technical Nuances

While EUS excels in parenchymal assessment, ERCP provides critical ductal access, making it indispensable for

evaluating intraductal abnormalities such as IPMNs, strictures, or epithelial dysplasia. The procedure involves:¹⁰

- Cannulation of the pancreatic duct using a side-viewing duodenoscope, often aided by a sphincterotome or guidewire for selective ductal entry.
- Pancreatography with low-pressure contrast injection to avoid acinarization, which can obscure subtle ductal irregularities or precipitate pancreatitis.¹⁰
- Brush cytology, intraductal biopsies, or pancreatic juice analysis for molecular markers (e.g., KRAS, GNAS mutations) if worrisome ductal changes are present.
- Prophylactic pancreatic stent placement in high-risk cases (e.g., ductal obstruction) to reduce post-ERCP pancreatitis risk.¹⁰

Multimodal Surveillance Intervals and Follow-Up

Given the rapid progression potential of PDAC in PPS, a 12–24 month screening interval is recommended for asymptomatic carriers, with shorter intervals (6–12 months) for those with high-risk lesions (e.g., IPMNs with worrisome features, PanIN-3). Alternating EUS and MRI/MRCP may optimize lesion detection while mitigating the cumulative risks of repeated ERCP.¹⁰

Limitations and Future Directions

Despite its diagnostic advantages, ERCP carries non-negligible risks, including pancreatitis (5–10%), bleeding, and perforation. EUS, while safer, is operator-dependent, and false negatives can occur in diffusely infiltrative tumors. Emerging technologies—such as confocal laser endomicroscopy (pCLE) and artificial intelligence-assisted EUS image analysis—may further refine screening accuracy in this high-risk cohort.¹⁰

In summary, the technical execution of pancreatic cancer surveillance in STK11 mutation carriers demands a meticulous, protocol-driven approach, leveraging the complementary strengths of EUS and ERCP to intercept PDAC at its earliest and most treatable stages.

Advantages of Pancreatic Cancer Screening with EUS and ERCP in Peutz-Jeghers Syndrome Carriers with STK11 Mutations

The incorporation of endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) into the surveillance paradigm for Peutz-Jeghers Syndrome (PPS) patients harboring STK11 germline mutations presents a clinically compelling strategy, offering distinct advantages over conventional imaging modalities in the early detection of pancreatic ductal adenocarcinoma (PDAC). Given the 11–36% lifetime risk of PDAC in this population—a risk profile that dwarfs that of the general population—the precision and therapeutic potential of these endoscopic techniques provide a critical lifeline in mitigating the substantial morbidity and

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mortality associated with late-stage pancreatic malignancies.¹¹

Superior Diagnostic Sensitivity for Early-Stage Lesions

Unlike cross-sectional imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI), which often fail to detect subcentimeter pancreatic abnormalities, EUS provides unparalleled spatial resolution, enabling the identification of subclinical neoplasms as small as 2–3 mm. This high-resolution capability is particularly advantageous in PPS, where pancreatic intraepithelial neoplasia (PanINs) and early invasive carcinomas may manifest as subtle parenchymal or ductal irregularities long before becoming clinically apparent. Furthermore, contrast-enhanced EUS (CE-EUS) improves the differentiation between benign cystic lesions (e.g., serous cystadenomas) and malignant or premalignant entities (e.g., intraductal papillary mucinous neoplasms [IPMNs] or solid pseudopapillary tumors), thereby reducing unnecessary interventions in low-risk cases while ensuring prompt management of high-risk findings.¹¹

Real-Time Tissue Acquisition and Molecular Profiling

A pivotal advantage of EUS-guided fine-needle aspiration (EUS-FNA) or biopsy (EUS-FNB) is the ability to obtain histopathological and molecular confirmation of suspicious lesions during the same procedural setting. This is of paramount importance in PPS, where the presence of STK11 loss-of-function mutations may accelerate tumorigenesis through dysregulated mTOR signaling. By facilitating KRAS, GNAS, or TP53 mutation analysis from pancreatic cyst fluid or solid lesions, EUS-guided sampling not only confirms malignancy but also helps risk-stratify lesions for subsequent management—whether through enhanced surveillance, surgical resection, or targeted therapy trials.¹¹

ERCP: Direct Ductal Evaluation and Therapeutic Potential

While EUS excels in parenchymal assessment, ERCP provides indispensable access to the pancreaticobiliary ductal system, allowing for direct visualization of main pancreatic duct (MPD) abnormalities—such as strictures, filling defects, or mucin extrusion—that may indicate high-grade dysplasia or early invasive carcinoma. Unlike non-invasive imaging, ERCP permits brush cytology, intraductal biopsies, and pancreatic juice collection for cytological and biomarker analysis, significantly enhancing the diagnostic yield in cases where ductal involvement is suspected but not clearly visualized on EUS or MRI.¹²

Moreover, ERCP offers therapeutic interventions that can alter the natural history of PDAC in PPS patients. For instance, prophylactic pancreatic duct stenting may be employed in cases of ductal obstruction to prevent acute pancreatitis, while ablation techniques (e.g., radiofrequency ablation [RFA] of dysplastic ductal epithelium) are being explored as potential preemptive measures in high-risk individuals.¹²

Dynamic Risk Stratification and Personalized Surveillance Intervals

The combination of EUS and ERCP enables a dynamic, risk-adapted surveillance strategy, wherein screening intervals can be adjusted based on lesion morphology, growth rate, and molecular markers. For example:

- Patients with no detectable abnormalities may continue surveillance every 12–24 months.¹²
- Those with low-risk IPMNs or PanIN-1/2 may benefit from annual EUS with intermittent ERCP.¹²
- Individuals with high-risk lesions (e.g., MPD dilation, mural nodules, or rapid cyst growth) may require 6-monthly evaluations or referral for surgical consideration.

This tailored approach optimizes resource utilization while minimizing the psychological and physical burden of excessive testing in low-risk individuals.¹²

Comparative Advantages Over Alternative Modalities

While MRI/MRCP is often advocated as a non-invasive screening tool, its limited sensitivity for subcentimeter solid lesions and inability to provide tissue diagnosis restrict its utility in PPS, where early intervention is paramount. Similarly, CT exposes patients to cumulative ionizing radiation, a non-trivial concern in a syndrome requiring lifelong surveillance. In contrast, EUS and ERCP avoid radiation exposure while offering diagnostic and therapeutic versatility unmatched by other modalities.¹²

Future Directions: Enhancing Early Detection Through Advanced Endoscopic Technologies

Emerging innovations—such as confocal laser endomicroscopy (pCLE), needle-based confocal microscopy (nCLE), and artificial intelligence (AI)-assisted EUS image analysis—promise to further refine the diagnostic accuracy of endoscopic screening in STK11 carriers. These technologies may enable real-time in vivo histology, allowing endoscopists to discriminate between low-grade dysplasia and advanced neoplasia during the initial procedure, thereby streamlining clinical decision-making.¹³

The integration of EUS and ERCP into the pancreatic cancer screening algorithm for PPS patients with STK11 mutations represents a paradigm shift in the management of this high-risk population. By combining unrivaled diagnostic precision, real-time tissue sampling, ductal evaluation, and therapeutic potential, these endoscopic techniques offer a proactive, personalized, and potentially life-saving approach to mitigating the formidable threat of PDAC in this vulnerable cohort. As endoscopic technology continues to evolve, the future of PPS-related pancreatic surveillance lies in the strategic fusion of advanced imaging, molecular diagnostics, and minimally invasive therapeutics—all anchored by the procedural expertise of dedicated endoscopists.¹⁴

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Limitations and Disadvantages of Pancreatic Cancer Screening with EUS and ERCP in Peutz-Jeghers Syndrome Carriers with STK11 Mutations

While endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) offer significant advantages for pancreatic cancer surveillance in STK11 mutation carriers with Peutz-Jeghers Syndrome (PPS), these modalities are not without substantial limitations that must be carefully considered in clinical practice. The inherent challenges span technical, procedural, and patient-specific factors that may compromise the efficacy, safety, and overall feasibility of long-term surveillance programs in this high-risk population.¹⁴

From a technical perspective, EUS remains highly operator-dependent, with significant interobserver variability in the interpretation of subtle pancreatic abnormalities. The learning curve for advanced endoscopic ultrasonography is notably steep, requiring extensive training to achieve competency in distinguishing between benign pancreatic parenchymal changes and early malignant lesions. This becomes particularly problematic in PPS patients, where the pancreatic tissue may demonstrate diffuse architectural distortion due to recurrent pancreatitis or widespread hamartomatous changes, potentially leading to both false-positive and false-negative interpretations. The sensitivity of EUS for detecting pancreatic intraepithelial neoplasia (PanIN)-1 and -2 lesions—considered precursor lesions to pancreatic ductal adenocarcinoma (PDAC)—remains suboptimal, with many early dysplastic changes occurring at a microscopic level beyond the resolution of current endoscopic ultrasound technology.¹⁴

The limitations of ERCP in this context are even more pronounced, primarily due to the procedure's invasive nature and associated complications. Post-ERCP pancreatitis occurs in 5-10% of cases, with higher rates anticipated in PPS patients who may have underlying pancreatic ductal anomalies or parenchymal vulnerability due to chronic subclinical inflammation. The risk profile is further exacerbated by the necessity for repeated procedures in a surveillance context, with cumulative exposure to contrast media, radiation, and mechanical trauma to the pancreatic ductal system. Unlike diagnostic ERCP alone, therapeutic interventions such as pancreatic duct stenting or brush cytology substantially increase the probability of adverse events, including hemorrhage, perforation, and infection, without guaranteed diagnostic yield. The procedure's utility is further constrained by its inability to reliably sample the pancreatic parenchyma, limiting its role to ductal abnormalities while missing potentially significant solid lesions.¹⁴

From a practical standpoint, the resource-intensive nature of comprehensive EUS-ERCP surveillance programs presents significant barriers to widespread implementation. The requirement for specialized endoscopic equipment, advanced

cytopathology support for rapid on-site evaluation (ROSE), and multidisciplinary team coordination renders these protocols feasible only in tertiary care centers with dedicated pancreatic disease programs. This creates substantial disparities in access to care, particularly for PPS patients in resource-limited settings where such infrastructure may be unavailable. The financial burden of repeated high-end endoscopic procedures, particularly in healthcare systems without universal coverage, may impose catastrophic out-of-pocket expenses on patients requiring lifelong surveillance.¹⁴

Patient-related factors further compound these challenges. The psychological toll of undergoing repeated invasive procedures—particularly when most examinations will not reveal malignancy—can lead to surveillance fatigue, non-adherence to recommended screening intervals, and diminished quality of life. Younger STK11 mutation carriers face decades of intensive monitoring, with each procedure carrying anxiety about potential cancer diagnosis while simultaneously providing no absolute assurance against interval PDAC development. The physical discomfort associated with ERCP, coupled with the necessity for conscious sedation or general anesthesia, creates additional barriers to compliance, particularly in patients with comorbidities that increase peri-procedural risks.¹⁴

Anatomically, certain PPS patients present unique technical challenges that may limit the effectiveness of endoscopic surveillance. Extensive jejunal polyposis can distort duodenal anatomy, making ampullary cannulation during ERCP technically difficult or impossible. Similarly, prior abdominal surgeries—common in PPS patients due to recurrent intussusception or polyp-related complications—may alter pancreaticobiliary anatomy, reducing both the feasibility and diagnostic accuracy of endoscopic procedures. In such cases, alternative imaging modalities must be considered, despite their well-documented inferiority for early pancreatic cancer detection.¹⁴

The evidence base supporting EUS-ERCP surveillance in PPS remains limited by the rarity of the syndrome and lack of prospective controlled trials demonstrating mortality benefit. Current recommendations extrapolate from other high-risk populations, potentially overestimating the effectiveness while underestimating the harms in this distinct patient group. Without robust longitudinal data, the optimal surveillance intervals, age at initiation, and criteria for discontinuing screening remain matters of conjecture rather than evidence-based practice.¹⁴

Emerging technologies such as artificial intelligence-assisted EUS interpretation and confocal laser endomicroscopy may eventually mitigate some limitations, but currently remain investigational with unproven benefit in routine PPS surveillance. Similarly, non-endoscopic alternatives like liquid biopsies for circulating tumor DNA, while promising,

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lack the sensitivity required to replace direct pancreatic evaluation in this ultra-high-risk population.^{15,16}

While EUS and ERCP represent the most sensitive tools currently available for PDAC surveillance in STK11 mutation carriers with PPS, their implementation is hampered by significant technical constraints, procedural risks, resource requirements, and patient burdens that collectively diminish their real-world effectiveness. These substantial disadvantages underscore the urgent need for less invasive, more cost-effective, and equally sensitive alternatives to revolutionize pancreatic cancer screening in this vulnerable population. Until such advances materialize, clinicians must carefully weigh the potential benefits against the considerable drawbacks when recommending intensive endoscopic surveillance protocols for individuals with this rare but devastating cancer predisposition syndrome.¹⁵

Conclusion: The Evolving Paradigm of Pancreatic Cancer Surveillance in Peutz-Jeghers Syndrome Through Advanced Endoscopic Modalities

The integration of endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) into the surveillance algorithm for pancreatic ductal adenocarcinoma (PDAC) in STK11 mutation carriers with Peutz-Jeghers Syndrome (PPS) represents both a critical advancement and an ongoing clinical challenge in the management of hereditary cancer predisposition syndromes. As our understanding of the molecular pathogenesis of PPS-associated malignancies continues to evolve, so too must our approach to early cancer detection in this exceptionally high-risk population. The current evidence, while limited by the rarity of the condition, strongly suggests that a proactive, multimodal endoscopic strategy offers the most viable pathway to mitigating the disproportionate burden of pancreatic cancer in STK11 mutation carriers.

The unique advantages of EUS—particularly its unparalleled spatial resolution for detecting subcentimeter pancreatic lesions and its capacity for real-time tissue acquisition—position it as the cornerstone of PDAC surveillance in this context. When combined with the ductal evaluation and therapeutic potential of ERCP, these modalities create a complementary diagnostic framework capable of identifying both parenchymal and ductal abnormalities at potentially curable stages. The ability to perform risk stratification through endoscopic findings and molecular analysis of acquired specimens represents a significant leap forward from reliance on conventional imaging modalities with their well-documented limitations in early pancreatic cancer detection.

However, the implementation of such surveillance protocols must be tempered by a realistic appraisal of their significant limitations. The operator-dependent nature of EUS, the non-trivial complication rates associated with ERCP, and the substantial resource requirements for sustained surveillance programs all pose considerable barriers to optimal care

delivery. These technical challenges are compounded by patient-specific factors including the psychological burden of lifelong surveillance, anatomical constraints posed by syndromic features of PPS, and the financial implications of repeated high-end endoscopic procedures.

The current landscape of PPS management thus presents a compelling argument for centralized care in specialized centers with multidisciplinary teams capable of navigating these complexities. Such an approach would ensure access to the necessary expertise while facilitating the collection of robust longitudinal data to refine surveillance protocols. Future directions must focus on minimizing invasiveness while maximizing diagnostic yield—through technological advancements in endoscopic imaging, the development of reliable biomarkers, and the judicious incorporation of emerging techniques such as confocal laser endomicroscopy and artificial intelligence-assisted image analysis.

Ultimately, the care of STK11 mutation carriers with PPS embodies the broader challenges and opportunities inherent in managing hereditary cancer syndromes. It demands a delicate balance between aggressive surveillance to prevent cancer mortality and thoughtful consideration of patient quality of life, between embracing cutting-edge technologies and acknowledging their current limitations, and between standardized protocols and personalized medicine. As we stand at this crossroads, the endoscopic surveillance of pancreatic cancer in PPS serves as both a model for other high-risk populations and a reminder of the work still required to optimize outcomes in rare genetic disorders.

The path forward must be guided by rigorous clinical research, technological innovation, and above all, a patient-centered approach that weighs the substantial benefits of early cancer detection against the very real costs—both personal and systemic—of intensive surveillance. Only through such balanced, evidence-based strategies can we hope to alter the natural history of PPS-associated pancreatic cancer while maintaining our fundamental commitment to first, do no harm.

REFERENCES

- I. Hruban RH, Canto MI, Goggins M, Schulick R, Klein AP. Update on familial pancreatic cancer. *Adv Surg*. 2010;44:293–311. doi: 10.1016/j.yasu.2010.05.011.
- II. Shindo K, Yu J, Suenaga M, Fesharakizadeh S, Cho C, Macgregor-Das A, Siddiqui A, Witmer PD, Tamura K, Song TJ, Navarro Almario JA, Brant A, Borges M, Ford M, Barkley T, He J, Weiss MJ, Wolfgang CL, Roberts NJ, Hruban RH, Klein AP, Goggins M. Deleterious germline mutations in patients with apparently sporadic pancreatic adenocarcinoma. *J Clin Oncol*. 2017;35(30):3382–3390. doi: 10.1200/jco.2017.72.3502.

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- III. Canto MI, Hruban RH, Fishman EK, Kamel IR, Schulick R, Zhang Z, Topazian M, Takahashi N, Fletcher J, Petersen G, Klein AP, Axilbund J, Griffin C, Syngal S, Saltzman JR, Morteale KJ, Lee J, Tamm E, Vikram R, Bhosale P, Margolis D, Farrell J, Goggins M. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. *Gastroenterology*. 2012;142(4):796–804. doi: 10.1053/j.gastro.2012.01.005.
- IV. Bipat S, Phoa SS, van Delden OM, Bossuyt PM, Gouma DJ, Lameris JS, Stoker J. Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis and determining resectability of pancreatic adenocarcinoma: a meta-analysis. *J Comput Assist Tomogr*. 2005;29(4):438–445. doi: 10.1097/01.rct.0000164513.23407.b3.
- V. Nawaz H, Fan CY, Kloke J, Khalid A, McGrath K, Landsittel D, Papachristou GI. Performance characteristics of endoscopic ultrasound in the staging of pancreatic cancer: a meta-analysis. *JOP*. 2013;14(5):484–497. doi: 10.6092/1590-8577/1512.
- VI. Tamburrino D, Riviere D, Yaghoobi M, Davidson BR, Gurusamy KS. Diagnostic accuracy of different imaging modalities following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. *Cochrane Database Syst Rev*. 2016;9(9):CD011515. doi: 10.1002/14651858.CD011515.pub2.
- VII. Rahman MIO, Chan BPH, Far PM, Mbuagbaw L, Thabane L, Yaghoobi M. Endoscopic ultrasound versus computed tomography in determining the resectability of pancreatic cancer: a diagnostic test accuracy meta-analysis. *Saudi J Gastroenterol*. 2020;26(3):113–119. doi: 10.4103/sjg.SJG_39_20.
- VIII. Rijkers AP, Valkema R, Duivenvoorden HJ, van Eijck CHJ. Usefulness of F-18-fluorodeoxyglucose positron emission tomography to confirm suspected pancreatic cancer: a meta-analysis. *Eur J Surg Oncol (EJSO)* 2014;40(7):794–804. doi: 10.1016/j.ejso.2014.03.016.
- IX. Santhosh S, Mittal BR, Bhasin D, Srinivasan R, Rana S, Das A, Nada R, Bhattacharya A, Gupta R, Kapoor R. Role of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in the characterization of pancreatic masses: experience from tropics. *J Gastroenterol Hepatol*. 2013;28(2):255–261. doi: 10.1111/jgh.12068
- X. Seo S, Doi R, Machimoto T, Kami K, Masui T, Hatano E, Ogawa K, Higashi T, Uemoto S. Contribution of 18F-fluorodeoxyglucose positron emission tomography to the diagnosis of early pancreatic carcinoma. *J Hepatobiliary Pancreat Surg*. 2008;15(6):634–639. doi: 10.1007/s00534-007-1339-x.
- XI. Matsumoto I, Shirakawa S, Shinzeki M, Asari S, Goto T, Ajiki T, Fukumoto T, Kitajima K, Ku Y. 18-Fluorodeoxyglucose positron emission tomography does not aid in diagnosis of pancreatic ductal adenocarcinoma. *Clin Gastroenterol Hepatol*. 2013;11(6):712–718. doi: 10.1016/j.cgh.2012.12.033.
- XII. Brentnall TA, Bronner MP, Byrd DR, Haggitt RC, Kimmey MB. Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer. *Ann Intern Med*. 1999;131(4):247–255. doi: 10.7326/0003-4819-131-4-199908170-00003
- XIII. Rulyak SJ, Brentnall TA. Inherited pancreatic cancer: surveillance and treatment strategies for affected families. *Pancreatology*. 2001;1(5):477–485. doi: 10.1159/000055851.
- XIV. Kimmey MB, Bronner MP, Byrd DR, Brentnall TA. Screening and surveillance for hereditary pancreatic cancer. *Gastrointest Endosc*. 2002;56(4 Suppl):S82–S86. doi: 10.1016/S0016-5107(02)70092-8.
- XV. Canto MI, Goggins M, Yeo CJ, Griffin C, Axilbund JE, Brune K, Ali SZ, Jagannath S, Petersen GM, Fishman EK, Piantadosi S, Giardiello FM, Hruban RH. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. *Clin Gastroenterol Hepatol*. 2004;2(7):606–621. doi: 10.1016/S1542-3565(04)00244-7.
- XVI. Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo C, Fishman EK, Brune K, Axilbund J, Griffin C, Ali S, Richman J, Jagannath S, Kantsevov SV, Kalloo AN. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clin Gastroenterol Hepatol*. 2006;4(6):766–781. doi: 10.1016/j.cgh.2006.02.005