Risk factors of familial pancreatic cancer and screening high risk patients

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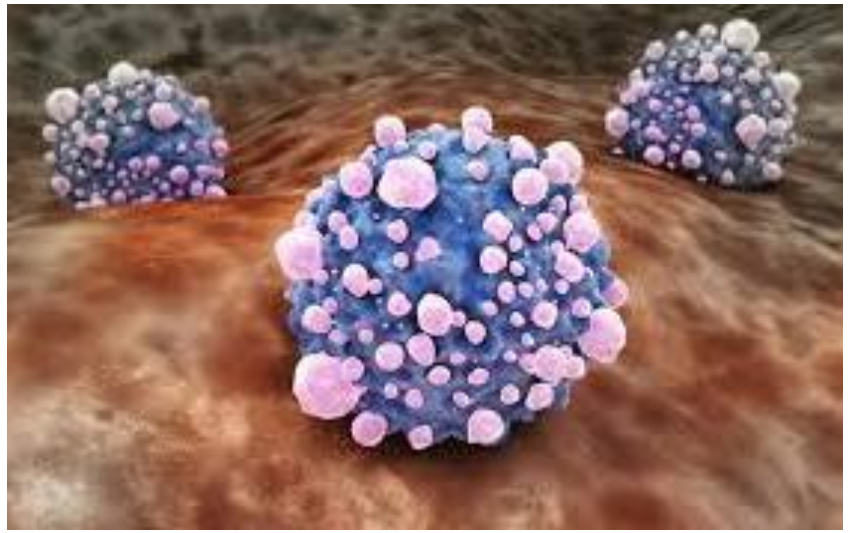
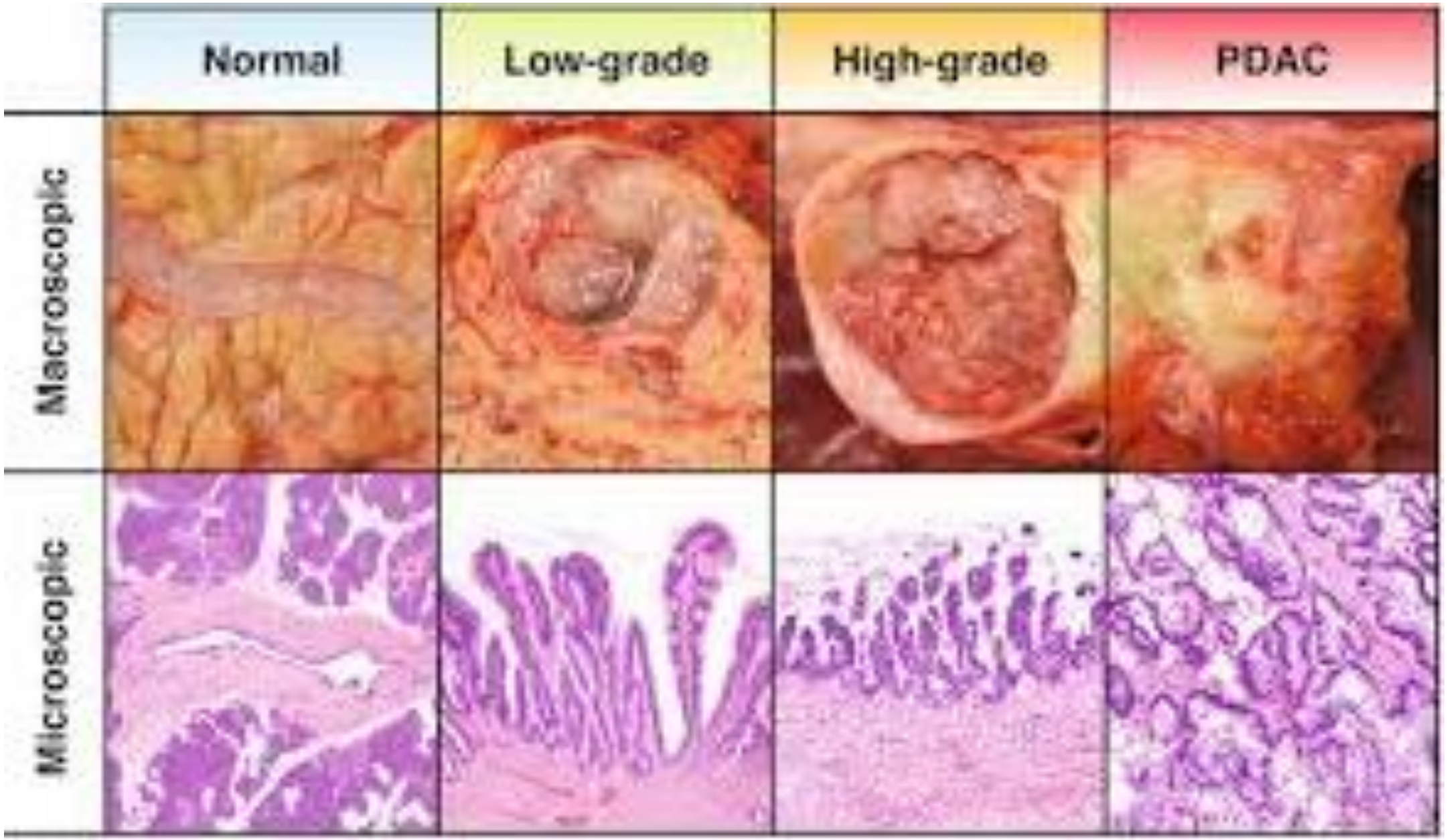


Screening and detection of asymptomatic, curable PC and precursors of PC

FH or **Genetic predisposition** increased risk for PC and
potential targets for selective screening

10 to 15 percent of PCs have genetic succeptibility
5 to 10 percent have FH of PC

- 3 precursor lesions for PDAC : pancreatic intra- epithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN).
- PanIN accounts for 90% of all PDAC and is defined as neoplasms involving the pancreas duct ,with progression from low-grade PanIN to high-grade PanIN to PDAC.
- IPMNs are macrocystic lesions that involve the pancreatic ductal system and account for 10% of all PDAC.


Normal
Low-grade
High-grade
PDAC
Macroscopic
Microscopic

RISK FACTORS FOR PANCREAS CANCER
Lifestyle and Chronic Disease Related

- smoking is associated with an increased risk of 1.7 to 2.2
- Heavy alcohol consumption, defined as greater than 9 drinks per day, is associated with a 1.6 increased risk
- Increased body mass index
- Chronic pancreatitis
- Diabet

GENETIC PREDISPOSITION SYNDROMES

- **Hereditary pancreatitis**
- Autosomal dominant disorder that accounts for a small fraction of cases of chronic pancreatitis.
- Most often associated with mutations in serine protease 1 gene (*PRSS1*) on chromosome 7q35, which encodes cationic trypsinogen.

- chronic pancreatitis before the age of 20 years and often before the age of five.
- Chronic infammation in hereditary pancreatitis leads to accelerated mutation accumulation and clonal expansion required for development of PC

Inherited cancer susceptibility syndromes

- Between 4 and 20 % with PC have germline mutations in known cancer predisposition genes
- **Hereditary breast cancer: BRCA and PALB2**
- Hereditary breast and ovarian cancer is characterized by the presence of germline mutations in one of two cancer susceptibility genes: breast cancer associated (*BRCA*) 1 and 2. The risk of PC may be elevated two- to threefold

- Breast cancer associated (*BRCA*) 1 and 2 genes are most commonly associated mutations, occurring in 13 to 19 % of FPC
- Median age for development of FPC is the same as that for sporadic PC (approximately 65 years)

- **Peutz-Jeghers syndrome**
- Germline mutations in the *STK11* gene are associated with (PJS), an autosomal dominant disorder
- 11 to 36 percent lifetime risk to age 70
- **Familial atypical multiple mole and melanoma syndrome**
- variant FAMMM-pancreatic carcinoma syndrome has been identified in families with a specific 19-base- pair deletion in the *p16* gene ,which is associated with pancreatic carcinoma of 21% by age 75

- **Lynch syndrome**
- Individuals with inherited germline mutations in mismatch repair (MMR) genes, in particular (*MLH1*), (*MSH2*), and (*MSH6*), have Lynch syndrome and are at increased risk of PC
- **Ataxia-telangiectasia**
- Monoallelic pathogenic variants in the ataxia-telangiectasia mutated (*ATM*) gene, are associated with an increased risk of PC

FAMILIAL PANCREATIC CANCER

- Familial pancreatic cancer (FPC) defined as PC in families in which there is at least a pair of first-degree relatives (FDRs) with pancreatic ductal adenocarcinoma (PDAC)
- In the absence of a known genetic susceptibility syndrome.

Pancreatic cancer genetic predispositions

Syndrome	Gene	% of Pancreas Cancer	Relative Risk (vs population)/ Lifetime Risk (%)
Familial pancreatic cancer	-	~10%	4.9×
Hereditary breast ovarian cancer syndrome	*BRCA1*	0.4%–1.0%	1.6–3.0×
Hereditary breast ovarian cancer syndrome	*BRCA2*	1.6%–5.7%	2.6–9.1×
—	*PALB2*	0.9%–1.6%	3.1–14.8×
—	*ATM*	2.0%–3.4%	3.4–9.0×
Lynch syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	1%	6–7×
Li-Fraumeni syndrome	*TP53*	<1%	6–7×
FAMM syndrome	*CDK2NA*	<1%	8.7–25.9×
Peutz-Jeghers	*STK11*	<1%	11%–36%
Familial pancreatitis	*PRSS1*, *SPINK1*	<1%	10% at age 50 y 54% at age 75 y

Syndrome	Gene(s)	cumulative lifetime risk of pancreatic cancer (%)	Gene locus
Hereditary breast/ovarian cancer	*BRCA2*, *BRCA1*	≤5 (*BRCA1*); 5 to 10 (*BRCA2*)	13q
	PALB2	2 to 10	16p
Familial atypical multiple mole melanoma syndrome	*CDKN2A*	10 to 21	9p
Peutz-Jeghers syndrome	*STK 11*	11 to 36	19p
Hereditary nonpolyposis colon cancer (Lynch syndrome)	DNA mismatch repair genes	<5 to 10 (highest [6.2%] for *MLH1*; lowest [0.5] for *MSH2*)	2p, 3p, 7p
Hereditary pancreatitis	*PRSS1*, *SPINK1*	25 to 44	7q, 5q

Individuals should be considered to be at high risk for hereditary PC :

- A known genetic syndrome associated with PC, including hereditary breast-ovarian cancer syndrome, familial atypical multiple melanoma and mole syndrome, Peutz- Jeghers syndrome (PJS), Lynch syndrome, and Li-Fraumeni syndrome, or the ataxia- telangiectasia mutated [*ATM*] gene)
- Two relatives with pancreatic adenocarcinoma, where one is an FDR
- Three or more relatives with PC on the same side of the family
- Hereditary pancreatitis

- one-half of patients with PC and pathogenic genetic variant have no FH of PC and/or do not meet clinical criteria for the hereditary syndrome
- In 2018 American Society of Clinical Oncology (ASCO)

"all patients diagnosed with pancreatic adenocarcinoma should undergo assessment of risk for hereditary syndromes

All hereditary cancer syndromes , should have screening and genetic testing



Understanding Pancreatic Cancer Screening: Who Needs It and When?

should not screen average-risk individuals for pancreas cancer.

Screening limited to HRIs, commonly defined as those with greater than 5% lifetime risk.

Importantly, limitations and risks of screening including overtreatment should be discussed

Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE
American Society for Gastrointestinal Endoscopy

ASGE guideline on screening for pancreatic cancer in individuals with genetic susceptibility: summary and recommendations



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Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

Recommendation :

- In individuals at increased risk of PC because of genetic susceptibility, suggest annual screening
- Starting age for screening should vary based on the underlining genetic condition
- Annual screening with EUS, MRI, or a combination of these modalities.

(a) *BRCA2* pathogenic variant: age 50 or 10 years earlier than the youngest relative with pancreatic cancer.
(b) *BRCA1* pathogenic variant: age 50 or 10 years earlier than the youngest relative with pancreatic cancer.
(c) *PALB2* pathogenic variant: age 50 or 10 years earlier than the youngest relative with pancreatic cancer.
(d) FPC syndrome: age 50 or 10 years earlier than the youngest relative with pancreatic cancer (screening is recommended for all first-degree relatives of affected family members).
(e) FAMMM syndrome: age 40 or 10 years earlier than the youngest relative with pancreatic cancer.
(f) Peutz-Jeghers syndrome: age 35 or 10 years earlier than the youngest relative with pancreatic cancer.
(g) Heterozygotes for *ATM* pathogenic variant with first- or second-degree relative with pancreatic cancer: age 50 or 10 years earlier than the youngest relative with pancreatic cancer.
(h) Lynch syndrome with first- or second-degree relative with pancreatic cancer: age 50 or 10 years earlier than the youngest relative with pancreatic cancer.
(i) Autosomal-dominant hereditary pancreatitis: age 40.

ATM, Ataxia-telangiectasia mutated; *EUS*, endoscopic ultrasound; *FAMMM*, familial atypical multiple mole melanoma; *FPC*, familial pancreatic cancer; *MRI*, magnetic resonance imaging

International Cancer of the Pancreas Screening (CAPS) Consortium

- Breast cancer associated (*BRCA*) 1,2 pathogenic variant with

If at least one affected first degree relative

OR , At least two affected relatives of any degree

AGA 2020

Genetic testing and counseling should be considered for familial pancreas cancer relatives.

A positive germline mutation is associated with an increased risk of neoplastic progression and may also lead to screening for other relevant associated cancers.

Best Practice Advice

screening should begin at age 50 years, or 10 years younger than the initial age of familial onset.

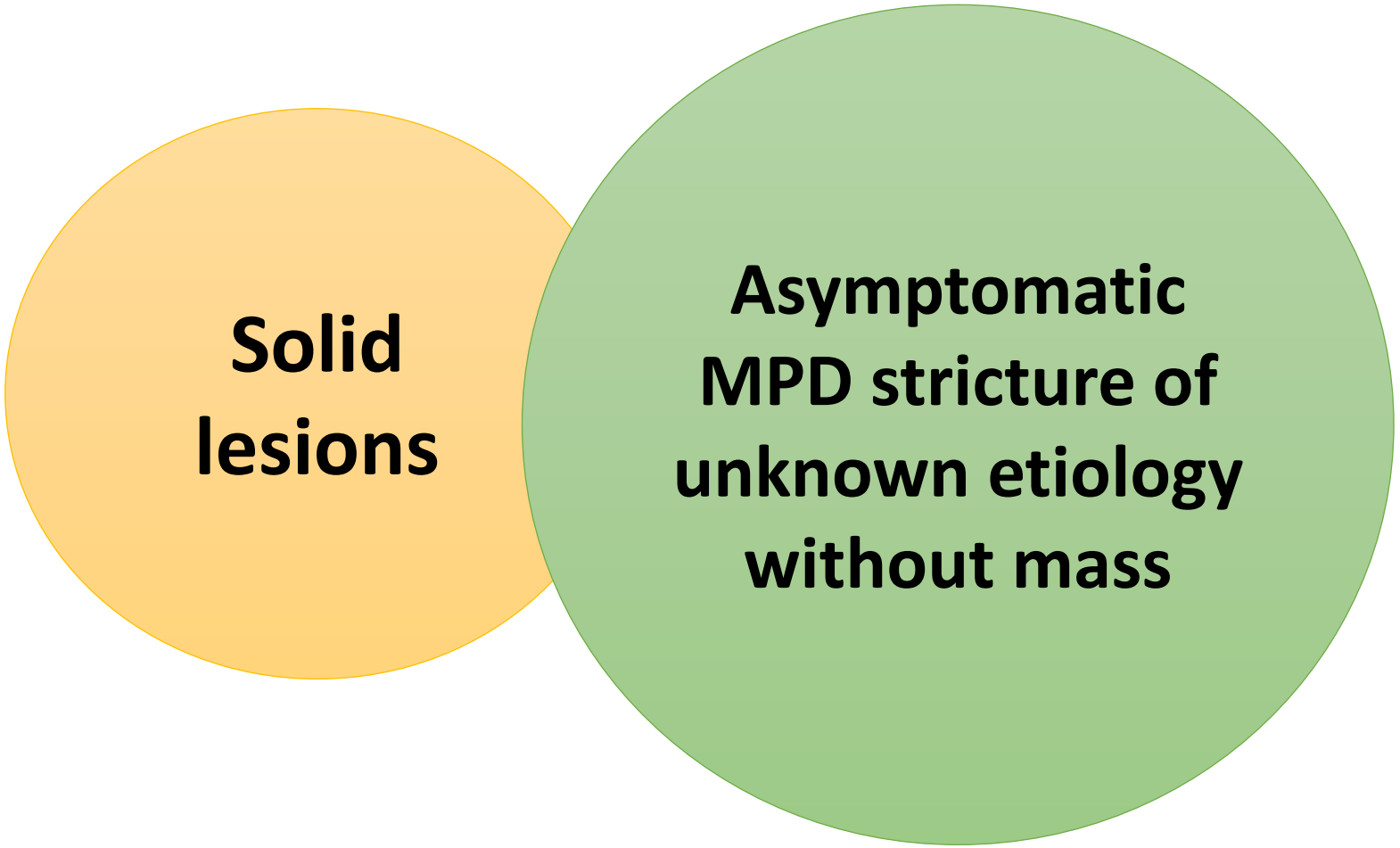
at age 40 years in CKDN2A and PRSS1 mutation carriers with hereditary pancreatitis and

age 35 years in the setting of Peutz–Jeghers syndrome.

AGA: Best Practice Advice

MRI and EUS, should be used in combination as the preferred screening modalities in individuals undergoing pancreas cancer screening.

CT only if :


Solid lesions
Asymptomatic MPD stricture of unknown etiology without mass

AGA: Best Practice Advice

- Screening intervals of 12 months ,when there are no pancreas lesions
- shortened intervals and/or EUS in 6–12 months directed towards lesions determined to be low risk (by a multidisciplinary team).
- EUS within 3–6 months for indeterminate lesions
- within 3 months for high-risk lesions, if surgical resection is not planned.
- New-onset diabetes in a high-risk individual should lead to additional diagnostic studies or change in surveillance interval.

Best Practice Advice

Decisions regarding therapy directed towards abnormal findings detected during screening should be made by a

- dedicated multidisciplinary team together
- with high-risk individual and their family.

AGA

Discontinuing screening when they are more likely to die of non-pancreas cancer–related causes due to comorbidity and/or are not candidates for pancreas resection.

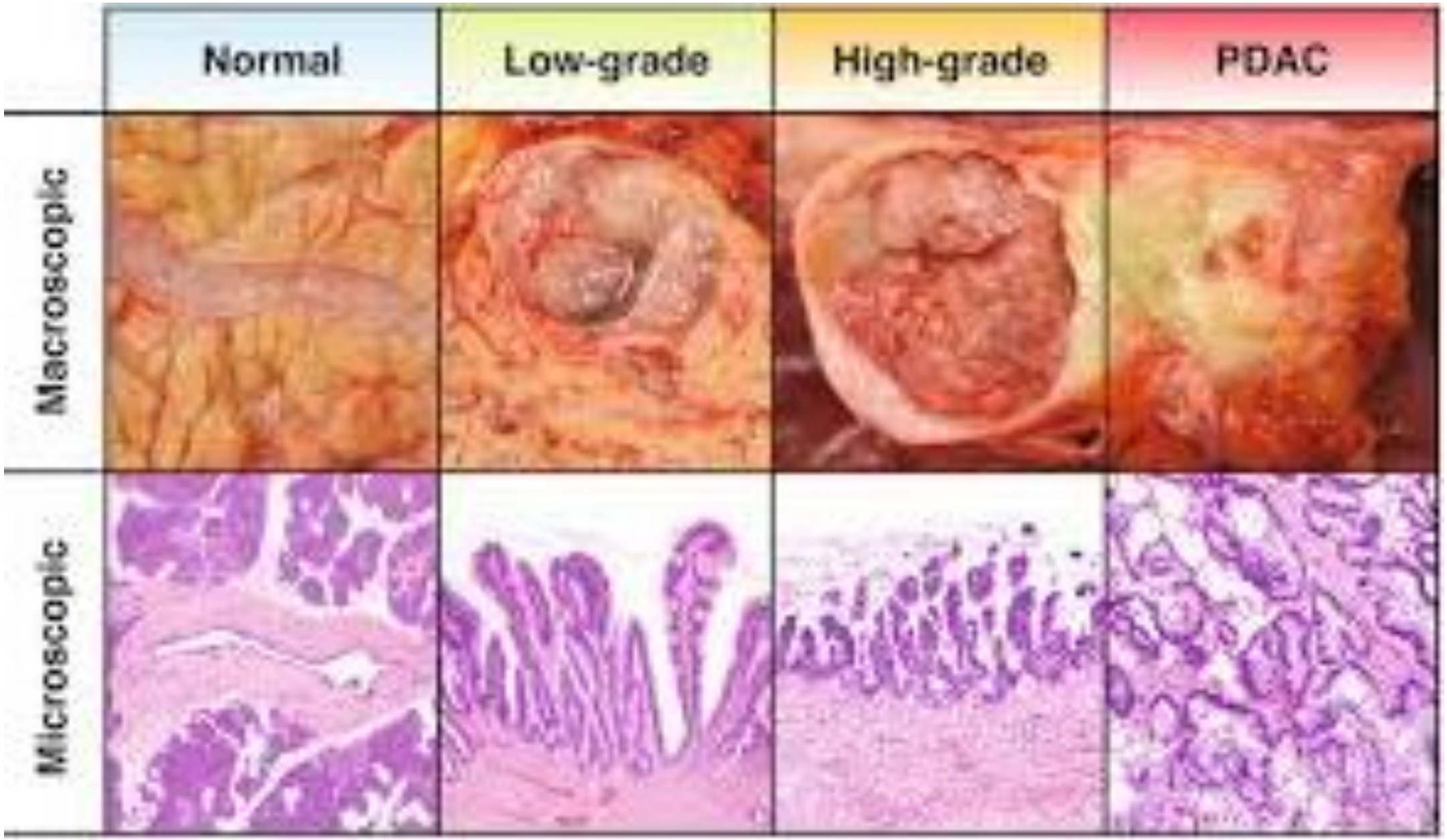
Evaluation of new-onset diabetes in patients undergoing screening

- Monitoring of blood glucose (FBS and/or hemoglobin A1C) can be considered at baseline and with continued surveillance
- New onset of diabetes may be indicative of an underlying pancreatic neoplasm in a high-risk individual.
- we perform urgent imaging (within two weeks) with EUS/MRCP/pancreatic protocol CT scan

Screening targets

Detect early resectable stage I invasive tumors and preinvasive lesions

- intraductal papillary mucinous neoplasms [IPMNs]
- pancreatic intraepithelial neoplasia [PanINs]) with high-grade neoplastic changes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Surg Clin N Am 104 (2024) 951–964

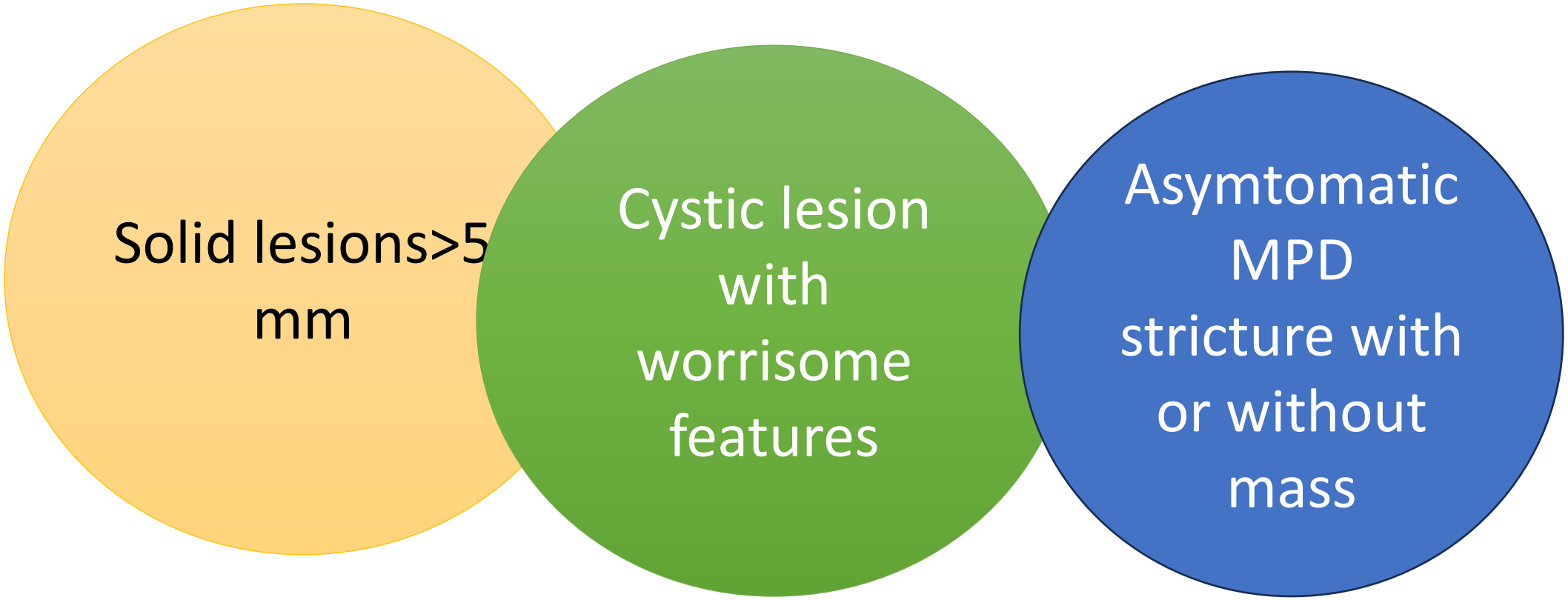
Pancreatic Cancer Screening among High-risk Individuals

Kevin M. Turner, MD[a,1], Sameer H. Patel, MD, FACS[a,b,*]

Table 2
Summary of societal recommendations

	Screening
Goals?	• Detection of precursor lesions with high-grade dysplasia (PanIN or IPMN) or Stage I PDAC (AGA, ASGE, and CAPS)
Whom?	• Patients with Peutz-Jeghers (*STK11*), FAMM (*CDK2NA*), or Familial Pancreatitis (*PRSS1*, *SPINK1*) • Patients with Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *EPCAM*), pathogenic mutations in *BRCA1*, *BRCA2*, *PALB2*, or *ATM and* $\geq$1 pancreas cancer affected FDR (AGA, CAPS) or SDR (NCCN) • Patients with FPC (ASGE, CAPS)
How?	• MRI/MRCP and EUS should be used in combination (AGA, ASGE, and NCCN) • Baseline MRI and EUS and fasting blood glucose/HbA1C with follow-up alternating MRI/EUS and routine fasting blood glucose/HbA1C (CAPS)
When?	• Peutz-Jeghers syndrome: Start at age 30–35 y or 10 y prior to the earliest exocrine pancreas cancer (AGA, ASGE, and NCCN); start at age 40 y (CAPS) • FAMM syndrome: Start at age 40 y or 10 y prior to the earliest exocrine pancreas cancer (AGA, ASGE, CAPS, and NCCN) • Familial pancreatitis: Start at age 40 y or 10 y prior to the earliest exocrine pancreas cancer (AGA, ASGE); Start at 20 y after initial symptoms or age 40 y, whichever is earliest (NCCN) • All other pathogenic variants: Start at age 50 y or 10 y prior to the earliest exocrine pancreas cancer (AGA, CAPS, NCCN); Start at age 45–50 y (ASGE) • FPC: Start at age 50–55 y or 10 y prior to the earliest exocrine pancreas cancer (CAPS)
Interval?	• Annual screening if no abnormalities/nonconcerning abnormalities (AGE, ASGE, CAPS, and NCCN) • 3–6 mo based on risk of abnormalities if surgery is not indicated (AGA, CAPS) • NOD in HRI should lead to diagnostic testing (AGA)
Completion?	• When patients are more at risk to die of nonpancreas cancer-related causes and/or not candidates for pancreas resection (AGA)

EUS-FNA only for:



- Excellent outcomes, 35% morbidity and 0% mortality rates, among screening HRI s have been reported.
- Serum CA 19-9:
  If concerning features on imaging
- CA 19-9 in conjunction with more novel markers such as thrombospondin-2, could aid in the diagnosis of early-stage disease.

Unlike common cancers, such as breast, colorectal, and lung cancer, screening for

early detection and prevention of pancreatic cancer remains

a challenge because it is a relatively rare disease that can be

difficult to diagnose, even when symptomatic.

Thanks for your attention

- IPMNs are commonly encountered incidentally. Their malignant potential is traditionally defined by clinical features, including main duct involvement, associated symptoms, and presence of mural nodules, among others.
- Advances in next generation sequencing of pancreatic cyst fluid has allowed increasingly accurate diagnosis of high-risk IPMNs.
- There is evidence to support progressive dysplasia associated with high-grade IPMNs as a direct precursor to PDAC.