# Familial Pancreatic Cancer

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# Pancreatic Cancer: Genetics

- Familial = at least 10% (syndromic and non-syndromic)
- Apparent "sporadic" = 6-7%: HNPCC & BRCA2 & other TBN
- Total genetic causes $\geq$ 17%

# Syndromes with Pancreatic Cancer

- Familial Adenomatous Polyposis (FAP): 5x increased risk
- Peutz-Jeghers: lifetime risk 36%
- HNPCC: unclear

# Syndromes with Pancreatic Cancer

- Hereditary pancreatitis: 53x (40%)
- Cystic Fibrosis:  32x (25%)

# Syndromes with Pancreatic Cancer

- Familial Atypical Mole Melanoma (FAMM): 13-20x (19%)
- Familial Breast Cancer (BRCA): 10x (5%)

# FPC: Spectrum of Syndromic Cancers

- Breast: often > age 50
- Lung
- Intestine
- Gastric
- Melanoma
- Osteosarcoma
- Prostate
- Ovarian
- Brain
- Other

# Some syndromes have pancreatic cancer---

But are most familial pancreatic cancers associated with syndromes?

# No!

Probably >70% of familial pancreatic cancer is caused by genes yet to be identified

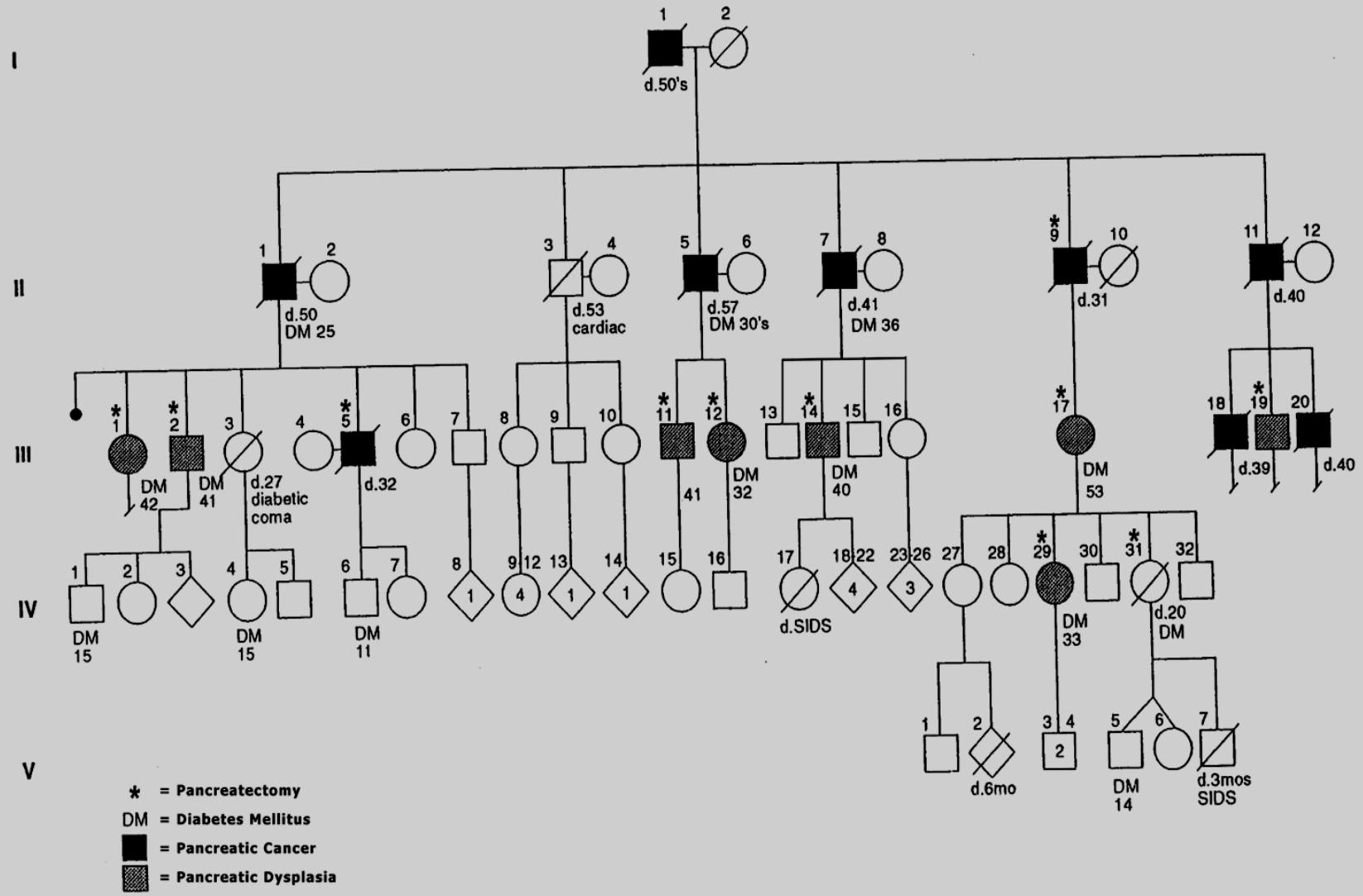
Pancreatic Cancer Gene Hunt!

# Non-syndromic: Familial Pancreatic CA (FPC)

- Family X: Large kindred at Univ of WA
  - 5 generations
  - 71 family members
- 9 deaths from pancreatic cancer
- screening program: 8 total pancreatectomies for dysplasia
- Gene identified: Palladin

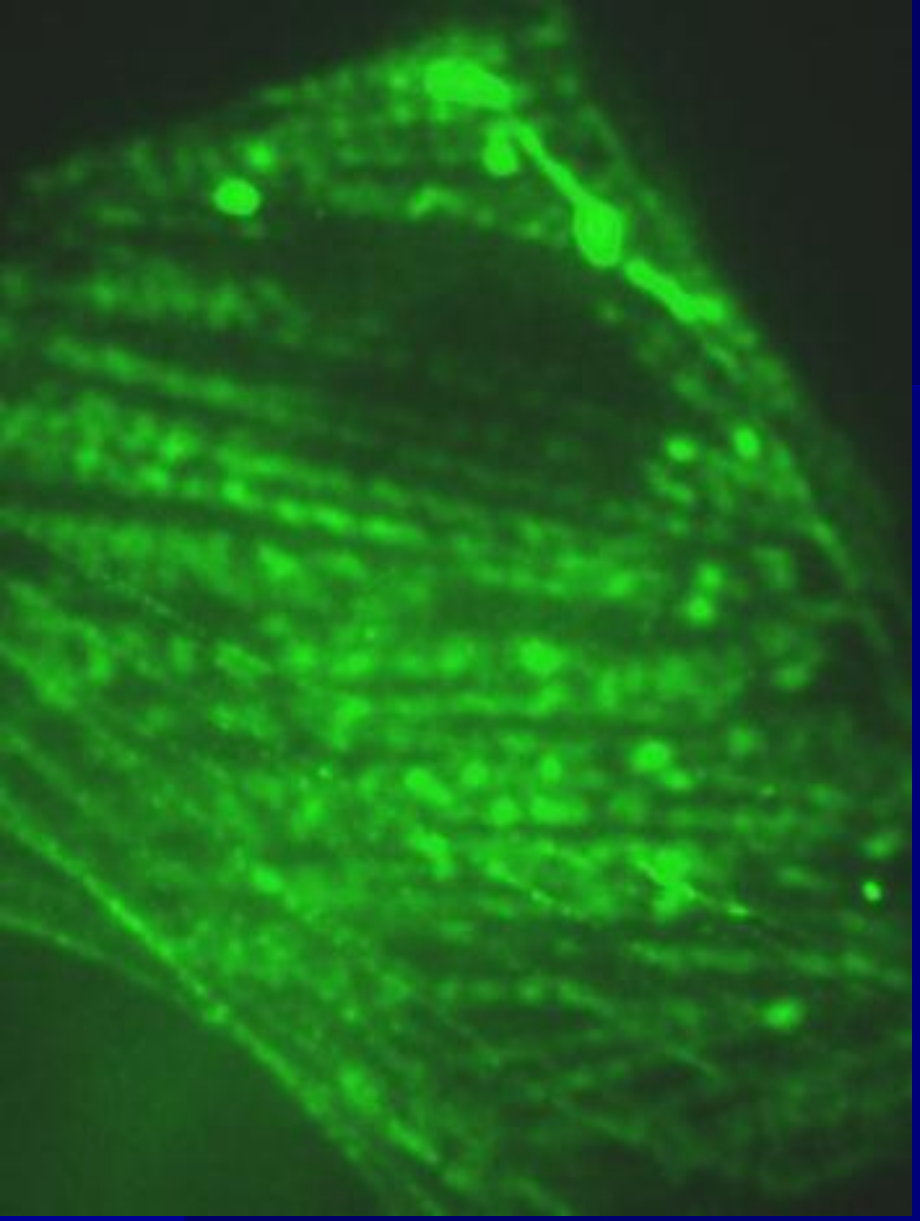

Brentnall TA, Bronner MP, et al. *Ann Int Med* 131:247, 1999.
Meckler KA, Bronner MP, et al. *Am J Surg Pathol* 25: 1047, 2001.
Eberle MA, Bronner MP, et al. *Am J Hum Genet* 70:1044-1048, 2002.
Pogue-Geile KL, Bronner MP, et al. *PLoS Med* 3: e516, 2006.

# Family X Pedigree

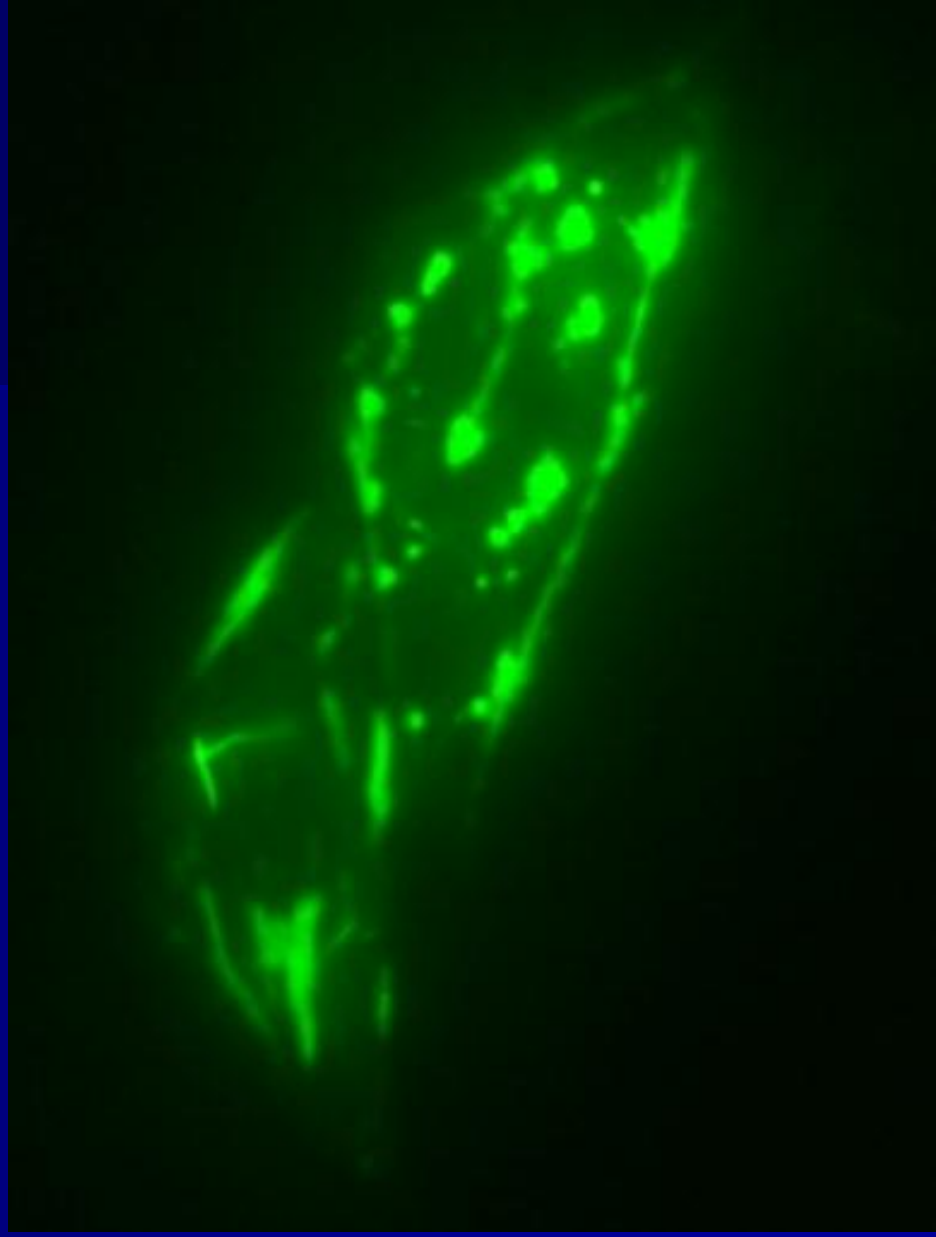


# Linkage Analysis and Gene ID

- Chromosome 4q32-34;  LOD 4.5
- Site excludes other known syndromes
- Causative gene identified: Palladin

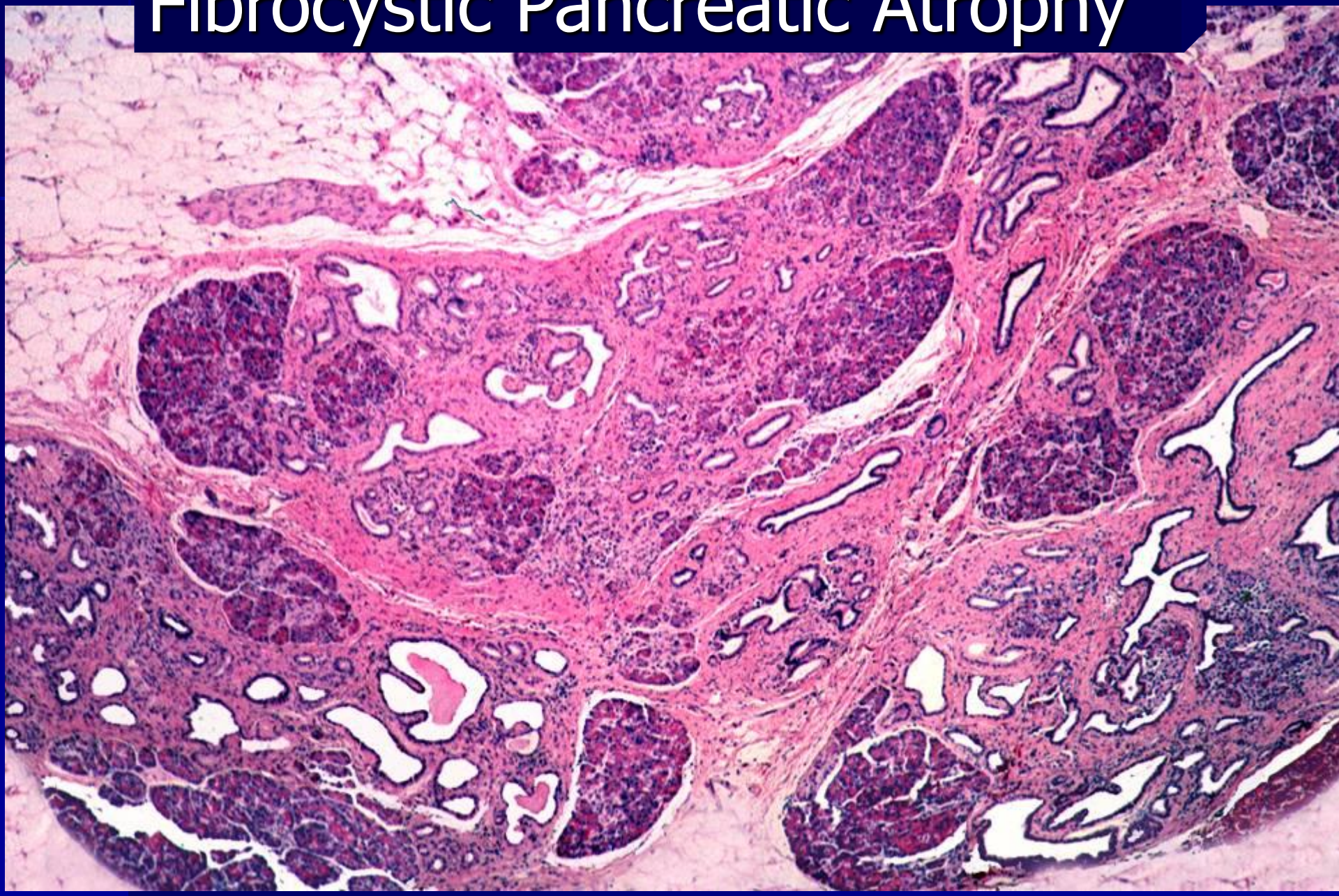


NORMAL Palladin



MUTATED Palladin

# Fibrocystic Pancreatic Atrophy



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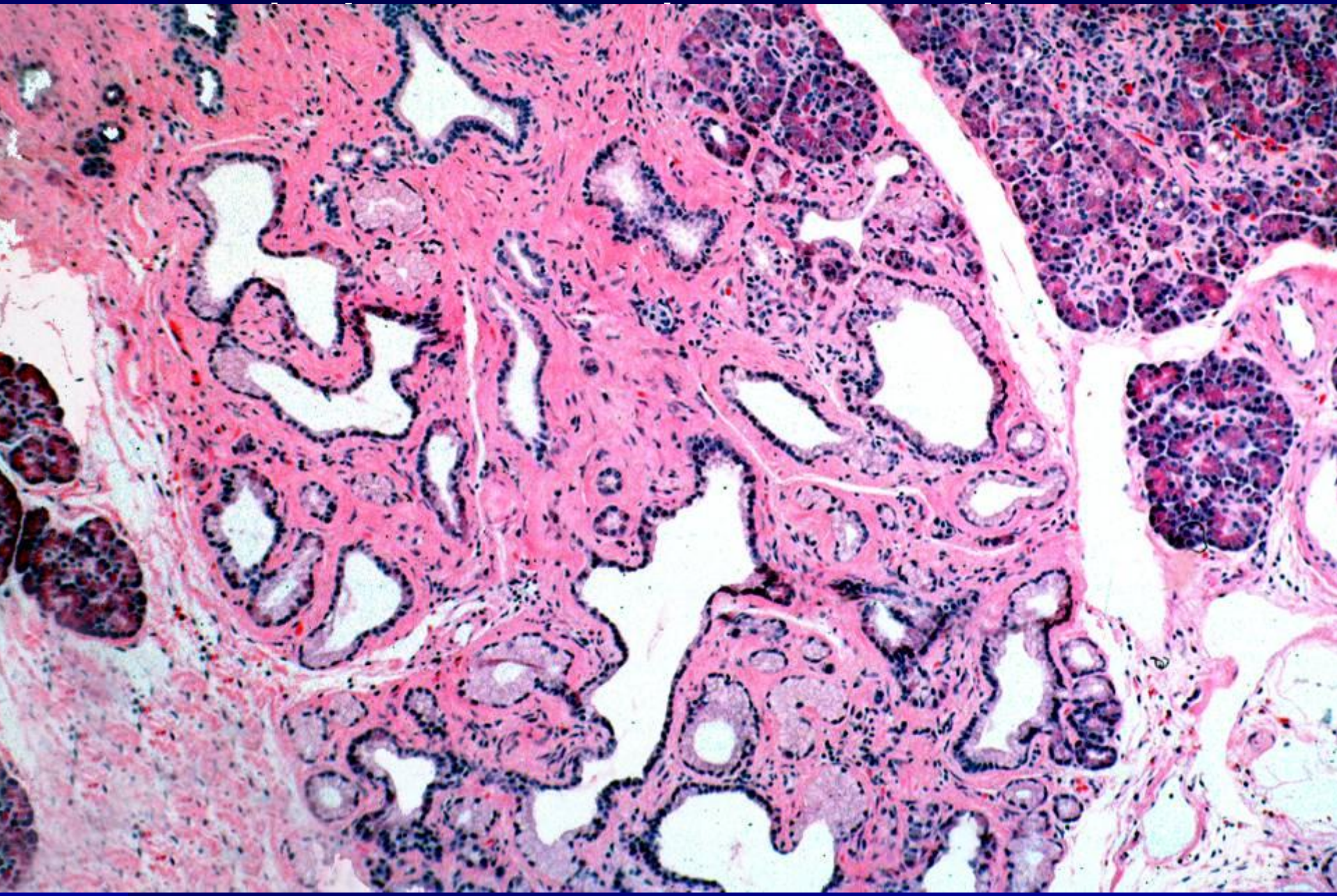
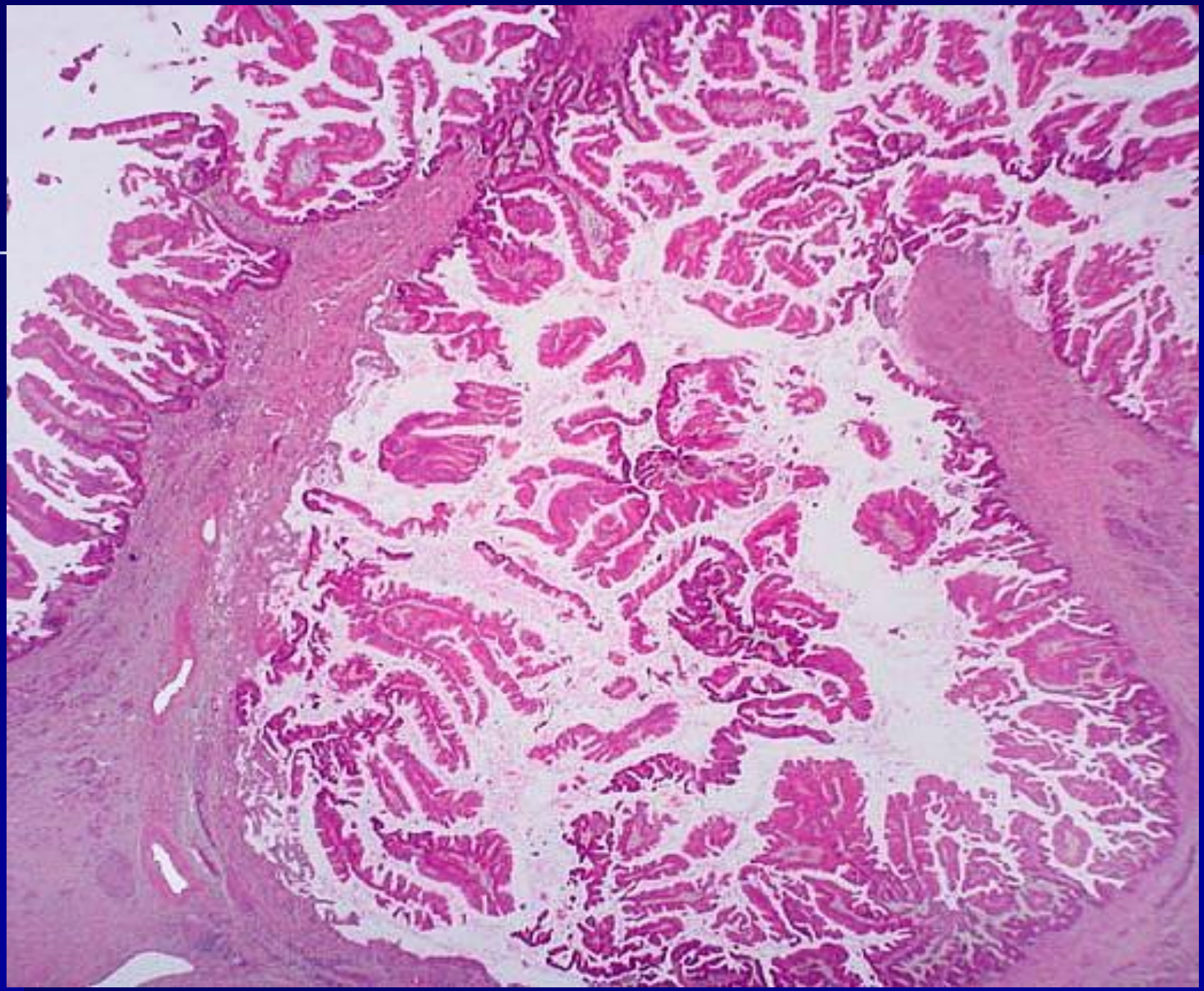
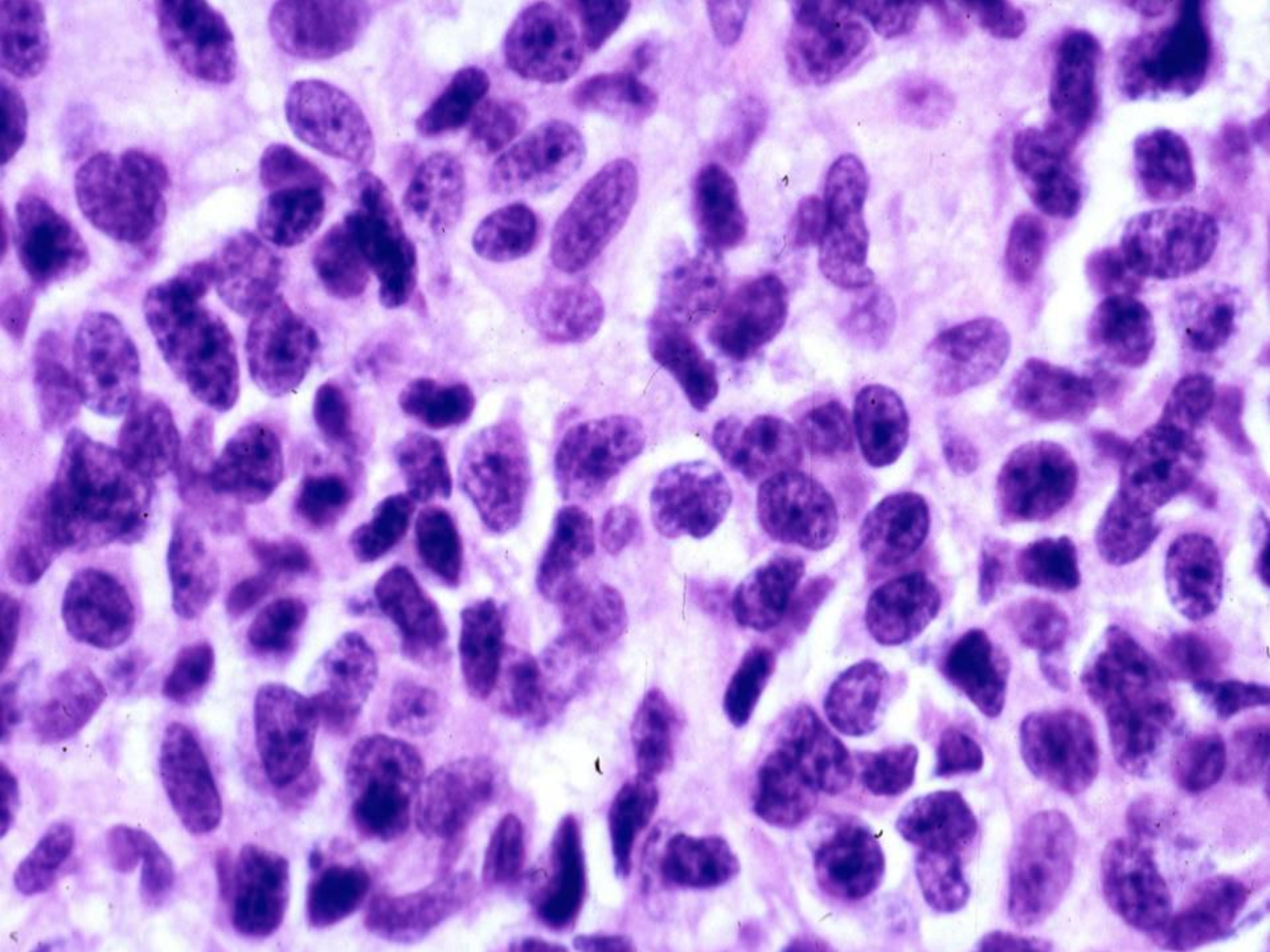


Meckler KA, Bronner MP, et al. *Am J Surg Pathol* 25: 1047, 2001.

# Family X: Dysplasia





# Pancreatic CA Screening: the task at hand

Identify high risk patients

….after they have started down the neoplastic pathway

…..*before the neoplasia becomes invasive and incurable*

# FPC screening: Patient eligibility

- 2 or more family members (1 first degree relative) with pancreatic cancer
- Gene mutation carriers conveying a high risk of pancreatic cancer

# 105 FPC patients

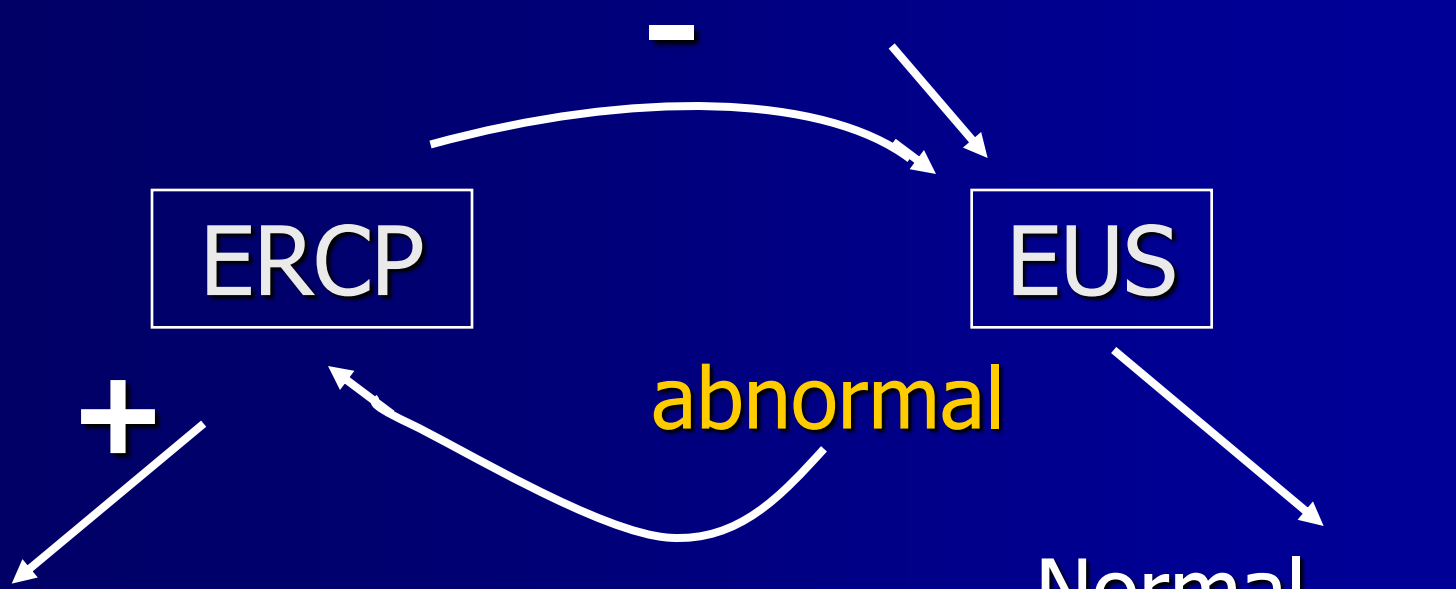
- 13 year program
- 73 different families
- Heterogeneous group of kindreds with different genetic causes
- Average years of surveillance = 5

# Known Genetic Causes (N=18)

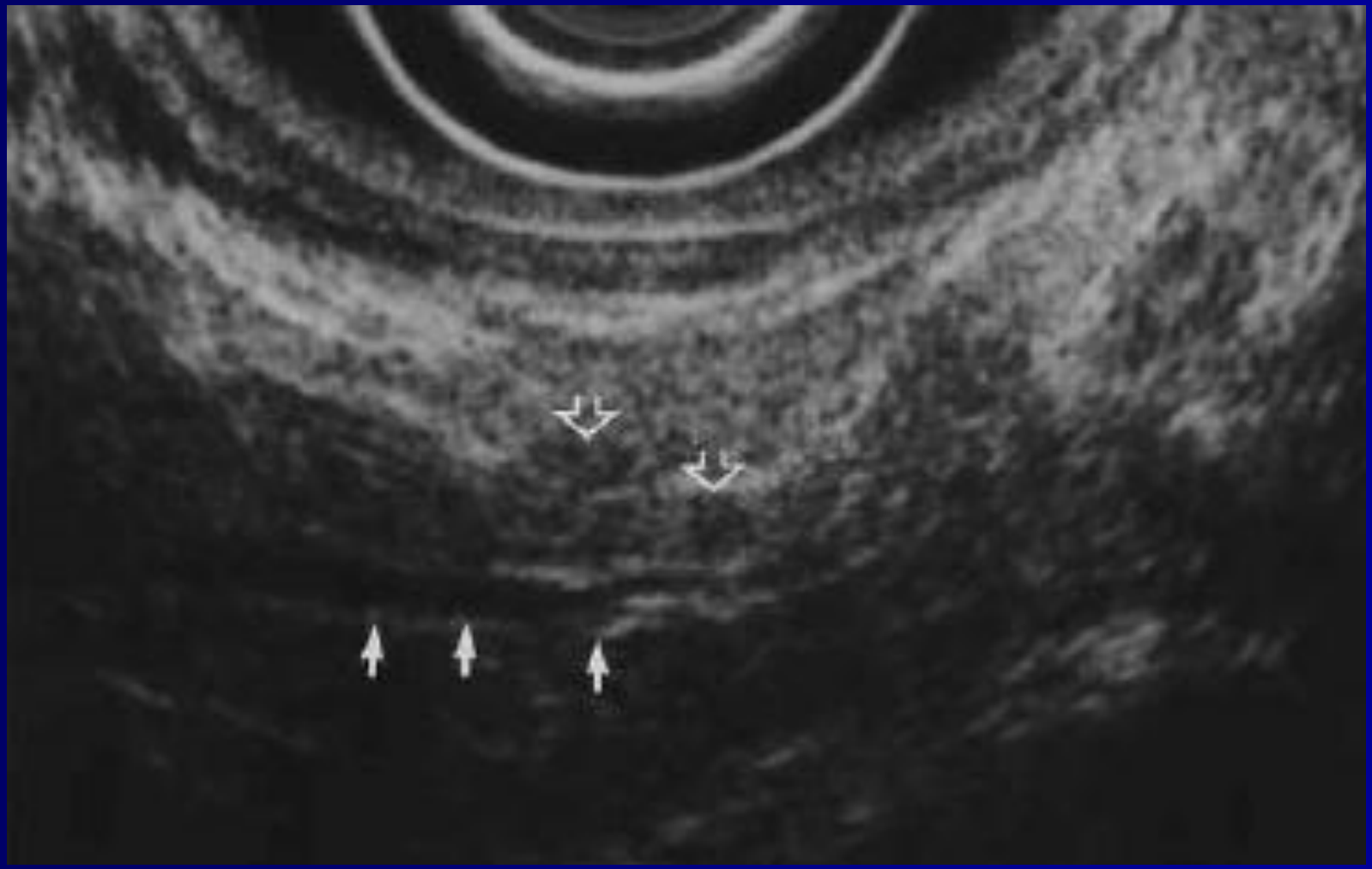
- 9 Family X, Palladin
- 5 BRCA 2
- 2 P16
- 1 HNPCC MLH1
- 1 Peutz-Jeghers

# Surveillance

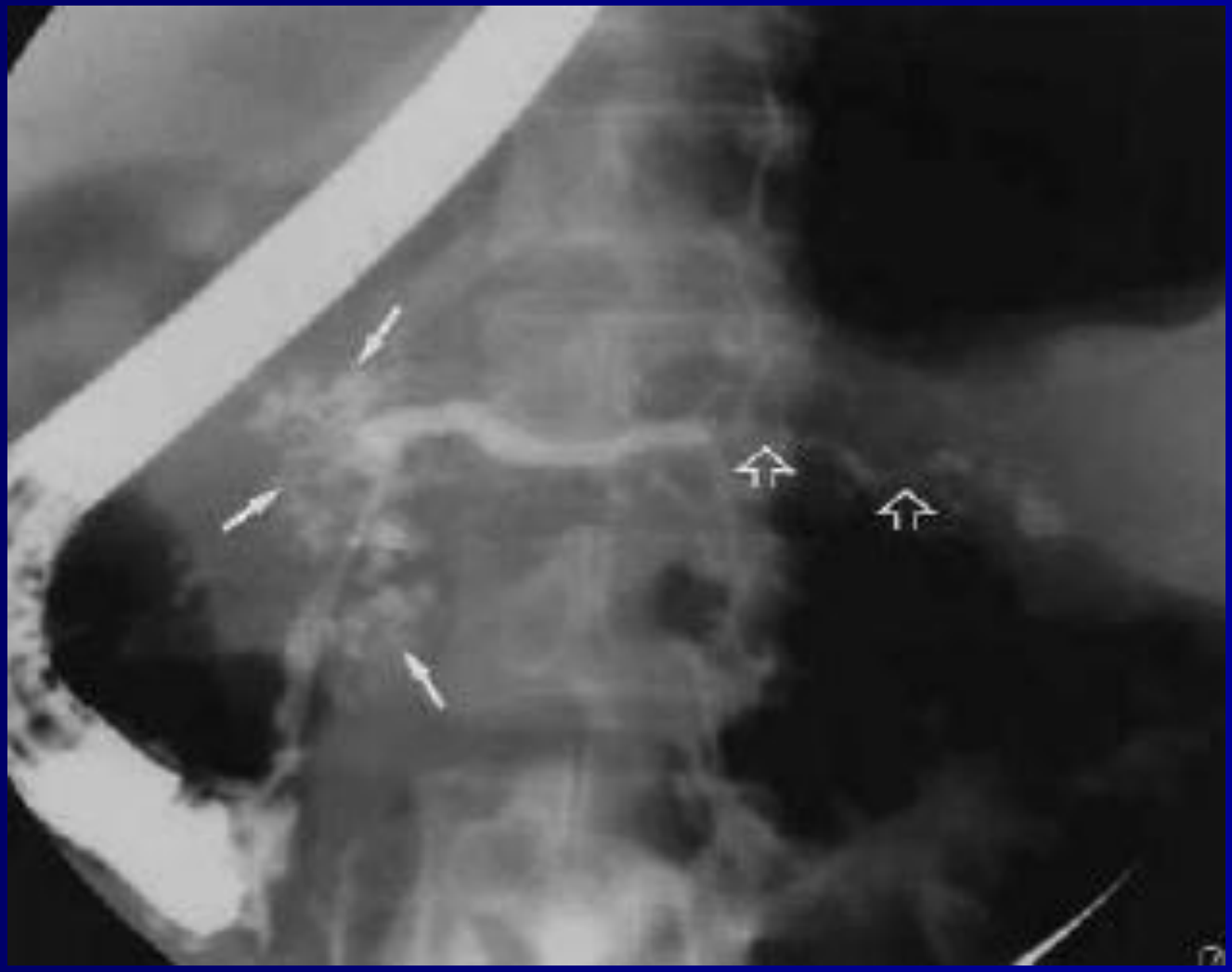
Positive family history,
one decade prior to earliest cancer



# EUS in FPC: Echogenic duct walls and hypoechoic lobules



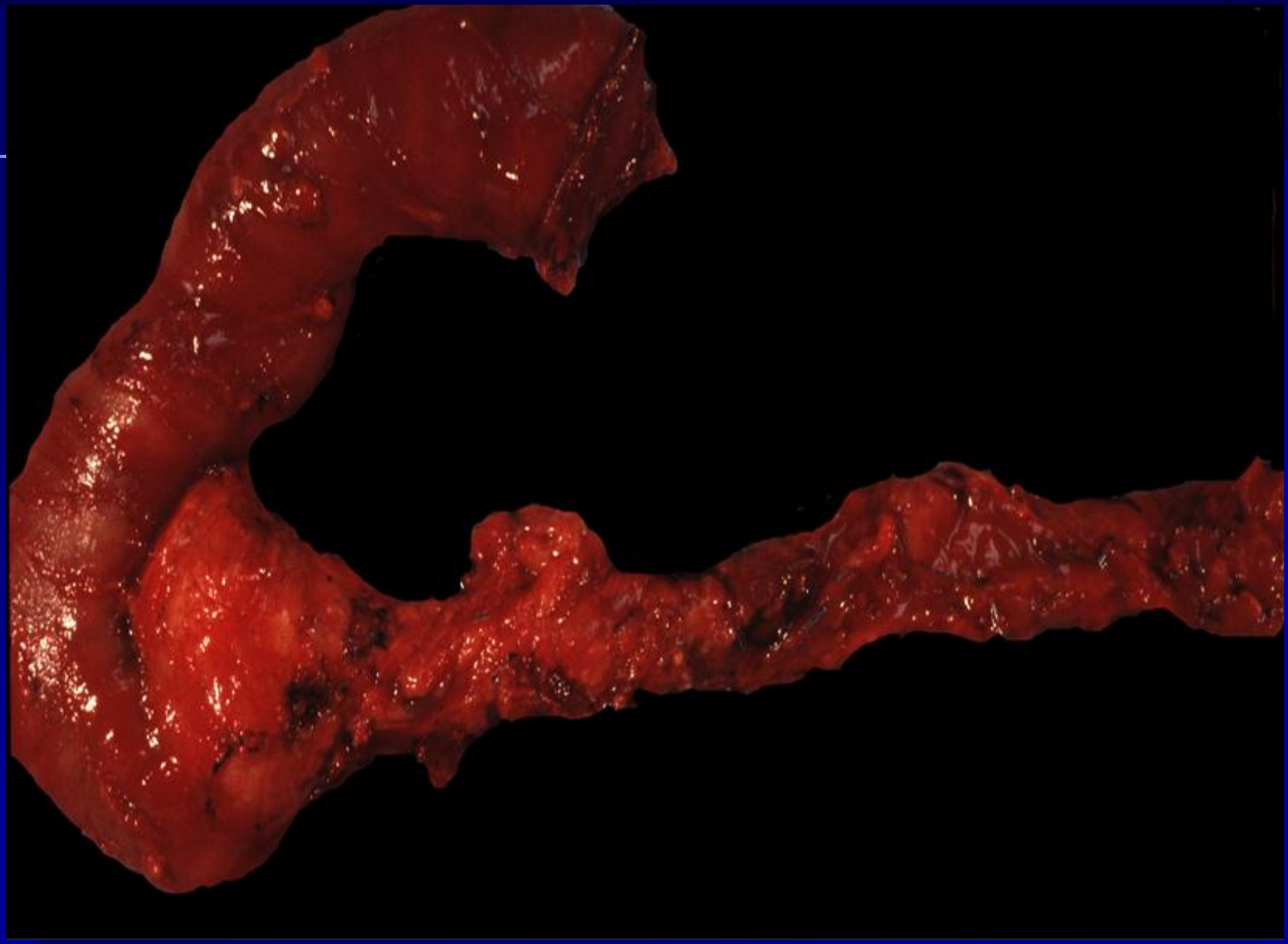
# ERCP in FPC: Ectatic side branches and main duct irregularity



# Treatment Goals

- Total pancreatectomy preferred
- Timing of surgery is key: *before* cancer *after* dysplasia

# Total Pancreatectomy & Duodenectomy



# Surgery

- Decision for pancreatectomy based on histology
- Two-phase operative approach:
  - Laparoscopic tail resection
  - +/- 2nd operation for completion

# Penetrance

- Variable penetrance in FPC kindreds
- Low penetrance with BRCA2
- Variable penetrance with FAMMM
- No specific spectra of mutations

*Brand & Lynch; Goggins*

# Does early detection improve curability?

105 total patients in high risk program

Surgical group n=21: No fu cancers (avg 7 yrs, 1-10 yr FU)

Cancers:

One metastatic: Alive at 1 year
One resectable: Alive at 2 years, NED

78 non-surgical cases: No cancers

# Yield of screening in high risk individuals

| Study | n | Modality | Diagnostic yield |
|---|---|---|---|
| Saunders et al | 100 | EUS | 22% |
| Canto et al | 78 | EUS | 10% |
| Canto et al | 36 | EUS | 5.3% |
| Poley et al | 44 | EUS | 23% |

*Saunders et al. Gastroenterol 2008; Canto et al. Clin Gastro Hepatol 2004; 2: 606; Canto et al. Clin Gastro Hepatol 2006; 4:766; Poley JW, et al. Am J Gastroenterol 2009;104:2175*

# Cost-effectiveness of pancreatic cancer screening in familial pancreatic cancer kindreds

Stephen J. Rulyak, MD, MPH, Michael B. Kimmey, MD, David L. Veenstra, PharmD, PhD, Teresa A. Brentnall, MD

*Seattle, Washington*

- Cost-effectiveness ratio= $17,000

(mammography $22K; pap smear $250K; CRC $6-92k)

- Procedure costs have limited impact
- Screening after age 70 is not cost effective

*GASTROINTESTINAL ENDOSCOPY*

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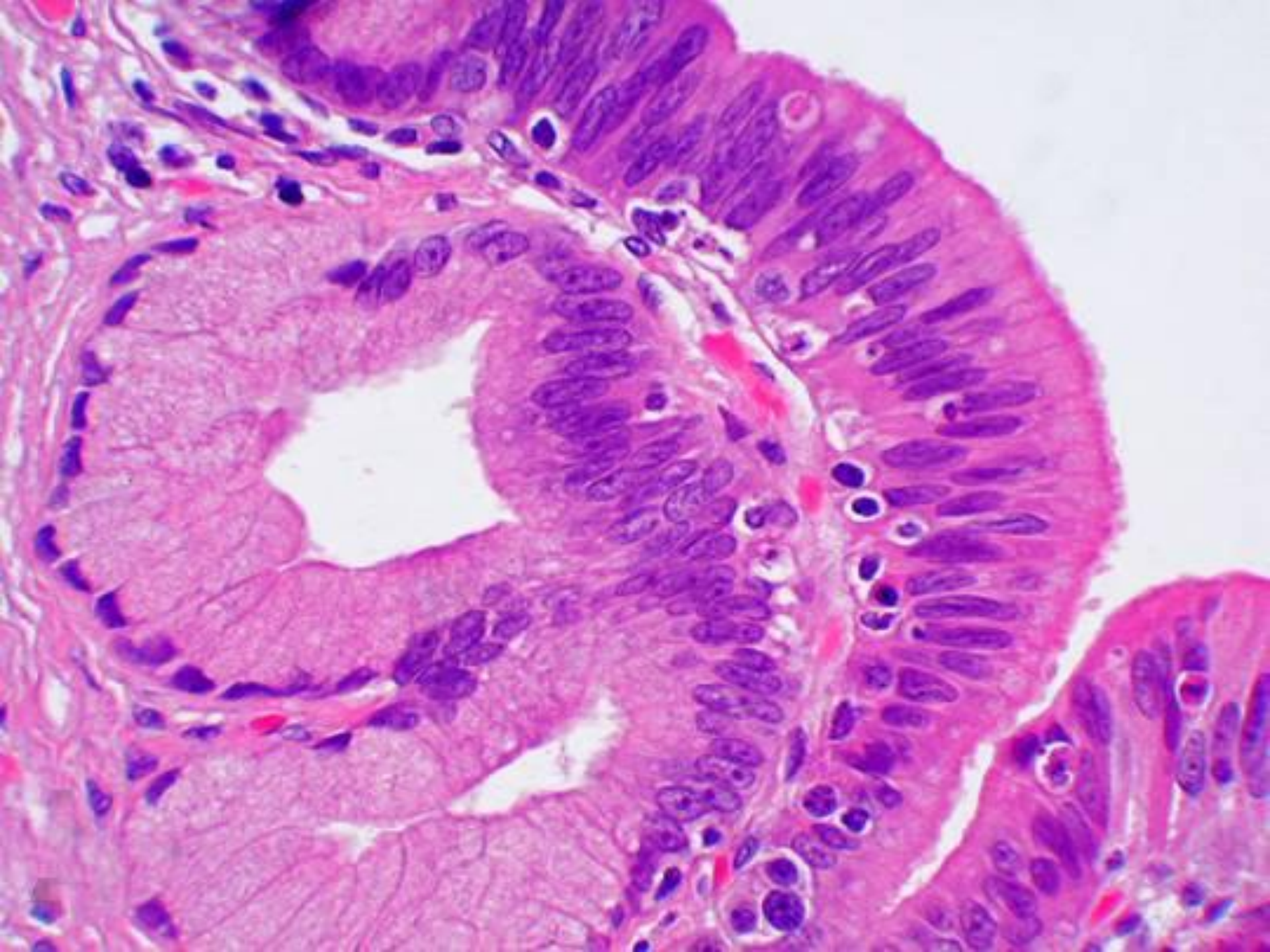
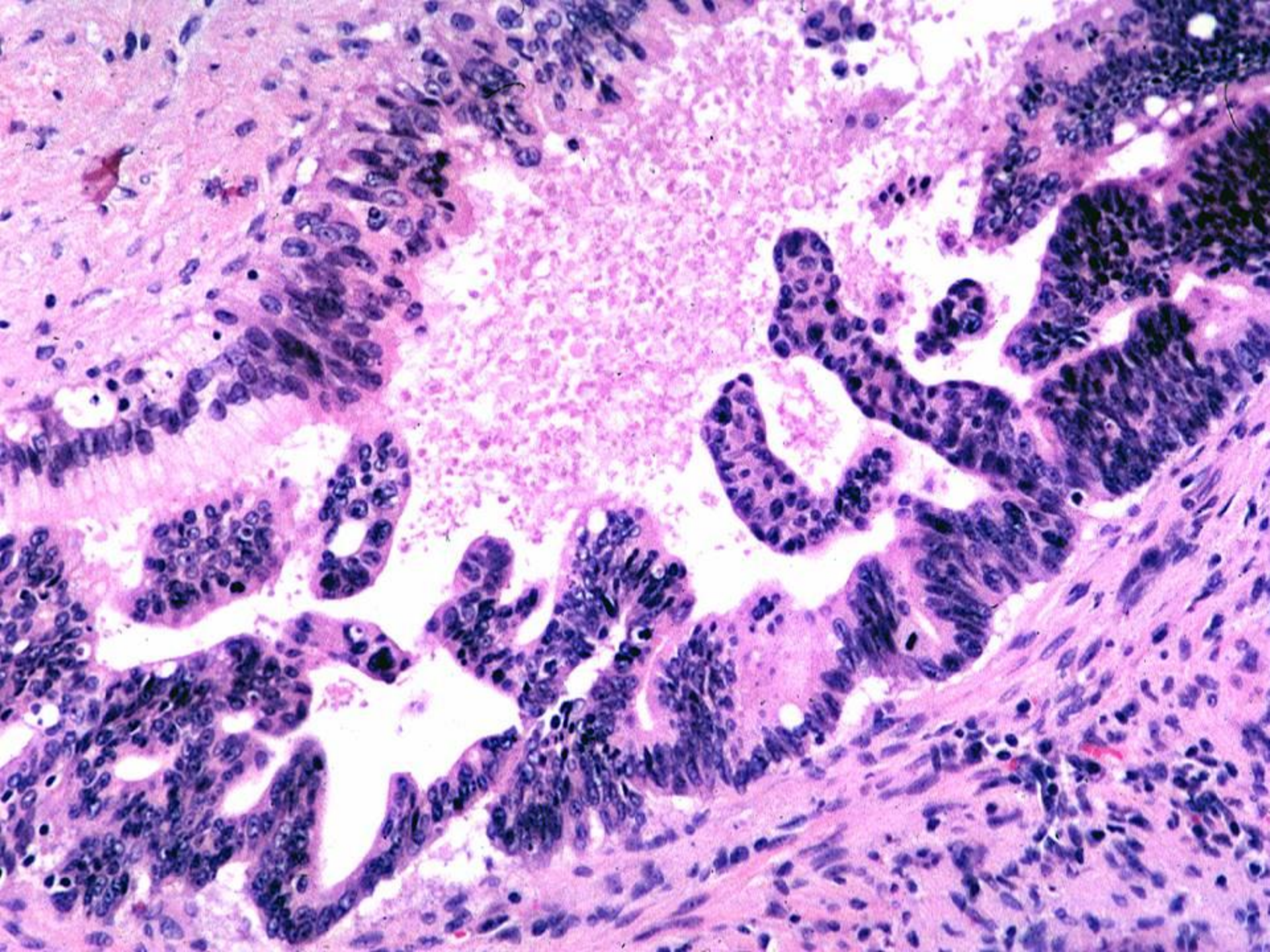
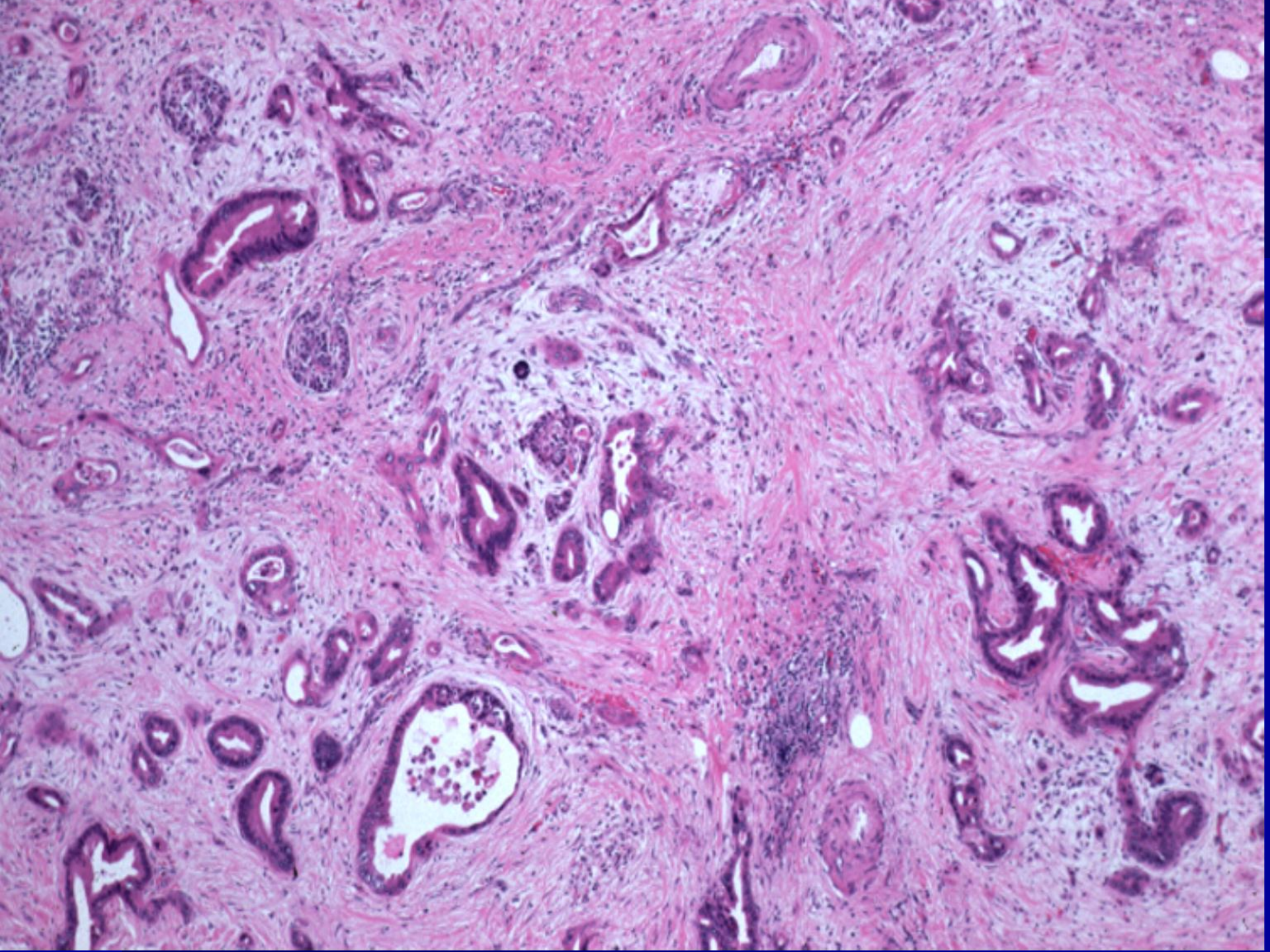
# PanIN: A Problematic Name

- PanIN I: *normal nuclei* + mucinous cytoplasm
- No other neoplasia grading system based on cytoplasm
- Low grade dysplasia = PanIN 2
- High grade dysplasia = PanIN 3 (CIS)
- Poor reproducibility: Kappas 0.4, 0.1, 0.4







# Summary: Early Detection of High Risk Patients

- Pre-invasive pancreatic neoplasia is diagnosable
- Early detection prevents pancreatic cancer
- Screening is cost effective if life time risk is at least 16%