Diagnosing Pancreatic Disease: Help from the Laboratory

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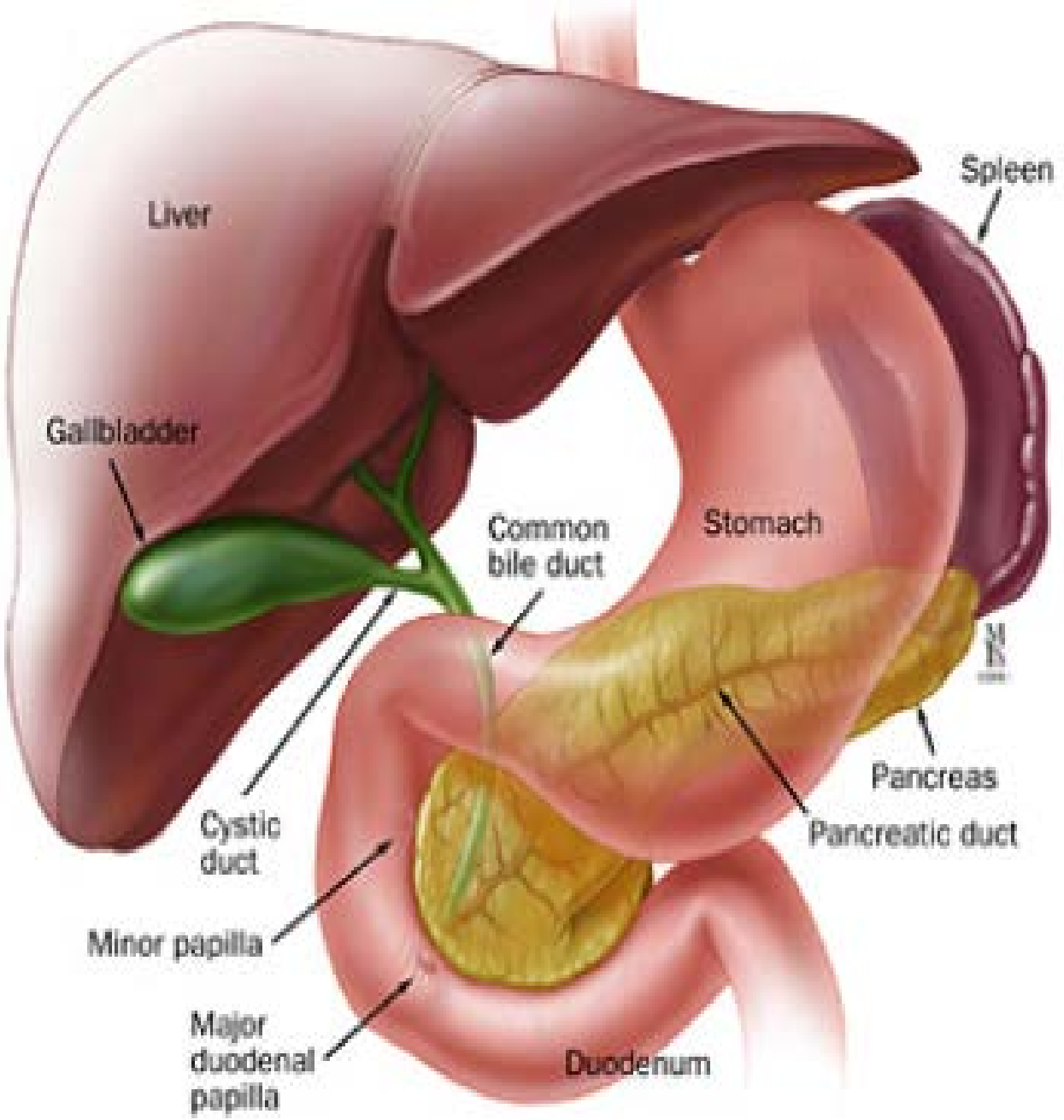
- Speakers are also expected to openly disclose intent to discuss any off-label, experimental, or investigational use of drugs, devices, or equipment in their presentations.
- This speaker has nothing to disclose.

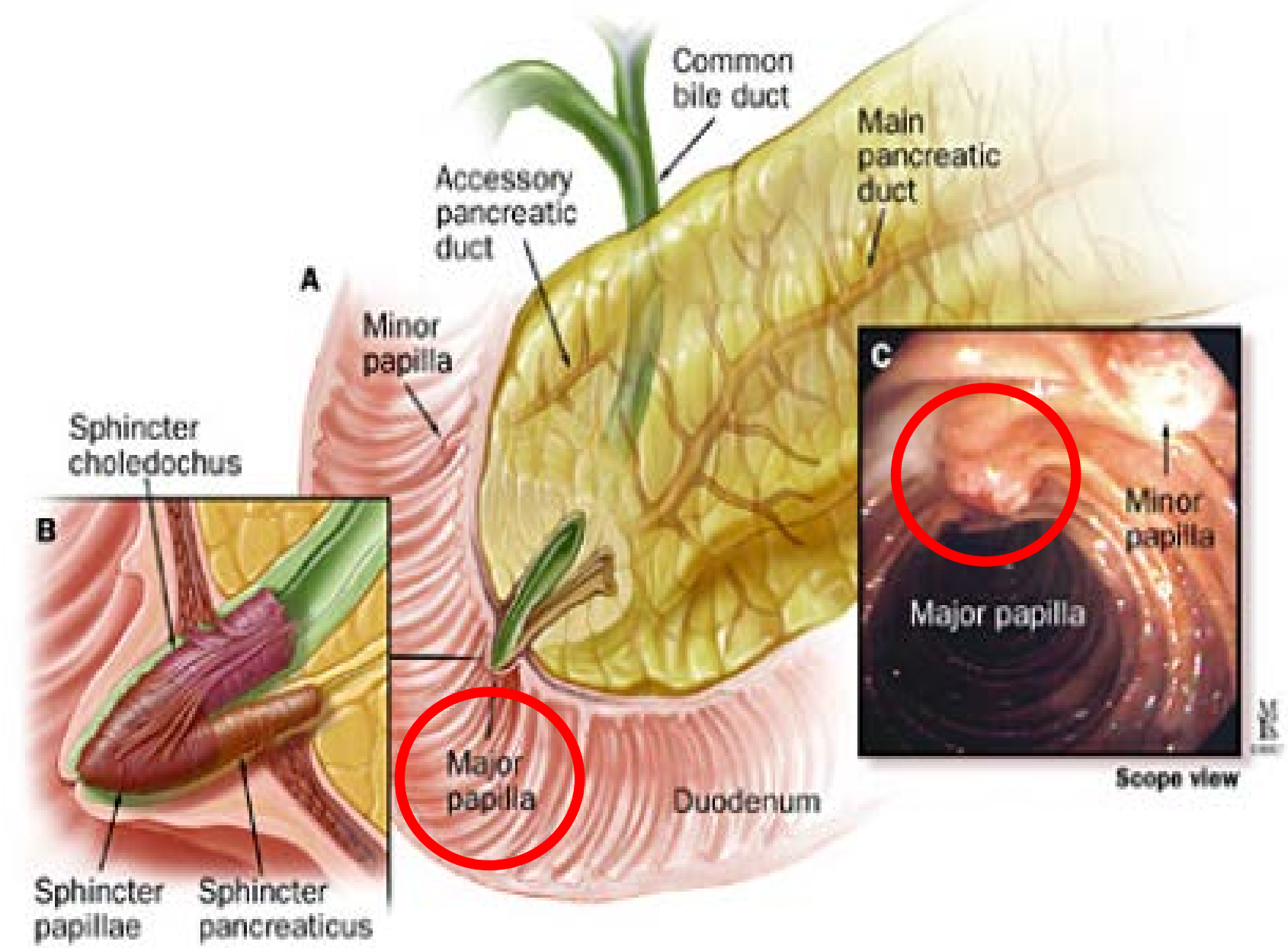
Objectives

1. Diagram basic gross and microscopic pancreatic anatomy
2. Given classic patient scenarios, compare and contrast pancreatic cancer and acute pancreatitis
3. When encountering a screening test in the lab, be able to evaluate advantages and disadvantages of the screening tests
4. List commonly used serum biomarkers for evaluating pancreatic disease

FIRST
Let’s do a quick review:

Anatomy
Histology
Physiology

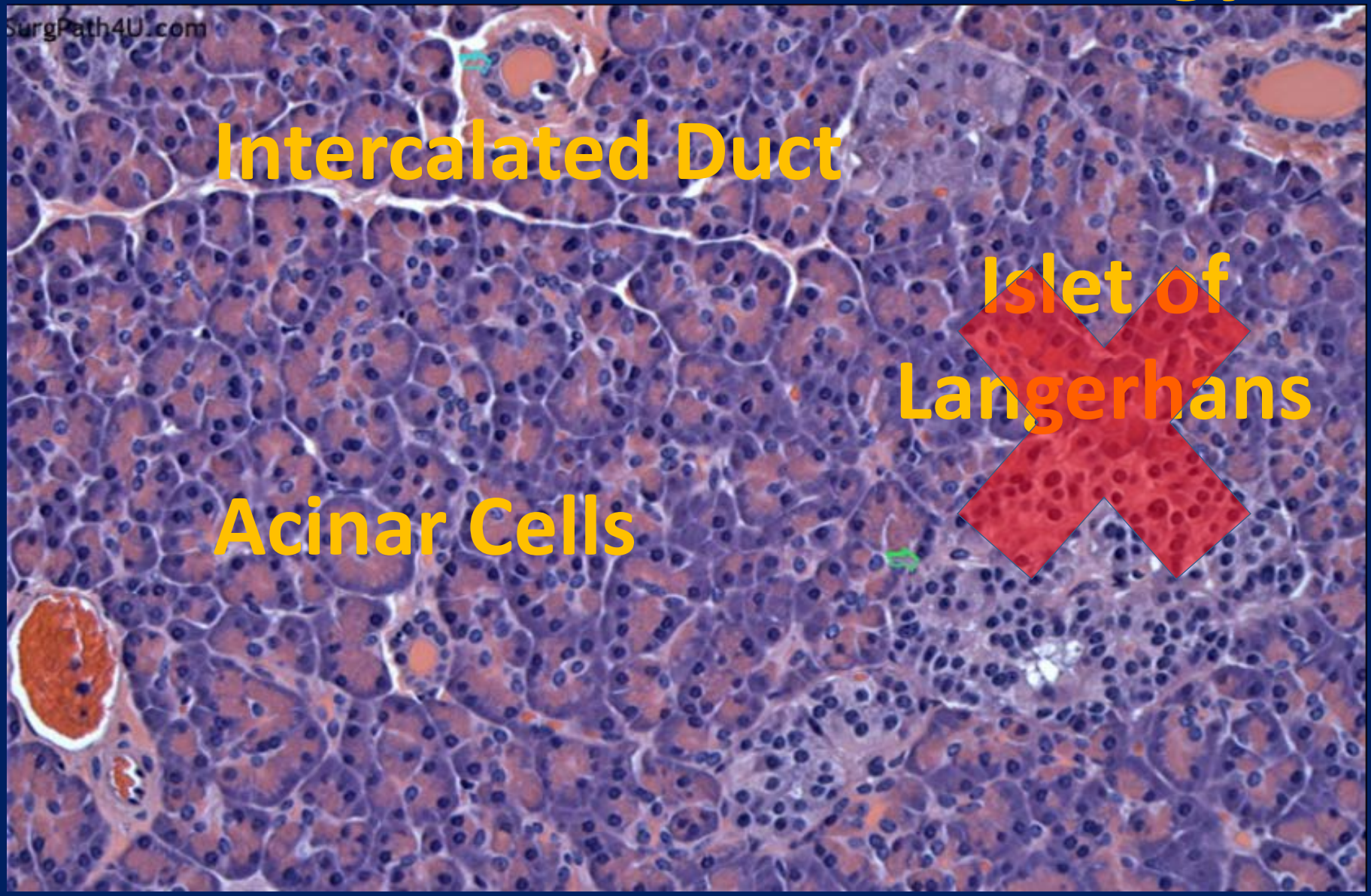

Liver
Spleen
Gallbladder
Common bile duct
Stomach
Pancreas
Cystic duct
Pancreatic duct
Minor papilla
Major duodenal papilla
Duodenum

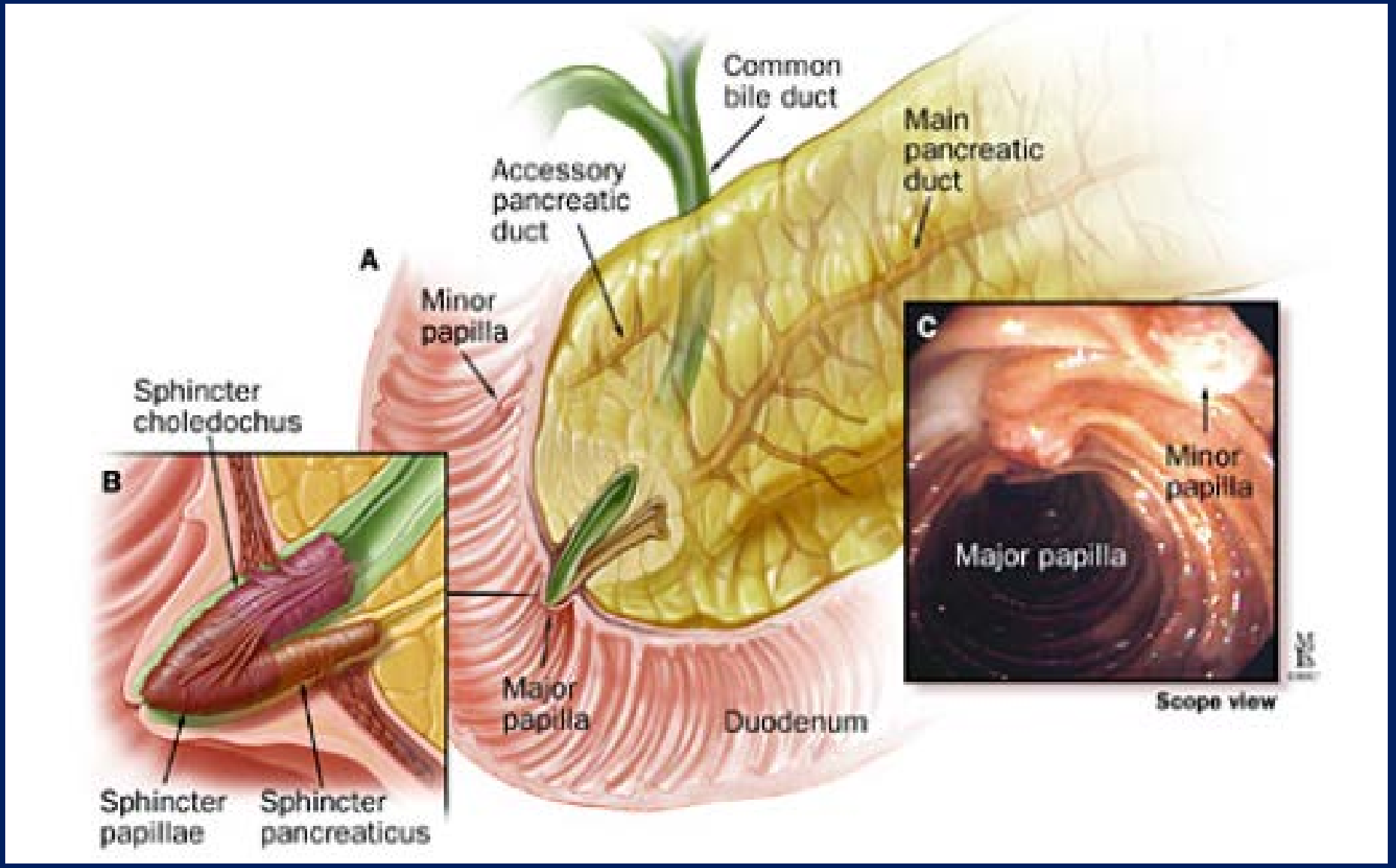


Major duodenal papilla = Ampulla of Vater, Sphincter of Oddi

http://www.hopkins-gi.org

Normal Pancreatic Histology



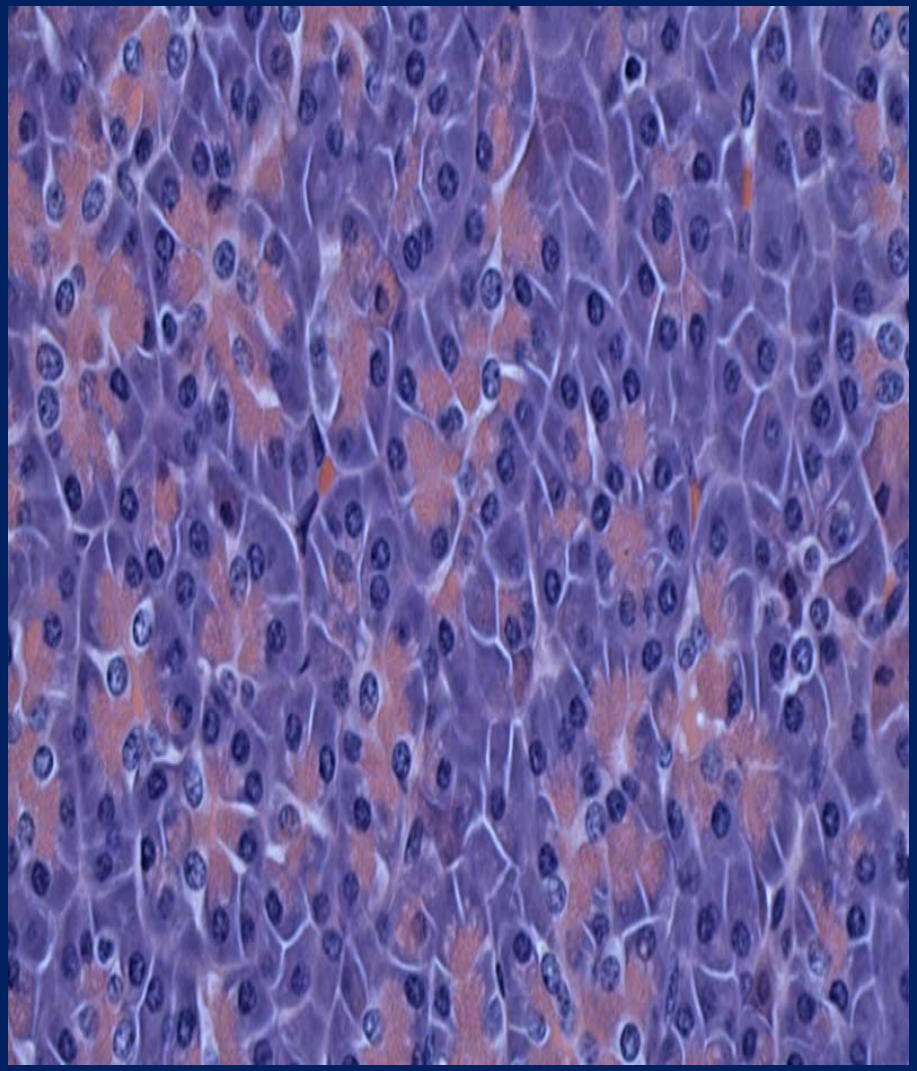


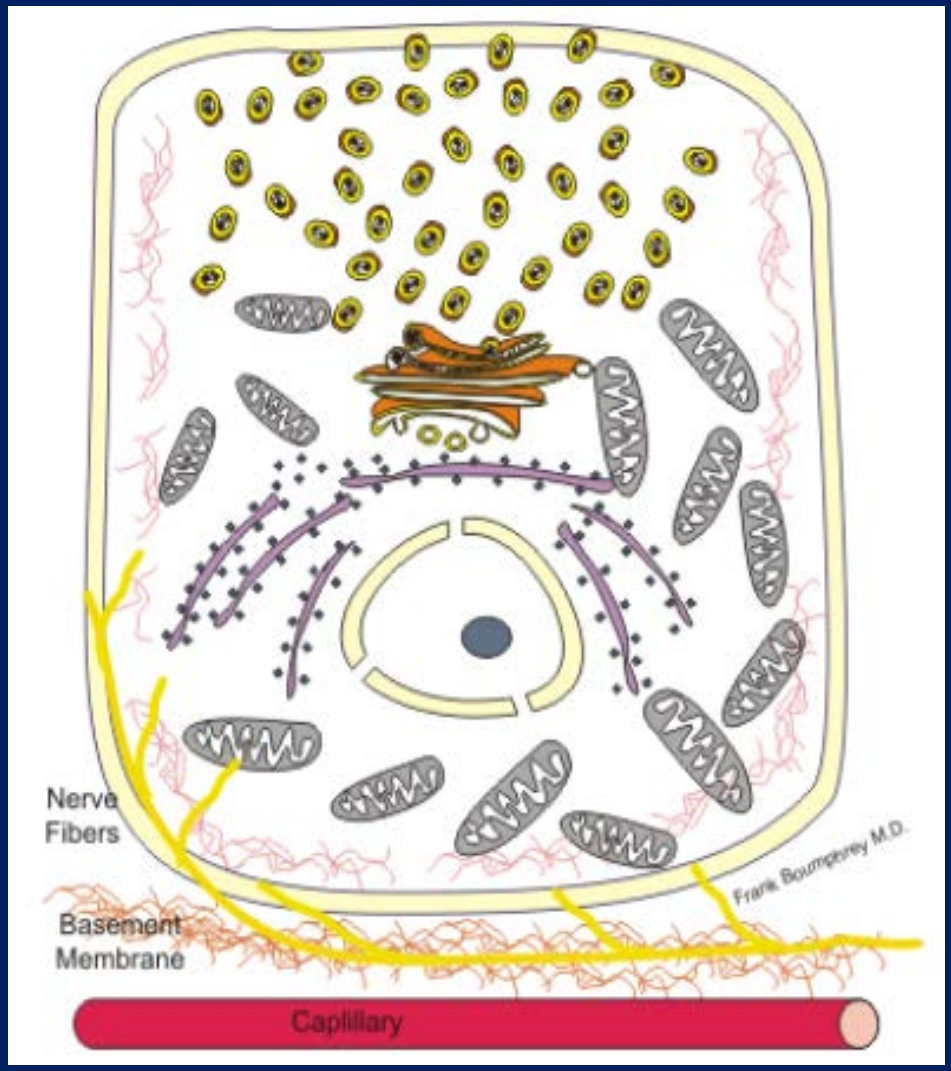
Conduit for acinar cell secretions:

Acinar lumen → intercalated ducts → interlobular ducts → main PD

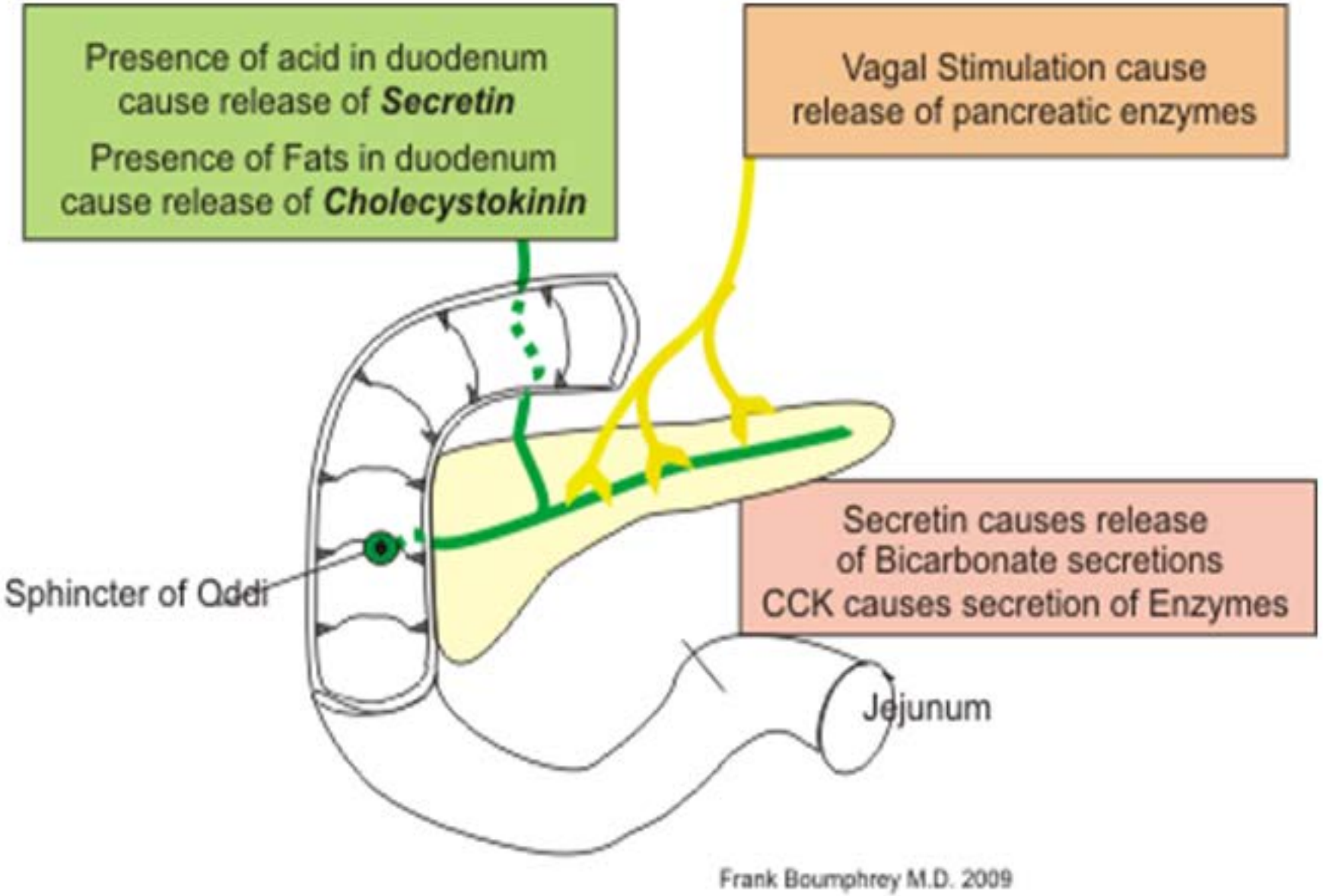
http://www.hopkins-gi.org

Normal Pancreatic Exocrine Histology





Pancreatic Exocrine Function



Pancreatic Exocrine Digestive Function

Nutrient	Enzyme	Product
Carbohydrates and Starch	Amylase	Saccharides
Fats	Lipase and Colipase	Triglycerides
Proteins	Trypsin (trypsinogen)	Peptides
	Chymotrypsin (chymotrypsinogen)	Peptides

Adapted from: http://en.wikibooks.org

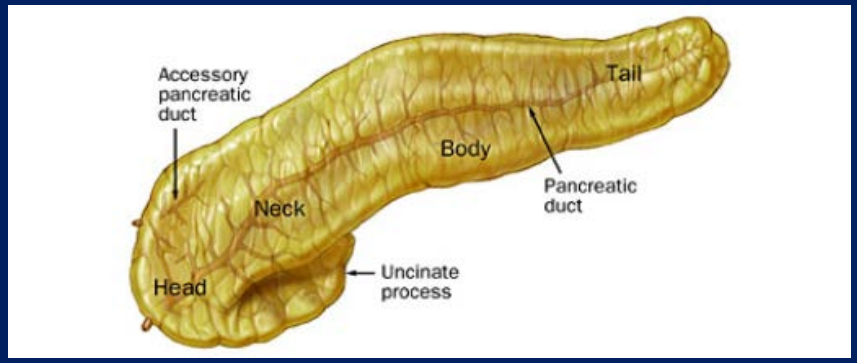
Done with the review:

What could possibly go wrong?

Case #1

- 48-year-old female presents to her primary care physician complaining of severe pain in her upper abdomen
  - Pain radiates to back
  - Present for the past 30 minutes
- Medical history: gallstones and obesity
- Family History: Not significant
- Social History: Negative tobacco and alcohol
- Review of Systems: Nausea, low grade fever

Case #1



- Physical Exam:
  - Abdominal tenderness and guarding
  - Decreased bowel sounds
- Labs:
  - Amylase- 6x upper limit normal
  - Lipase- 10x upper limit normal

DIAGNOSIS?

ACUTE PANCREATITIS

Acute Pancreatitis Pathogenesis

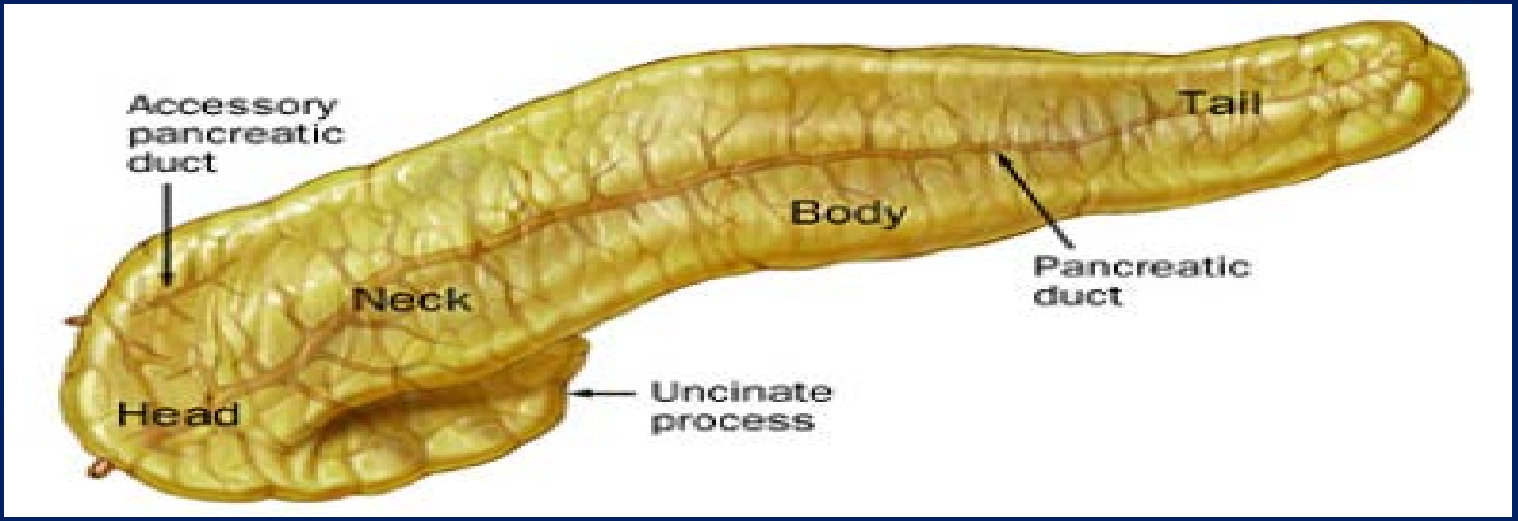
Mechanism - Auto Digestion

Co-localization of lysosomal proteases

Trypsinogen is activated to trypsin

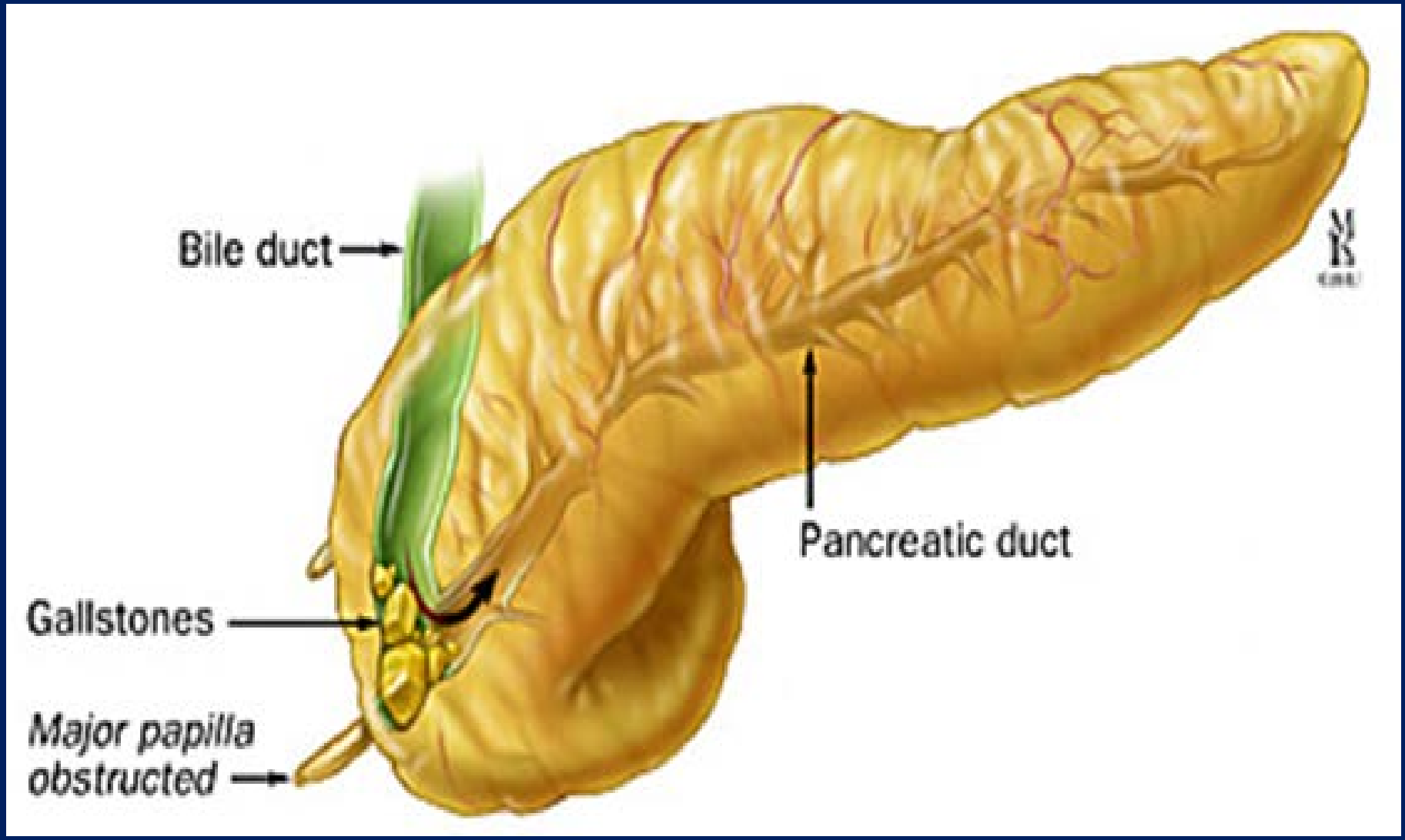
Extensive inflammatory response

Intrapancreatic and Extrapancreatic



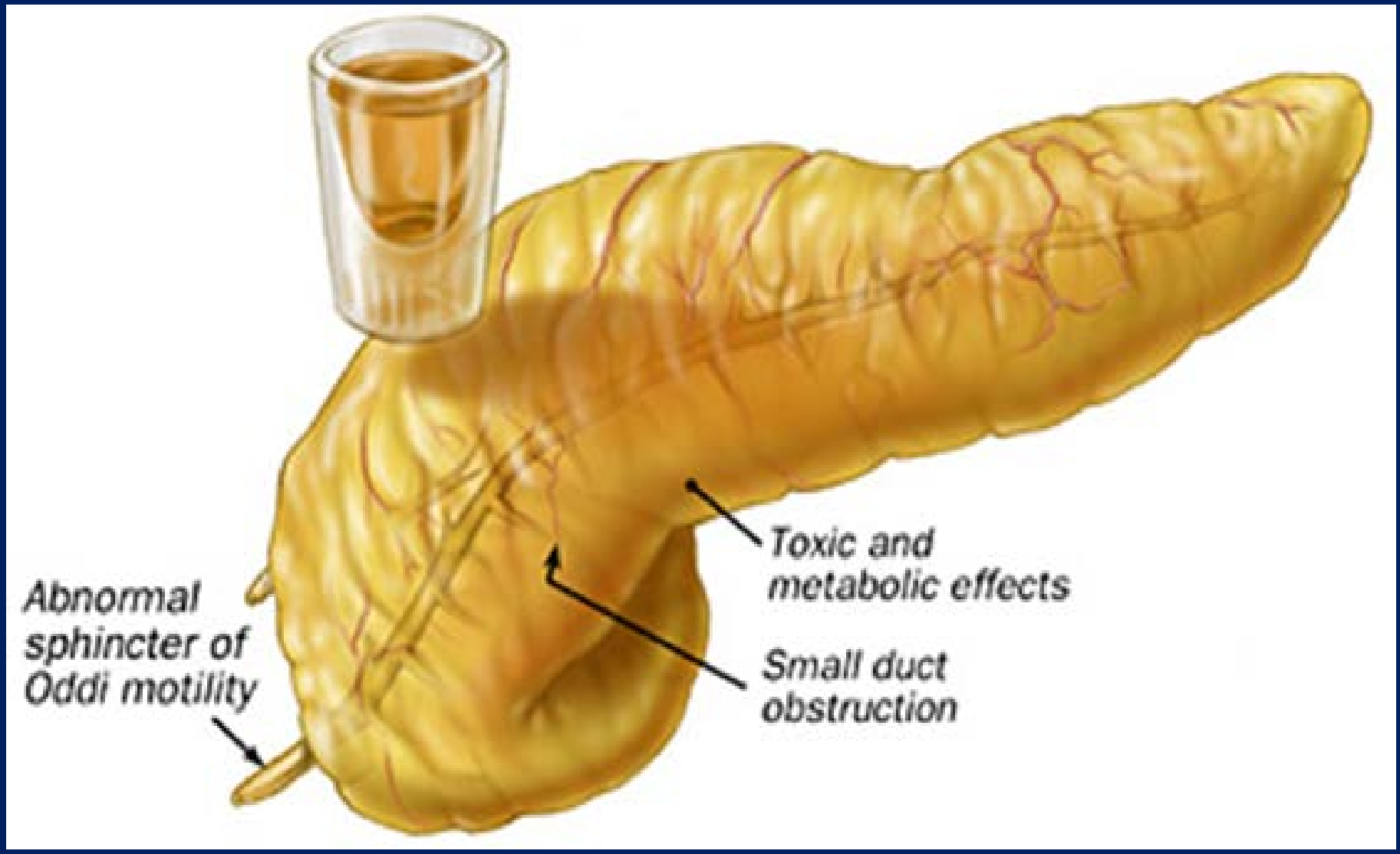
Causes Acute Pancreatitis

Gallstones: Duct obstruction, Reflux of bile



Causes Acute Pancreatitis

Alcohol: Toxic metabolites, sphincter dysmotility



Causes Acute Pancreatitis

Medications:
Azathioprine
6-Mercaptopurine
Bactrim (TMP-SMX)
Pentamidine
Dideoxyinosine (ddI)
Methyldopa

Miscellaneous:

Triglycerides > 1,000 mg/dL

Hypercalcemia

Organophosphates

Infection (Mumps, Ascaris)

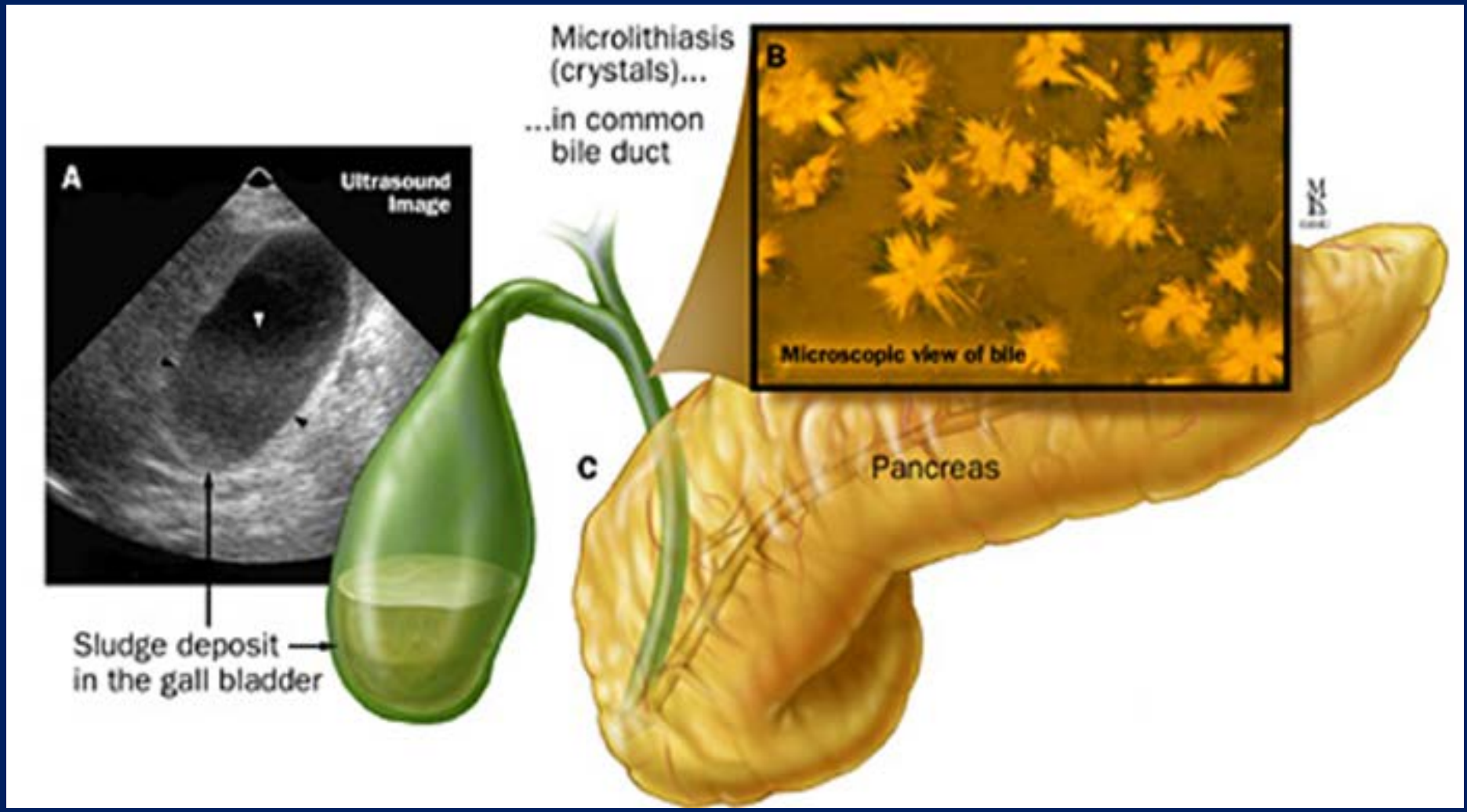
Cystic Fibrosis

Trauma

Scorpion sting

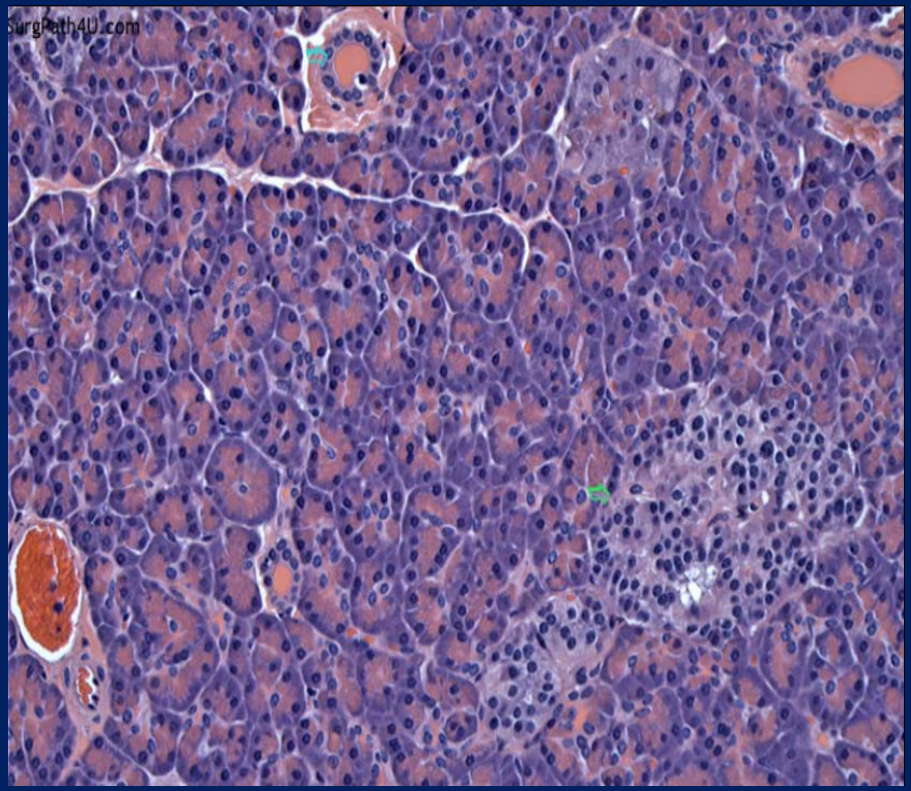
Causes Acute Pancreatitis

Idiopathic: Probable Microlithiasis (small stones)

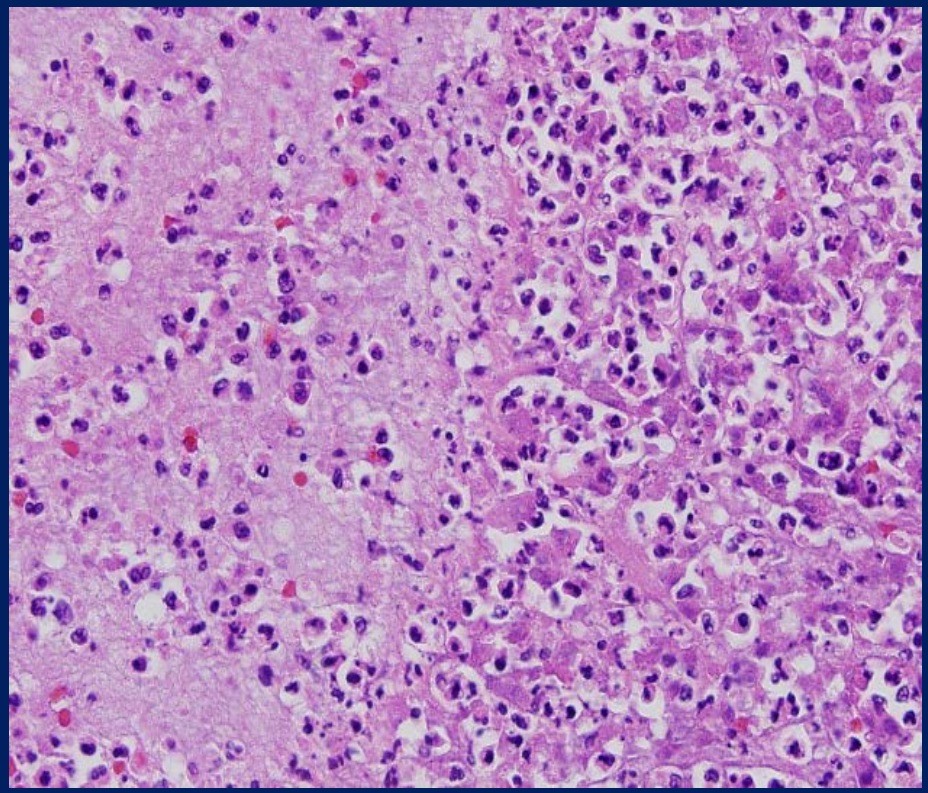


Acute Pancreatitis

- Pancreatitis ranges from mild (inflammatory process and edema) to severe (necrotic process and secondary extra pancreatic injury)



Normal Histology



http://www.musc.edu/pathology
http://www.surgpath4u.com

How could we diagnose our patient so quickly?

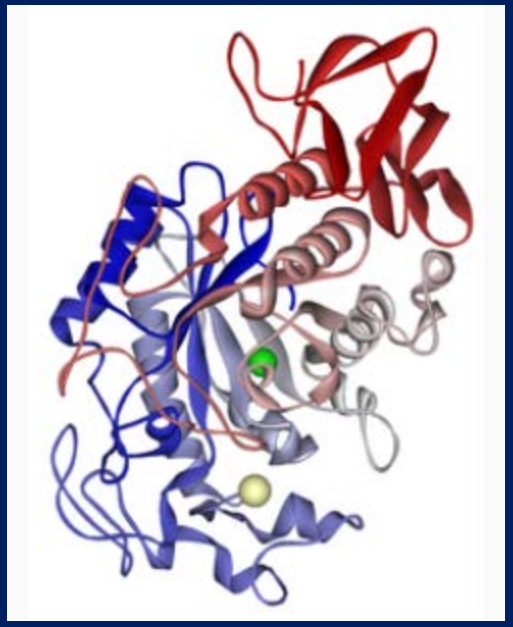
Severe abdominal pain

Elevated serum amylase & lipase levels

Initial diagnosis of acute pancreatitis

USEFUL LAB TEST:

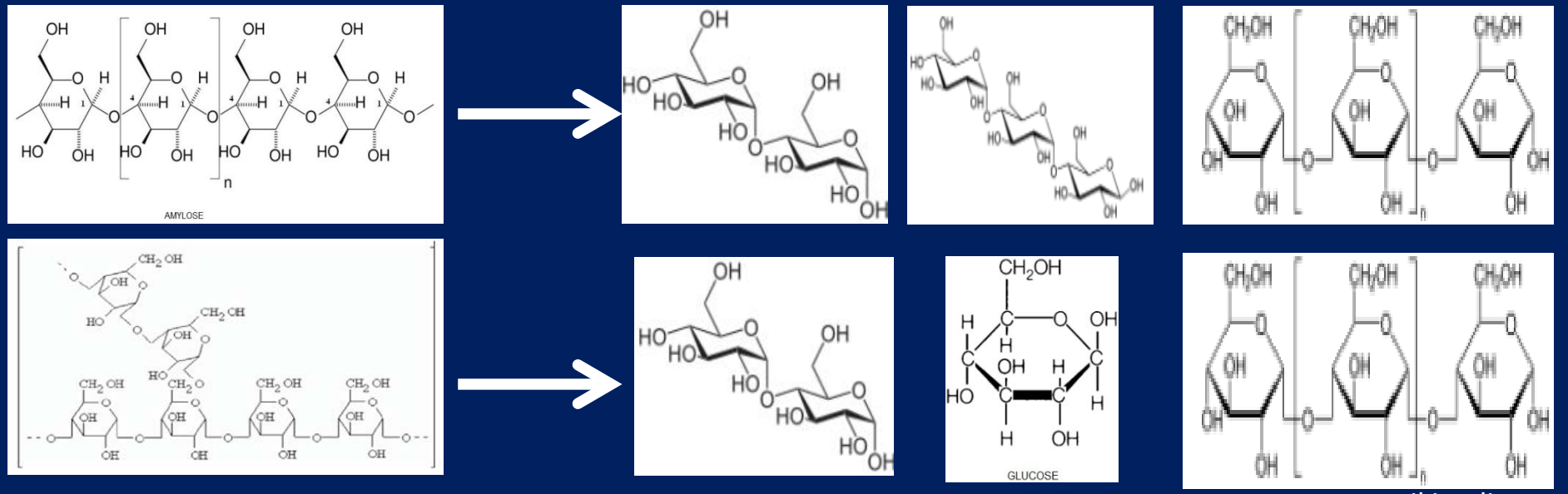
Amylase



www.wikipedia.org

Amylase

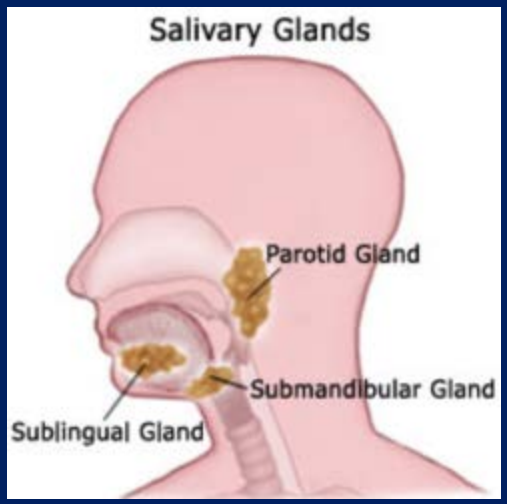
- Amylases are glycoside hydrolases
  - Alpha amylase
    - Ca^{2+} metalloenzyme (unable to function in absence of Ca2+)
    - Acts at random locations along a starch chain, yielding:
      - Maltotriose, maltose and limit dextrin from amylose
      - Maltose, glucose and limit dextrin from amylopectin

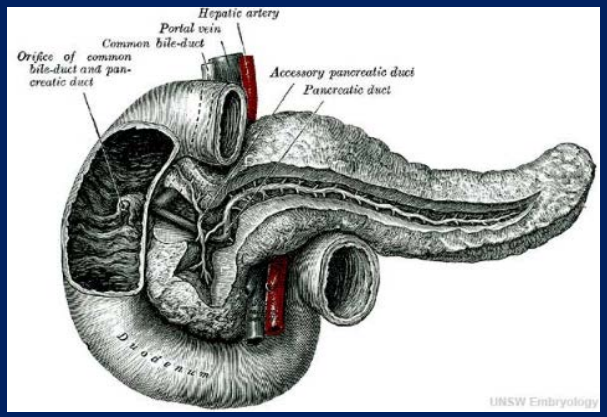


www.wikipedia.org

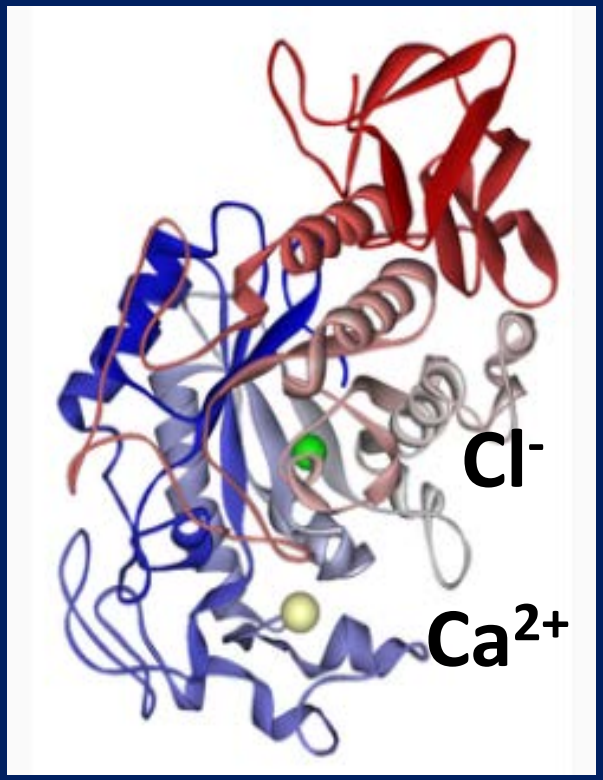
Amylase Sources/ Activators

- Salivary
  - S-amylase
- Pancreatic
  - P-amylase



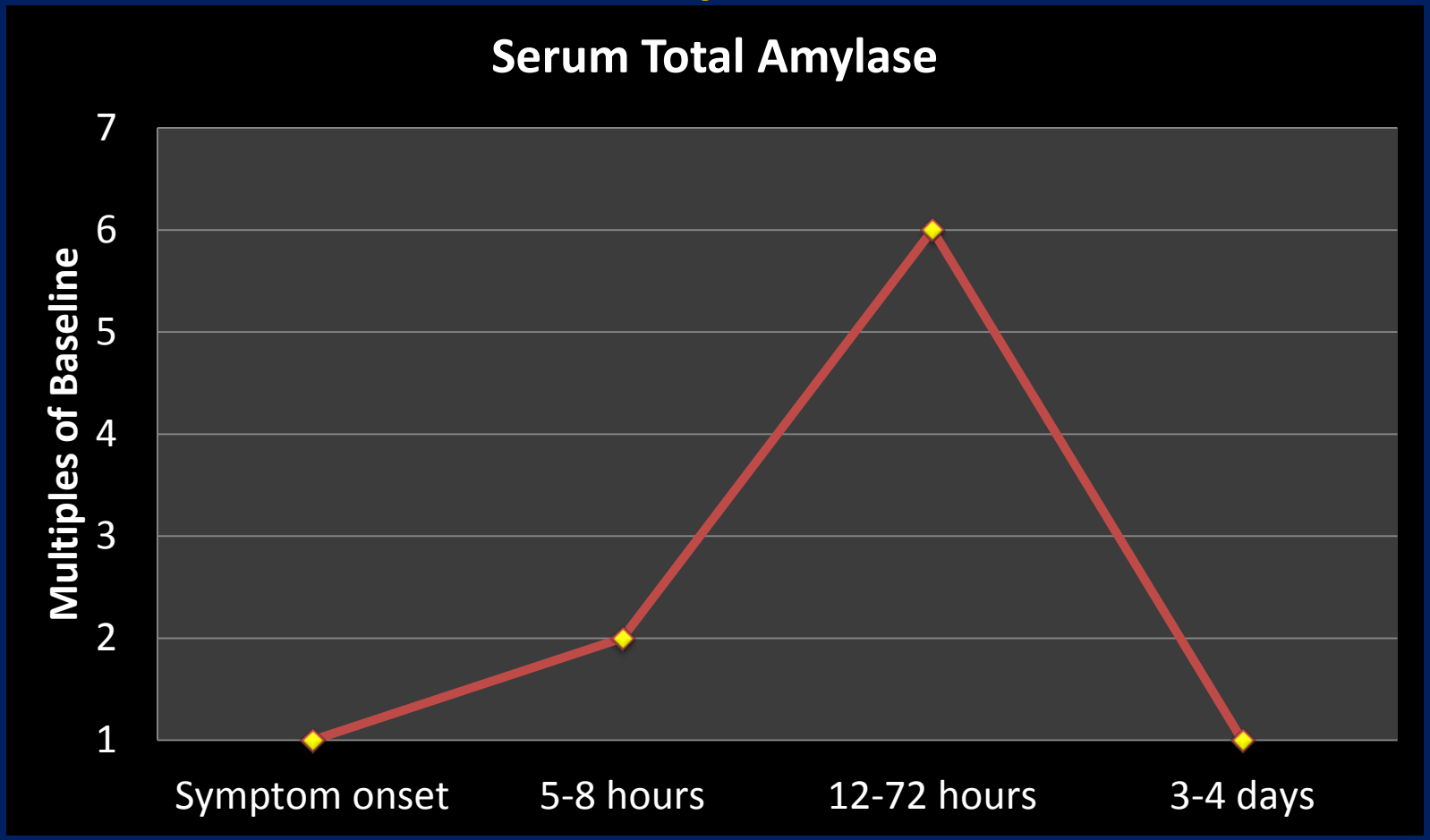


- CALCIUM AND
- Chloride

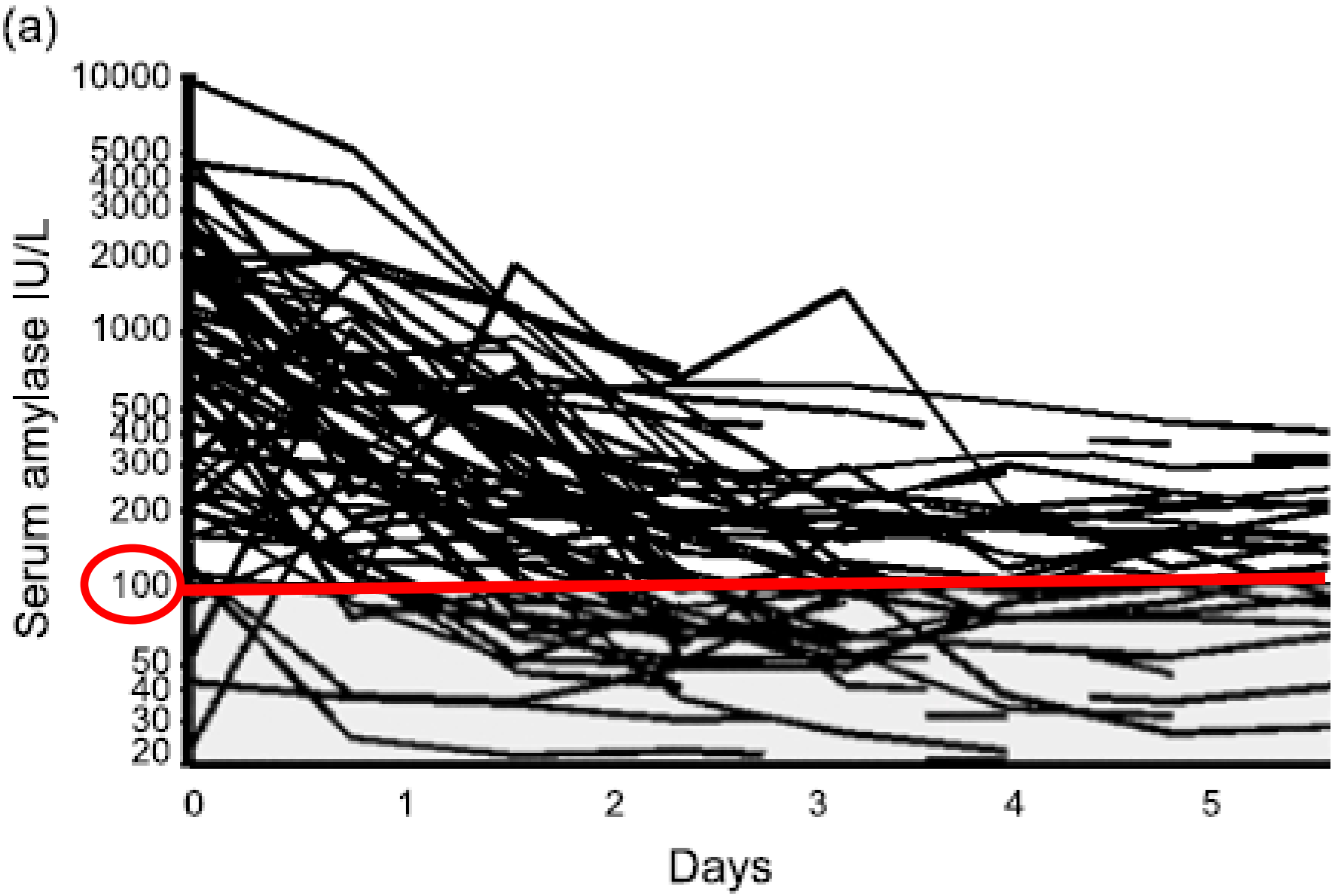


http://embryology.med.unsw.edu
http://leavingbio.net
www.wikipedia.org

Amylase



- Plasma enzyme found in the urine (small molecule- 54,000- 62,000 MW)
- Magnitude of elevation not correlated to severity
- Magnitude of elevation = greater probability acute pancreatitis



Should serum pancreatic lipase replace serum amylase as a biomarker of acute pancreatitis? Smith et al 2006

Causes of Increased Amylase

False positive test if looking for acute pancreatitis

Lack of specificity for total AMY

↑ Specificity (90%): P-AMY and 3x the upper ref limit

Pancreatic Disease	Pancreatitis (P-AMY)
	Pancreatic Trauma (P-AMY)
Other Intraabdominal Disease	Biliary Tract Disease (P-AMY)
	Intestinal Obstruction (P-AMY)
	Mesenteric Infarction (P-AMY)
	Perforated peptic ulcer (P-AMY)
	Gastritis, Duodenitis (P-AMY)
	Ruptured Aortic Aneurysm
	Acute Appendicitis
	Peritonitis
	Trauma
Genitourinary Disease	Ruptured Ectopic Pregnancy (S-AMY)
	Salpingitis (S-AMY)
	Ovarian Malignancy (S-AMY)
	Renal Insufficiency (mixed)
Misc	Salivary gland lesion, Acute alcoholic abuse, DKA, Macroamylasemia

Adapted from Teitz Textbook Ch 21 Enzymes

Macroamylasemia

- Complexes: amylase (usually S-type) and IgG or IgA
- Cannot filter through the glomeruli (MW > 200,000); ultrafiltration assay, decreased amylase to CrCl ratio (<1%), or urine amylase level
- No clinical symptoms associated
- 2.5% of hyperamylasemic patients and 1% of healthy subjects

Decreased Amylase

False Negatives:

Serum amylase may be normal (10% of cases)

Depleted acinar cell mass (necrosis)

Acute pancreatitis caused by high triglycerides

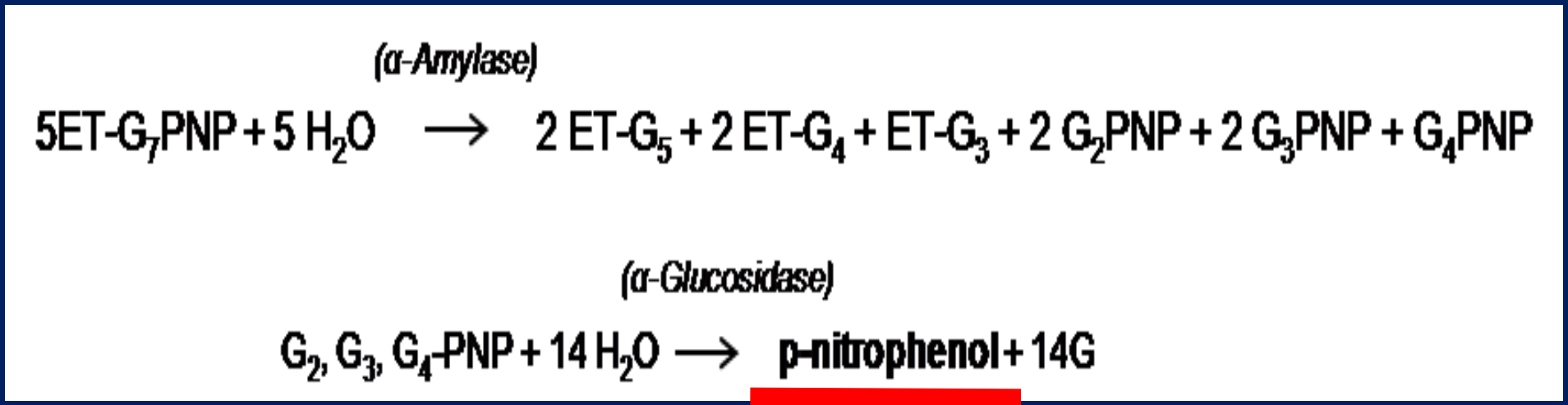
Take note of lipemic samples

Increase Sensitivity if use P-AMY, may be increased (in 80% of patients) up to 7-days post episode

Thank you Dr. Straseski

Amylase Method

- Can measure substrate decrease viscometrically, turbidimetrically, nephelometrically, amyloclastically
- Saccharogenic and kinetic (spectrophotometric) measurements used more commonly now
  - Saccharogenic assays measure glucose production
- Kinetic method correlates with HPLC measurement

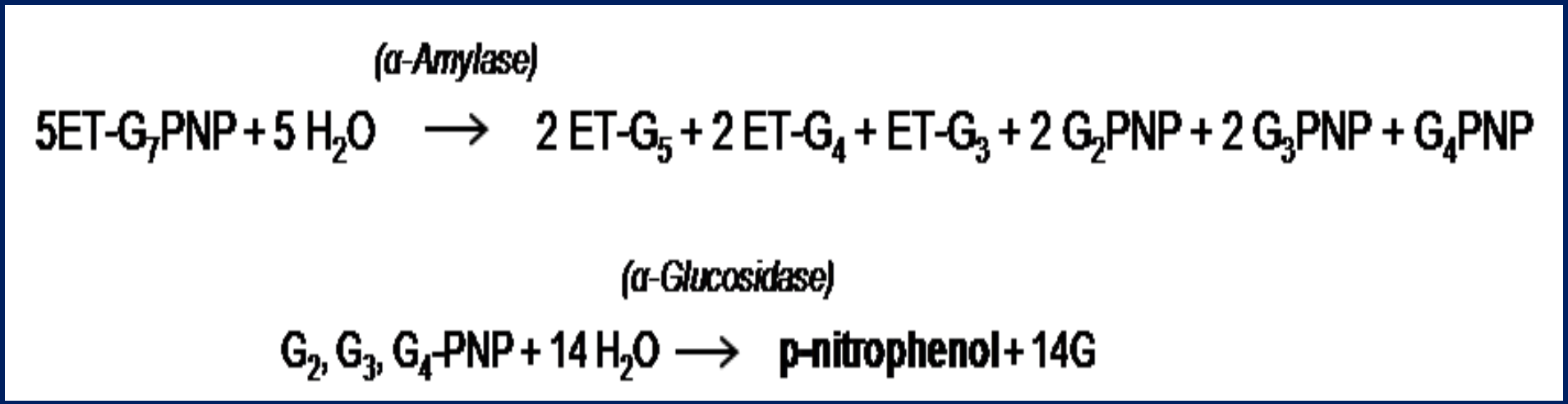


ET = ethylidene
G = glucose
PNP = p-nitrophenol

Measuring P-Amylase Activity

Inhibit S-AMY

with monoclonal antibodies



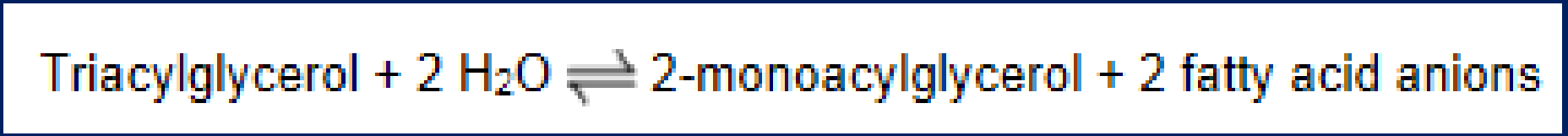
USEFUL LAB TEST:

Lipase

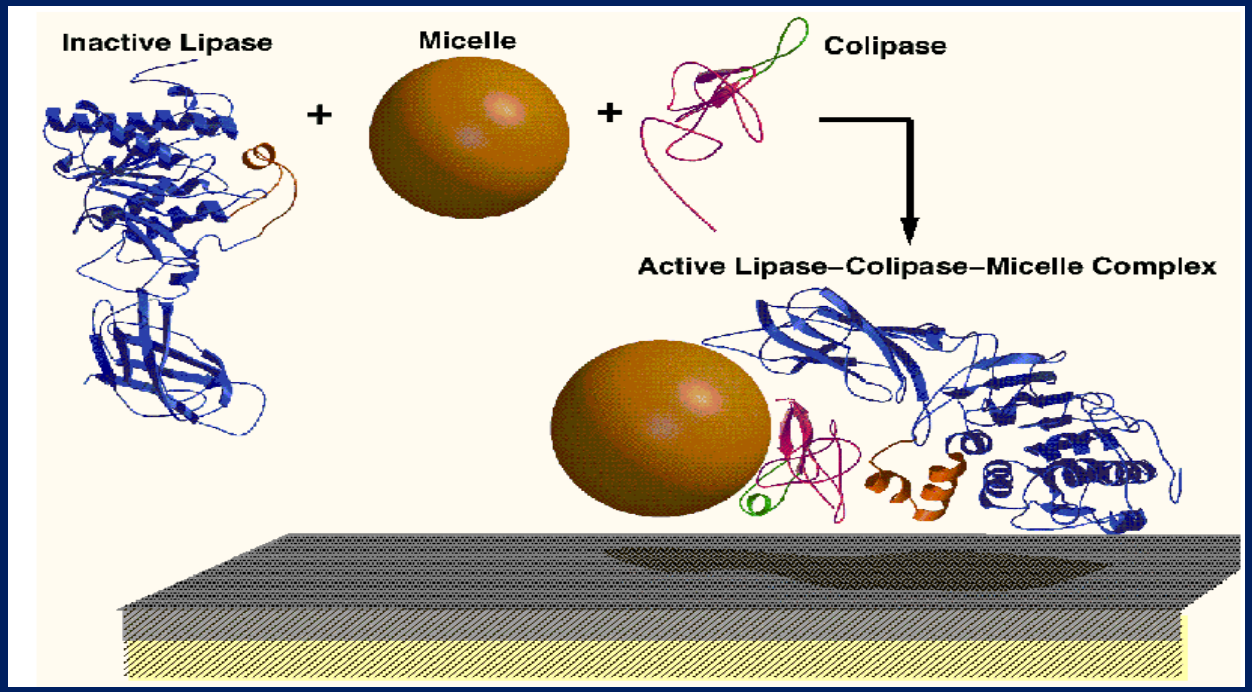
www.wikipedia.org

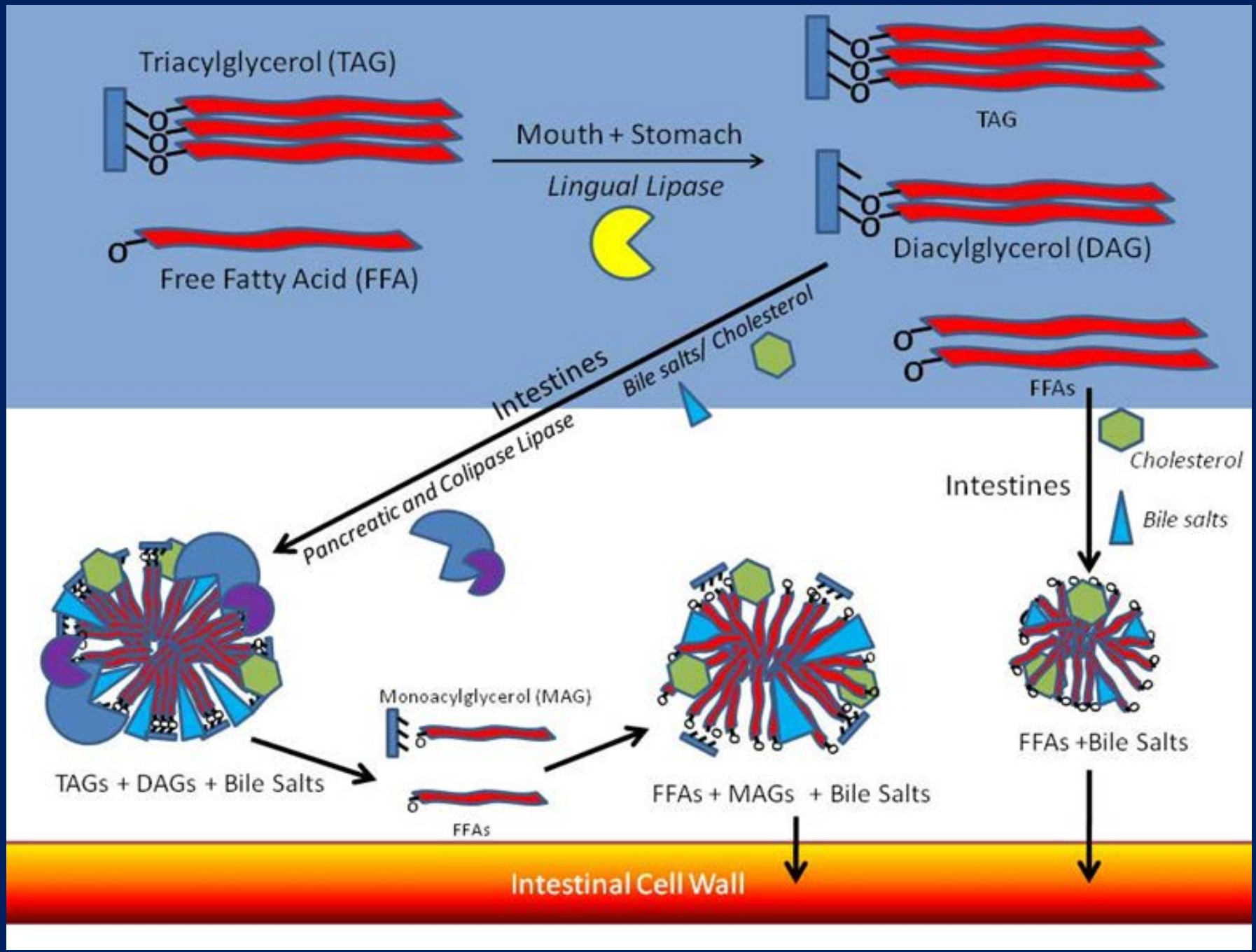
Human Pancreatic Lipase (HPL)

- Lipases are a subclass of the esterases; hydrolyze triglyceride substrates to monoglycerides and FFA

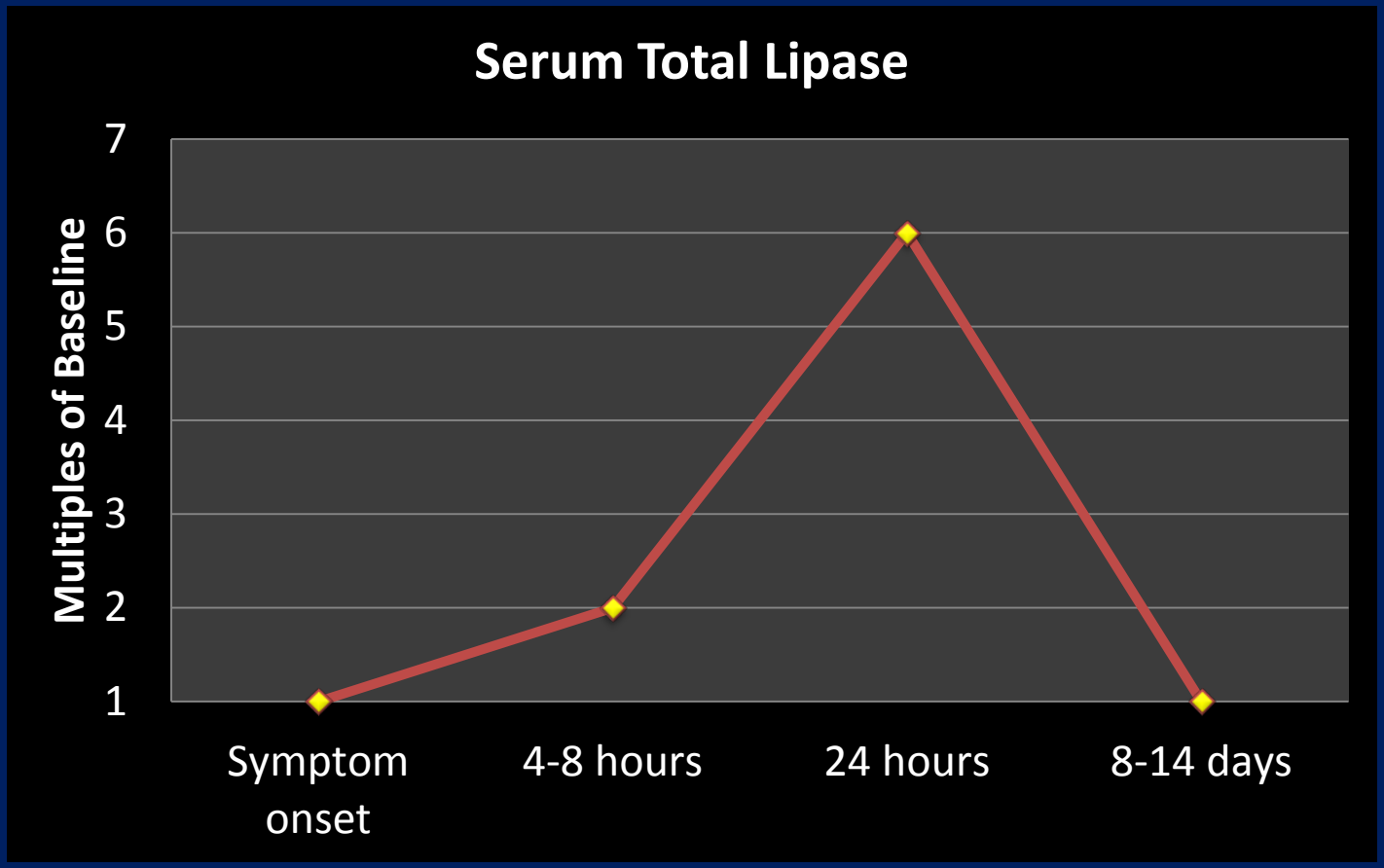


- Activated Ternary Complex
  - Lipase
  - Bile Salt Micelle
  - Colipase



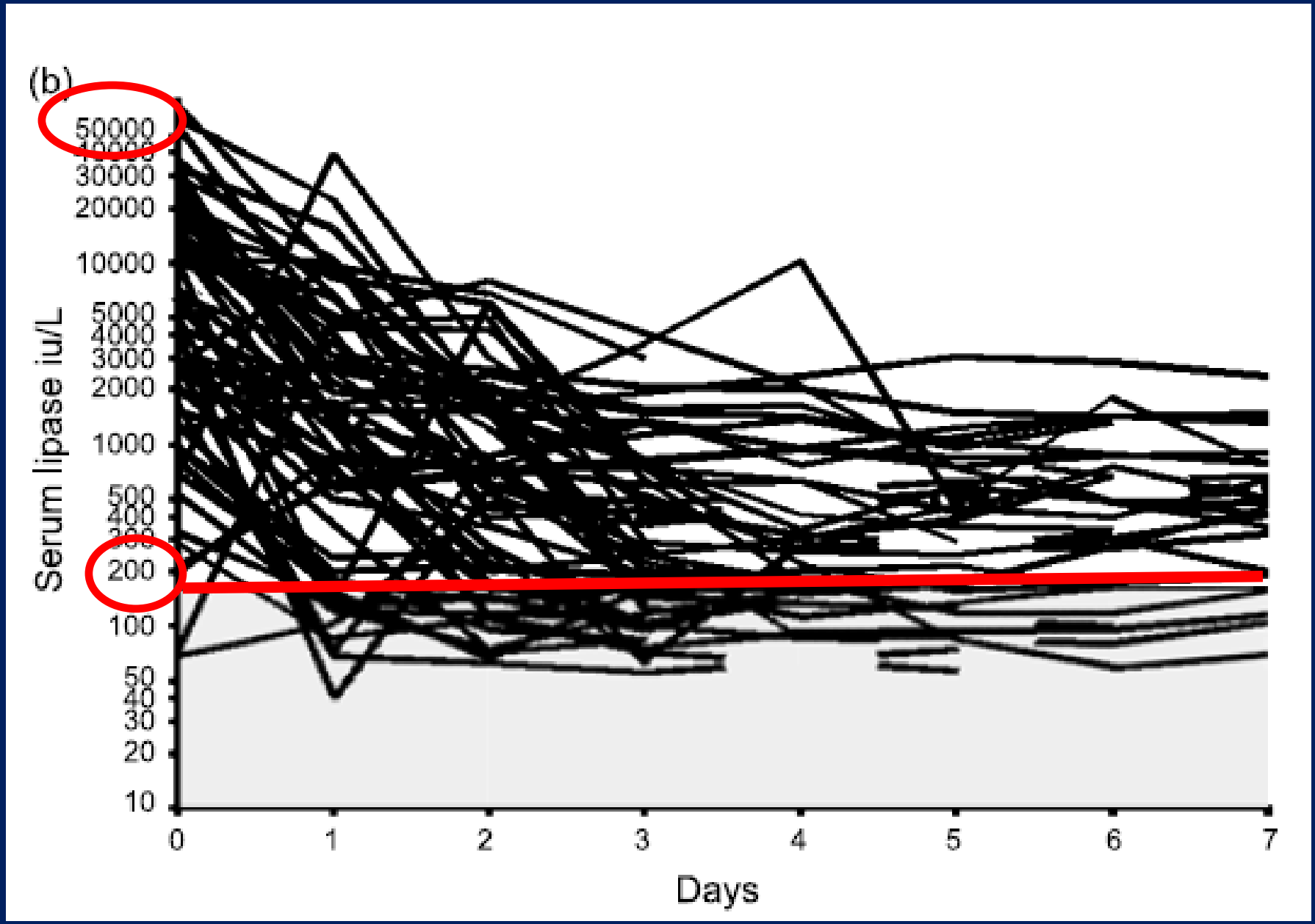


Lipase



Concentrations remain elevated longer than amylase

Magnitude of elevation not correlated to severity



Should serum pancreatic lipase replace serum amylase as a biomarker of acute pancreatitis? Smith et al 2006

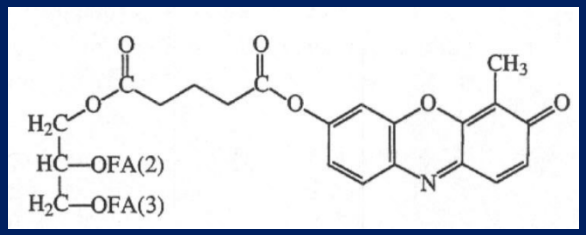
Lipase

- Sensitivity and Specificity are 80-100% depending on patient population and diagnostic cutoff
- Increased if use guideline- likely acute pancreatitis if >5x upper limit of reference range
- False positives: Obstruction of duct (carcinoma), reduced glomerular filtration rate, Opiates (cause sphincter of Oddi to contract)

Thank you Dr. Straseski

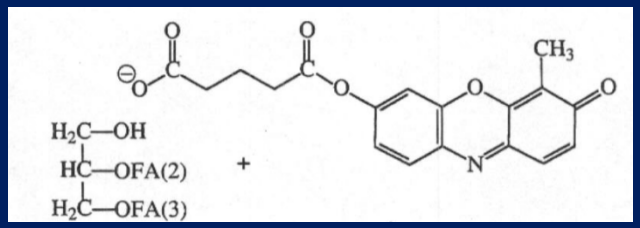
Lipase Activity: Laboratory Measurement

- Enzymatic method
- Cleavage of chromogenic lipase substrate emulsified with bile acid and colipase in alkaline medium
- Rate of color is directly proportional



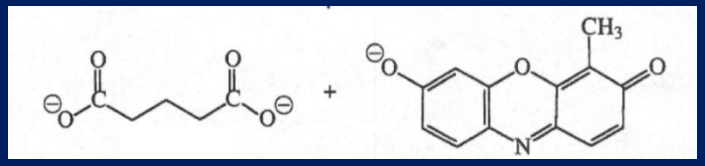
1,2-O-dilauryl-rac-glycero-3-glutaric acid-(6-methylresorufin) ester

Lipase →



1,2-O-dilauryl-rac-glycerol + glutaric acid-(6-methylresorufin) ester

Spontaneous decomposition ↓

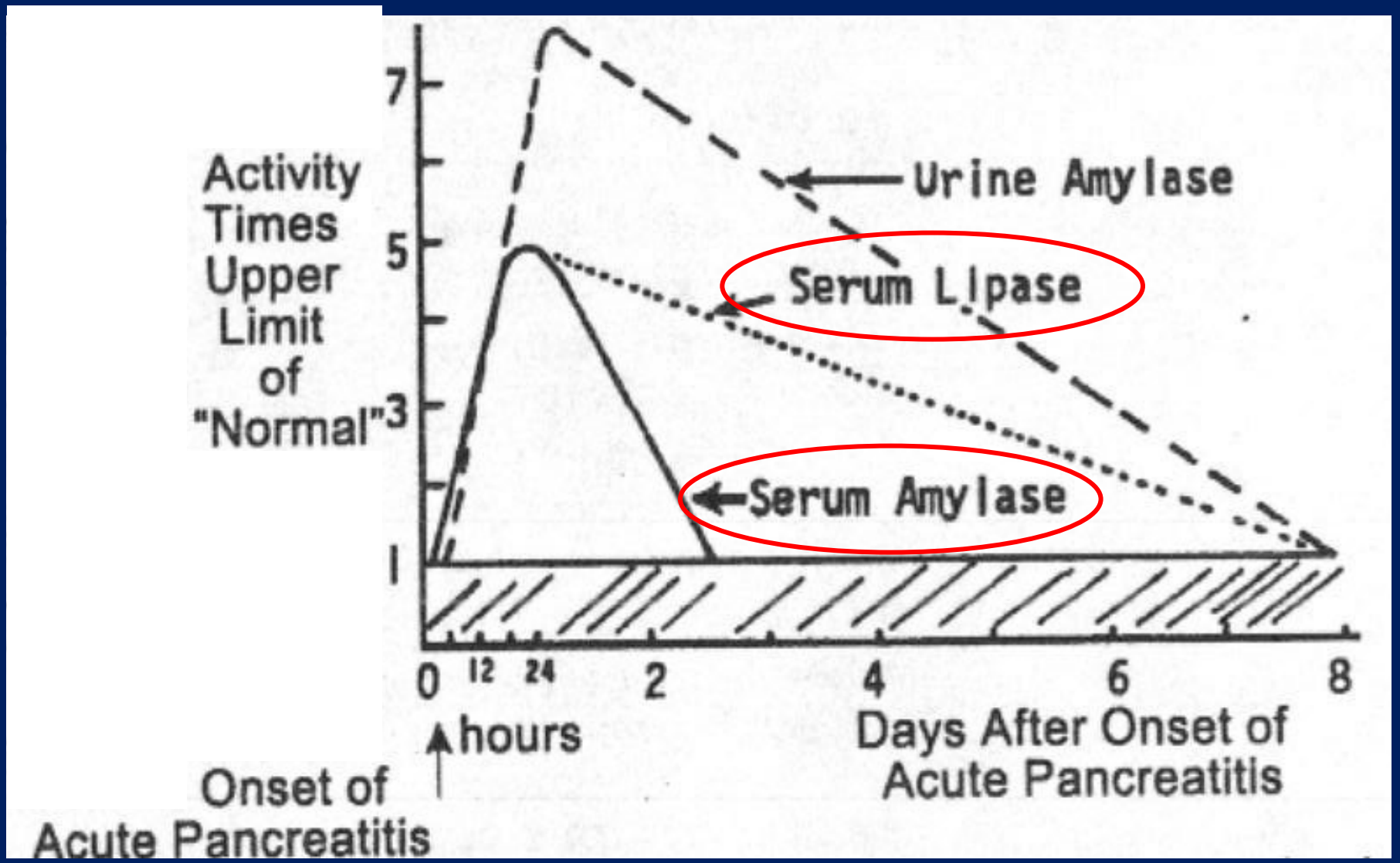


glutaric acid + **methylresorufin**

Red dye measured at 570 nm

Reference ranges = 16 – 63 IU/L

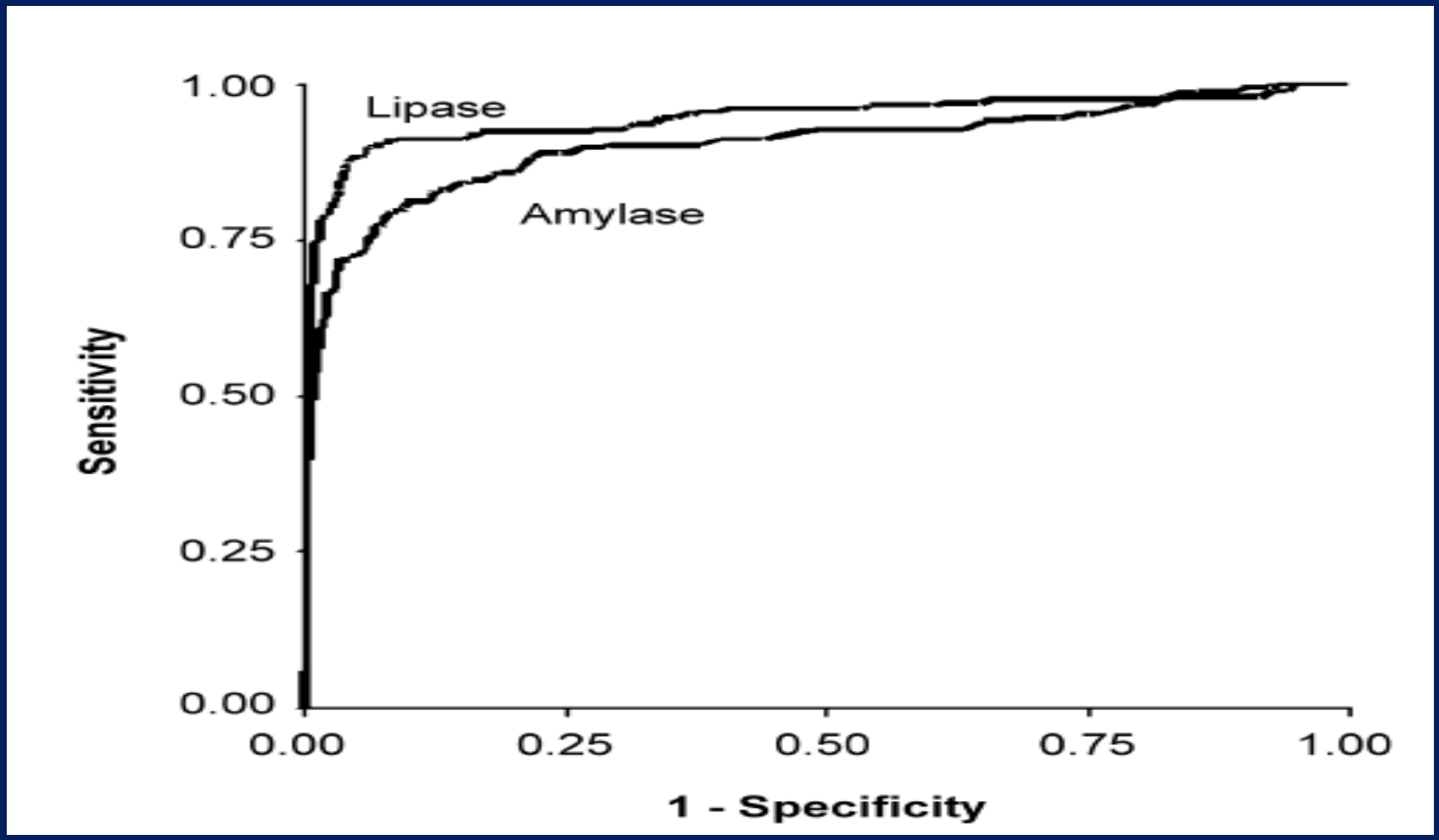
Diagnosis: Acute Pancreatitis



Thank you Dr. Straseski

Bakerman's ABC's, 4th edition, 2002.

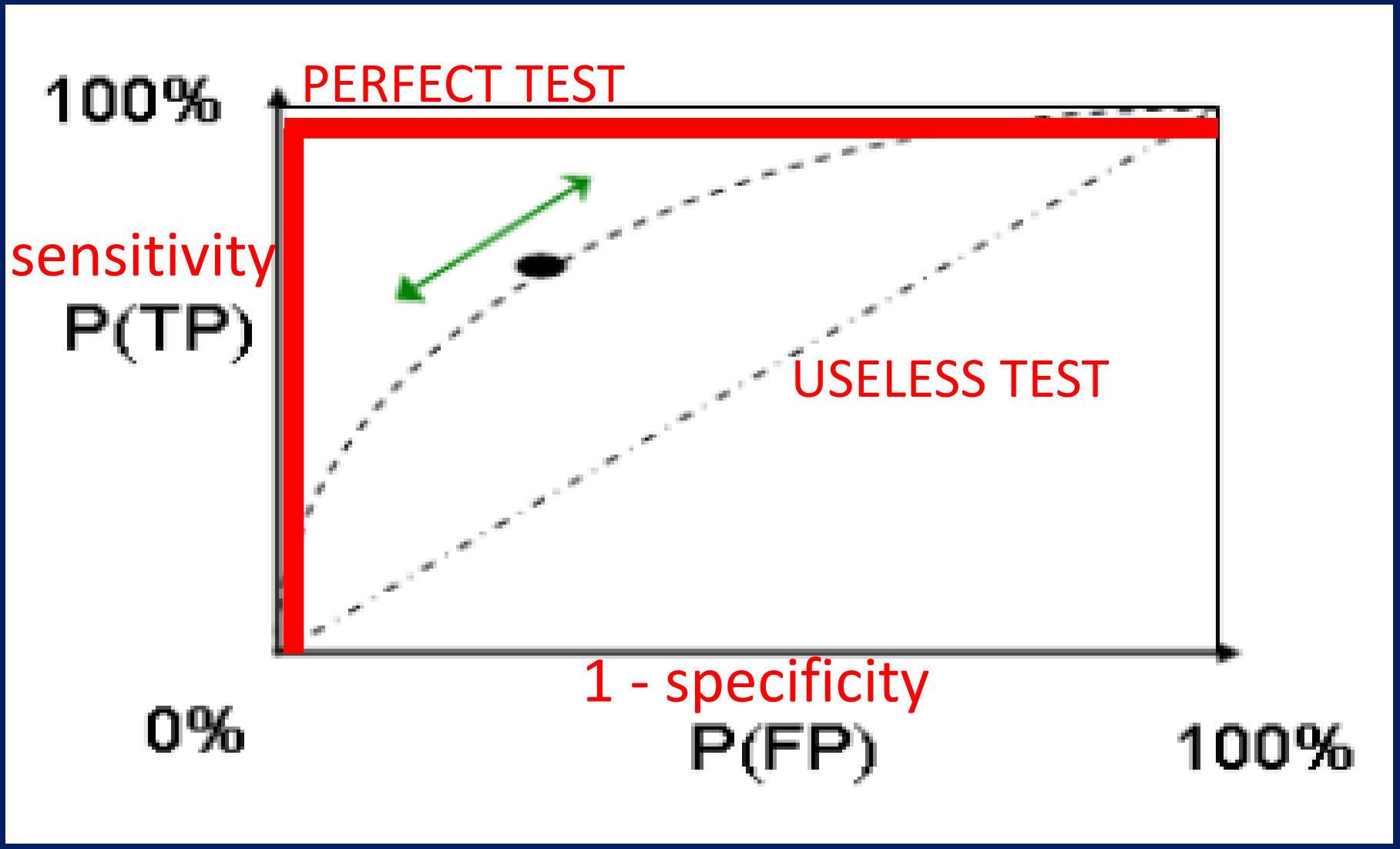
Receiver operator characteristic (ROC) curve



ER patients- Point of diagnostic threshold: Amylase set at 143 U/L with a sn of 0.690 and a sp of 0.966; Lipase set at 208 U/L where the sn was 0.861 and a sp of 0.936.

Should serum pancreatic lipase replace serum amylase as a biomarker of acute pancreatitis? Smith et al 2006

Review ROC curves, con't



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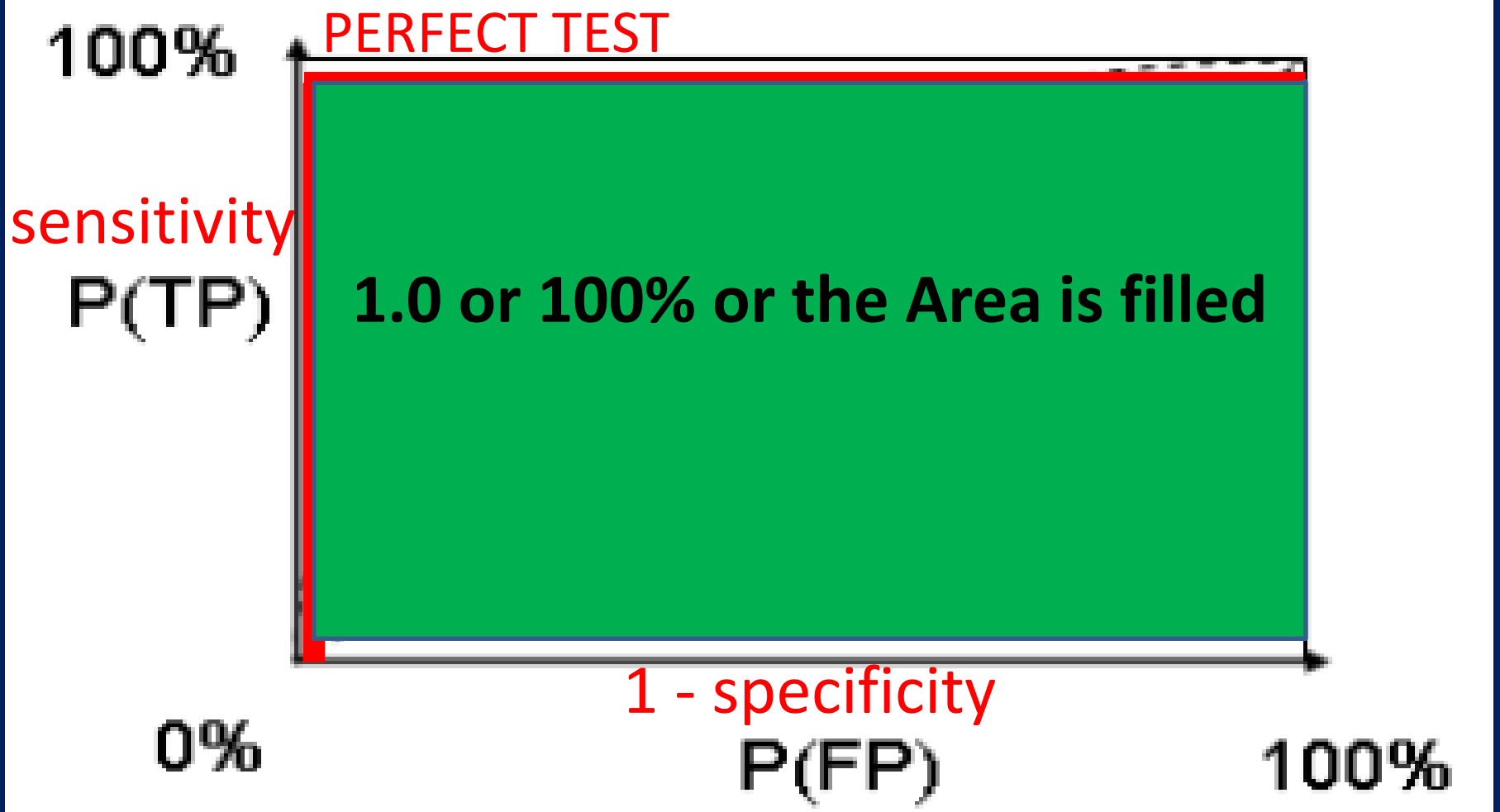
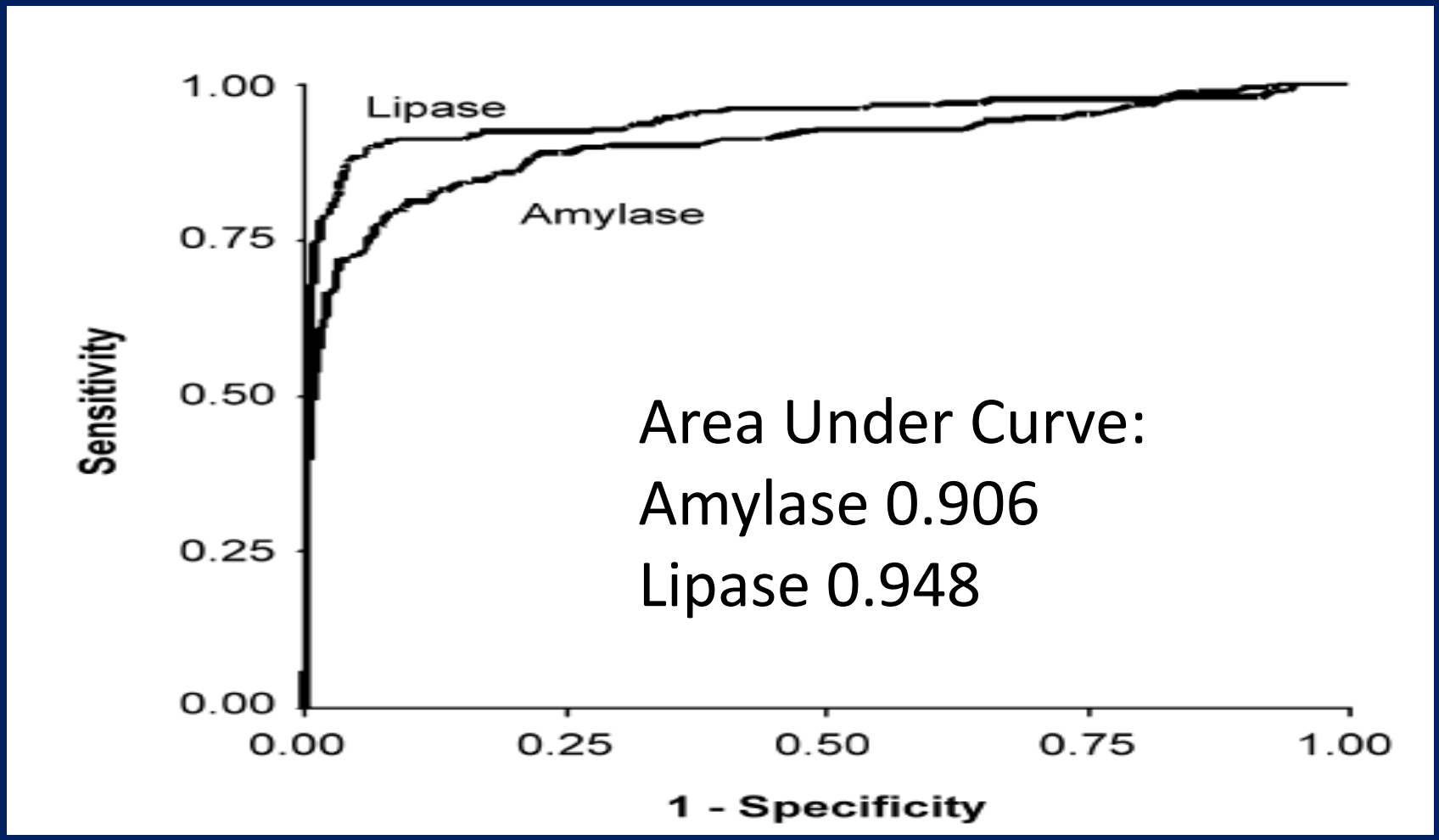


AUC: Increased Area = Better Test

Receiver operator characteristic (ROC) curve



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Should serum pancreatic lipase replace serum amylase as a biomarker of acute pancreatitis? Smith et al 2006

Amylase vs. Lipase Guidelines

"…not necessary to measure both …lipase may be preferable …serum lipase is thought to be more sensitive and specific …in the diagnosis of acute pancreatitis." -*Banks et al. American GI Society and American College of Gastroenterology (2006)*

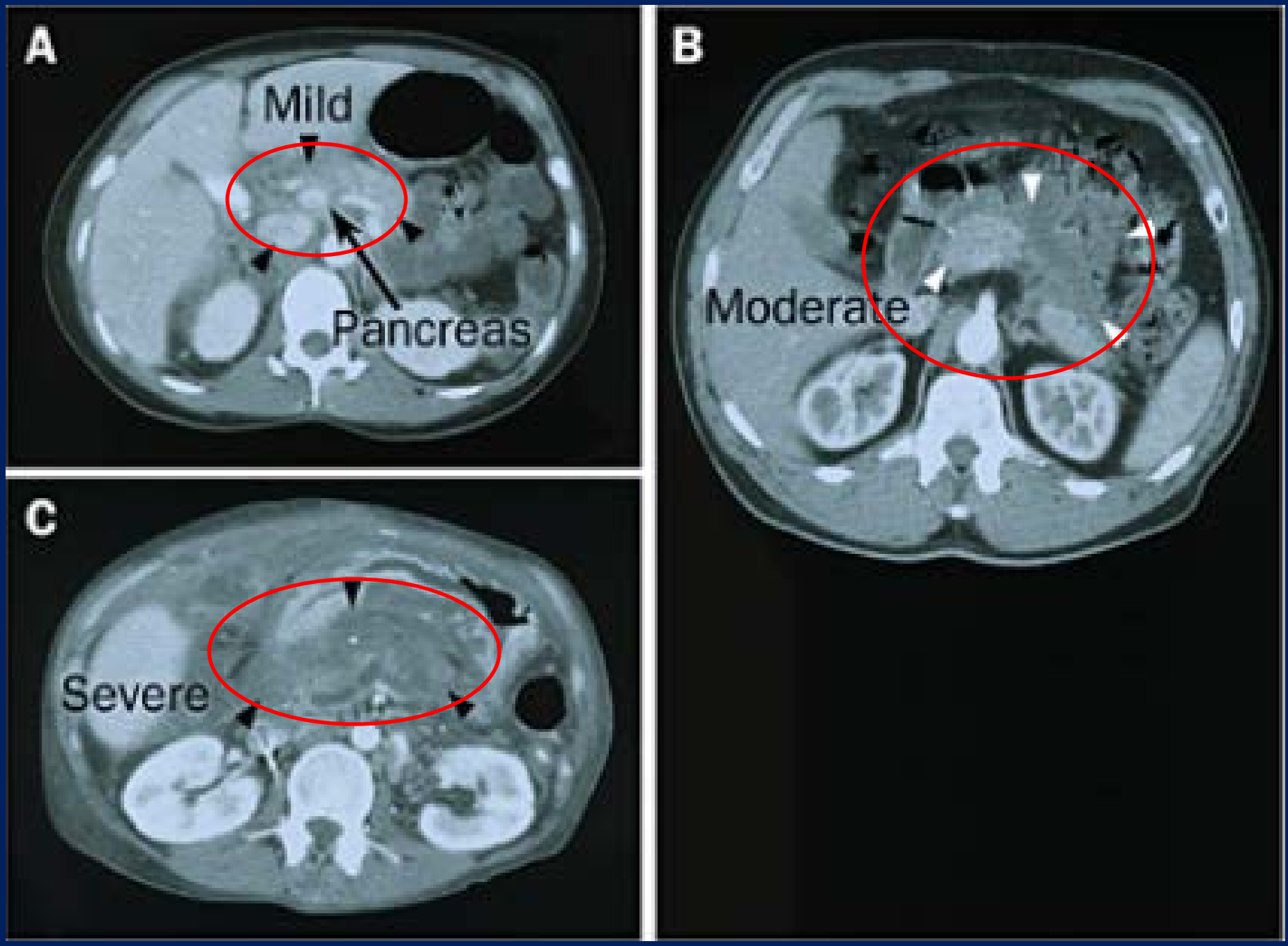
Although amylase is widely available and provides acceptable accuracy of diagnosis, where lipase is available it is preferred for the diagnosis of acute pancreatitis (recommendation grade A)" - *UK GI Party*

Acute Pancreatitis

Other Factors Contributing to the Diagnosis/ Risk:

Imaging

Additional Labs


A
Mild
Pancreas
B
Moderate
C
Severe

Risk Assessment

Ranson's Criteria

On Admission	Within 48 hours
Age >55 years	Hematocrit decrease by >10%
WBC > 16,000 mm^3	Urea Nitrogen increase >5 mg/dl
LDH > 350 U/L	Serum calcium < 8 mg/dl
Glucose > 200 mg/dl	Arterial PO_2 < 60 mm Hg
AST > 250 U/L	Base deficit > 4mmol/L
	Estimated fluid sequestration > 6 L

APACHE III Criteria (Acute Physiology and Chronic Health Eval.

Temperature	**Arterial pH**	**Leukocytes**
Mean BP	**Sodium/Potassium**	**Hematocrit**
Heart Rate	**Glucose**	**Albumin**
Respiratory Rate	**Creatinine**	**Bilirubin**
Oxygenation	**BUN**	**Age**

Mortality in Acute Pancreatitis

	Median (%)	Range (%)
All cases	5	2–9
Interstitial pancreatitis	3	1–7
Necrotizing pancreatitis	17	8–39
Infected necrosis	30	14–62
Sterile necrosis	12	2–44

Banks et al. Practice Guidelines in Acute Pancreatitis

Treatment

- Aggressive Intravenous Fluids
- Nil per os (“NPO”) = Nothing by mouth
- Parenteral Narcotics
- +/- Antibiotics (necrotizing pancreatitis)
- Transfer to ICU
- Look for Etiology

Pearls of Wisdom

Acute Pancreatitis

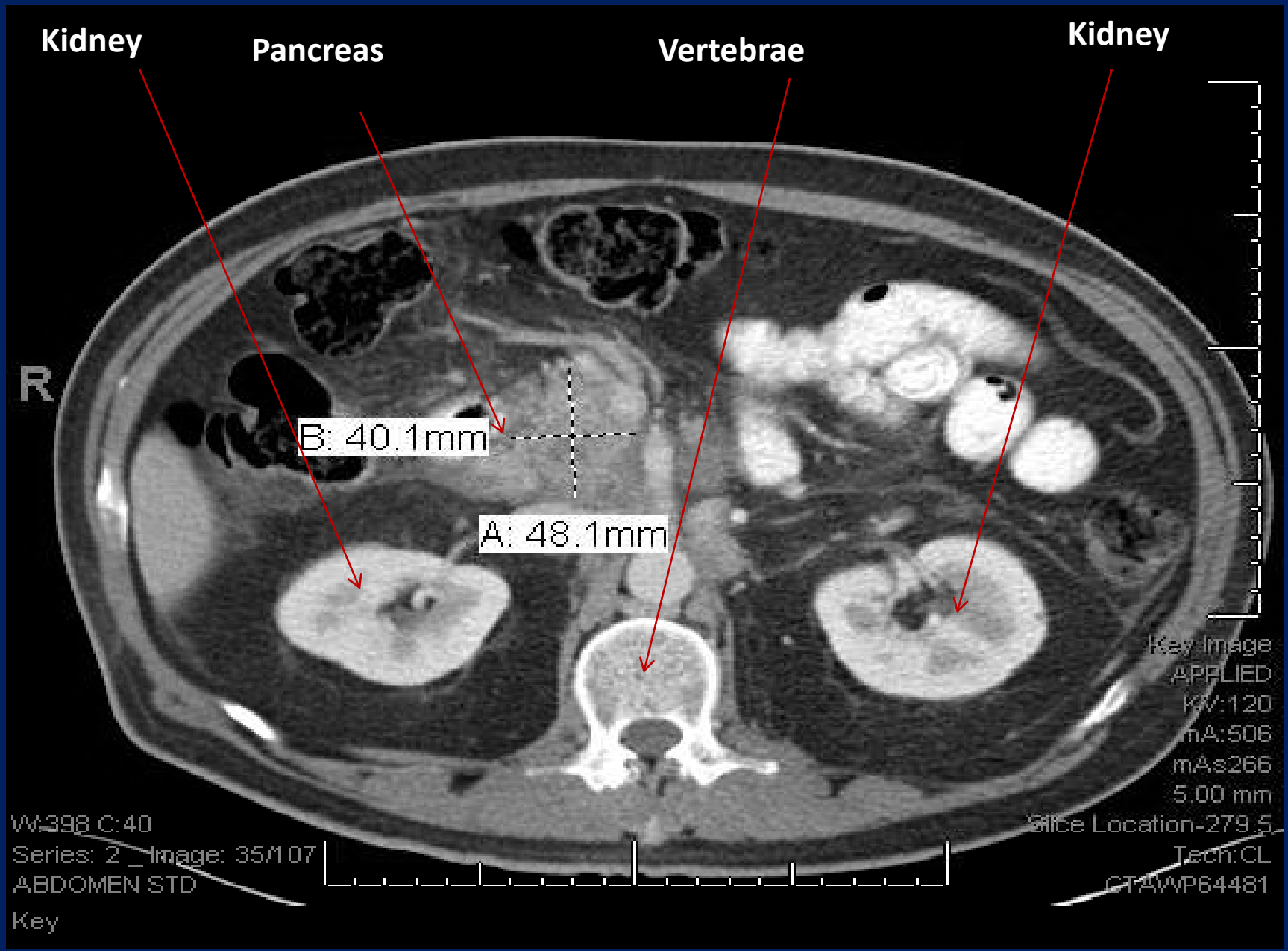
- Alcohol and Gallstones account for majority of cases
- Amylase greater than 3x upper limit of ref range
- Lipase greater sensitivity and specificity
- False positives exist for elevated levels of enzymes

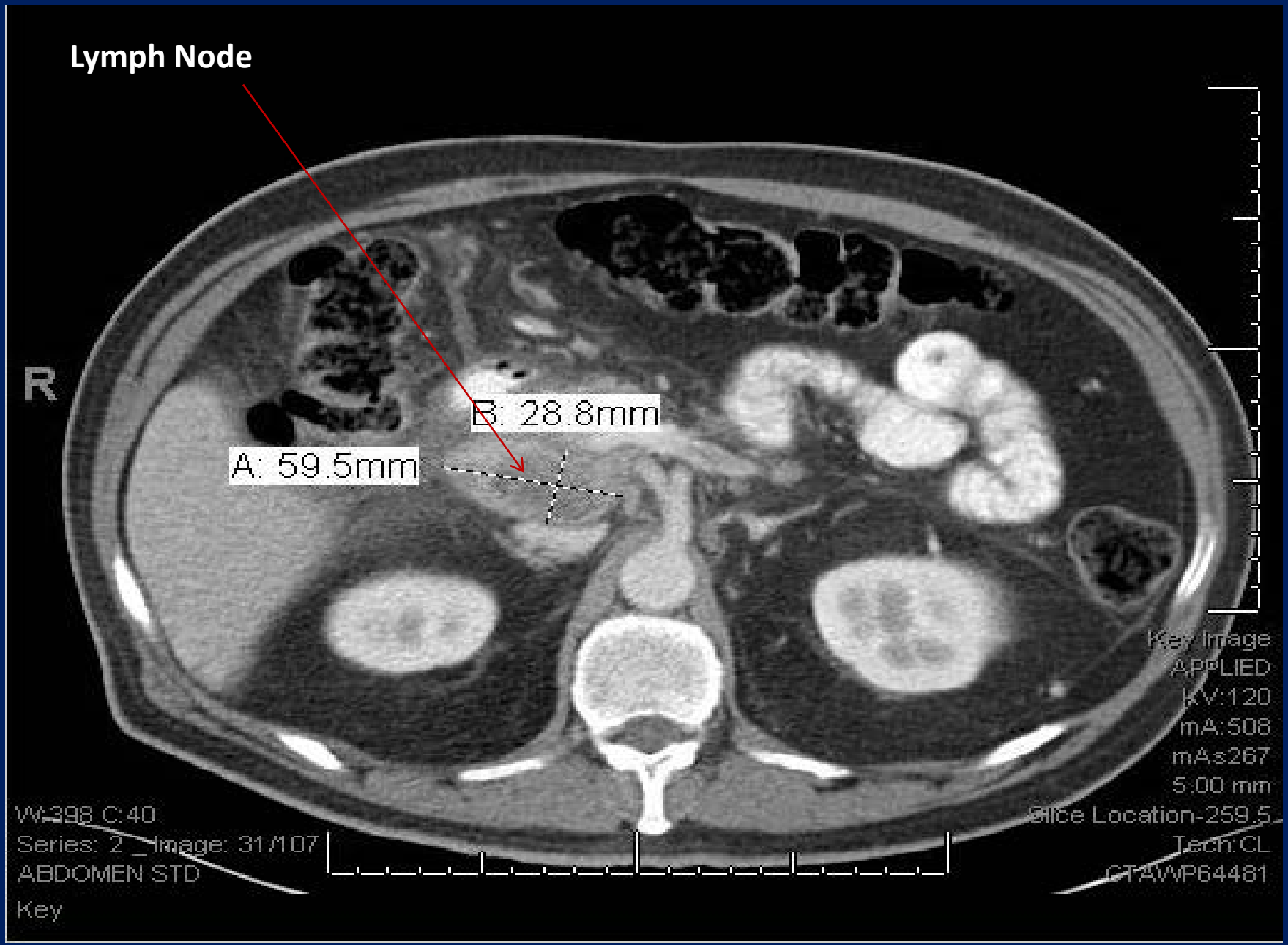
Case #2

- 61-year-old male presents to his primary care physician complaining of gradually increasing pain in his upper abdomen
  - Pain radiates to his back
- Medical history is significant for Hypertension
- Family History: Not significant
- Social History: (+) tobacco
- Review of Systems: weight loss; several week history of “painless jaundice” prior to pain starting

Case #2

- Physical Exam (Pertinent Positives):
  - Icteric sclera
  - Palpable left supraclavicular lymph (Virchow's) node
- Lab
  - Amylase and Lipase 1.5x the upper limit of normal
- Imaging
  - Pancreatic Protocol CT scan


Kidney
Pancreas
Vertebrae
Kidney
R
B: 40.1mm
A: 48.1mm
Key Image
APPLIED
KV:120
mA:506
mAs266
5.00 mm
Slice Location-279.5
Tech:CL
CTAVVP64481
W:398 C:40
Series: 2 Image: 35/107
ABDOMEN STD
Key


Lymph Node
R
B: 28.8mm
A: 59.5mm
Key Image
APPLIED
kV:120
mA:508
mAs267
5.00 mm
Slice Location-259.5
Tech:CL
CTAVP64481
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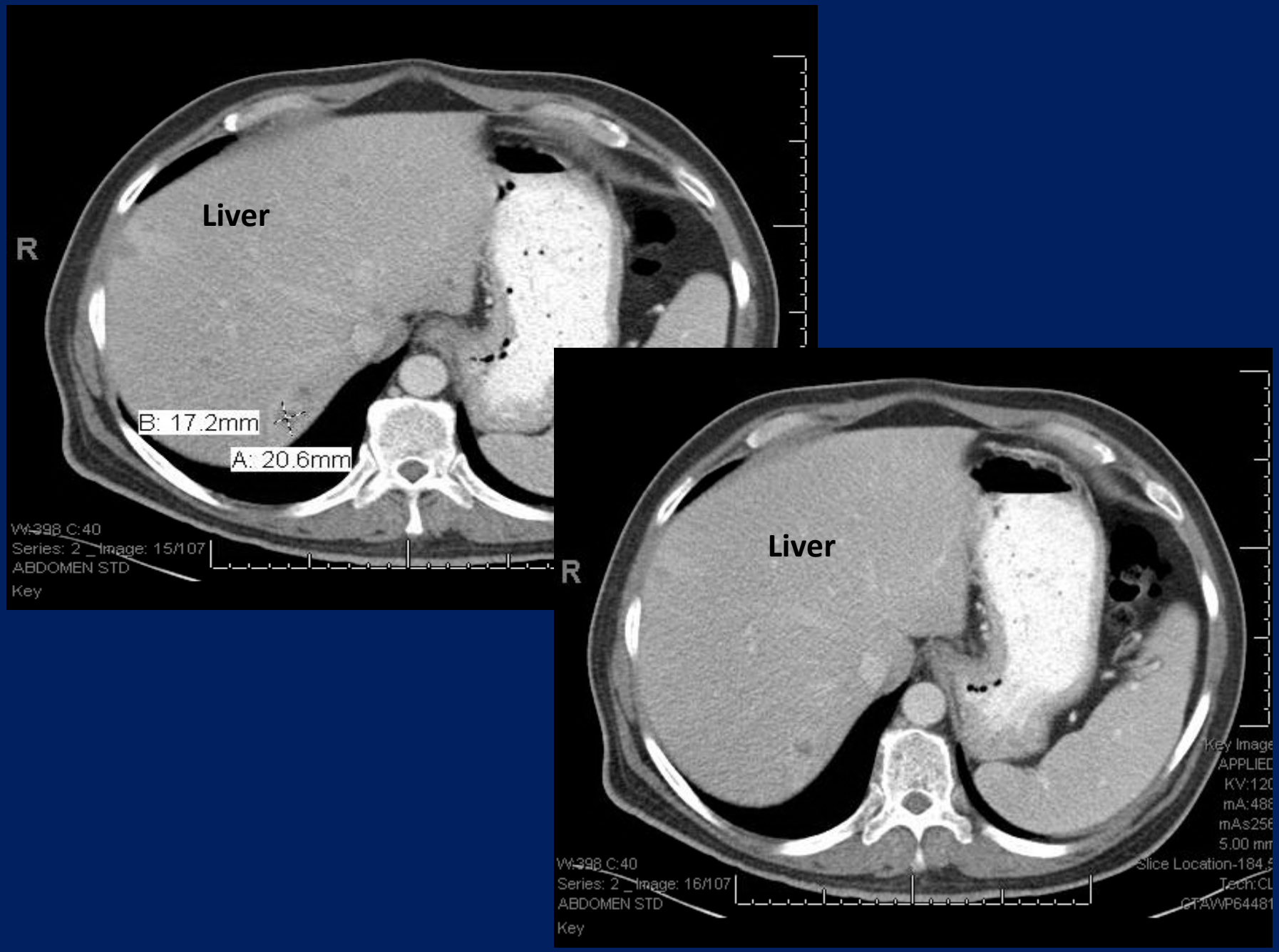
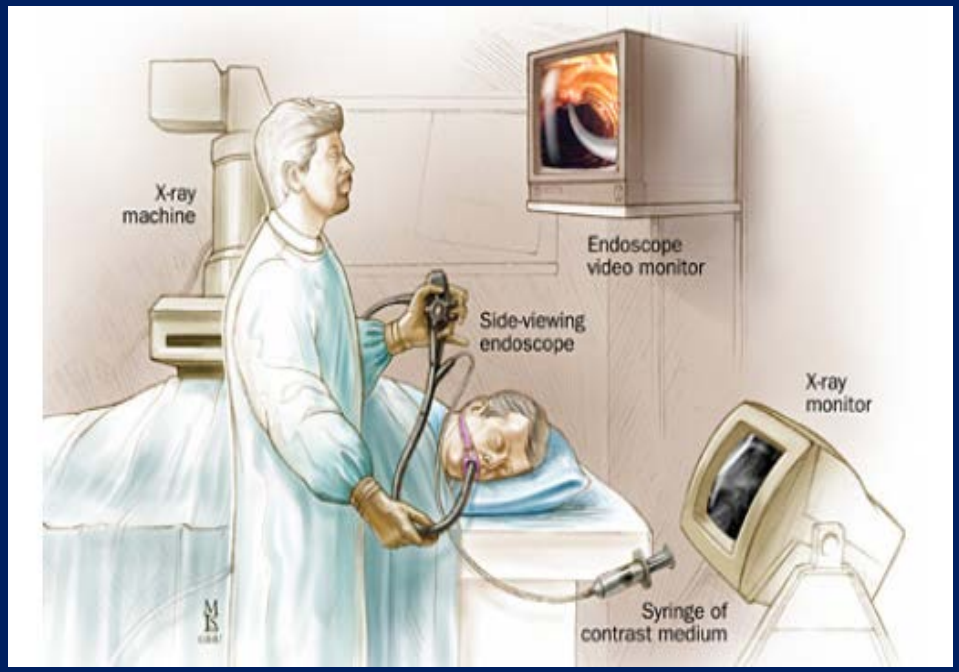
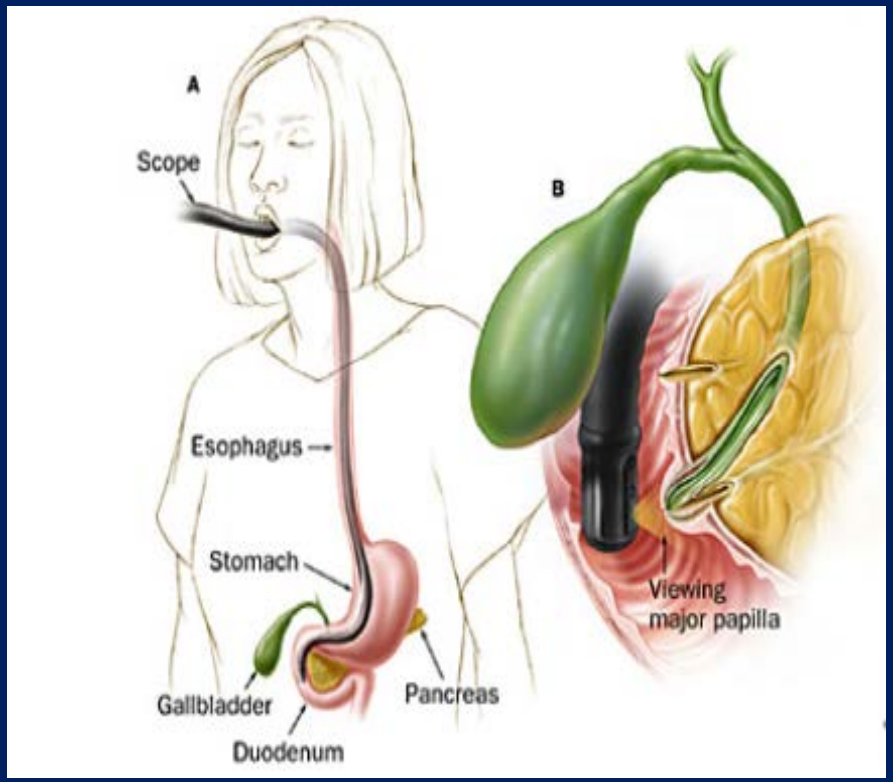
ABDOMEN STD
Key

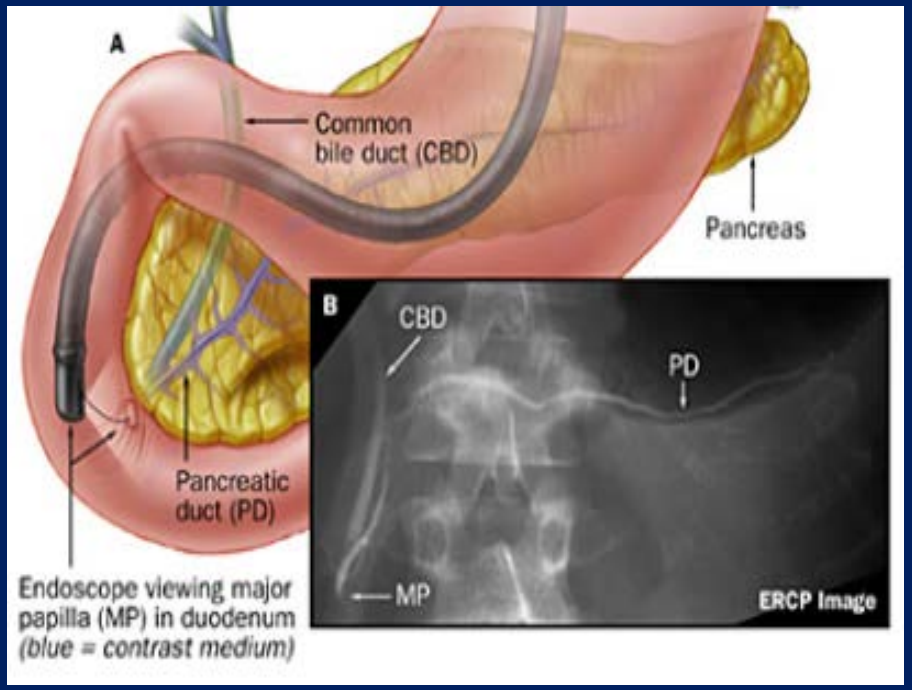

Liver
R
B: 17.2mm
A: 20.6mm
W:398 C:40
Series: 2 _ Image: 15/107
ABDOMEN STD
Key
Liver
R
W:398 C:40
Series: 2 _ Image: 16/107
ABDOMEN STD
Key

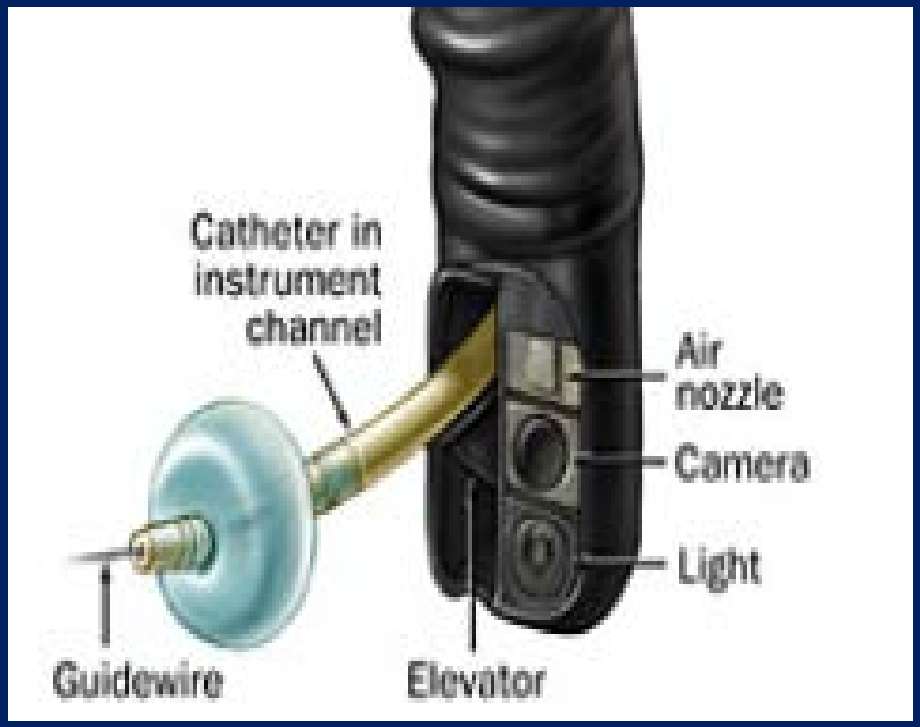
Biopsy via Endoscopic Ultrasound guided Fine Needle Aspiration



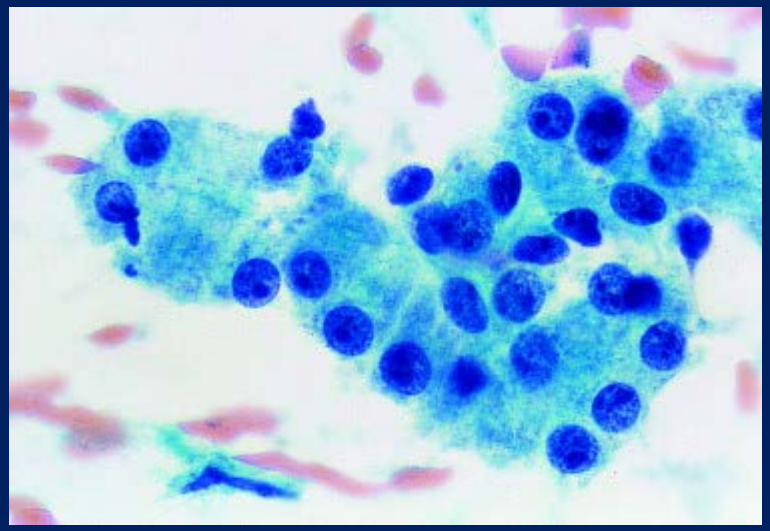


Biopsy via EUS guided FNA

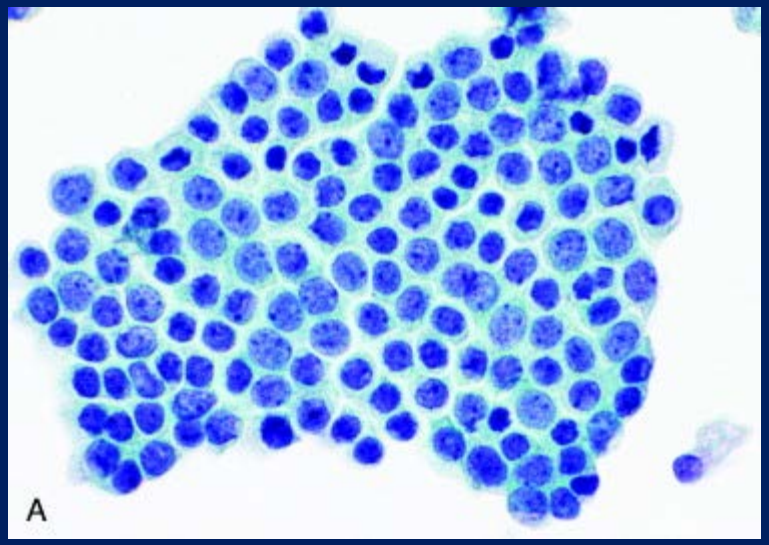


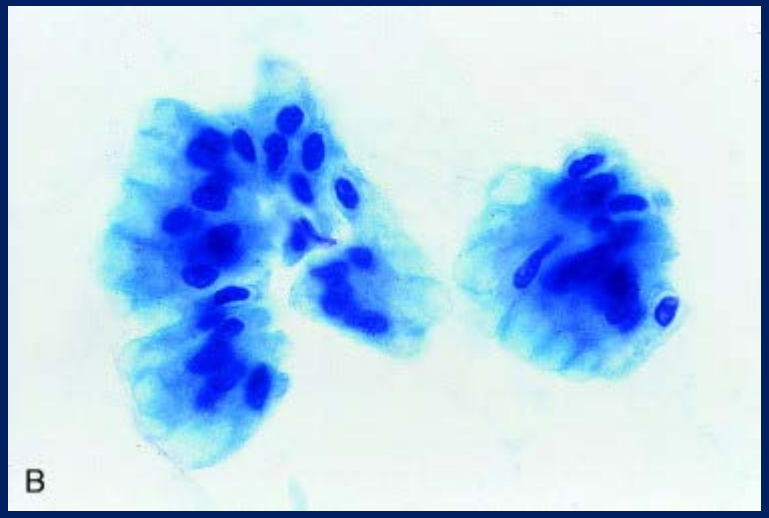


Normal Pancreas



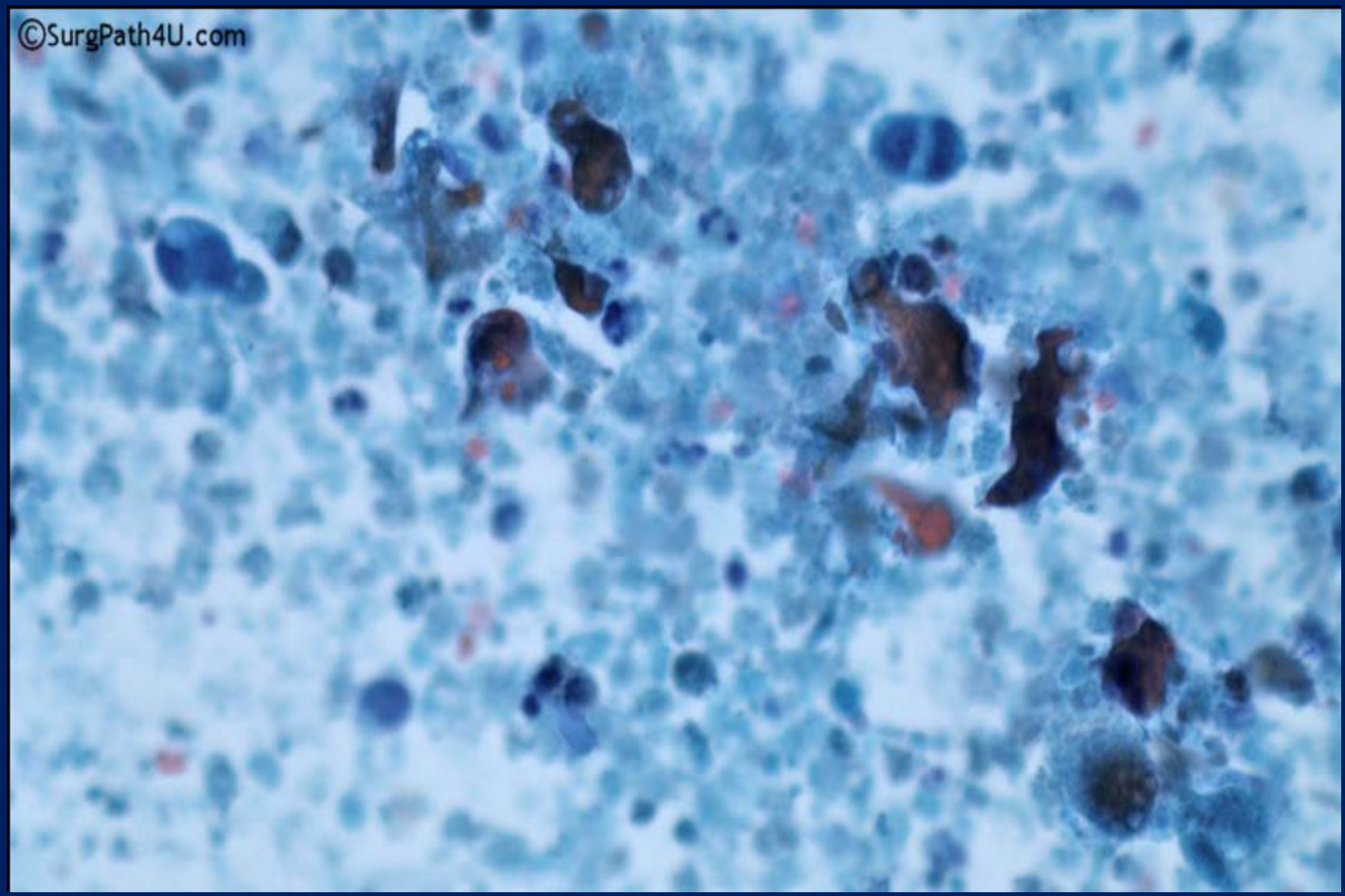
Acinar cells



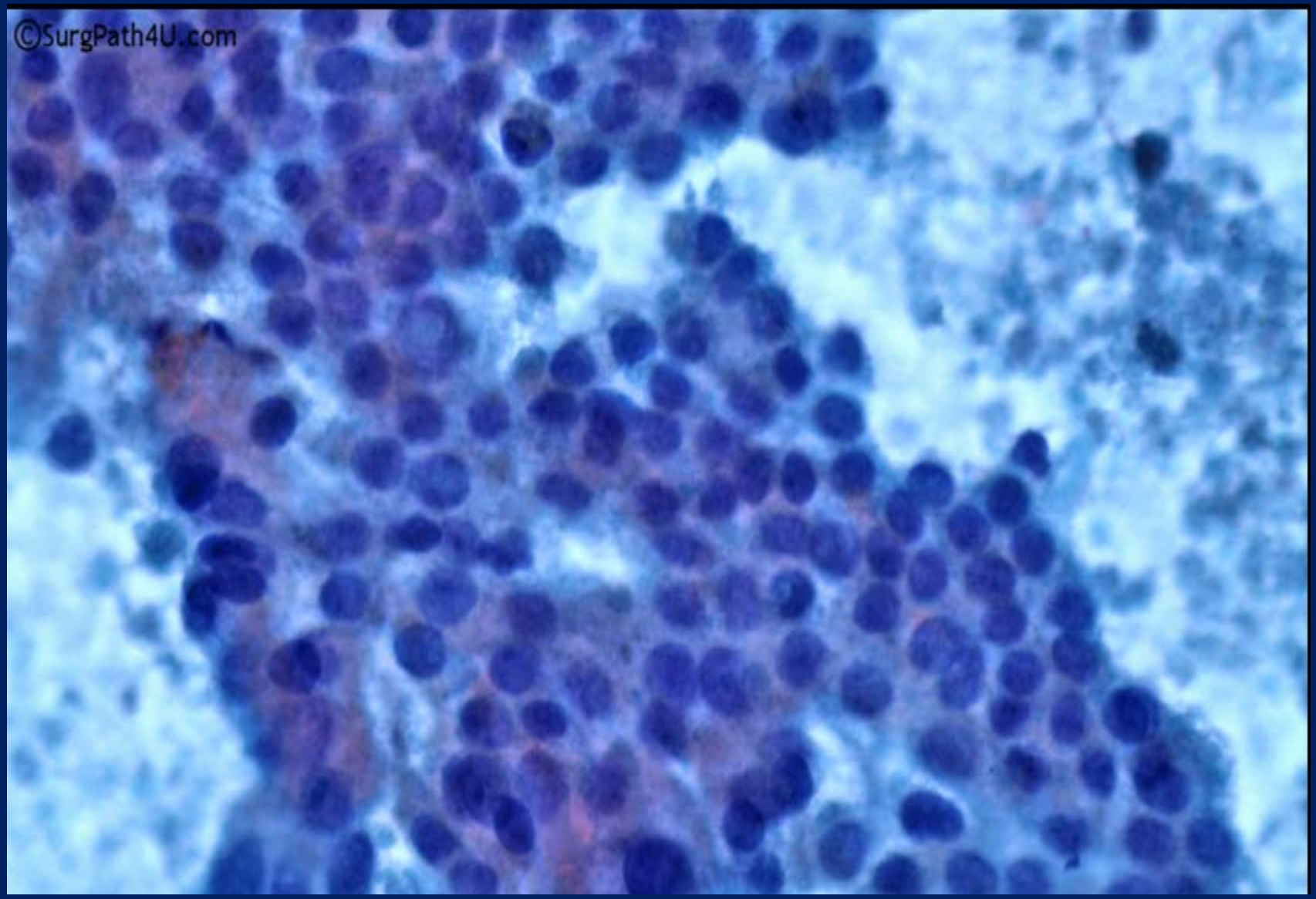


Ductal cells

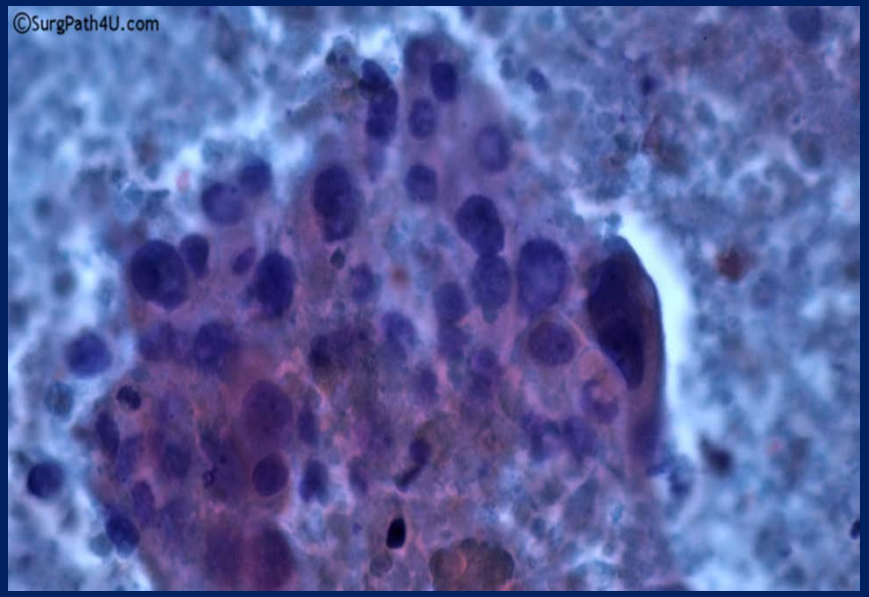
Pancreas is near the duodenum, liver, transverse colon, stomach, spleen, and kidneys



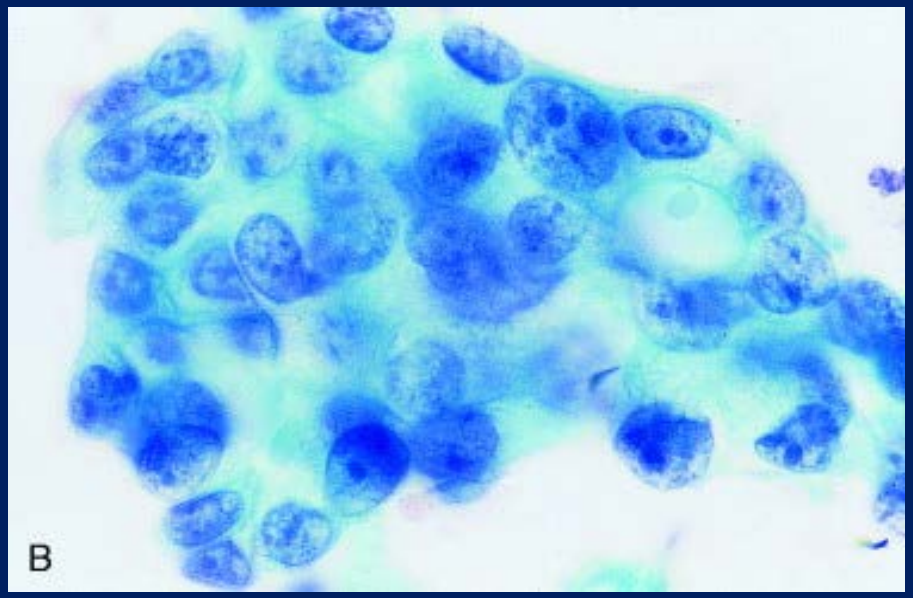
Necrosis



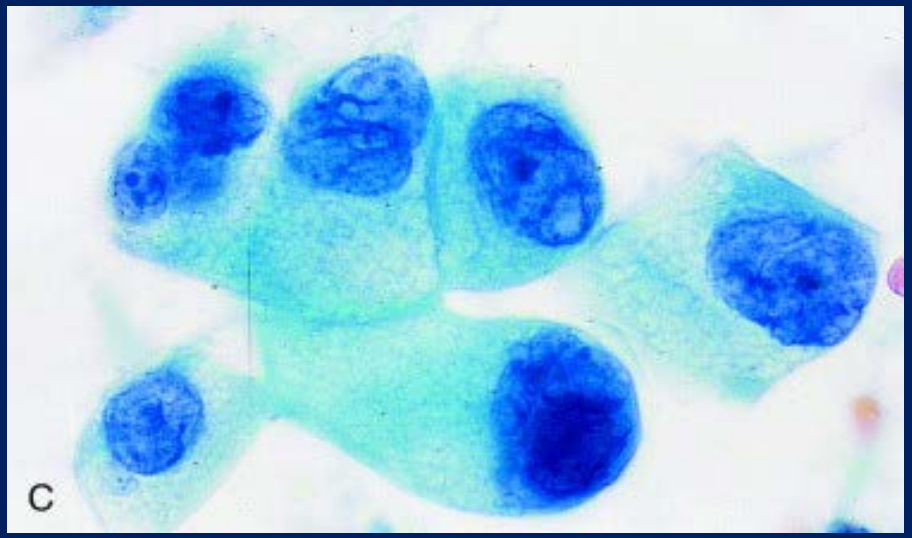
"Drunken Honeycomb"



Nuclear Pleomorphism



Nuclear Anisonucleosis



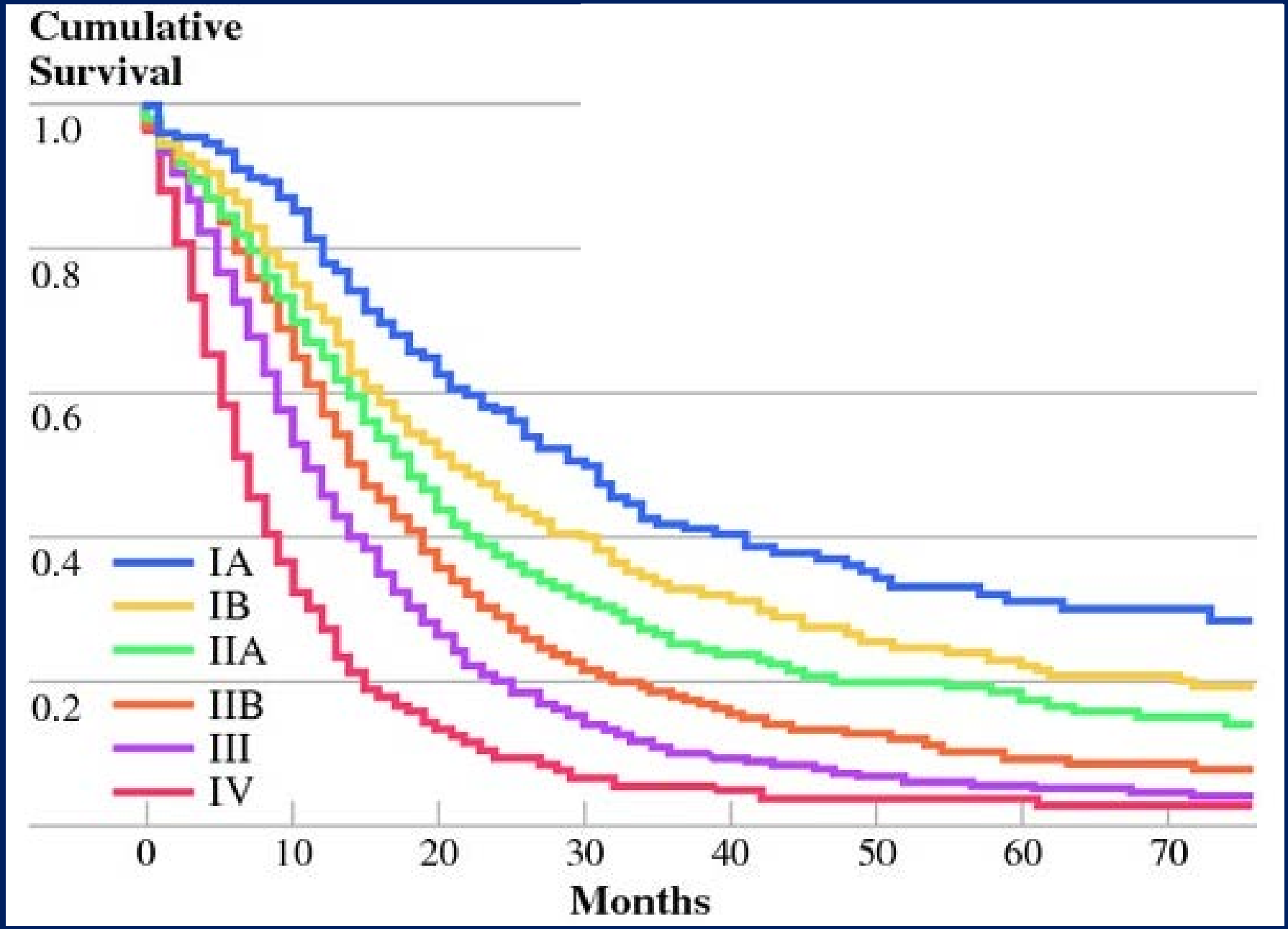
Clumped Chromatin

DIAGNOSIS?

PANCREATIC DUCTAL ADENOCARCINOMA

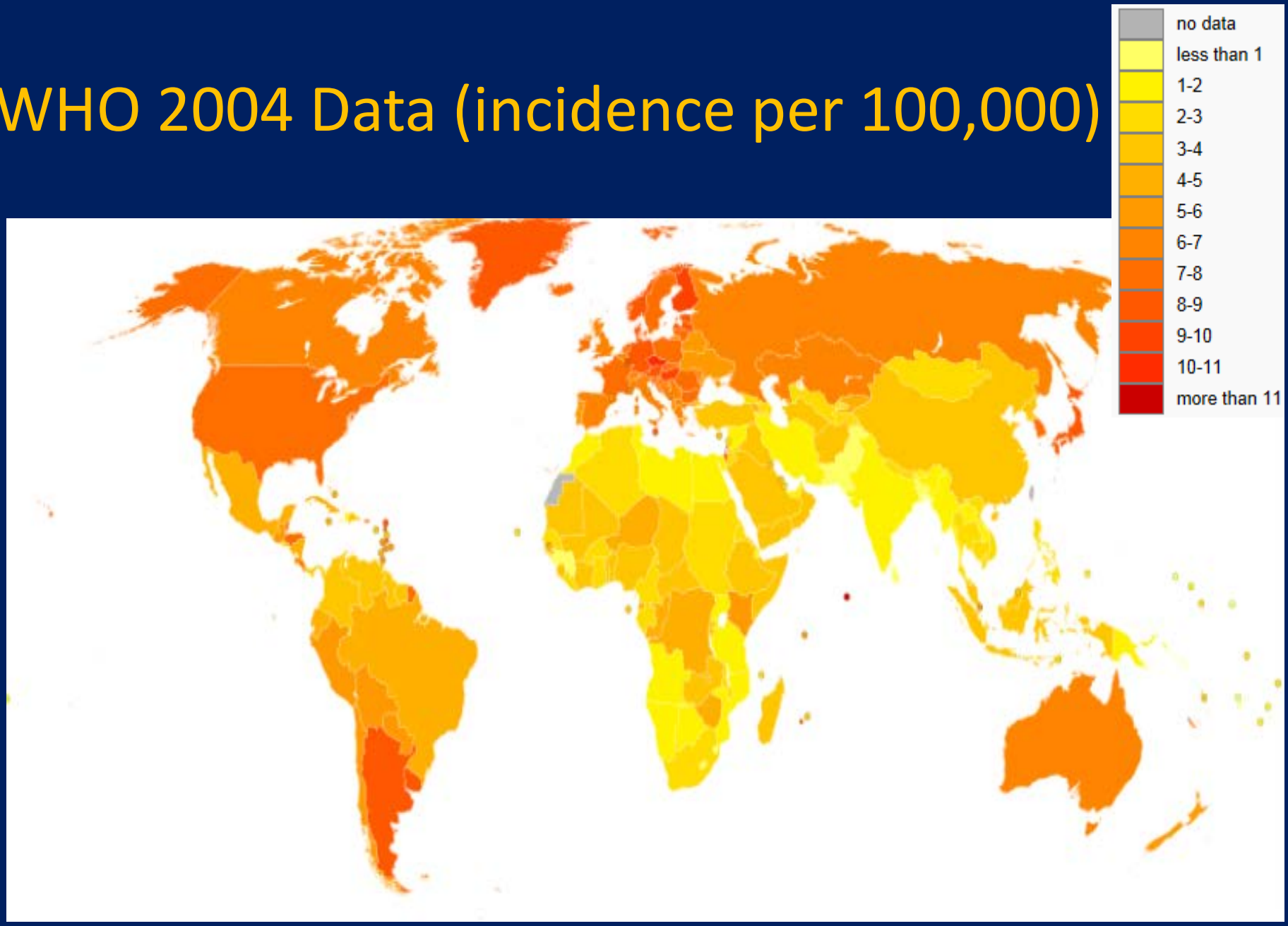
Pancreatic Ductal Adenocarcinoma (PDAC)

- 43,140 people are diagnosed annually in US
  - incidence 10–12 per 100,000 people
- Mortality rate of 36,800/year in US
- Mortality rate 227,000/year in World
- 4th on the list of cancer related causes of death
- 5 year survival rate is <5%



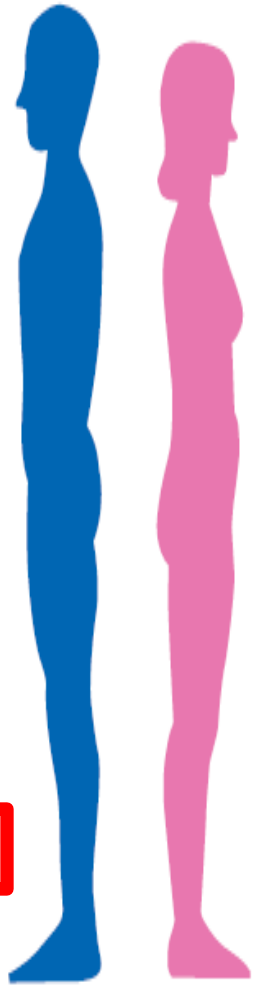
Wasif N, Ko CY, Farrell J, Wainberg Z, Hines OJ, Reber H, Tomlinson JS. Impact of tumor grade on prognosis in pancreatic cancer: should we include grade in AJCC staging?

WHO 2004 Data (incidence per 100,000)



Estimated New Cases*

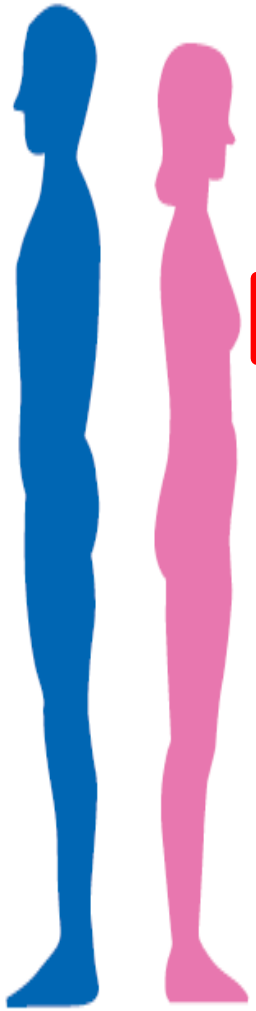
Males			Females		
Prostate	217,730	28%	Breast	207,090	28%
Lung & bronchus	116,750	15%	Lung & bronchus	105,770	14%
Colon & rectum	72,090	9%	Colon & rectum	70,480	10%
Urinary bladder	52,760	7%	Uterine corpus	43,470	6%
Melanoma of the skin	38,870	5%	Thyroid	33,930	5%
Non-Hodgkin lymphoma	35,380	4%	Non-Hodgkin lymphoma	30,160	4%
Kidney & renal pelvis	35,370	4%	Melanoma of the skin	29,260	4%
Oral cavity & pharynx	25,420	3%	Kidney & renal pelvis	22,870	3%
Leukemia	24,690	3%	Ovary	21,880	3%
Pancreas	21,370	3%	Pancreas	21,770	3%
All Sites	**789,620**	**100%**	**All Sites**	**739,940**	**100%**



Ahmedin Jemal, DVM, PhD et al Cancer Statistics, 2010

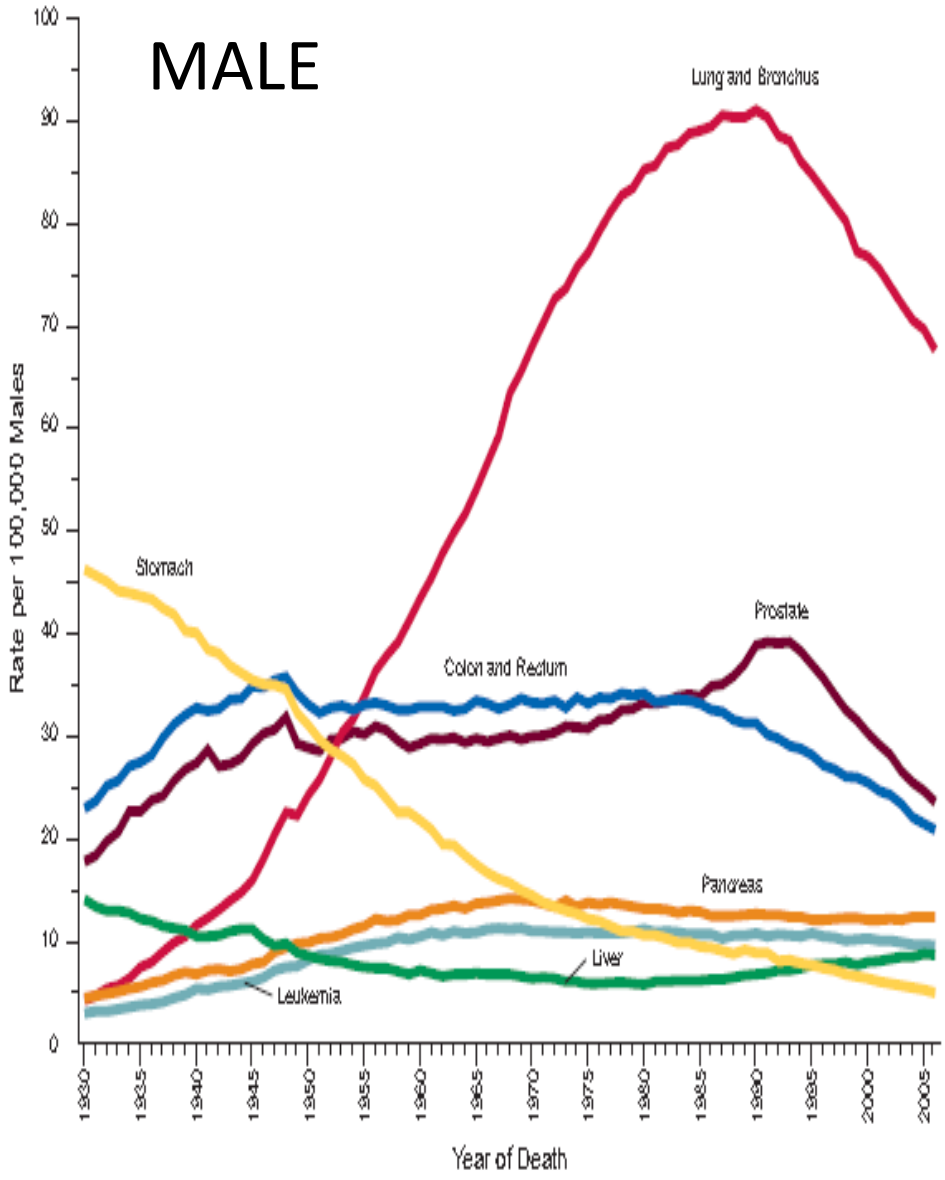
Estimated Deaths

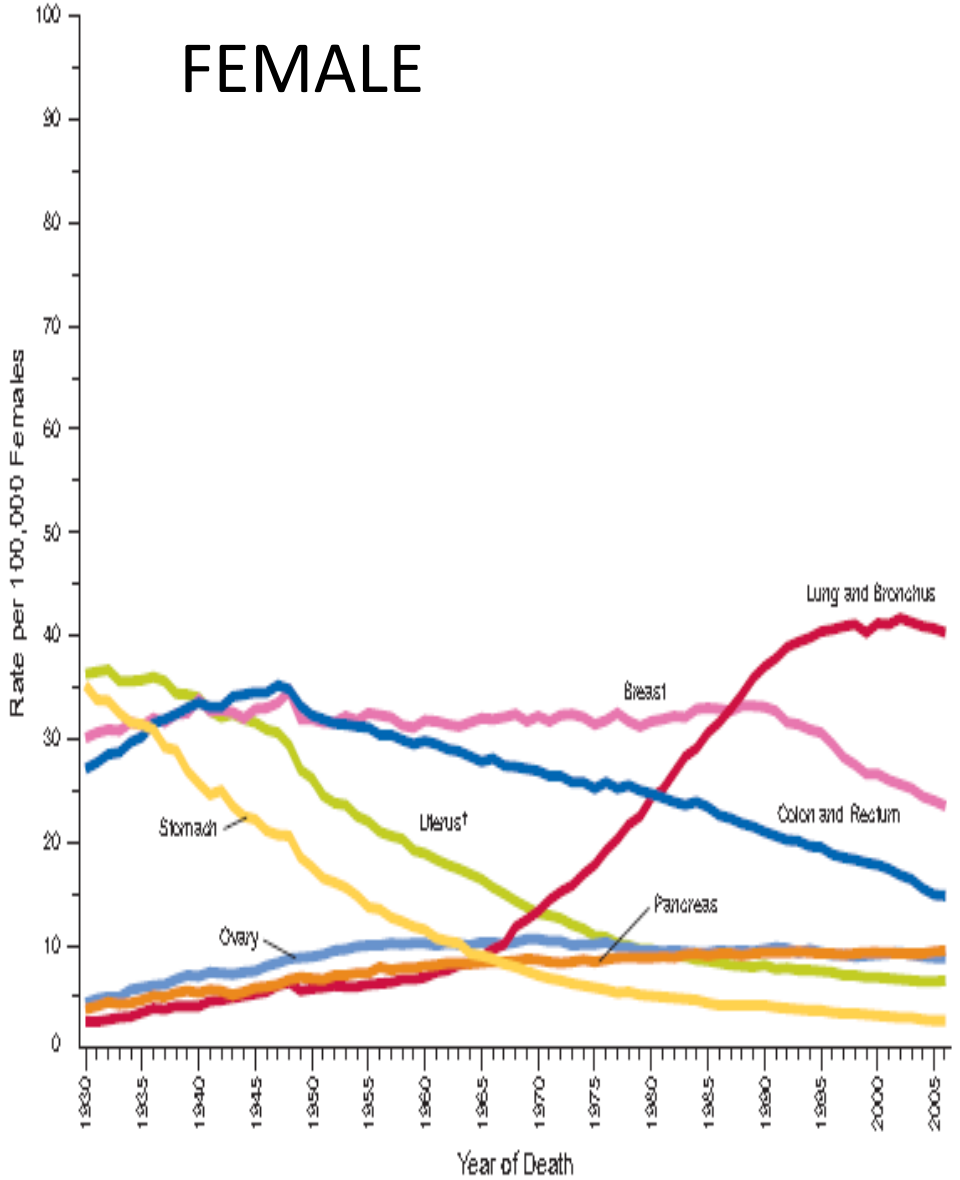
Males			Females		
Lung & bronchus	86,220	29%	Lung & bronchus	71,080	26%
Prostate	32,050	11%	Breast	39,840	15%
Colon & rectum	26,580	9%	Colon & rectum	24,790	9%
Pancreas	18,770	6%	Pancreas	18,030	7%
Liver & intrahepatic bile duct	12,720	4%	Ovary	13,850	5%
Leukemia	12,660	4%	Non-Hodgkin lymphoma	9,500	4%
Esophagus	11,650	4%	Leukemia	9,180	3%
Non-Hodgkin lymphoma	10,710	4%	Uterine Corpus	7,950	3%
Urinary bladder	10,410	3%	Liver & intrahepatic bile duct	6,190	2%
Kidney & renal pelvis	8,210	3%	Brain & other nervous system	5,720	2%
All Sites	**299,200**	**100%**	**All Sites**	**270,290**	**100%**



Ahmedin Jemal, DVM, PhD et al Cancer Statistics, 2010

Death Rate per 100,000 Males and Females



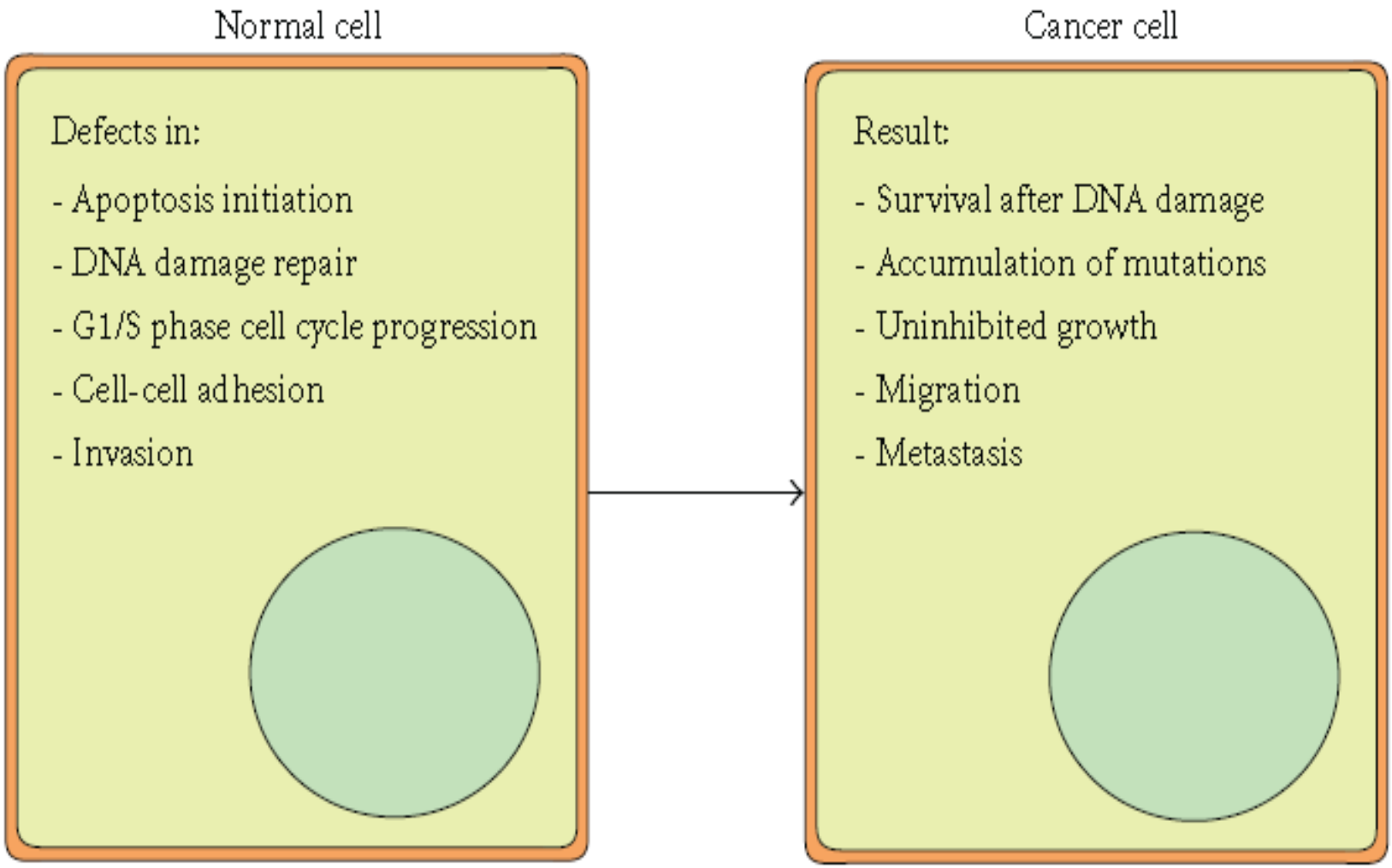


Ahmedin Jemal, DVM, PhD et al Cancer Statistics, 2010

PDAC: Implicated Factors

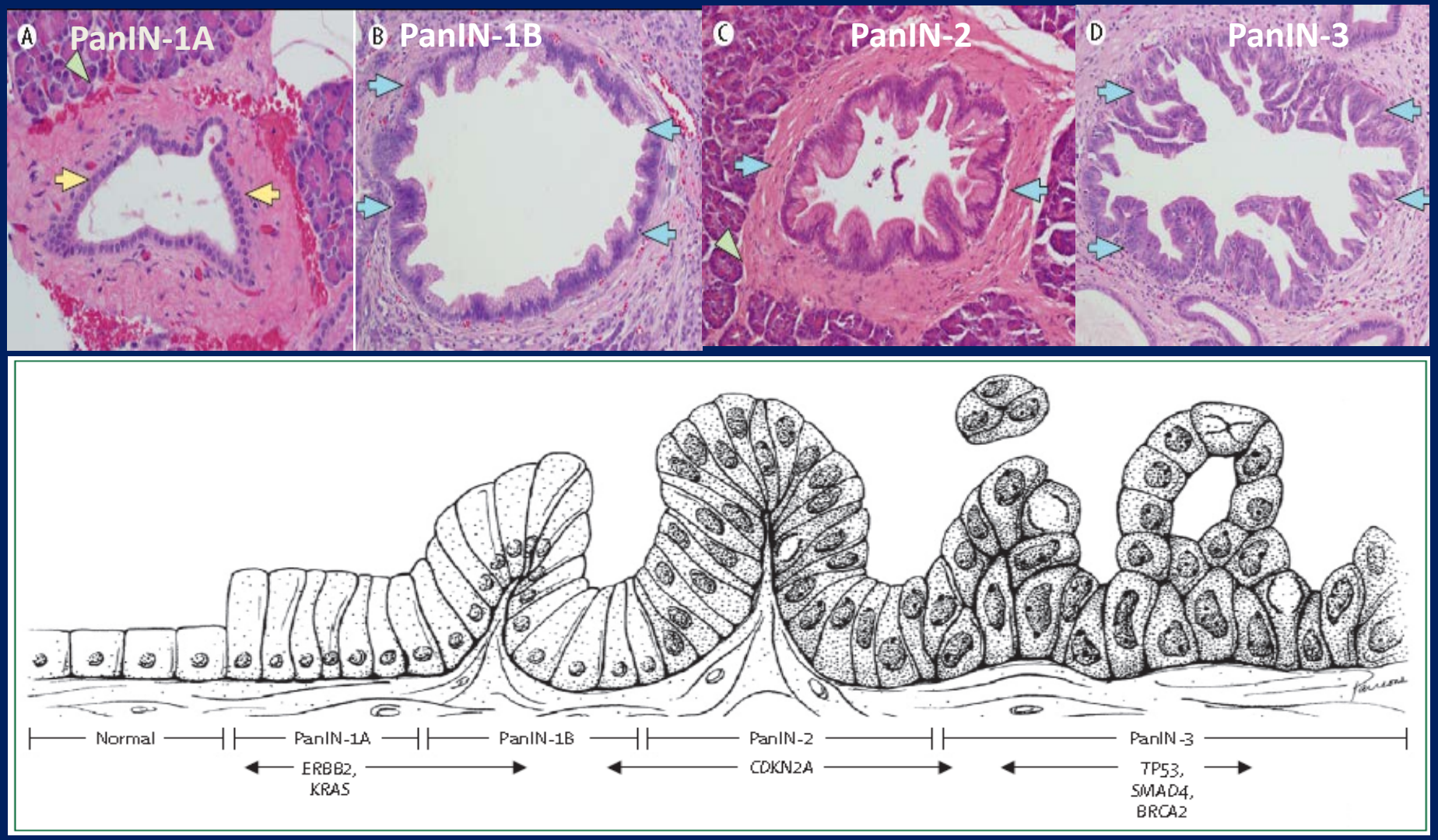
- Smoking (2.5-3.6 x increase risk)
- Family history, a pair of first-degree relatives = familial
- History of chronic pancreatitis, EtOH
- Advancing age
- Male sex
- Diabetes mellitus
- Obesity
- Non-O blood group
- Occupational exposures (eg chlorinated hydrocarbon solvents and nickel)
- African-American ethnicity
- Diet, high fat/high meat and low in vegetables and folate
- Possibly *Helicobacter pylori* infection
- Possibly periodontal disease

Becoming Cancer



Ottenhof NA et al. Molecular characteristics of pancreatic ductal adenocarcinoma

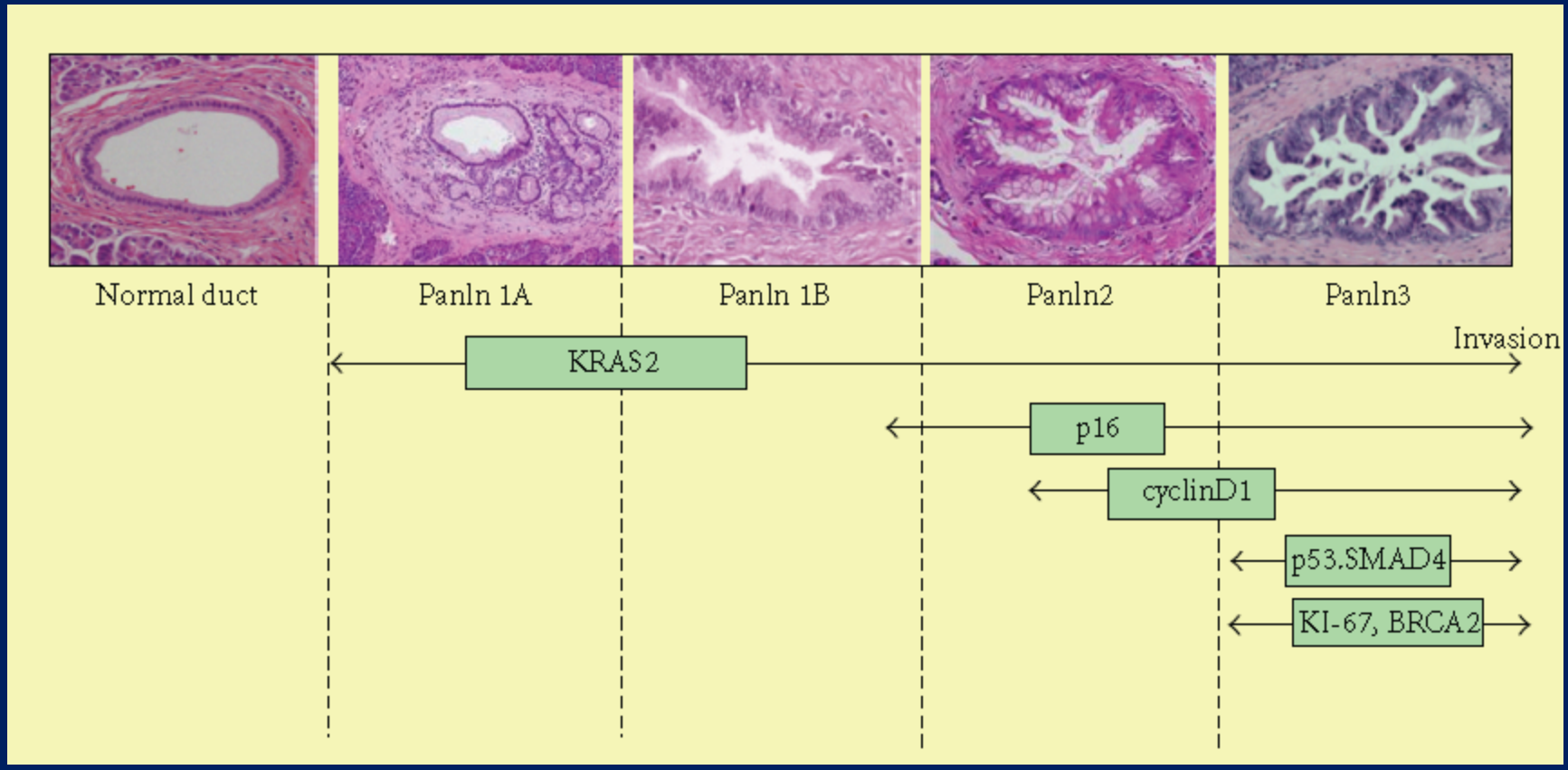
PDAC Pathophysiology



Precursors: PanINs, MCNs, and IPMNs

Vincent A et al, Pancreatic cancer

Molecular Features of PDAC

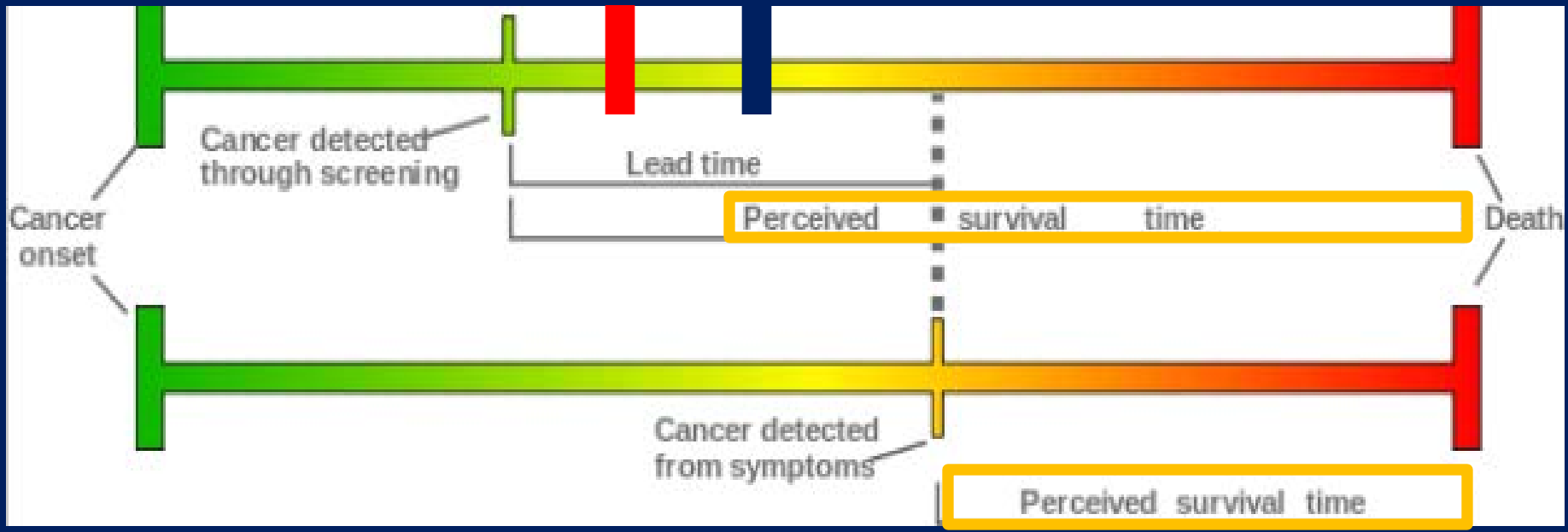


MORE THAN A DECADE TO PROGRESS… a guess

(creating a window for possible early detection)

Ottenhof NA et al. Molecular characteristics of pancreatic ductal adenocarcinoma

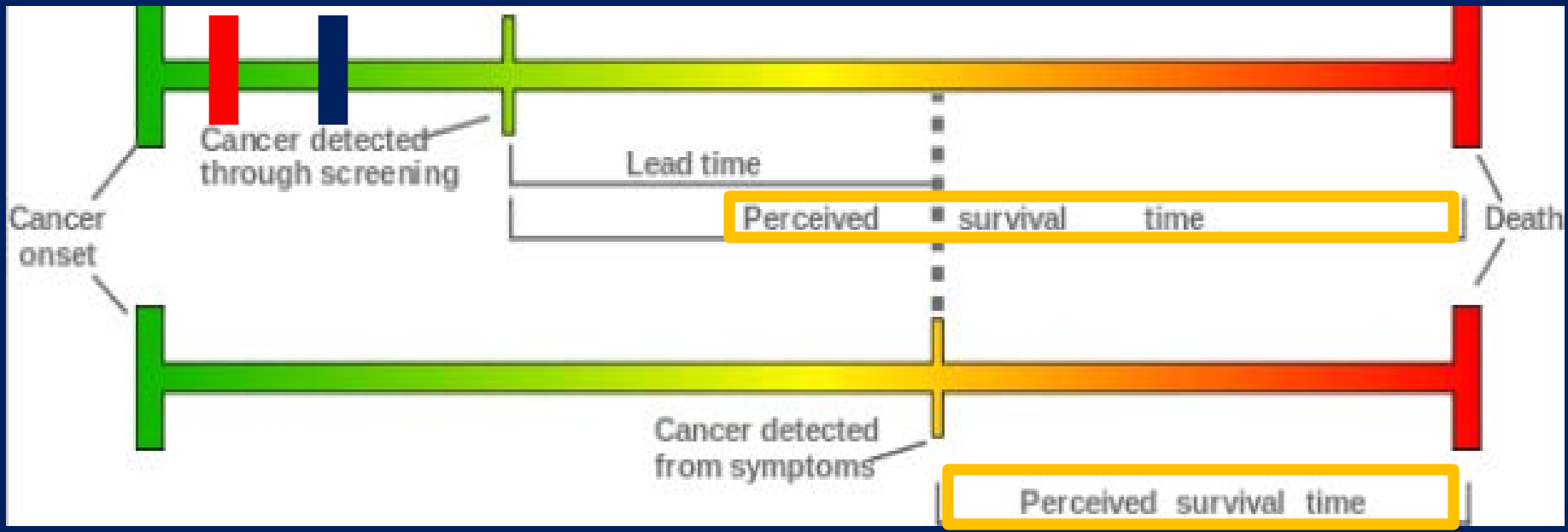
IF WE CAN DETECT DISEASE FOR DIAGNOSIS IS THERE EFFECTIVE TREATMENT? LEAD TIME BIAS



- Early-stage pancreatic cancer is usually clinically silent
- Disease becomes apparent after the tumor invades surrounding tissues or metastasizes to distant organs
  - 80% of the time has already metastasized

http://upload.wikimedia.org

IF WE CAN DETECT DISEASE FOR DIAGNOSIS IS THERE EFFECTIVE TREATMENT? LEAD TIME BIAS



- Early-stage pancreatic cancer is usually clinically silent
- Disease becomes apparent after the tumor invades surrounding tissues or metastasizes to distant organs

http://upload.wikimedia.org

World Health Organization — Principles of Screening (1968)

1. The condition should be an important health problem.
2. There should be a latent stage of the disease.
3. There should be a test or examination for the condition.
4. There should be a treatment for the condition.
5. There should be an agreed policy on whom to treat.
6. Facilities for diagnosis and treatment should be available.
7. The test should be acceptable to the population.
8. The natural history of the disease should be adequately understood.
9. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
10. Case-finding should be a continuous process, not just a "once and for all" project.

What Makes a Good Screening Test?

An ideal screening test for early pancreatic cancer would be a highly accurate (high sensitivity and specificity) marker that could be measured fairly non-invasively (blood, urine) in general population

Unfortunately, none to date have proven sufficiently specific

Nothing promising yet, lots of research being done

Proteins, aberrantly methylated DNA, autoantibodies, aberrantly glycosylated molecules, microRNAs

Screening those with familial risk

Syndrome	Germline Mutations	Relative Risk PDAC
Familial Atypical Multiple Melanoma and Mole Syndrome	CDKN2A	20-34
Peutz-Jeghers Syndrome	LKB1	>100
Hereditary pancreatitis	PRSS1/SPINK1	90
Familial Breast Cancer	BRCA 2	3-10
Lynch Syndrome	Mismatch repair	unknown

- Families with mutated susceptibility genes
  - Do NOT manifest a high penetrance of PDAC
  - Unexplained, Under reported, Underused
- Consensus guidelines have not been established for genetic testing of those at risk for inherited PDAC

Cancer of the Pancreas Screening Study (CAPS)- Imaging and DNA studies

- Multi-center, translational prospective controlled cohort study in **high risk patients**
- Pancreatic cystic lesions were detected more frequently with endoscopic ultrasound (93%) and MRI (81%) than with CT (27%)
  - Best sampled by EUS-FNA
- PanINs are usually not visible by imaging, research is attempting to identify markers in pancreatic fluid that could reliably identify high-grade PanINs

We need better screening tests

- <20% of patients qualify for surgical resection at diagnosis

- Surgical resection- only treatment to improve five-year survival rates
  - < 4% to 25–30%

- Chemo(radiation) therapy administered in (neo)adjuvant setting

We have no good screening tests.

What about tumor markers?

What is a tumor biomarker

- Levels increase with disease
- Lacks sensitivity/ specificity for diagnosis
- Used to monitor
  - treatment
  - progression
  - recurrence
- Not acute phase reactants
  - SAA, ICAM-1, CRP, osteoprotegerin

Carcinoembryonic Antigen (CEA)

Glycoprotein involved in cell adhesion

Produced during fetal life; decreases prior to birth

Can Measure in Serum or in Cyst Fluid

http://en.wikipedia.org

Carcinoembryonic Antigen (CEA)

CYST

Increased levels indicative of a mucinous cyst (does not distinguish benign from malignant)

ARUP- “body fluid” specimen category-off label

TUMOR MARKER	NON MUCINOUS CYST	MUCINOUS CYST
CEA	**Not Elevated**	**Elevated**

Carcinoembryonic Antigen (CEA)

SERUM

ELEVATED LEVEL = MALIGNANT	ELEVATED LEVEL = BENIGN
Colorectal Carcinoma	Ulcerative Colitis
Gastric Carcinoma	Crohn's Disease
Pancreatic Carcinoma	Pancreatitis
Lung Carcinoma	COPD
Breast Carcinoma	Cirrhosis
Medullary Thyroid Carcinoma	Smokers

Carbohydrate or Cancer Antigen (CA 19-9)

- False (+): Increased in colorectal cancer, esophageal cancer, hepatocellular carcinoma, pancreatitis, cirrhosis, and diseases or obstruction of the bile ducts.

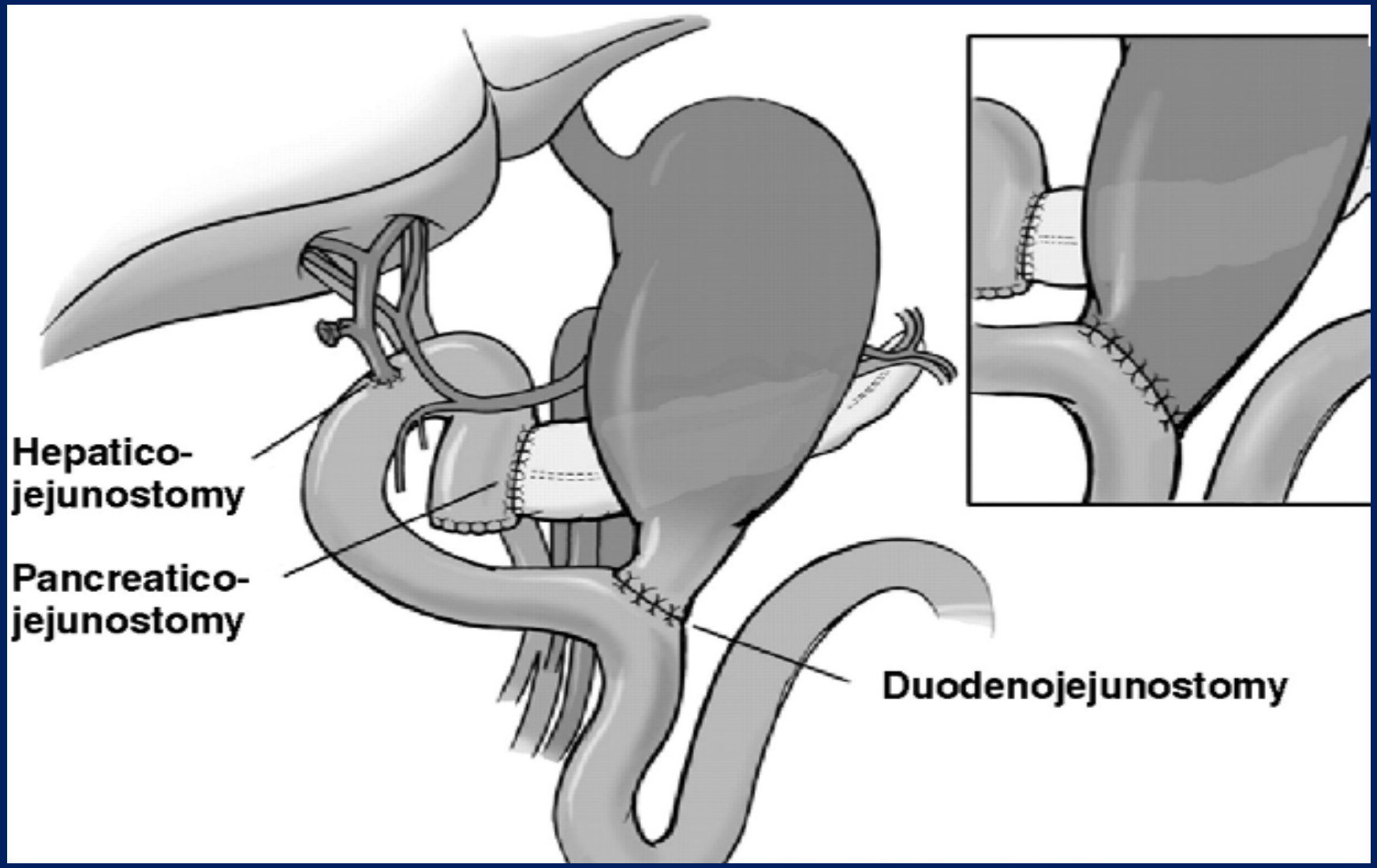
- False (-): CA 19-9 is sialylated Lewis (a) antigen (adsorbed RBC antigens)
  - 10% of the Caucasian population lacks the Lewis antigen (deficiency of a fucosyltransferase) = CA19-9 is not expressed

Carbohydrate or Cancer Antigen (CA 19-9)

- Preoperative amounts of carbohydrate antigen 19-9 (CA19-9) of more than 100–200 U/mL predict unresectability

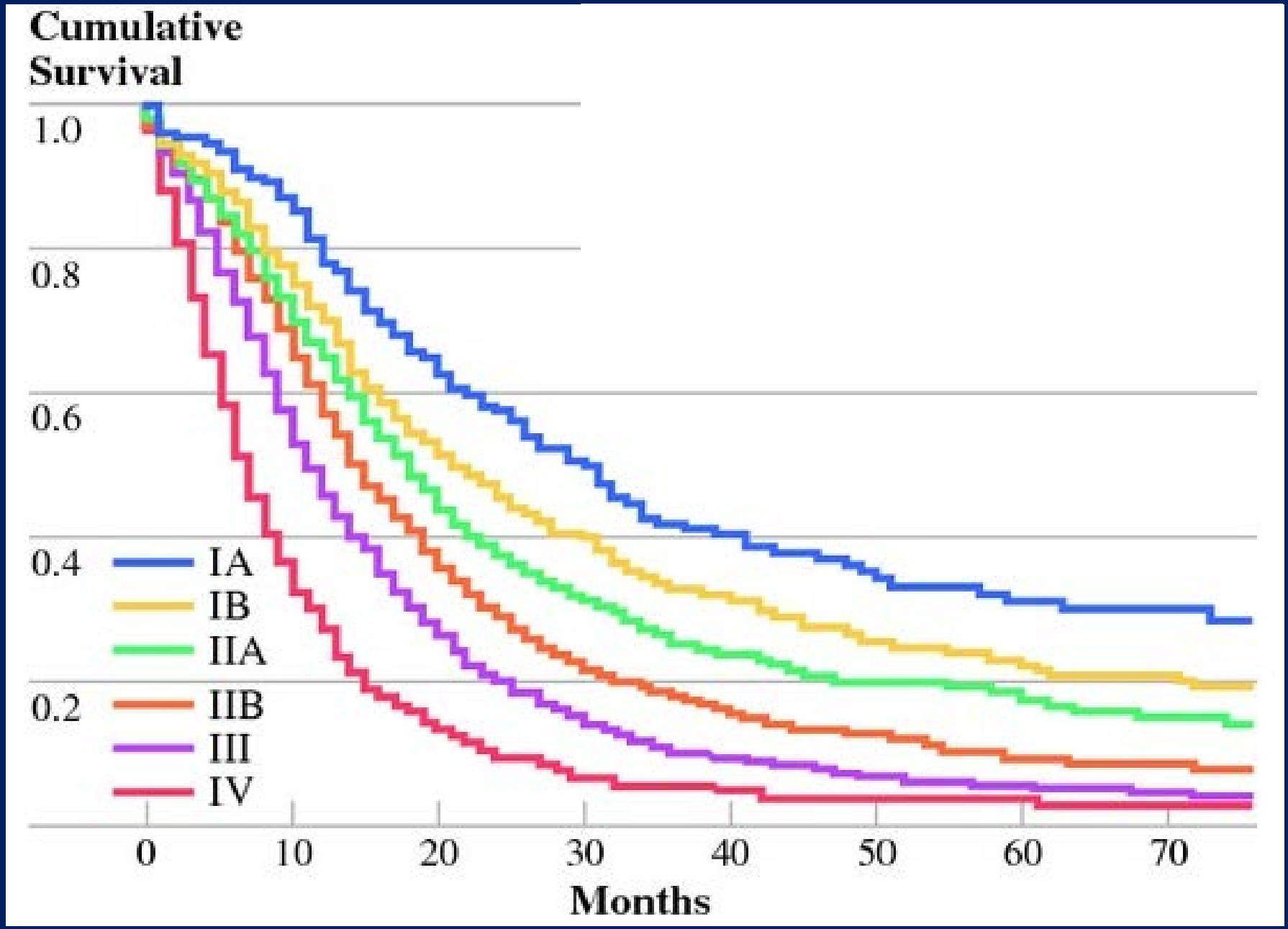
- Biliary drainage lowers nonspecific CA19-9 amounts, allowing for more reliable estimate of disease burden

Treatment- pancreaticoduodenectomy "WHIPPLE"



Staging of PDAC

Stage	Median Survival (mo)	Characteristics
IA	24.1	Limited to pancreas, <2 cm
IB	20.6	Limited to pancreas, >2 cm
IIA	15.4	Locally invasive, no involvement celiac or SMA
IIB	12.7	Locally invasive, Lymph Node metastasis
III	10.6	Celiac axis or SMA involved (unresectable)
IV	4.5	Distant Metastasis (unresectable)



Wasif N, Ko CY, Farrell J, Wainberg Z, Hines OJ, Reber H, Tomlinson JS. Impact of tumor grade on prognosis in pancreatic cancer: should we include grade in AJCC staging?

Treatment

- Chemotherapy after resection- gemcitabine

- The addition of erlotinib (small molecule inhibitor of EGFR) or fluoropyrimidine have shown slight improvements of overall survival
  - Erlotinib - modest survival improvement and increased level of toxicity has limited the acceptance

Pearls of Wisdom

- Mortality rate is extremely high; few survivors
- Research on screening for PDAC should focus of **PRE** invasive lesions
- Tumor markers are not synonymous with screening tests
- Much Room for Improvement
  - Screening
  - Biomarkers
  - Treatment

Summary

Commonly used tests for
diagnosing or evaluating pancreatic disease

Acute Pancreatitis

- Amylase and Lipase
- Imaging

Pancreatic Cancer

- No good screens (yet)
- EUS, cytopathology for diagnosis
- CEA, CA 19-9 for monitoring
- Imaging

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