

# Mission:Cure

Sep 24th, 2025

## High Triglycerides & Pancreatitis: Causes, Diagnosis & Treatments

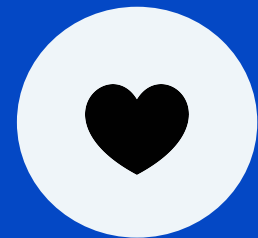


**Dr. Andres Gelrud**

**Pancreatologist and Director of  
the Pancreatic Disease Program**

# About Mission: Cure

Mission: Cure is a nonprofit founded in 2017 for & by patients to find treatments & improve the lives of people suffering from pancreatitis.



Awarded grant from Chan-Zuckerberg Initiative Science for high-potential patient-led rare disease organizations



Actively working with 6 pharma/biotech companies & 8 academic medical centers on drug development for chronic pancreatitis



Bringing new funding from impact investors to therapeutic development projects



**Megan & Eric**



**Linda & Amy**

# Agenda

Mission:Cure

**Pancreatitis & Triglycerides Basics**

**Dr. Andres Gelrud**

**Hypertriglyceridemia & Pancreatitis**

**Dr. Andres Gelrud**

**Causes, Symptoms, Diagnosis**

**Dr. Andres Gelrud**

**Treatment & Management**

**Dr. Andres Gelrud**

**Q&A Session**

**Dr. Gelrud & Megan Golden**

**Closing**

**Olivia Zeiden**

## OBJECTIVES

Mission:Cure

# Triglycerides & Pancreatitis

1. Understand TGs\* & their role
2. Learn how HTG\* increases risk of pancreatitis
3. Identify causes & forms of sHTG\*, including FCS
4. Review tests & diagnostic criteria for HTG\*
5. Inform on FDA-approved & emerging treatments
6. Strategies for long-term disease management

\*TGs: Triglycerides  
HTG: Hypertriglyceridemia  
sHTG: Severe Hypertriglyceridemia



# Understanding Hypertriglyceridemia & Pancreatitis

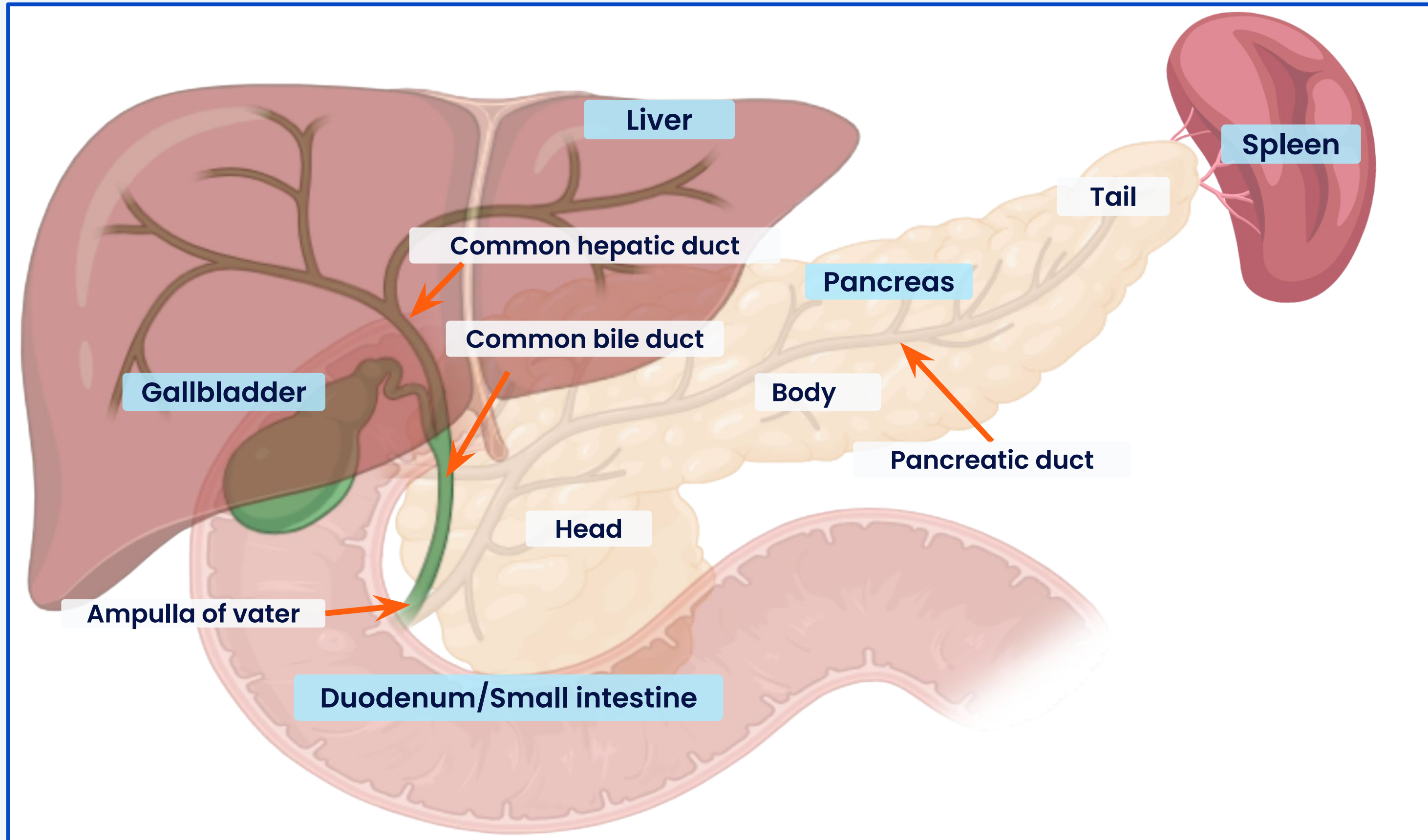


**Dr. Andres Gelrud**

Clinical pancreatologist, Gastro Health  
Director of the Pancreatic Disease Program, Miami Cancer  
Institute



# Pancreas Anatomy



# Pancreas Function

## Exocrine (Digestion)

The pancreas produces enzymes that help digest food

 Amylase

 Protease

 Lipase



## Endocrine (Hormonal)

The pancreas produces chemicals (hormones) that regulate blood sugar

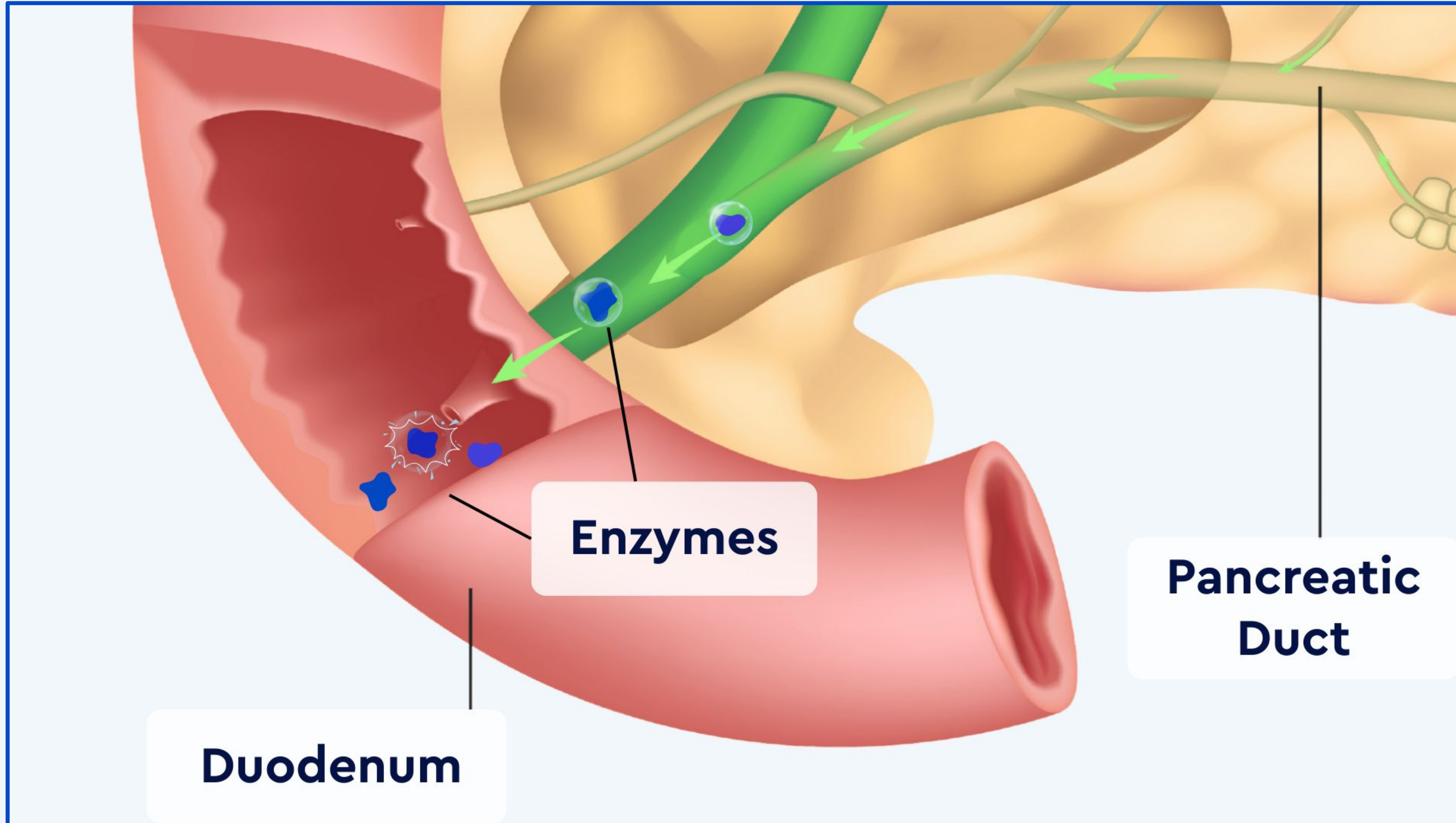
 Glucagon

 Insulin

 Somatostatin

 Pancreatic polypeptide

# Pancreas Function



# Pancreatitis: AP, RAP, CP

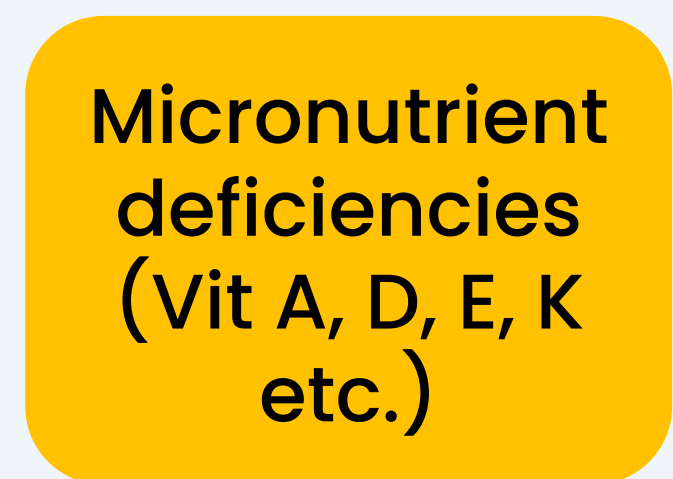
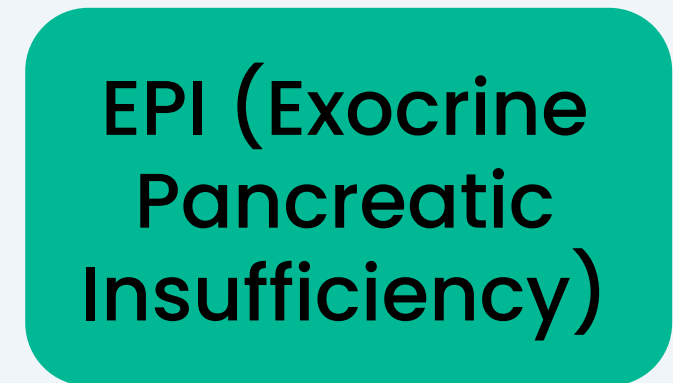
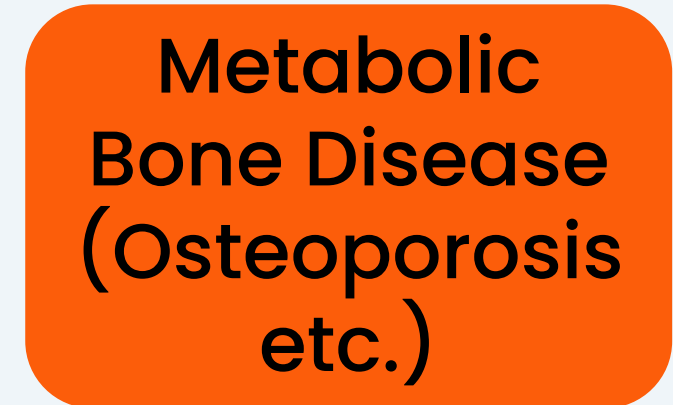
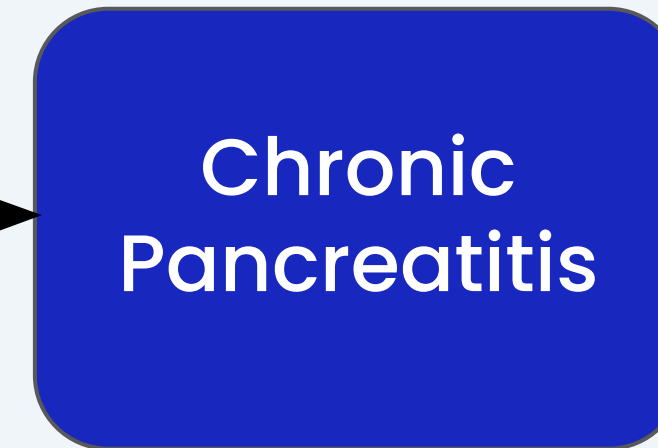
1 Episode



> 2 Episodes



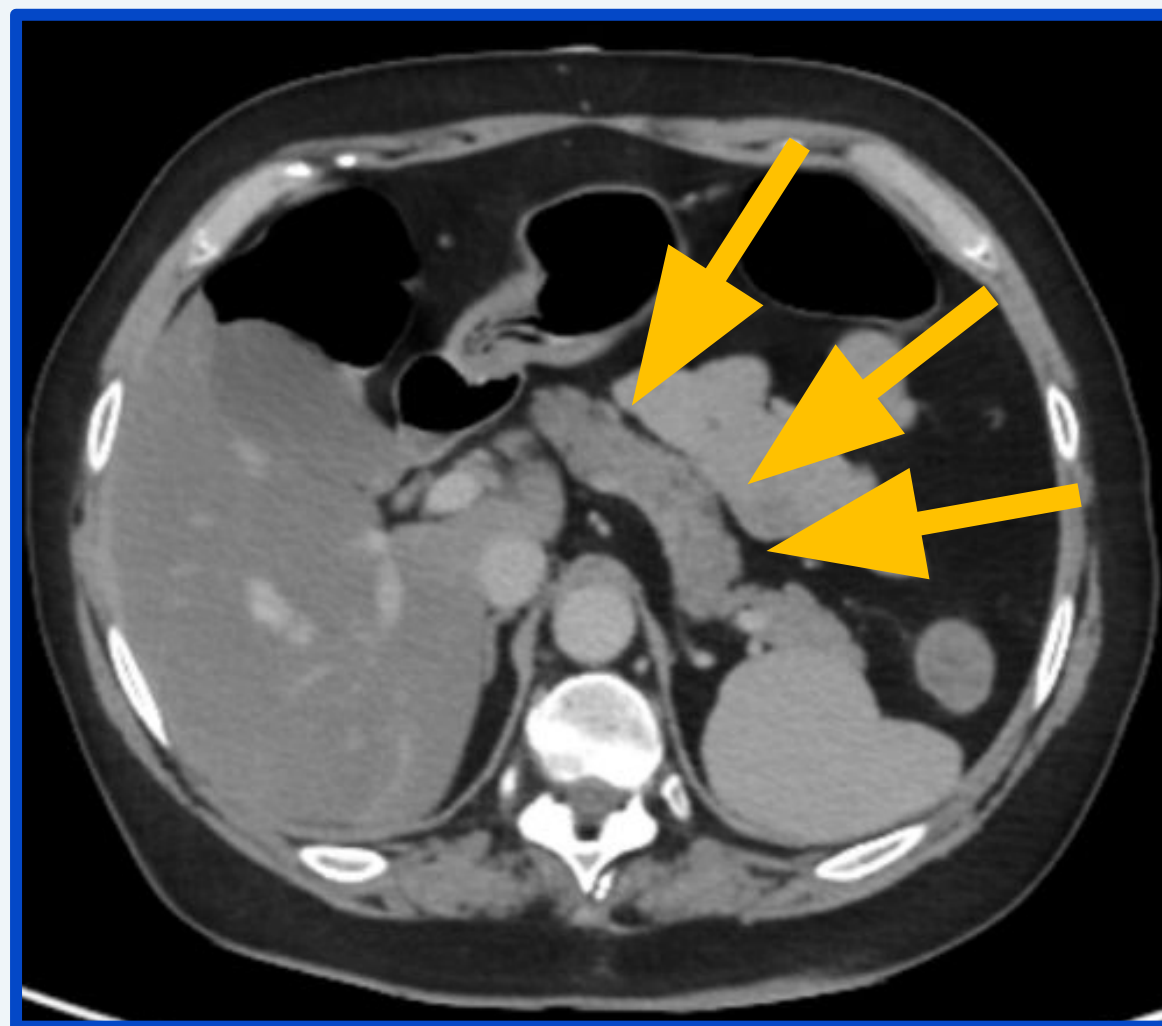
Established disease & complications



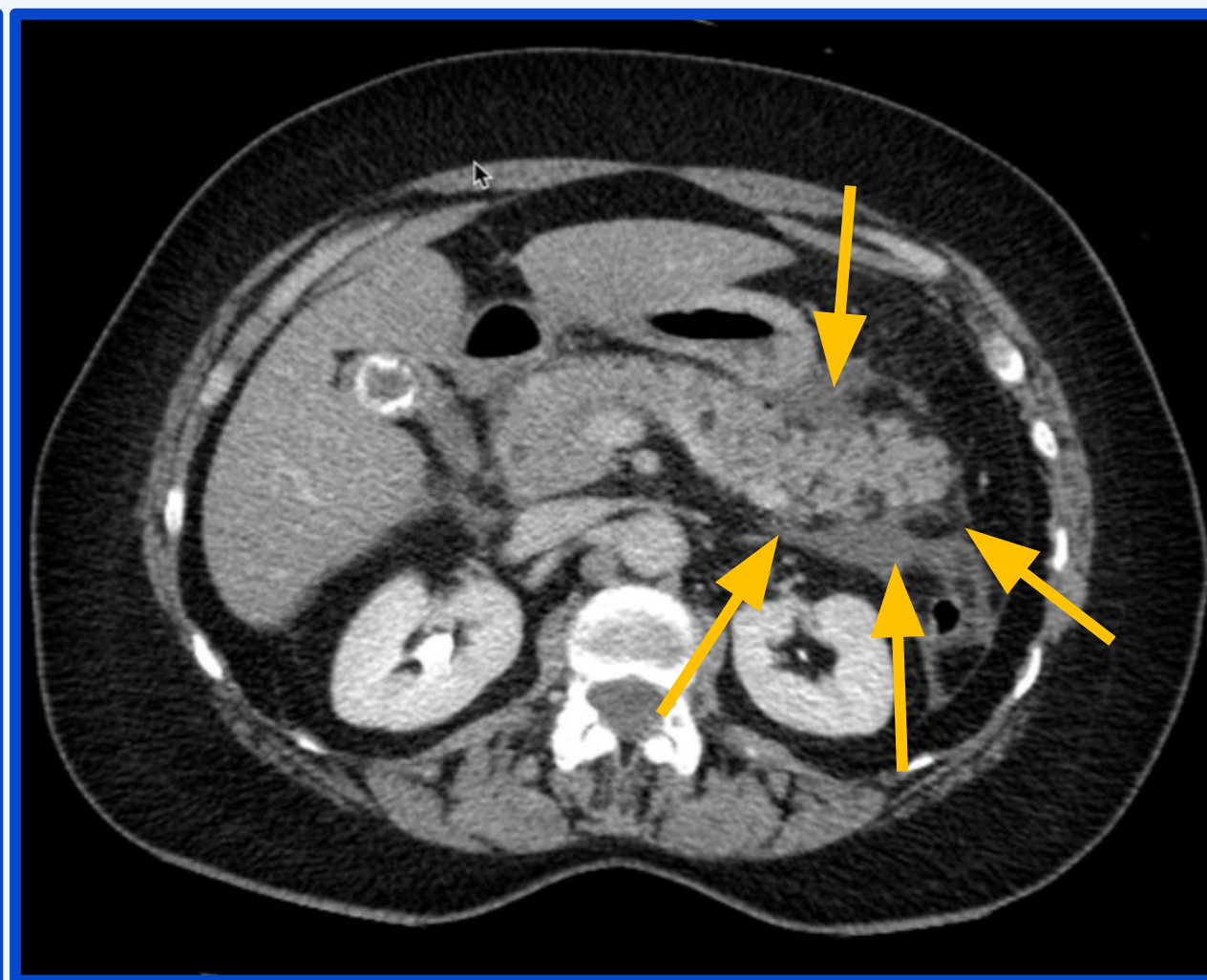
Diagnosis: \*2 or the below 3 = AP

- Abdominal pain
- Imaging with pancreatic inflammation
- $\geq 3$  times elevation of amylase/lipase

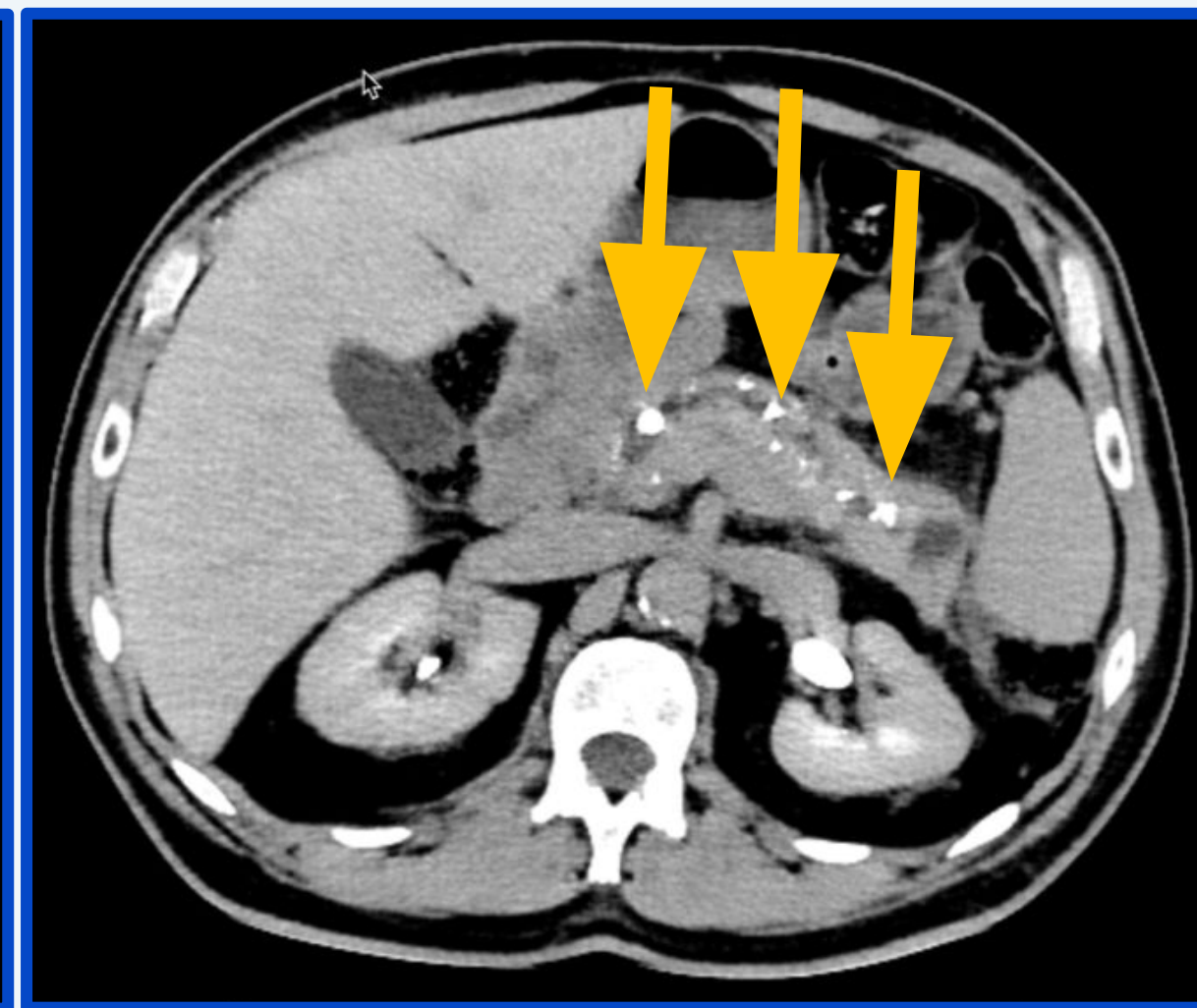
# Acute Pancreatitis: CT Imaging



**Normal Pancreas**

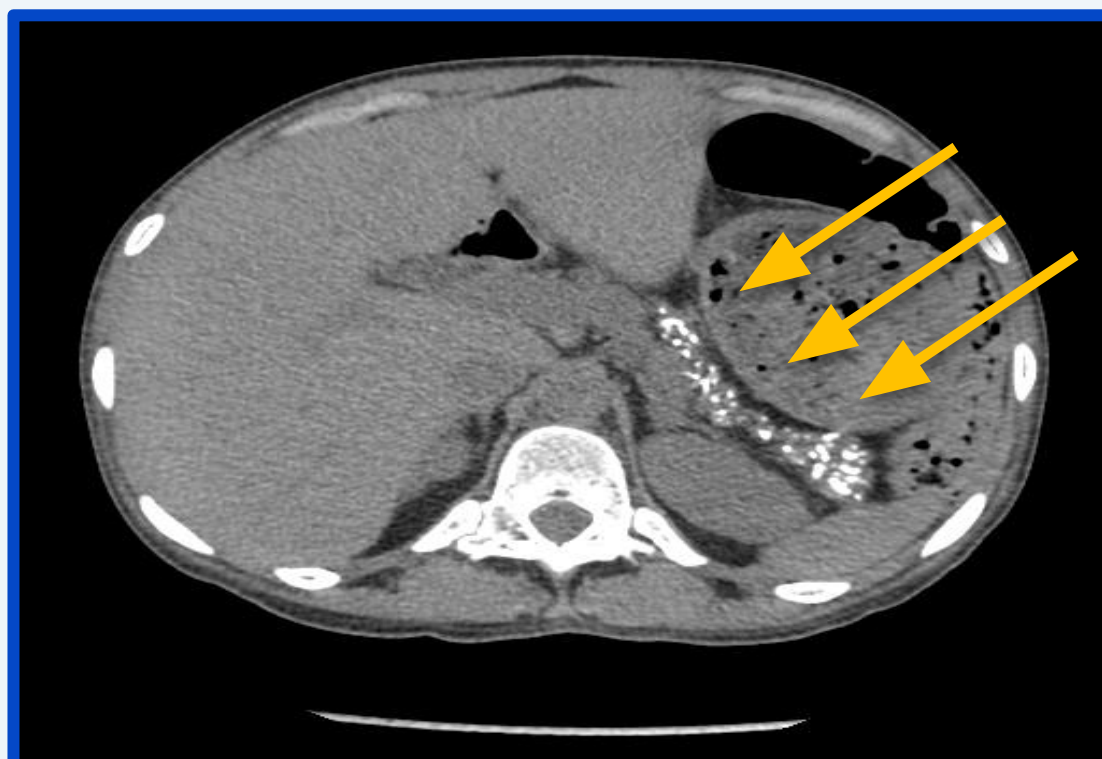
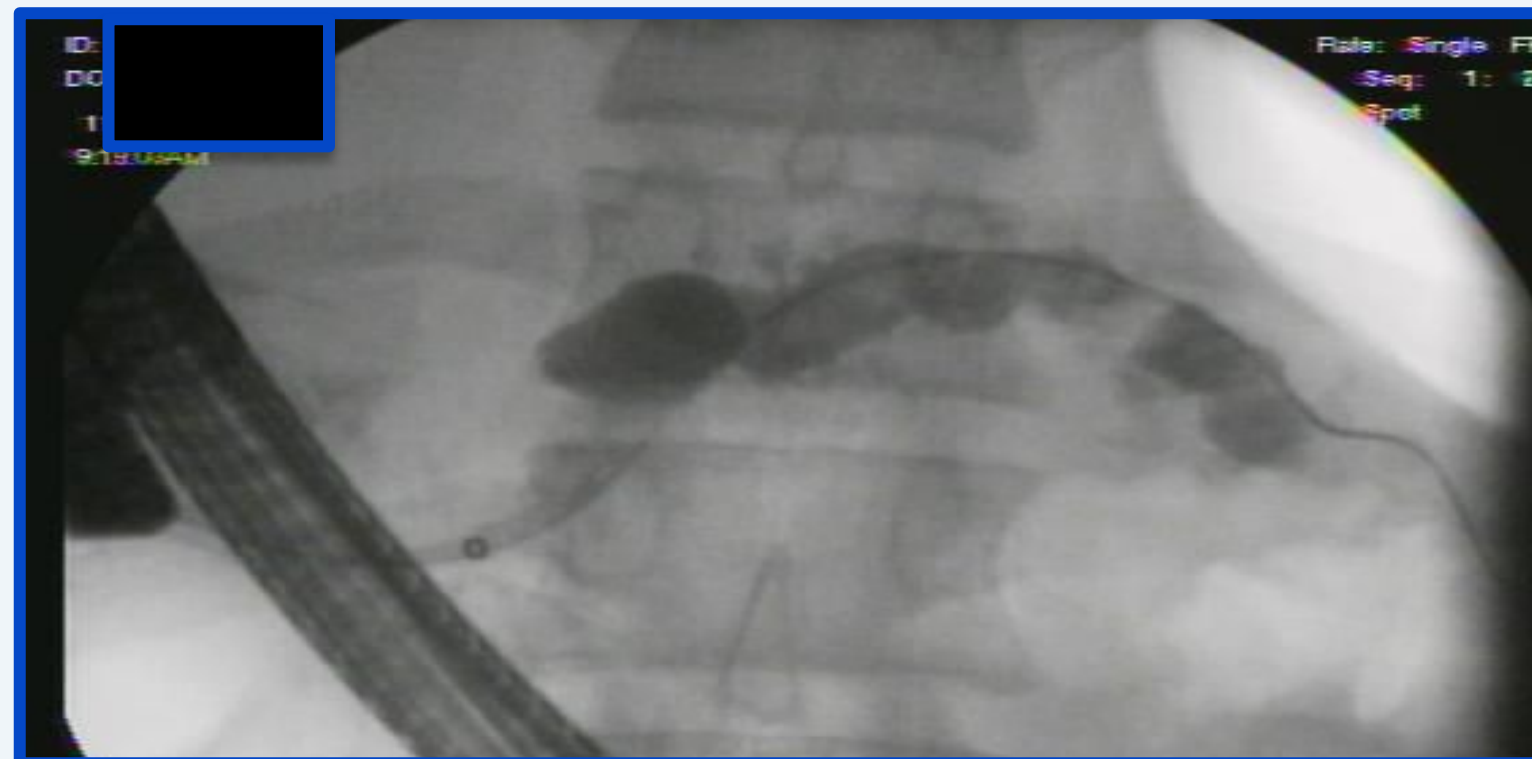
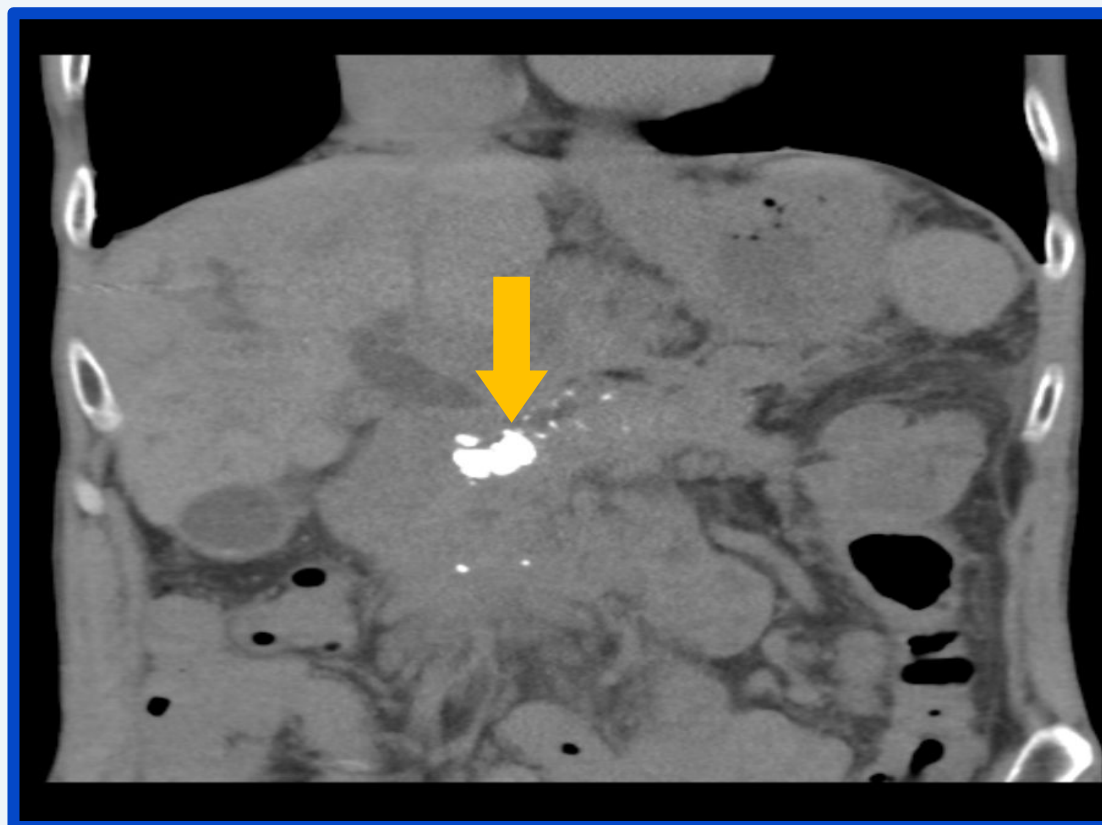


**Acute pancreatitis  
edema & stranding around  
pancreas**



**Dilated pancreatic duct with  
calcifications**

# Chronic Pancreatitis



# Natural History: After AP

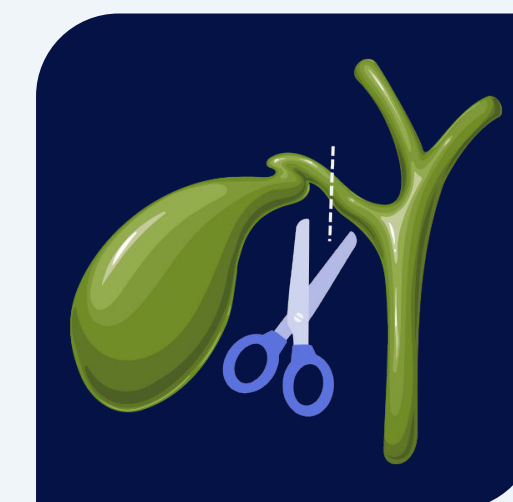
**Study: Yadav et al., Am J Gastroenterol 2012**  
(N=7,456, First AP Diagnosis 1996–2005, PHC4 Data)

## Results:

- First AP attack → Recurrent AP (~29%) → CP (~6–12.8%)
- Independent predictors for RAP & CP– Alcohol & Smoking
- Independent predictor for CP is RAP

## Prevention Opportunity:

- Stopping alcohol & smoking early may alter disease course
- In biliary AP (related to gallbladder & bile ducts), timely gallbladder removal (cholecystectomy) reduces recurrence



# Progression of AP- RAP- CP

Gastroenterology 2015;149:1490-1500

## **CLINICAL—PANCREAS**

### **Frequency of Progression From Acute to Chronic Pancreatitis and Risk Factors: A Meta-analysis**



Sharanya J. Sankaran,<sup>1</sup> Amy Y. Xiao,<sup>1</sup> Landy M. Wu,<sup>1</sup> John A. Windsor,<sup>1</sup> Christopher E. Forsmark,<sup>2</sup> and Maxim S. Petrov<sup>1</sup>

**Meta-analysis, 14 studies; N=8,492, 2015**

### **Results:**

- First AP attack → Recurrent AP (22%) → CP (10%)
- 36% of RAP cases progressed to CP
- Independent risk factors- Smoking, Alcohol use, Male sex

### **Conclusion:**

- ~1 in 10 patients with AP develop CP
- RAP substantially increases risk of CP progression

# AP Diagnosis: Basic Lab Tests

## Metabolic Workup:

- **Triglycerides**- Check for high levels & assess risk
- **Calcium**- Check for hypercalcemia trigger
- **TTG & IgA\***- Screen for celiac disease
- **TSH\***- Evaluate thyroid function (Hypothyroidism can raise triglyceride levels)
- **IgG4\***- Assess for autoimmune pancreatitis
- **Genetic Testing**- Identify inherited causes like FCS, MCS & other pancreatitis risk driving or causing genes



\*TTG: Tissue Transglutaminase

Antibody IgA: Immunoglobulin A

TSH: Thyroid Stimulating Hormone

IgG4: Immunoglobulin G Subclass 4

# What Are Triglycerides (TGs)?

*Main type of fat in the body & bloodstream*

**Sources:** From diet + Made by liver

**Transport:** Need to be carried by lipoproteins

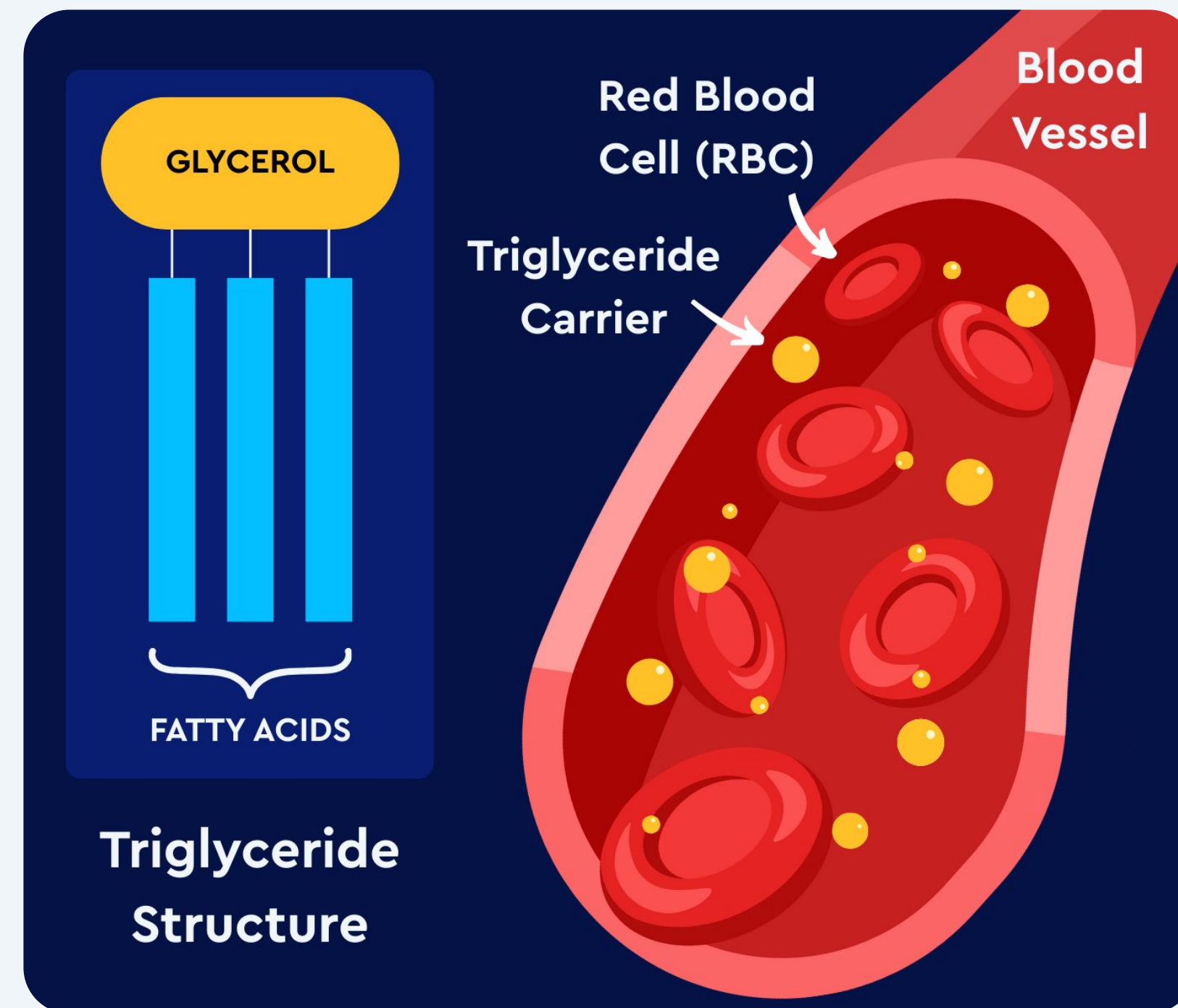
**Functions:**

- Fuel for muscles & energy storage (fat tissue)
- Protect & insulate organs
- Needed to absorb vitamins A, D, E, K

**TGs & Cholesterol:**

- TGs = Fuel = A lipid & fat
- Cholesterol = Structure = A lipid, not fat (*membranes, hormones, bile acids*)

*TGs & Cholesterol are transported in blood via lipoproteins*



# How TGs Travel

Lipoproteins = Fat + Protein

Role: Transport & Deliver Water-Insoluble TGs & Cholesterol to Tissues

High Levels = High Triglycerides  
**Pancreatitis Risk**

High Levels = Plaque Buildup  
 (Atherosclerosis)

TYPE OF LIPOPROTEIN →



TYPE OF LIPOPROTEIN	Chylomicron	Chylomicron Remnant	VLDL Very Low-Density Lipoprotein	IDL Intermediate-Density Lipoprotein	LDL Low-Density Lipoprotein	HDL High-Density Lipoprotein
<ul style="list-style-type: none"> <li> Phospholipids</li> <li> Cholesterol Esters</li> <li> Triglycerides</li> </ul>						
<b>DENSITY</b>	<0.93	0.93-1.006	0.93-1.006	1.006-1.019	1.019-1.063	1.063-1.210
<b>MAIN LIPIDS (FATS)</b>	Triglycerides	Triglycerides Cholesterol	Triglycerides	Triglycerides Cholesterol	Cholesterol	Cholesterol Phospholipids

# TG Metabolism

## Exogenous (From Diet)

Dietary fat → Intestine → Chylomicrons  
→ Broken down by lipoprotein lipase  
(LPL) → Fatty acids for energy/storage

## Endogenous (From Liver)

Liver makes TGs → VLDL (very low  
density lipoprotein) → Cleared by LPL →  
Fatty acids for use/storage

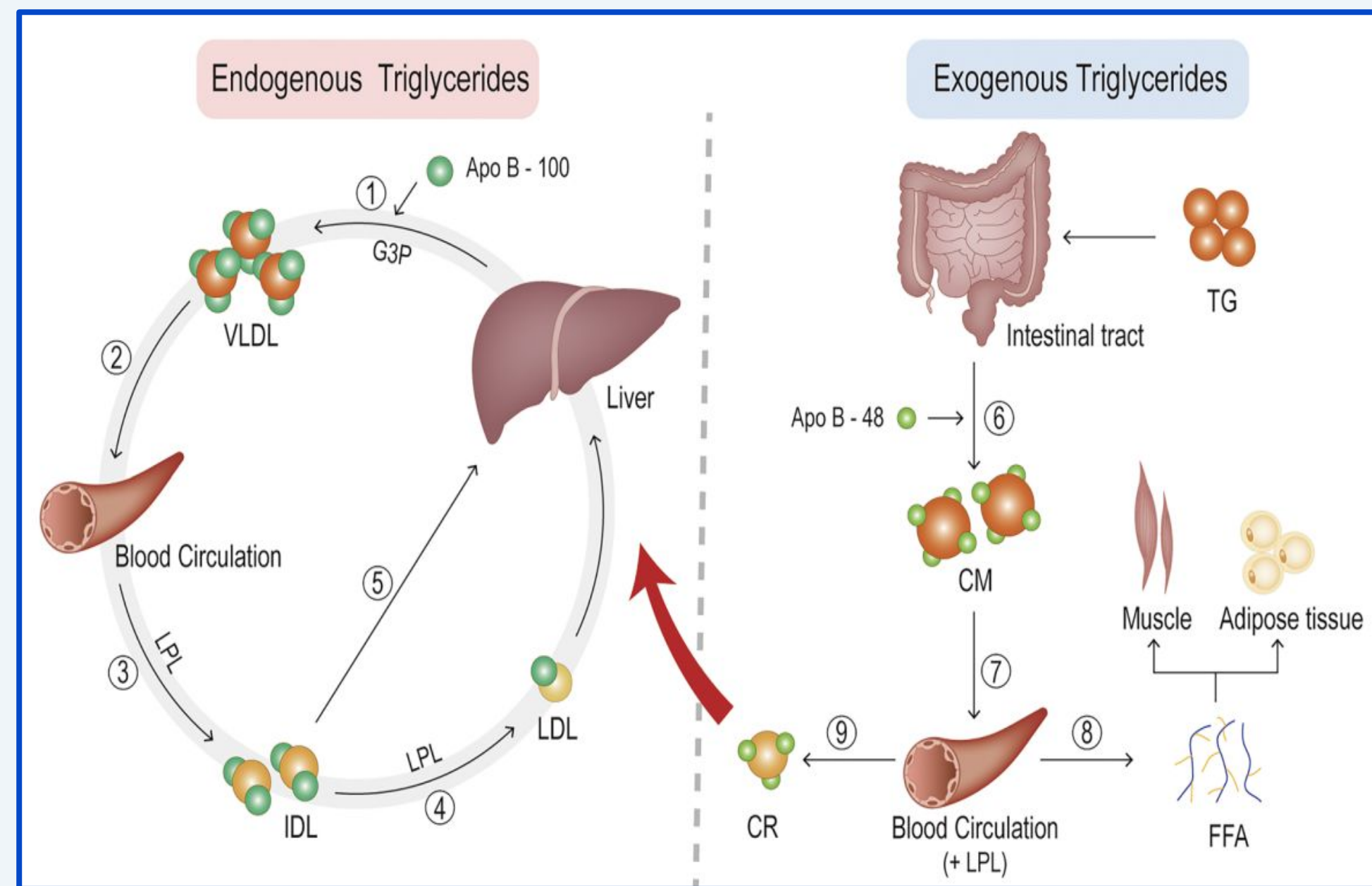


Figure 2, Qiu, Minhao & Zhou, Xiaoying & Zippi, Maddalena & Goyal, Hemant & Basharat, Zarrin & Jagielski, Mateusz & Hong, Wandong. (2023). Comprehensive review on the pathogenesis of hypertriglyceridemia-associated acute pancreatitis. *Annals of Medicine*. 55. 10.1080/07853890.2023.2265939.

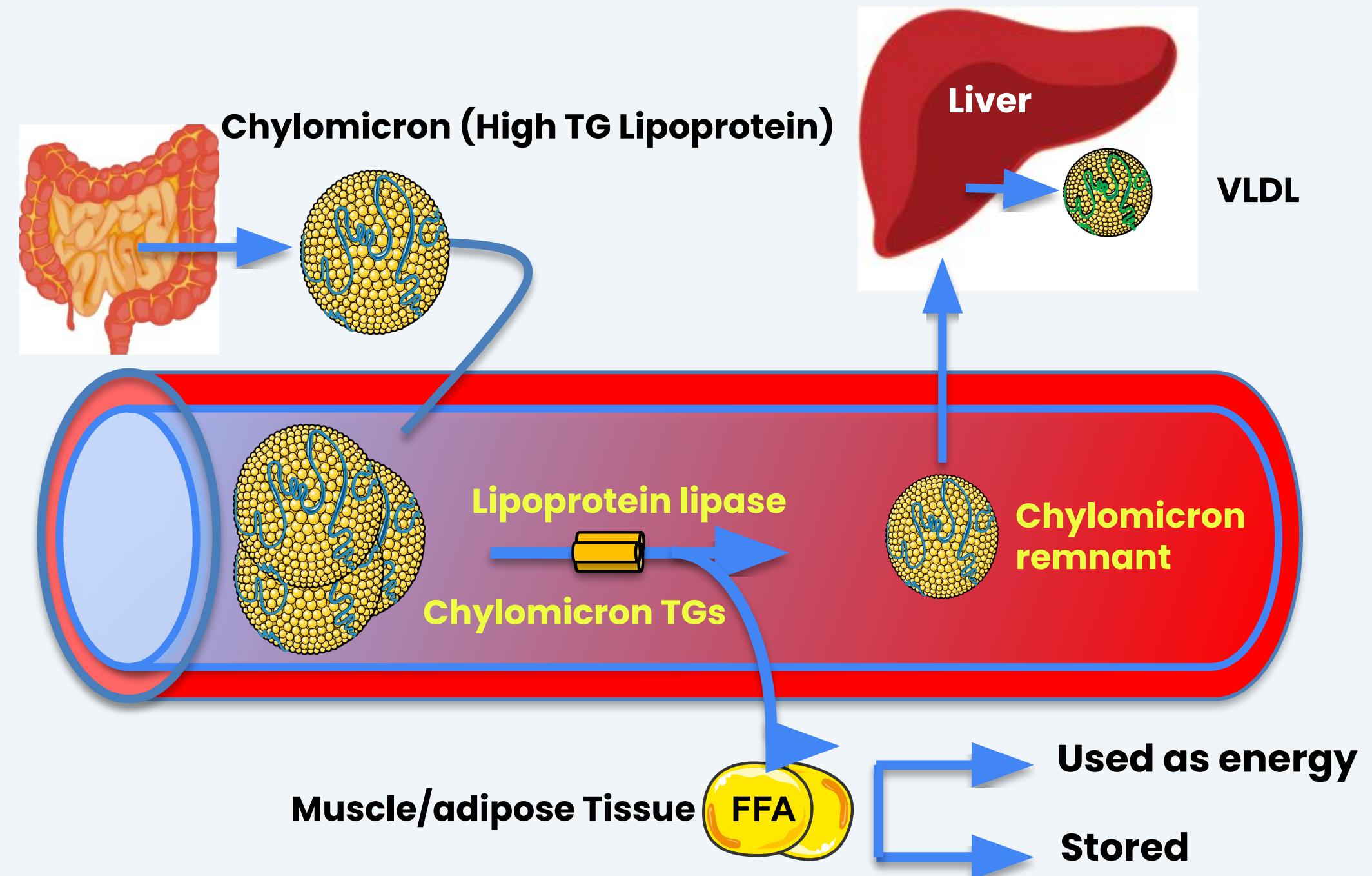
## Normally

LPL clears TG-rich particles efficiently → Blood TG returns to normal within hours after a meal

# In Healthy Individuals

## Chylomicrons: Large lipoproteins transporting TGs (from dietary fat)<sup>1,2</sup>

- Appear in circulation shortly after a meal; cleared after a few hours<sup>3</sup>
- LPL gene (or related genes like ApoC2, ApoA5, LMF1, GPIHBP1) normally make or support lipoprotein lipase (LPL)
- LPL enzyme breaks down TGs from chylomicrons & VLDL
- TGs broken down by LPL to FFAs are used by various tissues<sup>2</sup>



\*FFA: Free fatty acid; TG: Triglyceride; VLDL: Very low-density lipoprotein.

Adapted from Braham, Nat Rev Endocrinol, 2015.

# What is Hypertriglyceridemia (HTG)?

## High levels of triglycerides/TGs in blood (A form of dyslipidemia)

Too much dietary input (exo) or poor clearance from liver pathways (endo) → TGs accumulate → risk for AP

Level	Triglycerides	
	mg/dL	mmol/L
Optimal	<100	<1.1
Normal	<150	<1.7
Borderline-high triglycerides	150–199	1.7–2.3
High Triglycerides	200–499	2.3–5.6
Severe	>500	> 5.6
	>880 Chylomicronemia	>9.9



AP Risk Increases



# Why HTG Causes AP

## Established Mechanisms

- High TG → Excess free fatty acids (FFAs) → Toxic to pancreas & blood vessels
- Thickened blood & small vessel clogs reduce oxygen to pancreas
- Calcium overload inside cells turns on digestive enzymes too early
- Oxidative stress amplifies tissue damage

## Emerging Mechanisms

- Cell stress pathways may worsen injury
- Gut bacteria & genetics may influence severity

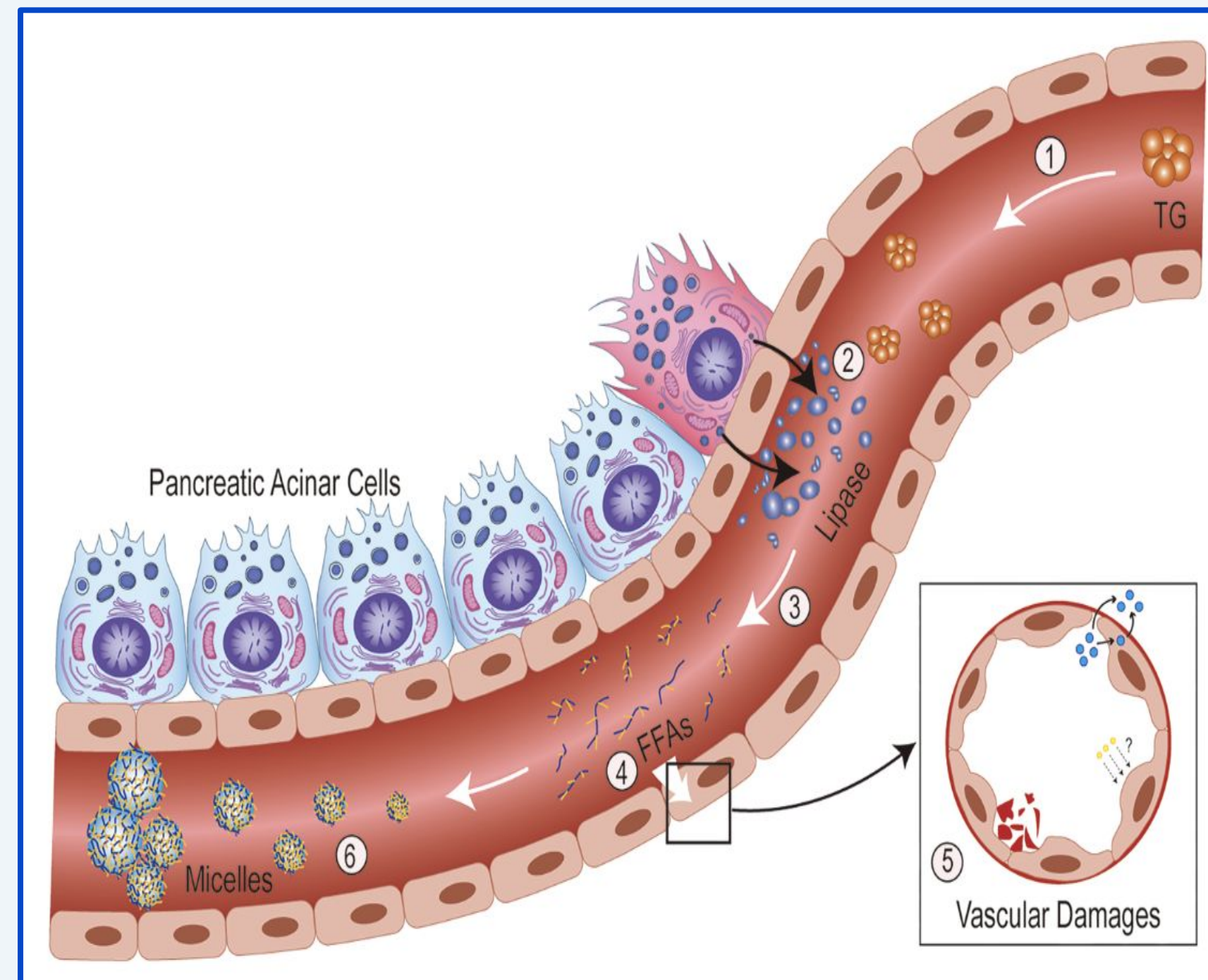


Figure 3, Qiu, Minhao & Zhou, Xiaoying & Zippi, Maddalena & Goyal, Hemant & Basharat, Zarrin & Jagielski, Mateusz & Hong, Wandong. (2023). Comprehensive review on the pathogenesis of hypertriglyceridemia-associated acute pancreatitis. *Annals of Medicine*. 55. 10.1080/07853890.2023.2265939.

# Common Causes of HTG

## Secondary Causes



**Alcohol**<sup>1-2</sup>



**Uncontrolled Diabetes**<sup>1-2</sup>



**Medications Known to Cause Hypertriglyceridemia**<sup>3</sup>

Atypical antipsychotic agents, beta-blockers, oral estrogens, protease inhibitors, bile acid binding resins, corticosteroids, L-asparaginase, retinoids, sirolimus, tamoxifen, propofol



**Medical Conditions**<sup>2-3</sup>

Chronic renal failure, Cushing syndrome, hypothyroidism, HIV infection, insulin resistance, metabolic syndrome, nonalcoholic fatty liver disease, pregnancy, systemic lupus erythematosus

## Primary

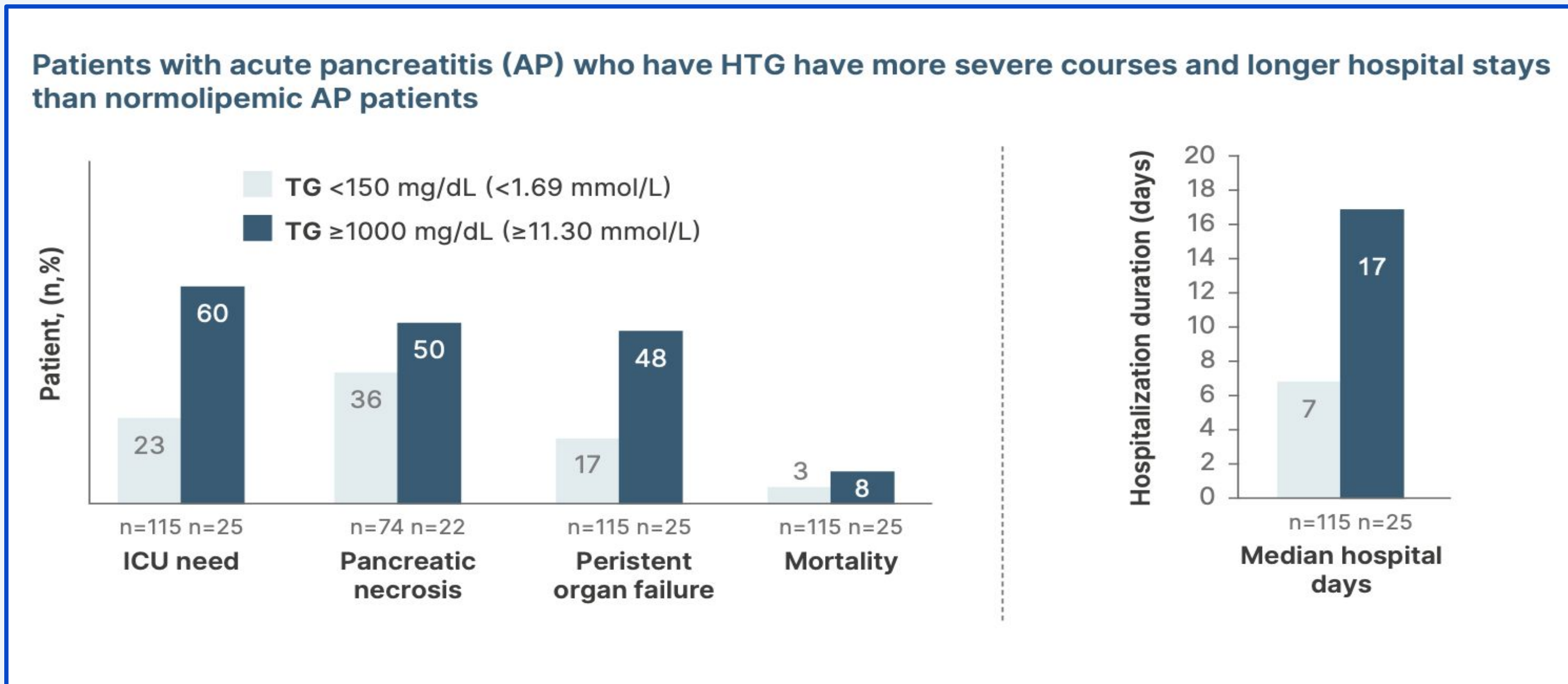
Causes



**Genetic**<sup>1</sup>

# HTG & AP Impact

- 3rd leading cause of AP; AP can be deadly
- Worse outcomes for patients with extremely high TG levels



# Severe Hypertriglyceridemia (sHTG)

Severe TGs: > 500 mg/dL or >5.6 mmol/L  
> 880 mg/dL or >9.9 mmol/L (Chylomicronemia)

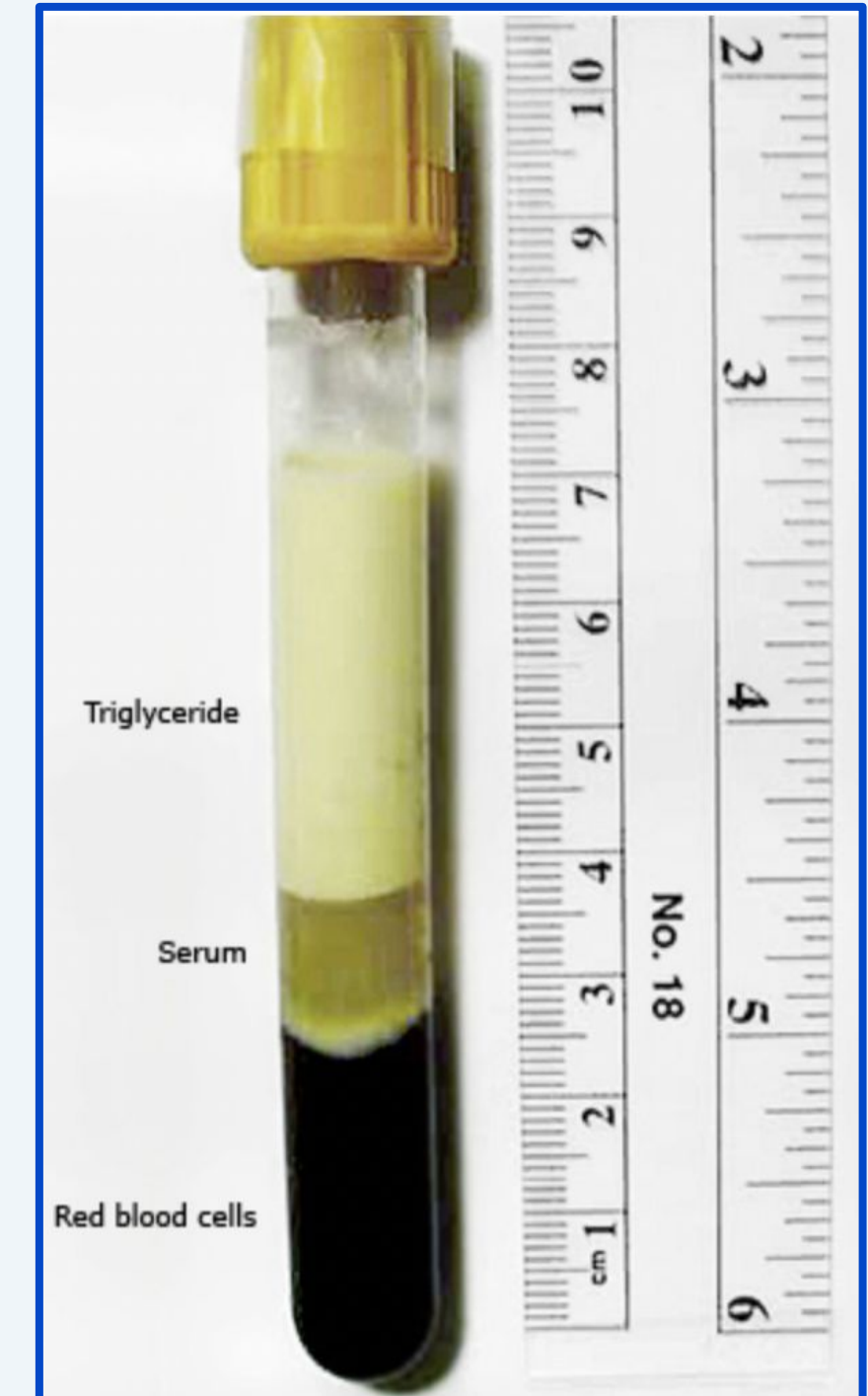
Blood Sample with TG of 1200 mg/dL

<p><b>1</b></p> <p><b>Familial Chylomicronemia Syndrome (FCS)</b></p>	<p><b>2</b></p> <p><b>Multifactorial Chylomicronemia Syndrome (MCS)</b></p>	<p><b>3</b></p> <p><b>Secondary Hypertriglyceridemia</b></p>
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Rare Disease  
Genetic Disorder

More Common Than FCS  
Genetic Factors + Lifestyle or Other Health Conditions

Most Common  
Other Underlying Medical Condition or External Trigger



# Familial Chylomicronemia Syndrome (FCS)

## Rare Inherited Genetic Disorder: Severe TG Elevation

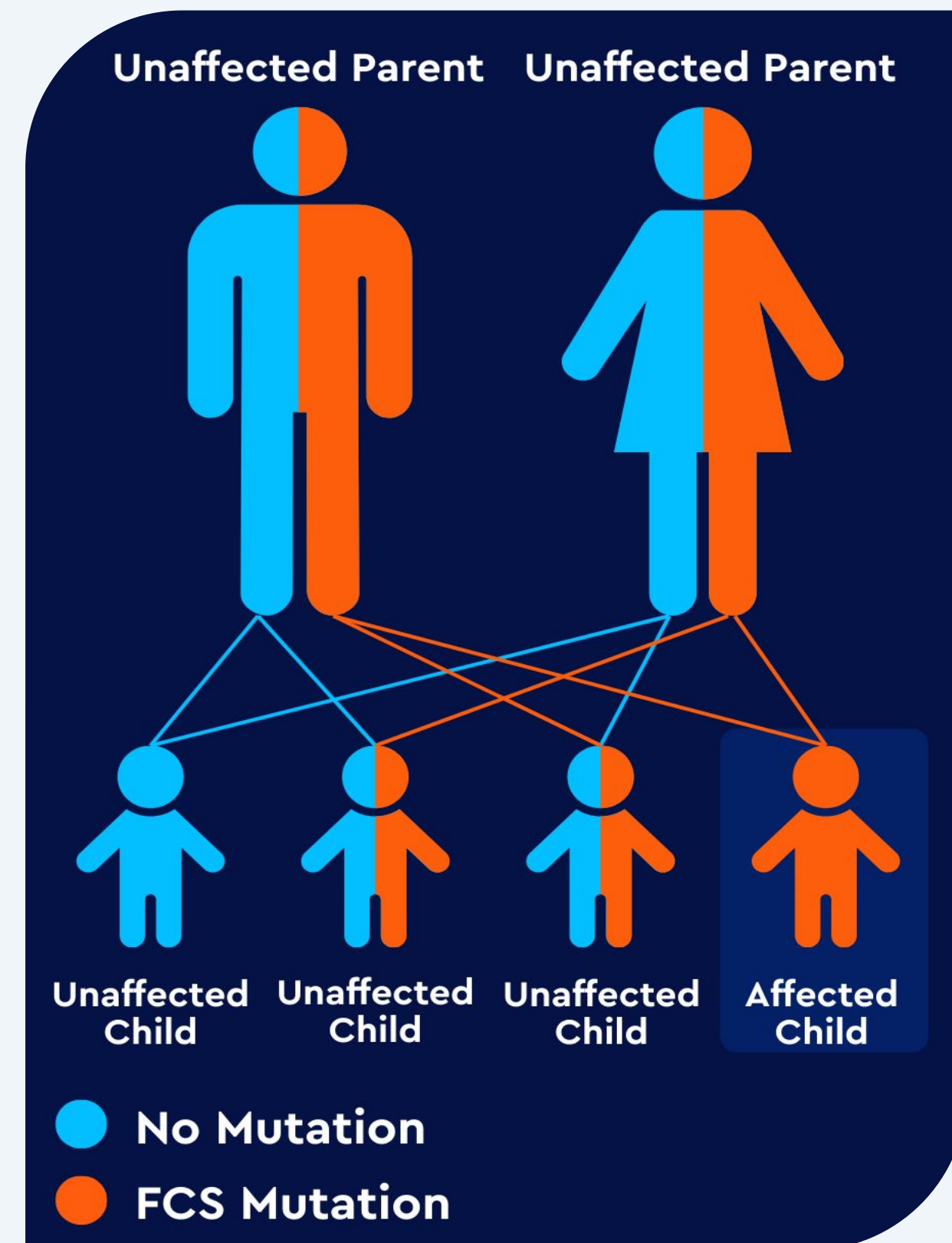
- Autosomal recessive genetic disorder
- TGs 10–100x greater than normal; sHTG = Pancreatitis risk
- Affects 1–8 people per million; Males & females equally affected

## Age of Onset

- 25% of affected children symptomatic by 1 yr of age
- Majority develop symptoms by 10 yrs of age
- Some show no symptoms until adulthood or pregnancy
  - Often present with abdominal pain, high TGs
    - *This inherited disease may be overlooked at this stage*

## Overall Mortality: 5% to 6%

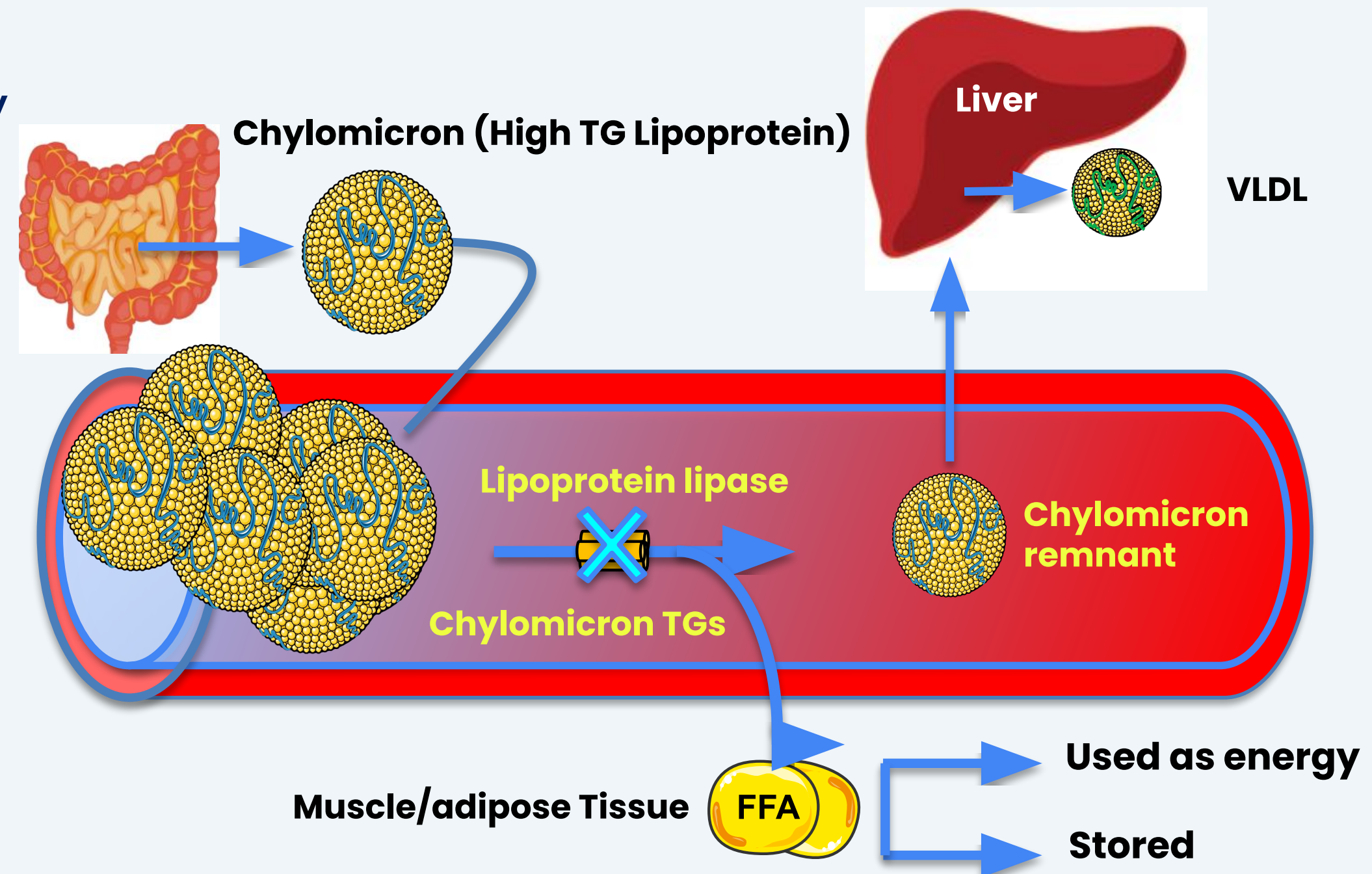
- 30% in subgroups with severe complications



# Individuals with Chylomicronemia

**Chylomicronemia: Persistence of chylomicrons in blood following 10 to 14 hours fasting<sup>1,2</sup>**

- In FCS, chylomicronemia is caused by inherited defects in chylomicron processing<sup>2</sup>
- Caused by mutations in the LPL gene (or related genes like ApoC2, ApoA5, LMF1, GPIHBP1)
- Without working LPL, body can't clear TGs from blood



\*FFA: Free fatty acid; TG: Triglyceride; VLDL: Very low-density lipoprotein.

Adapted from Brahm, Nat Rev Endocrinol, 2015.

# Diagnosing FCS

Severe, Refractory\* HTG, Presence of Key Clinical Symptoms, Not Due to Secondary Causes



**SEVERE =**  
Fasting TGs >880 mg/dL  
or 10 mmol/L



**\*REFRACTORY =**  
Not responsive to  
standard TG therapies

**History of AP**



**OR**

**History of recurrent  
abdominal pain without  
other explainable cause**

**Alcoholism**



**OR**

**Uncontrolled diabetes**

**OR**

**Medications or medical  
conditions known to cause HTG**

# Diagnostic Approach

## How

- Severely elevated levels of TGs ( $>880$  mg/dL)
- Unresponsive to standard lipid-lowering therapies
- “Refrigerator Test”– Confirms presence of chylomicrons
  - ◆ Blood samples in refrigerator overnight
  - ◆ Chylomicrons float to the top, forming a creamy layer

## When

- Severe TG levels in childhood or infancy
- Secondary causes (uncontrolled diabetes, alcohol abuse) ruled out
- Fasting TG levels  $>1000$  mg/dL or non-fasting  $>2000$  mg/dL
- Low or normal LDL, normal HDL
- Recurrent abdominal pain episodes, with or without recurrent pancreatitis
- Other symptoms present e.g., fatigue, malaise, cognitive impairment
- Family history of FCS



# Confirming FCS Diagnosis

1. Clinical Scoring Tools/Criteria
  - a. NAFCS- US & Canada
  - b. Moulin et al- EU
2. Refer to Lipid Specialist
3. Diagnostic Gold Standard (*not mandatory*)
  - a. Full LPL gene sequencing
  - b. Cofactor gene sequencing (*LMF1, GPIHBP1, ApoC2, ApoA5*)
4. If Patient Has FCS, Siblings Should Also Be Tested



# FCS Signs & Symptoms

## Clinical complications

- Recurrent abdominal pain
- Recurrent acute pancreatitis
- Pancreatic failure
- Diabetes
- Others



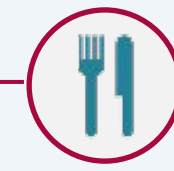
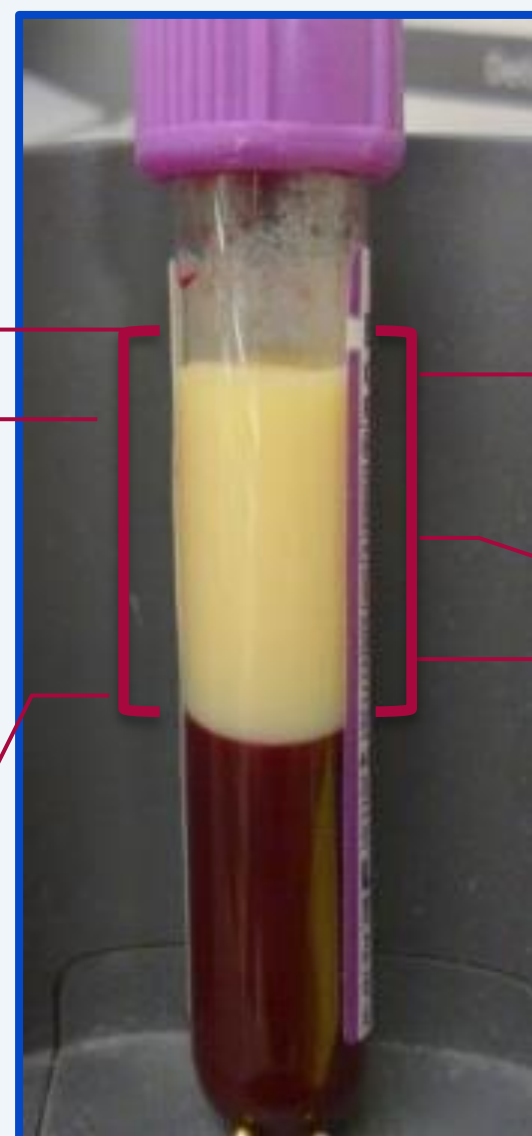
## Hematological manifestation

- Hyperviscosity
- Hemolysis
- Important platelet count variability
- Thrombocytosis
- Thrombocytopenia



## Neurological symptoms

- Cognitive impairment
- Memory loss
- Confusion
- Fatigue
- Peripheral neuropathy



## Clinical manifestation

- Eruptive xanthoma
- Lipemia retinalis
- Hepatosplenomegaly
- Fatty liver
- GI disturbances

## Emotional burden

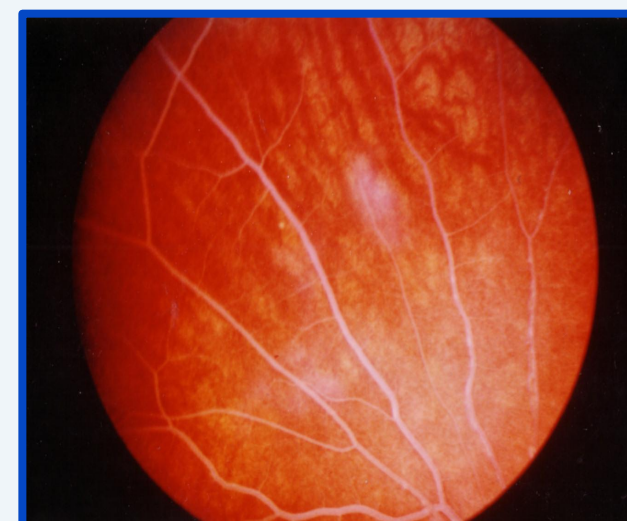
- Anxiety/depression
- Guilt
- Social constraints
- Decreased QOL

## Severe dietary restrictions

- <10-20g of total fat daily

## Financial burden

- Days missed from work
- ER/ICU visits
- Lengthy hospitalization
- Disability
- Under/unemployment



# FCS Challenges & Hope

- Difficult diagnosis to make; High symptom burden
- Hard to maintain very low fat diet (<20 g fat per day)
- Standard TG-lowering agents (Fibrates, Omega-3s/Fish Oil, Niacin) not effective
- Must avoid TG raising meds, alcohol intake, smoking
- Heavy social burden for the patient & family

## Treatment Timeline

**2019:** EU conditional approval of Volanesorsen (Waylivra)

**Until 2024:** No FDA approved therapies in US

**2025:** FDA & EMA approved FCS drugs available

- ➔ Olezarsen (Tryngolza) available in US & EU
- ➔ Plozasiran FDA new drug application decision awaited



**First FDA Approved  
FCS Treatment**



# New Therapies for FCS & sHTG

Clinical Trial > N Engl J Med. 2024 May 16;390(19):1781-1792. doi: 10.1056/NEJMoa2400201.

Epub 2024 Apr 7.

## Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome

Erik S G Stroes<sup>1</sup>, Veronica J Alexander<sup>1</sup>, Ewa Karwatowska-Prokopczuk<sup>1</sup>, Robert A Hegele<sup>1</sup>, Marcello Arca<sup>1</sup>, Christie M Ballantyne<sup>1</sup>, Handrean Soran<sup>1</sup>, Thomas A Prohaska<sup>1</sup>, Shuting Xia<sup>1</sup>, Henry N Ginsberg<sup>1</sup>, Joseph L Witztum<sup>1</sup>, Sotirios Tsimikas<sup>1</sup>; Balance Investigators

\*Hypertriglyceridemia Induced Acute Pancreatitis



TRYNGOLZA™ (olezarsen) approved in U.S. as first-ever treatment for adults living with familial chylomicronemia syndrome as an adjunct to diet

December 19, 2024

> N Engl J Med. 2024 Sep 2. doi: 10.1056/NEJMoa2409368. Online ahead of print.

## Plozasiran for Managing Persistent Chylomicronemia and Pancreatitis Risk

Gerald F Watts<sup>1</sup>, Robert S Rosenson<sup>1</sup>, Robert A Hegele<sup>1</sup>, Ira J Goldberg<sup>1</sup>, Antonio Gallo<sup>1</sup>, Ann Mertens<sup>1</sup>, Alexis Baass<sup>1</sup>, Rong Zhou<sup>1</sup>, Ma'an Muhsin<sup>1</sup>, Jennifer Hellowell<sup>1</sup>, Nicholas J Leeper<sup>1</sup>, Daniel Gaudet<sup>1</sup>; PALISADE Study Group



Arrowhead Pharmaceuticals Announces Acceptance of New Drug Application by U.S. FDA of Plozasiran for the Treatment of Familial Chylomicronemia Syndrome

January 17, 2025

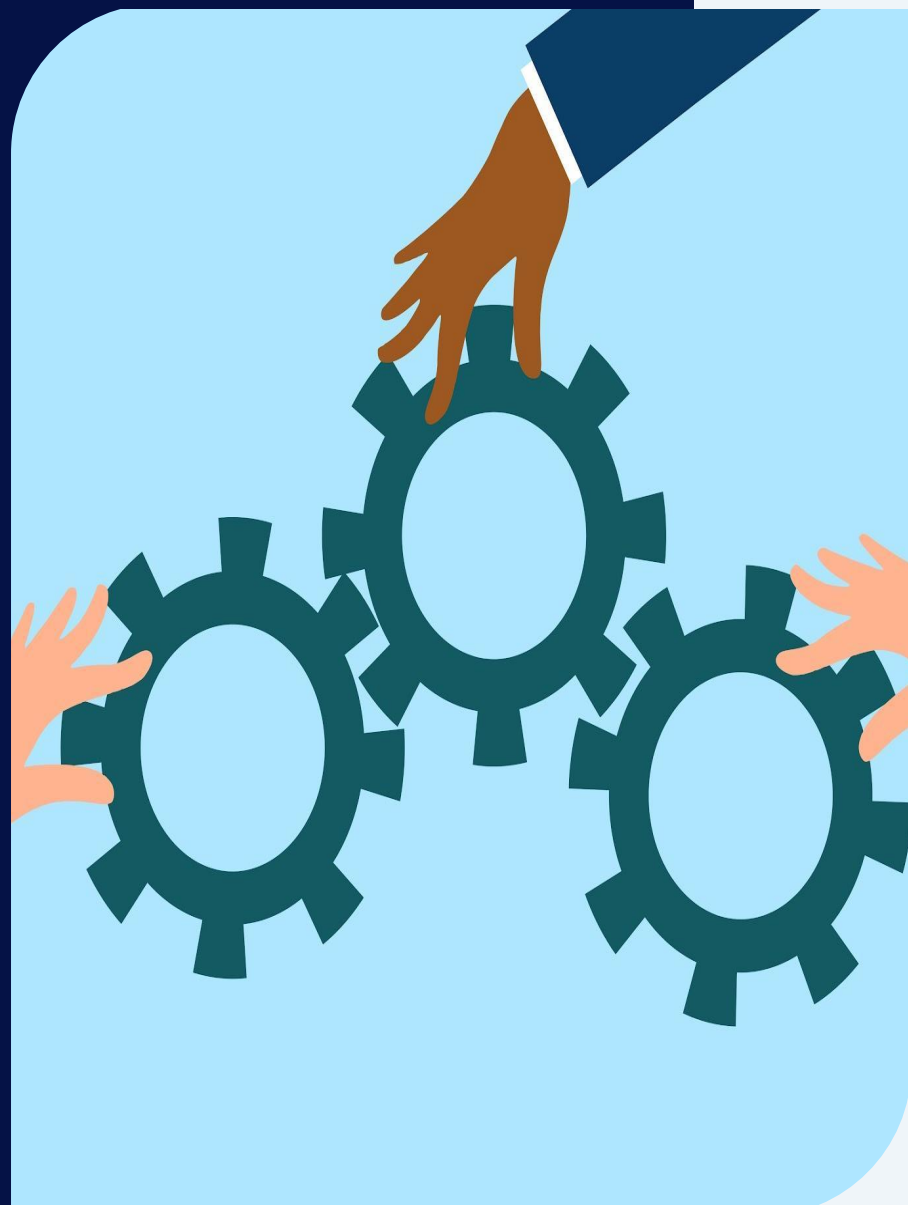
***Both drugs block APOC3 mRNA → Less ApoC-III protein (made by the APOC3 gene) → Better TG breakdown & clearance***

## Best Care with Multidisciplinary Team!

- Dietician
- Clinical Pancreatologist
- Lipid Expert (Lipidologist or Cardiologist)
- Endocrinologist, Certified Diabetes Educator (CDE)
- Surgical Pancreatologist
- Pain Specialist
- Radiology
- Social Service/Psychiatry/Mental Health Professionals

## Dietary Restrictions & Monitoring

- Sugar Restriction
- Low Fat Diet (In FCS < 20 g per day)
- Complete Alcohol Avoidance
- Monitor Fat-Soluble Vitamins Intake (A, D, E, K)



# Summary: Severe HTG (sHTG)

- **Think Early**
  - Suspect sHTG in pancreatitis, abdominal pain, very high TG levels
- **Find The Cause**
  - Rule out secondary factors
  - Genetic testing for severe levels/early-onset like FCS
  - Screen family when hereditary causes suspected
- **Prevent Progression**
  - Keep TGs low long-term; Cut pancreatitis & cardiovascular risk
- **Therapies (Existing & Pipeline)**
  - **HTG:** Lifestyle + Fibrates/Omega-3s (*± Statins for ASCVD risk*)
  - **FCS:** Lifestyle + Olezarsen (Tryngolza in US & EU); Volanesorsen (Waylivra in EU)
  - **Pipeline:**
    - Plozasiran late-stage for FCS/sHTG
    - Olezarsen shows positive Phase 3 results in sHTG
- Best outcomes with multidisciplinary care approach



# Resources

1. [Triglycerides, sHTG, Chylomicronemia Webpage](#) Newly Published!
2. FCS Treatments Blog: <https://mission-cure.org/fcs-treatment-ionis/>
3. FCS Foundation: [www.livingwithfcs.org](http://www.livingwithfcs.org)
4. FCS Support Facebook Group: <https://www.facebook.com/groups/livingwithfcs/>
5. Free Genetic Testing Program for FCS:  
<https://knowyourtgs.com/diagnosing-fcs/genetic-testing>
6. Advocacy Resource (Spotlight on FCS White Paper):  
<https://arrowheadpharma.com/wp-content/uploads/2025/02/Spotlight-on-FC S.pdf>
7. Nutritional Tips & Resources:  
<https://knowyourtgs.com/fcs-nutrition-and-lifestyle>  
<https://lowertriglycerides.com/patient/tips-resources/>
8. Accessing Olezarsen in US: <https://tryngolza.com/support-and-access/access>
9. If you're seeking a consultation with Dr. Andres Gelrud:  
<https://gastrohealth.com/physicians/andres-gelrud-md-mmhc>



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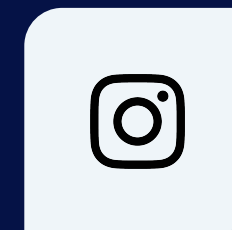
Resources shared here will be posted on Mission: Cure's website with the webinar recording

Thank You & Keep in Touch!

# Mission:Cure

For questions or comments please email:  
[info@mission-cure.org](mailto:info@mission-cure.org)

[MISSION-CURE.ORG](https://MISSION-CURE.ORG)



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pancreatitis-support