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Pancreatitis Overview

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Summary

The purpose of this overview is to increase the awareness of clinicians regarding pancreatitis and its genetic causes and management. The following are the goals of this overview.

Goal 1

Define pancreatitis.

Goal 2

Review the risk factors and etiologies of recurrent acute pancreatitis / chronic pancreatitis.

Goal 3

Provide an evaluation strategy to identify the genetic cause of pancreatitis in a proband (when possible).

Goal 4

Review management of pancreatitis.

Goal 5

Inform genetic risk assessment and surveillance of at-risk relatives for detection of early treatable manifestations of hereditary pancreatitis.

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1. Pancreatitis: Definitions

Pancreatitis is characterized by inflammation of the pancreas. In some individuals it may progress from acute (sudden onset; duration <6 months) to recurrent acute (>1 episode of acute pancreatitis) to chronic (duration >6 months). The range of symptoms and disease course vary from person to person.

Hereditary pancreatitis. The term hereditary pancreatitis is generally reserved for individuals and families with germline highly penetrant heterozygous gain-of-function variants in *PRSS1* (e.g., p.Asn29Ile, p.Arg122His).

Familial pancreatitis. Familial pancreatitis is used to describe kindreds with two or more closely related individuals (up to second-degree relatives) with pancreatitis. Other causes of pancreatitis must be excluded, including *PRSS1*-related hereditary pancreatitis, *CFTR*-related pancreatitis, gallstones, trauma, and other common etiologies.

Acute pancreatitis (AP) is diagnosed in the presence of two of the following three findings [Banks et al 2006]:

- Sudden onset of typical epigastric abdominal pain
- Elevation of serum amylase or lipase more than three times the upper limits of normal [Neoptolemos et al 2000]
- Characteristic findings of acute pancreatitis such as pancreatic edema, fat stranding, and peripancreatic fluid collections on abdominal imaging [O'Connor et al 2011, Banks et al 2013]

Manifestations of AP can range from vague abdominal pain lasting one to three days to severe abdominal pain, systemic inflammation, and multiorgan failure lasting days to weeks and requiring hospitalization with care in an intensive care unit (i.e., **severe acute pancreatitis** [SAP]).

Recurrent acute pancreatitis (RAP) is a condition defined by more than one episode of AP [Guda et al 2018]. In children, it is often called acute recurrent pancreatitis (ARP) to distinguish it from recurrent abdominal pain (often abbreviated as RAP).

Chronic pancreatitis (CP) has been redefined as a "pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental, and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress" [Whitcomb 2019]. The definition promotes the identification of disorders that may lead to CP before an irreversible stage is reached, and to guide targeted treatment of the cause rather than the symptoms. Clinical features of CP include pancreatic atrophy, fibrosis, pain, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction, and dysplasia.

Early CP. Individuals at risk for CP are initially asymptomatic with no disease features or symptoms. An event occurs (e.g., passing a gallstone), that initiates an AP attack. The immune system in the pancreas is activated, making the pancreas hypersensitive to future injury. This is typically followed by complete healing. However, some scarring may occur with continued inflammation, resulting in early CP. Early CP is poorly defined because the inflammation and fibrosis may be reversible, and the early imaging changes are nonspecific. While early CP cannot be accurately diagnosed as CP [Whitcomb et al 2018], it is possible to diagnose one of several underlying disorders that can be treated to prevent further progression.

Established CP represents progression to irreversible pancreatic damage, typically based on scarring or fibrosis identified with imaging studies. The clinical presentation can vary among affected individuals.

End-stage CP occurs when the function of the remaining cells (both exocrine and endocrine) falls below the physiologic needs of the affected individual, requiring both pancreatic enzyme replacement therapy and insulin.

In most populations, about one third of individuals with AP develop RAP, and about one third of individuals with RAP develop CP. Because of the high risk of progression to an irreversible condition, efforts to stop the progression should begin with the first episode of AP.

Clinical Features of CP

The pancreas has two cell types in the exocrine pancreas: acinar cells that secrete zymogens (inactive digestive enzymes), and duct cells that flush the zymogens into the small intestine where they become active. The endocrine pancreas has four cell types, collectively referred to as islet cells. Beta cells are the most important as they secrete insulin. Alpha cells secrete glucagon, an antagonist of insulin. The last two islet cell types secrete pancreatic polypeptide and somatostatin. In addition, the pancreas has a rich nerve innervation including sensory nerves. The inflammatory process can destroy any of the parenchymal cells, activate nerves causing pain, and cause DNA damage to acinar and duct cells, thereby increasing the risk for pancreatic ductal adenocarcinoma. Damage to islet cells may increase the risk for neuroendocrine tumors.

Exocrine pancreatic insufficiency (EPI) is the reduction in pancreatic enzyme quantity and/or activity to a level below the threshold required to maintain normal digestion. In CP, EPI occurs when the acinar cells cannot make sufficient zymogens and deliver them to the intestinal tract to digest food so that it can be absorbed and meet nutritional needs. Clinical signs include steatorrhea (fat and oil in the stool), symptoms of maldigestion (bloating, gas, cramps, and diarrhea), and nutritional deficiencies (e.g., fat-soluble vitamin deficiency including A, D, E and K, vitamin B_{12}, and protein malnutrition with low albumin, prealbumin, or retinal binding protein). Individuals with EPI require pancreatic enzyme replacement therapy.

Pancreatic endocrine insufficiency. With advanced CP, with or without surgical resection, insulin-producing beta cells are destroyed, resulting in insulin deficiency and pancreatogenic diabetes mellitus (type3c DM) [Andersen et al 2013]. In type3c DM, there is a reduction in insulin, glucagon, and pancreatic polypeptide. In earlier stages of CP, DM may develop as a result of selective dysfunction of the beta cells from autoantibodies (type 1 DM), beta-cell dysfunction from other genetic risk factors, peripheral insulin resistance similar to type 2 DM, or other rare types of diabetes. DM develops in about a third of individuals with CP, and most of these individuals have environmental/metabolic and/or genetic risks for type 2 DM [Bellin et al 2017, Goodarzi et al 2019].

Pain, the primary symptom in persons with CP, originates in the abdomen in response to pancreatic injury. Pain character, frequency, and severity are highly variable. As the disease progresses, pain may convert to constant neuropathic pain, which cannot be controlled even by major interventions such as spinal block or total pancreatectomy.

Pancreatic cancer risk is increased after age 50 years in those with longstanding chronic inflammation of the pancreas. Persons with hereditary pancreatitis are at high risk because their age at onset of CP is 20-30 years earlier than in sporadic forms of CP. Although an earlier study estimated lifetime risk for pancreatic cancer at 40%, this estimate was suspected to have been obtained in populations with high rates of smoking, a risk factor that doubles the risk for pancreatic cancer in individuals with hereditary pancreatitis [Lowenfels et al 2001]. For nonsmokers the lifetime risk may be below 20% [Rebours et al 2008, Rebours et al 2009, Shelton et al 2018].

2. Risk Factors and Etiologies of Recurrent Acute Pancreatitis / Chronic Pancreatitis

The common risk factors and etiologies of recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) are represented by the acronym **TIGAR-O** [Whitcomb & North American Pancreatitis Study Group 2019]. The presence of multiple TIGAR-O risk factors was common in individuals with RAP and CP, with one, two, and three or more risk factors observed in 27.6%, 47.6%, and 23.6% in one cohort, respectively [Conwell et al 2017].

- *T*oxic-metabolic factors (e.g., alcohol, smoking, hypercalcemia, chronic kidney disease)
- *I*diopathic
- *G*enetic risk factors (See Table 1 for genetic risk factors and Table 2 for syndromes associated with pancreatitis.)
- *A*utoimmune pancreatitis
- *R*ecurrent acute or severe acute pancreatitis
- Extra pancreatic etiology of duct *o*bstruction (e.g., pancreas divisum, ampullary stenosis, anatomic variants, tumors)

Table 1. Recurrent Acute Pancreatitis / Chronic Pancreatitis Genetic Risk Factors

% of Persons w/CP w/a Pathogenic Variant in Gene	Gene	MOI	Distinguishing Clinical Features	Other / Risk for Pancreatitis	References / Selected OMIM Links
44% of children; 2% of adults	*PRSS1*	AD	Onset age is ~10 yrs earlier.	Exon &/or multiexon deletions/duplications reported [1]	Schwarzenberg et al [2019], *PRSS1*-Related Hereditary Pancreatitis
~37% [2]	*CLDN2*	XL [3]	Assoc w/progression from RAP to CP	• Common variants assoc w/mild-to-moderate risk • ↑ risk w/alcohol abuse, esp in hemizygous males & homozygous females	Whitcomb et al [2012]
28% of children; 15% of adults	*CFTR*	AD AR [3]	May have sinusitis, respiratory symptoms, male infertility, constipation, indeterminate sweat chloride	• Heterozygotes are at ↑ risk. • Several pathogenic variants assoc w/ pancreatitis do not cause lung disease of cystic fibrosis. [4] • See footnote 5 for modifiers.	Miller et al [2020], Schwarzenberg et al [2019], Cystic Fibrosis
23% of children; 7% of adults	*SPINK1*	AD AR [3]	• ↑ risk for CP following AP • Early-onset aggressive pancreatitis assoc w/biallelic p.Asn34Ser	• Heterozygous & biallelic pathogenic variants reported w/↓ penetrance • Several common variants assoc w/mild-to-moderate risk • Founder variants reported in US, Europe, India, China, Japan, & Korea [6]	Schwarzenberg et al [2019], OMIM 608189
9.7% of children age ≤10 yrs; <1% of adults	*CPA1*	AD [3]	Early onset, nonalcoholic CP	• More common in Europe • Misfolding variants may cause AD CP.	Witt et al [2013], OMIM 114850

Table 1. continued from previous page.

% of Persons w/CP w/a Pathogenic Variant in Gene	Gene	MOI	Distinguishing Clinical Features	Other / Risk for Pancreatitis	References / Selected OMIM Links
8% of children; 1% of adults	*CTRC*	AD [3]	Early-onset CP	• Loss-of-function variants assoc w/ moderately ↑ risk • Common risk variant c.180C>T may ↑ risk for CP in persons w/ variants in *CFTR* or *SPINK1*.	Schwarzenberg et al [2019], OMIM 601405
<1% [7]	*CASR*	AD [3]		• Loss-of-function variants may ↑ risk in persons w/variants in *PRSS1*, *SPINK1*, or *CFTR*. • Common gain-of-function variant assoc w/moderate ↑ risk, particularly w/alcohol use.	Muddana et al [2008], OMIM 601199
<1%	*CEL*	AD [3]	• Diabetes mellitus • Pancreatic lipomatosis • Pancreatic exocrine, endocrine dysfunction • CP w/o severe malnutrition	• Exon &/or multiexon deletions/ duplications reported [1] • Nonallelic homologous recombination between *CEL* & adjacent pseudogene *CELP* → *CEL-HYB* assoc w/↑ risk [8]	See Maturity-Onset Diabetes of the Young Overview.
9.7% of early-onset CP; 2%-4.3% of adults	*TRPV6*	AR [3]	Early-onset nonalcoholic CP	Loss-of-function variants assoc w/↑ risk	Masamune et al [2020]

Table 1. continued from previous page.

% of Persons w/CP w/a Pathogenic Variant in Gene	Gene	MOI	Distinguishing Clinical Features	Other / Risk for Pancreatitis	References / Selected OMIM Links
<20%	Unknown	NA			

AD = autosomal dominant; AP = acute pancreatitis; AR = autosomal recessive; CP = chronic pancreatitis; MOI = mode of inheritance; RAP = recurrent acute pancreatitis

1. Ellard et al [2013]

2. Percentage of individuals with CP who have a common risk variant in *CLDN2*

3. Variant(s) in this gene increase the risk for recurrent acute and/or chronic pancreatitis and can be contributors to complex (e.g., multifactorial, polygenic) inheritance pattern.

4. CFTR pathogenic variants that affect bicarbonate conductance while maintaining chloride conductance (e.g., p.Arg75Gln [NM_000492.3:c.224G>A]) have major effects on the pancreas but minimal effects on the lungs. The functional effect of *CFTR* genotypes is determined by the least severe pathogenic variant; thus, either two bicarbonate-defective (BD) variants ($CFTR^{BD}$/$CFTR^{BD}$) or one BD and one severe variant ($CFTR^{BD}$/$CFTR^{sev}$) can result in a monogenic pancreatitis-predominant disorder.

5. SNPs in *SLC26A9* have been reported to modify exocrine pancreatic damage in individuals with cystic fibrosis [Miller et al 2015]. SLC26A9 interacts with CFTR and may increase anion flow in the absence of CFTR [Bertrand et al 2009]. Additionally, a variant *SLC26A9* modifies treatment response to ivacaftor [Strug et al 2016].

6. SPINK1 founder variant p.Asn34Ser (NM_003122.3:c.101A>G) is common in US, Europe, and India, with a minor allele frequency as high as 3%. Founder splice variant c.194+2T>C (NM_003122.3), (also known as IVS3+2T>C) is common in individuals of Chinese, Japanese, and Korean ancestry.

7. This percentage does not include the common gain-of-function variant associated with moderate increased risk for pancreatitis in those with alcohol use.

8. Fjeld et al [2015]

Table 2. Syndromes Associated with Recurrent Acute Pancreatitis / Chronic Pancreatitis

Disorder	Gene(s)	MOI	Distinguishing Clinical Features
Alagille syndrome	*JAG1* *NOTCH2*	AD	• Cholestasis • Congenital heart defects • Typical facial features • Butterfly vertebrae
Apolipoprotien C-II deficiency (OMIM 207750)	*APOC2*	AR	• Hepatosplenomegaly • Eruptive xanthomas • Hypertriglyceridemia • Lipemia retinalis
Childhood ataxia with central nervous system hypomyelination / vanishing white matter	*EIF2B1* *EIF2B2* *EIF2B3* *EIF2B4* *EIF2B5*	AR	• Progressive encephalopathy • Ataxia • Optic atrophy
Citrin deficiency	*SLC25A13*	AR	• Infantile intrahepatic cholestasis • Childhood failure to thrive • Dyslipidemia • Adult-onset hyperammonemia w/ neuropsychiatric symptoms
Cystic fibrosis	*CFTR* [1]	AR	• Bronchiectasis • Infertility in males • Chronic sinusitis
Hyperlipoproteinemia type 1 (See Familial Lipoprotein Lipase Deficiency.)	*LPL*	AR	• Severe hypertriglyceridemia • Recurrent acute pancreatitis • Xanthomata • Hepatosplenomegaly

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Distinguishing Clinical Features
Hyperlipoproteinemia type 1D (OMIM 615947)	*GPIHBP1*	AR	
Johanson-Blizzard syndrome (OMIM 243800)	*UBR1*	AR	• Congenital exocrine pancreatic inflammation & insufficiency • Multiple malformations incl nasal wing aplasia • Intellectual disability (frequently)
Isolated methylmalonic acidemia	*MCEE* *MMAA* *MMAB* *MMADHC* *MMUT*	AR	• Metabolic decompensation on protein-containing diet • Intellectual disability • Tubulointerstitial nephritis • Acute or chronic pancreatitis
Pearson syndrome (See Mitochondrial DNA Deletion Syndromes.)	mtDNA deletions/ duplications	Mat	• Exocrine & endocrine pancreatic dysfunction • Pancreatic fibrosis • Bone marrow failure • Sideroblastic anemia • Often fatal in infancy
Propionic acidemia	*PCCA* *PCCB*	AR	• Progressive encephalopathy • Metabolic crises • Cardiomyopathy
Shwachman-Diamond syndrome	*DNAJC21* *EFL1* *SBDS* *SRP54*	AR (AD)	• Exocrine pancreatic insufficiency • Pancreatic lipomatosis • Bone marrow failure • Skeletal abnormalities • Risk for myeloid leukemias
Wilson disease	*ATP7B*	AR	• Liver disease • Movement disorder or rigid dystonia • Psychiatric manifestations
Familial adenomatous polyposis (See *APC*-Associated Polyposis Conditions.)	*APC*	AD	• Gastrointestinal polyps • Cancers of (e.g.,) bowel, pancreas, thyroid

AD = autosomal dominant; AR = autosomal recessive; Mat = maternal; MOI = mode of inheritance
1. Individuals with symptoms of pancreatitis and a heterozygous *CFTR* pathogenic variant – without a *SPINK1, CTRC*, or *CASR* pathogenic variant – should be evaluated for additional manifestations of a *CFTR*-related disorder, such as bronchiectasis, infertility in males, and chronic sinusitis in the event that an undetected second pathogenic *CFTR* variant is present.

Emerging Genetic Risk Factors for Pancreatitis

In addition to the major known monogenic causes of pancreatitis (Table 1, Table 2) additional genes and susceptibility loci have been identified through genome-wide association studies (GWAS) and other research. Additional studies are needed to confirm and clarify the role of variants in these genes in pancreatitis causation. While these genes may appear on pancreatitis multigene testing panels, it is suggested that they not be included in molecular evaluation of pancreatitis because of their limited clinical utility (see Evaluation Strategies).

Case-control data. GWAS and case-control studies have implicated the following:

- ABO blood group [Greer et al 2011, Weiss et al 2015]
- *CTRB1-CTRB2* (chymotrypsin B1 and B2) [Rosendahl et al 2018]

- *GGT1*. Variation in *GGT1* was first implicated in pancreatic cancer, and *GGT1* variants were found to be significantly overrepresented in individuals with pancreatitis compared to controls [Brand et al 2013].
- *PNLIP* (pancreatic lipase) [Lasher et al 2019]
- *SLC26A9*. Variants in *SLC26A9* have been associated with exocrine pancreatic damage [Miller et al 2015].
- *PRSS2*. Protective effect of *PRSS2* p.Gly191Arg in Europeans [Witt et al 2006]

Case-level data. *CELA3B* (elastase 3B). A rare missense variant in *CELA3B* was found to cosegregate with pancreatitis in a large kindred with autosomal dominant chronic pancreatitis [Moore et al 2019].

3. Evaluation Strategies to Identify Genetic Risk Factors in a Proband with Pancreatitis

The evaluation of an individual at risk for chronic pancreatitis (CP) should begin at the time of the first episode of acute pancreatitis (AP), after common causes of AP have been ruled out such as a gallstone, trauma, hypertriglyceridemia, or hypercalcemia. If another etiology for AP is not identified, molecular genetic testing is indicated [Kleeff et al 2017, Guda et al 2018, Vivian et al 2019].

Establishing a specific genetic cause of pancreatitis:

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical and family history, physical examination, and genomic/genetic testing.

Medical and Family History

The most important part of the clinical evaluation is a careful family history and review of systems. The objective is to identify familial disorders such as hereditary pancreatitis, *CFTR*-related disorders, Shwachman-Diamond syndrome, or familial hypertriglyceridemia (see Table 2). Diabetes mellitus and pancreatic cancer may be surrogates for undiagnosed CP in older generations. The review of symptoms should focus on features of cystic fibrosis (e.g., sinorespiratory infections, nasal polyps, sinusitis, bronchiectasis, bronchitis, pneumonia, constipation, male infertility, pancreatitis symptoms) and Shwachman-Diamond syndrome (e.g., pancreatic insufficiency, short stature, maldigestion, neutropenia, frequent middle-ear and other infections, progressive marrow failure, myelodysplastic syndrome). The medical history may be able to exclude alternate etiologies of pancreatitis, such as biliary pancreatitis, hyperlipidemia, autoimmune disorders, obstructive pancreatitis, medications, or infections.

Early-onset pancreatitis (age <35 years) is often indicative of pancreatitis with an underlying genetic etiology (e.g., single-gene or polygenic disorder), whereas late-onset pancreatitis may indicate a complex pathology with both genetic and environmental causes.

Ongoing and high levels of alcohol and tobacco use may indicate an alcohol-related etiology, but excessive alcohol use does not exclude consideration of genetic risk for pancreatitis.

Molecular genetic testing for hereditary pancreatitis is indicated in a proband with pancreatitis and at least one of the following:

- An unexplained documented episode of acute pancreatitis in childhood
- Recurrent acute attacks of pancreatitis of unknown cause
- Chronic pancreatitis of unknown cause, particularly with onset before age 35 years without a history of heavy alcohol use (>5 drinks per day).
- A history of at least one relative with recurrent acute pancreatitis, chronic pancreatitis of unknown cause, or childhood pancreatitis of unknown cause

Physical Examination

The physical examination should focus on identifying syndromes associated with pancreatitis (see Table 2) since the pancreas cannot be directly evaluated on physical examination. These include assessment of growth and for signs of cystic fibrosis (nasal polyps, pulmonary examination).

Molecular Genetic Testing

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

- **Serial single-gene testing** can be considered if clinical findings and/or family history indicates that pathogenic variants in a particular gene are most likely (see Table 1). Sequence analysis detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis of *PRSS1* first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Note: (1) *PRSS1* has very high homology with other trypsinogen genes and pseudogenes, and the pathogenic variants often result from gene conversion events between trypsinogen genes or pseudogenes. Regardless of the sequencing method employed, primers must be carefully chosen and validated to amplify the fragment for the correct gene and transcript. Thus, a multistep method may be required to verify the presence of a pathogenic variant in *PRSS1*. (2) If a proband is reported to have a *PRSS1* pathogenic variant and the parents are negative for this pathogenic variant, the possibility of a false positive result in the proband can be evaluated by reviewing the test methodology (exome and genome sequencing may result in a false positive *PRSS1* result) and possibly retesting the proband.

- **A multigene panel** that includes some or all of the genes listed in the Table 1 is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of some of the genes associated with hereditary pancreatitis, some panels may not include these genes. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Note: Very few individuals with pancreatitis are found to have hereditary pancreatitis caused by a highly penetrant autosomal dominant pathogenic variant (e.g., *PRSS1* p.Arg122His). Individuals with variant(s) in *SPINK1, CFTR,* or *CTRC* associated with an increased risk for pancreatitis may only develop the disease in the

presence of additional risk factors (e.g., see Risk Factors and Etiologies of Recurrent Acute Pancreatitis / Chronic Pancreatitis).

4. Medical Management of Pancreatitis

Evaluations Following Initial Diagnosis

Imaging of the pancreas is one of the most useful tests for staging pancreatic disease (asymptomatic, acute pancreatitis / recurrent acute pancreatitis, [AP/RAP], early chronic pancreatitis [CP], established CP, end-stage CP) and detecting some complications [Frøkjær et al 2018].

- The initial test should be a CT scan to evaluate the size, shape and features of the pancreas including calcification, atrophy, pseudocysts, cysts, inflammatory masses, tumors, and extrapancreatic diagnoses.
- MRI and MR cholangiopancreatography (MRCP) provide additional information about the parenchyma. Secretin-stimulated MRCP is more accurate than standard MRCP in the depiction of subtle ductal changes and for diagnosing pancreatic divisum. MRI is not as useful as CT for diagnosing pancreatic calcifications.
- Endoscopic ultrasound (EUS) can also be used to diagnose parenchymal and ductal changes mainly during the early stage of the disease. The advantages of EUS include being able to add fine needle aspiration of suspicious lesions and diagnosis of microlithiasis in the biliary tree. However, early EUS changes are nonspecific and cannot be used to diagnose early CP.

Identifying changes in pancreatic function is often more challenging than imaging studies. The following evaluations are recommended:

- Referral to a gastroenterologist specializing in the pancreas for evaluation of pancreatic exocrine function using invasive or noninvasive testing
  - Clinical measures of pancreatic exocrine insufficiency include observation of steatorrhea (fat and oil in the stool), symptoms of maldigestion (bloating, gas, cramps, and diarrhea), and nutritional deficiencies (e.g., fat-soluble vitamin deficiency and protein malnutrition with low albumin, prealbumin, or retinal binding protein).
  - Fecal elastase-1 analysis. Can be falsely positive with diarrhea, but can be used while an individual is taking pancreatic enzyme replacement therapy. The test is insensitive for mild pancreatic exocrine insufficiency.
  - Secretin-stimulated pancreatic bicarbonate secretion testing. Requires intubation of the duodenum and careful measurement of pancreatic bicarbonate secretion over about an hour (depending on the method). It is considered very sensitive, but primarily assesses pancreatic duct function. The test is intended to document a loss of pancreatic parenchyma but should be interpreted in the context of the *CFTR* genotype since bicarbonate secretion is CFTR-dependent.
  - Serum trypsin or trypsinogen. A blood test that measures the leakage of pancreatic digestive enzymes (zymogens) into the blood stream. Under normal conditions a reduction in serum trypsin or trypsinogen levels reflects loss of parenchyma, with large reductions associated with exocrine pancreatic insufficiency. In some instances, abdominal pain is caused by mild acute pancreatitis flare and all pancreatic enzymes will be elevated in the blood, including trypsin and trypsinogen, possibly resulting in a pseudo-normalization of levels despite pancreatic insufficiency.
- Referral to an endocrinologist for evaluation of pancreatic endocrine function (i.e., assessment of glucose tolerance) and lipid disorders (e.g., hypertriglyceridemia)
  - Annual fasting blood sugar, hemoglobin A1C, and fasting lipid panel are recommended. In addition, risk for type 2 diabetes should be noted including ancestry, family history, and body mass index [Bellin et al 2017].

    - A standard glucose tolerance test or mixed meal test is recommended to evaluate beta-cell function and hormonal responses in individuals with pancreatitis. This can help sort out the cause of glucose intolerance including peripheral insulin resistance, beta-cell dysfunction, and/or islet cell loss.
    - Hypertriglyceridemia is a risk factor for RAP and CP. Endocrinologists typically measure fasting lipid levels as a risk for cardiovascular disease, whereas pancreatologists are more interested in peak levels as a risk for AP. There is no consensus on an approach. Endocrinologists, however, are the specialists who manage lipid disorders.
- Referral to a pancreatic cancer surveillance program in persons with longstanding chronic pancreatitis. Risk for pancreatic cancer is highest in individuals with a history of smoking, a familial cancer syndrome, a history of *Helicobacter pylori* infections, non-type O blood group, and hereditary pancreatitis [Maisonneuve & Lowenfels 2015].
- Referral to a clinical geneticist and/or genetic counselor if the individual has a family history of pancreatitis or pancreatic cancer, or genetic testing identifies a high-risk pathogenic variant

Treatment of Manifestations

Medical treatment and management for hereditary pancreatitis are similar to those for nonhereditary pancreatitis. AP is a sudden event that requires prompt evaluation by physicians trained in emergency medicine, gastroenterology, or abdominal surgery. Treatment of CP focuses on improving quality of life by managing pancreatic pain, maldigestion, and diabetes mellitus.

Pain can result from inflammation, ischemia, obstructed pancreatic ducts, pseudocysts, neuropathy, extrapancreatic locations from maldigestion, and central pain syndromes in some individuals.

- Obstruction of the pancreatic duct. Endoscopic treatment by a gastroenterologist (therapeutic endoscopist) is the first line of treatment for duct obstruction. Surgical treatment is indicated if endoscopic treatment fails or if there are significant pancreatic calcifications or an inflammatory mass.
- Analgesics are offered for other types of pain, using a step-up approach [Drewes et al 2017].
- Antioxidants have been reported to improve pain control in a few individuals with hereditary pancreatitis and nonalcoholic CP [Burton et al 2011, Shalimar et al 2017].
- Total pancreatectomy with islet autotransplantation (TPIAT) may be considered at specialized centers in individuals with severe pain and/or inflammation that cannot be controlled by other approaches [Bellin et al 2011]. Following TPIAT, individuals are at high risk for diabetes mellitus and must take full doses of pancreatic enzyme replacement therapy (PERT) with every meal indefinitely.

Maldigestion can result from pancreatic exocrine insufficiency.

- PERT improves digestion in those with pancreatic insufficiency who have pain with eating, steatorrhea, and/or diarrhea [Perrault 1994, Whitcomb et al 2010, Burton et al 2011].
- The amount of pancreatic enzyme replacement necessary depends on the diet and on the amount of residual pancreatic function (which diminishes over time). The normal amount of lipase secreted is about 750,000-1,000,000 units (USP) per meal. (Note that earlier papers used IU; 1 IU = 3 USP units [Pongprasobchai & DiMagno 2005].) Since a minimum of 10% of normal pancreatic enzyme output is needed to digest a meal, about 70,000-80,000 USP units of lipase are required for an average-sized adult (70 kg) with total pancreatic insufficiency. The amount can be reduced for smaller persons and those with residual pancreatic exocrine function – while monitoring symptoms and nutritional parameters.

Pancreatic endocrine insufficiency results in diabetes mellitus.

- Routine screening of individuals with chronic pancreatitis for glucose intolerance Recommendations for management and referral have been published [Rickels et al 2013b].

- Chronic pancreatitis with pancreatic exocrine insufficiency or pancreatic surgery may confound management of diabetes since the rate of nutrient digestion and absorption may be different from delivery of insulin (asynchrony). Attention to symptoms surrounding meals and multidisciplinary evaluation (gastroenterologists and endocrinologists) are needed to address these challenges. See also Rickels et al [2013a] for consensus guidelines on management of diabetes in pancreatitis.

Prevention of Primary Manifestations

The ability to prevent the primary manifestations of pancreatitis is limited. The following recommendations are for individuals with (or at risk for) hereditary pancreatitis. Following these recommendations from early childhood may help prevent attacks of acute pancreatitis:

- **Low-fat diet.** No formal guidelines for amount of dietary fat exist; however, some physicians recommend a low-fat diet to minimize pancreatic stimulation. If a low-fat diet is chosen, extra attention to providing fat-soluble vitamins (A, D, E, K) is needed. Some physicians recommend higher doses of PERT to compensate for altered pancreatic exocrine function.
- **Multiple small meals.** No evidence-based guidelines exist; however, small meals may minimize pancreatic exocrine stimulation.
- **Good hydration.** Maintaining good hydration may be helpful in minimizing attacks, especially since nausea, vomiting, and loss of appetite limit oral intake during an attack.
- **Antioxidants.** Antioxidant therapy is very low risk and low cost, may improve pain and reduce pancreatic injury, and thus is an appropriate first course of action [Bhardwaj et al 2009, Burton et al 2011, Shalimar et al 2017].
- **Cessation/abstinence from smoking and alcohol** is the strongest recommendation for all persons with pancreatitis. Substantial evidence shows that oxidative stress from alcohol and tobacco smoke is inherently linked to progression and pain in pancreatitis [Schoenberg et al 1995, Petrov 2010, Tandon & Garg 2011]. Smoking is also a major risk factor for pancreatic cancer [Lowenfels et al 2001]. Note: Men with one high-risk *CLDN2* variant and women with two high-risk *CLDN2* variants should be strongly urged to stop drinking immediately and directed to effective treatment programs.
- **Exercise, yoga, and other relaxation techniques** may increase quality of life in persons with pancreatitis [Sareen et al 2007]. Some individuals report that regular exercise, such as running, helps reduce the frequency of episodes of pancreatitis [Authors, unpublished].

Agents/Circumstances to Avoid

Alcohol and tobacco. Smoking increases the risk for pancreatitis in a dose-dependent manner, doubling the risk for recurrent acute pancreatitis in heavy smokers (>35 pack years) [Maisonneuve et al 2005, Yadav et al 2009]. In combination, smoking and alcohol use increase the risk of developing pancreatitis eightfold [Yadav et al 2009]. Alcohol and tobacco exacerbate existing pancreatitis [Lowenfels & Whitcomb 1997]. Tobacco use also increases the risk of early onset of pancreatic cancer [Lowenfels et al 2001]. In individuals with hereditary pancreatitis, smoking doubles the risk for pancreatic cancer [Lowenfels et al 2001].

Dehydration worsens episodes of acute pancreatitis. Poor hydration (e.g., during exercise) can lead to episodes of pancreatitis [Authors, unpublished].

Physical and emotional stresses aggravate pancreatitis [Applebaum et al 2000]. Avoiding these stressors in families with hereditary pancreatitis may prevent or delay worsening of symptoms and progression of disease.

5. Genetic Risk Assessment

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Modes of Inheritance

Pancreatitis can occur as an isolated finding or as part of a rare genetic syndrome. This section reviews genetic counseling issues associated with isolated pancreatitis.

Pathogenic variants associated with an increased risk for pancreatitis as an isolated finding may be inherited in an autosomal dominant, autosomal recessive, or polygenic manner. The risk to family members depends on the underlying etiology.

Autosomal dominant hereditary pancreatitis (HP) is associated with either of the following:

- Heterozygous gain-of-function *PRSS1* pathogenic variants (Generally, hereditary pancreatitis refers to *PRSS1*-HP.)
- Rare heterozygous variants in *CTRC*, *CPA1*, *PRSS1,* and *CEL* that generate misfolding of the protein and an unfolded protein response

Autosomal recessive familial pancreatitis is associated with either of the following:

- Biallelic pathogenic variants in *SPINK1*
- Biallelic pathogenic variants in *CFTR*, which can result in a monogenic pancreatitis-predominant disorder as a *CFTR*-related disorder. If diagnostic criteria for cystic fibrosis are met (e.g., 2 abnormal sweat chloride values ≥60 mEq/L), the diagnosis is classified as cystic fibrosis (see Table 1).

Polygenic inheritance is associated with either of the following:

- The presence of heterozygous pathogenic variants in two different pancreatitis-associated genes. Examples include: *CFTR* + *SPINK1* and *CFTR* + *CASR*.
- Additive or epistatic contributions of variants in multiple genes at different loci. Examples include *CFTR* + *CTRC* with a more severe course in the presence of a *PRSS1/2* risk allele that increases trypsinogen expression or the *CLDN2* risk allele.

Autosomal Dominant Inheritance (PRSS1-HP) – Risk to Family Members

Parents of a proband

- Many individuals diagnosed as having *PRSS1*-HP have an affected parent.
- Rarely, an individual diagnosed with *PRSS1*-HP has the disorder as the result of a *de novo* pathogenic variant.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing for the *PRSS1* variant identified in the proband. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation.

- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. (Although no instances of germline mosaicism have been reported, it remains a possibility.)

  Note: If a proband is reported to have a *PRSS1* pathogenic variant and the parents are negative for this pathogenic variant, the possibility of a false positive result in the proband can be evaluated by reviewing the test methodology (exome and genome sequencing may result in a false positive *PRSS1* result) and possibly retesting the proband (see Molecular Genetic Testing).

- Although most individuals diagnosed with *PRSS1*-related hereditary pancreatitis have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, late onset of the disease in the affected parent, or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed on the parents of the proband.

- If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected or has a *PRSS1* pathogenic variant, the risk to the sibs of inheriting the variant is 50%. However, sibs who inherit a *PRSS1* pathogenic variant may not develop pancreatitis because of reduced penetrance (penetrance of *PRSS1* varies; see *PRSS1*-Related Hereditary Pancreatitis, Penetrance).
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *PRSS1* pathogenic variant but are clinically unaffected, sibs of a proband are still at increased risk for *PRSS1*-related hereditary pancreatitis because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *PRSS1*-related hereditary pancreatitis has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or known to be heterozygous for a pathogenic *PRSS1* variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an individual diagnosed as having autosomal recessive familial pancreatitis are obligate heterozygotes (i.e., presumed to be carriers a single copy of a pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- The risk for pancreatitis in individuals heterozygous for a pathogenic variant in a gene associated with autosomal recessive inheritance is presumed to be similar to that of the general population. Note: The risk for pancreatitis may be slightly increased if the heterozygous individual has additional genetic risk factors (i.e., a second heterozygous pathogenic variant in a different hereditary pancreatitis-associated gene or additive contributions of variants in multiple genes at different loci).

Sibs of a proband

- If both parents are known to be heterozygous for a pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of not being a carrier.
- The risk for pancreatitis in individuals heterozygous for a pathogenic variant in a gene associated with autosomal recessive inheritance is presumed to be similar to that of the general population. Note: The risk for pancreatitis may be slightly increased if the heterozygous individual has additional genetic risk factors (i.e., a second heterozygous pathogenic variant in a different hereditary pancreatitis-associated gene or additive contributions of variants in multiple genes at different loci).

Offspring of a proband. The offspring of an individual with autosomal recessive hereditary pancreatitis are obligate heterozygotes for a pathogenic variant in a pancreatitis-related gene.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a pathogenic variant in a hereditary pancreatitis-related gene.

Heterozygote detection. Carrier testing for at-risk relatives requires prior identification of the pathogenic variants in the family.

Polygenic Inheritance – Risk to Family Members

Identification of heterozygous pathogenic variants in two different hereditary pancreatitis-associated genes or additive contributions of variants in multiple genes at different loci indicates complex disease and genetic risk assessment should be handled on a case-by-case basis. Specific combinations of genetic factors may be epistatic while others are additive. No systematic approach is available to predict the effects of most of these complex genotypes.

Related Genetic Counseling Issues

Risk assessment

- Genetic testing can only determine if a person has or has not inherited a variant that confers high risk for disease. Genetic testing cannot determine if the individual will develop disease, the age of disease onset, or disease severity.
- The assessment of risk to family members of developing pancreatitis depends on several variables: genetic risk factors, smoking, alcohol use, sex, and developmental differences such as pancreas divisum (incomplete pancreatic duct development resulting in two duct systems rather than one, with most of the pancreas draining through a high-resistance papilla), as well as unknown environmental and genetic risk factors. Thus, risk assessment needs to be tailored to each individual and family.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for hereditary pancreatitis are possible.

Note: The reduced penetrance and inability to predict the natural disease course or severity of disease based on a genetic test result generally make interpretation of prenatal testing indeterminate.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Pancreas Foundation (NPF)**
  101 Federal Street
  Suite 1900
  Boston MA 02210
  Phone: 866-726-2737 (toll-free); 617-342-7019
  Fax: 617-342-7080
  Email: info@pancreasfoundation.org
  www.pancreasfoundation.org

- **Pancreatica.org**
  149 Bonifacio Place
  Monterey CA 93940
  Phone: 831-658-0600
  Email: webmaster@pancreatica.org
  www.pancreatica.org

- **Pancreatic Cancer Action Network**
  2221 Rosecrans Avenue
  Suite 7000
  El Segundo CA 90245
  Phone: 877-272-6226 (toll-free); 310-725-0025
  Fax: 310-725-0029
  Email: info@pancan.org
  www.pancan.org

- **European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer**
  NIHR Pancreas Biomedical Research Unit, Royal Liverpool University Hospital
  5th Floor UCD Building
  Daulby Street
  Liverpool L69 3GA
  United Kingdom
  Phone: +44 (0) 151 706 4168
  Fax: +44 (0) 151 706 5826
  Email: europac@liverpool.ac.uk
  European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer

Chapter Notes

Author Notes

Dr Whitcomb is a physician-scientist who has dedicated his career to understanding the complexity of pancreatic physiology, pathophysiology, and pancreatic diseases in humans. He is the principal investigator of the Hereditary Pancreatitis Study and the North American Pancreatitis Study II (NAPS2), which includes over 25 major pancreas centers in the United States. He also serves as Chief, Division of Gastroenterology, Hepatology and Nutrition at the University of Pittsburgh and UPMC. He is the editor and webmaster of pancreas.org and co-editor, with Sheila Solomon, MS, CGC, of a patient-directed newsletter, Pancreas Education and Research Letter (PEaRL). Dr Whitcomb's work is focused on personalized medicine, with emphasis on early detection and prevention of a variety of pancreatic disorders using next-generation DNA sequencing, biomarkers, and comparative effectiveness research.

A specialized Pancreas Center of Excellence incorporating genetic testing and counseling early in the evaluation of pancreatic disease has been established [Whitcomb 2012].

Pancreas genetics research website. A summary of reported sequence variants in *PRSS1, PRSS2, SPINK1, CTRC,* and *CPA1* is available at www.pancreasgenetics.org.

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