Pancreatitis: TIGAR-O Version 2 Risk/Etiology Checklist With Topic Reviews, Updates, and Use Primers

David C. Whitcomb, MD, PhD[1], for the North American Pancreatitis Study Group

The Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis and Obstructive (TIGAR-O) Pancreatitis Risk/Etiology Checklist (TIGAR-O_V1) is a broad classification system that lists the major risk factors and etiologies of recurrent acute pancreatitis, chronic pancreatitis, and overlapping pancreatic disorders with or without genetic, immunologic, metabolic, nutritional, neurologic, metaplastic, or other features. New discoveries and progressive concepts since the 2001 TIGAR-O list relevant to understanding and managing complex pancreatic disorders require an update to TIGAR-O_V2 with both a short (S) and long (L) form. The revised system is designed as a hierarchical checklist for health care workers to quickly document and track specific factors that, alone or in combinations, may contribute to progressive pancreatic disease in individual patients or groups of patients and to assist in treatment selection. The rationale and key clinical considerations are summarized for each updated classification item. Familiarity with the structured format speeds up the completion process and supports thoroughness and consideration of complex or alternative diagnoses during evaluation and serves as a framework for communication. The structured approach also facilitates the new health information technologies that required high-quality data for accurate precision medicine. A use primer accompanies the TIGAR-O_V2 checklist with rationale and comments for health care workers and industries caring for patients with pancreatic diseases.

Clinical and Translational Gastroenterology 2019;10:e-00027. https://doi.org/10.14309/ctg.0000000000000027

INTRODUCTION

Many factors contribute to the etiology of acute pancreatitis (AP), recurrent AP (RAP), chronic pancreatitis (CP), and diseases with overlapping features. New understanding and approaches to medical management require a holistic approach to prevent complex chronic disease features (1). For this approach, it is critical to identify risk factors and etiologies causing the signs and symptoms at disease onset, such as the first episode of AP. Knowledge of these susceptibility and modifying factors facilitates diagnosis of organ-specific susceptibilities and pathogenic responses that are pathogenic and require targeted management before development of irreversible damage. These factors, properly analyzed within the clinical setting, provide insights for the prognosis and the potential prevention of RAP, CP, and their complications including pain syndromes, exocrine pancreatic insufficiency (EPI), diabetes mellitus (DM), and pancreatic cancer.

The spectrum of pancreatic diseases is more complex than previously imagined. Various combinations of genetic, epigenetic, metabolic, and environmental factors apparently converge to form a "perfect storm" that initiates and drives the inflammatory process and its consequences in multiple systems that normally regulate and maintain pancreatic function. Because of the random combination of severity and modifying factors, each patient is unique, and each one requires personalized assessment and management—the goal of precision medicine. Fortunately, most of the factors interact with known systems and pathogenic pathways so that effective management plans can be developed as new or repurposed therapies are evaluated and utilized using evidence-based strategies (2–4).

TIGAR-O Version 1 (TIGAR-O_V1) (List 1) is a pancreatitis-associated risk/etiology checklist first published in 2001 by Etemad and Whitcomb (5). TIGAR-O is an acronym for 6 categories of risk/etiology including Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis and Obstructive, with the latter category separated from the others with a dash to indicate extra-acinus etiologies (outside the acinar and proximal duct cells). The system was initially designed as a tool for the North American Pancreatitis Study II (NAPS2) projects (6) to capture and record each of the factors believed to confer risk (prepancreatitis) or contribute to etiology (postpancreatitis), based on a novel, mechanistic reverse engineering approach to complex diseases (7). The categories were organized in terms of expected prevalence. The list was also developed using the sentinel acute pancreatitis event (SAPE) model (8), allowing it to be used both for RAP and CP. This distinction is important because we now recognize that the global transition rate from the SAPE to RAP is ~20% and from RAP to CP is ~35% (1), whereas ~40%

[1]University of Pittsburgh, Division of Gastroenterology, Hepatology and Nutritions, Department of Medicine, Cell Biology and Molecular Physiology, and Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania. **Correspondence:** David C. Whitcomb, MD, PhD. E-mail: Whitcomb@pitt.edu.
Received December 2, 2018; accepted February 8, 2019; published online June 4, 2019

of patients with CP do not have a history of AP or RAP, and multiple risk and modifying factors determine these patterns of progression. The TIGAR-O risk/etiology checklist was included in all 3 phases of NAPS2 (6,9,10).

The TIGAR-O_V1 risk/etiology checklist has wide utility, being cited in more than 1,250 publications, used in major

LIST 1. TIGAR-O VERSION_V1 (ETEMAD AND WHITCOMB, 2001 (5))

Toxic-metabolic

- Alcoholic
- Tobacco smoking
- Hypercalcemia
  - Hyperparathyroidism
- Hyperlipidemia (rare and controversial)
- Chronic renal failure
- Medications
  - Phenacetin abuse (possibly from chronic renal insufficiency)
- Toxins
  - Organotin compounds (e.g., DBTC)

Idiopathic

- Early onset
- Late onset
- Tropical
  - Tropical calcific pancreatitis
  - Fibrocalculous pancreatic diabetes
- Other

Genetic

- Autosomal dominant
  - Cationic trypsinogen (Codon 29 and 122 mutations)
- Autosomal recessive/modifier genes
  - CFTR mutations
  - SPINK1 mutations
  - Cationic trypsinogen (codon 16, 22, 23 mutations)
  - α1-Antitrypsin deficiency (possible)

Autoimmune

- Isolated autoimmune chronic pancreatitis
- Syndromic autoimmune chronic pancreatitis
  - Sjögren syndrome–associated chronic pancreatitis
  - Inflammatory bowel disease–associated chronic pancreatitis
  - Primary biliary cirrhosis–associated chronic pancreatitis

Recurrent and severe acute pancreatitis

- Postnecrotic (severe acute pancreatitis)
- Recurrent acute pancreatitis
- Vascular diseases/ischemic
- Post-irradiation

Obstructive

- Pancreatic divisum
- Sphincter of Oddi disorders (controversial)
- Duct obstruction (e.g., tumor)
- Preampullary duodenal wall cysts
- Posttraumatic pancreatic duct scars

LIST 2. TIGAR-O_2L (LONG FORM)

Toxic-metabolic

- Alcohol-related (susceptibility and/or progression)
  - Categories
    1. 0 to <1 drink per day. Includes abstainers and occasional drinkers.
    2. 1–2 drinks/d
    3. 3–4 drinks/d
    4. 5 or more drinks/d
  - [__1; __2; __3; __4] Susceptibility (pre-acute pancreatitis)
  - [__1; __2; __3; __4] Progression (post-acute pancreatitis)
- Smoking (if yes, record pack-years: _____)
  - Non-smoker (<100 cigarettes in lifetime)
  - Past smoker
  - Current smoker
  - Other, NOS
- Hypercalcemia (total calcium levels >12.0 mg/dL or 3 mmol/L)
  - Hyperparathyroidism
  - Familial hypocalciuric hypercalcemia (by family history)
  - Other NOS
- Hypertriglyceridemia
  - Hypertriglyceridemic risk (Fasting >300 mg/dL; non-fasting >500 mg/dL)
  - Hypertriglyceridemic acute pancreatitis, history of (>500 mg/dL in first 72 hours)
  - Familial hypertriglyceridemia (by family history)
- Medications
  - NOS
- Toxins
  - Chronic kidney disease (CKD) (CKD Stage 5: end-stage renal disease, ESRD)
    - No dialysis
    - On dialysis
    - Kidney transplant
  - Oxidative stress–associated factors
    - Radiation/chemotherapy
    - Vascular insufficiency
    - Other factors
  - Other toxins, NOS
- Metabolic, other
  - Diabetes Mellitus (with the date of diagnosis if available)
    - Diet controlled
    - Medication controlled (oral agents)
    - Insulin requiring (≥10 U/d or ≥0.1 U/kg/d)
  - Diet (red meat ≥2 oz or 57 g per day; vegetarian, vegan)
  - Obesity (BMI >30 kg/m^2)
  - Visceral adiposity (e.g., apple-shaped obesity, see text)
  - Other, NOS
- Idiopathic
  - Early onset (<35 years of age)
  - Late onset (>35 years of age)
  - Other, NOS

Genetic

- Suspected; No or limited genotyping available
- Autosomal dominant (Mendelian inheritance—single gene syndrome)
  - PRSS1 mutations (Hereditary pancreatitis)

- *CEL*—MODY8 phenotype
- Other, NOS

Autosomal recessive (Mendelian inheritance—single gene syndrome)
- *CFTR,* 2 severe variants in *trans* (cystic fibrosis)
- *CFTR,* <2 severe variants in *trans* (CFTR-RD)
- SPINK1, 2 pathogenic variants in *trans*. (SPINK1-associated familial pancreatitis)
- Other, NOS

Complex genetics—(non-Mendelian, complex genotypes +/− environment)
- *CFTR* variant (1 variant or >1 all in *cis*)
- *CTRC* variants
- *CASR* variants
- *SPINK1* variant (1 variant or >1 all in *cis*)
- *CPA1* variants
- *CEL* or CEL-*HYB* variants
- Other, NOS

Modifier genes (pathogenic genetic variants)
- *PRSS1-PRSS1* locus
- *CLDN2* locus
- SLC26A9
- GGT1
- *ABO*—B blood type
- Other, NOS

Hypertriglyceridemia syndromes (pathogenic genetic variants)
- *LPL*—lipoprotein lipase deficiency
- *APOC2*—Apolipoprotein C-II deficiency
- Other familial chylomicronemia syndrome (FCS)
- Multifactorial chylomicronemia syndrome (MCS)
- Other, NOS

Rare, non-neoplastic pancreatic genetic variant-associated syndromes
- Shwachman-Diamond syndrome
- Johanson-Blizzard Syndrome
- Mitochondrial disorders (e.g., Pearson's Marrow-Pancreas Syndrome)
- Other, NOS

Autoimmune pancreatitis (AIP)/Steroid responsive pancreatitis

AIP Type 1—IgG4-related disease
- Isolated to the pancreas
- Associated with other organs (IgG4-related disease)

AIP Type 2
- Isolated to the pancreas
- With Crohn's disease
- With ulcerative colitis
- Associated with other organs

AIP-NOS (Steroid responsive, not Type 1 or Type 2)

Recurrent acute pancreatitis (RAP) and severe acute pancreatitis (SAP)

Acute pancreatitis (single episode, including date of event if available)
- AP without persistent MOF and <30% PNec
- AP without persistent MOF and >30% PNec
- SAP (persistent MAF with <30% PNec)
- SAP (persistent MAF with ≥30% PNec)

AP Etiology—Extra-pancreatic (excluding alcoholic, HTG, hypercalcemia, genetic)
- Biliary pancreatitis
- Post-ERCP
- Traumatic
- Ischemic (acute, such as postsurgical, hypotension)
- Infectious: Viral, other (not secondary infection)
- Undetermined or NOS

Recurrent acute pancreatitis (number of episodes, frequency, and dates of events if available)

Obstructive

- Pancreas divisum
- Ampullary stenosis
- Main duct pancreatic stones
- Widespread pancreatic calcifications
- Main pancreatic duct strictures
- Localized mass causing duct obstruction
  - Pancreatic ductal adenocarcinoma
  - IPMN
  - Other tumor
- Mass effect, NOS
- Anatomic Variants (other than pancreas divisum)
- Other NOS

TIGAR-O Version 2 risk/etiology classification–Long form—The list is updated Version 1 proposed by Etemad and Whitcomb in 2001 to reflect new discoveries and clarification of older categories (5). Patients typically have multiple risk factors from the list that contribute to recurrent acute and CP. All contributing etiologies should be documented in each patient. The list should be dated, complemented by further documentation in the patient record or case report form, and updated and dated with new information or changes in risk or etiology. See text.

epidemiology studies, and recommended for use by leading experts and major societies (3,11–18). A modification of TIGAR-O, with the classes reorganized to spell M-ANNHEIM (19), has also been included in a more extensive disease severity classification system and used in similar ways (20–23).

The TIGAR-O_V1 risk/etiology checklist was designed for capturing information associated with RAP and CP gleaned from the 20th century literature. The NAPS2 projects and other studies generated many new insights into pancreatitis risk and disease mechanisms, especially regarding the quantitative risk of alcohol for susceptibility vs progression, the independent role of smoking, the importance of hypertriglyceridemia (HTG), the classification of autoimmune pancreatitis (AIP), many genetic discoveries and new insights into complex genotypes, the need to specify types of injuries leading to RAP or severe acute pancreatitis (SAP), and further definition and delineation of obstructive etiologies. Diabetes mellitus and pancreatic cancer also affect the pancreas, and some features overlap with features of CP.

As the cutting edge of pancreatitis translational research approaches clinical utility in the precision medicine paradigm, it

LIST 3. TIGAR-O VERSION 2.0—SHORT FORM (TIGAR-O_V2-SF)

Toxic-metabolic

- Alcohol-related (susceptibility and/or progression)
  - 3-4 drinks/d
  - 5 or more drinks/d
- Smoking (if yes, record pack-years)
  - Non-smoker (<100 cigarettes in lifetime)
  - Past smoker
  - Current smoker
  - Other, NOS
- Hypercalcemia (total calcium levels >12.0 mg/dL or 3 mmol/L)
- Hypertriglyceridemia
  - Hypertriglyceridemic risk (Fasting >300 mg/dL; non-fasting >500 mg/dL)
  - Hypertriglyceridemic acute pancreatitis, history of (>500 mg/dL in first 72 hours)
- Medications (name)
- Toxins, other
  - Chronic kidney disease (CKD)—(CKD Stage 5: end-stage renal disease, ESRD)
  - Other, NOS
- Metabolic, other
  - Diabetes Mellitus (with the date of diagnosis if available)
  - Other, NOS

Idiopathic

- Early onset (<35 years of age)
- Late onset (>35 years of age)

Genetic

- Suspected; No or limited genotyping available
- Autosomal dominant (Mendelian inheritance—single gene syndrome)
  - *PRSS1* mutations (Hereditary pancreatitis)
- Autosomal recessive (Mendelian inheritance—single gene syndrome)
  - *CFTR,* 2 severe variants in *trans* (cystic fibrosis)
  - *CFTR,* <2 severe variants in *trans* (CFTR-RD)
  - *SPINK1,* 2 pathogenic variants in *trans.* (SPINK1-associated familial pancreatitis)
- Complex genetics—(non-Mendelian, complex genotypes +/− environment)
- Modifier Genes (list pathogenic genetic variants)
  - *PRSS1*-PRSS1 locus
  - *CLDN2* locus
  - Others:
- Hypertriglyceridemia (list pathogenic genetic variants)
  - Other, NOS

Autoimmune pancreatitis (AIP)/Steroid responsive pancreatitis

- AIP Type 1—IgG4-related disease
- AIP Type 2

Recurrent acute pancreatitis (RAP) and severe acute pancreatitis (SAP)

- Acute pancreatitis (single episode, including date of event if available)
- AP Etiology—Extra-pancreatic (excluding alcoholic, HTG, hypercalcemia, genetic)
  - Biliary pancreatitis
  - Post-ERCP
  - Traumatic
  - Undetermined or NOS
- Recurrent acute pancreatitis (number of episodes, frequency, and dates of events if available)

Obstructive

- Pancreas divisum
- Ampullary stenosis
- Main duct pancreatic stones
- Widespread pancreatic calcifications
- Main pancreatic duct strictures
- Localized mass causing duct obstruction

TIGAR-O Version 2 risk/etiology classification–Short form—As additional information is received, the patient's list should be transitioned to the longer form.

is necessary to update the risk and etiology list to reflect these advances. Coincident with the 20th anniversary of the initiation of the NAPS2 studies, the TIGAR-O_V1 checklist is being updated as TIGAR-O Version 2 long (TIGAR-O_V2-L, List 2) with comments and suggestions for checklist users. A short form (TIGAR-O_V2-S, List 3) can be used for initial screening in a busy clinic, with anticipation of expanding to the full list as additional information is received.

TIGAR-O_V2

The basic information supporting the elements of TIGAR-O_V1 and reported previously remains useful, and the reader is referred to these references for further discussion (5,17). Modifications in the classification with recommendations on completing the TIGAR-O_V2 checklist are given in List 2 and described below. A short form was also developed, at the request of some NAPS2 investigators List 3, to capture the more common and high-level information from busy clinicians who are not familiar with many of the details in the long form.

The TIGAR-O_V2 checklist is hierarchical. This organizational feature provides more specificity and accuracy related to the exact type of risk/etiology in a patient and some quantitative information within some categories. The nature of the items as risk or etiologic factors are not specified, while recognizing that some agents are primary drivers of injury or stress, others increase susceptibility by lowering tolerance to injury or stress, others affect protective responses, involve parallel or downstream systems or cells, limit regeneration or contribute to disease features in other ways. These data should be supplemented in patient histories, examinations, and objective measures. Each of the 6 categories and some subcategories include a "not otherwise specified" (NOS) section where unusual or other factors can be added.

Checklist users

Health care workers who intend to use TIGAR-O_V2 should become familiar with the list so that critical information is

collected at the time of the patient examination and all the relevant factors are checked efficiently. Typically, multiple factors will be checked in each patient. However, in most cases, a limited amount of information is available to the clinician at the time of an initial examination. Checking only the main categories and some subcategories with an initial visit is expected because additional testing is needed to check additional items in various categories. Thus, it is like a patient's problem list for pancreatitis-associated factors. As new information is received, the TIGAR-O_V2 checklist for the patient should be updated and dated. This provides progressively more accurate understanding of individual patients and the ability to develop time lines and assess treatment success in patients or groups of patients.

Instructions on the use of the checklist, along with evaluation and management considerations are included for each category (below), and a brief primer on the approach to pancreatitis is provided in the discussion. Medical decisions must be based on primary medical resources and guidelines with the checklist used as an additional tool. The health care provider's overall assessment and plans, based on their training and experience, must always take precedence in medical care.

TOXIC-METABOLIC FACTORS

The Toxic-metabolic risk and etiology category focuses on agents that specifically cause dysfunction or injury to components of the acinar or duct cells or alter the response of cells linked to the pancreas during the injury → inflammation → resolution → regeneration sequence (24). Updates from Version 1 include revisions to Alcohol, Smoking, Hypercalcemia, Hyperlipidemia, Medications, Toxins, and Other categories, with chronic renal failure moved to Toxins and a new Metabolic category to include diabetes mellitus, diet and obesity.

Alcohol

The "Alcohol" category was changed into "Alcohol-related" category with stratified levels of (i) 0 to <1 drink/d/occasional; (ii) 1–2 drinks/d; (iii) 3–4 drinks/d; and (iv) 5 or more drinks/d. The change was based on NAPS2 findings and other research demonstrating a possible threshold for susceptibility to alcoholic CP at approximately 4–5 drinks/d with increasingly higher risk with heaver drinking, drinking pattern (e.g., binge drinking), and duration (25–27). After the first episode of AP, continued alcohol drinking increases the risk of RAP, rates of progression to CP, and development of diabetes mellitus and other complications in a dose-dependent manner (28–30). After an episode of AP, and especially RAP, a safe level of drinking without risk of progression is yet to be established.

Many patients develop AP, RAP, and CP with alcohol drinking below the expected threshold levels of very heavy drinking. Occasional or social alcohol consumption is common among adults, whereas pancreatitis is uncommon—even among heavy alcohol users (31). Furthermore, in many populations, including the United States, most patients with RAP and CP do not have alcohol-related etiologies, indicating that additional factors or random triggering events are required to develop AP, RAP, and CP. These cases may be complex gene-environment interactions, and additional research and insights are required to provide more specific guidance.

Checklist users. The effects of alcohol differ with respect to susceptibility and progression. Because the effects are quantitative, all subjects should have their use recorded using 1 of 4 categories for susceptibility and progression.

Smoking

Use of TIGAR-O_V1 allowed the effects of smoking to be defined in the NAPS2 cohort, as well as a synergistic effect with alcohol in patients who both drink and smoke (25–27). Smoking is an independent risk factor for RAP and CP, with current smokers being at a higher risk than past smokers. The risk from smoking increases with the number of cigarettes smoked per day (25,26). The Other, NOS section can be used to record the smoking of cigars, pipes, or marijuana.

Checklist users. The category of "Past smoker" is intended to capture patients who were previously exposed to the effects of smoking that may have initiated the pancreatitis process. The category of "Current smoker" is intended to capture both past exposure and ongoing use. The risk/etiology should be further defined by recording the number of packs of cigarettes smoked per day and the number of years of smoking and recording the interval years. This establishes the pattern and exposure dose and can be used to calculate "pack-years," i.e., packs per day × years of smoking.

Hypercalcemia

Hypercalcemia is a well-known risk factor for AP and can lead to CP. In TIGAR-O_V2, hypercalcemia is listed as a risk factor when total ionized calcium levels are ≥12.0 mg/dL or 3 mmol/L. The value is well above the typical upper limits of normal (e.g., up to 10.2 mg/dL) because it is intended to reflect AP risk (32). Approximately 90% of cases of hypercalcemia are caused by primary hyperparathyroidism (PHPT) or hypercalcemia of malignancy (33), with a small subset associated with genetic disorders, sarcoidosis, chronic kidney disease (CKD), and other factors.

Hyperparathyroidism causes hypercalcemia (typically with hypophosphatemia), but AP generally occurs in less than 7% of people with PHPT (32,34–36). The risk of AP correlates with the highest serum calcium levels among patients with PHPT (e.g., 13.0 vs 12.1 mg/dL (32,36)).

Familial hypocalciuric hypercalcemia is a syndrome most often associated with specific mutations in the calcium-sensing receptor gene (*CASR*) (37–39). AP, RAP, and CP are not associated with *CASR* mutations *per se* (35), but pancreatitis has been documented in patients with PHPT and *CASR* mutations (40).

The CASR is a complex, pleotropic receptor used for different purposes in different cells (39,41,42). Therefore, it is possible to have a complex pancreatitis risk linked to *CASR* variants without hypercalcemia. In this case, only the *CASR* variant under genetic risk/etiology should be checked.

Other, NOS category is for identified causes of hypercalcemia such as parathyroid tumors (43), multiple endocrine neoplasia (MEN) type 1 or 2a (33,44), other cancers such as multiple myeloma (33,45), or rare causes of hypercalcemia.

Checklist users: Total and/or ionized calcium levels. Ionized calcium levels with associated dates of analysis and normal ranges for the laboratory should be recorded in the chart and/or case report form. Patients with hypercalcemia from medications (e.g., lithium and vitamin D overdose) should also be included under Toxic-metabolic > Medication and those with variants in genes affecting serum calcium (e.g., *CASR* and MEN syndromes) should be included under Genetics > Modifier Genes or Genetics > Other.

Clinical evaluation of hypercalcemia should be documented, as well as family history, medical history including

renal stones, medications including lithium and vitamin D use, and basic laboratory values including parathyroid hormone (PTH) levels and serum ionized calcium and phosphorus levels with urine calcium if familial hypocalciuric hypercalcemia is suspected. If the patient has hypercalcemia of malignancy (33), the tumor type should be recorded in the evaluation, consultation, and/or case report form.

Hypertriglyceridemia

Earlier literature suggested that hyperlipidemia was a rare and controversial cause of CP (5). However, in the NAPS2-Continuation and Validation (CV) study, hyperlipidemia was identified as a risk factor in 13% of subjects with CP (9). In TIGAR-O_V2, the term "hyperlipidemia" is changed to hypertriglyceridemia (HTG) and used as a clinical diagnosis. Controversy continues as to whether the critical triglyceride (TG) level is the trough (fasting levels recommended by endocrinologists) or peak (levels during pain and/or pancreatitis in the fed state as recommended by some gastroenterologist). In fasting patients, a threshold TG of >300 mg/dL represents the 95th percentile and HTG (to convert mmol/L to mg/dL, multiply by 88.6) (46). In the United States, 1.7% of the population have fasting TG > 500 mg/dL, and 0.4% have >1,000 mg/dL (47). Nonfasting TG levels confer increased risk of AP. Analysis of data from the Copenhagen City Heart Study suggests that the risk of AP begins with nonfasting mild-to-moderate HTG (>177 mg/dL), with hazard ratio (HR) 2.3 for TGs 177–265 mg/dL, HR 2.9 for TGs 366–353 mg/dL, HR 3.9 for TGs 354–442 mg/dL, and HR 8.7 for TGs > 442 mg/dL (48). The highest risk levels translate into an expected 12 events per 10,000 person-years (48).

Checklist users. HTG not only increases the risk of AP, RAP, and CP but also worsens the severity of an episode of AP in terms of pancreatic necrosis (PNec), systemic inflammatory response syndrome, multiple organ failure (MOF), intensive care unit (ICU) admissions, length of stay, and mortality (49–52). Therefore, identifying and managing HTG remains one of the most important actionable findings of patient evaluation.

Clinical evaluation should include a complete lipid panel at baseline (noting fasting or fed) and at the time of admission during an attack of AP. Pre-AP TG levels roughly correlate with HTG AP, but there is wide variability (53). Medications should be reviewed and documented. Family history of pancreatitis, HTG, DM, obesity (body mass index [BMI] >30 kg/m^2), and cardiovascular disease should be documented, and a dietary/nutrition history is recommended.

Medications

Medications are believed to cause both acute and CP through multiple mechanisms. Several mediations most strongly associated with severe AP and/or RAP including azathioprine (and its metabolite 6-mercaptopurine), 2′3′-dideoxyinosine (54), and L-asparaginase (55,56). More than 100 drugs have been implicated in AP and RAP, such as methylprednisolone, fenofibrate, angiotensin-converting enzyme inhibitors, statins, estrogens, and valproic acid, although direct, mechanistic cause-effect relationships are typically lacking and underlying cofactors such as genetic factors have not been excluded in most case reports (57–61). The medications taken by patients should be documented and tracked in anticipation of deeper understanding of complex disorders. No specific medication list is included in the TIGAR-O_V2 checklist, but the drugs listed above should be among the ones considered.

Checklist users should list the medications believed to be a risk factor or causative agent for RAP or CP in the NOS section, including dates of use and doses.

Toxins

Toxins include any agent that causes stress or injury to the acinar or duct cells, excluding alcohol and tobacco. The TIGAR-O_V1 checklist included "Organotin compounds (e.g., DBTC [dibutyltin dichloride])" as an example, which was not identified as a risk factor in NAPS2, although "Toxic" was selected in 3 patients with CP and 1 patient with RAP without indicating the suspected factor. The TIGAR-O_V2 checklist divides toxins into CKD, Oxidative stress-associated factors, and Other Toxins, with the Short Form including CKD, with the option to add additional information under NOS.

Chronic kidney disease. In TIGAR-O_V1, the term "Chronic renal failure" was used. In TIGAR-O_V2, the terminology is updated and the severity of CKD is specified as stage 5 or end-stage renal disease (ESRD). CKD may confer risk either through inability to clear pancreatic toxins or electrolyte imbalances such as hypercalcemia. CKD also presents challenges in fluid management and assessment of episodes of AP.

In the NAPS2-CV study, chronic renal failure was identified as a coexisting risk factor in ~2% of patients with CP and in ~5% of patients with idiopathic CP (9). The severity of disease was not well defined. For TIGAR-O_V2, a history of only the most severe forms of CKD is included. CKD stage 5 represents a person with ESRD with a glomerular filtration rate of 15 mL/minute or less. Further qualifications are included as to whether the subject is on dialysis or has had a kidney transplant at any time. A person with a kidney transplant should also be classified as "No dialysis" or "On dialysis" at the time of evaluation.

Oxidative stress-associated factors. Oxidative stress–associated factors are included as a separate category based on the observation that antioxidants seem to be useful in some studies (62). Postirradiation/chemotherapy-associated toxicity and ischemic risk (chronic, such as vascular disease), which were listed under Recurrent/SAP in TIGAR-O_V1, are now listed under the "Oxidative Stress" category. Factors that generate toxicity through oxidative stress mechanisms that are, or potentially mitigated by antioxidants, including some environmental factors, or toxic metals such as arsenic, cadmium, and chromium, which may also contribute to pancreatic cancer (63–66) should be listed here. These factors are not sufficient to cause pancreatitis alone, but likely contribute to disease in the context of alcohol, smoking, malabsorption, or dietary deficiencies in vitamins and antioxidants, exhaustive physical exercise, and/or genetic factors.

Other Toxins includes dose-dependent or idiosyncratic agents that cause AP, RAP, or CP by hyperstimulation (e.g., scorpion venom and anticholinesterase insecticides (67)). In addition, agents that are deemed to be toxic but are of unknown mechanism but contribute to risk can be listed under NOS.

Metabolic, other

This represents a new category to consolidate diabetes, obesity, metabolic syndrome, diet, and other factors likely associated with RAP and/or CP. HTG is listed as a separate category because of the unique mechanism of direct toxicity of fatty acids in AP (68) and a high incidence and morbidity in RAP and CP (9,50–53,69). The Short Form includes Diabetes, with the option to add additional information under NOS.

Diabetes mellitus. Diabetes Mellitus is broadly defined by elevated fasting glucose levels and/or hemoglobin A1c. This category of risk is new to TIGAR-O_V2 and is included because it can be a cause of pancreatic atrophy and fibrosis (e.g., exocrine pancreatopathy (70–72)), is associated with pancreatic exocrine insufficiency (73,74), and may be a biomarker for pancreatic cancer (75,76). The question of whether diabetes came before or after exocrine inflammation can be challenging in many cases (77), but the goal here is merely to document presence and severity as the features of exocrine pancreatic diseases are being evaluated (78). The term post-pancreatitis diabetes mellitus defines elevated blood glucose >3 months after an AP event (79). New-onset diabetes after pancreatitis is a study term that further defines the stage of pancreatitis (e.g., the first episode of AP [i.e., SAPE], RAP, or CP) (79). The 3 levels of therapy include Diet-controlled glucose intolerance, Medical control diabetes mellitus (oral agents), and Insulin requiring diabetes mellitus (≥10 units per day).

Checklist users may check more than 1 category. The date of onset of diabetes should be documented. The diagnosis of diabetes mellitus should follow the American Diabetes Association guidelines (80). Abnormal glucose levels are classified as diabetes with hemoglobin A1C ≥6.5%, fasting plasma glucose of ≥126 mg/dL, or oral glucose tolerance test with a 2-hour glucose of ≥200 mg/dL after 75 g of oral glucose. The term "prediabetes" is used to define a condition where the A1C or serum glucose is abnormal, but is not diagnostic of diabetes such as a hemoglobin A1C of 5.7–6.4%, fasting plasma glucose of 100–125 mg/dL, or oral glucose tolerance test with a 2-hour glucose of 140–199 mg/dL after 75 g of oral glucose. If the results are equivocal, they should be repeated. A random plasma glucose of ≥200 mg/dL is also diagnostic in a patient with symptoms of diabetes (80).

In some cases, the patient will have brittle diabetes due to loss of the islet alpha cells (glucagon producing) and subject to severe hypoglycemia (78). If the patient is at risk of level 2 hypoglycemia, defined as blood glucose <54 mg/dL (3.0 mmol/L), consider prescribed glucagon to be used as needed (80). The patient, family, caregivers, and other relevant individuals should be instructed on its location and when and how to administer it if needed (80).

Classifying the subtype of diabetes may be challenging in some patients, although the use of autoantibody testing and genetic analysis may be helpful. The patient's medical record or case report form should include relevant family histories and medical history of obesity, metabolic syndrome, propensity to hypoglycemia and diabetic ketoacidosis, HTG, and the timing and type of passed or planned pancreatic surgery, including total pancreatectomy with islet autotransplantation. New-onset diabetes mellitus with weight loss can be an early sign of pancreatic cancer (76).

Diet. Diet may be an important disease modifier, either directly or indirectly, such as effects on the gut biome. Diet is one of the most difficult factors to accurately measure. For this version, dietary risk factors for CP are limited to red meat consumption of >2 oz/57 g per day. The supporting data are the Multiethnic Cohort study in which a threshold of risk of RAP and CP was seen with the intake of >24.5 g/1,000 kcal/d, with a hazard ratio of 1.37 (1.01–1.87) (81). Two ounces of red meat is the threshold level for a 2,300 kcal/d diet, and "2 oz" was therefore arbitrarily defined as a reasonable risk threshold level for most adults. Between 40% and 50% of adults of all ethnic backgrounds will exceed this threshold. Once red meat intake increases above 2 oz/57 g in adults, the risk remains stable and does not seem to increase with higher red meat intake (81). A meat-rich diet is also associated with persistent organ failure in AP (82). In addition, a vegetarian/vegan diet should be noted as a possible protective factor.

Checklist users. Global measures of obesity such as BMI do not necessarily exclude malnutrition in patients with pancreatic disease. Patients with high intake of simple carbohydrates or who avoid fats may be overweight or obese and deny symptoms of maldigestion, while having protein and/or micronutrient deficiency, and especially in fat-soluble vitamins and vitamin B12. Thus, an elevated BMI should not preclude a complete nutrition analysis.

Obesity. Visceral adiposity, i.e., excess visceral adipose tissue (VAT) is associated with the risk of HTG, DM, metabolic syndrome, and other morbidities (83,84).

Visceral adiposity can be estimated by general morphology (e.g., "apple-" or "pear-" shaped obesity, with apple indicating VAT (85,86)), waist circumference, waist-to-hip ratio, computed tomography (CT), magnetic resonance imaging (MRI), or dual-energy x-ray absorptiometry (DXA), and others (84,87). VAT mass measured by DXA is comparable to MRI in a large, multiethnic cohort within a wide range of body fatness (87). DXA has the advantage of more rapid scanning, lower cost, and lower radiation exposure compared with MRI or CT while providing similar results (87).

Checklist users. Waist circumference is simple, measured 1 cm above the iliac crest with waist girth ≥102 cm for males and ≥88 cm for females indicating visceral obesity (84,87). Hip circumference is measured at the widest circumference of the buttocks at the area of the greater trochanters with waist-to-hip ratio >0.90 for men and >0.85 for women indicating visceral obesity (84,87).

IDIOPATHIC

The TIGAR-O_V1 checklist subclassified idiopathic pancreatitis as "Early onset," "Late onset," and "Tropical." In TIGAR-O_V2, the categories of early-onset and late-onset pancreatitis are the primary subcategory classes and defined by age <35 years or 35 years and older. The INSPPIRE group further subdivides pediatric cases into 3 age cohorts (<6, 6–11, and ≥12 years) based on published recommendations for age grouping in pediatric trials (88,89).

Tropical pancreatitis seems to be a complex genetic disorder and is not discussed under "Genetic > Rare, non-neoplastic pancreatic genetic variant-associated syndromes."

GENETIC

The last 20 years witnessed tremendous advances in understanding the genetics of pancreatitis, with most of the previous "Idiopathic" cases and many "Alcohol"-related cases having strong, pathogenic genetic factors. The TIGAR-O_V1 classification divided genetics into 2 subgroups, "Autosomal dominant" and "Autosomal recessive/modifier genes." With growing knowledge of genetics, especially within the domain of precision medicine, this classification is now outdated. The Short Form includes only high-level classification with opportunity to add additional information under NOS.

Suspected

TIGAR-O_V2 uses 8 Genetic categories. The first category, "Suspected," should be used to classify patients with suspected genetic factors, either while genetic testing is being considered, while the results are pending, or when the initial genetic test was too limited (e.g., only *PRSS1, CFTR, SPINK1*, and *CTRC*). Genetic etiologies should be suspected when there is early-onset pancreatitis

(age <35 years), if there are no other obvious causes (e.g., gallstones or trauma) such as idiopathic pancreatitis, when there is a positive family history of pancreatitis, diabetes, dyslipidemia, and pancreatic cancer, when unusual features suggest a genetic disorder (e.g., cystic fibrosis [CF]-related syndrome), or when the clinical course or response to treatment is unexpected or severe (90–92).

Autosomal dominant

The "Autosomal dominant" category is for mendelian syndromes including gain-of-function mutations in *PRSS1* (93,94) (see below for other *PRSS1* variants) or MODY8 phenotype-associated variants in *CEL* (95,96) (see below for other *CEL* variants).

Autosomal recessive

The "Autosomal recessive" diseases with mendelian inheritance include classic CF, CFTR-related disorders (CFTR-RD), and biallelic pathogenic *SPINK1* mutations.

Cystic fibrosis. Patients with 2 disease-causing *CFTR* variants on different alleles (*trans*) plus other criteria of clinical setting and functional defects in CFTR function have CF (97). Genomic *CFTR* locus sequence variants are now classified into 7 classes based on the effect on protein function, with classes I, II, III, and VII being severe (98). The term "atypical CF" is no longer used. Patients with *CFTR* genotypes with less than 2 severe mutations in *trans* but include other pathogenic *CFTR* variants of class IV, V, or VI are classified as CF if there is both clinical (i.e., signs and symptoms of CF in >1 typical organ) and functional evidence of CFTR dysfunction (e.g., sweat chloride testing) (97).

CFTR-related disorder. In some cases, the dominant disease feature in patients with *CFTR* variants is pancreatitis (99–101). The "CFTR <2 severe variants in *trans*" classification is for patients with at least 1 pathogenic *CFTR* variant (any class), including mutations of variable clinical consequence, variants of unknown significant, or no second identifiable variant, and in whom CFTR function testing is abnormal (typically a sweat chloride value in the intermediate range of 30–59 mmol/L). In TIGAR-O_V2, these are classified as a CFTR-RD if they do not qualify for classification as CF (e.g., it is monosymptomatic—affecting only 1 organ such as the pancreas). This category remains important because it may have specific therapeutic implications. Patients with male infertility and/or chronic sinusitis, in addition to RAP or CP, are classified here as CFTR-RD, with the other features noted (see LaRusch et al. (77)).

SPINK1-associated familial pancreatitis. Patients with 2 pathogenic *SPINK1* variance in *trans* are also classified as autosomal recessive pancreatitis. Heterozygous pathogenic SPINK1 variants are typically part of a complex, multigenic genotype.

Complex genetics

This category is emerging as one of the most important for all types of pancreatitis and other pancreatic diseases and is new in TIGAR-O_V2. Careful documentation of the risk and etiologic factors in individual patients is needed to continually improve the management of patients in the precision medicine paradigm. This category focuses on genetic variants that increase susceptibility to pancreatic injury, through the trypsin-dependent pathway (102), a protein misfolding pathway linked to the endoplasmic reticulum with a significant unfolded protein response (103), or other acinar or duct cell injury or stress mechanisms including calcium dysregulation (104,105). These represent disease drivers within the acinar or duct cells (e.g., causing recurrent injury), but do not include common variants that modify the severity of injury, the immune response, or other disease features such as diabetes mellitus or pancreatic ductal adenocarcinoma (see below). Only variants that are known to be pathogenic or are likely pathogenic should be included in this checklist (e.g., see www.pancreasgenetics.org). The full genetic testing report should be stored separately.

CFTR variants in this category include cases in which one or more pathogenic variants that are in *cis* (all on the same allele with the other allele being "wild type") and where there is either no functional information available (e.g., sweat chloride testing has not been performed) or when the functional testing of the genotype is normal (e.g., sweat chloride levels of <30 mmol/L). This category should also be checked if there are other pathogenic variants in this category (e.g., a single pathogenic *SPINK1* variant and *CTRC* variant) because *CFTR* variants may participate in multiple pathogenic pathways.

Other, NOS. This classification is for genetic variants that are considered susceptibility genes or disease drivers that are not listed above.

Modifier genes

Modifier genes differ from susceptibility genes in that do not independently cause RAP or CP, but make the disease phenotype worse. The list of pathogenic genetic variants selected for TIGAR-O_2 includes *CLDN2* (different genetics in men and women and linked to alcohol intake (106–108)), *SLC26A9* (linked with CF severity and their therapeutic responses (109,110)), *GGT1*, which likely requires generation of oxidative stress as the proximal cause and is associated with both pancreatitis and pancreatic cancer risk (111,112), and B blood type (associated with pancreatitis and pancreatic cancer) (113–115).

Other, NOS. This classification is for genetic variants that are considered modifier genes that are not listed above.

HTG syndromes

A clinical diagnosis of HTG should be included under "Toxic-metabolic > Hypertriglyceridemia." In TIGAR-O_V2, a new category of HTG syndromes is included to document genetic variants in the most common genes associated with familial chylomicronemia syndrome (lipoprotein lipase gene [*LPL*] and *APOC2*) with other less common single gene variants or complex combinations of variants listed separately (see Moulin et al. (116)).

Multifactorial chylomicronemia syndrome. This category includes both genetic and environmental cofactors in complex combinations. This category should be selected in patients with HTG, once genetic testing is completed or if there is strong clinical evidence of the phenotype in a patient with a known, strong inherited genetic risk.

Other, NOS is for variants that are documented in the patients records but do not fit into the above categories. Examples include *ANGPTL3, APOA5, APOB, CELSR2, FABP4, FADS1,2,3, GCKR, GPIHBP1, LMF1, MLXIPL, PPARG,* and others (116,117).

Rare, non-neoplastic pancreatic genetic variant-associated syndromes

This represents a new category in TIGAR-O_V2 and includes a group of distinct clinical syndromes that include pancreas dysfunctions and that can be caused by pathogenic variants in one or more genes.

Shwachman-Diamond syndrome. Shwachman-Diamond syndrome (SDS) is characterized by exocrine pancreatic insufficiency with hematologic abnormalities (e.g., cyclic neutropenia), skeletal

defects, and short stature (118). SDS is a rare autosomal recessive disorder associated with mutations in the *SBDS* gene (119) and likely other genes such as *DNAJC21, ELF1*, and *SRP54* (118). It does not cause pancreatitis but does disrupt exocrine pancreatic function.

Johanson-Blizzard syndrome. Johanson-Blizzard syndrome (JBS) is a rare autosomal recessive syndrome characterized by exocrine pancreatic insufficiency, typical facial features, dental anomalies, hypothyroidism, sensorineural hearing loss, scalp defects, urogenital and anorectal anomalies, short stature, and cognitive impairment of variable degrees (120). JBS is linked to mutations in the ubiquitin-ligase E3 (UBR1) gene, which is a key part of the unfolded protein response pathway for serine proteases (120,121). Pancreatic damage is characterized by pancreatic insufficiency and growth restriction, with lipomatous transformation of the pancreas rather than AP.

Mitochondrial disorders. The pancreas requires large amounts of energy to function. Adenosine triphosphate (ATP) is critical to calcium regulation, and deficits can predispose to trypsin activation (104). Mitochondrial dysfunction increases the risk of pancreatitis (122). The human prototype is Pearson marrow-pancreas syndrome, characterized by progressive, multiple system organ dysfunction and death in early childhood. This syndrome was caused by a 4977-bp deletion of mitochondrial DNA (mtDNA) encompassing portions of the genes coding for nicotinamide adenine dinucleotide (NADH) dehydrogenase, cytochrome oxidase, and ATPase (123). Less damaging genomic or mtDNA variants in patients with RAP or CP should be included here.

Other, NOS. In TIGAR-O_V1, the entity known as tropical pancreatitis was listed under "Idiopathic." Tropical pancreatitis is a historical term used to describe otherwise idiopathic CP in tropical regions. In many cases, these patients have complex genetic etiologies that are similar to other complex genetic pancreatitis cases (124,125). The term "tropical pancreatitis" is considered obsolete by many experts. From a phenotypic perspective, there are 2 distinct subtypes: "Tropical calcific pancreatitis" and "Fibrocalculous pancreatic diabetes." Further research is needed to determine whether these represent distinct syndrome that differ from other complex pancreatitis cases by genetic signatures or other factors that represent a disease sub-type (126).

AUTOIMMUNE PANCREATITIS

AIP describes a type of inflammation that is not directly linked to pancreatic injury, involves an abnormal B-cell response, and generally responds to steroid treatment. Two general types of AIP are recognized.

AIP type I is pathologically described as lymphoplasmacytic sclerosing pancreatitis, is usually associated with elevated IgG4 levels, and may be a part of a systemic IgG4-related disease syndrome with other organs also affected.

AIP type II is pathologically defined by the granulocyte epithelial lesion (GEL). There are currently no serum markers for AIP type II. Because a definitive diagnosis by pancreatic biopsy is a high-risk procedure, a trial of steroids is often preferred with a strongly positive response leading to a presumptive diagnosis. There is a high coincidence of inflammatory bowel disease with AIP type II. Medications used in treatment of inflammatory bowel disease, such as azathioprine, are associated with AP or RAP independent of AIP.

AIP-NOS

This category is for complex pancreatitis conditions in which an autoimmune component is demonstrated, but it does not meet the criteria for AIP type I or type II, such as patients with non-IgG4 antibodies to carbonic anhydrase and lactoferrin or other acinar or duct cell antigens (127–130).

RECURRENT ACUTE AND SEVERE AP

Among the strongest risk factors for the development of CP are RAP and severe AP (28,30,131,132). The risk of progression to CP after AP or RAP may also depend on the other etiologies (106,133). The goal of this category includes addressing the risk of progression to CP associated with different severity classifications of AP and with different etiologies of AP—including modifiable risk factors. RAP is >1 episode of AP, regardless of severity, and is a much stronger risk factor for CP then a single episode of AP (28,30,134).

The TIGAR-O_V1 class of "Postnecrotic (severe acute pancreatitis)" has been modified in the TIGAR-O_V2 checklist to include all cases of AP, with subclasses based on the severity criteria. SAP is defined as the presence of persistent systemic inflammatory response syndrome (≥48 hours) with MOF (lung, cardiovascular, and kidney) based on the modified Marshall score (see Banks et al. (135)) and the Determinant-Based Classification of AP Severity (136) that uses infected PNec or a new and persistent (≥48 hours) score (137) >2 to define organ failure. Four subcategories include patients with or without SAP and by the presence or absence of ≥30% PNec. The Short Form only includes a Yes/No option for previous AP.

Checklist users should check both AP and RAP if the patient has RAP. If they are using the Long Form, they should use <30% PNec if PNec is unknown. Use >30% if the patient developed a clinically significant pseudocyst or required surgery. Use SAP if the patient was admitted to the ICU for management. If not subcategory category can be selected with confidence, do not check any.

TIGAR-O_V1 included "Vascular diseases/ischemic" and "Post-irradiation" in Recurrent and Severe Acute Pancreatitis, but these have been moved to become examples of "Toxic-metabolic > Toxins > Oxidative stress-generating factors."

TIGAR-O_V2 includes a new category that captures the major etiologies of AP/RAP that are generated outside of the pancreatic acinar/duct and that are not Toxic-metabolic factors. This includes biliary AP, which is a major etiology of SAP, post–endoscopic retrograde cholangiopancreatography (post-ERCP), which many be linked to new risk etiologies, and others. Infectious includes viral and other with link to documentation. Note that bacteria as an etiology should not be confused with a secondary infections such as infected PNec.

Checklist users. Including information on SAPE, RAP, and CP is critical for the understanding of the pathobiology of individual patients because some patients progress from SAPE → RAP → CP, whereas others do not, and approximately 40% of patients present with CP without RAP or SAPE, suggesting that they have a different underlying disease process. It is important to document the dates and complications of each episode of AP and any new features that develop including diabetes mellitus, pancreatic exocrine insufficiency, or change in pain patterns. In addition, the frequency of attacks should be documented. These are important for evaluating the trajectory of disease, outcomes, and effectiveness of interventions (3,134,138).

OBSTRUCTIVE

The major changes between TIGAR-O_V1 and TIGAR-O_V2 are the replacement of "Sphincter of Oddi disorders

(controversial)" with "Ampullary stenosis" and the delineation of the location and etiology of factors that may obstruct the pancreatic ducts and contribute to obstructive CP.

Pancreatic calcifications develop within pancreatic ducts through poorly defined pathophysiological mechanisms. Because calcification/stone formation is highly variable, identifying patients with predominately large duct and predominately small duct (diffuse) calcifications is included.

Main pancreatic duct strictures are considered significant if there is upstream pancreatic duct dilation.

Localized masses can cause main pancreatic duct obstruction with permanent damage to upstream pancreatic tissue. Four categories are listed. Pancreatic ductal adenocarcinomas typically generate a desmoplastic reaction, which is not CP. Only localized pancreatic ductal adenocarcinomas with duct obstruction and residual CP pathology after tumor removal in patients should be included. If the patient had radiation therapy, also check the "Toxic-metabolic > Toxins, other > Oxidative stress-generating factors" category. Main duct intraductal papillary mucinous neoplasm (IPMN) should be localized, with upstream residual effects being due to obstruction.

Anatomic Variants is a new category within TIGAR-O_V2. This includes periampullary duodenal wall cysts, choledochoceles, Santoriniceles (focal cystic dilatation of the terminal portion of the dorsal pancreatic duct), anomalous pancreaticobiliary union, annular pancreas, and others, NOS. Pancreas divisum, a common variant and subject of ongoing studies, is retained within a separate category.

DISCUSSION

Our understanding of the spectrum of inflammatory diseases of the pancreas is undergoing a major revolution, driven in large part by the discovery that genetic variants play a major role in all aspects of pancreatic disease and that the spectrum of clinical features in patients with different diseases represents the interaction of multiple and common pathways. The complexity of chronic pancreatic diseases (17,24) and recognition of the importance of taking a holistic approach toward disease prevention and control (1) require a deeper understanding of disease mechanism, risk-etiology factors, and specific biomarkers of diseases activity and progressive state (139). The rationale for the TIGAR-O risk/etiology checklist is to provide mechanistic insights into a variety of pancreatic disorders with overlapping features and underling mechanisms. For example, neither atrophy, fibrosis, pancreatic exocrine insufficiency, pancreatic pain, nor diabetes mellitus is specific for CP, especially early in the disease (15). The differential for detection of these clinical signs and symptoms and disease biomarkers includes AIP, pancreatic insufficiency syndromes, diabetes mellitus, obstructing masses, IPMNs, cancers, and other disorders. Furthermore, more than 1 disease can exist in the same person at the same time, making the diagnoses and management based on clinical features alone challenging. Thus, identifying and classifying risk and etiologies allows for the relative probability of disorders in the differential to be ranked and verified, based on further investigation and established criteria.

The approach to patients with idiopathic AP, RAP, and CP should include a complete checklist of all of all the factors in each patient. Organizing and standardizing a checklist assists in the assessment of a complex patient, facilitates the recognition of interacting factors, and helps identify potentially modifiable factors for lifestyle changes or therapeutic targeting.

The checklist should always be dated and updated with subsequent evaluations to include new information (e.g., genetic testing results) or changes in risk status (e.g., stopped smoking, control of HTG, and removal of an obstruction). It therefore serves as a key to define pathogenic pathways in active pancreatic diseases and defines risk of progression to successive stages, severities, and complications of disease (24). The standardized TIGAR-O_V2 checklist also provides structure for analyzing and comparing groups of patients using comparative statistics and/or machine learning to better define disease mechanisms and to optimize treatments. Insights from population studies are invaluable for advancing the caring for individual patients and groups of patients.

Checklist users should sequentially check the category heading, the subheading, and the specific factor. For example, a patient with familial HTG and 1 episode of AP might have all of the following categories checked: Toxic-metabolic > HTG > and all 3 subcategories of risk: Hypertriglyceridemic risk (if the HTG was not yet controlled), Hypertriglyceridemic AP, history of; and Familial HTG. In addition, if the patient was found to have a mutation in the *LPL* gene, the checklist user would also check Genetic > HTG syndromes > LPL. Finally, the checklist user should record the pancreatitis pattern and severity under Recurrent and SAP if 1 or more criteria are met.

The benefit of using a standardized approach to pancreatitis disorders early in the course of disease is that it provides a critical component of the precision medicine paradigm needed for successful disease mitigation or effective management. By necessity, success in preventing disease development and progression, rather than supportive care, will increasingly depend on the use of new health information technologies that link the patient, the patient data, the health care team, and a world of information together. In addition, this formatted tool will give the clinician focused on patient-centered care tangible information to review with patients directly. They will have the opportunity to discuss etiology and risk factors and ways to mitigate their patient's individual risks directly.

CONFLICTS OF INTEREST

Guarantor of the article: David C. Whitcomb, MD, PhD.

Specific author contributions: D.C.W. planned and coordinated the study, collected the data, and drafted the manuscript and approved the final draft. The other contributors reviewed the manuscript and approved the final draft.

Financial support: This work was supported by the National Cancer Institute and National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award numbers U01DK108306, DK054709, and DK077906.

Potential competing interests: D.C.W. serves as a consultant for AbbVie, Regeneron, and Ariel Precision Medicine and is a cofounder of Ariel Precision Medicine and may have equity.

ACKNOWLEDGEMENTS

Ongoing collaborators and consultants associated with the North American Pancreatitis Study Group who reviewed and commented on the TIGAR-O_V2 list include Stephen Amann, MD, Peter A. Banks, MD, Melena D. Bellin, MD, Suresh Chari, MD, Gregory A. Cote, MD, MSc, Jeff Easler, MD, Christopher E. Forsmark, MD, Martin L. Freedman, MD, Nalini M. Guda, MD, Mark Haupt, MD, Jessica LaRusch, PhD, Michele D. Lewis, MD, Mark E. Lowe, MD, PhD, Thiruvengadam Muniraj, MD, PhD, Stephen Pandol, MD, Georgios I. Papachristou, MD, PhD, Vikesh Singh, MD, MSc, Adam Slivka, MD, PhD, C. Mel. Wilcox, MD, and Dhiraj Yadav, MD, MPH.

Study Highlights

WHAT IS KNOWN

- ✓ RAP and CP are complex inflammatory disorders.
- ✓ Multiple risk factors become etiologies once clinical disease begins.
- ✓ Complex gene and environment interactions drive RAP and CP through one or more disease mechanisms.
- ✓ Multiple disorders with features that overlap with the mechanistic definition of CP are considered in the differential diagnosis of CP.
- ✓ The TIGAR-O list of risk and etiologies provides an organizational tool for listing potential etiologies in patients, but new discoveries and insights are not included in the list.

WHAT IS NEW HERE

- ✓ The revised TIGAR-O Version 2 classification list is given.
- ✓ Clinically relevant details to understand the rationale and approach to complex risk factors, etiologies, and disease classifiers are discussed.
- ✓ Methods and specific cutoff values for documenting risks, potential etiologies, and clinical features are outlined.

TRANSLATIONAL IMPACT

- ✓ The TIGAR-O_V2 checklist provides a simple tool for busy physicians and health care workers to use in a clinical setting.
- ✓ A short form, TIGAR-O_V2-SF, can be used for initial risk/etiology/state classification while additional information is being gathered.
- ✓ The standardized format facilitates utilization of new health information technologies (HITs).
- ✓ The structured risk and etiologic format allows for epidemiological and systems biology studies to be conducted on the backend.
- ✓ Integration of the TIGAR-O_V2 system into clinical practice using health information technology, and linked to genomic data, biomarkers, clinical states, and other information will facilitate precision medicine.

REFERENCES

1. Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. Nat Rev Gastroenterol Hepatol 2019;16:175–84.
2. Abu-El-Haija M, Gukovskaya AS, Andersen DK, et al. Accelerating the drug delivery pipeline for acute and chronic pancreatitis: Summary of the working group on drug development and trials in acute pancreatitis at the National Institute of Diabetes and Digestive and Kidney Diseases Workshop. Pancreas 2018;47:1185–92.
3. Lowe ME, Goodman MT, Cote GA, et al. Accelerating the drug delivery pipeline for acute and chronic pancreatitis: Summary of the working group on drug development and trials in recurrent acute pancreatitis at the National Institute of Diabetes and Digestive and Kidney Diseases Workshop. Pancreas 2018;47:1193–9.
4. Forsmark CE, Andersen DK, Farrar JT, et al. Accelerating the drug delivery pipeline for acute and chronic pancreatitis: Summary of the working group on drug development and trials in chronic pancreatitis at the National Institute of Diabetes and Digestive and Kidney Diseases Workshop. Pancreas 2018;47:1200–7.
5. Etemad B, Whitcomb DC. Chronic pancreatitis: Diagnosis, classification, and new genetic developments. Gastroenterology 2001; 120:682–707.
6. Whitcomb DC, Yadav D, Adam S, et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). Pancreatology 2008; 8:520–31.
7. Whitcomb DC. What is personalized medicine and what should it replace? Nat Rev Gastroenterol Hepatol 2012;9:418–24.
8. Whitcomb DC. Hereditary pancreatitis: New insights into acute and chronic pancreatitis. Gut 1999;45:317–22.
9. Conwell DL, Banks PA, Sandhu BS, et al. Validation of demographics, etiology, and risk factors for chronic pancreatitis in the USA: A report of the North American Pancreas Study (NAPS) group. Dig Dis Sci 2017;62: 2133–40.
10. Wilcox CM, Sandhu BS, Singh V, et al. Racial differences in the clinical profile, causes, and outcome of chronic pancreatitis. Am J Gastroenterol 2016;111:1488–96.
11. Fernandez M, Arvanitakis M, Musala C, et al. The Belgian National Registry on chronic pancreatitis: A prospective multi-centre study covering more than 800 patients in one year. Pancreatology 2017;17:572–9.
12. Capurso G, Archibugi L, Pasquali P, et al. Prevalence of chronic pancreatitis: Results of a primary care physician-based population study. Dig Liver Dis 2017;49:535–9.
13. Delhaye M, Van Steenbergen W, Cesmeli E, et al. Belgian consensus on chronic pancreatitis in adults and children: Statements on diagnosis and nutritional, medical, and surgical treatment. Acta Gastroenterol Belgica 2014;77:47–65.
14. Lohr JM, Dominguez-Munoz E, Rosendahl J, et al. United European Gastroenterology Evidence-Based Guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United Eur Gastroenterol J 2017;5:153–99.
15. Whitcomb DC, Shimosegawa T, Chari ST, et al. International consensus statements on early chronic pancreatitis: Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group and European Pancreatic Club. Pancreatology 2018. [Epub ahead of print May 21, 2018.]
16. Conwell DL, Lee LS, Yadav D, et al. American pancreatic association practice guidelines in chronic pancreatitis: Evidence-based report on diagnostic guidelines. Pancreas 2014;43:1143–62.
17. Pham A, Forsmark C. Chronic pancreatitis: Review and update of etiology, risk factors, and management. F1000Res 2018;7.
18. Pezzilli R, Andriulli A, Bassi C, et al. Exocrine pancreatic insufficiency in adults: A shared position statement of the Italian Association for the Study of the Pancreas. World J Gastroenterol 2013;19:7930–46.
19. Schneider A, Lohr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: Introduction of a unifying classification system based on a review of previous classifications of the disease. J Gastroenterol 2007;42:101–19.
20. Hirth M, Vujasinovic M, Munch M, et al. Monitoring and predicting disease activity in autoimmune pancreatitis with the M-ANNHEIM-AiP-Activity-Score. Pancreatology 2018;18:29–38.
21. Olesen SS, Poulsen JL, Drewes AM, et al. The Scandinavian baltic pancreatic club (SBPC) database: Design, rationale and characterisation of the study cohort. Scand J Gastroenterol 2017;52:909–15.
22. He YX, Xu HW, Sun XT, et al. Endoscopic management of early-stage chronic pancreatitis based on M-ANNHEIM classification system: A prospective study. Pancreas 2014;43:829–33.
23. Diaconu BL, Ciobanu L, Mocan T, et al. Investigation of the SPINK1 N34S mutation in Romanian patients with alcoholic chronic pancreatitis. A clinical analysis based on the criteria of the M-ANNHEIM classification. J Gastrointestin Liver Dis 2009;18:143–50.
24. Whitcomb DC, Frulloni L, Garg P, et al. Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition. Pancreatology 2016;16:218–24.
25. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med 2009;169:1035–45.
26. Cote GA, Yadav D, Slivka A, et al. Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2010;9:266–73.
27. Yadav D, Whitcomb DC. The role of alcohol and smoking in pancreatitis. Nat Rev Gastroenterol Hepatol 2010;7:131–45.
28. Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. Am J Gastroenterol 2012;107:1096–103.

29. Takeyama Y. Long-term prognosis of acute pancreatitis in Japan. Clin Gastroenterol Hepatol 2009;7(11 Suppl l):S15–7.
30. Sankaran SJ, Xiao AY, Wu LM, et al. Frequency of progression from acute to chronic pancreatitis and risk factors: A meta-analysis. Gastroenterology 2015;149:1490–500.e1.
31. Yadav D, Eigenbrodt ML, Briggs MJ, et al. Pancreatitis: Prevalence and risk factors among male veterans in a detoxification program. Pancreas 2007;34:390–8.
32. Carnaille B, Oudar C, Pattou F, et al. Pancreatitis and primary hyperparathyroidism: Forty cases. Aust N Z J Surg 1998;68:117–9.
33. Zagzag J, Hu MI, Fisher SB, et al. Hypercalcemia and cancer: Differential diagnosis and treatment. CA Cancer J Clin 2018;68:377–86.
34. Bess MA, Edis AJ, van Heerden JA. Hyperparathyroidism and pancreatitis: Chance or a Causal Association? JAMA 1980;243:246–7.
35. Felderbauer P, Karakas E, Fendrich V, et al. Pancreatitis in primary hyperparathyroidism-related hypercalcaemia is not associated with mutations in the CASR gene. Exp Clin Endocrinol Diabetes 2007;115: 527–9.
36. Bai HX, Giefer M, Patel M, et al. The association of primary hyperparathyroidism with pancreatitis. J Clin Gastroenterol 2012;46: 656–61.
37. Pidasheva S, D'Souza-Li L, Canaff L, et al. CASRdb: Calcium-sensing receptor locus-specific database for mutations causing familial (benign) hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, and autosomal dominant hypocalcemia. Hum Mutat 2004;24:107–11.
38. Gorvin CM, Frost M, Malinauskas T, et al. Calcium-sensing receptor residues with loss- and gain-of-function mutations are located in regions of conformational change and cause signalling bias. Hum Mol Genet 2018;27:3720–33.
39. Hannan FM, Babinsky VN, Thakker RV. Disorders of the calcium-sensing receptor and partner proteins: Insights into the molecular basis of calcium homeostasis. J Mol Endocrinol 2016;57:R127–42.
40. Felderbauer P, Karakas E, Fendrich V, et al. Pancreatitis risk in primary hyperparathyroidism: Relation to mutations in the SPINK1 trypsin inhibitor (N34S) and the cystic fibrosis gene. Am J Gastroenterol 2008; 103:368–74.
41. Wang Y, Chandra R, Samsa LA, et al. Amino acids stimulate cholecystokinin release through the Ca2+-sensing receptor. Am J Physiol Gastrointest Liver Physiol 2011;300:G528–37.
42. Xie R, Dong X, Wong C, et al. Molecular mechanisms of calcium-sensing receptor-mediated calcium signaling in the modulation of epithelial ion transport and bicarbonate secretion. J Biol Chem 2014; 289:34642–53.
43. Gao Y, Yu C, Xiang F, et al. Acute pancreatitis as an initial manifestation of parathyroid carcinoma: A case report and literature review. Medicine 2017;96:e8420.
44. Dora JM, Siqueira DR, Meyer EL, et al. Pancreatitis as the first manifestation of multiple endocrine neoplasia type 2A. Arq Bras Endocrinol Metabol 2008;52:1332–6.
45. Goldner W. Cancer-related hypercalcemia. J Oncol Pract 2016;12: 426–32.
46. Johansen CT, Kathiresan S, Hegele RA. Genetic determinants of plasma triglycerides. J Lipid Res 2011;52:189–206.
47. Ford ES, Li C, Zhao G, et al. Hypertriglyceridemia and its pharmacologic treatment among US adults. Arch Intern Med 2009;169:572–8.
48. Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis. JAMA Intern Med 2016;176:1834–42.
49. Scherer J, Singh VP, Pitchumoni CS, et al. Issues in hypertriglyceridemic pancreatitis: An update. J Clin Gastroenterol 2014;48:195–203.
50. Nawaz H, Koutroumpakis E, Easler J, et al. Elevated serum triglycerides are independently associated with persistent organ failure in acute pancreatitis. Am J Gastroenterol 2015;110:1497–503.
51. Wan J, He W, Zhu Y, et al. Stratified analysis and clinical significance of elevated serum triglyceride levels in early acute pancreatitis: A retrospective study. Lipids Health Dis 2017;16:124.
52. Rawla P, Sunkara T, Thandra KC, et al. Hypertriglyceridemia-induced pancreatitis: Updated review of current treatment and preventive strategies. Clin J Gastroenterol 2018;11:441–8.
53. Sue LY, Batech M, Yadav D, et al. Effect of serum triglycerides on clinical outcomes in acute pancreatitis: Findings from a Regional Integrated Health Care System. Pancreas 2017;46:874–9.
54. Tenner S Drug induced acute pancreatitis: Does it exist? World J Gastroenterol 2014;20:16529–34.
55. Wolthers BO, Frandsen TL, Baruchel A, et al. Asparaginase-associated pancreatitis in childhood acute lymphoblastic leukaemia: An observational Ponte di Legno Toxicity Working Group study. Lancet Oncol 2017;18:1238–48.
56. Raja RA, Schmiegelow K, Frandsen TL. Asparaginase-associated pancreatitis in children. Br J Haematol 2012;159:18–27.
57. Gerstner T, Büsing D, Bell N, et al. Valproic acid-induced pancreatitis: 16 new cases and a review of the literature. J Gastroenterol 2007;42:39–48.
58. Badalov N, Baradarian R, Iswara K, et al. Drug-induced acute pancreatitis: An evidence-based review. Clin Gastroenterol Hepatol 2007;5:648–4 e3.
59. Chung EK, Lee JH, Jang DK, et al. Causative agents of drug-induced pancreatitis: A nationwide assessment. Pancreas 2018;47:1328–36.
60. Mallory A, Kern F. Drug-induced pancreatitis: A critical review. Gastroenterology 1980;78:813–20.
61. Andersen DK, Andren-Sandberg A, Duell EJ, et al. Pancreatitis-diabetes-pancreatic cancer: Summary of an NIDDK-NCI workshop. Pancreas 2013;42:1227–37.
62. Shalimar, Midha S, Hasan A, et al. Long-term pain relief with optimized medical treatment including antioxidants and step-up interventional therapy in patients with chronic pancreatitis. J Gastroenterol Hepatol 2017;32:270–7.
63. Aseervatham GS, Sivasudha T, Jeyadevi R, et al. Environmental factors and unhealthy lifestyle influence oxidative stress in humans: An overview. Environ Sci Pollut Res Int 2013;20:4356–69.
64. Carrigan PE, Hentz JG, Gordon G, et al. Distinctive heavy metal composition of pancreatic juice in patients with pancreatic carcinoma. Cancer Epidemiol Biomarkers Prev 2007;16:2656–63.
65. Liu R, Jia T, Cui Y, et al. The protective effect of selenium on the chicken pancreas against cadmium toxicity via alleviating oxidative stress and autophagy. Biol trace Elem Res 2018;184:240–6.
66. Chen QY, DesMarais T, Costa M. Metals and mechanisms of carcinogenesis. Annu Rev Pharmacol Toxicol 2019;59:537–54.
67. Khurana V, Barkin JS. Pancreatitis induced by environmental toxins. Pancreas 2001;22:102–5.
68. Navina S, Acharya C, Delany JP, et al. Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity. Sci Transl Med 2011;3:107ra10.
69. Vipperla K, Somerville C, Furlan A, et al. Clinical profile and natural course in a large cohort of patients with hypertriglyceridemia and pancreatitis. J Clin Gastroenterol 2016;51:77–85.
70. Mohapatra S, Majumder S, Smyrk TC, et al. Diabetes mellitus is associated with an exocrine pancreatopathy: Conclusions from a review of literature. Pancreas 2016;45:1104–10.
71. Hardt PD, Krauss A, Bretz L, et al. Pancreatic exocrine function in patients with type 1 and type 2 diabetes mellitus. Acta Diabetol 2000;37: 105–10.
72. Ewald N, Kaufmann C, Raspe A, et al. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). Diabetes Metab Res Rev 2012; 28:338–42.
73. Bellin MD, Whitcomb DC, Abberbock J, et al. Patient and disease characteristics associated with the presence of diabetes mellitus in adults with chronic pancreatitis in the United States. Am J Gastroenterol 2017; 112:1457–65.
74. Hardt PD, Hauenschild A, Jaeger C, et al. High prevalence of steatorrhea in 101 diabetic patients likely to suffer from exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations: A prospective multicenter study. Dig Dis Sci 2003;48:1688–92.
75. Chari ST, Leibson CL, Rabe KG, et al. Pancreatic cancer-associated diabetes mellitus: Prevalence and temporal association with diagnosis of cancer. Gastroenterology 2008;134:95–101.
76. Sharma A, Smyrk TC, Levy MJ, et al. Fasting blood glucose levels provide estimate of duration and progression of pancreatic cancer before diagnosis. Gastroenterology 2018;155:490–500.e2.
77. Das SL, Singh PP, Phillips AR, et al. Newly diagnosed diabetes mellitus after acute pancreatitis: A systematic review and meta-analysis. Gut 2014;63:818–31.
78. Rickels MR, Bellin M, Toledo FG, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: Recommendations from PancreasFest 2012. Pancreatology 2013;13:336–42.
79. Petrov MS. Diabetes of the exocrine pancreas: American diabetes association-compliant lexicon. Pancreatology 2017;17:523–6.
80. American Diabetes A. Standards of medical care in diabetes-2018 abridged for primary care providers. Clin Diabetes 2018;36:14–37.

81. Setiawan VW, Pandol SJ, Porcel J, et al. Dietary factors reduce risk of acute pancreatitis in a large multiethnic cohort. Clin Gastroenterol Hepatol 2017;15:257–65 e3.
82. Dugum M, Gougol A, Paragomi P, et al. Association of dietary habits with severity of acute pancreatitis. Curr Dev Nutr 2018;2:nzy075.
83. Shuster A, Patlas M, Pinthus JH, et al. The clinical importance of visceral adiposity: A critical review of methods for visceral adipose tissue analysis. Br J Radiol 2012;85:1–10.
84. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: An American Heart association/national Heart, lung, and blood Institute scientific statement. Circulation 2005; 112:2735–52.
85. Sangkum L, Klair I, Limsuwat C, et al. Incorporating body-type (apple vs. pear) in STOP-BANG questionnaire improves its validity to detect OSA. J Clin Anesth 2017;41:126–31.
86. Fu J, Hofker M, Wijmenga C. Apple or pear: Size and shape matter. Cell Metab 2015;21:507–8.
87. Neeland IJ, Grundy SM, Li X, et al. Comparison of visceral fat mass measurement by dual-X-ray absorptiometry and magnetic resonance imaging in a multiethnic cohort: The Dallas Heart study. Nutr Diabetes 2016;6:e221.
88. Giefer MJ, Lowe ME, Werlin SL, et al. Early-onset acute recurrent and chronic pancreatitis is associated with PRSS1 or CTRC gene mutations. J Pediatr 2017;186:95–100.
89. Williams K, Thomson D, Seto I, et al. Standard 6: Age groups for pediatric trials. Pediatrics 2012;129(Suppl 3):S153–60.
90. Choudari CP, Imperiale TF, Sherman S, et al. Risk of pancreatitis with mutation of the cystic fibrosis gene. Am J Gastroenterol 2004;99:1358–63.
91. Ballard DD, Flueckiger JR, Fogel EL, et al. Evaluating adults with idiopathic pancreatitis for genetic predisposition: Higher prevalence of abnormal results with use of complete gene sequencing. Pancreas 2015; 44:116–21.
92. Garg PK, Khajuria R, Kabra M, et al. Association of SPINK1 gene mutation and CFTR gene polymorphisms in patients with pancreas divisum presenting with idiopathic pancreatitis. J Clin Gastroenterol 2009;43:848–52.
93. Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet 1996; 14:141–5.
94. Gorry MC, Gabbaizedeh D, Furey W, et al. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. Gastroenterology 1997;113:1063–8.
95. Fjeld K, Weiss FU, Lasher D, et al. A recombined allele of the lipase gene CEL and its pseudogene CELP confers susceptibility to chronic pancreatitis. Nat Genet 2015;47:518–22.
96. Xiao X, Jones G, Sevilla WA, et al. A carboxyl ester lipase (CEL) mutant causes chronic pancreatitis by forming intracellular aggregates that activate apoptosis. J Biol Chem 2016;291:23224–36.
97. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: Consensus guidelines from the cystic fibrosis foundation. J Pediatr 2017;181S:S4–S15 e1.
98. De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. Lancet Respir Med 2016;4:662–74.
99. LaRusch J, Jung J, General IJ, et al. Mechanisms of CFTR functional variants that impair regulated bicarbonate permeation and increase risk for pancreatitis but not for cystic fibrosis. PLoS Genet 2014;10:e1004376.
100. Rosendahl J, Landt O, Bernadova J, et al. CFTR, SPINK1, CTRC and PRSS1 variants in chronic pancreatitis: Is the role of mutated CFTR overestimated? Gut 2013;62:582–92.
101. Masson E, Chen JM, Audrezet MP, et al. A conservative assessment of the major genetic causes of idiopathic chronic pancreatitis: Data from a comprehensive analysis of PRSS1, SPINK1, CTRC and CFTR genes in 253 young French patients. PLoS One 2013;8:e73522.
102. Hegyi E, Sahin-Tóth M. Genetic risk in chronic pancreatitis: The trypsin-dependent pathway. Dig Dis Sci 2017;62:1692–701.
103. Sahin-Toth M. Genetic risk in chronic pancreatitis: The misfolding-dependent pathway. Curr Opin Gastroenterol 2017;33:390–5.
104. Petersen OH, Sutton R. Ca2+ signalling and pancreatitis: Effects of alcohol, bile and coffee. Trends Pharmacol Sci 2006;27:113–20.
105. Gerasimenko JV, Gryshchenko O, Ferdek PE, et al. Ca2+ release-activated Ca2+ channel blockade as a potential tool in antipancreatitis therapy. Proc Natl Acad Sci U S A 2013;110:13186–91.
106. Whitcomb DC, Larusch J, Krasinskas AM, et al. Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. Nat Genet 2012;44:1349–54.
107. Derikx MH, Kovacs P, Scholz M, et al. Polymorphisms at PRSS1-PRSS2 and CLDN2-MORC4 loci associate with alcoholic and non-alcoholic chronic pancreatitis in a European replication study. Gut 2015;64:1426–33.
108. Giri AK, Midha S, Banerjee P, et al. Common variants in CLDN2 and MORC4 genes confer disease susceptibility in patients with chronic pancreatitis. PLoS One 2016;11:e0147345.
109. Pereira SV, Ribeiro JD, Bertuzzo CS, et al. Association of clinical severity of cystic fibrosis with variants in the SLC gene family (SLC6A14, SLC26A9, SLC11A1 and SLC9A3). Gene 2017;629:117–26.
110. Miller MR, Soave D, Li W, et al. Variants in solute carrier SLC26A9 modify prenatal exocrine pancreatic damage in cystic fibrosis. J Pediatr 2015;166:1152–7.e6.
111. Diergaarde B, Brand R, Lamb J, et al. Pooling-based genome-wide association study implicates gamma-glutamyltransferase 1 (GGT1) gene in pancreatic carcinogenesis. Pancreatology 2010;10:194–200.
112. Brand H, Diergaarde B, O'Connell MR, et al. Variation in the gamma-glutamyltransferase 1 gene and risk of chronic pancreatitis. Pancreas 2013;42:836–40.
113. Greer JB, LaRusch J, Brand RE, et al. ABO blood group and chronic pancreatitis risk in the NAPS2 cohort. Pancreas 2011;40:1188–94.
114. Weiss FU, Schurmann C, Guenther A, et al. Fucosyltransferase 2 (FUT2) non-secretor status and blood group B are associated with elevated serum lipase activity in asymptomatic subjects, and an increased risk for chronic pancreatitis: A genetic association study. Gut 2015;64:646–56.
115. Yeo TP. Demographics, epidemiology, and inheritance of pancreatic ductal adenocarcinoma. Semin Oncol 2015;42:8–18.
116. Moulin P, Dufour R, Averna M, et al. Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): Expert panel recommendations and proposal of an "FCS score". Atherosclerosis 2018; 275:265–72.
117. Johansen CT, Wang J, Lanktree MB, et al. Excess of rare variants in genes identified by genome-wide association study of hypertriglyceridemia. Nat Genet 2010;42:684–7.
118. Nelson AS, Myers KC. Diagnosis, treatment, and molecular pathology of shwachman-diamond syndrome. Hematol Oncol Clin North Am 2018; 32:687–700.
119. Boocock GR, Morrison JA, Popovic M, et al. Mutations in SBDS are associated with Shwachman-Diamond syndrome. Nat Genet 2003;33: 97–101.
120. Rommens M, Fiedler A, Guzmán C, et al. Mutations in the human UBR1 gene and the associated phenotypic spectrum. Hum Mutat 2014;35: 521–31.
121. Zenker M, Mayerle J, Lerch MM, et al. Deficiency of UBR1, a ubiquitin ligase of the N-end rule pathway, causes pancreatic dysfunction, malformations and mental retardation (Johanson-Blizzard syndrome). Nat Genet 2005;37:1345–50.
122. Biczo G, Vegh ET, Shalbueva N, et al. Mitochondrial dysfunction, through impaired autophagy, leads to endoplasmic reticulum stress, deregulated lipid metabolism, and pancreatitis in animal models. Gastroenterology 2018;154:689–703.
123. Rotig A, Colonna M, Bonnefont JP, et al. Mitochondrial DNA deletion in Pearson's marrow/pancreas syndrome. Lancet 1989;1:902–3.
124. Munnich V, Unnikrishnan AG, Thomas V, et al. Chronic pancreatitis: A prospective nationwide study of 1,086 subjects from India. JOP 2008;9: 593–600.
125. Midha S, Khajuria R, Shastri S, et al. Idiopathic chronic pancreatitis in India: Phenotypic characterisation and strong genetic susceptibility due to SPINK1 and CFTR gene mutations. Gut 2010;59:800–7.
126. Singh G, Bhat B, Jayadev MSK, et al. mutTCPdb: a comprehensive database for genomic variants of a tropical country neglected disease-tropical calcific pancreatitis. Database (Oxford) 2018;2018.
127. Frulloni L, Bovo P, Brunelli S, et al. Elevated serum levels of antibodies to carbonic anhydrase I and II in patients with chronic pancreatitis. Pancreas 2000;20:382–8.
128. Oracz G, Cukrowska B, Kierkuś J, et al. Autoimmune markers in children with chronic pancreatitis. Prz Gastroenterol 2014;9:142–6.
129. Hardt PD, Ewald N, Brockling K, et al. Distinct autoantibodies against exocrine pancreatic antigens in European patients with type 1 diabetes mellitus and non-alcoholic chronic pancreatitis. JOP 2008;9:683–9.
130. Nahon Uzan K, Levy P, O'Toole D, et al. Is idiopathic chronic pancreatitis an autoimmune disease? Clin Gastroenterol Hepatol 2005;3:903–9.
131. Bertilsson S, Sward P, Kalaitzakis E. Factors that affect disease progression after first attack of acute pancreatitis. Clin Gastroenterol Hepatol 2015;13:1662–9 e3.

132. Ahmed Ali U, Issa Y, Hagenaars JC, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clin Gastroenterol Hepatol 2016;14:738–46.
133. LaRusch J, Lozano-Leon A, Stello K, et al. The common chymotrypsinogen C (CTRC) variant G60G (C.180T) increases risk of chronic pancreatitis but not recurrent acute pancreatitis in a North American population. Clin Transl Gastroenterol 2015;6:e68.
134. Guda NM, Muddana V, Whitcomb DC, et al. Recurrent acute pancreatitis: International state-of-the-science conference with recommendations. Pancreas 2018;47:653–66.
135. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: Revision of the atlanta classification and definitions by international consensus. Gut 2013;62:102–11.
136. Dellinger EP, Forsmark CE, Layer P, et al. Determinant-based classification of acute pancreatitis severity: An international multidisciplinary consultation. Ann Surg 2012;256:875–80.
137. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001;286:1754–8.
138. Cote GA, Yadav D, Abberbock JA, et al. Recurrent acute pancreatitis significantly reduces quality of life even in the absence of overt chronic pancreatitis. Am J Gastroenterol 2018;113:906–12.
139. Whitcomb DC. Better biomarkers for pancreatic diseases. Pancreas 2015;44:1171–3.