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Accelerating the Drug Delivery Pipeline for Acute and Chronic Pancreatitis:

Summary of the Working Group on Drug Development and Trials in Recurrent Acute Pancreatitis (RAP) at the National Institute of Diabetes and Digestive and Kidney Diseases Workshop

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Abstract

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Recurrent acute pancreatitis (RAP) is a complex clinical syndrome with significant morbidity, unpredictable outcomes and limited treatment options. The National Institute of Diabetes and Digestive and Kidney Disease sponsored a workshop on July 25, 2018 in Pittsburgh, PA to address research gaps impeding development of effective therapies for pancreatitis. The RAP working group identified challenges to clinical progress using existing definitions, risk assessment, diagnostic and severity criteria, disease trajectories, outcomes and research methods. RAP includes all the risk of acute pancreatitis (AP) and often progresses to chronic pancreatitis (CP) with variable complications of chronic pain, exocrine insufficiency, diabetes and pancreatic cancer. However, the great variability among individuals with RAP requites better precision in defining the risks, individual episodes and their frequency, pathogenic pathways and specific outcome measures for each of the systems affected by pancreatic inflammation. Because of disease complexity, few patients are similar enough for traditional studies and methods to conduct clinical trials with small sample sizes are required. The need for genetic testing, biomarker development and better imaging methods was highlighted. Adaptive and N-of-one study designs, better endpoints and outcome measures including patient reported outcomes should considered early in developing future therapeutic trial design and include all stakeholders.

Keywords

Drug trials; Pancreatitis; Patient-reported outcomes

DEFINITION AND NATURAL HISTORY OF DISEASE

"Recurrent acute pancreatitis (RAP) is a syndrome of multiple distinct acute inflammatory responses originating within the pancreas in individuals with genetic, environmental, traumatic, morphologic, metabolic, biologic, or other risk factors who experienced 2 or more episodes of documented acute pancreatitis (AP), separated by at least 3 months."[1] The patient should be symptom and complication free during the interval between episodes. Each independent episode of AP after the first episode can be described as *acute recurrent pancreatitis*. Recurrent acute pancreatitis has important health consequences. Each episode exposes the patient to the morbidity and potential mortality associated with AP. Recurrent acute pancreatitis defines a group of patients with high risk of progression to chronic pancreatitis (CP). Definitions of RAP for clinical studies should focus on the documentation necessary to diagnose AP episodes, evidence of resolution between attacks and the minimal time between attacks to define distinct episodes.

While the human pancreas normally adapts to metabolic and environmental stressors, in susceptible individuals the pancreatic defense mechanisms are overwhelmed leading to activation of trypsinogen inside the pancreas and the associated injury and inflammation result in the first episode of AP.[2–6] This first attack sensitizes the pancreas to further attacks by one or more mechanisms (Sentinel Acute Pancreatitis Event [SAPE] model).[7] Recurrent acute pancreatitis may occur when the underlying modifiable, etiological factors are not effectively managed after the SAPE, such as clearing the biliary tree of gallstones, maintaining normal triglyceride levels or abstaining from alcohol consumption.[1] Typically,

about a third of patients with AP develop RAP, indicating a need for early recognition of patients at high-risk for RAP and development of effective management plans.

Chronic pancreatitis is, by traditional definition, irreversible.[8,9] The leading international pancreas societies recently adopted “The Mechanistic Definition of CP” that addresses the pathogenic processes linking asymptomatic risk factors to end-stage chronic pancreatitis.[10] The mechanistic definition defines the traditional characteristics of CP, but also defines the *essence* of CP as “a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.”[11] The new definition is linked with a progressive model that includes AP (SAPE) and RAP as important proximal risk factors for progressing to CP. The progressive model also anticipates “Early-CP”, which *cannot* be diagnosed by traditional definitions of CP.[10,12] Thus, the process leading to CP should be detected in patients with RAP or early-CP using the mechanistic definition and a more precise and personalized approach *before* the common features of established and advanced CP emerge. Knowledge of the mechanism facilitates targeted treatment. It is also true that the new definitions of RAP[1] and CP[11] are not mutually exclusive, and *both* syndromes can be present at the same time. Based on these new conceptual and technical advances, patients with RAP should be immediately evaluated for relevant genetic, environmental and metabolic risk factors,[1,13] and etiology-based therapies should be utilized when possible.

DIAGNOSTIC CRITERIA AND IDENTIFICATION OF COMPLICATION RISKS

Recurrent acute pancreatitis requires diagnosing independent episodes of AP on two or more independent occasions. A clinical diagnosis of AP using the revised Atlanta criteria requires 2 out of 3 features: (1) upper abdominal pain with or without radiation to the back; (2) amylase and/or lipase levels ≥3 times the upper limit of normal; (3) characteristic findings of AP on an abdominal imaging study including contrast-enhanced computed tomography (CT), MRI (magnetic resonance imaging), or abdominal ultrasound.[14] These criteria can result in significant challenges for researchers who must adjudicate possible prior episodes of AP from health records. The “characteristic pain” of AP is not well defined and overlaps with the pain in other acute gastrointestinal disorders.[15] Moderate elevations of amylase and/or lipase occur in a wide range of non-pancreatic conditions.[16–19] Imaging is not required for diagnosis of mild AP, and is deemed unnecessary for clinical management in mild AP. The lack of a highly specific biomarkers for AP and inconsistent use or documentation of accepted biomarkers, including imaging, may lead to the over diagnosis, under diagnosis or missed diagnosis of AP and RAP.

Recurrent acute pancreatitis is a complex disorder, affecting the acinar cells, ducts, islets, nervous system and quality of life. The complications of RAP include those of AP and progressive identification of various complications of CP. Common complications including pseudocysts, duct strictures, exocrine pancreatic insufficiency, diabetes mellitus, chronic pain syndromes and cancer risk.[20–23] Documentation of the date and context of the onset of these complications is important for understanding the natural history of the disease, justification for initiation of new, targeted therapies and for evaluating treatment effectiveness.

GENETICS AND OPPORTUNITIES FOR GENE INTERVENTION

The major and well-established environmental risks for RAP and progression to CP are continued alcohol consumption and smoking.[24,25] A number of genetic variants contribute to the etiology of RAP, particularly in patients with early disease onset.[1,26–28] As a consequence, genetic testing has become important in the evaluation of RAP and necessary in the evaluation of cases that were previously considered idiopathic RAP. The identification of novel genes associated with risk will assist in the development of directed therapeutics, as in cystic fibrosis.[29,30] Pathogenic genetic variants in patients with RAP provide insights into mechanisms of susceptibility to future attacks and risk of progression to CP and CP-associated complications. However, since RAP and CP are largely acquired diseases, truly relevant genetic variants can only be defined within a clinical context, including specific signs, symptoms and biomarkers as they are developed.

The list of pancreatitis susceptibility genes is constantly evolving, now includes: *PRSS1–2*,[31–33] *SPINK1*,[34,35] *CTRC*,[36] *CFTR*,[37] *CASR*,[38,39] *CPA1*,[40,41] *CEL*,[42,43] *CLDN2*,[44,45] *UBR1*,[46] *SBDS*,[47] and *GGT1*.[48] Variants in *PRSS1*, *CTRC*, *SPINK1*, and *CFTR* exhibit the strongest association with RAP. *CASR* and *CLDN2* represent risk modifying genes, particularly in the presence of environmental factors, such as alcohol or tobacco use.[44,45,49] Detailed descriptions of genetic variants associated with pancreatitis can be found elsewhere.[50–52] The genetic basis for RAP also includes inherited causes of hypertriglyceridemia, such as familial chylomicronemia syndrome.[53–55] The role of genetic variants in pancreatitis now goes beyond a simple association, as seen in classic Mendelian disorders. Specific genetic variants are tied to aberrant biologic pathways: trypsin regulation, unfolded protein response, oxidative stress, ductal dysfunction, and abnormal cell signaling.[3,56] These pathogenic pathways are potential targets for novel therapies. Early genetic testing can help identify likely disease-causing pathways in an individual patient so that directed therapies can be developed to mitigate the effects of the underlying pathology rather than just providing symptomatic relief of a progressive, destructive disease. Proof-of-concept studies have already been published for RAP in cystic fibrosis patients,[57] and additional studies are needed to determine the effectiveness of existing and new therapies directed at pathways identified by broad genotyping panels within a medical context.

Functional studies to elucidate the biological effects of genetic variants on disease etiology and outcomes are critical to the development of appropriate treatment strategies, particularly studies within genes that have multiple variants coding for non-synonymous changes in amino acid sequences. The need for these studies is best understood in the trypsin-dependent pathway, particularly for variants in *PRSS1,* in which variant specific mechanisms have been described.[3,58] Uncontrolled trypsin activity is associated with the p.R112H, p.A16V, p.N29I, p.D19A, p.D21A and p.K23R variants in *PRSS1.* In contrast, a small number of rare variants in *PRSS1*: p.K92N, p.D100H, and p.L104P increase ER stress through an unmitigated unfolded protein response. A thorough understanding of disease-causing or disease-modifying genetic variants provides a ‘window’ into the mechanism and serves as a starting point for identifying treatments that act upon these pathogenic pathways.[59]

The development of variant specific *CFTR*-modulator therapies for cystic fibrosis provides an excellent example of genomic-based drug discovery.[60,61] A detailed understanding and classification of *CFTR* dysfunction was required to identify potential targets and suitable biomarkers amenable for clinical trials. In addition to advances in pulmonary health associated with *CFTR*-modulator use, there is now emerging evidence to suggest *CFTR*-modulators may also influence gastrointestinal health, namely pancreatitis. In a small case series, ivacaftor reduced the frequency and recurrence rate of pancreatitis in patients with cystic fibrosis.[57]

Additional research is required to further the understanding of variant specific associations with mechanisms of disease in RAP. Better characterization of the genotype-phenotypic correlation may permit identification of specific targets for drug development or for the application of existing drugs for evaluation in clinical trials.[59,62] Systematic approaches are required to classify patients for potential studies, and prioritize potential treatments for patients within a class. Multicenter cooperative groups are needed to identify sufficient numbers of patients to perform adequately powered studies and identify individuals who are early enough in the disease course to prevent serious outcomes. Stronger academic-industry-government cooperative partnerships are essential to accomplish these goals. Despite the significant data generation still required, the diversity of RAP etiology is uniquely positioned for application of personalized medicine to treat the underlying mechanism of disease.

DEFINITION OF ENDPOINTS AND OUTCOMES

Clinician Reported Outcomes

In order to determine whether a treatment for RAP is effective, clinically relevant biomarkers of disease activity or progression and outcomes or surrogate outcomes must be accurately and quantitatively measured over time. Important variables in RAP include frequency (number of hospitalizations and hospital readmissions), duration of hospitalizations (length of stay), disease severity (using the revised Atlanta classification) and markers of progression toward CP.[14] While some components of these outcome measures are accurately measured (e.g., development of acute kidney injury), others (e.g., length of stay) may be influenced by non-biologic factors such as comorbidities unrelated to pancreatic disease, socioeconomic factors and physician practice patterns. The frequency of RAP may be affected by detection bias, as physicians differ on the threshold to perform laboratory tests in milder cases, or making a diagnosis without abdominal imaging, an objective biomarker of AP. Finally, measuring episode frequency (e.g., incidence rate ratio as the # episodes/time following an intervention ÷ # of episodes/time prior to intervention) is quantitative and objective, but requires accurate and long-term follow-up without other clinical interventions that could impact natural history. Thus, the disease definition, measurements, follow-up, and blinding present significant challenges when designing clinical trials.

Recurrent acute pancreatitis includes the pathology of each episode of AP and risk of developing CP with, roughly 10–20% of patients with RAP progress to CP within 3–5 years.[63] Progression from RAP to CP damages each of the specialized cells in the pancreas to

various degrees and at dissimilar rates in different patients. Clinically important outcomes include loss of exocrine function (exocrine pancreatic insufficiency (EPI), endocrine dysfunction (diabetes mellitus), progressive fibrosis, development of various pain syndromes and dysplasia with increased risk of pancreatic cancer. Although fibrosis, inflammation, loss of parenchymal tissue and dysplasia can be measured in tissue samples, core biopsies of the pancreas are technically difficult, have variable sensitivity and possess significant risk of iatrogenic pancreatitis and other complications. Abdominal imaging serves as a surrogate for tissue histology and includes CT, magnetic resonance imaging with cholangiopancreatography,[64,65] and endoscopic ultrasound (EUS), which is highly sensitive but less specific due to high intra- and inter-observer variability, and non-CP fibrosis.[66,67]

Imaging alone is a poor predictor of pancreatic function, especially in RAP or the early stages of CP.[10] Exocrine function can be measured quantitatively using a direct or indirect pancreatic function test. For example, an endoscopic pancreatic function test (ePFT), which directly measures the secretin-stimulated duct cell production of bicarbonate in the duodenum, can distinguish mild and severe chronic pancreatitis and can be combined with EUS to independently evaluate the extent of fibrosis.[68,69] However, the ePFT is time and labor intensive and performed infrequently in clinical practice. Its value in clinical practice remains unclear. Highly sensitive, reliable, and noninvasive measures of pancreatic exocrine function are still needed.

Imaging methods serve as surrogates of fibrosis but do not measure disease activity. Sensitive and specific biomarker panels to detect early inflammatory and fibrotic processes in the pancreas are needed. Potential sources include endoscope-based specimen collection for measurement of desmoplasia-associated extracellular matrix, growth factors, and inflammatory factors.[70,71] Pancreatic fluid cytokine levels may discriminate chronic pancreatitis from milder disease and pancreatic cancer from normal pancreas.[72,73] Glucose intolerance and pancreatogenic diabetes (Type 3c) resulting from compromised B-cell function can be measured by serial fasting glucose levels, HbA1c or glucose tolerance tests as markers of disease status and progression.[74,75] Validation of biomarker panels will require longitudinal cohorts with long-term follow-up, since many sequelae of acute pancreatitis are rare and delayed in their clinical manifestation.

Patient Reported Outcomes

Patient reported outcomes (PROs) refer to “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or someone else”.[76] Instruments to capture PROs range from single item symptom ratings to complex, multidimensional, health-related quality of life measures (Table 1). Disease-specific rather than generic instruments are typically more sensitive to changes and therefore better suited for use as endpoints in clinical trials and to potentially support a labeling claim.[76]

Patient reported outcomes may be considered as secondary endpoints in clinical trials of interventions aimed at modifying the natural history of RAP, whereas PROs may be considered as primary endpoints in studies aimed at modifying symptoms of RAP. While investigators have developed an instrument to measure PROs in chronic pancreatitis

(Pancreatitis Quality of Life Instrument; PANQOLI),[77,78] no such instruments exist for RAP. Developing and validating new instruments for RAP may be challenging due to the relatively low prevalence of the condition and heterogeneity of the patient population, which includes children, adolescents, and adults. Adapting existing instruments may be more feasible, and minor changes in wording may not necessitate full psychometric validation.

The episodic and erratic incidence of pancreatitis in RAP poses a challenge for ascertaining PROs. Daily diary assessments of symptoms and other aspects of quality of life may be needed to capture data for endpoints; event-driven reporting is an alternative but may be more challenging to implement. There is precedent for intensive ascertainment of intermittent symptoms in the sickle cell disease literature, where investigators have implemented daily reporting of PROs-- including pain, medication use, and health care utilization--averaged over two-week intervals.[79,80] Electronic data capture can facilitate this intensive reporting.

Other relevant, easily quantified endpoints such as missed days of school/work and use of analgesic and anti-emetic medications are relevant to families and patients. Investigators should also consider assessing the impact of RAP on family members and caregivers. Several instruments have been validated in other settings to ascertain the effects of a child's chronic illness on parents and other family members.[81,82] There are limitations to these measures since multiple factors may alter these outcomes and they may not directly reflect clinical benefit on the underlying disease process.

SUBJECT SELECTION FOR DRUG TRIALS AND LENGTH OF TREATMENT

Since recurrent acute pancreatitis is a syndrome with variable clinical manifestations, enrollment criteria, outcome measures, and follow-up intervals for intervention trials are interdependent.[83] These factors must be tailored to the study intervention and balance the need to optimize the study's internal and external validity.

Relationship Between Enrollment Criteria and Outcomes

The most stringent definition of acute pancreatitis requires the presence of clinical signs and symptoms along with specific radiographic manifestations. However, a substantial number of patients may have pancreatitis-type symptoms and only biochemical signs and cross sectional imaging may not be performed or be inadequate to detect mild changes.[18] At a minimum, a patient's biochemical signs, typically defined as a minimum three-fold elevation in serum lipase, amylase, or both, should accompany clinical symptoms on at least one occasion. In these cases, there should be documentation of normalization in serum amylase/lipase, to minimize the likelihood of alternate etiologies for the aberrant lab tests.[18] The most challenging patients are those who do not seek urgent medical attention but have consistent symptomatology that results in short-term disability. Although these events are measurable, some objective signs of acute pancreatitis must precede study enrollment in order to avoid confounding etiologies for pancreatitis-type abdominal pain.

In choosing the study enrollment criteria, the investigators must carefully consider their outcome measure(s). For example, if the intervention is hypothesized to prevent an episode

of acute pancreatitis defined radiographically, then patients with one or more antecedent episodes of acute pancreatitis having radiographic manifestations may be clinically relevant for enrollment in a trial. On the other hand, if the primary outcome relates to one or more PROs, the enrollment criteria and baseline assessment should require a quantitative assessment of PROs; in theory, such a study could have a less stringent definition of acute pancreatitis at baseline and during follow-up.

Length of Treatment and Follow-up

Most clinician reported outcome measures pertaining to RAP are time-dependent: longer follow-up will capture more events, whereas short-term follow-up is susceptible to type II statistical error. If a pharmacological agent is predicted to delay or prevent progression to overt chronic pancreatitis, patients who are likely to be amenable to long-term follow-up will be suitable for enrollment since the development of chronic pancreatitis may take years to develop. On the other hand, an intervention that is hypothesized to reduce the risk of subsequent acute pancreatitis – a time dependent outcome that may occur at any time – will require subjects who are available for long-term follow-up may only be required since the number of outcomes expected during a period of observation may be low. PROs may be measured at a pre-defined, short-term endpoint, but such studies will be limited by the issues outlined above. The same applies to physiological measures of inflammation and fibrosis, such as pancreatic cytokine panels; while these are more sensitive than clinical outcomes, the ideal pancreatitis biomarker panel will have consistent diagnostic and prognostic implications for patient care.

Single Subject or N = 1 Studies

There is a role for single subject or N-of-1 studies in RAP given its idiosyncrasies, complex pathobiology, and diverse clinical presentations. Unlike traditional population-based randomized controlled trials, which focus on average responses to an experimental and comparator intervention and essentially ignore inter (and intra) individual variability in response and the factors that may contribute to that variability, N-of-1 and aggregated N-of-1 trials focus on individual responses to an experimental intervention.[84] They are therefore more appropriate for testing ‘precision,’ ‘personalized’ or ‘individualized’ medicines. N-of-1 trials can exploit all the statistical technology leveraged in population-based randomized controlled trials, such as blinding, randomization, the use of washout periods and placebo controls.[85,86] They typically involve simple multiple cross-over designs in which an individual patient is provided an experimental intervention and then purposely provided a comparator intervention, and derive their power from the number of, and contexts in which, response measures are made while the patient is on and off the experimental intervention. N-of-1 trials can also leverage sequential testing of response without a comparator or placebo control by establishing ‘personal baselines’ or ‘personal thresholds’ derived from measures collected prior to providing the experimental intervention to a patient and determining if the experimental intervention exhibits an effect that deviates in a statistically significant way from the personal baseline values. They can also be aggregated so that patterns in response profiles can be explored, possibly to identify a factor or covariate (such as genotype) that can distinguish unequivocal responders and non-responders based on

the individual N-of-1 trial outcomes. Essential to N-of-1 trials are appropriate measures of response that can be collected in an efficient and cost-effective way.

REGULATORY ISSUES

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well-controlled trials to obtain marketing approval. Adequate and well controlled trials generally include a clear statement of objectives, appropriate control for comparison, selection of patients with the disease or who are at risk of developing the disease, methods to minimize bias, methods for assessment of response, and methods of analysis. A goal of a development program is to demonstrate the clinical benefit of the therapy on a meaningful aspect of how a patient feels, functions, or survives as a result of treatment. There are a variety of methods that can be proposed for use in clinical trial(s) to measure a clinical benefit including PROs. Many considerations factor into designing a clinical trial intended to support product approval and labeling. Early planning in the drug development process and collaboration with all stakeholders are critical to meet challenges associated with defining appropriate efficacy endpoints and outcome measurement.

GAPS IN KNOWLEDGE

There is a need to:

- Develop a uniform algorithm for subject definition to limit bias in identifying participants for trials.
- Develop sensitive, specific, quantitative biomarkers and imaging techniques to identify patients with RAP who will progress to CP, to stage disease, to identify complications, and to measure response to intervention.
- Improve understanding of RAP’s complex pathogenesis including deeper understanding of the multiple genetic risk variants, environmental, metabolic or toxic risk factors in various combinations.
- Define cellular expression patterns of genetic risk variants and how they impact cellular physiology.
- Delineate critical metabolic and cell-signaling pathways such as cell-death pathways and the inflammatory responses that are activated by various risk factors.
- Facilitate trial development by identifying targetable pathogenic pathways including those regulating inflammation and fibrosis.
- Improve and develop experimental models for recapitulating human disease. Mouse models rarely reproduce human disease and are prohibitively expensive and time-consuming for testing the growing number of low frequency genetic risk variants. Mathematical models offer promise, but these must be calibrated with accurate data from human subjects with known etiologies, disease stages and outcomes. Although investigators have progressed in directed differentiation

of human pluri-potent stem cells into pancreatic acinar cells as monolayers or organoids, these models are incompletely characterized and validated.[87] Further work on robust, reproducible methods to differentiate stem cells from patients into stable pancreatic acini is needed. Since RAP is a systemic disease, stem cell technology is not enough and appropriate animal models are still needed.

- Develop validated instruments to capture relevant patient reported outcomes that can be used as primary or secondary endpoints in trials.
- Develop novel, innovative approaches to clinical trials with small numbers of subjects.

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Abbreviations:

AP	acute pancreatitis
CP	Chronic pancreatitis
CT	computed tomography
EPI	Endocrine pancreatic insufficiency
ePFT	Endoscopic pancreatic function test
EUS	Endoscopic Ultrasound
ER	Endoplasmic reticulum
MRI	Magnetic resonance imaging
PROs	Patient reported outcomes
RAP	recurrent acute pancreatitis
SAPE	Sentinel acute pancreatitis event

REFERENCES

1. Guda NM, Muddana V, Whitcomb DC, et al. Recurrent Acute Pancreatitis: International State-of-the-Science Conference With Recommendations. *Pancreas*. 2018;47:653–666. [PubMed: 29894415]
2. Gukovskaya AS, Pandol SJ, Gukovsky I. New insights into the pathways initiating and driving pancreatitis. *Curr Opin Gastroenterol*. 2016;32:429–435.

3. Hegyi E, Sahin-Tóth M. Genetic Risk in Chronic Pancreatitis: The Trypsin-Dependent Pathway. *Dig Dis Sci*. 2017;62:1692–1701. [PubMed: 28536777]
4. Pandol SJ, Gorelick FS, Lugea A. Environmental and genetic stressors and the unfolded protein response in exocrine pancreatic function - a hypothesis. *Front Physiol*. 2011;2:8. [PubMed: 21483727]
5. Sah RP, Garg SK, Dixit AK, et al. Endoplasmic reticulum stress is chronically activated in chronic pancreatitis. *J Biol Chem*. 2014;289:27551–27561. [PubMed: 25077966]
6. Sahin-Tóth M Genetic risk in chronic pancreatitis: the misfolding-dependent pathway. *Curr Opin Gastroenterol*. 2017;33:390–395. [PubMed: 28650851]
7. Vipperla K, Papachristou GI, Easler J, et al. Risk of and factors associated with readmission after a sentinel attack of acute pancreatitis. *Clin Gastroenterol Hepatol*. 2014;12:1911–1919. [PubMed: 24815327]
8. Sarner M, Cotton PB. Classification of pancreatitis. Gut. 1984;25:756–759. [PubMed: 6735257]
9. Singer MV, Gyr K, Sarles H. Revised classification of pancreatitis. Report of the Second International Symposium on the Classification of Pancreatitis in Marseille, France, March 28–30, 1984. Gastroenterology. 1985;89:683–685. [PubMed: 4018507]
10. 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 5 21. [Epub ahead of print].
11. Whitcomb DC, Frulloni L, Garg P, et al. Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition. Pancreatology. 2016;16:218–224. [PubMed: 26924663]
12. Whitcomb DC. Peering Into the “Black Box” of the Complex Chronic Pancreatitis Syndrome. Pancreas. 2016;45:1361–1364. [PubMed: 27748718]
13. Etemad B, Whitcomb DC. Chronic pancreatitis: Diagnosis, classification, and new genetic developments. Gastroenterology. 2001;120:682–707. [PubMed: 11179244]
14. 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;62:102–111. [PubMed: 23100216]
15. Olesen SS, Krauss T, Demir IE, et al. Towards a neurobiological understanding of pain in chronic pancreatitis: mechanisms and implications for treatment. *Pain Rep*. 2017;2:e625. [PubMed: 29392239]
16. Cohen J, MacArthur KL, Atsawarungruangkit A, et al. Defining the diagnostic value of hyperlipasemia for acute pancreatitis in the critically ill. Pancreatology. 2017;17:176–181. [PubMed: 28237616]
17. Hameed AM, Lam VW, Pleass HC. Significant elevations of serum lipase not caused by pancreatitis: a systematic review. HPB (Oxford). 2015;17:99–112. [PubMed: 24888393]
18. Rompianesi G, Hann A, Komolafe O, et al. Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis. *Cochrane Database Syst Rev*. 2017;4:CD012010.
19. Steinberg WM, Nauck MA, Zinman B, et al. LEADER 3--lipase and amylase activity in subjects with type 2 diabetes: baseline data from over 9000 subjects in the LEADER Trial. Pancreas. 2014;43:1223–1231. [PubMed: 25275271]
20. 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;113:906–912. [PubMed: 29867178]
21. Das SL, Singh PP, Phillips AR, et al. Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. Gut. 2014;63:818–831. [PubMed: 23929695]
22. Shelton CA, Umapathy C, Stello K, et al. Hereditary Pancreatitis in the United States: Survival and Rates of Pancreatic Cancer. *Am J Gastroenterol*. 2018 7 18. [Epub ahead of print].
23. Yadav D, O’Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. *Am J Gastroenterol*. 2012;107:1096–1103. [PubMed: 22613906]

24. Coté 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*. 2011;9:266–273; quiz e27. [PubMed: 21029787]
25. Takeyama Y Long-term prognosis of acute pancreatitis in Japan. *Clin Gastroenterol Hepatol*. 2009;7(11 Suppl):S15–S17.
26. 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. [PubMed: 28502372]
27. Jalaly NY, Moran RA, Fargahi F, et al. An Evaluation of Factors Associated With Pathogenic PRSS1, SPINK1, CTFR, and/or CTRC Genetic Variants in Patients With Idiopathic Pancreatitis. *Am J Gastroenterol*. 2017;112:1320–1329. [PubMed: 28440306]
28. Kumar S, Ooi CY, Werlin S, et al. Risk Factors Associated With Pediatric Acute Recurrent and Chronic Pancreatitis: Lessons From INSPPIRE. *JAMA Pediatr*. 2016;170:562–569. [PubMed: 27064572]
29. Paranjape SM, Mogayzel PJ, Jr. Cystic fibrosis in the era of precision medicine. *Paediatr Respir Rev*. 2018;25:64–72. [PubMed: 28372929]
30. Spielberg DR, Clancy JP. Cystic Fibrosis and Its Management Through Established and Emerging Therapies. *Annu Rev Genomics Hum Genet*. 2016;17:155–175. [PubMed: 26905785]
31. Santhosh S, Witt H, te Morsche RH, et al. A loss of function polymorphism (G191R) of anionic trypsinogen (PRSS2) confers protection against chronic pancreatitis. Pancreas. 2008;36:317–320. [PubMed: 18362849]
32. Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat Genet*. 1996;14:141–145. [PubMed: 8841182]
33. Witt H, Sahin-Tóth M, Landt O, et al. A degradation-sensitive anionic trypsinogen (PRSS2) variant protects against chronic pancreatitis. *Nat Genet*. 2006;38:668–673. [PubMed: 16699518]
34. Pfützer RH, Barmada MM, Brunskill AP, et al. SPINK1/PSTI polymorphisms act as disease modifiers in familial and idiopathic chronic pancreatitis. Gastroenterology. 2000;119:615–623. [PubMed: 10982753]
35. Witt H, Luck W, Hennies HC, et al. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. *Nat Genet*. 2000;25:213–216. [PubMed: 10835640]
36. Masson E, Chen JM, Scotet V, et al. Association of rare chymotrypsinogen C (CTRC) gene variations in patients with idiopathic chronic pancreatitis. *Hum Genet*. 2008;123:83–91. [PubMed: 18172691]
37. Sharer N, Schwarz M, Malone G, et al. Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. *N Engl J Med*. 1998;339:645–652. [PubMed: 9725921]
38. Muddana V, Lamb J, Greer JB, et al. Association between calcium sensing receptor gene polymorphisms and chronic pancreatitis in a US population: role of serine protease inhibitor Kazal 1type and alcohol. *World J Gastroenterol*. 2008;14:4486–4491. [PubMed: 18680227]
39. Murugaian EE, Ram Kumar RM, Radhakrishnan L, et al. Novel mutations in the calcium sensing receptor gene in tropical chronic pancreatitis in India. *Scand J Gastroenterol*. 2008;43:117–121. [PubMed: 18938753]
40. Witt H, Beer S, Rosendahl J, et al. Variants in CPA1 are strongly associated with early onset chronic pancreatitis. Nat Genet. 2013;45:1216–1220. [PubMed: 23955596]
41. Wood NJ. Genetics: Global role for CPA1 variants in the pathogenesis of chronic pancreatitis. *Nat Rev Gastroenterol Hepatol*. 2013;10:567.
42. 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;47:518–522. [PubMed: 25774637]
43. Ragvin A, Fjeld K, Weiss FU, et al. The number of tandem repeats in the carboxyl-ester lipase (CEL) gene as a risk factor in alcoholic and idiopathic chronic pancreatitis. Pancreatology. 2013;13:29–32. [PubMed: 23395566]

44. 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;64:1426–1433. [PubMed: 25253127]
45. 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 12 2012;44:1349–1354. [PubMed: 23143602]
46. Sukalo M, Fiedler A, Guzman C, et al. Mutations in the human UBR1 gene and the associated phenotypic spectrum. *Hum Mutat*. 2014;35:521–531. [PubMed: 24599544]
47. Kayed H, Bekasi S, Keleg S, et al. Expression of the Shwachman-Bodian-Diamond syndrome (SBDS) protein in human pancreatic cancer and chronic pancreatitis. *Histol Histopathol*. 2008;23:819–826. [PubMed: 18437680]
48. Brand H, Diergaarde B, O'Connell MR, et al. Variation in the gamma-glutamyltransferase 1 gene and risk of chronic pancreatitis. Pancreas. 2013;42:836–840. [PubMed: 23462328]
49. Aghdassi AA, Weiss FU, Mayerle J, et al. Genetic susceptibility factors for alcohol-induced chronic pancreatitis. Pancreatology. 2015;15(4 Suppl):S23–S31. [PubMed: 26149858]
50. LaRusch J, Solomon S, Whitcomb DC. Pancreatitis Overview In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews((R)). Seattle, WA: University of Washington;1993.
51. LaRusch J, Whitcomb DC. Genetics of pancreatitis. *Curr Opin Gastroenterol*. 2011;27:467–474. [PubMed: 21844754]
52. Zator Z, Whitcomb DC. Insights into the genetic risk factors for the development of pancreatic disease. *Therap Adv Gastroenterol*. 2017;10:323–336.
53. Brahm AJ, Hegele RA. Chylomicronaemia--current diagnosis and future therapies. *Nat Rev Endocrinol*0 2015;11:352–362.
54. Chait A, Subramanian S, Brunzell JD. Genetic Disorders of Triglyceride Metabolism In: De Groot LJ, Chrousos G, Dungan K, et al., eds. Endotext. South Dartmouth, MA: MDText.com; 2000.
55. Ueda M, Dunbar RL, Wolska A, et al. A Novel APOC2 Missense Mutation Causing Apolipoprotein C-II Deficiency With Severe Triglyceridemia and Pancreatitis. J Clin Endocrinol Metab. 2017;102:1454–1457. [PubMed: 28201738]
56. Weiss FU, Skube ME, Lerch MM. Chronic pancreatitis: an update on genetic risk factors. Curr Opin Gastroenterol. 2018;34:322–329. [PubMed: 29901518]
57. Carrion A, Borowitz DS, Freedman SD, et al. Reduction of Recurrence Risk of Pancreatitis in Cystic Fibrosis With Ivacaftor: Case Series. J Pediatr Gastroenterol Nutr. 2018;66:451–454. [PubMed: 29045347]
58. Szabo A, Sahin-Toth M. Increased activation of hereditary pancreatitis-associated human cationic trypsinogen mutants in presence of chymotrypsin C. J Biol Chem. 2012;287:20701–20710. [PubMed: 22539344]
59. Dugger SA, Platt A, Goldstein DB. Drug development in the era of precision medicine. Nat Rev Drug Discov. 2018;17:183–196. [PubMed: 29217837]
60. Clancy JP, Cotton CU, Donaldson SH, et al. CFTR modulator theratyping: Current status, gaps and future directions. J Cyst Fibros. 2018 6 19. [Epub ahead of print].
61. Ong T, Ramsey BW. New Therapeutic Approaches to Modulate and Correct Cystic Fibrosis Transmembrane Conductance Regulator. Pediatr Clin North Am. 2016;63:751–764. [PubMed: 27469186]
62. Finan C, Gaulton A, Kruger FA, et al. The druggable genome and support for target identification and validation in drug development. Sci Transl Med. 2017;9 pii: eaag1166. [PubMed: 28356508]
63. Coté GA, Imperiale TF, Schmidt SE, et al. Similar efficacies of biliary, with or without pancreatic, sphincterotomy in treatment of idiopathic recurrent acute pancreatitis. Gastroenterology. 2012;143:1502–1509.e1. [PubMed: 22982183]
64. Sandrasegaran K, Tahir B, Barad U, et al. The Value of Secretin-Enhanced MRCP in Patients With Recurrent Acute Pancreatitis. AJR Am J Roentgenol. 2017;208:315–321. [PubMed: 27824485]
65. Sherman S, Freeman ML, Tarnasky PR, et al. Administration of secretin (RG1068) increases the sensitivity of detection of duct abnormalities by magnetic resonance cholangiopancreatography in patients with pancreatitis. Gastroenterology. 2014;147:646–654.e2. [PubMed: 24906040]

66. Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. Gastrointest Endosc. 2009;69:1251–1261. [PubMed: 19243769]

67. Stevens T, Lopez R, Adler DG, et al. Multicenter comparison of the interobserver agreement of standard EUS scoring and Rosemont classification scoring for diagnosis of chronic pancreatitis. Gastrointest Endosc. 2010;71:519–526. [PubMed: 20189510]

68. Albashir S, Bronner MP, Parsi MA, et al. Endoscopic ultrasound, secretin endoscopic pancreatic function test, and histology: correlation in chronic pancreatitis. Am J Gastroenterol. 2010;105:2498–2503. [PubMed: 20606675]

69. Conwell DL, Lee LS, Yadav D, et al. American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: evidence-based report on diagnostic guidelines. Pancreas. 2014;43:1143–1162. [PubMed: 25333398]

70. Apte MV, Wilson JS, Lugea A, et al. A starring role for stellate cells in the pancreatic cancer microenvironment. Gastroenterology. 2013;144:1210–1219. [PubMed: 23622130]

71. Castellanos JA, Merchant NB, Nagathihalli NS. Emerging targets in pancreatic cancer: epithelial-mesenchymal transition and cancer stem cells. Onco Targets Ther. 2013;6:1261–1267. [PubMed: 24049451]

72. Noh KW, Pungpapong S, Wallace MB, et al. Do cytokine concentrations in pancreatic juice predict the presence of pancreatic diseases? Clin Gastroenterol Hepatol. 2006;4:782–789. [PubMed: 16713745]

73. Paulo JA, Lee LS, Wu B, et al. Cytokine profiling of pancreatic fluid using the ePFT collection method in tandem with a multiplexed microarray assay. J Immunol Methods. 2011;369:98–107. [PubMed: 21569776]

74. Coté GA, Xu H, Easler JJ, et al. Informative Patterns of Health-Care Utilization Prior to the Diagnosis of Pancreatic Ductal Adenocarcinoma. Am J Epidemiol. 2017;186:944–951. [PubMed: 28541521]

75. Pan XF, He M, Yu C, et al. Type 2 Diabetes and Risk of Incident Cancer in China: A Prospective Study Among 0.5 Million Chinese Adults. Am J Epidemiol. 2018;187:1380–1391. [PubMed: 29304221]

76. U.S.Department of Health and Human Services Food and Drug Administration. Guidance for Industry. Patient-reported outcome measures: use in medical product development to support labeling claims. 2009; https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf. Accessed June 27, 2018.

77. Wassef W, Bova C, Barton B, et al. Pancreatitis Quality of Life Instrument: Development of a new instrument. SAGE Open Med. 2014;2:2050312114520856.

78. Wassef W, DeWitt J, McGreevy K, et al. Pancreatitis Quality of Life Instrument: A Psychometric Evaluation. Am J Gastroenterol. 2016;111:1177–1186. [PubMed: 27296943]

79. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med. 1995;332(:1317–1322. [PubMed: 7715639]

80. Smith WR, Ballas SK, McCarthy WF, et al. The association between hydroxyurea treatment and pain intensity, analgesic use, and utilization in ambulatory sickle cell anemia patients. Pain Med. 2011;12:697–705. [PubMed: 21481164]

81. Eccleston C, Crombez G, Scotford A, et al. Adolescent chronic pain: patterns and predictors of emotional distress in adolescents with chronic pain and their parents. Pain. 2004;108:221–229. [PubMed: 15030941]

82. Van Slyke DA, Walker LS. Mothers' responses to children's pain. Clin J Pain. 2006;22:387–391. [PubMed: 16691093]

83. Romagnuolo J, Guda N, Freeman M, et al. Preferred designs, outcomes, and analysis strategies for treatment trials in idiopathic recurrent acute pancreatitis. *Gastrointest Endosc*. 2008;68:966–974. [PubMed: 18725158]

84. Schork NJ, Goetz LH. Single-Subject Studies in Translational Nutrition Research. *Annu Rev Nutr*. 2017;37:395–422. [PubMed: 28715990]

85. Deaton A, Cartwright N. Reflections on Randomized Control Trials. *Soc Sci Med*. 4 28 2018.

86. Schork NJ. Randomized clinical trials and personalized medicine: A commentary on deaton and cartwright. *Soc Sci Med*. 2018;210:86–90. [PubMed: 29731150]

87. Hohwieler M, Illing A, Hermann PC, et al. Human pluripotent stem cell-derived acinar/ductal organoids generate human pancreas upon orthotopic transplantation and allow disease modelling. Gut. 2017;66:473–486. [PubMed: 27633923]

TABLE 1.

Examples of Patient Reported Outcome Instruments for Use in or Adaptation for Clinical Trials of Recurrent Acute Pancreatitis

Generic		Pancreas-Specific
Single Item	**Multidimensional**	**Multidimensional**
Visual analogue scale for pain	Patient-Reported Outcomes Measurement Information System (PROMIS)	Pancreatitis Quality of Life Instrument (PANQOLI) (chronic pancreatitis)
11-point pain scale	Pediatric Quality of Life Inventory (Peds QL)	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Pancreatic Modification (EORTC QLQ-PAN28(CP)) (pancreatic cancer module adapted for chronic pancreatitis)
Faces pain scale	Child Activity Limitations Interview (CALI); CALI-21	
	Bath Adolescent Pain Questionnaire (BAPQ)	
	Adult Responses to Children's Symptoms (ARC)	
	Bath Adolescent Pain-Parent Impact Questionnaire (BAP-PIQ)	
	Brief Pain Inventory short form	
	Pain Disability Index	
	McGill Pain Questionnaire	
	Revised Children's Anxiety and Depression Scale (RCADS)	
	Children's Depression Inventory (CDI)	
	Functional Disability Inventory (FDI)	