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Genetics and Treatments Options for Recurrent Acute and Chronic Pancreatitis

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Opinion Statement

Worldwide research efforts demonstrate a major role of gene-environment interactions for the risk, development, and progression of most pancreatic diseases, including recurrent acute and chronic pancreatitis. New findings of pancreas disease-associated risk variants have been reported in the *CPA1*, *GGT1*, *CLDN2*, *MMP1*, *MTHFR*, and other genes. These risk genes and their regulatory regions must be added to the known pathogenic variants in the *PRSSI*, *SPINK1*, *CFTR*, *CTRC*, *CASR*, *UBR1*, *SBDS*, *CEL*, and *CTSB* genes. This new knowledge promises to improve disease management and prevention through personalized medicine. At the same time, however, knowledge of an increasing number of pathogenic variants, and their complicated effects when present in combination, results in increasing difficulty in interpretation and development of recommendations. Direct-to-consumer marketing of genetic testing results also adds complexity to disease management paradigms, especially without interpretation and, in many cases, proven accuracy. While improvements in the ability to rapidly and accurately interpret complex genetic tests are clearly needed, some results, such as pathogenic *CFTR* variants – including a new class of bicarbonate-defective mutations – and *PRSSI* variants have immediate implications that direct management. In addition, discovery of pancreatitis-associated genetic variants in patients with glucose intolerance may suggest underlying type 3c diabetes, which also has implications for treatment and disease management.

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Human and Animal Rights and Informed Consent

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Keywords

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Introduction

Historically, it was assumed that acute pancreatitis was almost always caused by gallstones, and chronic pancreatitis by alcoholism. These simple, concrete causations exemplify the germ theory of disease, where a single factor causes a complex disease syndrome. In practice, however, it is clear that gallstones and alcohol are not always the proximal cause of pancreatitis. Furthermore, the clinical syndrome has unpredictably severity, duration, complications, and outcomes. Although studies have identified additional factors in the development of pancreatitis, it is clear that there are missing variables. Given that multiple variables affect each individual patient, how can the care and management of individual patients be accomplished?

Genetic susceptibility to pancreatitis and modification of the disease course by other genetic and environmental interactions plays a major role in the onset, severity, involvedness, and outcome of human pancreatic disease. Genetic tests differ from common medical tests used to evaluate pancreatic disease, such as measuring biomarkers (e.g., amylase, lipase), biopsies, or abdominal imaging tests. Such tests reveal structural changes or measure variable processes that are evaluated as indicators of normal biological, pathogenic, or pharmacologic responses to a therapeutic intervention [1]. Alternatively, genetic tests provide insights into the cellular blueprint that determines the molecular components that will be available for use under normal and abnormal conditions, as well as their functional qualities.

In most cases, adult pancreatic disease is not the result of abnormal pancreatic development. Rather, it is a disruption of the normal state of physiological function by stress or injury, with or without a failure to fully return to the normal state. For a given amount of stress or injury, pathogenic genetic variants disrupt optimal adaptation to stress, response to injury, regeneration, and/or post-injury return to the normal state. Thus, in pancreatic disease, biomarkers are most useful in determining the current state of function or dysfunction. On the other hand, genetics is useful in determining which underlying molecules or pathways are likely to function normally or abnormally in the current context as well as predicting which systems are most likely to respond normally or abnormally in the future. As such, optimal care must go beyond excluding gallstones and alcohol as the causative factor. Attention must be given to risk of recurrent acute pancreatitis (RAP), complications of altered anatomy (e.g., pancreatic necrosis, fluid collections), pathogenic persistence of inflammation and consequent fibrosis, atrophy, pain syndromes, diabetes mellitus (Type 3c) [2**], altered metabolism and nutrition, and cancer risk, all of which define chronic pancreatitis (CP).

As the conceptual framework and new methods of evaluating complex pancreatic diseases are being developed, there are economic, legal, and political forces that are changing the way complex medical conditions such as RAP and CP are evaluated and managed. Repeated use of abdominal imaging and function testing to diagnose and manage pancreatic diseases is expensive, potentially dangerous (ERCP, EUS with biopsy, radiation exposure) or insensitive, and provides information on severity of damage rather than etiology and prognosis. Large pancreatitis cohort studies such as the North American Pancreatitis Study II (NAPS2) [3] have established the complexity of RAP and progression to CP through the interaction of multiple genetic and environmental factors [4, 5]. The challenge is that complex genetics is complex, and busy physicians cannot easily keep up with all of the nuances and implications of various combinations of factors, their implications for other family members, and their prognostic implications for medical decision-making. Furthermore, the cost of genetic testing can be high, and insurance companies often refuse coverage of established tests by considering them “experimental.” In the case of individuals who wish to obtain genetic testing without a health professional intermediary, there have been restrictions placed on direct-to-consumer (DTC) genetic testing in some instances due to lack of proven analytic validity and concern for improper or potentially harmful self-care.

While it is clear that genetic evaluation of patients with early pancreatic disease will become increasingly important, the methods of obtaining the required genetic data and interpreting individual results have not been adequately defined. What is the state of the field, and what will be important in the future?

New pancreatitis disease genes

The list of genes with risk or protective variants associated with pancreatitis continues to grow. Based on data from extensive study and multiple replications, the primary risk genes include *PRSSI*, *CFTR*, *SPINK1*, and *CTRC* [4–7]. Additional genes with risk for pancreatic disease syndromes include *UBR1* [8], *SBDS* [9], and *CEL* [10]. Pancreatitis risk genes that have been reported but that are less well-studied include *MCPI* [11], *TNFA* [12], and *CTSB* [13]. Recently described genes include *CLDN2* [14], *CPA1* [15**], *GGT1* [16], *MYO9B* [17], *MMPI* [18], and *MTHFR* [19]. Among these genes there are multiple layers of complexity, variable replication among different populations, questions about gene-gene and gene-environmental interactions, and other debates.

The important role of key genes such as *PRSSI*, *CFTR*, and *SPINK1* are well-established [6, 20–22]. One of the most recent and exciting developments is the recognition that cystic fibrosis can be divided into two diseases. The first is the traditional severe syndrome with early onset and progressive dysfunction of pancreatic, respiratory, intestinal, male reproductive and other systems. This syndrome is caused by complete or nearly complete loss of CFTR function by two severe (class I–III) mutations in the CFTR gene (*CFTR^{sev}*). The second syndrome is caused by a group of mutations that specifically disrupt the ability of CFTR to transform from a chloride (Cl[−]) predominant channel into a bicarbonate (HCO₃[−]) predominant channel through activation by the intracellular sensor and channel regulating protein kinase WNK1 [23**, 24]. Members of the CFTR bicarbonate-defective genetic variants (*CFTR^{BD}*) include R74Q, R75Q, R117H, R170H, L967S, L997F, D1152H,

S1235R, and D1270N [23**, 25]. All of these are amino acid substitutions, which is consistent with the hypothesis that the mechanisms reflect a change in CFTR function rather than a change in amount or location. Patients with these pathogenic variants appear to be at increased risk of diseases with a recessive *CFTR* genotype (*CFTR^{BD}/CFTR^{BD}* or *CFTR^{BD}/CFTR^{sev}*), or with a compound trans-heterozygous genotype with *SPINK1* (e.g. *CFTR^{BD}/CFTR^{wt}* plus *SPINK1^{N34S}/SPINK1^{WT}*).

Several mechanisms lead to CFTR bicarbonate conductance deficits [23**]. Molecular simulation studies of the CFTR molecule suggest that one mechanism involves substitution of pore-lining amino acids with those that have larger side chains that project into the channel lumen and physically restrict the conductance of the larger HCO_3^- molecule but not the smaller Cl^- ion. Other mutations are located in the hinge region of the molecule and may restrict the dynamic movements necessary to transform the CFTR channel to the bicarbonate conductance-predominant conformation. Other mechanisms have not yet been explained [23**].

The new CF syndrome linked to the *CFTR^{BD}* variants appears to represent a subset of the primary CF syndrome, but is limited to organs that utilize CFTR for bicarbonate conductance such as the pancreas, sinuses (mucus hydration), and male reproductive system (sperm function) [23**]. In a comparison of patients with pancreatitis and controls, the presence of the *CFTR^{BD}* variants increased the risk for both rhinosinusitis (OR 2.3, $p < 0.005$) and male infertility (OR 395, $p < 0.0001$). However, there was no increase in lung disease. Since the evaluation and management of CF has been led by pulmonary physicians, it is likely that the scope and impact of the *CFTR^{BD}* variants will be increasingly recognized as they are evaluated by pediatricians, internists, and gastroenterologists.

These findings underscore the fact that new paradigms and new approaches will be needed to integrate the expanding realm of genetic factors into clinical practice and personalized medicine [5, 26**]. The opportunities for better management of pancreatic diseases are significant. Limitations to implementing therapeutic changes for pancreatic diseases include issues surrounding genetic testing, interpretation of genetic results, and developing new treatment plans that are aimed at both targeting defects and avoiding potential complications.

Genetic testing controversies

While genetic testing has the power to reveal lifelong potentially pathogenic variants, this utility is linked to potential dangers. These dangers are not necessarily associated with immediate physical injury but with underlying mechanisms. There can be long-term implications to a patient's self-concept as well as future health implications – an area of concern for health insurance, life insurance, employment, and other relationships. In some cases, such as the expanded trinucleotide repeat for glutamine in the Huntington's disease gene (*HTT*), the results of genetic testing predict a horrible death at a young age, with no good treatment options [27, 28]. In pancreatic diseases, knowledge of *gain-of-function* mutations in the cationic trypsinogen gene (*PRSSI*) indicating hereditary pancreatitis [29, 30], or two severe mutations in the cystic fibrosis transmembrane conductance regulator

gene (*CFTR*) indicating cystic fibrosis [31–33], have important and immediate implications for disease. However, knowledge of other genetic variants – especially common ones that may or may not play a role in various pancreatic diseases as a complex genotype or modifier – is difficult or impossible to interpret outside a well-defined context [5, 26].

In the examples above of mutations in the Huntington's gene, *PRSS1*, and *CFTR*, some genetic results provide clear, significant risk implications based on single-gene genotyping. Other pancreatic disease variants in genes such as *CTRC* [7*] or the *CLDN2* locus [14**] confer risk in combination with other pathogenic gene variants or strong environmental factors, and therefore have lower gene-specific risk. We believe that the knowledge of variants in the second group of genes alone, independent of the clinical context, has minimal predictive utility and therefore confers little risk.

The calculus that goes into genetic testing integrates the rights and needs of multiple stakeholders, and becomes more complicated when the potential results of extensive genotyping span the range of genetic risk profiles from minimal to life-changing. Years of experience have led to well-defined approaches to genetic tests of simple rare diseases [34]. This process includes careful pre-test counseling, as well as post-test disclosure and education that typically involve specialty-trained physicians, genetic counselors, and special resources. Consensus guidelines and expert guidance have been published for pancreatic disease such as hereditary pancreatitis [35–39]. The wide availability of accurate and inexpensive single-nucleotide polymorphism (SNP) testing on a chip and massively parallel next-generation sequencing (NGS) technologies now puts huge amounts of information into the hands of “everyone.” When, where, and how should this new and complex data be used, and by whom and for whom?

Direct-to-consumer genotyping

Given the high cost of detailed genetic sequencing obtained through healthcare channels, genetic testing companies, which provide individuals with the opportunity to obtain genetic results directly, may be an attractive alternative for patients motivated by curiosity and a desire learn about themselves without having to share such information with their health provider. Physicians should be aware of direct-to-consumer genetic testing and its controversies so that they are able to provide an optimal course of action for patients that divulge such results.

23andMe, founded in 2006, was among the first of the “direct-to-consumer” (DTC) personalized genetic testing companies in the United States. The company was highly successful, genotyping over 650,000 individuals [40]. Cost was controlled by the use of SNP chips, which initially allowed analysis of close to 600,000 polymorphisms [41]. The danger of reporting very high-impact and potentially serious results, such as Lynch syndrome, FAP, and other familial cancer syndrome-associated genetic variants, was avoided by not placing critical SNPs on the chip, and instead selecting tag SNPs that had proven associations with common disorders such as cardiovascular disease, diabetes, and obesity. In most of cases, the “risk” was relatively low because the relative risk of the disease was low or the impact of the results was self-evident (e.g., obesity).

The problem was that many of the conditions, such as risk of autoimmune disease, were distressing to individuals, especially those who had friends or family with complications of the particular disorder [42]. Additionally, although 23andMe marketed their testing as providing both medically meaningful and potentially actionable health reports, this marketing strategy was not approved by the FDA, as the company failed to prove the analytical validity and clinical utility of each SNP used to provide health information. Other major concerns from DTC genetic testing include inappropriate risk interpretation by consumers and incorrect or unwarranted health management decisions based upon DTC genetic testing reports. The magnitude of this problem was such that on November 13, 2013, the FDA ordered 23andMe to cease and desist from marketing and testing for health-related information. Consumers ordering testing on or after November 22, 2013 would not receive health information, but would still receive ancestry information and “uninterpreted raw genetic data.”

We believe that the stance of the FDA toward DTC genetic testing companies is warranted given that such testing typically is presymptomatic, provides results that are difficult to interpret, and does not involve a healthcare professional intermediary to provide guidance for the decision to test and results disclosure. The most important pathogenic variants are also excluded, possibly providing individuals with false assurance, and consumers are not required to seek genetic counseling with the disclosure of their test results. As such, individuals who undergo such DTC testing may incorrectly perceive predictive genetic testing results that prompt inappropriate and potentially harmful medical decisions.

DTC genetic testing companies may provide health information that individuals do not want to obtain through their healthcare provider because of huge price markups and required copays (i.e., financial barrier) or because they want to know their results prior to deciding if they want the results as part of their healthcare record (i.e., fear of genetic discrimination). Whether companies like 23andMe can align the “individual’s right to know” with FDA standards, and can provide both accurate and clinically useful results within an acceptable context, has not been resolved.

In summary, there is reasonable concern that the general population is not capable of fully understanding the risks and implications of complex genetic test results, and DTC genetic testing may drive unreasonable and unnecessary healthcare actions, and increase rather than alleviate anxiety and stress. Perhaps integrating DTC results with counseling will improve these outcomes [43*]. On the other hand, the question of whether an individual has the right to know details about their own body remains an important moral, ethical, legal, and social debate. Gastroenterologists should consider these points when faced with patients arriving with DTC genetic testing results for known genes involved in pancreatic disease, or patients expressing a desire to undergo DTC genetic testing for health-related information.

Pre-existing conditions

A major non-medical risk of genetic variant information is the potential penalty of having a “pre-existing condition” resulting in genetic discrimination. This is clearly one of the major concerns of patients, including those with risk for pancreatic disease [44]. The *Genetic*

Information Nondiscrimination Act of 2008 (GINA, Pub. L. 110–233) made it illegal to use genetic test results in consideration of health insurance rates or employment. However, patients are still concerned, and rightfully so, about life insurance, mortgages, and other potential areas of discrimination. The issue of discrimination also raises moral, ethical, social, and legal issues surrounding patient disclosure of DTC test results to their doctor, health plan, employer, and others, as noted above. Likewise, there are questions as to whether all genetic information from broad genome-wide sequencing tests by physicians and healthcare providers could be collected without disclosing all of the results to the patient. The American College of Medical Genetics (ACMG) currently recommends that their minimal list of medically-actionable findings be disclosed [45]. Implications of findings from any comprehensive genetic testing performed for pancreatic disease, therefore, may supersede issues specific to pancreatic disease.

Genetic testing for complex disorders

Most of the debate highlighted above revolves around genetic testing for simple Mendelian disorders or presymptomatic testing of a wide spectrum of common disorders with independently informative SNPs. There has been less debate and discussion on genetic testing for complex disorders, since there are very few well-defined disorders in which multiple genes and environmental factors are integrated into disease models that provide utility for managing these disorders. Should the same rules and guidelines apply for complex disorders? Who should own the results? How can they be interpreted by the physician and patient?

It is the authors' opinion that genetic testing is critical for understanding and managing complex disorders. It is the cornerstone of personalized medicine. It is central to predictive modeling for many conditions and disorders, such as pancreatic diseases, and many genes and regulator SNPs must be considered simultaneously to make accurate predictions in complex diseases. The field may become even more complex as epigenetics, regulatory elements, functional genomics, expression profiling, and the “omics” technologies enter the mix and must be interpreted [46, 47].

The greatest issue is that most physicians are not – and *cannot* be – adequately trained to interpret complex genetic data sets during a busy clinical session, especially when complex clinical and environmental factors contribute to variable risk and outcomes. With increasing focus on patient turnover and productivity, there is just not enough time to stay up to date on all of the important genetic factors and nuances of interpretation. However, there must be someone able to evaluate genetic data within the context of a clinical question or problem and to communicate the appropriate information in understandable terms to the healthcare provider and/or patient.

Pancreatitis genetics and their implications

Given the anatomical and functional simplicity of the pancreas as compared to other organs, and the relative protection from environmental factors, the pancreas provides an outstanding model for understanding complex disease [5, 26**]. The first observation is that the clinical features of acute, recurrent acute, and chronic pancreatitis center on the signs and symptoms

of inflammation, regardless of etiology. Management and prevention of recurrence necessitates addressing the underlying etiologies and patient-specific risk. Since the pancreas is protected from direct exposure to the environment, and because its function is to synthesize digestive enzymes and hormones rather than eliminate toxic metabolites or xenobiotics, the risk of injury and inflammation are largely linked to genetic variants. Appropriate genetic testing will provide information-rich data regarding these factors – but the key will be the interpretation of the data.

The second observation is that genetic risk factors for pancreatitis susceptibility and complications have different implications, and thus require individualized management. Autosomal dominant *PRSS1*-related hereditary pancreatitis provides a model for interpreting, counseling, and managing probands and families with a Mendelian disorder [39]. Likewise, cystic fibrosis, a recessive disorder of severe *CFTR* mutations, provides a model of a multi-system genetic syndrome with specific implications and treatments [48, 49]. Complex genotypes are common with variants in *CFTR*, *SPINK1*, *CTRC*, and other genes, both within and outside the context of smoking and drinking. Interpretation of the genes, variants, and context can be critical in immediately defining the reason for pancreatitis susceptibility and recurrence of progression, thereby limiting continued expensive and invasive evaluations or preventive procedures. The framework for understanding the effects and consequences of common and rare variants continues to evolve [6, 7, 38*, 49]. The work that has been done in identifying subsets of patients that are phenotypically similar to patients with single-gene pancreatic diseases [37, 50], but with more intricate genotypes, has made it possible to begin developing genetic counseling models for complex diseases as one option for managing complex genetic results [50].

Treatment options

There are several goals in genetic testing for pancreatic disease. The first is to identify a mechanistic etiology. It is important to compare the cost of a traditional evaluation comprising multiple office visits, biomarker studies, abdominal imaging tests, and procedures to determine etiology, with the cost of genetic testing. Of note, with the exception of very high levels of ionized calcium, IgG4, and triglycerides, most biomarkers are not linked with etiology. The issue with genetic testing early in the evaluation of pancreatitis without an obvious cause, such as gallstones, is that it is not a “medical necessity.” However, it does provide both diagnostic expedience and cost savings, and a positive genetic test eliminates the need for additional diagnostic testing and transitions the care plan to disease management and avoidance of complications.

Discovery of genetic syndromes such as CF, secondary forms of CF (e.g., *CFTR*^{BD} syndrome), or atypical CF have immediate implications for disease management as well as consideration of dysfunction of other organs. Treatment approaches for CF disease, for example, are well-established and may involve a referral to a CF center for full evaluation [49]. The new *CFTR* enhancers or correctors are intriguing, but have not been tested in predominantly pancreatic disease forms of CF and are prohibitively expensive.

A preliminary study was published on the use of amlodipine for management of hereditary pancreatitis from *PRSSI* gain-of-function mutations [51]. Use of this calcium channel blocker appeared to be safe, and trends toward benefit were observed. Additional trials have not been reported, but the author has received positive anecdotal reports. It is clear that prospective randomized double-blinded clinical treatment trials are needed to determine the most effective therapies for specific problems.

Genetic testing results may also have important implications for the treatment of diabetes mellitus. Chronic pancreatitis from any cause, including genetic, may result in type 3c diabetes mellitus, in which insufficient insulin production due to pancreatic disease or surgery diminishes the number of islets [2, 52]. A definitive diagnosis of CP is difficult unless there is severe RAP, significant morphologic distortions of the pancreas, or pancreatic calcifications. Diagnosis of CP based on steatorrhea, weight loss, or malnutrition is also an issue, as these signs and symptoms occur late in the disease when the exocrine pancreas is almost completely destroyed. Even with signs and symptoms that are obvious to a gastroenterologist, CP may not be appreciated by most endocrinologists, who are managing the glucose intolerance rather than pancreatic disease. Indeed, up to 9% of patients with diabetes may have unrecognized type 3c DM [53–55].

From a treatment standpoint, a correct diagnosis of type 3c diabetes is important for several reasons [2, 52, 56–58]. First, type 3c DM is associated with the loss of *all* islet cells, not just the beta cells. Therefore, these patients lack counter regulatory hormones such as glucagon and pancreatic polypeptide, and are thus susceptible to hypoglycemia and other metabolic dysfunctions. Second, there may be asynchrony between the ingestion of a meal, delivery of exogenous insulin, and nutrient absorption following meal digestion if there is a lack of pancreatic digestive enzymes (e.g., pancreatic exocrine insufficiency) and a significant delay in digestion. In this case, it seems reasonable to provide pancreatic enzyme supplements with meals to improve meal digestion and absorption in synchrony with the effects of insulin on clearance of glucose and fats from the bloodstream. Third, the use of incretins (GLP-1 agonists, DPP-4 inhibitors) to manage type 2 DM may be ineffective in type 3c DM, since levels of natural GLP-1 may already be high [59]. Fourth, there appears to be an increased risk of pancreatic ductal adenocarcinoma (PDAC) in patients with CP, and the risk of PDAC in DM may be linked to undiagnosed CP. Therefore, the use of genetic testing to assess the risk of RAP and CP in patients with DM and equivocal histories of episodes of RAP or CP should be considered.

The ultimate treatment for persistent, severe, or disabling CP with the threat of impending type 3c DM is total pancreatectomy with islet auto transplantation (TPIAT). This procedure, which was available at only two facilities a few years ago, is now conducted at over 20 medical centers. TPIAT involves the early removal of the pancreas before the number of islets is completely diminished, digestion of the pancreatic parenchyma and isolation of the islets, and reimplantation of the islets into the liver, abdomen, or other sites. The procedure, which is associated with significant dangers, exchanges one problem for another. Since the TPIAT alters gastrointestinal anatomy, some patients have major post-procedure motility problems, and all are committed to lifetime full-dose pancreatic enzyme replacement therapy with each meal and each snack. However, TPIAT typically provides relief from the

severe abdominal pain associated with pancreatitis and may prevent the development of diabetes. Guidelines for the evaluation and management of patients being considered for or who have undergone the procedure have recently been published [60].

Summary and conclusions

The low cost and wide availability of human genotyping offers new opportunities for rapid advances in personalized medicine. The hope is that the technology will lead to much better care and much lower costs. The reality is that the technology is far ahead of the ability to interpret the results, as witnessed in the controversy surrounding DTC genotyping by 23andMe. While the involved nature of complex disorders is aptly illustrated in pancreatic diseases, the simplicity of the pancreas provides the opportunity to model the management of a complex disorder by utilizing genetic information. However, it also reveals the challenge of interpreting large and complex data sets by busy physicians, which is likely functionally impossible. For the subset of data with clear implications, course of treatment is guided by the results. In some cases, management and care for patients with pancreatic disease should be coordinated with CF centers. Clinical trials are needed to determine the most useful therapies for specific disorders and genotypes. Recognition of CP in patients with DM is also important, as the management of type 3c DM is drastically different from that of type 2 DM, and may require TPIAT to save remaining islets and prevent brittle DM and other consequences of prolonged CP, such as PDAC.

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