Citation: Clinical and Translational Gastroenterology (2016) 7, e194; doi:10.1038/ctg.2016.51
 2155-384X/16

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EDITORIAL

Advances in Pancreatic Biomarker Measures: A Novel Approach to An Obscure Organ

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The pancreas remains a challenging organ to assess because of its retroperitoneal locations and cost of accessing the pancreatic duct for collection of biological samples. A novel and potentially useful approach to analysis of pancreatic juice proteins has been developed by Rocker *et al.* (*Clin Transl Gastroenterol* 7: e174; doi:10.1038/ctg.2016.27) using whole-gut lavage fluid from a colonoscopy prep. The widespread use of colonoscopy for colon cancer screening provides the opportunity to also screen the patient for benign and malignant pancreatic diseases using the fluid waste. New approaches are needed to assessing the pancreas, and wastes should not be wasted.

Clinical and Translational Gastroenterology (2016) **7,** e194; doi:10.1038/ctg.2016.51; published online 13 October 2016

Family history, genetics, and environmental factors such as excessive alcohol consumption and smoking confer increased risk for diseases of the pancreas, but they do not provide information on disease activity, disease state, or disease progression. To diagnose a disease and understand its nature requires the measurement of various biomarkers.

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[1] The pancreas is a small, soft gland located in the retroperitoneal of the upper abdomen making it impossible to evaluate on physical examination. Structural measures include abdominal imaging (computed tomography or magnetic resonance imaging), endoscopic ultrasound, or endoscopic retrograde pancreatography. The major functions of the pancreas are linked to secretion of its products either into the blood stream (e.g., insulin), or into the duodenum (e.g., pancreatic digestive enzymes and other proteins). Thus, measurements of pancreatic function have focused on serum markers such as blood glucose levels and insulin for endocrine function, or measures of pancreatic bicarbonate or enzyme secretion in the duodenum, signs of maldigestion (steatorrhea), or changes in pancreatic digestive enzyme levels in the stool (e.g., human fecal elastase).

Major clinical challenges include the early diagnosis of chronic pancreatitis (CP) before irreversible damage has been done, and the early diagnosis of pancreatic ductal adenocarcinoma (PDAC) before the malignant cells have spread throughout the body. Major efforts are under way to redefine CP in a more mechanistic way by detecting dysfunction of abnormal systems rather than by waiting until end-stage feature of pathogenic inflammation becomes obvious.[2] Likewise, efforts are under way to understand the mechanism in context of early progression to pancreatic cancer, so that effective interventions can be initiated. The problem is that the current approach to biomarker collection and assessment is technically challenging and expensive, and these approaches are not suitable for routine screening.[3–5]

Rocker *et al.*[6] describe a novel approach to assessing pancreatic exocrine function that is potentially simple, powerful, and possibly suitable to screen for some types of pancreatic diseases. Pancreatic proteins were found in whole-gut lavage fluid, which is the fluid from oral bowel preparation for colonoscopy. Surprisingly, two-thirds of the proteins in this fluid is of pancreatic origin! Furthermore, because of the gut lavage process, most of the other exogenous components of human stool have been eliminated. Using high performance liquid chromatography (LC)-mass spectrometry (MS)/MS, the authors demonstrate that pancreatic proteins could be identified and quantified in a reliable and reproducible way, and that their findings roughly matched the findings of others using a more invasive method. This could be a very exciting and potentially powerful approach to more comprehensive measures of biomarkers of pancreatic exocrine secretory function.

Although this paper provides exciting new possibilities, the approach requires replication and refinement to better establish the method, and to better understand normal variability among healthy patients as well as patients with common diseases such as diabetes mellitus. As the fluid is being collected during screening for colon cancer, the clinical questions that should and could be answered related to the pancreas in these patients are yet to be defined and justified. One obvious area of great need is in the early detection of PDAC. Potentially, either biomarkers of malignancy, such as proteins altered by acquired mutations, or changes in expression patterns from field effects might be useful. Detection of pancreatic exocrine insufficiency is also an important clinical problem and approaches to optimal measures should be considered. But as with all biomarker studies, the question of what biological feature each natural occurring analyte is measuring and within what biological context the sample is collected, and how it relates to normal biological

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Received 6 July 2016; accepted 6 July 2016

processes, pathogenesis, or pharmacologic responses to a therapeutic intervention must be rigorously tested.

Another interesting approach to noninvasive collection of biological samples is to assess pancreatic function in urine.[7–9] These early proof of principle studies suggest that urine may be useful in detecting biomarkers of pancreatic inflammation and fibrosis that measure disease activity rather than exocrine synthetic function. The advantage of urine is that the samples can be collected easily at convenient times rather than only during preparation for colonoscopy. However, the focus may be different and the results complementary.

Investigators in the field of pancreatic disease are beginning to witness some major advances in understanding the underlying processes, and measuring disease state and progression earlier and more accurately than ever before. The novel approach by Rocker *et al.*[6] is certainly contributing to possibilities of future tools.

CONFLICT OF INTEREST

Guarantor of the article: David C. Whitcomb, MD, PhD.
Specific author contributions: Both authors contributed to the writing of the editorial and approved the final draft submitted.
Financial support: None.
Potential competing interests: None.

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