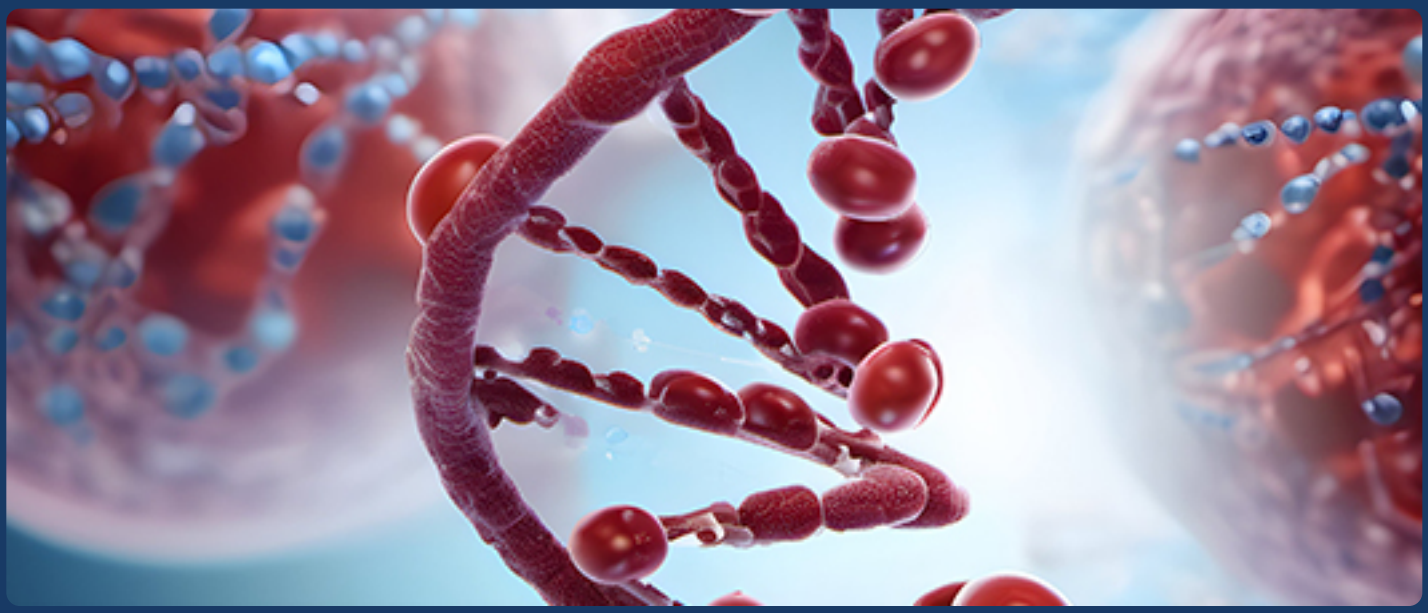
SMART-MD

Volume 1 / Issue 2

Summer, 2024

Journal of

Precision Medicine



Topic: Pancreatic Diseases and Pharmacogenetics

Editor: David C Whitcomb MD PhD

SMART Topic

Six Types of Pancreatitis Risk Factors in the Trypsinogen Gene Loci (*PRSS1–PRSS2–TRB*)
Andrea Geisz PhD , Maham Waqar MD and David C. Whitcomb MD PhD

SMART Approach

Pharmacogenetic Considerations in Beta-Blocker Therapy
Benyu Yang, MS and Jasmine Luzum, PharmD

Rational Use of Fecal Elastase-1 Testing for Exocrine Pancreatic Insufficiency (EPI)
C. Mel Wilcox MD

SMART Medical Reviews

Acute Pancreatitis: Assessment and Management in the First 24 Hours.
Peter J. Lee MBChB et al

Are your patients asking about Exocrine Pancreatic Insufficiency (EPI) and its symptoms? Symptoms of EPI may go undiagnosed or attributed to some other GI ailment.

- Excess fat content, feces are loose, floating and foul smelling
- Flatulence
- Bloating
- Abdominal pain
- Unexplained weight loss

Pertzye®, the only bicarbonate-buffered pancreatic enzyme, may benefit these patients.

Try Pertzye® (pancrelipase) for Pancreatic Enzyme Replacement Therapy (PERT). The bicarbonate-buffered enteric-coated microspheres may create an optimal pH microenvironment around the microspheres to maximize enzyme activity.

The most common adverse reactions (≥ 10%) are: diarrhea, dyspepsia, and cough.

Pertzye®
(pancrelipase)
Delayed-Release Capsules

Scan this code to download the Pertzye Sample Request Form

Indication

Pertzye® (pancrelipase) is indicated for the treatment of exocrine pancreatic insufficiency in adult and pediatric patients.

Important Safety Information

- Fibrosing Colonopathy is associated with high doses, usually over prolonged use and in pediatric patients with cystic fibrosis. Colonic stricture reported in pediatric patients less than 12 years of age with dosages exceeding 6,000 lipase units/kg/meal. Monitor during treatment for progression of preexisting disease. Do not exceed the recommended dosage, unless clinically indicated.
- Irritation of the Oral Mucosa may occur due to loss of protective enteric coating on the capsule contents. Do not crush or chew PERTZYE capsules or capsule contents.
- Hyperuricemia has been reported with high dosages, consider monitoring blood uric acid levels in patients with gout, renal impairment, or hyperuricemia.
- Risk of Viral Transmission: The presence of porcine viruses that might infect humans cannot be definitely excluded. However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic extracts have been reported.
- Hypersensitivity Reactions: Monitor patients with known reactions to proteins of porcine origin. If symptoms occur, initiate appropriate medical management; consider the risks and benefits of continued treatment.
- The most common adverse reactions (≥ 10%) are: diarrhea, dyspepsia, and cough.
- Do not substitute other pancreatic enzyme products for PERTZYE.

Please see Full Prescribing Information at www.pertzye.com.

DCI Digestive Care, Inc.
1120 Win Drive, Bethlehem, PA 18017-7059
Voice: 1-877-882-5950 | **Fax:** 610-882-0349 | **www.pertzye.com**

24027 | 12/2024

SMART Approach

Rational Use of Fecal Elastase–1 Testing for Exocrine Pancreatic Insufficiency (EPI)

C. Mel Wilcox MD[1]

[1]*Orlando Health Digestive Health Institute, Orlando, FL*

Overview

The diagnosis of exocrine pancreatic insufficiency (EPI) represents a stage in the progressive reduction in the delivery of pancreatic digestive enzymes to the intestine to digest food and deliver adequate micro- and macro-nutrients to meet metabolic needs.[1] One of the commonly used methods to diagnose is testing of the patient's stool to quantitate human fecal elastase-1 (FE). Key points discussed here include:

- All low FE is not pancreatic disease
- A watery stool makes the test very inaccurate
- EPI does not present with acute diarrhea
- A diagnosis of EPI is best made considering clinical history, risk factors and any pertinent imaging

Background

EPI has been traditionally diagnosed by characteristic symptoms and signs. [2] Symptoms of bloating, abdominal pain, and postprandial soft or loose stool are typical and when severe, weight loss could be reported and would be progressive if untreated. These symptoms are also chronic and not acute. Signs include loose stool, which is described as foul-smelling, difficult to flush and could contain frank oil droplets (steatorrhea). The stool oftentimes is described as orange in color. However, recognition of steatorrhea by the stool characteristics alone is inaccurate.[3] Fat soluble vitamin deficiencies could also be detected. These are patients with well-established chronic pancreatitis and/or with significant risk factors for pancreatic disease such as alcohol use disorder and or chronic tobacco use. [4] However, we also recognize that these symptoms and signs may overlap other common gastrointestinal conditions such as infections, endocrinopathies, maldigestive/malabsorptive conditions, and disorders of gut-brain interaction. [5] Thus, the diagnosis may not always be clear warranting additional investigation.

Testing for EPI

A variety of tests have been developed for the diagnosis of EPI. These tests can be categorized as indirect, direct, fecal, or even enzyme estimations in bodily fluids.[6] Many of these tests are not widely available or in the case of the 72-hour fecal fat collection, are cumbersome, difficult to perform and of variable compliance. The use of a qualitative fecal fat measurement may be helpful when performed appropriately but have gone out of favor.[7, 8] Accurate breath tests are available in Europe but are not used in the United States. Serum trypsinogen levels are accurate (when the patient is not having pancreatitis) but this test is no longer available.[9] Regardless of the type of test used, there is often a poor correlation between an abnormal test and fecal fat output. [10]

Human Fecal Elastase Stool Test.

The fecal elastase stool test (FE-1) has been available for ~ two decades. Previous investigations identified pancreatic elastase enzymes, which hydrolyze elastin, and are passed in the stool, bound by bile acids, not degraded during transit and remain stable for a week at room temperature.[6] Normative values have been established. FE-1 correlates well with pancreatic output of elastase as well as other pancreatic digestive enzymes. Importantly, pancreatic enzyme supplementation does not affect quantitative measurement of FE-1. Current commercial fecal elastase ELISA are specific for the isoform CELA 3 (chymotrypsin-like elastase family); thus, FE-1 is a misnomer. Compared against gold standard invasive (direct pancreatic function test) and noninvasive tests (72-hour fecal fat collection), in the appropriate setting, the sensitivity and specificity are high for severe EPI (FE-1 <100 mcg/g), but much less so for mild and moderate disease .[7, 11-13] When FE-1 testing is performed in a mixed population with low risk for disease (low pretest probability), the specificity is unacceptably low and a positive test is most likely a false positive. [14]

Abbreviations used in this paper. EPI, exocrine pancreatic insufficiency; FE-1, fecal elastase 1;

Key words: chronic pancreatitis, diarrhea, abdominal pain, fat soluble vitamins, maldigestion, malabsorption, pancreatic enzyme replacement therapy, precision medicine

ISSN 2997-2876 (online)
ISSN 2997-2868 (print)
DIO: https://doi.org/10.69734/hdhe8467
Website: www.SMART-MD.org

Unfortunately, there are critical nuances of the test which make interpretation potentially fraught with hazard and which are not widely recognized. In addition, measurements within stool as well as on separate days may also differ further underscoring the potential problems with this test.[15] Most importantly, we know that in the presence of a loose stool with high water content, the stool is diluted, and FE-1 will be low (falsely positive) as FE-1 measures the concentration of elastin in the stool. [16, 17] Therefore, appropriate interpretation based on stool characteristics is mandatory.

Differential Diagnosis of EPI.

Several nonpancreatic conditions have been associated with a low FE-1.[6, 18] These conditions include small bowel disease classically celiac disease, diabetes mellitus, prior gastrointestinal surgery, bacterial overgrowth, and disorders associated with enzyme inactivation or digestive asynchrony; perhaps abnormalities of FE-1 in these settings are better termed pancreatic exocrine dysfunction. Because of extrapancreatic lipolysis coupled with our excess digestive capacity, there can be a marked reduction in pancreatic secretion yet maintenance of adequate digestion. Thus, interpretation of FE must consider these other conditions as well and not just ascribe a low FE-1 to pancreatic disease.

FE-1 testing in patients with diarrhea.

Another problem with the current use of this test is that it is often bundled with other tests for evaluation of diarrhea. This panel typically may contain PCR testing for bacteria and viruses, alpha-1 antitrypsin, calprotectin as well as FE-1. These stool panels are typically ordered in patients with acute diarrhea, and as noted above, in this setting, FE-1 is much more likely to be inaccurate (watery stool).

Interpretation of FE-1 stool test as evidence of EPI

Recently a staging system for exocrine pancreatic dysfunction was published.[19] In patients with suggestive symptoms and signs but in whom FE-1 is greater than 200mcg/gm, other causes for their symptoms should be considered as EPI is essentially excluded. With a value between 100 mcg/gm and 200 mcg/gm, mild pancreatic dysfunction could be etiologic, but other causes of mildly low FE-1 should be first investigated as a FE-1 in this range in patients with mild pancreatic insufficiency is often not associated with any symptoms nor with vitamin deficiencies. These patients were termed pancreas sufficient. Patients with a FE-1 <100 mcg/gm and especially <50 mcg/gm are those most likely, in the appropriate setting, to have EPI. Patients with EPI and FE-1 <100 mcg/gm should generally be treated with pancreatic enzyme supplementation given the potential long-term complications. [20] For patients with a FE-1 between 100- 200 mcg/gm in the absence of symptoms or signs of maldigestion, enzyme supplementation is generally not warranted. Lastly, in some patients it may be very difficult to prove the diagnosis of EPI, and in this setting empirical use of appropriate doses of pancreatic enzymes may be reasonable recognizing the high placebo response rate.

How I use the FE-1 test.

When and in whom do I use the FE-1 test?

In patients with established recurrent acute, recurrent acute severe or chronic pancreatitis and in whom malabsorption may not be clinically evident, FE-1 testing would be appropriate. For those patients considered to have EPI but perhaps remain symptomatic and continue to lose weight, confirming the diagnosis and its severity is reasonable. Fecal elastase testing should be discouraged in patients with acute onset of diarrhea especially those without any risk factors for chronic pancreatitis as well as for patients with chronic diarrhea consistent with irritable bowel syndrome. A major issue for patients with a low risk of EPI in whom a low FE-1 is detected is that additional investigations including cross-sectional abdominal imaging or even endoscopic ultrasound are then recommended and expensive pancreatic enzymes prescribed potentially leading to further diagnostic confusion as well as costs. Repeating the stool test may be reasonable before embarking on these additional studies.

Summary

There is no ideal test to detect EPI. Rational use of FE-1 testing in conjunction with history, clinical symptoms and signs, and any prior cross-sectional abdominal imaging should guide its appropriate use and interpretation.

References:

1. Whitcomb D, Duggan S, Martindale R, Lowe M, Stallings V, Conwell D, et al. AGA-PancreasFest Joint Symposium on Exocrine Pancreatic Insufficiency. Gastro Hep Advances. 2023;2(3):395-411 D.O.I. PMID:
2. Whitcomb DC, Buchner AM, Forsmark CE. AGA Clinical Practice Update on the Epidemiology, Evaluation, and Management of Exocrine Pancreatic Insufficiency: Expert Review. Gastroenterology. 2023;165(5):1292-301 D.O.I: 10.1053/j.gastro.2023.07.007. PMID: 37737818
3. Lankisch PG, Droge M, Hofses S, Konig H, Lembcke B. Steatorrhoea: you cannot trust your eyes when it comes to diagnosis. Lancet. 1996;347(9015):1620-1 D.O.I. PMID: 8667884
4. Yadav D, Whitcomb DC. Diagnosis of chronic pancreatitis. . SMART-MD JPM. 2024;1(1):e4-e13 D.O.I: https://doi.org/10.69734/f83fbc79. PMID:
5. Brenner DM, Dominguez-Munoz JE. Differential Diagnosis of Chronic Diarrhea: An Algorithm to Distinguish Irritable Bowel Syndrome With Diarrhea

From Other Organic Gastrointestinal Diseases, With Special Focus on Exocrine Pancreatic Insufficiency. J Clin Gastroenterol. 2023;57(7):663-70 D.O.I: 10.1097/MCG.0000000000001855. PMID: 37115854
6. Leeds JS, Oppong K, Sanders DS. The role of fecal elastase-1 in detecting exocrine pancreatic disease. Nat Rev Gastroenterol Hepatol. 2011;8(7):405-15 D.O.I: 10.1038/nrgastro.2011.91. PMID: 21629239
7. Amann ST, Josephson SA, Toskes PP. Acid steatocrit: a simple, rapid gravimetric method to determine steatorrhea. Am J Gastroenterol. 1997;92(12):2280-4 D.O.I. PMID: 9399770
8. Fine KD, Ogunji F. A new method of quantitative fecal fat microscopy and its correlation with chemically measured fecal fat output. Am J Clin Pathol. 2000;113(4):528-34 D.O.I: 10.1309/0T2W-NN7F-7T8Q-5N8C. PMID: 10761454
9. Zhan W, Akshintala V, Greer PJ, Greer JB, Alkaade S, Anderson MA, et al. Low serum trypsinogen levels in chronic pancreatitis: Correlation with parenchymal loss, exocrine pancreatic insufficiency, and diabetes but not CT-based cambridge severity scores for fibrosis. Pancreatology. 2020;20(7):1368-78 D.O.I: 10.1016/j.pan.2020.08.025. PMID: 32967795
10. Benini L, Amodio A, Campagnola P, Agugiaro F, Cristofori C, Micciolo R, et al. Fecal elastase-1 is useful in the detection of steatorrhea in patients with pancreatic diseases but not after pancreatic resection. Pancreatology. 2013;13(1):38-42 D.O.I: 10.1016/j.pan.2012.11.307. PMID: 23395568
11. Lankisch PG, Schmidt I, Konig H, Lehnick D, Knollmann R, Lohr M, et al. Faecal elastase 1: not helpful in diagnosing chronic pancreatitis associated with mild to moderate exocrine pancreatic insufficiency. Gut. 1998;42(4):551-4 D.O.I: 10.1136/gut.42.4.551. PMID: 9616319
12. Chowdhury SD, Kurien RT, Ramachandran A, Joseph AJ, Simon EG, Dutta AK, et al. Pancreatic exocrine insufficiency: Comparing fecal elastase 1 with 72-h stool for fecal fat estimation. Indian journal of gastroenterology : official journal of the Indian Society of Gastroenterology. 2016;35(6):441-4 D.O.I: 10.1007/s12664-016-0714-4. PMID: 27878466
13. Gopi S, Singh N, Yegurla J, Tabish M, Agarwal S, Qamar S, et al. Utility of Fecal Elastase-1 to diagnose severe exocrine insufficiency in chronic pancreatitis: Real world experience. Pancreatology. 2023;23(2):151-7 D.O.I: 10.1016/j.pan.2023.01.002. PMID: 36610873
14. Vanga RR, Tansel A, Sidiq S, El-Serag HB, Othman MO. Diagnostic Performance of Measurement of Fecal Elastase-1 in Detection of Exocrine Pancreatic Insufficiency: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018;16(8):1220-8 e4 D.O.I: 10.1016/j.cgh.2018.01.027. PMID: 29374614
15. Hamwi A, Veitl M, Maenner G, Vogelsang H, Szekeres T. Pancreatic elastase 1 in stool: variations within one stool passage and individual changes from day to day. Wien Klin Wochenschr. 2000;112(1):32-5 D.O.I. PMID: 10689738
16. Brydon WG, Kingstone K, Ghosh S. Limitations of faecal elastase-1 and chymotrypsin as tests of exocrine pancreatic disease in adults. Ann Clin Biochem. 2004;41(Pt 1):78-81 D.O.I: 10.1258/000456304322664753. PMID: 14713391
17. Jones AM. The clinical and laboratory impact of reporting faecal elastase-1 in watery stool samples. Ann Clin Biochem. 2023;60(1):72-4 D.O.I: 10.1177/00045632221143678. PMID: 36424839
18. Kunovsky L, Dite P, Jabandziev P, Eid M, Poredska K, Vaculova J, et al. Causes of Exocrine Pancreatic Insufficiency Other Than Chronic Pancreatitis. J Clin Med. 2021;10(24) D.O.I: 10.3390/jcm10245779. PMID: 34945075
19. Khan A, Vege SS, Dudeja V, Chari ST. Staging exocrine pancreatic dysfunction. Pancreatology. 2022;22(1):168-72 D.O.I: 10.1016/j.pan.2021.11.005. PMID: 34916141
20. Erchinger F, Engjom T, Dimcevski G, Drewes AM, Olesen SS, Vujasinovic M, et al. Exocrine pancreas insufficiency in chronic pancreatitis - Risk factors and associations with complications. A multicentre study of 1869 patients. Pancreatology. 2022;22(3):374-80 D.O.I: 10.1016/j.pan.2022.02.003. PMID: 35216905

Further Reading:

1. Weiss FU, Budde C, Lerch MM. Specificity of a polyclonal Fecal Elastase ELISA for CELA 3. Plos One 2016;11:e0159363. PMID 27459204.

Correspondence

Address correspondence to: C. Mel. Wilcox MD, Orlando Health Digestive Health Institute. 1720 S. Orange Ave. Suite 200 Orlando, FL 32806.
Charles.Wilcox@orlandohealth.com

CRediT Authorship Contributions

C.M.W. contributed to all aspects of this report.

Conflicts of Interest

None related to the contents of this manuscript

Funding:
N/A