UNC MEDICAL CENTER GUIDELINE

Repeat Fecal Elastase Testing in Pediatric Patients on CFTR Modulator Therapy

This guideline is intended to review indications and timing of repeat fecal elastase-1 testing in cystic fibrosis patients being treated with CFTR modulator therapy.

BACKGROUND

Exocrine pancreatic insufficiency (PI) is a common feature of cystic fibrosis, occurring in roughly 85% of the CF population.[1] CF Foundation guidelines recommend screening all infants with CF under two years of age for pancreatic insufficiency via fecal elastase-1 (FE-1).[2] The development of highly effective CFTR modulators has begun to challenge the assumption that pancreatic insufficiency is irreversible, but as of yet there is no formal guidance as to when repeat fecal elastase testing may be indicated to confirm continued PI.

The first documented examples of improved pancreatic function come from the KIWI and KLIMB trials of ivacaftor (IVA) in children aged 2-5 years who possessed at least one gating mutation responsive to IVA.[3,4] In KIWI, after 24 weeks there was a statistically significant increase in mean fecal elastase-1 of 99.8 mcg/g. At the initiation of the study only one patient at baseline had FE-1 readings >200 mcg/g indicative of pancreatic sufficiency, but this increased to seven patients at week 24.[3] During KLIMB, the 84-week extension of KIWI, FE-1 continued to increase with a mean change of 56.8 mcg/g, but this was not statistically significant and no further patients became pancreatic sufficient.[4]

Rosenfeld et al. demonstrated a similar impact on pancreatic function in patients aged 12 to 24 months in the ARRIVAL trial. The mean change from baseline FE-1 at 24 weeks was 164.7 mcg/g and six children had their FE-1 levels increase from <50 mcg/g at baseline to >200 mcg/g indicative of a return to pancreatic sufficiency. Of note the increase in FE-1 was observed as early as two weeks after initiation of therapy with IVA.[5]

Several recent case reports also indicate that a restoration of pancreatic sufficiency is possible with CFTR modulator therapy. Munce et al. documented three cases of recovered pancreatic function in patients initiated on IVA at four, six, and seven years of age; the four- and six-year-olds demonstrated pancreatic sufficiency after two years of therapy and the last patient after just four months.[6] Megalaa et al. and Hamilton et al. both describe six-year-old patients who, after presenting with symptoms of acute pancreatitis, were found to have become pancreatic sufficient after four years of therapy with IVA.[7,8] Lastly, Smith et al. documents a patient, initiated on IVA at 12 years of age, who underwent repeat fecal elastase testing at age 17 and was found to have a FE-1 of 263 mcg/g after having an undetectable FE-1 at two years of age.[9]

The interval between initiation of CFTR modulator therapy and discovery of pancreatic sufficiency varies significantly in the literature, with the shortest interval from IVA initiation to documented fecal elastase >200 mcg/g being four months and the longest being five years.[6,9] However, based on the data from KIWI, KLIMB, and ARRIVAL it appears that the majority of improvement in FE-1 occurs within the first six months of therapy followed by more modest increases over time. Despite current data being limited to IVA, other highly effective modulators, e.g. elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), have

Authors: Kelly Baumberger, RD; Elisabeth Dellon, MD; Charissa Kam; PharmD; Alannah Mascarella, RD; Cameron McKinzie, PharmD; Michael Patti, PharmD; George Retsch-Bogart, MD; Vivek Shenoy, MD; Kimberly Stephenson, RD

Created March 2021

demonstrated similar improvements in respiratory function and other CF symptoms as IVA and it is reasonable to assume that ELX/TEZ/IVA may confer similar benefits in pancreatic function.

PATIENT CONSIDERATIONS

Consider repeat FE-1 testing in children in the following scenarios:

- Six months after initiation of any CFTR modulator therapy in children ≤ 12 years of age upon initiation of any CFTR modulator therapy
    - If initial 6 month repeat FE-1 continues to indicate insufficiency, it may be reasonable to repeat a FE-1 every 6-12 months.

- At any point during treatment in patients on any CFTR modulator, regardless of age upon initiation of CFTR, with previously documented pancreatic insufficiency presenting with any of the following clinical signs or symptoms suggesting return of pancreatic sufficiency:
    - Symptoms of acute pancreatitis such as abdominal pain and/or elevations in serum lipase or amylase [6-8]
    - If a patient is routinely missing doses of enzymes and not displaying symptoms of malabsorption such as poor weight gain, diarrhea, and oily or excessively foul smelling stools
    - A consistent change in the solidity of stool consistency from looser to more formed on the BSS scale (e.g. constipation unrelieved by laxatives in a patient with no prior history of constipation)
    - Excessive weight gain

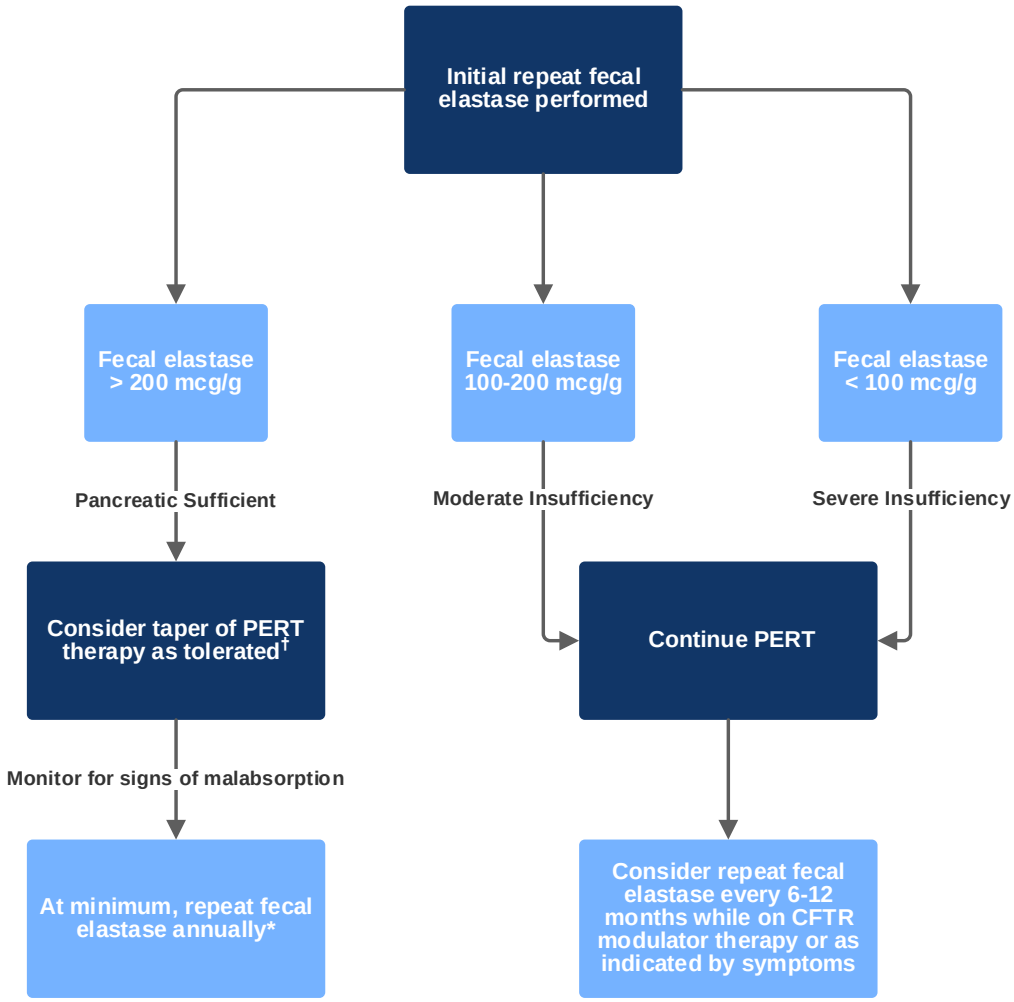
Patients will be provided a fecal elastase collection kit and step-by-step instructions for collection (Appendix A).

Table 1: Fecal Elastase Reference Values

Pancreatic Function Classification	Fecal Elastase Level
Pancreatic sufficiency	>200 mcg/g
Mild to moderate pancreatic insufficiency	100 – 200 mcg/g
Severe pancreatic insufficiency	<100 mcg/g

Authors: Kelly Baumberger, RD; Elisabeth Dellon, MD; Charissa Kam; PharmD; Alannah Mascarella, RD; Cameron McKinzie, PharmD; Michael Patti, PharmD; George Retsch-Bogart, MD; Vivek Shenoy, MD; Kimberly Stephenson, RD

Figure 1: Fecal Elastase Management



†**Suggested PERT taper:**

1) Decrease PERT dose by 50% for 1-2 weeks. Reassess for signs and symptoms of malabsorption.
2) If no signs and symptoms of malabsorption, stop PERT therapy.
3) At next follow-up visit after stopping PERT, recheck fat soluble vitamin levels. Dependent on repeat levels, consider switching to a regular multivitamin.

PERT = pancreatic enzyme replacement therapy

*Based on CF Foundation recommendations for annual FE-1 screening in pancreatic sufficient CF patients

Authors: Kelly Baumberger, RD; Elisabeth Dellon, MD; Charissa Kam; PharmD; Alannah Mascarella, RD; Cameron McKinzie, PharmD; Michael Patti, PharmD; George Retsch-Bogart, MD; Vivek Shenoy, MD; Kimberly Stephenson, RD

Created March 2021

REFERENCES

1. Singh VK, Schwarzenberg SJ. Pancreatic insufficiency in Cystic Fibrosis. *Journal of Cystic Fibrosis.* 2017;16:S70-S78.
2. Borowitz D, Robinson KA, Rosenfeld M, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr.* 2009;155(6 Suppl):S73-93.
3. Davies JC, Cunningham S, Harris WT, et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. *The Lancet Respiratory medicine.* 2016;4(2):107-115.
4. Rosenfeld M, Cunningham S, Harris WT, et al. An open-label extension study of ivacaftor in children with CF and a CFTR gating mutation initiating treatment at age 2-5 years (KLIMB). *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2019;18(6):838-843.
5. Rosenfeld M, Wainwright C, Higgins M, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. *Lancet Respir Med*. 2018;6:545-53.
6. Munce D, Lim M, Akong K. Persistent recovery of pancreatic function in patients with cystic fibrosis after ivacaftor. *Pediatr Pulmonol.* 2020;55(12):3381-3383.
7. Megalaa R, Gopalareddy V, Champion E, Goralski JL. Time for a gut check: Pancreatic sufficiency resulting from CFTR modulator use. *Pediatr Pulmonol.* 2019;54(8):E16-e18.
8. Hamilton JL, Zobell JT, Robson J. Pancreatic insufficiency converted to pancreatic sufficiency with ivacaftor. *Pediatr Pulmonol.* 2019;54(11):1654.
9. Smith H, Rayment JH. Sustained recovery of exocrine pancreatic function in a teenager with cystic fibrosis treated with ivacaftor. *Pediatr Pulmonol.* 2020;55(10):2493-2494.

Fecal Elastase Kit

Authors: Kelly Baumberger, RD; Elisabeth Dellon, MD; Charissa Kam; PharmD; Alannah Mascarella, RD; Cameron McKinzie, PharmD; Michael Patti, PharmD; George Retsch-Bogart, MD; Vivek Shenoy, MD; Kimberly Stephenson, RD

Created March 2021

Appendix A

Fecal Elastase Test

Why do you want my poop?

- This test will measure the amount of "elastase" that is in your stool. Elastase is a substance that is left over from the digestive enzymes that the pancreas makes and is present in stool.
- This test is specific for the enzymes that your own body makes, and does *not* measure the replacement enzymes that you take by mouth.
- You may do this test if you are taking a CFTR modulator like Kalydeco®, Orkambi®, Symdeko®, or Trikafta® to measure whether there is an improvement in your pancreas.
- You may also do this test when you are first diagnosed with Cystic Fibrosis.

The End Results

- Your CF team will give your specific instructions based on these results.
- If the value is >200, it is likely that you *do not* need replacement enzymes at this time.
- If the value is <200, it is likely that you *do* need replacement enzymes at this time.

Stinky Kit - Supplies

Item	Explanation
✓ Specimen cup with name label	Write date and time of collection
✓ Gloves	To keep your hands clean
✓ Wooden spatulas	To scrape the poop into the containers
✓ Collection "hat" for toilet	Place under back half of toilet seat for stool
✓ Two plastic bags	To double seal the jar of poop
✓ Refrigerator, ice, freezer pack	To keep the poop cold
✓ Instructions	To help you figure this out

Authors: Kelly Baumberger, RD; Elisabeth Dellon, MD; Charissa Kam; PharmD; Alannah Mascarella, RD; Cameron McKinzie, PharmD; Michael Patti, PharmD; George Retsch-Bogart, MD; Vivek Shenoy, MD; Kimberly Stephenson, RD

Created March 2021

Fecal Facts (or instructions)

1. Choose a day for stool collection that is within 3 days of when you can return to the lab.
2. Collect all the materials listed above and place in the bathroom near the toilet.
3. Label your container with your name, date, and time of stool collection.
4. When you are ready to poop, place the collection "hat" on the toilet. First raise the lid and the seat, then place the plastic "hat" so that the round edge covers the back half of the toilet, then lower the seat.
5. Now poop 💩
6. If you have diarrhea (very liquid stool), stop the collection and try another time.
7. Dispose of any toilet paper in the toilet bowl, not in the collection hat.
8. Put on clean, disposable gloves.
9. If there is urine in the hat, pour it into the toilet without losing the stool.
10. Use the wooden spatulas to scrape all of the stool into the labeled specimen cup.
11. You need to give us at least 10 grams of stool (about the size of a walnut, or 10 M&Ms).
12. Close the jar lid and seal it inside of 2 plastic lab bags, to decrease the smell.
13. Refrigerate the stool, or place it on ice.
14. Clean hat by rinsing with water. Dispose of your gloves.
15. Take the stool to the designated lab within 3 days, keeping it refrigerated or on ice the whole time.

What if my child is still in diapers or pull-ups?

When your child has a dirty diaper, put on clean gloves and use the wooden spatulas to scrape stool from the diaper into plastic collection jar. Close the jar lid, seal in 2 plastic bags, then refrigerate or put on ice.

Special Delivery

Bring your stool sample to the lab **within 3 days.** If it will be longer than 3 days, you must freeze the stool. Drop at a UNC lab or a designated Labcorp that has been arranged with your CF team. Please place this SPECIAL DELIVERY into the hands of a lab technician or pulmonary staff. Do not bring your stool sample if you have diarrhea, you are in the middle of a big "cleanout", or you forget to refrigerate it.

Questions?

Our CF Team is ready to answer questions about your 'dirty dilemmas.' You can contact us in the usual ways via Mychart or the Pediatric Pulmonary office phone 919-966-1055.

Authors: Kelly Baumberger, RD; Elisabeth Dellon, MD; Charissa Kam; PharmD; Alannah Mascarella, RD; Cameron McKinzie, PharmD; Michael Patti, PharmD; George Retsch-Bogart, MD; Vivek Shenoy, MD; Kimberly Stephenson, RD

Created March 2021