Potential of GI outcome measures in CFTR modulation

Is it possible to define a core set that should be evaluated in all studies?

Frank Bodewes
Pediatric GI

- No disclosures
- ESPGHAN Cystic Fibrosis Working group
- Clinical outcome measures
- (in vivo or ex vivo) CFTR function testing
  - Nasal potential
  - Organoid swelling
  - Intestinal current measurements (ICM)

Table 1
Schematic representation for the availability of the epidemiological qualities of gastrointestinal outcome measures for cystic fibrosis.

	Test	Outcome measured	CFTR related	Clinical relevance	Reliability	Validity	Reported response	Feasibility young age	Reference values
Downstream evidence of CFTR dysfunction	pH pill	Intestinal pH	+	?	+	+	+	−	+
	Scintigraphy	intestinal motility	+	+	+	?	?	−	+
	Wireless motility capsule	Intestinal motility	+	+	+	+/−	−	−	+
	Plasma C4	Fecal bile salt loss	?	?	+	?	?	+	+/−
	Plasma FGF19	Fecal bile salt loss	?	?	+	?	?	+	+/−
	Fecal calprotectin	Intestinal inflammation	?	?	+	?	?	+	+
	GI endoscopy	Intestinal inflammation	+	?	+	?	−	+/−	+
	Capsule endoscopy	Intestinal inflammation	+	?	+/−	+/−	−	−	+/−
	Fecal elastase-1	Exocrine pancreatic function	+	+	+	+	−	+	+
	CFA	Steatorrhoea	+/−	+	+/−	+	+	+/−	+
	Malabsorption blood test	Steatorrhoea	+/−	+	+/−	+/−	+	?	+
	Free fatty acid absorption test	PERT independent fat malabsorption	?	+	+/−	+/−	−	+	+
Direct measurement of CFTR function	Intestinal current measurement		+	?	+	+	?	+	+
	Intestinal organoid volume		+	?	?	?	+	+	?

+ evidence available.
− no evidence available.
? no information available.
C4: plasma 4-cholesten-3-one.
FGF19: Fibroblast growth factor 19.
CFA: coefficient of fat absorption.
PERT: pancreatic enzyme replacement therapy.

Additional endpoints needed

- GI tract phenotypically highly relevant in CF
  - Severe GI complication
  - Long term GI complication

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- Variation in drug responses
  - Intra-individual
  - Organ specific (lung≠intestine≠liver)

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- Limitations current end points
  - Sweat chloride not related to clinical outcome
  - FEV1 in young infants and children
  - Weight gain (multifactorial, not well explained)

GI related relevant clinical outcomes in CF

- Nutritional status
- CF related diabetes (CFRD)
- Intestinal malignancies
- Metabolic regulation
- Intestinal inflammation
- Bile acid metabolism

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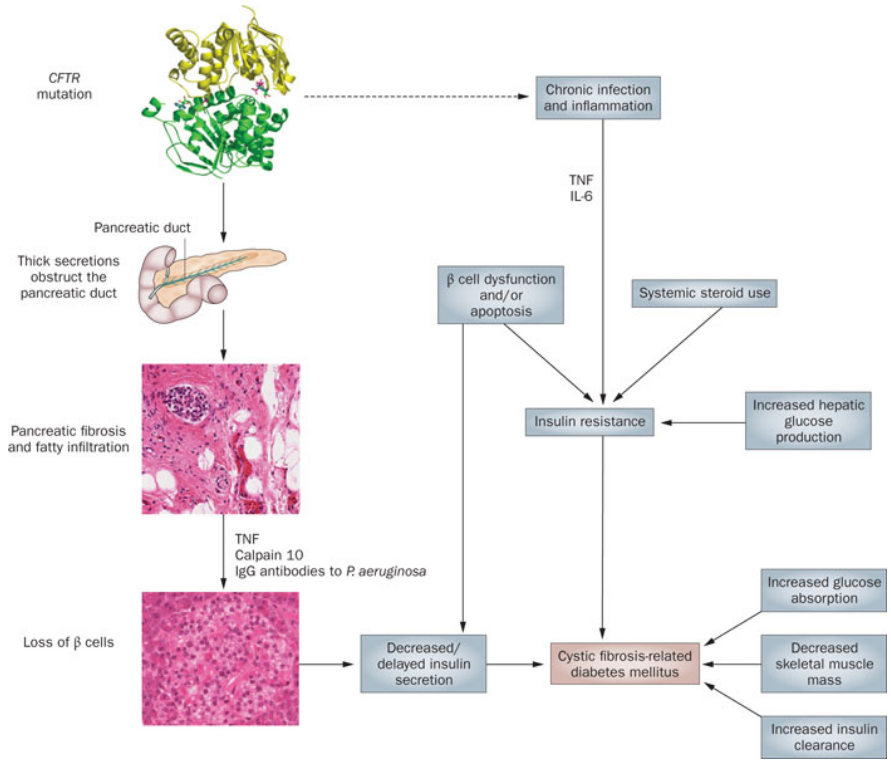
CF related diabetes (CFRD) associated with:

- Reduced growth and weight gain in children and adults
- Microvascular complication
- Reduced lung function
- Excessive reduced survival
  (minus: 2-15 years)

Increased mortality CFRD patient

Am J Respir Crit Care Med, 2015

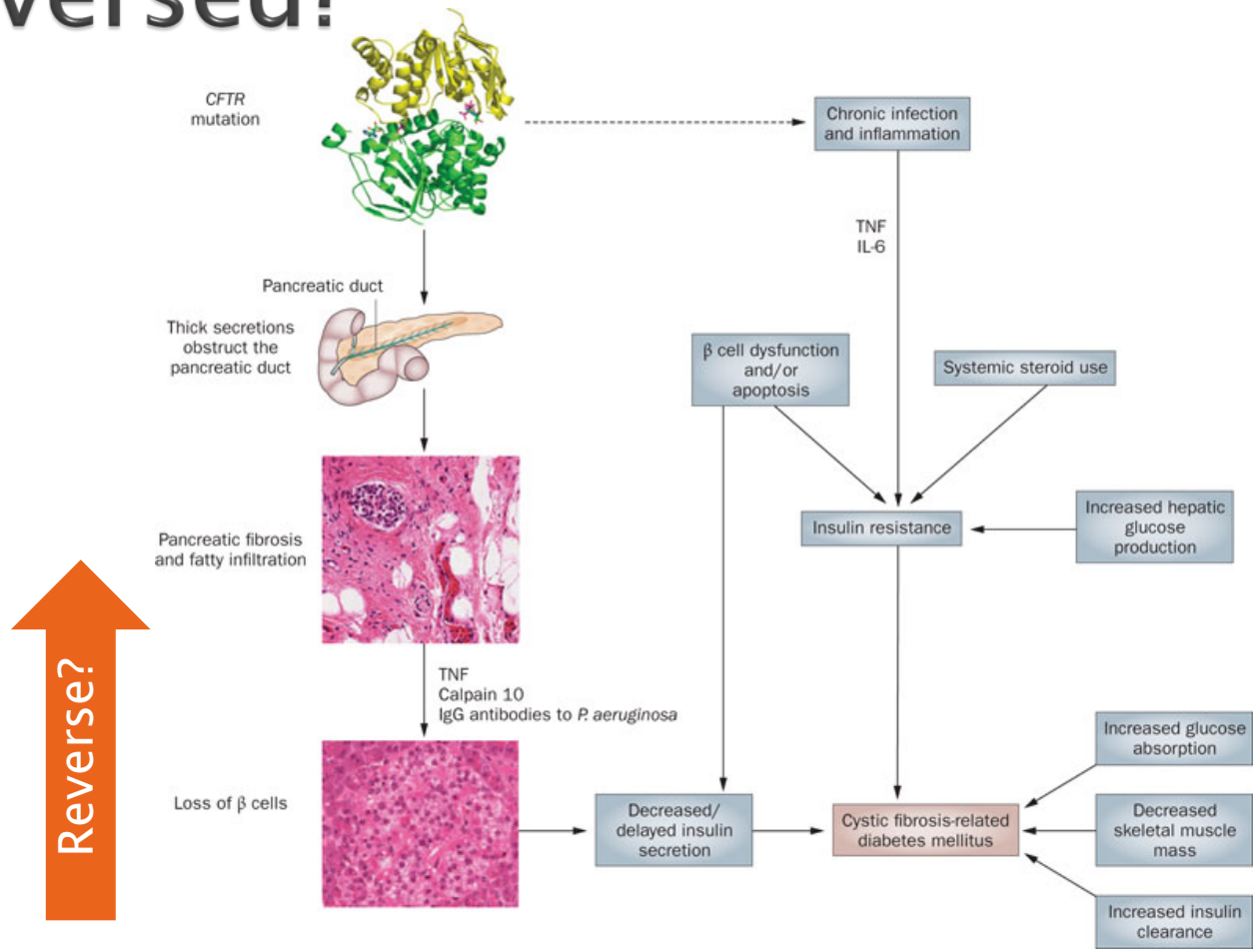
Development of CFRD is the final chapter of progressive pancreatic disease starting in utero and infancy



nature REVIEWS ENDOCRINOLOGY

Rana, M. *et al.* (2010) Cystic fibrosis-related diabetes in children—gaps in the evidence? *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2010.85

Development of CFRD can be reversed?



nature REVIEWS ENDOCRINOLOGY

Effective CFTR modulation may have an impact on the glycaemic health of patients with residual pancreatic endocrine function.

Barry, P. J., et al. "182 Impact of ivacaftor on glycaemic health in patients carrying the G551D mutation." *Journal of Cystic Fibrosis* 14 (2015): S104.

Methods

We conducted a prospective observational study of patients with the G551D mutation. Baseline measures were recorded including spirometric measures, weight and sweat chloride. Glycaemic control was **assessed using HbA1c and repeated measures were recorded at 1, 3, 6 and 12 months.**

Results

Of 24 subjects included, 16 had normal glucose handling as defined by oral glucose tolerance test, 5 subjects had a diagnosis of CF-related diabetes and. 3 subjects had impaired glucose tolerance prior to ivacaftorFEV_1, BMI and sweat chloride significantly improved at all timepoints compared to baseline. population, there was a significant decrease in HbA1c from baseline to 6 months: median 42.5 mmFor the whole ol/L vs 39.5 mmol/L, $p = 0.004$. In patients with normal glucose tolerance there was a significant reduction in HbA1c at 3 (-2.1 mmol/L, $p = 0.027$), 6 (-2.4 mmol/L, $p = 0.002$) and 12 months (-1.9 mmol/L, $p = 0.03$) compared to baseline. There were no significant changes in HbA1c or insulin requirements in the other subgroups.

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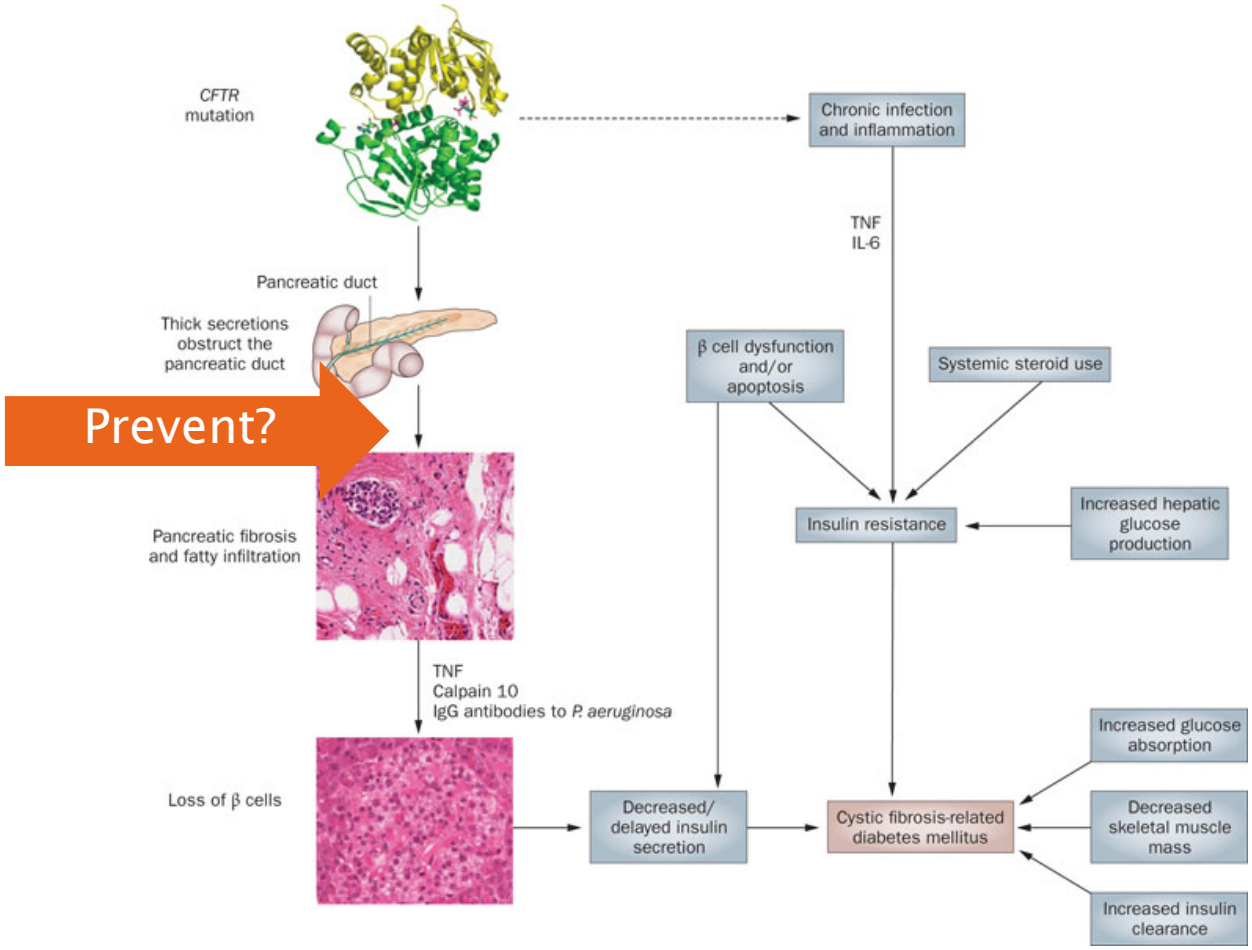
Risk of CFRD potentially prevented

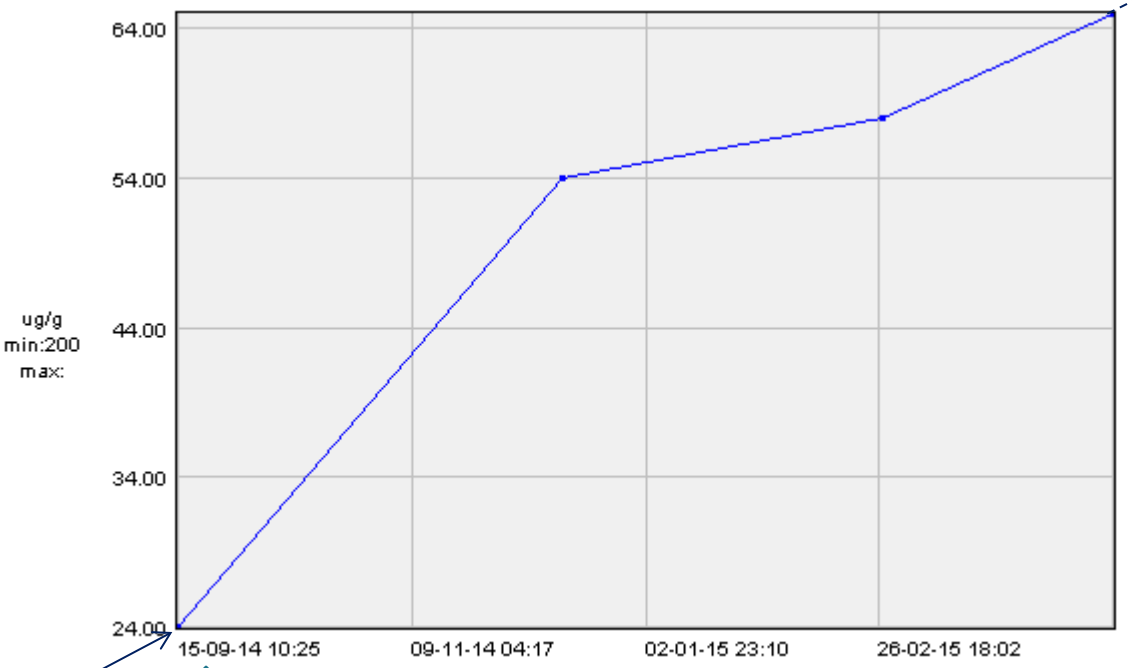


nature REVIEWS ENDOCRINOLOGY

Fecal elastase during Ivacaftor in 12 year old girl with gating mutation and EPI

Pancreas sufficient>200 µg/g

?



<15 ug/g

Start Ivacaftor

Preventing early pancreas destruction and EPI has high potential for preventing CFRD and improving survival

- Strong rational for evaluating fecal elastase in all age groups
- Strong rational for measure intestinal fat absorption

In CF patients with at least one G551D mutation, ivacaftor substantially improves fat intake and decreased fat excretion in near 80% of patients (normalizing in 3).

McKay, K., et al. "The effect of ivacaftor on exocrine pancreatic function in patients with cystic fibrosis and the G551D CFTR mutation who are naïve for ivacaftor." *Journal of Cystic Fibrosis* 14 (2015): S117.

- Ivacaftor treats the underlying defect in CFcaused by gating mutations of CFTR. Its use is associated with weight gain which may relate to decreased energy expenditure, increased appetite, but also a direct action of ivacaftor on pancreatic function.
- Methods
- An open-label two phase study was designed to elucidate pancreatic function **(weight gain, faecal elastase, and 3 day faecal fat excretion**) while taking ivacaftor. In Phase I (112 days) all participants commenced ivacaftor (150 mg BD) and in Phase II (112 days) those with evidence of normal pancreatic function **ceased pancreatic enzyme replacement therapy (PERT) while continuing ivacaftor**. 20 participants with established pancreatic insufficiency (fat excretion >10% of intake) aged 6–48 (11 male, 10 adults) with a G551D CFTR mutation.
- Results
- To date, 18 have completed phase I. At baseline, the mean weight was 52.8 kg, fat intake 93.8 g/day and fat excretion 39.3% of intake. At the end of Phase I, mean weight was 56.2 kg, fat intake 128.95 g/day, daily fat excretion was 30.4% of intake with 14 of 18 improving their fat absorption at the end of Phase I. In addition, 3 of 14 (17, 11 and 7 years) improved their fat absorption into the normal range (94.3, 94.9 & 91.2% of intake) and ceased PERT in Phase II. At the end of Phase II all 3 remain off PERT, maintain normal growth and are asymptomatic.
- Conclusions
- In CF patients with at least one G551D mutation, ivacaftor substantially improves fat intake and decreased fat excretion in near 80% of patients (normalising in 3). These are major factors contributing to the improved growth seen in these patients.
- **This study was supported by Vertex Pharmaceuticals.**

Intestinal fat absorption is the net result of lipolysis and post lpolytic processes

- Lipolysis
  - Pancreatic enzymes
  - EPI
- Post lipolysis
  - Luminal (bile acids microflora) and mucosal factors
  - Directly related to CFTR (dys)function

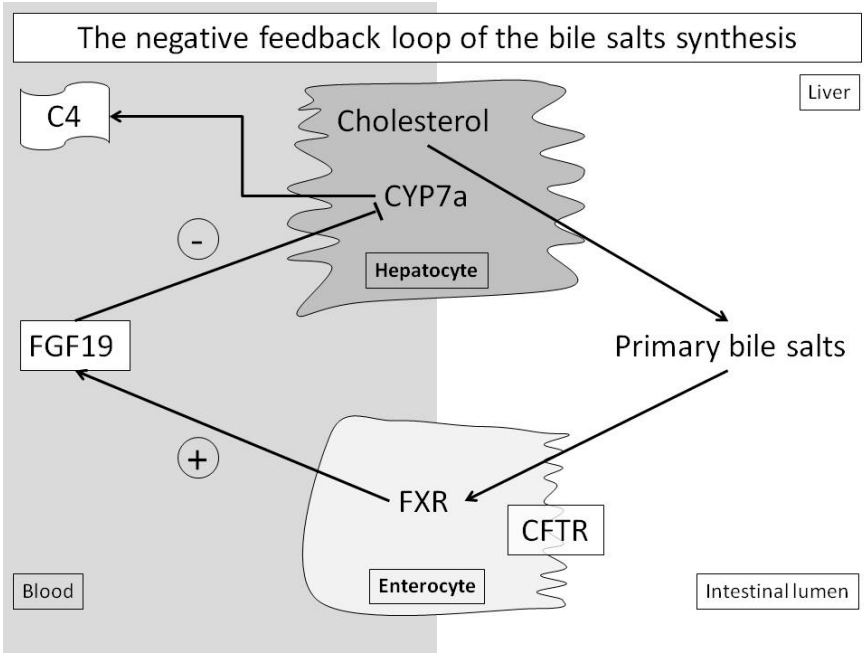
Wouthuyzen-Bakker, Marjan, Frank AJA Bodewes, and Henkjan J. Verkade. "Persistent fat malabsorption in cystic fibrosis; lessons from patients and mice." *Journal of Cystic Fibrosis* 10.3 (2011): 150-158.

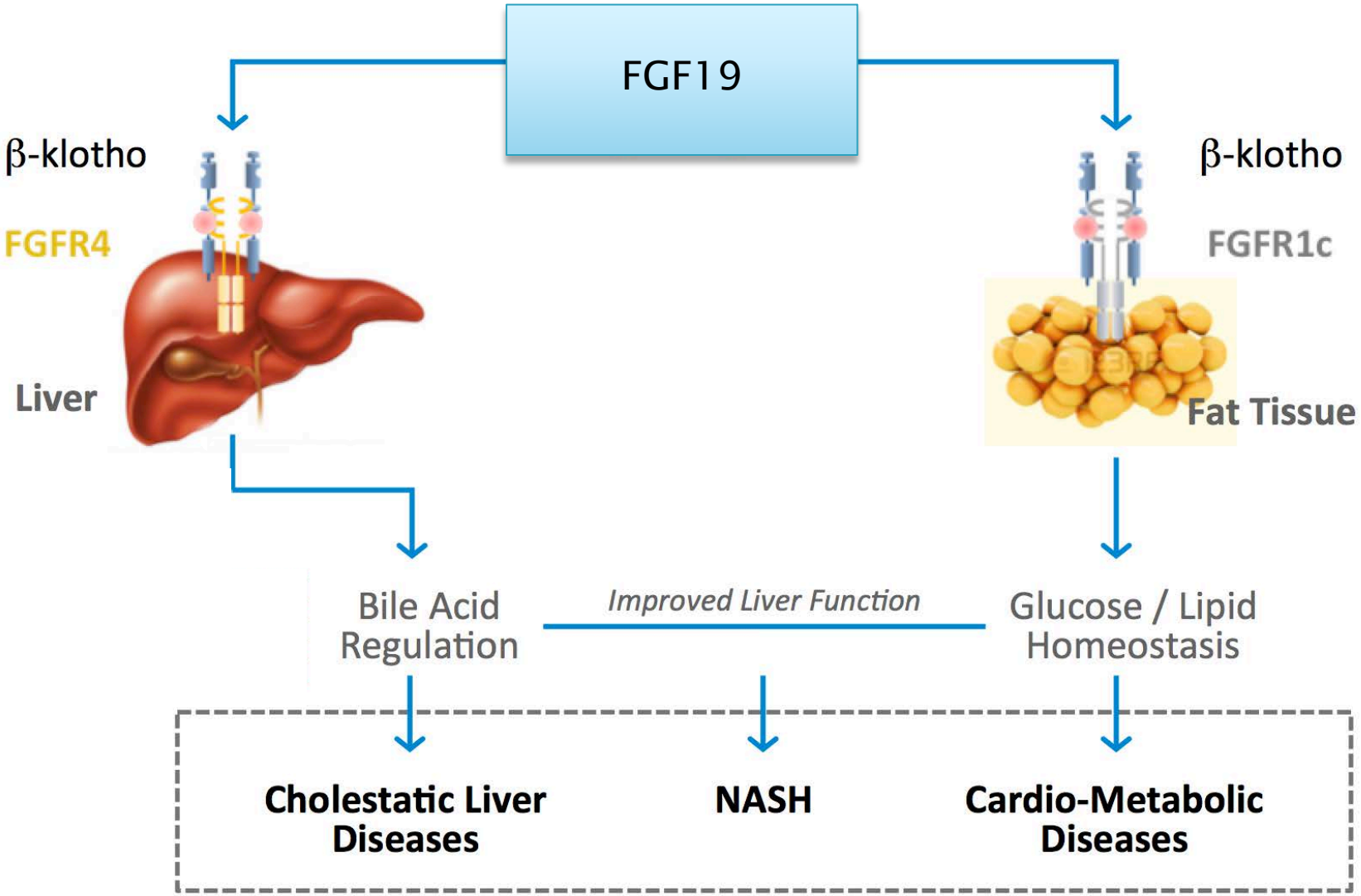
Bile salt are involved in intestinal fat absorption and regulation of glucose and lipids homeostasis

Disturbances of the normal homeostasis and enterohepatic circulation of bile salts are an intrinsic features the CF phenotype

FGF 19 and C4 in plasma marker of bile salt homeostasis

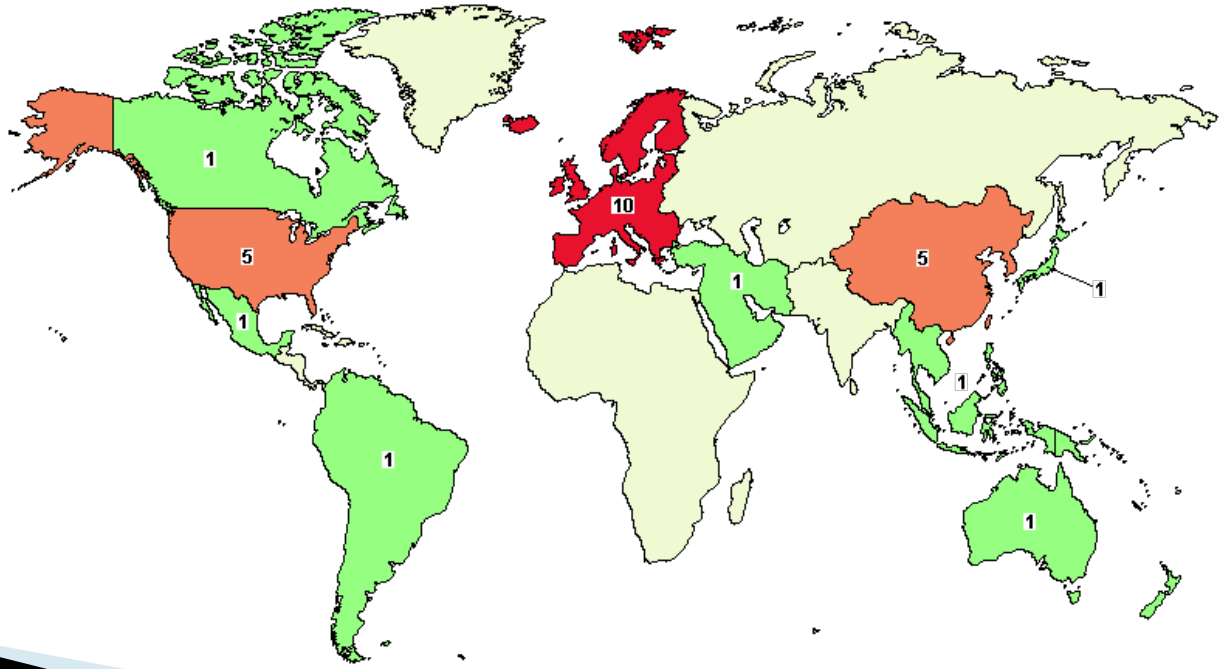
- **Plasma FGF19 (marker of intestinal bile salt absorption)**
  - ELISA, commercially available kit.
  - ~200 µl for duplicate
- **Plasma C4 (marker for hepatic bile salt synthesis)**
  - High-performance liquid chromatography-tandem mass spectrometry (XLC-MS/MS)
  - ~200 µl for duplicate




FGF19
β-klotho
FGFR4
Liver
β-klotho
FGFR1c
Fat Tissue
Bile Acid Regulation
Improved Liver Function
Glucose / Lipid Homeostasis
Cholestatic Liver Diseases
NASH
Cardio-Metabolic Diseases

FGF19 and C4 in Clinical trials

- **16 studies found for:** FGF19
- **2 studies found for:** C4



ClinicalTrials.gov

FGF19 Clinial trial study subjects

- Adenocarcinoma 2 studies
- Avitaminosis 1 study
- Bile Duct Cancer 2 studies
- Bile Duct Diseases 2 studies
- Biliary Tract Cancer 1 study
- Biliary Tract Diseases 2 studies
- Body Weight 2 studies
- Bone Diseases 1 study
- Bone Diseases, Metabolic 1 study
- Bronchial Neoplasms 1 study
- Calcium Metabolism Disorders 1 study
- Carcinoma 4 studies
- Carcinoma, Bronchogenic 1 study
- Carcinoma, Hepatocellular 2 studies
- Carcinoma, Non-Small-Cell Lung 1 study
- Cholangiocarcinoma 2 studies
- Cholestasis 3 studies
- Cholestasis, Intrahepatic 2 studies
- Connective Tissue Diseases 1 study
- Crouzon Syndrome 1 study
- Deficiency Diseases 1 study
- Diabetes Mellitus 3 studies
- Diabetes, Gestational 2 studies
- Diarrhea 1 study
- Digestive System Diseases 8 studies
- Digestive System Neoplasms 2 studies
- Endocrine System Diseases 2 studiesFatty Liver 2 studies
- Gastrointestinal Diseases 8 studies
- Gastrointestinal Neoplasms 2 studies
- Glucose Metabolism Disorders 2 studies
- Hypophosphatemia 1 study
- Insulin Resistance 1 study
- Intestinal Diseases 2 studies
- Intrahepatic Cholangiocarcinoma 1 study
- Intrahepatic Cholestasis of Pregnancy 1 study
- Liver Cancer 2 studies
- Liver Cirrhosis 1 study
- Liver Cirrhosis, Biliary 1 study
- Liver Diseases 6 studies
- Liver Neoplasms 2 studies
- Lung Diseases 1 study
- Lung Neoplasms 1 study
- Malabsorption Syndromes 2 studies
- Malnutrition 1 study
- Metabolic Diseases 4 studies
- Musculoskeletal Diseases 1 study
- Neoplasm Metastasis 1 study
- Neoplasms by Histologic Type 3 studies
- Neoplasms, Connective Tissue 1 study

"There is clear evidence of chronic intestinal inflammation in CF patients, possibly more strongly developed in those presenting pancreatic insufficiency"

- High-fat diet
- Gut microbiota
- Impact of intestinal inflammation on nutritional and pulmonary status.

Gut-liver-brain axis

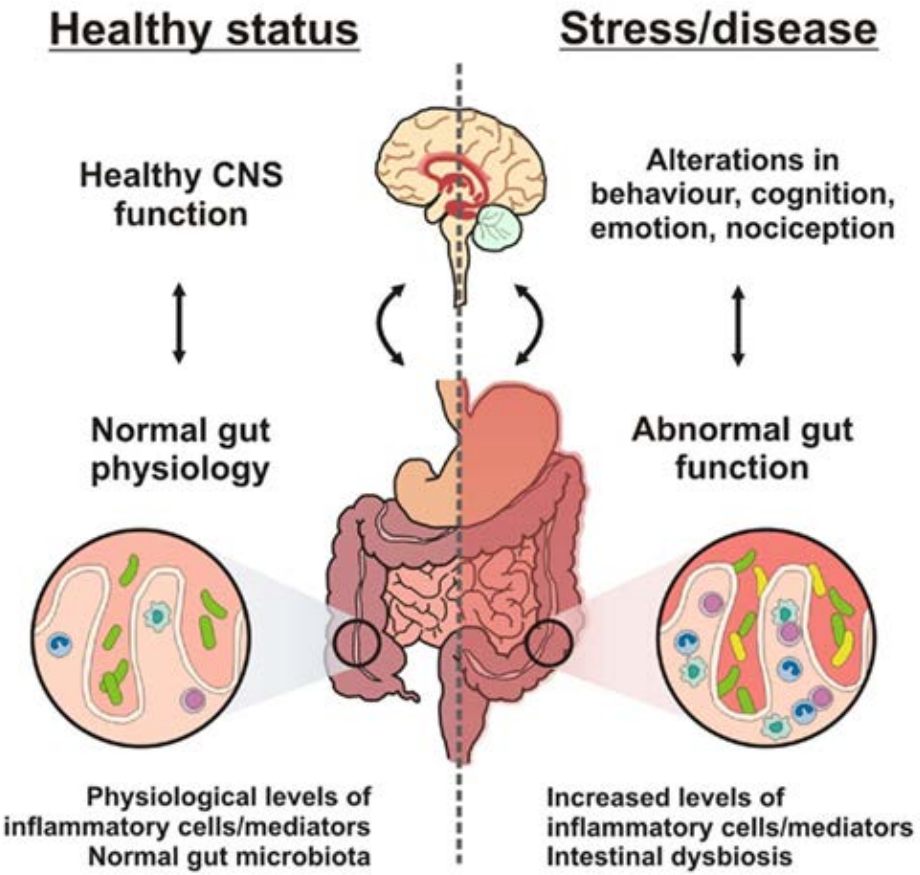
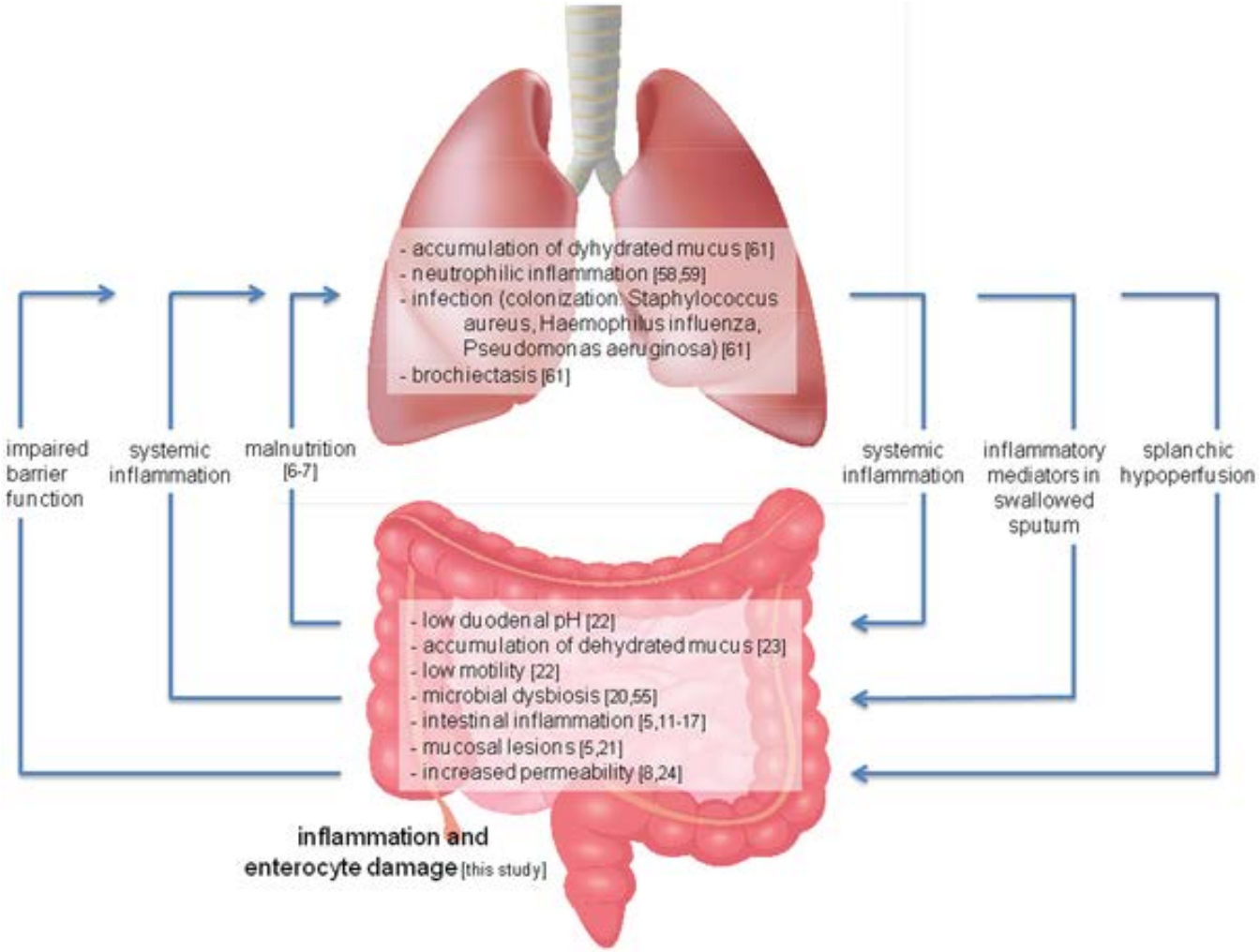


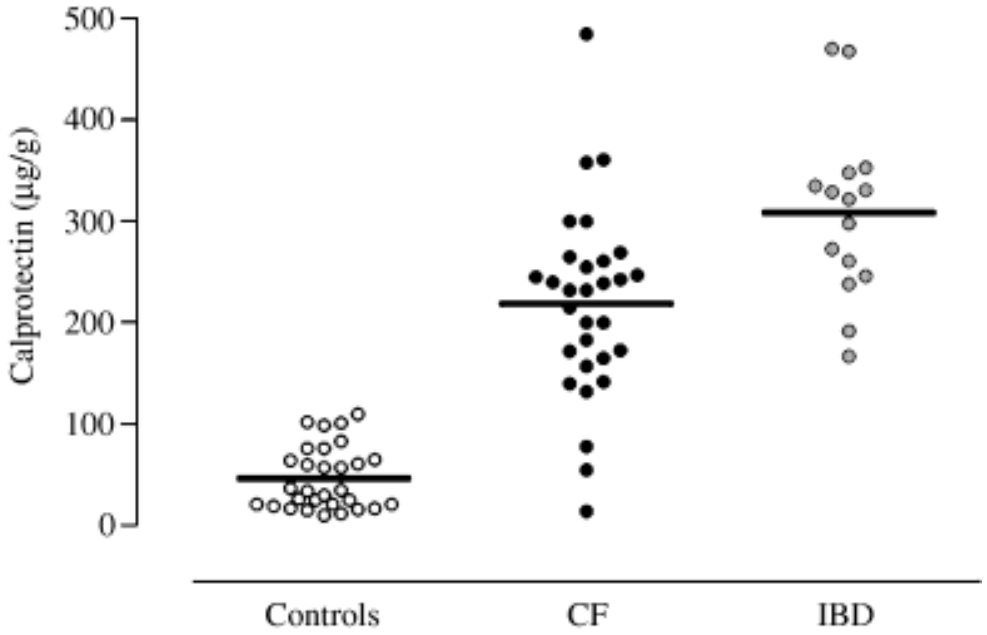
Fig 5. Proposed model for the interaction between intestinal and lung impairment in cystic fibrosis (CF).



Adriaanse MPM, van der Sande LJTM, van den Neucker AM, Menheere PPCA, Dompeling E, et al. (2015) Evidence for a Cystic Fibrosis Enteropathy. PLoS ONE 10(10): e0138062. doi:10.1371/journal.pone.0138062
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0138062

Fecal calprotectin is established marker for intestinal inflammation

Fecal calprotectin increased in Cystic fibrosis



Alimentary Pharmacology & Therapeutics
Volume 20, Issue 7, pages 813–819, 8 SEP
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2004.02174.x/full#f1

Conditions influencing intestinal inflammation in CF

Adriaanse MPM, et al. (2015) Evidence for a Cystic Fibrosis Enteropathy. PLoS ONE 10(10)

Increased risk for intestinal tract cancer in Cystic fibrosis

- Adenocarcinoma of the colon
- Standardized Incidence Ratio 2.5-3.5
- Comparable with IBD (standard screening)
- Higher after organ transplant
- Indication for screening CF patient ~30-35 years

Maisonneuve, Patrick, et al. "Cancer risk in cystic fibrosis: a 20-year nationwide study from the United States." *Journal of the National Cancer Institute* (2012): djs481.

Risk factors for adenocarcinoma of the colon in general population

Inflammation

Age

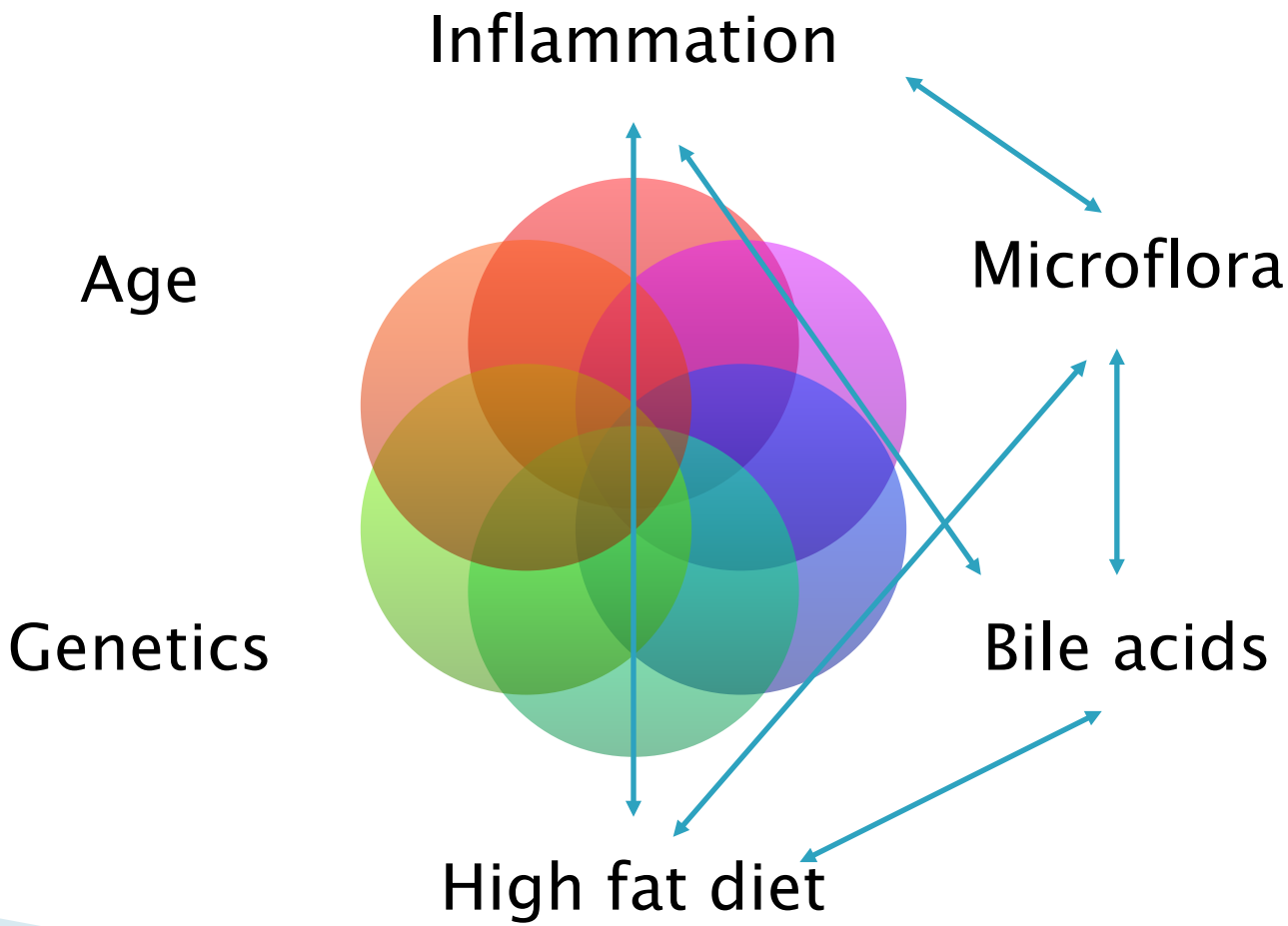
Microflora

Genetics

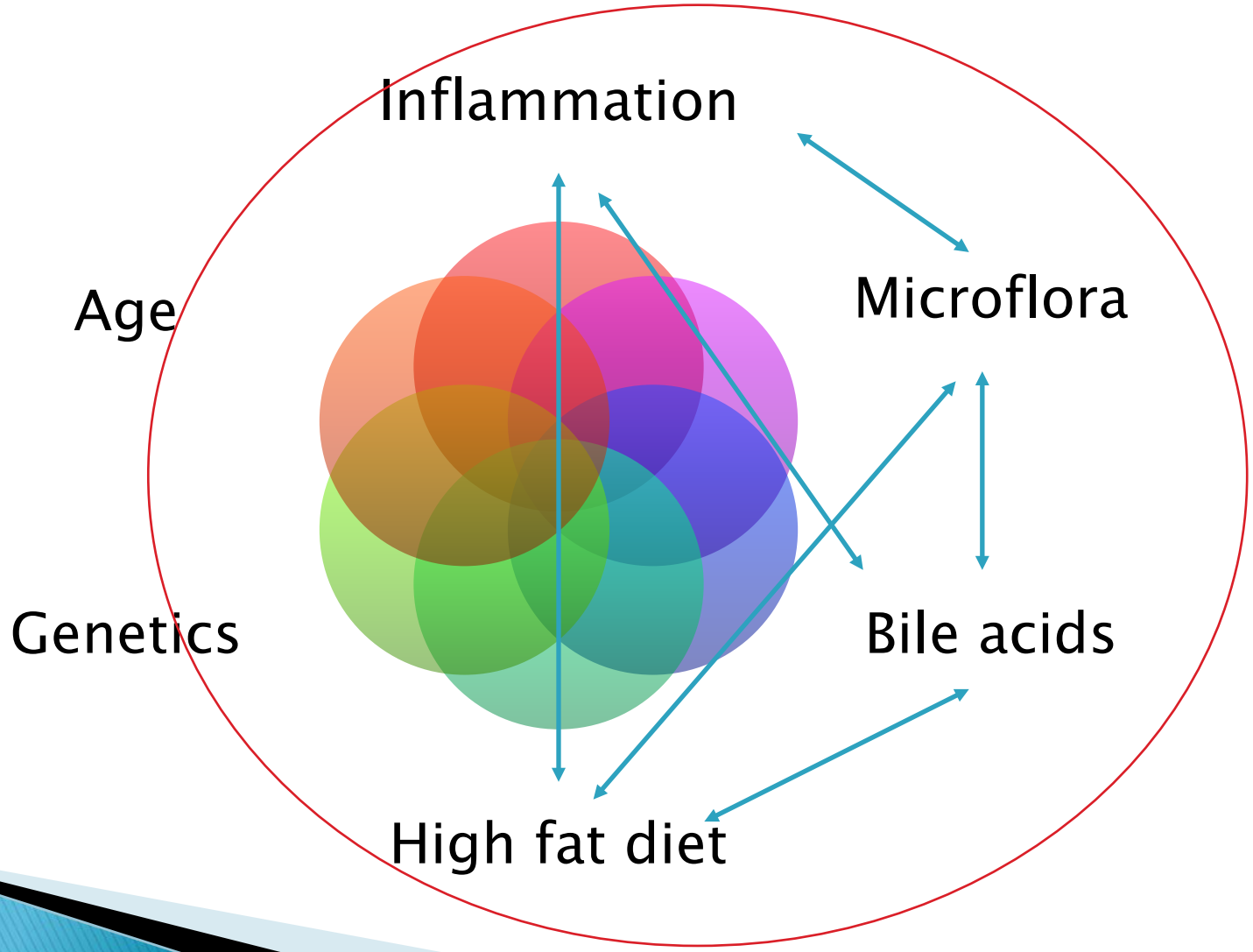
Bile acids

High fat diet

Risk factors for adenocarcinoma of the colon in general population



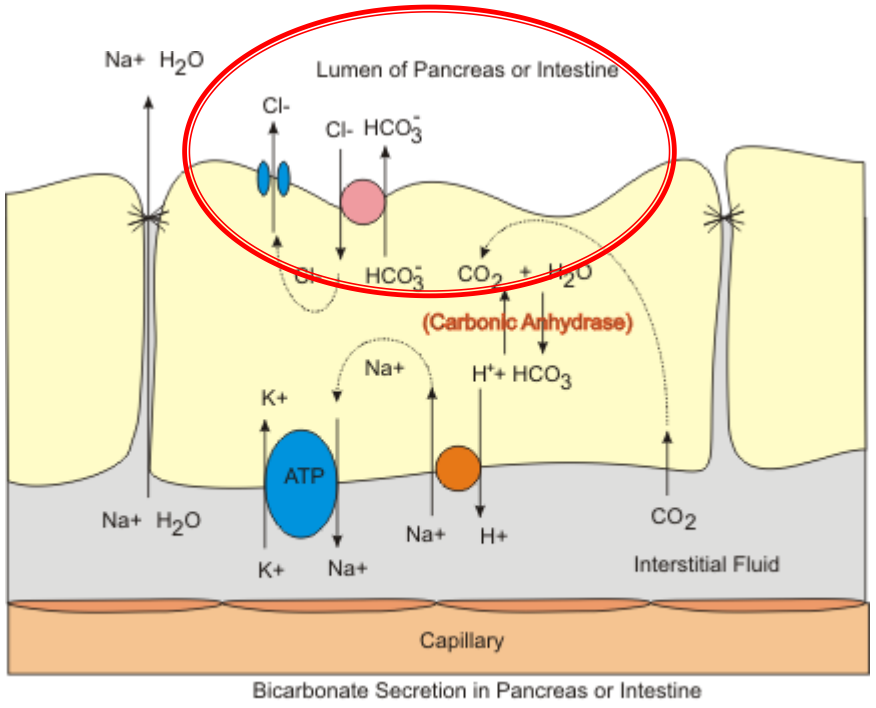
Risk factors for adenocarcinoma of the colon in Cystic fibrosis?



Intestinal pH influences:

- Digestive enzyme activity
- Bile salt conversion
- Micell formation
- Microflora composition

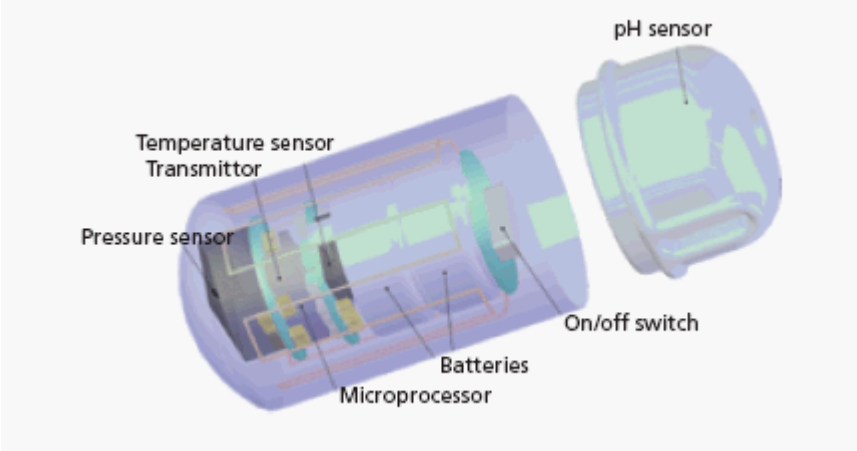
Gastric acid buffered by CFTR dependent intestinal and pancreatic bicarbonate



Bicarbonate Secretion in Pancreas or Intestine

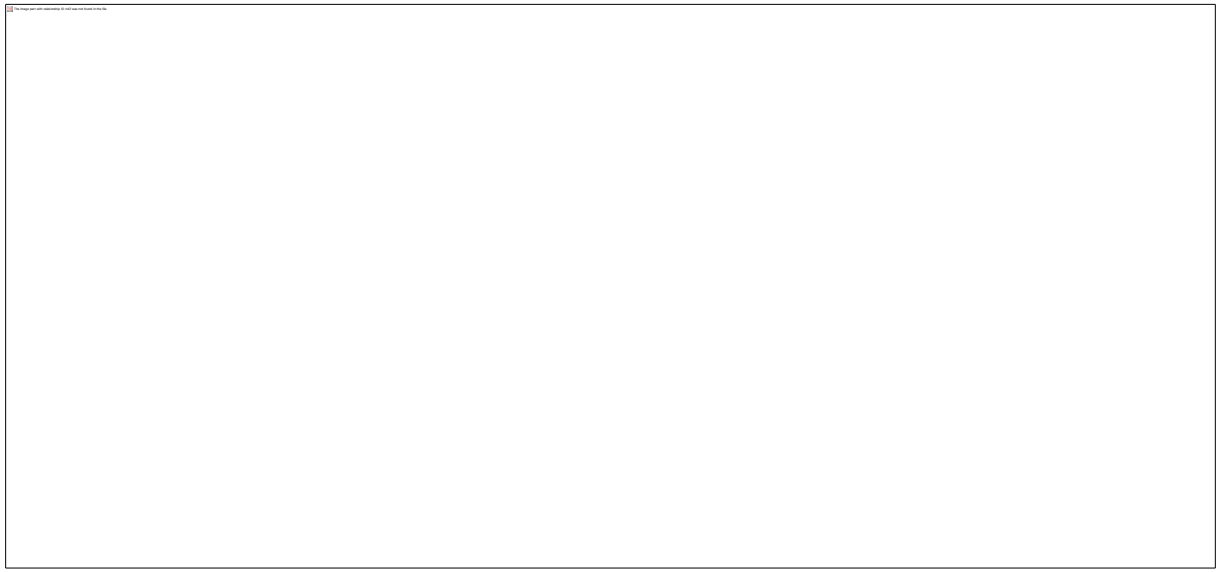
Frank Boumphrey M.D. 2009

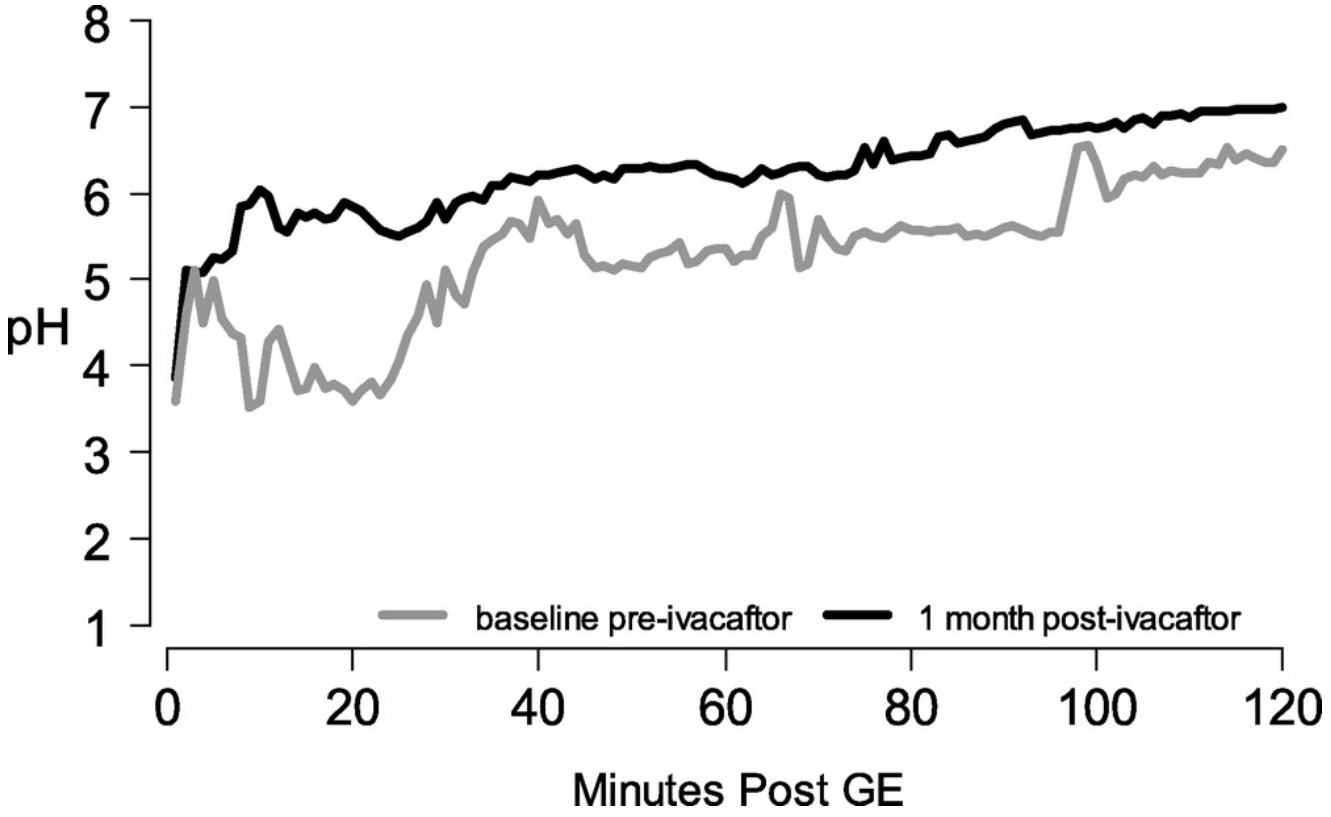
Smartpill



Dimensions 26 mm x 13 mm

Duodenal pH in CF is lower and displays a delayed neutralization





Am J Respir Crit Care Med, 2014

Goals of GI outcome measures in Cystic fibrosis

- Prevention or treatment of EPI
- Prevention or treatment of CFRD
- Treatment of intestinal fat absorption
- Prevention or treatment of inflammation
- Restoration of intestinal and bile salt metabolic regulation
- Prevention of intestinal malignancies

- Individual approach
  - Intra-individual variation
  - Organ specific responses

Discussion core set clinical outcome measures

- Dietary diaries (all ages)?

CFA	age < 2 years
Fecal elastase-1	all age groups
Serum FGF 19 and C4	>6 month
Fecal calprotectin	>3 years
Intestinal pH capsule	>6-8 years?

"Sweat chloride is not a useful marker of clinical response to Ivacaftor."

Barry, Peter J., et al. *Thorax* 69.6 (2014): 586-587.

"Changes in sweat chloride concentration at day 15 following treatment with ivacaftor **may have sufficient predictive potential** to identify individuals that show improvement in pulmonary function and weight gain after 16 weeks of treatment"

Seliger, Verena I., et al. "The predictive potential of the sweat chloride test in cystic fibrosis patients with the G551D mutation."
*Journal of Cystic Fibrosis*12.6 (2013): 706-713.