Pancreatic function testing has played an important role in the discovery of the mechanism of CF pancreatic pathophysiology. 

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patients with CF considered for lung transplantation were not included. Forty-one patients agreed to be included for prospective data collection. Nine patients did not perform EST. Cystic fibrosis diagnosis was evaluated according to the diagnostic criteria for CF defined in the CF foundation consensus report, discovering doubts about the correct CF diagnosis in 3 patients who either had sweat tests in the area between 40 and 60 mmol/L or lacked exact information of childhood sweat tests. One patient with intermediate range sweat test (46 mmol/L) and weak CF phenotypic characteristics was excluded. The other 2 patients had typical CF phenotype and were included. We thus included 40 patients for overview of the relation between genotype and exocrine status and 31 patients with CF for evaluation of EST.

Twenty-six HCs without gastrointestinal disease were also examined with EST. One HC was unable to fulfill the EST protocol and was excluded. Twenty-five HCs were included. The inclusion flow chart is illustrated in Figure 1. There was an age difference between the HC and CF groups performing EST as displayed in Table 1. The protocol was approved by the local ethics committee (approval number: REK 2010/2857-7) and the study was performed in accordance with the Helsinki Declaration. All subjects signed an informed consent. The protocol adheres to the STARD (STAndards for the Reporting of Diagnostic accuracy studies) statement.23

Methods
Before the examination medication, smoking habits, alcohol consumption, and body mass index were documented in all subjects. A review of the electronic patient journal was performed, and information on CFTR mutation and sweat-test values (Na⁺ and Cl⁻) were extracted from patient journals as documentation for the CF diagnosis. The genetic testing was performed over time, mostly by CF v3 Genotyping kit screening for 33 known CFTR mutations and collected retrospectively. Additional testing was performed for the CFTR mutations 4005+2T>C and R117H. Patients with unconfirmed mutation on screening performed whole gene sequencing for known CFTR mutations.

Fecal Elastase
Fecal elastase 1 (FE-1) was measured by a commercial monoclonal analysis kit (ScheBo Biotech, Giessen, Germany). We classified patients as exocrine pancreatic sufficient or insufficient by FE-1 concentration. Patients with FE less than 100 μg/g were considered pancreas insufficient.15

Short Endoscopic Secretin Test
The details of duodenal aspiration, duodenal juice handling, and analysis are described elsewhere19,20 but will be briefly described later.

The test procedure is illustrated in Figure 2. All procedures were performed by 4 experienced operators. Procedures were performed blinded to knowledge of pancreatic function status. Blinding to diagnosis and patient appearance was not possible. The patients received topical pharyngeal lidocaine (XYLOCAIN; AstraZeneca AB, Sweden) and conscious sedation with intravenous midazolam (MIDAZOLAM; Actavis Group HF, Island) 2 to 5 mg before the procedure. The study participants fasted for 8 hours before Secretin (Secrelux Sanochemia Diagnostics, Neuss, Germany; 1 CU/kg, maximum dose 70 CU) was administered 8 hours before Secretin (Secrelux Sanochemia Diagnostics, Neuss, Germany; 1 CU/kg, maximum dose 70 CU) was administered intravenously for 1 minute. Twenty-five minutes after secretin administration, we performed gastroscopy and carefully emptied the stomach and duodenum of fluid. Thirty minutes after secretin injection, the tip of the endoscope was placed distal to the papilla of Vateri and duodenal juice was aspirated through the working channel of the endoscope in three 5-minute sequences between 30 and 45 minutes after secretin stimulation. The samples were immediately stored on ice.

| TABLE 1. Results |
|------------------|------------------|------------------|------------------|
|                  | Patients         | Controls         |                  |
|                  | CFI (n = 13)     | CFS (n = 18)     | HC (n = 25)      |
| Age              | 21 (16–52)       | 22 (16–70)       | 38 (19–64)       |
| Sex, M/F         | 7/6              | 8/10             | 10/15            |
| Body mass index  | 21 (16–24)       | 23 (19–31)       | 24 (18–39)       |
| Sweat, CF        | 113 (89–157)     | 72 (59–89)       | —                |
| F-Elastase, μg/g | 0 (0–17)         | 560 (169–703)    | 553 (299–942)    |
| d-Bicarbonate, meq/L | 11 (0–24) | 118 (54.0–138)   | 114 (75.0–138)   |
| d-Lipase, 10⁷ U/mL | 0 (0–145) | 36.0 (6.90–175)  | 33.7 (14.1–120)  |
| d-Amylase, U/mL  | 14.9 (0–99)      | 281 (82.9–2200)  | 297 (89–1727)    |
| d-Elastase, U/mL | 0.0 (0–0.24)     | 0.17 (0.05–0.62) | 0.14 (0.03–0.57) |
| d-Chymotrypsin, U/mL | 0 (0–0.22) | 3.34 (0.73–15.0) | 2.85 (0.16–7.36) |
| Aspirated volume, mL | 1.7 (0–4.9) | 6.4 (3.00–13.7)  | 7.5 (3.20–9.90)  |
| Dry tap n = 3    | n = 3            | n = 0            |                  |

Results are expressed as medians (range) unless otherwise stated. CFCF indicates patients with CF with insufficient/sufficient pancreatic function defined by F-elastase cutoff value of 100 μg/g. ns indicates no significant difference.
Cutoffs between groups were made by student
results are expressed as median values with range. Simple compar-
of the samples was tested by Kolmogorov-Smirnov test. The
2011 Systat Software Inc., San Jose, Calif). Normal distribution
per 1.5 mL water added per milliliter duodenal juice).
Diagnostics, Mannheim, Germany; 0.2 mL solution of 1 tablet
inhibitor was added to one of these aliquots (Complete; Roche
zen more than 5 minutes after collection and stored on liquid nitro-
80°C until the day of analysis. The other 2 aliquots were snap fro-
stored on ice for bicarbonate analysis less than 3 hours after col-
Diagnoses, Mannheim, Germany; 0.2 mL solution of 1 tablet
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**RESULTS**

**Fecal Elastase**

When sorted by results of FE, the patients undergoing EST
were grouped as follows: CF pancreatic insufficient (CFI, n = 13) and CF pancreatic sufficient (CFS, n = 18). Demographic
data and FE results are displayed in Table 1.

**Duodenal Bicarbonate and Enzymes**

The values of duodenal bicarbonate concentration and lipase,
amylase, elastase, and chymotrypsin activities are presented in
Table 1 and Figure 3.

Using peak bicarbonate concentrations and peak duodenal
digestive enzyme activity levels, we were able to differentiate the
CFI group from both HCs and CFS patients (P < 0.001). The dif-
fences between CFS group and HC group were nonsignificant.
Duodenal bicarbonate correlates with volume aspirated
in EST. Duodenal bicarbonate concentration is the most direct CFTR
function measure. If we define an intermediate range of CFTR
function between 60 and 90 mEq/L, we identify 2 patients with
CF in this group. Both these subjects are classified as pancreas
sufficient by the FE cutoff value of 100 μg/g. The plot of bicar-
bonate against lipase activity demonstrates hyperconcentration
of the duodenal enzymes in the 2 patients with CF in the inter-
mediate bicarbonate level (Fig. 4).

**Diagnostic Accuracy**

Receiver operator curves were calculated for bicarbonate
concentrations and enzyme activities. Sensitivity and specific-
ity corresponded to suggested cutoff values are displayed in
Table 2. Compared with FE as standard for exocrine function,
bicarbonate has a sensitivity of 100% and a specificity of 88% with
the usual cutoff value set to 80 mEq/L (P < 0.001). The posi-
tive predictive value of the test was 91% and the negative pre-
dictive value was 100% compared with the same standard. D
enzymes have slightly lower sensitivities and specificities com-
pared with the FE standard, but the differences in ROC areas
between enzymes and bicarbonate are nonsignificant (Table 2).

**Genotype/Phenotype Analysis**

A list of known mutations organized according to pancreatic
phenotype for the whole group (n = 40) is displayed in Table 3.
There is a strong tendency toward pancreatic insufficient pheno-
type in the group with known, severe CF mutations on both alleles
(P < 0.001). The group with pancreatic sufficient phenotype has
the highest number of patients without a known CF mutation.
As noted earlier, the quality review of the CF diagnosis is accord-
ing to diagnostic criteria,25 discovering doubts about the correct
CF diagnosis in 3 patients (one excluded). Neither of these patient
had pancreatic insufficient phenotype. One patient had a patho-
genic mutation in one of the CFTR alleles; the other two had no
known CFTR mutation.
Adverse Events

The subjects reported mild abdominal discomfort and sensation of hunger connected to the secretin infusion. Most subjects also reported mild to moderate discomfort during the endoscopy. Heart rhythm, pulse, and oxygen saturation were observed in all subjects during the procedure. No complications or severe adverse events were reported.

DISCUSSION

In the present study, we demonstrate that a new, short EST is well tolerated and has a good diagnostic accuracy in assessing exocrine pancreatic function in patients with CF. We demonstrated a good correspondence between duodenal bicarbonate after secretin stimulation and the FE standards in the pancreas insufficient patients. Furthermore, duodenal enzyme concentrations also had fair correspondence with FE in both the pancreas sufficient groups and the patients with severe insufficiency. Among patients with CF with intermediate bicarbonate levels, we discovered 2 patients with CF with marked elevated pancreatic enzyme activity levels in all enzyme groups compared with other patients and controls. This phenomenon might prove to be a marker to identify patients with pancreatic sufficient CF at risk of or in the process of developing pancreatic insufficiency. Exocrine pancreatic test results were well correlated to the severity of CF genotype in our population.

Fecal elastase has previously demonstrated to be an excellent tool in repeated evaluation of exocrine pancreatic function in patients with CF and has more or less prevented the need for more complex, direct pancreatic function tests. However, FE has demonstrated weaknesses compared with the secretin-cholecystokinin test when aiming to follow progress in pancreatic failure or to detect early failure. Fecal elastase is not a tool to directly assess pancreatic ductal function. Development of the new, expensive CFTR modulators will increase the need of a clinical test to evaluate pancreatic CFTR function. Evaluation of the new, timed ESTs has to our knowledge previously not been performed in patients with CF. Schibli et al stated that tests with short sampling periods, concentration-based end points, and

FIGURE 3. Box and scatter plots for peak bicarbonate concentrations and peak duodenal pancreatic enzyme activities divided by groups.

FIGURE 4. The figure illustrates the correlation between peak duodenal bicarbonate concentration and duodenal lipase activity in the patients with CF. Mark especially the 2 patients with intermediate bicarbonate concentrations, aspirated volumes in the lower normal range and hyperconcentrated duodenal enzymes. White circles indicates CFI; black circles, CFS.
lacking evaluation of intestinal losses could create considerable errors when estimating pancreatic function in patients with CF, especially in the intermediate range. However, the short period analyzed in their study was confined to samples collected during the first 20 minutes after secretin stimulation, which later has been shown to be before the peak bicarbonate level in the duodenum in other studies including chronic pancreatitis patients.25,29 We claim that bicarbonate-concentration measure in duodenal juice is a physiological correct way to assess failure in CFTR function, because ductal secretion of water and bicarbonate is dependent of CFTR.8 Challenges in timing of duodenal collection and pollution from gastric ventricular fluid with low pH have been addressed in earlier works validating ESTs.21,30 The complex tube-based tests probably have better accuracy than shorter, concentration-based tests and should still be considered as criterion standard, but the fact that these tests have existed for decades without achieving widespread use justifies the search for simplified methods. We believe that our timed protocol can achieve acceptable results comparable with the more cumbersome and complex direct tests and that EST can prove to be a valuable direct CFTR-function test. To make a final conclusion on this issue, an evaluation of the FE and EST against the old quantitative direct tests must be conducted.

We chose FE as a standard for exocrine pancreatic function in our protocol because this is the simplest and most widespread test; thus, the protocol was not designed to compare the diagnostic accuracies of EST and FE. The conservative FE cutoff value of 100 μg/g gives a firm definition for the pancreas insufficient group. The influence of the possible low sensitivity in the FE test of early exocrine failure cannot be decided and specificity levels achieved for EST are influenced from reduced sensitivity of FE. Another accepted criterion standard for exocrine function in CF is the 3-day fecal-fat sample. Because of the lack of sensitivity of this test for mild to moderate failure, this standard will suffer from the same pitfalls as FE.

Analyses of pancreatic enzymes infer numerous practical pitfalls and require conscious handling of the duodenal samples.20 These analyses demonstrate lower diagnostic accuracy compared with bicarbonate. Still, we propose that pancreatic enzyme activity assessment gives valuable, additional information. Firstly, our procedure for analyzing duodenal enzymes requires only small amounts of fluid; thus, we are able perform analyses in patients with CF with severe volume output failure. Secondly, the phenomenon of enzyme hyperconcentration illustrates an etiological factor postulated to pre-exist the pancreatic destruction in CF. This may prove to be a sign of early volume output failure.

The correlation between CF genotype and pancreatic insufficient phenotype is well established in several studies.31–33 In the present study, the information on genotype was collected retrospectively from a patient registry, and the tests were performed for a period. The population has a number of unidentified CF mutations in the CFS group. Patients with CF in western Norway are earlier described to have a low prevalence of pancreatic insufficiency, possibly due to regional variations in genotype with a higher prevalence of milder CF mutations.34 We did not include patients with lung transplants or severe lung disease. Thus, the population presented is not a representative cohort of the whole CF population in our region. It is still interesting to note that also in our population, patients with CF with severe CF genotype have a high rate of exocrine pancreatic insufficiency and those milder mutations or unknown mutation status is a predictor pancreatic sufficiency; thus, the EST results fit the expectations when correlated to genotype.

We find all of the patients with CF-related disorder or doubtful CF diagnosis in the CFS group. We excluded one but chose to include the 2 others because of the presence of significant clinical signs of CF phenotype represented by classical organ manifestations and colonization from CF-associated pathogens strongly suggestive of CF. As noted by Ooi et al,35 the diagnostic guidelines provide guidance and promote rigorous evaluation for the diagnosis of CF but neither guideline should be regarded as dogma. The genetic diversity combined with a remaining uncertainty of the diagnosis in the CFS group may explain why we are not able to identify reduced bicarbonate levels in this group compared with HCs. Whether the presence of milder or heterozygote CFTR mutation can give partly reduced CFTR function and reduced duodenal bicarbonate compared with subjects with normal CFTR status remains unanswered.

### Table 2. Test Accuracy

| Enzyme          | Sensitivity (95% CI) | Specificity (95% CI) | Cutoff | AUC     |
|-----------------|---------------------|---------------------|--------|---------|
| D-Bicarbonate   | 1 (0.74–1)          | 0.88 (0.75–0.96)    | 80 meq/L | 1       |
| D-Lipase        | 1 (0.71–1)          | 0.92 (0.79–0.98)    | 15,000 U/mL | 0.99 |
| D-Amylase       | 1 (0.72–1)          | 0.93 (0.80–0.98)    | 100 U/mL   | 0.99 |
| D-Lactase       | 1 (0.69–1)          | 0.95 (0.83–0.99)    | 0.05 U/mL   | 1      |
| D-Chymotrypsin  | 1 (0.72–1)          | 0.90 (0.76–0.97)    | 1 U/mL     | 1      |

Diagnostic accuracy calculated from ROC curves for the CF group. Regarding duodenal bicarbonate, the cutoff is established in earlier studies. Regarding duodenal enzymes, the suggested cutoff values are extracted from our ROC calculations.

AUC, area under the curve calculated from ROC curves.

### Table 3. CFTR Mutations

| CF1 (n = 19) | CFS (n = 21) |
|-------------|-------------|
| ΔF508/ΔF508 (n = 10) | ΔF508/R117H (n = 1) |
| ΔF508/S912x (n = 3) | ΔF508/V232D (n = 1) |
| ΔF508/E60X (n = 1) | ΔF508/4005+2T>C (n = 2)* |
| ΔF508/G542x (n = 1) | ΔF508/3849+10kbc>T (n = 1)* |
| ΔF508/1525-SA>G (n = 1) | G551D/75Q (n = 1) |
| 621+1G>T/4005+2T>C (n = 1) | ΔF508- (n = 1) |
| 394delTT/S912x (n = 1) | 1525-47T>G- (n = 1) |
| R1162x/1525-2A>G (n = 1) | R117H- (n = 2) |

No mutation found (n = 0) | No mutation found (n = 11) |

Overall view of known mutation related to pancreatic phenotype.

*Patients with subnormal D-bicarbonate and enzyme hyperconcentration.
In the present study, we aimed to evaluate our short EST in a group of patients with CF with a well-established clinical diagnosis. Despite the fact that EST is an invasive test, the current version using less than 20-minute sampling time is feasible and can be performed in patients with CF with a low risk of patient hazard. Our study is the first evaluation of a timed short EST in patients with CF compared with HCs. Because of costs, test simplicity, and lack of patient hazard, FE will remain the first choice for assessing exocrine pancreatic function in patients with CF. We believe that the EST can be a valuable clinical supplement where the FE result leaves doubt whether there is pancreatic insufficiency or not. Particularly, the test might prove useful in selected patients with CF at risk if a combination of bicarbonate and enzyme values can give an indication on early or forthcoming exocrine pancreatic insufficiency. Whether the test can identify early or the risk of future pancreatic insufficiency remains unanswered. The effect of enzyme hyper concentration in the phase of early pancreatic failure needs further confirmation in a protocol with a higher number of patients in this phase of disease progression. An important near-future perspective can be to identify subjects to be targeted for therapeutic interventions with new CFTR modulators to preserve pancreatic function.

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