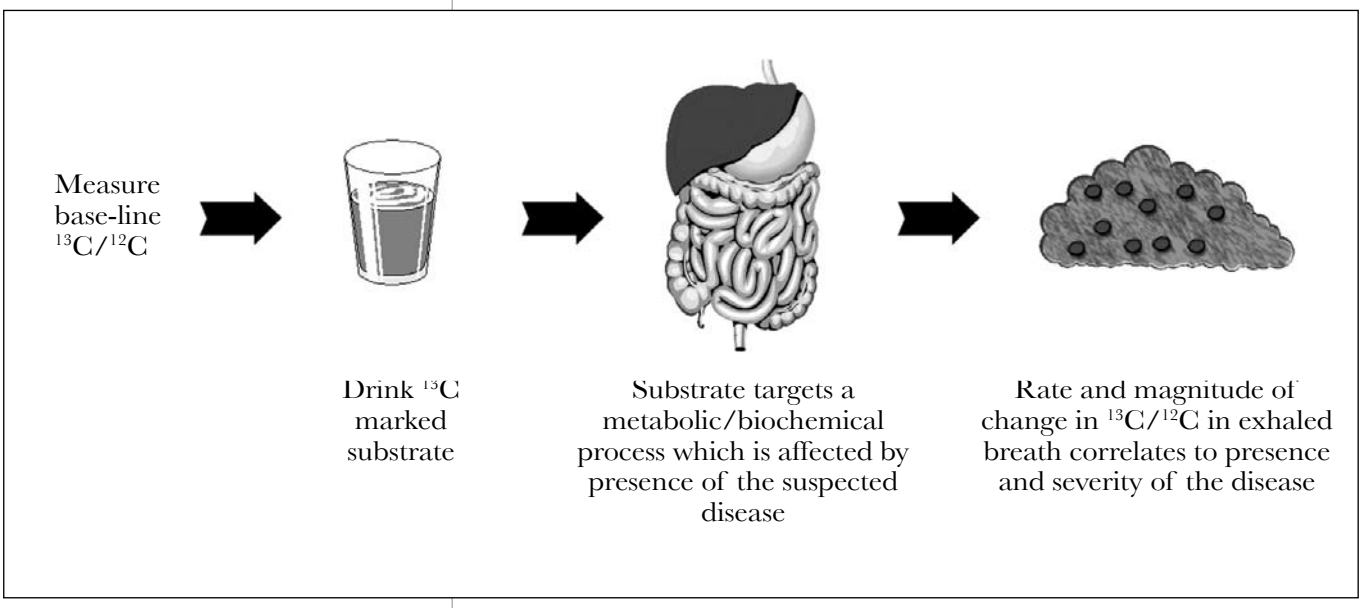
Use of ^{13}C Breath Tests for Current and Future Clinical Use

Carbon 13 (^{13}C) breath testing assists in monitoring metabolic organ function and processes in the liver and gastrointestinal tract. Non-invasive diagnostic tests based on the use of ^{13}C substrates present an extremely broad range of applications[1].
The only currently available ^{13}C application in routine clinical use is the ^{13}C-urea breath test (UBT) for detecting *Helicobacter pylori* bacteria in patients' stomachs.

The Concept Behind ^{13}C Breath Testing

The concept of ^{13}C breath testing is based on measuring the ratios of two non-radioactive isotopes of the Carbon atom in the form of CO_2: Carbon 12 (^{12}C) and Carbon 13 (^{13}C). Both isotopes naturally exist in normal breath, but their ratios are dissimilar: approximately 99% of exhaled breath is ^{12}C and only about 1% is isotope ^{13}C. Breath testing is based on changing this ratio by giving patients a test meal or drink that is enriched with ^{13}C. The $^{13}CO_2$ components of the substrate are extracted during absorption, gastro-intestinal transit, or metabolism of the absorbed substrate. The exhalation of $^{13}CO_2$ in patients' breath over a period of time reflects the function of the studied organ. This rate may indicate a particular organ's health and can be measured by devices such as the BreathID® to measure the ^{13}C enrichment in the exhaled air.



Several available ^{13}C-labeled substrates demonstrate the applicability and utility of the ^{13}C breath test. Some of these are described in the next page.

^{13}C Breath Testing Uses:

Helicobacter pylori: the ^{13}C-urea breath test is based on the detection of increased urease activity due to *H. pylori* infection[2]. This test is used for the initial diagnosis of *H. pylori* and serves as a follow-up tool to assess therapy results as well. Most breath-testing methods require the patient to exhale into two breath collection bags or tubes, before and after the ingestion of a test substrate (^{13}C-urea), which has been dissolved in a glass of water. Test duration is usually between 20 and 30 minutes, after which the test results are sent for analysis. If the samples are collected in tubes, samples are analyzed using an IRMS (Isotope Ratio Mass Spectrometer). If the samples are collected in bags, an NDIR (Non Dispersive Infrared Spectrometer) is used. The Exalenz BreathID® System* is unique in its ability to measure a patient's breath continuously and to provide immediate results at the end of the test. Test duration averages 10 minutes.

Gastroparesis (delayed gastric emptying): The ^{13}C-octanoic acid (solid meal) test was found to demonstrate a highly significant positive correlation to scintigraphy [3] and is a viable tool to assess solid emptying rate. Another substrate, the ^{13}C-sodium acetate (liquid meal) test may represent the liquid emptying rate. These are useful in diagnosing and monitoring gastroparesis, a disorder in which the stomach empties its contents slowly due to impaired gastric motor function. The current method for determining the gastric emptying rate is using scintigraphy, which is expensive and involves the consumption of radioactive test substrates. Both the ^{13}C-octanoic acid test and the ^{13}C-sodium acetate test are non-radioactive. They can be administered in any clinical setting and serve as practical tools in measuring the gastric emptying rate.

Liver impairment: A range of breath tests have been studied to monitor and quantify different states of reduced liver function and inductions and inhibitions of enzymes. These include ^{13}C-methacetin, ^{13}C-L-phenylalanine, ^{13}C-caffeine, ^{13}C-aminopyrine, and ^{13}C-galactose. Today, liver impairment is tested by standard serologic and biochemical serum liver tests, which do not provide an accurate assessment of liver function capacity and are relatively inaccurate in detecting hepatic disease severity. While liver biopsies are occasionally

^{13}C substrates may be used for the assessment of**:

- H. pylori
- Liver Impairment
- Liver Cirrhosis and Fibrosis
- Disease severity in fatty Liver
- Gastroparesis
- Gastric Accommodation
- Oral-Cecal Transit Time
- Bacterial Overgrowth
- B12 Insufficiency
- Pancreatic function
- Lipid Digestions

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Exalenz
Breathtaking Solutions

* *BreathID® System operating in PATIENT MODE (Hp FasTest)*

** *The only approved ^{13}C substrate for clinical use is the ^{13}C-UREA for detecting H. pylori all other substrates are limited to investigational use.*

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performed, their infrequent use and the added risk of complications limit their use as a standard follow-up test for monitoring disease severity. The ^{13}C substrate that is most often documented in literature is the ^{13}C-methacetin. It demonstrates the ability to measure P450 cytochrome activity, which is one of the most important metabolic pathways in the liver. Recently published literature involving the BreathID System suggests that the Methacetin Breath Test (MBT) can be used for identifying the degree of fibrosis, cirrhosis and inflammation[4] and can offer greater sensitivity than standard clinical tests for managing patients with severe acute liver disease[5] .

Assessment of disease severity in fatty liver disease: Fatty infiltration of the liver is a common cause for chronic liver disease. In some patients, inflammation or other types of injuries results in a "second hit" which causes further deterioration to the organ. Imaging may be used in order to assess fat accumulation in the liver, but it is limited in its ability to assess and manage fatty liver disease progress. Liver biopsies may be performed, but they have added risks of complications. The ^{13}C-sodium octanoate breath test has been used to assess liver mitochondrial beta oxidation. Alteration in mitochondrial beta oxidation may be correlated to disease severity.

Exocrine pancreatic function: Secretin test is the accepted gold standard in pancreatic testing, and is often used in assessing pancreatic function. Nevertheless, because it is time consuming, expensive and extremely cumbersome, it has not been accepted into routine clinical use. Indirect approaches, such as the diagnosis and differentiation of fat malabsorption using breath tests to evaluate the substrates of ^{13}C-labeled lipids (trioctanoin, triolein, and palmitic acid), provide a practical alternative to direct exocrine pancreas function assessment methods. Additionally, these tests can be valuable in the monitoring of pancreatic enzyme substitution therapy.

Bacterial overgrowth: a jejunal fluid culture is the standard method of assessing bacterial overgrowth. The fluid is obtained by intubating the jejunum under fluoroscopy with a closed-tube system, using a capsule for anaerobic collection. Gas-liquid chromatography of the fluid to identify volatile fatty acids is highly specific (100%) but insensitive (56%), as it only detects anaerobic activity. The ^{13}C-xylose breath test offers a diagnostic alternative to the microbiological analysis of jejunal fluid for the diagnosis of small bowel bacterial overgrowth; it also provides a practical way of serial testing a condition that is often chronic[2] .

References:

1 Fischer H. and Wetzel K.; The future of 13C-breath tests. Food and Nutrition Bulletin, vol. 23, no. 3 (supplement) © 2002, The United Nations University

2 Romagnuolo et al.; Using Breath Tests Wisely in a Gastroenterology Practice: An Evidence-Based Review of Indications and Pitfalls in Interpretation. AJG – Vol. 97, No. 5, 2002

3 Syed AA, Rattansingh A, Furtado SD.; Current perspectives on the management of gastroparesis. J Postgrad Med 2005; 51:54-60

4 G. Lalazar et al.; A Continuous 13C Methacetin Breath Test For Noninvasive Assessment Of Intrahepatic Inflammation And Fibrosis In Patients With Chronic HCV Infection And Normal ALT. Journal of Viral Hepatitis, 2008

5 G. Lalazar, T. Adar, Y. Ilan; Point-Of-Care Continuous ^{13}C-Methacetin Breath Test Improves Decision Making in Acute Liver Disease: Results of a Pilot Clinical Trial. World J Gastroenterol 2009 February 28; 15(8): 966-972

Disclaimer: The BreathID® System is intended for use in the qualitative detection of H. pylori. It has an approved 510(K) and an approved NDA for the 13C-urea Tablet and Citrica Powder. Certain applications are limited by Federal (of United States) Law to Investigational Use only.

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