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November 15, 2018

Dear Regina,

Welcome to BioMarketing Insight's monthly newsletter.

Last month, I covered "Highlights from Biotech Week, September 4 - 7, 2018" If you missed last month's article, click [here](#) to read it. This month we'll cover "Nonalcoholic Steatohepatitis (NASH): an Overlooked Disease."

Read on to learn more about this topic and other current news. The next newsletter will be published on December 15th, 2018.

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Sincerely,  
Regina Au  
Principal, New Product Planning/  
Strategic Commercial Consultant  
[BioMarketing Insight](#)



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## Developing a Product? Commercializing a Product?

If you are developing a product and have not conducted the business due diligence to determine commercial viability or success, contact [me](#) for an appointment. For successful commercial adoption of your product or looking to grow your business, contact [me](#) for an appointment.

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I am pleased to announce that my article entitled "Updates in Solving the Mystery of Alzheimer's Disease Pathology" was published in the International Journal of Clinical Pharmacology & Pharmacotherapy. This commentary reviews the "Updated Proposed timeline of biomarker abnormalities leading to cognitive impairment" and the involvement of both beta amyloid clearance and plaque, and tau clearance and tau-mediated neuronal injury and dysfunction. To read the article, click [here](#).

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### **Why Speed to IND Can Cause Major Issues and Risks Later in Development**

If you were unable to attend my presentation, here is a brief podcast interview with Dan Stanton from BPI on my presentation. To hear the podcast, click on my picture.

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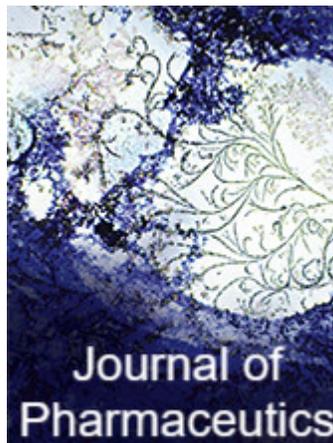


## Why Our Microbiome is Important to Our Physiology and Diseases

I am pleased to announce that my article entitled "Why Our Microbiome is Important to Our Physiology and Diseases" was published in the International Journal of Clinical Pharmacology & Pharmacotherapy. This article reviews the results of the Human Microbiome Project and the factors that affect our microbiome in relation to our healthy state and dysbiosis or disease state. To read the article, click [here](#).

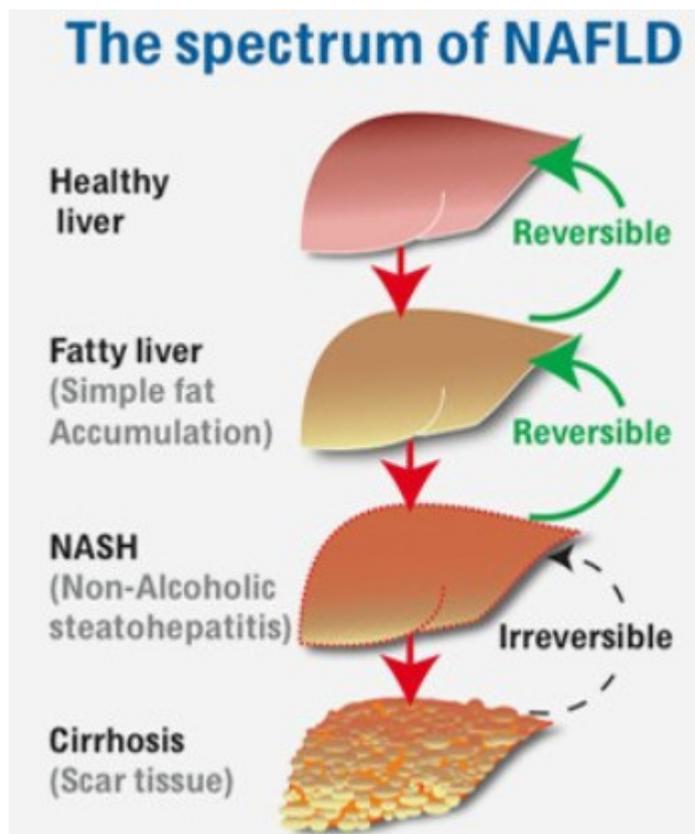
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## Immunooncology: Can the Right Chimeric Antigen Receptors T-Cell Design Be Made to Cure All Types of Cancers and Will It Be Covered?

I am pleased to announce that my article on "Immunooncology: Can the Right Chimeric Antigen Receptors T-Cell (CAR-T) Design Be Made to Cure All Types of Cancers and Will It Be Covered?" has been published in Journal of Pharmaceutics. This article reviews the mechanism, design and administration of CAR-T cells, and whether payers will pay for this new technology. To read the article, click [here](#).



## Nonalcoholic Steatohepatitis (NASH): an Overlooked Disease

Nonalcoholic Steatohepatitis (NASH), is a type of Nonalcoholic Fatty Liver Disease (NAFLD). NASH is a chronic condition where there is build up of fat in the liver, generally triglycerides processed by the liver for the body's future energy uses. [Too much fat](#) in the liver progresses on to inflammation of the liver and liver cell damage. [NAFL](#) can occur with or without inflammation and fibrosis. [NASH](#) occurs with inflammation, fibrosis and eventually cirrhosis. This disease resembles alcoholic liver disease but occur in people who don't drink or drink very little alcohol. [NASH](#) is most often diagnosed in patients between 40 yr and 60 yr but can occur in all age groups. [NASH](#) can also occur in children.

The reason NASH is an overlooked disease is because most patients who have NASH are asymptomatic. It is considered a common and "[silent](#)" killer. Affected individuals may have at least one risk factors such as obesity, type 2 diabetes and dyslipidemia. However, not all obese, type 2 diabetes and dyslipidemia patients go on to develop NASH.

### Prevalence

The National Institute of Diabetes and Digestive and Kidney Diseases ([NIDDK](#)) research estimates that between 30 percent and 40 percent of adults in the U.S. have fatty liver disease, and up to 12 percent of those adults will develop NASH.

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but confirmed diagnosis with most biopsy-based studies reported a prevalence of NASH of 3 to 5 percent. Worldwide, NAFLD has a reported a prevalence of 6 to 35 percent (median 20 percent).

According to one [study](#), the prevalence of NASH cirrhosis and NAFLD-associated advanced fibrosis has increase from a 2-fold to a 2.5-fold increase according to a 1999-2002 study compared to a 2009-2012 study respectively.

Since [2001](#), liver transplants attributed to NASH have increased tenfold in the U.S.

### Diagnosis

The [first sign](#) of suspecting NASH is elevated liver function tests (LFTs) that includes alanine aminotransferase (ALT) or aspartate aminotransferase (AST). However, not all NASH patients present with elevated LFTs. If a patient does have elevated LFTs, with no other reason for liver disease, an x-ray or imaging studies that include ultrasonography, CT, and MRI, may identify hepatic steatosis or fat in the liver. [However](#), these tests cannot identify the inflammation typical of NASH and cannot differentiate NASH from other causes of hepatic steatosis. To confirm the diagnosis of NASH a liver biopsy must be performed.

Since the prevalence of NASH is 3-5 percent of the reported NAFLD being 10-46 percent, physicians may be hesitant to do a biopsy which is an invasive test unless all tests, imaging studies warrant a biopsy. There is currently no diagnostic test to definitively confirm NASH.

However, a start-up company in Cambridge, MA called [Glympse Bio](#), spun out from the laboratory of MIT professor Sangeeta Bhatia, is developing a sensor technology that the company claims can give clinicians an early look at a developing disease. Glympse has developed bioengineered nanoparticles that circulate through the body, detect disease, and report their findings through a signal read by testing the patient's urine. Their lead disease target is NASH. Glympse also says its technology can monitor how a patient's disease is responding to a drug. If Glympse's technology comes through fruition, it would not only help to diagnose NASH a lot easier but earlier before it develops into cirrhosis and eventually a liver transplant making it too late to recover from this disease.

### Cause

The cause of NASH is unknown. NASH patients can have elevated blood lipids, such as cholesterol and triglycerides, and many have diabetes or prediabetes. However, not every obese person or every patient with diabetes has NASH. In fact, some patients with NASH are not obese, do not have diabetes, and have normal blood cholesterol and lipids. [NASH](#) can occur without any apparent risk factor.

These are the reasons, that NASH can be easily over looked since there is no consistent

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and dyslipidemia does because there are definitive signs of these diseases through laboratory tests, and risk factors such as obesity or medical history. Finding a treatment for an unknown mechanism of action, makes it hard to pinpoint a specific target.

While the causes of NASH is not known, several factors are possible candidates according to one [source](#):

1. insulin resistance
2. release of toxic inflammatory proteins by fat cells (cytokines)
3. oxidative stress (deterioration of cells) inside liver cells

Other [sources](#) hypothesis that possible mechanisms for steatosis include:

1. reduced synthesis of very low density lipoprotein (VLDL) and increased hepatic triglyceride synthesis (possibly due to decreased oxidation of fatty acids or increased free fatty acids being delivered to the liver).
2. inflammation may result from lipid peroxidative damage to cell membranes. These changes can stimulate hepatic stellate cells, resulting in fibrosis.

### Treatment

There is currently [no specific](#) treatment for NASH except to reduce the risk factors. The most important recommendations are the following:

1. reduce their weight (if obese or overweight)
2. follow a balanced and healthy diet
3. increase physical activity
4. avoid alcohol
5. avoid unnecessary medications

[New treatment](#) options are now being studied in clinical trials. These include the use of antioxidants (such as vitamin E, selenium, and betaine) and some newer antidiabetic medications (metformin, rosiglitazone, and pioglitazone) which treat insulin resistance.

There are no FDA-approved drugs for NASH, however, there are two companies that have drugs in clinical trials to treat NASH; Genfit Inc. and Intercept Pharmaceuticals.

### Genfit, Inc.

Genfit is developing Elafibranor, a dual agonist of the peroxisome proliferator-activated receptor- $\alpha$ (PPAR-alpha) and peroxisome proliferator-activated receptor- $\delta$ (PPAR- $\delta$  delta). PPAR agonists have been found to be one of the most promising classes of anti-diabetic drugs. [PPAR-alpha](#) plays a role in the breakdown and transport of fatty acids in the body. It also plays a role in reducing inflammation and ideal for the treatment of NASH which always has inflammation. [PPAR-delta](#), which is produced in cells throughout the body, plays a role in energy metabolism and reducing inflammation. PPAR have also shown to

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According to the [company](#), "in the rat, GFT505 (Elafibranor) demonstrated liver protection by acting on several pathways involved in NASH pathogenesis, reducing steatosis, inflammation, and fibrosis. GFT505 improved liver dysfunction markers, decreased hepatic lipid accumulation, and inhibited proinflammatory (interleukin-1 beta, tumor necrosis factor alpha, and F4/80) and profibrotic (transforming growth factor beta, tissue inhibitor of metalloproteinase 2, collagen type I, alpha 1, and collagen type I, alpha 2) gene expression."

In February 2014, the FDA granted Fast Track designation for GFT-505 for the treatment of NASH.

[Elafibranor](#) is currently in a phase 3 trial called RESOLVE-IT, a pivotal trial evaluating the efficacy of elafibranor in subjects with NASH Activity Score of  $\geq 4$  with F2 or F3 fibrosis. The trial's primary endpoint is NASH resolution under the new modified definition (ballooning = 0; inflammation = 0-1) without worsening of fibrosis.

Two thousand patients are being enrolled in the [RESOLVE-IT](#) trial with 1,000 patients for an interim analysis and data readout is expected in 2019 (interim analysis). The trial will remain blinded after interim analysis and will continue post-marketing to confirm the long-term benefits of NASH resolution with elafibranor 120 mg dose. If the data is positive, it would support elafibranor's marketing application in both the U.S. and Europe.

### **Intercept Pharmaceuticals**

Intercept Pharmaceuticals is developing obeticholic acid, a farnesoid X receptor (FXR) agonist for NASH. [Obeticholic acid](#) (OCA), a 6 $\alpha$ -ethyl derivative of the natural human BA chenodeoxycholic acid (CDCA) is the first-in-class selective FXR agonist that is about a 100-fold more potent than CDCA. Farnesoid X receptors (FXRs) are nuclear hormone receptors expressed in high amounts in body tissues that participate in bilirubin metabolism particularly in the liver, intestines, and kidneys. FXRs also play a critical role in carbohydrate and lipid metabolism and regulation of insulin sensitivity. FXRs modulate liver growth and regeneration during liver injury. Preclinical studies have shown that FXR activation protects against cholestasis-induced liver injury. In addition, FXR activation protects against fatty liver injury in animal models of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), and improved hyperlipidemia, glucose intolerance, and insulin sensitivity.

According to NIDDK, the FLINT trial, sponsored by the NIH's National Institute of Diabetes and Digestive and Kidney Diseases and partial funding from Intercept found that obeticholic acid (OCA) treatment was associated with improved liver function in people with NASH. Liver health improved in 45 percent of people on OCA versus 21 percent of the placebo group. "Although obeticholic acid did not eliminate liver disease in FLINT

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official for the NASH Clinical Research Network (NASH CRN), which performed the FLINT study. [OCA](#) was also associated with increases in itching and total cholesterol. More research is needed to determine whether OCA is a safe and effective treatment for NASH and to fully understand how OCA affects cholesterol.

In September 2015, Intercept started its Phase 3 trial called REGENERATE of obeticholic acid, or OCA, in NASH.

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### Closing Thoughts

Diagnosing NASH is difficult because there is no consistent parameters to indicate to a physician that a person may have NASH. Not every obese person or every patient with diabetes has NASH. In fact, some patients with NASH are not obese, do not have diabetes, and have normal blood cholesterol and lipids. NASH can occur without any apparent risk factor and at any age.

Many NASH patients are asymptomatic making it harder to diagnose early, since most physician will diagnose a disease when a patient complains of symptoms and the first sign of manifestation is portal hypertension or elevated LFTs, where the disease has probably progressed to cirrhosis and eventually lead to liver transplant.

To make things even more difficult, the only method to confirm a diagnosis of NASH is through a liver biopsy. I would presume that a physician would not order a biopsy unless there is a strong indication of NASH accompanied by abnormal lab tests, symptoms, and medical history because out of the 10-46 percent of the people who develop NAFLD, only 3-5 percent go on to develop NASH. This is a relatively small percentage and a physician would not want to put his patient through unnecessary pain to find out that the patient does

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make it hard for a physicians to readily diagnose this disease.

If Glympse Bio is successful with their sensory technology in diagnosing NASH, this diagnostic tool will definitely create a paradigm shift, since physicians would be able to diagnose NASH early in the course of the disease and not have to wait for a liver biopsy. Physicians could also starting treating this disease early even if it is lifestyle changes which can only help if patients have other co-morbidities. Patients with NASH also have a higher risk of developing Hepatocellular carcinoma (HCC). [NASH-induced](#) HCC can occur in non-cirrhotic stages of disease emphasizing the importance of treating NASH at earlier stages.

We need drugs that can treat NASH. However, because the cause is unknown, this makes it difficult to find the right target. Right now there are two drugs in clinical trials for NASH and there are a number of other companies (i.e. 89Bio and Akero Therapeutics, both working on a glycopegylated fibroblast growth factor 21 ([GFG21](#)), a protein that plays a key role in regulating metabolism and signaling throughout the body, and many large pharma companies such as Novartis and Pfizer) working on developing a drug for NASH. If Elafibranor and/or obeticholic acid gets approved, both will be successful since not all patients will respond to one medication, each having its own pros and cons. If Glympse Bio's technology can also monitor how well the patient is responding to a drug, this will help tremendously in identifying early whether a drug is working or not and then chose an alternative drug regimen.

There is enough room for both drugs or more to be successful in a potentially [\\$35-\\$40 billion](#) market. A combination of drugs could also be successful since the mechanism of action is unknown. Combination products tend to target multiple targets and used in lower doses which could alleviate unwanted side effects. The drug that will be the most successful is one that can not only halt the progression of the disease but reverse the disease even at the cirrhosis stage without the unwanted side effects if caught early enough. Which drug will achieve this profile? It's too early to know, only time will tell.

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Should you have any questions or need of assistance with your business due diligence, determining your product's value proposition and economic value of your product, feel free to contact me at 781-935-1462 or [regina@biomarketinginsight.com](mailto:regina@biomarketinginsight.com).

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