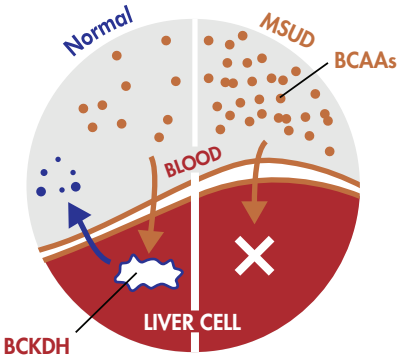
MAPLE SYRUP URINE DISEASE (MSUD)

the orphan disease center

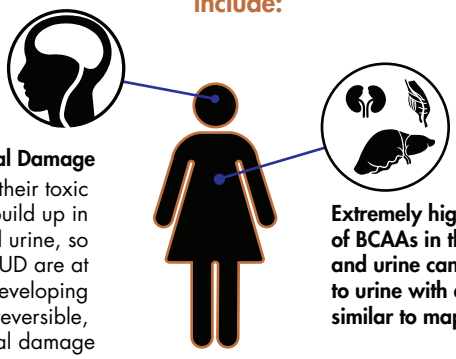
Maple Syrup Urine Disease (MSUD) is a rare genetic disease that leads to a build up of the branched-chain amino acids (BCAAs) in the blood and urine.

MSUD is caused by inherited mutations from both parents in one (or more) of three genes that produce proteins forming the branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex

Genetic mutations to one or more of the following genes prevents formation of a complex that is essential for breaking down the amino acids, leucine, isoleucine, and valine (the BCAAs):
- -BCKDHA
- -BCKDHB
- -DBT



Signs and Symptoms include:



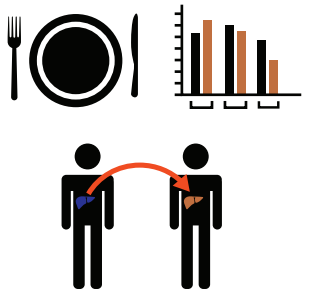
Neurological Damage
BCAAs and their toxic by-products can build up in the blood and urine, so patients with MSUD are at constant risk of developing severe irreversible, neurological damage

Extremely high levels of BCAAs in the blood and urine can lead to urine with an odor similar to maple syrup

Current treatments have limitations

Monitoring and Diet Control:
MSUD patients must constantly monitor the chemistry of their blood and urine, and carefully control their diet for management of BCAA levels.

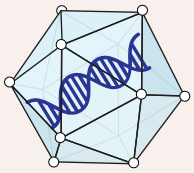
Liver Transplant
Limited availability, high risk



POTENTIAL NEW THERAPIES FOR MSUD

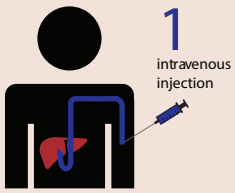
Experimental, molecular therapies, including delivery of messenger RNA (mRNA) and AAV gene therapy strive to overcome the genetic mutation(s) causing MSUD in different ways.

1.
a normal healthy copy of the gene(s) containing a mutation is produced and is inserted into either a harmless viral vector

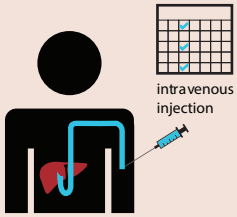


or a lipid nanoparticle containing an mRNA

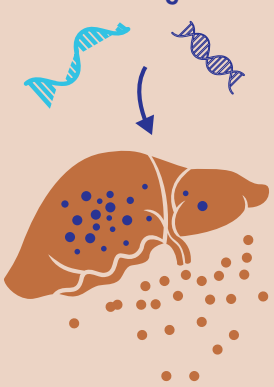
2.
AAV vector is delivered to the patient's body through the circulatory system with a **one-time** intravenous injection



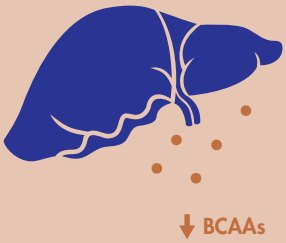
Lipid nanoparticles are routinely administered via intravenous injection **every few weeks**



3.
Liver cells (hepatocytes) take up vector and begin to express functional copies of the affected gene



4.
Functional proteins are produced and can break down the BCAAs and prevent a toxic build up of these amino acids and their by-products, lowering levels in the blood



Safety First

gene therapy has proven relatively safe and effective in animal models of MSUD

What's next?

Early clinical trials for MSUD evaluating safety in human subjects are next

Penn Medicine