cryobio

Additional Agreement to Use Donor WL 4011

We, _____ (Recipient), and _____ (Partner, if applicable), specifically request and accept frozen semen from Cryobio donor WL 4011. We understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor WL 4011. WL 4011 had expanded genetic carrier screening to determine their carrier status for 283 recessive genetic conditions. We have received genetic test results on this sperm donor, and we understand that donor WL 4011 has been found to be a carrier of the following recessive genetic conditions:

Biotinidase Deficiency
and
Progressive Familial Intrahepatic Cholestasis, Type 2.

Why carrier status is important: Carriers of genetic diseases have changes, called pathogenic variants or mutations, in a specific (or multiple) gene(s). Most of the genetic diseases that the Cryobio donors are tested for are inherited in an autosomal recessive pattern. Typically, we all have two copies of every gene---one from the egg source and one from the sperm source. Autosomal recessive diseases require a mutation in both copies of the same gene in order for it to cause disease. Therefore, individuals who carry just one mutation in a gene that causes recessive disease are 'carriers' of that specific disease. Carriers of most of the genetic diseases Cryobio donors are tested for do not typically show symptoms of the disease, i.e., they are asymptomatic, although there are rare exceptions. Some diseases tend to occur more in certain ethnicities, and some tend to occur evenly in all ethnicities. Most individuals are carriers for at least one if not multiple recessive genetic diseases.

Carrier status is important because if both the egg source and the sperm source are carriers for pathogenic variants or mutations in the same gene, then there is a 1 in 4 chance of the resulting child having that specific disease; a 2 in 4 chance of the resulting child being a carrier for that specific disease; and a 1 in 4 chance of the resulting child being neither a carrier or having that specific disease. Some of the diseases Cryobio donors are tested for have genotype-phenotype correlation, meaning that specific genetic pathogenic variations (the genotype) in a specific gene can be predictive of the type of specific disease that may present in the individual (the phenotype), but not all do.

Biotinidase Deficiency (*BTD* gene): Biotinidase deficiency is an autosomal recessive disorder caused by pathogenic variants in the gene *BTD*. Individuals from all ethnicities can be carriers for biotinidase deficiency. Individuals with biotinidase deficiency are unable to effectively "reuse" a vitamin, called biotin, in their body. Biotin is important in helping the body break down proteins, fats, and carbohydrates. If individuals with biotinidase deficiency are identified prior to developing symptoms; they typically remain asymptomatic if appropriate biotin therapy is started early (i.e. taking extra biotin for the body to use). Biotin supplements need to be continued throughout the individual's life.

If left untreated, biotinidase deficiency affects individuals within the first few months of life or in childhood. Severe forms of the disorder cause children to experience neurological abnormalities such as seizures, decreased muscle tone, developmental delay, vision problems, and even death. Other symptoms include hearing loss, respiratory problems, and abnormalities related to or affecting the skin such as rash and alopecia (hair loss). While effective treatment is available, symptoms such as vision problems, hearing loss, and developmental delay are irreversible once they have appeared. Also, sometimes even in treated individuals, hearing loss and vision problems may still arise. Several specific variants have been associated

with full or partial biotinidase deficiency, and therefore the severity of the disease may be predicted based on the genotype (the specific gene mutations the affected person has). Carriers are not expected to show symptoms of this disease. Biotinidase deficiency is recommended as part of the newborn screen in the United States, therefore most babies are screened for and diagnosed with the disease at birth.

Progressive familial intrahepatic cholestasis, Type 2 (*ABCB11* gene): Progressive familial intrahepatic cholestasis, type 2 (PFIC2) is an autosomal recessive, pan-ethnic disorder caused by pathogenic variants in the gene *ABCB11*. PFIC2 is a condition that affects the liver. Individuals with this disease experience recurrent episodes of cholestasis (blockage of bile flow) starting in infancy. Bile is made by the liver and it aids in the digestion of food. In individuals with PFIC2, excess bile salts are stored in the liver cells and leak into the bloodstream, resulting in severe itching, jaundice (a medical condition that causes yellowing of the skin and eyes), and an enlarged liver. Damage of the liver cells frequently leads to liver failure and sometimes liver cancer. Many patients will require a liver transplant, usually before adulthood. Some patients with two pathogenic *ACBC11* variants will develop a less severe disease known as benign recurrent intrahepatic cholestasis, type 2. These patients have recurrent cholestasis episodes but do not develop liver failure or cancer. It is sometimes possible to predict progressive versus benign disease based on the specific genetic variants, but it may not be possible to predict the severity of the disease in all patients. Life expectancy may be reduced in some patients in cancer, or those requiring liver transplants that experience complications.

Of Note: There has been evidence of the possibility of digenic inheritance in individuals with mild liver disease involving the *ABCB11* gene. Digenic inheritance means genetic variants in two different genes combined cause a disease. In one case report, disease was mild and easily treated. In another, no intervention was required, and disease resolved on its own. However, without larger scale studies, more evidence is needed to conclude digenic inheritance of these two genes in causing liver diseases. Situations like these highlight the complex nature of genetics, and how no amount genetic testing can rule out possibility of all diseases. If you have additional questions, please contact us for further information.

Carrier status frequency:
Carrier status frequency is the chance of an individual being a carrier for a genetic condition based on their ethnicity alone prior to any genetic screening. If an individual tests negative as a carrier for a condition or conditions, then the chance of being a carrier is significantly decreased. This remaining risk is known as residual risk, meaning what is the risk of being a carrier even after negative genetic testing. Residual risk data is available directly through sema4's website, sema4.com, or can be requested from Cryobio.

Biotinidase deficiency (*BTD* gene) carrier status frequency in different ethnicities, from Sema4's website:

Worldwide	1 in 13
African	1 in 52
Ashkenazi Jewish	1 in 15
East Asian	1 in 324
Finnish	1 in 9
European (Non-Finnish)	1 in 12
Native American	1 in 24
South Asian	1 in 7

Progressive familial intrahepatic cholestasis, Type 2 (*ABCB11* gene) carrier status frequency in different ethnicities, from Sema4's website:

Worldwide	1 in 306
African	1 in 295

East Asian	1 in 153
Finnish	1 in 835
European (Non-Finnish)	1 in 276
Native American	1 in 390
South Asian	1 in 654

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for both biotinidase deficiency (*BTD* gene) and progressive familial intrahepatic cholestasis, Type 2 (*ABCB11* gene) carrier status and consider genetic counseling. Please refer to Sema4's website, sema4.com, for more information and contact Cryobio with any questions or to arrange genetic counseling. We also strongly recommend that you discuss the donor's genetic carrier status results with your health care provider. Finally, we recommend that any future child be notified of this donor's carrier status once they are of reproductive age, as even if they do not have a recessive disease, they could be a carrier and their carrier status could be important to identify risks related to their own reproductive future.

Cryobio has advised us of the following:	Please initial to show your understanding and agreement:
The donor we have chosen has had positive results from genetic testing looking at carrier status for 283 conditions. These results indicate that the donor is a carrier for biotinidase deficiency and progressive familial intrahepatic cholestasis, Type 2.	Initials: _____ Initials: _____
These genetic conditions are inherited as recessive traits. This means that if both the egg source and the sperm source are carriers for the same condition, there is a significantly higher chance of the resulting child having that genetic condition.	Initials: _____ Initials: _____
By the donor testing positive for carrier status for biotinidase deficiency and progressive familial intrahepatic cholestasis, Type 2, the risk to a resulting child would now be higher than that of the general population.	Initials: _____ Initials: _____
Both the risk of being a carrier and the sensitivity of the genetic testing can vary depending on the individual's ethnicity. When an individual tests negative for carrier status, it does not completely eliminate their chance of being a carrier for that disease. Instead, their remaining (residual) risk of being a carrier is determined by their ethnic background. While a negative result decreases the likelihood that an individual is a carrier, how much that risk is reduced by can vary significantly. For more detailed information regarding the sensitivity of testing and remaining risk after negative screening, please see Sema4's website.	Initials: _____ Initials: _____
Genetic testing looking at a large panel of genes, including the genes/conditions that the donor has tested positive for, is available and could be done.	Initials: _____ Initials: _____
Genetic testing is *strongly recommended* for me (or the egg source, if different) to see if I am a carrier for biotinidase deficiency (*BTD* gene) and progressive familial intrahepatic cholestasis, Type 2 (*ABCB11* gene).	Initials: _____ Initials: _____

A negative genetic test result in the egg source significantly reduces the likelihood that the resulting child could be affected with these conditions. However, we fully understand that the risk cannot be completely eliminated.	Initials: _____ Initials: _____
Expanded genetic carrier screening is continuing to evolve, and at the time this donor entered the program this was the screening available. My health care provider may recommend an expanded carrier screen that includes/included more than the 283 genes screened for in this donor. It is my responsibility to share this information with my health care provider and review the risks and benefits of being screened for more (or fewer) genetic conditions.	Initials: _____ Initials: _____
While genetic testing can lower the likelihood for certain genetic diseases, no amount of genetic testing can guarantee that a child will be healthy or free of genetic disease.	Initials: _____ Initials: _____
Genetic counseling is available to us, either through Cryobio or Sema4, if we have additional questions regarding these test results and potential risks.	Initials: _____ Initials: _____
Both the donor's carrier status and whether the donor is acceptable for my use should be discussed with my health care provider.	Initials: _____ Initials: _____

We have read the above material and assume the risk of using donor sperm from a donor who has been found to be a carrier of genetic disorders. We are making the choice to use donor sperm from donor WL 4011 willingly and agree to release any legal claims, including negligence, that may arise from or are related to insemination or assisted reproduction using donor sperm from donor WL 4011.

We have read and had the chance to ask questions, and we understand and agree to the terms of this Additional Agreement to use donor WL 4011.

_____

Recipient Date

_____

Partner, if applicable Date

William C. Baird, PhD. 08-15-2022

Cryobio Date