cryobio

Additional Agreement to Use Donor WL 4012

We, _____ (Recipient), and _____ (Partner, if applicable), specifically request and accept frozen semen from Cryobio donor WL 4012. We understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor WL 4012. WL 4012 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 4012 has been found to be a carrier of the following recessive genetic condition:

Congenital Disorder of Glycosylation, Type Ia.

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.

Congenital disorder of glycosylation, Type Ia (*PMM2* gene): Congenital disorders of glycosylation (CDGs) are a group of genetic disorders that affect an important process in cells called glycosylation. Glycosylation is the process where "sugars" in the body are added to other proteins or fats, which ultimately is important and essential for a variety of functions in the body including normal growth and function of body tissues and organs. Different types of CDGs are caused by different genes, and are inherited in a variety of inheritance patterns. Congenital disorder of glycosylation, Type Ia (also known as *PMM2*-CDG) is the most common congenital disorder of glycosylation, and it is inherited in an autosomal recessive pattern caused by pathogenic variants in the gene *PMM2.* While patients have been reported from multiple ethnicities, this disease is more common in the Ashkenazi Jewish and Caucasian populations.

Congenital disorder of glycosylation, Type Ia can present differently at different periods of life, and the severity, symptoms present, and prognosis can vary greatly from one to person to another.
In infants, symptoms may include feeding problems resulting in babies failure to grow and gain weight, hypotonia (low muscle tone/"floppiness"), developmental delays, seizures, strabismus (abnormal alignment of the eyes), and abnormalities of the brain, kidney, liver, or other organs.

Later in infancy and/or childhood, the disease may manifest as hypotonia, ataxia (loss of full control of body movements), delayed language and motor development, intellectual disability (ranging from moderate to severe), stroke like episodes, retinitis pigmentosa (eye disease leading to vision impairment), and possible episodes of internal organ failure. Severely affected individuals may die in infancy or early childhood, but more mildly affected individuals may survive into adulthood with variable intellectual disability, spinal abnormalities, ataxia, endocrine dysfunction (lack of spontaneous puberty in girls) and coagulopathy (a condition where the ability to form blood clots is affected, which can lead to excessive bleeding or excessive clotting). There is currently no cure for congenital disorder of glycosylation, Type Ia, but treatments for specific symptoms may be implemented.

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.

Congenital disorder of glycosylation, type Ia (*PMM2* gene) carrier status frequency in different ethnicities, from Sema4's website:

Worldwide	1 in 80
African	1 in 245
Ashkenazi Jewish	1 in 66
East Asian	1 in 133
Finnish	1 in 58
European (Non-Finnish)	1 in 58
Native American	1 in 114
South Asian	1 in 278

Recommendation: Both Sema4 and Cryobio recommend that the recipient, or egg source if different than recipient, be tested for congenital disorder of glycosylation, type Ia **(*PMM2* 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. Because the donor was tested by Sema4, Cryobio recommends that the recipient or egg source should be tested by Sema4 as well. 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 congenital disorder of glycosylation, type Ia.	Initials: _____ Initials: _____

This genetic condition is inherited as a recessive trait. 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 congenital disorder of glycosylation, type Ia, 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 congenital disorder of glycosylation, type Ia (*PMM2* gene).	Initials: _____ Initials: _____
A negative genetic test result in the egg source significantly reduces the likelihood that the resulting child could be affected with this condition. 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 a genetic disorder. We are making the choice to use donor sperm from donor WL 4012 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 4012.

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 4012.

_____
Recipient

_____
Date

_____
Partner, if applicable

_____
Date

William C. Baird, PhD

_____
Cryobio

11-08-2022

_____
Date