cryobio

Additional Agreement to Use Donor WL 4004

We, _____ (Recipient), and _____ (Partner, if applicable), specifically request and accept frozen semen from Cryobio donor WL 4004. We understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor WL 4004. We reviewed the genetic test results on this sperm donor, and we understand that donor WL 4004 has been found to be a carrier of the following recessive genetic condition:

variant of Alpha-Thalassemia

Why carrier status is important: Carriers of genetic diseases have changes, called pathogenic variants or mutations, in a specific gene or multiple genes. 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 show symptoms of the disease, i.e., they are asymptomatic. 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 nor 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.

Alpha-thalassemia (HBA1 and HBA2 genes): Alpha-thalassemia is an autosomal recessive condition that affects the red blood cells. It can affect people of any ethnicity, but is more common in people who can trace their ancestry to Southeast Asia, India, equatorial Africa, the Mediterranean, or the Arabian Peninsula. Typically, individuals have 4 alpha (HBA) genes. Individuals who have all 4 working alpha genes are neither carriers nor are they affected with the disease. Individuals who are carriers have 2 or 3 working HBA genes and do not typically have symptoms of the disease, however, some carriers may have mild anemia. The two major and severe forms of alpha-thalassemia are hemoglobin Bart syndrome and alpha-thalassemia (also known as HbH disease). Hemoglobin Bart syndrome is caused by a loss of all 4 alpha-globin genes. It is very severe, and fetuses are either stillborn or die shortly after birth. Alpha-thalassemia (HbH disease) is caused by a loss of 3 alpha-globin genes. It results in anemia, an enlarged spleen, and mild jaundice. Most individuals are mildly disabled by this disease. Some people with more severe disease require frequent blood transfusions. The type of disease as well as the severity of symptoms can be predicted based on the genetic variants detected.

Donor WL 4004's specific variant: WL 4004 has an *extra* alpha-globin gene, and therefore carries a total of five (instead of four) alpha genes. *This does not cause any problems for him, but if the recipient (or egg source, if different than recipient) is a carrier for beta-thalassemia (caused by a mutation in a different gene called HBB), then the resulting child could inherit beta-thalassemia intermedia.* Beta-thalassemia intermedia varies in presentation, where some people have a mild form and others have a

more severe form and need blood transfusions. The beta genes code for a different aspect of red blood cells, and the number of alpha and beta genes that are made in the body need to be fairly balanced. If the recipient (or egg source, if different than recipient) carried a mutated HBB (beta) gene, while the donor had this extra HBA (alpha) gene, there is a chance that the baby could inherit the beta mutation (loss), along with the alpha duplication (gain). This would result in too many alpha-globin genes and not enough beta-globin genes, causing an imbalance in overall gene number and this then leads to abnormal hemoglobin protein.

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.

Beta-thalassemia (HBB gene) carrier status frequency in different ethnicities from Sema4's website:

Worldwide	1 in 81
African	1 in 97
Ashkenazi Jewish	1 in 28
East Asian	1 in 87
Finnish	1 in 1901
European (Non-Finnish)	1 in 214
Native American	1 in 438
South Asian	1 in 25

Recommendation: Both Sema4 and Cryobio recommend that the recipient (or egg source, if different than recipient), be tested for beta-thalassemia (HBB 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, if different than recipient) 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 for 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 positive results from genetic testing. These results indicate that the donor is a carrier for a variant of alpha-thalassemia.	**Initials:** _____ **Initials:** _____
This genetic condition is inherited as a recessive trait. Typically, this means that if both the egg source and the sperm source are carriers for the same gene, there is a significantly higher chance of the resulting child having that genetic condition. **In this case, I understand that the child would be at an increased for beta-thalassemia intermedia if I (or the**	**Initials:** _____ **Initials:** _____

egg source, if different than recipient) tested positive as being a carrier in an HBB gene.	
By the donor testing positive for carrier status for a variant of alpha-thalassemia, the risk to a resulting child **to inherit a blood disorder** 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 an 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 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 gene/condition that the donor has tested positive for, is available.	**Initials: _____ Initials: _____**
Genetic testing is ***strongly recommended*** for me (or the egg source, if different) to see if I am a carrier for beta-thalasemia (the HBB gene).	**Initials: _____ Initials: _____**
A negative genetic test result in me (or the egg source, if different) 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: _____**
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 diseases.	**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 4004 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 4004.

We have read, had the chance to ask questions, and we understand and agree to the terms of this Additional Agreement to use donor WL 4004.

_____
Recipient

_____
Date

_____
Partner, if applicable

_____
Date

William C. Baird, PhD

_____
Cryobio

10-06-2021

_____
Date