cryobio

Additional Agreement to Use Donor WL 4004

I, (_____ (Recipient), and _____ (Partner, if applicable)), specifically request and accept frozen semen from Cryobio donor WL 4004. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor WL 4004. WL 4004 had expanded genetic carrier screening to determine their carrier status for 283 recessive genetic conditions. Please note that Cryobio thoroughly evaluates each donor's results and assesses potential risks of any identified results before allowing donors to remain in our donor program.

I have reviewed genetic test results on this sperm donor, and I understand that donor WL 4004 has been found to be a carrier of the following recessive genetic condition:

A variant of alpha-thalassemia

Purpose of genetic carrier screening: Carriers of genetic conditions have changes, called pathogenic variants or mutations, in a specific (or multiple) gene(s). Most of the genetic conditions that the Cryobio donors are tested for are inherited in an autosomal recessive pattern (see Figure 1). Typically, we all have two copies of every gene---one from the egg source and one from the sperm source. Autosomal recessive conditions require a mutation in both copies of the same gene in order for it to cause the condition. Therefore, individuals who carry just one mutation in a gene that causes recessive genetic conditions are 'carriers' of that specific condition. Carriers of most of the genetic conditions Cryobio donors are tested for do not typically show symptoms of the condition, i.e., they are asymptomatic, although there are rare exceptions. Most individuals are carriers for at least one if not multiple recessive genetic conditions.

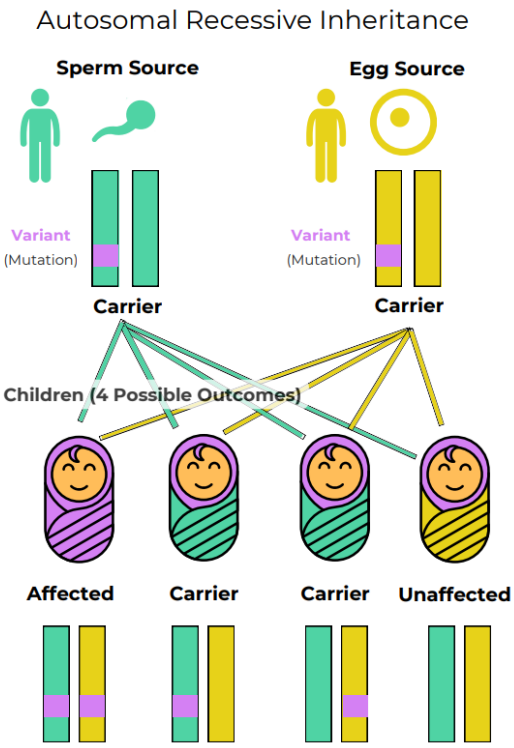

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

Carrier status is helpful to know 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 condition; a 2 in 4 chance of the resulting child being a carrier for that specific condition; and a 1 in 4 chance of the resulting child being neither a carrier or having that specific condition. Some of the conditions 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/specific features of a condition that may present in the individual (the phenotype), but not all do. Additionally, some of the genes can be linked to dominant conditions, meaning having a mutation in just one gene may increase the risk of a specific condition. If a specific change in a gene is linked to a dominant condition, it will be noted in this consent form.

Alpha-thalassemia (*HBA1* and *HBA2* genes): Alpha-thalassemia is an autosomal recessive condition that affects the red blood cells. It can cause anemia (deficiency of healthy red blood cells) and prevent the body from getting enough oxygen. Hemoglobin exists in our red blood cells to help carry oxygen from

our lungs throughout the rest of our body. Hemoglobin is made up of two alpha-globin chains and two beta-globin chains. We have specific genes in our body that contain the instructions for building these alpha- and beta-globin chains. A change in one of these instructions could cause an individual's hemoglobin to be different in structure or quantity, and this can cause health problems.

Generally, we have four functioning copies of the alpha-globin genes, two copies of *HBA1* and two copies of *HBA2*. Individuals with all four working alpha genes are neither carriers nor are they affected with the disease. Individuals who have two or three working HBA genes are carriers and do not typically have symptoms of the disease, however some carriers may have mild anemia. With alpha-thalassemia, the type of disease as well as the severity of symptoms can be predicted based on the genetic variants detected.

Alpha-thalassemia has two clinically significant forms: Hemoglobin H (HbH) disease and Hemoglobin Bart hydrops fetalis (Hb Bart) disease.

• Hemoglobin H (HbH) disease is caused by a loss of three alpha-globin genes. This means there is only one functioning alpha-globin gene. This results in anemia, an enlarged spleen, and mild jaundice. Most individuals are mildly affected by this condition, but some require frequent blood transfusions.

• Hemoglobin Bart (Hb Bart) disease is caused by a loss of all four alpha-globin genes. This means there are no functioning alpha-globin genes. It is very severe and results in stillbirth or death shortly after birth, without intervention.

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 general population risks or based on ethnicity, 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. There is still remaining risk called residual risk. Residual risk means the risk of being a carrier even after negative genetic testing for a condition. Residual risk data on the conditions the donor tested negative for can be requested from Cryobio. The carrier frequency provided is from the test provider. As with all genetic information, these carrier frequency numbers may change over time, and may slightly vary from lab to lab depending on the data used to curate them. Therefore, the carrier frequencies from this additional agreement are based on the numbers available from the performing laboratory on the date the donor's test results were reviewed by the lab.

Beta-thalassemia (*HBB* gene) carrier status frequency in different ethnicities from SEMA4:

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: 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 contact Cryobio with any questions or to arrange genetic counseling. Genetic counseling services can also be found through the National Society of Genetic Counselors. 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 help them 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 I have chosen has positive results from genetic testing looking at carrier status for 283 genes. 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 egg source, if different than recipient) tested positive as being a carrier in an *HBB* gene.**	Initials: _____ Initials: _____
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: _____
When an individual tests negative for carrier status, it does not completely eliminate their chance of being a carrier for that condition, however their remaining risk is greatly reduced. This remaining risk is called residual risk, and the residual risk can vary significantly from person to person. For more detailed information regarding the sensitivity of testing and remaining risk after negative screening, please contact Cryobio.	Initials: _____ Initials: _____
As genetic testing evolves and more data becomes available, I understand that there is the possibility of updated genetic information that may be uncovered for this donor for a variety of reasons. It is my responsibility to check back with Cryobio to see if any new genetic information is available for this donor.	Initials: _____ Initials: _____

Genetic testing for me (or the egg source, if different) can also be done to better understand and further reduce the risk to offspring.	Initials: _____ Initials: _____
Genetic testing is *strongly recommended* for me (or the egg source, if different) to see if I am a carrier for beta-thalassemia (the HBB gene).	Initials: _____ Initials: _____
Expanded genetic carrier screening is continuing to evolve, and at the time this donor entered the program this was the screening available. This donor had genetic testing with SEMA4 in 2019. 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: _____
The genetic testing done on the donor does ***not*** screen for all known 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 free of all genetic conditions.	Initials: _____ Initials: _____
Genetic counseling is available to me if I 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: _____

I 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 condition. I am 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.

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

_____

Recipient Date Email

_____

Partner, if applicable Date Email

William C. Baird, PhD, HCLD 10-06-2021

Cryobio Date