cryobio

Additional Agreement to Use Donor PC 506-B

I, (_____ (Recipient), and _____ (Partner, if applicable)), specifically request and accept frozen semen from Cryobio donor PC 506-B. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor PC 506-B. PC 506-B had expanded 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 PC 506-B has been found to be a carrier of the following recessive genetic conditions:

Alpha-thalassemia;

Biotinidase deficiency; and

Increased risk of being a silent carrier of spinal muscular atrophy

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.

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.

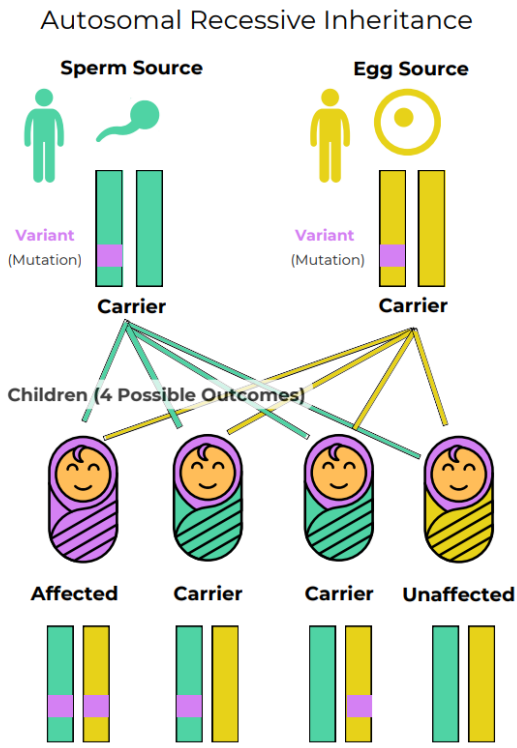

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

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*. This is often written as (aa/aa). There are typically two genes on each chromosome, so one chromosome in each pair comes from the egg source and one comes from the sperm source. **Note:** genes are "carried" on structures called chromosomes. Typically, individuals have 46 chromosomes, i.e., 23 pairs. Again, typically individuals inherit one set of chromosomes from the egg source, and one set of chromosomes from the sperm source.

A silent carrier for alpha-thalassemia has one gene deleted (-a/aa). An individual with alpha-thalassemia trait has two genes deleted and is considered a carrier. An individual with alpha-thalassemia trait may have both genes deleted from the same chromosome (--/aa) or one deletion from each chromosome (-a/-a). In all of these cases, we would not expect individuals to have any significant medical concerns related to their carrier status. However, some individuals who are carriers of alpha-thalassemia trait may present with mild symptoms (such as anemia), although most carriers do not. 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 (noted -a/--). This means there is only one functioning alpha-globin gene. This results in anemia (deficiency of healthy red blood cells), an enlarged spleen, and mild jaundice (yellow discoloration of the eyes, skin, etc.,). 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 (noted --/--). This means there are no functioning alpha-globin genes. It is very severe and results in stillbirth or death shortly after birth, without intervention.

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 condition. Biotinidase deficiency is recommended as part of the

newborn screen in the United States, therefore most babies are screened for and diagnosed with the condition at birth.

Increased risk of being a silent carrier for spinal muscular atrophy (*SMN1* gene): Spinal muscular atrophy (SMA) is a pan-ethnic, autosomal recessive disease caused by loss of function of the *SMN1* gene. In over 95% of cases, patients are missing both copies of the *SMN1* gene. The disease is characterized by the degeneration of alpha motor neurons of the spinal cord anterior horn cells, leading to progressive symmetric weakness, atrophy of the proximal voluntary muscles and early death. Age of onset can be anywhere on a continuum from the prenatal period to adulthood. Life expectancy varies from death before 6 months of age up to normal lifespan. Most patients, regardless of the severity of disease, have a deletion of both *SMN1* copies. Patients with later-onset disease usually have three or more copies of *SMN2*, which encodes a small amount of residual protein and lessens the severity of the symptoms. However, other factors besides *SMN2* copy number may affect the phenotype, and therefore the severity of the disease may not be able to be accurately predicted in all patients based on genotype.

Of Note: PC 506-B's variant of *SMN1* gene: PC 506-B has a variant of the *SMN1* gene that roughly doubles the chance that he is a silent carrier for SMA. He is not a carrier based on the testing performed, but he has an increased risk of being a carrier. Cryobio's genetic counselor still recommends that the recipient or the egg source, if different, be tested to determine their SMA carrier status.

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.

Alpha-thalassemia (HBA1 and HBA2 genes) carrier status frequency in different ethnicities, from SEMA4:

Caucasian	1 in 500
African American	1 in 30
Asian	1 in 20
Worldwide	1 in 25

Biotinidase Deficiency (BTD gene) carrier status frequency in different ethnicities, from SEMA4:

African	1 in 52
Ashkenazi Jewish	1 in 15
East Asian	1 in 324
Finnish	1 in 9
Caucasian	1 in 12
Latino	1 in 24
South Asian	1 in 7
Worldwide	1 in 13

Spinal muscular atrophy (*SMN1* gene) carrier status frequency in different ethnicities, from SEMA4:

African American	1 in 85
Ashkenazi Jewish	1 in 76
East Asian	1 in 53
Caucasian	1 in 48
Latino	1 in 63
South Asian	1 in 103
Sephardic Jewish	1 in 34

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for alpha-thalassemia (*HBA1* and *HBA2* genes); biotinidase deficiency (*BTD* gene); and SMA (*SMN1* 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 me 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 alpha-thalassemia; biotinidase deficiency; and is at an increased risk of being a silent carrier of SMA.	Initials: _____ Initials: _____
The genetic conditions tested for are inherited as recessive patterns. 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 alpha-thalassemia; biotinidase deficiency; and being at an increased risk of being a silent carrier of SMA, the risk to a resulting child 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 alpha-thalassemia (*HBA1* and *HBA2* genes); biotinidase deficiency (*BTD* gene); and SMA (*SMN1* 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 2020. 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 conditions, 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 genetic conditions. I am making the choice to use donor sperm from donor PC 506-B 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 PC 506-B.

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 PC 506-B.

_____ _____

Recipient Date Email

_____ _____

Partner, if applicable Date Email

William C. Baird, PhD, HCLD 10-18-2020

Cryobio Date