cryobio

Additional Agreement to Use Donor CB 954-B

I, (_____ (Recipient), and _____ (Partner, if applicable)), specifically request and accept frozen semen from Cryobio donor CB 954-B. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 954-B. This donor had expanded genetic carrier screening to determine their carrier status for 502 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 the genetic test results on this sperm donor, and I understand that donor CB 954-B has been found to be a carrier of the following recessive genetic conditions:

Alpha-thalassemia;
Deafness, autosomal recessive 59; and
Leber congenital amaurosis 8/Retinitis pigmentosa 12/Pigmented paravenous chorioretinal 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.

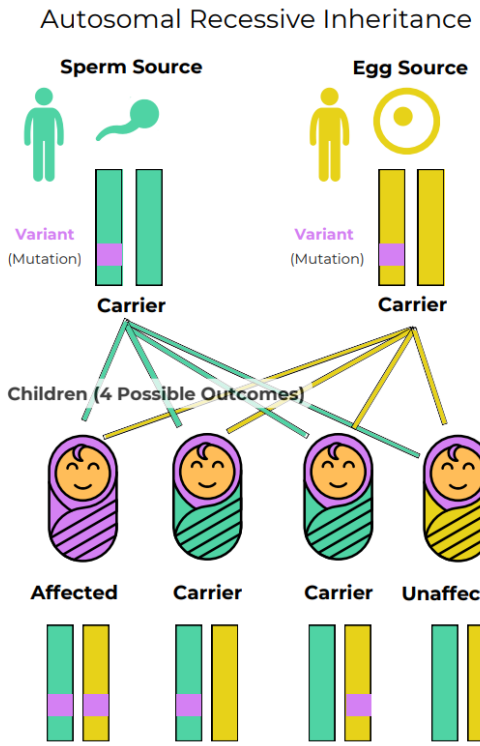

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

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.

Special note about CB 954-B's alpha-thalassemia carrier status: CB 954-B has alpha-thalassemia trait noted (-a/-a). An individual with alpha-thalassemia trait is not considered to have the disease alpha-thalassemia, they are considered to be a carrier. Remember, that of the four total alpha-globin genes, typically individuals have two *HBA1* genes and two *HBA2* genes. Donor CB 954-B carries a homozygous alpha 3.7 deletion, this means he is missing both copies of his *HBA2* gene. There were no deletions or sequence variants identified in his *HBA1* genes. Because CB 954-B is missing one copy of *HBA2* from each chromosome (-a/-a), a resulting child would always inherit a one gene deletion from him. This means they would be at least a silent carrier of alpha-thalassemia. The child's chance to have an alpha-thalassemia disease (Hemoglobin H disease or Hemoglobin Bart disease) would depend on the carrier status of the egg source. It would be unlikely for this child to have Hemoglobin Bart disease. **Cryobio recommends discussion with a genetic counselor for further clarification, and to best understand your risks when using this donor.**

Deafness, autosomal recessive 59 (*PJVK* gene): Deafness, autosomal recessive 59 is a disorder caused by pathogenic variants in the gene *PJVK*. The onset of this condition is typically at birth and the individual presents with mild to profound sensorineural hearing loss. In some cases, the hearing loss is progressive. Individuals with this form of hearing loss do not experience any other disease symptoms. Their lifespan is expected to be normal.

Leber congenital amaurosis 8/retinitis pigmentosa 12/pigmented paravenous chorioretinal atrophy (*CRB1* gene): Pathogenic variants in the gene *CRB1* are associated with three different autosomal recessive eye disorders known as *CRB1*-associated retinal dystrophies. Retinal dystrophies in general are a group of diseases of the retina (the part of the eye that helps convert light into electrical signals to your brain to help your brain create what you see). Common presentations among retinal disorders include night or color blindness, tunnel vision, and for some, progression to complete blindness. There are many different retinal dystrophies caused by a variety of genes. However, three different retinal dystrophies in particular can be caused by pathogenic variants in the *CRB1* gene: Leber congenital amaurosis 8, retinitis pigmentosa 12, and pigmented paravenous chorioretinal atrophy. Life expectancy is not reduced for any of these disorders. Some pathogenic variants have been associated with the development of one of the specific retinal dystrophies, and therefore the phenotype (specific type of disease) may be able to be predicted in some individuals based on the genotype (the specific gene mutation).

• **Leber congenital amaurosis 8 (LCA 8)** is the most severe of the three *CRB1*-associated retinal dystrophies. It manifests in infancy and individuals typically have profound loss of vision at birth/an early age that continues to progress/worsen to blindness. Many infants born with LCA 8 also present with nystagmus ("dancing"/wandering of the eyes), and the tendency to "rub" or "press" on their eyes.

• **Retinitis pigmentosa 12** typically presents with night blindness, which usually begins in early childhood, and progresses to tunnel vision and blindness later in adulthood.

• **Pigmented paravenous chorioretinal atrophy** can lead to a progressive loss of eyesight in some individuals, but most will not develop any symptoms. For asymptomatic individuals, diagnosis is typically made by specific findings during routine ophthalmology exams. Males are often affected more severely than females.

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 (*HBA 1/HBA 2* gene) carrier status frequency in different ethnicities:

Worldwide	1 in 25
African	1 in 30
East Asian	1 in 20
European (Non-Finnish)	1 in 500
South Asian	1 in 20

Deafness, autosomal recessive 59 (*PJVK* gene) carrier status frequency in different ethnicities:

Worldwide	1 in 1319
African	1 in 1046
East Asian	1 in 1458
European (Non-Finnish)	1 in 1138
Native American	1 in 2809
South Asian	1 in 1182

Leber congenital amaurosis 8 /retinitis pigmentosa 12 /pigmented paravenous chorioretinal atrophy (*CRB1* gene) carrier status frequency in different ethnicities:

Worldwide	1 in 190
African	1 in 116
Ashkenazi Jewish	1 in 389
East Asian	1 in 187
Finnish	1 in 1003
European (Non-Finnish)	1 in 158
Native American	1 in 263
South Asian	1 in 531

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for alpha-thalassemia (*HBA1* gene and *HBA2* gene); deafness, autosomal recessive 59 (*PJVK* gene); and Leber congenital amaurosis 8/retinitis pigmentosa 12/pigmented paravenous chorioretinal atrophy (*CRB1* 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.

Additional reference for alpha-thalassemia: Cryobio has changed genetic testing companies since this donor had testing done. This donor had testing done with Sema4. Our next genetic testing company, Invitae, has a pamphlet about alpha-thalassemia that includes helpful images of how inheritance works with alpha-thalassemia and different carrier types. We have attached this pamphlet to the donor's results solely as a reference to help you understand this condition, Invitae was not involved with testing this donor or the results report for this donor.

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 their carrier status for 502 conditions. These results indicate that the donor is a carrier for alpha-thalassemia; deafness, autosomal recessive 59; and Leber congenital amaurosis 8/retinitis pigmentosa 12/pigmented paravenous chorioretinal atrophy.	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 carrier status for alpha-thalassemia; deafness, autosomal recessive 59; and Leber congenital amaurosis 8/ retinitis pigmentosa 12/ pigmented paravenous chorioretinal atrophy, 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*/*HBA2* genes); deafness, autosomal recessive 59 (*PJVK* gene); and Leber congenital amaurosis 8/ retinitis pigmentosa 12/ pigmented paravenous chorioretinal atrophy (*CRB1* gene).	Initials: _____ Initials: _____
Based on CB 954-B's alpha-thalassemia carrier status (-a/-a), the resulting child will inherit at least one alpha chain deletion from the donor, and therefore will be at least a silent carrier of alpha-thalassemia. Carrier status of the recipient, or egg source if different, will help to further assess risks.	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 2022. My health care provider may recommend an expanded carrier screen that includes/included more than the 502 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 CB 954-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 CB 954-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 CB 954-B.

Recipient	Date	Email
Partner, if applicable	Date	Email
William C. Baird, PhD.	09-08-2023	
Cryobio	Date	