cryobio

Additional Agreement to Use Donor CB 559

I, _____ (Recipient), and _____ (Partner, if applicable), specifically request and accept frozen semen from Cryobio donor CB 559. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 559. I have received and reviewed genetic test results on this sperm donor, and I understand that donor CB 559 has been found to be a carrier of the following recessive genetic conditions:

Growth Hormone Deficiency, Type 1B,
and
Primary Coenzyme Q10 Deficiency 7.

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.

Growth Hormone Deficiency, type 1B (*GHRHR* gene): Growth hormone deficiency occurs in individuals when their bodies do not create enough growth hormone. The process of growth is complex, and an individual's height is influenced by a variety of genetic and environmental factors. As implied by the name, growth hormone deficiency can cause short stature and delayed bone age. Growth hormone deficiency, type 1B is an autosomal recessive disorder caused by pathogenic variants in the gene *GHRHR*. Growth failure in patients with type 1B is typically apparent in early to mid-childhood. Although growth hormone therapy is typically an effective treatment, response to the therapy can vary for everyone. Life expectancy depends on the severity of the clinical manifestations.

Of Note: Some carriers of single *GHRHR* mutations have been reported to have isolated growth hormone deficiency. However, most data suggests that carriers of *GHRHR* mutations are not found to be significantly shorter compared to that of the general population. One study reports a decreased height (4.2 cm difference) for GHRHR carriers in individuals between 60–80-years old, but not in carriers who are younger. Conversely, some studies suggested carriers of GHRHR mutations do have reduced body weight and reduced BMI when compared to normal controls, (see PMID: 17356054, 25761575).

Primary coenzyme Q10 deficiency, type 7 *(COQ4* gene): Primary coenzyme Q10 deficiencies are a group of autosomal recessive disorders that primarily result in deficiencies of the CoQ_{10} molecule. They can be caused by pathogenic variants in several genes. Coenzyme Q10 (CoQ_{10}) is an important molecule that is used throughout the body for a variety of important functions. Therefore, individuals who have deficiencies of the CoQ_{10} molecule typically have multisystem disease involvement.

Primary coenzyme Q10 deficiency, type 7 is caused by pathogenic variants in the *COQ4* gene. Symptoms of this condition typically present shortly after birth. Most individuals have severe cardiac symptoms, such as hypertrophic cardiomyopathy (thickened heart muscle), as well as neurological symptoms, such as seizures, severe hypotonia (low muscle tone), respiratory insufficiency, cerebellar hypoplasia (underdeveloped part of the brain), and slowly progressive neurologic deterioration. This disorder is typically fatal within the first few days of life. Although treatment is available using high-does oral CoQ_{10} supplementation, severe neurologic and kidney damage cannot be reversed.

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. 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, who was Sema4 who when the test was performed. 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.

Growth hormone deficiency, type 1B (*GHRHR* gene) carrier status frequency in different ethnicities:

Worldwide	1 in 673
African	1 in 724
East Asian	1 in 1044
European (Non-Finnish)	1 in 1181
Native American	1 in 897
South Asian	1 in 266

Primary coenzyme Q10 deficiency 7 (*COQ4* gene) carrier status frequency in different ethnicities:

Worldwide	1 in 547
African	1 in 2610
Ashkenazi Jewish	1 in 162
East Asian	1 in 314
Finnish	1 in 410
European (Non-Finnish)	1 in 741
Native American	1 in 633
South Asian	1 in 832

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for growth hormone deficiency, type 1B (*GHRHR* gene) and primary coenzyme Q10 deficiency 7 (*COQ4* 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 be important to 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. These results indicate that the donor is a carrier for growth hormone deficiency, type 1B and primary coenzyme Q10 deficiency 7.	Initials: _____ Initials: _____
These genetic conditions are inherited as recessive traits. 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 growth hormone deficiency, type 1B and primary coenzyme Q10 deficiency 7, 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 information regarding the remaining risk after negative screening, please contact Cryobio.	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 growth hormone deficiency, type 1B and primary coenzyme Q10 deficiency 7.	Initials: _____ Initials: _____
A negative genetic test result in the egg source significantly reduces the likelihood that the resulting child could be affected with these conditions. However, I fully understand that the risk cannot be completely eliminated.	Initials: _____ Initials: _____
Some carriers of single *GHRHR* mutations have been reported to have isolated growth hormone deficiency. Based on donor CB 559's carrier status for *GHRHR*, there is a 50% chance of any resulting child also being a carrier, and therefore potentially increased risk for isolated growth hormone deficiency.	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 2021. My health care provider may recommend an	Initials: _____ Initials: _____

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.	
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 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 disorders. I am making the choice to use donor sperm from donor CB 559 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 559.

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 559.

_____
Recipient

_____
Date

_____
Partner, if applicable

_____
Date

William C. Baird, PhD
_____
Cryobio

04-10-2023
_____
Date