cryobio

Additional Agreement to Use Donor CB 955-B

I, _____ (Recipient), and _____ (Partner, if applicable), specifically request and accept frozen semen from Cryobio donor CB 955-B. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 955-B. I have received and reviewed genetic test results on this sperm donor, and I understand that donor CB 955-B has been found to be a carrier of the following recessive genetic condition:

Homocystinuria (*CBS*-Related).

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.

Homocystinuria (*CBS*-Related) (*CBS* gene): Homocystinuria (*CBS*-related) is an autosomal recessive disorder caused by pathogenic variants in the *CBS* gene. Although pathogenic variants in a variety of other genes can also cause homocystinuria, *CBS*-related homocystinuria is the most common form.

Individuals affected with homocystinuria are unable to break down certain building blocks (called amino acids), which then cause increased amounts of homocysteine and other toxic materials to build up in their blood and urine. This build-up can affect a variety of organ systems, including the central nervous system, eyes, skeleton, and blood clotting system. Therefore, symptoms of CBS-related homocystinuria include intellectual disability/developmental delay, dislocated lenses of the eye/other eye problems, brittle bones/other skeletal abnormalities such as excessive height/scoliosis, and blood clots.

Some individuals present with more severe disease, known as B6-non-responsive type and develop symptoms during infancy, while others present with the milder B6-responsive disease and may not clinically develop symptoms until childhood or early adulthood. Affected individuals are treated with strict diets and supplements. Because prompt treatment can drastically improve outcomes, homocystinuria is recommended as part of the newborn screen in the United States. Therefore most babies are screened for and diagnosed with the disease at birth. However, treatment effectiveness and long-term outlook still

varies significantly. While some individuals who respond great to treatment may have normal development and normal lifespan, others with homocystinuria will have a shortened life expectancy due to complications of the disease.

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.

Homocystinuria (*CBS*-related) (*CBS* gene) carrier status frequency in different ethnicities:

Worldwide	1 in 179
African	1 in 188
Ashkenazi Jewish	1 in 330
East Asian	1 in 589
Finnish	1 in 336
European (Non-Finnish)	1 in 142
Native American	1 in 202
South Asian	1 in 523

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for homocystinuria (*CBS*-related) (*CBS* 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 looking at carrier status for 502 conditions. These results indicate that the donor is a carrier for homocystinuria (*CBS*-related).	Initials: _____ Initials: _____
This genetic condition is inherited as a recessive trait. 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 homocystinuria (*CBS*-related), 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 homocystinuria (*CBS*-related).	Initials: _____ Initials: _____
A negative genetic test result in the egg source significantly reduces the likelihood that the resulting child could be affected with this condition. However, I fully understand that the risk cannot be completely eliminated.	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: _____
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 955-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 955-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 955-B.

_____
Recipient

_____

Date

_____
Partner, if applicable

_____
Date

William C. Baird, PhD

_____
Cryobio

06-20-2023

_____
Date