cryobio

Additional Agreement to Use Donor CB 461

I (_____ (Recipient) and _____ (Partner, if applicable)), specifically request and accept frozen semen from Cryobio donor CB 461. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 461. CB 461 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 genetic test results on this sperm donor, and I understand that donor CB 461 has been found to be a carrier of the following recessive genetic conditions:

Homocystinuria (*CBS*-related);

Mucopolysaccharidosis type IVa; and

Schimke immunoosseous dysplasia.

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 nor 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.

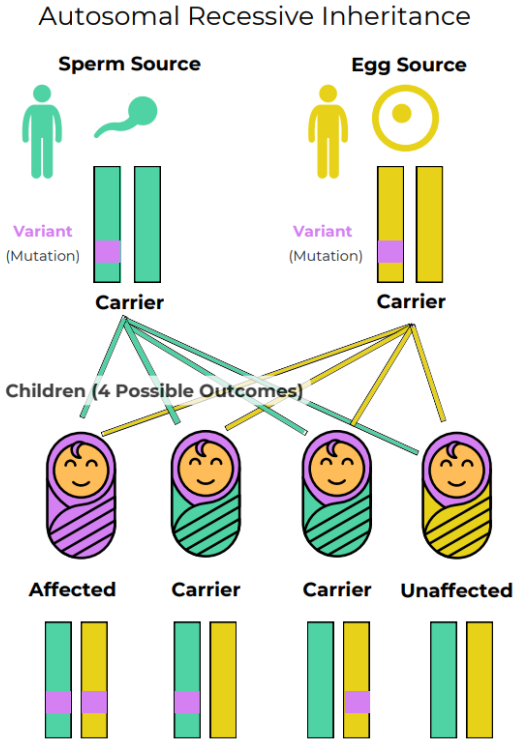

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

Homocystinuria (*CBS*-related) (*CBS* gene): Homocystinuria (*CBS*-related) is an autosomal recessive disorder caused by pathogenic variants in the *CBS* gene. It can occur in people of all ethnicities but is most common in people with Qatari and Caucasian ancestry. Although pathogenic variants in a variety of genes can cause homocystinuria, *CBS*-related homocystinuria is the most common form.

Individuals affected with homocystinuria are unable to process certain building blocks of proteins (called amino acids), which then cause increased amounts of the amino acids 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, brittle bones, and 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, screening for 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 respond great to treatment and may have normal development and normal lifespan, others with homocystinuria will have a shortened life expectancy due to complications of the condition, especially from blood clot events. Several specific variants have been associated with milder or more severe disease phenotypes, and therefore the disease severity may be predicted in some individuals based on the variant inherited.

Of note: The specific variant identified in donor CB 461 is a common variant found in individuals of Irish/Celtic descent and is associated with severe B6-nonresponsive type of homocystinuria. Carriers of homocystinuria are not expected to exhibit symptoms of the condition.

Mucopolysaccharidosis type IVA (*GALNS* gene): Mucopolysaccharidosis type IVA (MPS IVA) also known as Morquio syndrome, Type A, is an autosomal recessive disorder caused by pathogenic variants in the gene *GALNS*. MPS IVA is one of a group of lysosomal storage disorders. In general, lysosomal storage disorders are characterized by the bodies inability to break down particular nutrients. For individuals with MPS IVA, the body has an inability to break down certain sugars, called mucopolysaccharides. Because affected individuals cannot properly break down these sugars, it leads to a build up of these sugars and this can affect many parts of the body, primarily the skeletal system. The buildup of these sugars eventually leads to progressive damage to cells, tissues, and various organ systems.

Although MPS IVA can have variable age of onset, it is most commonly diagnosed during the second year of life. Affected individuals typically present with skeletal problems such as an abnormal curvature of the spine (kyphoscoliosis), lower leg abnormalities (knock-knee), a prominent breastbone (pectus carinatum), and joint looseness-all which can lead to short stature, pain, and arthritis. Over time, other organ systems can be affected, and may cause major respiratory problems, obstructive sleep apnea, valvular heart disease, hearing loss, visual impairment, dental abnormalities, and enlargement of the liver and spleen. Intelligence and early development are typically normal. Life expectancy varies based on the severity of the condition and quality of care individuals have access to. Generally, patients with the most severe form of the disorder do not survive beyond the third decade of life, while patients with a less severe form may survive past 70 years of age. Although there is no cure, there are treatments and therapies available that may improve quality of life.

Schimke immunoosseous dysplasia (*SMARCAL1* gene): Schimke immunoosseous dysplasia is an autosomal recessive disease caused by pathogenic variants in the *SMARCAL1* gene. Schimke immunoosseous dysplasia is primarily characterized by short stature, kidney disease, and a weakened immune system. Short stature is a result of abnormal development of the spine and the ends of the long bones (the big bones in your arms and legs). Kidney disease can progress to end stage renal (kidney) disease and life-threatening kidney failure. The weakened immune system is a result of the deficiency of T cells, which are a subgroup of white blood cells and play an important role in the body's immune response. An individual with a deficient immune response/system is more likely to get sick, and therefore affected individuals are at an increased risk for infections. Infection is often a common cause of death. Other common characteristics of this condition include abnormal curvature of the lower back (lumbar lordosis), darkened patches of skin (hyperpigmented macules), and distinctive facial features.

While the age of onset does not directly predict life expectancy, the severe form of the condition that presents in infancy usually results in reduced life expectancy. Individuals with mild presentation typically survive into adulthood if renal complications are treated. Treatment is based on symptoms as they arise. No direct genotype-phenotype correlations have been reported.

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.

Homocystinuria (*CBS*-Related) (*CBS* gene) carrier status frequency in different ethnicities, from SEMA4:

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

Mucopolysaccharidosis Type IVa (*GALNS* gene), carrier status frequency in different ethnicities, from SEMA4:

Worldwide	1 in 277
African	1 in 342
Ashkenazi Jewish	1 in 612
East Asian	1 in 286
Finnish	1 in 639
European (Non-Finnish)	1 in 256
Native American	1 in 333
South Asian	1 in 333

Schimke immunoosseous dysplasia (*SMARCAL1* gene) carrier status frequency in different ethnicities, from SEMA4:

Worldwide	1 in 547
African	1 in 699
Ashkenazi Jewish	1 in 174
East Asian	1 in 561
Finnish	1 in 717
European (Non-Finnish)	1 in 451
Native American	1 in 2123
South Asian	1 in 2565

Recommendation: Cryobio recommends that the recipient (or egg source, if different than recipient), be tested for homocystinuria (*CBS*-Related) (*CBS* gene), mucopolysaccharidosis type IVa (*GALNS* gene), and Schimke immunoosseous dysplasia (*SMARCAL1* 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 502 genes. These results indicate that the donor is a carrier for homocystinuria (*CBS*-related); mucopolysaccharidosis type IVa; and Schimke immunoosseous dysplasia.	Initials: _____ Initials: _____
These genetic conditions 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 homocystinuria (*CBS*-related); mucopolysaccharidosis type IVa; and Schimke immunoosseous dysplasia 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 homocystinuria (*CBS*-Related) (*CBS* gene), mucopolysaccharidosis type IVa (*GALNS* gene), and Schimke immunoosseous dysplasia (*SMARCAL1* 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 2021. 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 <u>*not*</u> 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 genetic conditions. I am making the choice to use donor sperm from donor CB 461 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 461.

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 461.

_____ _____ _____

Recipient Date Email

_____ _____ _____

Partner, if applicable Date Email

William C. Baird, PhD, HCLD 11-22-2021

Cryobio Date