cryobio

Additional Agreement to Use Donor CB 564

I, _____ (Recipient), and _____ (Partner, if applicable), specifically request and accept frozen semen from Cryobio donor CB 564. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 564. CB 564 had expanded genetic carrier screening to determine their carrier status for 502 recessive genetic conditions. I have received genetic test results on this sperm donor, and I understand that donor CB 564 has been found to be a carrier of the following recessive genetic conditions:

Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency, Non-Classic Form
and
Krabbe Disease.

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.

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form (*CYP21A2* gene): Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder which results from a deficiency in enzymes involved in cortisol production (a steroid hormone naturally produced by the body). Approximately 95% of cases of CAH are caused by defects in the *CYP21A2* gene, which leads to a deficiency of the steroid 21-hydroxylating enzyme. Approximately 1 in 12 individuals is a carrier of CAH. Symptoms of CAH vary based on the form of CAH, the age of diagnosis, and the sex of the individual.

Three different forms of CAH have been reported: a classic salt wasting form, a classic simple virilizing form, and a non-classic form.

- The classic salt wasting form of CAH is the most severe and presents with ambiguous genitalia (when an infant's external genitals don't appear to be clearly male or female), precocious puberty (puberty earlier than typical), excessive facial hair, and includes inadequate adrenal aldosterone secretion that can result in the body to be unable to retain enough salt which can result in a fatal health event called a "salt-wasting crises".

- The classic simple virilizing form involves prenatal virilization (the development of male physical characteristics (such as muscle bulk, body hair, and deep voice) in a female or precociously in a boy), ambiguous genitalia, precocious puberty, and excessive facial hair, but does not include the life-threatening salt-wasting crises.
- The mildest form, non-classic CAH, is often not diagnosed until later in childhood or adulthood. Individuals with the non-classic form may present with hyperandrogenism (too much testosterone in the body) and include features such as hirsutism (abnormal growth of hair on the face and body, especially on a woman), delayed menarche (the first period for females), and infertility.

Treatment for CAH usually includes steroids to replace the low hormones. The long-term prognosis for individuals with CAH is usually favorable, and with lifelong treatment, affected individuals typically have good health and normal lifespans. Often, individuals with non-classic CAH require no treatment at all. CAH is typically included on the newborn screen (check with your state/delivering hospital to be sure), so most individuals who have it will be diagnosed shortly after birth.

> **Of note:** Cryobio donor CB 564 tested positive as a carrier for a pathogenic variant typically associated with the non-classic type of CAH. This means that even when paired with another *CYP21A2* pathogenic variant associated with any type, the offspring would be at risk for the mild, non-classic form of CAH.

Krabbe disease (*GALC* gene): Krabbe disease is an autosomal recessive disorder caused by pathogenic variants in the *GALC* gene. Symptoms of the disease are caused by a deficiency in an enzyme involved in the breakdown of lipids (fats) in the brain, kidneys, and cells of the small intestine and colon. The majority of individuals with Krabbe disease have the classical form, but approximately 15% of patients have a later-onset form. While it has been identified in patients worldwide, it is more prevalent in specific groups of Druze and Muslim Arabs in Israel where the carrier frequency is estimated to be 1 in 6 individuals.

Two types of Krabbe disease have been reported: a classical infantile form and a later-onset variable form.

- The classical infantile form typically onsets before 12 months of age. After several months of normal development, infants become irritable and develop spasticity (stiffness of muscles) and rigidity. They begin to rapidly regress in their motor and cognitive skills over several weeks or months. Affected infants typically die in infancy or early childhood.
- Approximately 15% of patients have a later-onset form of the disease, although newer data suggests this may be higher. Both severity and symptoms are highly variable, and onset can occur anywhere between the age of 1 year and 70 years old. In the later onset form, deterioration tends to progress more slowly than the infantile form.

Treatment for the infantile form of Krabbe disease often includes hematopoietic stem cell transplantation (HSCT) within the first few weeks of life, as well as other supportive treatments based on specific symptoms. The outcome of HSCT depends on how early the disease is detected, the severity, and progression prior to treatment. While HSCT can lead to a delay in the progression of symptoms, treatment is not curative. Krabbe disease is on the newborn screen for several states but is not currently included on all newborn screens. Check with the state of your delivering hospital for more details.

> **Of note:** Specific variants have been determined to cause the infantile or late-onset forms of the disease, and therefore the phenotype (symptoms and characteristics) may be predicted for most genotypes (specific gene changes). Cryobio donor CB 564 tested positive as a carrier for a pathogenic variant that is typically considered mild, although presentations can vary for each individual based on the second GALC variant present.

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.

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (non-classic form) (*CYP21A2* gene) carrier status frequency in different ethnicities:

Worldwide	1 in 16
Ashkenazi Jewish	1 in 7
European (Non-Finnish)	1 in 11

Krabbe disease (*GALC* gene) carrier status frequency in different ethnicities, from Sema4's website:

Worldwide	1 in 77
African	1 in 158
Ashkenazi Jewish	1 in 777
East Asian	1 in 40
Finnish	1 in 146
European (Non-Finnish)	1 in 69
Native American	1 in 198
South Asian	1 in 35

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for congenital adrenal hyperplasia due to 21-hydroxylase deficiency (non-classic form) (*CYP21A2* gene) and Krabbe disease (*GALC* 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 had positive results from genetic testing looking at carrier status for 502 conditions. These results indicate that the donor is a carrier for congenital adrenal hyperplasia due to 21-hydroxylase deficiency (non-classic form) and Krabbe disease.	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 congenital adrenal hyperplasia due to 21-hydroxylase deficiency (non-classic form) and Krabbe disease, 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 detailed information regarding the sensitivity of testing and 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 congenital adrenal hyperplasia due to 21-hydroxylase deficiency, and Krabbe disease.	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: _____
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

564 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 564.

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 564.

_____
Recipient

_____
Date

_____
Partner, if applicable

_____
Date

William C. Baird, PhD
_____
Cryobio

06-29-2023
_____
Date