cryobio

Additional Agreement to Use Donor CB 557

I, _____ (Recipient), and _____ (Partner, if applicable), specifically request and accept frozen semen from Cryobio donor CB 557. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 557. I have received and reviewed genetic test results on this sperm donor, and I understand that donor CB 557 has been found to be a carrier of the following recessive genetic conditions:

Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency, Non-Classic Form,
Cystic Fibrosis,
and
Mucopolysaccharidosis VII.

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. 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 557 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.

Cystic Fibrosis (*CFTR* gene): Cystic fibrosis is an autosomal recessive disorder caused by pathogenic variants in the gene *CFTR*. Cystic fibrosis is typically a childhood-onset disease resulting in thickened secretions (mucus) in structures throughout the body. The most common clinical presentation of cystic fibrosis includes thick mucus accumulation in the lungs leading to progressive damage to the respiratory system which results in breathing difficulties and infection. Many individuals with cystic fibrosis also have significant digestive issues and poor growth due to deficiency of enzymes produced by the pancreas to digest food (pancreatic insufficiency). Symptoms range from mild to severe. Prognosis depends on the severity of symptoms as well as response to treatments; many affected individuals live well into adulthood. Intellect is not affected. CF is universally included on the newborn screen in the United States, so most individuals who have it will be diagnosed shortly after birth.

Milder forms of CFTR-related conditions include congenital absence of the vas deferens (CAVD) associated with male infertility, variable respiratory manifestations, and hereditary pancreatitis. Life span is not typically impacted with less severe CFTR-related conditions. The combination of variants identified in an affected individual impacts the observed clinical features and severity of the symptoms. Additional genetic and environmental factors are believed to play a role in determining the risk of developing these complex CFTR-related conditions.

Of Note: Current research suggests individuals with a single disease-causing *CFTR* variant (heterozygous carriers) may be at an increased risk for some cystic fibrosis-related conditions. However, most of these diseases are multifactorial, and an individual's risk depends on a variety of genetic and environmental factors. For example, some *CFTR* carriers may have an increased chance to develop inflammation of the pancreas (pancreatitis) compared to the average person, particularly if they have other environmental risk factors (such as alcohol consumption and/or smoking history) or variants in more than one gene associated with chronic and/or hereditary pancreatitis. The absolute risk of chronic pancreatitis for a *CFTR* carrier is low, and the vast majority will not develop this condition. Due to the potential of increased risks for specific health conditions, carriers may consider follow-up with a medical provider. (PMID: 35084992, 31882447, 20977904, 21520337, 11729110)

Mucopolysaccharidosis VII (*GUSB* gene): Mucopolysaccharidoses (MPS) are a group of genetic disorders in which the body cannot effectively recycle materials called mucopolysaccharides. The build-up of these materials can cause damage to multiple body systems and can ultimately lead to a reduced lifespan. MPS types are differentiated by clinical features, lab findings, and genetic testing.

Mucopolysaccharidosis (MPS) type VII, also known as Sly syndrome, is a rare autosomal recessive type caused by pathogenic variants in the gene *GUSB*. The severity and onset of this condition vary. The most severe cases present during pregnancy with hydrops fetalis (where large amounts of fluid buildup in the fetus' tissues and organs) and typically end in stillbirth or infants who die shortly after birth. Less severe cases of MPS VII present during early childhood and have a life expectancy into adolescence and early adulthood.

All affected individuals typically have short stature due to poor growth and skeletal abnormalities. Other characteristics include coarse facial features, hydrocephalus (increased fluid surrounding the brain), intellectual disability, hepatosplenomegaly (enlarged liver and/or spleen), heart abnormalities, spinal stenosis (narrowed space in the spine causing pressure), and respiratory issues. Additional features include corneal clouding which leads to significant vision loss and multiple skeletal abnormalities seen on x-ray (called dysostosis multiplex). The life expectancy depends on the severity of the condition but is typically significantly reduced. Treatment is based on an individual's symptoms. Enzyme replacement therapy was recently approved to treat pediatric and adult patients with MPS VII. However, due to the novelty of this treatment, its effectiveness is still under review.

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) (*CYP21A2* gene) carrier status frequency in different ethnicities:

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

Cystic Fibrosis (*CFTR* gene) carrier status frequency in different ethnicities:

Worldwide	1 in 33
African	1 in 58
Ashkenazi Jewish	1 in 24
East Asian	1 in 277
Finnish	1 in 75
European (Non-Finnish)	1 in 23
Native American	1 in 40
South Asian	1 in 73

Mucopolysaccharidosis VII (*GUSB* gene) carrier status frequency in different ethnicities:

Worldwide	1 in 593
African	1 in 589
East Asian	1 in 1704
Finnish	1 in 544
European (Non-Finnish)	1 in 525
Native American	1 in 662
South Asian	1 in 1283

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) (*CYP21A2* gene), cystic fibrosis (*CFTR* gene), and mucopolysaccharidosis VII (*GUSB* 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), cystic fibrosis, and mucopolysaccharidosis VII.	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), cystic fibrosis, and mucopolysaccharidosis VII, 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 congenital adrenal hyperplasia due to 21-hydroxylase deficiency (non-classic), cystic fibrosis, and mucopolysaccharidosis VII.	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: _____
Current research suggests individuals with a single disease-causing CFTR variant (heterozygous carriers) may be at an increased risk for some cystic fibrosis-related conditions, such as pancreatitis. Based on donor CB 557's carrier status for CFTR, there is a 50% chance of any resulting child also being a carrier, and therefore potentially increased risk for these health 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 557 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 557.

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 557.

_____
Recipient

_____
Date

_____
Partner, if applicable

_____
Date

William C. Baird, PhD

_____
Cryobio

04-13-2023

_____
Date