cryobio

Additional Agreement to Use Donor CB 569

I, _____ (Recipient), and _____ (Partner, if applicable), specifically request and accept frozen semen from Cryobio donor CB 569. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 569. **Special note**: At the time donor CB 569 was entering the donor program, Cryobio was in the process of choosing a new laboratory to perform genetic carrier screening through. Because of this, donor CB 569 had expanded genetic carrier screening from two different laboratories to determine their carrier status for a combined total of 689 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. Please see below for additional details regarding these two test results.

I have received genetic test results on this sperm donor, and I understand that donor CB 569 has been found to be a carrier of the following recessive genetic conditions:

Cystic fibrosis/*CFTR*-related conditions
Congenital adrenal hyperplasia due to 21-hydroxylase deficiency
Glycogen storage disease, Type II

Why carrier status is important: 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 condition 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.

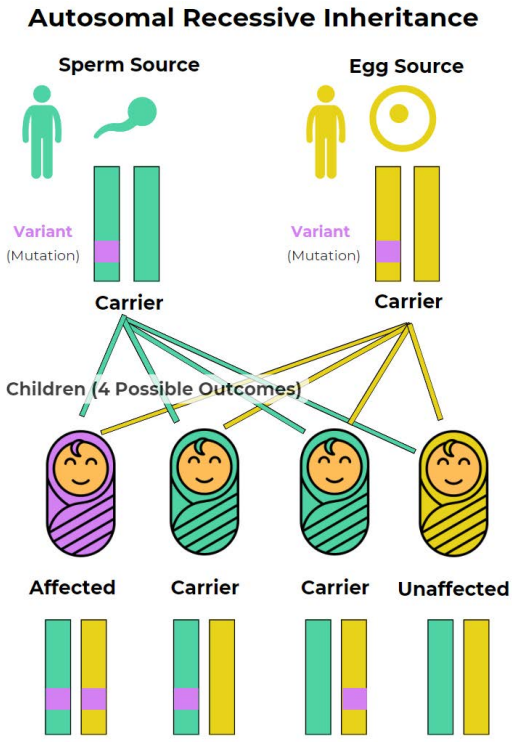

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

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 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 or 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 of specific 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.

Cystic fibrosis and *CFTR*-related conditions (*CFTR* gene): Cystic fibrosis (CF or cystic fibrosis) is an autosomal recessive condition caused by pathogenic variants in the gene *CFTR*. CF is typically a childhood-onset condition resulting in thickened secretions (mucus) in structures throughout the body. The most common clinical presentation of CF 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 CF 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.

Historically, pathogenic variants in the *CFTR* gene were only known to contribute to disease in individuals with a more classic form of CF as described above. However, as genetic testing has evolved and become more widely available, it is now understood that pathogenic variants in the *CFTR* gene can cause a "spectrum" of conditions, ranging from classic CF to milder forms of *CFTR*-related conditions including 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 CF-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)

Special note about CB 569's *CFTR* variant: Donor CB 569 has the *CFTR* 5T 12 TG variant. This variant involves the presence of 12 thymidine-guanine (TG) repeats in a specific region of the gene, which can result in altered *CFTR* protein function and contribute to the development of CF in some individuals. The *CFTR* 5T 12 TG variant is often associated with a milder form of the disease and may lead to less severe respiratory and digestive symptoms compared to other *CFTR* mutations. However, because it can still contribute to the development of CF-related complications, it should be considered in the clinical management and genetic counseling of affected individuals, or individuals who are identified as carriers of this variant. In the context of carrier screening, it's important to acknowledge that CB 569 is a carrier for CF and *CFTR*-related conditions.

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (*CYP21A2* gene): Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition which results from a deficiency in enzymes involved in cortisol production (a steroid hormone naturally produced by the adrenal glands). These hormones produced by the adrenal glands help regulate many essential functions in the body,

including sexual development and maturation. There are several types of CAH, which can be caused by changes in different genes, but 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. Individuals with the salt-wasting type lose large amounts of sodium (salt) in the urine, which can lead to "salt-wasting crises" that can be life-threatening in early infancy. Female infants with the classic type usually have external genitalia that do not look clearly male or female (ambiguous genitalia), while males typically have normal genitalia, although their testes may be smaller than typical. Individuals with the classic form may also have decreased fertility.
- 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, and excessive facial hair, and decreased fertility, 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 typically have typical external genitalia but 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), male pattern baldness, 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. Oftentimes 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 569 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.

Glycogen storage disease, type II (aka-Pompe disease) (*GAA* gene): Glycogen storage disease type II, also known as Pompe disease, is an autosomal recessive condition that is caused by pathogenic variants in the gene *GAA*. Glycogen storage disease (GSD) is a group of conditions in which the affected individuals' body is unable to convert/break down stored glycogen (a complex "sugar") into glucose (a more simple "sugar" that can be used by the body). A buildup of glycogen impairs the function of certain organs and tissues.

Pompe disease is historically classified into various subtypes based on the age of onset and severity, and they may not always have distinct names. However, they are commonly referred to as: classical or infantile-onset Pompe disease (IOPD) and nonclassical or late-onset Pompe disease (LOPD). The symptoms of Pompe disease can vary in age of onset and severity.

- IOPD typically appears in the first year of life and is characterized by poor feeding and failure to thrive (poor growth), hypotonia (low muscle tone), myopathy (muscle weakness), respiratory distress, and an enlarged heart. If untreated, the cardiac manifestations or breathing problems usually cause death in the first year of life.
- LOPD can begin any time after infancy (>12 months of age). These patients do not usually have cardiac problems, but have gradual, progressive muscle weakness that may result in wheelchair

dependency and difficulty breathing. Patients may reach adulthood, but life expectancy is reduced.

Although enzyme replacement therapy is available and may slow the disease progression, there currently is no cure for Pompe disease. Pompe disease 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.

Carrier status frequency: Carrier status frequency is the chance of an individual being a carrier for a genetic condition based on general population risks 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.

Carrier status frequency (as reported by Invitae):

Cystic Fibrosis and *CFTR*-related conditions (*CFTR* gene):

Pan-ethnic carrier frequency for classic cystic fibrosis: 1 in 45

Pan-ethnic carrier frequency for *CFTR* related disorder: 1 in 9

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CYP21A2 gene):

Pan-ethnic carrier frequency: 1 in 61

Glycogen storage disease, type II (*GAA* gene):

Pan-ethnic carrier frequency: 1 in 100

Special note about donor CB 569: As mentioned above, it is important to take notice that donor CB 569 has had genetic carrier screening done by two separate performing laboratories. While many of the genes on each lab's genetic carrier screens are the same, there are also a significant number of genes that are different. To review which genes donor CB 569 was specifically screened for, please refer to the gene list at the end of each available test report. Additionally, for the 3 conditions donor CB 569 screened positive as a carrier for on the Invitae carrier screen, the other laboratory (LabCorp) reported a negative result. Genetic testing is complex, and every lab is set up differently to decide which genetic variants should be reported. This is why referring to the specific laboratories residual risk after negative testing is important to keep in mind. Please refer to donor CB 569's results for more details. For other questions regarding this donor's carrier screening results, please contact Cryobio.

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for cystic fibrosis and *CFTR*-related conditions (*CFTR* gene), congenital adrenal hyperplasia due to 21-hydroxlyase deficiency (*CYP21A2* gene), and glycogen storage disease, type II (*GAA* 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 condition, 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 689 conditions. These results indicate that the donor is a carrier for cystic fibrosis and *CFTR*-related conditions, congenital adrenal hyperplasia due to 21-hydroxlyase deficiency, and glycogen storage disease, type II.	Initials: _____ Initials: _____
The genetic conditions tested for 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 cystic fibrosis and *CFTR*-related conditions, congenital adrenal hyperplasia due to 21-hydroxlyase deficiency, and glycogen storage disease, type II, 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 should I desire any additional information regarding this donor's genetic information status that may become available.	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 cystic fibrosis and *CFTR*-related conditions, congenital adrenal hyperplasia due to 21-hydroxlyase deficiency, and glycogen storage disease, type II.	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 Invitae and LabCorp in 2023. My health care provider may recommend an expanded carrier screen that includes/included more than the 689 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 *not* screen for all known genetic conditions.	Initials: _____ Initials: _____
While genetic testing can lower the likelihood for certain genetic conditions, no amount of genetic testing can guarantee that a child will be free of all 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 569'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: _____
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 569 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 569.

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 569.

_____

Recipient Date

_____

Partner, if applicable Date

William C. Baird, PhD. 06-15-2023

Cryobio Date