cryobio

Additional Agreement to Use Donor CB 567

I, _____ (Recipient), and _____ (Partner, if applicable), specifically request and accept frozen semen from Cryobio donor CB 567. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 567. CB 567 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. CB 567's genetic carrier screening revealed inconclusive results that required additional testing of family members to clarify his carrier status. Donor CB 567's parents agreed to testing, and with their results the genetic testing lab was able to determine that CB 567 is a carrier of for cystic fibrosis/*CFTR*-related condition(s). Please see below for additional details regarding his specific results and follow up family testing.

I have received and reviewed genetic test results on this sperm donor, and I understand that donor CB 567 has been found to be a carrier of the following genetic condition(s):

Cystic fibrosis/*CFTR*-related conditions

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. Cryobio thoroughly evaluates each donor's results and assesses potential risks of any identified results before allowing donors to remain in our donor program.

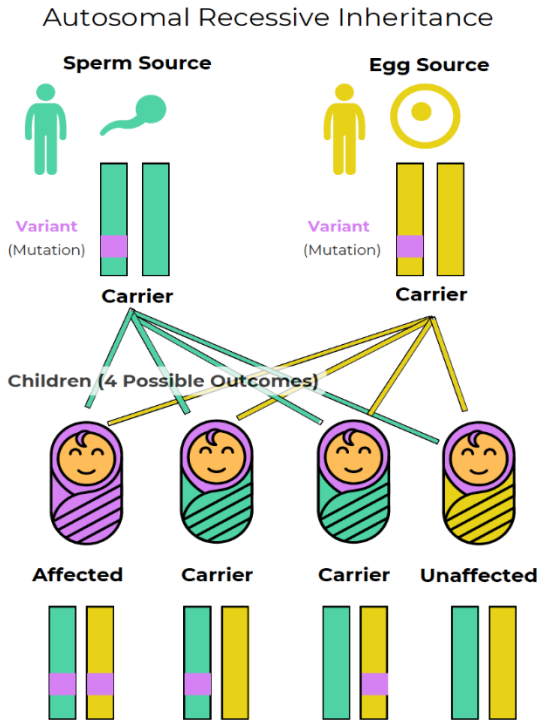

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

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 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/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.

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 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 cystic fibrosis-related conditions. However, most of these conditions 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)

Specific to CB 567's *CFTR* carrier status: Donor CB 567 was identified to have two variants in the *CFTR* gene, and his original carrier screening report stated that he "may exhibit clinical symptoms of disorders related to cystic fibrosis". Different combinations of specific *CFTR* variants can cause a spectrum of different CF-related conditions, ranging from classic CF to individuals who are asymptomatic (i.e.-has no identifiable features of CF or any CF-related conditions). Because donor CB 567 did not report having any symptoms of CF or *CFTR*-related conditions, Cryobio requested additional genetic testing from the donor and his parents to help better understand and define the variants identified in his carrier screening.

Reminder-typically, we all have two copies of every gene---one from the egg source and one from the sperm source. Individuals with CF/*CFTR*-related conditions typically have a mutation in both copies of their *CFTR* genes in order for it to cause the condition(s). Additional testing revealed that the two variants identified in CB 567 were inherited together (in cis) from one of his parents (See Figure 2). CB 567 carries two *CFTR* variants in the same gene copy (this is often referred to as a complex allele). **This means that donor CB 567 has one *CFTR* gene with two pathogenic variants identified, but a second *CFTR* gene with no pathogenic variants identified.**

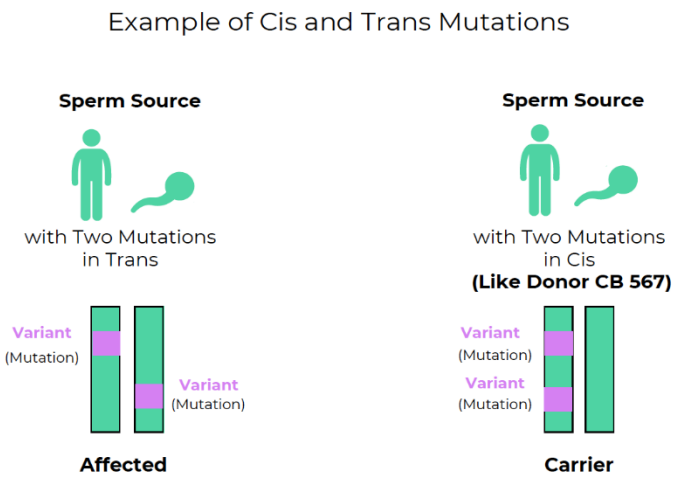

Figure 2. Representation of cis vs. trans mutation carriers.

Despite having a complex allele associated with cystic fibrosis, donor CB 567 should be handled similarly to other carriers of the *CFTR* gene. Cryobio recommends carrier screening for the recipient, or egg source if different, to better understand the risks of *CFTR*-related conditions in any offspring. All other information and risks regarding the *CFTR* gene as noted above apply. We have included donor CB 567's parents' results under his genetic testing profile for you and your health care provider to 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 first carrier frequency provided below is from the original test provider, Sema4, who was Cryobio's testing provider at the time the large panel test was performed. Cryobio changed lab providers during this time, and therefore the single gene test was done with Invitae, who typically reports carrier frequencies as a single, pan ethnic risk. 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.

Cystic fibrosis (*CFTR* gene) carrier status frequency in different ethnicities from Sema4:

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

Invitae carrier status frequency:

Panethnic classic cystic fibrosis	1 in 45
Panethnic classic cystic fibrosis **and** *CFTR* related disorders	1 in 9

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for cystic fibrosis (*CFTR* 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 cystic fibrosis/*CFTR*-related conditions.	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 for cystic fibrosis/*CFTR*-related conditions, 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 condition. 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 gene/condition 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 cystic fibrosis/*CFTR*-related conditions.	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 (and follow up testing with Invitae in 2023). 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: _____
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: _____
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 567's carrier status for *CFTR*, there is a 50% chance of any resulting child also being a carrier, and therefore being at a potentially increased risk for these related 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 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 a genetic condition. I am making the choice to use donor sperm from donor CB 567 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 567.

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 567.

_____

Recipient Date

_____

Partner, if applicable Date

William C. Baird, PhD. HCLD 08-30-2023

Cryobio Date