cryobio

Additional Agreement to Use Donor CB 487

I, (_____ (Recipient), and _____ (Partner, if applicable)), specifically request and accept frozen semen from Cryobio donor CB 487. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 487. CB 487 had expanded genetic carrier screening to determine their carrier status for 283 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 487 has been found to be a carrier of the following recessive genetic conditions:

Biotinidase deficiency;

Nephrotic syndrome (*NPHS2*-related)/Steroid-resistant nephrotic syndrome;

Propionic acidemia (*PCCB*-related); and

Zellweger syndrome spectrum (*PEX6*-related).

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.

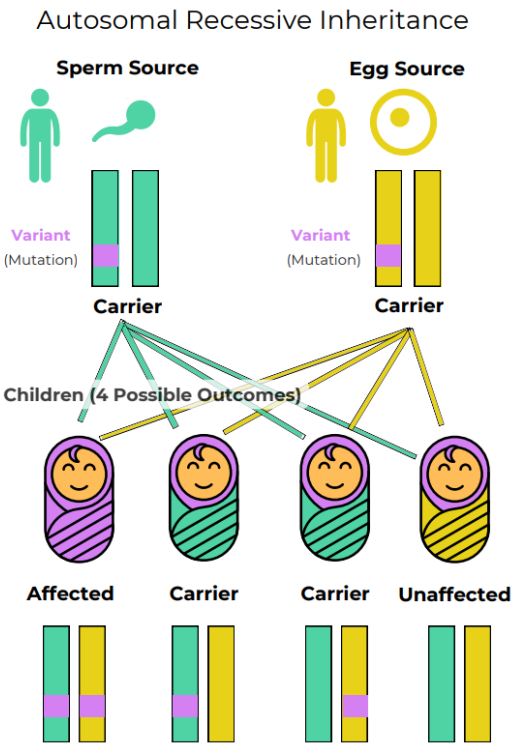

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

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.

Biotinidase deficiency (*BTD* gene): Biotinidase deficiency is an autosomal recessive disorder caused by pathogenic variants in the gene *BTD*. Individuals from all ethnicities can be carriers for biotinidase deficiency. Biotinidase deficiency affects individuals within the first few months of life or in childhood. Biotinidase deficiency is recommended as part of the newborn screen in the United States, so most babies are screened for and diagnosed with the condition at birth. Severe forms of the disorder cause children to experience neurological abnormalities such as seizures, decreased muscle tone, developmental delay, and vision problems. Other symptoms include hearing loss, respiratory problems, and abnormalities related to or affecting the skin such as rash and alopecia (hair loss). While effective treatment is available, symptoms such as vision problems, hearing loss, and developmental delay are irreversible once they have appeared. If individuals with biotinidase deficiency are identified prior to developing symptoms; they typically remain asymptomatic if appropriate biotin therapy is started early and continued throughout the individual's life. However, even in treated individuals, hearing loss and vision problems may still arise. Several specific variants have been associated with full or partial biotinidase deficiency, and therefore the severity of the condition may be predicted based on the genotype. Carriers are not expected to show symptoms of this condition.

Nephrotic syndrome (*NPHS2*-related)/Steroid-resistant nephrotic syndrome (*NPHS2* gene): Nephrotic syndrome (*NPHS2*-related), also known as steroid-resistant nephrotic syndrome, is a genetic disease caused by pathogenic variations or mutations in the *NPHS2* gene. It is inherited in an autosomal recessive inheritance pattern and individuals from all ethnicities can be carriers. Onset is usually during childhood or adolescence. Symptoms include loss of protein in the urine, which results in progressive kidney failure. Death will occur without a kidney transplant, usually by adolescence; however, many patients are cured after they have a kidney transplant. Several specific variants may be associated with an earlier or later age of onset of disease, but not all variants are known to have a genotype-phenotype correlation.

Of note: The specific variant identified in donor CB 487 (p.R229Q) is a common pathogenic variant which is known to cause disease with specific variants in the *NPHS2* gene but does not cause disease with all other variants of the *NPHS2* gene. Regardless, if the egg source were also identified to be a carrier of a *NPHS2* variant, we always recommend review of the information with a genetics professional to better understand the risks of disease to any resulting children. Carriers are not expected to show symptoms of this disease.

Propionic acidemia (*PCCB*-related) (*PCCB* gene): Propionic acidemia (*PCCB*-related) is an autosomal recessive condition caused by pathogenic variants in the gene *PCCB*. Individuals of all ethnicities can be carriers for propionic acidemia (*PCCB*-related). Age of onset is usually in infancy (infantile onset), but it may occur later in childhood or adolescence. Propionic acidemia is recommended as part of the newborn screen in the United States, so most babies are screened for and diagnosed with the condition at birth.

Individuals with propionic acidemia lack the ability to break down certain chemical "building blocks" (called amino acids) of proteins. Buildup of these amino acids then lead to the symptoms associated with the condition. Treatment is available and aims to reduce the amounts of build-up of toxic levels of amino acids. However, even with treatment, many individuals still experience brain damage.

- In the infantile onset form of the disease babies are born healthy but within several days these amino acids build up, they begin to vomit frequently, become lethargic, have diminished muscle tone (called hypotonia), and some may develop seizures. This metabolic crisis can lead to coma and death if not detected and treated. Metabolic crisis is more likely to occur during periods where the infant is sick or develops an infection.
- The later-onset form of the disease resembles the infantile onset disease in many ways, but it occurs after a period of relatively normal development. Symptoms of this form include developmental regression and cardiomyopathy (a disorder that affects the heart muscle).

As patients with propionic aciduria grow, they may have intellectual disability and seizures, as well as cardiomyopathy and pancreatitis. Some patients also have vision and/or hearing loss. Most patients need to be fed by various types of feeding tubes. Life expectancy is variable; for patients diagnosed before they experience a metabolic crisis, preventative treatment often results in a better outcome. Otherwise, life expectancy is limited, and some patients die in childhood. Carriers are not expected to show symptoms of this disease. Some genotype-phenotype correlation does exist, where specific variants are associated with early-onset and severe disease and others result in milder disease.

Zellweger syndrome spectrum (*PEX6*-related) (*PEX6* gene): Zellweger syndrome spectrum (*PEX6*-related) is spectrum of diseases inherited in an autosomal pattern cause by mutations in the *PEX6* gene. Mutations in the *PEX6* gene cause peroxisomal dysfunction. Peroxisomes are enzymes in the body responsible for many important biochemical processes. The Zellweger syndrome spectrum are disorders that are all caused by the same biochemical basis but are comprised of three conditions that make up a continuum of severity. The most severe form is referred to as Zellweger syndrome, the intermediate form is referred to as neonatal adrenoleukodystrophy, and the mildest form is referred to as infantile Refsum disease. Zellweger syndrome spectrum can be found in individuals of many different ethnicities, but it is most common in French Canadian individuals and Sephardic Jewish individuals from Yemen. While most variants do not have a clear genotype-phenotype correlation, several specific *PEX6* variants have been reported to be associated with a more severe phenotype.

• Zellweger syndrome is characterized by demyelination of structures in the brain leading to leukodystrophy, resulting in seizures and vision loss. Clinical features also include facial abnormalities, decreased muscle tone (hypotonia), cardiac problems, and jaundice/liver and kidney dysfunction. Death typically occurs in the first year of life.

• Neonatal adrenoleukodystrophy and infantile Refsum disease share many overlapping features. Onset of symptoms may be in infancy, or they may be noticed later in childhood. Features include developmental delay, hypotonia, seizures, and loss of vision and hearing; some children present with bleeding in the brain. The severity and course of the disease can vary between individuals; some may learn to walk and talk, and rarely, patients may survive to adulthood; while others never walk or talk. Many patients do not survive childhood. Symptoms tend to progress in severity over the course of the patient's life.

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.

Biotinidase deficiency (*BTD* gene) carrier status frequency in different ethnicities, from SEMA4:

Worldwide	1 in 13
African	1 in 52
Ashkenazi Jewish	1 in 15
East Asian	1 in 324
Finnish	1 in 9
European (Non-Finnish)	1 in 12
Native American	1 in 24
South Asian	1 in 7

Nephrotic syndrome (*NPHS2*-related)/steroid-resistant nephrotic syndrome (*NPHS2* gene) carrier status frequency in different ethnicities, from SEMA4:

Worldwide	1 in 16
African	1 in 77
Ashkenazi Jewish	1 in 9
East Asian	1 in 528
Finnish	1 in 7
European (Non-Finnish)	1 in 13
Native American	1 in 36
South Asian	1 in 18

Propionic acidemia (*PCCB*-related) (*PCCB* gene) carrier status frequency in different ethnicities, from SEMA4:

Worldwide	1 in 548
African	1 in 257
East Asian	1 in 192
Finnish	1 in 1080
European (Non-Finnish)	1 in 635
Native American	1 in 688
South Asian	1 in 1490

Zellweger syndrome spectrum (*PEX6*-related) (*PEX6* gene) carrier status frequency in different ethnicities, from SEMA4:

Worldwide	1 in 118
African	1 in 268
Ashkenazi Jewish	1 in 263
East Asian	1 in 595
Finnish	1 in 205
European (Non-Finnish)	1 in 83
Native American	1 in 239
South Asian	1 in 168
Worldwide	1 in 105

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for biotinidase deficiency (*BTD* gene); nephrotic syndrome (*NPHS2*-related)/steroid-resistant nephrotic syndrome (*NPHS2* gene); propionic acidemia (*PCCB*-related) (*PCCB* gene); and Zellweger syndrome spectrum (*PEX6*-related) (*PEX6* 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 283 genes. These results indicate that the donor is a carrier for biotinidase deficiency; nephrotic syndrome (*NPHS2*-related)/steroid-resistant nephrotic syndrome; propionic acidemia (*PCCB*-related); and Zellweger syndrome spectrum (*PEX6*-related).	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 biotinidase deficiency; nephrotic syndrome (*NPHS2*-related)/steroid-resistant nephrotic syndrome; propionic acidemia (*PCCB*-related); and Zellweger syndrome spectrum (*PEX6*-related), 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 biotinidase deficiency (*BTD* gene); nephrotic syndrome (*NPHS2*-related)/steroid-resistant nephrotic syndrome (*NPHS2* gene); propionic acidemia (*PCCB*-related) (*PCCB* gene); and Zellweger syndrome spectrum (*PEX6*-related) (*PEX6* 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 283 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: _____
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 487 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 487.

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 487.

_____ _____

Recipient Date Email

_____ _____

Partner, if applicable Date Email

William C. Baird, PhD, HCLD 9-14-2021

Cryobio Date