cryobio

Additional Agreement to Use Donor PC 1137

I, (_____ (Recipient), and _____ (Partner, if applicable)), specifically request and accept frozen semen from Cryobio donor PC 1137. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor PC 1137. PC 1137 had expanded 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 PC 1137 has been found to be a carrier of the following recessive genetic conditions:

Biotinidase deficiency;

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form;

Gitelman syndrome; and

Retinitis pigmentosa 25.

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.

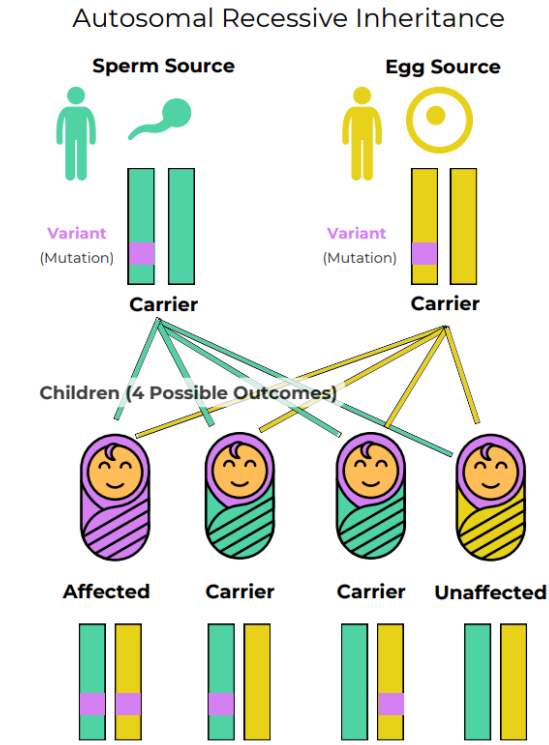

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

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 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. Individuals with biotinidase deficiency are unable to effectively "reuse" a vitamin, called biotin, in their body. Biotin is important in helping the body break down proteins, fats, and carbohydrates. If individuals with biotinidase deficiency are identified prior to developing symptoms; they typically remain asymptomatic if appropriate biotin therapy is started early (i.e., taking extra biotin for the body to use). Biotin supplements need to be continued throughout the individual's life.

If left untreated, biotinidase deficiency affects individuals within the first few months of life or in childhood. Severe forms of the disorder cause children to experience neurological abnormalities such as seizures, decreased muscle tone, developmental delay, vision problems, and even death. 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. Also, sometimes 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 (the specific gene mutations the affected person has). Carriers are not expected to show symptoms of this condition. Biotinidase deficiency is recommended as part of the newborn screen in the United States, therefore most babies are screened for and diagnosed with the condition at birth.

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 PC 1137 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.

Gitelman syndrome (*SLC12A3* gene): Gitelman syndrome is an autosomal recessive, pan-ethnic condition caused by pathogenic variants in the gene *SLC12A3*. In this condition, the kidney does not retain necessary particles/ions, causing an imbalance in the body. Symptoms usually begin in late childhood or adolescence, and include muscle spasms or cramps, tingling sensations, joint pain, and fatigue. Most patients have mild symptoms, but severe ion imbalances could lead to seizures or heart arrhythmias. With treatment, including dietary management, patients have a normal life expectancy. It is not currently possible to predict the severity of symptoms based on the variants inherited. Studies have suggested carriers of Gitelman syndrome may have a lower blood pressure compared to that of the general population. However, carriers are not expected to have clinical problems or symptoms of the condition.

Of note: There has been one case report of the possibility of digenic inheritance in an individual with Gitelman syndrome. Digenic inheritance means genetic variants in two *different* genes combined cause a disease. In this case report, it is *suspected* that one *SLC12A3* and one *CLCKNB* variant were the cause of disease. However, the pathogenicity (likelihood of the variant causing disease) of the *CLCKNB* gene could not be confirmed. More evidence is needed to conclude digenic inheritance as the cause of Gitelman syndrome. As an extra precaution, recipients should consider testing the recipient (or egg source if different) for *CLCKNB* carrier status in addition to *SLC12A3* carrier status.

Retinitis pigmentosa 25 (*EYS* gene): Retinitis pigmentosa refers to a group of inherited disorders and are the primary cause of hereditary blindness in adults. There are a variety of genes that can cause retinitis pigmentosa, and many different inheritance patterns. Retinitis pigmentosa 25 is inherited in an autosomal recessive pattern and is caused by pathogenic variants in the gene *EYS*. While it has been reported in populations worldwide, it is more prevalent in Spain and Sephardic Jewish populations from Morocco. Variants in the *EYS* gene have also been reported as the most frequent cause of inherited retinitis pigmentosa in Japanese populations.

Retinitis pigmentosa begins with the onset of night blindness in childhood and progresses to tunnel vision and blindness in adulthood. Age of onset and severity of vision loss may vary between patients. Some patients with retinitis pigmentosa 25 may develop cataracts. Life expectancy is not reduced. No genotype-phenotype correlation has been reported.

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:

African	1 in 52
Ashkenazi Jewish	1 in 15
East Asian	1 in 324
Finnish	1 in 9
Caucasian	1 in 12
Latino	1 in 24
South Asian	1 in 7
Worldwide	1 in 13

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

Ashkenazi Jewish	1 in 7
Caucasian	1 in 11
Worldwide	1 in 16

Gitelman syndrome (*SLC12A3* gene) carrier status frequency in different ethnicities:

African	1 in 138
Ashkenazi Jewish	1 in 121
East Asian	1 in 28
Finnish	1 in 239
Caucasian	1 in 73
Latino	1 in 131
South Asian	1 in 145
Worldwide	1 in 82

Retinitis Pigmentosa 25 (*EYS* gene) carrier status frequency in different ethnicities:

African	1 in 71
Ashkenazi Jewish	1 in 109
East Asian	1 in 53
Finnish	1 in 39
Caucasian	1 in 82
Latino	1 in 152
South Asian	1 in 168
Worldwide	1 in 77
Sephardic Jewish-Moroccan	1 in 42

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for biotinidase deficiency (*BTD* gene)**,** congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form (*CYP21A2* gene), Gitelman syndrome (including both the *SLC12A3* and *CLCKNB* genes), and retinitis pigmentosa 25 (*EYS* 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**;** congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form; Gitelman syndrome; and retinitis pigmentosa 25.	Initials: _____ Initials: _____
These genetic conditions 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**;** congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form; Gitelman syndrome; and retinitis pigmentosa 25, 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)**;** congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form (*CYP21A2* gene); Gitelman syndrome (including both the *SLC12A3* gene and the *CLCKNB* gene); and retinitis pigmentosa 25 (*EYS* 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 2019. 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 PC 1137 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 PC 1137.

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 PC 1137.

_____

Recipient Date Email

_____

Partner, if applicable Date Email

William C. Baird, PhD, HCLD 03-23-2023

Cryobio Date