cryobio

Additional Agreement to Use Donor PC 1134

I, (_____ (Recipient), and _____ (Partner, if applicable)), specifically request and accept frozen semen from Cryobio donor PC 1134. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor PC 1134. PC 1134 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 1134 has been found to be a carrier of the following recessive genetic conditions:

Medium chain acyl-CoA dehydrogenase deficiency; and
Congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form.

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.

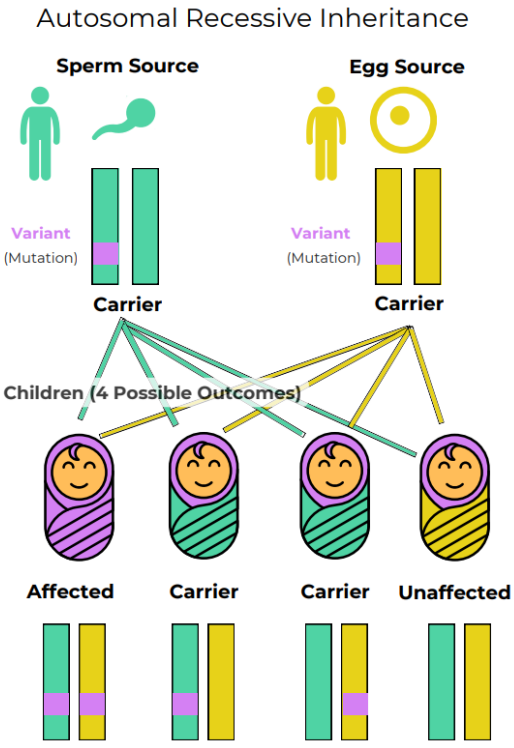

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

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.

Medium chain acyl-CoA dehydrogenase deficiency (*ACADM* gene): Medium chain acyl-CoA dehydrogenase (MCAD) deficiency is a pan-ethnic autosomal recessive condition caused by pathogenic

variants in the gene *ACADM*. MCAD is a metabolic disease that prevents the body from releasing and using energy from fats. Therefore, individuals with MCAD deficiency should limit the amount of time between meals so that their body does not need to rely on fat for energy. In individuals who are untreated, symptoms often begin in infancy, although the clinical presentation is highly variable, and some affected individuals do not show symptoms until adulthood-if at all. Untreated MCAD deficiency can cause metabolic crises, which present with lethargy and vomiting. Some undiagnosed infants may present with sudden death. Dietary management greatly reduces the risk of metabolic crises and allows affected individuals to live relatively normal lives. Although metabolic crises can be fatal, affected individuals who have a known diagnosis and receive proper care have normal life expectancy. Some *ACADM* variants are known to be associated with milder disease, although it is not possible to exactly predict the severity of disease based on the inherited variants. MCAD is also included on newborn screening, and therefore is now typically diagnosed 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 infant's external genitalia not appearing to be clearly male or female (ambiguous genitalia), puberty earlier than typical (precocious puberty), excessive facial hair, and includes inadequate adrenal aldosterone secretion that can result in the body not being able 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 too much testosterone in the body (hyperandrogenism). Hyperandrogenism may cause abnormal growth of hair on the face and body, especially on a woman (hirsutism), 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 1134 tested positive as a carrier for a pathogenic variant 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 only be at risk for the mild, non-classic form of CAH.

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.

Medium chain acyl-CoA dehydrogenase deficiency (*ACADM* gene) carrier status frequency in different ethnicities from SEMA4:

Worldwide	1 in 87
African	1 in 175
Ashkenazi Jewish	1 in 133
East Asian	1 in 262
Finnish	1 in 383
European (Non-Finnish)	1 in 57
Native American	1 in 130
South Asian	1 in 175

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form (*CYP21A2* gene) carrier status frequency in different ethnicities from SEMA4:

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

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for medium chain acyl-CoA dehydrogenase deficiency (*ACADM* gene) and congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form (*CYP21A2* gene) carrier status and consider genetic counseling. Please contact Cryobio with any questions or to arrange genetic counseling. 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 we have chosen has had positive results from genetic testing looking at carrier status for 283 genes. These results indicate that the donor is a carrier for medium chain acyl-CoA dehydrogenase deficiency and congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form.	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 medium chain acyl-CoA dehydrogenase deficiency and congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form, 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 medium chain acyl-CoA dehydrogenase deficiency (*ACADM* gene) and congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form (*CYP21A2* 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: _____

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 1134 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 1134.

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 1134.

Recipient	Date	Email

Partner, if applicable	Date	Email

William C. Baird, PhD, HCLD	07-28-2022
Cryobio	Date