cryobio

Additional Agreement to Use Donor PC 1131

We, _____ (Recipient), and _____ (Partner, if applicable), specifically request and accept frozen semen from Cryobio donor PC 1131. We understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor PC 1131. We have received genetic test results on this sperm donor, and we understand that donor PC 1131 has been found to be a carrier of the following recessive genetic conditions:

Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency,
Gaucher Disease,
and
Non-Syndromic Hearing Loss (GJB2-Related).

Why carrier status is important: Carriers of genetic diseases have changes, called pathogenic variants or mutations, in a specific (or multiple) gene(s). Most of the genetic diseases that the Cryobio donors are tested for are inherited in an autosomal recessive pattern. Typically, we all have two copies of every gene---one from the egg source and one from the sperm source. Autosomal recessive diseases require a mutation in both copies of the same gene in order for it to cause disease. Therefore, individuals who carry just one mutation in a gene that causes recessive disease are 'carriers' of that specific disease. Carriers of most of the genetic diseases Cryobio donors are tested for do not show symptoms of the disease, i.e., they are asymptomatic. Some diseases tend to occur more in certain ethnicities, and some tend to occur evenly in all ethnicities. Most individuals are carriers for at least one if not multiple recessive genetic diseases.

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 disease; a 2 in 4 chance of the resulting child being a carrier for that specific disease; and a 1 in 4 chance of the resulting child being neither a carrier or having that specific disease. Some of the diseases 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 disease that may present in the individual (the phenotype), but not all do.

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 1131 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.

Gaucher disease (GBA gene): Gaucher disease is an autosomal recessive disease caused by pathogenic variants in the gene GBA. While it is found in populations worldwide, it is most prevalent in individuals of Ashkenazi Jewish descent. Gaucher disease has variable clinical features and can be divided into the following subtypes.

- Type 1 is characterized by bone disease and absence of neurological involvement. The bone disease can vary in severity from asymptomatic to destruction of bone tissue and painful bone crises. Patients often have anemia and abnormal blood cell counts which may lead to frequent bleeding and may have lung disease. Other features may include delay in puberty, failure to grow, and an enlarged liver and spleen. Some patients may develop symptoms in early childhood to adulthood, while others may be asymptomatic.
- Type 2 is a severe form that begins in infancy and usually results in death by the age of 2 to 4. It is characterized by severe neurologic deterioration (which can present with abnormal eye movements, low muscle tone, and abnormal, spastic movements), seizures, anemia (lack of red blood cells and therefore lack of oxygen to parts of the body), poor feeding and failure to thrive. Other symptoms may include trouble breathing/lung problems, or skin problems called ichthyosis (dry, “scaly-like” skin).
    - The perinatal-lethal form is a more severe subtype of Type 2, where accumulation of fluid in the fetus results in death in utero or in the first several days of life. Some patients do not have the excess fluid, but die within three months.
- Type 3 is characterized by neurologic deterioration, as with Type 2, but onset may be anywhere from childhood to adulthood, and progresses more slowly. Patients develop seizures and declining intelligence. Patients also experience the bone disease and anemia seen in Type 1.
    - The cardiovascular form is a subtype of Type 3 that is characterized by calcification of the heart valves during adolescence. Patients may also have problems controlling their eye movements. The cardiac manifestations are usually fatal.

Some pathogenic variants are associated with a specific type of Gaucher disease. However, there is significant variability in the phenotypes (presentation/symptoms of the disease), even between identical twins. Therefore, it is not always possible to predict the severity of disease based on the specific genetic mutations.

IMPORTANT NOTE: Heterozygous carriers (i.e. individuals who have a single mutation in one GBA gene-like this donor) are not expected to exhibit symptoms of the disease, **but have an increased lifetime risk of developing Parkinson's disease.** This risk is approximately five times higher than the general population in heterozygous carriers (i.e. individuals who have a single mutation in one GBA gene-like this donor), and 10-20 times higher than the general population in homozygous carriers (i.e. individuals who have a pathogenic mutation in both copies of their GBA gene, but do not have symptoms of Gaucher disease). There is an association with an earlier age of onset and possibly more rapid progression with more dementia symptoms in individuals who have Parkinson's disease and are GBA mutation carriers compared to individuals with Parkinson's disease who are not GBA mutation carriers.

Parkinson's disease is a neurodegenerative disorder that affects the nervous system. It causes symptoms such as shaking, tremors, slow movement, balance problems and stiffness. It most frequently affects individuals who are over the age of 60 but can be diagnosed in individuals who are younger. There is currently no cure for Parkinson's disease, although medications are available to help control symptoms. It is the second most common neurodegenerative disorder, affecting up to 2-3% of individuals in the general population over the age of 65.

It is important to note that with a few rare exceptions, Parkinson's disease is understood to be inherited in a multifactorial inheritance pattern. This means that there typically *multiple* genetic (i.e. inherited) *risk factors* to develop the disease, and environmental risk factors (for example smoking, stress levels, exposure to chemicals, etc.) that increase the risk of disease. It is the combination of the genetic risk factors and the environmental risk factors that cause some individuals in families to develop the disease, while other individuals may not. It is estimated that up to 9% of all GBA carriers may develop Parkinson's disease in their lifetime. *However, carrying a GBA mutation is only one risk factor, and most carriers still do NOT develop Parkinson's disease in their lifetime. Family history of Parkinson's disease is another risk factor that can increase one's risk to develop the disease*. It is important to note that this donor did not report any personal or family history of Parkinson's disease or related symptoms. However, it is worth noting that if you, the recipient or egg source, if different, consider your own family history of Parkinson's disease before choosing to move forward with donor PC 1131. *We strongly encourage you to speak with a genetic counselor (through Cryobio or elsewhere) regarding this information before proceeding with donor PC 1131.* If you choose to use this donor, there is a 50% chance your child will be a carrier for his GBA gene mutation.

Non-syndromic hearing loss (GJB2-related) (GJB2/GJB6 gene): Non-syndromic hearing loss (*GJB2/GJB6*-related) is an autosomal recessive disorder that is caused by pathogenic variants primarily in the gene GJB2 and also, although more rare, deletions in the gene GJB6. Most commonly this hearing loss is caused by a mutation in both of an individual's GJB2 genes. However, there have been reports of individuals with one mutation in GJB2 and one mutation in GJB6 that resulted in hearing loss. It is found in individuals of many different ethnicities, but it is more prevalent in individuals of Ashkenazi Jewish descent, as well as Caucasians and Asians. Patients with this form of hearing loss do not experience any other disease manifestations. Hearing loss is usually present from birth and does not progress in severity over time. The level of hearing loss can vary between patients from mild to profound. Sometimes predictions can be made as to the severity of hearing loss based on the specific genetic variants present, but variability does exist and this prediction is not always accurate. Life expectancy is not reduced.

Of note: The specific variant identified in donor PC 1131 has been reported to have variable penetrance. This means some individuals with this mutation plus a second one in their other GJB2 (or GJB6) gene have presented with hearing loss, while others have not. Therefore, donor PC 1131 is still considered a carrier of GJB2-related non-syndromic hearing loss.

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. This remaining risk is known as residual risk, meaning what is the risk of being a carrier even after negative genetic testing. Residual risk data is available directly through sema4's website, sema4.com, or can be requested from Cryobio.

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form (CYP21A2 gene) carrier status frequency in different ethnicities from Sema4's website:

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

Gaucher disease carrier status frequency in different ethnicities, from Sema4's website:

Worldwide	1 in 158
Ashkenazi Jewish	1 in 15
European (Non-Finnish)	1 in 164

Non-syndromic hearing loss (GJB2-related) (GJB2 gene) carrier status frequency in different ethnicities, from Sema4's website:

Worldwide	1 in 18
African	1 in 56
Ashkenazi Jewish	1 in 13
East Asian	1 in 5
Finnish	1 in 16
European (Non-Finnish)	1 in 18
Native American	1 in 28
South Asian	1 in 55

Recommendation: Both Sema4 and Cryobio recommend that the recipient, or egg source if different than recipient, be tested for congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form; Gaucher disease; and non-syndromic hearing loss (GJB2-related which includes looking at both the GJB2 and GJB6 genes) carrier status and consider genetic counseling. Please refer to Sema4's website, sema4.com, for more information and contact Cryobio with any questions or to arrange genetic counseling. Because the donor was tested by Sema4, Cryobio recommends that the recipient or egg source should be tested by Sema4 as well. 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 health and reproductive future.

Cryobio has advised us of the following:	Please initial to show your understanding and agreement:
The donor we have chosen has had positive results from genetic testing. These results indicate that the donor is a carrier for congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form; Gaucher disease; and non-syndromic hearing loss	Initials: _____ Initials: _____

(GJB2-related which includes looking at both the GJB2 and GJB6 genes).	
These genetic conditions are inherited as recessive traits. 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 congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form; Gaucher disease; and non-syndromic hearing loss (GJB2-related which includes looking at both the GJB2 and GJB6 genes); 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 disease. 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 detailed information regarding the sensitivity of testing and remaining risk after negative screening, please see Sema4's website.	Initials: _____ Initials: _____
Genetic testing looking at a large panel of genes, including the genes/conditions 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 congenital adrenal hyperplasia due to 21-hydroxylase deficiency, non-classic form; Gaucher disease; and non-syndromic hearing loss (GJB2-related which includes looking at both the GJB2 and GJB6 genes).	Initials: _____ Initials: _____
A negative genetic test result in the egg source significantly reduces the likelihood that the resulting child could be affected with these conditions. However, we fully understand that the risk cannot be completely eliminated.	Initials: _____ Initials: _____
Carrier status of Gaucher disease can increase the risk of Parkinson's disease. Based on donor PC 1131's carrier status for Gaucher disease, there is a 50% chance of any resulting child also being a carrier, and therefore inheriting an increased risk of Parkinson's disease.	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 genetic disease.	Initials: _____ Initials: _____
Genetic counseling is available to us, either through Cryobio or Sema4, if we 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: _____

We 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. We are making the choice to use donor sperm from donor PC 1131 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 1131.

We have read and had the chance to ask questions, and we understand and agree to the terms of this Additional Agreement to use donor PC 1131.

_____
Recipient

_____
Date

_____
Partner, if applicable

_____
Date

William C. Baird, PhD
_____
Cryobio

04-11-2022
_____
Date