cryobio

Additional Agreement to Use Donor PC 1120

We, _____ (Recipient), and _____ (Partner, if applicable), specifically request and accept frozen semen from Cryobio donor PC 1120. We understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor PC 1120. We have received genetic test results on this sperm donor, and we understand that donor PC 1120 has been found to be a carrier of the following recessive genetic conditions:

Bartter Syndrome, Type 4A,
Non-Syndromic Hearing Loss (GJB2-Related),
and
Smith-Lemli-Opitz Syndrome.

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.

Bartter Syndrome, Type 4A (BSND gene): Bartter syndrome, type 4a is an autosomal recessive disorder caused by pathogenic variants in the gene BSND. Bartter syndrome is a term used to identify a group of genetic disorders that cause specific defects in kidney function. This altered kidney function causes imbalances in salt and electrolytes throughout the body. Salt and electrolyte concentration is crucial to a variety of processes in the body, and it can therefore lead to a variety of problems and potential life-threatening complications. Although severity and symptoms of the disease can vary from person to person, Bartter syndrome type 4a most often presents before birth or shortly after birth, and with more severe symptoms.

Abnormal kidney function in utero can lead to excess production of amniotic fluid, known as polyhydramnios, which often leads to premature birth. Individuals with type 4a also present with sensorineural deafness at birth. In infancy, the imbalances in the electrolytes can then cause failure to thrive (the failure to grow and gain weight appropriately), dehydration, constipation, bone weakness, and hardening of kidney tissue. Additionally, many individuals with type 4a will experience muscle weakness and cramping, as well as have intellectual disability. The severity of intellectual disability varies, and often correlates with the severity of prematurity. There is treatment available and when used and life-

threatening crises are avoided, then life expectancy is not reduced. There has been no genotype-phenotype correlation reported.

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. Some genotype-phenotype predictions can be made to predict the severity of hearing loss. However, the variability that exists between patients means that it may not be possible to predict the severity of an individual's hearing loss based on their genotype. Of note-the specific variant identified in donor PC 1120 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 1120 is still considered a carrier of GJB2-related non-syndromic hearing loss. Life expectancy is not reduced.

Smith-Lemli-Opitz Syndrome (DHCR7 gene): Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive disease caused by pathogenic variants in the gene DHCR7. The DHCR7 gene codes for an enzyme which plays a crucial role in the production of cholesterol, and individuals with SLOS do not produce enough cholesterol. Cholesterol is crucial for embryonic development and has important functions both before and after birth. Therefore, SLOS affects many parts of the body. While most patients have a severe phenotype and are identified at birth, more mildly affected patients who have been diagnosed in childhood or adolescence have been reported. While it is a pan-ethnic disease, it is identified more frequently in people of Caucasian or Ashkenazi Jewish ancestry.

Smith-Lemli-Opitz syndrome (SLOS) severity and number of symptoms can vary between indiviudals. However, it is generally characterized by prenatal and postnatal growth restriction, small head size (microcephaly), distinct facial features, cleft palate, extra and/or fused fingers and toes, gastrointestinal anomalies, and genital anomalies in males. Affected individuals may also have malformations of the heart and lungs, low muscle tone, feeding difficulties, and may grow more slowly than other infants. Individuals with SLOS often present with intellectual deficits and behavioral problems, including autistic features, self-harm behaviors and hyperactivity. Life expectancy varies with the severity of disease; it has been reported that approximately 25% of patients die in infancy, while others live to adulthood. There is currently no treatment for SLOS, however cholesterol supplementation may help, as well as other therapies based on symptoms. A clear genotype-phenotype correlation has not been reported.

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.

Bartter syndrome, type 4a (BSND gene) carrier status frequency in different ethnicities, from Sema4's website:

Worldwide	1 in 739

African	1 in 186
Ashkenazi Jewish	1 in 1641
East Asian	1 in 687
European (Non-Finnish)	1 in 916
Native American	1 in 2856
South Asian	1 in 733

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

Smith-Lemli-Opitz syndrome (DHCR7 gene) carrier status frequency in different ethnicities, from Sema4's website:

Worldwide	1 in 57
African	1 in 51
Ashkenazi Jewish	1 in 39
East Asian	1 in 357
Finnish	1 in 141
European (Non-Finnish)	1 in 46
Native American	1 in 118
South Asian	1 in 334

Recommendation: Both Sema4 and Cryobio recommend that the recipient, or egg source if different than recipient, be tested for Bartter syndrome, type 4a; non-syndromic hearing loss (GJB2-related which includes looking at both the GJB2 and GJB6 genes); and Smith-Lemli-Opitz syndrome 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 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 Bartter syndrome, type 4a; non-syndromic hearing loss (GJB2/GJB6-related); and Smith-Lemli-Opitz syndrome.	Initials: _____ Initials: _____

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 Bartter syndrome, type 4a; non-syndromic hearing loss (GJB2/GJB6-related); and Smith-Lemli-Opitz syndrome 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 Bartter syndrome, type 4a; non-syndromic hearing loss (GJB2/GJB6-related); and Smith-Lemli-Opitz syndrome.	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: _____
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 1120 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 1120.

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 1120.

_____
Recipient

_____
Date

_____
Partner, if applicable

_____
Date

William C. Baird, PhD

_____
Cryobio

03-30-2022

_____
Date