cryobio

Additional Agreement to Use Donor CB 956-B

I, (_____ (Recipient), and _____ (Partner, if applicable)), specifically request and accept frozen semen from Cryobio donor CB 956-B. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 956-B. I have received and reviewed genetic test results on this sperm donor, and I understand that donor CB 956-B has been found to be a carrier of the following recessive genetic conditions:

Cartilage-Hair Hypoplasia
Congenital Disorder of Glycosylation type Ia
and
Congenital Dyserythropoietic Anemia type Ia

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 typically show symptoms of the disease, i.e., they are asymptomatic, although there are rare exceptions. 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.

Cartilage-hair hypoplasia (*RMRP* gene): Cartilage-hair hypoplasia spectrum disorders are autosomal recessive disorders caused by pathogenic variants in both copies of the gene *RMRP*. It is typically divided into three clinical categories depending on the individual's features.

- Cartilage-hair hypoplasia (CHH)
- Metaphyseal dysplasia without hypotrichosis (MDWH)
- Anauxetic dysplasia (AD)

Generally, all individuals have disproportionately short limbs and stature, and most present with skeletal abnormalities, joint hypermobility/flexibility, abnormal immune system response that can lead to recurrent infections, and anemia (fewer red blood cells). Rarer symptoms include lymphomas (cancer involving the lymph system), Hirschsprung disease (characterized by bowel blockage or dysmotility), and intestinal malabsorption (inability to absorb nutrients from your food). Skeletal abnormalities will typically occur prenatally, while affected individuals may develop anemia, abnormal immune response, or Hirschsprung disease within the first few years of life. Some individuals may pass away in childhood due to abnormal immune response or cancer, but many live into adulthood. As clinical symptoms can vary within a family, it is difficult to predict the severity of the disease based on the inherited variants. There is currently no cure for cartilage-hair hypoplasia disorders, but treatments exist for specific symptoms.

Congenital disorder of glycosylation type Ia (*PMM2* gene): Congenital disorders of glycosylation (CDGs) are a group of genetic disorders that affect an important process in cells called glycosylation. Glycosylation is the process where “sugars” in the body are added to other proteins or fats, which ultimately is important and essential for a variety of functions in the body including normal growth and function of body tissues and organs. Different types of CDGs are caused by different genes and are inherited in a variety of inheritance patterns. Congenital disorder of glycosylation type Ia (also known as *PMM2*-CDG) is the most common congenital disorder of glycosylation and it is inherited in an autosomal recessive pattern caused by pathogenic variants in the gene *PMM2.* Congenital disorder of glycosylation type Ia can present at different periods of life and the severity, presenting symptoms, and prognosis can vary greatly from one person to another. In infants, symptoms may include feeding problems resulting in failure to grow and gain weight, hypotonia (low muscle tone/ "floppiness"), developmental delays, seizures, strabismus (abnormal alignment of the eyes), and abnormalities of the brain, kidney, liver, or other organs. Later in infancy and/or childhood, the disease may cause hypotonia, ataxia (loss of full control of body movements), delayed language and motor development, intellectual disability (ranging from moderate to severe), stroke like episodes, retinitis pigmentosa (eye disease leading to vision impairment), and possible episodes of internal organ failure. Severely affected individuals may die in infancy or early childhood, but more mildly affected individuals may survive into adulthood with variable intellectual disability, spinal abnormalities, ataxia, endocrine dysfunction (lack of spontaneous puberty in girls) and coagulopathy (a condition where the ability to form blood clots is affected, which can lead to excessive bleeding or excessive clotting). There is currently no cure for congenital disorder of glycosylation type Ia, but treatments for specific symptoms may be used.

Congenital dyserythropoietic anemia type Ia (*CDAN1* gene): Congenital dyserythropoietic anemia (CDA) is a group of rare, inherited conditions characterized by ineffective red blood cell production (erythropoiesis). This results in anemia, or fewer red blood cells and hemoglobin, which are important for carrying oxygen throughout the body. The different types of CDA are caused by different genes and inherited in different ways. Congenital dyserythropoietic anemia type Ia is an autosomal recessive disorder caused by pathogenic variants in the gene *CDAN1.* This disorder is characterized by moderate to severe anemia that typically is diagnosed in childhood. Rarely the disorder can be detected before birth, where it presents as hydrops fetalis (where large amounts of fluid build up in the baby’s tissues and organs causing significant swelling that can be seen on ultrasound). Individuals typically present with lifelong anemia, jaundice (yellow appearance of the skin and whites of the eye due to excessive amounts of bilirubin in the blood), and hepatosplenomegaly (swelling/enlargement of the liver and spleen). Rarely individuals are born with limb abnormalities and heart defects. Excess iron absorption can damage tissues and lead to arrhythmia (irregular heartbeat), congestive heart failure (inability of your heart muscle to pump blood as well as it should, liver cirrhosis (scarring and damage of the liver), and diabetes. Without proper treatment, complications from iron overload can cause early death. There is currently no cure for congenital dyserythropoietic anemia type Ia, but treatment for specific symptoms may be available.

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. 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, who was Sema4 who when the test was performed. 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.

Carrier status frequency of cartilage-hair hypoplasia (*RMRP* gene) in different ethnicities:

Worldwide	1 in 120
African	1 in 210
Ashkenazi Jewish	1 in 68
East Asian	1 in 165
Finnish	1 in 49
European (Non-Finnish)	1 in 143
Native American	1 in 157
South Asian	1 in 192

Carrier status frequency of congenital disorder of glycosylation type Ia (*PMM2* gene) in different ethnicities:

Worldwide	1 in 80
African	1 in 245
Ashkenazi Jewish	1 in 66
East Asian	1 in 133
Finnish	1 in 58
European (Non-Finnish)	1 in 58
Native American	1 in 114
South Asian	1 in 278

Carrier status frequency of congenital dyserythropoietic anemia type Ia (*CDAN1* gene) in different ethnicities:

Worldwide	1 in 290
African	1 in 657
Ashkenazi Jewish	1 in 1269
East Asian	1 in 425
Finnish	1 in 554
European (Non-Finnish)	1 in 204
Native American	1 in 348
South Asian	1 in 394

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for cartilage-hair hypoplasia (*RMRP* gene), congenital disorder of glycosylation type Ia (*PMM2* gene), and congenital dyserythropoietic anemia type Ia (*CDAN1* 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 be important to 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 502 conditions. These results indicate that the donor is a carrier for cartilage-hair hypoplasia, congenital	Initials: _____ Initials: _____

disorder of glycosylation type Ia, and congenital dyserythropoietic anemia type Ia.	
These genetic conditions are inherited as a recessive trait. 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 cartilage-hair hypoplasia, congenital disorder of glycosylation type Ia, and congenital dyserythropoietic anemia type Ia, 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 information regarding the remaining risk after negative screening, please contact Cryobio.	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 cartilage-hair hypoplasia, congenital disorder of glycosylation type Ia, and congenital dyserythropoietic anemia type Ia.	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, I fully understand that the risk cannot be completely eliminated.	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 2022. My health care provider may recommend an expanded carrier screen that includes/included more than the 502 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: _____
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 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 disorders. I am making the choice to use donor sperm from donor CB 956-B 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 956-B.

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 956-B.

_____

Recipient Date

_____

Partner, if applicable Date

William C. Baird, PhD. 05-26-2023

Cryobio Date