cryobio

Additional Agreement to Use Donor CB 571

I (_____ (Recipient), and _____ (Partner, if applicable)), specifically request and accept frozen semen from Cryobio donor CB 571. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 571. CB 571 had expanded genetic carrier screening to determine their carrier status for 556 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 CB 571 has been found to be a carrier of the following recessive genetic conditions:

Methylmalonic acidemia;
and
Primary ciliary dyskinesia.

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.

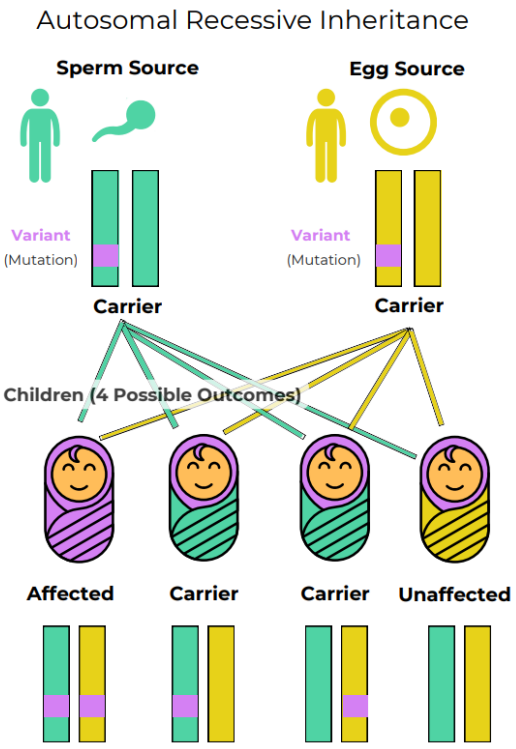

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

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.

Methylmalonic acidemia (MMA) (*MMAB* gene): Methylmalonic acidemia (MMA) is a condition in which the body is unable to properly process certain building blocks of proteins (amino acids) and fats (lipids). There are multiple forms of MMA, which are caused by changes in different genes. MMA caused by changes in the *MMAB* gene is also called cobalamin B type MMA. Symptoms of cobalamin B type MMA are variable in severity and may appear anytime from infancy through adulthood. Affected infants typically have vomiting, failure to thrive (poor growth), hypotonia (low muscle tone), lethargy (lack of energy), hepatomegaly (an enlarged liver), encephalopathy (brain dysfunction), and developmental delay. In some infants, these symptoms can be fatal. Affected individuals who survive infancy may experience periods of relative health followed by periods of potentially life-threatening illness (decompensation), often brought on by infections or stressors, such as injuries or surgery. Long-term complications can include intellectual disability, impaired growth, movement disorders, kidney disease, and pancreatitis (inflammation of the pancreas). Prognosis and life expectancy depend on the severity of symptoms. Dietary restriction of certain amino acids and supplementation with vitamin B12 and folate may help improve symptoms in some affected individuals, but there is currently no cure (although individuals with the MMAB sub-type are rarely responsive to vitamin B12 therapy). Methylmalonic acidemia 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.

Primary ciliary dyskinesia (PCD) (*DNAH5* gene): Primary ciliary dyskinesia (PCD) is part of a spectrum of conditions called ciliopathies, which involve defects in the microscopic, finger-like projections (cilia) that are located on the surface of cells and that are involved in cell movement and signaling. Ciliopathies affect many parts of the body.

PCD can be caused by changes in several different genes, but Donor 571 is specifically a carrier for one change in the *DNAH5* gene. *DNAH5*-related PCD is inherited in an autosomal recessive pattern. Affected individuals often experience breathing problems at birth. In childhood, symptoms of PCD typically include recurring respiratory infections that can damage the passages leading from the windpipe to the lungs (bronchiectasis), which can cause life-threatening breathing issues. Chronic otitis media (ear infections) are also common in childhood and may lead to hearing loss in adults with PCD. Approximately half of individuals affected with PCD have situs inversus totalis (a mirror-image reversal of their internal organs), in which, for example, the heart is on the right side of the body instead of on the left. In a smaller percentage of individuals with PCD, the internal organs are not arranged as expected in the chest and abdomen (heterotaxy). The organs involved often include the heart, lungs, spleen, liver, and/or intestines. The atypical position of these organs may lead to a variety of health complications. Males with PCD often experience infertility due to sperm that do not move properly. Infertility sometimes occurs in females with PCD, likely due to abnormal cilia in the fallopian tubes. There are no specific therapies or cure to correct ciliary dysfunction. Treatment focuses on treating the individual symptoms of PCD, such as infections.

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.

Carrier status frequency (as reported by Invitae):

Methylmalonic acidemia (*MMAB* gene):
Pan-ethnic carrier frequency: 1 in 456
Primary ciliary dyskinesia (*DNAH5* gene):
Pan-ethnic carrier frequency: 1 in 109

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for methylmalonic acidemia (*MMAB* gene) and primary ciliary dyskinesia (*DNAH5* 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 556 genes. These results indicate that the donor is a carrier for methylmalonic acidemia and primary ciliary dyskinesia.	Initials: _____ Initials: _____
The genetic conditions tested for 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 methylmalonic acidemia and primary ciliary dyskinesia, 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 methylmalonic acidemia and primary ciliary dyskinesia.	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 Invitae in 2023. My health care provider may recommend an expanded carrier screen that includes/included more than the 556 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 CB 571 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 571.

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 571.

_____

Recipient Date Email

_____

Partner, if applicable Date Email

William C. Baird, PhD, HCLD 06-16-2024

Cryobio Date