cryobio

Additional Agreement to Use Donor CB 591

I (_____ (Recipient), and _____ (Partner, if applicable)), specifically request and accept frozen semen from Cryobio donor CB 591. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 591. CB 591 had expanded genetic carrier screening to determine their carrier status for 557 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 591 has been found to be a carrier of the following recessive genetic conditions:

Cartilage-hair hypoplasia;
and
Oculocutaneous albinism types 1A and 1B

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.

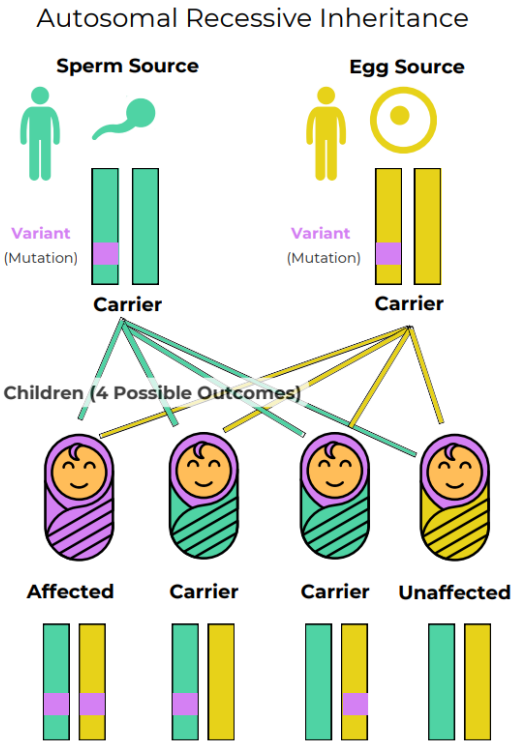

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

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.

Cartilage-hair hypoplasia (*RMRP* gene): Cartilage-hair hypoplasia is an autosomal recessive disorder caused by pathogenic variants in both copies of the gene *RMRP*. It is a disorder that affects the hair, bones, and the digestive and immune systems. It is often described as a spectrum of conditions 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 with these conditions 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). Individuals also often have abnormally fine, sparse, brittle, light-colored hair. 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. Metaphyseal Dysplasia without Hypotrichosis does not cause hair abnormalities, immune system or digestive problems, or anemia while Anauxetic Dysplasia causes more severe bone abnormalities and very short stature, distinct facial features, abnormalities of the teeth, and mild intellectual disability. There is currently no cure for cartilage-hair hypoplasia disorders, but treatments exist for specific symptoms.

Oculocutaneous albinism types 1A and 1B (*TYR* gene): Oculocutaneous albinism types 1A and 1B are autosomal recessive conditions that are caused by pathogenic variants (mutations) in the *TYR* gene. Oculocutaneous albinism is a group of conditions that affect coloring (pigmentation) of the skin, hair, and eyes. There are several different types of oculocutaneous albinism which are caused by mutations in different genes. Individuals with oculocutaneous albinism produce a reduced amount of melanin; melanin is a natural substance in our bodies that gives color to our skin, hair, and eyes. Individuals with oculocutaneous albinism have hypopigmentation (less color than usual) of their skin, hair, and eyes. All types of oculocutaneous albinism have similar ocular findings, including rapid involuntary eye movements (nystagmus), hypopigmentation of iris leading to iris translucency, reduced pigmentation of the retinal pigment epithelium, nearsightedness or farsightedness, and sometimes a degree of color vision impairment. Individuals with oculocutaneous albinism have an increased risk of skin damage and skin cancers, including an aggressive form of skin cancer called melanoma. Intelligence is not typically affected.

Cryobio donor CB 591 was found to have a mutation in the *TYR* gene. Mutations in the *TYR* gene are associated with oculocutaneous albinism type 1A and oculocutaneous albinism type 1B.

- Oculocutaneous albinism type 1A (OCA1A) is the most severe type, where no melanin is produced. OCA1A is often diagnosed during the first year of life and is characterized by white hair, very pale skin, and light-colored irises (typically blue in color).
- Oculocutaneous albinism type 1B (OCA1B) is less severe. Minimal melanin is produced, and the hair and skin may develop some pigment with time. OCA1B is characterized by white skin, white or light-yellow hair, and light-colored irises (typically blue in color).

Treatment is aimed at correcting vision and providing visual aids, or other visual resources. Sun protection is essential due to the increased risk of skin cancer.

Of note: Evidence of possible digenic inheritance with the *TYR* gene and another melanin related genes (specifically the *OCA2* or the *SLC45A2* gene) has been reported in individuals diagnosed with albinism

(PMID: 31719542; 23324268). Digenic inheritance means genetic variants in two different genes combined can cause a disease. One study suggests that in some families, family members with mutations in multiple melanin-related genes did not show any symptoms, while others did. This suggests that other genetic or environmental factors may also contribute to disease (PMID: 39349469). More evidence is needed to confirm this as a mode of inheritance at this time. For more information about digenic inheritance with the *TYR* gene, speak with your genetic counselor.

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 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 Natera):
Cartilage-hair hypoplasia (*RMRP* gene):
- General population carrier frequency: < 1 in 500
- Amish carrier frequency: 1 in 19
- Finnish carrier frequency: 1 in 76

Oculocutaneous albinism types 1A and 1B (*TYR* gene):
- General population carrier frequency: 1 in 20

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for cartilage-hair hypoplasia (*RMRP* gene) and oculocutaneous albinism types 1A and 1B (*TYR* 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 healthcare 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 557 genes. These results indicate that the donor is a carrier for cartilage-hair hypoplasia and oculocutaneous albinism types 1A and 1B.	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 cartilage-hair hypoplasia and oculocutaneous albinism types 1A and 1B, 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 cartilage-hair hypoplasia (*RMRP* gene) and oculocutaneous albinism types 1A and 1B (*TYR* 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 Natera in 2024. My healthcare provider may recommend an expanded carrier screen that includes/included more than the 557 genes screened for in this donor. It is my responsibility to share this information with my healthcare 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 <u>*not*</u> 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 healthcare 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 a genetic condition or genetic conditions. I am making the choice to use donor sperm from donor CB 591 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 591.

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 591.

Recipient	Date	Email
Partner, if applicable	Date	Email
William C. Baird, PhD, HCLD	11-08-2024	
Cryobio	Date	