cryobio

Additional Agreement to Use Donor CB 587

I (_____ (Recipient), and _____ (Partner, if applicable)), specifically request and accept frozen semen from Cryobio donor CB 587. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 587. CB 587 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 587 has been found to be a carrier of the following recessive genetic conditions:

COL11A2-Related Conditions and Ehlers-Danlos Syndrome Type VI

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 ***(please see below-as donor CB 587 has tested positive for one of these exceptions).*** Most individuals are carriers for at least one if not multiple recessive genetic conditions.

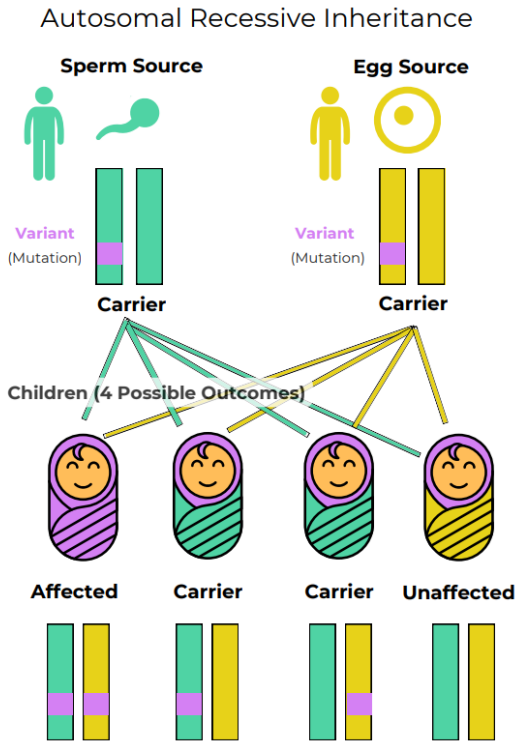

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

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.

***COL11A2*-Related Conditions (*COL11A2* gene):** Pathogenic variants, or mutations, in the *COL11A2* gene are associated with a range of autosomal dominant and recessive skeletal and auditory (hearing) conditions. Autosomal dominant conditions are conditions where you only need one copy of a changed gene from to have the condition. These gene changes may be passed down from a biological parent, but can also sometimes be *de novo* (new) to an individual. As reviewed above, autosomal recessive inheritance means you need to get two copies of a changed gene—one from the egg source and one from the sperm source—to have the condition.

The *COL11A2* gene helps make a part of type XI collagen, which is important for building strong cartilage/connective tissue and supporting normal hearing. Therefore, mutations in *COL11A2* disrupt collagen formation, leading to a spectrum of disorders that primarily affect the skeleton and hearing. Because this gene isn't active in the eyes, problems caused by *COL11A2* mutations usually affect the skeleton and ears, but not vision. For some individuals with *COL11A2* related conditions, symptoms start at birth, while others do not have health problems until later in life or at all.

Depending on the specific set of symptoms, different names are used for *COL11A2* conditions. *COL11A2*-related skeletal conditions include non-ocular Stickler syndrome (Stickler syndrome type III), Otospondylomegaepiphyseal dysplasia (OSMED), Weissenbacher-Zweymüller syndrome (WZS), and Fibrochondrogenesis 2.

These skeletal conditions have many overlapping features such as joint abnormalities, hearing loss, and other bone abnormalities. People with *COL11A2*-related conditions often have facial features that can sometimes make it hard to eat and breathe, like a small lower jaw and a flat middle face. They may also have problems with their spine and the bones in their arms and legs and are often shorter than most people. Some individuals with *COL11A2*-relatied conditions may have a lot of symptoms, while others may only have a few. Individuals with autosomal dominant forms of *COL11A2*-related conditions generally have fewer or milder symptoms. However, children of individuals with *COL11A2* mutations may have more or less severe symptoms than the biological parent.

COL11A2 related auditory disorders include autosomal recessive and autosomal dominant forms of non-syndromic hearing loss. In both the dominant and recessive forms of hearing loss related to the *COL11A2* gene, the condition affects an individual's ability to hear but does not affect any other part of the body.

Of note: At the time of CB 587's genetic test, the specific variant donor CB 587 is a carrier for has only been identified in individuals with autosomal recessive forms of disease.

Ehlers-Danlos Syndrome Type VI (*PLOD1* gene): Ehlers-Danlos Syndrome (EDS) Type VI (also denoted as kEDS-PLOD1) is one in a group of 13 heritable connective tissue disorders. The EDS conditions are caused by genetic changes in different genes that affect connective tissue. Each type of EDS has its own set of features with distinct diagnostic criteria. Some features are seen across all types of EDS, including joint hypermobility (joints having a greater range of motion than typical), skin hyperextensibility (skin that can be stretched beyond the typical range), and tissue fragility (the body's organs and tissues being more vulnerable to damage).

Ehlers-Danlos syndrome type VI is inherited in an autosomal recessive pattern. Individuals with type VI EDS typically have low muscle tone, early-onset kyphoscoliosis (curvature of the spine), and joint hypermobility. Lifespan may be normal, but affected individuals are at an increased risk of arterial dissection (a tear in the artery wall) and rupture, which can be life-threatening. Other features may include delayed motor development, eye problems, foot deformities such as clubfoot or flat feet, soft, stretchy, and fragile skin, and easy bruising. Intelligence is typically normal.

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 lab on the date the donor's test results were reviewed by that lab.

Carrier status frequency (as reported by Natera):
COL11A2-Related Conditions (*COL11A2* gene):
Pan-ethnic carrier frequency: 1 in ≤1 in 500
Ehlers-Danlos Syndrome Type VI (*PLOD1* gene):
Pan-ethnic carrier frequency: 1 in 158

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for *COL11A2*-related conditions (*COL11A2* gene) and Ehlers-Danlos Syndrome Type VI (*PLOD1* 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 557 genes. These results indicate that the donor is a carrier for *COL11A2*-related conditions and Ehlers-Danlos Syndrome Type VI.	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 *COL11A2*-related conditions and Ehlers-Danlos Syndrome Type VI, the risk to a resulting child would now be higher than that of the general population.	Initials: _____ Initials: _____
I understand that sometimes individuals with just one *COL11A2* mutation may may present with an autosomal dominant form of disease. Based on donor CB 587's carrier status for *COL11A2*-related conditions, there is a 50% chance of any resulting child also being a carrier and therefore inheriting an increased risk of a *COL11A2*-related disease.	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 *COL11A2*-related conditions and Ehlers-Danlos Syndrome Type VI.	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 health care 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 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 a genetic condition or genetic conditions. I am making the choice to use donor sperm from donor CB 587 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 587.

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 587.

Recipient	Date	Email

Partner, if applicable	Date	Email

William C. Baird, PhD, HCLD	05-21-2025
Cryobio	Date