cryobio

Additional Agreement to Use Donor PC 1145

I, _____ (Recipient), and _____ (Partner, if applicable), specifically request and accept frozen semen from Cryobio donor PC 1145. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor PC 1145. PC 1145 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 PC 1145 has been found to be a carrier of the following recessive genetic condition:

USH2A-related conditions.

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.

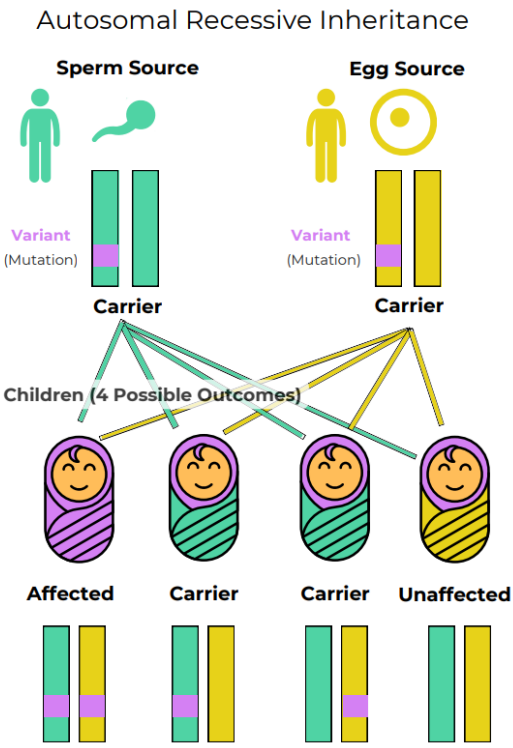

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

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.

***USH2A*-related conditions (*USH2A* gene):** *USH2A*-related conditions include Usher syndrome type IIA (USH2A) and autosomal recessive nonsyndromic retinitis pigmentosa (RP). They are autosomal

recessive conditions caused by pathogenic variants in the gene *USH2A*. Usher syndrome is a group of related conditions that causes deafness, progressive vision loss due to an eye disease called RP, and, in certain forms, balance difficulties due to inner ear problems (vestibular dysfunction). RP is a group of related conditions that affects the retina, which is the light-sensitive tissue that lines the back of the eye.

Individuals with USH2A are usually born with non-progressive deafness that ranges from mild to moderate in lower frequencies and from severe to profound in higher frequencies. Progressive vision loss due to RP typically begins during adolescence or adulthood. Severity of symptoms can vary, even between family members with the same genetic changes.

The first symptom of RP is often difficulty seeing in low light settings (night blindness), which usually occurs during childhood or adolescence. Vision loss continues over years or decades and typically progresses to a loss of side (peripheral) vision, causing tunnel vision. Ultimately, central vision loss occurs. Many affected individuals are legally blind by adulthood, though the severity of symptoms and age of onset varies by individual. Intelligence and life expectancy are not typically affected. For USH2A-related conditions, early initiation of medical, educational, and social services is recommended to maximize outcomes.

Of note: Digenic inheritance, which occurs when an individual has a genetic change in two different Usher syndrome-associated genes, has been reported (PMID: 15537665); however, the evidence available at this time is insufficient to confirm this as a mode of inheritance at this time. In addition, recent studies suggest the USH2A gene may be one risk factor that can contribute to mild hearing loss at low-level frequencies, which may or may not contribute to auditory processing/language development conditions. However, auditory and language conditions are understood to be multifactorial and complex, and it is unlikely that one USH2A gene mutation would be the sole risk factor/explanation for an auditory or language condition (PMID: 32313182).

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 Invitae):
USH2A-related conditions (*USH2A* gene):
Pan-ethnic carrier frequency: 1 in 112

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for USH2A-related conditions (*USH2A* 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 USH2A-related conditions.	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 USH2A-related conditions, 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 USH2A-related conditions.	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 <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 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. I am making the choice to use donor sperm from donor PC 1145 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 1145.

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 PC 1145.

_____ _____

Recipient Date Email

_____ _____

Partner, if applicable Date Email

William C. Baird, PhD, HCLD 05-14-2024

Cryobio Date