



Additional Agreement to Use Donor CB 576

I (_____ (Recipient), and _____ (Partner, if applicable)), specifically request and accept frozen semen from Cryobio donor CB 576. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor CB 576. CB 576 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 576 has been found to be a carrier of the following recessive genetic conditions:

Increased Carrier Risk for congenital adrenal hyperplasia due to 21-hydroxylase deficiency.

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.

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.

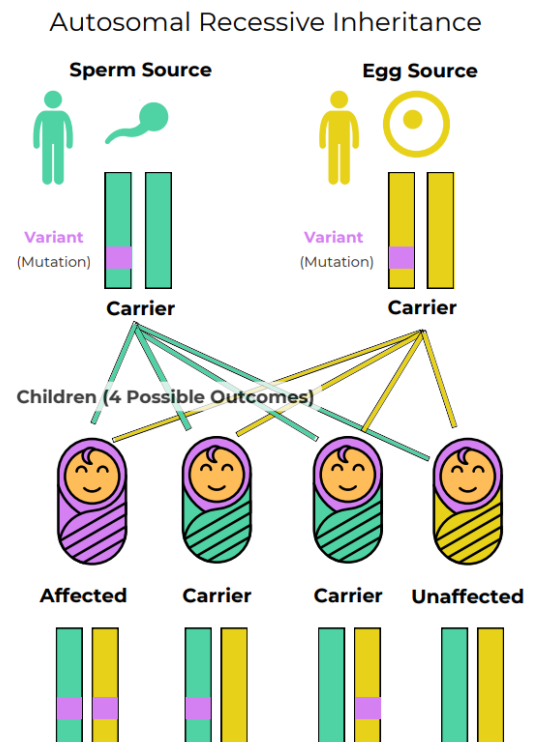


Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (*CYP21A2* gene): Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition which results from a deficiency in enzymes involved in cortisol production (a steroid hormone naturally produced by the adrenal glands). These hormones produced by the adrenal glands help regulate many essential functions in the body, including sexual development and maturation. There are several types of CAH, which can be caused by changes in different genes, but approximately 95% of cases of CAH are caused by defects in the *CYP21A2* gene which leads to a deficiency of the steroid 21-hydroxylating enzyme. Symptoms of CAH vary based on the form of CAH, the age of diagnosis, and the sex of the individual.

Three different forms of CAH have been reported: a classic salt wasting form, a classic simple virilizing form, and a non-classic form.

- The classic salt wasting form of CAH is the most severe. Individuals with the salt-wasting type lose large amounts of sodium (salt) in the urine, which can lead to “salt-wasting crises” that can be life-threatening in early infancy. Female infants with the classic type usually have external genitalia that do not look clearly male or female (ambiguous genitalia), while males typically have normal genitalia, although their testes may be smaller than typical. Individuals with the classic form may also have decreased fertility.
- The classic simple virilizing form involves prenatal virilization (the development of male physical characteristics (such as muscle bulk, body hair, and deep voice) in a female or precociously in a boy), ambiguous genitalia, and excessive facial hair, and decreased fertility, but does not include the life-threatening salt-wasting crises.
- The mildest form, non-classic CAH, is often not diagnosed until later in childhood or adulthood. Individuals with the non-classic form typically have typical external genitalia but may present with hyperandrogenism (too much testosterone in the body) and include features such as hirsutism (abnormal growth of hair on the face and body, especially on a woman), male pattern baldness, delayed menarche (the first period for females), and infertility.

Treatment for CAH usually includes steroids to replace the low hormones. The long-term prognosis for individuals with CAH is usually favorable, and with lifelong treatment, affected individuals typically have good health and normal lifespans. Oftentimes individuals with non-classic CAH require no treatment at all. CAH is typically included on the newborn screen (check with your state/delivering hospital to be sure), so most individuals who have it will be diagnosed shortly after birth.

Special note specific to CB 576’s *CYP21A2* carrier status: Based on donor CB 576’s results from this test, it was unable to be determined whether he is truly a carrier of CAH or not. The carrier screening identified one genetic mutation in one of donor CB 576’s *CYP21A2* genes. However, the test also identified one additional copy (a duplication) of donor CB 576’s *CYP21A2* gene. Therefore, donor CB 576 has three total copies of the *CYP21A2* gene, whereas individuals typically only have two copies. Having an additional copy of the *CYP21A2* gene does not cause an individual any problems.

Reminder-typically, we all have two copies of every gene---one from the egg source and one from the sperm source. All of our genes are packaged up on structures called chromosomes, and typically “groups” of genes are inherited together on chromosomes. Typically, individuals have 23 pairs of chromosomes, for a total of 46 chromosomes. We inherit half of our chromosomes from the egg source, and half from the sperm source. Because donor CB 576 has one additional *CYP21A2* gene, the test cannot determine whether he is carrier. If the two copies of the *CYP21A2* gene with no mutation (meaning they are working copies) are inherited together on the same chromosome, and the other copy with the mutation is inherited alone on the other chromosome, at most, donor CB 576 would be a carrier

of CAH and should be treated as any other carrier of this condition. However, if donor CB 576's *CYP21A2* gene is inherited with the additional/extra *CYP21A2* gene, he would have one working copy of the *CYP21A2* gene on each chromosome, meaning he would NOT be a carrier of CAH.

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):

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (*CYP21A2* gene):

Pan-ethnic carrier frequency: 1 in 61

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for congenital adrenal hyperplasia due to 21-hydroxylase deficiency (*CYP21A2* 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 at an increased risk to be a carrier for congenital adrenal hyperplasia due to 21-hydroxylase deficiency (<i>CYP21A2</i> gene).	Initials: _____ Initials: _____
Because the testing done cannot determine whether CB 576's two working copies of his <i>CYP21A2</i> genes are on the same chromosome, or whether one of them is on other chromosome, we cannot be sure whether donor CB 576 is a carrier of congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) or not. At most, donor CB 576 is a carrier of CAH. Carriers are not expected to have symptoms of this condition. Since we are unsure, he should be treated as a carrier of CAH, and we strongly recommend the egg source be tested for CAH carrier status to better understand the risks to future children.	Initials: _____ Initials: _____

<p>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.</p>	<p>Initials: _____ Initials: _____</p>
<p>By the donor testing positive for increased risk for carrier status for congenital adrenal hyperplasia due to 21-hydroxylase deficiency, the risk to a resulting child would now be higher than that of the general population.</p>	<p>Initials: _____ Initials: _____</p>
<p>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.</p>	<p>Initials: _____ Initials: _____</p>
<p>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.</p>	<p>Initials: _____ Initials: _____</p>
<p>Genetic testing for me (or the egg source, if different) can also be done to better understand and further reduce the risk to offspring.</p>	<p>Initials: _____ Initials: _____</p>
<p>Genetic testing is <i>strongly recommended</i> for me (or the egg source, if different) to see if I am a carrier congenital adrenal hyperplasia due to 21-hydroxylase deficiency.</p>	<p>Initials: _____ Initials: _____</p>
<p>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.</p>	<p>Initials: _____ Initials: _____</p>
<p>The genetic testing done on the donor does <i>not</i> screen for all known genetic conditions.</p>	<p>Initials: _____ Initials: _____</p>
<p>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.</p>	<p>Initials: _____ Initials: _____</p>
<p>Genetic counseling is available to me if I have additional questions regarding these test results and potential risks.</p>	<p>Initials: _____ Initials: _____</p>

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: _____
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I have read the above material and assume the risk of using donor sperm from a donor who has been found to have an increased risk of being a carrier of a genetic condition and should be treated as a carrier. I am making the choice to use donor sperm from donor CB 576 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 576.

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 576.

Recipient	Date	Email
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Partner, if applicable	Date	Email
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<i>William C. Baird, PhD, HCLD</i>	06-07-2024
Cryobio	Date