cryobio

Additional Agreement to Use Donor WL 4007

I (_____ (Recipient) and _____ (Partner, if applicable)), specifically request and accept frozen semen from Cryobio donor WL 4007. I understand that this Additional Agreement is an additional part of the Sperm Use Agreement specific to donor WL 4007. WL 4007 had expanded genetic carrier screening to determine their carrier status for 283 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 WL 4007 has been found to be a carrier of the following recessive genetic conditions:

Citrullinemia type 1;

Galactosemia; and

Limb-girdle muscular dystrophy type 2E.

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 nor 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.

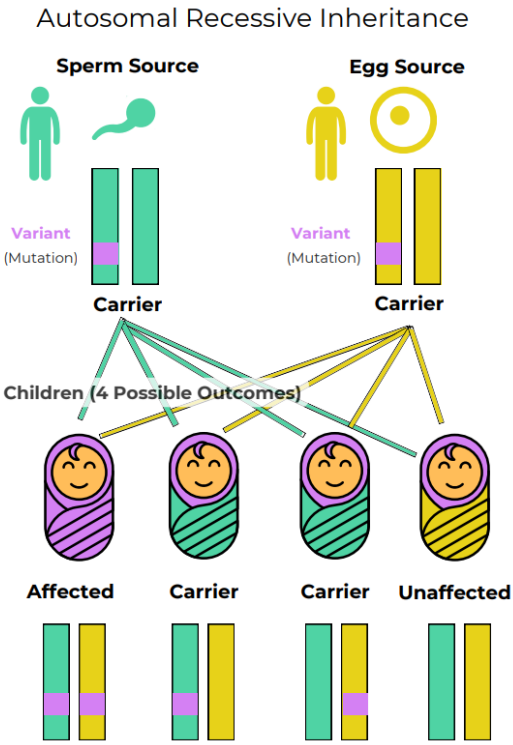

Figure 1. Graphic representing autosomal recessive inheritance of two carrier gametes.

Citrullinemia type 1 (*ASS1* gene): Citrullinemia, type 1 is an autosomal recessive, pan-ethnic disorder caused by pathogenic variants in the gene *ASS1*. Citrullinemia, type 1 causes ammonia and other toxic substances to accumulate in the blood and other body fluids such as cerebrospinal fluid. The accumulation of ammonia (called hyperammonemia) causes the variety of symptoms in individuals with Citrullinemia, type 1. There are a variety of different forms of the disease that include a neonatal acute (classic) form, a milder late-onset form, a form that begins during or after pregnancy, and an asymptomatic form. The neonatal "classic" form typically presents shortly after birth. Once babies develop hyperammonemia, they become progressively lethargic, have poor feeding, and may develop signs of intracranial pressure. Intracranial pressure may lead to spasticity (muscle stiffness), seizures, loss of consciousness, and even death. Individuals with the most severe form of the disease may experience neurologic deficits, even with prompt treatment. Later onset forms may also occur in adults, where the disease is characterized by periods of hyperammonemia, reduced alertness, slurred speech, headache, or migraine. Patients with adult-onset disease may also present with liver failure instead of neurological symptoms. Citrullinemia, type 1 that occurs during or shortly after pregnancy presents with the affected person experiencing repeated episodes of vomiting, lethargy, seizures, confusion, hallucinations, and potentially a coma. Some specific variants have been associated with the development of neonatal or adult-onset disease, although not all phenotypes can be accurately predicted based on genotype (i.e., the specific genetic mutations present). Although the disease can be managed with diet and medications, a liver transplant is the only current known cure. Liver transplantation cannot reverse any previous neurologic damage caused by a previous hyperammonemia episode. Citrullinemia, type 1 is typically included on the newborn screen, so most individuals are diagnosed at birth.

Galactosemia (*GALT* gene): Galactosemia is an autosomal recessive metabolic disorder caused by pathogenic variants in the *GALT* gene. While it is a pan-ethnic disease, it is found more commonly in patients from certain ethnicities, including African Americans and Irish Travelers. Individuals with galactosemia are unable to break down the sugar galactose into glucose (the form of sugar the body can then use for energy). Galactose is a major component of lactose, the sugar found in breast milk and formula. Therefore, infants with galactosemia who are on a diet that includes lactose (i.e., breast milk and formula) will develop lethargy and jaundice, feeding difficulties, will fail to gain weight, and possibly liver damage. Sepsis (infection) and death may occur if galactose is not removed from their diet. With removal of galactose from the diet, the neonatal signs such as lethargy, failure to thrive, potential liver damage, and death are prevented. However, affected children may still experience long-term complications, including cataracts, speech problems, developmental delay, or intellectual disability. Most adult people with ovaries with galactosemia also experience premature ovarian failure. With proper treatment, affected individuals will have a normal life expectancy, but may still exhibit some of the above complications. For patients with classical galactosemia, there is no known genotype-phenotype correlation. Classic galactosemia is typically included on the newborn screen, so most individuals are diagnosed at birth.

Limb-girdle muscular dystrophy type 2E (*SGCB* gene): Limb-gridle muscular dystrophies (LGMD) are a group of genetic diseases all characterized by weakness and wasting of the pelvic and shoulder girdle muscles. There are many subtypes of the disease determined by the gene involved in causing the disease, and the inheritance pattern in which the disease is passed through families. Limb-girdle muscular dystrophy, type 2E is an autosomal recessive, pan-ethnic disorder that is caused by pathogenic variants in the gene *SGCB*. This form of LGMD typically onsets in childhood, with symptoms usually present by the age of 12. However later adult onset/mild disease course has been reported. Wasting and weakness of muscles in the hips and shoulder areas are typically the first symptoms, which may present clinically with calf hypertrophy, tiptoe walking, tendon contractures, scapular winging, and scoliosis. Progression is variable, and patients are usually wheelchair bound within 5 to 25 years after onset of symptoms. Patients may also develop dilated cardiomyopathy as the disease progresses. Life expectancy is unknown, although most patients with limb-girdle muscular dystrophies have a shorter than natural lifespan. There

is no known treatment for LMGD, but management of symptoms and staying mobile can improve an individual's quality of life. Currently, it is not possible to predict the severity of the disease based on the genotype (specific genetic mutation).

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.

Citrullinemia type 1 (*ASS1* gene) carrier status frequency in different ethnicities, from SEMA4:

African	1 in 339
Ashkenazi Jewish	1 in 1669
East Asian	1 in 809
Finnish	1 in 2984
Caucasian	1 in 323
Latino	1 in 304
South Asian	1 in 192
Worldwide	1 in 339

Galactosemia (*GALT* gene) carrier status frequency in different ethnicities, from SEMA4:

African	1 in 87
Ashkenazi Jewish	1 in 181
East Asian	1 in 208
Finnish	1 in 4085
Caucasian	1 in 123
Latino	1 in 219
South Asian	1 in 342
Worldwide	1 in 156
Irish Travellers	1 in 11

Limb-girdle muscular dystrophy type 2E (*SGCB* gene) carrier status frequency in different ethnicities, from SEMA4:

African	1 in 653
East Asian	1 in 1437
Finnish	1 in 2092
Caucasian	1 in 628
Latino	1 in 3358
South Asian	1 in 373
Worldwide	1 in 558

Recommendation: Cryobio recommends that the recipient, or egg source if different than recipient, be tested for citrullinemia, type 1 (*ASS1* gene); galactosemia (*GALT* gene); and limb-girdle muscular dystrophy type 2E (*SGCB* 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 us of the following:	Please initial to show your understanding and agreement:
The donor we have chosen has had positive results from genetic testing looking at carrier status for 283 conditions. These results indicate that the donor is a carrier for citrullinemia type 1; galactosemia; and limb-girdle muscular dystrophy type 2E.	Initials: _____ Initials: _____
These genetic conditions 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 citrullinemia type 1; galactosemia; and limb-girdle muscular dystrophy, type 2E, 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 citrullinemia, type 1 (*ASS1* gene); galactosemia (*GALT* gene); and limb-girdle muscular dystrophy type 2E (*SGCB* 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 SEMA4 in 2020. My health care provider may recommend an expanded carrier screen that includes/included more than the 283 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 diseases, 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 WL 4007 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 WL 4007.

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 WL 4007.

_____ _____

Recipient Date Email

_____ _____

Partner, if applicable Date Email

William C. Baird, PhD, HCLD 07-28-2022

Cryobio Date