cryobio

Additional Agreement to Use Cryobio Donor LX 2064

I (_____ (Recipient), and _____ (Partner, if applicable)), specifically request and accept frozen sperm from Cryobio donor LX 2064.

Cryobio is providing you with this information so you can make an informed decision as to whether or not you feel comfortable using vials from donor LX 2064, in light of new information we received after the donor was available on our website. Cryobio received a report of a child that was born with multiple health issues after using Cryobio donor LX 2064 to conceive the pregnancy. These issues prompted genetic testing where a pathogenic variant (also called a genetic mutation) was identified in the *NIPBL* gene. Pathogenic variants in the *NIPBL* gene are associated with autosomal dominant Cornelia de Lange syndrome (CdLS) 1, and therefore the variant identified through genetic testing confirmed the suspected diagnosis for the child.

Features of CdLS 1 can vary for affected individuals from mild to severe but are typically apparent at birth. Associated symptoms and features include delays in physical development before and after birth, characteristic appearance of the head and facial area resulting in distinct facial features, upper limb defects (i.e. malformations of the hands and arms), and mild to severe intellectual disability. Some of the associated head and facial features include fusion of the eyebrows above the bridge of the nose (also known as synophrys), highly arched and/or thick eyebrows, long eyelashes, short nasal bridge with upturned nostrils, small widely spaced teeth, and a small head (also known as microcephaly). Individuals with a milder presentation may have less severe growth, cognitive, and limb involvement, but often have facial features consistent with CdLS.

CdLS 1 due to pathogenic variants in the *NIPBL* gene is inherited in an autosomal dominant inheritance pattern. Typically, individuals have two copies of every gene; one from the egg source and one from the sperm source. Genetic conditions can be inherited in a variety of ways. For example, autosomal recessive conditions require a genetic mutation in both copies of the same gene in order for an individual to be affected with the condition. Autosomal dominant conditions occur when a single copy of a gene with a mutation is sufficient to cause a trait or disorder, even if the other copy of the gene is normal. If an individual has an autosomal dominant genetic condition, there is a 50/50 chance that they will pass on the genetic mutation, and therefore genetic condition, to each pregnancy. Dominant conditions can be passed down to an affected individual from their egg source or sperm source, or they can be due to *de novo,* or new, genetic mutations that happen spontaneously at the time of conception. De novo mutations mean that the genetic condition was **not** inherited from either the egg source or the sperm source, and therefore the likelihood of the condition happening again is small. De novo mutations are not something that can be reliably screened for at this time, and therefore there is no way of knowing if/when they might occur.

The majority of individuals affected with CdLS due to pathogenic variants in the NIPBL gene have a de novo mutation. Fewer than 1% of individuals with autosomal dominant CdLS inherit the mutation from the egg source or sperm source. When the egg source or sperm source of an

individual affected with CdLS is clinically unaffected with the condition, the risk of being affected with CdLS to another child from the same egg source or sperm source is estimated to be 1-5%. This risk is due to the possibility of germline mosaicism. Germline mosaicism is a genetic phenomenon in which some of an individual's reproductive cells (sperm or eggs) carry a genetic mutation that is not present in the rest of the body's cells, i.e. the individual is not affected by the condition, but they can pass it on because the genetic mutation is in their reproductive cells.

Cryobio's policy when we receive a report of a serious health issue is to investigate and see if the health issues could be attributed to genetic or non-genetic factors from the donor. Donor LX 2064 does not report any clinical features of CdLS 1, nor did he report any symptoms in family members. Donor LX 2064 has not had genetic testing for CdLS, however based on his reported health history it is unlikely he is affected. **At this point in our investigation, Cryobio does not believe the health issues in the child are related to using donor LX 2064, although we cannot rule it out, due to the possibility of germline mosaicism.** Germline mosaicism is helpful to consider when determining where the mutation that caused the condition came from, and although we believe it is unlikely, we cannot definitively conclude that the sperm or egg source doesn't have the condition causing mutation.

While Cryobio does not have reason to believe LX 2064 had a role in this situation, there are several recommendations that could help reduce the risk of having a child with a serious health condition we wanted you to consider before proceeding with using LX 2064. You should discuss this situation with your health care provider and review the options that are available to lower the risk of having a child affected with CdLS 1, including using IVF to make embryos and having preimplantation genetic testing or choosing diagnostic testing such as chorionic villus sampling or amniocentesis during early pregnancy to pursue genetic testing for CdLS.

Also of note, as of October 2024, there have been 10 pregnancies reported using donor LX 2064, and births in at least 5 of those pregnancies. We have not received any reports of any health issues in any of these children, including no other diagnoses of CdLS.

Cryobio's donor selection process includes personal interviews, personal and family medical and social histories, physical exams, genetic disease and genetic carrier screening and testing for common recessive genetic conditions, and viral and sexually transmitted disease screening and testing. Cryobio relies on the donor to report their and their family's social and medical histories before, during, and after participating in the donor program.

It should be emphasized that we all carry genes that increase the risk for certain diseases or conditions, and generally, without further technological intervention, we have no control over what genes are passed on to our children. As technology advances, we are learning more about the genetic component to diseases, and while we may not have control over what genetic traits are passed on to our children, we may have the ability to potentially change the outcome of these traits by being proactive and getting early diagnoses and treatment. While some conditions, like CdLS are determined solely by changes in our genes, many other conditions such as birth defects, mental illness, heart disease, diabetes, and autoimmune diseases often result from a

combination of genetic factors and environmental factors that interact with each other to create a predisposition or increased risk in certain individuals.

Cryobio has advised me of the following:	Please initial to show your understanding and agreement:
Cryobio recommends that I discuss this information with the health care provider who is helping me attempt to get pregnant.	Initials: _____ Initials: _____
Cryobio recommends that I discuss this information with a genetic counselor.	Initials: _____ Initials: _____
Cryobio recommends that I let the OB/GYN handling my pregnancy know that I used a donor who was used by another person and that resulted in a child being born with Cornelia de Lange syndrome 1.	Initials: _____ Initials: _____
Cryobio recommends that I consider routine ultrasound screening and various testing procedures while I am pregnant.	Initials: _____ Initials: _____
Cryobio recommends that I discuss options for diagnostic testing for CdLS with my health care providers either before or during pregnancy.	Initials: _____ Initials: _____
Cryobio recommends contacting us with any questions or concerns.	Initials: _____ Initials: _____

I have read the above material and assume the risk of using donor sperm from a donor who was used in a situation where Cryobio received a report of a child diagnosed with Cornelia de Lange syndrome 1. I am making the choice to use donor sperm from LX 2064 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 LX 2064 in any resulting children.

I have read and signed the Sperm Use Agreement, and this consent is intended to function as an additional section of the Sperm Use Agreement. I have read, had the chance to ask questions, understand, and agree to the terms of this Additional Agreement to use donor LX 2064.

_____ _____

Recipient Date Email

_____ _____

Partner, if applicable Date Email

William C. Baird, PhD, HCLD 12-06-2024

Cryobio Date