Family Planning with Homocystinuria

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Once a genetic diagnosis is made in your family, whether by newborn screening or other means, many family members begin to think about the chances for their future children to be diagnosed with the same condition. As a genetic counselor, my job is to help the families I work with understand the condition in the family, who else may have a chance to have a child with this condition, and what options exist to help clarify that chance. Genetic counselors are trained to provide you with information and help you process what a diagnosis in the family means in the context of your life and your values and to help you make the personal decision that is best for you and your family.

If the condition in your family is homocystinuria (which we'll assume it is given where this is being published!), the likelihood for the condition to recur depends on two different factors: how closely related you are to the individual with the diagnosis and the carrier status of your partner. To fully understand how both of these factors impact your likelihood to have a child with homocystinuria (HCU), you first need to understand how this condition is inherited. HCU is inherited in an autosomal recessive manner. Every person has two copies of the *CBS* gene, one inherited from their mother and one from their father. When both copies of this gene are changed, the body cannot properly breakdown homocysteine and the person is diagnosed with HCU. Because one changed copy of the gene is inherited from each parent, we assume that each parent has a one copy of the gene that is changed and one copy that functions as expected. They are said to be asymptomatic carriers of the condition. For a child to be affected, both parents must be carriers. In this circumstance, each pregnancy the couple has together would have a 25% chance to have the condition.

Once a family member has been diagnosed with homocystinuria, others may choose to learn their carrier status. The closer an individual is to the person diagnosed, the more likely they are to be a carrier. First-degree relatives of the person with HCU (parents, siblings, and children), are more likely to be carriers than those more distantly related. Parents and children of people with this diagnosis are assumed to be carriers of the condition, while an unaffected sibling has a two-thirds or 66% to be a carrier. For anyone related to someone with HCU who wants to know the likelihood that they are a carrier, talk to your doctor or ask to see a genetic counselor and they can help clarify this possibility as well as discuss next steps with you should you want to pursue carrier testing.

Because both parents must be carriers of HCU for a child to be diagnosed with the condition, the carrier status of relatives to the person with the diagnosis is not the only factor to consider when determining the likelihood that a child could also have HCU. The partner's carrier status is equally important when calculating the chance for a couple to have a child with an autosomal recessive condition. Assuming your partner has no family history of HCU, the likelihood that they are a carrier is one in 250 (0.4%). Carrier testing should be pursued for both the partner and the relative of a person impacted by HCU to fully clarify that couple's chance to have a child with the condition.

There are a variety of options available to individuals pursuing carrier testing for HCU. Not all of these options are appropriate for every individual, and not every individual will want to pursue one of these options. The most straightforward approach to testing for the relative of an individual with HCU is called known familial variant analysis. In doing this, you are looking only for the gene changes known to cause HCU in the family. This testing does not look for other changes in the gene, but the likelihood of a relative carrying a different change is quite low, much less than 1%. To complete this testing, your provider would need to have a copy of the gene testing report for your relative with HCU to ensure the correct gene change is assessed. This option is not appropriate for the partner of someone with a family history, as a person from a different family would typically have different gene changes. This testing is often very affordable with some labs offering it for as little as $50.

For family members who do not have access to their relative's genetic testing report or for partners who are interested in carrier testing, gene sequencing is a good option. This testing is essentially spell check of the entire gene. While classic HCU is caused by changes in the CBS gene, there are also other genes which can cause elevated homocysteine levels, so you will want to confirm that the correct gene is being assessed. This testing, while still more expensive than the known familial variant analysis, has come down significantly with many labs offering the testing for $200-$300.

A final option that has become available in recent years in is an expanded carrier panel. These tests were designed to allow for couples to assess what conditions their children may be at risk for, regardless of their family history, by testing many genes (200+) all at once. There are multiple labs offering their own version of this test, but most include the CBS gene for classic HCU. If you're interested in this testing, it would be important to confirm that panel your provider is offering does include the gene for HCU. If it does not, a negative test may be falsely reassuring. Many labs do offer this testing for under $500. It would likely be the most expensive of the options, but it would also yield the most information since it looks beyond just HCU.

If you think you might be interested in pursuing any of these options for carrier testing or simply want more information, talk to your doctor and consider a referral to a genetic counselor. As genetic counselors, we are trained to walk you through all of these options, help determine what information is important to you, and work with your insurance to help ensure you have the lowest possible out of pocket cost. We will also help you interpret the results and talk about next steps for you to consider, as needed. Again, we recognize that carrier testing is not something every person is interested in pursuing. Our job is to help you make the best informed decision for yourself.

If both partners in a couple are identified as carriers of HCU, various options are available to them. Again, in this scenario, the decision a couple makes is deeply personal and should be made by them with their priorities and family in mind. Some couples choose to conceive naturally with the understanding that every pregnancy has a 25% chance to have HCU. From there, some may choose to pursue prenatal diagnosis by either chorionic villi sampling (CVS) or amniocentesis. These tests are invasive to the pregnancy, but they can tell prospective parents with greater than 99% certainty if the baby will have

HCU. Other parents will forego prenatal testing and wait until after the baby is born for newborn screening and confirmatory testing to learn the baby's status.

For parents not comfortable with the 25% chance, there are options available through fertility specialists to help lower this risk. Parents can consider using donor sperm from an unrelated individual or from a relative who is not a carrier. Donor sperm is a more affordable and less invasive option than donor egg or IVF, but it would mean that the father is not biologically the baby's father which can be difficult for some families to consider. Pursuing in vitro fertilization with genetic testing of the embryos by preimplantation genetic diagnosis also minimizes the chances that a baby would have HCU, but it is an invasive and expensive process.

There are many options that can help individuals and couples with an increased chance to have a child with homocystinuria. However, what may seem important or "high-risk" to one person, may not be perceived that way by others despite the risk assessment being the same numbers/chance. The decision to pursue carrier testing, prenatal diagnosis, or other options, is a very personal one. While not everyone is expected to make the same decisions, each person has the right to make an informed decision. A genetic counselor or physician familiar with genetics can help provide you with all the information you need to make the best decision for yourself and your family.