

## Making babies: having a family, the HD way



Making babies: HDBuzz's feature article on fertility technologies that can help at-risk people to have HD-free childr

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*For people at risk of Huntington's disease, having a baby who might inherit HD can make decisions around planning a family extremely difficult. Our HD fertility primer explains the options available, and how modern reproductive science can make a difference right now to families touched by HD.*

### Introduction

Many people with Huntington's disease, or at risk of it, would like to know if there are ways to have children without passing the disease on to the next generation.

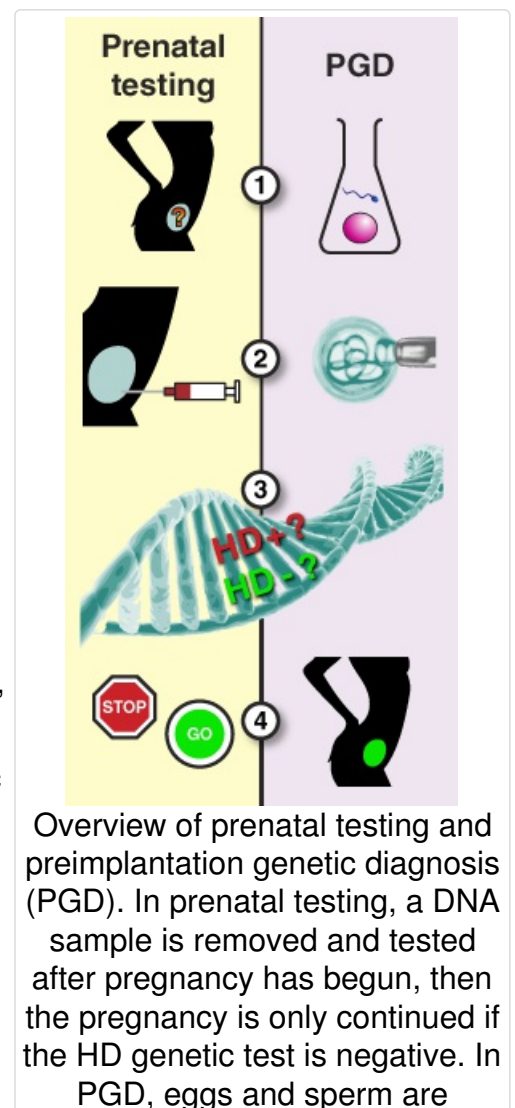
#### The short answer is yes!

'Assisted fertility' techniques are one area where scientific progress can make a real difference **right now** to the future of HD families. Several choices are available to people who are either at risk of Huntington's disease, or have had a positive gene test.

It may also come as a surprise to hear that **wannabe parents don't necessarily have to have an HD genetic test themselves** in order to use these fertility techniques to avoid passing HD to their children.

We hope this article will bring you up to speed on these options, but it's important to bear in mind that not all techniques are available everywhere, and in some countries, they can involve major expense. So if you're thinking about any of them, we recommend you contact a specialist genetic counselor for individual advice. The earlier you do, the more options you'll have.

#### The old-fashioned way



Deciding whether or not to have children who might be at risk of inheriting Huntington's disease is a dilemma that still faces prospective parents. Doing things the 'old-fashioned way' remains an option, and is of course free of charge and fun!

combined to form embryos in the lab. A single cell is removed from each embryo and genetically tested. Only embryos without the HD mutation are implanted into the womb.

As every HDBuzz article confirms, scientists are making real progress towards finding treatments for Huntington's disease. We believe a time will come when at-risk children are born into a world where HD is a treatable condition. However, there are no guarantees, and it's impossible to predict when disease-slowing treatments may become available.

Some people feel that they don't want to take any chances and would like to avoid the risk of passing on HD at all. That's where 'assisted fertility' techniques come in.

## Testing during pregnancy

It's possible to perform a genetic test during pregnancy to see whether the developing baby carries the gene that causes HD. This is called **prenatal testing**.

Deciding whether to test an unborn baby is a difficult decision. It is important to understand that prenatal testing in HD can only be performed when a couple feel sure they would terminate the pregnancy if the baby were found to carry the gene. That's a huge and intensely personal choice.

Importantly, the decision has to be made beforehand. That's because testing a pregnancy, but not going ahead with a termination after a positive test result, would take away the child's right to choose whether to have the genetic test, later in life. After all, most people at risk of HD choose not to have the test before they develop symptoms. We know that major difficulties can occur when a child is identified, from birth, as someone who will develop HD.

So, it's important to think carefully about prenatal testing for HD, and how you feel about pregnancy termination, in advance of getting pregnant.

Once a woman is pregnant, there is very little time to absorb the information about the prenatal test and make these important decisions, as the testing has to be carried out early during a pregnancy.

In addition, most testing in pregnancy can only be done if tests have been carried out on the couple (or other family members) beforehand. Often, there is not enough time to do this background work when a pregnancy has already started.

## How does prenatal testing work?

To test the developing baby, a procedure called **chorionic villus sampling** (CVS) is performed during early pregnancy. CVS involves collecting a small sample of the placenta (the 'afterbirth'), which has the same genes as the fetus.

CVS is done under local anesthetic and is a quick procedure in the outpatient clinic. Depending

on where the placenta is attached to the wall of the uterus, a very fine needle is passed either through the cervix or through the skin of the abdomen, using an ultrasound scanner to guide it. A small sample of cells is then collected from the placenta. These cells can be used to test for the HD genetic abnormality.

The main complication of the procedure is an increased risk of miscarriage, which happens after CVS in about 1 in 50 pregnancies.

CVS is usually carried out between 10 and 12 weeks into a pregnancy. At this stage, a pregnancy can still be kept private from family and friends. If the genetic test is positive, a termination can usually be carried out under general anesthetic until about 12-13 weeks - depending on the country's laws. Sometimes a termination can be carried out later.

## “HD-free with PGD”

**Pre-implantation genetic diagnosis** (PGD) is another way of going about things. It is a way of having an HD-free kid without having to think about terminating a pregnancy. It's more complicated, and more expensive than pre-natal testing and it can be a long and stressful process.

PGD involves using eggs and sperm to create embryos in a lab, then performing the HD test on the embryos, and putting only the HD-negative embryos into the woman's womb.

## The PGD Process

PGD is done as part of IVF (in-vitro fertilization). IVF is a medical procedure which involves a woman taking medications to cause the body to produce more eggs than normal.

The eggs are then collected and fertilized using a sperm sample given by the man. The fertilized eggs are left for a few days to develop into embryos.

The embryo is grown in the laboratory for two to three days until the cells have divided and the embryo has about eight cells. One or two cells are removed from each embryo at this stage. Removing cells at this early stage of development doesn't affect the way that the embryo develops.

The removed cells from each embryo are then tested genetically to see whether it has the HD mutation.

Finally, one or two embryos that don't have the mutation are transferred to the womb to allow them to develop.

Any healthy unaffected embryos can be frozen for later use.

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Expert genetic counseling helps understand the choices available locally. The earlier you get advice, the more options you'll have.

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About two weeks after the embryos are transferred, the woman will have a pregnancy blood test. If the transfer has been successful, pregnancy then carries on like normal.

## **The downside of PGD**

IVF - the process of stimulating egg release, collecting eggs, fertilizing them outside the body and returning embryos to the womb - is always a time-consuming and exhausting process. It can also be dangerous, carrying risks of the woman becoming unwell. Various things can go wrong, like not enough eggs or embryos being produced.

There's also more chance of having twins with IVF, which is harder work and more risky for the mother and babies.

On top of the risks of the IVF procedure, things can go wrong with the genetic bit of PGD. Embryos can be damaged when cells are removed, and sometimes the HD test doesn't work because there isn't enough DNA. Bad luck can mean that all the embryos have the HD mutation.

In the end, sometimes only one embryo is available for implantation - and sometimes none at all. To top it off, a pregnancy can fail after implantation.

Overall, each attempt at PGD gives a 20-30% chance of an HD-free pregnancy. Women under the age of 35 have the highest success rates - another reason to think ahead about fertility. Unfortunately, the chances of success over the age of 40 are nearly zero.

## **How much does PGD cost?**

PGD is expensive. The cost is somewhere in the region of US \$15,000 (£8,000 or €10,000) for each attempt. Health insurance usually doesn't cover the cost of PGD. In some countries like the UK, the public health care system will fund one or two PGD attempts, but even this can vary within individual countries, and may be limited to couples with no existing children.

## **What if I don't want to know my HD status?**

As we hinted at the top of this article, people at risk of Huntington's disease can take advantage of genetic technology to have HD-free kids, without having to be tested themselves. Doing so makes the process a bit more complicated, and makes it even more important to plan ahead and get expert advice early.

Both techniques we've described - prenatal testing (testing the fetus after pregnancy has begun) and PGD (testing embryos in the lab) - can be adjusted to avoid testing the prospective parents. The adjustments are called 'exclusion testing' and 'non-disclosure'.

## **Prenatal exclusion testing**

Prenatal exclusion testing involves taking DNA samples from the at-risk person, at least one of their parents and their partner. DNA is also collected from the unborn baby by CVS, as described above.

Testing the baby's DNA directly for the HD mutation can't be done, because if the test were positive, it would mean that the at-risk parent must have the HD mutation too - and we want to avoid doing that test.

So instead of doing the HD test directly, exclusion testing compares the DNA in the baby with the DNA of the parents and grandparents.

Inside each cell in the body, long strings of genes are tightly coiled into packages of DNA called chromosomes. A chromosome is a bit like a book - a small package containing lots of information. Cells contain 46 chromosomes; the two chromosomes containing the HD gene are both called number 4. When someone has a child, only one of the chromosomes is passed on.

Exclusion testing is done using DNA fingerprinting. It looks at chromosome 4 in all the DNA samples, without looking directly at the HD gene, and finds out whether or not the baby has inherited a copy of chromosome 4 from the grandparent with HD. Based on that, the baby is classified as high risk or low risk of developing HD, and a decision about whether to continue the pregnancy is made.

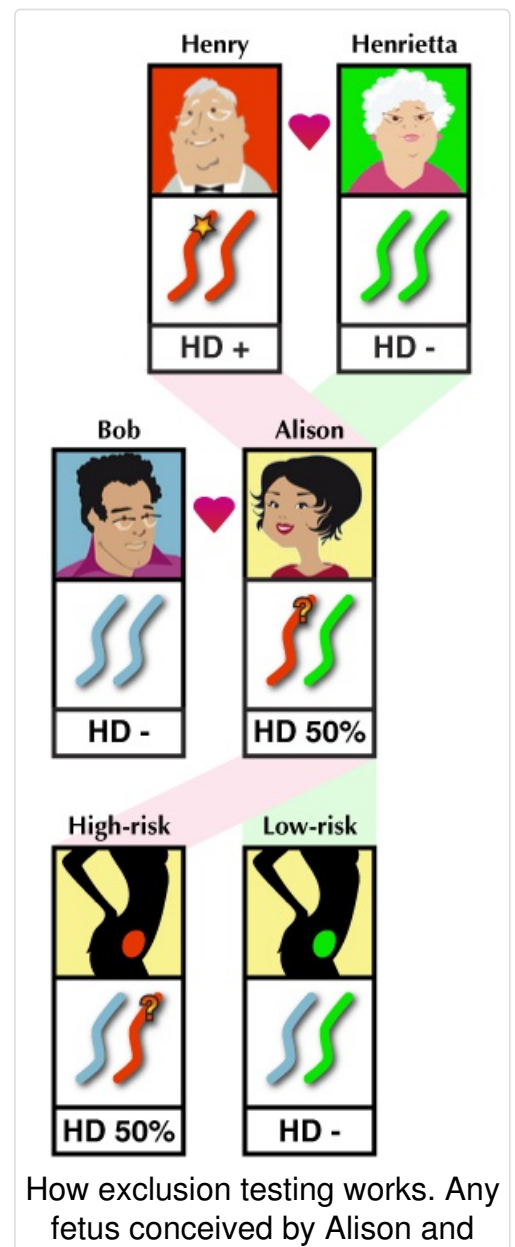
Let's explain it using an example. Alison and Bob want to have kids together but Alison's father, Henry, has Huntington's disease, and Alison doesn't want to have a genetic test for HD.

Alison has two copies of chromosome 4: one from her mother Henrietta, and one from her father Henry. The chromosome 4 she inherited from Henry was either the one with the HD mutation, or the normal one - the chance of each is 50%.

Alison, Bob and Henry all give blood samples, and Alison gets pregnant 'the fun way'. DNA is collected from the baby using CVS.

The fetus, too, inherits two copies of chromosome 4: one each from Alison and Bob. Neither of Bob's parents had HD, so we don't need to know any more about the chromosome the fetus has inherited from Bob.

But the chromosome 4 that the baby has got from Alison might have come from Henry or Henrietta. If it's Henrietta's, it won't have the HD mutation. But if it's from Henry, there's a 50% chance it's the one with the mutation. That's classified as a 'high risk' pregnancy, and would be terminated.



The difficulty with exclusion testing is that there is as much chance of terminating an unaffected pregnancy as an affected one. Giving any more certainty than that would require testing Alison for the mutation.

As you can see, exclusion testing makes it really important to think hard about how you feel about all the possible outcomes.

Like with normal prenatal testing, it can be dangerous to begin the procedure if you're not certain you'd be able to go ahead with a termination if the baby is found to be high risk. If a 'high risk' pregnancy is not terminated, and the parent goes on to develop HD, that means the child will also definitely get HD at some point during their life.

Bob will inherit a copy of chromosome 4 from either Henry or Henrietta. Chromosomes inherited from Henry may carry the HD mutation. Exclusion testing reveals which pregnancies have inherited Henrietta's copy of chromosome 4 and are therefore 'low risk' for inheriting the disease.

## Non-disclosure PGD

Non-disclosure is a twist on PGD that enables at-risk people to have HD-free children without finding out their own genetic status.

Suppose Alison and Bob decided to have non-disclosure PGD. Beforehand, Alison's blood would be tested for the HD mutation, but **Alison wouldn't be told the result**, and the doctors she sees directly won't know the result either- only the fertility lab knows. The PGD then begins, with egg collection and generation of embryos. If Alison's 'secret' test result was positive, the embryos are tested for HD, and only those without the mutation are replaced into Alison's womb.

Alison and Bob won't be told how many eggs are harvested, how many are successfully fertilized, or how many embryos are implanted. If there are no mutation-free embryos, the cycle stops there, and Alison and Bob are told that the fertilization failed, but not why. In vitro fertilization can fail for many reasons, so a failure to get pregnant can't be interpreted to mean Alison has the HD gene.

Not all clinics that perform PGD are able to offer non-disclosure PGD. Some offer PGD combined with exclusion testing instead.

## Other options

One way to have HD-free kids is to use **donor eggs or sperm** instead of those of the at-risk person.

Deciding to have a child with the help of a donor is a difficult decision, but avoids the need to consider termination of a pregnancy. It can be done for people who've had a positive predictive test, as well as those at risk who don't want to be tested themselves.

Like all choices, there's a downside. The child won't be genetically related to the at-risk parent, and the parents will need to think about how and when to share the information with the child.

There is plenty of support available to people who decide to go down this route, and this can be

discussed before deciding to embark on the process.

Many couples think about adopting children. In many places, couples with one partner at risk of HD are not allowed to adopt, because of the possible effect on the adopted child of a parent developing HD. However, at-risk couples may be able to be foster-carers for children.

## Summary

There are plenty of options available to people at risk of HD who wish to start a family.

The two main techniques for couples wishing to ensure HD-free kids are prenatal testing, where a pregnancy is genetically tested for HD using chorionic villus sampling, and preimplantation genetic diagnosis, where embryos created by in-vitro fertilization are tested and only HD-negative ones returned to the womb.

Either of these can be modified if the at-risk parent doesn't want to have an HD genetic test.

Expert advice, in the form of genetic counseling, will help you understand the exact options available to you locally. Your country's HD association can tell you how to get in touch with a genetic counselor. As with so many things in life, forward planning and understanding all the options is key.

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*The authors have no conflicts of interest to declare. For more information about our disclosure policy see our FAQ...*

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## Glossary

**Pre-implantation genetic diagnosis** A technique for preventing HD from being passed to children. Eggs and sperm are combined in a laboratory, and the embryos are tested genetically for the mutation. Only embryos without it are implanted into the mother's womb.

**chorionic villus sampling** A medical procedure used to get a sample of DNA from a developing baby during pregnancy. A needle passed through the skin of the abdomen, or through the cervix, is used to collect tissue from the placenta.

**In vitro fertilization** A medical procedure where eggs and sperm are combined in the laboratory, then embryos are implanted in the mother's womb.

**DNA fingerprinting** a method of discovering what chromosome came from what parent or grandparent, without testing for the HD genetic mutation.

**exclusion testing** an optional add-on to prenatal testing, where DNA from parents and grandparents is compared with the DNA of the embryo or fetus. Exclusion testing means that the at-risk parent doesn't have to have an HD genetic test to have HD-free children.

**prenatal testing** A technique for preventing HD from being passed to children. A DNA sample is taken during pregnancy and tested genetically. If the HD mutation is found, the pregnancy is terminated.

**Non-disclosure** an optional add-on to PGD, where an HD genetic test is performed on an at-risk parent but the result is kept secret. Non-disclosure PGD enables HD-free embryos to

be implanted without the at-risk parent having to learn their HD status.

**chromosomes** Long strings of genes, tightly coiled into packages of DNA inside cells. Each cell's DNA is stored as 46 chromosomes. The HD gene is on chromosome 4. Each chromosome has two copies, one inherited from each parent.

**placenta** the 'afterbirth', which supplies the fetus with oxygen and nutrients via the umbilical cord. The placenta's DNA is the same as the fetus's.

**embryo** the earliest stage during the development of a baby, when it consists of just a few cells

**uterus** womb

**cervix** the neck of the uterus (womb)

**fetus** a developing baby in the womb

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