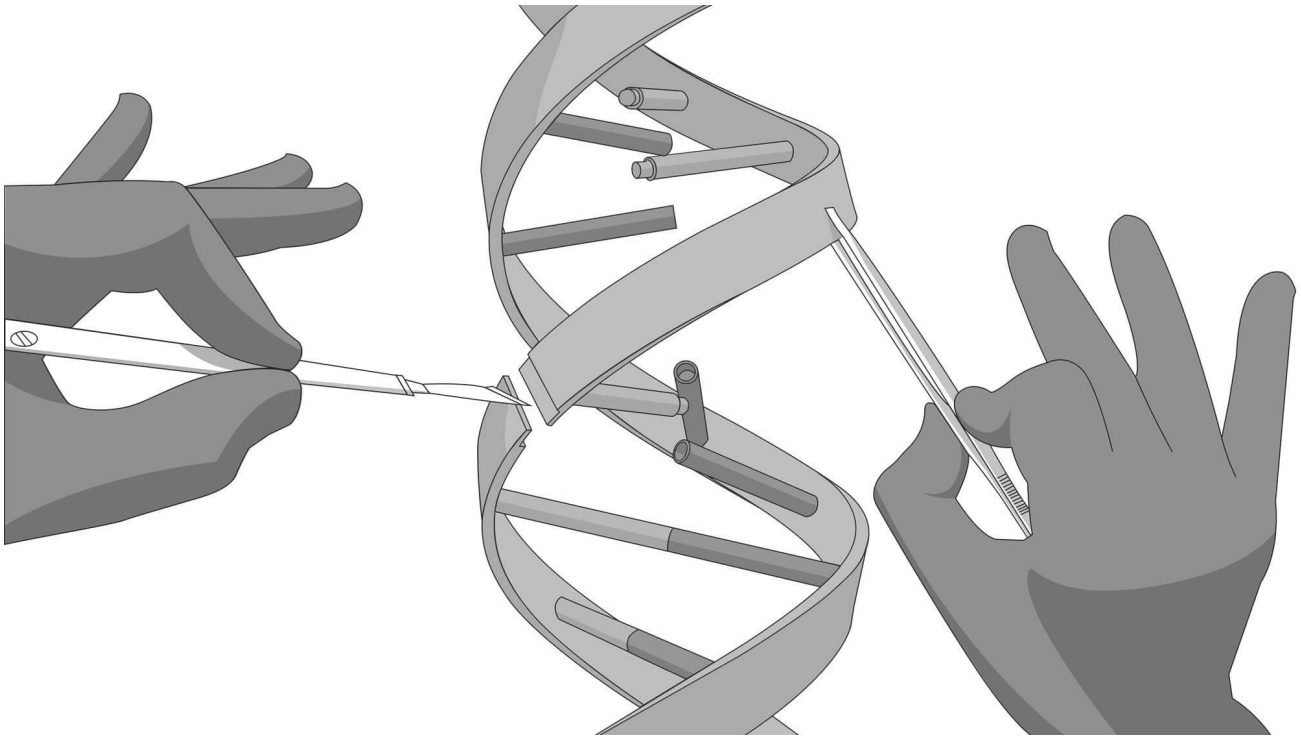
PASS IT ON

For Individuals and Families With a History of Cancer

Newsletter of the Cancer Genetic Counseling Service



CRISPR: THE GENE EDITING TOOL OF THE FUTURE

BY COURTNEY ATTARD, GENETIC COUNSELOR

In today's world, it can sometimes be difficult to distinguish between hype and hope when it comes to major medical advancements as portrayed by the media. CRISPR (pronounced "crisper") is the latest and greatest medical breakthrough that everyone seems to be discussing. So what is CRISPR and what do you need to know? What applications have promising potential for helping to treat disease and what belongs in futuristic sci-fi flicks?

In short- CRISPR (clustered regular-interspaced short palindromic repeats) is a gene editing technology. The CRISPR system was initially identified in E. coli as a natural immune system response that bacteria use to fight off their age-old nemesis, the virus.

At a very basic level, this is how it works:
When a virus attacks a bacteria, a snippet of the viral DNA is stored within the bacteria's own DNA code (within the CRISPR region)- effectively capturing a snapshot of the infection. Other proteins work together like a DNA scout, searching for a match to the virus. If the virus invades again, the scout complex easily recognizes the viral DNA and swiftly destroys it.

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"Many scientists are finding that CRISPR is not perfect quite yet and doesn't always make just the intended changes."

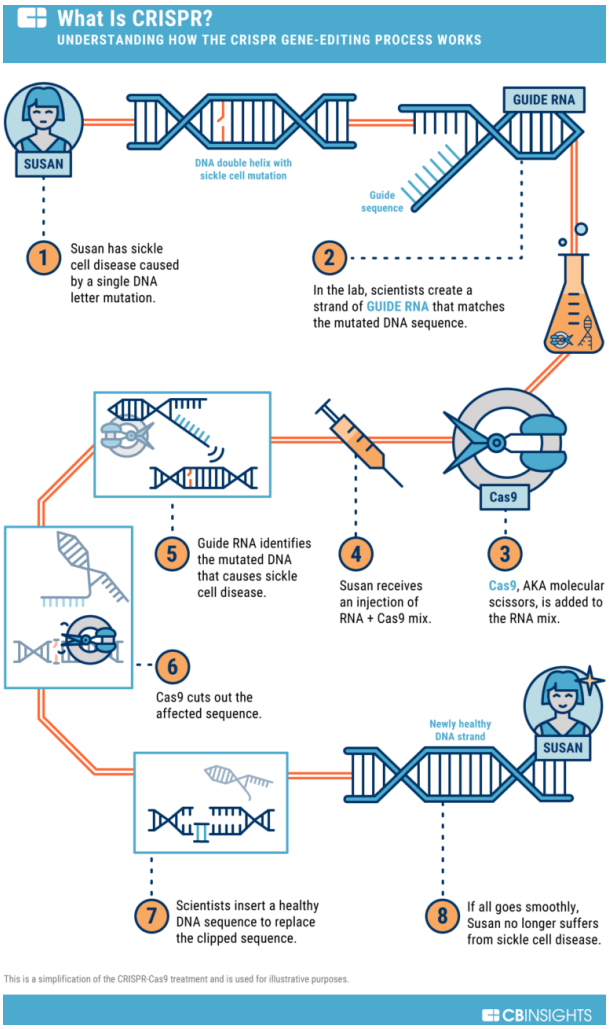
Recently, scientists have discovered how to manipulate this CRISPR system to target any DNA segment in virtually any organism. With the right information, this bacterial immune system becomes a precise gene editing tool, which can alter DNA and change specific genes by repairing DNA mistakes or even inserting a new copy of a gene.

In the scientific community, there is a lot of discussion about the appropriate use of such a technology and most agree there are obstacles that must be overcome before CRISPR can be used routinely in humans. The ability to fix DNA errors means that CRISPR could potentially create new treatments for diseases like sickle cell anemia or cystic fibrosis. While promising, more research is underway to study exactly what happens when genes are turned off or changed in an organism. Many scientists are finding that CRISPR is not perfect quite yet and doesn't always make just the intended changes, sometimes introducing "off-target" mutations elsewhere in the genome that could lead to unknown and undesirable outcomes.

There are also plenty of ethical considerations being debated by the scientific community. Most agree that the focus should be on helping to treat or cure disease. But others argue that it is a slippery slope. Some worry that this kind of technology could be used to produce babies with "enhancements"- that is, traits that might be considered desirable by parents which don't actually affect health or lifespan, such as eye and hair color or athletic ability and intelligence. Would such a technology be affordable to everyone or only the very wealthy? Could this lead to further inequalities in our society? Up until now, humans have not had a way to introduce heritable changes to our genetic code. These are changes that could be passed down to future generations, therefore altering the gene pool and possibly changing the course of evolution. Importantly, couples who are at high risk to have a child with a genetic disorder already have alternative options available such as in vitro fertilization with preimplantation genetic diagnosis (PGD). PGD is a procedure that screens embryos for specific genetic mutations and only implants embryos that do not carry that mutation.

While these are important discussions, most research is focused on how to use CRISPR to help treat individuals who are currently battling a disease. For example, there are studies investigating how CRISPR can be used to modify only the genes in lung cells in people with cystic fibrosis or only the blood cells in people with leukemia or sickle cell disease (**see Figure 1**). These are genetic changes aimed to help lessen some of the symptoms a person experiences related to their disorder; however, they are not heritable changes that could be passed down to future generations or that could change the gene pool at a population level. It is clear that CRISPR has a lot of potential to make a big impact on the medical field, but more research is needed in order to fully understand this tool. Stay tuned for future updates from our group!

Figure 1



GENE SPOTLIGHT: MUTYH

BY RACHEL REAGLE, GENETIC COUNSELOR

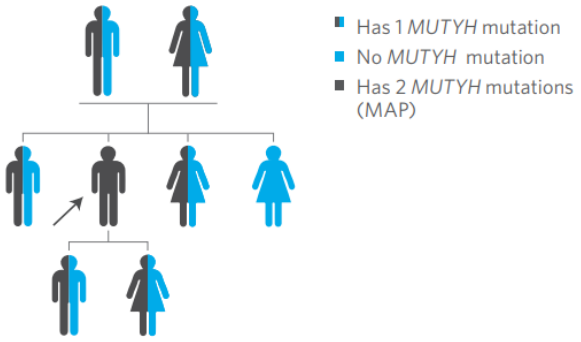
MUTYH is a hereditary cancer gene that increases the chance to develop colon cancer or colon polyps in individuals with a genetic mutation.

What are the risks associated with MUTYH?

The risk for colon cancer and/or colon polyps related to the *MUTYH* gene depends on how many genetic mutations a person inherits. A person with one *MUTYH* mutation has a slightly higher chance to develop colon cancer (10% lifetime risk) as compared to the general population risk of 4.5 percent. A person with two *MUTYH* mutations, one inherited from BOTH their mother & father, has a condition called *MUTYH*-Associated Polyposis (MAP). Individuals with MAP often develop 10-100s of colon polyps, also increasing their chances of developing colon cancer (43-100% lifetime risk).

Are my children at-risk for my MUTYH mutation?

A person with one *MUTYH* mutation has a 50% chance to pass the mutation on to each of their children. These children could also be at risk for having MAP if both parents happen to carry a *MUTYH* mutation. Importantly, both men and women are at-risk to inherit and pass on these mutations. The diagram below helps show how these *MUTYH* mutations may be passed down in a family.



How would a MUTYH mutation change medical care?

For individuals with one MUTYH mutation, a colonoscopy is recommended at least every 5 years beginning at age 40. For those with two mutations or MAP, colonoscopy is recommended every 1-2 years starting around age 25-30. Colon surgery may also be suggested for some people with MAP who develop a large number of colon polyps.

SO MY GENETIC TEST RESULTS WERE INCONCLUSIVE...

According to laboratories, 27% - 38% of individuals have an inconclusive result or "variant of uncertain significance (VUS)" in at least one of the genes tested for.

WHAT IS A VUS?

VUS stands for Variant of Uncertain Significance. It means that a genetic change was found in one or more of your genes, but the laboratory does not have enough evidence to classify your result as positive or negative. **A VUS is an inconclusive test result.**

HOW OFTEN IS A VUS RECLASSIFIED?

Over time, the laboratories collect evidence about the different genetic changes in hopes of eventually reclassifying it as positive or negative. According to various labs, 80% of VUS results are reclassified to a negative result.

HOW DOES THIS AFFECT MY MEDICAL CARE?

Put simply, it doesn't. An inconclusive result means that the cancer risk associated with the identified gene variant has not yet been determined. We don't use these results to change your medical management or screening recommendations & instead use your personal and family history.

WHAT IF MY VUS IS NOT RECLASSIFIED?

The laboratory will continue to investigate your result and will let your healthcare provider know of any updates. Remember that a VUS is neither good or bad in terms of your future health.

DOES MY FAMILY NEED TESTING FOR A VUS?

Short answer: No. Until your VUS is further characterized, test results of other relatives would be difficult to interpret. There may be other reasons to test your family members, such as a strong personal or family history of cancer.

If you have additional questions about a VUS result, you can always reach out to your genetic counselor for more information!

Infographic by Mallory Wagner

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