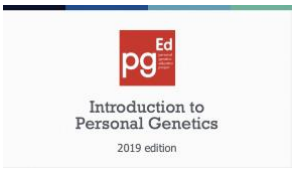
VIDEO TRANSCRIPT

Introduction to Personal Genetics

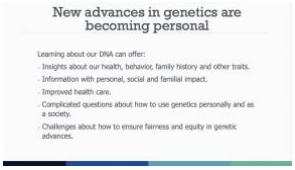
Link to video.

Slide 1



PGED's Introduction to Personal Genetics lesson gives an overview of many of the ways in which genetics may become relevant to our everyday lives. Our aim is to examine how new advances in personal genetics may impact our lives, our medical decisions, and society.

Slide 2

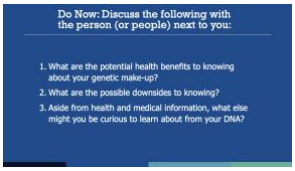


The scientific advances of the past few decades have brought us to a time in which individuals have more access to their personal genetic information than ever before. Learning about our DNA can offer insights about our health, behavior, family history and other traits. This information can improve our health care and has personal, social, and familial impact. In this lesson we'll use "personal genetics" as a broad term, encompassing the many choices that individuals may face as healthcare consumers and as members of society.

While learning about your DNA is highly personal, the ability to do so raises complicated questions about how we as a society should handle access to genetic information. For example, if you learn about your risk for Alzheimer's disease, this may raise concerns for your biological relatives, who might not want to know anything about their risk. Might easy access to genetic predispositions affect dating relationships? Should insurance companies be able to know information

about your DNA? Would everyone have equal access to personal genetic information and the benefits of new genetic technologies? These are a few of the issues that this lesson will explore.

Slide 3



Before delving into the presentation, we like to pause to allow people to reflect on a few questions that we will be addressing.

Here, we pose three questions:

1. What are the potential health benefits to knowing about your genetic make-up?
2. What are the possible downsides to knowing?
3. Aside from health and medical information, what else might you be curious to learn about from your DNA?

You may want to pause here to think about your own answers to these questions.

Typically, for question one, we hear ideas related to taking steps to prevent or seek early treatment for a potential health condition.

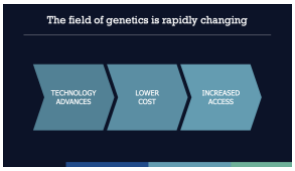
As for the downsides, we frequently hear concerns related to privacy and discrimination, as well as the potential emotional burden of learning about a predisposition for a genetic condition without current treatment, although some people suggest that in this case they could choose to become active in clinical trials or advocacy work.

Another idea that frequently surfaces here is the idea that genetics will give a person definitive life-altering answers, often including a specific cause of death. It is important to

clarify that genes are one part of a very complex puzzle, and other factors related to environment and lifestyle also play an important role in health outcomes.

For the third question, people frequently mention learning about their ancestry and finding biological relatives.

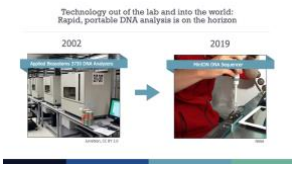
Slide 4



Technological advances that have lowered the cost of genome analysis are paving the way for people to have greater access to genetic information. For example, when the Human Genome Project was completed in 2003, it cost 3 billion dollars and took about 13 years.

In 2020 sequencing a human genome can cost as little as $700-$1,000 US and can be done in a matter of days, sometimes less, and both the cost and the time for analysis continue to decrease.

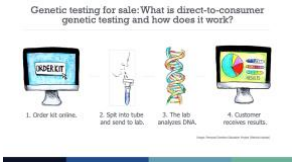
Slide 5



The machines that sequence DNA are becoming smaller, cheaper, and more accessible. The first sequence of the human genome was achieved with hundreds of sequencing machines working for years. Now, a single machine can sequence a full human genome in a matter of days. Some companies are developing DNA analysis machines, capable of providing a partial analysis (rather than a full genome sequence), that are the size of a USB drive.

These handheld genome sequencers can be useful in emergency medical situations, for rapid diagnosis in an emergency room or to track the spread of a virus (such as the recent outbreaks of Ebola and COVID-19).

Slide 6



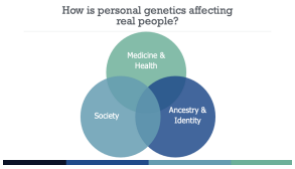
Genetic tests have become so accessible that you can now buy testing kits online or in pharmacies and department stores across the US. Some of these direct-to-consumer (DTC) tests can be purchased without a doctor's request or participation, while others require consulting with a doctor or genetic counselor about results. Samples are collected usually in the form of spit in tubes, which are then analyzed in a lab, and results are returned to customers by logging onto a website.

These products may provide information about risk for cancer or other conditions, or carrier status for genetic variants that, if inherited from both parents, can cause serious diseases in their children. Other tests offer an analysis of your possible ancestry or may provide interesting but not particularly consequential information about your traits, such as whether or not you're likely to sneeze when in bright sunlight or if you are likely to enjoy the taste of cilantro.

There has been much debate over DTC genetic testing since it first emerged in the early 2000s. Millions of individuals have sent in their DNA samples seeking information about their traits, ancestry, and health. While many people are excited to learn about their genetic make-up and believe they have the right to know whatever information may be in their DNA, others are concerned about the safety of providing individuals with genetic health information without the supervision of a healthcare professional. Worries persist that individuals will misinterpret results, feel a false sense of security, or make medical decisions based on the limited information provided by these tests.

If you'd like to learn more about direct to consumer genetic testing, check out PGED's lesson on "Consumer Genetics."

Slide 7



As we have seen in the previous slides, the field of genetics is changing rapidly and recent technological advances mean that we have faster and cheaper access to more genetic information than ever before.

These technological and scientific advances in genetics are impacting healthcare and medicine, adding exciting and complicated layers to concepts of identity and history, and having an impact on public life – particularly, the criminal justice system. We will discuss these topics in the coming slides.

Slide 8

One major use of genetic testing is to determine whether an illness has a genetic cause, or whether a person's genetic make-up may affect how well a particular treatment works for them.

Slide 9

Individuals with rare genetic disorders often undergo a long "diagnostic odyssey", seeing physician after physician and being subjected to test after test in search of answers.

Tess Bigelow, pictured here, (second row, third from the left) had her genome analyzed in search of a genetic cause for a number of complex health issues and developmental delays. Tess's genetic analysis revealed a change in her USP7 gene that caused it to malfunction. Disorders of the USP7 gene are very rare, so Tess's father, Bo, made a social media post

in search of other children with the same genetic variant as Tess. The following day, someone who saw Bo's post connected him with a researcher studying this gene, and Bo learned that there were seven other children known to have the same condition.

Like many families with a rare genetic disease, the Bigelow family have become activists, in addition to champions for Tess and her medical journey, seeking to find and connect families all over the world who might be affected by this genetic variant. They launched a foundation and created a community of other affected families in hopes of one day finding enough patients to populate a research study.

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While some people have their genomes analyzed to look for answers to the health problems they are currently experiencing, others seek genetic testing to identify future health risks. In May 2013, actor Angelina Jolie revealed that she had undergone a double mastectomy because she carries a mutation in the BRCA1 gene that greatly increases her risk of breast and ovarian cancer. Some believe a preemptive double mastectomy was a dramatic and potentially unnecessary choice since Jolie neither had cancer nor knew with certainty that she ever would. However, instead of waiting to see if she would develop cancer, she opted for a surgery that greatly decreased her chances. She has since also had her ovaries removed for the same reason. Jolie advocates for making genetic testing more accessible to all who want it.

Slide 11

Many people have had the experience of taking a medication that seems to work well for other people, only to find it does not work for them. The reason could be because of genetics. Certain genes control the rate at which a person's body metabolizes a drug, and this can affect the dosage they will need or whether the medicine should be prescribed at all.

A specific example is codeine, an opioid drug frequently prescribed for pain. For the drug to be effective, the body must convert the codeine to morphine. This is done with the help of an enzyme called CYP2D6. Variants in the CYP2D6 gene can dramatically affect how quickly an individual metabolizes this drug, and it can have serious, sometimes lethal, consequences if the dosage is not calibrated correctly.

Those with a version of CYP2D6 making them a typical metabolizer will get the expected effects from the typical dose of the medication. Those that are slow metabolizers will convert codeine to morphine at a much slower pace, meaning that they will get limited effect from the same dose of drug as a typical metabolizer. But those who are rapid metabolizers will convert that same dose of codeine into morphine at a much faster pace, causing a spike of morphine in the patient's body that is potentially life-threatening.

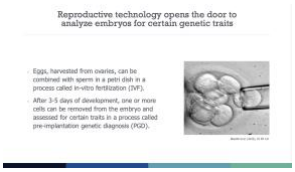
The FDA has cleared genetic tests to determine if a person is a rapid metabolizer, but they are not routinely used in the clinic. Individuals who have a personal or family history of not responding to medications as expected may want to seek genetic analysis for a possible explanation.

Slide 12

DNA testing can also be used to learn about future generations. A test known as non-invasive prenatal testing (NIPT) makes information about the genetic make-up of a fetus available at earlier stages of pregnancy than ever before.

How does NIPT work? All of us have small fragments of DNA, released from cells in our body, that circulate in our bloodstream. When a person is pregnant, a small fraction of this cell-free DNA originates from cells of the placenta, an organ formed by embryonic cells that connects the developing embryo (and later fetus) to the uterus. By obtaining a blood sample from the arm of the pregnant person, physicians and researchers can analyze its cell-free DNA to reveal information about the developing fetus. For this reason, this test can also be referred to as cell-free fetal DNA testing.

Slide 13



Genetic testing can also be used to learn about the genetic makeup of embryos created by in vitro fertilization (IVF). In some cases, a genetic testing technique called preimplantation genetic diagnosis (PGD) is performed prior to transferring embryos to the uterus. For PGD, one or more cells are removed from embryos created by IVF, and DNA from these cells is then tested for various genetic markers. First performed in 1990, PGD is often used in an effort to avoid genetic disorders, including deadly or debilitating childhood diseases such as Tay-Sachs and cystic fibrosis, as well as adult–onset diseases such as Huntington's disease and breast cancer.

Access to IVF and PGD remains quite limited due to cost. In 2020, the average cost of IVF and PGD, combined, was

$20,000-30,000 US. Unless it is covered by their health insurance, many people are not able to afford this procedure.

PGED's lesson "Reproductive Genetic Screening: Technology, Access & Decision Making" has more on this topic.

Slide 14

Whereas the previous examples focused on medical decisions based on reading the genetic code, this next story focuses on recent developments in genetic technologies that allow us to edit or engineer the genome.

The case of Layla Richards symbolizes the potential promise of genome engineering for treating diseases. Diagnosed at 14 weeks old with leukemia, a type of cancer that affects blood and bone marrow, Layla Richards was 11 months old when all conventional treatments had failed. Layla became the first child to be treated for leukemia via donated immune cells that were genetically engineered specifically for her body and type of cancer - a kind of treatment called immunotherapy. The cells, called CAR-T cells, were engineered to attack Layla's cancer cells. The cells were also altered to ensure Layla's immune system would not perceive them as dangerous and reject them. The transplant was a success, and as of the most recent report in early 2017, Layla remained cancer-free.

Slide 15

Ancestry testing is another dimension of personal genetics. In 2020, DNA ancestry tests often cost $100 US or less. For some, genetics can add a layer of information onto decades or centuries of records of family history. Others - because of adoption, migration, or other family circumstances such as donor-assisted conception - might be seeking unknown relatives from all over the world. For example, because of the history of slavery in the US, many people of African ancestry do not know in what part of Africa their ancestors lived. DNA testing may provide some information towards filling in these gaps and may allow people to feel more connected to a past of which they were previously unaware. On the other hand, DNA testing can also complicate or even contradict a person's sense of identity if results are unexpected or unwelcome. At the same time, some ethnic groups, particularly many Indigenous American nations, place a greater emphasis on cultural belonging and familial lineage rather than genetic ancestry when considering questions of ethnic identity.

Slide 16

These maps illustrate the point that while some people's ancestry can be seen via a world map looking at human migration patterns in the ancient past, others will see the history of their families more clearly in a map of the slave trade.

Using a combination of the archaeological record and DNA analysis, scientists have been able to track human movements out of Africa, believed to have started around 60,000-70,000 years ago, to eventually most areas of the world (except for Antarctica). The image on the left illustrates our current understanding of ancient human migration across the globe, showing the approximate date when a

particular island or part of a continent is believed to have been first inhabited by humans.

The second map illustrates the most common transatlantic slave trade routes during the 17th-19th centuries. During this time, 10-15 million people were forcibly moved from one part of the world to another. Today, there are many more millions of descendants of this slave trade whose genealogical and cultural history have been impacted by this forced migration. Taken together, these maps illustrate some of the many historical events that have shaped the genetic ancestry of populations across the world today.

Slide 17

There is a complex relationship between nationality, ethnicity, ancestry, and physical traits seen in countries formed as a result of European colonization, such as Mexico and the US. Such countries are not ethnically-uniform, but are instead multicultural and multiethnic countries with varied percentages of ancestral origins in their populations. National/ethnic identities such as "Mexican" can encompass dozens of languages and cultures, a mix of ancestries (including African, Indigenous American, European and/or Asian ancestry), and a wide diversity of traits. The variation in traits such as skin color is seen on this slide. In the US, many people of Mexican and other Latin American origins may identify or be identified as "Latino." The term "Latino" came into use largely as a category in the US Census; it does not easily map onto common notions of race and geography and is not broadly used across the globe.

Slide 18

This slide provides links to two videos in which young people are learning about their genetic ancestry via direct-to-consumer genetic tests. Both videos include people reflecting on how their results from a DNA ancestry test might fill in important pieces of their personal story, give them a sense of belonging, or differ from their family stories and concepts of ethnicity and identity. Also, both videos mention the history of colonization and slavery, and how painful that can be within families. The two videos both reinforce the idea that people are more alike than different from a genetic perspective.

You may choose to watch one or both of them now or later.

For a deeper dive into this topic, check out the PGED lessons "How does Ancestry Testing Work?" and "Consumer Genetics."

Slide 19

In the final part of this presentation we will look at some of the societal implications of genetics. We will explore examples that highlight 1) new law enforcement techniques, 2) past failures in research ethics, 3) the struggle for healthcare access, and 4) new models of community participation in genetics.

Slide 20

The case of the Golden State Killer is an example of how genetics can be used as a forensic tool to identify suspects.

The "Golden State Killer" is a serial killer and rapist who committed at least 13 murders and over 50 rapes between 1974 and 1986 in California. After failing to find a match in the government-created databases, investigators in this case

uploaded the perpetrator's DNA to an open-source genealogy database, called GEDmatch. GEDmatch is a privately-created database that welcomes people to upload their DNA analysis from private companies like 23andMe or Ancestry.com, in the hopes of building a large community for people seeking familial connections.

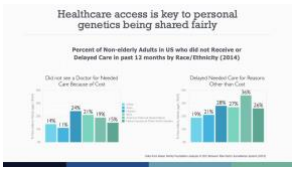
Law enforcement found a genetic connection in the database – a distant cousin of the suspected killer. Using genealogical research to construct a family tree, investigators narrowed down the possible suspects and, with additional DNA testing, an arrest was made. In 2020, Joseph James DeAngelo pleaded guilty in exchange for a sentence of life in prison instead of the death penalty.

This case is an example of how quickly a new technique can take hold. Though GEDmatch was not developed to be a legal tool, in the months after the arrest of the "Golden State Killer", law enforcement agencies used the database to make arrests in several other "cold cases." Some people have reacted positively to this news by saying that any and all methods are justified in the pursuit of solving crimes. Others have voiced concern regarding the fact that if even one biological relative uploads their DNA to a genealogy database like GEDmatch, then some of their shared DNA is also part of a system that is now being used for law enforcement reasons.

GEDmatch later changed its terms of service so that DNA profiles are now by default opted out of use for law enforcement investigations. Users can choose to opt-in, but only a small percentage have chosen to do so. GEDmatch has since been taken over by the forensic genomics firm

Verogen, raising new concerns over privacy and the use of personal data.

Slide 21



Another important societal issue surrounding personal genetics is that of access. Many people in the US, across ethnicities, cannot access the healthcare services they need. This remains a pervasive problem, and one that should be included in the discussion of how the potential of personal genetics to improve health remains out of reach for many until these underlying issues of access and economics are addressed.

Slide 22

In addition to limited access, past mistreatment and exploitation of minority communities have led to distrust and fear of biomedical researchers and resulted in a much lower rate of participation in clinical research or drug trials among ethnic minority communities than white communities.

One particularly egregious example of this mistreatment is the Tuskegee Syphilis Study, a study of the natural course of untreated syphilis run by the US Public Health Service from 1932-1972. Over 600 disenfranchised African American men were enrolled in the study under the promise of free healthcare and burial insurance. Many of the men were not told they were part of a study, nor where they informed about the risks or advised that they could leave the study. By 1947, penicillin had become the standard treatment for syphilis, but it was withheld from the men in the study. Many of the men died, 40 of their wives were infected as well, and 19 children were born with congenital syphilis. The study came to an end in 1972 after it was reported in the press.

In 1976, a national commission released the Belmont Report which provides principles and guidelines for the ethical treatment of human subjects. President Clinton formally apologized to the survivors in 1997.

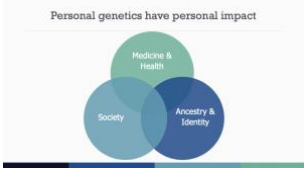
Researchers continue to strive to increase the diversity of research participants by increasing awareness and building trust with communities.

Slide 23

Collaboration between researchers and communities that emphasizes trust, access and transparency is an emerging model in genetic research. An example of this approach to genetic research is being implemented by the Diné (also known as the Navajo Nation). Navajo leaders have proposed lifting the ban on genetic research that the nation had put in place since 2002 so their community can benefit from advances in genetics. Tribal leaders are devising a new model of participation in research to avoid potentially unwanted or inappropriate use of their DNA. In this model, Navajo Nation would have the power to approve or reject research studies and retain control over their DNA samples. They are also conducting public meetings and hearings to gather input.

A collaborative approach is also being used in Massachusetts, New Zealand and sub-Saharan Africa where genetic technologies are being considered to solve environmental issues with insect-borne disease and invasive species. These collaborative projects are placing the wishes of the people living in the impacted areas in the center of the discussions about if and how a project will proceed.

Slide 24



Whether seeking answers to medical questions, tracing our ancestry or addressing larger community-level issues like access and law enforcement, personal genetics is playing an ever-increasing role in our daily lives.