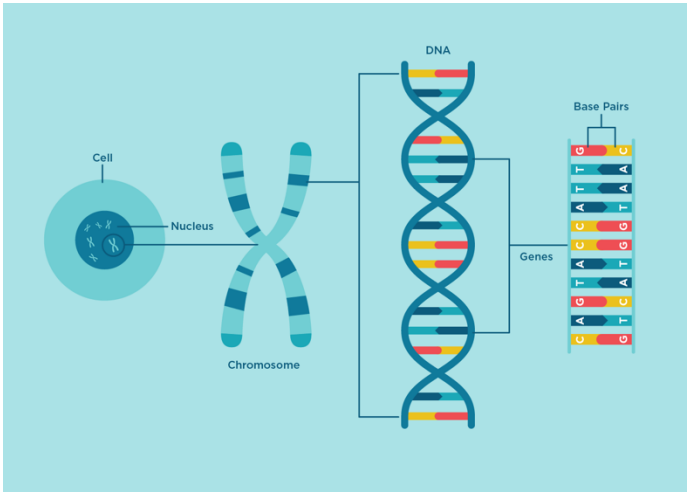
Genetic and Protein Testing: Should I take the tests?

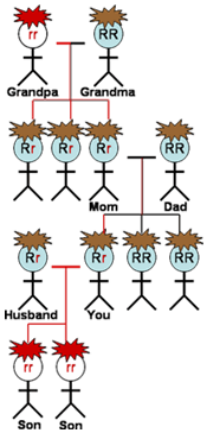
Understanding Genetics and Genetic Testing



I am about to make you all science nerds... assuming that you aren't one already. If you are already a science nerd, you still just might need a refresher! Are you ready?

Most of our cells have a nucleus and in each of those nuclei, there are 23 chromosomes, see the blue square, from blog.color.com. Chromosomes exist in pairs with one chromosome from your mother and one from your father. Chromosomes are comprised of long strands of DNA, that are made up of base pairs – adenine, thymine, cytosine, and guanine. Various base pair combinations code for billions of genes, 20,000 of which give us our unique appearance, traits and health.

By examining our genes, we can learn about who are relatives are and our ancestral homelands. Companies like Ancestry.com and 23andme.com have been marketing this information for years. Genes can also be used to determine diseases that could potentially arise and the likelihood of you developing these diseases. They can also let you know if you are a carrier of a disease that you do not have, but could pass on to your children or grandchildren.



Sometimes a single gene determines a characteristic like whether you have freckles, are lactose intolerant or have blue eyes. Please allow me some editorial license to give you an example for demonstration purposes (it's not 100% scientifically accurate). Take a look at the pedigree chart below. In this family, Grandpa has red hair. He inherited two recessive genes for red hair from his parents. Grandma has two dominant genes for brown hair that she got from her parents. All of their children have one red hair gene and one brown hair gene. Because brown hair is dominant over red hair, the recessive gene, all of their children have brown hair. The person labeled "You" in the chart got one brown hair gene from dad and a red hair gene from mom, so "you" too have brown hair. Coincidentally, so does your husband. Because both of you carry the silent red hair gene, you are able to pass that gene on to your children. Your children just happen to both receive 2 copies of the recessive red hair gene and have red hair. Red hair seems to have magically skipped two generations!

Diseases work the same way. In some cases, diseases are transmitted through recessive genes, but they can also be from a dominant gene. To complicate our understanding of genetics, multiple genes are involved in most traits and diseases such as with height, weight, skin color, blood pressure, cancer, type 2 diabetes, etc.

Genetic Testing Options

If you are interested in looking into the fortune teller's magic globe, you have many options to choose from for genetic testing. Let us review the various genetic tests that I personally have explored and that we have been using with patients. These comments reflect only my opinions and personal experience as a consumer. (Of note, I do not have any financial interest in any of the companies that I mention below.)

1. Health information available through commercial companies like Ancestry.com and 23andme.com
    - These companies are restricted in the types and amount of information that they are allowed to share with customers. These restrictions are in place, because the information is provided directly to the customer and without medical counseling.
    - Overall, I would say that these health and wellness reports are *not* worth the money
    - ~$150

2. Targeted testing for specific risks like Color.com or Invitae.com
    - Color uses some of your DNA to assess risk for cancer and heart disease and your personal Medication Response.
        - For example, I am much more sensitive to ibuprofen and caffeine than the average person
    - Invitae uses some of your DNA to assess risk for a broader range of diseases including cancer, heart disease, neurologic disease, pediatric genetic disease, metabolic, immunology, blood disease, skin disease and eye disease
    - These tests look for the most common mutations in a gene
        - For example, these were recommended due to my family history, but missed detecting an inherited cancer gene. These tests look for the most common mutations in the BRCA gene and not the entire gene, so the patient being tested could still have a rare mutation
    - ~$250

3. Broad DNA analysis that only assesses SNPs
    - SNP stands for single nucleotide polymorphisms, where one base pair in your genes is different resulting in a trait or a disease, eg. an adenosine is now a cytosine (see the blue square for a reminder)
    - Fairly comprehensive, but it does not assess DNA abnormalities including deletions, duplications or rearrangements
    - I can take your raw DNA from Ancestry.com or 23andme.com and compare your genetics to every NIH study available (Don't pay for the health and wellness profile, just the basic raw data). This focuses on SNPs.
    - Cheapest, just takes time for Jeannette to review
    - Done once, not routinely updated
    - ~$20 to pay for the computer server to organize data files

4. Most comprehensive sequencing of your entire DNA, (e.g. New Amsterdam Genomics)
    - Includes analysis of SNPs, deletions, duplications, and rearrangements

- Like #2 and #3 it includes your risk for various disease, if you carry a disease that you don't have but could pass on to your children, but is more comprehensive than #2
- Includes tips on your response to medications like #2 and #3
- Uniquely includes a list of very specific behavior changes you can make based on your genetic risks
- May help solve mysterious symptoms by identifying rare diagnoses
- Includes tips on your response to medications like #2 and #3
- Uniquely provides the exact data, with referenced journal articles, regarding every finding for your exploration and understanding
- Continuously updated
- Most expensive ~$2500

Here are some illustrative examples that represent patients that I have worked with but don't reference any specific patient.

Case 1
Jennifer is a 40 year old woman with a personal history of migraines since her early teens. Her mother, grandmother, and maternal aunt also suffered from migraines. Jennifer asked Jeannette to run her SNP genetics (#3). She learned that she has 10 genes that put her at high risk for migraines. She also had her genetics run through New Amsterdam (#4) and learned that she has a specific vitamin deficiency, based on her genetic profile. Since replacing this vitamin, her migraines have improved.

Case 2
Paul, a 31 year old gentleman reported that his mother went blind from Macular Degeneration at an unusually young age. He wanted to know if he too might go blind. Jeannette ran his SNP genetics (#3) and he learned that he is a carrier for a rare disease called Stargardt disease that leads to premature macular degeneration and blindness. While he still needs regular eye exams, he should not get the disease as it is recessive and he only has one gene for the disease, where his mother likely had two. He can also make sure that his future mate is screened prior to having children. If she were to have Stargardt disease as well, genetic testing of embryos and invitro fertilization would be recommended to protect future children from developing Stargardt disease.

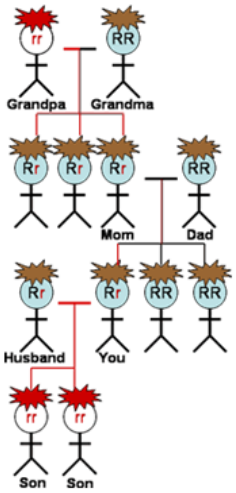
Case 3
A 72 year old female named Anabelle who wanted to better understand recent weight gain completed the New Amsterdam genetic testing (#4), only to learn incidentally that she has a previously unknown blood clotting disorder – Factor V Leiden Deficiency. This will better inform further preventative health measures, such as taking blood thinners for long car rides and flights and carefully watching for blood clots. She can also inform her children, so that they too can be tested by their physicians.

Case 4
A 75 year old woman named Sue asked Jeannette to use her Ancestry.com raw data to analyze her genetics (#3). The analysis showed that her genes did *not* put her at risk for lung cancer. She exclaimed, "but, I have had lung cancer -" to which Jeannette reminded her that she also smoked

2 packs of cigarettes a day for 60 years and she chuckled. Remember genes are only part of the story.

Genetics Versus Proteomics

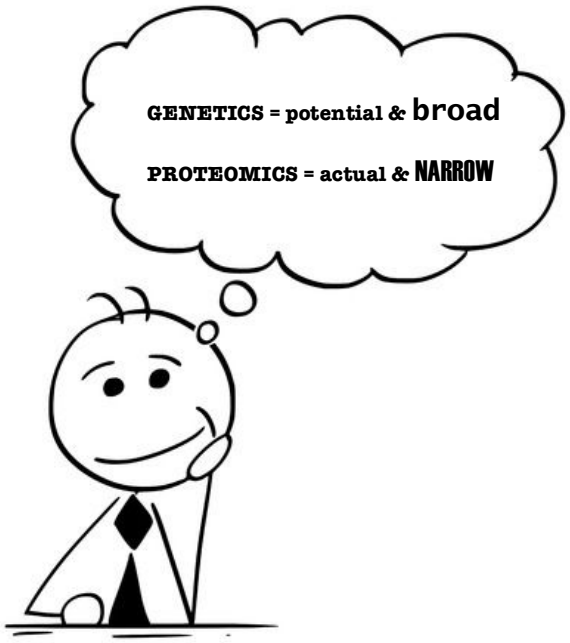
Yes, genes are only part of the story. And even genes aren't as simple as I have made them sound. The first genetic concept is whether or not you have a gene for a disease, or multiple genes for a disease. These genes can be inherited from your mother or your father or can arise through spontaneous mutations. The next two concepts to discuss are penetrance and variable phenotypic expression. Just because you have a gene, doesn't necessarily mean that it will be expressed. Not all genes penetrate and become visible. Secondly, of the genes that do penetrate, there may be variability in the way they are expressed.



Let us go back to the pedigree chart that we looked at for red and brown hair. Does every brown-haired person you know have the same shade of brown hair? No, that is variable expression of the brown hair gene. Penetrance would mean for example, that you have one dominant gene for brown hair and recessive gene for red hair, but the brown hair gene decides not to penetrate. As a result, despite genes that suggest you should have brown hair, you have beautiful red locks instead.

Why am I telling you all of this? It is important to understand if you want to differentiate between genetic testing and protein (AKA proteomics) testing. Genes, given penetrance and variable expression, tell you what you could potentially get, but just because you have the gene doesn't guarantee that you will get the disease. A risk level is predicted instead. As in Case 1, a person with 10 genes for migraines has a higher risk of having migraines than someone who just has 2.

Proteomics testing bypasses the question of which genes will penetrate and how they will be expressed by looking at the proteins your genes are actually making! Currently, the technology is more limited. With proteomics, predictions can be made about less diseases.



Proteomic Testing

We have traditionally used a company out of Boulder called SomaLogics to assess the following:

- Primary Cardiovascular Risk – if you *have not* had heart or vascular disease
- Secondary Cardiovascular Risk – if you *have* had heart or vascular disease
- Liver Fat – Do I have excess liver fat?
- Cardiorespiratory Fitness (VO2 Max) - What is my aerobic fitness level?
- Percent Body Fat – What is my body fat percentage?
- Lean Body Mass – What is my lean body mass?
- Alcohol Impact – Is my body showing the effects of my weekly alcohol consumption?
- Glucose Tolerance – If I have simple sugars, does my blood glucose spike to unhealthy levels?
- Visceral Fat - How much fat is around my organs?
- Resting Energy Rate – How many calories does my body burn at rest when I am not doing physical activity?

All of this information can be determined from a blood sample alone by looking at the proteins that your DNA produces! It costs about $200. The technology ceases to amaze us and will continue to grow exponentially as more disease are incorporated into their testing profiles.

Case Example 5
John, a 63 year old male, completed the SomaLogic proteomics testing and discovered that his health was below that of his age and gender matched peers. In fact, he was in the 30th percentile. He set a goal of improving his cardiovascular fitness and reducing visceral fat over the next year, when he plans to get retested to assess his progress.

Case Example 6
Gabe, a 57 year old, completed the testing under spousal pressure. There was a family dispute over whether Gabe drank too much draft beer from the local breweries. SomaLogic proteomics testing revealed that the alcohol was doing a number on Gabe's liver. This was the needed motivation to cut down on drinking and to ask for help.

Case Example 7
Ellen is a 58 year old female from a large close knit family. She is a nurse and knows her personal and family medical history very well. She developed Burning Mouth Syndrome, which causes a burning, raw feeling in her mouth. The pain was not relieved by pain medication, or

traditional therapies but by eating. She decided to have her genetics and proteomics explored. She did not learn any new information that would help her understand why the condition developed or how better to treat it.

As with all things in medicine, no test is perfect and results are often presented as probabilities rather than a "yes" or "no". The same is true for genetics. The other thing to know about medical tests is that they all come with pros and cons.

PROS	CONS
Opportunity for early detection and treatment	May increase anxiety and stress
Ability to notify family members	Results may be inconclusive or uncertain
Prevent spreading disease to subsequent generations	Discrimination*
Relief from uncertainty	
Information to make informed medical and lifestyle decisions	

*Though the Genetic Information Nondiscrimination Act (GINA) was signed into federal law in 2008 prohibiting health insurers and most employers from discriminating against individuals based on genetic information, it does NOT cover life, disability of long-term care insurance.

I wanted to make this newsletter COVID 19 free. But since we are talking about genetics and proteomics, you may find it interesting to know that some consumer genomics companies and university laboratories are offering free genetic testing to people hospitalized with COVID 19. They hope to understand why some people get sicker than others. Scientist believe our genes hold the answer to why some people become more ill from the virus, why some people have higher viral loads, and why others are more likely to get infected in the first place.

Initially, there was speculation that blood type or ACE (angiotensin converting enzyme) influenced the severity of COVID 19. Genetic testing has shown that there is no evidence to support these hypotheses. Another idea involves HLAs (human leukocyte antigen) genes. Like blood types, we have different types of HLA. Our HLAs contain instructions on how to build proteins that bind to viruses which then alert the immune cells of a virus invader. More to come on whether different HLA types cause individuals to respond differently to COVID 19.

The good news is that COVID 19 is being researched and targeted from multiple different angles to ensure a healthier future. Sorry to be so long winded… but I picked a big topic that can get complicated fast. I hope that I was able to make it understandable, without my markers and flipchart for sketching!