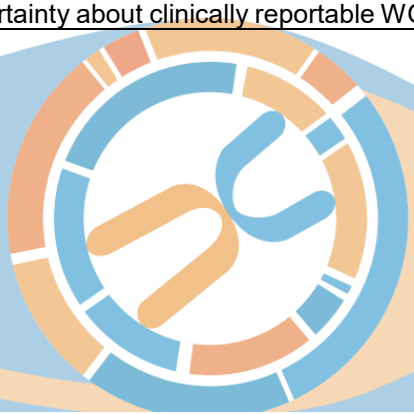
Genomics F.A.Q.

Our goal is to make our doctors experts in genomics and Precision Medicine, so we are pleased to present answers to some commonly asked questions. If you have a question that is not addressed here, contact Kristopher Faulend at kfaulend@nagenomics.com or (347) 507-8438.

Q. What are the different types of sequencing?

A. There are four major types of sequencing, described in the table below:

Genotyping	Examples: 23andMe, Ancestry.com, Pathway Discussion: Genotyping is technology from about 2008. It only looks at single nucleotide polymorphisms (i.e. do you have an A, C, G, or T) at a particular location. This can't detect insertions and deletions (which can have larger impact than SNPs). This also doesn't detect rare mutations that each person inevitably has, which also can have much higher impact. In general, the results that come out of genotyping have small odds ratios and are not very clinically important.
Gene Panels	Examples: Myriad, Counsyl, Color Discussion: Gene panels look at full gene sequences for just a few genes. Their price is often not much less than Whole Exome. In addition, many diseases are caused by many different genes. So even if you're only interested in investigating one problem, there is a good chance a gene panel won't find it. Cancer is a great example: there are over 1000 known tumor suppressor genes plus oncogenes that can influence a person's risk.
Whole Exome	Examples: N.A.G., Harvard University, Baylor University Discussion: Whole Exome sequencing looks at the coding region of all 22,000 genes of your DNA. The coding region is just 2% of the entire genome, but it encompasses the vast majority of disease causing mutations. Next Generation Sequencing technology has made the cost of sequencing your whole exome cheaper than doing multiple gene panels.
Whole Genome	Examples: *The Genomic Alliance has concluded Whole Genome is not ready for clinical use at this time.* Discussion: Whole Genome sequencing may initially seem more attractive than Whole Exome, given that it sequences more. However, Whole Genome has a number of problems. First, we have found that organizations advertising Whole Genome often do not actually analyze the whole genome, only a subset of genes (counterintuitively making them less broad than Whole Exome). Second, even if they did actually analyze the full genome, Whole Genome scans typically compromise on coverage, bringing it down to 30X, which is below what we believe is necessary to confidently call mutations (especially when someone's life is on the line!). Here is a paper describing more: http://jama.jamanetwork.com/article.aspx?articleid=1840236 . Some quotes: "In this exploratory study of 12 volunteer adults, the use of WGS was associated with incomplete coverage of inherited disease genes, low reproducibility of genetic variation with the highest potential clinical effects, and uncertainty about clinically reportable WGS findings."



"... fewer than one-third of insertion/deletion variants in inherited disease genes were confirmed by the second sequencing platform. This finding suggests that genetic variants of a type that are quite likely to be pathogenic are more often inconsistently identified. Other investigators have made similar observations about potential loss-of-function mutations. This may be particularly pronounced in individuals with low prior probability of inherited disease or when no clear diagnostic end point is pursued. Thus ... there is a persistent need for technical confirmation of potentially significant findings and supplementation with other genetic assays to achieve clinical grade sensitivity and specificity."

Q. Other than differences in sequencing, how else should I evaluate DNA tests?

A. N.A.G. has several other key advantages:

- Breadth and volume of genomic annotations
- Provides not just risk assessments, but often actions a person can take to mitigate their highest risks
- Ability to prioritize results so you can quickly understand which are most important
- Affiliation with the Genomic Alliance, meaning you are kept up to date with all the latest best practices in genomics
- Results that auto-update every two weeks based on the latest scientific findings
- Service: we are responsive to individual requests from our doctors

Q. What do you test for?

A. We test for tens of thousands of different medical conditions, so it's hard fully capture the breadth in a quick answer. Nevertheless, here's an overview. We test for risks of cancers, coronary heart disease, heart arrhythmias, structural heart disease, hypertension, blood problems, diabetes, kidney function, respiratory problems, autoimmune diseases, stroke, eye problems, dementia, and neurodegenerative diseases. We test for rare Mendelian disorders – the US government estimates 10% of the population has one. We test for medication responses, i.e. whether a person will metabolize a drug safely and whether that drug will be effective in treating a particular problem. We test for diet, exercise, and lifestyle annotations, e.g. the effects of dietary fat vs cholesterol, animal fat, saturated fat, and whole grains; weight loss suggestions; abnormal sugar desire; the effects of caffeine, alcohol, and aspirin; vitamin deficiencies and altered metabolism; endurance markers; strength and power markers; muscle problems; optimal sport choices; and longevity markers. We test for recessive traits a patient carries in their DNA but doesn't express themselves, which can be useful for family planning. We also test for ancestry, comparing a person's DNA to 52 ethnicities from around the globe. All told, 40% of people who take our test have a life changing result, a figure far beyond anyone else.

Q. Is this a good test for healthy patients?

A. You are the final judge, of course, but about 2/3 of our patients are generally healthy. There is so much a person can learn from our test, even if they feel and seem healthy.

Q. Which patients should I speak to first about getting tested?

A. While we believe that anyone can potentially benefit from our test, there are certain groups of people that have higher likelihood of getting more benefit. Those groups include: cancer patients (since cancer is such a serious disease, we analyze all of a patient's tumor suppressor genes, and we have special expertise with cancer), people with unexplained symptoms (since we analyze such a broad amount of DNA, we can direct you to an answer quicker and cheaper), and science / technology / finance people (since they work with data in their jobs, they enjoy looking at the data of their own bodies).

Q. Which other doctors are using N.A.G.?

A. Hundreds of doctors across the country use N.A.G. Some references can be found on our website (http://nagenomics.com). Ask us if you seek testimonials specific to a certain topic.

Q. How does standard of care change when a patient's DNA is revealed to a doctor?

A. One of the main reasons the Genomic Alliance was formed was to answer this question. The answer will evolve as we learn more, but your involvement in the Genomic Alliance will guarantee that you are both engaged in the discussion and aware of any great best practices your peers come up with. The current best practice is that you start by reviewing and evaluating any high impact genomic finding found on the patient's concise report. Any finding you believe is legitimate, accurate, and substantial we recommend you corroborate by family history, patient symptoms, or a follow-up test. For any corroborated finding, we recommend you consider developing steps toward mitigation, if such steps exist. If there is a significant finding that you aren't able to corroborate, then you should carefully weigh the costs/benefits of taking a possible mitigation step. Sometimes there are individualized mitigation steps available for a patient's particular health problem on their Diet, Exercise, and Lifestyle webpage. It is completely fine to outsource any result that is outside your domain of expertise to a specialist. Despite this, the Genomic Alliance believes primary care doctors are in great position to see a person's DNA results first, given that DNA touches so many facets of health.

Q. What about ethics?

A. Ethics is something we take very seriously. This is why we have developed the industry's best ethical policy. We have validated this ethical policy by discussing it with the members of the Genomic Alliance. Each patient, at time of test requisition, has the choice of three different levels

for which information they want returned to them. Those choices are Show Everything, Only Actionable, and Comfortable and Fun. You as the doctor help them choose. Factors to consider include the patient's psychology, the patient's family history, and the patient's support network (i.e. whether they have potential caretakers in the case of a bad finding). In general, the spirit of our test is that we hope to find as many mitigation steps as possible for the health risks a person has. It is true that oftentimes, people find health risks they didn't know about. However, we have also found that patients feel empowered knowing they are doing the best they can, and patients often feel relieved by learning they are genetically clear of problems they thought they had.

Q. What is epigenetics?

A. Epigenetics confuses many people. Epigenetics is defined as factors a person inherits that are not the A, C, G, and T sequence data of someone's DNA. Examples include the methylation patterns on someone's DNA and how a person's DNA is structured in three dimensions.

It is important to emphasize that the "methylation pathways" that some DNA tests report on is a different concept that unfortunately sounds similar. Methylation pathway tests do not test epigenetics, they test sequence variation of DNA, and thus are, generally speaking, a subset of what we test. The reason that these tests are called methylation pathway tests is because they look at DNA mutations that affect the methylation of many different molecules (proteins, enzymes, and also DNA). They do not test DNA methylation patterns; they test DNA mutations that could affect the methylation patterns of all sorts of cellular molecules.

Epigenetics is a biological subject with real phenotypic effects, but we believe it is not yet ready for use in the clinic. An example of a phenotype that people suspect is related to epigenetics is homosexuality; however, to our knowledge, there is no epigenetics test testing for that. Many years from now, it is likely that epigenetics will be used in the clinic.

Q. What is microbiome analysis?

A. The microbiome is the diverse microorganisms symbiotic with a person, present in several different areas of the body. Most interest in microbiome research is on the gastrointestinal tract. While there is real science here – a person's microbiome certainly impacts their health – we believe research has not yet advanced to the point where microbiome testing is valuable for many patients. There have not been enough studies that have proven associations between properties of the microbiome and clinically useful conclusions. Another key limitation is that a person's microbiome changes over time (e.g. in response to foods they eat and medications they take), meaning the microbiome is not a stable indicator of a patient's health.