DTC Genetic Testing – Dr. Fran Kendall

Dr. Fran Kendall is one of the pioneers in the field of mitochondrial medicine and a specialist in metabolic mitochondrial inherited disorders. Harvard-trained and board certified as a clinical biochemical geneticist, she also founded the very first mitochondrial disease clinic in the United States, and one of the first commercial laboratories focused on rare metabolic and mitochondrial disorders. She is also a founder of VMP Genetics, which is a private practice specializing in rare genetics with foci on direct patient care, education, and physician to physician support. Dr. Kendall serves as the head of genetics for a large hospital system. She has authored chapters on mitochondrial medicine for medical texts, written numerous research articles and also lectures at medical and nursing schools. She is a frequent guest speaker at medical conferences on mitochondrial disease and autism. Dr. Kendall often acts an expert witness in federal court cases and has appeared on national news outlets to offer expert opinion. She currently sees children and adult patients from around the world in either her VMP Genetics clinic offices in Atlanta, Georgia, or by telemedicine.

Dr. Fran Kendall

Direct-to-consumer genetic testing (DTC) is a topic that comes up frequently, both in the general population and in the mitochondrial community. DTC testing refers to genetic tests that are advertised and sold directly to the public. Tests offer information such as ancestry, one's risk for developing certain conditions, carrier status for some autosomal recessive diseases, predicted drug response, and non-disease phenotype traits such eye color. These tests are not considered diagnostic and offer risk information for only a limited set of conditions. There are a number of entities offering DTC genetic testing including 23 & Me, Ancestry, Color, Mayo Clinic, GeneGuide, and My Heritage.

Benefits: One potential benefit of DTC testing is promoting awareness of genetic disease. It could also provide personalized information about overall individual health, disease risk, and other traits. It can potentially allow consumers to take a more proactive role in their health care. Certainly it offers a means for people to learn about their ancestral origins. These tests don't require approval from an insurance company or a health care provider, (and the results are available relatively quickly, usually within six weeks. Data can be added to a large database, which could be used for further medical research. Depending on the company, the databases may represent up to several million participants, which is a large group of patients to glean data from.

Limitations: There are also significant limitations to DTC testing. First, a user might receive unexpected information relating to family relationships, health, or ancestry that might be disturbing. Stories abound about the impact of people learning that the person they think is their father, is not, or that they are adopted. The second limitation, and it's a significant one from the perspective of a geneticist, is that people could make important decisions about disease treatment or prevention based on test results that offer inaccurate, incomplete, or misunderstood information. Furthermore, there is currently little oversight or regulation of testing companies. In addition, unproven or invalid tests can be misleading. For example, there could be insufficient scientific evidence linking a particular gene change to a given disease or trait, but that is not provided in testing company's report.

There is also the risk that genetic privacy may be compromised if a testing company uses acquired genetic information in an unauthorized way or if data is stolen. For example, testing companies could sell data to other corporations or research groups or law enforcement could request and gain access to genetic information. There have been cases reported (including a previously unsolved murder case in California) that were solved based on information on family relationships gleaned from direct-to-consumer testing. While this could be considered a positive, individuals need to be aware that their information can be compromised or released without authorization. Results of genetic testing could also impact one's ability to obtain life, disability, or long term care insurance. There is not yet enough data yet to know if this will be the case.

It is also important to note that in the United States, the FDA restricts DTC companies from offering products that function as diagnostic tests. Nonetheless in April 2017, the FDA did authorize 23 & Me to market genetic health risk tests for ten different diseases, including Parkinson's, Alzheimer's, Celiac Disease, and Goucher's. The risk assessment the company provides for these ten diseases is based on the presence or absence of a limited list of genetic variants in the sample, which are statistically higher and effective versus healthy people. But this alone is not necessarily causal of the conditions because not only do other factors, including lifestyle and environmental influences play a role, but these test are not genetically comprehensive.

All that the results can provide is some general type of health risk and it is essential for users to be aware of the limitations of the data and to understand how to interpret that data for personal use. None of the genes associated with these conditions are comprehensively sequenced nor are they analyzed with the detail that would be available from a diagnostic laboratory. In addition, the tests do not include all of the genes and variants that have been associated with these conditions. This is especially important because some diseases have multiple genes associated with them. So an individual (with concerns about a disease because of clinical symptoms or a family history) who relies on DTC testing, may be led to think that they are not at risk, when in fact they could have a variant of an uncommon gene associated with that disease that was not tested for.

An example of Gene Risk Analysis can be seen in 23 & Me's genetic health risk tests for Parkinson's. In their testing, they report just one variant in each of two genes (LRRK2 and GBA) which are both linked to Parkinson's phenotype or clinical presentation. But there are other known pathogenic variants in these two genes that they don't report and they do not report out changes in other genes known to be linked to Parkinson's disease like NCA and the Park2 and ParkN gene. The point that bears repeating is that DTC testing only looks at some of the more common or known pathogenic changes. It is not a comprehensive genetic risk assessment. This is in comparison to diagnostic tests, which are comprehensive, with analysis of the full coding sequences of all genes associated with a disease. These results may then be used by the clinician or provider to guide disease management or surveillance.

Raw Data Analysis: Although the FDA prohibits most companies from offering diagnostic genetic tests, some companies will provide, upon request, what is referred to as raw data. Patients can then pay separately for interpretive services by a third-party company. Here again, there are issues. A 2017 study that looked at third-party companies found that they operate by looking at publicly available databases (that are not considered accurate medical databases). The study also found that the majority of classifications in some of these databases are incorrect, resulting in, for example, the interpretation of some of these changes as pathogenic when they may just be benign variants or benign polymorphisms,

(meaning that changes in the gene are not disease-linked). These companies also assume that the raw data show true abnormalities rather than considering the possibility of false positives. The bottom line is that patients may be receiving incorrect interpretations, leading them to believe that there is cause for concern, when in fact, there may not be.

23andme made a statement in XXXX regarding the clinical utility of their testing. It says:

> "The test is not intended to tell you anything about your current state of health or to be used to make medical decisions, including whether or not you should take a medication, how much of a medication you should take or determine any treatment. And these carrier reports are not intended to tell you anything about your risks for developing the disease in the future, the health of your fetus or your newborn child's risk of developing a particular disease later in life."

To look at this in further detail, there was a 2018 study published in *Genetics in Medicine* by Ambry Genetics. (Ambry Genetics is one of the larger commercial clinical diagnostic genetic laboratories, a group which also includes GeneDx and Baylor Genetics Lab). Ambry looked at analyzed variants previously identified by DTC testing and raw data analysis in 49 patients between January 2014 and December 2016. Almost 92% of the patients were female and almost 74%were unaffected by disease (meaning not reporting disease and/or having no symptoms). Just over 53 percent were between 30 and 49 years of age. In about 45% of the cases, a single site analysis was ordered to confirm the raw data findings of DTC testing. In other words, the DTC tests showed that these individuals had some variant in one gene and the clinicians of these patients asked Ambry Genetics to look at this variant, in essence, to double check the work. (Almost 88% of the testing was for cancer genes; around 8% were looking at cystic fibrosis genes; and 2% each looked at connective tissue disorders and Familial Mediterranean Fever genes.) Ambry found that 60% of the variants were confirmed, which means that 40% of them were false positives. Of the false positives, they were most commonly found in the more common BRCA1 and 2 breast cancer genes. Not only did Ambry's study show a misclassification of the variants by the third-party interpretation services, but it also showed that some of the variants were found in the general population at frequencies much too high to be associated with disease. For example, one BRCA2 gene variant is found in 25% of the general population. So 60% of the variants that were found by this testing were actually present, but in 40%, they were completely false positives. That means that either the variants were not found at all or the variants that were present and had been classified as something of concern, were actually just population variance, meaning something that a good percentage of the population has as a variant that is not associated with disease.

In summary, this study demonstrates that raw data analysis conducted by a third party company based on publicly available non-medical databases shows:

- A very high false positive rate. (40% is not an acceptable rate for a test).
- A high incidence of discrepant classification or misinterpretation of variants from both the companies and third-party services.

Again, these genetic tests do not include comprehensive gene analysis so it is critical that clinical confirmatory testing be performed on any variants that are reported in the raw data provided by a DTC company prior to any changes in medical management.

The concern is about the number of people may make poor decisions based on false positive data. This includes not only people who do testing on their own but also those who have tests done at the suggestion of healthcare providers who are not familiar with the

limitations of this testing. Bottom line: It is critical that genetic testing be interpreted by somebody who not only understands data, but can also interpret it in the context of other factors such as individual personal and family medical history.

With regard specifically to mitochondrial diseases, like other diseases, variants in mitochondrial genes that may show up in at home testing doesn't necessarily confer disease. Diagnostic criteria for mitochondrial disease are fairly specific – very specific gene mutations, biochemical abnormalities, histological changes – and this information cannot be obtained from DTC testing and clinicians can't use it. Similarly, without access to the proper databases, raw data cannot be properly analyzed.

The American Society of Human Genetics, the American College of Medical Genetics and the NIH have each put out important statements regarding the pitfalls and the powers of this testing.

The American Society of Human Genetics stated:

> "Because of the fragmented regulatory environment for genetic testing in general, there is concern that the quality of the tests offered DTC may be inadequate. For a test to be of good quality, the laboratory performing it must be able to obtain the correct answer reliably, meaning that it detects a particular genetic variant when it is present and does not detect the variant when it is absent. A test's accuracy is referred to as "analytic validity". Further, there must be adequate scientific evidence to support the correlation between the genetic variant and a particular health condition or risk – the so-called clinical validity."
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> Claims made regarding DTC genetic tests may in some cases be exaggerated or unsupported by scientific evidence. Exaggerated or unsupported claims may lead consumers to get tested inappropriately or to have false expectations regarding the benefits of testing. Further, consumers may make unwarranted, and even irrevocable, decisions on the basis of test results and associated information, such as the decision to terminate a pregnancy, to forgo needed treatment, or to pursue unproven therapies"

The American College of Medical Geneticists said:

> "Due to the complexities of genetic testing and counseling, the self-ordering of genetic tests by patients over the telephone or the Internet, and their use of genetic "home testing" kits, is potentially harmful. Potential harms include inappropriate test utilization, misinterpretation of test results, lack of necessary follow-up, and other adverse consequences."

National Institutes of Health (NIH) released the following statement:

> "DTC genetic testing may promote awareness of genetic diseases, allow consumers to take a more proactive role in their health care, and offer a means for people to learn about their ancestral origins." However, "consumers are vulnerable to being misled by the results of unproven or invalid tests" and "may make important decisions about treatment or prevention based on inaccurate, incomplete or misunderstood information about their health."

Role of the Federal Government: As kits have become more popular, issues such as consumer privacy have arisen. In November 2017, Senator Chuck Schumer called on the Federal Trade Commission to regulate consumer DNA testing. Schumer cautioned that these kits put consumer privacy at risk because the DNA testing firms could potentially sell personal and genetic information because it's not really regulated. He was calling on the Federal Trade Commission to investigate and ensure that the privacy policies are clear, transparent, and fair to consumers. His statement is as follows:

When it comes to protecting consumers privacy from at home DNA test kits, services, the federal government is behind," Schumer stated. "Besides putting your most personal genetic information in the hands of third-parties for their exclusive use raises a lot of concerns from the potential for discrimination by employers all the way to health insurance. That's why I'm asking the Federal Trade Commission to take a serious look at this relatively new kind of service and ensure that these companies have clear, fair privacy policies and standards for all kinds of at home DNA test kits. We don't want to impede research, but we also don't want to empower those looking to make a fast buck or an unfair judgment of your genetic information. We can find the right balance here and we must."

Again, as a geneticist, that is certainly of concern to me. But my concerns are more specifically in alignment with those concerns that the NIH expressed in terms of the false utility of that information and making decisions. To my understanding, there' hasn’t been too much movement there.

Should an individual choose to use DTC testing, it is worth asking the following questions about the testing companies:

1. How are they positioning themselves? What are they offering?
2. What do they claim to analyze?
3. How do they validate their results or do they validate their results with standardized testing?
4. Who interprets their data?
5. What databases do they use?