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Cancer-related Genetic Testing and Counseling

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Gail Javitt, Esq., Law and Policy Director, Genetics and Public Policy Center, Johns Hopkins University: Implications of Home Tests and Direct-to-Consumer Advertising: I am going to talk about the policy implications of direct-to-consumer (DTC) genetic testing, particularly focusing on tests for cancer. DTC genetic testing actually means different things to different people. There is DTC that is advertising-only - to promote awareness and demand - and the test must be ordered by, and delivered to, a health care provider. Then there is DTC in which everything is DTC: Consumers can order the test without a doctor and get the results without a doctor. And finally, there is a hybrid, where consumers order, generally through a website, without their own health care provider, but there is a counselor and/or provider on the staff of the company that is providing the service who authorizes the transaction. The results go straight back to the consumers without going to their personal physicians.

The only example of advertising-only DTC I am aware of is that of Myriad Genetic Laboratory, which ran an ad campaign in Atlanta, Denver, Raleigh-Durham, and Seattle for BRCA tests in 2002 in order to raise awareness about the importance of early disease detection. There have been some studies about what impact that had. The CDC did a phone survey that showed increased awareness in the cities where the advertising campaign was piloted, but not necessarily more interest in getting tested (MMWR, 2004). There was also a Kaiser mail survey showing a small negative impact in terms of anxiety and an increase in inappropriate testing (Mouchawar et al., 2005).

But other than that example, the trend in DTC has been both advertising and sale of tests. There are many non-health related examples which I am not going to focus on: ancestry and paternity testing, for example. There are also tests that are health related and health profiling - for disease-related genes, predictive genes, and profiling, pharmacogenetic tests, tests for your heart health, your bone health, and even tests for athletic performance - which sport is right for you or should you just sit out gym.

Reporters frequently ask me whether DTC advertising is growing. Certainly in terms of the different types of tests that are being offered, it has grown since we started looking at it. Whether more people are getting tests is more difficult to know. Tests range from the typical genes that are well-accepted by health care providers - cystic fibrosis, factor V Leiden (a blood coagulation abnormality) - to athletic performance as I just mentioned, so they are all over the place. My favorite poster child for DTC is the baby gender test, to give you the extreme end of the spectrum, which purports to detect fetal gender as early as five weeks of pregnancy by detecting free fetal DNA in the mother's blood, which apparently works less well than when my grandmother used to look at our bellies and say boy or girl.

I went back and looked through the tests that are available and advertised in order to identify which ones are being offered specifically for cancer, and found four examples: BRCA testing, CyP2D6 testing for tamoxifen dosing, colon cancer screening, although not HNPCC, and nutrigenetic tests which make some cancer prevention-cancer risk claims. DNA Direct happens to be offering three out of these four examples (although the tests themselves are performed for DNA Direct by Laboratory Corporation of America), so I will be spending a little time on this

website so you can get a sense of what claims are being made.

This company offers testing for the BRCA mutations. The site offers a choice of full sequencing, multi-site testing and single-site testing. It says that full sequencing is appropriate when you are the first person in your family to test and you are not Ashkenazi Jewish. It says that multi-site testing looks at the three specific gene changes in the BRCA-1 and -2 genes that are associated with most cases of hereditary breast cancer in people of Ashkenazi Jewish ancestry, and that single-site testing is done when a specific BRCA gene change has been identified in your family. I'm not drawing conclusions on the merit of these claims. You are the doctors and experts, and you can draw your own conclusions.

The site provides an online questionnaire that the consumer takes in order to determine whether to test and what test is appropriate. I didn't try every single permutation, but I tried two. If you fill out the risk factor questionnaire saying no to every risk factor except that you are Ashkenazi Jewish, it recommends multi-site testing. That costs $695.

Dr. Greene: In the absence of any history of cancer either in yourself or your family?

Ms. Javitt; That's right, you say no to everything except Ashkenazi Jewish ancestry. You receive a personalized report. The company states that it has board certified genetic counselors on staff and provides post-test consultation as part of the service. If you fill out the online questionnaire answering no to every question except that you were diagnosed with breast cancer after age 50 – for example, no to any family history and things like that – the site recommends full gene sequencing because you are the first person in the family to be tested, and you don't have Ashkenazi Jewish ancestry. The cost for that testing is $3,456, including personalized report and phone consult.

There has been recent evidence that women with certain variants in their Cytochrome P450 2D6 genes had a shorter time to recurrence of breast cancer after treatment with tamoxifen, a hormonal therapy to reduce recurrence of some breast cancers. Recently an FDA advisory panel recommended a change in the label, saying that some woman with certain variants of 2D6 may be poor metabolizers of tamoxifen (to its active form, endoxifem) and thus at higher risk of breast cancer recurrence, and that genetic testing is available to help determine this. Studies have not shown that prospective genotyping for 2D6 prior to selection of therapy improves outcomes, and the FDA has not yet made any label change. Nevertheless, DNA Direct is offering 2D6 testing for women taking or considering taking tamoxifen, claiming that genetic testing can predict whether tamoxifen is likely to be an effective treatment. That is $300. My very cursory understanding is that there is a lot of controversy about these findings. They are from small studies, and clinicians are not yet routinely testing for this purpose, but yet a woman can be tested through a DTC route.

There is another site, Genelex Corporation, that offers an extended CyP panel for $1,000. This company is not making specific tamoxifen claims. Its claims are limited to antidepressant efficacy, i.e., that testing for CyP variants can aid in drug selection and dosing. AHRQ just came out with a report concluding there are a lack of data supporting a benefit for CyP testing for antidepressants. So you could, if you were a woman who knew about it, also get CyP2D6 testing

from this site as well.

My third example is for colon cancer screening, also offered by DNA Direct. This is a screen for 23 DNA markers that the company states are associated with colon cancer and precancerous polyps. These are mutations in the APC, K-ras, and P53 genes, one microsatellite instability marker in BAT-26 for HNPCC like colorectal cancer, and one long DNA marker. I filled out the online questionnaire as if I were an applicant who was under age 50 without risk factors; the response said I was at general population risk and recommended the PreGen-Plus as a non-invasive option for interim screening, either between colonoscopies or if colonoscopy is declined. That is $575. From facial expressions here, I gather that is not a persuasive case.

Dr. Greene: Is that a blood test?

Ms. Javitt: No, it is a stool test. They don't get too explicit about how you collect your sample at home.

Ms. Bennett: I ordered a kit once. It is a large box.

Ms. Javitt: The final example is the nutrigenetic test that makes diet and lifestyle recommendations based on testing a 19-gene panel. One of the groups is for antioxidant detoxification, looking at variants in six different genes. The claim is that these variants may reduce removal of toxins from the body that can be associated with cancer. Based on your profile, they recommend that you eat certain vegetables and fruits and avoid tobacco smoke or stop smoking. Some companies recommend certain supplements. Based on my looking at two examples, prices appear to vary between $300 and $400.

Nutrigenetic tests have gotten press recently because of a report that the Government Accountability Office issued last summer, and the hearing that was then held by the Senate Special Committee on Aging, looking at the nutrigenetic tests from four companies, although one lab was doing the tests for three out of the four companies. The GAO report concluded that the tests they purchased made misleading predictions that were medically unproven and so ambiguous that they were not providing meaningful information to consumers. On the same day, the Federal Trade Commission issued an alert that said, essentially, “buyer beware,” explaining that some of the tests lack scientific validity, and others provide results that are meaningful only in the context of a full medical evaluation.

Who is using these tests? This is a question we would really like to answer, but there are very few data. At the most recent American College of Medical Genetics meeting last week, a group from CDC reported on a 5,000-consumer survey and a separate survey of health care providers, both on nutrigenetic testing. Among consumers, they found 14 percent were aware of nutrigenetic tests, and 0.6 percent who had used them. Among providers, 44 percent were aware, 41 percent had never had a patient come to them asking about these tests, and 74 percent had not discussed results with patients. Nevertheless, the population estimate based on 0.6 percent is about two million. So even though it’s a small percent, a lot of people are apparently using these tests. CDC will go on and do a broader survey and refine their instrument to try to get a handle on who is using these tests. As far as the other DTC tests, we don't have much data about who is

using them; the companies have those data, but they are not necessarily sharing them.

To put this in context, the number of conditions for which there are genetic tests now exceeds 1,300, not just for cancer but overall, and continues to grow. DTC testing is just a method of marketing the tests. As the number of tests grows, the number of things that potentially could be out there direct-to-consumer grows as well. The gene test laboratory directory now comprises slightly over 600.

Let's talk about regulation. Is there government oversight of genetic testing? Not just DTC testing, but genetic testing more broadly. There is some, but there are lots of gaps. Who are the players who could, or are, or should be involved in overseeing genetic testing? They are at the Department of Health and Human Services at the federal level - FDA, CDC, and CMS. They each have a piece of the puzzle, but there are lots of pieces that are not under any of their jurisdictions. FDA, as you all know, regulates drugs, devices, and biological products as well as human tissue, and they are the device authority that is potentially in play when it comes to genetic testing. CDC serves in an advisory capacity to CMS over the implementation of something called the Clinical Laboratory Improvement Amendments of 1988, or CLIA, which gives CMS authority to certify all clinical laboratories and set standards for them, including quality control/quality assurance standards, and personnel requirements.

A clinical laboratory under CLIA is any lab that examines materials derived from the human body in order to provide information for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of, human beings. Genetic testing labs are clinical laboratories if the result is being returned to a patient, clearly. There is a basic group of requirements that all genetic testing laboratories must meet, including validation and documentation of procedures, personnel, and the like. Furthermore, because genetic tests are complex, the labs are considered high complexity laboratories by CMS. Most high complexity laboratories under CLIA are subject to something called a specialty area, where means there is a specification of quality control and personnel requirements, and, perhaps most importantly, proficiency testing requirements. That involves the laboratory analyzing test specimens that are sent to it to assess the accuracy of its determinations. However, there is not a specialty area for molecular and biochemical genetic tests, and there is no clear mandate under CLIA that genetic testing laboratories perform proficiency testing. CLIA also does not look at clinical validity. The regulations have been implemented to focus on laboratory performance, not tests for clinical validity.

The issue of CMS oversight for genetic testing oversight has been looked at for about ten years. The Genetics and Public Policy Center is not the first one to examine this. There have been recommendations from an NIH/DOE task force (1997) and from the Secretary's Advisory Committee on Genetic Testing (2000) for strengthening oversight at both the FDA and CMS level. CMS issued a notice of intent to develop a specialty area for molecular and biochemical genetic tests in 2000, and in April 2006 got as far as putting it formally on their regulatory agenda with a release date of November 2006. However, in September 2006, they announced that they would not be issuing a specialty area. At that point, we, along with two other organizations, filed what is called a petition for rulemaking formally asking the agency to issue a rule for a genetic testing specialty.

We wanted to know how the genetic testing labs were performing - maybe a specialty area really doesn't matter. We fielded a survey of clinical genetic testing laboratories (Hudson et al., 2006) and got responses from 190 laboratories. Only two-thirds of those surveyed reported participating in all available proficiency-testing programs, such as, for example, the formal program from the College of American Pathologists, which sends out test specimens and grades performance. In the absence of a formal program, there are informal ways such as sharing with another laboratory or splitting samples. We asked, if a formal program was not available, does the lab use some other method, and almost a quarter said they did not always perform proficiency testing using some other method. We also asked the labs what has been their most frequent type of error in the last two years, dividing it into errors that could be considered pre-analytical, analytical, and post-analytic errors, and a strong predictor of whether analytic errors were the most common was how much proficiency testing laboratories did, if they said 100 percent of the tests they offered or something less.

Dr. Greene: How did they know that they made an analytic error?

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Ms. Javitt: It is self reported error. Under CLIA you are supposed to keep records of errors you are aware of. Sometimes it is hard to know. The laboratory does not always find out.

I mentioned that FDA also has a piece of the puzzle. The agency regulates the components that laboratories use to make tests, general purpose reagents, and also a class of reagents that the agency has categorized as analyte specific reagents (ASRs), which they consider to be the key ingredient of an assay. Regulation does not mean clinical validity of that component is monitored in this case; rather, it is what is claimed for the component, whether it is made under good manufacturing practices, and is sold only to appropriate laboratories. In a draft guidance document, FDA has recently cracked down on the way the ASR provision has been used; the agency means it to apply only for single analytes. Some vendors have been combining their ASRs in labeling, instructing use of one ASR with another - that is, selling a test kit. A test kit is a package of reagents with labeling and directions for use that a laboratory can use to perform a test, in our case a genetic test. Test kits are also subject to FDA regulations. Those regulations involve more than just looking at labeling and Good Manufacturing Practices. FDA reviews the analytic and clinical validity of the test kit. Either premarket notification, which is like premarket review, or something more formal called the premarket approval application is required.

Only a few genetic tests, about five or six, have gone the test kit route and been approved by the FDA. Otherwise, of the more than a thousand genetic tests, the vast majority are what are termed laboratory developed assays or home brew assays. FDA has gone back and forth regarding jurisdiction over laboratory developed tests. Currently they are exercising what they call enforcement discretion and not looking at them, although they have recently issued a fairly controversial draft guidance document on a class that they have called in vitro diagnostic multivariate index assays (IVDMIAs). These have particular relevance for this discussion, because the first example of an IVDMIA was a test that claimed to determine whether a woman is likely to have a recurrence of breast cancer. The Oncotype DX assay is claimed to analyze the expression of a panel of 21 genes and predict the likelihood of recurrence of stage I or II estrogen

receptor positive breast cancer. FDA is concerned about this type of test, because it examines multiple signals and then uses an algorithm (which is not transparent to the clinician) to make a treatment decision. In view of this, FDA is considering the assay a test kit, even though it is developed by a laboratory and would traditionally have been lightly regulated.

Dr. Greene: Is this similar to FDA action against the OvaCheck proteomics assay?

Ms. Javitt: An IVDMIA does not have to be a genetic marker. It could be any type of marker where you take multiple signals and analyze them.
One can conceptualize these regulatory approaches toward home brew tests, home brew tests with ASRs, and test kits by using baking a cake as an example. If you buy the box of Betty Crocker cake mix off the shelf, and you make a cake, that is a test kit. The mix goes to FDA. If you are pooling the eggs, flour, and other ingredients together on your own, it is a home brew and FDA has no involvement. If you are using Hershey's chocolate (an ASR) with the generic ingredients (a home brew), FDA looks at the ASR. So, same test, different way of getting the test, vastly different regulatory structure.

Dr. Parkinson: And business model, I might add.

Ms. Javitt: Right, that is a good point. The home brew is under CLIA, but CLIA is looking at the kitchen, not at the cake. In the absence of a genetic testing specialty area, they are restricted in how they look at the kitchen. If it is an ASR you get kitchen inspection plus ASR oversight, and then finally if you are a test kit you get CLIA and FDA. These different degrees of regulation have implications for the cost of test development and pricing.

FDA, despite having a relatively low level of oversight for genetic testing, has started thinking about how genetic information can improve drug development and therapy and improve safety and effectiveness of drugs. The agency has issued several guidance documents, a final guidance on pharmacogenomics data submissions in 2005 and a draft guidance for pharmacogenetics tests and genetic tests for heritable markers in 2006. These have been primarily aimed at the drug side, requesting data about genetic markers that affect drug efficacy and safety. An IVDMIA draft guidance in 2006 looked at the device side of things, in an attempt to strengthen oversight.

How does the Federal Trade Commission fit in here? They are not a DTC test regulatory agency, but they have generalized authority to prohibit false and misleading claims, anything that creates an unfair or deceptive trade practice. They have not taken any enforcement actions against DTC companies. In one instance, we know that complaints were filed about the Baby Gender Mentor case, but other than the consumer beware document that I mentioned earlier, FTC has not intervened in nutrigenetics testing. There is a class action suit on Baby Gender Mentor, so maybe the tort system will help us here.

We mustn't forget about the states. They oversee the practice of medicine generally. Different states through their laboratory practice laws also regulate who can order a test and who can receive the test results. So that affects whether you can do DTC testing in various states. About half the states allow a laboratory to receive a sample directly from a patient and return the result. Further, on Baby Gender Mentor, New York State prohibits DTC testing and has sent letters to

Baby Gender Mentor (located in Massachusetts) warning against selling in New York. The company would be liable for fines every day. In practice, that is a very hard thing to enforce, especially when dealing with Internet commerce.

Two professional societies, the American College of Medical Genetics (ACMG) and the American Society of Human Genetics (ASHG) both have considered draft statements of policy on DTC genetic testing suggesting transparency or, in the case of ACMG, announcing that testing should be ordered, received, and interpreted by qualified health professionals. In theory, these societies could influence DTC practices.

When asked whether direct-to-consumer genetic testing is regulated, one needs to clarify: regulation of what? Regarding advertising product claims, that is the Federal Trade Commission's bailiwick. If it is a test kit, FDA would have some involvement. If it is about clinical validity, FDA evaluates it only if it is a test kit; CLIA does not. If it is about the laboratory, CLIA could establish a genetic testing specialty but has not. As the GAO report and the Senate hearing pointed out, some of the laboratories that were offering the DTC tests that came under scrutiny were not even CLIA certified, and there is not a transparent process for either doctors or patients to determine whether a laboratory they are using is CLIA certified. Whether labs can do DTC business, give a patient the results, get a sample from a patient without a provider intermediary - those are questions of state law.

Is DTC testing good or bad? There are arguments in favor of it and arguments against it, and I have tried to identify the issues. There is certainly a concern about false and misleading claims, and I have presented some examples. There may be a lack of counseling and context because there is no requirement that a company offering DTC tests provide counseling, although some do. There is the risk of inappropriate test selection, if the consumer does not have a provider or a counselor helping with that. An opportunity to get treated, for example, might be missed if the PreGen-plus test provided an assurance that there was no risk of colon cancer, and the patient skipped a recommended colonoscopy. There is concern about laboratory certification and test validity. There is also a concern about the potential to undermine the provider-patient relationship. For example, this could happen, if it hasn't happened already - a patient who gets the 2D6 assay might tell her oncologist that she feels she shouldn't be on tamoxifen. It's the wrong drug for her, and she wants a different drug because she is a poor metabolizer of CyP2D6. The provider may disagree. I think there is not consensus among physicians about whether this testing is clinically useful. Certainly, there is an opportunity for tension between patient and physician. Finally, we shouldn't forget about wasted money. Is it really necessary to spend $3,400 on whole-genome sequencing?

On the other hand, there are those that argue that DTC can increase consumer access to testing and give consumers more choice about what tests they get. It can also give them more information than they might otherwise have, and armed with that information they may seek treatment earlier. Perhaps an informed patient is a provider's best customer. Certainly an informed patient can improve the provider-patient relationship, and potentially, although it doesn't sound like it in some of the examples, testing costs might decrease if the clinician intermediary was eliminated. Privacy and confidentiality, I put on the borderline between the pros and cons. This is because some of these DTC sites make claims that privacy is more

protected through the Internet because results do not get in the medical record. As we heard earlier, there is a lot of fear about genetic discrimination. However, I question the premise that DTC testing necessarily is more privacy-protective. The HIPAA Privacy Rule specifically protects health information in medical records, and includes significant penalties for misuse. Consumers may not know very much about the company they are sending samples to over the Internet, nor what legal protections for confidentiality and privacy they have. In addition, if patients receive a worrisome result they are likely to take that to their clinician and so it gets into the medical record anyway.

So why doesn't somebody just pass a law? There are two bills being considered in Congress at the moment. One, introduced this past month by Senators Kennedy and Smith, gives FDA jurisdiction over laboratory developed tests and would require CMS to issue a genetic testing specialty. It also would require FDA to provide premarket review of tests sold DTC. Second, legislation that was just introduced by Senators Obama and Burr gives the Secretary of HHS a mandate to improve oversight, and would direct CDC to study the impact of DTC on consumers, among other things.

In summary, DTC is basically just a method of marketing a genetic test. A variety of concerns have been raised about it, but there are very few limits on its practice. It is also a good lens for looking at the state of oversight of genetic testing more generally, and the gaps that exist. I think we can all agree that we would like accurate information to diagnose, treat and prevent disease; that laboratories should be qualified; that providers and patients ought to have adequate information about genetic tests; and that we need a regulatory system that encourages doing a good job, rather than the current one, where the incentive is to do less and not to go through FDA. Overall, there is a need for risk-based regulation, because not every test is going to merit the same level of scrutiny. And there needs to be a mechanism for postmarket reporting so that we know when errors are occurring.

Dr. Scott Ramsey, Member, Fred Hutchinson Cancer Research Center: This is just to be a little controversial, but I will give you my economist's perspective on this. I think DTC and genetic testing are a little bit of a tempest in a teapot. While we all can find anecdotes with people doing dumb things with tests, in terms of a major societal impact I'm not sure that DTC is ever going to be a big problem. The reasons are two, and they have to do with barriers to this market. The one barrier on the supplier side is the cost of advertising. Anybody can get on the Web and it is very inexpensive to advertise, but we know that the uptake of that in our society as an advertising medium is pretty modest. The other approach is through mass marketing, like Viagra at the Superbowl, which is where you reach a lot of people, but the barriers to that are huge because the costs are huge. Even the biggest company in this whole field, which is Myriad, had a marketing campaign and spent millions of dollars. We haven't seen them do that again, and there must be a reason. They actually presented the data on their advertising at a genome conference that I attended a couple of years ago, and I asked one of their people, how many more people did you get from this for these tests, and they wouldn't tell me.

Ms. Bennett: They are planning another one.

Dr. Ramsey: But these are going to be one-off things. I think they are just very expensive, even

for a company of that size to undertake. The other barrier, which is not insignificant, is the cost to the individual. These aren't reimbursed by insurance in general, certainly not buying directly, where you bypass everything. This is not like buying clothes at Land's End. This is a very different product, and I think people have pause going to a website and buying it. So there will always be people who will buy this stuff, but whether it rises to the level of something that we should spend an extraordinary amount of effort to control, I'm just not sure right now.

Ms. Lochner-Doyle: I was intrigued with your pros and cons. Regarding the cons, I thought to myself, those are all true for regular genetic testing, not limited to direct to consumer testing. Just a comment.

Ms. Javitt: I think there is a commonality in these two points. I think we don't know what impact DTC is going to have, that is absolutely right. CDC is trying to get some data on who is using it and what kind of effect it has. It may wind up being small. But we have looked at it as a real tool for looking nationally at the flaws in genetic testing oversight more broadly, flaws which I think are affecting the public health and need to be fixed. So it is serving that role, in addition to just being an interesting phenomenon.

Dr. Ferrell, Research Scientist, City of Hope National Medical Center: Just like Dr. Ramsey, to be the devil's advocate in this conversation and probably out of my ignorance, I have two comments. The primary reason that this didn't seem to be a public health concern is the market issue. It is so expensive that there is not huge consumer demand What if next year, there was a new business plan that delivered a very inexpensive technology? Then suddenly this would be a whole different picture that might have real implications.

Second, in this country we still have significant problems of people getting cancer information and diagnoses early in the course of their disease. As this field is explored, is there a potential or an opportunity, if these companies are going to mount their million dollar campaigns to get their messages to the public about cancer, to send correct messages to the consumer about cancer. If DTC is part of our future, is there a proactive way to harness it that might help the things that we really care about in this field?

Ms. Javitt: I think the ASHG statement that is being worked on gets at that point: ‘don’t stop it entirely, but if we are going to do it, here are some guidelines for how to do it responsibly.’