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DECODING FDA DTC POLICY

The COMPLETE SERIES

The following is a compilation of five blog posts published between November 12 - 16, 2018. We have compiled them together here in a complete article for those who would like to read through the full content with minimal clicks.

In this article we digest some recent FDA movement in the direct-to-consumer (DTC) genetic testing space. This is a space that we work directly with several of our collaborators, so we felt it was an important area to highlight.

If you are interested in re-posting this article in your own blog, please do so - we simply ask that you include prominent links back to this original source and do not change the contents of the post itself.

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PART 1: PHARMACOGENETICS ARE HERE!

While many of us were heading out to dish out candy (or tricks) to local goblins and superheroes this past Halloween, the FDA rounded out their suite of De Novo reclassification orders on DTC genetic testing. The latest announcement adds Personal Genome Service Pharmacogenetic Reports (PGSPR) to the existing regulations for Carrier Screening and Genetic Health Risk (GHR) tests (including a specific case of Genetic Health Risk Report for BRCA1/BRCA2).

The full FDA classification order for these new Pharmacogenetic Tests can be found here. As has been the case for the past few years now - the company leading the way with these authorizations is 23andMe.

FDA regulations are about as fun to read as the foreign language instructions to your new Cuisinart mixer. So we have collected some of the best minds in the field to digest and summarize the key takeaways for those who do work in this area, and we have summarized what is going on in the field.

While the expansion of 23andMe's test panel was perhaps not surprising— the FDA added some intrigue to the story on the following day - November 1, 2018 - when they released two additional communications about pharmacogenetics testing. We'll return to those shortly, but first, let's summarize the new authorization...

The Pharmacogenetic Report Authorization

So what exactly did the FDA just authorize? The short story is this: 33 direct-to-consumer tests for variants located on 8 genes that are all linked to how some medicines work in your body.

The nitty gritty details are below — links will bring you to relevant entries in the NIH Genetics Home Reference where you can find even more detail.

Approved Genes/Variants:

- CYP2C19 *2, *3, *17
- CYP2C9 *2, *3, *5, *6, rs7089580
- CYP3A5 *3
- UGT1A1 *6, *28
- DPYD *2A, rs67376798
- TPMT *2, *3C
- SLCO1B1 (see "other disorders") *5
- CYP2D6 *2, *3, *4, *5 , *6, *7, *8, *9, *10, *11, *15, *17, *20, *29, *35, *40, *41

If this level of detail is too much - all you need to know is that most of these variant/gene references have something to do with how your body metabolizes certain drugs. This may mean (for someone with one of the variants) that certain drugs may not work as they do in others, resulting in your doctor potentially wanting to start you on a higher or lower dose, or change your existing medication or dosage.

In comparison with previous GHR DTC reports, these tests do contain a more extensive set of limitations. Consumers are warned that the reports do not describe whether or not a person will or will not respond to the specific drug, and they strongly warn that these reports are not a substitute for seeing your doctor, and that they should not be used to start, stop or change any course of treatment on their own. The FDA is limiting the report to "inform discussions with a healthcare provider", and not what action should be taken as a result of the test.

PART 2: WHAT ARE USER COMPREHENSION STUDIES? AND ARE PHARMACOGENETIC TEST REPORT REQUIREMENTS DIFFERENT THAN PREVIOUS FDA REGULATIONS?

What Are User Comprehension Studies and Why are they Required by the FDA?

Unlike tests that are overseen by health care professionals where a conversation may take place about the meaning of results, direct-to-consumer tests bypass the traditional patient-doctor relationship and deliver results directly to patients (or consumers). A well-known example of a direct-to-consumer test is a pregnancy test that one may purchase at any pharmacy or similar retail store.

The FDA is charged with identifying and reducing risks to consumers with such direct-to-consumer tests. To do that, they require test manufacturers to conduct "controls" or "special controls" prior to marketing a test for a specific purpose -- all designed to reduce risk. One common special control is the ***user comprehension study***. Such studies are designed to ensure that the information being presented in the test report is done so in a way such that the average consumer understands and interprets the results accurately.

User comprehension studies are defined as a special control in all FDA DTC authorization processes. Most recently, in the Genetic Health Risk (GHR) protocol, the FDA identifies risks to the user of obtaining these reports as including "incorrect understanding of the device and test system" and "incorrect interpretation of the test results". To help mitigate these risks, they propose special controls for the test manufacturer to take - Special Control #3 focuses on the comprehension of the test results.

Specifically, they require that naive, untrained users must be used to conduct comprehension testing. The testing must include sufficient numbers of cases and represent diversity of age and education level.

The user comprehension testing must evaluate a representative sample of the contents that are generated as the report, which must include a public facing website including test details, definition of terms, a pre-purchase page, a frequently asked questions page, technical details, as well as the test report itself.

The GHR authorization specifies that participants must be evaluated to ensure that they are capturing 90% comprehension on items in the following five domains (topics):

- Test limitations
- Test purpose
- Appropriate actions (next steps)
- Other factors that may have an impact on the test results
- Test results

According to the FDA, the details of what concepts should be included in the report within these domains is left to a "physician and/or genetic counselor that identifies the appropriate general and variant-specific concepts contained within the material tested in the user comprehension study."

For example - the ***purpose*** of the test is a domain that the FDA requires. However, they do not indicate what the specific purpose for the test should be. Using 23andMe's publicly presented example report for Parkinson's Disease, we can find several pieces of information that describe the purpose of the test. The concepts of two genetic variants, increased risk of developing the condition, as well as specific gene variants that the test looks for are examples of content that relate to the test purpose. The decision to include these concepts (and not others) was made, presumably, by a physician and/or genetic counselor who understands how to communicate these kinds of results to patients.

The FDA leaves the specific questions and methods for how to capture comprehension among these domains to the professionals (presumably to the expert questionnaire designers/researchers) involved in designing the study. However, they do provide some details that they feel are important things to consider in the design. We recommend you talk with someone who has experience in such designs to learn more about these details. However, if you would like to drink it directly from the FDA fire hose, most of these details above can be found on pages 20-22 in the GHR DEN160026 Reclassification Order.

User Comprehension for Personal Genome Service Pharmacogenetic Reports (PGSPR)

This brings us to the recent authorization for 23andMe's PGSPR. There is no difference in primary concept to the previous GHR protocol described above— however, one change in language does show up that may have an impact on those involved in user comprehension studies for these new reports.

Where the GHR authorization defines the domains of the special control user comprehension study (limitations, purpose, next steps, other factors, and results), the language used in the PGSPR authorization around user comprehension is that it must cover

"***all result comprehension concepts that are critical for safe use of the device***." They do not specifically reference the domains of comprehension previously used in the GHR protocol.

It is too early to tell what this may actually mean. More details may be revealed once the FDA Decision Summary on the PGSPR is released. The Decision Summary is a follow-up document that comes after an initial authorization and often includes more complete details that relate to the specific authorization given to 23andMe.

PART 3: THE NOVEMBER 1 WARNING SHOTS

The FDA Safety Communications

One day following the Personal Genome Service Pharmacogenetic Reports (PGSPR) approval release, on Thursday, November 1, 2018, Jeffrey Shuren, M.D., J.D. (the Director of the FDA's Center for Devices and Radiological Health), together with Janet Woodcock, M.D., (the Director of the FDA's Center for Drug Evaluation and Research) published a statement to warn "consumers about genetic tests that claim to predict patient's responses to specific medications." This statement specifically calls out tests that are being "marketed directly to consumers or offered through health care providers that claim to predict how a patient will respond to specific medications". They elaborate that "Tests that make such claims that have not been evaluated by the FDA and are not supported by prescribing recommendations in the FDA-approved drug label, may not be supported by scientific and clinical evidence and may not be accurate."

They specifically call out two examples where the FDA believes a genetic test can inform drug prescribing. The first is genetic testing for warfarin sensitivity to inform initial drug dosing. The second example described is the October 31, 2018 PGSPR 23andMe authorization. While warfarin sensitivity tests are typically ordered by the patient's physician, the PGSPR can be ordered by a consumer directly. The FDA points to a list of cleared and approved tests published here.

The FDA statement also cautions that "many" tests that are not approved and make claims of links between genetic variant and drug response that ***are not supported by the science***. FDA does not distinguish between PGSPR tests offered DTC and those ordered by a provider, implying that tests that physicians currently rely on are unproven.

It may be that the FDA is attempting to raise concerns (which they may or may not pursue later) in how non-DTC tests are being marketed. Or, this could be a warning to companies working under a 3rd party network physician model where physicians oversee the care/implementation of the test. Because consumers have a much more significant role in the identification and purchase of these tests (often online), the influence of the marketed claims may be getting the FDA's attention.

At about the same time as the letter described above, a warning was also issued by the FDA as an official "FDA Safety Communication" (release here). This is a more general statement from the FDA that supports and expands upon the letter. It claims to be aimed at raising patients and physician's awareness of the same issue.

One interesting item that captured our attention about this warning was that it extended the claim of the "problem" with unapproved genetic tests to third party software platforms that interpret previously collected genetic data. A recent paper in Genetics in Medicine raised questions about such platforms. Clearly the FDA is paying attention there as well.

The FDA Safety Communication does not introduce any new points about the problem in this communication — but it does extend a list of recommendations to patients, health care providers and laboratories, as well as test manufacturers.

The recommendations highlight one area where test manufacturers can focus. They suggest that a test may be authorized if the drug that is targeted by the genetic test already has FDA-approved label contents that reference genetic variant links. When such label contents exist - it seems possible that the FDA is suggesting that a test may be supported without additional authorization (or at least with a reduced number of special controls).

In reading this, we wondered whether any of the recent 23andMe tests overlapped with these previously existing and approved links. At this time, however, we just don't know. Given that 23andMe sought and obtained approval to market these tests, it is likely that these were new connections that were not previously established.

It will be interesting to monitor what comes next -- especially if any specific regulatory action emerges from these general warnings.

PART 4: THE PHYSICIAN/GENETIC COUNSELOR PERSPECTIVE

The National Society of Genetic Counselor's position statement on DTC testing from 2015 states that consumers have the right to make an informed decision on DTC genetic testing. As with other DTC tests based on SNP array technology, it is important that companies offering these tests are very clear when discussing their limitations. For instance, the 23andMe Personal Genome Service Pharmacogenetic Reports (PGSPR) panel is limited to those SNPs that are detectable by their array and is by no means an exhaustive list of all possible PGSPR variants within the genes investigated on this panel. It should also be noted that there are many PGSPR genes that are not being evaluated on this panel.

That said, the information consumers learn from this test could prove meaningful to their future health. For this reason, genetic counselors urge anyone who is considering this test to talk with their doctor or a genetic counselor either before or after purchasing a kit. Since PGx is still an emerging area of clinical genetics, many clinicians may not yet be comfortable discussing these results. Thus, it is ideal to start the discussion before testing and a genetic counselor is specially trained for such discussions. Independent networks of fully licensed genetic counselors and physicians who are experts in genetics like Genome Medical are now available in all 50 states.

There are groups outside of the FDA who are working hard to inform the public about genetic links to health risks as well as pharmacogenetics. The Clinical Pharmacogenetics Implementation Consortium (CPIC) publishes a list of guidelines.

PART 5: FINAL THOUGHTS

Commentary: Final Thoughts

Over the course of this week, we have covered a variety of related topics that arose from the recent FDA activity around direct-to-consumer (DTC) genetic testing. Because this is so new, much is yet unknown, so the best we can do today is speculate. However, we thought we would wrap up today with a few parting ideas to consider.

1. **If you are in the DTC genetic test business, get familiar with these rulings.**
   The big news for you this week is that there is now a pathway to pharmacogenetic reports. While this presents an obvious pathway for others, do pay attention to the small differences that seem to be emerging. They may well be significant.

2. **The FDA has come to maturity with a regulatory journey that started in 2010.**
   With the Personal Genome Service Pharmacogenetic Reports (PGSPR) authorization, the FDA has now completed what it started in 2010 when it issued its Warning Letter to 23andMe after they went to market with hundreds of tests. Eighteen years later, the FDA now has regulations in place to provide test manufacturers with a pathway to go to market with these tests.

3. **Consider using the FDAs guidance as a set of best practices in the development of genetic testing reports.**
   Whatever your role is in genetic testing, there now exists a framework that can be considered as a "best practice" for reducing risk to consumer/patients with these tests. Even if you do not currently fall under the FDA with what you are doing - it may not be a bad idea to use this framework to help guide what you do.

   Even physician ordered (non-DTC) test manufacturers may find it useful to conduct user comprehension studies - to ensure that once the report is in the hands of the patient and away from the medical professionals - the consumer is not mistaken when they pick the report up weeks or months later.

4. **If you are involved in providing software designed to interpret genetic data, start paying attention to this FDA space.**
   This is a new and growing field -- and the FDA has not raised it in previous DTC related rulings. But now that they have, expect it to be an area of focus. If you do provide such a platform, you may want to consider significant legal warnings about the platform being an entertainment or education only environment -- or consider proceeding through the DTC protocols to obtain FDA authorization.

5. **If you are in the healthcare profession, these letters may cause an inconvenience and potentially some confusion for you.**
   Patients will now be receiving more personal genetic tests than ever before, and the pharmacogenetic test will have warnings that indicate that the test cannot be used for any medical purpose. Get familiar with them and consider how you will respond when they show up.

By the way, for those who are really interested in this topic, which probably means ***you*** if you got to this final paragraph of this series, the FDA has a growing and well stocked page that details all of their DTC actions and positions (see it here).