Genetics inMedicine | COMMENT

Attention: Direct-To-Consumer patrons: Proceed with caution

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In this issue, Tandy-Connor et al. from Ambry Genetics (a fully accredited molecular diagnostic laboratory) share initial findings detailing their diagnostic experience in confirming sequence variants originally identified via Direct-To-Consumer (DTC) testing.[1] The variants in question were considered to be clinically significant based on indications from their DTC provider, or by extension an independent third party interpretation service. The first take-away from this report is that 40% of variants identified on a DTC platform were technically false-positives based on confirmatory testing performed by Ambry. If that does not catch your attention please reread the previous sentence: 40% of variants that were initially thought to be real are, in fact, not truly present based on targeted testing in a reputable clinical setting! How can that be? Does anyone think that 40% in this context is acceptable? Are the rules different for DTC laboratories than they are for diagnostic laboratories? Let's take a further look to see what can be collectively made of this information and how it has an impact on our intertwined fields of human, medical, and recreational genetics.

There is no doubt that many individuals believe they have certain unalienable Rights that include Life, Liberty, and the Pursuit of Genomic Information. For those concerned about how different individuals absorb genetic information and what DTC companies intend to accomplish with their massive data sets that is a different conversation. The old adage that the train has already left the station when it comes to what genetic consumers expect is the reality of the world we live in. That said, consumers expect the quality of the data in question, no matter its origin, to be accurate—what they decide to do with it is their own personal business. Going even further beyond this aspect, let's not forget the larger societal concern regarding the potential negative impact of high-volume, low-value DTC testing has on the medical system as a whole.[2] Moreover, while the DTC community is convinced that they are doing all of us a favor with this medical model, there are many elsewhere that are not even remotely confident that this is the most appropriate method to disseminate information with potentially important medical consequences.

But let's face it, occasional misses due to technical reasons happen as do user errors and clerical mistakes that unfortunately lead to false-positives and false-negatives. Moreover, to be clear, this is not a phenomenon limited to only laboratories performing genetic studies. It should also be clearly stated that some DTC labs are likely better than others, and before casting dispersions on all DTC facilities as a whole more information needs to come to light. Labs continually strive to do better by implementing quality improvement measures to avoid making the same recurrent mistakes. Are we perfect? Absolutely not. But a 40% false-positive rate is scary stuff, regardless of the context. If a study found that any given diagnostic lab had such a missed call rate that would be quite an indictment. That lab's reputation would be significantly downgraded for the foreseeable future and you can bet their referral volume would be influenced. Am I reaching too far on this, given the relatively small sample size of the Ambry study? Maybe. Am I being overly provocative? I hope so. The reason being is that each of us in our own way contributes to the overall reputation of the field of genetics. If DTC-based testing is ultimately deemed to be casually interesting, but not overly reliable that undermines a lot of the other good work being done as the field strives to make Personalized/Precision Medicine a greater reality.

The relatively modest sample size of the study by Tandy-Connor should give us pause to question why this concern has not received more attention sooner. Perhaps, the volume of testing being performed is not as great as some of the companies would like us to believe? Alternatively, maybe individuals using DTC testing are, in general, more intrigued about things like their alcohol flush reaction or caffeine sensitivity than they are about more serious health-related findings. Maybe there is something unique about the genes or variants involved with these false-positives? If so, it's not immediately apparent, but it should be noted that three variants involving three different genes had more than one false-positive in this reasonably small cohort. Are each of the false-positives with greater than one case possibly attributed to the same DTC laboratory? If so, is there a technical explanation that predisposes these particular variants to incorrect calls? It's not possible to discern this level of detail from the current study, but hopefully in time this type of information will become more apparent. And if this is not concerning enough, add into the mix the frightening notion that many consumers may simply take their DTC results at face-value while remaining oblivious to the need for further

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clinical validation (despite the not-so convenient disclaimers provided).

In the meantime, consider the following: what if only 1% of all DTC users with data in-hand have a clearly pathogenic alteration in a well-defined gene that predisposes them to a significant health concern. This equates to 10,000 individuals per million tested that have a variant that warrants confirmatory testing (assuming the DTC users get that far with their data). If 40% of those variants turn out to be false-positives, there should be some explaining to do. The problem is, the companies providing DTC testing will say "it's not our problem—talk to someone else—we warned you this could happen". The historically paternalistic genetic establishment side will say this sounds like a classically modern case of "sorry-not sorry". All sarcasm aside, most will agree that all parties can do better on this front so let's allow the evidence to speak for itself. Other large commercial laboratories are the most likely to have the greatest collective data/experience to replicate or dispute the results from Tandy-Connor and colleagues. If the trend continues, it should be possible to investigate in finer detail to determine the true source of these false-positives. To be fair, if there are high-quality DTC performers, they certainly do not want their reputations tarnished simply by being lumped under the DTC umbrella when there are likely labs of questionable quality generating significant amounts of data with sub-optimal reliability.

Another finding, of equivalent concern, is the fact that some variants were designated as being "increased risk" alleles by a third party interpretive service, although Ambry along with other strong supporting evidence indicate that they are benign. Variant interpretation continues to be a challenging area, but when clinical providers have a strong consensus for any given alteration and a questionably qualified service provider has a different opinion something seems amiss. It's clear that most independent third party vendors rely on automated variant interpretation algorithms and by playing the odds they are much more likely to be right than wrong. Even so, this oversimplified strategy does not make any sense when so much is on the line when considering the clinical relevance for many of these variants. The ACMG guidelines for variant interpretation have been given significant attention and much has been done to improve the field's collective ability to interpret rare variants, but many clearly benign alterations continue to be called pathogenic or associated with "increased risk" even though the evidence is to the contrary. Guilt by association is no longer sufficient—third party services please take note.

In the end, it is probably fair to say we all want the same things when it comes to genomic information. First, we want it to be accurate. This often remains easier said than done for numerous technical reasons, which means for the time being we all need to remain vigilant in terms of accepting and understanding different sources of data. Simply put, not all data are created equally. Secondly, we want as much consistency as possible in interpreting the significance of variants, especially when they are found in genes that strike immediate fear when discussed. The current report is a stark reminder that the clinical providers will continue to be the voice of reason when it comes to confirming and interpreting variants of questionable significance. A common theme these days is: "If you see something, say something". It is probably fair to say that this should hold true when it comes to inaccuracies that arise from genomic testing—whether it be via DTC or otherwise. Hopefully, the report by the Ambry group will inspire others to shed additional light on this subject in future reviews. Doing so will give everyone a chance for themselves to understand the truth of what happens when clinically significant variants are brought to light via DTC-based testing.

CONFLICT OF INTEREST

The author declares no conflicts of interest.

REFERENCES

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