CASE PRESENTATION

Case Report: Direct Access Genetic Testing and A False-Positive Result For Long QT Syndrome

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Abstract We report the case of a woman who pursued direct access genetic testing and then presented with concerns regarding a positive test result for Long QT syndrome. Although the result ultimately proved to be a false positive, this case illustrates that costs associated with follow-up of direct access genetic testing results can be non-trivial for both the patient and for health care systems. Here we raise policy questions regarding the appropriate distribution of these costs. We also discuss the possibility that, when confronted by a direct access genetic test result that reports high risk for one or more actionable diseases, a family physician might feel compelled to act out of a desire to avoid liability, even when information regarding the accuracy and validity of the testing were not easily accessible. This case outlines lessons that can easily be translated into clinical practice, not only by genetic counselors, but also by family physicians, medical specialists and members of the public.

Keywords Direct access genetic testing · False positive · Health economics · Public policy · Long-QT syndrome · Secondary findings · Testing accuracy · Positive predictive value

Introduction

Long QT Syndrome (LQTS) is an inherited cardiac arrhythmia syndrome characterized by an increased susceptibility to syncope and sudden death, which manifests as a prolonged QT interval on electrocardiogram (ECG). Clinical diagnosis is based on personal medical history, family history and on the ECG findings of a QT interval ≥ 480 ms. Functional mutations in cardiac ion channels can delay repolarization of the cardiac muscle (Morita et al. 2008) and thus confer a susceptibility to arrhythmias. Notably, the first presentation in an affected family may be sudden death, with no prior signs or symptoms, and these deaths commonly occur in the first three decades of life. There are 15 genes associated with long QT syndrome (Nakano and Shimizu 2015). LQTS has variable clinical expression and penetrance; up to 40 % of gene carriers may have a normal QT interval, so individuals who are heterozygous for a known pathogenic mutation may be symptom-free with a normal ECG, but still be at risk for sudden death (Gollob 2011). Individuals who are clinically unaffected, but have a proven pathogenic mutation for LQTS, are recommended to pursue cardiac surveillance for early detection of the LQTS phenotype (Ingles et al. 2011); prophylaxis may include implantable defibrillators, which are considered by many centres to be superior to pharmacoprevention (Pundi et al. 2015).

Direct access companies offer genetic testing at a cost to the individual consultand, without facilitation from a medical professional. This practice has made genetic testing much more widely available than it was previously, and the National Society of Genetic Counselors has enacted a policy regarding testing (NSGC Headquarters, 2015). In the context of traditional clinical testing, careful distinctions are made between “primary findings” (defined as those directly related to the indication for testing) and “secondary findings” (SFs, defined as those considered reportable and potentially actionable, but...
not directly related to the indication for testing). Importantly, direct access testing offers a new and different context than traditional clinical testing. The reasons why an individual might pursue direct access testing are highly heterogeneous, including personal curiosity, early uptake of technology, interest in family/population history, and concerns regarding current or future health status (Su 2013). There is currently no consensus regarding whether the terms “indication,” “primary finding,” and “secondary finding” even apply in the situation of direct access genetic testing. Nonetheless, if the testing method interrogates genes of medical relevance, then medically actionable results can be generated. The possibility of such (apparently) actionable results may or may not have been anticipated by the direct access customer. The first action to be taken may appear straightforward, namely to consult a licensed health care practitioner regarding the result. The practitioner then faces three choices: 1) refuse to act on the result(s), on the grounds that the data are not clinical grade, 2) accept the results without additional confirmation, and proceed with subsequent testing and interventions, or 3) request specific clinical-grade confirmation prior to any additional action. Option 1) treats all direct access results with suspicion; many practitioners may feel uncomfortable with this option because of an existing therapeutic alliance with the customer/patient, and because some fraction of direct access results may represent true positive results that are actionable. By taking the result at “face value,” option 2) treats all direct access results as true positives, even though the test or the provider may not be certified by an accredited body. The following case report outlines the experience of a woman who received a result from her direct access genetic testing that was unrelated to the primary reason for her original health-related curiosity. The variant was predicted to place her at highly elevated risk for developing LQTS. We discuss the patient history and the investigations she underwent subsequent to the finding but prior to Sanger validation of the result, which determined it to be a false positive. We believe that specific clinical-grade confirmation should be sought prior to any additional action from a direct access result (option 3), and discuss how such additional testing might be accommodated in publicly-funded health care systems.

Transcription

Because the classification of a finding as primary or secondary can be influenced by the rationale for the testing in the mind of the requestor (whether physician or not), and because the consultand had had a number of tests performed at a variety of centers that were not linked by a common medical record, three of the authors (SP, SH and WG) interviewed the consultand over the telephone to capture the details of the process. Highlighting the consultand’s rationale for testing is important in the direct access genetic testing realm. This knowledge would assist in determining whether the results are primary (or pursued), or are secondary. This interview was transcribed verbatim and is included in the Supplementary Materials (Supplemental Material S1).

Case history

Our consultand is of Zimbabwean, South African, and European descent and was in her late 40s at the time of testing. She was introduced to the idea of direct access genetic testing through a marketing presentation made to a leadership organization of which she was a member. She was in good health when she pursued the testing, and said that her objective was to gain more information on her own future health risks, in addition to those of her children. Specifically, she was concerned about her own risk for Alzheimer disease and breast cancer, due to a family history of these diseases in two of her grandparents. In this context, then, variants predicted to confer risk for these two diseases could arguably be considered “primary” findings. Similarly, variants predicted to confer risk for other diseases could arguably be considered “secondary” findings. Some of her other family members also took up direct access genetic testing, including her husband, her two daughters, and her father-in-law. She did not consult with a health professional prior to the testing (Supplemental Materials S1). Subsequent review of her family history revealed that the onset and course of these illnesses was typical of “polygenic-multifactorial” disease, i.e. not sufficiently early or atypical as to expect a strong risk of identifying one or more rare DNA variants of large effect on risk.

Whole genome SNV analysis was completed through a genetic ‘Wellness and Longevity Panel’ run on a proprietary Nexus DNA Chip and described by the company as “Full Genome Analysis.” Worthy of note is that the genetic testing laboratory was also reported to be CLIA-certified. The report issued by the company to the consultand in November of 2011 described 895 SNVs and 10 haplotypes associated with 1217 syndromes, diseases and traits. The report also stated that a p.R243C mutation in KCNQ1 had been identified, which carried an increased risk for LQTS (as reported in 15 published studies referenced in the report). The result was presented with the explicit recommendation for her to have a comprehensive workup for LQTS, and to have her medications reviewed to ensure that none of them had negative side effects when combined with LQTS. The report also stated that she was at an increased risk for heart attack (either coronary artery disease or myocardial infarction), predicting a 61 % chance compared to the general population risk of 25 %.
Medical History

After learning of her results, she became quite anxious with the magnitude of the risks quoted to her for her own health, and also became concerned about how to discuss them with her family (including her two children). After consulting her family members about her risks for sudden death, and about the potential for cascade testing, the consultand pursued cardiac screening (Supplemental Materials S1). She was referred to a cardiologist in 2013. History taking at that time found that she had experienced some shortness of breath and lightheadedness, as well as infrequent chest pain under her rib cage. She had never fainted, but did report experiencing palpitations and lightheadedness during long walks and runs. She was on no medications, and had had an uneventful surgery on one of her elbows. There was no reported family history of syncope, pre-syncope, palpitations, sudden infant death syndrome (SIDS), or recurrent pregnancy loss. There was no information on her paternal family history, other than death syndrome (SIDS), or recurrent pregnancy loss. There was no reported family history of syncope, pre-syncope, palpitations, sudden infant death syndrome (SIDS), or recurrent pregnancy loss. There was no information on her paternal family history, other than a paternal grandmother with late-onset breast cancer. Her two daughters, aged 19 and 10 years, were in good health. She recalled that her elder daughter becomes lightheaded when she stands up rapidly. However, neither of her daughters’ genetic direct access results had identified the mutation flagged in the consultand’s report.

Cardiac Investigations

Physical exam at her first visit to a cardiologist found a heart rate of 54 BPM, blood pressure in the right arm 90/60 mmHg and left arm 92/64 mmHg, a normal apex with no thrills or heaves, normal S1 and S2 heart sounds, and no evidence of S3, S4 or murmurs. Her lungs were clear, her pulses palpable and equal bilaterally, and no carotid or abdominal bruits were heard. An ECG earlier that year had found a normal sinus bradycardia at 52 BPM, and a corrected QT interval (QTc) of 421 milliseconds (ms). An ECG at the clinic that day also found a normal sinus bradycardia at 54 BPM with a QTc of 405 ms with no T-wave abnormality.

An exercise stress test later that same year found a normal rhythm and normal ST segments. Echocardiogram found normal heart structures. A third ECG showed a QTc of 422 ms, R wave of 75 ms, sinus rate of 67 ms and QRS of 80 ms. At a second exercise stress test her resting heart rate of 76 BPM rose to 179 BPM at peak exercise, with a QTc of 422 ms after 4 min of recovery.

Later in 2013, she was referred to the British Columbia Inherited Arrhythmia Program, where she saw a cardiologist and genetic counselor, who arranged for Sanger sequencing to validate the variant. Clinical-grade genetic testing in a CLIA-accredited laboratory in 2014 reported that the putative R243C mutation in KCNQ1 was not, in fact, present in the consultand’s DNA. Though she was relieved once the putative mutation was confirmed to be absent, she then began to question the accuracy of the remaining direct access genetic testing results and of those of her family members.

Discussion

Much debate has been sparked around disclosure of direct access results (Hogarth et al. 2008; Roberts and Ostergren 2013); as the resolution of these tests improves over time, the potential for benefits and harms would be expected to increase. Some companies restrict their test offerings to markers for genetic-relatedness, whereas others appear to market their tests as having health benefits, including risk assessments for disease (Myers 2011). Some direct access genetic testing companies have even made forays beyond single nucleotide variant (SNV) and gene panel analysis to include whole exome sequencing (van den Berg et al. 2014). Testing at this level of detail does have the potential for uncovering rare variants of large effect on disease risk. If truly present, such mutations would be considered actionable in a health care context, even if they were originally identified outside of such a context.

However, one nuanced aspect of testing that may not be appreciated by direct access customers is the epidemiological relationship between population prevalence, test positivity and actionability. As the population prevalence of a particular disease decreases, the proportion of apparently positive test results that are true positives will also decrease (i.e. the false positivity rate increases and positive predictive value diminishes). So if a test integrates genes of medical relevance, and if a large proportion of the test’s consumers are at a low a priori risk for a pathogenic mutation, then most results that flag a potentially actionable pathogenic mutation will be false positives. The prior probability of monogenic diseases is much lower in the general population than in the subpopulation with “traditional” genetic risk factors (such as a family history of a monogenic disease) that would be considered eligible for physician-ordered genetic testing. In the setting of clinical testing for LQTS, guidelines and protocols surround which family member may be the best to test, and for which conditions testing is indicated, based on family history (Ackerman et al. 2011). The prior probability of a potentially actionable SNV being found by broad and high-resolution genetic analysis among individuals not selected specifically for monogenic diseases has been estimated to be 1–2 %, depending on ancestral background (Amendola et al. 2015). The prior probability of a potentially actionable SNV being found in someone eligible for physician-ordered clinical genetic testing is between one and two orders of magnitude higher than this. Such differences in prior probability of pathogenic allele(s) lead to an important difference in the risk-benefit ratio for clinical genetic testing versus direct access genetic testing.
particularly in the situation of adult-onset dominant conditions that may be asymptomatic at time of testing.

Unless the customer specifically pre-specifies a thoughtful question that he or she wishes to have answered by the test, it could be argued that all results of a direct access test are actually secondary findings (SFs). The American College of Medical Genetics and Genomics (ACMG) guidelines on reporting SFs outline that these should be reported when they could be verified by other diagnostic means and have medical intervention (Green et al. 2013). Frequently-cited reasons to refrain from disclosing SFs outside of the clinical setting include the potential to cause psychological harm, and the possibility that non-clinical providers (such as private companies and research settings) may lack expertise in the relevant diseases (Christenhusz et al. 2013; Kohane et al. 2006; Lohn et al. 2013). Thus, independent clinical-grade confirmation of any direct access testing result (ideally on a second sample) is advisable, and is certainly necessary for actionable results. Such confirmation should be completed swiftly, to avoid causing undue anxiety and unwarranted medical costs by reporting of false positive results. Had validation of the putative mutation been pursued prior to the report being issued, the consultand’s additional medical costs and anxiety would have been avoided (Supplemental Material S2) (Aviva Health UK 2012; Centers for Medicare and Medicaid Services 2015; Fair Health Consumer Cost Lookup 2015; Federal Executive Council of the Commonwealth of Australia 2014; Medical Services Commission 2014). The company that provided the testing described here has since declared bankruptcy in California Central Bankruptcy Court (Company Bankruptcy Information for Existence Genetics, LLC., n.d.). However, new companies are still entering the direct access genomics market, so the risk of similar false positive results remains (Sanfilippo et al. 2015; Vrecar et al. 2015).

The United States Food and Drug Administration (FDA) has issued warning letters to a variety of direct access providers, and went further to issue a full “cease and desist” order to a provider because of concerns over the true validity of direct access SNV panels that might be interpreted by the general public as having medical utility (Gutierrez 2013). The testing performed on our consultand was an SNV panel; although it incorporated genotypes at multiple SNVs associated with disease risk by Genome-Wide Association Studies (GWAS), it also appears to have included rare SNVs of large effect on risk (a.k.a. pathogenic mutations). Because the effect on risk for each GWAS-derived variant is small, a false result for any particular common SNV should have a minimal effect on the overall reported risk for disease. However, concerns regarding analytical validity become more prominent when rare SNVs of large effect on disease risk might be reported out, as was the case here.

Direct access genetic testing companies operate in a number of countries, but regulations differ surrounding the provision of test results without prior assessment and referral by a health care provider. Many European jurisdictions ban genetic testing without the involvement of a medical professional, whereas the United States FDA places regulations around direct access genetic testing and monitors the market (Borry et al. 2012). In Canada, there is no legislation in place, although the need for such has been recently highlighted (The Education, Ethics and Public Policy committee of the Canadian College of Medical Geneticists 2015). Express or implied claims of health benefits from direct access genetic testing are still largely unregulated in many jurisdictions. At this time, direct access genetic tests are still being advertised for “inherited risk factors and how you might respond to certain medications” and “to better manage your health and wellness” (23andMe-UK 2015; 23andMe-Canada 2015). Some companies explicitly encourage customers to approach their family physician with questions after they receive their results, so recipients of direct access results may misinterpret them as being equivalent to medical testing, and may pursue further testing and interventions as follow-up (Kaufman et al. 2012). Care providers (especially primary care providers with little formal training in genetics) may have difficulty determining whether the consultand’s variant(s) are variants of unknown significance (VUS), pathogenic variants, or genetic markers with a weak association to disease, and they will almost certainly be unable to appraise the validity of risk calculations without a thorough understanding of the algorithms used by the direct access genetic testing provider. In the case history presented here, health care practitioners assumed clinical validity of a direct access result (option “2” in the Introduction). Acting on this assumption, they ordered a variety of follow-up diagnostic tests. The financial costs of these tests were borne by the public health care system in which the consultand resided, and we have attempted to quantify these (see below and Supplemental Material S2). We do note that without private or public health insurance, these costs might well have been incurred directly by the consultand. We present her own assessment of the emotional costs in Supplemental Material S1.

In countries with a publicly funded healthcare system like Canada, the United Kingdom and Australia, the costs of any tests ordered by physicians to follow up on direct access genetic results will be borne by the public insurance provider. Furthermore, even the process of having a licensed health care provider look at the direct access genetic test result(s) to decide on actionability places some additional burden on public resources. We estimate the actual costs associated with the cardiac follow-up and genetic validation, for this woman to have been approximately $1200 USD. Our estimates are based on Canadian billing codes, though projected costs would vary by jurisdiction were a similar situation to occur elsewhere (Supplemental Material S2). Supporters of direct access genetic testing claim that the health risk estimates should increase adherence to healthier lifestyle choices. They also claim that any increase in costs (e.g. for lifestyle advice, lipid profiles and glucose tests) would be minor and are likely to be offset by long-term benefits (Kaufman et al. 2012). To our
knowledge, downstream costs associated with direct access genetic testing are not tracked systematically in any jurisdiction. However, the type of detailed studies that are likely to be ordered to work up a high-penetration variant of major effect on an organ system are neither inexpensive (e.g. specialist consultations, MRI) nor risk-free (e.g. CT scans, endoscopy). Because of the variety of direct access genetic testing companies and tests on the market, and the variety of practitioners a recipient might consult after-the-fact (e.g. nutritionist, nurse, counsellor, family physician, specialist, etc.), it is difficult to estimate the systematic costs of followup of direct access testing results. Given that some direct access genetic testing companies derive income from a service that then “offloads” subsequent costs onto other payers, publicly-funded health care systems and private insurance companies could consider refusing coverage for the evaluation and follow up of direct access genetic test results (Bloss et al. 2011). However, an ethically-motivated practitioner is likely to feel a strong obligation to provide some level of assessment and care if an actionable mutation is reported to them by an anxious consultand, even if the test result was not issued by an accredited laboratory. Furthermore, a practitioner might have significant concerns about liability for failure to act on a genetic direct access testing result that, if true, flagged a serious and treatable risk for disease or death. Ordinarily, a mutation that predisposed to cardiac arrhythmia would require immediate follow-up with cardiac screening, and it is likely that few practitioners would feel truly comfortable dismissing the lab result described here with no further action.

This case illustrates the need for policies to be developed regarding the followup care for recipients of direct access genetic testing results. We believe that an ethical solution must protect patients by minimizing the risk that a true positive result (whatever its source) might be ignored. At the same time, practitioners must be able to allocate time and other resources effectively; they cannot be expected to field questions regarding an ever-changing variety of direct access tests, especially if proteomic and metabolomic tests enter the consumer space alongside genomic tests. Furthermore, publicly-funded health care systems can and should take proactive steps to maximize cost-efficiency; extensive follow-up of direct access test results that are not clinically validated is not cost-effective. As we outline above, most positive test results from a low-prevalence population will be false positives, as was the case here.

We believe that the most cost-effective and ethical solution would be for clinical validation of any potentially actionable direct access genetic testing result to be performed on a second sample by an independent CLIA-certified laboratory, prior to any further investigations being completed. The presence or absence of individual DNA variants can now be confirmed in a variety of clinically certified labs worldwide at a reasonable cost (typically $150–$350 US, Source: www.Genetests.org). Clinical confirmation typically includes interpretation of the variant’s pathogenic status, to the extent that is known. The price of such clinical testing is in a range similar to that of the direct access tests; upward pressure on public health care costs could be avoided by having the consultand pay privately for the clinical confirmation for any rare variant for which follow-up testing would be sought. Follow-up testing (such as EKGs, exercise testing, etc. in cases similar to this one) would only be ordered in the case of confirmed true positive results.

**Role of the Genetic Counselor in Direct Access Genetic Testing**

The exact role for genetic counseling services within the direct access genetics context has yet to be defined, although there are many points in the process at which counselors might be involved—either through the companies themselves, or post-result disclosure at the consumer’s own local clinic (Harris et al. 2013; Hogarth et al. 2008). Genetic counseling has been found to benefit consumers who are trying to understand their genetic direct access results (Weaver and Pollin 2012). However, this is unlikely to be pursued prior to testing by all direct access consumers (Darst et al. 2013), and the subset who are particularly attracted by marketing that emphasizes rapid turnaround of results may be even less likely to seek prior counseling. Counseling should be strongly considered prior to pursuing testing, for discussion of the types of conditions the direct access genetic testing panel interrogates, and to prepare in advance for various possible results. Post-test counseling would aid the consultand in interpreting the result, and in comprehending the implications and advisable follow-up (such as clinical validation and cascade testing among family members).

Had genetic counseling been available to our consultand earlier in the process, the need for Sanger validation would likely have been appreciated early on, and the financial costs to the system and psychological costs to the family would have been reduced appreciably. This case illustrates that validation of any potentially actionable direct access genetic result should occur early in the process, regardless of who ordered the test and definitely prior to other action being taken. We appreciate that expecting consumers to cover the cost of clinical validation prior to follow-up appointments will not be without controversy, but we believe it could be implemented without extreme cost to the consumer, thereby improving the cost-effectiveness of the public health system.

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**Conflict of Interest** Author Predham, Author Hamilton, Author Elliott and Author Gibson declare that they have no conflict of interest.
Informed Consent  Informed consent was obtained from the participant for being included in the report. Prior to first submission, the consultand was shown the transcription and manuscript to be published.

Human and Animal Rights  No animal studies were carried out by the authors for this article.

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**Comments**

This manuscript has been submitted solely to the Journal of Genetic Counseling and has not been published elsewhere. The manuscript’s contents have not been previously published and are not anticipated to be published elsewhere.