Written evidence submitted by the British Pharmacological Society to the Science and Technology Select Committee inquiry on Commercial Genomics

About us

The British Pharmacological Society (BPS) is the primary UK learned society concerned with research into drugs and the way they work. The Society has around 4,000 members working in academia, industry, regulatory agencies and the health services, and many are medically qualified. The Society covers the whole spectrum of pharmacology, including laboratory, clinical, and toxicological aspects. Pharmacology is a key knowledge and skills base for developments in the pharmaceutical and biotech industries, and is therefore fundamental to a thriving UK industry and R&D. The Society publishes three scientific journals: the British Journal of Pharmacology, the British Journal of Clinical Pharmacology, and Pharmacology Research and Perspectives.

Key points

1.1 This submission outlines the safeguards we think need to be put in place to protect individuals who have genomic tests. These safeguards are related to:

A. False positive and false negative results
B. False reassurance
C. Inaccurate interpretation and limited sensitivity
D. Indication-driven versus preventive screening
E. Benefit versus harm of genomic screening of healthy individuals
F. Privacy and confidentiality
G. Wider impact on NHS services

1.2 The Society would be happy to support the inquiry going forward. For further input, please contact: Natalie Harrison, Education, Engagement and Policy Officer, e. natalie.harrison@bps.ac.uk, t. +44 (0)20 7843 0493.

A. False positive and false negative results

2.1 Genomic tests are far less deterministic than is generally believed. A recent study found that 40% of variants reported by direct-to-consumer testing companies were incorrect[1]. As such, more onus should be put on test providers to ensure that the reporting and interpretation of results are transparent and clear, and especially to inform on false positive and false negative rates of testing. Inaccurate information provided by these companies may lead to major impact on the NHS (eg, increased outpatient and GP appointments, increased time for genetic counselling, and additional genomic and non-genomic testing), and this will need to be monitored.

[1] Tandy-Connor S, Guiltinan J, Krempely K, et al (2018). False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. *Genet Med* 20(12): 1515-1521.

B. False reassurance

3.1 Conversely, it is also important to avoid false reassurance; unrealistic claims about gene tests encourage a false sense of genetic determinism. There is a big difference between telling a patient they are not at risk for a condition and telling them no genetic factors that increase their risk were identified; however, this distinction is often not made clear by providers or is misunderstood by users. This confusion can result in individuals believing that they are not at increased risk—or are entirely free of risk—for a condition. This false reassurance can cause patients to forego other types of screening that would normally be recommended, including mammograms and colonoscopies[2].

C. Inaccurate interpretation and limited sensitivity

4.1 A 2010 report by the US Government Accountability Office[3] found that "identical DNA samples yield contradictory results" from four different direct-to-consumer testing companies, and that the results were "misleading and of little or no practical use". Further, a 2013 study found that predictions of disease risk from different direct-to-consumer genetic testing companies still varied significantly[4].

4.2 Commercial testing or interpretation companies should provide a clear picture of how comprehensive their test or interpretation is. If a test only assesses limited variants within a gene, a possible variant could be missed. Some pharmacogenomic tests only test for CYP2C19 and CYP2D6 common variants while others offer a panel of more than 20 genes covering more than 300 medications[5,6,7]. Current evidence suggests that in pharmacogenomics, genotype information on approximately 12 genes (including CYP2D6, CYP2C19, CYP2C9, VKORC1, SLCO1B1, TPMT, DPYD and HLA) is of most value for prescribers[8], but this is likely to increase even in the short-term. Coverage of rare variants (including those more common in non-Europeans) is also going to be

[2] Butterfield RM, Evans JP, Rini C, et al (2018). Returning negative results to individuals in a genomic screening program: lessons learned. *Genet Med* doi: 10.1038/s41436-018-0061-1.
[3] US Government Accountability Office. Direct-to-consumer genetic tests: misleading test results are further complicated by deceptive marketing and other questionable practices. Available at: https://www.gao.gov/products/GAO-10-847T (last accessed 11 April, 2019).
[4] Kalf RR, Mihaescu R, Kundu S, de Knijff P, Green RC, Janssens AC (2014). Variations in predicted risks in personal genome testing for common complex diseases. *Genet Med* 16(1):85-91.
[5] Gross T, Daniel J. (2018) Overview of pharmacogenomic testing in clinical practice. *Ment Health Clin* 8(5):235-241.
[6] Thermo Fisher Scientific. Pharmacogenomics. Available at: https://www.thermofisher.com/uk/en/home/clinical/clinical-translational-research/pharmacogenomics.html (last accessed 15 April, 2019).
[7] Illumina. Pharmacogenomics Screen. Available at: https://www.illumina.com/content/dam/illumina-marketing/documents/clinical/trugenome-intended-use-pharmacogenomics-screen.pdf (last accessed 15 April, 2019).
[8] Swen JJ, Nijenhuis M, van Rhenen M, et al (2018). Pharmacogenetic Information in Clinical Guidelines: The European Perspective. *Clin Pharmacol Ther* 103(5):795-801.

important[9,10]. It is therefore crucial that whatever testing is provided, it needs to keep pace with the rapid advances that are being made.

4.3 As the science develops further, retesting or reanalysis of genome sequence data may be of benefit to some individuals and further decrease the number of false negatives, which is already small.

D. Indication-driven versus preventive screening

5.1 Genetic testing is appropriate and can be life-saving when doctors and genetic counsellors interpret complex results and map out the various courses of action.

5.2 Studies are needed to assess the risks and benefits of direct-to-consumer genomic screening of healthy individuals when this is not offered as part of a shared decision-making process with a health-care provider.

5.3 The presentation of results for drug interactions and efficacy needs to be sufficiently detailed and clear to enable a prescriber to make decisions that are in the best interest of the patient. Some commercial genomic testing companies present results to customers using a simple traffic light system. However, this system does not allow prescribers to fully interrogate and interpret the results and can lead them to choose a drug that has a green light despite not being the best option for the patient[11]. For example, this system may result in a prescriber choosing a more expensive, branded product when a generically available product given in smaller doses would not cause adverse effects for the patient. Full disclosure of interests and connections between genetic testing companies and pharmaceutical manufacturers should be mandatory. A useful test interpretation should be comprehensible and informative to both physician and patient. This aspect needs careful attention by the test provider.

5.4 In terms of risk prediction, most polygenic risk scores relating to disease susceptibility offered by commercial genetic testing companies have been derived from a white European population. This raises issues about generalisability of the tests and could exacerbate health disparities[12,13]. There is a need for culturally appropriate educational material about the use of genetic testing.

5.5 Commercial genetic companies present genetic risks to the customer as relative risks which may suggest a high risk for a disease. However, the real risk, usually presented as absolute risk may be vanishingly small for the genetic variant or indeed for

[9] Ingelman-Sundberg M, Mkrtchian S, Zhou Y, Lauschke VM (2018). Integrating rare genetic variants into pharmacogenetic drug response predictions. *Hum Genomics* 12(1):26.
[10] Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ (2019). Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet* 51(4):584-591.
[11] Gross T, Daniel J. (2018) Overview of pharmacogenomic testing in clinical practice. *Ment Health Clin* 8(5):235-241.
[12] Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ (2019). Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet* 51(4):584-591.
[13] Canedo JR, Miller ST, Myers HF, Sanderson M (2019). Racial and ethnic differences in knowledge and attitudes about genetic testing in the US: Systematic review. *J Genet Couns*. doi: 10.1002/jgc4.1078.

a polygenic risk score. Further, the small effects of polygenic risks on individual risk has been likened to genetic astrology[14] rather than rigorous science. This is an evolving area of science, and the degree of uncertainty in any predictive estimates need to be made clear to customers.

E. Benefit versus harm of genomic screening of healthy individuals

6.1 Women who have BRCA mutations are reported by commercial genetics companies as having a significantly elevated risk of developing breast cancer, yet most of these women will not go on to develop cancer (only about 5-10% of breast cancers are linked to BRCA variants[15]). In addition, only a limited number of variants associated with cancer are tested by some providers so both negative and positive findings may be misleading[16]. Nonetheless, Angelina Jolie's announcement in May 2013 that her BRCA1 mutation led her to have a preventative double mastectomy caused what is now known as the "Angelina Jolie effect", with the number of DNA tests for breast cancer mutations increasing by two-and-a-half times[17]. However, this may not have been equally distributed with respect to socioeconomic indicators, again leading to exacerbation of health disparities.

6.2 One of the FDA's explicit concerns is that some of the women worried about their risk of these cancers will opt for direct-to-consumer genetic tests and receive overly deterministic or inaccurate information, leading to unnecessary surgeries, treatments, or screenings[18].

6.3 The effects of perceived genetic risk on outcomes is sometimes greater than the effects associated with actual genetic risk. One study showed that merely receiving genetic risk information changed individuals' cardiorespiratory physiology, perceived exertion and running endurance during exercise, and changed satiety physiology and perceived fullness after food consumption in a self-fulfilling manner[19].

6.4 It should be made clear that when apparently healthy individuals pursue genomic screening to improve their health, there is no primary clinical question or indication that provides a clear probability of benefit. Most genetic tests lack long-term studies demonstrating robust evidence of improved outcomes or survival.

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14 Babovic-Vuksanovic D (2019). Genomics as a Scientifically Based Fortune-teller. *Mayo Clin Proc* 94(1):7-9.
15 Peto J, Collins N, Barfoot R, et al (1999). Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. *J Natl Cancer Inst* 91(11):943-9.
16 Fisher A. 23andMe Risk Test Misses Almost 90 Percent of BRCA Mutation Carriers. Available at: https://forward.com/fast-forward/422211/23andme-brca-breast-cancer-ashkenazi/ (last accessed 12 April, 2019).
17 Evans DG, Wisely J, Clancy T, et al (2015). Longer term effects of the Angelina Jolie effect: increased risk-reducing mastectomy rates in BRCA carriers and other high-risk women. *Breast Cancer Res* 17:143.
18 US Food and Drug Administration. FDA authorizes, with special controls, direct-to-consumer test that reports three mutations in the BRCA breast cancer genes. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm599560.htm (last accessed 15 April, 2019).
19 Turnwald BP, Goyer JP, Boles DZ, Silder A, Delp SL, Crum AJ (2019). Learning one's genetic risk changes physiology independent of actual genetic risk. *Nat Hum Behav* 3(1):48-56.

F. Privacy and confidentiality

7.1 Privacy of genomic data and issues of informed consent for the disclosure and use of genomic information should be considered. For example, genomic data can impact biologically related family members even if they have not accessed genomic testing themselves.

7.2 The complexity of ethical, legal, and social issues surrounding consent for genomic testing indicate that substantial effort is required to ensure adequate understanding of the test by consumers. Depending on how many of these issues apply, professional genetic counselling may be crucial for obtaining truly informed consent for genomic tests. Genetic counselling is less important, and unlikely to be required, when only pharmacogenomic tests are being provided; however, for pharmacogenomic testing, there is a need to have expertise in prescribing, and clear decision support on how to interpret the results.

7.3 With regards to identity, commercial genetic testing companies need to define processes to ensure that the DNA sample analysed is from the person who submitted the sample. There have been cases where samples have been sent for analyses that did not belong to the customer[20].

7.4 Up to 62% of consumers use third-party applications to interpret the raw data obtained from commercial genetic companies[21].

7.5 If commercial genetic testing has the potential to cause psychological distress, companies should provide access to genetic counselling as part of the service[22].

G. Wider impact on NHS services

8.1 There are broader implications in terms of impacts on already stretched NHS services. People will seek reassurance, request advice, further tests or treatments; all of which have potential cost implications to the NHS. This is concerning in the context of the value of commercial genomic testing not having been assessed.

8.2 As with other private health care, where patients pay for genetic tests, they must be made aware of the implications of also having to meet the costs of any NHS staff involved in the provision of the care, and any treatment, tests or counselling needed as a result of having had a genetic test[23].

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[20] Rutherford A. How Accurate Are Online DNA Tests? Available at: https://www.scientificamerican.com/article/how-accurate-are-online-dna-tests/ (last accessed 11 April, 2019).
[21] Wang C, Cahill TJ, Parlato A, et al (2018). Consumer use and response to online third-party raw DNA interpretation services. *Mol Genet Genomic Med* 6(1):35-43.
[22] Middleton A, Mendes Á, Benjamin CM, Howard HC (2017). Direct-to-consumer genetic testing: where and how does genetic counseling fit? *Per Med* 14(3):249-257.
[23] NHS. Guidance on NHS patients who wish to pay for additional private care. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/404423/patients-add-priv-care.pdf (last accessed 11 April, 2019).