Submission to the TGA Consultation on the Review of the regulation of certain self-testing IVDs in Australia

Andrea Belcher, Tiffany Boughtwood, John Christodoulou, Matilda Haas, Chriselle Hickerton, Sylvia Metcalfe, Ainsley Newson and Kathryn North*, on behalf of the Australian Genomics Health Alliance (Australian Genomics) and the Genioz Study*

This submission, which can be made public, focusses on the regulation of genetic self-tests (direct to consumer (DTC) genetic tests).

Summary of this submission

Australian Genomics and Genioz would suggest that:

- the current regulatory approach is only partially restricting access to tests that are deemed to require management by health professionals
- advances in technology, increasing availability and decreasing costs for DTC genetic tests are likely to have created the need for a new regulatory approach
- the Genioz study showed that Australians are accessing personal genomic testing online from overseas providers, are uploading their raw data to third-party re-interpretation sites and are seeking help with interpretation of results from many different types of health practitioners
- the TGA should take a precautionary approach to allowing the supply of DTC genetic tests in which genetic tests for diagnostic purposes and tests for which results are highly predictive should continue to be excluded from supply as DTC tests and should instead be mediated by a suitably trained health professional
- there is merit in considering whether a risk-based regulatory approach similar to the EU could be adopted in Australia, consisting of regulation (validation, control), support (counselling, education) and downstream evaluation to monitor the impact of the approach

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Addressing the Consultation Questions

Is the Excluded Purpose Specification fit for purpose?

The objective of the Excluded Purposes Specification (EPS) was to restrict access to tests that were deemed to require management by health professionals including pre- and post- test counselling. There are two reasons why it could be argued that the current regulatory approach is only partially achieving this objective.

First, while the EPS may have limited the availability of health-related genetic self-tests in Australia to an extent, the current approach has not prevented consumers accessing tests (which are likely of variable quality) online from providers outside Australia. The consultation paper recognises that some consumers are accessing these tests via the internet and importing them into Australia for personal use, thereby circumventing the EPS.

Second, consumers can already access health-related re-interpretation of information obtained from genetic self-tests that fall outside the current medical devices regulations and EPS, via so-called third-party re-interpretation services. These companies take 'raw data'[1] from tests not precluded under the EPS (such as those for dietary management, athleticism, paternity and ancestry) and provide consumers with further results, including health-related analysis, based on this information. This circumvents the EPS and indeed could be said to challenge the very framework of an EPS.

[1] Currently this data is often generated using genotyping arrays that detect single nucleotide polymorphisms (SNPs). While there are a variety of test types, each detecting different SNPs, the raw data files contain the same type of information (five fields-RSID (SNP name), chromosome number, position, allele 1 and allele 2). This raw data can be reanalysed by third party re-interpretation services to provide a specific set of results, per the test description.

There are a number of difficulties that can arise as a result of Australian consumers seeking tests and third-party re-interpretation services from overseas suppliers (some of which are noted in the consultation paper):

- reliability of the tests
- unknown quality and performance standards
- clinical utility of the information
- access to appropriate qualified clinical geneticist and genetic counsellor services
- consumers using this information to obtain further interventions that are unnecessary
- risks to data ownership, privacy and secondary use
- implications for family members and impact on insurances

In determining whether the current approach remains fit for purpose, another relevant consideration is consistency with approaches in other jurisdictions. There are a number of approaches being adopted internationally ranging from complete bans (in France and Germany) through to the use of existing general laws relating to health care services and patients' rights[2]. However, it would seem there is a trend towards the use of risk classification systems. The new EU Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices, which came into force in 2017 and will fully apply from May 2022, introduces a risk classification system. Similarly, the US Food and Drug Administration's (FDA) approach is to review DTC tests for moderate to high risk medical purposes to determine the validity of test claims, while allowing tests for non-medical, general wellness or low risk medical purposes to be offered without FDA review.

Should the TGA allow the legal supply in Australia of direct to consumer genetic tests?

In determining whether to allow the legal supply of direct to consumer (DTC) genetic tests 'onshore' in Australia, it is important to keep in mind that the EPS is currently not able to stop consumers accessing these tests from overseas, which could be considered a form of medical tourism. That said, a solution to a concern about medical tourism may not always be to offer the same intervention onshore – particularly if it is of poor quality. Other options, such as better consumer education as to benefits and concerns with testing could also be considered.

It may also be appropriate to consider the way regulation is currently thought about, which is largely based on regulating the purpose of the test. It is highly likely that this approach will become irrelevant with i) decreasing costs of testing, ii) advances in sequencing technology enabling the move from genotyping arrays to whole exome and whole genome sequencing, iii) the evolution of third-party re-interpretation services including the use of improved algorithms to mine the literature for variant data and, in the not-too-distant future, iv) the potential to aggregate genomic data with other data types. Indeed, the impact of these changes may already be seen in the blurring of the distinctions between the four subtypes of self-testing IVDs currently defined in the EPS.

The DTC market has changed since the 2003 AHMAC recommendation so it is appropriate to reconsider the goal of regulating access to DTC genetic tests. In framing that goal, it would be helpful to understand in greater detail why people feel the need to have this type of testing without health professional involvement, particularly given the likelihood they could be paying for a test they don't need. Findings from the Genioz study indicated that participants did not experience any serious harms from the use of personal genomic testing, but this may be explained by the fact that the majority of Genioz study participants were accessing ancestry testing. There is growing evidence globally of DTC

[2] Kalokairinou L, Howard HC, Slokenberga S, et al. Legislation of direct-to-consumer genetic testing in Europe: a fragmented regulatory landscape. *J Community Genet*. 2018;9(2):117–132. doi:10.1007/s12687-017-0344-2

genetic testing causing harms such in a health context such as unnecessary treatments or false reassurance[3] [4].

There is no simple answer to the question of whether to allow DTC testing. There is a difficult balance to be struck between supporting consumer choice over what tests they can purchase and how they interact with the health system and a wider system-view (focused on consumer protection) that questions whether there is sufficient evidence of the safety and value of many of the DTC genetic tests being sold.

What does the research on public expectations of personal genetic testing tell us?

Research conducted by the Genioz study provides the following insights:

- of more than 2,800 Australians who responded to the Genioz survey, 373 Australians had accessed personal genomic testing (PGT) with carrier testing (defined as a test for someone where there was no clinical indication (i.e. no family history)) and ancestry testing the two most common types of testing reported by respondents[5]
- individuals had gone to multiple information sources (including different types of health practitioners, such as non-medical, non-genetics specialists) for help with interpretation of testing results
- consumers were given confusing information about where to go for help with interpretation and DTC companies often suggested consumers go to their healthcare provider for follow-up and advice, however the Australian health workforce is not currently adequately prepared/resourced to support consumers with this type of testing
- some health practitioners advertised online that they offered PGT[6]
- consumers were buying online DNA tests and were able to download their raw data (for example from an ancestry test) and upload it to a third-party re-interpretation site for very little money to find out health-related information, without a health professional being involved
- the tests were commercial tests available to consumers via an online search and as a consequence, seeking help with interpretation was mainly consumer driven – this is a very different model for ordering medical tests in Australia
- many different types of health practitioners were helping individuals with interpretation of test results – nutritionists, naturopaths, dieticians, pharmacists, private genetic specialists, GPs and GPs practising integrative medicine

Further research conducted by Australian Genomics provided the following insights about the above practitioners:

- They operate within their own modalities and differ in their approach to interpretation and the type of support provided can differ greatly between each practitioner. These differences could be reflective of varying knowledge, interest of the practitioner and differing approaches

[3] Moscarello, T., Murray, B., Reuter, C.M. et al. Direct-to-consumer raw genetic data and third-party interpretation services: more burden than bargain? Genet Med 21, 539–541 (2019) doi:10.1038/s41436-018-0097-2

[4] Schleit, J., Naylor, L.V. & Hisama, F.M. First, do no harm: direct-to-consumer genetic testing. Genet Med 21, 510–511 (2019) doi:10.1038/s41436-018-0071-z

[5] Savard, J., Hickerton, C., Tytherleigh, R. et al. Australians' views and experience of personal genomic testing: survey findings from the Genioz study. Eur J Hum Genet 27, 711–720 (2019) doi:10.1038/s41431-018-0325-x

[6] Tutty, E. , Hickerton, C. , Adamski, M. M. and Metcalfe, S. A. (2019), Personal genomic testing for nutrition and wellness in Australia: A content analysis of online information. Nutr Diet, 76: 263-270. doi:10.1111/1747-0080.12516

to using the genetic results (some interpret the results in the context of other information about the individual while others provide generic advice based solely on the genetic results). This also raises the question of whether all of these practitioners fall within the definition of "health professional" in the MD Regulations

- Education and training for practitioners varied but most were getting their training from the testing companies (a requirement of some companies to be a registered practitioner and order through them), sales representatives from the companies, self-learning on the Internet, or from journal articles . Receiving training and education from the testing companies could suggest a conflict of interest and it could also suggest that the information/training, including the way they critically evaluate the information, could vary greatly
- Some practitioners have reported having to mediate consumer expectations of DTC test results while also outlining the limitations when a report is brought to them. Limitations of testing are often not stated by testing companies due to the way they are marketed, with an emphasis on empowerment rhetoric[7]

Other Research that may contribute to the knowledge base

Australian Genomics was invited by the Australian Government to administer the Mackenzie's Mission project in partnership with the University of NSW, The University of Western Australia and the Murdoch Children's Research Institute. Mackenzie's Mission is a research study in which couples will be offered reproductive genetic carrier screening to identify those with an increased chance of having children with severe genetic conditions.

While this project is a research study and does not investigate DTC carrier testing (couples will be invited to participate by a health practitioner) it will generate evidence of diagnostic yield, clinical utility, consumer and health professional education and acceptance, psychosocial impacts, ethical aspects and health economics of carrier screening delivered through the health system. In the future, this evidence could be used as a comparator for assessments of DTC carrier tests that may seek to be approved for supply, if the TGA establishes a regulatory approach.

Are there any tests that should not be available and why?

In principle, having a regulatory approach in which the TGA evaluates DTC genetic tests against criteria such as specificity, sensitivity and clinical utility could enable identification of tests that should not be made available directly to consumers. We would urge the TGA to take a precautionary approach, in which a DTC test is only made legal for supply once it is shown that harm is unlikely to occur. In our view, genetic tests for diagnostic purposes and tests for which results are highly predictive should continue to be excluded from DTC genetic testing and should instead be mediated by a health professional who has sufficient expertise in this area. We would also support requirements that any DTC predictive testing should require adequate pre- and post- test counselling by appropriately qualified counsellors, who may be located in a health service (public or private) or accessed via the testing companies.

[7] Tutty, E. , Hickerton, C. , Adamski, M. M. and Metcalfe, S. A. (2019), Personal genomic testing for nutrition and wellness in Australia: A content analysis of online information. Nutr Diet, 76: 263-270. doi:10.1111/1747-0080.12516

What are the risks to consumers and how can they be mitigated?

Based on our research and experience we perceive a number of risks for consumers and potential mitigation strategies:

Risks	Mitigations
Consumers misunderstanding the purpose or gravity of the test being offered - the 'recreational' nature of DTC genetic testing and ease of access can mean consumers may not be fully aware of the gravity of the health-related results they may receive. Consumers have reported approaching the health-related testing as an 'optional extra' and that they 'may as well get as much information from the test as possible' without considering the complexity or implications of the health information they may receive	Requirements for test companies to provide clear distinctions between test types (diagnostic tests, predictive tests and other self-tests that) and information on the range of possible results
Consumers misunderstanding or misinterpreting the test results	Guidance to test companies relating to the content and language to be used in DTC test reports
Consumers not understanding the potential lack of quality control and accuracy associated with some DTC tests - evidence such as that produced by Tandy-Connor et al (2018)[8] illustrates some of the existing problems such as rates of false positive results reported in DTC raw data	Requirements for test companies to provide performance evaluation documentation, including data on scientific validity and analytical performance, as part of any assessment by the TGA prior to inclusion of a test into the ARTG Development of consumer information on the quality and reliability of available tests
Consumers not understanding implications of the results for family members	Requirements for test companies to provide referrals to counselling services in situations where there are family implications
Consumers not understanding implications for insurance	A national regulatory approach in place to ensure DTC genetic test results do not negatively impact on consumers' ability to access individually assessed life insurance and related policies (noting the Financial Services Council currently has a moratorium in place until 2024 on disclosing genetic test results, including those from DTC tests, for life insurance policies up to set financial limits)

[8] Tandy-Connor S, Guiltinan J, Krempely K, et al. False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. *Genet Med*. 2018;20(12):1515–1521. doi:10.1038/gim.2018.38

Risks	Mitigations
Consumers not understanding where the testing is being done, who owns the data, where it is being stored and what else it can be used for (e.g. access by law enforcement officials, sold to other commercial entities etc)	Requirements for test companies to provide clear information up front (not deep within the T&Cs) about: - data ownership , storage and secondary use - location of testing Requirements for test companies to provide mechanisms for consumers to exercise a degree of control over the use of their data if they wish to (dynamic consent)
Consumers lacking access to accurate and unbiased information on which to make good decisions when considering testing	Mandatory provision of accurate and non-biased consumer information and referrals to health professional services including genetic counselling Availability of resources that encourage consumers to critically reflect on what tests they need and why Further research on which entities and types of information consumers trust, how and who can regulate the available information and how access to unregulated information can be controlled
Consumers experiencing a disparity between actual results and what they expect tests can tell them, which may be due to the provision of biased or misleading consumer information	Marketing standards with penalties that are enforced when fraudulent claims in advertising occur
Consumers experiencing a lack of equity in access to DTC genetic testing *- the commercial basis of DTC testing leads to consumers who can afford tests being able to purchase them while others are excluded*	Schemes to support low-income Australians to access tests that would otherwise exacerbate health disparities
Consumers may experience delays when approaching the health care system to assist them with interpretation, confirmation and follow up of DTC genetic testing results	Assessment is needed of the additional demands placed on clinical genetics services and accredited laboratories as a consequence of DTC test results requiring confirmatory testing to support clinical action and to avoid potential harm from unreliable results Greater workforce education is needed to prepare health professionals so they can engage with consumers about this type of testing

Risks	Mitigations
Consumers may be presumed to have improved understanding and decision making merely as a result of information being provided to them *- however, there are known problems with the relationship between information provision and subsequent understanding and sound decision-making*	Further research is needed to inform strategies that support effective consumer education and behaviour change
Consumers may experience overdiagnosis and overtreatment as a result of DTC genetic tests reporting *- e.g. reporting of variants of unknown significance or utility in healthy/asymptomatic individuals)*	Requirements for test companies to provide clinical evidence to support the intended purpose of the test as part of any assessment by the TGA prior to inclusion of a test into the ARTG Reinforcement to consumers when a test result is probabilistic
Consumers being unclear about which health professionals have appropriate knowledge and capacity to help them interpret their DTC result or raw data	Requirement for test companies to inform consumers that not all health practitioners have the capacity or knowledge to help with test interpretation Consideration of a range of additional resources to support consumers with questions from DTC testing including information from test companies such as FAQs, genetic counsellor helplines, chatbots etc More research to assess consumer preferences and to understand which health practitioners are best placed to support consumers that use DTC tests
Consumers may still purchase overseas services of unknown quality and performance if they are cheaper (as a result of lower regulatory burdens, larger markets etc)	Development of consumer information on the quality and reliability of available tests

Conclusions

DTC genetic testing for health purposes appears to be here to stay and it seems problematic to consider that it operates outside the healthcare system. The Genioz research and experience internationally shows that many consumers will approach their local healthcare system for support with interpretation, confirmation of results and to manage health-related outcomes following DTC genetic testing (changes to screening, new or changed treatments, lifestyle changes, reproductive planning etc).

Different views are emerging on how to respond to the consumer demand for DTC genetic testing and its impact on health services. In October 2019, the UK Royal College of General Practitioners (RCGP) released a Position Statement on Direct to Consumer Genomic Testing that recommended health professionals should exercise caution when asked to offer, or provide, clinical expertise about the results of Direct to Consumer (DTC) genomic or genetic testing. In contrast, the US National Academies of Science, Engineering and Medicine's Roundtable on Genomics and Precision Health held a workshop in October to Explore the Current Landscape of Consumer Genomics. Here the conversation explored the idea of DTC genetic testing as being another consumer access point to the healthcare continuum, alongside health practitioner-initiated genetic testing. It should be noted that the conversation in the US occurred in the context of a 'user pays' and highly privatised healthcare system, where there are significant health disparities but also very large numbers of consumers who have purchased a DTC genetic test. It seems reasonable to suggest that any discussion about whether, and how, to regulate the supply of DTC genetic tests in Australia should also consider how results and data from these tests could be integrated with clinical care and what challenges that will create.

On balance, we would suggest that there is merit in considering whether a regulatory approach similar to the EU could be adopted in Australia. Given the TGA's expertise in regulating therapeutics, medical devices and IVDs, it would seem well placed to design and implement a risk-based approach to classification, evaluation and regulation of genetic self-tests. We would suggest that such a system should include appropriate regulation (validation, control), support (counselling, education) and downstream evaluation to monitor of the impact of allowing the supply of DTC genetic tests on the consumer testing market, the healthcare system and consumers. We would also suggest that the following principles that should be incorporated into the regulatory approach:

- transparency around the TGA's evaluation processes including a public register of approved and unapproved tests (similar to the public summary documents published by MSAC and PBAC)
- enforcement provisions with substantial penalties for marketing unapproved tests as well as providing fraudulent or misleading information in Australia
- an expectation of similar standards for tests mediated by health professionals and provisions for spot checks of compliance

Appendix 1

Background information on the organisations that contributed to this submission

Australian Genomics Health Alliance (https://www.australiangenomics.org.au)

The Australian Genomics Health Alliance (Australian Genomics) is a national research collaboration of clinicians, researchers, geneticists, counsellors and patient advocates working together to provide evidence for the equitable, effective and sustainable delivery of genomic medicine in healthcare. Australian Genomics is funded by the National Health and Medical Research Council (NHMRC) (2016-2020; GNT1113531).

Australian Genomics' research encompasses four main Programs of work:

1. Establishing a national diagnostic and research network in genomics;
2. Developing a national approach to genomic data federation and analysis;
3. Informing health policy, conducting health economic analyses, applying implementation science methods and addressing ethical implications; and
4. Evaluating the needs of the genomic workforce.

This research program is embedded in clinical practice, with patients with rare diseases and cancers being prospectively recruited for genomic testing in clinical Flagship projects. Information from the clinical Flagships in turn drives the four Programs of work. Australian Genomics engages a network of more than 400 clinicians, researchers, diagnosticians and genetic counsellors to coordinate the recruitment of more than 5,000 patients for genomic testing across Australia.

Australian Genomics activities and expertise relevant to DTC genetic testing include:

- Research relating to the implementation of genomics into Australian healthcare including evaluations of the methods and outcomes covering, but not limited to, workforce understanding and education, system capacity and processes, public engagement and data security/information management
- Development of consumer education materials on DTC testing
- exploring the landscape of community practitioners such as Integrative GPs, private genetic specialists, pharmacists, naturopaths, nutritionists and dieticians, who currently offer, or could offer support to individuals who have had an online DTC test. This Australian Genomics study has been led by investigators with cross-membership in the Genioz Research Team.
- Development of a Position Statement on the use of Genomic Information in Life Insurance and interaction with the Financial Services Council on its Insurance Moratorium
- Contribution to the development of the National Health Genomics Policy Framework
- Working with State/Territory and Federal Governments through the Project Reference Group on Health Genomics, which has been appointed by AHMAC to progress the National Health Genomics Policy Framework Implementation Plan.

Genioz Study (https://www.genioz.net.au)

The Genioz study was led by a team of Australian and international researchers that used focus groups, a survey, interviews and forums with the public to investigate the Australian public's expectations of personal genomics. The research helped define educational strategies to support and empower the Australian public so they can make informed decisions in their use of personal genomic technologies. This evidence base can also inform national policy for personal genomics. The Genioz study was funded by the Australian Research Council Grant Number DP150100597.

Genioz activities and expertise relevant to DTC genetic testing include:

- Investigating the views and experiences of >3000 Australians on personal genomics using focus groups, a survey, interviews and public fora
- Contributing to the development of a Human Genetic Society of Australasia's (HGSA) position statement: 'Online DNA Testing' which expressed the view that individuals/consumers and healthcare professional/providers should be supported to make informed choices about online DNA testing and that adequate and ongoing education should be available
- Contributing to the development of the National Health Genomics Policy Framework
- Authoring 5 publications (plus 1 in press, 1 submitted and others in preparation) relating to online DNA testing and contributing to several media articles as well as presenting at conferences
- Developing evidence-based community resources to be used by anyone considering buying an online/DTC test and any health practitioner or other organisation that may have discussions with individuals who are considering buying/ordering an online/DTC test