Regulating direct-to-consumer genetic tests: What is all the fuss about?

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Abstract: The number of genetic tests available direct-to-consumer has burgeoned over the last few years, prompting numerous calls for tighter regulation of these services. However, there is a lack of consensus about the most appropriate and achievable level of regulation, particularly given the global nature of the market. By consideration of potential for direct and indirect harms caused by genetic susceptibility or genomic profiling tests, in this study we offer an overarching framework that we believe to be feasible for the regulation of direct-to-consumer genetic tests and likely to be relevant to other forms of predictive testing. We suggest that just five key requirements would adequately protect the consumer: a proportionate set of consent procedures; formal laboratory accreditation; evidence of a valid gene-disease association; appropriately qualified staff to interpret the test result; and consumer protection legislation to prevent false or misleading claims. ***Genet Med*** **2011:13(4):295–300.**

Key Words: *DTC, consumer, regulation, susceptibility, genetic test, genome profiling*

Energized by the sudden explosion in genetic profiling services available direct-to-consumer (DTC) through the internet,[1,2] which purport to assess an individual's risk of numerous diseases and traits, there has been a concomitant rise in calls for tighter regulation of this "consumer genomics" movement.[1–6] Although the issue of increasing complexity of genetic (and other biomarker) tests has been extensively highlighted by numerous commentators, particularly in cases where interpretation of the results is highly complex and the clinical utility of testing is unproven,[7,8] the regulatory environment has not developed as quickly as the technology itself.[2,9] This has left policy makers divided over how to proceed. There is a lack of consensus as to the extent to which regulators should be involved, what minimum standards should and could be required across an international and predominantly internet-based market, and the role of legislation versus self-governance or voluntary guidance within an appropriate regulatory framework.[5,6,10]

Although the market for DTC genetic profiling services is currently fairly small,[11] analysis of the sector suggests that some existing services provided by commercial providers are substandard, indicating that some regulatory oversight of this sector may be needed. A survey on DTC genetic testing commissioned by the European Parliament reported that the majority of these services failed to provide sufficient information to consumers regarding the nature of the genetic test, interpretation of the results, and implications arising from the test itself.[12] Moreover, a systematic review of the evidence supporting the gene-disease association from seven DTC genetic testing companies found that, of those reviewed in meta-analyses (57%), the minority (38%) were found to be statistically significant.[13]

Numerous organizations including the UK Human Genetics Commission (established by and linked to the UK Department of Health) and the US Personalized Medicine Coalition (funded by private companies) are working in collaboration with commercial stakeholders to devise voluntary standards or codes of practice.[6,14] However, existing legislation varies widely between countries. In Europe, a number of states within the Council of Europe that are signatories to the Convention on Human Rights and Biomedicine have signed or ratified additional voluntary legislation relating to genetic tests. The Additional Protocol on Genetic Testing requires that genetic tests that are carried out for health purposes satisfy generally accepted criteria of scientific and clinical validity (Article 5) and that an essential criterion of offering a test should be its clinical utility (Article 6).[15] The protocol also states that a genetic test for health purposes "may only be performed under individualized medical supervision" (Article 7) and with the provision of relevant information and nondirective genetic counseling in the case of predictive, susceptibility, or carrier testing (Article 9).[15] If widely adopted within Europe, these provisions "could have significant implications for certain DTC tests."[16] Although the Convention on Human Rights and Biomedicine and the Additional Protocol have been made in the interests of greater harmonization within the auspices of the Council of Europe, they are open for signature and ratification by a wider group of countries including the United States and Canada. To date, however, it is notable that neither Germany nor the United Kingdom have either signed or ratified the Convention or the Additional Protocol. Moreover, in Germany, access to genetic tests by the consumer has already been banned by law.[17]

In the United States, there is federal oversight of clinical laboratories through the Clinical Laboratory Improvements Amendment (CLIA), which regulates clinical laboratories to ensure accuracy, reliability, and timeliness of patient test results. However, different states have taken very different approaches toward the regulation of DTC genetic testing, particularly in terms of who can order the test. Most notably, the states of New York and California have tried to directly regulate DTC genetic testing services, and multiple "cease and desist" letters were sent out to companies in both states notifying them that they need to meet the specific requirements of the state to be licensed to receive DNA samples from residents for analysis.[5] In early 2010, the National Institutes of Health announced the creation of a public Genetic Testing Registry, to which laboratories can voluntarily submit information, which aims to improve the levels of information accessible to the public about the availability, validity, and usefulness of genetic tests.[18]

Within the context of this ongoing international debate, in this study we offer a conceptual analysis of the area leading to an overarching framework for the regulation of DTC genetic tests, which we believe could also be applied more generally to tests for other predictive biomarkers. The term regulation as

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used in this article encompasses more than the use of legal instruments—which we term statutory regulation—and includes other mechanisms that will influence the extent to which tests are taken up by patients and consumers. The funding of health services when informed by a robust evidence base, whether by commissioners (as with the National Health Science in the United Kingdom), medical insurers (in Europe and elsewhere), or health maintenance organizations (in the United States) may be considered such a tool. Clinical guidelines and the education of physicians and patients can also be considered as a regulatory tool but at the level of the clinical consultation. It is not the purpose of the article to discuss in detail the operation of such tools but to lay a framework and to point to five points of access where our three sets of regulatory tools (statutory, funding, and clinical) might be made to work.

Our intention is neither to provide a detailed critique of national and international variations in current legislation nor a comprehensive review of the positions held by different professional stakeholders, as these have been covered elsewhere.[2,19] In addition, this paper does not cover non-consensual testing (including testing of minors, adults who are unable to give consent, or third parties), but confines itself to the issues associated with legal, voluntary and consensual testing of competent adults. We focus on the key issues involved and offer a simple and widely applicable framework to the oversight of DTC genetic tests, which grapples with the competing demands of the need for proper regulation and concerns about an overly paternalistic approach which unnecessarily limits individual choice. Each element of our framework will need more detailed consideration as to how it might be work in practice in different countries, but the crux of our proposal is that appropriate regulation will need to be provided across all the elements of the clinical pathway: from the assay, through the determination of clinical validity and utility, and to the interpretation of the test in a clinical context.

ANALYSIS

Much of the angst over the regulation of genetic tests has resulted from conflation of "traditional" genetic tests for highly penetrant monogenic inherited diseases, with "new" genomic tests for common variants with low penetrance that confer modest susceptibility to multifactorial diseases. Although the line between these categories is already blurry, and may ultimately disappear as whole-genome sequencing becomes widely available, we believe that the distinction is still useful with respect to current genetic susceptibility tests. The former "traditional" tests are either essentially diagnostic or strongly predictive and generally relate to extremely rare, severe phenotypes where often no treatment exists; in this study, the clinical utility of the test lies in the provision of information about the likely course of disease, in improved management once symptoms arise, and in its potential to aid reproductive choice. It follows that providing advice and support for patients with these mutations is crucial.

In contrast, the latter are weakly probabilistic and often relate to a small risk of developing very common phenotypes at some point in the future. Although genetic risk profiling is new and still largely unproven, public health interventions and preventative treatments for some of the diseases in question are well established, and generic advice to eat a balanced diet and take more exercise seems to be an effective way of reducing the risk of many common complex diseases regardless of genotype. Except for the subgroup of diseases caused by high-penetrance single-gene variants, where the exceptionally high risk conferred by the variant requires specific modes of clinical management, most genetic variants will individually only cause risk of disease to be slightly increased or decreased.

We explicitly exclude tests for the purpose of diagnosing an existing ailment (which we assume will largely remain the preserve of formally regulated national or state medical providers) or for inherited single-gene disorders; the focus of this article is on genomic/genetic testing for common, low-penetrant variants conferring only modest susceptibility to multifactorial diseases, which represents the majority of DTC genetic tests.[20] Even if the risk scores themselves are not predictive enough for clinical purposes, it has been argued that evidence of a weak risk association might be sufficient to motivate individual diet and lifestyle modifications. However, systematic evidence is still needed to show that long-term, beneficial behavior change occurs in response to these tests.[21]

Two distinctions are helpful in both the evaluation of DTC testing services and discussion of how they should be regulated.

Assays versus tests

First, there is an important difference between an assay, the technical measurement of a biomarker (e.g., sequencing the *BRCA1* gene), and a test, the application of that assay for a particular disease (or trait), in a particular population, for a particular purpose[22] (e.g., testing for inherited breast cancer in a woman with a family history of the disease to counsel her about her risk and available preventative options). A single assay can, therefore, be used in various different tests. Ideally, an evaluation of test performance should include not only the analytical validity of the assay but also the characteristics of the disorder, the clinical validity, and utility of the test in a particular context, and any ethical, legal, and social issues raised by the test. Evidence for each stage of this evaluation process is provided by different sectors of the scientific and medical community (Fig. 1),[23] each with their own funding and regulatory mechanisms. This ACCE framework,[24] initially developed by the US Centers for Disease Control and Prevention, has been successfully applied to genetic test evaluation for single-gene disorders by the Genetic Testing Network in the United Kingdom,[25] and by Evaluation of Genomic Applications for Practice and Prevention project in the United States.[26] Although multigenic risk profiling raises some different issues from testing for monogenic inherited disorders,[27] the general principles enshrined in the ACCE framework are applicable to the process of evaluation of any health-related test including multigenic genomic susceptibility tests.[28]

Products versus services

Second, it is useful to make the distinction between a product, the kit, or device for measuring or quantifying a particular biomarker (e.g., polymerase chain reaction or SNP chip), and a service, the broad overarching context in which a test is offered. Importantly, the clinical interpretation of the test result is provided by the service not the product itself. Although medical devices are regulated by legislation, such as Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices,[29] services are at present significantly less formally regulated, although general consumer protection and advertising standards regulations may still apply. Although this situation may be relatively unproblematic within the context of national health care systems, where both laboratory and clinical services are generally governed by professional bodies and internal controls, the regulatory framework within the private sector is much less well defined.

Unlike test kits sold DTC (often over the counter), the distinctive nature of DTC genetic test provision is such that, in addition to providing an assay, there is also an interpretation service being offered to the consumer. Therefore, an additional

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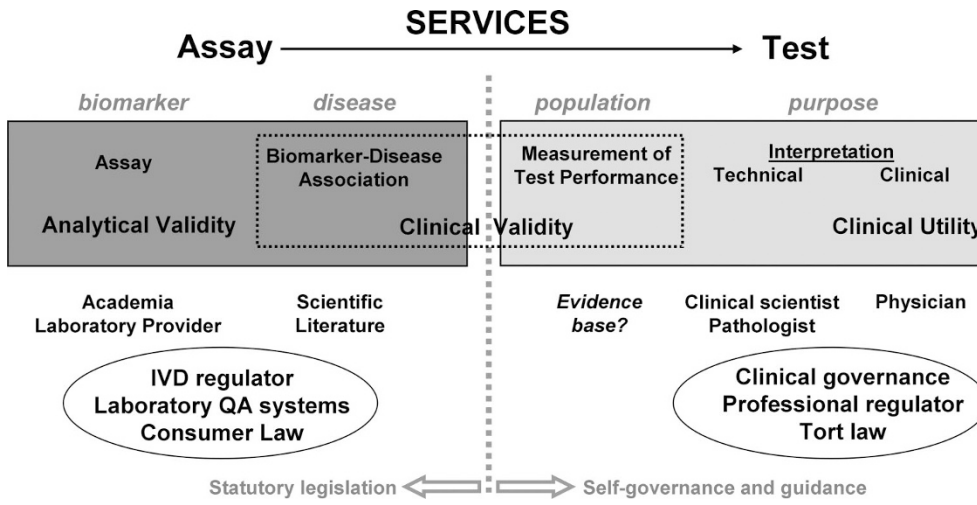

Fig. 1. Outline of the evaluation framework, adapted from the ACCE model, and the relevant regulatory vehicles available at each stage.[23]

factor that needs to be taken into consideration in the case of a DTC test provider, beyond the standard regulations relating to self-contained testing kits, is the service itself, to ensure that the results of the test are correctly interpreted and appropriately protected. The importance of this distinction has been highlighted by a bill (SB 482) introduced to the California State Senate in early 2009 to amend the Business and Professions Code, specifically to address entities providing personal genome services.[30] If enacted, this would define a new category of business—one that provides postproduction bioinformatics services for data interpretation as distinct from the production of that data—and exempt such businesses from requirements applicable to traditional clinical laboratory service providers.

REGULATORY SPECTRUM

Regardless of the prevailing method of health care delivery within any jurisdiction, the key question remains—how should we regulate private DTC genetic testing services (by which we mean tests marketed directly at citizens rather than health care professionals) that detect genetic variants? Conceptually, there are three discernable positions along the spectrum of options:

1. Extreme libertarianism: all genetic tests should be allowed on the market, without any regulation or requirement for evaluation, as the test itself causes no direct harm (e.g., unlike pharmaceuticals or x-rays).
2. Extreme conservatism: no genetic tests should be allowed on the market without proven clinical utility and appropriate medical support because of the potential for consequential harms (including psychological harm and the possibility of erroneous results) arising from the impact of information from the tests and from any subsequent management decisions.
3. Intermediate position: genetic tests should be treated similar to other tests that purport to produce medically relevant information, with regulations being limited to the safety and accuracy of the test itself, and the validity of any marketing claims.

It should be noted that the positions highlighted above are not specific to genetic tests and could equally well be applied generically to any health-related test. Indeed, our starting point is that regulation of genetic tests with potential clinical relevance should be treated the same as other in vitro medical tests with the potential to yield results of similar clinical accuracy and personal sensitivity[31,32] (Position 3 above). This is not least because of the difficulty of adequately and appropriately defining what we mean by the term "genetic" in the context of a test[33,34]; certainly, it seems nonsensical to give special treatment to a test simply by virtue of the fact that the underlying assay is based on DNA, rather than any other analyte. Rather than nucleic acids being the important factor, the relevant issues should be the diagnostic or predictive accuracy of the test, the potential for harm, and the impact of the results on family members (which is directly related to the first two points).

Thus, as with all products, the potential harm resulting directly from the device or assay itself should be considered, along with its technical accuracy. These issues are addressed for medical devices through CE marking in the European Union and 510(k) approval in the United States. Additionally, the validity of any medical (or other) claims made by the service provider should be verified, which is not a direct requirement of medical device legislation but could be undertaken by consumer protection organizations. To date, there has been no formal regulation of so-called laboratory developed tests (LDTs)—in vitro diagnostic tests that are manufactured and offered in-house, of which genetic tests are a subcategory. Nonetheless, the US Food and Drug Administration has now adopted a more stringent approach: it has recently sent enforcement letters to the major DTC personal genomics providers, equating the services with medical devices under section 201(h) of the Federal Food, Drug, and Cosmetic Act and is considering formal oversight of all LDTs.[35] At this time, however, it is unclear what form this oversight will take and how DTC services will be handled.

Factors that are often cited in support of more robust regulation of genetic tests include the fact that the results are highly complex to interpret, are of unproven clinical utility, might cause physical or psychological harm to the individual and their family, and that insurance companies might use the results to increase premiums. However, we suggest that these arguments are equally valid for numerous other biological measurements used to predict the risk of future disease,[32] including weight, height, cholesterol level, and blood pressure, for which tests are

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currently available DTC from multiple retailers. Indeed, the psychological harm resulting from a high blood cholesterol reading or a large waist measurement is potentially substantially higher than that resulting from a genetic profile, as the perceived or actual risks of disease may be significantly larger than those conferred by common genetic polymorphisms. Even a visit to an official National Statistics website may reveal substantially higher age-specific rates of disease mortality than many individuals are aware of. Moreover, in practice, the results may be equally complex to interpret, and the implications for family members and insurance companies may be similar (ranging from highly significant to irrelevant). Rather, empirical evidence suggests that weakly predictive genetic susceptibility tests do not have a major negative psychological impact on individuals.[36] Moreover, follow-on interventions that could cause indirect harm and may be undertaken as a consequence of testing should be considered separately from the harm of the test itself and are often already formally regulated (e.g., food and drug regulation and professional physician registration). Thus, we conclude that the indirect harms likely to arise from the results of genetic tests for susceptibility to common complex diseases are neither sufficient nor sufficiently different from other types of information, as to require additional statutory regulation.

Additionally, within the context of a free market economy, a lack of proven clinical utility would seem insufficient to justify banning the sale of any test given that (with the notable exception of pharmaceuticals) the requirement for such a high threshold for clinical efficacy is not replicated in most other arenas. Recently, the concept of personal utility has been introduced for DTC genetic tests, which augments the classical medical view of utility and includes nonmedical benefits of testing that may vary significantly between individuals based on their values and temperament.[37] Thus, the overall utility of a DTC genetic testing service should be considered for individuals as well across society.

Another common argument for the need to regulate genetic testing services is that wider access to genetic testing, coupled with poor data security might jeopardize individual privacy and confidentiality.[38] Although ownership or custodianship of an individual's genetic data are an extremely controversial area, this concern is not unique to genetics but applies to all forms of medical information. The principles governing confidentiality should be the same as for any other service that has access to personal, identifying information—be it credit card details, medical records, or purchasing habits—rather than being a function of the product itself, and an individual should be allowed to decide where to draw the line regarding the confidentiality of their own information.

Therefore, we suggest that any regulatory framework for DTC genetic test services must be informed by, and consistent with, the regulation of all health-related DTC testing services, which claim to be predictive and do not pose any direct harm to the consumer. Nonetheless, because the majority of the current discourse is centered around genetic tests, where there is currently wide medical, commercial, public, and political interest, we have, therefore, focused our recommendations on DTC genetic testing services. However, we believe that they are also relevant to any type of predictive tests and that DTC genetic testing services could provide an exemplar of how other DTC testing services should be evaluated and regulated.

RECOMMENDATIONS

The novelty of the area and the speed with which DTC genetic testing has developed suggests that researching, implementing, and assessing an evidence-based regulatory framework may be impossible. Rather, we took a deliberative approach and sought to consider the issues broadly and transparently to propose a pragmatic, consistent, and appropriate regulatory framework. Nonetheless, we believe that evidence of harm should inform the implementation of regulatory processes that might curtail individual freedom. We have assumed that the DTC genetic testing market will be global, and services will be available across the boundaries between jurisdictions and, thus, in practice attempts to be overly restrictive may fail. We have also assumed that DTC genetic tests themselves pose no direct harm to the consumer caused by the testing device and that the indirect harms (and clinical utility) will be limited for susceptibility testing for common complex diseases.

We suggest that, to appropriately protect the citizen, the following five points of entry in the development and provision of a genetic test should be addressed in the regulation of private genomic profiling services (Fig. 2):

1. Information: Appropriate information and a proportionate set of consent procedures should be in place before testing, such that the citizen is unambiguously informed about the nature of what he or she will receive by way of information and its possible implications. In this study, the word "proportionate" is used to imply that the level of information required for consent differs between different tests, e.g., *BRCA* testing for risk of breast cancer versus *TCF7L2* testing for risk of type 2 diabetes. The complexity of the information provided about the test, the interpretation, and the use to which it will be put depend in part on the sensitivity of the information likely to be obtained as a result of the test, its predictive or diagnostic validity and utility, the extent to which the consumer and others will seek to rely on those results in the future, and the severity of the disease at issue. Thus, tests that confer strongly predictive information about significant health problems which are almost certain to arise in the future, or which will be used for the purpose of reproductive choice,

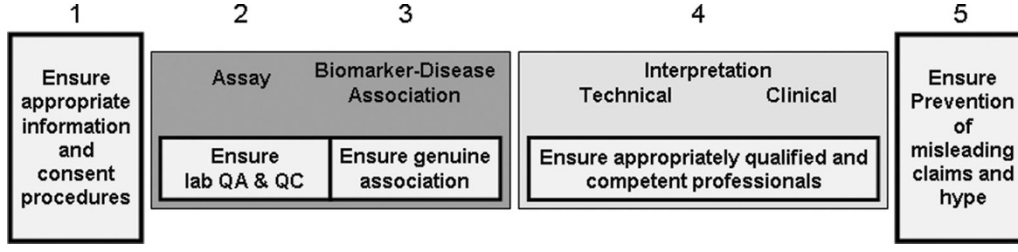

Fig. 2. Five-step proposal for the regulation of DTC genetic risk profiling for multifactorial disease. The five points are organized with reference to the evaluation framework outlined in Figure 1.

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require a more comprehensive engagement from both consumers and providers than perhaps a service that offers "recreational" genetic tests for ancestry tracing.

Provision of transparent and evidence-based information through publically available registries, such as the Genetic Testing Registry,[18,39] will be increasingly important as the breadth of possible information arising from a particular test expands (e.g., future complete genome sequencing versus current genome scanning technologies), so that individuals can make informed autonomous decisions regarding management of their own health. Transparency is also critical for knowing which population the test is applicable to (i.e., age, sex, ethnicity, country of origin, etc.), both in terms of disease incidence rates and relative risks associated with genetic variants.[40]

It is debatable whether existing institutions should be explicitly tasked with monitoring and policing the quality of the evidence provided to the consumer, such as consumer protection organizations or medical regulators, and whether rational standards can be set. However, by enabling transparency, both patients and physicians might be directed toward dealing with companies that provide "adequate" evidence for the validity and utility of the test offered and away from those that provide little or nothing by way of an evidence base.

2. Analytical validity: Laboratories providing an assay service should undergo accreditation procedures and subject themselves to stringent quality assurance requirements, the details of which are publically available, such that citizens themselves can have confidence in the assay results that are generated. For example, in the United States, the Centers for Medicare & Medicaid Services regulate all clinical laboratory testing through CLIA certification, and this should be a formal requirement for DTC testing laboratories; in Europe, oversight of laboratory certification is generally country specific, but the Organization for Economic Co-operation and Development has produced a set of guidelines for quality assurance in molecular genetic testing.[41] In practice, the degree of oversight may be less than desirable, but the basis of the recommendation is that no laboratory should be allowed to provide tests to the public without participation in a validated quality assurance scheme. This aspect of regulation should be a statutory requirement, akin to that for clinical laboratories, and enforceable by the relevant regulatory authorities in each country.
3. Scientific validity: Statutory regulations should be put in place to ensure that the scientific validity of the clinical claim is established, i.e., the link between the disorder and the genetic variant is established as a true and real relationship, and thus, the claimed association is valid (which is currently not the case for some DTC genetic testing services[13]). Appropriate tools already exist to determine a threshold for the validity of a gene-disease association, such as the Venice criteria,[42] which is a necessary—although not sufficient—condition of clinical validity, and, thus, should form a bare minimum evidentiary requirement. Without this, it seems to us that it may not be an overstatement to regard the service as fraudulent. This requirement pertains just to the validity of the claimed association between genetic variant and disease, and the size of the effect; it does not encompass all the evidence required for clinical validity, such as test performance (sensitivity, specificity, and predictive values), which we believe to be too great a burden to place on test developers to gather before launch. Thus, its clinical interpretation and utility are a separate matter and cannot be regulated through statutory means. However, both patient and physician need to know whether an association is valid, without which information no further judgment as to clinical relevance can be made. This aspect of validity (as distinct from clinical test performance and subsequent interpretation) has not previously been explicitly recognized or evaluated by medical regulators, but we believe that it could and should be in future.
4. Access to advice: All providers should ensure that consumers have access to named and appropriately qualified professionals with the necessary competence to interpret the assay measurement and provide advice and support to consumers regarding the interpretation of the test result to consumers. This function has previously been termed a "post-CLIA bioinformatics service,"[30] and because it can be provided completely independently from laboratories offering just the assay service, it requires separate regulatory consideration. Our view is that the process of interpretation consists of two elements that should be considered separately: technical interpretation, including not only determination of the genetic variant (or biomarker level) but also its relevance with respect to the disease in question and the population of interest, and clinical interpretation, including determination of the implications of the result for an individual and providing advice regarding interventions for prevention or management. Because of the enormous and potentially overwhelming amount of information presented to consumers following a genome profile, this support might include the offer of genetic counseling, as recently recommended for health-related tests by the UK Human Genetics Commission in its Common Framework of Principles for DTC genetic testing services.[14] This would be particularly crucial in the case of strongly predictive tests for inherited diseases or full genome sequencing, where highly penetrant diseases could be potentially uncovered in asymptomatic individuals. However, the type of professional advice provided should relate to the test itself, and obtaining medical advice should not be a prerequisite to accessing genomic information, particularly where the test is of limited or no medical use.
5. Claims: Guidelines and consumer protection regulations should either be strengthened to prevent misleading claims for the product or service, including unsubstantiated and overhyped assertions concerning clinical utility, or action should be taken to ensure that existing regulatory powers are enforced. This includes empowering bodies such as the US Federal Trade Commission, The UK Consumer Protection Agency, and the European Union Directorate General for Health and Consumers to be able to identify and prevent fraudulent, deceptive, and unfair business practices in the DTC genetic testing marketplace.

This framework can be distinguished from that proposed by others, such as that from the American College of Medical Genetics,[43] in several key respects. Many statements made by professional bodies stress the importance of a knowledgeable professional being involved in ordering the genetic tests. We do not believe that this should be a requirement for all genetic tests because of the enormous variability in the predictive ability and clinical utility of the tests (as discussed previously), which should ultimately guide the level of involvement of medical professionals. Our framework can also be distinguished from

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those commentators, including the UK House of Lords Science and Technology Committee,[44] who have proposed generic reforms to the European In Vitro Diagnostics directive,[29] such that all genetic tests are reclassified as being medium risk and, therefore, subject to independent premarket review.[12] Even if resources could be found to put such premarket reviews in place, this regulatory response is overly simplistic in our view because it fails to take account enormous variation in significance and sensitivity between different genetic tests; the fact that genetic tests are based on the analysis of nucleic acids does not, in itself, justify a blanket regulatory response. However, our framework is broadly in line with the recent recommendations from a National Institute of Health and Centers for Disease Control and Prevention expert workshop relating to targeted research into the scientific foundation for personal genomics.[45] We do not believe that existing medical device legislation is appropriate for the regulation of consumer genomics services but welcome the Food and Drug Administration's initiative to consider oversight of all clinical LDTs and hope that the framework outlined in this study will assist them in their deliberations.

CONCLUSION

When deciding on national and international regulations with respect to DTC genetic (and other biomarker) tests, policymakers must consider both the potential harms associated with these tests relative to other medical services or health-related information and the practicalities of regulating a global market. Although simple, we believe that this set of five overarching principles is practically enough to be feasible and would adequately protect the consumer from fraudulent products and incompetent services.

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