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making science work for health

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Response from the PHG Foundation to the Request for Information on the NIH Plan to Develop the Genetics Testing Registry (GTR)

Introduction

The Foundation for Genomics and Population Health (PHG Foundation) is the successor body to the Public Health Genetics Unit. Its overarching purpose is to foster and enable the application of biomedical science, particularly genome-based technologies, for the benefit of human health. Among its specific objectives is the promotion of a social and regulatory environment that is receptive to innovation, without imposing an undue or inequitable public burden. The Foundation has a particular interest in the way that new technologies are translated within health services, in genetic research and its impact upon clinical and public health services.

The Foundation strongly supports the development of such a register for all diagnostic tests, the establishment of which was one of the main recommendations of a Diagnostics Summit held with the Royal College of Pathologists in 2008 (see www.phgfoundation.org/reports/4982). This position was re-iterated in our more recent report on Genomic Medicine, published in May 2010 in response to the UK House of Lords Science and Technology Committee 2009 Report, in which we recommended that the UK Department of Health should support the establishment and maintenance of a 'National Laboratory Medicine Catalogue' to provide up-to-date guidance on offering, performing and interpreting tests (see www.phgfoundation.org/reports/5431).

Comments

1. *Are there any types of genetic tests that should not be included in the GTR?*

For the purpose of the registry, the NIH's stated working definition of a 'genetic test' is: "*a test that involves an analysis of human chromosomes, deoxyribonucleic acid, ribonucleic acid, genes and/or gene products (e.g., enzymes, other types of proteins, and selected metabolites), which is predominantly used to detect heritable or somatic mutations, genotypes, or chromosomal variations in structure or number related to disease, health, and/or personalized medicine.*" If this definition remains (see Q14.) the GTR should exclude ancestry tests and tests for genetic-relatedness – such as siblingship and paternity – where the primary purpose is to determine the nature of a social relationship, rather than determine a medical or health risk. This limitation would be consistent with the health-focused purpose of the GTR.

2. *What are the potential uses of the GTR for (1) researchers, (2) patients/consumers, (3) health care providers, (4) clinical laboratory professionals, (5) payers, (6) genetic testing entities/data submitters, (7) policy makers, and (8) electronic health records?*

No detailed comment. However we note that if siblingship, relationship and paternity tests remain within the remit of the GTR that there would be wider implications for many state institutions, such as for the judicial system (in terms of

child custody and maintenance orders) and for state and federal funding of child benefits and payments.

3. *What data elements are critical to include for use by (1) researchers, (2) patients/consumers, (3) health care providers, (4) clinical laboratory professionals, (5) payers, (6) genetic testing entities/data submitters, (7) policy makers, and (8) electronic health records?*

No comment.

4. *What are the potential benefits and risks associated with facilitating public access to information about the: a. Availability and accessibility of genetic tests? b. Scientific basis and validity of genetic tests? c. Utility of genetic tests?*

The main benefits of facilitating public access to this type of information would be:

- To allow consumers of tests to have an authoritative source to turn to for independent information regarding the validity and utility of tests
- To encourage testing companies to ensure that information about their test is transparent and thus discourage false or misleading claims
- To provide physicians with an authoritative summary of availability and evidence behind different tests
- To facilitate future clinical genome annotation for the interpretation of whole genome sequencing results based on the individual genetic tests currently available.

We consider that the risks of facilitating public access to this type of information are minimal. However, our main concern is that providing such an authoritative home for this information automatically gives it legitimacy. Indeed if claims are made by manufacturers without verification, they might well form the basis for negligence or consumer protection claims to be made against manufacturers regarding the fitness for purpose or efficacy of a product or service. It is therefore important that, wherever possible, information and evidence submitted to the GTR is independently verified to ensure it is trustworthy, and that contradictory evidence is neither deliberately nor accidentally omitted. Providing a simplistic independent assessment of the quality or level of evidence associated with a test, and the level of independent evaluation of the data (including stating when this has not occurred) would be a good way to alleviate this problem, and could be achieved, for example, by using wiki-style model or a panel of experts.

5. *What is the best way to distinguish between data fields left blank because of an absence of data/evidence and those left blank for other reasons? How important is this distinction for enhancing transparency, including for the purpose of identifying research opportunities?*

Where there is an absence of evidence, this should be explicitly stated as “no evidence”, rather than leaving the data field blank. This is critical for both transparency and identifying research opportunities.

6. *To adequately and accurately describe a genetic test, which of the following data elements should be included in the GTR? Are there other data elements that should be added? What information is necessary to represent adequately each data element?*

It would be extremely valuable to use the tried and tested UK Genetic Testing Network (UKGTN) Gene Dossier method as a basis for collecting the relevant data, available at www.ukgtn.nhs.uk/gtn/Information/Services/Gene+Dossiers/Forms. One of the significant insights that the UKGTN reached through using this process was the importance of having testing criteria, *i.e* describing why and under what circumstances the test would be used. This is critical to measures of both clinical validity and utility.

We agree with the list (a-p) of information to be provided to the GTR, as previously outlined by the NIH, but wish to make the following additional points.

First, within the concept of *clinical validity, we* commend a distinction that has not been well recognised in the literature, namely its separation into two components: (a) *scientific validity* - the determination of the relationship between genetic variant and genotype and (b) *test performance* - the empirical determination of the clinical sensitivity, specificity and predictive value (both positive and negative) of a test. This distinction is not currently stated in the list, and we believe that explicitly separating these components is crucial for transparency and evaluation. We suggest that *scientific validity* should include information about the odds ratio, study size and level of replication, whilst emphasising that this information is NOT equivalent to clinical validity. Robust evidence of a gene-disease association based on a case-control or cohort study cannot be used to directly compute *test performance,* particularly where the test uses multiple variants identified in different studies, which must be carried out as a separate empirical study in different populations or different clinical contexts.

Second, metrics for establishing *personal* utility have yet to be established, whilst numerous metrics and dimensions are well documented relating to *clinical* utility (which describe both the test itself and its mechanism of delivery, associated clinical services and the presence of appropriate therapeutic options). It may therefore be advisable to separate these two aspects of utility into two separate questions. Although it is unclear what level of information or evidence should be provided to the GTR regarding the utility and effectiveness of different behavioural or therapeutic options recommended following testing, or their availability and cost, this is clearly critical to measuring utility and should be explicitly recognised in the question. Moreover, it will be important to distinguish between claimed (or isolated individual cases of) utility and proven utility for which robust evidence is available.

Third, the register should be transparent as to whether the test or gene sequence is subject to existing or pending patent protection and whether providers are offering the test under licence. The inclusion of patent application numbers would allow relevant searches to be undertaken by potential consumers or prospective licensors of the test. The co-development of targeted pharmaceutical drugs and companion diagnostic tests represents one model for the emerging pharmacogenetics market. However within the direct-to-consumer market numerous instances have arisen of co-marketing of nutritional supplements or other products or services, to purportedly address the concerns that may have been highlighted by the test. Where goods or services are offered by the company or a related company as a consequence of those test results, details should be included in the register.

Fourth , a further question could be added at the end of the list regarding any specific ethical considerations relating to the test (*e.g.* relevance for family members).

Finally, if the register is to be publically available outside the USA, alternate trade names of drugs or tests used in other jurisdictions, or alternate disease descriptions should also be included.

7. *What types of information might be difficult for test providers to submit and why?*

We do not believe that any evidence is inherently difficult to submit, but test providers may have difficulty knowing how to decide systematically what constitutes robust evidence. In addition, due to the commercial nature of many test providers, we are concerned that, where multiple studies of the same test show varying degrees of association between a gene variant and disease, that evidence supporting a test is more likely to be submitted by test manufacturers and suppliers in preference to evidence refuting it. This bias could result in tests for variants which actually have a weak (or non-existent) association with a particular disease appearing to have evidence of a strong association from early studies. Whether this can be fixed by explicitly asking test providers to submit any evidence they know of that refutes their test, or whether independent expert evaluation is required (as suggested above), needs to be established.

8. *What are the advantages and disadvantages of collecting and providing information on the molecular basis of genetic tests, such as detailed information about what the test detects and the specific methods employed?*

No comment.

9. *In addition to the data elements, would it be helpful to reference other resources, and if so, which ones (e.g., published studies, recommendations from expert panels such as the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, U.S. Preventive Services Task Force, or Evaluation of Genomic Applications in Practice and Prevention Working Group)?*

Linked references to all of the above would be extremely valuable, in addition to references to internet databases such Lab Tests Online and disease-specific support groups or charities. Where a specific gene or genes are tested, proving a link to the location of the gene(s) in a genome browser might also be useful.

10. *As the GTR is being designed, what are the important processes to consider to make the submission of data as easy as possible for the data provider (e.g., the capability of linking to information that has been submitted to other agencies, such as the Food and Drug Administration and the Centers for Medicare and Medicaid Services, or a master file of data common to particular tests)?*

In other contexts, the use of integrated electronic systems has increased compliance and overall stakeholder satisfaction. For example, in the UK, the use of an integrated system for managing applications by researchers for multiple approvals (from research ethics committees, research and development and the National Information Governance Board) has greatly increased researcher

compliance, researcher satisfaction and overall transparency. Provided that care is taken in framing the construction of the questions between different agencies to avoid unnecessary duplication, streamlining the process could have a significant impact on uptake.

11. *Which potential benefits and risks would be most likely to affect the decisions of researchers, test developers, and manufacturers on whether to submit data to the GTR, and what factors will best encourage submission of complete and accurate data?*

We believe that reputable test providers will support the GTR and will be keen to submit data. However, it is possible that researchers, test developers and manufacturers might be reluctant to submit data to the GTR on the basis that sensitive commercial interests might be threatened if the scientific and clinical basis for a genetic test is publicised at too early a stage of development. Early publication could compromise patent protection, and assist competitors to develop tests which could circumvent reliance on the initial test and thus avoid contributing to the development costs involved in that process. In the UK, the exemption from patent protection for so-called 'home brew' tests could aggravate manufacturers' reluctance to be transparent.

However, if these hurdles are negotiated successfully, registration within the GTR could be viewed as a potent marketing tool which could be used to undermine unregistered competitors. The balance of risks and harms involved may well be dependent upon how the majority of stakeholders respond.

12. *What are the most effective methods to ensure continued stakeholder input into the maintenance of the GTR?*

Within Europe, the use of a CE mark denotes conformity with relevant in-vitro diagnostic devices directives. The GTR could pilot a similar system, or at least offer recognition to those test providers who have submitted information, and embark upon a programme of public engagement with health care providers and potential consumers to educate them about the value of registration. However, there would still need to be acknowledgement that in practice, at least in initial stages of development, there may be substantial evidential gaps.

13. *For what purpose(s) would you use the Registry to support your professional efforts?*

No comment.

14. *Are there any other issues that NIH should consider in the development of the GTR?*

We have the following points for further consideration:

- *Definition of a 'genetic test' (see Q1. above):* this definition may be too broad to be manageable, as it include protein-based assays of which there are thousands. Although ideally the GTR would eventually expand to include all *in vitro* medical tests, it may be worth limiting the definition initially to direct analyses of nucleic acids.

- *Whole genome profiling:* it is unclear how providers of whole genome services (*e.g.* genotyping microarrays, SNP-typing, whole exome, whole genome, etc) will submit information to the GTR. In such cases, the service provider may be offering an open-ended assay to which a large number of specific closed questions (tests) can be put. Should the test provider enter information for every analysis they offer? – for example, this would already require a company such as 23andme to submit many hundreds of entries into the GTR, which would doubtless become rapidly out-dated. We cannot see how this can be avoided if evidence is to be provided about every analysis, but providing a layered system such that common data (name, address, analytical validity, *etc.*) are shared under a single test provider's heading is essential. This issue is further confounded where the assay and analysis service providers are independent (*e.g.* a genome sequence is directly purchased from Illumina, but analysed by 23andme). Since these type of services are likely to increase in the future, careful consideration should be given to how they can be encouraged to submit data to the GTR.

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