



## **HUMAN GENETICS SOCIETY OF AUSTRALASIA**

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The liability of members is limited

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The Royal College of Pathologists of Australasia

NIH GTR RFI Comments,  
National Institutes of Health,  
Office of Science Policy,  
6705 Rockledge Drive,  
Room 750,  
Bethesda, MD 20892.

[GTR@od.nih.gov](mailto:GTR@od.nih.gov)

July 30, 2010

Dear Sir/Madam,

**Re: Response to Request for Information on the NIH Plan to Develop the Genetic Testing Registry**

The Human Genetics Society of Australasia (HGSA) is grateful for the opportunity to Comment on the NIH plan to develop the Genetic Testing Registry (GTR). The Human Genetics Society of Australasia is the peak Australasian professional body to provide a forum for the various disciplines related human genetics. We are submitting this response with another Australasian organization with a professional interest in genetic testing, the Royal College of Pathologists of Australasia.

We believe that the NIH Plan to Develop the Genetic Testing Registry is a potentially very useful enterprise, and we are strongly supportive of this initiative. Given the rapid proliferation and commercialization of a plethora of genetic tests and the advent of direct-to-consumer (DTC) genetic testing, there is an urgent need for a centralized public resource, such as the one planned by the NIH, to be established. Such a resource undoubtedly has the potential to greatly benefit clinicians, researchers, test developers and the public alike.

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There has been an upsurge of start-up biotechnology companies offering DTC genetic tests. Some genetic tests marketed DTC were already available in clinical practice, such as tests to predict single gene disorders, for example, Tay Sachs disease and cystic fibrosis, but many other tests offered DTC for multifactorial disorders lack published data to support clinical validity. There is clearly a need for a centralized resource to provide high-quality and easily accessible information on the validity and utility of such tests to ensure that test users are in the best possible position to make informed choices about whether or not use particular tests.

A recent report published by the National Health and Medical Research Council, Australia's peak body for supporting health and medical research, outlines the regulatory framework for genetic tests (<http://www.nhmrc.gov.au/publications/synopses/e99syn.htm>). At present, the accreditation of laboratories and regulation of test kits is limited to medical laboratories which provide tests in the context of a clinical service provided by a medical practitioner.

The report also outlines potential ethical, social and legal implications of DTC testing in detail, which include potential psychological and medical risks to consumers from receiving adverse results in the absence of genetic counseling and concerns regarding the scientific validity and potentially misleading claims of some DTC genetic tests. A centralized Registry would go some way in preventing potential misuse and misapplication of genetic tests.

We would also like to take this opportunity to respond to the specific points on which the NIH is seeking input:

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

The definition of a "genetic test" is vexed. A DNA-based assay is simply a methodology. The major concerns regarding inappropriate marketing of tests or the appropriate ethical utilization of tests relates to tests about heritable disorders. We recommend that the GTR catalogue include information about tests for heritable disorders or for heritable risk of disorders. This then precludes the Registry from holding information about somatic genetic tests, but paves the way for information about biochemical, cytogenetic, or molecular genetic assays that identify heritable variants that place a person at increased risk of disease.

**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?**

(1) The GTR could provide information for researchers about the availability of testing for a disease of interest, or of laboratories with an interest in a

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particular condition. By enforcing consistent nomenclature and standards for reporting, the GTR could also provide a benchmark against which researchers could measure their own activities.

- (2) The GTR would provide essential information about the availability and clinical utility of investigations.
  - (3) A “market-driven” system is inequitable for families with uncommon genetic disorders and creates inefficiencies for the counseling services working with these families. As noted by the American College of Medical Genetics, “... many clinical genetic services spend a good deal of time and effort – usually without reimbursement – trying to assist patients in their quest for medically necessary but esoteric laboratory tests. This scenario has become a barrier for accessibility to needed but esoteric tests for many patients, especially Medicaid patients, since inadequate reimbursement levels preclude access to tests performed by out-of-state reference laboratories.” (American College of Medical Genetics: Manual on Reimbursement for Medical Genetics Services, 2002. Ed. M Williams. Kendall/Hunt Publishing. pp 60-61.)
  - (4) Ditto. In addition, knowledge about what other laboratories are doing can help other facilities decide what tests are worth developing in-house, and which ones would be more appropriately outsourced.
  - (5) The same information about test utility and availability is essential for payers to make rational decisions about funding of investigations.
  - (6) By enforcing consistent nomenclature and standards of reporting, the GTR would assist in the deposition of consistent data regarding genetic variants identified during clinical testing.
  - (7) Information about the utility of investigations, availability, and the funding will be essential for policymakers.
  - (8) Electronic health records require national consistency regarding test nomenclature, gene names, and variant nomenclature. The Registry could be an essential driver for developing this consistency.
- 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?**

At the very least, all users will require the following information:

- The name of the gene, locus, protein, or analyte being analyzed using consistent international nomenclature.
- Scope of testing provided by the laboratory, preferably using consistent national nomenclature.

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- Clinical indication for testing, preferably using consistent international nomenclature regarding disease names.
- Potential clinical utility of the investigation. This will be the most difficult component to implement consistently. It is particularly important that the strengths and, in particular, limitations of the investigation in clinical decision-making be articulated for the benefit of the public.
- Sample requirements, turnaround time.
- Name of associated local clinical service providers; however this could be difficult to achieve in a competitive market.
- Pre-test requirements for genetic counseling and informed consent, if any. Details on of how consumers can access genetic counseling for further information and support should also be included.
- The usual contact details etc for the laboratory.
- Cost of the test, and information regarding reimbursement by insurers or other agencies.
- Relevant resources such as locus-specific databases.
- Relevant national or international guidelines that may impact on the delivery or utilization of the test result.

**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 database would facilitate the identification of particular tests by health professionals and allow them to make targeted comparisons in relation to the performance characteristics, including costs, of the tests being offered. The availability of, and easy access to, data on the validity and utility of genetic tests available will ensure that tests users (consumers and their health professionals) are in the best possible position to make informed choices about whether or not use particular tests.

- a. The public may seek tests which are available but which are of little utility. Conversely, patients may be more proactive than their clinicians in identifying investigations that may be useful. This is particularly the case with rare disorders.
- b. The risks of providing scientific information about the investigation, and the clinical utility, are related to potential confusion. With care, it would be possible to avoid most of these difficulties. In particular, patients should be advised to seek expert advice from the relevant health care professional to explore the utility of the test in the particular patient's situation.
- c. It is hard to pin down the utility of investigation with clinicians, let alone with the general public. Nonetheless, the GTR should develop a consistent framework for describing the potential utility and limitations of the test. This would be very useful for the clinicians as well.

**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**

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**reasons? How important is this distinction for enhancing transparency, including for the purpose of identifying research opportunities?**

We agree that data fields left blank because of a lack of currently available data should be clearly marked as such.

**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?**

**a. Contact information (e.g., location, name of the laboratory director, and contact information for the laboratory performing the test).**

Agree

**b. Laboratory certifications (e.g., Federal or State certification of the laboratory that performs the test)**

Agree. This may even include a link to an explanatory glossary of the various systems of certification, which are likely to be of varying standards in different regions. If the register is opened up to other countries, there should be a clear indication whether the relevant test has been produced by a laboratory that has met certification standards in the relevant jurisdiction. Moreover, links to the various documents that provide information on certification standards in those different jurisdictions should be provided.

**c. Name of the test (e.g., common test name, commercial name, marketing materials about the test and/or genetic testing entity, standard identifier (e.g. CPT codes, LOINC<sup>ii</sup>))**

Each test will have a different name. There may be a common test name, the laboratory's name for the test, the analyte or gene to be assessed, and links to other regulatory and marketing codes.

**d. Regulatory clearances (e.g., for tests reviewed by the Food and Drug Administration, the 510(k) or premarket approval (PMA) number).**

Agree. Once again, if the register is opened up to international access, there should be a clear reference to the relevant jurisdiction in which the clearance was obtained and the regulatory standards that are applicable.

**e. Intended use of the test (e.g., diagnosis, screening, drug response)**

We do not agree with the wording of this item. The intended use of the test is determined by the clinician and a clinical setting. This is in contrast

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to the purpose of the test which could be defined by the laboratory. We suggest that the laboratory describe the purpose of the test (selecting from one or more pre-defined options), and that this be related generally to the potential use of the test in different clinical settings (again selecting from one or more pre-defined options).

**f. Recommended patient population**

The "target" population needs to be defined in terms of clinical setting, intended use, age, ethnicity, gender etc. A standardized way of describing these populations would be preferable.

**g. Limitations of the test (e.g., is the test validated only for certain subpopulations or limited to particular uses such as screening but not diagnostic testing?)**

Agree.

**h. Test methodology.**

This needs to be in two parts. First, a brief summary statement or phrase regarding the scope of testing (eg "complete sequencing of gene", "test for common variants in gene") that is taken from a pre-defined list of options. Second, a free text description of what the laboratory will actually do, including relevant references.

**i. Analyte(s)—What is being measured in the test (e.g., genetic sequence)**

Agree.

**j. Specimen requirements (e.g., blood, saliva, tissue samples, amniotic fluid)**

Agree, but clinicians will also need to know details such as the types of tubes for collection, conditions for dispatch (e.g. temperature), maximum delay before receipt by the laboratory etc.

**k. Availability (e.g., is the submitter the sole provider of the test or are there multiple providers?)**

This will presumably be derived automatically from the list of investigations held by the Registry.

**l. Accessibility (e.g., accessible through a health provider, public health mandate, and/or direct-to-consumer)**

Agree.

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## **m. Performance characteristics<sup>1</sup>**

We suggest that this whole section include plain English explanations if it is anticipated that non-clinicians will use this resource.

- i. Analytical sensitivity**
- ii. Analytical specificity**
- iii. Accuracy**
- iv. Precision**
- v. Reportable range of test results**
- vi. Reference range**
- vii. Method used for proficiency testing (e.g., formal PT program, alternative assessment) and score**

## **n. Clinical validity<sup>1</sup>**

- i. Clinical sensitivity**
- ii. Clinical specificity**
- iii. Positive and negative predictive value in different populations.**

This will be the challenging part as a clinical validity can vary enormously depending on which patient population is being tested.

### **iv. Prevalence**

This is not an attribute of the test. It is an attribute of the clinical syndrome (clinical features which take a person to see a health care provider) or an attribute of the mutation (which may or may not take a person to see a health care provider, depending on the clinical features).

### **v. Penetrance**

This is not an attribute of the test. It is an attribute of the underlying mutation. We do not see a benefit in including this information

### **vi. Modifiers**

This is not an attribute of the test. It is a description of the genetic basis for a disease, and it would be better housed in a related database describing the genetic basis of different diseases.

## **o. Utility (e.g., clinical and/or personal utility) or outcomes**

This is the most important section, and it will be essential that the Registry has some structured way for providing this information in a consistent and defensible manner. It might be advantageous to provide links to websites that explain these parameters for related

condition(s). It may also be appropriate to mention recommendations for further testing depending on the test result.

- i. Benefits**
- ii. Harms**
- iii. Added value, compared with current management without genetic testing**
- iv. Cost (e.g., price of the test, health insurance coverage)**

Whilst this will be a complex item because of the complexity of healthcare funding in the US (and elsewhere), it is essential that this information is provided and is updated.

If possible each of these details should be included, where available because it is important for laboratories to define the performance characteristics of an investigation before it is provided in a clinical context. However, it may be very difficult for laboratories to provide meaningful data on some performance characteristics for tests, particularly for rare conditions. For example, the clinical validity can be difficult to establish in the case of rare disorders. In this case, it may only be possible to provide limited information regarding clinical validity. As another example, it may not be possible to provide meaningful data about sensitivity for very rare disorders, where the laboratory may have only tested 3 or 4 affected patients. In this case, the laboratory could give all data (e.g. 4 cases detected between 2000 and 2009, and no known false negative results). It is not possible to provide predictive values meaningfully either, unless the prevalence of the disorder is known.

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

Please refer to earlier comments.

**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?**

The collation of all relevant details regarding genetic tests as part of a 'one stop shop' is likely to be a time efficient means of providing health professional with up-to-date and accurate information on the characteristics of genetic tests. Few practicing health professionals, in particular GPs, will have the time and resources to undertake independent research to collate and evaluate details on the validity and utility of genetic tests.

**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.**

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## **Preventive Services Task Force, or Evaluation of Genomic Applications in Practice and Prevention Working Group)?**

We feel it would be very helpful if links were provided to relevant documents resources.

Links need to go to the following categories of resources:

- information about the diseases associated with the test
- information about resources for patients and family members concerned about this disease
- information about informed consent and genetic counseling resources that may be appropriate for this test
- information about accreditation programs that are used by laboratories
- information about "best practice" guidelines or standards for the management of patients and families with the disorder in question
- information about funding policies and programs to cover the test costs
- availability of pre-implantation genetic diagnosis (PGD) and relevant links
- legal advisory for tests involving paternity issues
- DNA or tissue banking

### **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)?**

It is essential that, where possible, data be entered only once. However, the Registry is not managed by the FDA or jointly with other regulatory agencies. This means that there will, of necessity, be some duplicate data entry because one agency is not in a position to "trust" the data provided by another agency. It would be helpful to identify information that could be brought into the Registry from other sources and identify information, which could be linked out to other sources.

### **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?**

Submitting data to the GTR may be perceived as potentially time-consuming, so the submission process needs to be as user-friendly as is possible.

This is a Federal government initiative (in the US) and submission of data (and maintenance of this information) should be made a condition of receiving federal funding in any form. This is a strong position, but the Registry will only be as useful as the information it contains. If the laboratory

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chooses not to submit information on the Registry, then the role of the Registry in providing comprehensive information for the benefit of health-care providers and patients will be lost. We agree that the submission should be simple, efficient (hence the need for linkages to other data sources) etc. These are the incentives that need to be in place. But if more complete participation is needed to validate the development of the Registry, it could be argued there should also be penalties for not submitting. Failure to submit data should lead to ineligibility for Federal funding and accreditation.

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

There should be an advisory committee made up of laboratories, clinicians, patients, regulators and other relevant stakeholders to oversee the operation of the Registry. If the appropriate linkages could be made between the Registry and other databases that laboratories must maintain, then the efficiency of using the Registry as a portal for information will encourage laboratories to remain engaged. To ensure that data, including test availability, is updated, there should be reporting mechanism, for example for clinicians who use the resource and find that laboratories listed no longer provide the required test.

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

The predominant issue for clinicians is to identify if the test is available, whether the test can be provided by an accredited laboratory, and the cost of testing. The principles of issue for patients are: (i) to identify if the test is available for a particular condition, and whether that test would be useful in managing their condition; and (ii) to be informed about appropriate local services that are available to provide counseling and support.

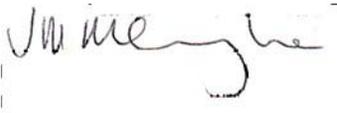
**14. Are there any other issues that NIH should consider in the development of the GTR?**

This has the potential to be an international resource. Making this resource an international resource would, of course, create more complexities. But we already have DNA samples crisscrossing the world for genetic testing. We recommend that the NIH consider developing this is an international resource with the potential for laboratories in other countries to lodge their test details on the Registry. Issues around intellectual property, curating of data and managing discontinuation of tests would also need to be considered prior to development.

Yours sincerely,

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