



**BlueCross BlueShield
Association**

An Association of Independent
Blue Cross and Blue Shield Plans

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

Dear Dr. Collins:

On behalf of the Blue Cross and Blue Shield Association (BCBSA) – which is made of 39 independent locally-owned and operated Blue Cross and Blue Shield companies that collectively provide healthcare coverage to 98 million Americans – I am pleased to respond to the National Institutes of Health (NIH) Request for Information on the NIH plan to develop a genetic testing registry.

BCBSA speaks for potential stakeholders in such a registry, including:

- **the 39 independent BCBS Plans**, who need accurate, evidence-based sources of information for researching reimbursement policy, and
- **the Technology Evaluation Center (TEC)**, which conducts evidence-based health technology assessments of a variety of medical interventions including genetic tests. Since 1997, TEC has published 24 Assessments and Special Reports addressing various genetic tests on its publicly available website (www.bcbs.com/tec), with documents from the most recent 3 years remaining accessible at any given time.

We strongly believe that the plan responds to an important information gap identified by the Secretary's Advisory Committee on Genetics, Health, and Society's (SACGHS) 2008 report on the *U.S. System of Oversight of Genetic Testing* and their recommendation for a "publicly available, Web-based registry for laboratory tests."

We note, however, some discrepancies with the SACGHS recommendations and emphasize their reconsideration.

- **BCBSA supports a mandatory registry.** SACGHS recommended a mandatory registry as "the best approach to address these information gaps in the availability of tests and their analytical and clinical validity." Most genetic tests currently are offered as laboratory-developed tests and there is no requirement to make public any information regarding the

analytic or clinical validity of the test. Mandatory posting of such information in a registry would even the playing field with those manufactured test kits that require Food and Drug Administration (FDA)-clearance and an FDA-cleared summary of analytic and clinical validity (in the kit insert, usually also available online). At the same time, mandatory posting would ensure more rapid participation in the registry with consequent benefit to all stakeholders. We recognize NIH currently lacks regulatory authority for such a mandate and recommend NIH partner with a regulatory agency (CMS or FDA) within the Department of Health and Human Services (DHHS) to develop this authority.

- **BCBSA recommends considering the best location for the registry.** “The Committee [SACGHS] also discussed whether such a database should reside at CDC, CMS, or FDA, but recognized that unresolved issues . . . require further analysis . . . about how and where to implement the registry.” Because the registry would be used as a source of information for testing that would be used to directly manage patient care, accuracy and accountability of the information will be extremely important. A voluntary, non-curated registry managed by a research organization (no matter how excellent that organization!) may not be the best solution. A stakeholder process should be used to decide the appropriate location.

BCBSA recommends that a method be devised to encourage accuracy of submitted data. Because the information in this registry will have direct patient impact, it is vital that submitted data be accurate, and not highly selected. A completely voluntary, non-curated registry may not meet this expectation. One possibility may be to coordinate with CMS administrated CLIA or CLIA-deemed laboratory inspections during which randomly selected validation packages for laboratory tests are closely inspected. The data, analysis, and summary information reviewed during the inspection procedure could be compared with the information on the registry, with followup of any discrepancies. Because selection of tests during inspection is random, this would encourage accuracy of all data submissions. Another possibility might be to contract with either the New York State Department of Health, the Food and Drug Administration, or with one or more professional organizations to audit and quality control this data base.

BCBSA also recommends that a CLIA laboratory license be a required element for registry participation. Congress passed the Clinical Laboratory Improvement Amendments (CLIA) in 1988 establishing quality standards for all laboratory testing to ensure the accuracy, reliability and timeliness of patient test results regardless of where the test was performed. A laboratory is defined as any facility which performs laboratory testing on specimens derived from humans for the purpose of providing information for the diagnosis, prevention, treatment of disease, or impairment of, or assessment of health (http://www.cms.gov/CLIA/07_Program_Descriptions_Projects.asp#TopOfPage). Essentially any laboratory providing genetic testing results to a patient or a provider meets this definition and should be licensed under CLIA. Some so-called direct-to-consumer businesses have avoided licensure by claiming that their tests are educational rather than intended for medical decision-making, but recent actions by the FDA suggest that direct-to-consumer tests may be considered medical devices, in which case laboratory licensure will be necessary. **It is important not to include tests in development or research tests that are not used to direct patient care in this registry;** any entry in the registry will be assumed by the user to have some level of vetting for clinical use.

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BCBSA recommends separating the elements of clinical utility and personal utility. Clinical utility is, as noted in the RFI, the net balance of risks and benefits associated with using a test and indicates if/how patient medical outcomes are improved when the test is used to influence management decisions compared to no testing. Such information is critical to evidence-based health technology assessment, formulating medical practice guidelines, and to decisions regarding reimbursement policy. Personal utility (e.g. the desire “to know,” decision-making regarding jobs, purchasing long-term care insurance, etc.) is very important to the patient but is not typically part of medical policy or decision-making.

Thank you for providing this opportunity to offer our perspective; our responses to the specific items for comment listed in the RFI are in the attachment immediately following.

Very truly yours,



Allan M. Korn, MD, FACP
Senior Vice President Clinical Affairs and Chief Medical Officer

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Enclosure

Emailed to: GTR@od.nih.gov

ATTACHMENT: Specific items requested for comment:

1. As noted above, tests in development, research tests not used to direct patient care (i.e. results are not returned to the patient or provider), and any test not run/interpreted in a CLIA-licensed laboratory should not be included. In terms of immediate planning, BCBSA recommends beginning with tests that are not part of neonatal public health testing and those not listed in the GeneTests database. The registry could be planned for eventual expansion to include all genetic or, indeed, all laboratory tests.
2. Potential uses for BCBSA include data for evidence-based health technology assessment; for BCBS Plans, educational information for Plan policy staff regarding scientific basis, test use, patient indications, etc and an evidence base to help develop reimbursement policy.
3. A) CLIA licensure for participating laboratories is a critical gateway.
B) Appropriate information supporting clinical utility is key. It should be clear that evidence that associates the test result with a patient outcome (e.g. odds, risk, hazard ratio) is always considered clinical validity. Clinical utility is either direct evidence (e.g. a randomized controlled trial of test use vs. no test use) or an indirect evidence chain showing that use of the test to change patient management improves outcomes that matter to the patient like morbidity, mortality, or quality of life. One way to show clinical utility may be to measure samples from an already completed randomized controlled clinical trial and conduct a net reclassification improvement analysis (Pencina et al. 2008).
4. A potential risk may be the need for educating patients/other public users regarding the need for evidence and for test ordering/counseling by a provider.
5. Elements for which information is required to exist (e.g. under CLIA regulations for the validation package for a laboratory-developed test) but is not entered should read 'INFORMATION WITHHELD' to make it clear to the database user that existing information was deliberately not entered. In a mandatory registry, all such information should be required.
6. a) Yes
b) Required for participation
c) Name of test. Separate element: new CPT code (in progress; available in 2012)
d) Yes
e) General category (risk assessment; disease diagnosis; prognostic; screening; pharmacogenomic; etc). Specific disease/patient description. Specific intent of test in clinical scenario. Divide into elements as appropriate.
f) Yes. Be very specific.
g) Yes
h) Yes
i) Yes
j) Yes
k) Yes; relevant patents
l) Yes
m) As required by CLIA validation package for laboratory developed tests; see also required elements for manufactured kit inserts
n) Yes
o) See 3B above for information regarding clinical utility, and paragraph above recommending

separation of personal and clinical utility elements. Additional information regarding clinical validity vs. clinical utility can be found in Teutsch et al. 2008.

- p) May be able to ask participants to place test cost within broad ranges. However, as laboratories negotiate costs with clients and do not share this information publicly, exact ranges and costs are unlikely to be available. Coverage policy may vary from plan to plan, and within the same plan, reimbursement may vary depending upon the contract negotiated (which can override coverage policy). Thus, coverage information is not likely to be available, uniform, or helpful.
7. See notes above.
 8. General, non-proprietary information regarding the scientific basis of the test and methods employed are necessary to understand the scope and limitations of the test result, as well as the likely accuracy of the method. Comparison to other similar types of tests ensure that the data submitted for the test of interest are not unusual.
 9. Yes; all known resources should be referenced where relevant including USPSTF and AHRQ systematic reviews, guidelines that incorporate genetic tests (e.g. NCCN, ASCO), and test recommendations (EGAPP). TEC Assessments and Special Reports are accessible via the public website www.bcbs.com/tec .
 10. The registry should include a standard template which ideally would include many elements similar to those included in the device decision summary currently posted on the FDA web page (as appropriate.) Links to GeneTests.org as well as to relevant CMS, CDC (EGAPP) and other related web sites should be considered.
 11. See recommendation above for accuracy of submitted data.
 12. Mandatory registry
 13. See item 2 above
 14. See initial recommendations, pages 1 and 2.

REFERENCES

Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008 Jan 30;27(2):157-72.

Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. *Genet Med*. 2009 Jan;11(1):3-14. Available at www.egappreviews.org .