

Response to Request for Information  
**Genetic Test Registry**

National Institutes of Health

NIH GTR RFI Comments  
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**Background and Context for Response:** The McKesson Health Solutions (MHS) division of McKesson Corporation is entirely devoted to providing information technology and knowledge management services to a wide variety of healthcare entities. The Advanced Diagnostics Management (ADM) business unit of MHS was explicitly launched three years ago to address key infrastructure requirements involving Molecular Diagnostics Testing and Clinical Care Management.

Two years ago, ADM began offering a Master Catalog for Diagnostics Laboratory testing to the commercial market with the following goals (also see Figure 1, Appendix 1):

- Improve the clinical care process by offering objective, evidence-based decision support to clinicians at the point of care - based on access to a comprehensive catalog of tests that includes test selection criteria and practical information about the laboratories that perform the selected tests.
- Improve the transparency of the involved business processes: provide real-time access to patient eligibility and coverage for services; confirm health plan benefits determination related to the specific clinical circumstances of specific patients; and, establish the availability and suitability of the selected tests.
- Provide a mechanism for clinical laboratories to determine pre-authorization requirements and meet reimbursement criteria for more than 400 tests with clinical care criteria and clinical evidence summaries on a payer specific basis.
- Create a specific unique test identifier that would be assigned to each unique test as a tracking code. A test inventor would be assigned a unique tracking code when a new test application is developed and submitted. On-line utilities to manage the Catalog database are in development to permit online data entry by a variety of user roles; assess and document the analytic and clinical utility of the test; provide tools for Tech Assessment personnel; and permit health plans, oversight entities and other entitled entities to enter data regarding health plan benefits and coverage determinations, validation of technical assessments, and manage other pertinent information about catalog entities.

Based on our rapidly accumulating experience with more than 2000 test codes in the Master Catalog, more than 400 Clinical Evidence Summaries, and extensive customer feedback, we wish to respond to the RFI on 3 levels:

- Share information and observations about our experience, pertaining to the RFI questions
- Explore collaborative mechanisms to make the NIH Genetic Test Registry an indispensable resource to the healthcare community
- Explore opportunities for assisting the National Institutes of Health in this initiative, either as a strategic partner, technology services vendor, or application development collaborator.

We appreciate this opportunity to provide our thoughts. At the very least, we would like to link our Master Catalog to the GTR, and, perhaps, at best, we can create or provide the architecture and/or the open web services-based infrastructure for the GTR. We would like the opportunity to discuss these matters with you as the process proceeds.

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The NIH is seeking input and advice on the following items:

1. Are there any types of genetic tests that should not be included in the GTR?  
It is unclear in the RFI whether non-human genetic testing will be included; we believe every effort should be made to include each unique genetic test in the GTR. Expanded categories in the GTR might include:
  - a) DNA / RNA analytics, human
  - b) DNA / RNA analytics, infectious agents
  - c) DNA / RNA analytics, other species, of research and pathological interest
  - d) Chromosome testing and morphology
  - e) Pharmacogenetic (PGx) testing
  - f) Tumor Markers, including DNA/RNA, as well as cell surface and other genetic marker deviations
  - g) Matrix / multi-gene profiles
  - h) Risk Panel Assessment tests

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) policymakers, and
  - 8) electronic health records?

In Figure 1 (below), we have taken a systems approach to stakeholder analysis. We have done extensive work on each of these stakeholders. We believe that there is strong potential for creating additional value for each of these user types in collaborative use cases. An enabling requirement for collaboration is for each unique analytic test to have a unique identifier. The current CPT and HCPCS coding systems do not do this. To the extent that each of the above users contributes to the development and use of new and refined assays for characterizing the molecular basis for biological growth, health, and illness, a systemic method of classifying and identifying each unique assay is ESSENTIAL.

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) policymakers, and
  - 8) electronic health records?

Each of the user categories identified above has unique requirements; the exact list of these attributes will evolve over time – functionality must be provided in the GTR to add fields (attributes), readily access public fields, and maintain private and/or secure fields that contain proprietary information necessary for certain users but not all users.

4. What are the potential benefits and risks associated with facilitating public access to information about the:
  - 1) Availability and accessibility of genetic tests?
    - i. **Benefit:** Systematic organization and presentation of complex and technical information is a critical step in making this data available and intelligible to users in a wide variety of roles. From an ethical perspective, allowing the public to access this information (which we believe is highly desirable) should also be associated with information and references to Genetic Counseling and other ‘expert’ resources.
    - ii. **Risk:** Establishing, maintaining, and (?) credentialing the accuracy of supporting data; inaccurate or misrepresentation may lead to healthcare decisions with unfortunate consequences.
  - 2) Scientific basis and validity of genetic tests?
    - i. **Benefit:** We believe that objective transparency about what information a test does or does not provide is important to all stakeholders.
    - ii. **Risk:** However, not all users of the Registry may have the technical expertise to use Registry information properly, if a scientific format is the primary mode of data presentation.

- 3) Utility of genetic tests?
  - i. **Benefit:** Having clear information about when a test changes the clinical care of a patient and differentiates between alternative therapies is essential to medical decision support when all stakeholders, including patients, are involved.
  - ii. **Risk:** Depending on the accuracy and objectivity of the technical assessment protocols, preliminary assessments may be misleading or subject to change with accumulating clinical experience; this may be confusing or perplexing for some users (e.g., health plans may decide not to cover promising tests if information is perceived to be ‘preliminary’ or ‘not adequately proven.’)

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?

The nomenclature and syntax of the Registry must be readily apparent to users. For example, as is true in other coding systems, the following abbreviations might be considered, as examples:

**NA** = not available  
**NOC** = not otherwise classified  
**NS** = available, but not submitted  
**P** = pending

In other words, all data fields should have an entry.

6. To describe adequately and accurately 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?

We believe that ALL of the following components are critical to the usefulness of the Registry. We are equally clear that this area will be dynamic, over time, as technology evolves, and will look forward to the community responses to this question – we would be pleased to discuss our own experience and approach in detail.

- 1) Contact information (e.g., location, name of the laboratory director, and contact information for the laboratory performing the test)
- 2) Laboratory certifications (e.g., Federal or State certification of the laboratory that performs the test)
- 3) 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))
- 4) Regulatory clearances (e.g., for tests reviewed by the Food and Drug Administration, the 510(k) or pre-market approval (PMA) number)
- 5) Intended use of the test (e.g., diagnosis, screening, drug response)
- 6) Recommended patient population
- 7) 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?)
- 8) Test methodology
- 9) Analyte(s)—What is being measured in the test (e.g., genetic sequence)
- 10) Specimen requirements (e.g., blood, saliva, tissue samples, amniotic fluid)
- 11) Availability (e.g., is the submitter the sole provider of the test or are there multiple providers?)
- 12) Accessibility (e.g., accessible through a health provider, public health mandate, and/or direct-to-consumer)
- 13) Performance characteristics
  - 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  
 This type of information is vital to **any** user’s understanding of the proper use of the test.
- 14) Clinical validity
  - i. Clinical sensitivity
  - ii. Clinical specificity
  - iii. Positive and negative predictive value
  - iv. Prevalence
  - v. Penetrance
  - vi. Modifiers  
 This type of information is vital to any **clinical** user’s understanding of the proper use of the test.

- 15) Utility (*e.g.*, clinical and/or personal utility) or outcomes
    - i. Benefits
    - ii. Harms
    - iii. Added value, compared with current management without genetic testing  
This type of information is vital to any *clinical* user's understanding of the proper use of the test.
  - 16) Cost (*e.g.*, price of the test, health insurance coverage)
7. What types of information might be difficult for test providers to submit and why?  
In some cases, this information is not available. In other cases, certain participants in the system may have inherent conflicts of interest: a test inventor/owner may be unwilling to share known or suspected objective information about limitations or inaccuracies of particular tests. Not all parties are well-suited, qualified, or motivated to provide, validate, and maintain information in the GTR. Some users may be unwilling to provide specific information about proprietary procedures involved in performing a test – unless there are very clear policies for functional and physical privacy and security protocols in place for appropriate data elements.
  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 principle advantage is to permit test users to fully understand the clinical validity and utility of a test – particularly in relation to comparative effectiveness and pricing. Although full transparency may be resisted by test inventors and laboratories that offer a test commercially, the appropriate and prudent use of a test requires substantial if not full disclosure regarding the fundamentals of the testing process. Providing secure and limited access to selectively defined proprietary information (*e.g.* trade secrets) may significantly promote acceptance and use of the Registry.
  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)?  
Yes. Also, it would be extremely helpful to have this information displayed in a summary box with checkboxes (or comparable symbols) indicating additional information available with links to a second level detail layer. There are also valid use cases for including references and access to commercial sources and information generated from the community of users.
  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)?  
This is an appealing, but not essential feature. In most cases, the GTR should come to be the primary source for data capture and retrieval of all information of this type. Allowing suitable information to be downloaded or copied electronically into suitable formats is very appealing.
  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?  
Health plans and other organizations that require submission of a complete test application to the GTR before any consideration is given to technical assessment and reimbursement for commercial purposes would be a major driver for participation in the Registry. For example, having CMS require a GTR entry for any test to be reimbursed through the Medicare or Medicaid program would be a significant incentive for participation. In addition, there are a number of clinical and economic use cases that would serve to provide motivation for participation. Vendors, such as McKesson, are actively exploring a number of these use cases – that depend on uniquely and correctly identifying each test.
  12. What are the most effective methods to ensure continued stakeholder input into the maintenance of the GTR?  
Creating or endorsing a multi-layer "wiki" option would accomplish this – modeled after the format of Wikipedia, with tabs at the top of each page indicating the available layers. Information for the general public in non-technical terms might be displayed at the top level; information for physicians and health professionals at a clinical indications and utility level might be layer two; technical and methodological information would be the bottom layer. Some fields may be 'sacred' or unchangeable, particularly in association with a certification or validation process. However, a blog format for other comments that would permit emerging information to be posted would be very appealing. Some moderation of this site would be essential to ensure suitable content integrity and editorial congruity.

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

McKesson currently uses our Master Catalog as the foundation of a variety of healthcare transaction management applications provided at the point of care (see Appendix A, Figure 1). McKesson Advanced Diagnostics Management would very much like to partner as a key development collaborator of the GTR. In McKesson's 177 years as a business, we have served and been a central connector for all stakeholders of care. For example, we played a key strategic role in the development of the National Drug Code (NDC), and have extensive expertise and experience we wish to bring to this project. At the very least, we would like to link our Master Catalog to the GTR, and, perhaps, at best, we can create or provide the architecture and/or the open web services-based infrastructure for the GTR. Details provided upon request.

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

- i. There must be explicit policies and procedures for identifying obsolete data elements or tests.
- ii. An audit trail, accessible to privileged users, that documents and timestamps ALL database changes is essential. A case can be made for read-only access to the change logs by the general public.

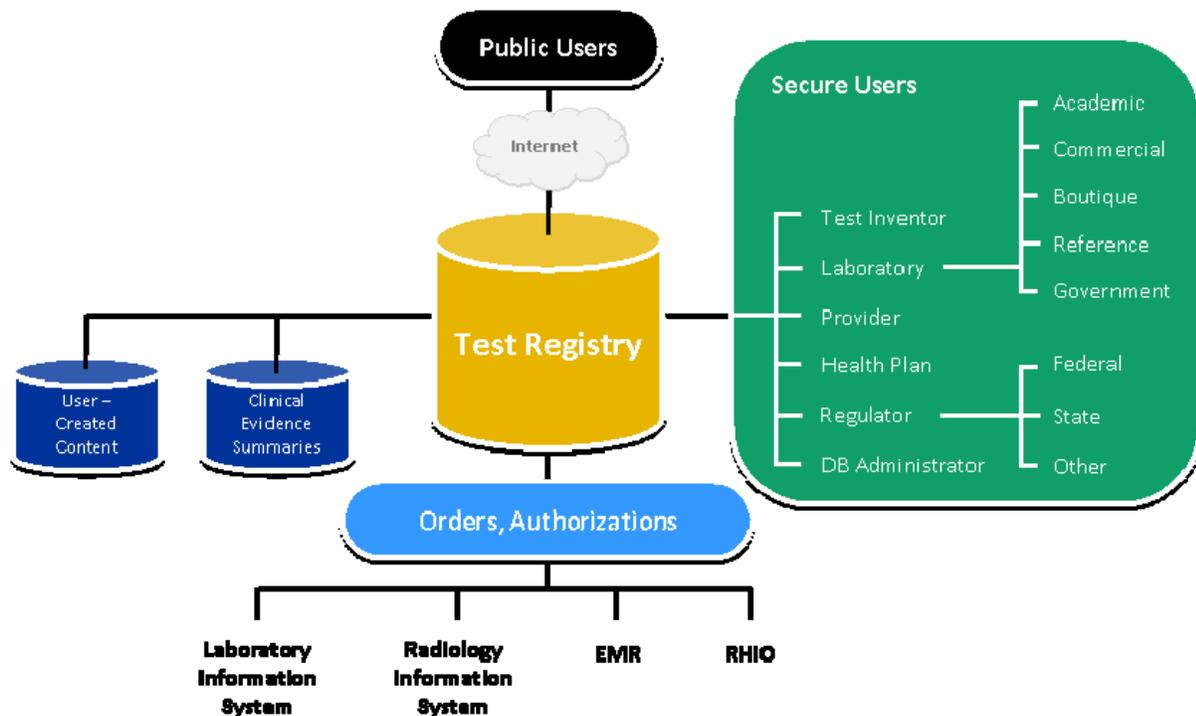
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## Appendix 1: Supplemental Materials

Figure 1: Master Catalog – Global Perspective



The Advanced Diagnostics Management group within McKesson Health Solutions currently offers commercially available software for Point of Care Decision Support – based on a knowledge base architecture depicted in Figure 1.

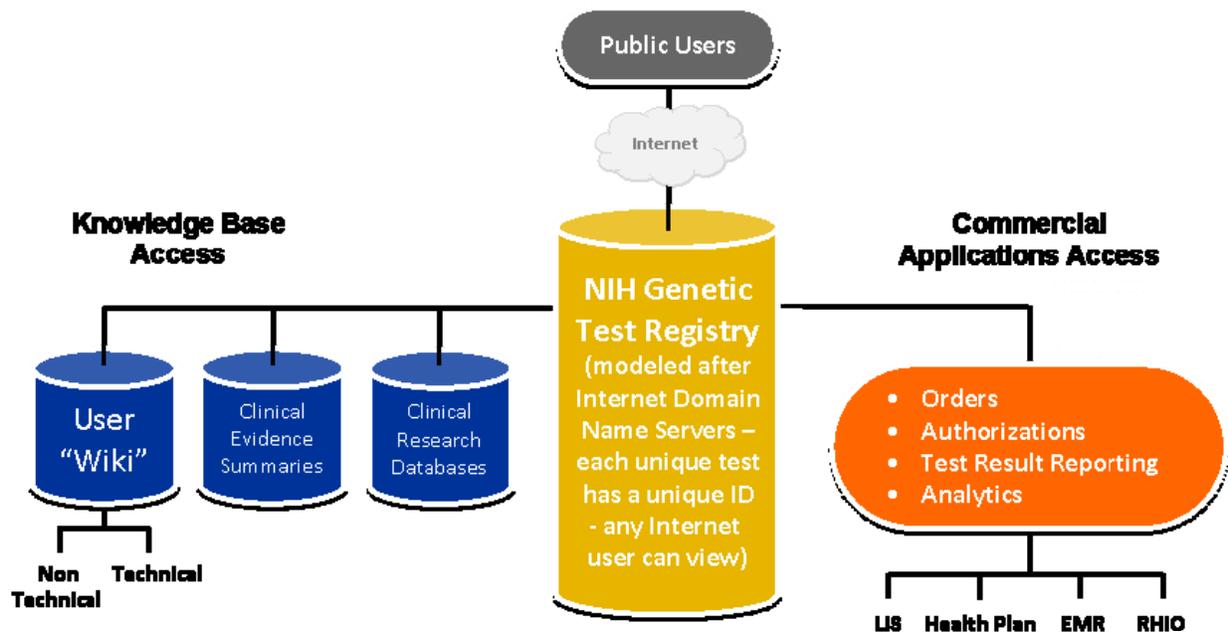
A unique identifier (primary key) is created in the Test Registry for each unique test. This unique identifier is a 5-character alphanumeric code, beginning with the letter 'Z,' and is assigned to any molecular diagnostic test, as a unique identifier and tracking code - if a unique identifier for the test does not already exist as a CPT or HCPCS code. This approach was modeled after the approach utilized for the HCPCS 'S' (or Sxxxx) codes, whereby a defined group of stakeholders (e.g. AHIP, Blue Cross Blue Shield Assn, and others) can request a HIPAA-compliant code – as a 'temporary national code' without explicit endorsement by CMS.

There is no classification schema within the code itself: critical 'identifier' attributes and functions related to the use of these codes are defined in the Master Catalog in dependent data fields linked to the primary identifier (primary key); all other non-critical attributes and functions also reside in dependent but separate fields or files, linked to the primary key identifier – similar to the manner in which Internet developers use the Domain Name Registry (DNR) 'name server' data base as a starting point for developing Internet-based knowledge base linkages. In fact, by defining all attributes dynamically, more than one classification system overlay can be defined for each test – through the use of secondary attribute fields in the Master Catalog. As an example, one classification schema might be devised for the type of laboratory methodology employed, and another classification schema would be related to physiological or pathological categories.

The Z-codes, under suitable circumstances, might be promoted from a unique identifier to full status as HIPAA transaction compliant codes for a variety of purposes including medical service reporting and billing activities. As 5-character alphanumeric codes, they are immediately available for addition to current billing and claims system without further software modifications. If capital letters "I" and "O" are excluded in order to avoid confusion with numerals "1" and "0," more than 1.3 million code combinations are still possible with 34 characters available in positions 2-5.

There are no plans by McKesson to print manuals of these codes or attributes – hard copies of this information would be out-of-date nearly before they are printed.

Figure 2: Master Catalog – Connectivity Opportunities



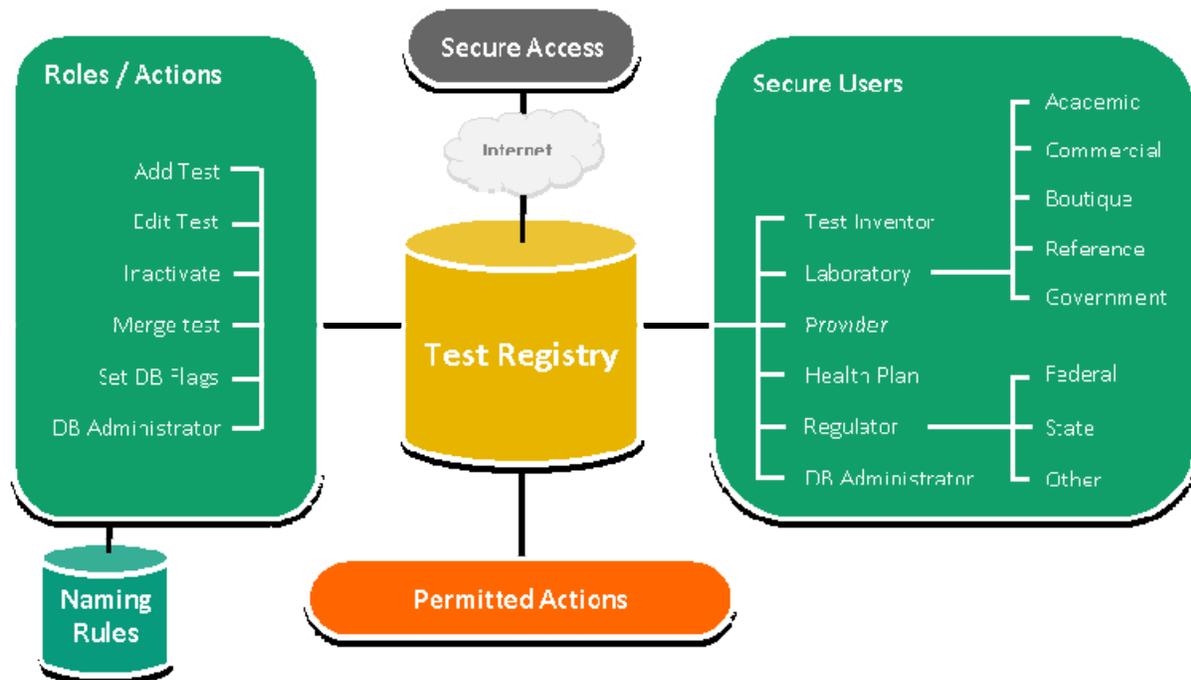
Although the current NIH proposal calls for voluntary registration of tests, there are very important reasons why a single process for standardizing the naming, identification, and utilization of each unique molecular diagnostic test within a single registry would have significant value for the healthcare industry overall. By having a ‘point-of-truth’ in identifying a test in the universal Master Catalog, any confusion about which test is under consideration is eliminated when the possibility of more than one test identifier, as occurs now, is eliminated. Furthermore, this concept should be applied to all laboratory tests with clinical research or commercial value, not just ‘genetic’ tests. In addition to DNA and RNA linked tests, the Registry should include cellular and subcellular markers (e.g. protein, glycoprotein or other complex compounds) such as tumor surface markers and other markers of phenotypic expression. Infectious disease probes and corresponding antibodies would be included. Tests for a variety of pharmacogenomic purposes would be included, as would any other staging or predictive markers for cell behavior. Although more thinking may be needed on the approach to multi-test matrix assays and risk profiling models, these assays may also be important to include in a standardized catalog.

Acknowledging that the NIH may not currently have the authority (or interest) for mandating the registration of all tests mentioned in the preceding paragraph does not mean that such a requirement should not be anticipated or considered in developing the current registry.

The value in having a comprehensive Master Catalog for ALL molecular tests would make the process for building additional applications and connections much simpler over time. It is only important, currently, to consider this connectivity opportunity – not to define every possible future use of the Registry along these lines. In fact, simply standardizing the Catalog will create additional uses that cannot be currently considered until such a possibility is both real and practical.

In the Figure above, several possible linkages are portrayed as examples of the possibilities – not as any suggestion that this number can be fully quantified now or later.

Figure 3: Master Catalog – User Perspective

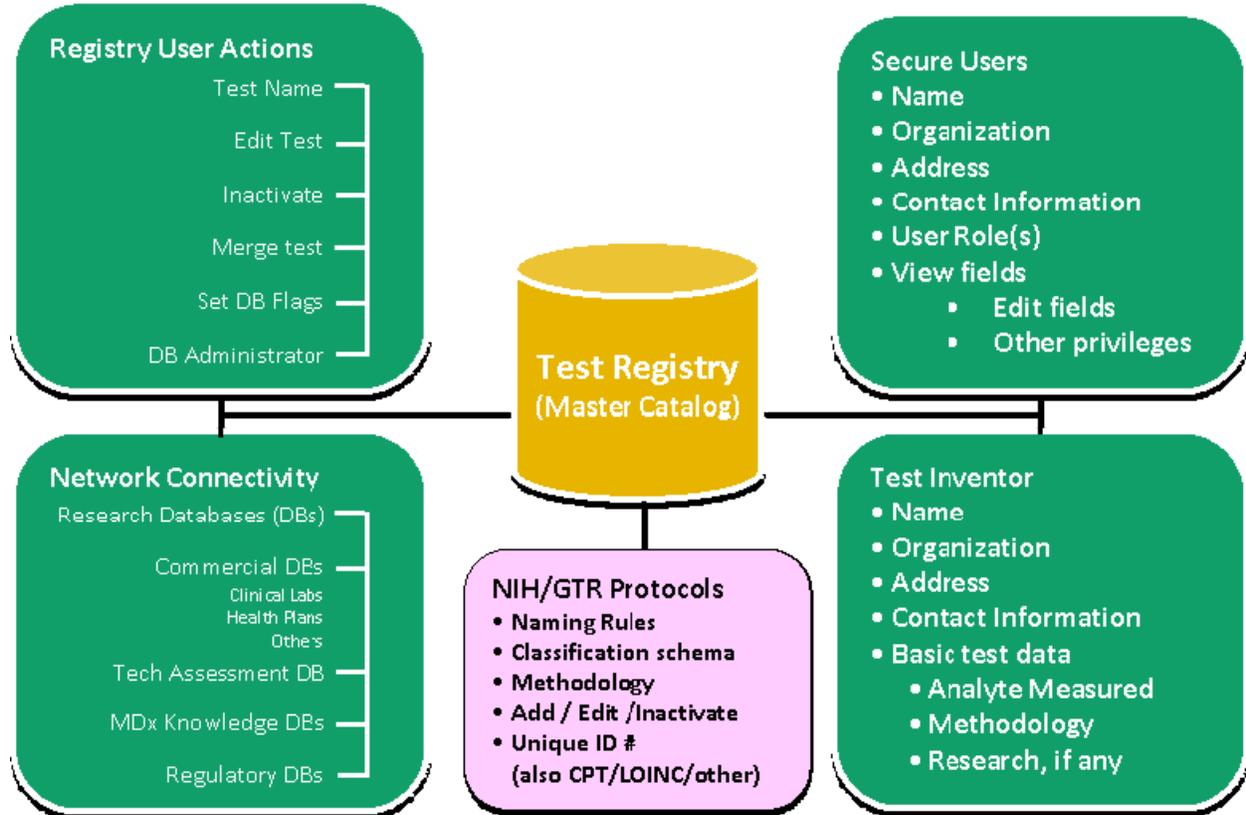


The Test Registry or Master Catalog that we envision would require all of the usual functions and user roles that characterize any database of this type. However, if the concept matures that *this* Registry will ultimately be the universal Master Catalog for all such tests, then additional attention to Which Users may do WHAT becomes important.

For example, a test inventor may be allowed to complete an online application for a new test by submitting sufficient data about the new test that it can be distinguished as unique and distinct from all existing tests already listed in the Registry. Preliminary data provided in a test application under development may need to 'locked' when the final application is submitted; further changes would occur only thru a permitted protocol with change 'logging' and options for administrative oversight in order to maintain knowledge base integrity and security.

Additional detailed considerations of the issues to be considered here are beyond the scope of this RFI but should be considered during the catalog design phase.

Figure 4: Master Catalog – Data Perspective / Data Model



The NIH has an opportunity to define a naming and classification process for molecular testing and test certification that is unprecedented in this field. The lack of such integrity currently is the source of considerable confusion about ‘which test is which test’ when multiple laboratories or users are involved.

For the healthcare community to properly assess and establish the value of various molecular assays (test utility and accuracy, clinical utility and value, as well as economic utility and value), a strong data foundation is required for establishing objective and reproducible user assessments and functions – clearly, this must be a collaborative process involving key stakeholders with many perspectives and interests. Standardizing the data and data management protocols for Molecular Testing is a vital requirement for the ongoing development and productive use of these tests.