

The New NIH Genetic Testing Registry: Peering into the black box of genetic tests

Public Health Genomics Interest Group Seminar Series
NCI Division of Cancer Control and Population Sciences

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The following relationship(s) exist related to this presentation:
No relationships to disclose.

Outline

- Recognizing the black box is a problem, and deciding to do something about it
- Finding out what's in the black box (GTR live demo)
- Thinking outside the box

The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention?

Muin J. Khoury, MD, PhD, Marta Gwinn, MD, MPH, Paula W. Yoon, PhD, MPH, Nicole Dowling, PhD, Cynthia A. Moore, MD, PhD, and Linda Bradley, PhD

T1

From Gene
Discovery to
Health
Application

T2

From Health
Application to
Evidence-based
Guideline

T3

From Guideline
to Health
Practice

T4

From Practice
to Health
Impact

Gene discovery → Genetic tests

Khoury MJ et al. *Genetics in Medicine*, 2007

Some problems

- Pervasive belief that $T1 = T4$
 - Manifest destiny of genetics and genomics

Some problems

Extrapolation from a single example to all of health care



Ransohoff & Khoury v. Gulcher & Stefannson
Eur J Clin Invest 2010

Some problems

Extrapolation from a single example to all of health care, when disease prediction matches disease diagnosis

- Therefore, all predictions are true
- All opportunities to intervene are effective and lifesaving
- All individuals will rationally pursue avenues toward better health
- Numeracy and risk perception are ideal
- No potentially adverse effects need to be considered
- Every observed association will translate into better public health

Genetic test is a basic unit or 'analyte' of genomic medicine

- Subject of a study
- Component of a study

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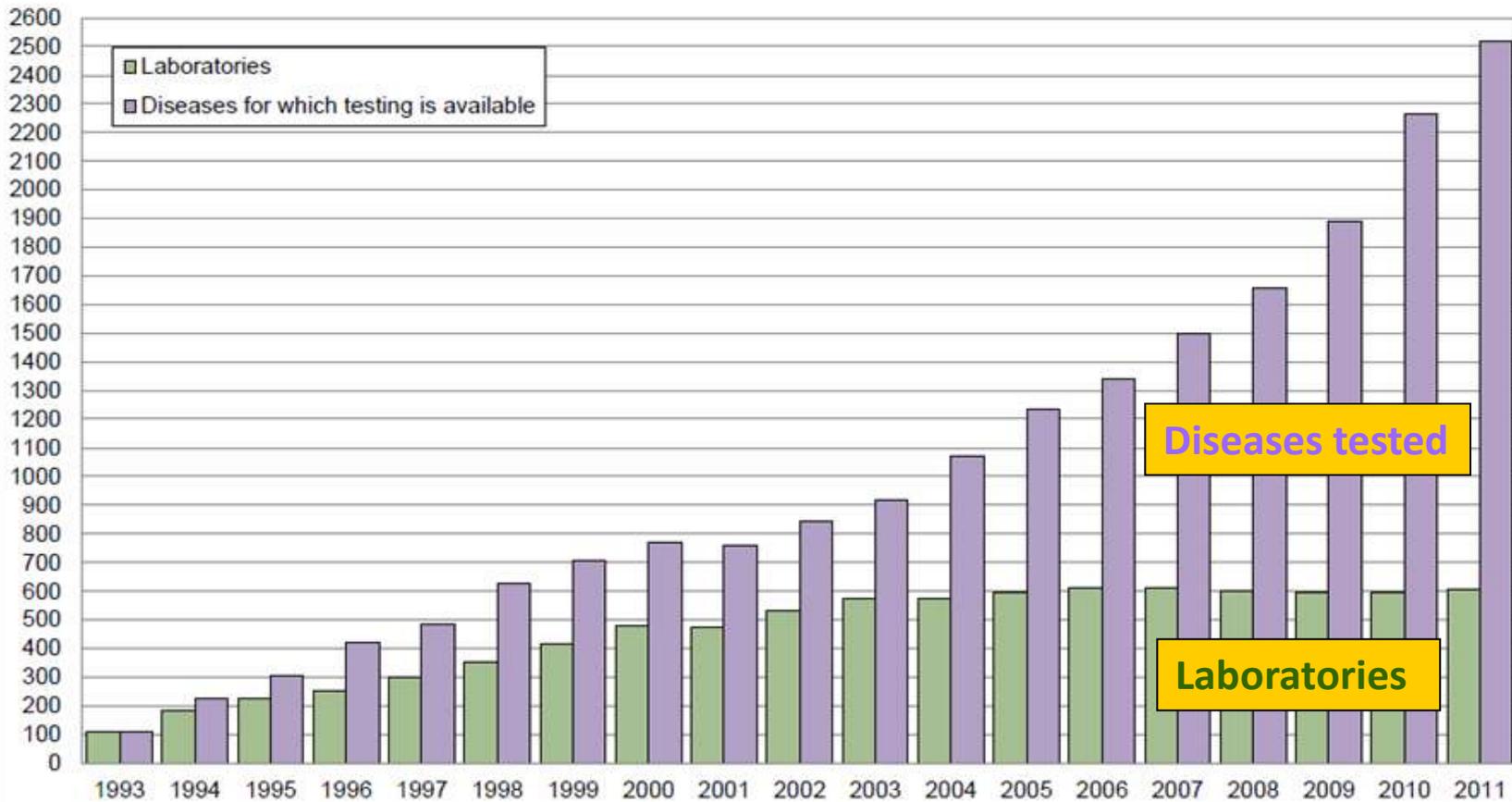
Some more problems

- Information void
 - How many genetic tests are clinically available?

How many genes? How many tests?



Growth of Laboratory Directory



Data source: GeneTests database (2011)/ www.genetests.org

<http://www.ncbi.nlm.nih.gov/sites/GeneTests/>

Some more problems

- Information void
 - How many genetic tests are clinically available?
 - How are these tests performed (methods)?
 - What is the purpose?
 - Are there health benefits?
 - What is the evidence?

Yet more problems

- Which genes have clinically valid tests?
- Which conditions have clinical utility for genetic testing?
- Which variants are pathogenic and which are not?

Yet more problems

- Which genes have clinically valid tests?
- Which conditions have clinical utility for genetic testing?
- Which variants are pathogenic and which are not?

Thinking outside the box

One piece of the puzzle



Recognizing the black box is a problem, and deciding to do something about it

The Call for a Test Registry

Currently, there are tests for more than 2,000 genetic conditions but no single source of information about these tests.

A 2008 Secretary's Advisory Committee on Genetics, Health, and Society report recommended that HHS establish a test registry to increase the transparency of genetic testing.

http://oba.od.nih.gov/oba/sacghs/reports/sacghs_oversight_report.pdf

Other policy and advocacy groups have called for a registry that includes tests across the risk continuum and comprehensive information to enable informed decision making regarding genetic testing.

Javitt G et al. Developing the blueprint for a genetic testing registry. *Public Health Genomics*. 2010;13(2):95-105.

Zonno K. Call for Action from Genetic Alliance. *Registry of Genetic Tests: A Critical Stepping Stone to Improving the Genetic Testing System*. *Genet Test Mol Biomarkers*. 2009; 13(2): 153–154.

Clinical Genomics

- Need database anchored on tests, not diseases
- Must accommodate complex information
 - Arrays
 - Whole genome and whole exome tests

NIH Responds

NIH developed a voluntary genetic testing registry to:

- Encourage providers of genetic tests to enhance transparency by publicly sharing information about the availability and scientific basis of their tests;
- Provide an information resource for health care providers, researchers, and patients to locate laboratories that offer particular tests; and
- Facilitate research and new scientific discoveries.

GTR Development Steps

Date	Step
March 18, 2010	NIH announcement to develop the GTR
June-August 2010	RFI public comment period
November 2, 2010	Public stakeholder meeting
April 2011	Initiated Paperwork Act Reduction process
January 18, 2012	604 labs participating in GeneTests notified of plan to transition to the GTR None opted out
February 7, 2012	Soft launch of the GTR website Tests transitioned from GeneTests to GTR, GTR navigation features, resource links integrated
Feb-March 2012	Open submission site pending approval by the Office of Management and Budget to collect information
Mid- 2012	Realize full potential of the GTR as labs migrate and fully register GTR tests

Stakeholder Input

Input from diverse stakeholders (e.g., test developers, health care providers, industry) throughout GTR development

- 84 public comments from 3 *Federal Register* notices
- 17 public comments from public stakeholder meeting
- 95 comments through “Contact GTR”
- 19 meetings/teleconferences with stakeholder groups
- 3 meetings with other government agencies
- Feedback from presentations at 7 professional meetings
- 10 consultations with two clinical advisory groups

GTR Team

- NIH Office of the Director – Policy oversight
- Jim Ostell, PhD
 - Chief, NCBI Information Engineering Branch
 - Directs NCBI's suite of genome tools and resources
GenBank, dbSNP, dbGaP, RefSeq, PubMed, PubMed Central, etc.
- Wendy Rubinstein, MD, PhD
 - GTR Director
- Donna Maglott, PhD
 - Lead, Database development
- Jennifer Lee, PhD
 - Lead, Web development
- Brandi Kattman, MS, CGC
 - Genetic counselor
- Adriana Malheiro, MS
 - Genetic counselor
- Team of programmers, web developers, usability experts

GTR Advisory Groups

NCBI Medical Genetics Working Group

Christine Seidman, M.D.
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Bryan Traynor, M.D., M.M.Sc.
Tiina Urv, Ph.D.

Phased Approach

Initial phase

- Single-gene tests for heritable mutations, including pharmacogenetic tests
- Multiplex panels and arrays

Subsequent phases

- Tests for somatic mutations (e.g., solid tumors, hematological malignancies)
- Direct-to-consumer tests
- Whole exome sequencing / whole genome sequencing

Data Elements

- Designed to collect the maximum amount of information while taking into consideration
 - Burden on the submitters
 - Input from a variety of stakeholders
- Distinctions between minimal, recommended, and optional fields
- Not included
 - Test price
 - Patents and licensing agreements
 - Turn-around time
 - Proprietary information

Overview of GTR Information

Test information

- Intended use
- Target population
- Assay Limitations
- Methodology
- Analytical validity
- Clinical validity
- Clinical utility
- Ordering information
- Test credentials (e.g., FDA approved/cleared)

Laboratory information

- Contact information
- Certification(s), license(s)

Additional resources

- Other NLM resources and professional practice guidelines well integrated in the GTR

Intended Audience

- Initial target audience is health care providers
- GTR aims to serve a wider audience and to increase usability for
 - Non-genetics health care providers
 - Patients/consumers

Quality of Information

- Code of Conduct
Information that is accurate and not misleading
- Professional organization 'stamp of approval' invited

Code of Conduct

Code of Conduct

Test submitters providing test information to the Genetic Testing Registry (GTR) agree to abide by a code of conduct. Failure to honor this code of conduct may result in the removal of the submitter's test information from the GTR. Submitters agree to the following terms in the code of conduct:

- To uphold the integrity of the GTR through the submission of information that is accurate and not misleading.
- To assure the accuracy of the data at the time of submission and to review and, if necessary, update the submitted information at least once a year.
- To make no explicit or implicit claims that the National Institutes of Health, the Department of Health and Human Services, or the U.S. Government approves or endorses tests listed in, or any other information submitted to, the GTR.

Key features of GTR navigation

- Global search and tabbed searches
- Autocomplete dictionary
- Quickly limit disease search results
 - Tests, OMIM, or *GeneReviews* available
- Quickly filter test results
 - > Condition/Phenotype
 - > Clinical or Research test
 - > Test purpose
 - > Test method
 - > Certifications e.g., NY CLEP-certified
 - > Laboratory Location
- Compare labs and their methodology menus
 - Plan sequential testing in proband and family

Key features of GTR navigation

- Detailed Test pages with overview and tabs
- Discovery Panel – context-specific
 - Clinical practice guidelines e.g., ACMG, EGAPP, CPIC
 - Automated searches e.g., *GeneReviews*, OMIM, Orphanet, PubMed
- Locate a genetics professional
 - ACMG, NSGC, GeneTests, NCI, ABMG, ABGC
- Consumer Resources
 - Print information for your patient from Genetics Home Reference
- Access to NCBI's suite of molecular tools and resources
 - Variation
- Login to MyNCBI to save preferences for displays and retrieval sets
- Stable accession and version history

Nomenclature and Standards

- Challenging!
 - Many overlapping nomenclatures and varied conventions
- The GTR strongly endorses use of established standards
 - GTR will continue GeneTests practice of using the HGNC standard for gene symbols and UniProt for protein names
 - Whenever available, GTR will use disease names from SNOMED CT, and HGVS expressions for variations. Searches by alternate terms will continue.
- We use SNOMED CT - a standard vocabulary for use in Electronic Medical Records
 - Support other standard health record keys such as ICD codes, and LOINC codes
 - Forward-looking to direct connections between electronic health systems and the GTR

All GTR

Tests

Conditions/Phenotypes

Genes

Labs

GeneReviews

Search All GTR

Find all types of GTR records, including tests, conditions/phenotypes, genes, and labs.

 [GTR overview and search tips](#)

Disclaimer: NIH does not independently verify information submitted to the GTR; it relies on submitters to provide information that is accurate and not misleading. NIH makes no endorsements of tests or laboratories listed in the GTR. GTR is not a substitute for medical advice. Patients with specific questions about a genetic test should contact a health care provider or a genetics professional.

<http://www.ncbi.nlm.nih.gov/gtr/>

Finding out what's in the black box
Live demo of GTR

Solving some problems

Secondary (incidental) variants:

which to disclose (and in which settings)?

$\Sigma \rightarrow$ **Whole genome tests**

Solving some problems

- Which genes have clinically valid tests?
Which conditions have clinical utility for genetic testing?

Solving some problems

- Which genes have clinically valid tests?
Which conditions have clinical utility for genetic testing?
- Tests, genes, and variants in GTR
 - Claims and evidence provided by test submitters
 - Stable versioning, can reference unique tests and review as if an analyte
 - Aggregate info per similar tests for professional group
 - ∫ Integrate information by professional group
- ACMG workgroup taking on this task?
 - GTR will display professional stamp of approval

Solving some problems

- Which variants are pathogenic and which are not?

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AATTTGTA CTGATGGTATGGGGCCAAGAGA  
GCCAAGGACAGGTACGGCTGTCATCACTTAG  
CAGGAGCCAGGGCTGGGCATAAAAGTCAGG  
ACAGACACCATGGTGCATCTGACTCCTGA  
GCCCTGGGCAGGTTGGTATCAAGGTTACAA  
TCTGATAGGCACTGACTCTCTGCCTATT
```

ClinVar

ClinVar aggregates information about sequence variation and its relationship to human health.

- ClinVar represents the relationship of genotype, phenotype, and clinical interpretation based on supporting evidence
 - Aggregating information about medically important human variation
 - Structured observations are recorded to facilitate aggregation, comparison, search, and re(evaluation)
- ClinVar is an archive, not an interpretation tool
 - Layers of assertions: Confidence in any assertion is indicated as a range from a single source submission to practice guidelines
- Attribution: Sources are acknowledged, with gateways to publications and external databases
- Terminology consistent with community standards
- Unrestricted availability: Data can be downloaded and integrated into external databases and local analysis pipelines
- Will be a distinct web resource later this year
- Companion resource with Genetic Testing Registry