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Update on Mapping the Landscape of Genetic Tests for Non-Cancer Diseases/Conditions

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Update on Mapping the Landscape of Genetic Tests for Non-Cancer Diseases/Conditions

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This report is based on research conducted by the Tufts Evidence-based Practice Center under contract to AHRQ, Rockville, MD (HSSA 290 2007 10055 I). The findings and conclusions in this document are those of the authors, who are responsible for its contents. The findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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Peer Reviewers

We wish to acknowledge individuals listed below for their review of this report. This report has been reviewed in draft form by individuals chosen for their expertise and diverse perspectives. The purpose of the review was to provide candid, objective, and critical comments for consideration by the EPC in preparation of the final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

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Introduction

Over the past decade, research efforts such as the Human Genome Project and the International Haplotype Map (HapMap) project, coupled with concomitant advances in genomic technologies and bioinformatics, have contributed to an explosive growth in the field of human genomics.[1-3] These developments have resulted in cheaper and more efficient genomic technologies, and they, along with other innovations in medical diagnostics and therapeutics, will soon play a substantial role in everyday clinical practice. Genetic tests can be used for a variety of purposes including screening, diagnosis, disease monitoring, risk stratification, and therapeutic management. In addition, genetic tests can be helpful in predicting outcomes and can be used as clinical decisionmaking tools. As new assays become available for clinical use, it is crucial for patients, clinicians, and payers to be well informed as to the breadth of genetic testing available and the appropriate contexts in which they should be used.

To that end, the Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested the Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ) map the landscape of genetic tests available for non-cancer diseases/conditions. AHRQ assigned this project to the Tufts Medical Center Evidence-based Practice Center (Contract Number: HHSA 290 2007 10055 I). The current report presents an updated list of genetic tests for non-cancer conditions, adding those identified since the 2007 and 2010 horizon scan reports on Genetic Testing for Non-Cancer Conditions sponsored by the CMS and funded through the AHRQ.[4,5] A report concerning genetic tests for cancer conditions is forthcoming in 2013. The goal was to identify genetic tests for non-cancer conditions that are already in clinical practice and are applicable to the Medicare population. Eligible tests were reviewed and summarized for inclusion in an electronic database.

Objectives

The main objective of this report is to provide a broad but succinct overview of each identified genetic test, and to provide a preliminary estimate of the amount of published literature currently available for each genetic test. The report and the accompanying database serve as a ready reference for decisions on generating future topics for systematic reviews. The contents of the database reflect data obtained from manufacturers' Web sites or other Internet sources and should not be construed as definitive clinical evidence. This report is not meant to serve as an in-depth or systematic review. A systematic evaluation of the topic or of selected tests is left to future reviews.

Methods

We adopted the 2007 and 2010 horizon scan report on Genetic Testing for Non-Cancer Conditions as a model for this report.[4,5] We adopted all the terminologies used in the previous report. As part of this project, we also developed an internal database to collect information on genetic tests. The current report represents the updated state of this database of genetic tests for non-cancer conditions and provides concise summaries for all newly identified tests since 2010. For readers' convenience, some sections from the 2010 horizon scan report on Genetic Testing for Non-Cancer are reproduced in this section.

Terminologies, Definitions, and Eligibility Criteria

Genetic Test Definition

We adopted the National Institutes of Health (NIH) working definition for genetic tests drawn from the 2008 Report of the Secretary's Advisory Committee on Genetics, Health, and

Society (http://oba.od.nih.gov). (Please note that this definition may change as technologies continue to evolve.)

> "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."

Eligibility Criteria

Inclusion Criteria

We included genetic tests already in use in clinical practice and would impact the health outcomes of the population of interest (adults in the Medicare age group). We included genetic conditions that could manifest in adulthood, such as Huntington's disease (a degenerative brain condition). We also included genetic tests for diseases/conditions whose symptoms may be recognized until adulthood, even though the onset may have begun at an early age (e.g., Marfan syndrome, a connective tissue disorder). We included tests that aided in the diagnosis, treatment, prediction, and prognosis of non-cancer disease conditions in adult patients of the Medicare age group, and which met the following criteria:

1) Cleared by the U.S. Food and Drug Administration (FDA), or
2) Conducted in Clinical Laboratory Improvement Amendments (CLIA) certified labs and requiring a physician order, or
3) Conducted by an Internet-based genetic testing service and requiring a physician order.

Exclusion Criteria

We excluded tests performed for the purpose of identifying carrier status of heritable diseases, prenatal diagnosis, and conditions that affect only newborns and children that result in early deaths (e.g., Canavan disease, a degenerative brain disease). We excluded tests targeted for cancer conditions. These tests will be considered in a subsequent report. We excluded tests that are still in research development.

Clinical Applications of Genetic Tests

For the clinical applications of genetic tests that are covered in this report, we mostly adopted the terminologies used in the previous horizon scan reports on Genetic Testing for Non-Cancer Conditions. The following categories were used to describe the different applications for the various eligible genetic tests:

1) **Prevention:** To detect inherited susceptibility to adult-onset non-cancer conditions in persons who do not have the disease in order to initiate appropriate interventions.
2) **Diagnosis and management:** Includes confirming, classifying, and predicting the typical course of a disease; choosing type of treatment (e.g., lifestyle modifications or medical therapy); monitoring response to therapy; and predicting outcomes (predictive tests).

Tests that were categorized as aiding in diagnosis and management were further classified into diagnostic, prognostic, and monitoring.

1) **Diagnostic:** Test used to confirm or aid in the diagnosis of the particular disease.
2) **Prognostic:** Information from the test can be used to determine or predict the aggressiveness of the disease or overall outcome of the disease, at the time of initial

diagnosis and prior to initiation of treatment. Prognostic information can then be used to determine a particular or individualized treatment plan.

3) **Predictive**: Information from the test can be used to determine or predict overall outcome of the disease with treatment.
4) **Monitoring:** Test used to monitor tumor and/or patient response to treatment.

Searches

We conducted focused searches of grey literature sources, including online genetic databases, registries, and laboratories, to identify new genetic tests that are currently in clinical use. One definition of grey literature is, "that which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers".[6] Listed below are Web sites that were frequently visited to gather information on new genetic tests.

Description of Grey Literature Sources

1) **Genetic Testing Registry:** Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr) is a Web site funded by the National Institutes of Health (NIH), with an overarching goal to advance public health and research into the genetic basis of health and disease. The NIH Genetic Testing Registry (NIH GTR) has been available since February 2012 as a central location for genetic test information submitted voluntarily by providers. The current scope includes the purpose, methodology, validity, and evidence of usefulness of the tests, as well as laboratory contacts and credentials. This Web site also includes materials that were previously available at the GeneTests.org.

2) **GeneTests:** GeneTests (http://www.genetests.org) is a Web site funded by the NIH and sponsored by the University of Washington in Seattle. The current Web site includes links to the International Laboratory Directory, the International Genetics Clinic Directory, GeneReviews, and Educational Materials. The purpose of this Web site is to provide medical genetics information to physicians, other healthcare providers, and researchers. GeneTests.org is available free of charge to all interested persons. GeneReviews is authored and reviewed by experts in the field of genetics, updated and/or revised periodically as clinically relevant material emerges. GeneReviews allows searches to be conducted by disease name, gene symbol, chromosomal locus, protein name, feature, Online Mendelian Inheritance in Man (OMIM) number, author, or title. The GeneTests.org reports that the International Laboratory Directory is a voluntary listing of laboratories offering molecular genetic testing, specialized cytogenetic testing, and biochemical testing for inherited disorders. We obtained information related to testing, clinical uses, and other resources from the GeneReviews section of the GeneTests.org Web site. We also utilized the links to commercial diagnostic laboratories that were provided by testing sources to explore the specimen collection methods, methodology, and genetic disease/condition descriptions.

3) **Google News:** We searched Google News (http://www.news.google.com) using the following search terms: ("gene OR genetic OR genomic test OR epigenetic OR proteomic") AND ("FDA cleared OR clearance"). The news items and their links were automatically deposited into an email system to give daily email alerts. The alerts were screened periodically (weekly or biweekly basis). We visited Web links listed in the news

items. We also visited Web sites for relevant laboratories that appeared in the news items to identify any new genetic tests.

4) **Commercial diagnostic laboratories:** These laboratory Web sites were screened to identify genetic tests that are available for routine clinical use. We also identified the Web sites of companies or major commercial laboratories in the US, such as Roche Diagnostics®, Quest Diagnostics®, LabCorp®, and Arup Laboratories. A complete list of systematically queried laboratories and their Web sites can be found in **Table 1**. For any potential genetic tests that were mentioned in these Web sites, we conducted focused Internet searches by including the specific test names to find more information, including other manufacturers, suggested uses, and press releases.

5) **Other Internet sites:** At the direction of experts in the field of genetics, we searched for news tests available at the following Web sites: PHG Foundation (phgfoundation.org) and EGAPP Reviews (egappreviews.org).

6) **The Office of In Vitro Diagnostics Device Evaluation and Safety (OIVD):** OIVD (http://www.fda.gov/cdrh/oivd/consumer-otcdatabase.html) is part of the FDA Center for Devices and Radiological Health. The OIVD regulates all aspects of in-home and laboratory diagnostic tests (*in vitro* diagnostic devices, or IVDs), helps new IVDs reach the medical marketplace, prevents the sale of unsafe or ineffective IVDs, and categorizes the complexity of IVDs according to the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88), which defines the type of regulatory oversight applied. The OIVD Web site (http://www.fda.gov/cdrh/oivd) was explored to identify genetic tests currently cleared by the FDA. The search of this Web site for approved genetic tests requires

unique product-specific queries. Further explorations of the Genomics Web site at the FDA were also conducted.

7) **FDA Pre-market Approval:** We searched the FDA's online pre-market approval database (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm). The Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act established three regulatory classes for medical devices. The amendments define a Class III device as "one that supports or sustains human life or is of substantial importance in preventing impairment of human health or presents a potential, unreasonable risk of illness or injury." All devices placed into Class III are subject to pre-market approval requirements. Pre-market approval by the FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices.

8) **PharmGKB:** PharmGKB (www.pharmgkb.org) is a Web site maintained by Stanford University. The two currently developing fields of pharmacogenetics (focuses on single genes) and pharmacogenomics (focuses on multiple genes) were identified as possibly providing insights into the inter-individual variability of drug responses. As such, we also culled genetic tests from the PharmGKB (www.pharmgkb.org) Web site.

9) **American Medical Association's (AMA) Current Procedural Terminology (CPT) Editorial Panel 2012:** We reviewed the list of genetic tests available in the AMA CPT Editorial Panel 2012 and examined those against the tests that were previously available in our genetic test database.

10) **GAPP Finder:** GAPP Finder (http://www.hugenavigator.net/GAPPKB/topicStartPage.do) is an online resource of a searchable knowledge base of genomic applications in practice and prevention. The

GAPP Finder is supported by Center for Disease Control Office of Public Health Genomics.

Updating the Database

Horizon scanning has been ongoing since 2007 by the Tufts EPC, and our internal database is continuously updated as genetic tests are identified. The results of grey literature searches, along with concise summaries of each identified test, are added to this database monthly.

Tracking the Evolution

We conducted grey literature searches in March 2012 to identify whether the 90 genetic tests (targeting 101 different diseases, herein referred as test-disease combination) identified in our 2007 report remained available. In addition, we searched the FDA Web site to identify whether these tests have been cleared by the FDA.

Table 1. Web sites that were investigated to identify new genetic tests for non-cancer conditions

Description	*URL*
Quest Diagnostics®	http://www.questdiagnostics.com
LabCorp®	http://www.labcorp.com
Roche Diagnostics®	http://www.roche-diagnostics.us
Athena Diagnostics, Inc.	http://www.athenadiagnostics.com
GeneDx	http://www.genedx.com
Google News	http://news.google.com
FDA News	http://FDAnews.com
Genetic Testing Registry	http://www.ncbi.nlm.nih.gov/gtr
GeneTests	http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests
Ambry Genetics	http://www.ambrygen.com
Harvard Medical School Lab for Molecular Medicine	http://www.hpcgg.org
Mayo Clinic Medical Labs	www.mayomedicallaboratories.com
NeuroMark	www.neuromark.com
Kimballgenetics	www.kimballgenetics.com
Ilgenetics	www.ilgenetics.com
Genelex	http://www.healthanddna.com
Epigenomics	http://www.epigenomics.com
Correlogic	http://www.correlogic.com
DeCODE	http://www.decode.com

Individual Test Summaries

Once the list of current genetic tests was updated, a series of concise summaries of each test in the database was compiled using data extracted from various sources, including manufacturers' and other publically available Web sites. Included in these summaries was a more detailed description of the test and its clinical use. Each summary included the following items:

- **Test name:** The majority of the clinically available genetic tests were identified either by the disease/conditions or by the disease-causing genes, without any specific test name. Hence, gene names, protein, and disease/conditions often served as surrogate identifiers for genetic tests. When available, we recorded the specific test name.
- **Test description:** A brief summary of a genetic or genomic test and its association with the non-cancer condition.
- **Purpose:** The clinical applications of genetic tests include primary or secondary prevention, diagnostic, prognostic, recurrence, and monitoring.
- **Availability:** A brief list of laboratories, including commercial and academic laboratories in the US and other countries.
- **Specimen:** The specimen (e.g., whole blood, buccal swab, etc.) that was utilized to evaluate gene-disease condition.
- **Diseases:** A list of disease conditions for which a genetic test was utilized (e.g., dilated cardiomyopathy, psoriatic arthritis, etc.).
- **Clinical uses:** Applications in a clinical setting (e.g., routine use, investigational use, etc.).

- **Source:** A list of additional sources that was typically consulted for information about a genetic test application.
- **Exploratory PubMed® search:** The exploratory PubMed search included the name of a genetic or molecular marker, the disease, and the terms "non-cancer condition [mh]" (e.g., dilated cardiomyopathy) and "humans [mh]" connected with the Boolean operator "AND." For tests that use a panel of genetic or molecular markers, we used the brand name of the panel crossed with the search terms. All searches were repeated on 3/1/2012. These search strategies were exploratory, and the number of citations returned was used as a rough estimate of the volume of scientific literature available on each test-disease condition.
- **FDA cleared:** Indicating whether a genetic test has been cleared by the FDA for clinical use.

Description of the Electronic Database

We developed an in-house electronic database that resides within Tufts EPC for the efficient storage and retrieval of the previously described summary information on eligible genetic tests. For convenience, we developed a user-friendly interface that allows for browsing and searching of the database without the need for programming.

MySQL Database

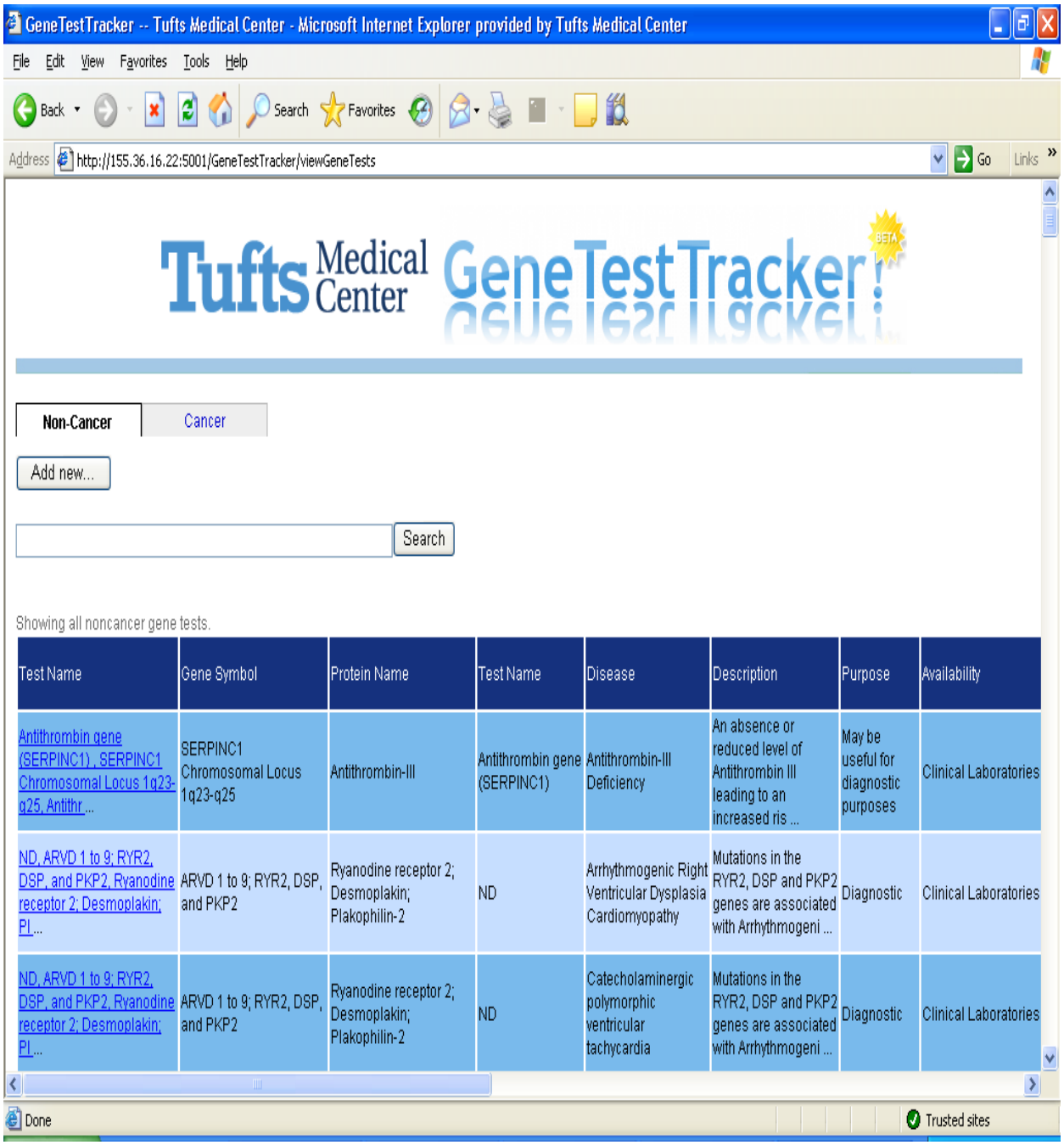
We have created a MySQL (http://www.mysql.com) database to store the collected genetic test information. In this genetic test database, data are separated into cancer and non-cancer genetic tests. We keep a record of all the data needed to generate the summaries for each genetic test.

Front End

While our internal MySQL database stores and indexes genetic tests, accessing the data is not necessarily straightforward for those unfamiliar with MySQL (and the SQL query language). To make the database more widely accessible, we have developed a user-friendly interface through which to access the database, dubbed the "GeneTestTracker." The front end is Web-based and written in the Python programming language (http://python.org), using the Pylons (http://pylonshq.com) Web framework. Having a Web-based program is advantageous because it allows for remote access (via any standard Internet browser), is platform independent, and can be easily updated without requiring users to reinstall software.

Upon logging into the password-protected site, users can see genetic tests in a tabular format; the non-cancer tests are displayed on one tabbed page (**Figure 1**). From this screen, users can add a new genetic test by simply clicking the "Add new" button. Furthermore, users can click on an existing gene test to bring up the corresponding one-page summary. This summary can then be edited or deleted by the user. Additionally, a Microsoft© Word-friendly Rich Text Format (RTF) document can be automatically generated from the summary page, which the user can print out or download to their computer locally. After including appropriate search terms, the database interfaces with PubMed so as to automatically generate the number of citations a search in PubMed turns up for a specific gene test.

Figure 1. The front end to GeneTestTracker, the electronic database that lists genetic and genomic tests.



After logging into the password-protected site, the user sees an HTML page depicting a table. Each row pertains to a specific genetic test. The columns list the test name, gene symbol, protein name, test name, non-cancer condition and description of disease, purpose of the test, availability, specimen, methodology, clinical use, sources, marker, organ, PubMed search

strategies, the number of PubMed hits, the date of update, and the FDA approval status for the test. Above the columns is a search window where the user may search the database for any genetic test within two categories, cancer and non-cancer. The database may be searched using the test name, gene symbol, disease, or laboratory as keywords to find a specific test or any number of tests currently available for a specific disease. The database is currently available for internal use only.

Results

Through grey literature searches, we identified 15 new genetic tests (targeting 17 diseases) for non-cancer conditions available since our 2010 horizon scan report on Genetic Testing for Non-Cancer Conditions. These tests are used to assess non-cancer disease risk associations (13 tests assessing a panel of genes) and pharmacogenomic applications (2 tests). Concise summaries of relevant information concerning these tests are compiled in our internal genetic test database (see Appendix A).

We also confirmed that all 90 genetic tests (101 test-disease combinations) that were listed in our 2007 report remain available for clinical use. In addition, a search of the FDA Web site indicated that only five (targeting three disease conditions) of the 90 tests have been cleared by the FDA. These include: the factor V and MTHFR genetic tests for thrombophilia, UGT1A1 for Crigler-Najjar syndrome and Gilbert syndrome, and a panel of 11 genes in XDx Allomap Molecular Expression testing for acute cellular organ transplant rejection. These are listed in Appendix B, Table 1. For additional information on genetic tests cleared by the FDA, readers of this report should refer to the FDA Web site. The list of pharmacogenomic biomarkers in drug labels posted at the FDA Web site is included in Appendix C, Table 1.

Discussion

Genetic testing is a rapidly emerging field with the potential to dramatically influence clinical decisionmaking. Most of the information for each of the tests we identified was gathered from various public and proprietary Web sites. Laboratories offering genetic testing services provided most of the information on the description of the specific gene(s) involved with a particular disease. The Web sites we used were mostly identified in our previous horizon scan reports on Genetic Testing for Non-Cancer Conditions. Our list encompasses both gene associations of potential biomarkers that are available in clinical use and tests that predict response to clinical use. Our report indicates that there has been an increase in the number of genetic tests for specific non-cancer conditions (e.g., cardiovascular diseases). Compared with earlier reports, recent grey literature searches indicate that many genetic tests are currently being marketed as multi-panel tests (panel of multiple gene evaluations).

A number of efforts to catalogue information on genetic tests have been undertaken by varying national agencies. These online resources provide genetic test information to keep stakeholders abreast of available tests. While all these databases gather information on genetic tests, their methodologies are quite different. The earliest online resource was GeneTests.org, funded by the NIH and sponsored by the University of Washington in Seattle gathers information volunteered by testing providers. More recently, though still nascent, the NIH GTR, which relies solely on information volunteered by testing providers, came online since February 2012.[7] Another, the GAPP Finder, supported by the Center for Disease Control Office of Public Health Genomics, gathers information on genomic tests through systematic surveillance of the Internet.[8] For all these databases, the data gathered can include information on both tests in development and in clinical use.

Because research into genetics progresses rapidly, the logistics of identifying a comprehensive list of genetic tests poses a significant challenge. Our database includes genetic tests identified through active searches conducted in grey literature sources. The present report is valuable as an up-to-date listing and description of genetic tests in current clinical use with a specific applicability to older adults. Although our database is not publicly available (efforts are currently ongoing to make it freely accessible), its contents are updated monthly, peer-reviewed, and then published as reports, biennially. Furthermore, we have used our electronic database for critical evaluation of genetic tests using evidence-based methodology.[9-11]

Potential limitations of this report include the lack of an empirical structure providing guidance on how to conduct optimal grey literature searches of the Internet. For example, searches using modern search engines such as Google are not strictly reproducible. This has been partially overcome by storing Web addresses along with access dates in our database. Another limitation stems from our reliance on Internet searching without further contact with the manufacturers of genetic tests. Currently, this process limits our ability to identify a test with multiple commercial names (for example, a test that has been licensed from one company to another company but carries a different commercial name for the same test) or to identify if changes were made to a test but the name remains unchanged (for example, when additional single-nucleotide polymorphisms are added to a test).

In summary, the current report is a valuable source of genetic tests in current clinical use with specific applicability to older adults. However, we believe that further efforts should be undertaken to integrate different online databases funded through various agencies into one comprehensive registry of genomic tests. In addition, further empirical research is needed to assess the optimal evidence sources for identifying newly clinically available genetic tests.

Progress in translational research will be made only if new products or technologies are used in clinical practice, which requires education and awareness. Health care providers, patients, payers, decision-makers, and consumers can all benefit from staying abreast of the rapidly expanding field of genetic testing.

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Appendix A. One-page summaries of genetic tests for non-cancer conditions

(All Medline searches were conducted on 3/1/2012)

Gene Test Information:

Test Name: Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Testing

Gene Symbol: Five genes (*PKP2; DSP; DSC2; DSG2; TMEM43)*

Protein Name: plakophilin; desmoplakin; desmocollin 2; desmoglein 2; transmembrane protein 43

Description: Arrythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) is an autosomal dominant genetic disorder that affects the desmosomes of cardiac muscle and accounts for approximately 20% of sudden cardiac deaths in young individuals and athletes. Commonly, the presenting symptom of ARVD/C is sudden cardiac death, and therefore genetic testing can detect at-risk individuals whose family members have a history of sudden cardiac death under age 45 or diagnosed ARVD/C.

Purpose: Primary prevention; diagnostic

Availability: Commercial labs

Specimen: Whole blood

Methodology: Amplification by polymerase chain reaction; sequencing of entire protein-coding region; deletion/duplication analysis.

Diseases: Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

Clinical Uses: Can be used to screen patients at risk for sudden cardiac death who may benefit from primary implantable cardiac defibrillator.

Sources: correlagen.com

Medline Searches: (PKP2[All Fields] OR "dsp"[All Fields]) OR DSC2[All Fields] OR DSG2[All Fields] OR TMEM43[All Fields]) AND ("cardiomyopathies"[MeSH Terms] OR "cardiomyopathies"[All Fields] OR "cardiomyopathy"[All Fields]) AND "humans"[MeSH Terms] = 99

FDA Cleared: No

Gene Test Information:

Test Name: Atrial Septal Defect with Atrioventricular Block testing

Gene Symbol: *NKX2-5*

Protein Name: Transcription factors for NKX2-5.

Description: Atrial Septal Defect with Atrioventricular Block is characterized by a congenital opening in the atrial septum in addition to defects in the atrioventricular node. *NKX2-5* mutations are associated with atrial septal defect with atrioventricular block as well as sudden cardiac death. Therefore, testing in symptomatic individuals or those with a family history of the disease may be warranted for possible treatment by percutaneous closure of the septal defect.

Purpose: Diagnostic testing

Availability: Correlagen

Specimen: Whole blood

Methodology: Amplification by polymerase chain reaction; sequencing of entire protein-coding region.

Diseases: Atrial Septal Defect with Atrioventricular Block testing

Clinical Uses: Confirm diagnosis of atrial septal defect; alert risk of potential atrioventricular defect.

Sources: correlagen.com

Medline Searches: NKX2-5[All Fields] AND ("heart septal defects, atrial"[MeSH Terms] OR ("heart"[All Fields] AND "septal"[All Fields] AND "defects"[All Fields] AND "atrial"[All Fields]) OR "atrial heart septal defects"[All Fields] OR ("atrial"[All Fields] AND "septal"[All Fields] AND "defect"[All Fields]) OR "atrial septal defect"[All Fields]) AND "humans"[MeSH Terms] = 46

FDA Cleared: No

Gene Test Information:

Test Name: Celiac Disease Profile-HLA Linkage Disequilibrium: DQA/DQB

Gene Symbol: *HLA-DQ2; HLA-DQ8*

Protein Name: Human Leukocyte Antigens HLA-DQ2; HLA-DQ8

Description: *HLA-DQ2; HLA-DQ8* genes, though common, have a strong association with the development of Celiac Disease, an autoimmune disorder characterized by gastrointestinal symptoms in response to consumption of gluten, a protein found in many grains. It is thought that the HLA-DQ2 and HLA-DQ8 antigens tightly bind, and present gluten peptides to antigen-specific T-cells, which induces T-cell proliferation and resulting inflammation and symptoms.

Purpose: Diagnosis

Availability: LabCorp; Quest Diagnostics

Specimen: Blood; mouth swab

Methodology: Not reported

Diseases: Celiac Disease

Clinical Uses: With high negative predictive value, testing may be performed to rule out Celiac Disease to alternative diagnoses.

Sources: World J Gastroenterol. 2011 May 14;17(18):2259-72; LabCorp.com

Medline Searches: (HLA-DQ2[All Fields] OR ("HLA-DQ8 antigen"[Supplementary Concept] OR "HLA-DQ8 antigen"[All Fields] OR "hla dq8"[All Fields])) AND ("coeliac disease"[All Fields] OR "celiac disease"[MeSH Terms] OR ("celiac"[All Fields] AND "disease"[All Fields]) OR "celiac disease"[All Fields]) AND "humans"[MeSH Terms] = 414

FDA Cleared: No

Gene Test Information:

Test Name: Corus™ CAD

Gene Symbol: 23 genes (IL18RAP; TNFAIP6; CASP5; IL8RB; TNFRSF10C; TLR4; KCNE3; S100A8; S100A12; CLEC4E; NCF4; RPL28; AQP9; SLAMF7; KLRC4; SPIB; CD79B; TMC8; CD3D; AF289562; HNRPF; TFCP2; TSPAN16)

Protein Name: N/A

Description: Corus™ CAD by CardioDX is a blood-base gene expression that integrates the expression levels of 23 genes and other patient characteristics to assess whether individual patient's symptoms may be due to obstructive coronary artery disease (CAD). The patient's blood sample is generally obtained in a primary care or cardiology clinic setting. Given that RNA levels are altered when obstructive CAD is present, the Corus CAD score aids clinicians in the diagnosis of obstructive coronary artery disease. Corus CAD is the first sex-specific test for CAD that accounts for key biological differences between men and women.

Purpose: Diagnosis

Availability: CardioDx, Inc

Specimen: Blood sample

Methodology: Quantitative real time polymerase chain reaction (qRT-PCR)

Diseases: Coronary Artery Disease

Clinical Uses: The test is intended to be used in an outpatient setting with non-diabetic, stable patients who present with typical or atypical symptoms suggestive of CAD, have no history of prior myocardial infarction (MI) or revascularization procedure, and are not currently taking steroids, immunosuppressive agents or chemotherapeutic agents.

Sources: CardioDx® ; Annals of internal medicine citation

Medline Searches: 4 citations available from manufacturer's Web site.

FDA Cleared: No

Gene Test Information:

Test Name: deCODE Cardio test Panel

Gene Symbol: Five markers detected by deCODE AF™; CYP2C19 *2, *3, *4 and *8, and one SNP designated *17 detected by deCODE Clopidogrel™; DNA markers detected by deCODE MI™; DNA markers detected by deCODE T2™; two SNPs on chromosome 9 associated with increased risk of the development of abdominal aortic aneurysm; The deCODEC IA markers that include three SNPs (rs10757278, rs10958409, rs9298506) on chromosomes 8 and 9 associated with risk of IA; the F5 gene encoding factor V deCODE's VTE test.

Protein Name: Cytochrome P-450 enzymes and others

Description: Many genetic variants, or SNPs, affect susceptibility to cardiovascular disease. The deCODE Cardio Scan measures the most comprehensive and up-to-date set of validated genetic risk factors for a range of CV diseases, including all of the risk markers for all of deCODE's individual CV disease tests.

Purpose: Diagnosis and risk assessment

Availability: deCODE

Specimen: Whole blood, buccal swab

Methodology: ND

Diseases: Cardiovascular risk factor assessment

Clinical Uses: Informing, monitoring, and treatment strategies of cardiovascular diseases

Sources: decodehealth.com

Medline Searches: Not conducted due to multiple markers.

FDA Cleared: No

Gene Test Information:

Test Name: deCODE Clopidogrel™

Gene Symbol: CYP2C19 *2, *3, *4 and *8 (loss-of-function alleles), and one SNP designated *17 (the gain-of-function alleles)

Protein Name: Cytochrome P-450 enzymes

Description: Clopidogrel (trade name: Plavix), is an anti-platelet agent used in the treatment for coronary artery disease, peripheral vascular disease and cerebrovascular disease. Clopidogrel requires biotransformation to an active metabolite by cytochrome P-450 enzymes.Recent studies have shown that patients treated with Clopidogrel with a reduced function CYP C219 genetic variant had lower levels of the active metabolite resulting in a reduced antiplatelet response to the drug and a three-fold risk of stent thrombosis. The increased risk for recurrent cardiovascular events in patients with reduced anti-platelet response has been confirmed by several studies.

Purpose: Therapeutic management

Availability: deCODE Health

Specimen: Not documented

Methodology: Not documented

Diseases: Poor metabolizers to clopidogrel / plavix

Clinical Uses: Personalizing Clopidogrel dosing using pharmacogenetics may be an effective method of rationalizing treatment.

Sources: http://www.decodehealth.com/clopidogrel-response

Medline Searches: (CYP2C19[All Fields] OR (("cytochrome p-450 enzyme system"[MeSH Terms] OR ("cytochrome"[All Fields] AND "p-450"[All Fields] AND "enzyme"[All Fields] AND "system"[All Fields]) OR "cytochrome p-450 enzyme system"[All Fields] OR ("cytochrome"[All Fields] AND "p450"[All Fields]) OR "cytochrome p450"[All Fields]) AND 2C19[All Fields])) AND ("clopidogrel"[Supplementary Concept] OR "clopidogrel"[All Fields]) AND "humans"[MeSH Terms] = 254

FDA Cleared: No (has added a Boxed Warning to the label of clopidogrel)

Gene Test Information:

Test Name: deCODE MI™

Gene Symbol: Chromosome 9p21 variants

Protein Name: Not documented

Description: deCODE MI™ can detect genetic component to overall susceptibility to heart attack, risk that appears to be independent of well known risk factors such as elevated cholesterol and hypertension. Large clinical cohort studies have demonstrated that testing even for only the 9p21 markers included in deCODE MI™ shifts a significant proportion of patients either up or down in risk category, impacting guideline LDL targets and statin dosing.

Purpose: Therapeutic management

Availability: deCODE Health

Specimen: Not documented

Methodology: Not documented

Diseases: Risk assessment of heart attack [myocardial infarction (MI)]

Clinical Uses: Risk assessment of heart attack and management of cardiovascular risk factors.

Sources: http://www.decodehealth.com/myocardial-infarction

Medline Searches: (("chromosomes"[MeSH Terms] OR "chromosomes"[All Fields] OR "chromosome"[All Fields]) AND 9p21[All Fields]) AND (acute[All Fields] AND ("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields])) AND "humans"[MeSH Terms] = 10

FDA Cleared: No

Gene Test Information:

Test Name: DNA Drug Sensitivity Testing™

Gene Symbol: Multiple genes including CYP2D6, CYP2C9, CYP2C19, NAT2, UGT1A1, DPD, 5HTT, and CYP1A2

Protein Name: Cytochrome P-450 enzymes and others

Description: Screening of the following genes such as CYP2D6, CYP2C9, CYP2C19, NAT2, UGT1A1, DPD, 5HTT, and CYP1A2 can help predict a person's particular response to many prescription, OTC (over-the-counter) and herbal medicines including those used to treat depression, anxiety, seizures and psychoses; heart disease, cancer, diabetes, and pain. Screening for the aforementioned genes can identify the type of metabolizer including normal, intermediate, poor, and ultraextensive.

Purpose: Therapeutic management

Availability: Genelex.com

Specimen: Buccal swab

Methodology: Not documented

Diseases: Adverse drug reactions to prescription or OTC medications

Clinical Uses: Personalizing treatment and dosing using may be an effective method of treatment.

Sources: http://www.healthanddna.com

Medline Searches: (("cytochrome p-450 cyp2d6"[MeSH Terms] OR ("cytochrome"[All Fields] AND "p-450"[All Fields] AND "cyp2d6"[All Fields]) OR "cytochrome p-450 cyp2d6"[All Fields] OR "cyp2d6"[All Fields]) OR CYP2C9[All Fields] OR CYP2C19[All Fields] OR NAT2[All Fields] OR UGT1A1[All Fields] OR DPD[All Fields] OR 5HTT[All Fields] OR ("cytochrome p-450 cyp1a2"[MeSH Terms] OR ("cytochrome"[All Fields] AND "p-450"[All Fields] AND "cyp1a2"[All Fields]) OR "cytochrome p-450 cyp1a2"[All Fields] OR "cyp1a2"[All Fields])) AND ("pharmacogenetics"[MeSH Terms] OR "pharmacogenetics"[All Fields] OR "pharmacogenomics"[All Fields]) AND "humans"[MeSH Terms] = 1559

FDA Cleared: No (but the aforementioned genes are labeled on medications as Boxed Warning label)

Gene Test Information:

Test Name: Familial Dilated cardiomyopathy

Gene Symbol: Associated with any of at least 24 genes, including *ACTC; LMNA; MYH7; TNNT2; MYBPC3; TNNI3; TPM1*.

Protein Name: Includes lamin A; cardiac myosin heavy chain, beta; cardiac troponin T; myosin binding protein C.

Description: Dilated cardiomyopathy (DCM) is characterized by an enlarged left ventricle with diminished ability to pump blood, leading to progressive heart failure. While there are several types of DCM, familial DCM accounts for approximately 30-60% of cases. Screening at-risk individuals for familial mutations in any one of these 24 genes may identify affected individuals for treatment.

Purpose: Diagnostic

Availability: Available at major lab testing centers

Specimen: Whole blood

Methodology: Amplification by polymerase chain reaction (PCR); sequencing of entire protein-coding region

Diseases: Dilated cardiomyopathy

Clinical Uses: Test may be used to identify sporadic versus familial DCM.

Sources: correlagen.com; NCBI Genetic Testing Registry

Medline Searches: (ACTC[All Fields] OR LMNA[All Fields] OR MYH7[All Fields] OR TNNT2[All Fields] OR MYBPC3[All Fields] OR TNNI3[All Fields] OR TPM1[All Fields]) AND ("cardiomyopathy, dilated"[MeSH Terms] OR ("cardiomyopathy"[All Fields] AND "dilated"[All Fields]) OR "dilated cardiomyopathy"[All Fields] OR ("dilated"[All Fields] AND "cardiomyopathy"[All Fields])) AND "humans"[MeSH Terms] = 189

FDA Cleared: No

Gene Test Information:

Test Name: Familial Hypercholesterolemia

Gene Symbol: *LDLR; APOB; (PCSK9*)

Protein Name: Low-density lipoprotein receptor; apolipoprotein

Description: Familial Hypercholesterolemia is an autosomal co-dominantly inherited disease. Gene *LDLR* codes for the low-density lipoprotein receptor (LDLR), the main mediator for clearance of low-density lipoprotein from the plasma. Individuals heterozygous for a mutation in *LDLR* show diminished expressivity of LDLR, and therefore have high LDL cholesterol levels. Homozygous individuals have even higher levels. Significantly high levels of LDL often lead to coronary heart disease.

Purpose: Diagnosis

Availability: Wide use

Specimen: Blood

Methodology: To verify genetic bases for hypercholesterolemia and to guide treatment

Diseases: Hypercholesterolemia

Clinical Uses: Amplification by polymerase chain reaction; sequencing of entire protein-coding region.

Sources: correlagen.com

Medline Searches: (LDLR[All Fields] OR ("apolipoproteins b"[MeSH Terms] OR "apolipoproteins b"[All Fields] OR "apob"[All Fields]) OR PCSK9[All Fields]) AND ("genes"[MeSH Terms] OR "genes"[All Fields]) AND ("familial hypercholesterolaemia"[All Fields] OR "hyperlipoproteinemia type ii"[MeSH Terms] OR ("hyperlipoproteinemia"[All Fields] AND "type"[All Fields] AND "ii"[All Fields]) OR "hyperlipoproteinemia type ii"[All Fields] OR ("familial"[All Fields] AND "hypercholesterolemia"[All Fields]) OR "familial hypercholesterolemia"[All Fields]) AND "humans"[MeSH Terms] = 297

FDA Cleared: No

Gene Test Information:

Test Name: Long QT Syndrome gene analyses (CPT code: 812XX)

Gene Symbol: Duplication-deletion variants - KCNQ1, KCNH2, SCN5A, KCNE1, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, ANK2

Protein Name: N/A

Description: This test is an add-on to the original diagnosis test of Romano Ward Syndrome with the addition of the following genes: KCNQ1, KCNH2, SCN5A, KCNE1, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1 and ANK2.

Purpose: Diagnostic, Prognostic

Availability: Clinical laboratories

Specimen: Blood

Methodology: Duplication/Deletion Variants

Diseases: Romano Ward (Long QT) Syndrome

Clinical Uses: Clinical use(s) for the Medicare population: (a) Confirmatory diagnostic testing; (b) Predictive testing

Sources: American Medical Association's (AMA) Current Procedural Terminology (CPT) Editorial Panel 2012

Medline Searches: (KCNQ1[All Fields] OR KCNH2[All Fields] OR SCN5A[All Fields] OR KCNE1[All Fields] OR KCNJ2[All Fields] OR CACNA1C[All Fields] OR CAV3[All Fields] OR SCN4B[All Fields] OR AKAP[All Fields] OR SNTA1[All Fields] OR ANK2[All Fields]) AND ("genes"[MeSH Terms] OR "genes"[All Fields]) AND ("long qt syndrome"[MeSH Terms] OR ("long"[All Fields] AND "qt"[All Fields] AND "syndrome"[All Fields]) OR "long qt syndrome"[All Fields]) AND "humans"[MeSH Terms] = 333

FDA Cleared: Yes

Gene Test Information:

Test Name: Long QT Syndrome gene analyses (familial sequence variant)

Gene Symbol: Familial sequence variant - KCNQ1, KCNH2, SCN5A, KCNE1, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, ANK2

Protein Name: N/A

Description: This test is an add-on to the original diagnosis test of Romano Ward Syndrome with the addition of the following genes: KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1 and ANK2.

Purpose: Diagnostic, Prognostic

Availability: Clinical laboratories

Specimen: Blood

Methodology: Full Sequence Analysis

Diseases: Romano Ward (Long QT) Syndrome

Clinical Uses: Clinical use(s) for the Medicare population: (a) Confirmatory diagnostic testing; (b) Predictive testing

Sources: American Medical Association's (AMA) Current Procedural Terminology (CPT) Editorial Panel 2012

Medline Searches: (KCNQ1[All Fields] OR KCNH2[All Fields] OR SCN5A[All Fields] OR KCNE1[All Fields] OR KCNJ2[All Fields] OR CACNA1C[All Fields] OR CAV3[All Fields] OR SCN4B[All Fields] OR AKAP[All Fields] OR SNTA1[All Fields] OR ANK2[All Fields]) AND ("genes"[MeSH Terms] OR "genes"[All Fields]) AND ("long qt syndrome"[MeSH Terms] OR ("long"[All Fields] AND "qt"[All Fields] AND "syndrome"[All Fields]) OR "long qt syndrome"[All Fields]) AND "humans"[MeSH Terms] = 333

FDA Cleared: Yes

Gene Test Information:

Test Name: Long QT Syndrome gene analyses (CPT code: 812XX)

Gene Symbol: KCNQ1, KCNH2, SCN5A, KCNE1, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, ANK2

Protein Name: N/A

Description: This test is an add-on to the original diagnosis test of Romano Ward Syndrome with the addition of the following genes: KCNQ1, KCNH2, SCN5A, KCNE1, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2

Purpose: Diagnostic, Prognostic

Availability: Clinical laboratories

Specimen: Blood

Methodology: Known Familial Sequence Variant

Diseases: Romano Ward (Long QT) Syndrome

Clinical Uses: Clinical use(s) for the Medicare population: (a) Confirmatory diagnostic testing; (b) Predictive testing

Sources: American Medical Association's (AMA) Current Procedural Terminology (CPT) Editorial Panel 2012

Medline Searches: (KCNQ1[All Fields] OR KCNH2[All Fields] OR SCN5A[All Fields] OR KCNE1[All Fields] OR KCNJ2[All Fields] OR CACNA1C[All Fields] OR CAV3[All Fields] OR SCN4B[All Fields] OR AKAP[All Fields] OR SNTA1[All Fields] OR ANK2[All Fields]) AND ("genes"[MeSH Terms] OR "genes"[All Fields]) AND ("long qt syndrome"[MeSH Terms] OR ("long"[All Fields] AND "qt"[All Fields] AND "syndrome"[All Fields]) OR "long qt syndrome"[All Fields]) AND "humans"[MeSH Terms] = 333

FDA Cleared: Yes

Gene Test Information:

Test Name: The Ambry test: Marfan Syndrome and Marfan-Related Disorders Next-Gen Sequencing Panel

Gene Symbol: ACTA2, CBS, FBN1, FBN2, MYH11, COL3A1, SLC2A10, SMAD3, TGFBR1 and TGFBR2 genes

Protein Name: Not documented

Description: Marfan Syndrome is an autosomal dominant, multisystem disorder characterized by cardiovascular, skeletal, and ocular abnormalities. One of the major features of Marfan syndrome (MFS) and the majority of Marfan- related disorders is an increased risk for Thoracic Aortic Aneurysms (TAAs), which if left untreated, has a high morbidity and mortality rate. Three genes have been associated with familial nonsyndromic TAAs: TGFBR2 in TAA2, ACTA2 in TAA4, MYH11 in familial TAA and patent ductus arteriosus. Sporadic forms of TAAs have also been reported. To date, ten genes (ACTA2, CBS, FBN1, FBN2, MYH11, COL3A1, SLC2A10, SMAD3, TGFBR1, and TGFBR2) have been associated with various forms of MFS and Marfan-related syndromes.

Purpose: Prognosis, Therapeutic management

Availability: Ambry Genetics™

Specimen: Whole blood, buccal swab

Methodology: Polymerase chain reaction (PCR) and Next-Gen sequencing and Sanger sequencing

Diseases: Marfan Syndrome (MFS) and Marfan Syndrome related disorders

Clinical Uses: Can aid diagnosis and management in patients suspected to have Marfan Syndrome and Marfan Syndrome related disorders. The test may also be considered for differential diagnosis, carrier testing for individuals with a family history.

Sources: http://www.ambrygen.com/panels/marfan-syndrome-and-marfan-related-disorders-next-gen-sequencing-panel

Medline Searches: (ACTA2[All Fields] OR CBS[All Fields] OR FBN1[All Fields] OR FBN2[All Fields] OR MYH11[All Fields] OR COL3A1[All Fields] OR SLC2A10[All Fields] OR SMAD3[All Fields] OR TGFBR1[All Fields] OR TGFBR2[All Fields]) AND MARFAN[All Fields] AND "humans"[MeSH Terms] = 366

FDA Cleared: No

Gene Test Information:

Test Name: Narcolepsy Profile

Gene Symbol: *HLA-DRB1*15; DQB1*0602*

Protein Name: Not documented

Description: Narcolepsy is a nervous system disorder characterized by excessive sleepiness and frequent daytime sleep attacks. The etiology is not fully known, though it is associated with the *DRB1/DQB1* alleles.

Purpose: Research purpose, Therapeutic management

Availability: LabCorp and other international laboratories

Specimen: whole blood

Methodology: Polymerase chain reaction – targeted mutation analysis

Diseases: Narcolepsy, cataplexy

Clinical Uses: Diagnosis; research.

Sources: labcorp.com; PubMed

Medline Searches: (HLA-DRB1*15[All Fields] OR ("HLA-DQB1 antigen"[Supplementary Concept] OR "HLA-DQB1 antigen"[All Fields] OR "dqb1 0602"[All Fields])) AND ("genes"[MeSH Terms] OR "genes"[All Fields]) AND ("narcolepsy"[MeSH Terms] OR "narcolepsy"[All Fields]) AND "humans"[MeSH Terms] = 57

FDA Cleared: No

Gene Test Information:

Test Name: Pan Cardiomyopathy Panel

Gene Symbol: Pan Cardiomyopathy Panel - 46 genes (HCM panel 18 genes; DCM panel 24 genes; ARVC/CPVT panel 8 genes; and LVNC panel 10 genes)

Protein Name: N/A

Description: Hypertrophic cardiomyopathy (HCM) is characterized by unexplained left ventricular hypertrophy (LVH) in a non-dilated ventricle. To date, over 1000 variants have been identified in genes causative of HCM, most of which affect the sarcomere, the contractile unit of the cardiac muscle. Dilated cardiomyopathy (DCM) is characterized by ventricular chamber enlargement and systolic dysfunction with normal left ventricular wall thickness. To date, over 40 genes have been demonstrated to cause DCM. Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is characterized by replacement of myocytes by fatty or fibrofatty tissue, mainly in the right ventricle. The resulting manifestations are broad and include ventricular tachyarrhythmias and sudden death in young individuals and athletes. ARVC is typically inherited in an autosomal dominant fashion with incomplete penetrance and variable expressivity and to date, 5 ARVC genes (DSP, DSC2, DSG2, PKP2, TMEM43) have been identified. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is typically characterized by exercise induced syncope due to ventricular tachycardia in individuals without structural heart disease. Two CPVT genes are known to date (RYR2 – autosomal dominant; CASQ2 – autosomal recessive). Left ventricular noncompaction (LVNC) has recently been established as a specific type of cardiomyopathy and is often familial, and the genetic spectrum is beginning to emerge although it is not yet well defined. LVNC genes reported to date include ACTC, DTNA, LDB3, MYBPC3, MYH7, TAZ, and TNNT2.

Purpose: Clinical diagnosis, Therapeutic management

Availability: Center for Personalized Genetic Medicine, Harvard Medical School.

Specimen: Whole blood

Methodology: A combination of next generation sequencing technology and Sanger sequencing

Diseases: Hypertrophic cardiomyopathy (HCM); Dilated cardiomyopathy (DCM); Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC); Catecholaminergic polymorphic ventricular tachycardia (CPVT); and Left ventricular noncompaction (LVNC)

Clinical Uses: Patients with unclear diagnosis and those who have a family history where the number of living affected relatives would allow segregation analysis to establish or rule out pathogenicity.

Sources: http://pcpgm.partners.org/lmm/tests/cardiomyopathy

Medline Searches: Not conducted due to many genes.

FDA Cleared: No

Gene Test Information:

Test Name: Pulmonary Arterial Hypertension (BMPR2)

Gene Symbol: BMPR2 DD

Protein Name: Bone morphogenetic protein

Description: Primary pulmonary arterial hypertension (PAH) is caused by wide spread occlusion/destruction of the smallest pulmonary arteries that increases resistance to blood flow. Most heritable PAH (75%) is caused by a mutation in *BMPR2*. Heritable PAH is autosomal dominant. Retrospective studies suggest that persons with PAH who have a *BMPR2* mutation exhibit more severe disease.

Purpose: Diagnosis

Availability: Arup laboratories; Ambry genetics

Specimen: Whole blood

Methodology: Polymerase Chain Reaction/Multiplex Ligation-dependent Probe Amplification to detect Deletion/Duplication

Diseases: Primary pulmonary arterial hypertension

Clinical Uses: Detection of PAH and management

Sources: Arup laboratories; *GeneReviews*

Medline Searches: (("bone morphogenetic protein receptors, type ii"[MeSH Terms] OR ("bone"[All Fields] AND "morphogenetic"[All Fields] AND "protein"[All Fields] AND "receptors"[All Fields] AND "type"[All Fields] AND "ii"[All Fields]) OR "type ii bone morphogenetic protein receptors"[All Fields] OR "bmpr2"[All Fields]) AND ("genes"[MeSH Terms] OR "genes"[All Fields] OR "gene"[All Fields]) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields]))) AND "humans"[MeSH Terms] = 159

FDA Cleared: No

Appendix B. Evolution of Tests that were identified in the 2007 report

Table 1A. Evolution of Tests that were identified in the 2007 report

Disease	Gene	FDA cleared	Currently available (2011)
Alpha-1-antitrypsin deficiency	SERPINA1	n	y
Alport Syndrome	COL4A5	n	y
Alzheimer's Disease	Phosphorylated-Tau protein, Total-Tau protein and Aß42 peptide	n	y
Alzheimer's Disease Late onset disease	ApoE2, E3, E4 alleles	n	y
Antithrombin-III Deficiency	SERPINC1	n	y
Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy	ARVD 1 to 9; RYR2, DSP, and PKP2	n	y
Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)	CHRNA4, CHRNB2	n	y
Bardet-Biedl Syndrome	BBS10	n	y
Cardiovascular risk assessment	ACE I and II	n	y
Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)	BBS2	n	y
	BBS10	n	y
CADASIL	NOTCH3	n	y
Cerebral Cavernous Malformations	CCM2	n	y
	CCM3 / PDCD10	n	y
Familial Cerebral Cavernous Malformation 1 (CCM1)	CCM1 / KRIT1	n	y
Crigler-Najjar Syndrome	UGT1A1	y	y
Crohn Disease	CARD15	n	y
Cystinosis	CTNS	n	y
Cystinuria	SLC3A1	n	y
	SLC7A9	n	y
Dent disease	CLCN5	n	y
	OCRL	n	y
Dentatorubral-Pallidoluysian Atrophy (Naito-Oyanagi Disease)	ATN1	n	y
Familial Cold Urticaria	CIAS1	n	y
Autosomal dominant frontotemporal dementia.	MAPT	n	y
Rare forms of thalassemia	Hemoglobin E	n	y
Hereditary Inclusion Body Myopathy	GNE gene	n	y
ACVRL1-Related Hereditary Hemorrhagic Telangiectasia	ACVRL1 (ALK1)	n	y

Disease	Gene	FDA cleared	Currently available (2011)
ENG-Related Hereditary Hemorrhagic Telangiectasia (Osler Rendu Weber Syndrome)	ENG	n	y
Hereditary Sensory Radicular Neuropathy Type I, HSN1	SPTLC1	n	y
Gilbert syndrome	UGT1A1	y	y
Hexosaminidase A Deficiency or GM2 Gangliosidoses (Hexosaminidase A-Deficient)	HEXA	n	y
HFE-Associated Hereditary Hemochromatosis	HFE	n	y
Huntington Disease	HD	n	y
Huntington disease-like 2, HDL2	JPH3	n	y
Hyperbilirubinemia, rotor type	nd	n	y
Hyperlipoproteinemia Type III Risk Factor (APOE)	ApoE	n	y
Hypokalemic Periodic Paralysis Type 1	CACNA1S	n	y
Hypokalemic Periodic Paralysis Type 2	SCN4A	n	y
Krabbe Disease	GALC	n	y
Lecithin Cholesterol Acyltransferase Deficiency or Fish-Eye Disease or Norum Disease	LCAT	n	y
Marfan Syndrome	FBN1	n	y
MASS Syndrome	FBN1	n	y
Medullary Cystic Kidney Disease	UMOD	n	y
Membranoproliferative Glomerulonephritis, Type II	CFH	n	y
Metachromatic leukodystrophy	ARSA	n	y
Motor neuropathy	nd	n	y
Dilated cardiomyopathy	MYBPC3	n	y
Dilated cardiomyopathy	MYH7	n	y
Myoclonus-Dystonia	SGCE	n	y
Myotonic dystrophy type 1	DMPK	n	y
Myotonic dystrophy type 2	ZNF9	n	y
Nemaline myopathy	NEB	n	y
Oculopharyngeal Muscular Dystrophy	PABPN1	n	y
Osteoporosis	VDR	n	y
Paget Disease of Bone	PDB1	n	y
	PDB2	n	y
LRRK2-Related Parkinson Disease	LRRK2	n	y
Pink1-Related Parkinson Disease	PINK1	n	y

Disease	Gene	FDA cleared	Currently available (2011)
Patterned Dystrophy of Retinal Pigment Epithelium or Butterfly-Shaped Pigmentary Macular Dystrophy	RDS	n	y
Polycystic Kidney Disease	PKD1 and PKD2 genes	n	y
Polycystic liver disease	PRKCSH and SEC63 genes	n	y
Pompe Disease	GAA	n	y
Porphyria cutanea tarda or idiosyncratic porphyria	UROD	n	y
Primary open angle glaucoma	GLC1B	n	y
	OPTN	n	y
	MYOC	n	y
Primary pulmonary hypertension	BMPR2	n	y
Red cell antigen genotyping (Duffy)	FY	n	y
Red cell antigen genotyping (Kidd)	SLC14A1	n	y
Red cell antigen genotyping (Rh-e)	RHCE	n	y
Renal Tubular Acidosis, Distal, Autosomal Dominant	SLC4A1	n	y
Renal Tubular Acidosis, Distal, Autosomal Recessive	ATP6V0A4	n	y
Retinitis pigmentosa - PRPF3-Related Retinitis Pigmentosa	PRPF3	n	y
Romano Ward (Long QT) Syndrome	KCNQ1	n	y
	KCNH2	n	y
	SCN5A	n	y
	KCNE1	n	y
	KCNE2	n	y
Sialuria	GNE	n	y
SOD1-Related Amyotrophic Lateral Sclerosis	SOD1	n	y
Spastic Paraplegia Type 4	SPAST	n	y
Spinal Muscular Atrophy 4	SMN1 (SMNt)	n	y
Spinal and Bulbar Muscular Atrophy	AR	n	y
Spinocerebellar Ataxia Type 2	ATXN2	n	y
Spinocerebellar Ataxia Type 3	ATXN3	n	y
Spinocerebellar Ataxia Type 6	CACNA1A	n	y
Spinocerebellar Ataxia Type 7	ATXN7	n	y
Spinocerebellar Ataxia Type 10	ATXN10	n	y
Spinocerebellar Ataxia Type 12 (SCA12)	PPP2R2B	n	y
Spinocerebellar ataxia type 14 (SCA14)	PRKCG	n	y
Spinocerebellar Ataxia Type 17	TBP	n	y

Disease	Gene	FDA cleared	Currently available (2011)
Spastic Paraplegia 3	SPG3A	n	y
Spastic Paraplegia 4	SPAST	n	y
Thrombophilia	MTHFR	y	y
Thrombophilia	PROS1	n	y
Thrombophilia	F5	y	y
Transthyretin amyloidosis	TTR	n	y
Tuberous sclerosis I	TSC1	n	y
Tuberous sclerosis 2	TSC2	n	y
XDx Allomap Molecular Expression testing for acute cellular organ transplant rejection	11 different genes	y	y

Appendix C. Pharmacogenomic Biomarkers in Drug Labels from the FDA Web site

Table 1. Pharmacogenomic Biomarkers in Drug Labels from the FDA Web site

Drug	Therapeutic area	Biomarker
Desloratadine and Pseudoephedrine	Allergy	CYP2D6
Celecoxib	Analgesics	CYP2C9
Codeine	Analgesics	CYP2D6
Tramadol and Acetaminophen	Analgesics	CYP2D6
Quinidine	Antiarrhythmics	CYP2D6
Terbinafine	Antifungals	CYP2D6
Voriconazole	Antifungals	CYP2C19
Chloroquine	Antiinfectives	G6PD
Rifampin, Isoniazid, and Pyrazinamide	Antiinfectives	NAT1; NAT2
Abacavir	Antivirals	HLA-B*5701
Boceprevir	Antivirals	IL28B
Maraviroc	Antivirals	CCR5
Peginterferon alfa-2b	Antivirals	IL28B
Telaprevir	Antivirals	IL28B
Carvedilol	Cardiovascular	CYP2D6
Clopidogrel	Cardiovascular	CYP2C19
Isosorbide and Hydralazine	Cardiovascular	NAT1; NAT2
Metoprolol	Cardiovascular	CYP2D6
Prasugrel	Cardiovascular	CYP2C19
Pravastatin	Cardiovascular	ApoE2
Propafenone	Cardiovascular	CYP2D6
Propranolol	Cardiovascular	CYP2D6
Ticagrelor	Cardiovascular	CYP2C19
Cevimeline	Dermatology and Dental	CYP2D6
Dapsone	Dermatology and Dental	G6PD
Fluorouracil	Dermatology and Dental	DPD
Tretinoin	Dermatology and Dental	PML/RARα
Dexlansoprazole (1)	Gastroenterology	CYP2C19
Dexlansoprazole (2)	Gastroenterology	CYP1A2
Esomeprazole	Gastroenterology	CYP2C19
Omeprazole	Gastroenterology	CYP2C19
Pantoprazole	Gastroenterology	CYP2C19
Rabeprazole	Gastroenterology	CYP2C19
Sodium Phenylacetate and Sodium Benzoate	Gastroenterology	UCD (NAGS; CPS; ASS; OTC; ASL; ARG)
Sodium Phenylbutyrate	Gastroenterology	UCD (NAGS; CPS; ASS; OTC; ASL; ARG)
Lenalidomide	Hematology	Chromosome 5q
Warfarin (1)	Hematology	CYP2C9
Warfarin (2)	Hematology	VKORC1
Atorvastatin	Metabolic and Endocrinology	LDL receptor

Drug	Therapeutic area	Biomarker
Carisoprodol	Musculoskeletal	CYP2C19
Carbamazepine	Neurology	HLA-B*1502
Clobazam	Neurology	CYP2C19
Dextromethorphan and Quinidine	Neurology	CYP2D6
Galantamine	Neurology	CYP2D6
Phenytoin	Neurology	HLA-B*1502
Tetrabenazine	Neurology	CYP2D6
Aripiprazol	Psychiatry	CYP2D6
Atomoxetine	Psychiatry	CYP2D6
Chlordiazepoxide and Amitriptyline20	Psychiatry	CYP2D6
Citalopram (1)	Psychiatry	CYP2C19
Citalopram (2)	Psychiatry	CYP2D6
Clomipramine	Psychiatry	CYP2D6
Clozapine	Psychiatry	CYP2D6
Desipramine	Psychiatry	CYP2D6
Diazepam	Psychiatry	CYP2C19
Doxepin	Psychiatry	CYP2D6
Fluoxetine	Psychiatry	CYP2D6
Fluoxetine and Olanzapine	Psychiatry	CYP2D6
Fluvoxamine (1)	Psychiatry	CYP2C9
Fluvoxamine (2)	Psychiatry	CYP2C19
Fluvoxamine (3)	Psychiatry	CYP2D6
Iloperidone	Psychiatry	CYP2D6
Imipramine	Psychiatry	CYP2D6
Modafinil (1)	Psychiatry	CYP2C19
Modafinil (2)	Psychiatry	CYP2D6
Nefazodone	Psychiatry	CYP2D6
Nortriptylin	Psychiatry	CYP2D6
Paroxetine	Psychiatry	CYP2D6
Perphenazin	Psychiatry	CYP2D6
Pimozide	Psychiatry	CYP2D6
Protriptylin	Psychiatry	CYP2D6
Risperidon	Psychiatry	CYP2D6
Thioridazine	Psychiatry	CYP2D6
Trimipramine	Psychiatry	CYP2D6
Valproic Acid	Psychiatry	UCD (NAGS; CPS; ASS; OTC; ASL; ARG)
Venlafaxine	Psychiatry	CYP2D6
Indacaterol	Pulmonary	UGT1A1
Ivacaftor	Pulmonary	CFTR (G551D)
Azathioprine	Rheumatology	TPMT
Flurbiprofen	Rheumatology	CYP2C9