Technology Assessment

Technology Assessment Program

Genetic Tests for Non-Cancer Diseases/Conditions: A Horizon Scan

Agency for Healthcare Research and Quality
540 Gaither Road
Rockville, Maryland 20850

August 28, 2007

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FINAL REPORT
August 28, 2007

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This report is based on research conducted by the Tufts-New England Medical Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0022). The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decision-makers; patients and clinicians, health system leaders, and policymakers, make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Introduction

The Center for Medicare and Medicaid Services (CMS) requested the Tufts-New England Medical Center Evidence-based Practice Center (Tufts-NEMC EPC) to conduct a horizon scan on the use of genetic tests for non-cancer diseases/conditions. CMS would like the report to be a ready reference for their discussions in this area. This report aims to provide a broad review with sufficient information on each test, and to estimate the amount of potential literature available on each test. This report is not meant to be an in-depth review to assess the analytic validity, clinical validity, clinical utility, and ethical issues of each test. In-depth reviews of a test or group of tests would be the subject of future focused reviews. The 2005 horizon scan report on Genetic Testing for Cancer is to be used as a model for this report.(1)

According to the National Human Genome Research Institute, a genetic test is defined as follows (http://www.genome.gov/10002405):

> The analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. Such purposes include predicting risk of disease, identifying carriers, establishing prenatal and clinical diagnosis or prognosis. Prenatal, newborn, and carrier screening, as well as testing in high-risk families, are included. Tests for metabolites are covered only when they are undertaken with high probability that an excess or deficiency of the metabolite indicates the presence of heritable mutations in single genes. Tests conducted purely for research are excluded from the definition, as are tests for somatic (as opposed to heritable) mutations, and testing for forensic purposes.

The population of interest in this report is Medicare age adults in which a genetic test result would directly impact their health outcomes. We included tests that are performed to aid diagnosing, treating, and prognosticating of adult patients. We excluded tests that are performed for the purpose of identifying carrier status of heritable diseases, prenatal diagnosis, conditions that affect only newborns and children resulting in early deaths such as Canavan disease, a degenerative brain disease. We excluded genetic disease/conditions that could lead to cancer conditions such as Birt-Hogg-Dubé (fibrofolliculoma) syndrome. However, we included genetic tests whose symptoms may not have been recognized as a syndrome until adulthood even though the onset could have been at an early age such as Marfan syndrome, a connective tissue disorder. We also included genetic conditions that could manifest in adulthood such as Huntington disease, a degenerative brain disease. This report will also exclude gene-based biomarkers since the aforementioned definition excludes somatic and protein-based tests. Similarly excluded were genetic tests for infectious disease; these were considered beyond the scope of this report.

The aim of this report was to identify genetic tests for non-cancer diseases/conditions that are already in clinical practice, currently in development for clinical care, and/or currently in preclinical stages, with biomarkers being tested for possible genetic associations with various non-cancer conditions. For each of these genetic tests, we gathered information to create a one-page summary. In general, the genetic tests for non-cancer diseases/conditions have no specific names and are usually named after the genetic disease/condition and/or by the gene and methodology of the

specific genetic test. Thus the name of a genetic test can vary from one laboratory to another.

In the 2005 horizon scan report on Genetic Testing for Cancer, we have identified the grey literature as an important source of information. Grey literature can be any documentary material issued by government, academia, business, and industry that includes technical reports, working papers, business documents, and conference proceedings and is not published or indexed commercially.(2) The process of identifying grey literature can be quite challenging, and difficult to locate and obtain. In addition, the lack of an editorial process can limit its reliability and authenticity, thus making it necessary for users to learn the skills for assessing the quality and credibility. Nonetheless, grey literature remains an important source of information produced by researchers and practitioners in the field.

METHODS

Unlike genetic testing for cancer, identifying genetic testing for non-cancer conditions is more challenging due to myriad diseases/conditions and the lack of specific genetic test name. A literature search employing strategies generally used to search for diagnostic test studies yielded over 20,000 citations for genetic testing. Screening a sample of these citations revealed that many of these citations were irrelevant to the current topic. Since there is no published guidance on formulating optimal search strategies for this topic, we took the following approaches to review the grey literature sources:

1. We reviewed “grey literature” for the genetic tests in non-cancer disease/conditions and consulted appropriate experts including neurologists, hematologists, cardiologists, endocrinologists, nephrologists, gastroenterologists, clinical pathologists, and geneticists to ascertain additional genetic tests being used or being marketed for use in the clinics.
2. We identified genetic tests from websites known to have comprehensive genetic testing information such as www.genetests.org (also known as www.genetest.com), commercial laboratories and other relevant sources identified in our previous 2005 genetic testing for cancer conditions.
3. We compiled an initial list of genetic tests identified from various sources and consulted the clinical geneticist at Tufts-NEMC to identify a preliminary and a potential list of genetic tests for non-cancer diseases/conditions that are most applicable to the Medicare population.
4. We reviewed the preliminary list with the staff at CMS for additional input and finalized the list of tests for genetic diseases/conditions.
5. We searched the Food and Drug Administration (FDA) website and consulted FDA staff to ascertain genetic tests that have been approved for clinical use in non-cancer conditions in target population of interest.

We report the genetic tests for non-cancer diseases/conditions that are most applicable to the Medicare age group by the following definitions: disorders solely presented in adulthood, or whose symptoms may not have been recognized as a syndrome until adulthood, and had a mean survival age of greater than 40 or more years. The

disorders that presented in childhood but led to end-stage renal disease (a disease condition covered by the Medicare) were also deemed applicable.

We conducted a grey literature search to identify genetic tests for non-cancer conditions that are either currently available or in development for clinical care. The most efficient method for identifying such tests was to search for genetic tests from websites of the major commercial diagnostic laboratories in the U.S., including but not limited to, Genzyme®, LabCorp®, and Specialty Laboratories®. Early in this process we contacted neurologists, hematologists, cardiologists, endocrinologists, nephrologists, gastroenterologists, clinical pathologists, and geneticists, all or majority of whom directed us to the website www.genetests.org for a comprehensive information on currently available genetic tests. In addition, we explored other company websites, such as Diagene and Genzyme, and www.genedx.com. Several other websites identified in our previous 2005 horizon scan report on Genetic Testing for Cancer was also searched. We used UpToDate® (http://www.utdol.com/application/search.asp), Online Mendelian Inheritance in Man (OMIM), and http://ghr.nlm.nih.gov/ at National Library of Medicine (NLM) to identify the onset and clinical manifestations of genetic diseases that were identified in the grey literature search.

Below is a list of all grey literature sources explored for this part of the project along with a brief description of their contents.

Description of grey literature sources

1. GeneTests (www.genetests.org) is a website funded by the National Institutes of Health and sponsored by University of Washington in Seattle. GeneTests started, as

Helix in 1993 as a national directory of medical genetics laboratories and the name was later changed to GeneTests. The directory went online in October 1996. The current website includes the International Laboratory Directory, the International Genetics Clinic Directory, GeneReviews, and Educational Materials. The purpose of this website is to provide medical genetics information for physicians, other healthcare providers, and researchers. This website is available free of charge to all interested persons. GeneReviews are 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, OMIM number, author, or title. The GeneTests Laboratory Directory is a voluntary listing of laboratories offering molecular genetic testing, specialized cytogenetic testing, and biochemical testing for inherited disorders. Posted on this website are the tests for which laboratories contact GeneTests and provide information. The laboratories are requested to update their information once a year, and to send GeneTests information about new tests that are offered between annual updates. This website provides information on "New Lab Listings" that links to a list of new diseases and services added to the GeneTests Laboratory Directory in the past 30 days. GeneTests do not actively seek out new laboratories or new genetic tests. The "New in GeneReviews" provides information on newly posted reviews, updated reviews, and revised reviews in the past 60 days. We searched the GeneReviews section of this website for each disease/condition or related gene that is linked to the following source of information: testing, research, reviews, and resources sections. We also utilized the links to commercial diagnostic

laboratories provided by testing sources to explore further on the specimen collection methods, methodology and genetic disease/condition descriptions. In addition we contacted the staff at the GeneTests to clarify and obtain more information about the website.

2. Commercial diagnostic laboratories – these laboratories websites were screened to identify genetic tests that are available for routine clinical use. Websites we searched include:

    - Athena Diagnostics – http://www.athenadiagnostics.com
    - Diagene – http://www.diagene.com
    - Genzyme – http://www.genzymegenetics.com
    - LabCorp – http://www.labcorp.com
    - Roche – http://www.roche-diagnostics.com
    - Specialty Labs – http://www.specialtylabs.com
    - Tm Bioscience – http://www.tmbioscience.com
    - GeneDx – http://www.genedx.com
    - Quest diagnostics – http://www.questdiagnostics.com/
    - Mayo clinic – http://www.mayoclinic.org/
    - ARUP Labs – http://www.aruplab.com/

3. LexisNexis (http://www.lexisnexis.com) - LexisNexis provides access to legal, news, public record, and business information through a set of searchable databases that contains several thousands of print material. Sources include public records, The New York Times, CNN, Bloomberg, Dun & Bradstreet, The Associated Press, Biotech Week, and NewsRx, etc. This tool is the global legal information division of

Reed Elsevier. For further information on relevant tests, we visited the developer's website to obtain more information.

4. Web of Knowledge (www.isiwebofknowledge.com) - ISI Web of Knowledge is an integrated website that delivers easy access to high quality, diversified scholarly information in the sciences, social sciences, and arts and humanities, as well as search and analysis tools. This site encompasses both multidisciplinary and specialized content as well as external collections, covering journals (including open access titles) books, proceedings, patents, chemical structures, evaluated Web content, grant funding, and preprints.

5. National Research Register (NRR) (http://www.nrr.nhs.uk/search.htm) - The National Research Register is a database of ongoing and recently completed research projects funded by, or of interest to, the United Kingdom's National Health Service (NHS).

6. Online Computer Library Center (OCLC)'s FirstSearch (http://www.oclc.org/firstsearch/): The OCLC FirstSearch database retrieves records from worldwide conferences, symposia, meetings, expositions, and congresses. This database covers a number of disciplines including the Arts, Humanities, Social Sciences, and Physical and Life Sciences.

7. Google News (http://www.news.google.com) - Google News gathers stories from worldwide and automatically arranges them to present the most relevant news first. Results are compiled solely by computer algorithms, without human intervention, and include articles that have only appeared within the past 30 days.

8. Canadian Institute of Scientific and Technical Information (CISTI) (http://cisti-icist.nrc-cnrc.gc.ca/main_e.html) - CISTI is a source for information in all areas of science, technology, engineering and medicine. CISTI began over 75 years ago as the library of the National Research Council of Canada and became the National Science Library in 1957. It contains several thousands of different serial titles, books, conference proceedings and technical reports, and 2 million technical reports from around the world.

9. ClinicalTrials.gov (http://www.clinicaltrials.gov): ClinicalTrials.gov provides regularly updated information about federally and privately supported clinical research in human volunteers. ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and phone numbers for more details.

10. NY Academy of Medicine (http://www.nyam.org): The Grey Literature Report is a quarterly publication of The New York Academy of Medicine Library alerting readers to new grey literature publications in public health as they are acquired. This report was first published in 1999 and acquires materials from various organizations publishing grey literature and gives them special cataloging treatment.

11. GreyLit Network (http://greylit.osti.gov): The GreyLIT Network is a portal for technical report information generated through federally funded research and development projects. It was developed by the Department of Energy's Office of Scientific and Technical Information (OSTI), in collaboration with the Department of Defense/ Defense Technical Information Center (DOD/DTIC), NASA, and the EPA.

12. Health Services Research Projects in Progress (HSRProj) (http://www.academyhealth.org/hsrproj/search.htm): HSRProj contains descriptions

of research in progress funded by federal and private grants and contracts for use by policy makers, managers, clinicians and other decision makers. It provides access to information about health services research in progress before results are available in a published form.

13. The Office of In Vitro Diagnostics Device Evaluation and Safety (OIVD) (http://www.fda.gov/cdrh/oivd/consumer-otcdatabase.html) OIVD is part of the U.S. Food and Drug Administration's Center for Devices and Radiological Health. 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), thereby defining the type of regulatory oversight applied to the product. The website http://www.fda.gov/cdrh/oivd/ was explored to identify currently approved genetic tests from the FDA. The search of this website for approved genetic tests requires unique product specific queries. The staff at the FDA was contacted through email communication with regard to queries for the website, and regulatory requirements for the non-approved gene tests or “home-brew” tests. Discussions were relevant to pertinent issues such as “home brew” vs. FDA approval, the future of genomic testing, and co-development of drug and diagnostic test. Further exploration of the pharmacogenomic website at FDA and the update websites were also conducted.

14. FDA Pre-market Approval (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 (the 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 FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices.

15. The Office of Rare Diseases (ORD) (http://rarediseases.info.nih.gov/asp/resources/rardis_info.asp) was established in 1993 within the Office of the Director of the National Institutes of Health (NIH). The goals of ORD are to stimulate and coordinate research on rare diseases and to support research to respond to the needs of patients who have any one of the more than 6,000 rare diseases known today. This website provides links to several other websites that provides information on genetic tests in rare diseases/conditions.

16. National Laboratory Network for Rare Disease Genetic Testing (http://www.rarediseasetesting.org/about.php) includes 6 charter laboratories that provides genetic testing needs of families and individuals affected by rare (or orphan) diseases for which genetic testing is not routinely available in appropriately accredited laboratories. NLN member laboratories comply with all accreditation and licensure programs applicable to their region and specialty.

Description of genetic tests for non-cancer diseases/conditions currently available/in development for clinical care

1. We adopted the one-page descriptive summary from our previous 2005 horizon scan report on Genetic Tests for Cancer and summarized information for each currently available genetic test.
2. We conducted MEDLINE search for published literature on currently available genetic tests in non-cancer diseases/conditions to estimate the number of studies on each relevant genetic test.
3. We conducted additional searches and explored further sources of information when needed, depending on results from the above steps.

The one-page summary included the following items: 1) Gene symbol; 2) Protein Names; 3) Disease; 4) Description; 5) Purpose; 6) Availability; 7) Specimen; 8) Methodology; 9) Other Diseases; 10) Clinical use(s) for the Medicare population; 11) Source of Information; and 12) Exploratory Medline Search. The majority of the clinically available genetic tests were identified either by the disease/ conditions or their disease causing genes without any specific test name. Hence the gene names, protein, and disease/conditions served as the surrogate for the genetic testing identifier. These names were used to search for relevant information for each of the items one through three on the description page (items #1-3). The source of the genetic test description for the item four (item #4) as it relates to the disease included National Center of Biotechnology Information: OMIM, GeneTests.org, National Library of Medicine Genetics Home Reference, and UpToDate. GeneTests.org also served as the source for the purpose of the testing, availability, methodology, and clinical use (items #5,6,8,9,10). Supplemental resources for these items included:

- Center for genetic testing at Saint Francis

(http://www.sfh-lab.com/molecular%20test%20listing%201.htm),

- Medical Genetics Laboratory at the Baylor College of Medicine http://www.bcm.edu/geneticlabs/tests/alltests.html
- Athena Diagnostics – http://www.athenadiagnostics.com
- GeneDx – http://www.genedx.com

Though blood is assumed to be universally adequate for genetic testing, preferred specimen data appropriate for corresponding diseases were collected when links to the laboratories were available (item #7).

A crude MEDLINE search was conducted to estimate the number of potentially relevant publications on the topic of genetic testing for the corresponding disease. In electronic searches, we used terms for the specific diseases/conditions (e.g. Marfan syndrome), filtered for specific gene terms (e.g. FBN1), and limits applied to humans. This report lists an estimate of citations available for each of the currently available genetic tests for non-cancer conditions and thus a thorough screening of the abstracts was not conducted for relevancy.

Results

We searched the “grey literature” websites to identify currently available genetic tests and generated a list of tests to be included in this report. Among the websites we searched, GeneTests (www.genetests.org) provided the most comprehensive data on genetic tests currently available for common as well as several rare genetic diseases/conditions. The website lists over 1,000 diseases/conditions with clinically available genetic tests. Three hundred and fifty genetic tests for non-cancer diseases/conditions met our inclusion criteria and were deemed probably applicable to the Medicare population. We created one-page descriptive summary for each of these tests. (Appendix-A). For example, one-page summary for the genetic test of cardiovascular risk assessment or ACE gene testing has the following items included: Gene symbol was identified as the ACE gene located on chromosome 17, protein name as angiotensin-converting enzyme, and the disease as cardiovascular disease or coronary artery disease risk factor. A brief description of the gene association with the disease was obtained from sources including OMIM and UptoDate. The purpose of the genetic test was identified as diagnostic and/or prevention for the disease condition, and availability was assessed for clinical use. The source of information with regard to the specimen collection and methodology were obtained from the clinical laboratories that perform this test. The clinical and Medicare applicability was assessed to be adequate for this population. All the sources utilized for the aforementioned description were also documented and a preliminary MEDLINE search yielded 1,354 potentially relevant published citations available in humans assessing this genetic test for cardiovascular risk assessment. We

further narrowed the list to about 90 genetic tests that were most relevant to the Medicare population (Table 1).

Four tests were identified as currently approved by the FDA: Roche AmpliChip™, the Tag-It Cystic Fibrosis Kit, Factor V Leiden, and Prothrombin polymorphism for Thrombophilia. The first test, Roche AmpliChip Cytochrome P450 Genotyping test for use on the Affymetrix GeneChip Microarray Instrumentation System is a new laboratory test system manufactured by Roche Diagnostics (Basel, Switzerland) and was approved by the FDA in January 2005. The Roche AmpliChip Cytochrome P450 Array analyzes two genes CYP2C19 and CYP2D6, which encode drug-metabolizing enzymes involved in the metabolism of approximately 25% of all prescription drugs, including antidepressants, antipsychotics, beta-blockers, and some chemotherapy drugs. This test aids in identifying people with variations in this gene that can cause a person to metabolize these drugs abnormally fast, abnormally slow, or not at all. For example, while the same dose that is safe for a patient with one variation might be too high and therefore toxic to a patient with a different variation who cannot metabolize the drug. The second test, the Tag-It Cystic Fibrosis Kit is manufactured by Tm Bioscience Corporation of Toronto, Canada and approved by FDA on May 9, 2005. Cystic fibrosis is a serious genetic disorder affecting the lungs and other organs that often leads to an early death. This test was not deemed of interest to this report. In addition to the AmpliChip and CF for carrier screening, the FDA has cleared tests for detection for Factor V Leiden and Prothrombin polymorphism for Thrombophilia. These tests were deemed of limited Medicare applicability to this report.

In the remainder of the websites including – Web of Knowledge, National Research Register (NRR), Google News, Canadian Institute of Scientific and Technical Information (CISTI), ClinicalTrials.gov, NY Academy of Medicine, GreyLit Network, Health Services Research Projects in Progress (HSRProj) – the search did not identify any new additional tests.

Table 1: Genetic tests for non-cancer conditions with high likelihood applicability to the Medicare population

ID	Disease	Gene	Specimen	DNA methodology[1]
1	Alpha-1-antitrypsin deficiency	SERPINA1	Blood	Mutation analysis, Sequence analysis, Linkage analysis
2	Alport Syndrome	COL4A5	Blood	Sequence analysis
3	Alzheimer's Disease	Phosphorylated-Tau protein, Total-Tau protein and Aß42 peptide	CSF	*ELISA*
4	Alzheimer's Disease Late onset disease	ApoE2, E3, E4 alleles	Blood, buccal swab	*Serial Invasive Signal Amplification Reaction (SISAR)*
5	Antithrombin-III Deficiency	SERPINC1	ND	Sequence analysis, Deletion/duplication analysis
6	Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy	ARVD 1 to 9; RYR2, DSP, and PKP2	Blood	Mutation analysis, Sequence analysis, Linkage analysis, Deletion/duplication analysis
7	Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)	CHRNA4 CHRNB2	Serum	Sequence analysis
8	Bardet-Biedl Syndrome	BBS10	Blood	Mutation analysis, Sequence analysis, Linkage analysis
9	Cardiovascular risk assessment	ACE I and II	Blood	Mutation analysis, Deletion/duplication analysis
10	Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)	BBS2 BBS10	Blood	Mutation analysis, Sequence analysis, Linkage analysis
11	Cerebral Cavernous Malformations	NOTCH3	Blood, extracted DNA	Sequence analysis
12	Cerebral Cavernous Malformations	CCM2 CCM3 / PDCD10	Blood	Mutation analysis, Sequence analysis, Linkage analysis
13	Familial Cerebral Cavernous Malformation 1 (CCM1)	CCM1 / KRIT1	Blood	Mutation analysis, Sequence analysis, Linkage analysis
14	Crigler-Najjar Syndrome	UGT1A1	Blood	Mutation analysis, Sequence analysis, Mutation scan
15	Crohn Disease	CARD15	Blood	Sequence analysis, Mutation scan
16	Cystinosis	CTNS	Cultured cells, skin biopsy	Mutation analysis
17	Cystinuria	SLC3A1 SLC7A9	Blood, urine	Mutation analysis Sequence analysis, Deletion/duplication analysis

1. Methodology other than DNA appears in italics.

Table 1: Genetic tests for non-cancer conditions with high likelihood applicability to the Medicare population (continued)

ID	Disease	Gene	Specimen	DNA methodology[1]
18	Dent disease	CLCN5 OCRL	Blood, buccal swab	Mutation analysis, Sequence analysis, Linkage analysis, Deletion/duplication analysis
19	Dentatorubral-Pallidoluysian Atrophy (Naito-Oyanagi Disease)	ATN1	Blood	Sequence analysis, Deletion/duplication analysis
20	Familial Cold Urticaria	CIAS1	Blood, buccal swab	Sequence analysis
21	Autosomal dominant frontotemporal dementia.	MAPT	Blood	Sequence analysis
22	Rare forms of thalassemia	Hemoglobin E	Blood	Mutation analysis, Sequence analysis
23	Hereditary Inclusion Body Myopathy	GNE gene	Blood, buccal swab	Mutation analysis, Sequence analysis, PCR
24	ACVRL1-Related Hereditary Hemorrhagic Telangiectasia	ACVRL1 (ALK1)	Blood	Sequence analysis, Linkage analysis, Deletion/duplication analysis, Mutation scan
25	ENG-Related Hereditary Hemorrhagic Telangiectasia (Osler Rendu Weber Syndrome)	ENG	Blood	Sequence analysis, Linkage analysis, Deletion/duplication analysis, Mutation scan
26	Hereditary Sensory Radicular Neuropathy Type I, HSN1	SPTLC1	Blood	Sequence analysis
27	Gilbert syndrome	UGT1A1	Blood	Mutation analysis
28	Hexosaminidase A Deficiency or GM2 Gangliosidoses (Hexosaminidase A-Deficient)	HEXA	Blood, serum	Sequence analysis, Mutation scan
29	HFE-Associated Hereditary Hemochromatosis	HFE	Blood	Mutation analysis, Sequence analysis, Mutation scan
30	Huntington Disease	HD	Blood	Mutation analysis
31	Huntington disease-like 2, HDL2	JPH3	Blood	Mutation analysis
32	Hyperbilirubinemia, rotor type	nd	Urine	*High-Performance Liquid Chromatography (HPLC)*
33	Hyperlipoproteinemia Type III Risk Factor (APOE)	ApoE	Blood	Mutation analysis
34	Hypokalemic Periodic Paralysis Type 1	CACNA1S	Blood	Mutation analysis, Sequence analysis, Linkage analysis, Mutation scan
35	Hypokalemic Periodic Paralysis Type 2	SCN4A	Blood	Mutation analysis, Sequence analysis, Linkage analysis, Mutation scan
36	Krabbe Disease	GALC	Blood	Mutation analysis
37	Lecithin Cholesterol Acyltransferase Deficiency or Fish-Eye Disease or Norum Disease	LCAT	Blood	*Enzymatic Calorimetric*

1. Methodology other than DNA appears in italics.

Table 1: Genetic tests for non-cancer conditions with high likelihood applicability to the Medicare population (continued)

ID	Disease	Gene	Specimen	DNA methodology[1]
38	Marfan Syndrome	FBN1	Blood	Sequence analysis, Mutation scan
39	MASS Syndrome	FBN1	Blood	Sequence analysis
40	Medullary Cystic Kidney Disease	UMOD	Blood	Sequence analysis
41	Membranoproliferative Glomerulonephritis, Type II	CFH	Blood	Sequence analysis
42	Metachromatic leukodystrophy	ARSA	Blood	*Enzymatic activity with p-nitrocatechol sulfate*
43	Motor neuropathy	nd	Serum	*Western Blot; ELISA*
44	Dilated cardiomyopathy	MYBPC3	Blood	Sequence Analysis
45	Dilated cardiomyopathy	MYH7	Blood	Sequence Analysis
46	Myoclonus-Dystonia	SGCE	Blood	Sequence Analysis, Deletion / Duplication analysis
47	Myotonic dystrophy type 1	DMPK	Blood	Mutation analysis, Linkage analysis
48	Myotonic dystrophy type 2	ZNF9	Blood	Mutation analysis
49	Nemaline myopathy	NEB	Blood, buccal swab	Mutation analysis
50	Oculopharyngeal Muscular Dystrophy	PABPN1	Blood	Mutation analysis
51	Osteoporosis	VDR	ND	Mutation analysis
52	Paget Disease of Bone	PDB1 PDB2	Blood	Mutation analysis
53	LRRK2-Related Parkinson Disease	LRRK2	Blood	Mutation analysis, Sequence Analysis
54	Pink1-Related Parkinson Disease	PINK1	Blood	Sequence Analysis
55	Patterned Dystrophy of Retinal Pigment Epithelium or Butterfly-Shaped Pigmentary Macular Dystrophy	RDS	Blood	Sequence Analysis, Mutation scan
56	Polycystic Kidney Disease	PKD1 and PKD2 genes	Blood	Sequence Analysis, Linkage analysis
57	Polycystic liver disease	PRKCSH and SEC63 genes	Blood	Sequence Analysis, Mutation scan
58	Pompe Disease	GAA	Skin fibroblasts, tissue samples	Mutation analysis, Sequence Analysis
59	Porphyria cutanea tarda or idiosyncratic porphyria	UROD	Blood	Sequence Analysis, Mutation scan
60	Primary open angle glaucoma	GLC1B OPTN MYOC	Blood	Sequence Analysis, Mutation scan
61	Primary pulmonary hypertension	BMPR2	Blood	Sequence Analysis, Deletion / Duplication analysis
62	Red cell antigen genotyping (Duffy)	FY	Blood	NA
63	Red cell antigen genotyping (Kidd)	SLC14A1	Blood	NA
64	Red cell antigen genotyping (Rh-e)	RHCE	Blood	Mutation analysis
65	Renal Tubular Acidosis, Distal, Autosomal Dominant	SLC4A1	Blood	Sequence Analysis, Deletion / Duplication analysis

1. Methodology other than DNA appears in italics.

Table 1: Genetic tests for non-cancer conditions with high likelihood applicability to the Medicare population (continued)

ID	Disease	Gene	Specimen	DNA Methodology[1]
66	Renal Tubular Acidosis, Distal, Autosomal Recessive	ATP6V0A4	Blood	Sequence Analysis, Deletion / Duplication analysis
67	Retinitis pigmentosa - PRPF3-Related Retinitis Pigmentosa	PRPF3	Blood	Sequence Analysis, Linkage analysis
68	Romano Ward (Long QT) Syndrome	KCNQ1 KCNH2 SCN5A KCNE1 KCNE2	Blood	Sequence Analysis, Deletion / Duplication analysis
69	Sialuria	GNE	Blood	Sequence Analysis
70	SOD1-Related Amyotrophic Lateral Sclerosis	SOD1	Blood	Mutation analysis, Sequence Analysis
71	Spastic Paraplegia Type 4	SPAST	Blood	Sequence Analysis Mutation scan
72	Spinal Muscular Atrophy 4	SMN1 (SMNt)	Blood	Mutation analysis, Sequence Analysis
73	Spinal and Bulbar Muscular Atrophy	AR	Blood	Mutation analysis
74	Spinocerebellar Ataxia Type 2	ATXN2	Blood	Mutation analysis, Linkage analysis, Mutation scan
75	Spinocerebellar Ataxia Type 3	ATXN3	Blood	Mutation analysis, Mutation scan
76	Spinocerebellar Ataxia Type 6	CACNA1A	Blood	Mutation analysis, Mutation scan
77	Spinocerebellar Ataxia Type 7	ATXN7	Blood	Mutation analysis, Linkage analysis, Mutation scan
78	Spinocerebellar Ataxia Type 10	ATXN10	Blood	Mutation analysis, Mutation scan
79	Spinocerebellar Ataxia Type 12 (SCA12)	PPP2R2B	Blood	Mutation analysis
80	Spinocerebellar ataxia type 14 (SCA14)	PRKCG	Blood	Sequence Analysis
81	Spinocerebellar Ataxia Type 17	TBP	Blood	Mutation analysis, Mutation scan
82	Spastic Paraplegia 3	SPG3A	Blood	Mutation analysis, Sequence Analysis
83	Spastic Paraplegia 4	SPAST	Blood	Sequence Analysis, Mutation scan
84	Thrombophilia	MTHFR;	Blood	Mutation analysis
85	Thrombophilia	PROS1	Blood	Mutation analysis, Sequence Analysis
86	Thrombophilia	F5	Blood	Mutation analysis
87	Transthyretin amyloidosis	TTR	Blood	Mutation analysis, Sequence Analysis
88	Tuberous sclerosis I	TSC1	Blood	Mutation analysis, Sequence Analysis
89	Tuberous sclerosis 2	TSC2	Blood	Sequence Analysis, Deletion / Duplication analysis
90	XDx Allomap Molecular Expression testing for acute cellular organ transplant rejection	11 different genes[2]	Blood	*Messenger RNA (mRNA) expression*

1. Methodology other than DNA appears in italics.
2. ITGA4, PDCD1, PF4, G6b, MIR, WDR40A, SEMA7A, ILIR-2, ITGAM, FLT3, RHOU

Identification of genes encoding drug-metabolizing enzymes, drug transporters, or drug targets

Two currently developing fields such as pharmacogenetics that focuses on single genes and pharmacogenomics that focuses on multiple genes may provide insights into the inter-individual variability in drug responses. Table 2 identifies a list of very important drug metabolizing enzyme biomarkers or gene encoding drug transporters that may determine drug efficacy and toxicity. This is not meant to be an exhaustive list but includes biomarkers or genes encoding drug metabolizing enzymes or drug transporters and are frequently cited in the reviews or at the website PharmGKB (www.pharmgkb.org) maintained by the Stanford University.

Table 2. Examples of genes encoding drug-metabolizing enzymes, drug transporters, or drug targets *

Gene	Role of the gene	Drug	Effect of polymorphism on response to drug
ABCB1 (*MDR1*)	Drug transporter	Digoxin	Increased bioavailability, atrial arrhythmias, and heart failure
		Fexofenadine	Associated with lower plasma concentrations
		Nelfinavir; Efavirenz	Associated with lower plasma concentrations and greater rise in CD4 responses
		Antiepileptic drugs	Associated with drug resistant epilepsy
ABCA1	Drug transporter	Statins	High adjusted mean change
ACE	Drug target	Angiotensin-converting–enzyme inhibitors	Decreased blood pressure; reduction in left ventricular mass; survival after cardiac transplantation; renal protection (All effects most pronounced with D/D genotype)
		Statin	Decreased LDL levels and regression of atherosclerosis
ADRB2	Drug target	ß2-Adrenergic agonists	Vasodilation and bronchodilation
APOE	Drug target	Statins	Decreased LDL levels and reduced mortality after myocardial infarction
CETP	Drug transporter		Progression of coronary-artery atherosclerosis
CYP3A4	Drug metabolism	Testosterone	Variability in activity
CYP3A5	Drug metabolism	Tacrolimus; Cyclosporine	Associated with higher plasma concentrations
CYP2A6	Drug metabolism	Nicotine	Variability in plasma concentrations
CYP2B6	Drug metabolism	Efavirenz	Associated with higher plasma concentrations
CYP2C8	Drug metabolism	Repaglinide	Associated with lower plasma concentrations

Table 2. Examples of genes encoding drug-metabolizing enzymes, drug transporters, or drug targets (continued)*

Gene	Role of the gene	Drug	Effect of polymorphism on response to drug
CYP2C19 / CYP2D6	Drug metabolism	Multiple drugs	Poor metabolism of anticonvulsants
KCNE2 (*MiRP-1*)	Drug transporter	Clarithromycin	Long-QT syndrome and ventricular fibrillation
		Sulfamethoxazole	Long-QT syndrome
OATP-C	Drug transporter	Pravastatin	Associated with lower clearance
Factor V	Pathway none	Anticoagulants	Need for increased therapy after major surgery
VKORC1	Drug metabolism	Warfarin	Associated with variability in dosing and response
CYP2C9			

*The examples shown are illustrative and not representative of all available genes encoding drug-metabolizing enzymes, drug transporters, or drug targets

Summary and Discussion

This report identifies and emphasizes the role of various public websites that provide an important resource to identify genetic tests. These tests are either currently clinically available or in research phases of development that may have clinical impact in the very near future. We focused our search to websites and grey literature, and identified 91 genetic tests with high likelihood of applicability to the Medicare population and many more potential candidates. Most of the information for each of the genetic tests was gathered from various public and proprietary websites. The website, GeneTests.org provided most of the information on the description of the gene involved with the disease, the laboratories offering genetic testing service and their methodology used. When available, links to the clinical laboratory websites offering genetic testing service were accessed to locate information pertaining to specimen requirements. Although the list of tests we identified in this report is fairly comprehensive with regard to the diseases/conditions for which currently a clinical genetic testing is available, this report provides only a small sample genetic biomarkers in drug metabolizing enzymes and drug transporters. In terms of the gene associations of potential biomarkers, there may be information that is not relevant, given that so few biomarkers ever make it to the clinical application stage.

References:

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