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

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

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None of the investigators has any affiliations or financial involvement related to the material presented in this report.
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**

Rapid progress in genetic research has been gained through the completion of the Human Genome Project (1) and by the International Haplotype Map (HapMap) project, resulting in the rapid proliferation of lower cost and more efficient genomic technologies. (2) The number of available genetic tests that can be used in every day clinical practice is increasing. The genetic tests are used for a variety of purposes that may include screening, diagnosis, risk stratification, and therapeutic management. In addition, the genetic tests can be used as a clinical decision-making tool to aid disease monitoring and prognosis of patient.

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) for an update of the horizon scan of genetic tests for cancer and non-cancer diseases/conditions and with alternate year update reports on cancer and non-cancer conditions. AHRQ assigned this project to the Tufts Medical Center Evidence-based Practice Center (Contract Number: HHSA 290 2007 10055 I). The current report updates genetic tests for non-cancer conditions that were identified since the 2007 horizon scan report on Genetic Testing for Non-Cancer Conditions. (3) CMS would like the report and the accompanying database to be a ready reference for their internal discussions in this area and for decisions on future topics for systematic reviews. The main objective of this report is to provide a broad overview with sufficient information on each identified genetic test, and to provide a preliminary estimate on the amount of published literature available on each genetic test. This report is not meant to be an in-depth review. Systematic search of published literature and systematic review of
selected tests will be subject to future focused reviews. The contents in the database reflect the data obtained from the manufacturer’s websites or other websites and should not be construed as definitive clinical evidence.

The aim of this report is to identify genetic tests for non-cancer conditions that are already in clinical practice and are applicable to the Medicare population. The eligible tests are reviewed to obtain additional details of individual tests and to create a one-page summary of genetic tests for non-cancer conditions in an electronic database.

**Methods**

We adopted the 2007 horizon scan report on Genetic Testing for Non-Cancer Conditions as a model for this report. We adopted all the terminologies used in the previous report. The current report updates the database of genetic tests for non-cancer conditions, and provides concise summaries for all newly identified tests since 2007. For reader’s convenience, some sections from the 2007 horizon scan report on Genetic Testing for Non-Cancer are reproduced in the methods section. The items that are bold-faced and italicized pertain to new entries in the methods section.

**Terminologies, definitions, and eligibility criteria**

**Genetic test definition**

We adopted specific sections of the updated genetic test definition from the 2008 Report of the Secretary’s Advisory Committee on Genetics, Health, and Society (http://oba.od.nih.gov/).
“A genetic or genomic test involves an analysis of human chromosomes, deoxyribonucleic acid, ribonucleic acid, genes, and/or gene products (e.g., enzymes and other types of proteins), which is predominately used to detect heritable or somatic mutations, genotypes, or phenotypes related to disease and health. The purpose of genetic tests includes predicting risk of disease, screening newborns, directing clinical management, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations. Excluded from the definition are tests conducted exclusively for forensic and identity purposes as well as tests conducted purely for research. Also excluded are tests that are used primarily for other purposes but that may contribute to diagnosing a genetic disease or disorder (e.g., blood smears, certain serum chemistries). For example, cholesterol screening in the general population is not considered a genetic test, but it may reveal a genetic disorder such as an inherited form of hypercholesterolemia.”

**Eligibility criteria**

**Inclusion criteria**

We included in this report genetic tests that are already in clinical practice. The population of interest is adults in the Medicare age group, in which a genetic test result would directly impact their health outcomes. However, we included genetic tests for diseases/conditions 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. We
included tests that are performed to aid in diagnosing, treating, and prognosticating adult patients. In addition, we also included tests that were utilized to monitor patient status and detect disease recurrence. For the current update report we used the following criteria:

1) Genetic tests that have been cleared by FDA
2) Genetic tests that are conducted in CLIA certified labs and require physician order
3) Internet based test sites that usually offer a mix of genetic testing services, but inclusion of genetic tests will be limited to those that specifically require physician order.

Exclusion criteria

We excluded tests that are 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 such as Canavan disease, a degenerative brain disease. We excluded tests performed for the purpose of identifying cancer conditions syndrome.

Clinical Applications of Genetic Tests

For the clinical applications of genetic tests that are covered in this report, we adopted the 2007 horizon scan report on Genetic Testing for Non-Cancer. The following categories were used to describe the different applications for various genetic tests:

i. Prevention - Primary or Secondary: to detect inherited susceptibility to adult-onset non-cancer conditions in persons who do not have the disease in order to initiate appropriate interventions.

ii. Diagnosis and management: includes confirming, classifying, and predicting the typical course of a disease, choosing type of treatment (e.g. life-style
modifications or with medical therapy), monitoring response to therapy,
choosing the right drug in the right dose at the right frequency
(pharmacogenomics).

They were further classified into diagnostic, prognostic, and monitoring categories:

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) Monitoring: test used to monitor tumor and/or patient response to
treatment.

**Literature searches**

Our previous experience suggests that systematic searches of the published
scientific literature are not a practical way to identify new genetic tests for the following
reasons: 1) there are no specific pre-defined search strategies to identify genetic tests that
are currently available in clinical use; 2) there is a very large number of publications on
genetic, genomic, proteomic and related molecular markers and panels, which can be
resource intensive to review them all; 3) typically publications referring to specific
patented technologies may not be indexed by their genetic test names, as the main focus
may be to study molecular expression patterns or gene-disease associations; 4) even if a
test is currently in clinical use and there are studies that pertain to the test of interest,
there may still be a time lag until their publication; and 5) many potentially evaluated
gene-disease associations may not have matured to a clinically useful genetic test.

Based on our experience with two prior technology assessment reports on genetic
tests for cancer and non-cancer, focused searches of the grey literature are preferable to
searches of the published scientific literature for the identification of new genetic tests.

**Description of grey literature sources**

1) GeneTests ([www.genetests.org](http://www.genetests.org)) is a website funded by the National Institutes of
Health and sponsored by the University of Washington in Seattle. This website was
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 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, OMIM number, author, or title. The
International Laboratory Directory is a voluntary listing of laboratories offering
molecular genetic testing, specialized cytogenetic testing, and biochemical testing for
inherited disorders. The “New in GeneReviews” provides information on newly posted,
updated, 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
sources of information: testing, research, reviews, and resources sections. 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.

2) We searched the Internet websites using the following algorithm. We first searched Google News (http://www.news.google.com) for “gene OR genetic OR genomic test”, and “FDA cleared genetic test.” The news items with their links were automatically deposited into an email system to give daily email alerts. We visited web links listed in the news items. We also visited the relevant laboratories that appeared in the news items to identify any new genetic tests.

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

<table>
<thead>
<tr>
<th>Description</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quest Diagnostics&quot;</td>
<td><a href="http://www.questdiagnostics.com/">http://www.questdiagnostics.com/</a></td>
</tr>
<tr>
<td>LabCorp&quot;</td>
<td><a href="http://www.labcorp.com/">http://www.labcorp.com/</a></td>
</tr>
<tr>
<td>Roche Diagnostics&quot;</td>
<td><a href="http://www.roche-diagnostics.us/">http://www.roche-diagnostics.us/</a></td>
</tr>
<tr>
<td>Athena Diagnostics, Inc</td>
<td><a href="http://www.athenadiagnostics.com">http://www.athenadiagnostics.com</a></td>
</tr>
<tr>
<td>GeneDx</td>
<td><a href="http://www.genedx.com">http://www.genedx.com</a></td>
</tr>
<tr>
<td>Google News</td>
<td><a href="http://news.google.com">http://news.google.com</a></td>
</tr>
<tr>
<td>FDA News</td>
<td><a href="http://FDAnews.com">http://FDAnews.com</a></td>
</tr>
<tr>
<td>Ambry Genetics</td>
<td><a href="http://www.ambyrgen.com">http://www.ambyrgen.com</a></td>
</tr>
<tr>
<td>Harvard Medical School Lab for Molecular Medicine</td>
<td><a href="http://www.hpcgg.org">http://www.hpcgg.org</a></td>
</tr>
<tr>
<td>Mayo clinic Medical Labs</td>
<td><a href="http://www.mayomedicallaboratories.com/">www.mayomedicallaboratories.com/</a></td>
</tr>
<tr>
<td>NeuroMark</td>
<td><a href="http://www.neuromark.com">www.neuromark.com</a></td>
</tr>
<tr>
<td>Kimballgenetics</td>
<td><a href="http://www.kimballgenetics.com">www.kimballgenetics.com</a></td>
</tr>
<tr>
<td>Ilgenetics</td>
<td><a href="http://www.ilgenetics.com">www.ilgenetics.com</a></td>
</tr>
<tr>
<td>Gensona</td>
<td><a href="http://www.Gensona.com">www.Gensona.com</a></td>
</tr>
<tr>
<td>PsoriasisDx</td>
<td><a href="http://www.psoriasisdx.com/">http://www.psoriasisdx.com/</a></td>
</tr>
<tr>
<td>Genelex</td>
<td><a href="http://www.healthanddna.com">http://www.healthanddna.com</a></td>
</tr>
<tr>
<td>Epigenomics</td>
<td><a href="http://www.epigenomics.com/">http://www.epigenomics.com/</a></td>
</tr>
<tr>
<td>Correlogic</td>
<td><a href="http://www.correlogic.com/">http://www.correlogic.com/</a></td>
</tr>
<tr>
<td>DeCODE</td>
<td><a href="http://www.decode.com/">http://www.decode.com/</a></td>
</tr>
</tbody>
</table>

4) Other internet sites: At the direction of experts in the field of genetics, we included tests available at the following websites **PHG Foundation** ([phgfoundation.org](http://www.phgfoundation.org)) and **EGAPP Reviews** ([egappreviews.org](http://www.egappreviews.org))

5) The Office of In Vitro Diagnostics Device Evaluation and Safety (OIVD): ([http://www.fda.gov/cdrh/oivd/consumer-otcdatabase.html](http://www.fda.gov/cdrh/oivd/consumer-otcdatabase.html)) is part of the U.S. Food and
Drug Administration's (FDA) 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), which defines the type of regulatory oversight applied. 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. Further explorations of the Genomics website at the FDA were also conducted.

6) 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 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 to 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.

7) The two currently developing fields of pharmacogenetics (focus on single genes) and pharmacogenomics (focus on multiple genes) may provide insights into the inter-individual variability in drug responses. We identified genetic tests from the PharmGKB (www.pharmgkb.org) website maintained by Stanford University.
Individual test summaries

Once the list of current genetic tests was updated, a series of one-page summaries of each test in the database was completed using data extracted from various sources, including commercial websites and manufacturers. Data included in these summaries are a more detailed description of the test and its clinical use. The “one-page summary” included the following items:

1) 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 the gene names, protein, and disease/conditions served as the surrogate for the genetic testing identifier. When available, we recorded the specific test name.

2) Description: Includes a brief summary of the genetic or genomic test and its association with the non-cancer condition.

3) Purpose: The clinical applications of genetic tests include primary or secondary prevention, diagnostic, prognostic, recurrence, and monitoring.

4) Availability: Includes a brief list of laboratories including commercial and academic laboratories in the US and other countries.

5) Specimen: The specimen was utilized to evaluate the gene-disease condition, which included whole blood, serum, tumor tissue, etc.

6) Diseases: Included a list of disease conditions for which the genetic test was utilized (e.g. dilated cardiomyopathy, psoriatic arthritis, etc.).

7) Clinical uses: This included genetic test applications in a clinical setting (e.g. routine use, investigational use, etc.).
8) Source: A list of additional sources that were typically consulted for information about the genetic test application.

9) Marker: This included the list of possible genetic test names, genes, and biomarkers that will be used for Medline search strategy.

10) Organ: Included a list of specific organ(s) affected by the gene-disease association.

11) Exploratory Pubmed search: The exploratory Pubmed search includes the name of the 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 3/1/2010. These search strategies are exploratory and the number of citations returned is an estimate of the scientific literature available on each test-disease condition. However, this number is preliminary and would be subject to change from the use of a more fully developed search strategy and the application of specific screening criteria.

**Description of the electronic database**

We developed an electronic database for efficient storage and retrieval of the aforementioned information on eligible genetic tests. For convenience, we developed a user-friendly front end (interface) that allows browsing and searching of the database without the need to use low-level programming commands.

**MySQL database**

We have created a MySQL (http://www.mysql.com/) database to store the collected genetic test information. MySQL is a relational database management system that is free, open-source, well documented, extremely robust, and widely used. It is often
held to be a *de facto* standard for databases. Furthermore, the embedded SQL query language allows for quick and flexible querying of the stored data. For example, the end user can easily request information for all tests related to a specific non-cancer condition, with an arbitrarily complex set of limits. MySQL databases can be exported to a myriad of other formats, including a Microsoft© Excel readable CommaSeparated Values (CSV) format.

In the genetic test database, data is separated into cancer and non-cancer genetic tests. For each, we keep a record of all the data needed for one-page summaries of genetic tests.

**Front end**

While the MySQL database stores and indexes all of the genetic tests, it is not necessarily straightforward for those unfamiliar with MySQL (and the SQL query language) to access this data once collected. We have developed a user-friendly interface to interact with 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 theoretically allows remote access to the database (via any standard internet browser), is platform independent, and software updates need only be dropped onto the server (rather than installed manually by end users).

Upon logging in the password-protected site, users can see all of the 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.

We have also been working on interfacing with PubMed so as to automatically generate plots showing the number of hits a search in PubMed turns up for a gene test over time.

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

Figure 1 is a snapshot of Gene Test Tracker, the front end to the electronic database that lists genetic and genomic tests. After logging in the password-protected site, the user sees an html page depicting a table. Each row pertains to a specific 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.
Results

Through grey literature searches, we identified 22 new genetic tests for non-cancer conditions available since our 2007 horizon scan report on Genetic Testing for Non-Cancer Conditions report. The electronic database contains 106 different genetic tests. A brief summary is available in Appendix B Table 1 and 2. In addition, 22 are new tests identified from 2008 to the present and a brief overview of each of the new tests identified is also included in Table 2a – 2b. These tests are used in a variety of non-cancer disease conditions and pharmacogenomic applications. Eleven tests were for pharmacogenomic applications, and the remaining 11 tests evaluated the association of relevant genotypes and non-cancer disease. The Database also compiles one-page summaries for each of the 22 genetic tests (Appendix A). The one-page summaries provide additional details on the individual genetic tests, including further discussion on their clinical use. Based on our 2007 horizon scan report on Genetic Testing for Non-Cancer Conditions, the CMS identified and requested the TAP at the AHRQ for full systematic reviews of two pharmacogenomic tests for non-cancer conditions. (4; 5) These topics were chosen based on both high clinical relevance and sufficient numbers of potentially eligible publications to conduct systematic reviews. The topics for which systematic reviews were conducted are listed in Table 3.
Discussion

We performed Internet-based grey literature searches and updated 22 new genetic tests in non-cancer conditions since 2007. The horizon scan for genetic tests for cancer- and non-cancer-related diseases/conditions, with biannual updates, adds important information on emerging tests. Genetic testing is a rapidly emerging field with the potential to dramatically influence clinical decision-making. Most of the information for each of the genetic tests was gathered from various public and proprietary websites. The laboratories offering genetic testing services provided most of the information on the description of the gene involved with the disease. These sites were identified from our 2007 horizon scan report on Genetic Testing for Non-Cancer Conditions and through Google News searches. Our list encompasses both gene associations of potential biomarkers, and pharmacogenomic tests. In terms of tests of gene associations, only few biomarkers ever make it to the clinical application stage. Thus the list of tests we identified in this report along with genetic tests identified in our 2007 report, are fairly comprehensive with regard to the diseases/conditions for which currently a clinical genetic testing is available.

Potential limitations of our report include lack of empirical structure providing guidance on how to conduct optimal grey literature searches of the Internet. Following are the caveats to our grey literature searches: Internet searches in Google are not strictly reproducible. This has been partially overcome by storing web links along with access dates in our database. However, for searches conducted within a reasonably short time period, the web pages will be more or less the same. To overcome these limitations related to searches conducted in Google, we supplemented Internet searches with review
of websites of major companies that manufacture genetic and molecular tests, and by searching the FDA website.

There is an inherent subjectivity in identifying emerging genetic tests. A plethora of genetic and molecular markers and panels are being associated with non-cancer conditions. We have selected those that have known clinical use for screening, diagnosis, prognosis, disease management, or patient monitoring as tests for non-cancer diseases by commercial or academic laboratories and manufacturers. In addition to grey literature searches, our discussion with local experts as well as the external panel of reviewers helped us identify this comprehensive list of genetic tests.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Role of the gene</th>
<th>Drug</th>
<th>Effect of polymorphism on response to drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP450 2C19</td>
<td>Drug metabolism</td>
<td>Clopidogrel</td>
<td>Patients who have CYP2 C19 poor metabolizer status is associated with diminished response to clopidogrel and greater risk of cardiovascular events</td>
</tr>
<tr>
<td>HLA-B* 1502</td>
<td>Drug metabolism</td>
<td>Carbamazepine</td>
<td>HLA-B*1502 allele presence is associated with serious dermatologic reactions such as Stevens-Johnson Syndrome and toxic epidermal necrolysis.</td>
</tr>
<tr>
<td>Thiopurine S-methyltransferase gene</td>
<td>Drug metabolism</td>
<td>Azathioprine</td>
<td>TPMT deficiency or lower activation due to gene mutation increases myelotoxicity in patients undergoing azathioprine therapy.</td>
</tr>
<tr>
<td>CYP2 D6</td>
<td>Drug metabolism</td>
<td>Antidepressants</td>
<td>Depending on certain allelic variants will show normal, decreased or no CYP2D6 function, which can affect the plasma concentrations of the drug.</td>
</tr>
<tr>
<td>CYP2 D6</td>
<td>Drug metabolism</td>
<td>Pain medications</td>
<td>Depending on certain allelic variants will show normal, decreased or no CYP2D6 function, which can affect the plasma concentrations of the drug.</td>
</tr>
<tr>
<td>Androgen receptor gene</td>
<td>Drug target</td>
<td>Finasteride</td>
<td>Finasteride therapy is effective in patients with a shorter CAG repeat number than those with a longer CAG repeat number.</td>
</tr>
<tr>
<td>HLA-B*5701</td>
<td>Drug metabolism</td>
<td>Abacavir</td>
<td>Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir.</td>
</tr>
<tr>
<td>Low density lipoprotein receptor (LDLR) Gene</td>
<td>Drug target</td>
<td>Atorvastatin</td>
<td>Atorvastatin attenuates the inflammatory reaction and development of atherosclerosis in hypercholesterolemic patients, but in patients with LDLR gene polymorphism, this effect is more profound.</td>
</tr>
<tr>
<td>GRIK2 and GRIA3</td>
<td>Drug target</td>
<td>Citalopram or selective serotonin reuptake inhibitor (SSRI)</td>
<td>Kainate receptor gene, GRIK2 and GRIA3 increases the odds for suicidal thinking in patients taking citalopram or other SSRI</td>
</tr>
<tr>
<td>CYP2 C19</td>
<td>Drug metabolism</td>
<td>Second generation SSRI</td>
<td>Depending on certain allelic variants will show normal, decreased or no CYP2C19 function, which can affect the plasma concentrations of the drug.</td>
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<tr>
<td>CYP2 C19</td>
<td>Drug metabolism</td>
<td>Proton-pump inhibitors</td>
<td>Depending on certain allelic variants will show normal, decreased or no CYP2C19 function, which can affect the plasma concentrations of the drug.</td>
</tr>
<tr>
<td>Disease/Condition</td>
<td>Gene/Genes</td>
<td>Specimen</td>
<td>Methodology</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>Psoriasis Arthritis</td>
<td>MICA-A9</td>
<td>Buccal Swab</td>
<td>Not reported</td>
</tr>
<tr>
<td>Dilated cardiomyopathy (DCM)</td>
<td>Multiple genes</td>
<td>Whole blood</td>
<td>DNA sequence analysis</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Multiple genes</td>
<td>Whole blood</td>
<td>Dideoxy DNA sequence analysis</td>
</tr>
<tr>
<td>General nutrition assessment</td>
<td>5-10-methylenetetrahydrofolate reductase gene (MTHFR) and transcobalamin 2 gene</td>
<td>Whole blood</td>
<td>SNP analysis</td>
</tr>
<tr>
<td>Heart disease and acute coronary events</td>
<td>Interleukin 1 (IL1) genes</td>
<td>Whole blood</td>
<td>Not reported</td>
</tr>
<tr>
<td>Periodontal disease</td>
<td>Interleukin-1A and interleukin-1B</td>
<td>Buccal swab</td>
<td>DNA analysis for variations in the interleukin-1 genes</td>
</tr>
<tr>
<td>Narcolepsy and other sleep disorders</td>
<td>Human leukocyte antigen (HLA)</td>
<td>Whole blood</td>
<td>DNA testing using PCR analysis</td>
</tr>
<tr>
<td>Recurrent acute pancreatitis and Chronic pancreatitis</td>
<td>PRSS1, SPINK1, and CFTR</td>
<td>Blood, saliva</td>
<td>DNA mutation analyses</td>
</tr>
<tr>
<td>DeCODE-AF™</td>
<td>SNPs rs2200733; rs100233464</td>
<td>Blood, Buccal</td>
<td>Not reported</td>
</tr>
<tr>
<td>DeCODE glaucoma™</td>
<td>LOXL1 gene</td>
<td>Blood, Buccal</td>
<td>sequencing utilizing the Illumina Hap300 SNP chip</td>
</tr>
<tr>
<td>DeCODE T2™</td>
<td>TCF7L2, PPARG, CDKAL1, and CDKN2A</td>
<td>Blood, Buccal</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

| Table 3. Topics for which a focused review of pharmacogenetics was conducted or is currently in progress |
|-----------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Disease                                             | Test                                                                                         | Target drugs   | Potentially eligible Medline citations | Final inclusion |
| Warfarin Responsiveness                             | CYP2C9 genotype                                                                               | Warfarin       | 270                                     | 29              |
| Warfarin Responsiveness                             | VKORC1 genotype                                                                               | Warfarin       | 288                                     | 28              |
| Cardiovascular Disease                              | Apo E genotype                                                                               | Statins        | 262                                     | 44              |
References


Appendix A. One-page summaries of the genetic tests for non-cancer conditions.
Figure 1. Gene Test Information: INFINIT(TM) CYP450 2C19, CYP 2C19, cytochrome P-450 enzymes, Resistance to clopidogrel plavix (pharmacogenetic test)

**Test Name:** INFINIT(TM) CYP450 2C19  
**Gene Symbol:** CYP 2C19  
**Protein Name:** cytochrome P-450 enzymes  
**Description:** Clopidogrel 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.

**Purpose:** Research purpose, Therapeutic management  
**Availability:** Autogenomics Inc., Genelex.com  
**Specimen:** whole blood, buccal swab  
**Methodology:** ND  
**Diseases:** Resistance to clopidogrel plavix (pharmacogenetic test)  
**Clinical Uses:** Personalizing Clopidogrel dosing using pharmacogenetics may be an effective method of rationalizing treatment.

**Sources:** medicalnewstoday.com; genelex.com  
**Medline Searches:** (CYP2C19 OR cytochrome P450 2C19) AND (clopidogrel)  
**FDA Cleared:** Yes

![This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.](image)
Figure 2. Gene Test Information: HLA-B 1502 Genotype, Carbamazepine Hypersensitivity (Pharmacogenetic test), HLA-B 1502 Genotype, Human Leukocyte Antigen-B, Carbamazepine Hypersensitivity

**Test Name:** HLA-B 1502 Genotype, Carbamazepine Hypersensitivity (Pharmacogenetic test)

**Gene Symbol:** HLA-B 1502 Genotype

**Protein Name:** Human Leukocyte Antigen-B

**Description:** The presence of the HLA-B*1502 allele prior to receiving carbamazepine, a drug used to treat epilepsy, manic bipolar disorders, and neuropathic pain. Individuals positive for the *1502 allele have an increased risk of developing a skin reaction resulting in toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS), a milder form of TEN, when treated with carbamazepine.

**Purpose:** Therapeutic management

**Availability:** Commercial labs in the US

**Specimen:** whole blood

**Methodology:** 5 multiplexed allele-specific PCR amplifications of HLA-B regions

**Diseases:** Carbamazepine Hypersensitivity

**Clinical Uses:** Identifying individuals of Asian ancestry who are at risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis when administered carbamazepine therapy

**Sources:** PharmGKB, mayo medical laboratories

**Medline Searches:** HLA-B 1502 Genotype AND Carbamazepine

**FDA Cleared:** Yes

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 3. Gene Test Information: Thiopurine Methyltransferase (TPMT), Erythrocytes, TPMT gene, Thiopurine S-methyltransferase, Pharmacogenetic testing for therapy of thiopurine drugs

**Test Name:** Thiopurine Methyltransferase (TPMT), Erythrocytes  
**Gene Symbol:** TPMT gene  
**Protein Name:** Thiopurine S-methyltransferase  
**Description:** Azathioprine (Imuran) and 6-mercaptopurine (6-MP, Purinethol) are thiopurine drugs used to treat neoplasms such as acute lymphoblastic leukemia and a variety of rheumatologic, dermatologic, and neurologic diseases. The metabolic conversion of azathioprine or 6-MP to purine nucleotides and the subsequent incorporation of these nucleotides into DNA plays an important role in both the therapeutic efficacy and the toxicity of these drugs. A competitive catabolic route for the metabolism of thiopurines is catalyzed by the enzyme thiopurinemethyltransferase (TPMT), which inactivates them by thiomethylation. A balance must be established between these 2 competing metabolic pathways so that sufficient amounts of drug are converted to the nucleotide to act as an antimetabolite, yet the levels antimetabolite do not become so high as to cause potentially lethal bone marrow suppression.  
**Purpose:** Therapeutic management  
**Availability:** Commercial labs in the US  
**Specimen:** Whole blood  
**Methodology:** ND  
**Diseases:** Pharmacogenetic testing for therapy of thiopurine drugs  
**Clinical Uses:** Detection of individuals with low TPMT activity who will have excessive myelosuppression when taking azathioprine (Imuran) and 6-MP (Purinethol)  
**Sources:** Mayo clinic laboratories, PharmGKb  
**Medline Searches:** Thiopurine Methyltransferase gene AND thiopurine[dt]  
**FDA Cleared:** Yes

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 4. Gene Test Information: CYP2D6, CYP2D6, Cytochrome P-450, Pharmacogenetic testing for tricyclic antidepressants

**Test Name:** CYP2D6  
**Gene Symbol:** CYP2D6  
**Protein Name:** Cytochrome P-450  
**Description:** Poor metabolizers have more adverse effects than ultrarapid metabolizers. Poor metabolizers will have higher concentrations of tricyclic antidepressants and increased side effects.  
**Purpose:** Therapeutic management  
**Availability:** Commercial laboratories  
**Specimen:** blood or buccal swab  
**Methodology:** ND  
**Diseases:** Pharmacogenetic testing for tricyclic antidepressants  
**Clinical Uses:** Therapeutic dose adjustment  
**Sources:** www.pgxlab.com  
**Medline Searches:** CYP2D6 AND (tricyclic antidepressant OR antipsychotics OR SSRI)  
**FDA Cleared:** Yes

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 5. Gene Test Information: CYP2D6, CYP2D6, Cytochrome P-450, Pharmacogenetic testing of opioids

**Test Name:** CYP2D6  
**Gene Symbol:** CYP2D6  
**Protein Name:** Cytochrome P-450  
**Description:** Poor metabolizers are unable to convert codeine to morphine and have no pain relief. Ultrarapid metabolizers have increased sedation and opioid toxicity.  
**Purpose:** Therapeutic management  
**Availability:** Commercial laboratories  
**Specimen:** Blood  
**Methodology:** Cytochrome P-450 2D6 DNA mutation panel  
**Diseases:** Pharmacogenetic testing of opioids  
**Clinical Uses:** Dosage adjustment  
**Sources:** www.healthanddna.com  
**Medline Searches:** CYP2d6 AND opioids  
**FDA Cleared:** Yes

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Test Name: HairDX (RxR) Genetic Test
Gene Symbol: androgen receptor gene
Protein Name: androgen receptor

Description: The HairDX (RxR) Genetic Test for Finasteride response examines a small genetic sequence in the androgen receptor gene. The result of the genetic analysis, called a CAG repeat score, aids predicting Finasteride response. Published studies have shown that finasteride has a better therapeutic effect on individuals with a shorter CAG repeat number than on individuals with a longer CAG repeat number.

Purpose: Diagnostic
Availability: www.hairdx.com
Specimen: Buccal swab
Methodology: ND
Diseases: Finasteride response in androgenetic alopecia

Clinical Uses: The test results as CAG repeat score helps to predict Finasteride response in androgenetic alopecia

Sources: www.hairdx.com

Medline Searches: Androgen receptor gene AND (finasteride OR hair loss)

FDA Cleared: No

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 7. Gene Test Information: HLA-B*5701 test, human leukocyte antigen (HLA) B*5701 allele, human leukocyte antigen (HLA), Abacavir hypersensitivity

**Test Name:** HLA-B*5701 test

**Gene Symbol:** human leukocyte antigen (HLA) B*5701 allele

**Protein Name:** human leukocyte antigen (HLA)

**Description:** HLA-B*5701 allele of the major histocompatibility complex (MHC) genes codes for a highly variable set of cell surface glycoproteins (HLAs) that play a critical role in presenting antigens to T-cell receptors to elicit an immune response. Susceptibility to abacavir hypersensitivity appears to be mapped specifically to the HLA-B*5701 allele. Published studies have found that the HLA-B*5701 test for increased risk of abacavir hypersensitivity may be clinically useful in identifying HIV patients at risk of developing a hypersensitivity reaction to abacavir. The test can be used for genetic risk stratification prior to initiating abacavir therapy.

**Purpose:** Primary prevention, diagnostic

**Availability:** Labcorp; other commercial labs

**Specimen:** whole blood or buccal swab

**Methodology:** Polymerase chain reaction (PCR) sequence-specific oligonucleotide probes (SSOP)

**Diseases:** Abacavir hypersensitivity

**Clinical Uses:** Identifying increased risk of abacavir hypersensitivity in HIV patients at risk of developing a hypersensitivity reaction.

**Sources:** www.labcorp.com

**Medline Searches:** HLA-B*5701 AND abacavir

**FDA Cleared:** Yes

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 8. Gene Test Information: Low density lipoprotein receptor (Pharmacogenetic test), Low density lipoprotein receptor (LDLR) Gene, Low-density lipoprotein receptor class A domain-containing protein 3, Pharmacogenetic testing to evaluate response to atorvastatin (lipitor) therapy.

**Test Name:** Low density lipoprotein receptor (Pharmacogenetic test)

**Gene Symbol:** Low density lipoprotein receptor (LDLR) Gene

**Protein Name:** Low-density lipoprotein receptor class A domain-containing protein 3

**Description:** Familial Hypercholesterolemia (FH) can occur in either the heterozygous or homozygous state, with 1 or 2 mutant LDLR alleles, respectively. FH heterozygotes are often treated with 3-hyroxy-3-methylglutaryl CoA reductase inhibitors (i.e., statins), either in monotherapy or in combination with other drugs such as nicotinic acid and inhibitors of intestinal cholesterol absorption.

**Purpose:** Therapeutic management

**Availability:** Clinical labs in the US

**Specimen:** whole blood

**Methodology:** DNA testing

**Diseases:** Pharmacogenetic testing to evaluate response to atorvastatin (lipitor) therapy

**Clinical Uses:** Genetic testing of individuals at risk for known LDLR familial mutation(s) and therapeutic management with atorvastatin

**Sources:** mayomedical laboratories, PharmGKb website

**Medline Searches:** Low density lipoprotein receptor (LDLR) Gene AND atorvastatin

**FDA Cleared:** Yes

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 9. Gene Test Information: Mark-C(TM) test, GRIK2 and GRIA3, glutamate in ionotropic glutamate receptors. A pharmacogenetic test that can identify suicidal ideation when a patient is prescribed the antidepressant drug, citalopram.

**Test Name:** Mark-C(TM) test  
**Gene Symbol:** GRIK2 and GRIA3  
**Protein Name:** glutamate in ionotropic glutamate receptors  
**Description:** Two of the markers probed by the Mark-C test reside in genes that encode receptors for the excitatory neurotransmitter glutamate. These are the genes GRIK2 and GRIA3, both of which encode ionotropic glutamate receptors, the most prominent neuronal membrane receptors in the mammalian brain activated by normal neurophysiologic processes. Both genes regulate how the brain processes glutamate, an amino acid that helps mediate communication between neurons in the brain.  
**Purpose:** prognostic, secondary prevention  
**Availability:** www.neuromark.com  
**Specimen:** Buccal swab  
**Methodology:** A DNA test.  
**Diseases:** A pharmacogenetic test that can identify suicidal ideation when a patient is prescribed the antidepressant drug. citalopram  
**Clinical Uses:** The genetic test identifies people at risk of suicidal ideation (thoughts of committing suicide) when prescribed an antidepressant drug citalopram.  
**Sources:** www.neuromark.com; Google  
**Medline Searches:** (GRIK2 OR GRIA3) AND citalopram  
**FDA Cleared:** No

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 10. Gene Test Information: CYP2C19, CYP2C19, Cytochrome P-450, Pharmacogenetic testing of second-generation antidepressants

**Test Name:** CYP2C19  
**Gene Symbol:** CYP2C19  
**Protein Name:** Cytochrome P-450  
**Description:** Poor metabolizer have accumulation of antidepressants and more side effects. Ultrarapid metabolizer have lack of response.  
**Purpose:** Therapeutic management  
**Availability:** Commercial Laboratories  
**Specimen:** Blood or buccal swab  
**Methodology:** Cytochrome P-450 2C19 DNA test  
**Diseases:** Pharmacogenetic testing of second-generation antidepressants  
**Clinical Uses:** Dosage adjustment  
**Sources:** PGXL lab; healthdna.com  
**Medline Searches:** CYP2C19 AND antidepressants  
**FDA Cleared:** Yes

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
**Test Name:** CYP2C19  
**Gene Symbol:** CYP2C19  
**Protein Name:** Cytochrome P-450  
**Description:** Cytochrome P450 2C19 (CYP2C19) accounts for large differences in the pharmacokinetics of a number of clinically important drugs. Ultrarapid metabolizers have treatment failure. Extensive metabolizers require more frequent doses than poor metabolizers  
**Purpose:** Therapeutic management  
**Availability:** Commercial laboratories  
**Specimen:** Blood or buccal swab  
**Methodology:** Cytochrome P-450 2C19 DNA test  
**Diseases:** Pharmacogenetic testing for proton pump inhibitors  
**Clinical Uses:** Dosage management  
**Sources:** PGXL labs; healthdna.com  
**Medline Searches:** CYP2C19 AND proton pump inhibitors  
**FDA Cleared:** Yes

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This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 12. Gene Test Information: PsoriasisDX, MICA-A9, class I major histocompatibility complex chain-related protein, Psoriatic arthritis

**Test Name:** PsoriasisDX  
**Gene Symbol:** MICA-A9  
**Protein Name:** class I major histocompatibility complex chain-related protein  
**Description:** Positive tests for the MICA-A9 variant result in an approximately 60% chance of developing PsA, while negative tests for the MICA-A9 variant result in an approximately 70% chance of not developing Psoriatic arthritis. Psoriatic arthritis is a progressive irreversible joint disease associated with psoriasis. It is estimated that 20% to 40% of psoriasis patients will eventually develop Psoriatic arthritis.  
**Purpose:** Diagnostic screening, therapeutic management  
**Availability:** www.psoriasisdx.com  
**Specimen:** buccal swab  
**Methodology:** Not reported  
**Diseases:** Psoriatic arthritis  
**Clinical Uses:** identifying those at highest risk for developing psoriatic arthritis, allowing the use of medications before joint damage occurs.  
**Sources:** www.psoriasisdx.com  
**Medline Searches:** MICA-A9 AND Psoriasis  
**FDA Cleared:** No

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 13. Gene Test Information: Dilated cardiomyopathy (DCM) panel, LMNA, MYH7, TNNT2, ACTC1, DES, MYBPC3, TPM1, TNNI3, ZASP, TAZ, PLN, TTR, LAMP2, SGCD, MTTL1, MTTQ, MTTH, MTTK, MTTS1, MTTS2, MTND1, MTND5 and MTND6, ?-cardiac actin (ACTC1); ?- myosin (MYH7); cardiac myosin-binding protein C (MYBPC3); heavy chain ?-tropomyosin (TPM1); and troponins T (TNNT2) and I (TNNI3), Dilated cardiomyopathy

**Test Name:** Dilated cardiomyopathy (DCM) panel

**Gene Symbol:** LMNA, MYH7, TNNT2, ACTC1, DES, MYBPC3, TPM1, TNNI3, ZASP, TAZ, PLN, TTR, LAMP2, SGCD, MTTL1, MTTQ, MTTH, MTTK, MTTS1, MTTS2, MTND1, MTND5 and MTND6

**Protein Name:** ?-cardiac actin (ACTC1); ?- myosin (MYH7); cardiac myosin-binding protein C (MYBPC3); heavy chain ?-tropomyosin (TPM1); and troponins T (TNNT2) and I (TNNI3)

**Description:** Hereditary dilated cardiomyopathy can be caused by mutations in genes coding for cardiac proteins. To date, 23 genes have been identified to have potential association of DCM.

**Purpose:** Diagnostic

**Availability:** GeneDx

**Specimen:** Blood

**Methodology:** DNA sequence analysis

**Diseases:** Dilated cardiomyopathy

**Clinical Uses:** diagnosis of DCM and risk assessment of asymptomatic family members

**Sources:** www.GeneDX.com

**Medline Searches:** (LMNA OR MYH7 OR TNNT2 OR ACTC1 OR DES OR MYBPC3 OR TPM1 OR TNNI3 OR ZASP OR TAZ OR PLN OR TTR OR LAMP2 OR SGCD OR MTTL1 OR MTTQ OR MTTH OR MTTK OR MTTS1 OR MTTS2 OR MTND1 OR MTND5 OR MTND6) AND dilated cardiomyopathy

**FDA Cleared:** No

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 14. Gene Test Information: Hypertrophic cardiomyopathy panel (HCM), MYH7, TNNT2, MYBPC3, TNNI3, TPM1, ACTC, MYL3, MYL2, LAMP2, PRKAG2, GLA, CAV3, MTTG, MTTI, MTTK, TNNC1 and TTR, myosin-binding protein C (MYBPC3), regulatory and essential light chains (MYL2, MYL3), Beta-myosin heavy chain (MYH7) (thick filament), actin (ACTC), tropomyosin (TPM1), troponin I (TNNI3), and troponin T (TNNT2) (thin filament), Hypertrophic cardiomyopathy

**Test Name:** Hypertrophic cardiomyopathy panel (HCM)

**Gene Symbol:** MYH7, TNNT2, MYBPC3, TNNI3, TPM1, ACTC, MYL3, MYL2, LAMP2, PRKAG2, GLA, CAV3, MTTG, MTTI, MTTK, TNNC1 and TTR

**Protein Name:** myosin-binding protein C (MYBPC3), regulatory and essential light chains (MYL2, MYL3), Beta-myosin heavy chain (MYH7) (thick filament), actin (ACTC), tropomyosin (TPM1), troponin I (TNNI3), and troponin T (TNNT2) (thin filament)

**Description:** To date, mutations in 17 genes have most commonly been identified in adult HCM patients. Mutations in genes coding for sarcomeric proteins of the heart muscle, and their regulators and interaction partners can lead to HCM.

**Purpose:** Diagnostic

**Availability:** GeneDX

**Specimen:** Blood

**Methodology:** dideoxy DNA sequence analysis

**Diseases:** Hypertrophic cardiomyopathy

**Clinical Uses:** Confirmation of diagnosis of HCM and risk assessment for asymptomatic family members

**Sources:** www.GeneDx.com

**Medline Searches:** (MYH7 OR TNNT2 OR MYBPC3 OR TNNI3 OR TPM1 OR actc OR MYL3 OR MYL2 OR LAMP2 OR PRKAG2 OR GLA OR CAV3 OR mttg OR mtti OR mttk OR tnnc OR TTR) AND hypertrophic cardiomyopathy

**FDA Cleared:** No

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 15. Gene Test Information: Gensona(TM) General Nutrition Genetic Test, 5-10-methylenetetrahydrofolate reductase gene (MTHFR), transcobalamin 2 gene (TCN2), manganese superoxide dismutase 2 (SOD2), glutathione s-transferase M1 (GSTM1), paroxanase 1 (PON1), and x-ray repair cross complementing gene (XRCC1), ND, General nutrition status and general health status

**Test Name:** Gensona (TM) General Nutrition Genetic Test

**Gene Symbol:** 5-10-methylenetetrahydrofolate reductase gene (MTHFR), transcobalamin 2 gene (TCN2), manganese superoxide dismutase 2 (SOD2), glutathione s-transferase M1 (GSTM1), paroxanase 1 (PON1), and x-ray repair cross complementing gene (XRCC1)

**Protein Name:** ND

**Description:** The variantion of the MTHFR gene has been associated with less efficient activity of certain enzymes that depend on B vitamins for optimal function. The variant of the TCN2 gene has been associated with affecting the body’s need for vitamin B-12. A Positive result for one or more of the variants of four genes (glutathione s-transferase M1 (GSTM1), paroxanase 1 (PON1), and x-ray repair cross complementing gene (XRCC1)) indicates cells may be less efficient at protecting against damage from oxidative stress.

**Purpose:** Primary prevention

**Availability:** Gensona testing services through Quixtar USA and Quixtar Canada

**Specimen:** Blood

**Methodology:** SNP analysis

**Diseases:** General nutrition status and general health status

**Clinical Uses:** Variations in several genes are used to predict their influence how the body uses vitamins and micronutrients. Also evaluates an individual’s ability to withstand oxidative stress

**Sources:** www.Gensona.com

**Medline Searches:** (5-10-methylenetetrahydrofolate reductase gene OR MTHFR OR transcobalamin 2 gene OR TCN2 OR manganese superoxide dismutase 2 OR SOD2 OR glutathione s-transferase M1 OR GSTM1 OR paroxanase 1 OR PON1 OR x-ray repair cross complementing gene OR XRCC1) AND Health

![Line Graph]

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Test Name: Gensona(TM) Heart Health test
Gene Symbol: interleukin 1 (IL1) genes
Protein Name: ND
Description: Inflammation is one of the risk factors for heart disease. The genes variations identify an individual’s predisposition for over-expression of inflammation and risk for cardiovascular disease. The test may not be useful for diagnosis of specific heart diseases.
Purpose: Monitoring
Availability: Gensona testing service available through Quixtar USA and Quixtar Canada
Specimen: Blood
Methodology: ND
Diseases: Heart disease and acute coronary events
Clinical Uses: The genetic test provides risk information independent of traditional risk factors
Sources: www.ilgenetics.com
Medline Searches: interleukin 1 genes AND cardiovascular disease

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 17. Gene Test Information: PST (R) Genetic Test, interleukin-1A and interleukin-1B genes, interleukin-1A and interleukin-1B, Periodontal disease

**Test Name:** PST (R) Genetic Test  
**Gene Symbol:** interleukin-1A and interleukin-1B genes  
**Protein Name:** interleukin-1A and interleukin-1B  
**Description:** Variations in the interleukin-1A and interleukin-1B genes increases the risk for periodontal disease 3 to 7-fold and for tooth loss 3-fold.  
**Purpose:** Diagnostic, primary prevention  
**Availability:** Kimball genetics  
**Specimen:** Buccal swab  
**Methodology:** DNA analysis for variations in the interleukin-1 genes  
**Diseases:** Periodontal disease  
**Clinical Uses:** Diagnosis of periodontitis, aid in advanced surgical or complex restorative procedures, and prevention of chronic periodontitis  
**Sources:** www.kimballgenetics.com  
**Medline Searches:** (interleukin-1A OR interleukin-1b genes) AND (periodontitis OR tooth loss)  

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 18. Gene Test Information: Narcolepsy DNA test, human leukocyte antigen (HLA) alleles DQB10602 and DQA10102, human leukocyte antigen (HLA), Narcolepsy

**Test Name:** Narcolepsy DNA test

**Gene Symbol:** human leukocyte antigen (HLA) alleles DQB10602 and DQA10102

**Protein Name:** human leukocyte antigen (HLA)

**Description:** Individuals with narcolepsy have DQB1*0602 and DQA1*0102 and studies have found that these alleles have been associated with narcolepsy. Usually diagnosed in adulthood, narcolepsy is the most common disorder of excessive daytime sleepiness

**Purpose:** Diagnosis

**Availability:** Kimball genetics

**Specimen:** Blood

**Methodology:** DNA testing using PCR analysis

**Diseases:** Narcolepsy

**Clinical Uses:** diagnosis of narcolepsy from other sleep disorders

**Sources:** www.kimballgenetics.com

**Medline Searches:** (HLA DQB1*0602 OR HLA DQA1*0102) AND narcolepsy

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 19a. Gene Test Information: The Ambry Test(R) Pancreatitis Amplified, PRSS1, SPINK1, and CFTR, ND, idiopathic

**Test Name:** The Ambry Test(R) Pancreatitis Amplified

**Gene Symbol:** PRSS1, SPINK1, and CFTR

**Protein Name:** ND

**Description:** Mutations in three genes PRSS1, SPINK1, and CFTR predispose to pancreatitis. Pancreatitis due to PRSS1 results from premature activation and or impaired degradation of trypsin and related enzymes. SPINK1 is a risk modifier gene that inhibits trypsinogen activation within the pancreas. CFTR, a cystic fibrosis gene may contribute to pancreatitis by restricting adequate flushing of enzymes from the pancreatic ductules.

**Purpose:** Diagnostic, recurrence, and target therapy

**Availability:** Ambry Genetics

**Specimen:** Blood, saliva

**Methodology:** DNA mutation analyses

**Diseases:** idiopathic

**Clinical Uses:** For diagnosis, target treatment, screening of family member with regard to idiopathic, chronic, and recurrent acute pancreatitis

**Sources:** www.ambrygen.com

**Medline Searches:** (PRSS1 OR SPINK1 OR CFTR) AND pancreatitis

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 19b. Gene Test Information: The Ambry Test(R) Pancreatitis Amplified, PRSS1, SPINK1, and CFTR, ND, chronic

**Test Name:** The Ambry Test(R) Pancreatitis Amplified  
**Gene Symbol:** PRSS1, SPINK1, and CFTR  
**Protein Name:** ND  
**Description:** Mutations in three genes PRSS1, SPINK1, and CFTR predispose to pancreatitis. Pancreatitis due to PRSS1 results from premature activation and or impaired degradation of trypsin and related enzymes. SPINK1 is a risk modifier gene that inhibits trypsinogen activation within the pancreas. CFTR, a cystic fibrosis gene may contribute to pancreatitis by restricting adequate flushing of enzymes from the pancreatic ductules.  
**Purpose:** Diagnostic, recurrence, and target therapy  
**Availability:** Ambry Genetics  
**Specimen:** Blood, saliva  
**Methodology:** DNA mutation analyses  
**Diseases:** chronic  
**Clinical Uses:** For diagnosis, target treatment, screening of family member with regard to idiopathic, chronic, and recurrent acute pancreatitis  
**Sources:** www.ambrygen.com  
**Medline Searches:** (PRSS1 OR SPINK1 OR CFTR) AND pancreatitis

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Figure 20. Gene Test Information: deCODE AF, SNPs rs2200733 and rs100233464- chromosome 4q25, ND, Atrial Fibrillation

**Test Name:** deCODE AF  
**Gene Symbol:** SNPs rs2200733 and rs100233464- chromosome 4q25  
**Protein Name:** ND  
**Description:** Alleles (bases) of two SNPs, rs2200733 and rs100233464, both located near the PITX2 gene on chromosome 4q25, were found to be significantly more common in AF patients than in control subjects. The PITX2 gene is known to play a role in cardiac development.  
**Purpose:** diagnostic  
**Availability:** DECODE  
**Specimen:** blood or buccal swab  
**Methodology:** ND  
**Diseases:** Atrial Fibrillation  
**Clinical Uses:** Genetic testing of individuals at risk for AF  
**Sources:** www.decodediagnostics.com AF-risk.php  
**Medline Searches:** atrial fibrillation AND 4Q25

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Test Name: deCODE Glaucoma
Gene Symbol: LOXL1 gene on chromosome 15q24
Protein Name: Lysyl oxidase-like protein 1
Description: Two non-synonymous changes in exon 1 of the LOXL1 gene on chromosome 15q24.1 confer risk to exfoliation glaucoma, possibly through the exfoliation syndrome. Exfoliation syndrome is characterized by accumulation of abnormal microfibrillar deposits that line the aqueous bathed surfaces of the anterior segment of the eye.
Purpose: diagnostic
Availability: DECODE
Specimen: blood or buccal swab
Methodology: sequencing utilizing the Illumina Hap300 SNP chip
Diseases: exfoliation glaucoma
Clinical Uses: diagnosis (risk prediction)
Sources: www.decodediagnostics.com GL.php
Medline Searches: glaucoma AND LOXL1

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
**Test Name:** deCODE T2  
**Gene Symbol:** TCF7L2, PPARG, CDKAL1, and CDKN2A  
**Protein Name:** PPAR Receptors  
**Description:** The DNA markers included in deCODE T2 are located in or near the following genes: TCF7L2, PPARG, CDKAL1, and CDKN2A and have each been widely replicated in 10 to 40 independent populations. TCF7L2 is the strongest genetic risk factor discovered so far for Type 2 diabetes and has been validated in over 40 populations spanning several ethnicities. The TCF7L2 marker correlates with lower insulin secretion in response to oral glucose. deCODE T2 combines the risk due to TCF7L2 with the three other widely validated genes.  
**Purpose:** screening  
**Availability:** DECODE  
**Specimen:** blood or buccal swab  
**Methodology:** ND  
**Diseases:** Type 2 Diabetes  
**Clinical Uses:** High-risk patients may benefit from more aggressive management either through lifestyle modification or drug treatment.  
**Sources:** www.decodediagnostics.com T2.php  
**Medline Searches:** diabetes AND (TCF7L2 OR PPARG OR CDKAL1 OR CDKN2A)

This line graph shows medline hits on the y-axis versus dates on the x-axis. The number of medline hits has increased over time.
Appendix B. Genetic tests from 2007 horizon scan report on Genetic Testing for Non-Cancer Conditions report.
Table 1. Pharmacogenetic tests for non-cancer conditions

<table>
<thead>
<tr>
<th>Gene</th>
<th>Role of gene</th>
<th>Drug</th>
<th>Effect of polymorphism on response to drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB1</td>
<td>Drug transporter</td>
<td>Digoxin</td>
<td>Increased bioavailability, atrial arrhythmias, and heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fexofenadine</td>
<td>Associated with lower plasma concentrations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nelfinavir, Efavirenz</td>
<td>Associated with lower plasma concentrations and greater rise in CD4 responses</td>
</tr>
<tr>
<td>ABCA1</td>
<td>Drug transporter</td>
<td>Statins</td>
<td>High adjusted mean change</td>
</tr>
<tr>
<td>ACE</td>
<td>Drug target</td>
<td>Angiotensin-converting–enzyme inhibitors</td>
<td>Decreased blood pressure; reduction in left ventricular mass; survival after cardiac transplantation; renal protection (All effects most pronounced with D/D genotype)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statin</td>
<td>Decreased LDL levels and regression of atherosclerosis</td>
</tr>
<tr>
<td>ADRB2</td>
<td>Drug target</td>
<td>82-Adrenergic agonists</td>
<td>Vasodilation and bronchodilation</td>
</tr>
<tr>
<td>APOE</td>
<td>Drug target</td>
<td>Statins</td>
<td>Decreased LDL levels and reduced mortality after myocardial infarction</td>
</tr>
<tr>
<td>CETP</td>
<td>Drug transporter</td>
<td>Testosterone</td>
<td>Progression of coronary-artery atherosclerosis</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Drug metabolism</td>
<td>Tacrolimus; Cyclosporine</td>
<td>Associated with higher plasma concentrations</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Drug metabolism</td>
<td>Nicotine</td>
<td>Variability in plasma concentrations</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>Drug metabolism</td>
<td>Effavirenz</td>
<td>Associated with higher plasma concentrations</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Drug metabolism</td>
<td>Repaglinide</td>
<td>Associated with lower plasma concentrations</td>
</tr>
</tbody>
</table>

B-2
<table>
<thead>
<tr>
<th>Gene</th>
<th>Role of the Drug</th>
<th>Drug</th>
<th>Effect of polymorphism on response to drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19/CYP2D6</td>
<td>Drug metabolism</td>
<td>Multiple drugs</td>
<td>Poor metabolism of anticonvulsants</td>
</tr>
<tr>
<td>KCNE2 (MiRP-1)</td>
<td>Drug transporter</td>
<td>Clarithromycin, Sulfamethoxazole</td>
<td>Long-QT syndrome and ventricular fibrillation, Long-QT syndrome</td>
</tr>
<tr>
<td>OATP-C</td>
<td>Drug transporter</td>
<td>Pravastatin</td>
<td>Associated with lower clearance</td>
</tr>
<tr>
<td>Factor V</td>
<td>Pathway none</td>
<td>Anticoagulants</td>
<td>Need for increased therapy after major surgery</td>
</tr>
<tr>
<td>VKORC1</td>
<td>Drug metabolism</td>
<td>Warfarin</td>
<td>Associated with variability in dosing and response</td>
</tr>
<tr>
<td>CYP2C9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2: Genetic tests for non-cancer conditions with high likelihood applicability to the Medicare population

<table>
<thead>
<tr>
<th>ID</th>
<th>Disease</th>
<th>Gene</th>
<th>Specimen</th>
<th>DNA methodology¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alpha-1-antitrypsin deficiency</td>
<td>SERPINA1</td>
<td>Blood</td>
<td>Mutation analysis, Sequence analysis, Linkage analysis</td>
</tr>
<tr>
<td>2</td>
<td>Alport Syndrome</td>
<td>COL4A5</td>
<td>Blood</td>
<td>Sequence analysis</td>
</tr>
<tr>
<td>3</td>
<td>Alzheimer's Disease</td>
<td>Phosphorylated-Tau protein, Total-Tau protein and Aβ42 peptide</td>
<td>CSF</td>
<td>ELISA</td>
</tr>
<tr>
<td>4</td>
<td>Alzheimer's Disease Late onset disease</td>
<td>ApoE2, E3, E4 alleles</td>
<td>Blood, buccal swab</td>
<td>Serial Invasive Signal Amplification Reaction (SISAR)</td>
</tr>
<tr>
<td>5</td>
<td>Antithrombin-III Deficiency</td>
<td>SERPINC1</td>
<td>ND</td>
<td>Sequence analysis, Deletion/duplication analysis</td>
</tr>
<tr>
<td>6</td>
<td>Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy</td>
<td>ARVD 1 to 9; RYR2, DSP, and PKP2</td>
<td>Blood</td>
<td>Mutation analysis, Sequence analysis, Linkage analysis, Deletion/duplication analysis</td>
</tr>
<tr>
<td>7</td>
<td>Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)</td>
<td>CHRNA4, CHRN82</td>
<td>Serum</td>
<td>Sequence analysis</td>
</tr>
<tr>
<td>8</td>
<td>Bardet-Biedl Syndrome</td>
<td>BBS10</td>
<td>Blood</td>
<td>Mutation analysis, Sequence analysis, Linkage analysis</td>
</tr>
<tr>
<td>9</td>
<td>Cardiovascular risk assessment</td>
<td>ACE I and II</td>
<td>Blood</td>
<td>Mutation analysis, Deletion/duplication analysis</td>
</tr>
<tr>
<td>10</td>
<td>Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)</td>
<td>BBS2, BBS10</td>
<td>Blood</td>
<td>Mutation analysis, Sequence analysis, Linkage analysis</td>
</tr>
<tr>
<td>11</td>
<td>Cerebral Cavernous Malformations</td>
<td>NOTCH3</td>
<td>Blood, extracted DNA</td>
<td>Sequence analysis</td>
</tr>
<tr>
<td>12</td>
<td>Cerebral Cavernous Malformations</td>
<td>CCM2, CCM3, PDCD10</td>
<td>Blood</td>
<td>Mutation analysis, Sequence analysis, Linkage analysis</td>
</tr>
<tr>
<td>13</td>
<td>Familial Cerebral Cavernous Malformation 1 (CCM1)</td>
<td>CCM1, KRIT1</td>
<td>Blood</td>
<td>Mutation analysis, Sequence analysis, Linkage analysis</td>
</tr>
<tr>
<td>14</td>
<td>Crigler-Najjar Syndrome</td>
<td>UGT1A1</td>
<td>Blood</td>
<td>Mutation analysis, Sequence analysis, Mutation scan</td>
</tr>
<tr>
<td>15</td>
<td>Crohn Disease</td>
<td>CARD15</td>
<td>Blood</td>
<td>Sequence analysis, Mutation scan</td>
</tr>
<tr>
<td>16</td>
<td>Cystinosis</td>
<td>CTNS</td>
<td>Cultured cells, skin biopsy</td>
<td>Mutation analysis</td>
</tr>
<tr>
<td>17</td>
<td>Cystinuria</td>
<td>SLC3A1, SLC7A9</td>
<td>Blood, urine</td>
<td>Mutation analysis, Sequence analysis, Deletion/duplication analysis</td>
</tr>
</tbody>
</table>

¹ Methodology other than DNA appears in italics.
Table 2: Genetic tests for non-cancer conditions with high likelihood applicability to the Medicare population (continued)

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

1. Methodology other than DNA appears in italics.
Table 2: Genetic tests for non-cancer conditions with high likelihood applicability to the Medicare population (continued)

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

1. Methodology other than DNA appears in italics.
<table>
<thead>
<tr>
<th>ID</th>
<th>Disease</th>
<th>Gene</th>
<th>Specimen</th>
<th>DNA Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td>Renal Tubular Acidosis, Distal, Autosomal Recessive</td>
<td>ATP6V0A4</td>
<td>Blood</td>
<td>Sequence Analysis, Deletion / Duplication analysis</td>
</tr>
<tr>
<td>67</td>
<td>Retinitis pigmentosa - PRPF3-Related Retinitis Pigmentosa</td>
<td>PRPF3</td>
<td>Blood</td>
<td>Sequence Analysis, Linkage analysis</td>
</tr>
<tr>
<td>68</td>
<td>Romano Ward (Long QT) Syndrome</td>
<td>KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2</td>
<td>Blood</td>
<td>Sequence Analysis, Deletion / Duplication analysis</td>
</tr>
<tr>
<td>69</td>
<td>Sialuria</td>
<td>GNE</td>
<td>Blood</td>
<td>Sequence Analysis</td>
</tr>
<tr>
<td>70</td>
<td>SOD1-Related Amyotrophic Lateral Sclerosis</td>
<td>SOD1</td>
<td>Blood</td>
<td>Mutation analysis, Sequence Analysis</td>
</tr>
<tr>
<td>71</td>
<td>Spastic Paraplegia Type 4</td>
<td>SPAST</td>
<td>Blood</td>
<td>Sequence Analysis, Mutation scan</td>
</tr>
<tr>
<td>72</td>
<td>Spinal Muscular Atrophy 4</td>
<td>SMN1 (SMN1)</td>
<td>Blood</td>
<td>Mutation analysis, Sequence Analysis</td>
</tr>
<tr>
<td>73</td>
<td>Spinal and Bulbar Muscular Atrophy</td>
<td>AR</td>
<td>Blood</td>
<td>Mutation analysis</td>
</tr>
<tr>
<td>74</td>
<td>Spinocerebellar Ataxia Type 2</td>
<td>ATXN2</td>
<td>Blood</td>
<td>Mutation analysis, Linkage analysis, Mutation scan</td>
</tr>
<tr>
<td>75</td>
<td>Spinocerebellar Ataxia Type 3</td>
<td>ATXN3</td>
<td>Blood</td>
<td>Mutation analysis, Mutation scan</td>
</tr>
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<td>76</td>
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<td>Spastic Paraplegia 4</td>
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<td>Tuberous sclerosis 2</td>
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<td>90</td>
<td>XDx Allomap Molecular Expression testing for acute cellular organ transplant rejection</td>
<td>11 different genes $^*$</td>
<td>Blood</td>
<td>Messenger RNA (mRNA) expression</td>
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1. Methodology other than DNA appears in italics.
2. ITGA4, PDCD1, PF4, G6b, MIR, WDR40A, SEMA7A, ILIR-2, ITGAM, FLT3, RHOU