Technology Assessment

Technology Assessment Program

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

Technology Assessment Report

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Tufts Medical Center

Evidence-based Practice Center

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This report is based on research conducted by the Tufts Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290 2007 10055 I). 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. 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.

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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) 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

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

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) and ***EGAPP Reviews*** (egappreviews.org)

5) The Office of In Vitro Diagnostics Device Evaluation and Safety (OIVD): (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 Comma Separated 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.

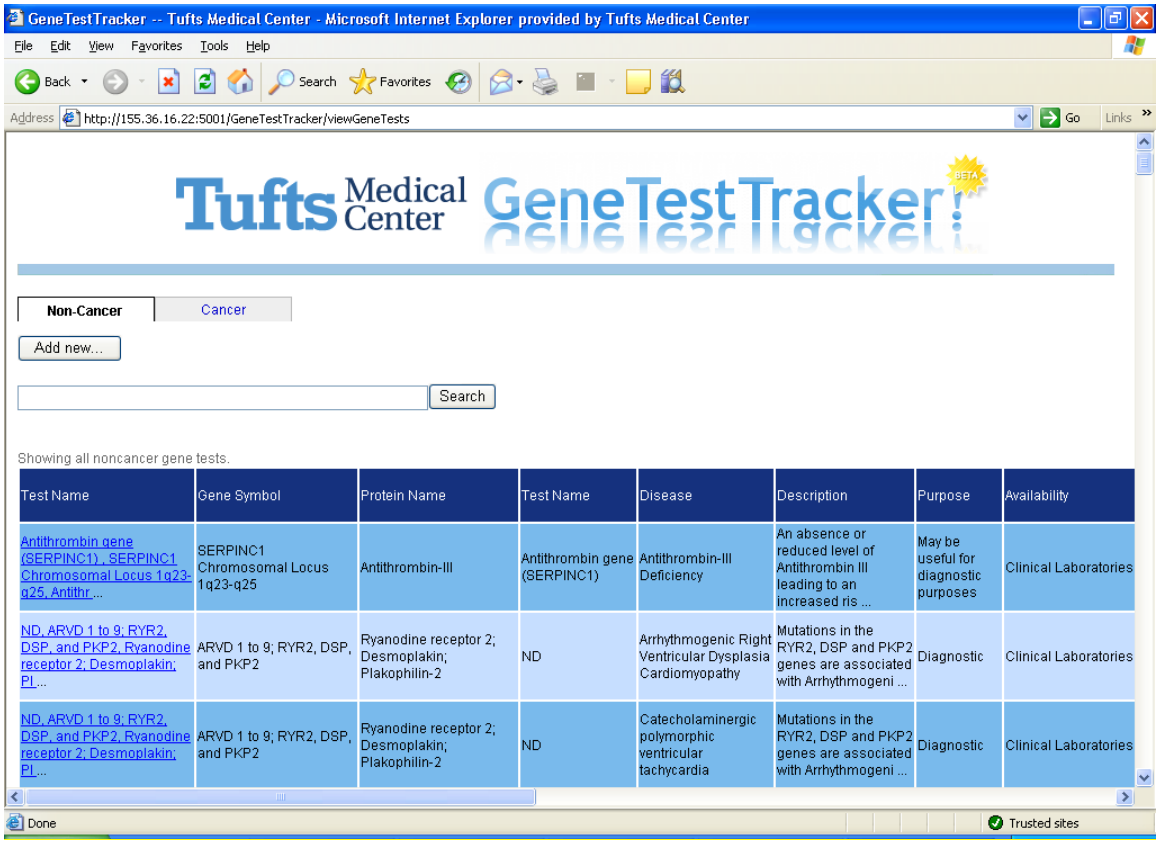

Figure 1 is a snapshot of Gene Test Tracker, the front end to the electronic database that lists genetic and genomic tests. After logging in the password-protected site, the user sees an html page depicting a table. Each row pertains to a specific test. The columns list the

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 2a. Pharmacogenetic tests for non-cancer conditions

Gene	Role of the gene	Drug	Effect of polymorphism on response to drug
CYP450 2C19	Drug metabolism	Clopidogrel	Patients who have CYP2 C19 poor metabolizer status is associated with diminished response to clopidogrel and greater risk of cardiovascular events
HLA-B* 1502	Drug metabolism	Carbamazepine	HLA-B*1502 allele presence is associated with serious dermatologic reactions such as Stevens-Johnson Syndrome and toxic epidermal necrolysis.
Thiopurine S-methyltransferase gene	Drug metabolism	Azathioprine	TPMT deficiency or lower activation due to gene mutation increases myelotoxicity in patients undergoing azathioprine therapy.
CYP2 D6	Drug metabolism	Antidepressants	Depending on certain allelic variants will show normal, decreased or no CYP2D6 function, which can affect the plasma concentrations of the drug.
CYP2 D6	Drug metabolism	Pain medications	Depending on certain allelic variants will show normal, decreased or no CYP2D6 function, which can affect the plasma concentrations of the drug.
Androgen receptor gene	Drug target	Finasteride	Finasteride therapy is effective in patients with a shorter CAG repeat number than those with a longer CAG repeat number.
HLA-B*5701	Drug metabolism	Abacavir	Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir.
Low density lipoprotein receptor (LDLR) Gene	Drug target	Atorvastatin	Atorvastatin attenuates the inflammatory reaction and development of atherosclerosis in hypercholesterolemic patients, but in patients with LDLR gene polymorphism, this effect is more profound.
GRIK2 and GRIA3	Drug target	Citalopram or selective serotonin reuptake inhibitor(SSRI)	kainate receptor gene, GRIK2 and GRIA3 increases the odds for suicidal thinking in patients taking citalopram or other SSRI
CYP2 C19	Drug metabolism	Second generation SSRI	Depending on certain allelic variants will show normal, decreased or no CYP2C19 function, which can affect the plasma concentrations of the drug.
CYP2 C19	Drug metabolism	Proton-pump inhibitors	Depending on certain allelic variants will show normal, decreased or no CYP2C19 function, which can affect the plasma concentrations of the drug.

Table 2b. Gene disease association tests for non-cancer conditions with high likelihood applicability to the Medicare population

Disease/Condition	Gene	Specimen	Methodology
Psoriasis Arthritis	MICA-A9	Buccal Swab	Not reported
Dilated cardiomyopathy (DCM)	Multiple genes	Whole blood	DNA sequence analysis
Hypertrophic cardiomyopathy	Multiple genes	Whole blood	Dideoxy DNA sequence analysis
General nutrition assessment	5-10-methylenetetrahydrofolate reductase gene (MTHFR) and transcobalamin 2 gene	Whole blood	SNP analysis
Heart disease and acute coronary events	interleukin 1 (IL1)genes	Whole blood	Not reported
Periodontal disease	interleukin-1A and interleukin-1B	Buccal swab	DNA analysis for variations in the interleukin-1 genes
Narcolepsy and other sleep disorders	human leukocyte antigen (HLA)	Whole blood	DNA testing using PCR analysis
Recurrent acute pancreatitis and Chronic pancreatitis	PRSS1, SPINK1, and CFTR	Blood, saliva	DNA mutation analyses
DeCODE-AF™	SNPs rs2200733; rs100233464	Blood, Buccal	Not reported
DeCODE glaucoma™	LOXL1 gene	Blood, Buccal	sequencing utilizing the Illumina Hap300 SNP chip
DeCODE T2™	TCF7L2, PPARG, CDKAL1, and CDKN2A	Blood, Buccal	Not reported

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

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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

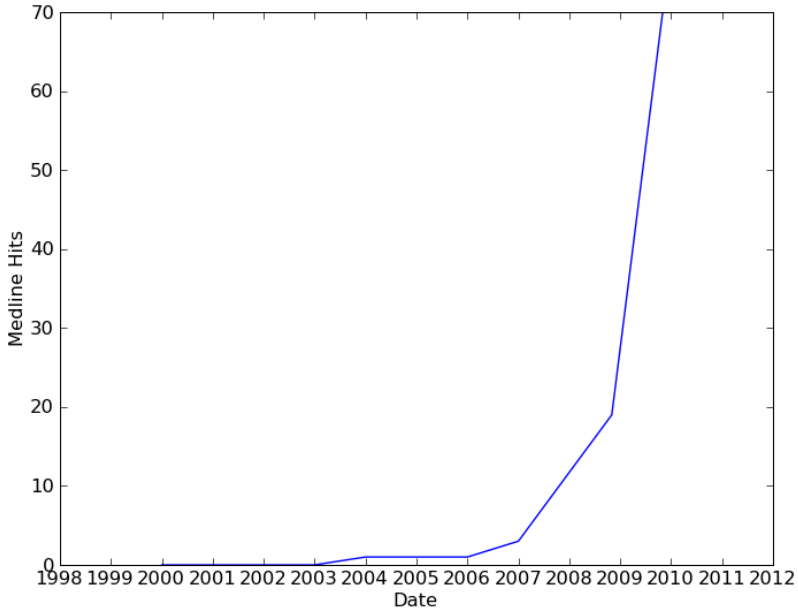
Diseases: Resistance to clopidogrel plavix (pharmacogenetic test)

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.

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

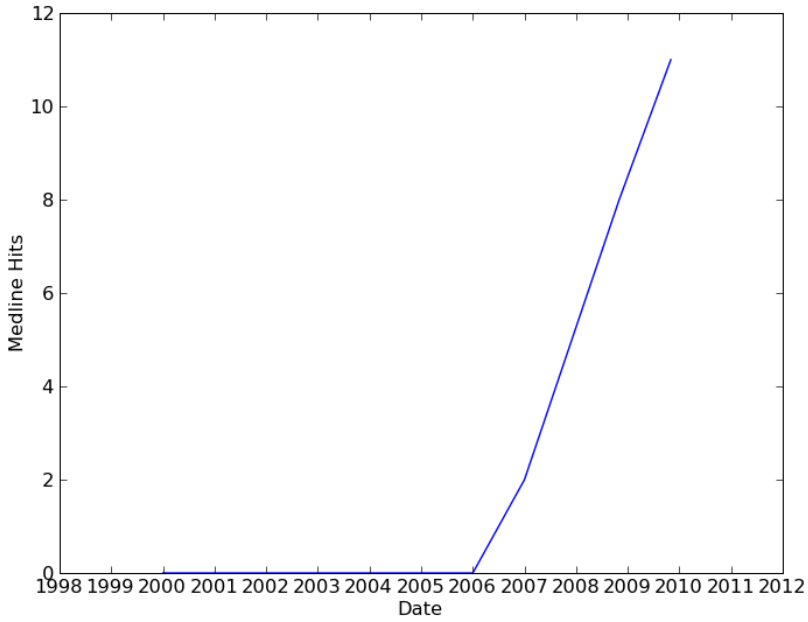
Diseases: Carbamazepine Hypersensitivity

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

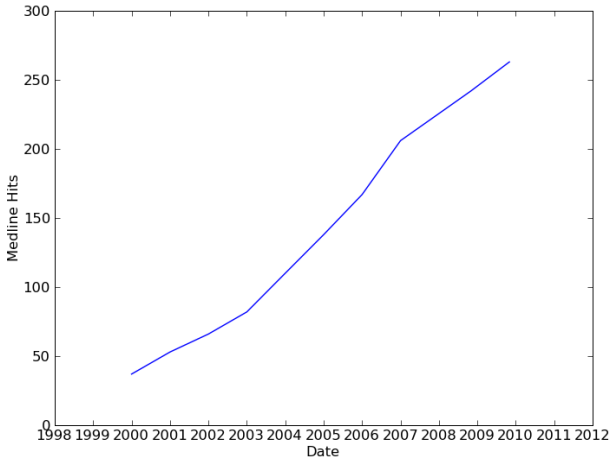
Diseases: Pharmacogenetic testing for therapy of thiopurine drugs

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 metaolizers. 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

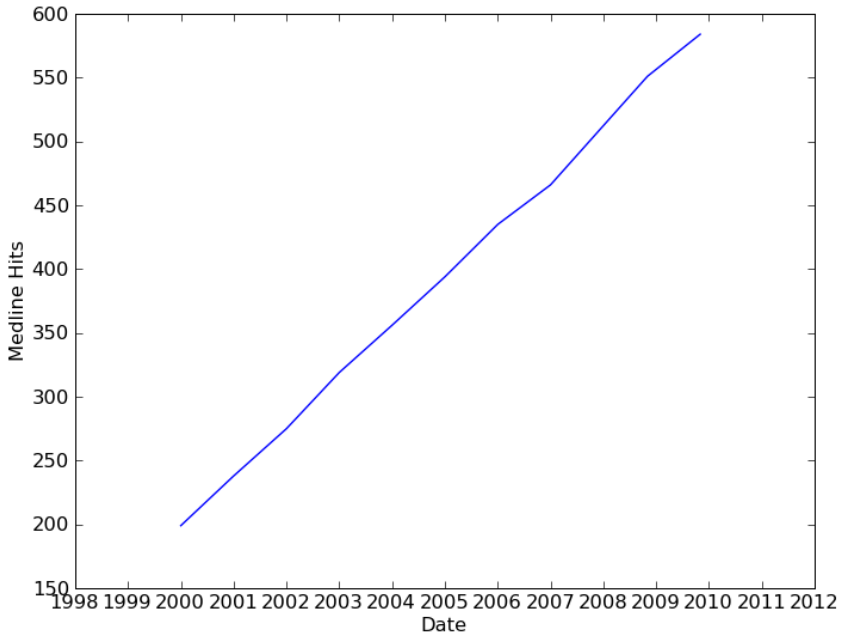
Diseases: Pharmacogenetic testing for tricyclic antidepressants

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

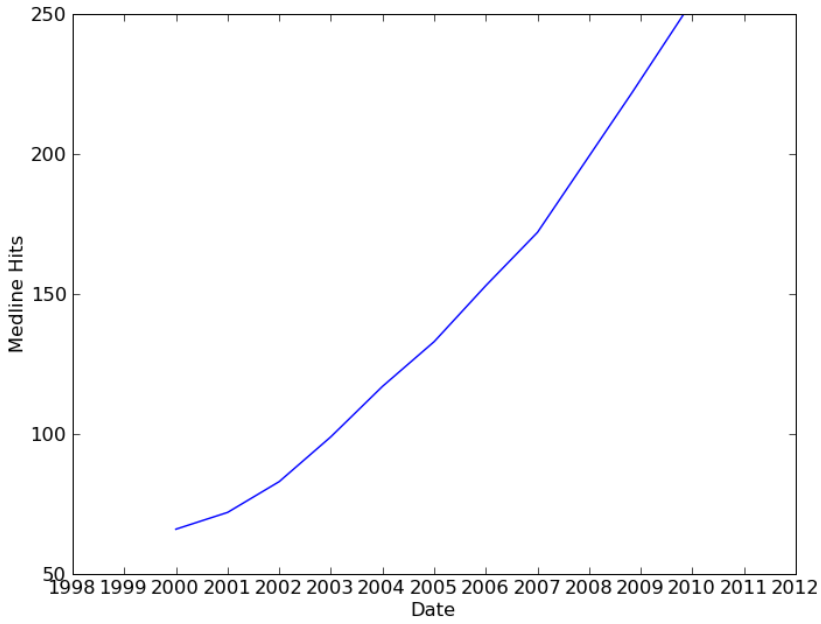
Diseases: Pharmacogenetic testing of opioids

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.

Figure 6. Gene Test Information: HairDX (RxR) Genetic Test, androgen receptor gene, androgen receptor, Finasteride response in androgenetic alopecia

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

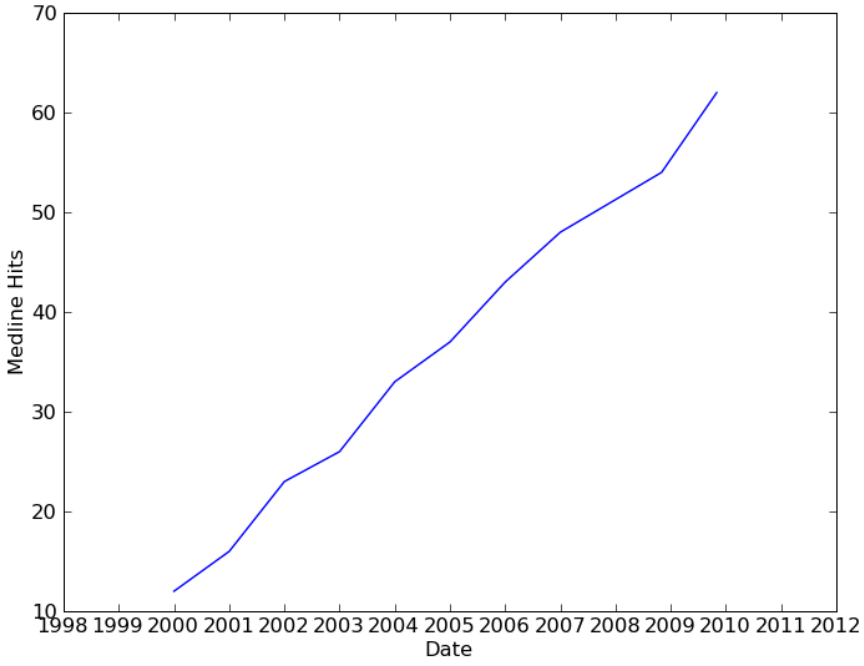
Diseases: Finasteride response in androgenetic alopecia

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 HLAB*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)

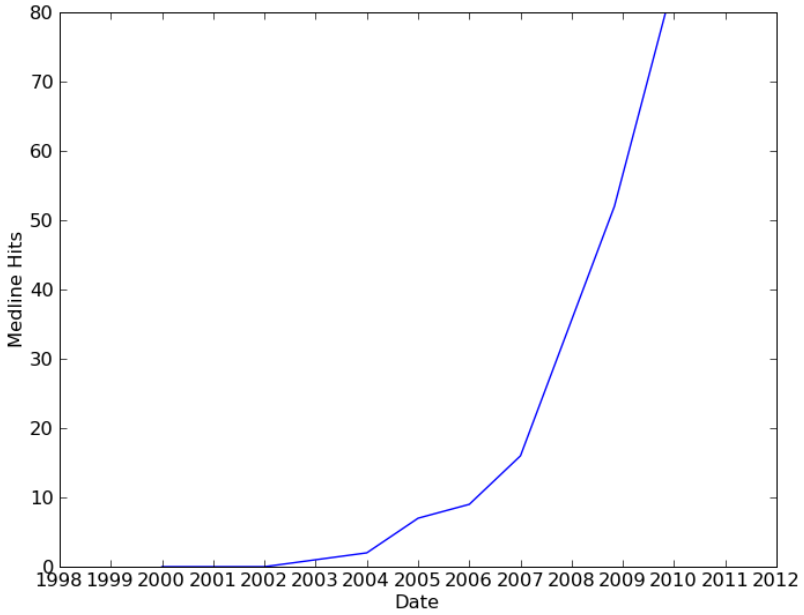
Diseases: Abacavir hypersensitivity

Clinical Uses: Identifying increased risk of abacavir hypersensitivityin 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

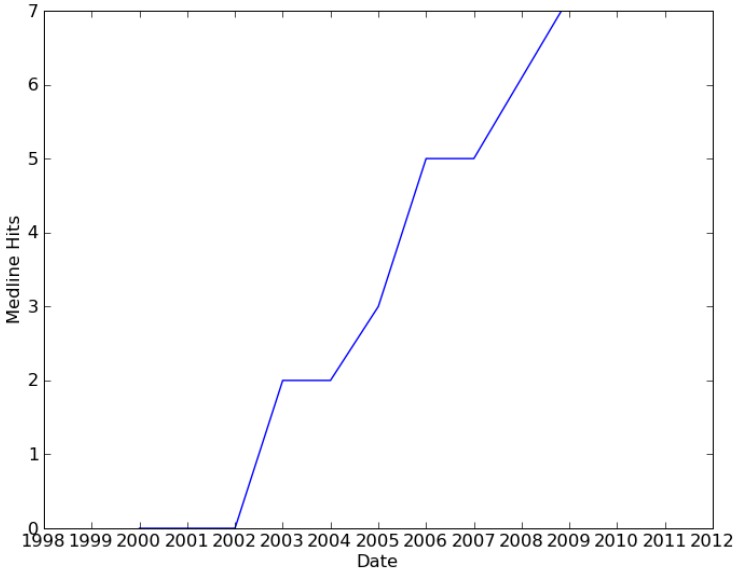
Diseases: Pharmacogenetic testing to evaluate response to atorvastatin (lipitor) therapy

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.

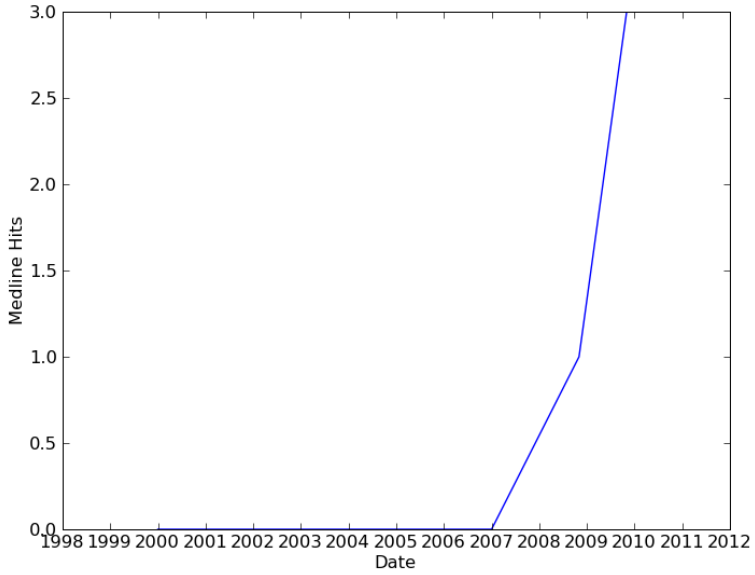
Diseases: A pharmacogenetic test that can identify suicidal ideation when a patient is prescribed the antidepressant drug. citalopram

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

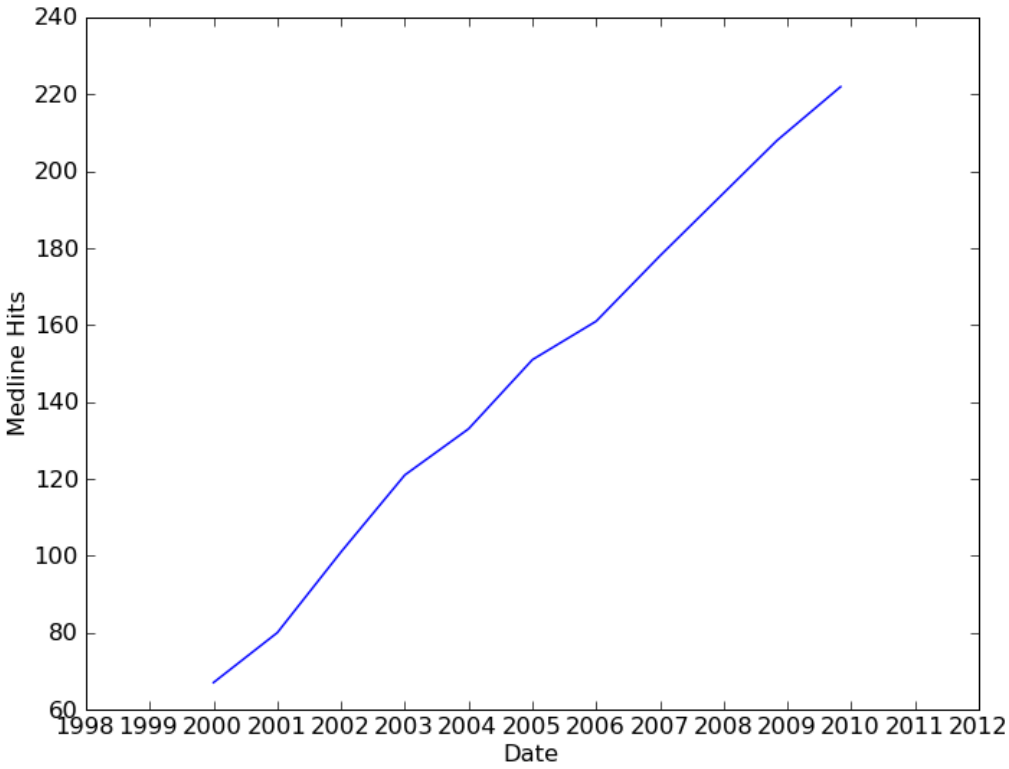
Diseases: Pharmacogenetic testing of second-generation antidepressants

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.

Figure 11. Gene Test Information: CYP2C19, CYP2C19, Cytochrome P-450, Pharmacogenetic testing for proton pump inhibitors

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 thatn poor metabolizers

Purpose: Therapeutic management

Availability: Commercial laboratories

Specimen: Blood or buccal swab

Methodology: Cytochrome P-450 2C19 DNA test

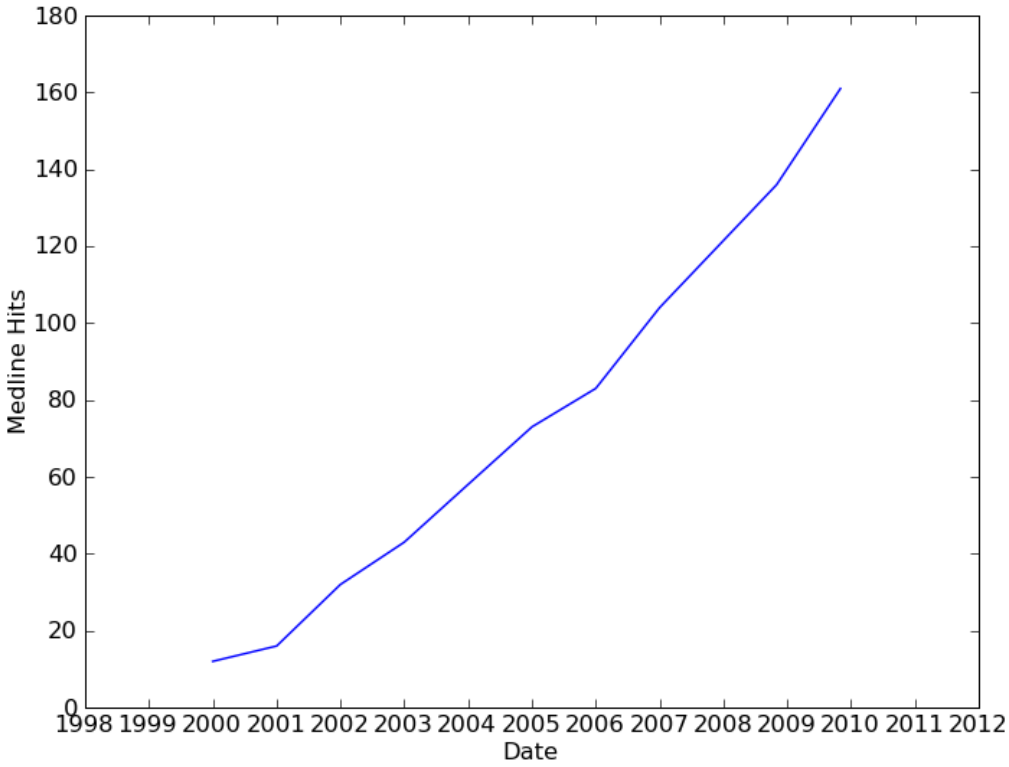
Diseases: Pharmacogenetic testing for proton pump inhibitors

Clinical Uses: Dosage management

Sources: PGXL labs; healthdna.com

Medline Searches: CYP2C19 AND proton pump inhibitors

FDA Cleared: Yes



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

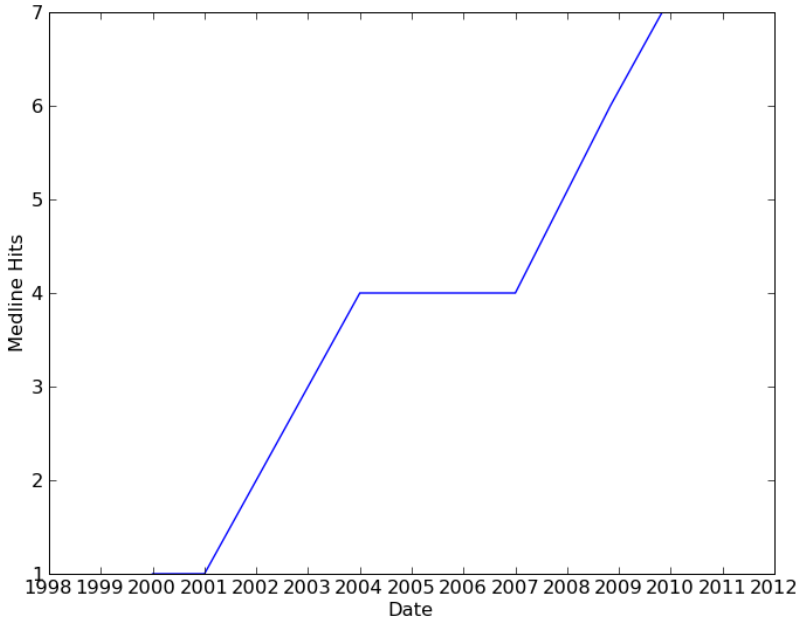
Diseases: Psoriatic arthritis

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

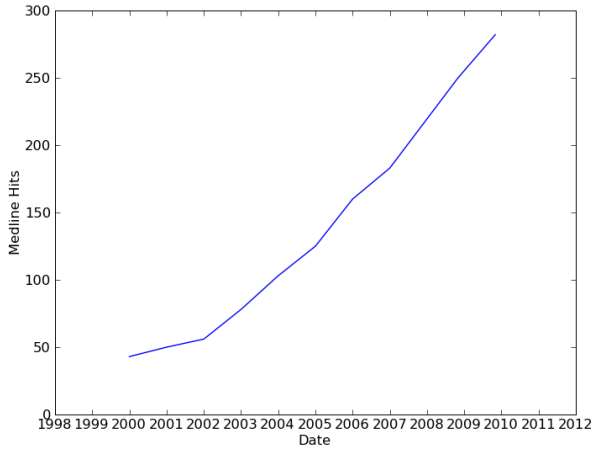
Diseases: Dilated cardiomyopathy

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 (TNN13), 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 (TNN13), 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 heartmuscle, and their regulators and interaction partners can lead to HCM.

Purpose: Diagnostic

Availability: GeneDX

Specimen: Blood

Methodology: dideoxy DNA sequence analysis

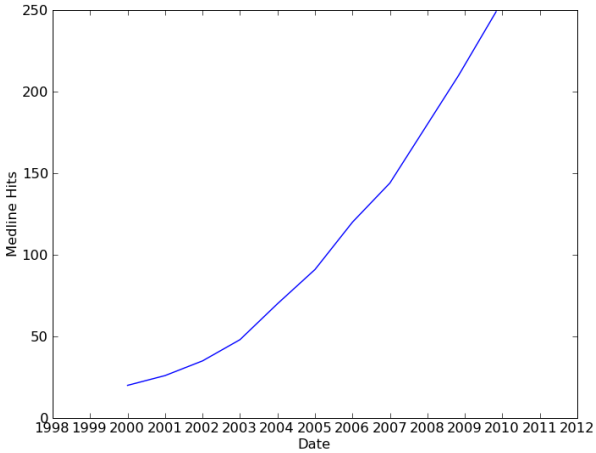
Diseases: Hypertrophic cardiomyopathy

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

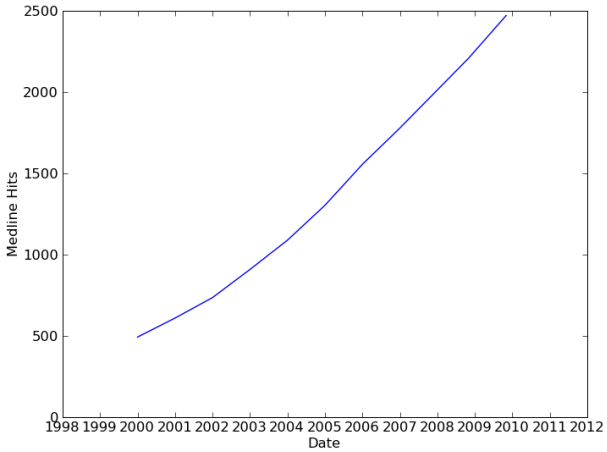
Methodology: SNP analysis

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



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 16. Gene Test Information: Gensona(TM) Heart Health test , interleukin 1 (IL1)genes, ND, Heart disease and acute coronary events

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

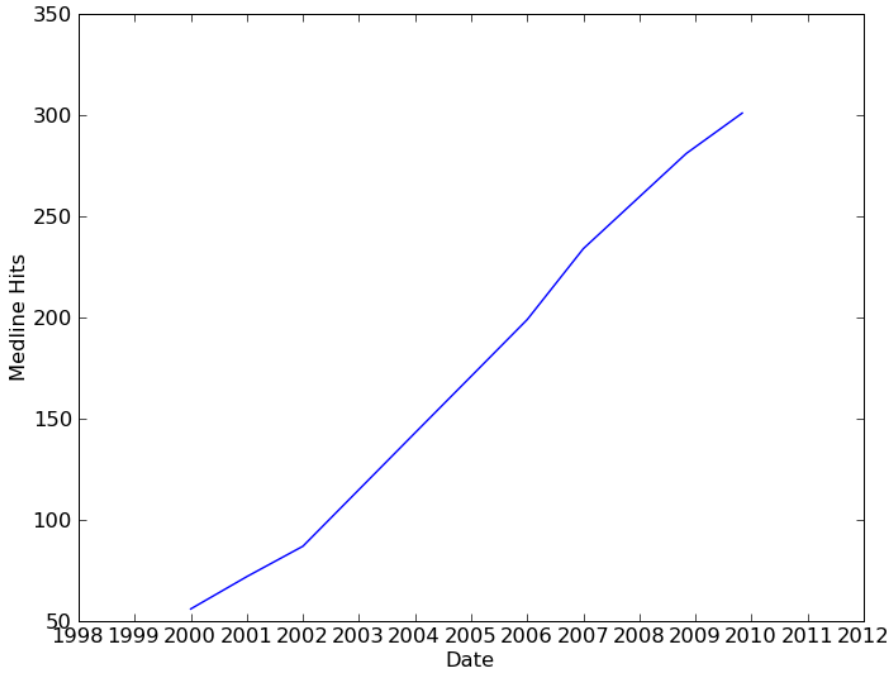
Methodology: ND

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

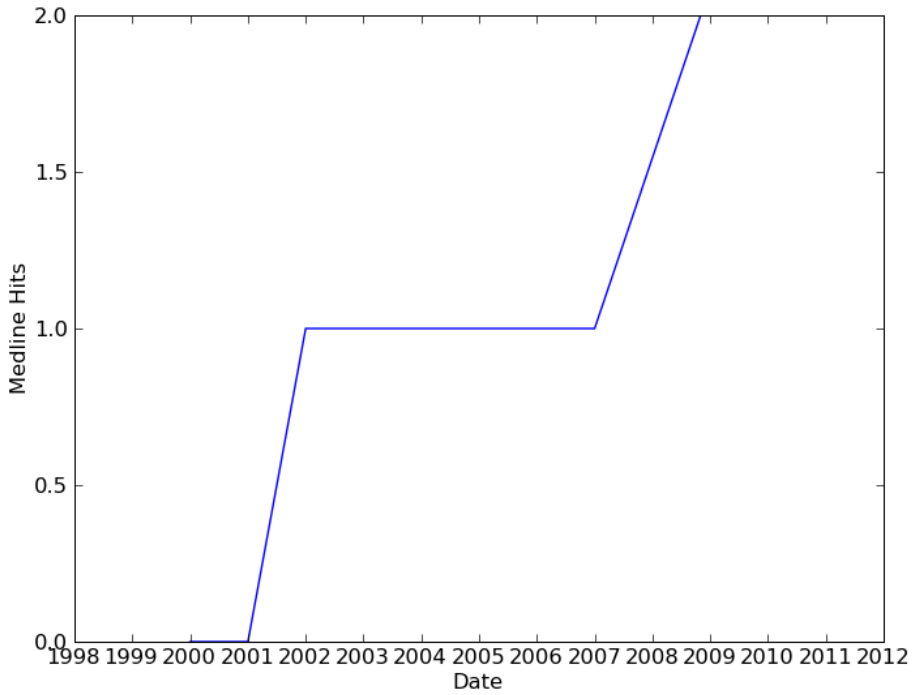
Methodology: DNA analysis for variations in the interleukin-1 genes

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

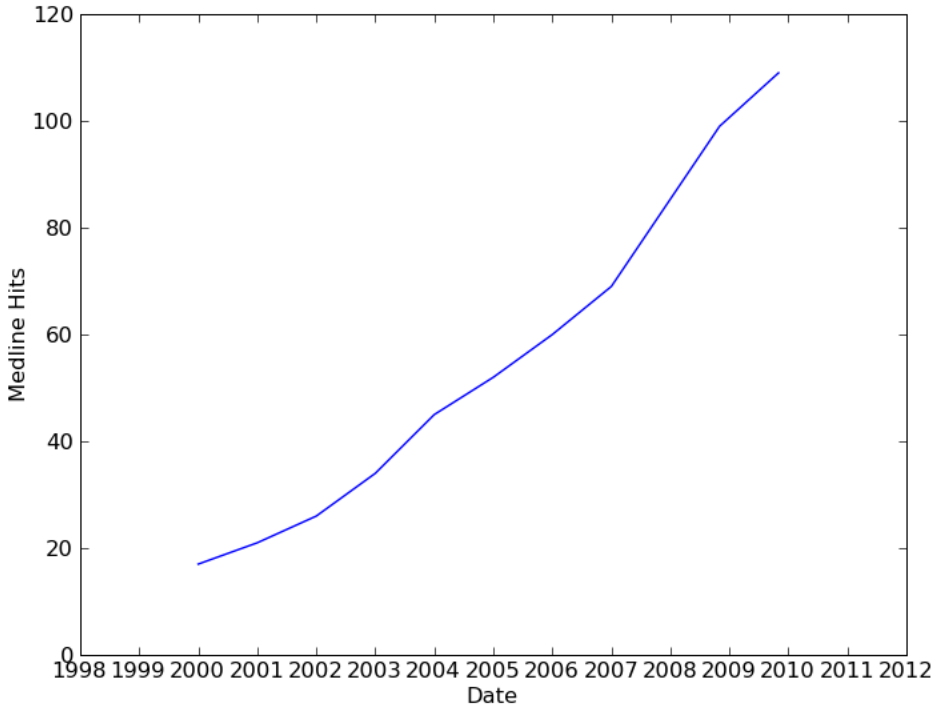
Methodology: DNA testing using PCR analysis

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

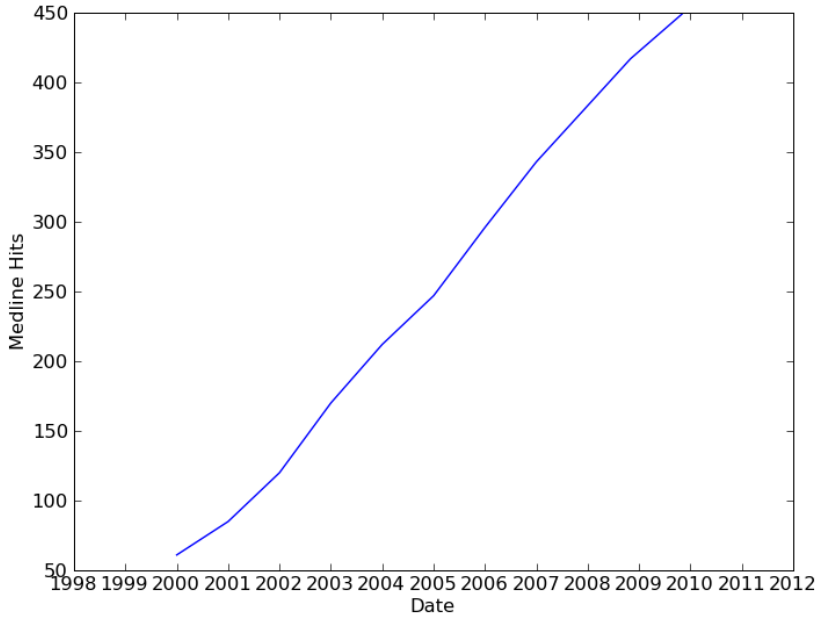
Methodology: DNA mutation analyses

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

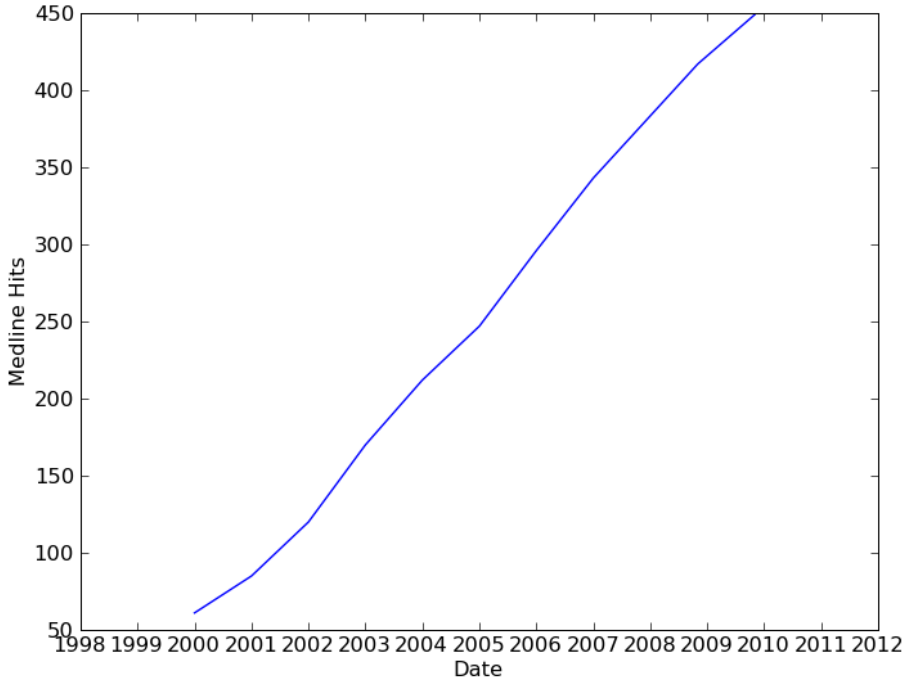
Methodology: DNA mutation analyses

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

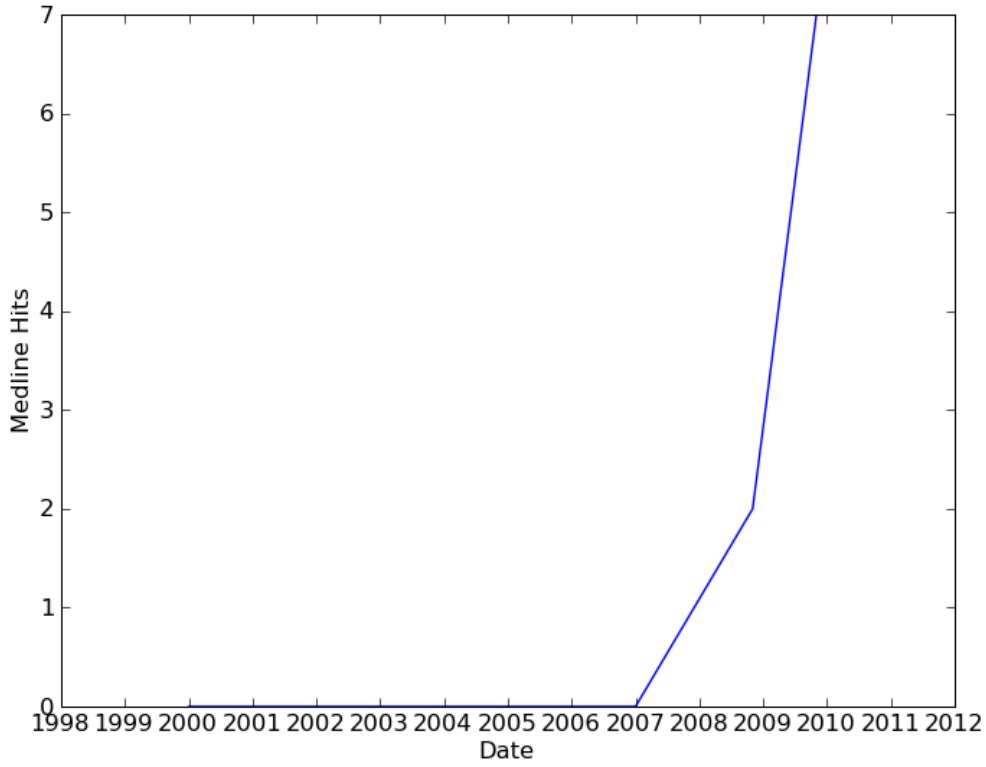
Methodology: ND

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.

Figure 21. Gene Test Information: deCODE Glaucoma, LOXL1 gene on chromosome 15q24, Lysyl oxidase-like protein 1 , exfoliation glaucoma

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

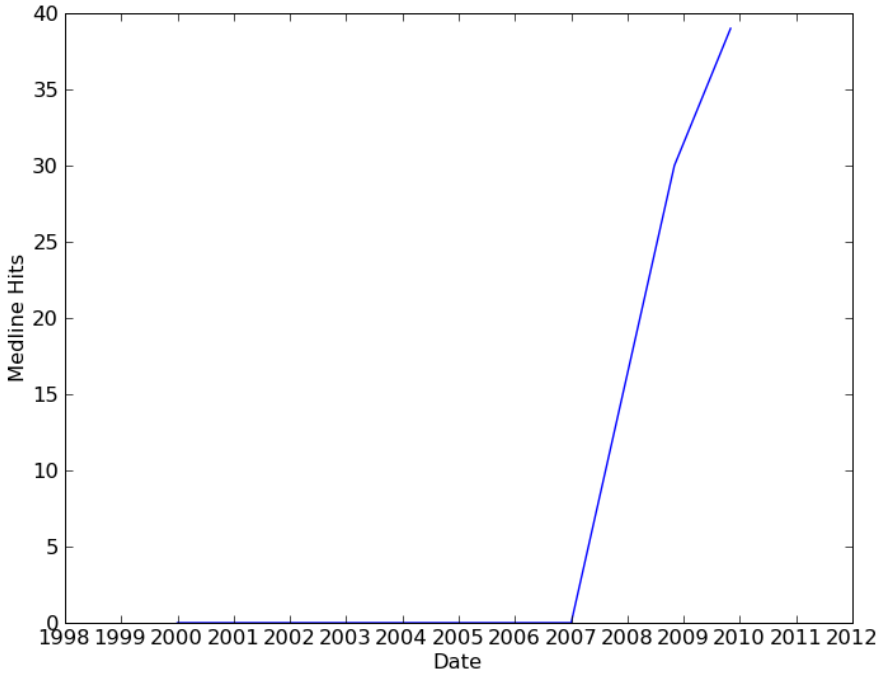
Methodology: sequencing utilizing the Illumina Hap300 SNP chip

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.

Figure 22. Gene Test Information: deCODE T2, TCF7L2, PPARG, CDKAL1, and CDKN2A, PPAR Receptors, Type 2 Diabetes

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

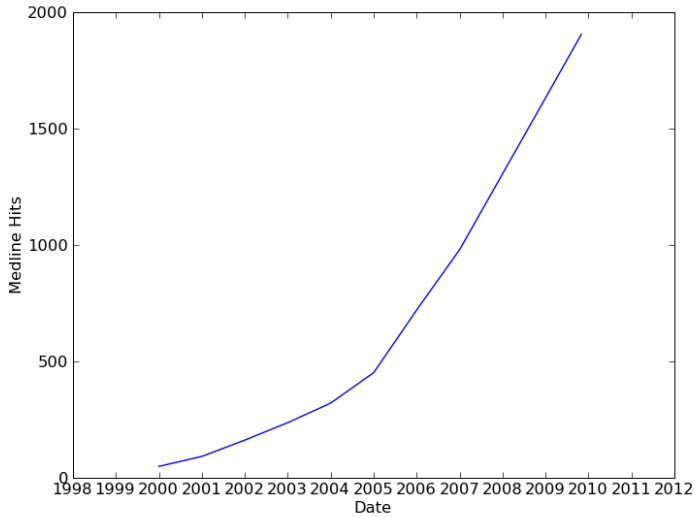
Methodology: ND

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

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 1. Pharmacogenetic tests for non-cancer conditions (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			

Table 2: 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 2: 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 2: 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 2: 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