Technology Assessment

Technology Assessment Program

Genetic Tests for Cancer

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

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

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INTRODUCTION

The Centers for Medicare & Medicaid Services (CMS) has asked the Agency for Healthcare Research & Quality (AHRQ) and the Tufts-NEMC EPC to perform a horizon scan of gene-based tests in cancer that are currently in clinical use, are being promoted for clinical use, or are being developed for clinical use. CMS has expressed the need for the deliverable to be a ready reference tool to inform discussions in this area.

Aim

The aim of this horizon scan is to identify the different genomic tests that are being promoted for clinical use in cancer prevention, diagnosis, and management. As outlined in the Detailed Workplan, the project was organized into two distinct parts with separate aims and methodologies. The goal of Part I was to answer the key question: What genetic tests are currently available for cancer prevention, diagnosis and treatment? The goal of Part II of this project was to answer the key question: What genetic tests are in development for cancer?

Definition of a Genetic test:

An essential step early in our project was to establish a definition for genetic test. To this end, we refer to the Secretary's Advisory Committee on Genetic Testing (SACGT)'s broad definition:

> "A genetic test is an analysis performed on human DNA, RNA, genes, and/or chromosomes to detect heritable or acquired genotypes, mutations, phenotypes, or karyotypes that cause or are likely to cause a specific disease or condition. A genetic test also is the analysis of human proteins and certain metabolites, which are predominantly used to detect heritable or acquired genotypes, mutations, or phenotypes. The purposes of these genetic tests include predicting risks of disease, screening of newborns, directing clinical management, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations." [1]

This definition includes tests for molecular or biochemical biomarkers. It also includes cytogenetic, genomic, genome-based and gene-based tests. We have found that the terms "genetics" and "genomics" are often used interchangeably in the literature and both can refer to tests for molecular or biochemical biomarkers, as well as cytogenetic and gene-based tests. This review will use the term genetics to also mean genomics.

Clinical applications of genetic tests to be covered by the review:

Based on our discussions with AHRQ and feedback from CMS, the following three categories were used to describe the different applications for the various genetic tests:

i. Primary prevention: to detect inherited susceptibility to cancer in persons who do not have cancer in order to initiate appropriate interventions (prophylactic surgery, drug treatment or intensive and earlier screening)

ii. Secondary prevention: early detection of cancer in persons who have early stage (asymptomatic) cancer

iii. Diagnosis and management: includes confirming cancer, classifying cancer, predicting typical course of cancer, choosing type of treatment (e.g. surgery alone or with adjuvant chemotherapy), monitoring response to therapy, choosing right drug in right dose at right frequency (pharmacogenomics).

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) Recurrence: to detect disease recurrence in a patient who has already been diagnosed and treated for cancer. This is a more focused application that could be considered a subset of tests for the above mentioned "diagnosis and management" category
4) Monitoring: test used to monitor tumor and/or patient response to treatment

The focus of this horizon scan was primarily to review the genetic applications used for disease diagnosis, management and recurrence, and secondarily on disease prevention.

PART I : Genetic tests currently available for clinical use

AIM

The aim of Part I of the project was to identify genetic tests already in clinical practice or tests that are being marketed for use in clinical practice. As detailed in the Detailed Workplan, the goal of this part of the project was to generate (1) a database of current genetic tests for cancer, and (2) a series of one page summaries for each test in the database, providing additional detail of the individual tests including potential literature search strategies.

METHODS

I. Database of genetic test currently available

We considered 3 different categories of information for identifying current genetic tests widely available for cancer use:

1. scientific literature search
2. grey literature search
3. expert interviews and scientific meetings

1. scientific literature search

We conducted preliminary searches for genetic tests in sources from the three different categories. A quick Medline search for “cancer genetic test” revealed thousands of citations of reporting on various genetic polymorphisms and their possible association with different cancers. Examples of a few citations include “XPC polymorphisms and lung cancer risk,” ”Breast cancer risk associated with genotypic polymorphism of the mitosis-regulating Aurora-A/STK15/BTAK,” and “Genetic alteration of p53, but not over-expression of intratumoral p53 protein, or serum p53 antibody is a prognostic factor in sporadic colorectal adenocarcinoma.” It was quickly apparent that further efforts to explore the scientific databases was likely to reveal thousands of abstracts describing or identifying various gene or genome associations with cancer biology or tumorigenesis. However, most of these reported gene associations or potential tumor biomarkers are likely years removed from becoming a widely available clinically validated test for commercial cancer use. As a result, we determined that the scientific databases would not be useful for the purposes of this part of the project.

2. grey literature search

The Fourth International Conference on Grey Literature in Washington, DC, in October 1999 defined grey literature as: "That which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers."[2] Grey literature can include reports,

memoranda, conference proceedings, standards, technical documentation, and government documents.

According to Alberani et al., grey literature publications are "non-conventional, fugitive, and sometimes ephemeral publications. They may include, but are not limited to the following types of materials: reports (pre-prints, preliminary progress and advanced reports, technical reports, statistical reports, memoranda, state-of-the art reports, market research reports, etc.), theses, conference proceedings, technical specifications and standards, non-commercial translations, bibliographies, technical and commercial documentation, and official documents not published commercially (primarily government reports and documents)".[3]

For the purpose of this report we created a functional definition of grey literature that included a variety of traditional grey literature databases, as well as a variety of sources for reports and publications that are not peer-reviewed. In fact, we found that the most useful and efficient method for identifying genetic tests currently in use for cancer care, was to search for detailed listings of cancer genetic tests from the corporate websites of the major commercial diagnostic laboratories in the U.S. such as Quest Diagnostics® (Teterboro, NJ) and LabCorp® (Burlington, NC). Supplemental information and additional tests were found in other company websites such as Myriad Genetics (Salt Lake City, UT) and Genomic Health (Redwood City, CA), or other pertinent resources available online such as UpToDate® and www.genetest.org.

In constructing our list of grey literature sources for Part II of this project, we referred to the National Library of Medicine's Health Technology Assessment Information Resources.[5] In their Etext on grey literature for health technology assessments, NLM describes a general approach to searching grey literature and internet resources. Traditional types of grey literature identified by NLM include: theses and dissertations, census, economic and other data sources, databases of ongoing research, electronic networks, informal communications (telephone conversations, meetings, etc.), conference proceedings and abstracts, newsletters, research reports (completed and uncompleted), technical reports and translations. Tables B and C within NLM's document, lists databases and other sources that include grey literature. Furthermore, we supplemented this list of grey literature sources with additional databases through conversations with AHRQ (LexisNexis) and internal investigations (Google News, Early Research Detection Network, Cambridge HealthTech). The methods section of Part II of this report includes a more comprehensive list and description of the grey literature databases used for this project.

3. expert interviews and scientific meetings

At the outset of this project, we anticipated that a scientific literature based approach would be labor intensive and likely low yield. As a result, we focused our search to company websites, expert interviews, and attending specialty conferences. In addition to the grey literature obtained from the internet, we attended two scientific meetings during the course of this project in attempt to further expand the breadth of our search. The first conference was a workshop on "Pharmacogenomics in Drug Development," jointly sponsored by the Drug Information Association, FDA, Pharmacogenetic Working Group, PhRMA, and the Biotechnology Industry

Organization. The theme of this workshop and its focus on diagnostic pharmacogenomic test and drug co-development was relevant to the aims of Part II of our project. The second conference attended, the 2005 American Society of Clinical Oncology (ASCO) Annual Meeting, was applicable to both the first and second parts of this horizon scan. In particular, the ASCO conference exhibit hall featured over 400 commercial displays, with representatives from various pharmaceutical, medical diagnostics, and commercial laboratories involved in cancer care. During the exhibit hall sessions, we were able to speak with representatives from companies involved in genetic testing for cancer such as Quest Diagnostics, LabCorp, Genomic Health, US Labs, Roche Diagnostics, and Veridex.

Finally, we spoke with different experts representing commercial laboratories, academic hospitals, and the FDA. During these interviews, our goal was to verify our database of genetic tests available, as well as to obtain knowledge about cancer genetic tests in development that would apply to Part II of our project. From our discussions with these experts and our initial explorations with the scientific and grey literature, it became evident that the most useful and efficient method for compiling a comprehensive list of genetic tests for cancer was to focus our search to the comprehensive test catalogs of the largest commercial diagnostic laboratories in the US, such as Quest Diagnostics® and LabCorp.® In addition, one of the advantages of using these test catalogs as a resource is that both catalogs include tests offered or developed by other reference laboratories (e.g. Myriad Genetics and Exact Sciences) and are used by Quest and LabCorp for sendouts.

II. Individual test summaries

Once a the list of current genetic tests was compiled, a series of one page summaries of each test in the database was completed using data extracted from a variety of sources including commercial websites and current medical text. Data included in these summaries are a more detailed description of the test and its clinical use. In addition, examples of Medline searches using exploratory search terms and the number of citations generated is provided to give an estimate of the scientific literature available on each test. 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.

RESULTS

The main results for this part of the project can be found in two attachments:

I. Database of genetic tests currently available (Database I):

Database I contains an overview of cancer-related genetic tests currently available for clinical use in oncology. This database contains 62 genetic tests. These tests are used in a variety of solid tumors and hematologic malignancies. Fifteen tests have applications for breast cancer, 5 in prostate, 9 in lung, 15 in colorectal, 12 in pancreas, 7 in ovarian, 5 in liver, 11 in lymphoma, and 11 in leukemia.

These tests have applications in primary prevention, secondary prevention, and in the diagnosis and management of disease. The majority of tests (87%, 54 of 62) are utilized for the diagnosis and management of cancer, while 18% (11 of 62) of tests can be used for secondary prevention and 8% (5 of 62) for primary prevention. Among the tests used in the diagnosis and management of cancer, 54% (29 of 54) have diagnostic roles, 57% (31 of 54) have prognostic roles, 41% (22 of 54) may be used to detect disease recurrence, and 52% (28 of 54) are used to monitor patient and disease status.

II. Individual test summaries (Database II):

Database II is a compilation of one-page summaries for each of the 62 tests listed in Database I. The one-page summaries provide additional detail on the individual genetic tests, including further discussion on their clinical use and potential literature search strategies for future investigation of that particular genetic test.

SUMMARY

After considering the three types of data sources (scientific literature, grey literature, and expert interviews) and the limited time allocated for this project, we chose a very focused approach to compiling a database of cancer genetic tests currently available for clinical use. We found 62 genetic tests for 9 different cancers. One-third of the tests are used in hematologic malignancies (leukemia, lymphoma) while the remaining tests have applications in the solid tumors (breast, lung, colorectal, pancreas, etc). Approximately one-fourth of the tests may be used for primary or secondary prevention of cancer. However, the majority of genetic tests that we found can be used to provide diagnostic and prognostic information, as well as to monitor patient status and detect disease recurrence.

PART II: Genetic tests in development for clinical use

AIM

The aim of Part II of this project was to identify genetic tests currently in development for clinical cancer care. During this part of the project, one challenge was how to identify genetic tests "in development" that were pertinent to the purposes of this horizon scan. The methods section of this report details the systematic process that we developed and applied to the scientific and grey literature, in attempt to identify cancer genetic tests with more immediate clinical and commercial potential.

The final product of this part of the project is a database of genetic tests currently in clinical development for cancer care. These tests were identified during our search of the scientific and grey literature as well as through other additional resources such as expert interviews and scientific conferences. The focus of this database was to find genetic tests that are currently under investigation for clinical utility. By the time most medical tests in development reach testing for clinical utility, the new technology in development usually is associated with commercial interests. As a result, the focus of our search for genetic tests in development, centered around the LexisNexis® database, which provides access to authoritative legal, news, public record, and business information via a set of searchable databases that contains over 36,000 sources of print media including newspapers, magazines, and legal documents.

METHODS

Our approach to identify genetic cancer tests in this section can be divided into three separate processes:

1. searching the scientific literature
2. searching the grey literature
3. scientific meetings and expert interviews

We began with a search of the scientific literature. However, as we learned from our efforts during the Part I of this project, a systematic search of the scientific literature was not likely to be useful for the purposes of this horizon scan. As a result, the focus of our search for genetic tests in development centered on a systematic review of the grey literature and in particular, LexisNexis, as the source of information most applicable to our horizon scan project.

1. Scientific Literature search

A Medline search was conducted on July 12, 2005 to address the key question of identifying genetic tests in development for cancer. Briefly, we used search terms from 3 categories:

1. diagnostic test (ie. sensitivity and specificity, mass screening, diagnosis, predictive value, ROC curve, likelihood ratio)
2. gene or genetic or genomic test
3. top 10 cancers by mortality (lung, colon, breast, pancreas, prostate, leukemia, lymphoma, ovarian, esophagus, liver)*****

***** top 10 cancers in estimated deaths based on data from American Cancer Society Surveillance Research, US Mortality Public Use Data Tapes, 1969-2002, and National Center for Health Statistics, CDC, 2004

The complete search strategy used is detailed in Appendix A4**.** The results of this initial exploratory search of the scientific literature was presented and discussed at an interim conference call with AHRQ. Based on a sampling of the abstracts from the Medline search, it was revealed that many of the studies identified, as potentially of interest, were preclinical exploratory reports of potential tumor biomarkers or genes/genomic arrays with possible associations with tumor diagnosis or activity. However, the chances that any of these early preclinical biomarker reports will eventually evolve into clinically validated and useful tests are slim.[4] As a result, a significant majority of these reports would not be of interest or useful for the purposes of our particular horizon scan. Together with AHRQ, we thus decided to focus our energies towards searching grey literature sources.

2. Grey Literature search

As discussed earlier in Part I, in constructing our list of grey literature sources, we started with grey literature sources identified by the NLM's Health Technology Assessment Information Resources.[5] Furthermore, we supplemented this list of grey literature sources with additional databases through conversations with AHRQ (LexisNexis) and internal investigations (Google News, Early Research Detection Network, Cambridge HealthTech). By the end of this project, we identified 39 databases of interest. However, this list is not designed to be comprehensive. Below is a brief description of each grey literature source explored and the search strategies that we employed for each database.

For the purposes of this report, we have organized the grey literature sources that we examined into three categories:

Category I: (High utility for the horizon scan)

a. LexisNexis (http://www.lexisnexis.com)

LexisNexis provides access to authoritative legal, news, public record, and business information via a set of searchable databases that contains over 36,000 sources of print media including newspapers, magazines, and legal documents. Sources include public records, The New York Times, CNN, Bloomberg, Dun & Bradstreet, The Associated Press, Biotech Week, and NewsRx. This tool is the global legal and information division of Reed Elsevier.

We searched LexisNexis under the Medical News and Business News headings. Business News contained additional subheadings of interest: Industry News, Business and Finance, Mergers and Acquisitions, and Knight Ridder. For the purpose of our search, we began with the key terms "cancer" AND "test" covering a one year time period. We started with these terms to cast the widest net possible. However, if more than 1000 articles are returned for a search, LexisNexis does not provide individual title results. When this result occurred, we first altered the timeframe of our search and second, added an addition search term in order to be more specific in our request. If >1000 articles were returned for 6 months of records, our search terms were changed to "cancer" AND "gene" AND "test." With either the two or three term combinations, we were able to generate a list of titles for a 1 year time period. (A time period of 1 year was chosen in the hope of capturing references to genetic tests that are more advanced in the clinical development process and perhaps more likely to be commercial available within a relatively short time. Therefore, by limiting our search to 1 year, we hoped to find genetic tests that might be relevant to CMS within the next 1-2 years, using the most efficient method possible.)

Two reviewers screened the list generated by the LexisNexis search for relevant titles. Complete articles were then retrieved for the titles identified as potentially applicable for our project. Articles were then read by two reviewers and a group decision was made regarding whether to include or exclude the test from our database. When a test was identified for inclusion, pertinent test information was extracted from the report and entered into the database. If additional data on a particular technology was needed, we often were able to extract missing information from the developer's website.

b. Cambridge Healthtech Institute (CHI) (http://www.healthtech.com/)

The Cambridge Healthtech Institute has developed and released the "CHI ToolBar." The CHI Toolbar allows users to search eight different databases including the Biomedical NewsAnalyzer, which is a fully searchable, on-line database containing all press releases from many companies in the pharmaceutical, biotechnology, bioinformatics, diagnostics, medical device, equipment, drug delivery, contract research and manufacturing industries. Additionally, this tool provides access to the Biomedical Industry Analyzer, a directory of over 4600 companies in these sectors.

We searched the CHI database with the key terms "cancer," "test," and "gene." These searches were limited to the field of oncology. We screened all of the titles that were obtained from these searches to identify reports of interest. Next, we retrieved and reviewed the full articles identified by our title screening and extracted pertinent information on potential genetic tests into our database.

Category II: (Low to moderate utility for the horizon scan)

c. Computer Retrieval of Information on Scientific Projects (CRISP) (http://crisp.cit.nih.gov/)

CRISP provides a listing of federally funded research projects conducted at universities, hospitals, and other research institutions in the biomedical fields. This database is maintained by the Office of Extramural Research at the National Institutes of Health and includes projects funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), Agency for Health Care Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

We searched CRISP using the combination of key terms "cancer" AND "test" AND "gene." Two reviewers screened the titles for potential relevance and retrieved the complete reports for a sampling of projects. From the initial sampling of retrieved reports, it became evident that the CRISP database was limited to projects mainly investigating preclinical exploratory biomarkers or genomic arrays that might have an association with tumor diagnosis or activity. In this sense, CRISP provided information similar to a Medline search or other traditional scientific literature databases. Therefore, after consulting with AHRQ, we decided that CRISP would be less useful to our specific task of identifying genetic tests in development.

d. Web of Knowledge (http://www.thomsonisi.com/)

ISI Web of Knowledge encompasses both multidisciplinary and specialized content as well as external collections, covering journals (including open access titles) books, proceedings, patents, chemical structures, evaluated Web content, grant funding, and preprints. All content in this database, including over 8,700 journals and 22 million patents, must meet editorial requirements to be included.

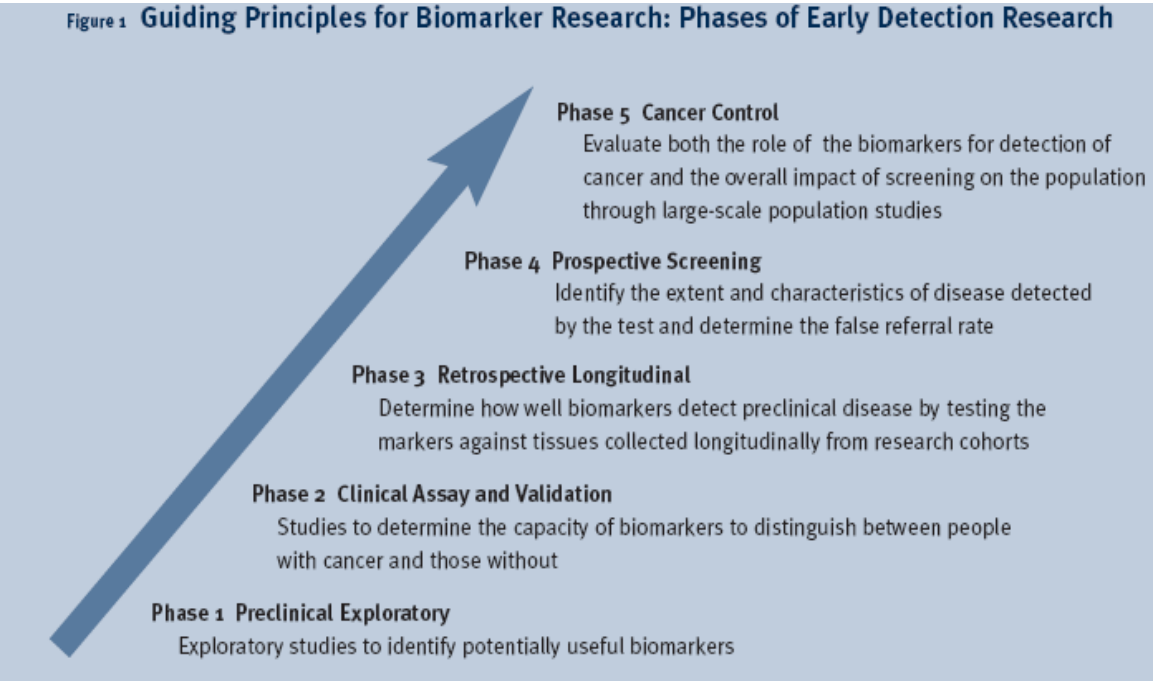
We searched Web of Knowledge using the key terms "cancer" AND "test" AND "gene" for a time period of one year. We screened a sampling of the titles that were obtained from these searches to identify reports of interest. We then retrieved the complete reports from a sampling of articles that represented promising leads for cancer genetic tests in development. From this sample of articles, it became evident that the Web of Knowledge is useful for identifying research of potential biomarkers that are mainly in the preclinical phase of development and far from establishing clinical utility or commercial development. In this respect, Web of Knowledge may be considered similar to Medline searches and therefore, it was decided that this resource would not be useful for our purposes and further exploration of Web of Knowledge was discontinued.

e. Early Detection Research Network (EDRN)
(http://www3.cancer.gov/prevention/cbrg/edrn/)

EDRN is a multi-disciplinary collaborative effort organized by the National Cancer Institute to identify and validate potential cancer biomarkers. EDRN focuses on speeding laboratory discoveries and their subsequent translation to clinical biomarkers. In addition, the goal of EDRN is to "provide timely, cost-effective clinical tests for early detection of cancer and identification of high-risk individuals."[6] This network is comprised of the following main components: 1) Biomarkers Developmental Laboratories, which develop

and characterize new biomarkers or refine existing biomarkers; 2) Biomarkers Reference Laboratories, which serve as a resource for clinical and laboratory validation; 3) Clinical Epidemiology and Validation Centers, which conduct and support early phases of clinical and epidemiological research on the application of biomarkers; 4) a Data Management and Coordinating Center, which provides statistical, logistics, information support, and develops theoretical statistical approaches to pattern analysis of multiple markers simultaneously; and 5) an Informatics Center led by investigators at the National Aeronautics and Space Administrations Jet Propulsion Laboratory serving as the lead for the informatics component.

Since the goals of EDRN appeared to be similar to the goal of our horizon scan, we decided to search the most recent EDRN report (March 2005) to identify potential genetic biomarkers and tests that could be added to our database. In order to stay consistent with our justifications for discontinuing extensive explorations of databases such as Medline and Web of Knowledge, we only extracted biomarkers that had proceeded beyond the preclinical exploratory stage (phase one of development) and were at least being studied for clinical validity and utility (phase two and beyond). [Figure 1.]



***** Figure 1 from National Cancer Institute, Division of Cancer Prevention. The Early Detection Research Network: Translational Research to Identify Early Cancer and Cancer Risk. Third Report. March 2005. p15

f. National Research Register (NRR) (http://www.nrr.nhs.uk/search.htm)

The National Research Register is a database of ongoing and recently completed research projects funded by, or of interest to, the United Kingdom's National Health Service (NHS).

We searched The National Research Register using the combination of key terms "cancer," "test," and "gene." We screened the titles to identify reports of interest. Next, we retrieved and reviewed the full articles that held potential for tests to be included in

our database. However, the majority of potentially relevant articles, as hinted by their titles, referred to early preclinical, exploratory studies to identify potentially useful tests. As a result, we decided to discontinue further exploration of this resource.

g. Canadian Institute of Scientific and Technical Information (CISTI) (http://cisti-icist.nrc-cnrc.gc.ca/main_e.html)

CISTI is a source for information in all areas of science, technology, engineering and medicine. CISTI began over 75 years ago as the library of the National Research Council of Canada and became the National Science Library in 1957. It contains over 50,000 different serial titles, over 600,000 books, conference proceedings and technical reports, and 2 million technical reports from around the world.

We searched Canadian Institute for Scientific and Technical Information using the combination of key terms "cancer" AND "test" AND "gene." We screened all of the titles that were obtained from this search to identify reports of interest and pulled the full reports of articles that might fit our inclusion criteria above. Similar to NRR, the majority of titles screened in CISTI referred to phase I exploratory studies and were thus far from either commercial development or establishing clinical utility. We decided to discontinue further exploration of the CISTI database because of its limited utility to our horizon scan.

h. Google (www.news.google.com)

Google News gathers stories from more than 4,500 news sources in English worldwide and automatically arranges them to present the most relevant news first. Results are compiled solely by computer algorithms, without human intervention, and include articles that have only appeared within the past 30 days.

We searched Google News using the key terms "cancer" AND "test" AND "gene." We screened all of the titles that were obtained from this search for reports of interest. We then pulled the full articles of all titles of interest. Tests extracted from these articles of interest revealed significant overlap between Google and LexisNexis. In addition to this redundancy with LexisNexis, the Google search engine did not allow a search beyond 30 days. As a result of these limitations, we did not further explore Google for this horizon scan.

i. Clinical Laboratory Improvement Amendments (CLIA) (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/Search.cfm)

CLIA regulates all laboratory testing (except research) performed on humans in the U.S. In total, CLIA covers approximately 175,000 laboratory entities. The Division of Laboratory Services, within the Survey and Certification Group, under the Center for Medicaid and State Operations has the responsibility for implementing the CLIA Program.

We searched CLIA using the simple search function with the key term "cancer." We screened all of the titles that were obtained from this search and pulled the full reports of

all articles that might fit our inclusion criteria above. Review of these articles and tests of interest, revealed that these sources focused mainly on genetic tests currently in use. Therefore, the CLIA database was probably more applicable and useful for Part I of this project.

j. The Office of In Vitro Diagnostics Device Evaluation and Safety (OIVD) (http://www.fda.gov/cdrh/oivd/consumer-otcdatabase.html)

OIVD is part of the U.S. Food and Drug Administration's Center for Devices and Radiological Health. OIVD regulates all aspects of in-home and laboratory diagnostic tests (in vitro diagnostic devices or IVDs), helps new IVDs reach the medical marketplace, prevents the sale of unsafe or ineffective IVDs, and categorizes the complexity of IVDs according to the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88), thereby defining the type of regulatory oversight applied to the product.

We searched OIVD with the key term “cancer.” We screened all of the titles that were obtained from this search and retrieved the full reports of all articles that had titles of interest. Review of these reports quickly revealed that all of the relevant reports in the OIVD database referred to tests already available for clinical use, thus making OIVD a resource more applicable for Part I of this project.

k. FDA Pre-market Approval (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm)

The Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act (the act) established three regulatory classes for medical devices. The amendments define a Class III device as one that supports or sustains human life or is of substantial importance in preventing impairment of human health or presents a potential, unreasonable risk of illness or injury. All devices placed into Class III are subject to pre-market approval requirements. Pre-market approval by FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices.

We searched the Pre-market Approval Database with the key terms “cancer,” “test,” and “gene.” We screened all of the titles that were obtained from this search and retrieved the full reports of all articles of interest. Similar to OIVD, we found that the Pre-market Approval database identified tests already available for clinical use, thus making it a resource more applicable for Part I of this project.

l. ClinicalTrials.gov (www.clinicaltrials.gov)

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

We searched clinicaltrials.gov using the combination of key terms “cancer” AND “test” AND “gene.” We screened all of the titles that were obtained from this search strategy and retrieved the full reports of the titles of interest. Similar to databases like

NRR and CISTI, most reports in ClinicalTrials.gov refer to genetic tests in preclinical phase I exploratory studies and could be considered too premature from either commercial development or establishing clinical utility. Therefore, we limited further exploration of ClinicalTrials.gov database due to its limited utility to our particular horizon scan.

m. Online Computer Library Center (OCLC)'s FirstSearch (http://www.oclc.org/firstsearch/)

The OCLC FirstSearch database retrieves records from worldwide conferences, symposia, meetings, expositions, and congresses. This database covers a number of disciplines including the Arts, Humanities, Social Sciences, and Physical and Life Sciences.

Within the FirstSearch database, we searched PapersFirst from 2004-2005 using the key terms "cancer" AND "test" AND "gene." We screened all of the titles that were obtained from this search but were unable to proceed further because the database did not allow access or retrieval of abstracts or full text reports.

n. Health Technology Assessment Database (HTA) (http://www.york.ac.uk/inst/crd/htahp.htm)

The Health Technology Assessment (HTA) database contains information on healthcare technology assessments and is produced in collaboration with The International Network of Agencies for Health Technology Assessment (INAHTA) Secretariat, based in Sweden. The database contains records of ongoing projects being conducted by members of INAHTA as well as publications reporting completed technology assessments carried out by INAHTA members and other health technology assessment organizations.

We searched this database using the key terms: "cancer" AND "test" AND "gene." We also applied the same search terms to the Data Abstracts of Reviews of Effects and Health Assessment Technology Database. As indicated by their titles, these technology assessments review analytical and clinical utility data on genetic tests already in use. Therefore, the HTA database would be more relevant for Part I of this project.

o. NY Academy of Medicine (http://www.nyam.org/)

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

We searched the Grey Literature section of the Academy using the terms "cancer," "test," and "gene." We screened all of the titles that were obtained from this search and retrieved the full reports of all articles of interest. A quick review of these titles and abstracts revealed that this database produced reports that were not specific to genetic

tests in development. The few reports that did involve genetic testing usually contained clinical and analytical data for already established technologies.

p. GreyLit Network (http://greylit.osti.gov/)

The GreyLIT Network is a portal for technical report information generated through federally funded research and development projects. It was developed by the Department of Energy's Office of Scientific and Technical Information (OSTI), in collaboration with the Department of Defense/ Defense Technical Information Center (DOD/DTIC), NASA, and the EPA. The GreyLIT Network was released in early response to recommendations from a May 2000 workshop on the concept of a "Future Information Infrastructure for the Physical Sciences" held at the National Academy of Sciences.

We searched the GreyLit Network with the combination of terms: "cancer," "test" and "gene." We screened all of the titles that were obtained from these searches and retrieved the full reports of a sampling of articles of interest. Abstracts from the GreyLit Network mainly referred to tests in a preclinical exploratory phase of development, similar to several databases mentioned earlier. As a result, we did not choose to explore this database in further detail for the purposes of this project.

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

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

We searched HSRProj with the terms "cancer," "test," and "gene." We screened all of the titles that were obtained from this search and pulled the full reports of a sampling of articles that might fit our inclusion criteria above. The HSRProj database identifies research focused on health services research and not on test development. As a result, we limited our use of this resource for this horizon scan.

Category III: (Not useful for the horizon scan)

r. Other

We identified several additional grey literature tools available to explore. However, further investigation of these sources revealed that none of the resources would be useful for our horizon scan project. Table C lists these grey literature resources that we identified but did not use for any part of this project. Reasons for not using some of these resources include; they did not contain a search engine, were subscription services that we were unable to access, or were clearly oriented towards literature that was not applicable to our horizon scan on genetic testing in cancer.

III. Opinion leaders and scientific conferences

Interviews were conducted with different experts representing commercial laboratories, academic hospitals, and the FDA. Academic and government leaders were identified during our scientific and grey literature searches, including the EDRN network of principal investigators and consultants. Opinion leaders were affiliated with the University of Chicago, the FDA, Quest Diagnostics, and Roche Diagnostics. In addition, we attended two scientific meetings; (1) "Pharmacogenomics in Drug Development," a workshop jointly sponsored by the Drug Information Association, FDA, Pharmacogenetic Working Group, PhRMA, and the Biotechnology Industry Organization, and (2) the 2005 American Society of Clinical Oncology (ASCO) Annual Meeting.

RESULTS

I. Scientific Literature

Based on the search strategy detailed in Appendix A4, a total of 4492 citations were initially produced for cancer genetic tests in development as they applied to the top 10 cancers by mortality. Briefly, there were 4492 citations produced for the 10 cancers. In attempt to reduce this total, we limited the database timeframe to years 2000 to 2005, which resulted in 2519 citations for 3 of the top 10 cancers. Finally, we sampled citations for three of the cancers:

Using a broad definition for genetic tests "in development," we sampled 3 cancers:

1. esophageal: 45/55 (81%) citations were screened in
2. pancreas: 77/110 (70%) citations were screened in
3. liver: 92/123 (75%) citations were screened in

Examples of abstracts screened in, include "development of a quantitative three-tiered algorithm and multi-gene RT-PCR to discriminate between Barrett's esophagus and esophageal adenocarcinoma," "chemokine receptor CXCR4 expression in colorectal cancer demonstrated significant associations with recurrence, survival and liver metastasis," and "use of microsatellite marker of loss of heterozygosity and k-ras codon 12 mutation analysis of PCR in accurate diagnosis of pancreaticobiliary malignancy."

Based on the sampling of the abstracts from the Medline search, we found that many of the papers were preclinical reports investigating different genes that may explain biological pathways of tumor development or reports of microarray investigations that are searching for genes of interest. Additionally, these reports of basic science and tumor cell are far from implementation and presentation as commercial projects. As a result, a significant majority of these papers would be excluded from our report.

II. Grey Literature

Category I**:** High utility

LexisNexis and Cambridge Healthtech Institute

We comprehensively searched these databases using the methods described above. These databases had the highest yield in returning tests of interest.

A. LexisNexis: Using the combination of key words "cancer," "test," and "gene," we obtained the following results within the different subheadings of LexisNexis:

1. Medical News (1 year) = 1132 citations
2. Business News/ Industry News (1 year) = 1241 citations

3. Business News/ Mergers and Acquisitions (1 year) = 233 citations
4. Business News/ Business and Finance (1 year) = 251 citations
5. Business News/ Knight Ridder (1 year) = 94 citations

Table A provides further detail of our search of LexisNexis. We scanned a total of 2951 titles from the combination of LexisNexis sources and identified 879 articles of interest. From the articles of interest, we extracted 142 tests of interest and ultimately 50 unique genetic tests. Database III provides a listing of the genetic tests that were obtained from the LexisNexis search.

B. Cambridge HealthTech Institute:

Table A also details our search strategy using the CHI Toolbar. Using the combination of "cancer," "test," and "gene," we scanned a total of 494 titles and found 52 articles of interest. From these articles of interest, we identified 24 genetic tests of interest and 10 unique genetic tests.

Database III provides a listing of genetic tests in development for cancer as identified by both LexisNexis and CHI resources. Table 1 below demonstrates the distribution of cancer indications for all genetic tests found using LexisNexis and CHI databases. The ten most deadly cancers in the U.S. account for 80% (49 of 61) of the test indications, with breast cancer accounting for 20% (12 of 61) of these indications. The 'other' cancers being investigated include bladder, cervical, GIST, mesothelioma, and tumors of unknown origin. There were 17.6 tests of interest found for every 1000 titles scanned.

Table 1: Distribution of cancer targets for Category I genetic tests

Cancer	# of tests	% of total
Breast	12	24%
Prostate	10	15%
Lung	10	15%
colorectal	10	18%
pancreas	0	0%
Ovarian	4	6%
esophagus	0	0%
liver	1	1%
lymphoma	0	0%
leukemia	2	3%
Other	12	19%
total indications	*61	100%

*total # of indications may be greater than total # of tests in the database because some tests may have multiple indications

Table 2 summarizes the distribution for test purpose among the genetic tests in found using LexisNexis and CHI. A significant majority (94%) of the investigations

identified with LexisNexis and CHI were for disease diagnosis or management. Further information on test specifics was limited since clinical utility has yet to be established for most of these tests.

Table 2: Distribution of indicated use for Category I genetic tests

Use	# of tests	% of total
diagnosis/ management	52	95%
primary prevention	3	5%
total tests	55	100%

Category II: Low to moderate utility

EDRN, CLIA, ClinicalTrials.gov, Google and others

Table B lists the category II grey literature resources investigated and summarizes the search strategies and results for each database. Initial literature searches of these databases found over 200,000 titles. However, after re-focusing our methods and discontinuing further exploration of low yield sources, we identified 190 abstracts of interest from 8 grey literature sources (Google, CISTI, CLIA, EDRN, FDA pre-market, ClinicalTrials.gov, and NY Academy of Medicine.) and found 39 unique genetic tests which are included in Database III.

The Early Detection Research Network publication identified 75 genetic tests in development; however, almost 80% (59 of 75) of these tests are in pre-clinical exploratory phase of drug development, while only 21% (16 of 75) are in at least phase 2 clinical validation studies. Only the latter tests, in at least phase 2 of clinical development studies, were included in Database III. Google News and clinicaltrials.gov also contributed to our category II grey literature database with 5 and 13 tests, respectively. The CLIA database identified 1 test in development that was of interest to our database while the FDA pre-market approval site identified 2 tests. The ten most deadly cancers in the U.S. account for 82% (40 of 49) of the total test indications; while ovarian cancer accounts for 22% (11 of 49) of these indications (Table 3 below). The ‘other’ cancers being investigated include bladder, cervical/ endometrial, kidney, and tumors of unknown origin.

Although it appears that almost all of the Category II genetic tests are associated with the diagnosis and management of cancer, it may be too premature to assign a definitive role for any of these tests since most are only in pre-clinical phase of development and have yet to establish any clinical validity or utility data.

Table 3: Distribution of cancer indication among Category II genetic tests

Cancer	# of tests	% of total
Breast	7	14%
prostate	7	14%
Lung	5	10%
colorectal	8	16%
pancreas	0	0%
ovarian	11	22%
esophagus	0	0%
liver	1	2%
lymphoma	0	0%
leukemia	1	2%
Other	9	18%
total indications	49	100%

*total # of indications may be greater than total # of tests in the database because some tests may have multiple indications

Category III: Not applicable

These resources did not yield any search results because they were either non-operational websites or contained information not applicable to this particular report.

III. Interviews, conferences

A. Interviews:

We conducted interviews with different experts representing commercial laboratories, academic hospitals, and the FDA.

1. Olufunmilayo Olopade, MD, Director of Cancer Risk Clinic, Univ. of Chicago
2. Steve Gutman, PhD, Director of OIVD, FDA
3. Richard Bender, MD, Medical Director, Quest Diagnostics
4. Gerd Moss, MD, Austin Finley, PhD, John Rich, Roche Diagnostics

During these interviews, we discussed issues concerning current genetic tests available (Part I), as well as tests in clinical development (Part II). Drs. Olopade and Gutman both reviewed draft versions of our current genetic test database from Part 1. Meanwhile, Dr. Bender from Quest Diagnostics suggested looking at the commercial websites for information on current genetic tests.

Dr. Olopade is a member of the EDRN Network Consulting Team and she is the Director of the Cancer Risk Clinic at the University of Chicago. During our interview with Dr. Olopade, we discussed a wide range of issues involved with genetic testing. Particular tests discussed were Oncotype Dx, Mammaprint, OvaChek, BRCA1 and 2, and Her2-neu. Additional topics mentioned included: the impact of Myriad's Genetic direct-to-consumer marketing campaign for its BRCA testing for breast cancer screening, direct-to-consumer genetic test companies such as DNA Direct, Genetests.org as a source for genetic tests research, and the future of pre-implantation genetic testing. Finally, Dr. Olopade also mentioned a new pharmacogenomic test in development, involving gene polymorphisms for metabolizing CPT-11 (Camptosar, irinotecan) chemotherapy used in advanced colon cancer.

Dr. Bender is the Medical Director for Hematology/Oncology at Quest Diagnostics. We spoke with Dr. Bender at the ASCO Annual Meeting where we discussed issues involving genetic testing from a commercial laboratory standpoint. In particular, we discussed future pharmacogenomic testing and some of the challenges in validating these new tests. Dr. Bender introduced an upcoming 7-gene pharmacogenomic panel for evaluating response in chemotherapy for colon cancer. More specifically, this pharmacogenomic panel looks for several gene polymorphisms (ERCC1, UGT1A1, TS, XPD, GST-P1, XRCC1, and DPD) in order to evaluate the likelihood of toxicity and/or response to 5FU, oxaliplatin and irinotecan chemotherapy.

Dr. Gutman is Director of OIVD at the FDA. Due to confidentiality reasons, Dr. Gutman was not allowed to speak about specifics of individual genetic tests available or in development. However, he did discuss pertinent issues such as "home brew" vs. FDA approval, direct-to-consumer genetic test companies such as DNA Direct, the future of genomic testing, and co-development of drug and diagnostic test. Dr. Gutman also received a preliminary draft of the genetic test database for review.

We held a conference call with representatives from Roche Diagnostics to discuss current and future genetic tests in cancer. Involved in the call were the head of oncology test development (Moss), director of sales and reimbursement (Rich), and the director of public policy (Finley). Roche Diagnostics is currently testing their AmpliChip technology in large multi-center international clinical trials for leukemia patients. Roche's aim is to develop their Amplichip technology for use in leukemia patients, in clinical trials to help classify leukemia patients and correlate to outcomes. Genetic tests for cancer using Roche's Amplichip technology, as well as other cancer genetic tests in development identified by expert review of this report by Roche, have been included in Database III.

B. Conferences:

1. Pharmacogenomics in Drug Development and Regulatory Decision Making

This meeting was jointly sponsored by the Drug Information Association, FDA, Pharmacogenetic Working Group, PhRMA, and the Biotechnology Industry Organization. The focus of this workshop was on the implementation and integration of pharmacogenomics in the mid to late clinical phases of the development of new drugs, biologics, and associated devices. A draft version of the FDA's "Drug-Diagnostic Co-Development Concept Paper" was provided for discussion.

2. The 2005 American Society of Clinical Oncology (ASCO) Annual Meeting

Numerous opportunities to gather information about genetic testing were available at the ASCO Annual Meeting. With the recent design, development, and clinical evaluation of several new targeted agents in oncology, more specific tests are needed to select the patients most appropriate for these agents and to evaluate their response to these molecularly targeted therapies.

From a scientific standpoint, the ASCO meeting featured many important studies and abstracts in which the integration of diagnostic tests with specific and targeted types of therapies was the focus of the presentation. Among the tests presented included: BRCA1 and pancreatic cancer risk, circulating tumor cell assay for breast cancer, EGFR expression in colon cancer and response to cetuximab, BCR/abl mutations and imatinib (Gleevec) resistance, and pharmacogenetic studies for 5-FU based chemotherapy regimens. In addition to abstracts, the ASCO meeting also featured several presentations relevant to our project as part of their cancer genetics track. Examples of presentation titles include, “Beyond anatomic staging: is it time to take the leap into the molecular era?” and “Clinical relevance of genetics and genomics in gastrointestinal cancer: current and future biologic paradigms.”

The ASCO meeting also provided excellent opportunity to make contacts with several of the commercial vendors involved in genetic testing for cancer. In particular, the meeting featured over 400 corporate exhibits where attendees could visit booths, speak with representatives from the various pharmaceutical, medical diagnostic, and commercial laboratories, and obtain clinical and commercial literature regarding specific tests. There were numerous companies involved in genetic testing for cancer present at the corporate exhibitor hall, such as Quest Diagnostics, LabCorp, Genomic Health, US Labs, Roche Diagnostics, and Veridex.

Summary

Our initial exploration of the scientific literature led to our realization that Medline searches would be more useful for collecting information of various biomarker and genetic tests in the pre-clinical stage of development. We concluded that for the purposes of this report, a different search strategy would have to be employed in order to more efficiently identify genetic tests in later phases of development that may have clinical impact in the very near future. As a result, we focused our search to the grey literature and were able to identify 104 genetic tests in development. Among these 104 tests, over two-thirds (60 of 104, 68%) were identified from the LexisNexis (n=50) and Cambridge Healthtech Institute (n=10) databases. Another 39 tests (38%) in development were found among 8 additional grey literature databases. The remaining 5 tests (4%) were added through additional alternative resources such as interviews with opinion leaders and attendance at national conferences. Three-quarters of the tests (84 of 104, 76%) were being developed for only five of the top 10 most common cancers by mortality. Breast, prostate, lung, colorectal, and ovarian accounted for these 5 most

common indications. Finally, although it appears that almost all of these genetic tests in development are associated with the diagnosis and management of cancer, it would be speculative to assign a more definitive role for most of these tests since clinical validity or utility has yet to be established.

DISCUSSION

Searching the grey literature (for this horizon scan): LexisNexis, CHI vs. others

For our project, the meaning of grey literature evolved into referring to "any literature which is not peer reviewed." However, given the broad definitions for key terms such as "grey literature," "genetic test," "biomarker," and "in development," one of the early challenges of this project was to identify grey literature which was appropriate and applicable to our particular task order. To this end, we found little precedent or guidance for systematic searching of the grey literature for the purpose of a horizon scan in genetic testing for cancer.

In the NLM's Etext on Health Technology Assessment Information resources, finding the grey literature is demonstrated through the HTA example, which starts with the HTA Database.[5] We began our search with the NLM report and continued to add grey literature resources to this list as our project evolved. We carefully documented our methods in searching the grey literature for this project because we believe that our report may serve as a novel yet useful example of how to perform a grey literature search for a horizon scan project. After rigorous exploration of numerous databases and resources, we were able to identify a handful of grey literature sources that could be loosely categorized into 3 different categories of utility for our project: high utility, low to moderate utility, and not applicable.

For the purposes of our horizon scan, we found that the LexisNexis and CHI databases to have the greatest utility for finding cancer genetic tests of interest to our project. One final caveat, our particular method for searching the grey literature is not meant to be definitive or apply universally to all projects. Instead, our report is meant to provide one example of how the grey literature can be searched for the purposes of a horizon scan on diagnostic genetic tests in clinical development for cancer.

Genetic tests for cancer

Part I: current genetic tests

In both parts of this project, we started our search with the same approach of reviewing the scientific and grey literature while also attending scientific conferences and interviewing expert opinions. In order to accomplish the first goal of identifying genetic tests currently available for cancer care, we found that the commercial literature and websites for the largest diagnostic test companies to be the most useful for addressing the first part of this project. We found 62 genetic tests for 9 different cancers. Given the broad definition for genetic test that we used, it should not be a surprise that we found such a wide range of genetic tests available, from basic protein biomarkers like AFP, to the new multi-gene assay, Oncotype Dx, for predicting disease recurrence in breast cancer. The compilation of one-page summaries provides more detailed information on each genetic test currently available in the database. In addition, each summary contains a brief synopsis of different search strategies and the amount of literature that may be

indicative of the amount of time and effort that would be needed to focus on potential projects such as a systematic review of the clinical validity and utility studies for an individual genetic test.

Part II: genetic tests in development

One of the challenges that we encountered during this second part of the project, was trying to determine what genetic test was appropriate for being "in clinical development" for cancer. Earlier, we discussed the 5 different phases of development that a genetic test or biomarker must achieve in order to eventually gain clinical acceptance [Figure 1]. The evaluation and testing of a diagnostic test can be a long and time consuming process; therefore, a horizon scan for genetic tests in development may only be interested in tests that are emerging from later phases of clinical development (phases 2-5) in order to identify tests with the greater likelihood of having more immediate clinical impact.

The next challenge we faced was to then find the most efficient resources and databases that would identify genetic tests in development relevant to our project. As we gained experience with the scientific literature, grey literature, and professional meetings and interviews, we discovered that Medline searches were useful for finding information of pre-clinical exploratory biomarker and genetic tests. However, we also found that Medline and other databases that search the scientific literature were not as efficient in identifying genetic tests in the later phases of development. Instead, the grey literature, and in particular LexisNexis and CHI, were the most useful in identifying genetic tests in development and with more immediate commercial potential. The results for Part II of this project can be found in Database III, which is a compilation of genetic tests identified through various grey literature resources and expert interviews.

Finally, we found 104 genetic tests in development through our systematic search of the grey literature and other sources. We discovered that the LexisNexis and CHI resources had the highest utility for identifying genetic tests in development that may have more immediate commercial impact. However, we are aware that despite all our efforts, these lists are not necessarily comprehensive and that it is possible that a handful of promising genetic tests for cancer exist but do not appear in our database. Perhaps, this is to be expected since we are entering a time of unprecedented growth for the medical diagnostic industry as physicians, patients, and society are just beginning to benefit from the fruits of labor stemming from the completion of the Human Genome Project in 2003.

APPENDIX

A1. Glossary of acronyms used

Tests

EIA	Enzyme immunoassay
FISH	Fluorescence in-situ hybridization
ICC	Immunocytochemistry
ICMA	Immunochemiluminometric assay
IHC	Immunohistochemistry
IRMA	Immunoradiometric assay
MEIA	Microparticle enzyme immunoassay
PCR	Polymerase chain reaction
RIA	Radioimmunoassay
RT-PCR	Reverse transcriptase polymerase chain reaction

Diseases

ALL	Acute lymphocytic leukemia
AML	Acute myelogenous leukemia
APL	Acute promyelocytic leukemia
CLL	Chronic lymphocytic leukemia
CML	Chronic myelogenous leukemia
CTCL	Cutaneous T-cell lymphoma
FAP	Familial adenomatous polyposis
HNPCC	Hereditary non-polyposis colon cancer
MM	Multiple myeloma
NHL	Non-Hodgkin's lymphoma
PNH	Paroxysmal nocturnal hemoglobinuria

A2. Synopsis of select commercial diagnostic laboratories
(information from company websites)

Quest Diagnostics (Teterboro, NJ) www.questdiagnostics.com

Quest Diagnostics is the nation's leading provider of diagnostic testing, information and services. The information we provide to health care practitioners and consumers enables them to make better decisions and improve care. With $4.7 billion in annual revenues, Quest Diagnostics offers the broadest access to clinical testing services through its national network of 30-plus regional laboratories, approximately 155 rapid response laboratories and almost 2,000 patient service centers. Quest Diagnostics is the leading provider of specialty testing, including gene-based testing, and is the leader in routine medical testing, drugs of abuse testing, and anatomic pathology testing. Through partnerships with pharmaceutical, biotechnology and information technology companies, Quest Diagnostics provides support to help speed the development of health care insights and new therapeutics.

Laboratory Corporation of America®, LabCorp® (Burlington, NC) www.labcorp.com

LabCorp is a pioneer in genomic testing and the commercialization of new diagnostic technologies. LabCorp is one of the world's largest clinical laboratories, with annual revenues of $3.1 billion in 2004. Headquartered in Burlington, North Carolina, LabCorp has more than 23,500 employees and offers more than 4,400 clinical tests ranging from routine blood analyses to the most sophisticated molecular diagnostics. LabCorp tests more than 340,000 specimens daily for over 220,000 clients nationwide.

Specialty Laboratories (Valencia, CA) www.specialtylabs.com

Specialty Laboratories is a leading hospital-focused clinical reference laboratory, performs highly advanced, clinically useful testing services for hospitals, laboratories and physician specialist communities nationwide. With an extensive menu of clinical tests for the diagnosis and treatment-management of disease, Specialty offers clients a single-source solution for their esoteric testing needs. Specialty also supports its test offering with distinguished R&D capabilities. Through internal research programs and technology partnerships, Specialty develops new and enhanced clinical tests for reliable and cost-effective patient assessment

A3. Additional companies and websites

Abbot	http://www.abbottdiagnostics.com/
Adnagen	http://www.adnagen.com/
Agendia	http://www.agendia.com/
AMDL	http://www.amdl.com/
Applied Imaging Corp	http://www.aicorp.com/
AstraZeneca	http://www.astrazeneca.com/
BioCurex	http://www.biocurex.com/
Cangene Biotech	http://www.cangene.com/
CeMines	http://www.cemines.com/
ChondroGene	http://www.chondrogene.com/
Ciphergen Biosystems	http://www.ciphergen.com/
Corixa	http://www.corixa.com/
Correlogic	http://www.correlogic.com/
Cytogen	http://www.cytogen.com/
DakoCytomation	http://www.dako.com/
Diagene	http://www.diagene.com/
DiagnoCure	http://www.diagnocure.com/
Epigenomics	http://www.epigenomics.com/
Exagen	http://www.exagendiagnostics.com/
Fujirebio Diagnostics	http://www.fdi.com/
GenoID	http://genoid.net/eng/welcome.html
Genomic health	http://www.genomichealth.com/
Gen-Probe	http://www.gen-probe.com/
Genzyme	http://www.genzyme.com/
GMP Companies	http://www.gmpcompanies.com/
Health discovery Corporation	http://www.healthdiscoverycorp.com/
Healthtronics	http://www.healthtronics.com/
IMI Medical	http://www.imimedical.com/
Immunicon	http://www.immunicon.com/
Intergenetics	http://www.intergenetics.com/
LabCorp	http://www.labcorp.com/
Matritech Inc.	http://www.matritech.com/
Medicorp	http://www.medicorp.com/
Metagenex	http://www.metagenex.fr/
Methexis	http://www.methexis-genomics.com/
Microprevention Tests	no website found
Myriad Genetics	http://www.myriad.com/
Orion Genomics	http://www.oriongenomics.com/
Power3	http://www.power3medical.com/
Procyon	http://www.procyonbiopharma.com/
Qualigen	http://www.qualigeninc.com/
Quest diagnostics	http://www.questdiagnostics.com/
Roche	http://www.roche-diagnostics.com/
Sequenom	http://www.sequenom.com/

Specialty Laboratories	http://www.specialtylabs.com/
Tessera	http://www.tesserainc.com/
Tm Bioscience	http://www.tmbioscience.com/
Tripath Imaging	http://www.tripathimaging.com/
US LABS	http://www.uslabs.net/
Veridex	http://www.veridex.com/
ViroLogic	http://www.monogrambio.com/
Vitatex	http://www.vitatex.com/
Wako	http://www.wakousa.com/

A4. Exploratory Medline search strategy: genetic tests for 10 cancers

Ovid MEDLINE(R) 1966 to June Week 5 2005

#	Search History	Results
1	exp "sensitivity and specificity"/	182609
2	exp Predictive Value of Tests/	61018
3	exp ROC CURVE/	7998
4	exp Mass Screening/	69062
5	exp diagnosis/	3543147
6	exp REPRODUCIBILITY OF RESULTS/	106784
7	exp false negative reactions/ or false positive reactions/	24280
8	predictive value.tw.	26661
9	(sensitivity or specificity).tw.	386606
10	accuracy.tw.	90063
11	screening.tw.	150990
12	roc.tw.	5785
13	reproducibility.tw.	23848
14	(false positive or false negative).tw.	27567
15	likelihood ratio.tw.	2116
16	or/1-15	3980953
17	exp genetic screening/	12094
18	((gene or genes or genetic$) and (diagno$ or test$ or screen$)).tw.	169073
19	or/17-18	174880
20	exp cell culture techniques/	11135
21	exp cell line/	355216
22	In Vitro/	330724
23	exp biological assay/	24262
24	exp tumor stem cell assay	3161
25	or/20-24	707287
26	(16 and 19) not 25	70418
27	limit 26 to humans	16623
28	26 not 27	53795
29	limit 28 to english language	48399
30	limit 29 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or guideline or interview or lectures	

	or legal cases or legislation or letter or meta analysis or news or newspaper article or patient education handout or periodical index or practice guideline or "review" or review, academic or "review literature" or review, multicase or "review of reported cases" or review, tutorial)	12504
31	29 not 30	35895
32	exp prostate neoplasms/	46076
33	31 and 32	352
34	limit 33 to yr=" 2000-2005"	255
35	exp ovarian neoplasms/	39000
36	31 and 35	573
37	limit 36 to yr=" 2000-2005"	354
38	exp colonic neoplasms/	45633
39	31 and 38	361
40	limit 39 to yr=" 2000-2005"	164
41	exp lung neoplasms/	101151
42	31 and 41	428
43	limit 42 to yr=" 2000-2005	258
44	exp leukemia/	141459
45	31 and 44	922
46	limit 45 to yr=" 2000-2005	400
47	exp lymphoma, non-hodgkin/	53794
48	31 and 47	491
49	limit 48 to yr=" 2000-2005"	256
50	exp breast neoplasms/	122806
51	31 and 50	1501
52	limit 51 to yr=" 2000-2005"	902
53	exp esophageal neoplasms/	22840
54	31 and 32	88
55	limit 33 to yr="2000 - 2005"	52
56	exp liver neoplasms/	79138
57	31 and 35	210
58	limit 36 to yr="2000 - 2005"	123
59	exp pancreatic neoplasms/	31833
60	31 and 38	171
61	limit 39 to yr="2000 - 2005"	110
62	33 or 36 or 39 or 42 or 45 or 48 or 51 or 54 or 57 or 60	4492
63	34 or 37 or 40 or 43 or 46 or 49 or 52 or 55 or 58 or 61	2519

A5. Sample titles from searches of the grey literature databases

a. LexisNexis

"Collaboration to focus on the role of DNA in colon cancer detection"
"Tm Bioscience to manufacture novel breast cancer risk testing reagents for Intergenetics"
"Matritech says study data show its bladder-cancer test is cost-effective"

b. Cambridge Healthtech Institute (CHI)

"Abbott Data Published in Nature Reveals A Promising New Approach to Cancer"
"ACADIA Pharmaceuticals Expands Technology Platform to Target Tyrosine Kinase Linked Receptors"
"Broad Institute to Conduct Large-Scale Genotyping Project Using Affymetrix Technology."

c. Computer Retrieval of Information on Scientific Projects (CRISP)

"Genetic Abnormalities Early on the Path of Breast Cancer"
"CYP1A1 and CYP1B1 genes in race-related Prostate Cancer"
"LEF/TCF Expression in Colon Cancer"

d. Web of Knowledge

"Induction of Th1-type immunity and tumor protection with a prostate-specific antigen DNA vaccine"
"Pituitary tumor transforming gene (PTTG) induces genetic instability in thyroid cells"
"Novel mechanism of inhibition of nuclear factor-kappa B DNA-binding activity by diterpenoids isolated from Isodon rubescens"

e. Early Detection Research Network (EDRN)

f. National Research Register (NRR)

"Analysis of BRCA1 gene mutations in familial and early onset breast cancer"
"An investigation of susceptibility genes for prostate cancer"
"Analysis of expression of RNA profiles in primary breast cancer"

g. Canadian Institute of Scientific and Technical Information (CISTI)

"Detection of Metastatic Potential in Breast Cancer by Rho-GTPase and WISP3 Proteins"
"Identification of HP1 Target Genes Involved in Progression of Breast Cancer"
"Investigation of Alpha6 Integrins and Their Signaling Intermediates as Prognostic Markers for Breast Cancer"

h. Google

"New Test Predicts Breast Cancer Risk"
"New Gene Chip may be Cancer Diagnostic Tool"
"Silenced Gene Suggests Greater Risk, Possible Marker For African-Americans With Prostate Cancer"

i. Clinical Laboratory Improvement Amendments (CLIA)

"Abbott Architect I2000 system (Fujirebio Diagnostics Inc, Architect CA 15-3 reagent kit)"
"Asymmetrx prostate-63 cancer diagnostic reagent"
"TOSOH AIA-360 (ST AIA Pack 27.29)"

j. The Office of In Vitro Diagnostics Device Evaluation and Safety (OIVD)

"Dakocytomation HER2 FISH PharmDx Kit"
"Urovysion bladder cancer kit"
"Architect CA 15-3 assay"

k. FDA Pre-market Approval

"immunochemistry analyzer"
"prostate specific antigen (PSA) for detection and management of prostate cancers"
"digital mammographic x-ray system"

l. ClinicalTrials.gov

"Microarray Analysis for Human Genetic Disease"
"Genetic and Environmental Risk Assessment for Colorectal Cancer in Healthy Participants"
"Microsatellite Analysis of Urinary Sediment in Detecting Bladder Cancer"

m. Online Computer Library Center (OCLC)'s FirstSearch

"Novel Pentablock Copolymers as Non-Viral Vectors for Gene Therapy against Cancer"
"451-034: Fuzzy Neural Network Applications for Gene Selection and Cancer Classification"
"APC, K-ras, and p53 Gene Mutations in Colorectal Cancer Patients: Correlation to Clinicopathologic Features and Postoperative Surveillance"

n. Health Technology Assessment Database (HTA)

"Screening for ovarian cancer: a systematic review"
"Genetic diagnosis by PCR," and "Colorectal cancer screening."

o. NY Academy of Medicine

“Community health profiles: the health of Southwest Brooklyn”
“FDA hinders cancer vaccines”
“Fulfilling the potential of cancer prevention and early detection: an American Cancer Society and Institute of Medicine Symposium”

p. GreyLit Network

“Cancer risk assessment: Should new science be applied? A workgroup summary”
“Targeting human breast cancer cells that overexpress HER-2/neu mRNA by an antisense iron responsive element”
"Investigation of the candidate tumor suppressor gene PRK in prostate cancer”

q. Health Services Research Projects in Progress (HSRProj)

“Improving palliative care in chronic critical illness”
“Mammography disparities in elderly African American women”
“Socio-ecological variables/cancer screening behaviors”

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Database I

GENETIC TESTS FOR CANCER

Database of genetic tests currently available

NAME	Other names	Primary prevention	Secondary prevention	Diagnostic	Prognostic	Recurrence	Monitoring	Specimen
Acid phosphatase, total and prostatic	PAP				x	x	x	serum
Adrenocorticotropic hormone	ACTH			x				plasma
Alpha fetoprotein	AFP		x		x	x	x	serum
AML1/ETO translocation	t(8;21)			x	x	x	x	blood, marrow
B-cell gene rearrangement				x	x	x		blood, marrow, tissue
BCL-1/JH gene rearrangement	t(11;14)			x	x		x	blood, marrow, tissue
BCL-2 translocation	t(14;18)			x	x	x	x	blood, marrow, tissue
BCR/ABL gene rearrangement	Philadelphia chromosome			x	x	x	x	blood, marrow
Beta human chorionic gonadotropin	b-HCG			x		x	x	serum
Beta-2 microglobulin				x	x			serum
Bladder tumor antigen	BTA					x	x	urine
BRCA Analysis	BRCA1, BRCA2	x			x			blood
Calcitonin			x	x	x	x		serum
Cancer antigen 125	CA 125					x	x	serum
Cancer antigen 15-3	CA 15-3					x	x	serum
Cancer antigen 19-9	CA 19-9					x	x	serum
Cancer antigen 27.29	CA 27.29					x	x	serum
Carcinoembryonic antigen	CEA		x		x	x	x	serum
Cathepsin D					x			tissue
CBFB/MYH11 fusion protein	inv(16), t(16;16)			x	x		x	blood, marrow
CD 117, c-kit	Gleevec sensitivity			x				tissue
CD 20	Rituxan sensitivity			x				blood
CD 25	Ontak sensitivity			x				blood, marrow, tissue
CD 33	Mylotarg sensitivity			x				blood, marrow
CD 52	Campath sensitivity			x				blood, marrow
Chromosome 18q assay	18q/RER, DCC			x	x			blood, tissue
Colaris	MLH1, MSH2		x	x				blood
Colaris AP	APC, FAP		x	x				blood
Cyclin-D1				x	x			tissue
E-cadherin					x			tissue
Epidermal growth factor receptor	EGFR pharmDx, HER-1, Erbitux sensitivity			x				tissue
Estrogen/progesterone receptor	ER/PR			x	x			tissue
Fecal globin	InSure, FOBT		x					stool
FLT 3 mutation					x			blood
HER-2/neu	c-erbB-2, PathVysion, Herceptin eligibility			x	x			tissue
5-HIAA	5-hydroxyindoleacetic acid			x	x			urine
Human papillomavius hybrid capture	HPV, ThinPrep		x					pap smear
IgVH mutation analysis					x			blood, marrow
Immunocyt	mucin, CEA					x	x	urine

NAME	Other names	Primary prevention	Secondary prevention	Diagnostic	Prognostic	Recurrence	Monitoring	Specimen
Kappa/lambda light chain							x	blood,tissue
LAP	leukocyte alkaline phosphatase			x			x	blood, marrow
Lipid associated sialic acid	LASA, LSA					x	x	serum
Melaris	p16	x						blood
MIB-1 antibody	Ki-67 antigen				x			tissue
Micrometastasis detection	cytokeratins					x	x	marrow, tissue
Microsatellite instability	MSI, BAT-26, RER+, HNPCC	x	x	x	x			blood, tissue
MLH1, MSH2, MSH6 mutations	HNPCC mismatch repair gene	x						blood
Neuron specific enolase	NSE						x	serum
Nuclear matrix proteins	NMP 22			x		x	x	urine
Oncotype Dx	Breast cancer assay				x			tissue
p53 tumor suppressor gene	p53				x			issue
PML/RARA translocation	t(15;17)			x	x		x	blood, marrow
PreGen-26	MSI, BAT-26	x	x				x	stool
PreGen-Plus	k-ras, APC, p53		x				x	stool
Prostate-specific antigen	PSA free, total, ultrasensitive,HAMA		x		x	x	x	blood
T-cell recepter gene rearrangment				x				blood, marrow, tissue
TEL/AML1 gene fusion	t(12;21)			x	x		x	blood, marrow
Thyroglobulin						x	x	serum
Tumor antigen 90 immune complex	TA90-IC				x	x	x	serum
Urokinase plasminogen activator	uPA, PAI-1(plasminogen activitor inhibitor)				x			tissue
Urovysion	Vysis Urovysion					x		urine
ZAP-70					x			blood, marrow

NAME	Test type	Breast	Prostate	Lung	Colorectal	Pancreas	Ovarian	Esophagus	Liver	Lymphoma	Leukemia
Acid phosphatase, total and prostatic	ICMA,spectphoto		x								
Adrenocorticotropic hormone	ICMA			x		x					
Alpha fetoprotein	ICMA			x	x	x			x		
AML1/ETO translocation	PCR										x
B-cell gene rearrangement	PCR									x	
BCL-1/JH gene rearrangement	PCR									x	
BCL-2 translocation	PCR									x	
BCR/ABL gene rearrangement	PCR, FISH										x
Beta human chorionic gonadotropin	ICMA			x		x	x		x		
Beta-2 microglobulin	ICMA									x	
Bladder tumor antigen	cytology, EIA										
BRCA Analysis	PCR	x				x	x				
Calcitonin	ICMA										
Cancer antigen 125	MEIA, ICMA	x		x	x	x	x				
Cancer antigen 15-3	ICMA	x									
Cancer antigen 19-9	EIA				x	x			x		
Cancer antigen 27.29	ICMA	x		x		x	x		x		
Carcinoembryonic antigen	ICMA	x		x	x	x	x				
Cathepsin D	IHC	x									
CBFB/MYH11 fusion protein	PCR										x
CD 117, c-kit	IHC										
CD 20	flow cytometry									x	
CD 25	IHC,flow cytometry									x	
CD 33	flow cytometry										x
CD 52	flow cytometry										x
Chromosome 18q assay	PCR				x						
Colaris	PCR				x						
Colaris AP	PCR				x						
Cyclin-D1	IHC									x	
E-cadherin	IHC		x								
Epidermal growth factor receptor	IHC	x	x	x	x						
Estrogen/progesterone receptor	IHC	x									
Fecal globin	IHC				x						
FLT 3 mutation	PCR										x
HER-2/neu	IHC,FISH,EIA	x					x				
5-HIAA	liquid chromatography										
Human papillomavius hybrid capture	DNA probe										
IgVH mutation analysis	PCR										x
Immunocyt	cytology, ICC										

NAME	Test type	Breast	Prostate	Lung	Colorectal	Pancreas	Ovarian	Esophagus	Liver	Lymphoma	Leukemia
Kappa/lambda light chain	IHC									x	
LAP	enzyme assay					x					
Lipid associated sialic acid	spectrophotometry	x		x	x	x	x		x	x	x
Melaris	PCR					x					
MIB-1 antibody	IHC	x								x	
Micrometastasis detection	IHC	x									
Microsatellite instability	PCR				x						
MLH1, MSH2, MSH6 mutations	PCR				x						
Neuron specific enolase	RIA			x		x					
Nuclear matrix proteins	EIA										
Oncotype Dx	PCR	x									
p53 tumor suppressor gene	IHC	x	x		x						
PML/RARA translocation	PCR										x
PreGen-26	PCR				x						
PreGen-Plus	PCR				x						
Prostate-specific antigen	ICMA,IRMA,EIA		x								
T-cell recepter gene rearrangment	PCR									x	
TEL/AML1 gene fusion	FISH										x
Thyroglobulin	ICMA										
Tumor antigen 90 immune complex	EIA										
Urokinase plasminogen activator	EIA	x									
Urovysion	FISH										
ZAP-70	flow cytometry										x

NAME	Other cancers
Acid phosphatase, total and prostatic	
Adrenocorticotropic hormone	carcinoid, thyroid, pituitary
Alpha fetoprotein	testicular germ cell cancer
AML1/ETO translocation	acute myelogenous leukemia
B-cell gene rearrangement	B-cell malignancies
BCL-1/JH gene rearrangement	mantle cell lymphoma
BCL-2 translocation	B-cell lymphomas
BCR/ABL gene rearrangement	chronic myelogenous leukemia, acute lymphoblastic leukemia
Beta human chorionic gonadotropin	testis, uterus, stomach
Beta-2 microglobulin	multiple myeloma, CLL and other indolent lymphomas
Bladder tumor antigen	bladder
BRCA Analysis	
Calcitonin	medullary carcinoma of thyroid
Cancer antigen 125	endometrial, cervical, primary peritoneal carcinoma
Cancer antigen 15-3	
Cancer antigen 19-9	gastric
Cancer antigen 27.29	
Carcinoembryonic antigen	
Cathepsin D	
CBFB/MYH11 fusion protein	acute myelomonocytic leukemia (AML subtype M4E0)
CD 117, c-kit	gastrointestinal stromal tumors (GISTs): c-kit-positive
CD 20	B-cell non-Hodgkin's lymphoma
CD 25	cutaneous T-cell lymphoma
CD 33	acute myeloid leukemia
CD 52	chronic lymphocytic leukemia
Chromosome 18q assay	
Colaris	hereditary non-polyposis colon (HNPCC), endometrial cancer
Colaris AP	familial adenomatous polyposis (FAP) associated cancer
Cyclin-D1	mantle cell lymphoma
E-cadherin	prostate
Epidermal growth factor receptor	head and neck
Estrogen/progesterone receptor	
Fecal globin	
FLT 3 mutation	acute myelogenous leukemia
HER-2/neu	
5-HIAA	carcinoid tumors
Human papillomavius hybrid capture	cervical cancer
IgVH mutation analysis	chronic lymphocytic leukema
Immunocyt	bladder cancer

NAME	Other cancers
Kappa/lambda light chain	multiple myeloma, lymphoproliferative disease
LAP	testicular germ cell cancer
Lipid associated sialic acid	melanoma, neuroblastoma, uterine, sarcoma
Melaris	melanoma
MIB-1 antibody	anaplastic large cell non-Hodgkin's lymphoma
Micrometastasis detection	
Microsatellite instability	hereditary non-polyposis colon cancer
MLH1, MSH2, MSH6 mutations	hereditary non-polyposis colon cancer
Neuron specific enolase	melanoma, neuroblastoma, thyroid, neuroendocrine
Nuclear matrix proteins	bladder
Oncotype Dx	
p53 tumor suppressor gene	bladder
PML/RARA translocation	acute promyelocytic leukemia (APL)
PreGen-26	hereditary non-polyposis colon cancer
PreGen-Plus	
Prostate-specific antigen	
T-cell recepter gene rearrangment	T-cell malignancies
TEL/AML1 gene fusion	acute lymphoblastic leukemia
Thyroglobulin	thyroid carcinoma
Tumor antigen 90 immune complex	melanoma
Urokinase plasminogen activator	
Urovysion	bladder cancer recurrence
ZAP-70	chronic lymphocytic leukemia

NAME	Clinical use
Acid phosphatase, total and prostatic	monitor course of disease and treatment progress
Adrenocorticotropic hormone	diagnosis of ectopic ACTH syndrome seen in lung, pancreas, carcinoid, and thyroid tumors
Alpha fetoprotein	management of testicular cancer, monitor patients with hepatocellular cancer
AML1/ETO translocation	diagnosis of AML with t(8;21) translocation, monitor response to treatment, predict relapse
B-cell gene rearrangement	diagnosis of B-cell malignancies, determine prognosis and treatment, detect recurrence
BCL-1/JH gene rearrangement	diagnosis of mantle cell lymphoma, monitor minimal residual disease, predict relapse
BCL-2 translocation	diagnosis and characterization of lymphomas, detect residual disease
BCR/ABL gene rearrangement	diagnosis of CML and ALL, assess prognosis, monitor disease, predict relapse
Beta human chorionic gonadotropin	diagnosis of germ cell neoplasm, monitor for recurrence
Beta-2 microglobulin	may be useful for prognosis, monitor response to therapy, surrogate for disease activity
Bladder tumor antigen	monitor patient with history of bladder cancer
BRCA Analysis	screen for hereditary cancer in women already diagnosed with breast and ovarian cancer
Calcitonin	diagnosis and management of medullary carcinoma of the thyroid
Cancer antigen 125	monitor ovarian cancer for residual disease and recurrence
Cancer antigen 15-3	monitor patients with breast cancer
Cancer antigen 19-9	monitor patients with pancreatic or gastrointestinal cancer
Cancer antigen 27.29	monitor metastatic breast cancer patients, early detection of recurrence
Carcinoembryonic antigen	primarily used to monitor patients with colon cancer
Cathepsin D	predict survival in node negative breast cancer
CBFB/MYH11 fusion protein	diagnosis of AML with inv(16) or t(16;16)(ie CBFB/MYH11)
CD 117, c-kit	determine eligibility for Gleevec (imatinib mesylate)
CD 20	determine eligibility for Rituxan (rituximab, anti-CD20)
CD 25	determine eligibility for Ontak (denileukin diftitox, anti CD25)
CD 33	determine eligibility for Mylotarg (anti-CD33, semtuzumab ozogamicin)
CD 52	determine eligibility for Campath (alemtuzumab, anti-CD52) in patients with CLL
Chromosome 18q assay	determine prognosis, guide therapy
Colaris	genetic susceptibility test for HNPCC and endometrial cancer
Colaris AP	genetic susceptibility test for FAP-associated cancer
Cyclin-D1	used for diagnosis of mantle cell lymphoma
E-cadherin	prognostic assessment for prostate cancer
Epidermal growth factor receptor	determine eligibility for Erbitux (cetuximab, EGFR inhibitor) for colorectal cancer, breast cancer prognosis
Estrogen/progesterone receptor	determine prognosis in breast cancer, predict response to hormonal therapy
Fecal globin	screen for lower gastrointestinal bleeding associated with colorectal cancer and other conditions
FLT 3 mutation	prognostic information for AML
HER-2/neu	determine eligibility for Herceptin, assess prognosis, predict survival in chemotherapy patients
5-HIAA	monitor patients with carcinoid tumors
Human papillomavius hybrid capture	assess cervical cancer risk
IgVH mutation analysis	assess prognosis for CLL
Immunocyt	early detection and management of bladder cancer

NAME	Clinical use
Kappa/lambda light chain	monitor disease activity
LAP	help determine disease prognosis
Lipid associated sialic acid	monitor tumor burden in a variety of malignacies, including Hodgkin's, leukemia, melanoma
Melaris	screen for hereditary melanoma
MIB-1 antibody	predict survival breast cancer, diagnosis of anaplastic NHL, assess tumor cell proliferation
Micrometastasis detection	detect micrometastases of epithelial cell origin, predict recurrence, survival
Microsatellite instability	monitor HNPCC patients, assess need to test relatives for HNPCC
MLH1, MSH2, MSH6 mutations	differentiate HNPCC from non-HNPCC, assess risk of family members
Neuron specific enolase	monitor disease in small cell lung cancer, also elevated in neuroblastoma, pancreatic, thyroid, others
Nuclear matrix proteins	diagnosis of bladder cancer, monitor for recurrence
Oncotype Dx	predict likelihood of recurrent disease in early stage breast cancer patients
p53 tumor suppressor gene	prognostic marker for prostate cancer and other tumor
PML/RARA translocation	diagnosis of APL, predict response to all trans retinoic acid (ATRA)
PreGen-26	used as adjunct to colonoscopy for monitoring HNPCC
PreGen-Plus	enhance detection of colorectal cancer
Prostate-specific antigen	screening, diagnosis, management of prostate cancer, detect residual and recurrent disease
T-cell recepter gene rearrangment	diagnosis of T-cell malignancies, detect minimal residual disease or recurrence
TEL/AML1 gene fusion	diagnosis, prognosis, monitor ALL patients
Thyroglobulin	detect presence of residual papillary-follicular carcinoma of thyroid
Tumor antigen 90 immune complex	assess prognosis for malignant melanoma, monitor for recurrence
Urokinase plasminogen activator	assess risk of recurrence, assess need for therapy, predict teatment response
Urovysion	detect bladder cancer recurrence
ZAP-70	assess prognosis and need for aggressive treatment in CLL

Database II

GENETIC TESTS FOR CANCER

One page profiles of genetic tests currently available

Glossary of test acronyms used in this database

Tests

EIA	Enzyme immunoassay
FISH	Fluorescence in-situ hybridization
ICC	Immunocytochemistry
ICMA	Immunochemiluminometric assay
IHC	Immunohistochemistry
IRMA	Immunoradiometric assay
MEIA	Microparticle enzyme immunoassay
PCR	Polymerase chain reaction
RIA	Radioimmunoassay
RT-PCR	Reverse transcriptase polymerase chain reaction

1. Test name: **Acid phosphatase, total and prostatic**

2. Other names: PAP

3. Description: Elevated levels of this enzyme are found in patients with metastatic prostate cancer. PAP determination, in conjunction with PSA measurements, is useful in assessing the prognosis of prostate cancer. Concentrations of both the prostatic and nonprostatic forms of acid phosphatase may be differentiated using tartrate. The activity of the prostatic form of the enzyme is inhibited in the presence of tartrate.

4. Purpose: prognostic, recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: Serum, frozen

7. Methodology: ICMA
spectrophotometry - alpha-naphthol phosphate substrate with tartrate inhibition for prostatic AcP determination

8. Cancers: prostate cancer

9. Other cancers:

10. Clinical use(s):
    a) Routine:

        - used as an adjunct in confirming the clinical staging of prostate cancer
        - used with PSA to detect recurrence of prostate cancer in patients who have been treated

11. Source of information: LabCorp, Specialty Laboratories, UpToDate™ websites

12. Exploratory Medline search (5/25/05):
    a) "Acid phosphatase" = 2010 citations, "prostate" = 6127 citations
    b) "Acid phosphatase" and "prostate" = 102 citations
    c) "Acid phosphatase" and "prostatic neoplasm" (24856) = 111 citations
    d) "Total acid phosphatase" (21) and "prostatic neoplasm" = 4 citations

1. Test name: **Adrenocorticotropic hormone**

2. Other names: ACTH hormone

3. Description: ACTH has been used in diagnosing disorders of the hypothalamic-pituitary system. It is useful in the differential diagnosis of Cushing syndrome, ectopic ACTH syndrome, Addison disease, hypopituitarism, and ACTH-producing pituitary tumors (eg, Nelson syndrome). The most common causes of ectopic ACTH syndrome are small (oat)-cell carcinomas, carcinoid tumors, particularly bronchial carcinoids, islet cell tumors, and pulmonary tumorlets.

4. Purpose: diagnostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: plasma

7. Methodology: ICMA

8. Cancers: pituitary, adrenal

9. Other cancers: carcinoid, thyroid, pulminary, pancreas

10. Clinical use(s):
    a) Routine:
        - used in the diagnosis of ectopic ACTH syndrome associated with small cell carcinoma, carcinoid tumors, and islet cell tumors

11. Source of information: Quest Diagnostics, LabCorps, Specialty Laboratories, UpToDate™

12. Exploratory Medline search (5/26/05):
    a) "corticotropin" = 6949 citations, "pituitary gland" = 11858 citations
    b) "pituitary neoplasm" = 4542 citations
    c) "corticotropin" and "pituitary gland" = 1873 citations
    d) "corticotropin" and "pituitary neoplasm" = 423 citations
    e) "corticotropin" and "ACTH syndrome, ectopic" = 84 citations

1. Test name: **Alpha-Fetoprotein**

2. Other names: AFP

3. Description: Elevated serum AFP levels are most closely associated with non-seminomatous testicular cancer and hepatocellular cancer. The rate of clearance from serum after treatment is an indicator of the effectiveness of therapy. Conversely, the growth rate of progressive disease can be monitored by serially measuring serum AFP concentrations over time.

4. Purpose: secondary prevention, prognostic, recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum protein

7. Methodology: ICMA

8. Cancers: non-seminomatous testicular, hepatocellular

9. Other cancers: AFP may also be elevated in malignant germ cell tumors of ovary and testis, gastrointestinal, pancreatic, pulmonary cancer

10. Clinical use(s):
    a) Routine:
        - distinguish between seminomatous and non-seminomatous testicular germ cell cancer
        - monitor effectiveness of therapy and detect recurrence in individuals with non- seminomatous testicular germ cell cancer
        - monitor effectiveness of therapy in individuals with hepatocellular carcinoma
        - monitor hepatitis B carriers for evidence of liver cancer
    b) Investigational:
        - elevated serum concentrations of AFP are found in 23% of patients with pancreatic, gastric (18%), bronchogenic (7%) and colonic carcinoma (5%), compared to 75% of patients with non-seminomatous testicular cancer and 72% of patients with hepatocellular cancer

11. Source of information: Quest Diagnostics, LabCorp, Specialty Laboratories websites

12. Exploratory Medline search (5/12/05):
    a) "alpha-Fetoproteins" = 2608 citations, "testicular neoplasms" = 4401 citations
    b) "alpha-Fetoproteins" and "testicular neoplasm" = 113 citations
    c) "alpha-Fetoproteins" and "carcinoma, hepatocellular" (13840) = 704 citations
    d) "alpha-Fetoproteins" and "pancreatic neoplasms" (12117) = 27 citations
    e) "alpha-Fetoproteins" and "gastrointestinal neoplasms" (64300) = 133 citations
    f) "alpha-Fetoproteins" and "lung neoplasms" (36152) = 46 citations
    g) "alpha-Fetoproteins" and "ovarian neoplasms"(15334) = 64 citations

1. Test name: **AML1/ETO translocation**

2. Other names: t(8:21)

3. Description: The translocation t(8;21)(q22;q22) is one of the most common structural chromosomal aberrations in patients with Acute Myeloid Leukemia (AML). AML with t(8;21) has a mean onset age of about 30 years and is most common in children and younger adults; it is relatively rare in elderly patients. The presence of t(8;21) is associated with the highest complete remission rate (90%) and the highest probability (50%-70%) of remaining in complete remission at 5 years. However, the disease may become resistant to therapy upon relapse.

4. Purpose: diagnostic, prognostic, recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: whole blood, bone marrow

7. Methodology: PCR

8. Cancers: acute myeloid leukemia

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - diagnosis of acute myeloid leukemia (AML) with t(8;21) chromosome translocation
        - monitor treatment response
        - detect minimal residual disease (MRD or evidence for the presence of residual cancer cells, even when so few malignant cells are present that they cannot be detected by routine means)
        - predict early relapse

11. Sources of information: Quest Diagnostics, LabCorp, UpToDate

12. Exploratory Medline search (6/01/05):
    a) "AML1" = 853 citations, "ETO" = 469 citations
    b) "Leukemia, Myelocytic, Acute" = 4057 citations
    c) "fusion protein" = 12573 citations
    d) "Leukemia, Myelocytic, Acute" and "fusion protein" = 138 citations
    e) "AML1" and "ETO" = 138 citations

1. Test name: **B-cell gene rearrangement**

2. Other names:

3. Description: These additional studies are used to establish a definitive diagnosis. They include molecular analysis of tumor material using PCR technology to identify gene rearrangements known to be associated with B-cell malignancies. Additionally the special tests can sometimes help to establish both the lineage and the presence of prognostically significant subtypes of malignant lymphoma.

4. Purpose: diagnostic, prognostic, recurrence

5. Availability: commercial laboratories, academic hospitals

6. Specimen: whole blood, bone marrow, or tissue

7. Methodology: PCR

8. Cancers: B-cell malignancies

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - diagnosis of B-cell malignancies
        - assist in determining disease prognosis and thus influence treatment selection
        - detection of minimal residual disease or recurrent disease

11. Source of information: Quest Diagnostics, LabCorps websites

12. Exploratory Medline search (6/01/05):
    a) "B-Lymphocytes" = 17852 citations, "leukemia" = 38022 citations
    b) "B-Lymphocytes" and "leukemia" = 1047 citations
    c) "gene rearrangement" = 6400 citations
    d) "B-Lymphocytes" and "gene rearrangement" = 1285 citations
    e) "leukemia" and "gene rearrangement" = 1044 citations

1. Test name: **bcl-1/JH t(11;14) Gene Rearrangement**

2. Other names: t(11;14)

3. Description: The t(11;14)(q13;q32) rearrangement causes deregulation of the bcl-1 gene and over-expression of cyclin D1, which may in turn lead to lymphoma genesis. The bcl-1 translocation is specific for mantle cell lymphoma

4. Purpose: diagnostic, prognostic, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: whole blood, bone marrow, tissue

7. Methodology: PCR

8. Cancers: mantle cell lymphoma

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - diagnosis of mantle cell lymphoma
        - assessment of therapeutic response
        - detect minimal residual disease (MRD)
        - predict early relapse

11. Source of information: Quest Diagnostics, LabCorp

12. Exploratory Medline search (6/01/05):
    a) "genes, bcl-1" = 124 citations, "translocation" = 7571 citations
    b) "mantle cell lymphoma" = 522 citations
    c) "cyclin D1" = 2811 citations
    d) "mantle cell lymphoma" and "cyclin D1" = 84 citations

1. Test name: **BCL-2 translocation**

2. Other names: t(14:18)

3. Description: The bcl-2 gene translocation, t(14;18), is the rearrangement of the bcl-2 proto-oncogene on chromosome 18 with the immunoglobulin heavy chain region on chromosome 14. The bcl-2 translocation is a characteristic of B-cell lymphomas. It is observed in 70 to 90% of follicular non-Hodgkin B-cell lymphomas, 20 to 30% of large diffuse B-cell lymphomas, and 50% of undifferentiated B-cell lymphomas, but not in other lymphomas.

4. Purpose: diagnostic, prognostic, recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood, marrow, tissue

7. Methodology: PCR

8. Cancers: B-cell lymphomas

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - distinguish lymphoma from benign lymphoid hyperplasia
        - distinguish B-cell lymphoma from T-cell lymphoma
        - determine prognosis for patients with B-cell lymphomas
        - monitor B-cell lymphoma patients for minimal residual disease or evidence of recurrence

11. Source of information: Quest Diagnostics, UpToDate websites

12. Exploratory Medline search (6/01/05):
    a) "Translocation, Genetic"= 7571 citations
    b) "BCL-2 gene" = 1894 citations
    c) "Lymphoma, B-Cell"= 9217 citations
    d) "BCL-2 gene" and "Lymphoma" = 92 citations

1. Test name: **BCR-ABL**

2. Other names: Philadelphia chromosome

3. Description: Bcr/abl fusion gene, formed by rearrangement of the breakpoint cluster region (bcr) on chromosome 22 with the c-abl proto-oncogene on chromosome 9, is present in 95% of CML patients and 30% of ALL patients. Identification of bcr/abl rearrangement is important for the diagnosis of CML, whereas in ALL, presence of bcr/abl is associated with poor prognosis and may warrant more aggressive therapy. In both diseases, increasing levels of bcr/abl may be associated with clinical progression.

4. Purpose: diagnostic, prognostic, recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: whole blood, bone marrow RNA

7. Methodology: PCR, FISH

8. Cancers: Chronic Myelogenous Leukemia (CML)
   Acute Lymphocytic Leukemia (ALL)

9. Other cancers:

10. Clinical use(s):
    a) Routine:
       - assist in diagnosis of CML
       - assess prognosis in ALL patients
       - detect minimal residual disease and monitor effectiveness of therapy
       - predict early relapse

11. Source of information: Quest Diagnostics, LabCorp, Specialty Labs websites, UpToDate™

12. Exploratory Medline search (5/12/05):
    a) "fusion proteins, bcr-abl" or "Philadelphia Chromosome" = 2008 citations
    b) "leukemia, myeloid, chronic" = 4926 citations
    c) "leukemia, lymphocytic, acute" = 4027 citations
    d) "fusion proteins, bcr-abl" or "Philadelphia Chromosome" and "myeloid leukemia, chronic" = 1119 citations
    e) "fusion proteins, bcr-abl" or "Philadelphia Chromosome" and "leukemia, lymphocytic, acute" = 151 citations

1. Test name: **Beta human chorionic gonadotropin**

2. Other names: beta-HCG

3. Description: beta-hCG is detectable in the serum of 70% of patients with non-seminomatous germ-cell tumors. Patients with a prolonged half life of beta -hCG (>3.5 days) have an inferior overall and disease-free survival and may be candidates for high dose chemotherapy. In germ cell tumors in the male, beta-hCG and alpha-fetoprotein are both useful tumor markers

4. Purpose: diagnostic, recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum

7. Methodology: ICMA

8. Cancers: germ cell tumors (e.g. teratoma, struma ovarii, dysgerminoma, yolk sac tumor, embryonal carcinoma, and choriocarcinoma)

9. Other cancers: lung, pancreas, liver, stomach

10. Clinical use(s):
    a) Routine:
        - assist in the diagnosis of germ-cell tumors
        - monitor response to trophoblastic tumor therapy
        - detect disease recurrence

    b) Investigational:
        - monitor lung, pancreas, liver, stomach cancers

11. Source of information: LabCorp, UpToDate, Specialty Labs websites

12. Exploratory Medline search (6/01/05):
    a) "germinoma" = 2695 citations
    b) "Chorionic Gonadotropin, beta Subunit, Human" = 1148 citations
    c) "Chorionic Gonadotropin, beta Subunit, Human" and "germinoma" = 67 citations

1. Test name: **Beta 2-microglobulin**

2. Other names:

3. Description: Beta 2-microglobulin is increased nonspecifically in active chronic lymphocytic leukemia in which there is increased lymphocyte turnover. Elevated levels of beta 2-microglobulin can be found in cerebral spinal fluid (relative to serum) in acute lymphoblastic leukemia, lymphoma and other lymphoproliferative disorders. (Lymphoproliferative disorders refers to a group of malignant diseases involving the lymphoid cells and cells from the reticuloendothelial system, including lymphoma and post-transplant lymphoproliferative disorder). Increased serum concentrations of beta 2-microglobulin are good predictors of complete response and time to treatment failure in low-grade lymphoma.

4. Purpose: diagnostic, prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum

7. Methodology: ICMA

8. Cancers: lymphoma, Hodgkin's and Non-Hodgkin's Lymphoma

9. Other cancers: multiple myeloma, chronic lymphocytic leukemia, and other indolent lymphomas

10. Clinical use(s):
    a) Routine:
        - assist in diagnosis of lymphoma and other lymphoproliferative diseases
        - predictive of response of low grade lymphoma

11. Source of information: LabCorp, Specialty Labs, UpToDate

12. Exploratory Medline search (6/01/05):
    a) "Lymphoproliferative Disorders" = 57926 citations
    b) "Leukemia, Lymphocytic, Chronic" = 3353 citations
    c) "beta 2-Microglobulin" = 2093 citations
    d) "Lymphoproliferative Disorders" and "beta 2-Microglobulin" = 195 citations
    e) "Leukemia, Lymphocytic, Chronic" and "beta 2-Microglobulin" = 19 citations

1. Test name: **Bladder Tumor Antigen**

2. Other names: BTA

3. Description: A biomarker that is currently being investigated for use in surveillance following initial treatment of superficial bladder cancer.

4. Purpose: recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: urine

7. Methodology: cytology, EIA

8. Cancers: bladder

9. Other cancers: kidney and ureter

10. Clinical use(s):

    b) Investigational:
        - detection of tumor recurrence

11. Source of information: Quest Diagnostics, LabCorp, UpToDate websites

12. Exploratory Medline search (6/01/05):
    a) "bladder neoplasms" = 9404 citations
    b) "tumor markers, biological" = 50524 citations
    c) "bladder neoplasms" and "tumor markers, biological" = 1090 citations

1. Test name: **BRCA Analysis**

2. Other names: BRCA1, BRCA2

3. Description: BRCA1 and BRCA2 are two susceptibility genes for breast cancer that are inherited in an autosomal dominant fashion and account for one-fifth of the familial risk of breast cancer. BRCA mutations are found in between 1 and 3.3 percent of American women with breast cancer who are unselected for family history. However, the prevalence of a deleterious BRCA1 or BRCA2 mutation in women of Ashkenazi Jewish (Eastern European) descent is approximately 2 percent.

4. Purpose: primary prevention, prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: whole blood

7. Methodology: PCR

8. Cancers: breast, ovarian

9. Other cancers: prostate, lymphoma, melanoma, cancers of the gallbladder, pancreas, stomach

10. Clinical use(s):
    a) Routine:
        - detection of BRCA1 and BRCA2 mutations which are associated with the majority of hereditary breast and ovarian cancers
        - presence of BRCA1/2 gene mutations in patients with breast cancer may influence their treatment and management of their disease
        - presence of BRCA1/2 gene mutations in a cancer patient may also result in additional testing for the mutation in family members of the BRCA positive patient

11. Source of information: Quest, LabCorp, UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "Breast Neoplasms" = 57,232 citations
    b) "genes, BRCA1 or genes, BRCA2" = 2188 citations
    c) "Breast Neoplasms" and "genes, BRCA1 or genes, BRCA2" = 1597 citations

1. Test name: **Calcitonin**

2. Other names:

3. Description: High concentrations of calcitonin occur in patients with malignant parafollicular or C-cell tumors of the thyroid gland. The doubling time of serum levels of this hormone correlates with recurrence of tumors.

4. Purpose: secondary prevention, diagnostic, prognostic, recurrence

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum, frozen

7. Methodology: ICMA

8. Cancers: thyroid gland

9. Other cancers: lung, breast, carcinoids, islet cell tumors, APUDomas

10. Clinical use(s):
    a) Routine:
        - detection of C-cell hyperplasia (the precursor of medullary carcinoma of thyroid)
        - used as a tumor marker for diagnosis and management of medullary carcinoma of the thyroid gland
    b) Investigational:
        - preoperative serum calcitonin is reported to roughly correlate with tumor weight or extent of disease

11. Source of information: LabCorps, Specialty Laboratories, Quest, UpToDate websites

12. Exploratory Medline search (08/02/05):
    a) "calcitonin" = 2434 citations
    b) "thyroid neoplasms" = 9062 citations
    c) "calcitonin" and "thyroid neoplasms" = 311 citations

1. Test name: **Cancer Antigen 125**

2. Other names: CA 125

3. Description: CA 125 is expressed by >80% of non-mucinous ovarian epithelial neoplasms. Approximately half of women with metastatic ovarian cancer have an elevated CA 125 level.

4. Purpose: recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum

7. Methodology: MEIA, ICMA

8. Cancers: ovarian

9. Other cancers: lung, colorectal, pancreas, primary peritoneal carcinoma

10. Clinical use(s):
    a) Routine:
        - monitor response to treatment for patients with ovarian cancer
        - detect recurrence of ovarian cancer

11. Source of information: Quest Diagnostics, Specialty Laboratories, UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "CA-125 antigen" = 1391 citations
    b) "ovarian neoplasms" = 15,743 citations
    c) "CA-125 antigen" and "ovarian neoplasms" = 793 citations

1. Test name: **Cancer Antigen 15-3**

2. Other names: CA 15-3

3. Description: Elevated serum CA 15-3 concentrations are found in 5% of stage I, 29% of stage II, 32% of stage III and 95% of stage IV carcinoma of the breast. Most (96%) patients with a CA 15-3 increase of greater than 25% have disease progression. Most (nearly 100%) patients with a CA 15-3 decrease of greater than 50% are responding to treatment.

4. Purpose: recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum

7. Methodology: ICMA

8. Cancers: breast

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - tumor marker used to monitor clinical course in patients with metastatic disease
        - change in CA 15-3 over time is predictive of response to therapy or progression of disease
        - serum concentration correlates with tumor bulk

11. Source of information: Specialty Laboratories, LabCorps, UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "CA-15-3 antigen" = 1629 citations
    b) "breast neoplasm" = 57,603 citations
    c) "CA-15-3 antigen" and "breast neoplasm" = 449 citations

1. Test name: **Cancer Antigen 19-9**

2. Other names: CA 19-9

3. Description: CA 19-9 is a mucin-glycoprotein first identified from a human colorectal carcinoma cell line and is present in epithelial tissue of the stomach, gall bladder, pancreas and prostate. Concentrations are increased in patients with pancreatic, gastric, and colon cancer as well as in some non-malignant conditions. Increasing levels generally indicate disease progression, whereas decreasing levels suggest therapeutic response.

4. Purpose: recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum or plasma

7. Methodology: EIA

8. Cancers: colorectal, pancreatic, liver

9. Other cancers: gastric

10. Clinical use(s):
    a) Routine:
        - monitor effectiveness of therapy in individuals with pancreatic cancer
        - monitor effectiveness of therapy in selected individuals with gastric and colon cancer

11. Source of information: Quest Diagnostics, LabCorps, and UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "CA-19-9 antigen" = 816 citations
    b) "colorectal neoplasm" = 37,826 citations
    c) "CA-19-9 antigen" and "colorectal neoplasm" = 122 citations

1. Test name: **Cancer Antigen 27.29**

2. Other names: CA 27.29

3. Description: Elevated CA 27.29 levels are primarily associated with metastatic breast cancer, where it can be used to monitor the course of disease, response to treatment, and detect disease recurrence. Elevated serum CA 27.29 concentrations are found in 95% of stage IV breast cancer. In addition, CA 27.29 has been found to be elevated in lung (43%), pancreas (47%), ovarian (56%), and liver (55%) cancer.

4. Purpose: recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum protein

7. Methodology: ICMA

8. Cancers: breast

9. Other cancers: may also be elevated in lung, pancreas, ovarian, and liver cancer

10. Clinical use(s):
    a) Routine:
        - in patients with metastatic breast cancer and an elevated level of this tumor marker, CA 27.29 can be used to monitor response to treatment, determine whether tumor has become resistant to therapy or whether a patient has progressive disease.

11. Source of information: Quest Diagnostics, LabCorp, Specialty Labs websites

12. Exploratory Medline search (5/12/05):
    a) "CA 27 29" or "CA 27-29" or "cancer antigen 27 29" = 18 citations
    b) "breast neoplasm" = 55886 citations
    c) "CA 27 29" and "breast neoplasms" = 16 citations
    d) "CA 27 29" and "lung neoplasms"(36152) = 0 citations
    e) "CA 27 29" and "pancreas neoplasms" (12117) = 0 citations
    f) "CA 27 29" and "ovarian neoplasms" (15334) = 1 citations
    g) "CA 27 29" and "liver neoplasms" (28088) = 2 citations

1. Test name: **Carcinoembryonic Antigen**

2. Other names: CEA

3. Description: CEA is an oncofetal glycoprotein present in the gastrointestinal tract and body fluids of the embryo and fetus. It is also present in certain adult gastrointestinal cells, including the mucosal cells of the colorectum, and small amounts are present in blood. Blood levels are often elevated in patients with disseminated cancers and in some patients with non-malignant disease.

4. Purpose: secondary prevention, prognostic, recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum

7. Methodology: ICMA

8. Cancers: breast, lung, colorectal, pancreas, ovarian

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - monitor persistent, metastatic, or recurrent adenocarcinoma of the colon following curative surgery
        - recommended for staging/prognosis, detecting recurrence, monitoring therapy, and screening for hepatic metastases in patients with colon cancer

    b) Investigational:
        - if CEA is elevated at the time of diagnosis and prior to initiation of treatment, it may be used to monitor response to therapy in patients with breast, lung, pancreas, ovarian cancers

11. Source of information: Quest Diagnostics, LabCorps, and UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "carcinoembryonic antigen" = 2785 citations
    b) "breast neoplasm" or "lung neoplasm" or "colorectal neoplasm" or "pancreas neoplasm" or "ovarian neoplasm" = 162,473 citations
    c) "carcinoembryonic antigen" and (b) = 1504 citations

1. Test name: **Cathepsin D**

2. Other names:

3. Description: This enzyme plays a critical role in protein catabolism and tissue remodeling. Over-expression is associated with non-ductal carcinoma and metastasis at the time of breast cancer diagnosis.

4. Purpose: prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: tissue (formalin-fixed, paraffin-embedded)

7. Methodology: IHC

8. Cancers: breast

9. Other cancers:

10. Clinical use(s):
    b) Investigational:
        - high levels may have clinical significance in predicting decreased metastasis-free survival and decreased overall survival in women with node-negative breast cancer

11. Source of information: Quest Diagnostics, LabCorps, and UpToDate websites

12. Exploratory Medline search (8/2/05):
    a) "cathepsin D" = 1001 citations
    b) "breast neoplasm" = 57,603 citations
    c) "cathepsin D" and "breast neoplasm" = 203 citations

1. Test name: **CBFB/MYH11 fusion protein**

2. Other names: inv(16), t(16;16)

3. Description: This inversion results in fusion of the core binding factor ß (CBFß) gene on 16q22 with the smooth muscle myosin heavy chain gene (MYH11) on 16p13. This fusion protein accounts for 16% of the chromosomal aberrations associated with AML and patients with inv(16) or t(16;16) generally have relatively good response and long-term disease-free survival rates.

4. Purpose: diagnostic, prognostic, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood, marrow

7. Methodology: PCR

8. Cancers: acute myleomonocytic leukemia (AML subtype M4E0)

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - diagnosis of acute myelomonocytic leukemia (AML) with abnormal eosinophils, with inv(16) or t(16;16)
        - monitor effectiveness of treatment
        - monitor minimal residual disease
        - predict early relapse

11. Source of information: Quest Diagnostic and UpToDate websites

12. Exploratory Medline search (8/2/05):
    a) "oncogene proteins, fusion" = 3798 citations
    b) "leukemia, myelocytic, acute" = 4151 citations
    c) "oncogene proteins, fusion" and "leukemia, myelocytic, acute" = 172 citations

1. Test name: **CD 117, c-kit**

2. Other names: Imatinib mesylate (Gleevec) sensitivity

3. Description: The glycoprotein c-kit (CD117) is a member of the receptor tyrosine kinase subclass III family and has been implicated in a number of malignancies. Imatinib mesylate, a tyrosine kinase inhibitor, is effective in treating GISTs and other tumors that express c-kit

4. Purpose: diagnostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: tissue

7. Methodology: IHC

8. Cancers: gastrointestinal stromal tumors, c-kit positive

9. Other cancers:

10. Clinical use(s):
    a) Routine:
    - determine eligibility for treatment with imatinib mesylate in patients with c-kit-positive gastrointestinal stromal tumors (GISTs)

11. Source of information: Quest Diagnostics, UpToDate websites

12. Exploratory Medline search (8/2/05):
    a) "proto-oncogene protein c-kit" = 2022 citations
    b) "gastrointestinal neoplasm" = 66,189 citations
    c) "proto-oncogene protein c-kit" and "gastrointestinal neoplasm" = 367 citations

1. Test name: **CD 20**

2. Other names: rituximab (Rituxan) sensitivity

3. Description: Rituximab is a genetically engineered, chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B-cell lymphocytes. Since non-Hodgkin's Lymphoma (NHL) subtypes may differ in their response to rituximab, determination of drug sensitivity is important for choosing therapy.

4. Purpose: diagnostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood

7. Methodology: flow cytometry

8. Cancers: B-cell non-Hodgkin's lymphoma

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - determine eligibility for rituximab (Rituxan; anti-CD20) treatment in patients with B-cell non-Hodgkin's lymphomas (NHL)

11. Source of information: Quest Diagnostics, UpToDate websites

12. Exploratory Medline search (8/2/05):
    a) "antigens, cd20" = 1022 citations
    b) "lymphoma, Non-Hodgkin" = 22,160 citations
    c) "antigens, cd20" and "lymphoma, Non-Hodgkin" = 475 citations

1. Test name: **CD 25 (immunohistochemistry and flow cytometry)**

2. Other names: denileukin diftitox (Ontak) sensitivity

3. Description: Denileukin diftitox (Ontak) is a cutaneous T-cell lymphoma (CTCL) therapy that targets the high-affinity interleukin-2 (IL-2) receptor. The IL-2 receptor may exist in a low-affinity form (CD25), an intermediate-affinity form (CD122/CD132), and a high-affinity form (CD25/CD122/CD132). Patients whose malignant cells express the CD25 component of the IL-2 receptor may respond to Ontak therapy

4. Purpose: diagnostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: tissue (IHC), blood or marrow (flow cytometry)

7. Methodology: IHC or flow cytometry

8. Cancers: cutaneous T-cell lymphoma

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - determine eligibility for denileukin diftitox treatment in patients with persistent or recurrent CTCL

11. Source of information: Quest Diagnostics and UpToDate websites

12. Exploratory Medline search (8/2/05):
    a) "receptors, interleukin-2" = 4221 citations
    b) "lymphoma, t-cell, cutaneous" = 2157 citations
    c) "receptors, interleukin-2" and "lymphoma, t-cell, cutaneous" = 25 citations

1. Test name: **CD 33**

2. Other names: Gemtuzumab (Mylotarg) sensitivity

3. Description: Gemtuzumab consists of a recombinant, humanized IgG kappa antibody conjugated to a cytotoxic anti-tumor antibiotic, calicheamicin, which binds specifically to the CD33 antigen. This antigen is found on the surface of leukemic blasts and immature normal cells of myelomonocytic lineage, but not in normal hematopoietic stem cells.

4. Purpose: diagnostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood, marrow

7. Methodology: flow cytometry

8. Cancers: acute myeloid leukemia (AML)

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - determine eligibility for gemtuzumab (Mylotarg, anti-CD33) treatment in patients with acute myeloid leukemia

11. Source of information: Quest Diagnostics and UpToDate websites

12. Exploratory Medline search (8/2/05):
    a) "antigens, cd" = 88,193 citations
    b) "leukemia, myelocytic, acute" = 4151 citations
    c) "cd 33.mp" = 27 citations
    d) "antigens, cd" and "leukemia, myelocytic, acute" = 435 citations

1. Test name: **CD 52**

2. Other names: alemtuzumab (Campath) sensitivity

3. Description: CD52 is an antigen that can be expressed at high density on the surface of malignant CLL cells. Alemtuzumab is a humanized antibody targeted against CD52 and its binding is necessary for cell death and therapeutic response

4. Purpose: diagnostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood, marrow

7. Methodology: flow cytometry

8. Cancers: chronic lymphocytic leukemia (CLL)

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - determine eligibility for alemtuzumab (Campath, anti-CD52) treatment in patients with chronic lymphocytic leukemia

11. Source of information: Quest Diagnostics and UpToDate websites

12. Exploratory Medline search (8/2/05):
    a) "antigens, cd" = 88,193 citations
    b) "leukemia, lymphocytic, chronic" = 3422 citations
    c) "cd 52.mp" = 13 citations
    d) "antigens, cd" and "leukemia, lymphocytic, chronic" = 646 citations

1. Test name: **Chromosome 18q assay**

2. Other names: 18q/RER, DCC

3. Description: Colorectal cancer patients having tumors with chromosome 18 deletion are more likely to have disease recurrence and have a shorter disease-free survival period when compared to patients with two copies of this chromosome

4. Purpose: diagnostic, prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood, tissue

7. Methodology: PCR

8. Cancers: colorectal cancer

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - diagnosis of colorectal disease
        - predict recurrence of disease

11. Source of information: LabCorps and UpToDate websites

12. Exploratory Medline search (8/2/05):
    a) "chromosomes, human, pair 18" = 1824 citations
    b) "colorectal neoplasms" = 37,826 citations
    c) "chromosomes, human, pair 18" and "colorectal neoplasms" = 108

1. Test name: **Colaris**

2. Other names: MLH1, MSH2

3. Description: Hereditary nonpolyposis colorectal cancer (HNPCC) accounts for about 3% to 5% of colorectal cancers (CRCs) and is caused by defects in mismatch repair (MMR) enzymes. These defects may also increase the risk of endometrial, cervical, stomach, ovarian, and other forms of cancer. About 90% of individuals with HNPCC have mutations in 1 of 2 MMR genes, MLH1 or MSH2

4. Purpose: secondary prevention, diagnostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood

7. Methodology: PCR

8. Cancers: colorectal

9. Other cancers: endometrial, cervical, stomach, ovarian

10. Clinical use(s):
    a) Routine:
        - differentiate hereditary nonpolyposis colorectal cancer (HNPCC) from non-HNPCC colorectal cancer (CRC)
        - assess risk of HNPCC in family members of individuals with HNPCC

11. Source of information: Quest Diagnostics, LabCorps, UpToDate websites

12. Exploratory Medline search (8/2/05):
    a) "colorectal neoplasm, hereditary nonpolyposis" = 1363 citations
    b) "base pair mismatch" = 2251 citations
    c) "colorectal neoplasm, hereditary nonpolyposis" and "base pair mismatch" = 268 citations

1. Test name: **Colaris AP**

2. Other names: APC, FAP

3. Description: Used to identify patients who may have disease causing mutations by sequencing the coding region of the APC gene. Individuals with mutations in this gene are at risk for developing early onset of colon cancer. Identifying these mutations makes allows for presymptomatic diagnosis of familial adenomatous polyposis (FAP).

4. Purpose: secondary prevention, diagnostic

5. Availability: LabCorp

6. Specimen: blood

7. Methodology: PCR

8. Cancers: colorectal

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - identify genetic predisposition to colorectal cancers associated with FAP

11. Source of information: LabCorp website

12. Exploratory Medline search (8/2/05):
    a) "genes, apc" = 1167 citations
    b) "colorectal neoplasm, hereditary nonpolyposis" = 1363 citations
    c) "genes, apc" and "colorectal neoplasm, hereditary nonpolyposis" = 57citations

1. Test name: **Cyclin D1**

2. Other names:

3. Description: D-type cyclins are predominantly expressed in the G1 phase of the cell cycle. The expression pattern of cyclin D1 has been extensively studied in certain cancer types including lymphoma and non-small cell lung cancer. Approximately 30% of breast carcinomas are Cyclin D1 positive. Over expression of Cyclin D1 is now a well established criterion for the diagnosis of Mantle Cell Lymphoma, a malignant, non-Hodgkin's lymphoma which is characterized by a unique chromosomal translocation t(11;14).

4. Purpose: diagnostic, prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood, tissue

7. Methodology: FISH

8. Cancers: mantle cell lymphoma

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - diagnosis of mantle cell lymphoma
        - predict recurrence of disease

11. Source of information: LabCorp and UpToDate websites

12. Exploratory Medline search (8/2/05):
    a) "cyclin d1" = 2877 citations
    b) "lymphoma, mantle cell" = 539 citations
    c) "cyclin d1" and "lymphoma, mantle cell" = 85 citations

1. Test name: **E-cadherin**

2. Other names:

3. Description: E-cadherin is a calcium-dependent epithelial cell-cell adhesion molecule that is associated with tumor invasiveness and disease progression. E-cadherin under-expression appears to be associated with poor tumor differentiation, progression following radical prostatectomy, and diminished overall survival.

4. Purpose: prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: tissue

7. Methodology: IHC

8. Cancers: prostate

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - determine prognosis, predict tumor behavior and response to therapy

11. Source of information: Quest Diagnostics and UpToDate websites

12. Exploratory Medline search (8/2/05):
    a) "cadherins" = 4880 citations
    b) "prostatic neoplasm" = 25,690 citations
    c) "cadherins" and "prostatic neoplasm" = 115 citations

1. Test name: **Epidermal growth factor receptor**

2. Other names: EGFR pharmDx, HER-1, Cetuximab (Erbitux) sensitivity

3. Description: Dysregulation of the EGFR signaling pathway due to EGFR overexpression, genetic aberrations, or other causes leads to malignant transformation. Cetuximab inhibits binding of EGFR by EGF and transforming growth factor-α, thereby blocking downstream signal transduction pathways and arresting cell growth.

4. Purpose: diagnostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: tissue

7. Methodology: IHC

8. Cancers: breast, prostate, lung, colorectal

9. Other cancers: head and neck

10. Clinical use(s):
    a) Routine:
       - determine eligibility for cetuximab (Erbitux™') treatment

11. Source of information: Quest Diagnostics and UpToDate websites

12. Exploratory Medline search (8/2/5):
    a) "receptor, epidermal growth factor" = 6983 citations
    b) "lung neoplasms or colorectal neoplasms or breast neoplasms or prostatic neoplasms" = 151,099 citations
    c) "receptor, epidermal growth factor" and (b) = 1358 citations

1. Test name: **Estrogen/ progesterone receptor**

2. Other names: ER/PR

3. Description: Breast cancers are dependent upon estrogen and/or progesterone for growth and that this effect is mediated through ERs and progesterone receptors (ER/PR). Both receptors may be over-expressed in malignant breast tissue.

4. Purpose: diagnostic, prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: tissue

7. Methodology: IHC

8. Cancers: breast

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - predicts response to hormone therapy for women with advanced breast cancer and those receiving adjuvant treatment
        - prognosticates the aggressiveness of a tumor

11. Source of information: UpToDate website

12. Exploratory Medline search (8/2/05):
    a) "receptors, estrogen" = 10,705 citations
    b) "receptors, progesterone" = 3898 citations
    c) "breast neoplasms" = 57,603 citations
    d) "receptor, estrogen" and "receptors, progesterone" and "breast neoplasm" = 1452 citations

1. Test name: **Fecal globin**

2. Other names: InSure, FOBT

3. Description: Cancerous and precancerous colorectal lesions tend to cause low-level bleeding. Annual screening with a fecal occult blood test (FOBT) can decrease colorectal cancer mortality by up to 33%.

4. Purpose: secondary prevention

5. Availability: commercial laboratories, academic hospitals

6. Specimen: stool

7. Methodology: IHC

8. Cancers: colorectal

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - screen for lower gastrointestinal bleeding associated with colorectal cancer, adenomas, polyps, and other lower gastrointestinal conditions

11. Source of information: Quest diagnostics, UpToDate websites

12. Exploratory Medline search (8/2/05):
    a) "occult blood" = 1087 citations
    b) "colorectal neoplasm" = 37,826 citations
    c) "occult blood" and "colorectal neoplasm" = 825 citations

1. Test name: **FLT 3 mutation**

2. Other names:

3. Description: Mutations in FLT3 are common in AML and have been associated with poorer survival in children and in younger adults with normal cytogenetics receiving intensive chemotherapy

4. Purpose: prognostic

5. Availability: Quest Diagnostics

6. Specimen: blood

7. Methodology: PCR

8. Cancers: acute myelogenous leukemia (AML)

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - predict survival in AML patients

11. Source of information: Quest Diagnostics and UpToDate websites

12. Exploratory Medline search:
    a) "receptor, protein, tyrosine kinase" = 28,203 citations
    b) "leukemia, myelocytic, acute" = 4151 citations
    c) "receptor, protein, tyrosine kinase" and "leukemia, myelocytic, acute" = 125 citations

1. Test name: **HER-2/neu**

2. Other names: c-erbB-2, trastuzumab (Herceptin) eligibility, HercepTest, PathVysion®

3. Description: HER-2/neu is an oncogene encoding a growth factor receptor related to epidermal growth factor receptor (EGFR) and is amplified in approximately 25-30% of node-positive breast cancers. Over-expression of HER-2/neu is associated with decreased disease-free and overall survival. Over-expression of HER-2/neu may be used to identify patients who may be may benefit from trastuzumab (Herceptin™) and/or high dose chemotherapy. Trastuzumab is a humanized monoclonal antibody targeting the HER 2/neu (c-erbB-2) oncogene.

4. Purpose: diagnostic, prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: tumor tissue, serum

7. Methodology: IHC, FISH, EIA

8. Cancers: breast

9. Other cancers: HER2/neu may also be expressed in ovarian, gastric, colorectal, endometrial, lung, bladder, prostate, and salivary gland cancers

10. Clinical use(s):
    a) Routine:
        - assess prognosis of stage II, node positive breast cancer patients
        - predict disease-free and overall survival in patients with stage II, node positive breast cancer treated with adjuvant cyclophosphamide, doxorubicin, 5-fluorouracil chemotherapy
        - determine patient eligibility for Herceptin treatment
        - College of American Pathologists (CAP) recommends FISH as an optimal method for HER2/neu testing; therefore, positive IHC results are usually confirmed by FISH testing
    b) Investigational:
        - HER2/neu may also be expressed in ovarian, gastric, colorectal, endometrial, lung, bladder, prostate, and salivary gland

11. Source of information: Quest Diagnostics, LabCorp, Specialty Labs websites, UpToDate™

12. Exploratory Medline search (5/12/05):
    a) "receptor, erbB-2" = 4028 citations
    b) "receptor, erbB-2" and "breast neoplasms" (55886) = 1905 citations
    c) "receptor, erbB-2" and "ovarian neoplasms" (15334) = 239 citations

1. Test name: **5-HIAA**

2. Other names: 5-hydroxyindoleacetic acid

3. Description: A serotonin analysis is most frequently performed for the diagnosis of carcinoid tumors of the small intestine. These tumors release large amounts of serotonin, which can produce the clinical syndrome of flushing, diarrhea, and right sided heart failure. 5-HIAA is the final metabolite of serotonin and is the most frequently used diagnostic test for carcinoid tumors.

4. Purpose: diagnostic, prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: urine

7. Methodology: liquid chromatography

8. Cancers: carcinoid tumors

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - diagnosis of metastatic carcinoid tumors
    b) Investigational:
        - may be used as a prognostic factor in this disease; however, poor correlation exists between 5-HIAA level and clinical severity of carcinoid syndrome

11. Source of information: LabCorp, UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "Hydroxyindoleacetic Acid" = 1270 citations
    b) "Carcinoid tumor" = 2255 citations
    c) "Hydroxyindoleacetic Acid" and "Carcinoid tumor" = 78 citations

1. Test name: **Human papillomavirus hybrid capture**

2. Other names: HPV, ThinPrep

3. Description: Human papillomavirus (HPV) infection is a common infection that is associated cancer. Although HPV infection does not always progress to cancer, >93% of cervical cancer cases are associated with HPV. This test detects 13 viral strains that are associated with an intermediate to high risk of cancer.

4. Purpose: secondary prevention

5. Availability: commercial laboratories, academic hospitals

6. Specimen: pap smear

7. Methodology: DNA probe cocktail

8. Cancers: cervical cancer

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - determine need for colposcopy in individuals with atypical squamous cells of uncertain significance (ASCUS) found on Pap test
        - assist in guiding patient management (as adjunct to cervical cytology)

11. Source of information: Quest Diagnostics, UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "Papillomavirus, Human" = 6318 citations
    b) "Cervix Neoplasms" = 12280 citations
    c) "Papillomavirus, Human" and "Cervix Neoplasms" 2661 citations

1. Test name: **IgVh mutation analysis**

2. Other names:

3. Description: Chronic lymphocytic leukemia (CLL) patients can be divided into 2 basic groups on the basis of the mutational status of the immunoglobulin heavy-chain variable-region (IgVH) gene in leukemic cells. Patients with IgVH mutations have longer survival than those without IgVH mutation. Thus, mutation analysis may be useful for planning management strategies.

4. Purpose: prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood, marrow

7. Methodology: PCR

8. Cancers: chronic lymphocytic leukemia (CLL)

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - assess prognosis for patients with CLL

11. Source of information: Quest Diagnostics and UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "Immunoglobulin Variable Region" = 3919 citations
    b) "Leukemia, Lymphocytic, Chronic" = 3422 citations
    c) "Immunoglobulin Variable Region" and "Leukemia, Lymphocytic, Chronic" = 126 citations

1. Test name: **ImmunoCyt**

2. Other names: mucin, CEA

3. Description: An immunocytochemistry assay for the detection of tumor cells shed in the urine of patients previously diagnosed with bladder cancer. This test is intended to augment the sensitivity of cytology for the detection of tumor cells in the urine of individuals previously diagnosed with bladder cancer.

4. Purpose: recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: urine

7. Methodology: cytology, ICC

8. Cancers: bladder cancer

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - detection of tumor cells in the urine of individuals previously diagnosed with bladder cancer
        - indicated for use in conjunction with cytoscopy as an aid in the management of bladder cancer

11. Source of information: LabCorp and UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "Carcinoembryonic Antigen" = 2785 citations
    b) "Bladder Neoplasms" = 9483 citations
    c) "Carcinoembryonic Antigen" and "Bladder Neoplasms" = 33 citations

1. Test name: **Kappa/lambda light chain**

2. Other names:

3. Description: Elevated serum levels of monoclonal free light chains are associated with malignant plasma cell proliferation (eg. multiple myeloma), primary amyloidosis and light chain deposition disease. The appearance of higher levels of free light chains in the urine may be indicative of kidney disease or malignant lymphoproliferative disease such as multiple myeloma.

4. Purpose: monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum, tissue, urine

7. Methodology: IHC

8. Cancers: multiple myeloma, lymphoproliferative disorders

9. Other cancers: primary amyloidosis, light chain deposition disease

10. Clinical use(s):
    a) Routine:
        - detection of multiple myeloma

11. Source of information: Quest Diagnostics, UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "immunoglobulins, light chains" = 2376 citations
    b) "multiple myeloma" = 6154 citations
    c) "lymphoproliferative disorders" = 59,066 citations
    d) "immunoglobulins, light chains" and "multiple myeloma" = 258 citations
    e) "immunoglobulins, light chains" and "lymphoproliferative disorders" = 534 citations

1. Test name: **LAP**

2. Other names: leukocyte alkaline phosphatase

3. Description: Low LAP scores have been associated with CML, PNH, and thrombocytopenic purpura. In CML, regardless of the total WBC, the LAP score remains low. High LAP scores have been seen in polycythemia vera, myelofibrosis, aplastic anemia, hairy cell leukemia, leukemoid reactions, and Hodgkin's disease.

4. Purpose: diagnostic, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood, bone marrow

7. Methodology: enzyme assay

8. Cancers: chronic myelocytic leukemia (CML)

9. Other cancers: polycythemia vera, myelofibrosis, aplastic anemia, paroxysmal nocturnal hemoglobinuria, hairy cell leukemia, leukemoid reactions, lymphoma

10. Clinical use(s):
    a) Routine:
        - aids in differential diagnosis of chronic myelocytic leukemia vs. leukamoid reaction
        - aids in evaluation of polycythemia vera, myelofibrosis with myeloid metaplasia, and paroxysmal nocturnal hemoglobinuria

    b) Investigational:
        - serial LAP scores can be a useful adjunct in evaluating the activity in Hodgkin's disease, as well as its response to therapy.

11. Source of information: Quest Diagnostics, UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "alkaline phosphatase " = 7889 citations
    b) "testicular neoplasm " = 4487 citations
    c) "alkaline phosphatase " and "testicular neoplasm" = 34 citations

1. Test name: **Lipid associated sialic acid**

2. Other names: LASA; Lipid-Bound Sialic Acid

3. Description: Elevations in blood LASA levels have been reported in patients with mammary (63%), gastroenteric (65%), pulmonary (79%), and ovarian (94%) neoplasms as well as those with leukemia (86%), lymphoma (87%), melanoma (84%), sarcoma (97%), and Hodgkin disease (91%). As a result, this assay may not have high specificity or sensitivity necessary for cancer detection.

4. Purpose: recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum

7. Methodology: spectrophotometry

8. Cancers: breast, lung, colorectal, pancreas, ovarian, liver, lymphoma, leukemia, melanoma, neuroblastoma, uterine, sarcoma

9. Other cancers:

10. Clinical use(s):
    a) Investigational:
        - monitoring the course of therapy
        - detecting disease recurrence

11. Source of information: LabCorps website

12. Exploratory Medline search (8/02/05):
    a) "lipid associated sialic acid.mp" = 15 citations
    b) "N-acetylneuraminic acid" = 1496 citations
    c) "neoplasms" = 571,042 citations
    d) "lipid associated sialic acid.mp" and "neoplasms" = 9 citations
    e) "N-acetylneuraminic acid" and "neoplasms" = 194 citations

1. Test name: **Melaris**

2. Other names: p16

3. Description: p16 is a tumor suppressor gene that regulates cellular proliferation and growth by acting as a cyclin-dependent kinase 4 (CDK4) inhibitor. This test determines if a patient has a p16 gene mutation, indicating a predisposition for melanoma and pancreatic cancer.

4. Purpose: primary prevention

5. Availability: myriadtests.com

6. Specimen: blood

7. Methodology: PCR

8. Cancers: melanoma, pancreas

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - screening for hereditary melanoma

11. Source of information: Myriad Tests website

12. Exploratory Medline search (8/02/05):
    a) "genes, p16" = 990 citations
    b) "melanoma" = 17,770 citations
    c) "neoplasms, pancreatic" = 12,470 citations
    d) "genes, p16" and "melanoma" = 136 citations
    e) "genes, p16" and "pancreatic neoplasms" = 66 citations

1. Test name: **MIB-1 antibody**

2. Other names: Ki-67 antigen

3. Description: There is a strong correlation between proliferation rate and clinical outcome in a variety of tumor types and measurement of cell proliferative activity is an important prognostic marker. This marker correlates with flow cytometric S-phase

4. Purpose: prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: tissue

7. Methodology: IHC

8. Cancers: breast, lymphomas, anaplastic large cell non-Hodgkin's lymphoma

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - tissue marker for large cell non-Hodgkin's lymphoma
        - assess tumor proliferative rate, determine disease prognosis
        - direct disease management

11. Source of information: Quest Diagnostics, LabCorp, Specialty Laboratories Websites

12. Exploratory Medline search (8/02/05):
    a) "Ki-67 Antigen" = 4840 citations
    b) "Lymphoma, Non-Hodgkin" = 22160 citations
    c) "Ki-67 Antigen" and "Lymphoma, Non-Hodgkin" = 117 citations

1. Test name: **Micrometastasis detection**

2. Other names: cytokeratins

3. Description: Cytokeratins are expressed by both normal and malignant epithelial cells, but not by lymph node or bone marrow cells. Thus, the presence of cytokeratin-positive cells in lymph nodes or the bone marrow is suggestive of metastatic tumor. Multiple chromosomal aberrations in these suspected cytokeratin-positive micrometastases further substantiate that these cells are tumor cells.

4. Purpose: recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: marrow, tissue

7. Methodology: IHC

8. Cancers: breast

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - detect micrometastases of epithelial cell origin (e.g., breast cancer)
        - determine the stage of epithelial cancers
        - predict cancer recurrence/relapse and overall prognosis

11. Source of information: Specialty Laboratories, Quest Diagnostics websites

12. Exploratory Medline search (8/02/05):
    a) "cytokeratin" or "keratin" = 8784 citations
    b) "Breast Neoplasms" = 57603 citations
    c) "Neoplasm Metastasis" = 32119 citations
    d) "cytokeratin" or "keratin" and "Breast Neoplasms" and "Neoplasm Metastasis" = 263 citations

1. Test name: **Microsatellite instability**

2. Other names: MSI, BAT 26, RER+

3. Description: MSI is a marker for faulty DNA repair and is found in 90% of patients with hereditary non-polyposis colorectal cancer (HNPCC) but in only 15% of sporadic colorectal tumors. HNPCC (Lynch syndrome) is characterized by an autosomal dominant inheritance pattern of early-onset predisposition to colorectal cancer (average age 44 years). MSI is helpful in determining if colorectal cancer is due to HNPCC and whether further genetic testing of patients or their family members for HNPCC-associated mutations

4. Purpose: primary and secondary prevention, diagnostic, prognostic

5. Availability: commercial labs, academic institutions

6. Specimen: blood, tumor tissue DNA

7. Methodology: PCR

8. Cancers: hereditary non-polyposis colorectal cancer

9. Other cancers:

10. Clinical use(s):
    b) Investigational:
    - identify colorectal tumors with high microsatellite instability
    - identify individuals at risk for HNPCC
    - identifying HNPCC in affected patients is also important since close surveillance of at-risk family members has been found to reduce the rate of colorectal cancer and overall mortality by >60%

11. Source of information: Quest Diagnostics, LabCorp, Specialty Labs websites, UpToDate™

12. Exploratory Medline search (5/12/05):
    a) "microsatellite repeats" = 15030 citations
    b) "colorectal neoplasms" = 36712 citations
    c) "colorectal neoplasms, hereditary nonpolyposis" = 1318 citations
    d) "microsatellite repeats" and "colorectal neoplasms" = 1217 citations
    e) "microsatellite repeats" and "colorectal neoplasms, hereditary nonpolyposis" = 410 citations

1. Test name: **MLH1, MSH2, MSH6 mutations**

2. Other names: HNPCC mismatch repair gene

3. Description: About 90% of individuals with HNPCC have mutations in 1 of 2 mismatch repair (MMR) genes, MLH1 or MSH2. Mutations in MSH6, PMS1, and PMS2 have also been implicated in this malignancy. These genes are responsible for correcting nucleotide base mispairs and small insertions or deletions that occur during DNA replication. The lifetime risk of colorectal cancer in individuals with an MMR gene mutation is about 80%.

4. Purpose: primary prevention

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood

7. Methodology: PCR

8. Cancers: colorectal

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - differentiate hereditary non-polyposis colorectal cancer (HNPCC) from non-HNPCC colorectal cancer
        - assess risk of HNPCC in family members of individuals with HNPCC

11. Source of information: Quest Diagnostics and UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "MLH1" = 1285 citations
    b) "MSH2" = 887 citations
    c) "MSH6" = 294 citations
    d) "colorectal neoplasm" = 37826 citations
    e) ("MLH1" or "MSH2" or "MSH6") and "colorectal neoplasms" = 792 citations

1. Test name: **Neuron specific enolase**

2. Other names: NSE

3. Description: NSE is a glycolytic enzyme that catalyzes the conversion of phosphoglycerate to phosphoenol pyruvate. Elevated NSE concentrations are observed in patients with neuroblastoma, pancreatic islet cell carcinoma, medullary thyroid carcinoma, pheochromocytoma and other neuroendocrine tumors. Additionally, NSE levels are frequently increased in patients with small cell lung cancer (SCLC) and infrequently in patients with non-SCLC.

4. Purpose: monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum

7. Methodology: RIA

8. Cancers: lung, pancreas

9. Other cancers: neuroblastoma, carcinoma, medullary thyroid carcinoma, pheochromocytoma and other neuroendocrine tumors

10. Clinical use(s):
    a) Routine:
        - monitor disease progression and therapy in individuals with small cell lung cancer
        - monitor effectiveness of therapy in various other cancers

11. Source of information: Specialty Laboratories, Quest Diagnostics Websites

12. Exploratory Medline search (8/02/05):
    a) "neuron specific enolase" = 1577 citations
    b) "lung neoplasms" = 37232 citations
    c) "neuron specific enolase" and "lung neoplasms" = 223 citations

1. Test name: **Nuclear matrix proteins**

2. Other names: NMP 22

3. Description: Nuclear matrix proteins (NMPs) are associated with functions such as DNA replication and RNA synthesis. Identification of increased concentrations of NMP 22 can aid in the management of patients with transitional cell carcinoma of the urinary tract and also in the differential diagnosis of persons with symptoms or risk factors for transitional cell carcinoma of the bladder

4. Purpose: diagnostic, recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: urine

7. Methodology: EIA

8. Cancers: bladder

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - diagnosis of bladder cancer
        - monitor patients for bladder cancer recurrence

11. Source of information: Quest Diagnostics, LabCorp websites

12. Exploratory Medline search (8/02/05):
    a) "nuclear matrix-associated proteins"= 830 citations
    b) "NMP 22" = 25 citations
    c) "bladder neoplasms" = 9483 citations
    d) "NMP 22" and "neoplasms, bladder" = 23 citations
    e) "nuclear matrix-associated proteins" and "bladder neoplasms" = 3 citations

1. Test name: **Oncotype DX™**

2. Other names: breast cancer assay

3. Description: Oncotype DX is an assay that quantifies the likelihood of breast cancer recurrence in women with newly diagnosed, stage I or II, node negative, estrogen receptor positive breast cancer who will be treated with Tamoxifen. The assay analyzes the expression of a panel of 21 genes and the results are provided as a Recurrence Score™ (0-100). Using the Recurrence score, patients are classified into low, intermediate, and high risk categories for likelihood of disease recurrence.

4. Purpose: prognostic

5. Availability: limited commercial availability via Genomic Health (Redwood City, CA), academic institutions participating in clinical trials

6. Specimen: tumor tissue RNA

7. Methodology: PCR

8. Cancers: breast

9. Other cancers:

10. Clinical use(s):
    a) Investigational:
        - to assess risk of recurrence in certain breast cancer patients and thus aid in treatment planning

11. Source of information: Genomic Health website and promotional material

12. Exploratory Medline search (5/12/05):
    a) "gene assay" = 599 citations
    b) "breast neoplasms" = 55,886 citations
    c) "gene assay" and "breast neoplasms" = 33 citations
    d) "oncotype dx" or "oncotype" = 4 citations
    e) company website = 11 citations: 2 publications, 9 abstracts

1. Test name: **p53 tumor suppressor gene**

2. Other names: p53

3. Description: p53 is a tumor suppressor gene and normally has an inhibitory influence on the cell cycle. Once this gene is deleted or its function reduced, normal control mechanisms are altered. Alterations of the p53 tumor suppressor gene have been shown to serve as a powerful prognostic marker in a wide variety of tumor types such as colorectal, breast, prostate, and bladder. Additionally, alterations of p53 are associated with tumor recurrence and shorter disease-free survival.

4. Purpose: prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: tissue

7. Methodology: IHC

8. Cancers: breast, prostate, colorectal

9. Other cancers: bladder

10. Clinical use(s):
    a) Routine:
        - determine prognosis in patients with colorectal, breast, prostate, bladder cancers
        - predict disease recurrence
        - predict disease free survival

11. Source of information: Quest Diagnostics, LabCorp, and UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "genes, P53" = 7910 citations
    b) "colonic neoplasms" = 15,654 citations
    c) "genes, P53" and "colonic neoplasms" = 276 citations

1. Test name: **PML/RARA translocation**

2. Other names: t(15;17)

3. Description: More than 99% of (acute promyelocytic leukemia) APL patients harbor a translocation between chromosomes 15 and 17, which fuses the retinoic acid receptor alpha (RARA) gene on chromosome 17 with the PML gene on chromosome 15. Historically one of the most lethal forms of acute myeloid leukemia, APL leads to disseminated intravascular coagulation and death when not diagnosed and treated. Treatment with all-trans-retinoic acid substantially improves survival in patients who have failed anthracycline chemotherapy or for whom anthracycline is contraindicated.

4. Purpose: diagnostic, prognostic, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood, marrow

7. Methodology: PCR

8. Cancers: acute promeylocytic leukemia

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - diagnosis of acute promyelocytic leukemia (APL)
        - predict response to all-trans-retinoic acid or arsenic trioxide therapy
        - assess effectiveness of therapy
        - detection of minimal residual disease (MRD)
        - predict early relapse

11. Source of information: Quest Diagnostics, UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "translocation, genetic" = 7693 citations
    b) "leukemia, promyelocytic, acute" = 1954 citations
    c) "translocation, genetic" and "leukemia, promyelocytic, acute" = 274 citations

1. Test name: **PreGen-26**

2. Other names: MSI, BAT-26

3. Description: Isolates human DNA in stool and detects microsatellite instability usually associated with HNPCC and in a subset of sporadic colorectal cancers. PreGen-26 identifies alterations in the BAT-26 mononucleotide marker, believed to be the most frequent alteration found in tissue in HNPCC. BAT-26 microsatellite instability is present in as many as 90% of the colorectal cancers that occur in patients with HNPCC. PreGen-26 results can help to determine which patients are likely to have the presence of cancer with BAT-26 MSI.

4. Purpose: primary and secondary prevention, monitoring

5. Availability: LabCorp

6. Specimen: stool DNA

7. Methodology: PCR

8. Cancers: colorectal

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - adjunct to colonoscopy for monitoring patients with HNPCC and family members of patients with HNPCC
        - may be used as an alternative method to monitor patients with known or suspected HNPCC syndrome who are non-compliant with current screening recommendations

11. Source of information: Exact Sciences, LabCorp websites

12. Exploratory Medline search (8/02/05):
    a) "microsatellite repeats" = 15,424 citations
    b) "colorectal neoplasms" = 37,826 citations
    c) "microsatellite repeats" and "colorectal neoplasms" = 1265 citations

1. Test name: **PreGen-Plus™**

2. Other names: DNA-based colorectal cancer test

3. Description: PreGen-Plus is a noninvasive screening test designed to detect clinically significant colorectal cancer. PreGen-Plus consists of a panel of 23 individual tests, each looking for the presence of mutations in human DNA isolated from stool. Three distinct technologies look for the presence of mutations in the k-ras oncogene, the APC and p53 tumor suppressor genes, shortened forms of BAT-26 (microsatellite instability), and a novel marker for disordered apoptosis.

4. Purpose: secondary prevention, monitoring

5. Availability: developed by EXACT Sciences, available commercially at LabCorp exclusively

6. Specimen: stool DNA

7. Methodology: PCR

8. Cancers: colorectal

9. Other cancers:

10. Clinical use(s):
    b) Investigational:
        - detection of clinically significant colorectal neoplasia in asymptomatic, average-risk patients 50 years old and older
        - an adjunctive test for those patients who receive an fecal occult blood test (FOBT), flexible sigmoidoscopy, or colonoscopy
        - may enhance current methods for early detection of colorectal cancer

11. Source of information: Exact Sciences, LabCorp websites

12. Exploratory Medline search (5/12/05):
    a) "genes, ras" or "genes, apc" or "genes, p53" or "microsatellite, repeats" = 26861 citations
    b) "colorectal neoplasms" = 36712 citations
    c) "feces" and "DNA" = 1162 citations
    d) "feces" and "DNA" and "colorectal neoplasms" = 62 citations
    e) a) and d) = 25 citations

1. Test name: **Prostate Specific Antigen**

2. Other names: PSA: free, total, ultra-sensitive, with HAMA

3. Description: PSA is elevated in about 30% of all cases with nodular prostatic enlargement. Circulating PSA exists as two major forms: complexed and free. Bound PSA is found in higher concentrations in patients with prostate cancer and free-PSA concentrations are higher in patients with Benign prostatic hypertrophy (BPH). PSA can be used to aid in the management of patients following surgical or medical treatment for prostate cancer.

4. Purpose: secondary prevention, prognostic, recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood

7. Methodology: ICMA, IRMA, EIA, MEIA

8. Cancers: prostate

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - detection of early prostate cancer
        - improve accuracy of staging prior to surgery
        - monitor patient response to therapy
        - detect disease recurrence

11. Source of information: Quest Diagnostics, Specialty Labs, Abbott Diagnostics, UpToDate

12. Exploratory Medline search (8/02/05):
    a) "prostate-specific antigen" = 7096 citations
    b) "prostatic neoplasms" = 25,690 citations
    c) "prostate-specific antigen" and "prostatic neoplasms" = 6084 citations

1. Test name: **T-cell receptor gene rearrangement**

2. Other names:

3. Description: Study intended to provide some evidence that can help to distinguish between benign lymphadenopathy and malignant lymphoma. Specifically used to detect clonal gene rearrangements in the T-cell receptor beta-chain constant region. The presence of a monoclonal gene rearrangement usually, but not always, reflects the presence of a T-lymphocytic neoplasm while polyclonal gene rearrangement patterns are found in benign reactive conditions.

4. Purpose: diagnostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood, marrow, tissue

7. Methodology: Southern blot analysis

8. Cancers: T-cell malignancies, lymphomas and leukemias

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - diagnosis of T-cell malignancies
        - leukemia and lymphoma lineage determination for prognosis and treatment selection
        - detection of minimal residual disease or recurrent disease

11. Source of information: LabCorp and UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "Gene Rearrangement, T-Lymphocyte" = 1735 citations
    b) "Lymphoma, T-Cell" = 4837 citations
    c) "Gene Rearrangement, T-Lymphocyte" and "Lymphoma, T-Cell" = 303 citations

1. Test name: **TEL/AML 1 gene fusion**

2. Other names: t(12;21)

3. Description: The TEL/AML1 is a gene fusion resulting from a t(12;21)(p13;q22) chromosomal translocation. Although it occurs in only about 3% of adult acute lymphoblastic leukemia (ALL) cases, it is the most common genetic rearrangement in B-lineage pediatric ALL (frequency ~25%). The TEL/AML1 gene fusion is associated with a more favorable prognosis as evidenced by a significantly lower relapse rate.

4. Purpose: diagnostic, prognostic, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood, marrow

7. Methodology: FISH

8. Cancers: leukemia, acute lymphoblastic leukemia

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - differential diagnosis of acute lymphoblastic leukemia (ALL)
        - determine prognosis of patients with ALL
        - monitor patients with ALL

11. Source of information: Quest Diagnostics, UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "Oncogene Proteins, Fusion" = 3798 citations
    b) "Leukemia, Lymphocytic, Acute" = 7786 citations
    c) "Oncogene Proteins, Fusion" and "Leukemia, Lymphocytic, Acute" = 453 citations

1. Test name: **Thyroglobulin**

2. Other names:

3. Description: Thyroglobulin is elevated in differential thyroid tumors. Thyroglobulin is a tumor marker useful to assess the presence of residual papillary-follicular carcinoma of thyroid, following resection, including tumors that fail to concentrate radioiodine. Additionally, thyroglobulin assays are used to monitor postoperative thyroid carcinoma patients.

4. Purpose: recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum

7. Methodology: ICMA

8. Cancers: thyroid carcinoma

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - detection of residual disease following resection
        - monitor therapeutic response
        - detect disease recurrence

11. Source of information: LabCorp and UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "Thyroglobulin" = 1501 citations
    b) "Thyroid neoplasms" = 9062 citations
    c) "Thyroglobulin" and "Thyroid neoplasms" = 578 citations

1. Test name: **Tumor antigen 90 immune complex**

2. Other names: TA90-IC

3. Description: TA90 is a 90-kd tumor-associated antigen that is expressed by >70% of melanomas. After curative resection of malignant melanoma, patients with occult metastasis may exhibit elevated levels of a TA90-IgG immune complex. TA90-IC is a sensitive and specific marker of recurrence in patients with malignant melanoma and is associated with shortened survival.

4. Purpose: prognostic, recurrence, monitoring

5. Availability: commercial laboratories, academic hospitals

6. Specimen: serum

7. Methodology: EIA

8. Cancers: melanoma

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - assess prognosis after curative resection of malignant melanoma
        - monitor patients for melanoma recurrence after curative resection

11. Source of information: Quest Diagostics and UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "Melanoma" = 17,770 citations
    b) "Antigens, Neoplasm" = 25,465 citations
    c) "Melanoma" and "Antigens, Neoplasm" = 1128 citations

1. Test name: **Urokinase plasminogen activator**

2. Other names: uPA, PAI-1 (plasminogen activator inhibitor)

3. Description: The serine protease urokinase-type plasminogen activator (uPA) and its primary inhibitor, plasminogen activator inhibitor-1 (PAI-1), have shown promise for risk assessment and prediction of therapeutic response in primary breast cancer. High levels of uPA or PAI-1 in primary tumor tissue are associated with an aggressive disease course and poor prognosis in both node-positive and node-negative breast cancer.

4. Purpose: prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: tissue

7. Methodology: EIA

8. Cancers: breast

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - assess risk of breast cancer recurrence after primary treatment
        - assess need for adjuvant therapy in women with lymph node-negative breast cancer
        - predict therapeutic response to adjuvant chemotherapy

11. Source of information: Quest diagnostics

12. Exploratory Medline search (8/02/05):
    a) "Plasminogen Activator Inhibitor 1" = 3320 citations
    b) "Urinary Plasminogen Activator" = 3442 citations
    c) "Breast Neoplasms" = 57,603 citations
    d) "Plasminogen Activator Inhibitor 1" and "Breast Neoplasms" = 142 citations

1. Test name: **Urovysion**

2. Other names: Vysis Urovision

3. Description: Detects chromosomal abnormalities associated with the development and progression of bladder cancer. Specifically, this test detects aneuploidy of chromosomes 3, 7, 17, and loss of the 9p21 locus. It detects high grade pT1 and pTis tumors that can be overlooked with traditional diagnostic methods and have high progression rates to muscle-invasive cancer

4. Purpose: recurrence

5. Availability: commercial laboratories, academic hospitals

6. Specimen: urine

7. Methodology: FISH

8. Cancers: bladder

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - detection of bladder cancer recurrence

11. Source of information: Quest Diagnostics, Urovision, and UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "Urovysion" = 17 citations
    b) "Bladder Neoplasms" = 9483 citations
    c) "Urovysion" and "Bladder Neoplasms" = 16 citations

1. Test name: **ZAP-70**

2. Other names:

3. Description: ZAP-70 is a 70-kD member of the Syk family of protein tyrosine kinases. It is expressed primarily in T-cells and natural killer (NK) cells and is critical for signal transduction following T-cell receptor engagement. In CLL B-cells, elevated ZAP-70 expression appears to predict the need for therapy as effectively as IgVH mutation status. Although ZAP-70 expression is strongly correlated with IgVH mutation status, the combination of the 2 markers may provide greater prognostic value than either marker alone. Positive ZAP-70 results predict an aggressive disease course.

4. Purpose: prognostic

5. Availability: commercial laboratories, academic hospitals

6. Specimen: blood, marrow

7. Methodology: flow cytometry

8. Cancers: CLL

9. Other cancers:

10. Clinical use(s):
    a) Routine:
        - assess prognosis and need for aggressive therapy in patients with chronic lymphocytic leukemia (CLL)

11. Source of information: Quest Diagnostics and UpToDate websites

12. Exploratory Medline search (8/02/05):
    a) "Protein-Tyrosine Kinase" = 45983 citations
    b) "Leukemia, Lymphocytic, Chronic" = 3422 citations
    c) "Protein-Tyrosine Kinase" and "Leukemia, Lymphocytic, Chronic" = 62 citations

Database III

GENETIC TESTS FOR CANCER

Database of genetic tests in development

Name	Other name	Use	breast	prostate	lung	colorectal	pancreas	ovarian	esophogus	liver	lymphoma	leukemia	other
AFP-L3		primary prevention								x			
alpha Catenin	methylation marker	prognosis	x										
APC		detection				x							
BAT-26	microsatallite instability	detection				x							
bladder cancer test		diagnosis											x
BladderChek	NMP22	diagnosis											x
Breast Cancer Detection	Nipple Aspirate Fluid	diagnosis	x										
Breast Cancer Outcome Prediction Test	PIX2/TTF1	diagnosis	x										
Cancer antigen 72-4	CA 72-4	diagnosis											x
CDK family	cyclin dependent kinase family	management			x								
CDKN24	methylation marker	detection				x							
CDP/Cux		diagnosis	x										
CellSearch	circulating tumor cells	diagnosis	x										
CeMines CellCorrect Lab		diagnosis			x								
chromosome 8q gain		management						x					
c-Kit pharmDx	Gleevec sensitivity test	management											x
colorectal cancer test		diagnosis				x							
colorectal gene panel	7 gene pharmacogenomic panel	management				x							
Colorectalert		diagnosis				x							
Conversion Analysis	Conversion Technology	diagnosis				x							
Cox-2 RNA	stool	detection				x							
cPSA	complexed PSA	management		x									
CupPrint		management											x
Cyfra 21-1	cytokeratin fragment 19	diagnosis			x								
Cytokeratin 20	CK 20	diagnosis				x							
CytoVision		diagnosis										x	
des-gamma carboxyprothrombin		detection								x			
DNA methylation	Oncomethylome	detection		x	x			x					x
DNA methylation	Second Code	diagnosis		x	x	x							
EEF1A2	elongation factor	management	x										
EGFR	Genzyme	detection			x			x					x
EGFR		management			x								
EPCA		diagnosis		x									
eTag		management	x		x								

Name	Other name	Use	breast	prostate	lung	colorectal	pancreas	ovarian	esophogus	liver	lymphoma	leukemia	other
Genomic Test	3q, 7q, 16q, 17pter-q21	diagnosis						x					
GOS	stool	detection				x							
GSTM1		prediction			x								
GSTP1		management		x									
Her-1, Her-2, Her-3, Her-4		diagnosis	x										
HLA-E		prognosis											x
HP1alpha		management	x										
HPV test	DNA with Pap Test	diagnosis											x
HPV test	human papilloma virus cell swab	diagnosis											x
IGF-II		prediction											x
IMI breast cancer test		diagnosis	x										
Immunocyt/ uCyt		diagnosis											x
Iressa test		management			x								
Key2		diagnosis	x										
K-ras		detection			x	x							
Leukemia Affymetrix Chip		diagnosis										x	
Leukemia blood test	MRD test	recurrence										x	
lung cancer test		diagnosis			x								
lung cancer test	Electronic Nose	diagnosis			x								
LungAlert		diagnosis			x								
lysophopholipids	LPA	detection						x					
M2-PK		primary prevention				x							
MammaPrint		management	x										
matrix metalloproeinases	MMP	detection						x					
Melanoma inhibiting antigen	MIA	diagnosis											x
melastatin	mRNA expression	management											x
MESOMARK		diagnosis											x
MGMT	methylation marker	detection				x							
Microsatelitte Analysis	Urine MicroSatellite Analysis	detection											x
MLH1	methylation marker	detection				x							
MN protein		detection						x					
MSA		management											x
MSA analysis	microsatellite DNA	diagnosis											x
NAF test		diagnosis	x										

Name	Other name	Use	breast	prostate	lung	colorectal	pancreas	ovarian	esophogus	liver	lymphoma	leukemia	other
NMP179		diagnosis											x
NMP22	Matritek's Bladderchek test	detection											x
NMP35		diagnosis				x							
NMP48		diagnosis		x									
NMP66		diagnosis	x										
OncoVue breast cancer risk test	Tagit	primary prevention	x										
Ovacheck		diagnosis						x					
ovarian cancer biomarker test		diagnosis						x					
ovarian cancer test		diagnosis						x					
ovarian cancer test	Ovarian Cancer Prognostic Profile	management						x					
ovarian pap test		detection						x					
p16, p15, p14 deletions		management										x	x
p202		management		x									
p53 Affymetrix Chip		diagnosis	x										
Prostate 63	AsymmetRx	management		x									
prostate biomarkers		management		x									
Prostate Cancer Blood Test	ProteomeDx	diagnosis		x									
Protein Profile test	lysophosphatidic acid (LPA)	recurrence						x					
PSA testing	in office	diagnosis		x									
PSMA	prostate specific membrane antigen	management		x									
PSP94	prostate secratory protein	diagnosis		x									
PTEN tumor suppressor		management		x									
PyloriProbe	DR70	diagnosis				x							
Recaf	alpha feto protein receptor	diagnosis	x	x	x	x							
RhoC GTPase		management	x										
S100		diagnosis											x
SELDI-TOF-MS	molecular profiling using SELDI	management	x	x	x			x					
SurePath		diagnosis											x
telomerase	hTR, HTerRT	diagnosis											x
TGF genes		prognosis	x										
TUO test		diagnosis											x
uPM3	PCA3 assay	diagnosis		x									
urinary plasminogen activator	suPAR	detection						x					
urine test for cervical cancer		diagnosis											x
VEGF		management				x							
WISP3		management	x										

Name	other cancer	Developer	Data source
AFP-L3		Wako	LexisNexis
alpha Catenin			EDRN
APC			EDRN
BAT-26			EDRN
bladder cancer test	bladder	ChondroGene, MSKCC	LexisNexis
BladderChek	bladder	M.D. Anderson C.C, Matritech Inc.	LexisNexis
Breast Cancer Detection		IMI International	CHI
Breast Cancer Outcome Prediction Test		Epigenomics, Roche Diagnostics	LexisNexis
Cancer antigen 72-4	stomach	Roche Diagnostics	Roche Diagnostics
CDK family		M.D. Anderson	LexisNexis
CDKN24			EDRN
CDP/Cux		DiagnoCure, McGill U.	LexisNexis
CellSearch		Immunicon, Veridex. Quest Diagnostics	LexisNexis, CHI
CeMines CellCorrect Lab		CeMines	LexisNexis
chromosome 8q gain			clinicaltrials.gov
c-Kit pharmDx	GIST	DakoCytomation	LexisNexis
colorectal cancer test		Microprevention Tests	LexisNexis
colorectal gene panel		Quest diagnostics	LexisNexis
Colorectalert		IMI Medical	LexisNexis, CHI
Conversion Analysis		GMP Companies, Cleveland Clinic	LexisNexis
Cox-2 RNA			EDRN
cPSA			FDA
CupPrint	tumor of unknown origin	Agendia	LexisNexis
Cyfra 21-1		Roche Diagnostics	Roche Diagnostics
Cytokeratin 20		Roche Diagnostics	Roche Diagnostics
CytoVision		Applied Imaging Corp	LexisNexis
des-gamma carboxyprothrombin			EDRN
DNA methylation	kidney		google news, CHI
DNA methylation		Orion Genomics, Methexis, Roche, Sequenom	LexisNexis, CHI
EEF1A2			CISTI
EGFR	cervical, endometrial		EDRN, clinicaltrials.gov, CHI
EGFR		Genzyme, DFCI, MGH	LexisNexis
EPCA		Tessera, Johns Hopkins U	LexisNexis
eTag		ViroLogic, AstraZeneca	LexisNexis, CHI

Name	other cancer	Developer	Data source
Genomic Test			clinicaltrials.gov
GOS			EDRN
GSTM1			google news
GSTP1			EDRN, google news
Her-1, Her-2, Her-3, Her-4		Roche Diagnostics	Roche Diagnostics
HLA-E	gliomas		google news
HP1alpha			CISTI
HPV test	cervical	Diagene, GenoID	LexisNexis
HPV test	cervical	Roche Diagnostics	Roche Diagnostics
IGF-II	cervical, endometrial		EDRN
IMI breast cancer test		IMI Medical	LexisNexis
Immunocyt/ uCyt	bladder	DiagnoCure, Gen-Probe	LexisNexis
Iressa test		U of Tokyo, AstraZeneca	LexisNexis
Key2		Exagen	LexisNexis
K-ras			EDRN
Leukemia Affymetrix Chip		Roche Diagnostics	Roche Diagnostics
Leukemia blood test		Genzyme	CHI
lung cancer test		Cangen Biotech, Olympus	LexisNexis
lung cancer test		Cleveland Clinic	LexisNexis
LungAlert		IMI Medical	LexisNexis
lysophopholipids			clinicaltrials.gov
M2-PK		Giessen U	LexisNexis
MammaPrint		Agendia, Transbig, Molecular Profiling Institute	LexisNexis
matrix metalloproeinases			clinicaltrials.gov
Melanoma inhibiting antigen	melanoma	Roche Diagnostics	Roche Diagnostics
melastatin	melanoma		clinicaltrials.gov
MESOMARK	mesothelioma	Fujirebio Diagnostics	LexisNexis
MGMT			EDRN
Microsatelitte Analysis	bladder		clinicaltrials.gov
MLH1			EDRN
MN protein			clinicaltrials.gov
MSA	bladder		EDRN, clinicaltrials.gov
MSA analysis	bladder	Cangen Biotech	LexisNexis
NAF test		Power3	LexisNexis

Name	other cancer	Developer	Data source
NMP179	cervical	Matritech Inc.	LexisNexis
NMP22	bladder		FDA/ CHI
NMP35		Matritech Inc.	LexisNexis
NMP48		Matritech Inc.	LexisNexis
NMP66		Matritech Inc.	LexisNexis, CHI
OncoVue breast cancer risk test		Tm Bioscience/ Intergenetics	LexisNexis, CHI
Ovacheck		Quest, LabCorp, Correlogic	LexisNexis
ovarian cancer biomarker test		Ciphergen Biosystems, Johns Hopkins	LexisNexis
ovarian cancer test		Yale U	LexisNexis
ovarian cancer test		Beth Israel Deaconess Medical Center	LexisNexis
ovarian pap test			clinicaltrials.gov
p16, p15, p14 deletions	ALL		clinicaltrials.gov
p202			CISTI
p53 Affymetrix Chip	others	Roche Diagnostics	Roche Diagnostics
Prostate 63			CLIA
prostate biomarkers		Health discovery Corporation/ Stanford U	CHI
Prostate Cancer Blood Test		Correlogic	CHI
Protein Profile test			clinicaltrials.gov
PSA testing		Qualigen, Healthtronics	LexisNexis
PSMA		Cytogen	CHI
PSP94		Procyon, Medicorp	LexisNexis
PTEN tumor suppressor			CISTI
PyloriProbe		AMDL	LexisNexis
Recaf		Abbot, BioCurex	LexisNexis
RhoC GTPase			CISTI
S100	melanoma	Roche Diagnostics	Roche Diagnostics
SELDI-TOF-MS			EDRN
SurePath	cervical	Tripath Imaging	LexisNexis
telomerase	bladder	Roche Diagnostics	Roche Diagnostics
TGF genes			google news
TUO test	tumor of unknown origin	US LABS	LexisNexis
uPM3		DiagnoCure, Gen-Probe	LexisNexis
urinary plasminogen activator			clinicaltrials.gov
urine test for cervical cancer	cervical	U. Washington	LexisNexis
VEGF		Quest	LexisNexis
WISP3			CISTI

Name	Other
AFP-L3	detects AFP-L3 presence
alpha Catenin	
APC	
BAT-26	
bladder cancer test	gene expression profiling in blood cells
BladderChek	urine test for protein NMP22
Breast Cancer Detection	
Breast Cancer Outcome Prediction Test	DNA methylation markers that correlate closely with prostate cancer aggressivness
Cancer antigen 72-4	
CDK family	measures activity of CDK family enzymes which potentially assesses chemotherapy activity
CDKN24	
CDP/Cux	proteins abnormally expressed in breast cancers
CellSearch	circulating tumor cells
CeMines CellCorrect Lab	test detects molecular fingerprints of disease-related autoantibodies in blood
chromosome 8q gain	
c-Kit pharmDx	qualitatively identifies c-kit protein/ CD117 expression
colorectal cancer test	detect surface layer exfoliated epithelial cells
colorectal gene panel	evaluate likelihood of toxicity/response to 5FU, oxaliplatin, irinotecan
Colorectalert	sampling of rectal mucus/ clinical trial with EDRN initiated
Conversion Analysis	improved detection of genetic mutations associated with hereditary cancer
Cox-2 RNA	
cPSA	
CupPrint	gene expression
Cyfra 21-1	
Cytokeratin 20	
CytoVision	autosomal chromosomal analysis using FISH
des-gamma carboxyprothrombin	
DNA methylation	
DNA methylation	detects DNA methylation
EEF1A2	
EGFR	
EGFR	EGFR gene mutations
EPCA	blood test for EPCA
eTag	technology to improve analysis of HER factor family receptor

Name	Other
Genomic Test	
GOS	
GSTM1	
GSTP1	
Her-1, Her-2, Her-3, Her-4	
HLA-E	
HP1alpha	
HPV test	HPV detection with Pap smear, identifies 51 types of HPV
HPV test	
IGF-II	
IMI breast cancer test	identifies cancer associated sugar in nipple aspirate fluid
Immunocyt/ uCyt	urine test for bladder cancer recurrence
Iressa test	determine response to Iressa
Key2	detects changes in DNA copy number
K-ras	
Leukemia Affymetrix Chip	
Leukemia blood test	
lung cancer test	hybrid DNA and protein test for detection of lung cancer
lung cancer test	detects 'smell prints' of numerous organix compounds in exhaled breath
LungAlert	sputum test for lung cancer
lysophopholipids	
M2-PK	M2-PK protein in stool blood
MammaPrint	70 gene expression signature
matrix metalloproeinases	
Melanoma inhibiting antigen	
melastatin	
MESOMARK	blood test for soluble mesothelin related proteins
MGMT	
Microsatelitte Analysis	
MLH1	
MN protein	
MSA	
MSA analysis	urine test using microsatelitte DNA analysis
NAF test	analyses 14 biomarkers found in breats ductal fluid

Name	Other
NMP179	test for protein NMP179
NMP22	
NMP35	blood test for protein NMP35
NMP48	blood test for protein NMP48
NMP66	blood test for protein NMP66
OncoVue breast cancer risk test	breast cancer risk test/ mouthwash DNA test
Ovacheck	genomic blood test for detection of ovarian cancer
ovarian cancer biomarker test	protein array for detecting ovarian cancer
ovarian cancer test	blood test for 4 biomarkers
ovarian cancer test	gene expression profile (115 gene array) for prognosis
ovarian pap test	
p16, p15, p14 deletions	
p202	
p53 Affymetrix Chip	
Prostate 63	
prostate biomarkers	
Prostate Cancer Blood Test	
Protein Profile test	
PSA testing	measures PSA levels
PSMA	
PSP94	blood test for PSP94
PTEN tumor suppressor	
PyloriProbe	quantifies fibrin degradation products in serum by a proprietary antibody
Recaf	potential biomarker for new cancer diagnostic tests
RhoC GTPase	
S100	
SELDI-TOF-MS	
SurePath	biomarkers associated with cervical cancer
telomerase	
TGF genes	
TUO test	gene expression profiling of RNA for classification of Tumors of unknown origin
uPM3	urine test for PCA3 gene and PSA mRNA
urinary plasminogen activator	
urine test for cervical cancer	urine test for high risk cervical cancer
VEGF	predict response to bevacizumab
WISP3	

Tables

GENETIC TESTS FOR CANCER

Grey literature resources: search strategies and results

Table A. Search strategy and results for Category I grey literature resources

Search Tool	Date	Timeframe	Search	Notes	Hits	Reports of Interest	Tests of Interest
LexisNexis (http://www.lexisnexis.com/)	7/8/05	6 months	gene! or geno! and test! and cancer!	Medical News	>1000		
	7/8/05	1 year	gene! or geno! and test! and cancer!	Medical News	>1000		
	7/18/05	1 year	Cancer and gene and test	Medical News	1132	586	17
	7/19/05	1 year	Cancer and test	Business News/ Industry News	1241	147	61
	7/19/05	1 year	Cancer and test	Business news/ Mergers and Acquisition	233	38	22
	7/19/05	1 year	Cancer and test	Business news/ Business and Finance	251	102	41
	7/19/05	1 year	Cancer and test	Business news/ Knight Ridder	94	6	1
Cambridge Health Tech Institute (CHI) (http://www.healthtech.com/)	7/26/05	3 months	Cancer	limit to oncology	466	36	13
	7/11/05	3 months	Cancer, test	limit to oncology	26	14	9
	7/11/05	3 months	Cancer, test, gene	limit to oncology	2	2	2

Table B. Search strategy and results for Category II grey literature resources

Search Tool	Date	Timeframe	Search terms	Notes	Hits	Reports of interest	Tests of interest
Google (www.news.google.com)	7/14/05	past 30 days	Cancer		59,200		
	7/14/05	past 30 days	Cancer, test		4,010		
	7/14/05	past 30 days	Cancer, test, gene		267	7	5
Canadian Institute of Scientific and Technical Information (CISTI) (http://cisti-icist.nrc-cnrc.gc.ca/main_e.html)	7/14/05	2004-2005	Cancer		14,780		
	7/14/05	2004-2005	Cancer, test		977		
	7/14/05	2004-2005	Cancer, test, gene		255	8	0
Clinical Laboratory Improvement Amendments (CLIA) (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/Search.cfm)	7/11/05	Since 2000	Cancer	Simple search	63	1	1
	7/11/05	Since 2000	Cancer, test	Simple search	0		
Office of In Vitro Diagnostics (OIVD) (http://www.fda.gov/cdrh/oivd/consumer-otcdatabase.html)	7/11/05		Cancer	Captures tests already available (Part I)	69	0	0
	7/11/05		Cancer, test		16	0	0
	7/11/05		Cancer, test, gene		2	0	0

Search Tool	Date	Timeframe	Search terms	Notes	Hits	Reports of interest	Tests of interest
FDA pre-market approval (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm)	7/11/05		Cancer	Simple search	124	2	2
	7/11/05		Cancer, test	Simple search	32	0	0
	7/11/05		Cancer, test, gene	Simple search	0		
Early Detection Research Network (EDRN) (http://www3.cancer.gov/prevention/cbrg/edrn/)	March 2005		Biomarkers, Phase II or greater developmental status	Summary tables by organ site from the Third Report, March 2005		75	14
ClinicalTrials.gov (http://www.clinicaltrials.gov)	7/12/05		Cancer		2588	*	
	7/12/05		Cancer, test		347	43	11
	7/12/05		Cancer, test, gene		57	0	0
Computer Retrieval of Information on Scientific Projects (CRISP) (http://crisp.cit.nih.gov/)	7/13/05	From 1972	Cancer		10,582	*	
	7/13/05	From 1972	Cancer, test		2661	*	
	7/15/05	From 1972	Cancer, test, genetic		969	165	*
National Research Register (NRR) (http://www.nrr.nhs.uk/search.htm)	7/11/05		Cancer		20,835	*	
	7/11/05		Cancer, test		1212	*	
	7/11/05		Cancer, test, gene		79	0	0

* Further data extraction was discontinued (see Methods for detailed explanation for each individual resource)

Search Tool	Date	Timeframe	Search terms	Notes	Hits	Reports of interest	Tests of interest
FirstSearch (OCLC) (http://www.oclc.org/firstsearch/)	7/26/05	2004-2005	Cancer	PaperFirst- titles only	47,181	*	
	7/26/05	2004-2005	Cancer, test		141	*	
	7/26/05	2004-2005	Cancer, test, gene		1	0	0
ISI Web of Knowledge (http://www.thomsonisi.com/)	7/18/05	year to date	Cancer	Cross Search searches patents and scientific abstracts	96,230	*	
	7/18/05	year to date	Cancer, test		3751	*	
	7/18/05	year to date	Cancer, test, gene		610	*	
Health Technology Assessment (http://www.york.ac.uk/inst/crd/htahp.htm)	7/11/05		Cancer, test, genetic	no limits. TA contain clinical data	745	*	
			Cancer, test, genetic	Data Abstracts of Reviews of Effects and Health Assessment Technology Database	213	*	
NY Academy of Medicine (http://www.nyam.org/)	7/11/05		Cancer	keyword limited to Gray Literature	135	1	0
	7/11/05		Cancer, test		3	0	0
	7/11/05		Cancer, test, gene		0	0	0

* Further data extraction was discontinued (see Methods for detailed explanation for each individual resource)

Search Tool	Date	Timeframe	Search terms	Notes	Hits	Reports of interest	Tests of interest
GrayLit Network (http://graylit.osti.gov/)	7/11/05		Cancer	Limit to DTIC and DOE databases	200	*	
	7/26/05		Cancer, test	Limit to DTIC and DOE databases	7	1	0
	7/11/05		Cancer, test, gene	Limit to DTIC and DOE databases	248	*	
Health Services Research Projects in Progress (HSRProj) (http://www.academyhealth.org/hsrproj/search.htm)	7/11/05		Cancer		494	*	
	7/11/05		Cancer, test		115	0	0
	7/11/05		Cancer, test, gene		0	0	0

* Further data extraction was discontinued (see Methods for detailed explanation for each individual resource)

Table C. Category III grey literature resources

Search Tool	Description	Notes
National Guidelines Clearinghouse (www.guideline.gov)	A public resource for evidence-based clinical practice guidelines	Guidelines are formed from clinical and analytical utility data. Tests that are in development do not yet have this data available
Networked Digital Library of Theses (http://www.ndltd.org/index.en.html)	Organization dedicated dissemination and preservation of electronic analogues to the traditional paper-based theses and dissertations	Theses are preliminary reports from academic research programs. The majority are not commercially active and those that are will be seen in other reports
System for Information on Grey Literature in Europe (SIGLE) (http://www.york.ac.uk/services/library/guides/sigle.htm)	Computerized index to reports and other grey literature produced in Europe	Grey Literature search tool that requires a subscription
TheseNet (http://www.sudoc.abes.fr/)	French Theses collection. Now called Systeme Universitaire de Documentation.	Non-English.
AMICUS (National Library of Canada) (http://amicus.collectionscanada.ca/aaweb/aalogine.htm)	Canadian national library catalogue	Library holdings overlap significantly with Medline and reports contained therein are based on clinical and analytical data
Australian National Library Catalog (http://catalogue.nla.gov.au/)	Australian national library catalogue	Library holdings overlap significantly with Medline and reports contained therein are based on clinical and analytical data
CABOT (Canadian Research Database) (http://cahspr.ca/cabot/)	Canadian research database.	This website had a nonfunctional search tool.

Search Tool	Description	Notes
British Library (http://www.bl.uk/)	British library catalogue	Library holdings overlap significantly with Medline. Similar to searching NLM
FDA OIVD new products (http://www.fda.gov/cdrh/oivd/consumer-otcdatabase.html)	New OIVD products as of 7/1/05	Web site still under construction
National Library of Medicine's LocatorPlus (http://locatorplus.gov/)	Search for book, journal and audiovisual titles in the NLM collections	Searches NLM. This source will return a similar dataset to other library holdings
Database of Abstracts of Reviews of Effects (DARE) (http://www.york.ac.uk/inst/crd/darehp.htm)	Structured abstracts of quality-assessed reviews	Included in HTA database search above
CMA Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp)	Canadian Clinical Practice Guidelines.	Guidelines are formed from clinical and analytical utility data. Tests that are in development do not yet have this data available
BIREME Databases (http://www.bireme.br/bvs/bireme/I/homepage.htm)	Scientific and technical health information with the countries and among the countries of the Latin America and the Caribbean region	We are only interested in Health Sciences Section. The search tools used are Medline and LILACS.
Search Adobe PDF Online (http://www.searchpdf.adobe.com)	Searches PDF files on line	Nonfunctional search tool
DIMDI databases (http://www.dimdi.de/static/en/db/recherche.htm)	German Institute of Medical documentation and information.	Not In English and uses Medline
DIRLINE (http://dirline.nlm.nih.gov/)	Directory of Health Organizations Online.	Not applicable to our report. Organized by National Library of Medicine

Search Tool	Description	Notes
Directory of Database of Research (JAPAN) (http://read.jst.go.jp/EN/)	Listing of research taking place in Japan.	Reports similar to those of Medline
Dissertation Abstracts (http://library.dialog.com/bluesheets/html/bl0035.html)	Subject, title, and author guide to virtually every American dissertation accepted at an accredited institution since 1861.	Dissertations are preliminary reports from academic research programs. Utility of dissertations for purposes of this report is unclear.
ERIC database (http://www.eric.ed.gov/)	Education literature.	Not applicable to our report
DrugResearcher.com (http://www.drugresearcher.com/)	Drug development in Europe.	This site is not directed towards biomarker development and thus is not applicable to our report.
ThePinkSheet.com (http://www.thepinksheet.com)	Prescription pharmaceuticals and biotechnology information.	A subscription is needed for information beyond the title
Reuters Health (www.reutershealth.com)	Supplier of health and medical news on the Internet	A subscription is needed for information beyond the title