

Molecular Testing in the Community Oncology Setting
Annotated Bibliography

Molecular Oncology Testing: *Annotated Bibliography*

Literature review databases: (PubMed, CINAHL, Health and Psychosocial Instruments, Google Scholar, Cochrane Review, PsycInfo) and hand search of bibliographies.

Sample of keywords searched: *oncology, molecular testing, biomarkers, barriers, quality, measures, metrics, indicators, quality improvement, personalized medicine, decision-making, companion diagnostics, clinical utility, policy, genetic testing.*

Only a handful of published articles are substantially relevant (most dealt with clinical aspects of molecular testing in oncology which was beyond the scope of this project).

The following articles bearing some relevance are organized by date of publication and then alphabetically by author.

The overriding themes of the articles presented include the following, although some articles cover multiple concerns:

- Barriers to Molecular Testing in Oncology
- Environmental Barriers to Personalized Medicine
- Clinical Utility and Decision-Making
- Quality Assurance and Quality Improvement
- Regulatory and Reimbursement Issues
- Efficiency and Effectiveness
- Economics and Cost Implications.

1. Cohen J, Wilson A, Manzillo K. Clinical and economic challenges facing pharmacogenomics. *Pharmacogenomics J.* 2012 Jan 10; doi:10.1038/tpj.2011.63. [Epub ahead of print]

In this paper, Cohen and colleagues examine the clinical and economic challenges that face developers of and payers for personalized drugs and companion diagnostics. They review and summarize clinical, regulatory and reimbursement issues with respect to eight, high profile personalized medicines and their companion diagnostics. Subsequently, they determine Medicare parts B and D reimbursement of the eight drugs from publicly available databases. Finally, they utilize surveys—each tailored to three key stakeholders; payers, drug and diagnostic developers, and pharmacogenomic expert analysts—to assess reimbursement of diagnostics, analyze the role that different kinds of evidence have in informing prescribing and reimbursement decisions, as well as the specific clinical, regulatory and economic challenges that confront pharmacogenomics as it moves forward. Cohen et al. found that Medicare beneficiary access to physician-administered (Medicare part B) drugs is relatively unfettered, with a fixed patient co-insurance percentage of 20%. More reimbursement restrictions are placed on self-administered (Medicare part D) drugs, which translates into higher and more variable cost sharing, more use of prior authorization and quantity limits. There is a lack of comprehensive reimbursement of companion diagnostics, even in cases in which the diagnostic is on the label and recommended or required by the Food and Drug Administration. Lack of evidence linking diagnostic tests to health outcomes has caused payers to be skeptical about the clinical usefulness of tests. Expert analysts foresee moderate growth in post-hoc development of companion diagnostics to personalize already approved drugs, and limited growth in the concurrent co-development of companion diagnostics and personalized medicines. Lack of clinically useful diagnostics as well as an evidence gap in terms of knowledge of drug and diagnostic clinical effectiveness appear to be hindering growth in personalized medicine. An increase in comparative effectiveness research may help to close the evidence gap.

2. Cohen JP. Overcoming regulatory and economic challenges facing pharmacogenomics. *N Biotechnol.* 2012 Sept 15; 29(6)751-6. Epub 2012 Feb 19.

The number of personalized medicines and companion diagnostics in use in the United States has gradually increased over the past decade, from a handful of medicines and tests in 2001 to several dozen in 2011. However, the numbers have not reached the potential hoped for when the human genome project was completed in 2001. Significant clinical, regulatory, and economic barriers exist and persist. From a regulatory perspective, therapeutics and companion diagnostics are ideally developed simultaneously, with the clinical significance of the diagnostic established using data from the clinical development program of the corresponding therapeutic. Nevertheless, this is not (yet) happening. Most personalized medicines are personalized post hoc, that is, a companion diagnostic is developed separately and approved after the therapeutic. This is due in part to a separate and more complex regulatory process for diagnostics coupled with a lack of clear regulatory guidance. More importantly, payers have placed restrictions on reimbursement of personalized medicines and their companion diagnostics, given the lack of evidence on the clinical utility of many tests. To achieve increased clinical adoption of diagnostics and targeted therapies through more favorable reimbursement and incorporation in clinical practice guidelines, regulators will need to provide unambiguous guidance and manufacturers will need to bring more and better clinical evidence to the marketplace.

3. Tanner NT, Pastis NJ, et al. The role of molecular analyses in the era of personalized therapy for advanced NSCLC. *Lung Cancer*. 2012 May;76(2):131-7. Epub 2011 Dec 15.

Platinum-based doublet chemotherapy is the traditional treatment of choice for advanced non-small cell lung cancer (NSCLC); however, the efficacy of these regimens has reached a plateau. Increasing evidence demonstrates that patients with sensitizing mutations in the epidermal growth factor receptor (EGFR) experience improved progression-free survival and response rates with first-line gefitinib or erlotinib therapy relative to traditional platinum-based chemotherapy, while patients with EGFR-mutation negative tumors gain greater benefit from platinum-based chemotherapy. These results highlight the importance of molecular testing prior to the initiation of first-line therapy for advanced NSCLC. Routine molecular testing of tumor samples represents an important paradigm shift in NSCLC therapy and would allow for individualized therapy in specific subsets of patients. As these and other advances in personalized treatment are integrated into everyday clinical practice, pulmonologists will play a vital role in ensuring that tumor samples of adequate quality and quantity are collected in order to perform appropriate molecular analyses to guide treatment decisions. This article provides an overview of clinical trial data supporting molecular analysis of NSCLC, describes specimen acquisition and testing methods currently in use, and discusses future directions of personalized therapy for patients with NSCLC.

4. Tian Q, Price, ND, Hood L. Systems cancer medicine: towards realization of predictive, preventive, personalized and participatory (P4) medicine. *J Intern Med*. 2012; 271(2): 111-121.

A grand challenge impeding optimal treatment outcomes for patients with cancer arises from the complex nature of the disease: the cellular heterogeneity, the myriad of dysfunctional molecular and genetic networks as results of genetic (somatic) and environmental perturbations. Systems biology, with its holistic approach to understanding fundamental principles in biology, and the empowering technologies in genomics, proteomics, single-cell analysis, microfluidics, and computational strategies, enables a comprehensive approach to medicine, which strives to unveil the pathogenic mechanisms of diseases, identify disease biomarkers, and begin thinking about new strategies for drug target discovery. The integration of multidimensional high-throughput 'omics' measurements from tumor tissues and corresponding blood specimens, together with new systems strategies for diagnostics, enables the identification of cancer biomarkers that will enable pre-symptomatic diagnosis, stratification of disease, assessment of disease progression, evaluation of patient response to therapy, and the identification of reoccurrences. While some aspects of systems medicine are being adopted in clinical oncology practice through companion molecular diagnostics for personalized therapy, the mounting influx of global quantitative data from both wellness and diseases is shaping up a transformational paradigm in medicine termed 'predictive,' 'preventive,' 'personalized,' and 'participatory' (P4) medicine, which requires new strategies, both scientific and organizational, to enable bringing this revolution in medicine to patients and to the healthcare system. P4 medicine will have a profound impact on society—transforming the healthcare system, turning around the ever escalating costs of healthcare, digitizing the practice of medicine and creating enormous economic opportunities for those organizations and nations that embrace this revolution.

5. Beckman RA, Clark J, Chen C. Integrating predictive biomarkers and classifiers into oncology clinical development programmes. *Nat Rev Drug Discovery*. 2011. Sept 30;10(10): 735-748.

The future of drug development in oncology lies in identifying subsets of patients who will benefit from particular therapies, using predictive biomarkers. These technologies offer hope of enhancing the value of cancer medicines and reducing the size, cost and failure rates of clinical trials. However, examples of the failure of predictive biomarkers also exist. In these cases the use of biomarkers increased the costs, complexity and duration of clinical trials, and narrowed the treated population unnecessarily. Here, Beckman and colleagues present methods to adaptively integrate predictive biomarkers into clinical programs in a data-driven manner, wherein these biomarkers are emphasized in exact proportion to the

evidence supporting their clinical predictive value. The resulting program demands value from predictive biomarkers and is designed to optimally harvest this value for oncology drug development.

6. Chen B, Richards CS, Wilson JA, Lyon E. Quality assurance and quality improvement in U.S. clinical molecular genetic laboratories. *Curr Protoc Hum Genet.* 2011 Apr; Chapter 9: Unit 9.2.

A robust quality-assurance program is essential for laboratories that perform molecular genetic testing to maintain high-quality testing and be able to address challenges associated with performance or delivery of testing services as the use of molecular genetic tests continues to expand in clinical and public health practice. This unit discusses quality-assurance and quality-improvement considerations that are critical for molecular genetic testing performed for heritable diseases and conditions. Specific discussion is provided on applying regulatory standards and best practices in establishing/verifying test performance, ensuring quality of the total testing process, monitoring and maintaining personnel competency, and continuing quality improvement. The unit provides a practical reference for laboratory professionals to use in recognizing and addressing essential quality-assurance issues in human molecular genetic testing. It should also provide useful information for genetics researchers, trainees, and fellows in human genetics training programs, as well as others who are interested in quality assurance and quality improvement for molecular genetic testing.

7. Chiang A, Million P. Personalized medicine in oncology: next generation. *Nat Rev Drug Discov* 2011; Dec 1;10(12): 895-896.
8. Duncan PR, Lin JT. Ingredients for success: a familial cancer clinic in an oncology practice setting. *J Oncol Pract.* 2011;7(1): 39-42.

Genetic cancer risk assessment (GCRA) has become increasingly important in clinical cancer care. Almost all published information on genetic risk assessment has come from academic institutions. However, a majority of patients with cancer are seen in the community practice setting. Dun and Lin describe the evolution of a community oncology practice GCRA clinic. Over a 10-year period, 445 patients were seen for a possible genetic cancer syndrome. This included 325 patients with family history of breast or ovarian cancer, 92 patients with family history of colorectal cancer or polyposis, and 28 families with another familial cancer predisposition. Fifty-three unique families with a genetic mutation were identified.

CONCLUSION: A GCRA clinic can be incorporated into an oncology practice setting and can enhance the standard of care for the entire community. Duncan and Lin present data reflecting a 10-year experience with such a clinic and provide recommendations for establishing a successful one.

9. Engstrom PF, Bloom MG, et al. NCCN molecular testing white paper: effectiveness, efficiency, and reimbursement. *J Natl Compr Canc Netw.* 2011; 9 Suppl 6: S1-16.

Personalized medicine in oncology is maturing and evolving rapidly, and the use of molecular biomarkers in clinical decision-making is growing. This raises important issues regarding the safe, effective, and efficient deployment of molecular tests to guide appropriate care, specifically regarding laboratory-developed tests and companion diagnostics. In May 2011, NCCN assembled a work group composed of thought leaders from NCCN Member Institutions and other organizations to identify challenges and provide guidance regarding molecular testing in oncology and its corresponding utility from clinical, scientific, and coverage policy standpoints. The NCCN Molecular Testing Work Group identified challenges surrounding molecular testing, including health care provider knowledge, determining clinical utility, coding and billing for molecular tests, maintaining clinical and analytic validity of molecular tests, efficient use of specimens, and building clinical evidence.

10. Freeman RA. Personalized medicine and therapeutic decision-making in oncology: a commentary on key environmental issues. *J Oncol Pharmacy Practice.* 2011; 17(3): 295-297.

11. Majewski JJ, Bernards R. Taming the dragon: genomic biomarkers to individualize the treatment of cancer. *Nat Med.* 2011; 17(3): 304-312.

The gradual shift from cytotoxic drugs to highly selective, targeted therapeutic agents for cancer requires a parallel effort to characterize cancers at the molecular level to guide the choice of therapy for the individual patient. Majewski and Bernards review the genomic technologies that can be used to develop these drug response indicators, or biomarkers. The authors also discuss hurdles in the development and the implementation of biomarkers in clinical practice.

12. McDermott U, Downing JR, et al. Genomics and the continuum of cancer care. *New Engl J Med.* 2011;364(4): 340-350.
13. Toyooka ST, Mitsudomi T, Soh, J, et al. Molecular oncology of lung cancer. *Gen Thorac Cardiovasc Surg.* 2011; 59(8): 527-537.

Progress in genetic engineering has made it possible to elucidate the molecular biological abnormalities in lung cancer. Mutations in KRAS and P53 genes, loss of specific alleles, and DNA methylation of the tumor suppressor genes were the major abnormalities investigated between 1980 and the 2000s. In 2004, mutations in the epidermal growth factor receptor (EGFR) gene that cause oncogene addiction were discovered in non-small-cell lung cancers (NSCLCs), especially in adenocarcinomas. Because they are strongly associated with sensitivity to EGFR-tyrosine kinase inhibitors (EGFR-TKIs), a great deal of knowledge has been acquired in regard to both EGFR and other genes in the EGFR family and their downstream genes. Moreover, in 2007 the existence of the echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) fusion gene was discovered in NSCLC; and the same as EGFR-TKIs, ALK inhibitors are being found to be highly effective in lung cancers that have this translocation. These discoveries graphically illustrate that molecular biological findings are directly linked to the development of clinical oncology and to improving the survival rates of lung cancer patients. Here, Toyooka and colleagues review the remarkable progress in molecular biological knowledge acquired thus far in regard to lung cancer, especially NSCLC, and the future possibilities.

14. Trosman, JR, Van Bebber SL, et al. Health technology assessment and private payers' coverage of personalized medicine. *J Oncol Pract.* 2011;7(3 Suppl): 18s-24s.

Health technology assessment (HTA) plays an increasing role in translating emerging technologies into clinical practice and policy. Private payers are important users of HTA whose decisions impact adoption and use of new technologies. Trosman and colleagues examine the current use of HTA by private payers in coverage decisions for personalized medicine, a field that is increasingly impacting oncology practice. The study design featured a literature review and semistructured interviews. The authors reviewed seven HTA organizations used by private payers in decision-making and explored how HTA is used by major US private payers (n = 11) for coverage of personalized medicine. All payers used HTA in coverage decisions, but the number of HTA organizations used by an individual payer ranged from one (n = 1) to all seven (n = 1), with the majority of payers (n = 8) using three or more. Payers relied more extensively on HTAs for reviews of personalized medicine (64%) than for other technologies. Most payers (82%) equally valued expertise of reviewers and rigor of evaluation as HTA strengths, whereas genomic-specific methodology was less important. Key reported shortcomings were limited availability of reviews (73%) and limited inclusion of non-clinical factors (91%), such as cost-effectiveness or adoption of technology in clinical practice.

CONCLUSION: Payers use a range of HTAs in their coverage decisions related to personalized medicine, but the current state of HTA to comprehensively guide those decisions is limited. HTA organizations should address current gaps to improve their relevance to payers and clinicians. Current HTA shortcomings may also inform the national HTA agenda.

15. Wegwarth O, Day RW, et al. Decisions on pharmacogenomic tests in the USA and Germany. *J Eval Clin Pract.* 2011;17(2): 228-235.

With the increase in molecular genetic understanding of disease, diagnostic test development and availability are growing rapidly. This study investigated oncologists' decision-making on using pharmacogenomic tests for cancer treatment and examined cross-cultural differences between the U.S. and Germany. Study methods: Pilot studies revealed that the following cues play a role in decisions on pharmacogenomic tests: stage of cancer, availability of treatment options, cost of the treatment options, severity of side effects of the treatments, therapeutic consequence of the test, cost of the test, and guideline recommendation specifying use of the test. All cues were used for designing the main study comprising nine scenarios, for each of which oncologists were asked to decide whether they would order a pharmacogenomic test. Results: On average, U.S. oncologists opted for the test in 6.5 out of the nine scenarios (SE = 0.2), and German oncologists in 5.4 scenarios (SE = 0.2). The majority of oncologists' decisions in both the U.S. (76.1%) and Germany (64%) were best explained by a simple sequential model (heuristic strategy). In the U.S., the information about cost of the test was most influential on the decisions; in Germany it was the guideline recommendation of the test. When the side effects of therapy B were described as being more severe within the scenarios, choices in favor of a non-recommended test increased by about 20% within both samples.

CONCLUSION: Both U.S. and German oncologists were highly inclined to use pharmacogenomic tests, but differed in what information influenced their decisions—a difference possibly explained by the differences in the health insurance systems. Although many oncologists' heuristic decisions were based on the valid cue of a test's guideline recommendation, an alarming number abandoned it when a therapy had potentially severe side effects.

16. MacDonald DJ, Blazer KR, et al. Extending comprehensive cancer center expertise in clinical cancer genetics and genomics to diverse communities: the power of partnership. *J Natl Compr Canc Netw*. 2010; 8(5): 615-624.

Rapidly evolving genetic and genomic technologies for genetic cancer risk assessment (GCRA) are revolutionizing the approach to targeted therapy and cancer screening and prevention, heralding the era of personalized medicine. Although many academic medical centers provide GCRA services, most people receive their medical care in the community setting. However, few community clinicians have the knowledge or time needed to adequately select, apply, and interpret genetic/genomic tests. This article describes alternative approaches to the delivery of GCRA services, profiling the City of Hope Cancer Screening & Prevention Program Network (CSPPN) academic and community-based health center partnership as a model for the delivery of the highest-quality evidence-based GCRA services while promoting research participation in the community setting. Growth of the CSPPN was enabled by information technology, with video-conferencing for telemedicine and Web conferencing for remote participation in interdisciplinary genetics tumor boards. Grant support facilitated the establishment of an underserved minority outreach clinic in the regional county hospital. Innovative clinician education, technology, and collaboration are powerful tools to extend GCRA expertise from a National Cancer Institute-designated Comprehensive Cancer Center, enabling diffusion of evidence-based genetic/genomic information and best practice into the community setting.

17. Meckley LM, Neumann PJ. Personalized medicine: factors influencing reimbursement. *Health Policy*. 2010;94(2): 91-100.

Personalized medicine (PM) has attracted tremendous interest, but yielded few marketed products. We examined factors influencing the reimbursement of existing PM technologies. Methods: Meckley and Neumann conducted six case studies of the following paired genetic tests and treatments: HER2/neu with trastuzumab (Herceptin); hepatitis C genotyping with ribavirin/pegylated interferon; Oncotype DX with chemotherapy; UGT1A1 with irinotecan (Camptosar); VKORC1/CYP2C9 with warfarin; BRCA1/2 with prophylactic surgical measures; and Oncotype DX with chemotherapy. The authors developed a framework for categorizing PM technology, and assessed factors influencing reimbursement, including quality of evidence, type of regulatory oversight, presence of clinical guidelines, and cost-effectiveness.

RESULTS: PM is not a monolithic concept, but rather encompasses different types of technology. The strength of evidence available for existing PM technology varies widely and, along with endorsement of clinical guidelines, appears to be the strongest predictor of reimbursement. In the absence of reimbursement, direct-to-consumer marketing has continued for some PM technology. The type of regulatory oversight and the results of cost-effectiveness analysis do not appear to be associated with reimbursement to date.

CONCLUSION: To date, the promise and hype of PM has outpaced its evidentiary support. In order to achieve favorable coverage and reimbursement and to support premium prices for PM, manufacturers will need to bring better clinical evidence to the marketplace and better establish the value of their products.

18. Quinn, B. Payers and the assessment of clinical utility for companion diagnostics. *Clin Pharmacol Ther.* 2010;88(6): 751-754.

The decision makers who approve or deny payment for healthcare services review many new technologies. Reimbursement for companion diagnostics for expensive drugs (“personalized medicine”) is already under close policy scrutiny, in line with long-standing concerns about overuse of diagnostic tests. Evaluation of diagnostic tests adds some complexities to the payer's comparative-effectiveness evaluation for drugs alone. Currently, decision-making frameworks suitable for companion diagnostics are being developed for practical application by payer policy makers.

19. Sturgeon C, Hill R, et al. Taking a new biomarker into routine use—a perspective from the routine clinical biochemistry laboratory. *Proteomics Clin Appl.* 2010;4(12): 892-903.

There is increasing pressure to provide cost-effective healthcare based on “best practice.” Consequently, new biomarkers are only likely to be introduced into routine clinical biochemistry departments if they are supported by a strong evidence base and if the results will improve patient management and outcome. This requires convincing evidence of the benefits of introducing the new test, ideally reflected in fewer hospital admissions, fewer additional investigations, and/or fewer clinic visits. Carefully designed audit and cost-benefit studies in relevant patient groups must demonstrate that introducing the biomarker delivers an improved and more effective clinical pathway. From the laboratory perspective, pre-analytical requirements must be thoroughly investigated at an early stage. Good stability of the biomarker in relevant physiological matrices is essential to avoid the need for special processing. Absence of specific timing requirements for sampling and knowledge of the effect of medications that might be used to treat the patients in whom the biomarker will be measured is also highly desirable. Analytically, automation is essential in modern high-throughput clinical laboratories. Assays must therefore be robust, fulfilling standard requirements for linearity on dilution, precision, and reproducibility, both within- and between-run. Provision of measurements by a limited number of specialized reference laboratories may be most appropriate, especially when a new biomarker is first introduced into routine practice.

20. Trosman JR, Van Bebber SL, et al. Coverage policy development for personalized medicine: private payer perspectives on developing policy for the 21-gene assay. *J Oncol Pract.* 2010;6(5): 238-242.

Personalized medicine is changing oncology practice and challenging decision making. A key challenge is the limited clinical evidence for many personalized medicine technologies. This study describes the strategies private payers employed to develop coverage policy for personalized medicine using the example of the 21-gene assay in breast cancer. Trosman and colleagues examined the coverage policies of six private payers for the 21-gene assay. They then interviewed senior executives (n = 7) from these payers to elucidate factors informing coverage decisions. Additionally Trosman et al. focused on the timing of payer decisions compared with the timing of evidence development, measured by publication of primary studies and relevant clinical guidelines.

RESULTS: The 21-gene assay became commercially available in 2004. The interviewed payers granted coverage between 2005 and 2008. Their policies varied in structure (e.g., whether prior authorization was required). All payers reported clinical evidence as the most important factor in decision making, but all used some healthcare system factors (e.g., physician adoption or medical society endorsement) to inform decision-making as well. Payers had different perceptions about the strength of clinical evidence at the time of the coverage decision.

CONCLUSION: Coverage of the 21-gene assay is currently widespread, but policies differ in timing and structure. A key approach private payers use to develop coverage policies for novel technologies is considering both clinical evidence and healthcare system factors. Policy variation may emerge from the range of factors used and perception of the evidence. Future research should examine the role of healthcare system factors in policy development and related policy variations.

21. Downing GJ, Boyle SN, et al. Information management to enable personalized medicine: stakeholder roles in building clinical decision support. *BMC Med Inform Decis Mak.* 2009;9: 44.

Advances in technology and the scientific understanding of disease processes are presenting new opportunities to improve health through individualized approaches to patient management referred to as personalized medicine. Future health care strategies that deploy genomic technologies and molecular therapies will bring opportunities to prevent, predict, and pre-empt disease processes but will be dependent on knowledge management capabilities for healthcare providers that are not currently available. A key cornerstone to the potential application of this knowledge will be effective use of electronic health records. In particular, appropriate clinical use of genomic test results and molecularly-targeted therapies present important challenges in patient management that can be effectively addressed using electronic clinical decision support technologies.

DISCUSSION: Approaches to shaping future health information needs for personalized medicine were undertaken by a work group of the American Health Information Community. A needs assessment for clinical decision support in electronic health record systems to support personalized medical practices was conducted to guide health future development activities. Further, a suggested action plan was developed for government, researchers and research institutions, developers of electronic information tools (including clinical guidelines, and quality measures), and standards development organizations to meet the needs for personalized approaches to medical practice. This article focuses these activities on stakeholder organizations as an operational framework to help identify and coordinate needs and opportunities for clinical decision support tools to enable personalized medicine.

SUMMARY: This perspective addresses conceptual approaches that can be undertaken to develop and apply clinical decision support in electronic health record systems to achieve personalized medical care. In addition, to represent meaningful benefits to personalized decision-making, a comparison of current and future applications of clinical decision support to enable individualized medical treatment plans is presented. If clinical decision support tools are to impact outcomes in a clear and positive manner, their development and deployment must therefore consider the needs of the providers, including specific practice needs, information workflow, and practice environment.

22. Issa AM, Tufail W, et al. Assessing patient readiness for the clinical adoption of personalized medicine. *Public Health Genomics.* 2009;12(3): 163-169.

Although pharmacogenomics-based diagnostics and therapeutics are increasingly being translated into personalized medicine applications, relatively little evidence exists about how novel pharmacogenomics-based technologies will be accepted and adopted by patients. It is important to understand the characteristics of genomic diagnostics and targeted therapeutics that might impact utilization or serve as barriers to adoption of these novel technologies in order to formulate appropriate policies and procedures. The objective of this study was to investigate patients' understanding and knowledge of personalized

medicine and the process of decision-making regarding pharmacogenomics testing and targeted therapeutics and to better understand how patients value receiving pharmacogenomics-based care.

METHODS: For this study, 4 focus groups with 8-10 individuals in each group were conducted with patients recruited from outpatient clinics at The Methodist Hospital in Houston, Tex., U.S.

RESULTS: The use of genomic diagnostics and targeted therapeutics to facilitate personalized medicine has considerable support from patients. However, the study data revealed that participants were concerned with issues surrounding privacy and confidentiality of genetic test results, particularly with respect to access of information by insurers, with potential costs of testing and issues related to accuracy of test results. Questions regarding willingness to pay revealed that patients would be more willing to pay out-of-pocket if the disease associated with pharmacogenomic testing for treatment was perceived to be high risk (e.g., colorectal cancer) versus a chronic condition that was perceived as lower risk (e.g., high cholesterol).

CONCLUSION: As the personalized medicine approach is increasingly incorporated into healthcare, understanding patients' needs and their readiness to adopt these novel technologies will become progressively more important for the development of appropriate health policies.

23. Kawamoto K, Lobach DF, et al. A national clinical decision support infrastructure to enable the widespread and consistent practice of genomic and personalized medicine. *BMC Med Inform Decis Mak.* 2009; 9:17.

In recent years, the completion of the Human Genome Project and other rapid advances in genomics have led to increasing anticipation of an era of genomic and personalized medicine, in which an individual's health is optimized through the use of all available patient data, including data on the individual's genome and its downstream products. Genomic and personalized medicine could transform healthcare systems and catalyze significant reductions in morbidity, mortality, and overall healthcare costs.

DISCUSSION: Critical to the achievement of more efficient and effective healthcare enabled by genomics is the establishment of a robust, nationwide clinical decision support infrastructure that assists clinicians in their use of genomic assays to guide disease prevention, diagnosis, and therapy. Requisite components of this infrastructure include the standardized representation of genomic and non-genomic patient data across health information systems; centrally managed repositories of computer-processable medical knowledge; and standardized approaches for applying these knowledge resources against patient data to generate and deliver patient-specific care recommendations. Here, we provide recommendations for establishing a national decision support infrastructure for genomic and personalized medicine that fulfills these needs, leverages existing resources, and is aligned with the Roadmap for National Action on Clinical Decision Support commissioned by the U.S. Office of the National Coordinator for Health Information Technology. Critical to the establishment of this infrastructure will be strong leadership and substantial funding from the federal government.

SUMMARY: A national clinical decision support infrastructure will be required for reaping the full benefits of genomic and personalized medicine. Essential components of this infrastructure include standards for data representation; centrally managed knowledge repositories; and standardized approaches for leveraging these knowledge repositories to generate patient-specific care recommendations at the point of care.

24. Miller FA, Krueger P, et al. Postal survey of physicians and laboratories: practices and perceptions of molecular oncology testing. *BMC Health Serv Res.* 2009;9:131.

Molecular oncology testing (MOT) to detect genomic alterations underlying cancer holds promise for improved cancer care. Yet knowledge limitations regarding the delivery of testing services may constrain the translation of scientific advancements into effective health care. **Methods:** Miller and colleagues conducted a cross-sectional, self-administered, postal survey of active cancer physicians in Ontario, Canada (N = 611) likely to order MOT, and cancer laboratories (N = 99) likely to refer (i.e.,

referring laboratories) or conduct (i.e., testing laboratories) MOT in 2006, to assess respondents' perceptions of the importance and accessibility of MOT and their preparedness to provide it. Results: 54% of physicians, 63% of testing laboratories, and 60% of referring laboratories responded. Most perceived MOT to be important for treatment, diagnosis, or prognosis now, and in 5 years (61% - 100%). Yet only 45% of physicians, 59% of testing labs, and 53% of referring labs agreed that patients in their region were receiving MOT that is indicated as a standard of care. Physicians and laboratories perceived various barriers to providing MOT, including, among 70% of physicians, a lack of clear guidelines regarding clinical indications, and among laboratories, a lack of funding (73% - 100%). Testing laboratories were confident of their ability to determine whether and which MOT was indicated (77% and 82% respectively), and perceived that key elements of formal and continuing education were helpful (75% - 100%). By contrast, minorities of physicians were confident of their ability to assess whether and which MOT was indicated (46% and 34% respectively), and while majorities considered various continuing educational resources helpful (68% - 75%), only minorities considered key elements of formal education helpful in preparing for MOT (17% - 43%).

CONCLUSION: Physicians and laboratory professionals were enthusiastic about the value of MOT for cancer care but most did not believe patients were gaining adequate access to clinically necessary testing. Further, study results suggest that many were ill equipped as individual stakeholders, or as a coordinated system of referral and interpretation, to provide MOT. These challenges should inspire educational, training, and other interventions to ensure that developments in molecular oncology can result in optimal cancer care.

25. Perez-Soler R. Individualized therapy in non-small-cell lung cancer: future versus current clinical practice. *Oncogene*. 2009;28 Suppl 1:S38-45.

Despite advances in the management of non-small-cell lung cancer (NSCLC), including the introduction of targeted therapies such as epidermal growth factor receptor tyrosine kinase inhibitors, improvements in survival are marginal and the overall prognosis for patients remains poor. Tailoring therapy to the individual patient is a promising approach for selecting the most appropriate therapeutic regimens to maximize efficacy and minimize toxicity. The identification of predictive biomarkers that can guide treatment decisions is an important step for individualized therapy and in ultimately improving patient outcomes. Genomic and proteomic studies provide a means for the molecular profiling of tumor tissue from patients with NSCLC, and allow tailoring of therapy whereby the most appropriate treatment is administered to each individual patient. Although there are still significant challenges to implementing genomic and proteomic testing in clinical practice, the rapid development of newer technologies provides hope for overcoming these barriers.

26. Sturgeon, CM, Hoffman BR, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for use of tumor markers in clinical practice: quality requirements. *Clin Chem*. 2008; 54(8): e1-e10.

This report presents updated National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines summarizing quality requirements for the use of tumor markers. Methods: One subcommittee developed guidelines for analytical quality relevant to serum and tissue-based tumor markers in current clinical practice. Two other subcommittees formulated recommendations particularly relevant to the developing technologies of microarrays and mass spectrometry. Results: Prerequisites for optimal use of tumor markers in routine practice include formulation of the correct clinical questions to ensure selection of the appropriate test, adherence to good clinical and laboratory practices (e.g., minimization of the risk of incorrect patient and/or specimen identification, tube type, or timing), use of internationally standardized and well-characterized methods, careful adherence to manufacturer instructions, and proactive and timely reactions to information derived from both internal QC and proficiency-testing specimens. Highly desirable procedures include those designed to minimize the risk of the reporting of erroneous results attributable to interferences such as heterophilic antibodies or hook effects, to facilitate the provision of informative clinical reports (e.g., cumulative and/or graphical reports, appropriately derived reference intervals, and interpretative comments), and when possible to integrate these reports with other patient information

through electronic health records. Also mandatory is extensive validation encompassing all stages of analysis before introduction of new technologies such as microarrays and mass spectrometry. Provision of high-quality tumor marker services is facilitated by dialogue involving researchers, diagnostic companies, clinical and laboratory users, and regulatory agencies.

CONCLUSION: Implementation of these recommendations, adapted to local practice, should encourage optimization of the clinical use of tumor markers.

27. Wordsworth SJ, Buchanan, et al. Molecular testing for somatic mutations in common cancers: the views of UK oncologists. *J Clin Path.* 2008;61(6):761-765.

Somatic mutations are important determinants of cancer behavior and response to therapy. However, molecular testing in this context has a relatively low profile within the clinical community, despite publicity surrounding targeted therapies such as Herceptin. As the testing process affects many stakeholders, especially oncologists, this paper examines current test request patterns and views of such testing. **Methods:** A postal questionnaire was mailed to 582 UK oncologists and hematologists, achieving a 20% response rate. **Results:** The survey revealed that immunohistochemistry and fluorescent in situ hybridization are the most commonly requested tests (used by 70% and 55% of respondents, respectively), especially for breast cancer. Availability of suitable treatment options is the main factor influencing the decision to test (selected by 62% of respondents). Respondents were generally positive about future demand for immunohistochemistry, fluorescent in situ hybridization, microarray analysis and DNA-based tests, but uncertain about the prospects for microsatellite instability and ploidy testing.

CONCLUSION: Overall, respondents thought that somatic mutation testing could have a significant and positive effect on oncology and hematology departments and patient care, especially with better treatment and tumor classification. However, lack of supportive scientific evidence and funding were considered key barriers to widespread testing. Further research is clearly required on both the resource implications of this increase in demand and the best model of service delivery to ensure the most efficient use of health service resources.

28. Wordsworth S, Papanicolas I, et al. Molecular testing for somatic cancer mutations: a survey of current and future testing in UK laboratories. *J Clin Path.* 2008;61(3) 373-376.

Genetics clinical practice has paid limited attention to non-inherited aspects of cancer, namely mutations occurring during carcinogenesis. These somatic mutations are likely to be the primary determinants of cancer behavior and treatment response, with a recent example being HER2/Neu gene status and response to Herceptin in breast cancer.

AIM: To assess the feasibility of widespread testing of tumors by surveying U.K. histopathology and genetics laboratories. **Methods:** The questionnaire asked: which of the common cancers or other malignancies are routinely assessed; which molecular and cytogenetic methods are used; who orders and funds testing; what is the future demand for somatic testing; and what are the barriers to widespread testing?

RESULTS: Of 50 laboratories surveyed, 33 responded, 22 of which are currently using molecular tests. The survey shows that the most common tests are immunohistochemistry, fluorescence in-situ hybridization, and DNA testing of somatic mutations. Most laboratories predict testing will increase over the next 10 years, particularly for DNA testing using microarrays. Respondents perceived the main barriers to expanding molecular testing were a lack of laboratory funding and scientific evidence and testing not considered an NHS priority.

CONCLUSION: These results provide important information for healthcare commissioners faced with managing demand for molecular testing of cancers.