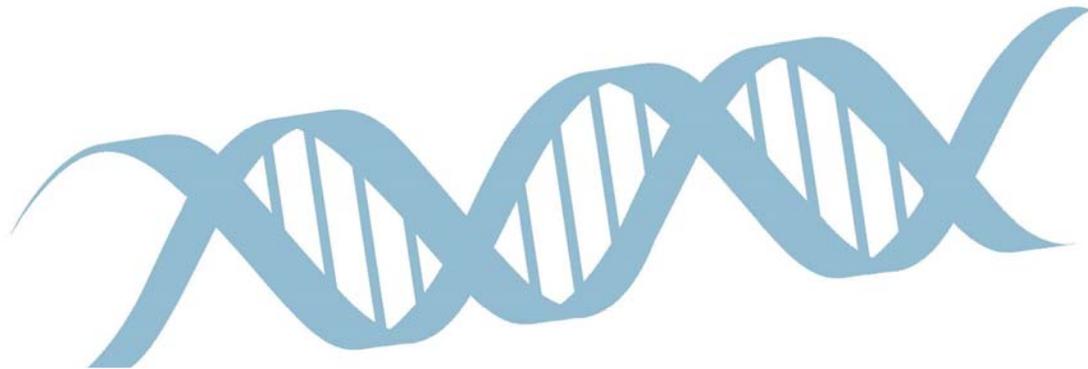




Molecular Diagnostics in
Cancer: Informing the Issues
of Personalized Medicine



Background Briefing Document

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Research Advocacy Network

Advancing Patient-Focused Research



Molecular Diagnostics in Cancer: Informing the Issues of Personalized Medicine

About this document:

To set the context for discussions of current issues of clinical utility in molecular diagnostics for cancer, the Research Advocacy Network commissioned this document and literature search. In addition, to inform the development of this document and to further elucidate the issues, interviews were conducted with experts in the field.

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The rapidly advancing field of personalized medicine is poised to fundamentally change how cancer is prevented, diagnosed and treated. In its broadest sense, 'personalized medicine' tailors medical treatment to the characteristics of an individual patient, often moving beyond standard treatment approaches. By incorporating a patient's genetic information, physicians can better predict cancer and its prognosis, and select cancer treatments most likely to be of benefit to that individual. Scientists and oncologists often use the term 'personalized medicine' interchangeably with 'genomic medicine', 'precision medicine' and 'precision oncology'. Dr. Richard Schilsky, Chief Medical Officer for the American Society of Clinical Oncology further explains the terminology, "Molecular diagnostics is the broad term and implies any tests that uses a molecular technique to detect the substance of interest. The term genomic implies looking for a variation in DNA. A genomic test is a molecular test but all molecular tests are not genomic tests." Thus, here we will use the broader term 'molecular diagnostics'.

Molecular diagnostics can provide specific detail about how susceptible a person may be to a disease and how they are expected to respond to a particular treatment. This will lessen the chance of patients having to undergo unnecessary interventions and experience adverse events. It offers enormous potential benefit in meeting the goals of prevention, early diagnosis, treatment and improving the overall performance and efficiencies of the cancer care system.¹

Testing patients and including their biological information to tailor interventions has raised several issues due to the complex nature of this type of individualized care. Based on recent findings in the medical literature and in-depth interviews with experts and key opinion leaders, here we examine issues identified in translating these findings into the clinic, and the challenges that lay ahead for molecular diagnostics in cancer.

Test Selection and Clinical Utility

Genetic testing can be a valuable tool in the detection and treatment of cancer. The tests are used to identify and measure the presence of genetic variations/mutations known as biomarkers and they can be extremely beneficial in guiding treatment decisions. A well-known genetic biomarker is the *HER2* gene, in breast cancer.² With the increasing number of tests available, oncologists have to determine which test should be used for a specific patient and how the information provided by the test will inform clinical decision-making.^{1,3}

Even though a test has been analyzed in a laboratory and validated in a research trial, clinicians describe successful demonstration of clinical utility to be a diagnostic test that results in an improvement in patient outcomes. The Centers for Medicare & Medicaid Services provide a guideline for the evaluation of diagnostic tests focusing on whether the evidence provided delivers accurate diagnostic information. Meaning, that diagnostic accuracy alone is not sufficient, the important factor is whether test results lead to changes in practice resulting in improved health outcomes. Dr. Noah M. Hahn is an Associate Professor of Oncology and Urology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore and he has found that clinicians are looking for, "Documentation that the test adds value beyond what is currently available. The test needs to show that patients respond better in a specific patient population than in an unselected patient population (e.g. in lung cancer where 10 to 20% of the population have an *ALK* mutation, we need to show that those patients respond better with the targeted agent than with standard chemotherapy)."

In a broad sense, demonstrating utility may be as simple as showing that a test provides equivalent or increased sensitivity and specificity (leading to equivalent or improved management decisions); is less invasive (incurs less patient harm); is less costly (provides the same benefit with fewer resources); or is more widely or easily available

(more likely to be used to make management decisions).⁴ Similarly, Dr. Schilsky shared his insight into the factors that will bring a test into clinical use. He states, “The test must clearly inform a medical decision. Someone has to pay for the test to be done and in the future, regulatory issues may be a hurdle.” He adds, “The biggest barriers are developing persuasive clinical evidence that can be measured and will be informative to a medical decision.”

An improvement in outcomes will help a test to gain acceptance from clinicians, payers, and patients and demonstrating the clinical value of a test may potentially reduce the waste of health care resources from inconsistent or unnecessary use of other tests. A major limiting factor for the use of these tests has been a lack of consensus among stakeholders regarding both the evidence needed to move a test into clinical practice and the acceptable methodologies to collect and validly demonstrate this evidence. Some tests have succeeded in clinical uptake better than others, Dr. Schilsky explains, “There is the need for all large clinical trials to collect biospecimens because that is the foundation of developing a useful test. Most tests don't fail because of technology. They fail because they haven't been tested in appropriate samples often because the samples are not available. Additionally, tests should also be developed in the same patient population intended to be used in.”

“The specialty of oncology is becoming more fragmented, among those treating different types of cancers and those practicing in academic institutions compared to those in community settings,” explains Amy Sing, MD, Senior Director-Medical Affairs for Genomic Health, adding that, “Clinical setting is a determinant of test use, as many community oncologists see so many patients and such a variety of patients they stick with what they know. New testing methods are more likely to be accepted and used by specialists in academic settings earlier because of the infrastructure and resources available to them.” Dr. Bryan Schneider, Director of Personalized Medicine Center at Indiana University Cancer Center explains that, “tests need to be easily understandable, have good scientific basis and not be too time consuming in order to facilitate clinical uptake or acceptance.” This is echoed by Dr. Hahn, “The test has to be simple for both patient and physician (user-friendly) so that it can be implemented in real time in the clinic.”

Dr. Sing has found that, “physicians will incorporate a test into routine practice if it provides information they can use when making patient treatment decisions. In early stage disease there are different criteria than metastatic and the definition of useful changes.” She adds, “Every physician has a different threshold for ‘useful’. Some find just information useful. They can use it to talk to patients about other options for treatment, or they might think it was useful because they can talk to patients about the nature and character of the tumor and what drugs or clinical trials might be available.”

Another barrier to test use is that clinicians may also feel that they do not have access to adequate education regarding testing methods, test selection or interpretation of results. Dr. Bert O'Neil is a Professor of Oncology and a Professor of Medicine at the Indiana University School of Medicine, in Indianapolis and has found that, “Getting the education through to clinicians is a barrier as they are being bombarded by new knowledge, so they have to filter out the “noise” and determine the best test to use.” In order to address the challenge of educating physicians and support staff, Dr. O'Neil suggests successful strategies may include information provided by CME courses; dissemination of results at conferences/meetings and symposia; sales reps and gaining access to review articles in peer reviewed journals.

It is important to note that tumors can exhibit mixed test results, because of variability within tumors and over the lifetime of a cancer, which poses significant challenge to the validity of molecular diagnostics.⁵ This irregularity complicates the understanding of cancer pathways, and anticipated drug response and resistance, adding greater difficulty to refining personalized therapeutic targets.⁶ This means that a single biopsy may not be representative of the genetic composition of the cancer and a single snap-shot biopsy at a single time-point may no longer be sufficient. Longitudinal tumor sampling approaches will be essential to decipher the impact of tumor variability on

cancer evolution, and this will necessitate the development of minimally invasive methods to profile tumor genomes.

Successfully directed targeted therapy depends largely on the availability of specific tests to determine which patients express the drug target (biomarker), and on evidence that these patients display a differential response to the drug compared with those patients who lack the biomarker.⁷⁻⁹ Also, even if a test proves not to be predictive for response to a new treatment, the test may still be useful in development of the therapeutic if it can identify those patients who have relatively poor response to standard-of-care, and the new therapeutic improves that outcome.

It has been suggested that as more variants are being discovered, a framework of acceptable evidence, particularly for the most promising markers, needs to be agreed upon by payers and test developers. This issue is further complicated by regulatory approval issues, at a national and institutional level. Currently, diagnostic tests are not required to demonstrate evidence from large clinical trials, which creates a challenge for institutional review boards, payers and physicians of determining how and when to implement a new test into their practice or facility. Dr. Hahn has suggested, “The creation of a ‘just in time’ IRB model in order to alleviate the long delays in the institutional review process and address the urgency to provide answers and find the best treatment for the mutation.”

The experts agreed that a good example of a successfully developed test is Oncotype Dx. Dr. Schilsky explains that it was, “Good strategy because they partnered with a research group for biospecimens where the outcome was known and have repeatedly run the test to validate. So they used a prospective - retrospective approach to validate. The same strategy was used in *KRAS* testing for colorectal cancer.” Dr. Schneider agrees, “Oncotype Dx provides clear answers and is understandable by physicians.” Dr. Donna Messner from the Center for Medical Technology and Policy adds, “Oncotype Dx is an example of a company with a good laid out strategy going from payer to payer with the evidence they needed. When confronted with good evidence they will write a policy to use it.”

Communication and Informed Consent

As the scientific information and promising results surrounding the use of molecular diagnostics becomes increasingly available and publicized in mainstream media, patients and their families expect a greater knowledge from their front-line health care providers. There is a growing need for oncology health care providers to become comfortable with incorporating information about genetics/genomics into their clinical practice and patient education. Additionally, increased expectations in cancer care and outcomes are created. The experts interviewed agreed that clear explanation and setting of reasonable expectations is key. Patients have greater access to medical information than ever before, but they may lack the ability to appropriately decipher and make valid conclusions from what they read or hear. These expectations are often difficult to meet, particularly in view of limited health care resources. The increased focus on evidence-based and personalized cancer care exaggerates public and professional expectations, potentially creating a credibility gap. As such, organizations like the European Society for Medical Oncology were compelled to release a statement on World Cancer Day in 2013, dispelling the myth that personalized medicine is ‘already a reality for all cancer types and all patients with cancer’.

Oncologists, teachers, and associations are required to fill the credibility gap through communication with individual patients and families, as well as through education of the public and oncologists in training. Appropriate communication between physicians and their patients and caregivers regarding treatment improvements, whether marginal or doubtful and the associated costs is recommended in order to refrain from perpetuating false hopes about new treatments.¹¹ Cherny and colleagues recently published their description of the relationship between

personalized medicine and biologically personalized therapeutics. They set out areas of a biopsychosocial model of medicine that must be as personalized as the genetically informed biological care, stressing that each patient has individual needs for communication, for psychological and emotional wellbeing, social functioning, and spiritual expression and care; noting that in very few cases would the exact same approach work for all people with a similar condition.¹² Dr. Sing suggests that, “We need to communicate to the patient in a way that makes them feel like a member of the decision-making team. Don’t say you must do something in an absolute way, use more recommendations.”

In a study from early 2014, McGowan and colleagues conducted in-depth interviews with 117 stakeholders from a wide variety of institutional and professional settings to analyze their experiences and perspectives related to personalized medicine in oncology.¹³ They found that despite a considerable enthusiasm for the shift toward personalized medicine, promoters, monitors, and providers had heightened ethical and social concerns, related to informed consent for cancer genomic testing; privacy, confidentiality, and disclosure of genomic test results; access to genomic testing and targeted therapies in oncology; and the costs of scaling up pharmacogenomic testing and targeted cancer therapies. These results indicate that a great deal of work is still needed in these areas.

There is also confusion about the difference between molecular diagnostics and genetic testing. Patients need to understand the implications for the type of test being proposed. Receiving informed consent for genetic testing from patients can be complex and time consuming. The American Society of Clinical Oncology has developed a list of elements of informed consent for cancer genetic testing, including (1) information on the specific test being performed, (2) implications of positive or negative results, (3) possibility that the test will not be informative, (4) options for risk estimation without genetic testing, (5) risk of passing a mutation to children, (6) technical accuracy of the test, (7) fees involved in testing and counseling, (8) risks of psychological distress, (9) risks of insurer or employment discrimination, (10) confidentiality issues, and (11) options and limitations of medical surveillance and screening following testing.¹⁰

Test Specimens and Biobanking

Molecular diagnostic tests are performed on appropriately collected and stored biospecimens (blood or tissue from a tumor removed, spinal fluid, urine, or nail clippings). In order for testing to be performed, the specimen must meet the specific requirements of the molecular test with respect to the amount of tissue or fluid and be handled, prepared, stored and shipped in a precise way in order to preserve the sample. Coordinating the collection and handling of a sample requires excellent communication between multiple healthcare professionals and support staff. Tissue handling guidelines are often in place to minimize logistic issues.

Biobanks are sophisticated systems of programmed storage of a large number of archive specimens and corresponding health data. In cancer research, these biobanks are a key resource for genomic studies and development of therapeutic targets, biomarkers and drug discovery. The confidentiality of a patient’s biobanked information is critical and researchers must have protocols in place to ensure data is kept secure and private. Specimens are connected to patient data (including family health history and clinical treatment-related data) accurately and efficiently, and then it is ‘de-identified’ when researchers access it. This ‘de-identification’ is an extremely important step and ensures patient privacy and confidentiality. A recent US study found that participants cared about the confidentiality of their data, in part because it gave them a feeling of retaining some control over their information. Additionally, patients expressed a need to be protected from the possible dangers of disclosure, particularly for insurance and employment discrimination.⁷

In an effort to address some of these types of concerns, The Genetic Information Nondiscrimination Act (GINA) of 2008 was established and protects the provision of health insurance and employment against discrimination based on genetic information. More specifically, the Act prohibits access to an individual's personal genetic information by insurance companies and by employers and prohibits insurance companies from requesting that applicants for group or individual health coverage plans be subjected to genetic testing or screening and prohibits them from discriminating against health plan applicants based on individual genetic information.¹⁴

Interpretation of Results

As noted above, experts agree that in order for a test to be used by clinicians, the results need to be easily interpretable and understandable. The interpretation of test results can be complex and in many larger institutions and care centers a tumor board has been established. Tumor boards integrate expertise from medical, surgical and radiation therapy oncologists, biostatisticians, radiologists, pathologists, clinical geneticists, basic and translational science researchers, and bioinformatics and pathway analysis specialists to discuss the intricacies of tumor genetics and inform and recommend a personalized treatment plan. For challenging cases or for clinicians who may not have access to a local tumor board, web-based interactive tumor boards for expert consultation are being developed. Additionally, cancer gene databases have been established that provide details about clinically significant gene variants and their relationship to outcomes, treatments and ongoing clinical trials.¹⁵

Patients are key stakeholders in molecular diagnostics and their understanding and perception of the tests and results are vital. Dr. Schneider stresses the importance of good doctor/patient communication, "The patient expects a decision to be made, a 'yes' or 'no' from using the test. We must provide an alternative to the problem identified. People do not understand relative risk reduction, and absolute numbers are easier to understand. We won't ever get to 100% or 0%, but patients can handle 10% - 90%." Communication of test results to the patient requires the clinician have a thorough understanding of the ethical, legal, and social implications of genetic testing and the ability to provide accurate responses to complex questions and issues that may arise during the process of risk assessment and counseling.

Patients are unlikely to understand the statistical methods used to calculate relative risk and what the actual implications will mean to them. A recent study by Bombard et al demonstrated that in a group of early stage breast cancer patients undergoing gene expression profile testing for estimating baseline recurrence risk, patients tended to overestimate the truth-value of the testing based on misperceptions of its validity.¹⁶ They stated that they valued the test because it provided them with certainty amidst confusion, with options and a sense of empowerment, and with personalized, authoritative information. As well, they commonly believed that the test was better and fundamentally different from other clinical tests, attributing to it unique power and truth-value.

Consideration of the patient's psychological and emotional ability to handle the testing and results disclosure process can help avoid doing harm. Predictive testing for cancer susceptibility presents a challenge because of the hereditary nature of the diseases being tested and the implications of genetic risk for family members. Physicians are faced with a duty to warn or to act to prevent foreseeable harm. One practical suggestion for facilitating family-based communication is providing patients with education and information materials to facilitate disease susceptibility discussions with family members.

Access to Treatment

By defining the molecular pathways driving tumor growth, drug targets (biomarkers) can be identified. Drugs able to specifically inhibit such drivers of disease are offering exciting new therapies for many forms of cancer, such as it has for *HER2*-receptor positive breast cancer.²

Once a treatment plan has been made, based on the patient's molecular profile, it can be challenging to obtain the drugs predicted to be the most beneficial. Often, these drugs will be prescribed off-label or as investigational agents only available through participation in clinical trials. Dr. Hahn indicates that, "Advocacy is needed to assist patients with the practical and often logistical issues that may prohibit their clinical trial participation." Rarely, pharmaceutical companies can make these agents available through an expanded access program.¹⁴ The American Society of Clinical Oncology recently developed a new access program and registry to facilitate use of off-label cancer drugs and its hope is to serve as a model for medical specialty societies that would serve as intermediaries between drug companies and patients seeking early access to experimental medicines. Dr. Messner further explains, "A network is needed where oncologists can say there is an off label use and agree to become part of clinical trial. There is a need to establish these networks with regional hubs that collect patient information and studies."

Direct to Consumer Tests

Oncology researchers and clinicians find that the 'direct to consumer' genetic testing kits (23andMe, etc.) available to the general public may provide general information but offer no guidance. Dr. O'Neil has found that not many of his patients come to him with questions or have these tests performed. This type of testing does not deliver quality information needed for good decision making. Additionally, Dr. Hahn expressed concerns that, "When testing is done in this way, the medical and scientific community loses the opportunity to collect that data to build biobanks and inform science."

The Economics of Molecular Diagnostics

Ultimately, personalized cancer therapy is anticipated to become the financially preferred model, by treating the patient with the right therapy, the first time, achieving prolonged responses, and ultimately leading to cures. Unfortunately this is not yet established because longitudinal accounting, which would enable payers to capture long-term cost savings is lacking.

The economics of testing and treatment remains a multifaceted issue, due to disconnects in the system between payers, test developers, academic centers and local community practices. Dr. Messner explains, "We are missing dots that connect all those things. Each major academic center is developing their own biomarkers and their own way of using them for patients. Payers have policies that work for local community practices but not academic medical centers because they are in the investigational space. All disconnects are a problem." Dr. Schneider mentioned the hurdles of developing tests in an academic setting but there is no clear pathway to get a test on the market so it can ultimately benefit patients.

The associated costs and reimbursement for molecular diagnostic testing can be unaffordable to payers and the individual. Targeted therapy benefits only a subpopulation of patients with biomarkers that indicate sensitivity, and these benefits are frequently transient. Thus, making it difficult to demonstrate the cost benefit of particular approaches. However, it is important to note that molecular marker approaches have the potential to indicate which patients will not benefit from expensive therapies, and that will provide a major opportunity for cost savings. For example, several multivariate assays have been developed that indicate patients who do not need and will not be likely to benefit from chemotherapy, thus decreasing both cost and morbidity.¹⁷⁻²¹ Similarly, patients with *KRAS* mutations are unlikely to benefit from EGFR-targeted therapy, thus sparing the high costs of targeted therapy.²²

An intriguing approach that has recently been implemented is to link reimbursement of drug costs to demonstrated benefit for the individual patient. This method, which is currently applied solely to drug costs, could

be combined to determine the level of reimbursement for molecular diagnostics. Despite clinicians and patients having access to genomic resources, personalized medicine may be cost prohibitive, particularly if patients' results indicate expensive targeted therapeutics that fall outside the standard of care, are not covered by insurance, or both. Because severe financial burdens are imposed on many patients with cancer and their family caregivers, it is critical for the healthcare team to learn how to communicate properly and ethically about treatment costs, benefits and risk. As an example, genome sequencing and tumor typing are especially appealing to cancer patients who have exhausted the standard therapies, but these approaches are rarely covered by insurance plans. These types of situations further highlight inequalities in patient access to targeted therapeutics based on an inability to pay, thus creating an ethical dilemma.¹³ Dr. Messner stresses the importance of advocacy in this area, "Advocates need to try to convince payers that there needs to be more flexibility from payers around biomarkers that are important. Advocates can be helpful in working with both entities, payers and test developers in these areas." Further advocacy is needed in this area, to advise payers that meaningful clinical evidence can be provided by well-designed observational studies.

Biomarkers and molecular diagnostic medicine are replacing the "one size fits all" healthcare model. It is predicted that in the next decade oncology will move from a reactive to a proactive discipline and become predictive, personalized, preventive and participatory (P4). New tools, for implementing preemptive medicine based on genetic and molecular diagnostics and interventions will emerge and these will improve prevention, early detection, and access to care. The role of advocates in this area will be instrumental in building information networks and providing connections to inform the different stakeholders, facilitate access and improve patient care.

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