A Health Services Research Agenda for Cellular, Molecular and Genomic Technologies in Cancer Care

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Key Words

Genomics · Health services research · Emerging
technologies · Translational research

Abstract

Background: In recent decades, extensive resources have been invested to develop cellular, molecular and genomic technologies with clinical applications that span the continuum of cancer care. **Methods:** In December 2006, the National Cancer Institute sponsored the first workshop to uniquely examine the state of health services research on cancer-related cellular, molecular and genomic technologies and identify challenges and priorities for expanding the evidence base on their effectiveness in routine care. **Results:** This article summarizes the workshop outcomes, which included development of a comprehensive research agenda that incorporates health and safety endpoints, utilization patterns, patient and provider preferences, quality of care

and access, disparities, economics and decision modeling, trends in cancer outcomes, and health-related quality of life among target populations. **Conclusions:** Ultimately, the successful adoption of useful technologies will depend on understanding and influencing the patient, provider, health care system and societal factors that contribute to their uptake and effectiveness in 'real-world' settings.

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Introduction

Within the past 30 years, extensive resources have been invested to develop cellular, molecular and genomic (CMG) technologies with clinical applications that span the continuum of cancer care [1]. The capacity for innovation stems largely from our rapidly expanding knowledge base in molecular carcinogenesis [2] and biotechnology. However, there are many challenges to trans-

lating this knowledge into clinically useful and well-implemented interventions for cancer prevention, early detection, diagnosis and treatment [3].

The National Institutes of Health (NIH) have emphasized that translation and integration of new technologies are major priorities. Currently, 2 of 4 components in the NIH Core Strategic Vision directly address integration of research innovations into health care delivery, emphasizing the need to 'accelerate translation of findings from the bench to the bedside to the community' as well as 'provide the evidence and knowledge base to allow for a rational transformation of our healthcare system' (<http://www.nih.gov/about/director/newsletter/Spring2007.htm>).

In December 2006, the National Cancer Institute (NCI) sponsored the first workshop of researchers to focus on the delivery of CMG interventions in cancer care. The goals were to examine the current state of health services research (HSR) on CMG interventions and to identify research priorities and challenges to expand our limited knowledge base about their effectiveness in 'real-world' settings. Participants were primarily from academia and government, with expertise in HSR, including clinical decision making, economics, clinical and translational medicine, technology assessment, policy, and other areas. The workshop addressed cutting edge issues from a wide range of perspectives and also developed recommendations for advancing a comprehensive HSR agenda on cancer-related CMG interventions. The objective of this report is to summarize the main workshop conclusions, beginning with a discussion of knowledge gaps surrounding the use of CMG interventions, followed by research needs and challenges, and ending with recommendations for a comprehensive HSR agenda to advance our understanding of their effectiveness. Several relevant areas are not addressed in this report because of limited coverage during the workshop. Their importance, however, is acknowledged in the section on workshop limitations.

The Scope of HSR

HSR is defined by AcademyHealth (the primary professional organization for HSR) as 'the multidisciplinary field of scientific investigation that studies how societal factors, financing systems, organizational structures and processes, health technologies, and personal behaviors affect access to health care, the quality and cost of health care, and ultimately, our health and well-being' (<http://www.academyhealth.org/about/whatishsr.htm>). Box 1

lists the main areas of HSR, as described by the Blue Cross Blue Shield Association (<http://www.bcbs.com/about/foundation/health-services-research-definition.html?templateName=template-28719196&print=t>).

Box 1: Components of Health Services Research

- Costs, cost-effectiveness, cost-benefit and other economic aspects of health care
- Patient and population health status/quality of life
- Outcomes of health care technologies/interventions
- Practice patterns and diffusion of technologies/interventions
- Quality assurance programs/techniques designed to test generalizable attributes
- Guidelines, standards and criteria for health care
- Patient compliance with treatment
- Need and demand for health care
- Availability and accessibility of health care
- Utilization of health care
- Patient preferences for treatments, providers, settings and so forth
- Organization and delivery of health care (for example, managed care vs. fee for service)
- Health care workforce
- Financing of health care (for example, public and private third-party payment, capitation)
- Health care administration and management
- Health education and patient instruction
- Health professions education
- Health planning and forecasting
- Legal and regulatory changes affecting the health care system (for example, anti-trust laws)
- Data and information needed for health care decision making (for example, report cards)
- Studies of whether new health care technologies/interventions (including randomized controlled trials) can produce a desired outcome in real-world settings of general or routine clinical practice

The traditional methods employed in HSR to evaluate familiar interventions like mammography or chemotherapy are, for the most part, applicable to research on CMG technologies. However, the latter may have distinguishing features that require new methodologies or adaptations to existing ones. Such features may include: limited insurance coverage (for example, genetic counseling) and inadequate coding systems (for example, laboratory genetic testing) that make it difficult to track or

identify an intervention in claims databases, the need to analyze and condense massive amounts of data points (for example, microarray-based gene polymorphism and expression assays), low power due to risk stratification of patients into multiple groups (for example, pharmacogenetics), rapid translation to clinical use with little clinical outcome data (for example, laboratory genetic testing), heightened concerns about genetic discrimination, and the complexities inherent to studying families rather than individuals (for example, predictive genetic testing for cancer risk assessment). Clearly, the strategies for HSR will vary by technology.

The Scope of CMG Technologies in Cancer Care

Public and private funding has supported extensive research to develop a broad spectrum of CMG clinical applications, although progress has been uneven across cancer sites and technologies. Applications in cancer care range from primary prevention and early detection of malignancy to confirming diagnosis, selecting type and dose of treatment, and monitoring treatment effectiveness. Commercially available tools for primary prevention include predictive genetic tests for hereditary high-risk mutations [4], nucleic acid and protein-based tests for oncogenic infectious agents [5–7], and recombinant prophylactic vaccines against human papillomavirus [8] and hepatitis B [9].

There has also been considerable research on biomarker tests for early detection of cancer, where the challenges of developing highly sensitive and specific tests have limited the number of clinical applications currently in practice [10, 11]. A recent ‘horizon scan’ on genetic tests for cancer performed by the Agency for Healthcare Research and Quality (AHRQ) technology assessment program lists 11 screening tests that rely on DNA or protein-based technologies, including the widely used prostate-specific antigen test (<http://www.ahrq.gov/clinic/ta/gentests/gentests.pdf>).

The majority of cancer biomarker tests, including 54 listed in the AHRQ report, are used for the diagnosis and/or treatment of cancer. Some diagnostic tests identify abnormal gene expression in tumors that may respond to targeted therapies, such as trastuzumab for HER2-positive breast cancers [12]. The BCR-ABL gene test can be used to diagnose chronic myelogenous leukemia as well as monitor response to the tyrosine kinase inhibitor drug imatinib that targets the BCR-ABL protein [13]. Several gene expression-profiling tests detect and analyze pat-

terns of multiple genes expressed in early-stage breast tumors, providing a prognostic score to identify potentially more aggressive tumors for which adjuvant chemotherapy is indicated [14, 15]. Other genetic tests identify germline polymorphisms associated with drug toxicity or nonresponse, enabling early dose adjustment or selection of alternative therapies [16, 17].

CMG applications also include targeted and supportive therapies to treat cancer. Targeted therapies, such as monoclonal antibodies or drugs, are designed to interfere with specific molecular pathways important to the growth and survival of tumor cells. Several targeted therapies that inhibit kinase enzyme activity (such as trastuzumab, imatinib, erlotinib in epidermal growth factor receptor-positive non-small-cell lung cancer) have received Food and Drug Administration (FDA) approval and are in clinical use. Promising approaches to targeted drug delivery include chemotherapy molecules conjugated to natural or synthetic nanoparticles, which are efficiently taken up by tumor cells with fewer toxic side effects than drug formulations requiring solvents [18–20]. Supportive care therapies, such as hematopoietic stem cell transplants and growth factor therapies, are used to replace stem cells or stimulate production of red and white blood cells destroyed by chemotherapy or radiotherapy [21–23].

Functional imaging and optical technologies have diverse applications, ranging from detection of early lesions and metastatic disease to monitoring response to treatment. In vivo functional imaging techniques enable visualization of molecular pathway activities, enhancing characterization of the disease state when used in conjunction with structural imaging data [24, 25].

Not unexpectedly, the number of CMG innovations in the developmental pipeline that are described in the literature exceeds the number currently used in clinical care. Although a strong scientific rationale often exists for their use, some technologies are not sufficiently developed to yield clinically useful results or improvements over existing interventions [26]. Nevertheless, contextual factors, such as direct-to-consumer and provider marketing [27, 28], press coverage, or advocacy and lobbying activities, may drive their diffusion into clinical practice before their safety and efficacy are well understood.

Gaps in Efficacy Research

A major concern for many emerging CMG interventions is the limited amount of published premarketing clinical data about safety and efficacy, which provides the

basic evidence that new technologies have net benefit (that is, improve health outcomes). Premarketing safety and efficacy data are evaluated in technology assessments, which are critical for decision making about appropriate clinical uses of new technologies, coverage and reimbursement by insurers, and evidence-based guidelines. Technology assessments also identify existing gaps in both premarketing efficacy data and real-world effectiveness data. Gaps in premarketing research on CMG technologies are summarized in box 2. Three areas with significant gaps include targeted therapies, screening interventions and gene-based tests.

Box 2: Research Gaps for CMG Technologies

Limited published data on analytic and clinical validity as well as clinical utility of diagnostic and predictive tests, and devices:

- Lack of gold standards with which to assess analytic validity
- Studies of analytic validity often not published or otherwise publicly available
- Studies of clinical validity often small and not designed to yield definitive results
- Studies on clinical utility (that is, impact of diagnostic tests on subsequent treatment decisions or patient outcomes) seldom done
- In the United States, evidentiary standards for regulatory (that is, FDA) approval of laboratory tests and devices are less stringent than those for approval of therapeutics; in addition, laboratory tests may avoid FDA regulation entirely if developed in a laboratory and offered as a service by the same lab

Limited published randomized controlled trial data on safety and efficacy of therapeutics:

- Studies often have small sample size, restrictive inclusion criteria, short duration and surrogate outcomes
- Concerns about market segmentation may serve as disincentives for conducting pharmacogenetic drug trials

Limited data on outcomes and effectiveness in routine clinical care:

- Standards of care needed in the early stages of diffusion cannot be developed in the absence of clinical data

- Minimal HSR has been done to examine whether appropriate levels of care are being provided, what the determinants are of disparities in outcomes and care, and what organizational or other changes are needed to optimize care
- Minimal surveillance has been conducted to monitor long-term outcomes of new interventions related to health, safety and quality of life
- Minimal economic studies have been done to assess incremental costs and cost-effectiveness of new technologies

With respect to therapeutics, FDA approval requires data from randomized controlled trials (RCTs) to establish the safety and efficacy of new oncology drugs and biological therapies. Yet, RCTs of novel therapeutics often lack the power to detect uncommon adverse events and are not designed to assess off-label uses [29]. Short trial duration and use of surrogate markers as primary endpoints can also limit understanding of therapeutic outcomes. Furthermore, the generalizability of trial results may be affected by restrictive inclusion criteria that cause key demographic subgroups to be underrepresented. Unfortunately, these subgroups, such as elderly patients or those with comorbidities, may actually comprise a large proportion of users in routine care. In addition, incentives to assess pharmacogenomic differences in drug response may be tempered by industry concerns about market segmentation if fewer patients are found to benefit from treatment [30].

Gene-based tests to detect abnormalities in a single gene or a broader array of genes represent an area of growing importance for treatment decision making. Data from observational studies are typically used to obtain FDA approval for in vitro diagnostic test kits. However, laboratory-developed tests that are not marketed as kits, such as breast cancer (BRCA) tests for breast/ovarian cancer risk assessment and OncotypeDX™ for breast cancer prognosis, are not currently subject to FDA clearance. In contrast to test kits, laboratory-developed tests may enter the market with minimal published information about analytic and clinical validity [31, 32].

With the widespread availability of different high-throughput genomic and proteomic platforms and analytic techniques, and the lack of a gold standard for comparison to genomic expression data (or with current gold standards that are not adequately sensitive and/or specific), it can be difficult to establish analytic validity of a test. Furthermore, although the association of new biomarkers with patient outcomes (that is, clinical validity)

often provides the incentive for test development, the predictive value of a test is likely to differ in high- versus low-risk populations, thus requiring costly large samples to assess genetic, demographic or other variation. Other issues can limit validation studies as well. As an example, a recent AHRQ evidence report on genomic tests for ovarian cancer found that studies had small sample sizes and spectrum biases, which affected the estimates of test sensitivity and specificity. These studies also had unrealistically high disease prevalence, which affected predictive value (<http://www.ahrq.gov/clinic/tp/genovctp.htm>).

Finally, validation studies alone cannot assess the clinical utility of diagnostic tests, which addresses test impact on subsequent treatment decisions and patient outcomes. Most tests lack information on clinical utility when first introduced into clinical practice. The same AHRQ evidence report on ovarian cancer found that the use of genomic tests to guide management decisions, and improvements in patient outcomes (compared to standard management), had not been evaluated in the context of diagnosis, or primary or secondary prevention. These limitations are not unique to genomic tests. Validation studies of optical technologies and molecular imaging devices also require costly large samples to examine sources of variability, and there are similar challenges to selecting appropriate gold standards and surrogate endpoints [33, 34].

Gaps in Effectiveness Research

Even with promising premarket safety and efficacy data about many CMG interventions, the actual net benefit observed in real-world settings is typically less than the expected net benefit obtained from RCTs, for several reasons. First, the former includes a more diverse, often sicker, patient population exhibiting less adherence and persistence with therapy, drug-drug interactions or pharmacogenetic factors, and variations in delivery of care due to provider practices, coverage and reimbursement, or access. Furthermore, the short-term surrogate endpoints examined in RCTs may correlate imperfectly (or even poorly) with long-term health outcomes, especially if the natural history of the disease is not well understood or the clinical course is heterogeneous. The potential for differences between RCT and clinical practice results underscores the need to monitor the effectiveness of CMG interventions in routine care. Research on effectiveness also evaluates whether appropriate care is being provided

to those who need it, resulting in improved health and health-related quality of life.

Gaps in effectiveness research are summarized in box 2. For many CMG interventions, relatively few studies have examined uptake and patterns of care or associated clinical outcomes in routine care [35]. Similarly, the incremental costs, life expectancy and quality-adjusted life expectancy gains associated with CMG interventions, relative to clinical practice without their use, have not been evaluated; these will be necessary to conduct economic evaluations, such as cost-effectiveness and cost-utility analyses [36].

One explanation for knowledge gaps about effectiveness is that funded cancer research focusing on the delivery of CMG interventions has been minimal. In a search of the NCI cancer research portfolio database (<http://researchportfolio.cancer.gov/>) from 2000 to 2006, only 12 HSR or related grants were identified that focused on delivery of care involving CMG technologies [Ambs and Wideroff, pers. commun.]. These grants, which totaled USD 12 million, were found by independently entering 19 biotechnology search terms (such as genetic tests, pharmacogenetics, biological therapies, cancer vaccines and nanotechnology) and restricting results to grants and contracts with research-type codes for patient care and survivorship, surveillance, cost analyses, health care delivery, education, communication, resources or infrastructure. No additional grants were found when the search term 'health disparities' was added to each technology. One caveat is that projects conducted within large research infrastructures, such as cancer centers or P01 grants, cannot be individually identified in abstracts, which possibly results in some underestimation. Nevertheless, to put this in perspective, total NCI research expenditures for the same period were approximately USD 18.29 billion (NCI Annual Fact Book, <http://obf.cancer.gov/financial/factbook.htm>; see 2001 link: Total Research Grants, page 6/iv, for fiscal year 2000 and 2001 expenditures; see 2003 link: Total Research Grants, page 7/v, for 2002 and 2003; see 2004 link: Subtotal Research Grants, page 41/B-4, for 2004; see 2005 link: Subtotal Research Grants, pg. 53/B-4, for 2005; see 2006 link: Subtotal Research Grants, page 53/B-4, for 2006).

How to Address HSR Gaps

A strong HSR agenda is needed to evaluate clinical utility and reduce uncertainty about the net benefits of CMG interventions. Box 3 summarizes ways that HSR

can contribute to the knowledge base for CMG interventions. The HSR agenda should include postmarketing surveillance to systematically monitor adverse events of new therapies, devices and tests. Such research is needed to determine the balance of risks versus benefits of emerging CMG interventions among the heterogeneous populations that receive care in community settings (http://www.nap.edu/catalog.php?record_id=11897#toc). For example, postmarketing surveillance research has yielded valuable information about the risks and benefits of hematopoietic growth factors used in association with adjuvant chemotherapy [37, 38].

Box 3: Ways to Address Research Gaps in CMG Technologies

Conduct postmarketing surveillance to systematically assess CMG technologies within well-defined target populations:

- Monitor clinical endpoints to assess safety and health outcomes
- Monitor patient-reported outcomes, such as functional impact and psychosocial and economic burden

Broaden research to evaluate the effectiveness and clinical utility of CMG technologies, by determining if appropriate care is being delivered to the target populations, with improvements in health and health-related quality of life:

- Assess prevalence and determinants of patient and provider use, knowledge, and attitudes
- Monitor trends in health plan and government policy toward coverage
- Determine economic impact, including incremental cost, cost-effectiveness and cost-utility
- Assess the multiple dimensions of access to care, particularly among medically underserved and target populations (that is, affordability, availability, acceptability, access by target populations, and accommodation of practice-to-patient constraints and preferences)
- Determine the occurrence, determinants and consequences of disparities in care, and test interventions to reduce or eliminate them
- Evaluate net benefit based on population trends in incidence, mortality, survival, and quality of life

Expand use of decision analysis in premarketing and postmarketing research to model the effectiveness of CMG technologies that add to or substitute existing standards of care:

- Change the model parameters to assess relative costs and benefits of interventions
- Compare interventions in populations with varying economic and health care resources and sociocultural practices

Yet, HSR must go well beyond postmarketing surveillance to assess the adoption and impact of emerging CMG interventions at the patient, provider, health system and population levels. A wide range of outcomes should be studied, including patient-reported quality of life indicators (such as functional impact, psychosocial and economic burden) [39], trends in patient and provider uptake and use, knowledge, attitudes and other determinants that might facilitate or hinder adoption and appropriate use in specific settings [40], trends in health plan and government policy toward coverage and regulation, incremental cost, cost-effectiveness and cost-utility [41, 42], and net benefit based on population trends in incidence, mortality, survival and quality of life [43].

The knowledge obtained from this approach would be useful for defining standards of care and measuring the quality of care involving CMG interventions. In this regard, the Institute of Medicine described 6 aims for health care: safety, effectiveness, patient-centeredness, timeliness, efficiency and equity (<http://www.iom.edu/CMS/8089/5432.aspx>). To measure how well those goals are being met, a link must be made between a given process of care, such as administration of a genomic test or treatment, and an outcome. These links can be difficult to establish. Additionally, the development and testing of quality measures is resource intensive, particularly for interventions that improve decision making and knowledge (<http://mdm.sagepub.com/content/vol27/issue5/>) [44, 45]. However, these links are essential for efficient identification, adoption and promotion of new CMG technologies that can positively impact patients' lives.

Access to health care will remain an important factor in improving overall population health care quality and outcomes. Broadly defined, access covers the dimensions of affordability, availability of services and their access by the target population, acceptability to patients, providers and the health care system, and accommodation of practice to patient constraints and preferences [46, 47]. Although there is currently little research about access to most CMG technologies, many of the issues are very rel-

evant [36]. High costs and limited insurance coverage may impose particular constraints on affordability. For example, biological therapies currently represent some of the highest expenditures in cancer treatment [48]. The monoclonal antibody trastuzumab, indicated for metastatic HER2-positive breast cancer [49], was estimated to cost USD 50,000 per year for a 70-kg woman [50], which potentially limits access for uninsured and underinsured patients.

Availability of health services is another notable constraint to access, particularly for medical specialties with existing or projected work force supply deficits, such as genetic counseling and oncology [51, 52]. With respect to genomic tests, it will be important to have access to high-quality clinical labs that deliver results rapidly, so that the results can influence treatment decisions as near to real time as feasible. This is particularly challenging for single-source tests offered by labs that conduct only 1 or a few tests and do not have an established shipping network. At the patient level, cultural and other factors, perhaps undefined, may also influence access. One study noted a 5-fold higher uptake of genetic counseling for breast cancer 1 and 2 testing in white women, relative to African Americans, that was not explained by socioeconomic or behavioral variables [53].

Inequities in access to care due to socioeconomic, geographic, cultural, racial-ethnic or other factors can ultimately lead to disparities in cancer incidence, mortality and health-related quality of life [54]. Therefore, studies that describe the occurrence, determinants and consequences of disparities, as well as those that test strategies to reduce or eliminate disparities, should be an integral part of an HSR agenda [55]. Although some research has addressed disparities in genetic testing and follow-up care [56], little is currently known about disparities in utilization of most CMG technologies.

Decision-analytic modeling can play an important role in evaluating the incremental costs and cost-effectiveness of an emerging CMG intervention [57]. In a model-based decision analysis, information about the disease, effectiveness of treatment, performance and costs of both new and existing technologies are combined with other relevant demographic and epidemiological characteristics of a target population. These models can be used to comparatively assess the relative costs and benefits of technologies that add to or substitute existing standards of care [58, 59]. Decision analysis can also be used to compare public health strategies in countries or populations with varying economic and health care resources and sociocultural practices [60].

Challenges in Addressing Gaps

Although the rationale to expand HSR on emerging CMG technologies is clear, there is less clarity about how to do this with the available resources. Administrative claims databases have been a mainstay of HSR [61], but may require substantial adaptations to accommodate CMG information, such as: specific standardized coding for new test procedures, and information on patient diagnosis and intent of the test; electronic linkages to additional data sources; incorporation of genetic and family history data. Cancer registries may need to be modified to allow their use for HSR research on CMG technologies, by incorporating data on tumor biomarkers, pharmacy claims and other data elements [62]. Images and multiplex molecular test results may need to be incorporated into electronic medical records systems [63], which are already facing the complexities of interoperability across systems as well as tensions between patient privacy and accessibility to researchers [64, 65]. The more expansive the data required to personalize care based on hereditary and molecular tumor characteristics, the more complex and costly the data systems can become, with potentially long lag times required to implement changes. Even with extensive informatics adaptations, some research questions can only be answered by collecting questionnaire data or other types of information not recorded in the usual databases [66].

Another challenge concerns selection of the appropriate time to initiate HSR in the developmental trajectory of a new CMG technology. Unfortunately, the opportunity to generate published HSR in the technical development and testing phase is often missed because translational studies are typically restricted in scope and do not incorporate HSR disciplines [67, 68]. Consequently, data that directly address health care delivery are often absent from translational medicine conferences and publications. Several conceptual models have described the translation of emerging CMG technologies into health practice, emphasizing the continuum of translational research that could incorporate HSR at various stages [68, 69]. Certain types of HSR, such as decision analysis and assessment of quality of life and acceptability, could be readily integrated into premarket clinical studies. In fact, decision-analytic models can be used to extend the knowledge from empirical studies of CMG technologies to a broader array of clinical situations, and can allow for the extrapolation of costs and health effects beyond the time horizon of a single study. Models can formally relate biological and clinical information, provide quantitative

insight into the relative importance of different uncertain variables, and investigate how results will change if values of key parameters are changed. By identifying the most influential parameters, they can be used to help prioritize and guide data collection efforts as well as assist with the design of randomized trials [70].

Data on costs can certainly be collected during clinical trials, although the highly controlled experimental conditions may not mirror the real-world practice conditions needed for economic analyses [71]. Model-based analyses inevitably rely on uncertain assumptions and parameters; as such, it is imperative that analysts be as transparent as possible and assess the impact of parameter and model uncertainty. The purpose and stage of development of CMG technologies will greatly influence the economic evaluation, due to differences in target populations, amount of available data on clinical outcomes and other variables of interest [72]. Standardization of cost measures and analytic methods can ensure better comparability across economic studies [73].

Incorporation of HSR into premarket clinical studies, and early in the diffusion curve when clinical guidelines and public health policies are nascent, can best be achieved through a scientific, team-based approach that brings together collaborating experts in translational and applied research. Early collaboration could facilitate timely modifications of databases used for postmarketing surveillance to rapidly respond to information needs. Challenges to implementing a transdisciplinary team approach include cross-disciplinary differences in terminology and research culture, complexities in working across institutions, and competing needs of tenure-track investigators to obtain grants and publications in their own specific fields [74, 75]. Also, due to increasing data complexity, the teams may require expansion to include disciplines not previously considered, such as bioinformatics, systems biology and the social sciences.

Understanding the use and impact of CMG technologies among medically underserved populations, such as racial or ethnic minorities and the uninsured, presents further challenges. These populations are often underrepresented in research due to limited access to health care, prioritization of social needs such as food or housing, distrust in the health care system, or other factors [76–78]. Tailored and community-based approaches to recruiting may improve representation in various types of research [79]. Inclusion of underserved populations in basic and translational cancer research can help ensure that HSR addresses relevant questions about health disparities. This is particularly important

when the underserved populations are at highest risk of incidence and/or mortality, as is well-illustrated in the case of African American men and prostate cancer [80].

CMG technologies are evolving in a changing regulatory and policy environment that may or may not facilitate HSR [81]. Regulatory changes favoring pharmacoeconomic information on drug labels may lead to increased opportunities for collaborative HSR. In contrast, exclusion of interventions such as genetic counseling and testing from insurance coverage limits availability of data in claims databases. Ultimately, the growth of HSR on CMG technologies hinges on its perceived importance, the availability of interested research groups and funding resources.

One of the greatest challenges to expanding HSR is constrained government funding [82]. Creative mechanisms for funding HSR research, such as public-private partnerships or interagency federal initiatives, must be explored during this period of tightened budgets. Furthermore, funding agencies should promote initiatives that specifically prioritize health care delivery research on CMG technologies, in both the translational and post-marketing phase. The NIH program announcement, ‘Understanding the Effects of Emerging Cellular, Molecular, and Genomic Technologies on Cancer Health Care Delivery’, is one such example that aims to stimulate grant applications (<http://grants.nih.gov/grants/guide/notice-files/NOT-CA-06-039.html>; <http://grants.nih.gov/grants/guide/pa-files/PA-06-281.html>).

In addition, AHRQ has started a new DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) research network as part of its Effective Health Care program to conduct accelerated studies about the outcomes, comparative clinical effectiveness, safety and appropriateness of health care services (<http://effectivehealthcare.ahrq.gov/aboutUs.cfm?abouttype=decidecert>). AHRQ has also recently solicited proposals to fund demonstration projects that advance understanding of how best to incorporate clinical decision support into the delivery of health care (<http://www.fbo.gov/spg/HHS/AHRQ/DCM/AHRQ%2D07%2D10045/Attachments.html>). Such projects could specifically address funding needs for emerging CMG interventions. Since the workshop described in this article, the Centers for Disease Control and Prevention National Office of Public Health Genomics released several other relevant funding initiatives, under the Genomic Applications in Practice and Prevention program, including one entitled ‘Translation Research’ (<http://www.cdc.gov/od/pgo/funding/GD08-001.htm>)

and a second one entitled ‘Translation Programs in Education, Surveillance, and Policy’ (<http://www.cdc.gov/od/pgo/funding/GD08-801.htm>).

Recommendations for Advancing HSR on CMG Technologies

Box 4 summarizes the recommendations of workshop participants for strengthening HSR on emerging CMG technologies, with recognition that specific strategies depend on the type of technology and its stage of development. HSR should systematically examine the benefits and harms of CMG technologies in routine clinical care. A wide range of outcomes must be studied, including preferences, utilization, access and disparities, quality of care, cost as well as trends in incidence, mortality, survival and health-related quality of life among target populations. Demographically and biologically heterogeneous populations must be studied, using tailored community-based approaches to facilitate recruitment of the medically underserved.

Box 4: A Proposed Health Services Research Agenda for CMG Technologies

- Certain HSR areas, such as assessment of patient and provider preferences, patient-reported outcomes, economic modeling and decision analysis, should be routinely incorporated in the premarketing phases of product development and efficacy testing. The methodologies should be transparent, and the findings should be made publicly available.
- Outcomes should include: patient-reported quality of life indicators; prevalence and determinants of patient and provider use, knowledge, and attitudes; health plan and government policy toward coverage and regulation; incremental cost, cost-effectiveness and cost-utility; net benefit based on population trends in incidence, mortality, survival and quality of life.
- Disparities in access to care and health outcomes should be routinely monitored, with special attention given to inclusion of racial/ethnic minorities and other underserved populations in studies.
- A full range of outcomes should be considered when developing and evaluating quality measures of progress related to CMG technologies.

- Administrative databases of patient records should be systematically evaluated and modified to include infrastructure, data elements and electronic linkages that facilitate HSR. Standard HSR data sources may need modifications to be effectively used.
- Funding agencies and investigators should explore ways to further transdisciplinary team science that bridges discovery, development and delivery research.
- Funding agencies and researchers should explore ways to fund HSR, with creative approaches emphasized during times of budget restrictions. Mechanisms for priority funding should be considered to encourage HSR in both pre- and postmarketing studies.

A transdisciplinary team science approach can help ensure that these critical research needs are met. Certain areas, such as evaluation of patient and provider preferences as well as decision-analytic modeling, can be successfully incorporated into both pre- and postmarketing clinical research. Other areas, such as utilization, access to care and population trends in cancer outcomes are inherently suited for the postmarketing phase. Adaptations may be needed to effectively use standard HSR data sources, such as claims databases, population-based cancer registries and health systems’ electronic medical records.

Workshop Limitations

Given time limitations, some areas were not addressed but should be a focus of further research. Although evidence synthesis and its application in practice are valid forms of HSR, the workshop and its recommendations focused mostly on the primary research enterprise that allows data to be collected for this purpose. Other areas that were not covered include dissemination and communications research, the role of practical clinical trials in building the evidence base for technology assessment [83], and reimbursement policy where evidence is limited. International comparisons were also not addressed, but could shed light on variability in adoption and effectiveness of CMG technologies in countries with different research priorities, clinical practices and health care systems. Specific bioinformatics tools, such as natural language processing, were not discussed in detail, although such tools may be critical to improving the availability and validity of electronic medical records for HSR on emerging CMG

technologies. Institutional review board and privacy policies were not addressed in depth, although their impact on the research climate is significant.

Conclusions

This workshop identified a comprehensive research agenda to better understand the delivery of care for emerging CMG interventions. Meaningful expansion of HSR on CMG technologies hinges on its perceived importance, the availability of interested research groups and funding resources. Ultimately, the successful adoption of appropriate technologies will depend on understanding and informing the patient, provider, health care system as well as societal factors that contribute to effectiveness and uptake in routine clinical care.

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Acknowledgements

We would like to thank Darrell Anderson and Marcia Feinleib of the Scientific Consulting Group Inc., Gaithersburg, Md., USA for editorial assistance.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the NCI, Centers for Disease Control and Prevention as well as the AHRQ.

The study was funded by the NCI (263-MQ-610769 to K.A.P.; 263-MQ-612315 to K.A.; 263-MQ-612317 to C.L.B.; 263-MQ-700870 to M.S.D.; 263-MQ-701381 to M.F.; 263-MQ-612321 to S.J.G.; 263-MQ-611969 to R.A.H.; 263-MQ-612316 to H.L.M.; 263-MQ-612323 to I.P.; 263-MQ-611964 to D.S.; 263-MQ-612324 to K.A.S.; 263-MQ-611967 to the University of York; HHSN261200700005C to Scientific Consulting Group for organizational and editorial assistance).

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