Translating Genomics in Cancer Care

Yvonne Bombard, PhD; Peter B. Bach, MD, MAPP; and Kenneth Offit, MD, MPH

Abstract
There is increasing enthusiasm for genomics and its promise in advancing personalized medicine. Genomic information has been used to personalize health care for decades, spanning the fields of cardiovascular disease, infectious disease, endocrinology, metabolic medicine, and hematology. However, oncology has often been the first test bed for the clinical translation of genomics for diagnostic, prognostic, and therapeutic applications. Notable hereditary cancer examples include testing for mutations in BRCA1 or BRCA2 in unaffected women to identify those at significantly elevated risk for developing breast and ovarian cancers, and screening patients with newly diagnosed colorectal cancer for mutations in 4 mismatch repair genes to reduce morbidity and mortality in their relatives. Somatic genomic testing is also increasingly used in oncology, with gene expression profiling of breast tumors and EGFR testing to predict treatment response representing commonly used examples. Health technology assessment provides a rigorous means to inform clinical and policy decision-making through systematic assessment of the evidentiary base, along with precepts of clinical effectiveness, cost-effectiveness, and consideration of risks and benefits for health care delivery and society. Although this evaluation is a fundamental step in the translation of any new therapeutic, procedure, or diagnostic test into clinical care, emerging developments may threaten this standard. These include “direct to consumer” genomic risk assessment services and the challenges posed by incidental results generated from next-generation sequencing (NGS) technologies. This article presents a review of the evidentiary standards and knowledge base supporting the translation of key cancer genomic technologies along the continuum of validity, utility, cost-effectiveness, health service impacts, and ethical and societal issues, and offers future research considerations to guide the responsible introduction of NGS technologies into health care. It concludes that significant evidentiary gaps remain in translating genomic technologies into routine clinical practice, particularly in efficacy, health outcomes, cost-effectiveness, and health services research. These caveats are especially germane in the context of NGS, wherein efforts are underway to translate NGS results despite their limited accuracy, lack of proven efficacy, and significant computational and counseling challenges. Further research across these domains is critical to inform the effective, efficient, and equitable translation of genomics into cancer care. (JNCCN 2013;11:1343–1353)

Genomics in Cancer Care
There is increasing enthusiasm for genomics and its promise in advancing personalized medicine.1–3 However, the application of genomics in health care is not a novel concept. Genetic testing and risk assessment based on family history has been an established part of standard medical care for decades. Genomics in health care builds on the principles established by the integration of genetics into medical practice.4 What is novel, however, is the scale of genomic analysis with regard to the amount of information considered. Although “classic” genetics evaluates genes in isolation, genomics assesses multiple genes or individuals’ entire genetic sequences and the interactions between genes and epigenetic interactions with the environment, to improve the prevention, diagnosis, and treatment of disease.

Many examples exist of the use of genomic information to personalize health care; these span the fields of cardiovascular disease, infectious disease, endocrinology, metabolic medicine, and hematology.5 However, oncology has often been the first test bed for
the clinical translation of genomics for diagnostic, prognostic, and therapeutic applications (Table 1). Notable hereditary cancer examples include testing for mutations in BRCA1 or BRCA2 in unaffected women to identify those at significantly elevated risk for developing breast and ovarian cancer, and screening patients with newly diagnosed colorectal cancer for mutations in mismatch repair genes (including MLH1, MSH2, EPCAM, MSH6, and PMS2) to reduce morbidity and mortality in their relatives. These examples characterize high-penetrant germline mutations that are associated with large increases in cancer risk (relative risks of 9–33 based on various ages), for which detection facilitates risk-reducing surgeries and/or use of surveillance technologies.

Germline genomic testing is distinct from somatic genomic testing of tumors to predict prognosis and treatment response. Somatic genomic testing is increasingly used in oncology. For example, gene expression profiling (GEP) of breast tumors examines expression levels of a panel of prognostically relevant genes to establish the likelihood of benefit from chemotherapy and recurrence risk within 10 years among node-negative, estrogen receptor–positive patients. A second example is testing for somatic mutations in the EGFR gene to predict response to tyrosine kinase inhibitors, such as gefitinib in first-line therapy or erlotinib in the second- or third-line setting, in patients with advanced non–small cell lung cancer (NSCLC). These applications represent commonly used genomic technologies in cancer care.

### Genomic Translation and Health Technology Assessment

The translation of genomic technologies to health care is typically established through the development of clinical practice and policy guidance. Health technology assessment (HTA) provides a rigorous means to inform clinical and policy deci-

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Target</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Risk assessment</td>
<td>BRCA1, BRCA2</td>
<td>Risk-reducing surgery for breast and ovarian cancers</td>
</tr>
<tr>
<td></td>
<td>MLH1, MSH2 (including EPCAM), MSH6, PMS2</td>
<td>Intensified colonoscopic screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer)</td>
</tr>
<tr>
<td></td>
<td>CDH1</td>
<td>Preventive surgery for hereditary gastric cancer</td>
</tr>
<tr>
<td>Screening</td>
<td>HPV genotypes</td>
<td>Screening for cervical cancer</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>BCR-ABL, E2A-PBX1, TEL-AML1, MLL fusions and rearrangements</td>
<td>Individualizing Rx for leukemia</td>
</tr>
<tr>
<td></td>
<td>Gene expression profiles</td>
<td>Individualizing Rx for subtypes of breast cancer and lymphomas</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Gene expression profiles</td>
<td>Individualizing Rx for breast, colon, and prostate cancers and lymphomas</td>
</tr>
<tr>
<td></td>
<td>HER2/neu, ER, PR</td>
<td>Individualizing Rx for breast cancer</td>
</tr>
<tr>
<td>Treatment</td>
<td>EGFR mutations</td>
<td>Targeting Rx with gefitinib, erlotinib treatment for lung cancer and glioblastoma</td>
</tr>
<tr>
<td></td>
<td>KIT, PDGFR mutations</td>
<td>Targeting Rx for imatinib, nilotinib, sunitinib, sorafenib treatment for sarcomas gliomas, liver cancer, renal cancer, and melanoma</td>
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<tr>
<td></td>
<td>BRAF mutations</td>
<td>Targeting Rx with RAF inhibitors in melanoma</td>
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<td></td>
<td>BCR-ABL translocation</td>
<td>Targeting Rx with imatinib for chronic myelogenous leukemia</td>
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<tr>
<td></td>
<td>KRAS mutations</td>
<td>Precluding need for EGFR inhibition in colorectal cancer</td>
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<tr>
<td></td>
<td>BRCA mutation</td>
<td>Targeting Rx with PARP inhibitors for breast, ovarian, prostate, and pancreatic cancers</td>
</tr>
<tr>
<td></td>
<td>HER2</td>
<td>Targeting Rx with Herceptin (trastuzumab) for HER2+ breast cancer</td>
</tr>
</tbody>
</table>

Abbreviations: ER, estrogen receptor; HPV, human papillomavirus; PARP, poly (ADP-ribose) polymerase; PR, progesterone receptor; Rx, treatment. Adapted from refs. 4,5,7
sion-making through systematic assessment of the supporting evidentiary base, including consideration of clinical effectiveness (eg, validity, utility, safety), cost-effectiveness (eg, economic evaluation), and risks and benefits for health care delivery and society (eg, impact on health services, consistency with societal and ethical values) (Table 2). The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) was established as an advisory body to the Office of Public Health Genomics at the Centers for Disease Control and Prevention to provide evidence reviews for genomic technologies. This independent group adopted review methods similar to HTA frameworks, although HTA frameworks typically include broader considerations of health service delivery, economic analysis, and ethical or social issues. Although evaluation of the evidentiary base of a technology is a fundamental step in the translation of any new therapeutic, procedure, or diagnostic test into clinical care, emerging developments may threaten this standard.

## Emerging Issues in Genomics Translation: Cancer as Harbinger

Genome-wide association studies have defined hundreds of single nucleotide polymorphisms (SNPs) as low-penetrance genetic markers of risk for cancer and common disease. Unlike high- and intermediate-penetrance mutations, SNPs associated with disease risk are common in the population but, in isolation, confer small increases in risk, which vary based on environmental and lifestyle factors. More than 100 SNPs are currently associated with cancer risk, but these tests have uncertain clinical validity, and are therefore not currently considered part of standard oncology or preventive care. However, commercial laboratories currently offer these tests as part of their genomic risk assessment services, termed direct to consumer (DTC) testing.

A second emerging development is massively parallel sequencing technologies of exomes or whole genomes, collectively termed next generation sequencing (NGS). To date, NGS has largely

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### Table 2 Health Technology Assessment Dimensions, Aims, and Methods in Genomics

<table>
<thead>
<tr>
<th>HTA Precept</th>
<th>Aims</th>
<th>Methods</th>
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<tbody>
<tr>
<td><strong>Validity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analytic validity</td>
<td>Accuracy and reliability of the test in detecting the genetic changes of interest</td>
<td>Analytic sensitivity and specificity, assay reproducibility, robustness, and laboratory proficiency testing</td>
</tr>
<tr>
<td>Clinical validity</td>
<td>Accuracy and reliability of the test in identifying patients with the disorder of interest</td>
<td>Specificity, sensitivity, genotype/phenotype relationships, and predictive values</td>
</tr>
<tr>
<td><strong>Utility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical utility</td>
<td>Likelihood that use of the test will significantly improve health-related outcomes</td>
<td>Morbidity, mortality, clinical outcomes, and quality-of-life data</td>
</tr>
<tr>
<td>Personal utility</td>
<td>Benefits of information beyond clinical utility, such as richer self-knowledge, relieving uncertainty, enabling reproductive and life planning, or empowering risk-reducing behaviors</td>
<td>Metric does not exist though (actual or hypothetical) participation rates and satisfaction may be proxies</td>
</tr>
<tr>
<td>Economic evaluation</td>
<td>Value for money: health gain (benefit), relative to resources consumed for a particular health technology (costs) compared with available alternatives</td>
<td>Cost/benefit analysis, cost-effectiveness analysis, and cost-utility analysis</td>
</tr>
<tr>
<td>Health services impact</td>
<td>Feasibility of adopting a genomic technology or implementing a genomic screening program into the health system</td>
<td>Operational and economic feasibility, net budget impact</td>
</tr>
<tr>
<td>Ethical and social values</td>
<td>Consistency of adopting a genomic technology with broadly shared moral and societal values</td>
<td>Primary research, secondary analyses, expert advice/report, and public engagement</td>
</tr>
</tbody>
</table>

been directed toward the discovery of the genetic cause of specific disorders.\textsuperscript{15} NGS is also increasingly applied clinically to panels of genes for the simultaneous analysis of multiple susceptibility genes (multiplex testing)\textsuperscript{16} and to identify mutations in tumors to guide therapy. In the process, comparisons are typically made between the tumor genome and the germline genetic sequence to distinguish causative mutations.\textsuperscript{17} However, in the course of sequencing, NGS reveals incidental germline information, including genetic variants associated with unrecognized current disease, drug response, future risk for common diseases, and variants of unknown significance, on the scale of thousands of variants per individual\textsuperscript{18} (although few would be considered medically actionable). Consequently, oncologists will likely be the first line of health providers to be confronted by dozens of incidental inherited susceptibilities for which their patients with cancer did not necessarily request testing. In a research setting, these incidental findings may be anticipated in discussions of informed consent. However, whether in a research or clinical context, a major challenge has emerged regarding whether incidental NGS results should be actively sought or analyzed, and whether and how these should be disclosed to individuals whose genomes or exomes have been sequenced.\textsuperscript{19–25} Policy guidance has increasingly taken the position that investigators have a duty to disclose actionable incidental results.\textsuperscript{18} In fact, recent recommendations from the American College of Medical Genetics have delineated a minimum set of clinically actionable incidental results that laboratories are required to seek and report in patients they are clinically sequencing.\textsuperscript{26} These developments will create significant ethical and clinical challenges for providers and institutions.\textsuperscript{19,27,28}

Collectively, these emerging issues threaten to undermine the evidence-based translation of genomics in health care because a potential surge of genomic information will be disseminated, which will not have established efficacy based on evidentiary standards required before translation. Furthermore, translation of genomic information of limited clinical validity or utility threatens to create undue pressure on the health care system if DTC users or recipients of NGS incidental results return to their health care providers to request follow-up tests and procedures that may be unnecessary or even harmful. Commentators have posited that this incidental genomic information may lead to a cascade effect, resulting in inappropriate follow-up that would constitute an unjustified use of health care resources.\textsuperscript{27,29}

Thus, because of the advent of tumor sequencing to target therapies and resulting generation of incidental findings, cancer care will continue to chart the course for the translation of genomics in health care. This article presents a comprehensive review of the evidentiary standards and knowledge base supporting the translation of key cancer genomic technologies along the continuum of validity, utility, cost-effectiveness, health service impacts, and ethical and societal issues (Table 3), and offers future research considerations for the responsible introduction of NGS technologies into health care.

**Translating Genomics in Cancer Care: Evaluating the Evidence**

**Analytical Validity**

Analytic validity of a genomic test focuses on the accuracy and reliability of the test in detecting the genetic changes of interest (genotype or analyte).\textsuperscript{13} Measures typically include analytic sensitivity and specificity, assay reproducibility, robustness, and laboratory proficiency testing.

**Examples:** Tumor-Based Screening for Lynch Syndrome: EGAPP found that the overall analytic validity of the preliminary and diagnostic tests for Lynch syndrome is high based on the analytic performance of microsatellite instability (MSI) testing and DNA sequencing, respectively.\textsuperscript{30} However, the analytic validity of the diagnostic sequencing and the Multiplex Ligation-Dependent Probe Amplification (MRC-Holland; Amsterdam, The Netherlands) was not assessed. EGFR Testing to Predict Response to Treatment for NSCLC: A review by Blue Cross Blue Shield Association (BCBSA) found sequencing to have sufficient evidence to support the predictive value of EGFR mutation testing for gefitinib therapy based on sensitivity, specificity, positive predictive value, and negative predictive value of mutation presence compared with its absence.\textsuperscript{31}

**Future Research and Considerations:** Although DNA (Sanger) sequencing remains the gold standard for diagnostic testing, external proficiency testing programs for sequencing do not exist. Furthermore, there is often a lack of a gold standard in genomic technologies, which remains a significant limitation in evaluating an-
Table 3  
Selected Evidence for Genetic and Genomic Technologies, Across Health Technology Assessment Domain

<table>
<thead>
<tr>
<th>Examples</th>
<th>Analytic Validity</th>
<th>Clinical Validity</th>
<th>Clinical Utility</th>
<th>Economic Evaluation</th>
<th>Health Service Delivery</th>
<th>Ethical and Social Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hereditary Cancer Genomics</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tumor-based screening for Lynch syndrome</td>
<td>High (EGAPP)</td>
<td>Adequate (EGAPP)</td>
<td>Adequate (EGAPP)</td>
<td>Cost-effective (ICER $25,000 per life year) (EGAPP)</td>
<td>$41–$281 million (EGAPP)</td>
<td>Informed consent, psychological distress, uptake (EGAPP)</td>
</tr>
<tr>
<td>BRCA testing for breast and ovarian cancer susceptibility</td>
<td>None found</td>
<td>None found</td>
<td>Fair (USPSTF)</td>
<td>Cost-effective</td>
<td>None found</td>
<td>Mixed psychosocial response, low risk of harms (USPSTF)</td>
</tr>
<tr>
<td><strong>Somatic Cancer Genomics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGF testing to predict response to treatment for NSCLC</td>
<td>Sufficient (BCBS)</td>
<td>No conclusions reached (BCBS)</td>
<td>No conclusions reached (BCBS)</td>
<td>Cost-effective (ICER of $46,021 per life year) (OHTAC)</td>
<td>$4.6–$8.1 million (OHTAC)</td>
<td>Improved QoL (OHTAC)</td>
</tr>
<tr>
<td>GEP for recurrence risk in breast cancer</td>
<td>Inadequate evidence (EGAPP)</td>
<td>Adequate (EGAPP)</td>
<td>Inadequate evidence (EGAPP)</td>
<td>Inconclusive evidence (EGAPP)</td>
<td>$4.14 million (OHTAC)</td>
<td>Inadequate evidence (EGAPP)</td>
</tr>
</tbody>
</table>

Abbreviations: BCBS, Blue Cross Blue Shield Association; EGAPP, Evaluation of Genomic Applications in Practice and Prevention; EGF, epidermal growth factor receptor; GEP, gene expression profiling; ICER, incremental cost-effectiveness ratio; NSCLC, non–small cell lung cancer; OHTAC, Ontario Health Technology Advisory Committee; QALY, quality-adjusted life year; QoL, quality of life; USPSTF, US Preventative Services Task Force.

1Evidence relates to reduced morbidity and mortality.
2Based on a study commissioned by EGAPP.
3Total programmatic costs, depending on testing strategy adopted.
4EGAPP review did not conduct a review but commented on these issues in its considerations of the contextual issues.
5Evidence relates to prophylactic surgeries in reducing breast and ovarian cancer risk.
6Based on one analysis on preventative surgeries for women with BRCA1/2, taking a societal perspective.
7Or ICER of $81,071 per QALY.
8Budget impact assuming yearly incidence of advanced NSCLC in Ontario from 2011 to 2015 would be the same as that in 2010, and EGF gene mutation testing was performed once for any patients newly diagnosed with advanced NSCLC from 2011 to 2015.
9Evidence relates to MammaPrint and Oncotype DX.
10Evidence relates to Oncotype DX (no evidence found for MammaPrint and H:1 Ratio Tests).
11Budget impact assuming an update rate of 25%.

alytic validity. Heterogeneity both within and between tumors is a significant confounder in somatic genomic testing, including for patients undergoing EGFR testing. Importantly, neither SNP testing nor NGS have been fully validated. In the case of SNP risk assessment, different risk estimates have been obtained from the same individual’s sample, largely because of variations in analytic algorithms and differences in SNPs analyzed. In the case of NGS, exome sequencing platforms vary in capture efficiency and may fail to detect structural genomic changes or distinguish mutations on the same or different chromosomes. No proficiency testing currently exists in the United States for NGS.

**Clinical Validity**

Clinical validity of a genomic test aims to ensure the accuracy and reliability of the test in identifying patients with the disorder or outcome of interest. Key metrics include clinical specificity, clinical sensitivity, genotype/phenotype relationships, and predictive values.

**Examples:**

- **Tumor-Based Screening for Lynch Syndrome:** EGAPP determined that adequate evidence of clinical validity exists for the preliminary and diagnostic tests to identify Lynch syndrome, wherein sensitivity of preliminary immunohistochemical (IHC) testing was 83% and specificity was 89%. The sensitivity and specificity of preliminary MSI testing varied according to mismatch repair mutations present, and ranged from 55% to 81% and 89% to 90%, respectively. However, EGAPP did not find enough evidence to recommend one preliminary screening strategy over another (eg, MSI vs IHC).

- **GEP for Recurrence Risk in Early-Stage Breast Cancer:** Clinical validity for GEP relies on the ability of the
tests to predict overall or recurrence-free survival 5 to 10 years after surgery versus avoidance of chemotherapy toxicity. Several GEP tests are available, which use real-time PCR or microarray analysis. EGAPP found adequate quality evidence to support the association between recurrence scores produced by Oncotype DX and MammaPrint and rates of 5- or 10-year metastasis. EGAPP also found adequate evidence to support the association between recurrence scores produced by Oncotype DX and chemotheraphy benefit. 

**Future Research and Considerations:** Given the relatively low prevalence of genetic risk factors in the population, highly specific screening tests are required to avoid excessive false-positive results. This is a particularly challenging issue with NGS because of the high rate of false-positive and -negative results, and indeterminate results from computational limitations in assessing novel variants for functional consequences. Family history, clinical information, and alignment of the sequence data with reference databases are commonly used to filter germline variants. Although sequencing remains the gold standard for minimizing false-positive results, its capacity is dwarfed by NGS, creating a need for alternative high-throughput genotyping approaches to validate NGS findings. Validating somatic data is more challenging because of the genetic heterogeneity and purity of the tumors. Comparison with germline tissue from the same patient can filter variants, but this can also result in the identification of incidental, inherited predispositions. Minimizing false-negatives is more complex, and as yet cannot be accomplished given the coverage and quality issues inherent in NGS of exomes or whole genomes. In contrast, NGS technologies applied to panels of genes (multiplex testing) currently have better depth of coverage and accuracy than NGS applied to exomes and whole genomes. 

**Clinical Utility**
Clinical utility focuses on safety, effectiveness, burden of illness, and need. Typical assessments include morbidity, mortality, clinical outcomes, and quality-of-life data. In the case of genomics, clinical utility is based on the likelihood that use of the test will significantly improve health-related outcomes. 

**Examples:** BRCA Testing for Breast and Ovarian Cancer Susceptibility: Despite the fair quality of supporting evidence, the US Preventive Services Task Force (USPSTF) concluded that BRCA testing has clinical utility. This decision was based on evidence indicating that prophylactic bilateral mastectomy in high-risk women has resulted in an 85% to 100% reduction in risk for breast cancer. Similarly, oophorectomy was shown to reduce ovarian cancer risk by 85% to 100% and breast cancer risk by 53% to 68%. GEP for Recurrence Risk in Early-Stage Breast Cancer: EGAPP found no direct evidence to support GEP’s clinical utility. However, in assessing indirect, retrospective evidence for Oncotype DX, they noted a benefit associated with chemotherapy and a 27% reduction in 10-year recurrence rates for women with a high recurrence score who had node-negative, receptor-positive disease. 

**Future Research and Considerations:** Supportive evidence for clinical utility in the hereditary disease context is generally limited by low incidence rates and, by extension, small sample sizes. Although cancer is highly prevalent, assessment of genomic technology often requires cases to be stratified by molecular subtypes, also limiting sample size. Thus, efficacy even for common tumor types may be difficult to demonstrate. For new genotyping technologies, these research gaps will necessarily lead to delays in demonstrating clinical utility. Nonetheless, additional research is needed to assess how individuals use the results of genomic tests in medical decision-making and lifestyle choices, and their associated clinical outcomes (whether testing is provided clinically or DTC, or results are generated incidentally from NGS). Further research on how genomic testing could be incorporated into behavioral interventions (eg, diet, exercise, smoking cessation, cancer screening) support would also be important for determining the clinical value of these technologies. 

**Personal Utility**
Although not a traditional precept of HTA, proponents of genomic technologies have advanced the concept of personal utility, arguing that clinical utility is too restrictive a metric to use in judging the possible benefits of genomic information. Personal utility is believed to offer richer self-knowledge and to empower risk-reducing behaviors, and has gained prominence as a justification for disclosing genomic information in the absence of an evidentiary base or proof of a direct influence on health outcomes. 

**Examples:** Although considered an emerging justification by some, the notion of personal utility
is an established concept in genetics. Provision of genetic tests for untreatable, fatal diseases (eg, Li-Fraumeni syndrome, Huntington disease) and diseases with complex environmental interactions (eg, hereditary melanoma) was predicated on the fact that, despite medical intervention, there is personal utility in knowing one’s risk for a future illness to empower risk reducing behaviors, relieve uncertainty, and inform reproductive, career, or financial decisions.\(^4^\)\(^1\)–\(^4^\)\(^4\) Although a metric for personal utility does not exist, emerging literature suggests the presence of perceived benefits from genetic testing for fatal and complex diseases,\(^4^\)\(^2\)–\(^4^\)\(^4\) and uptake of risk-reducing strategies among individuals with a genetic predisposition.\(^4^\)\(^4\)\(^5^\)

**Future Research and Considerations:** Broader considerations are required regarding whether personal utility is a valid justification for translating genomic technologies, and what weight should be given to this purported benefit in relation to other HTA precepts. This is especially important given the increasing public interest in learning genomic results of uncertain or low utility\(^4^\)\(^6\)–\(^4^\)\(^8\) through commercial DTC companies, or through research efforts designed to return incidental research findings to participants. The desire to improve health has been cited as a common motivator for pursuing DTC testing or participating in genome sequencing research,\(^4^\)\(^9\)–\(^5^\)\(^2\) although research supporting these outcomes has been limited. Given the increasing popularity of DTC testing for low to moderate penetrance alleles and the magnitude of incidental findings from NGS technologies, justifications based on personal utility ought to be weighed against the potential harms of false alarm, false reassurance, and adverse psychological sequelae,\(^4\) in addition to the unjustified use of health care resources.\(^2^\)\(^9\) Longitudinal, comparative effectiveness research on the benefits, harms, and health care use after the receipt of DTC or incidental results from NGS is needed, including comparative observational and randomized trials; assessment of patient-reported outcomes and health service use; decision modeling; and economic analyses.\(^5^\)\(^3\) These studies would build the evidence base supporting the translation of genomic technologies, and could inform the fundamental question of whether these technologies result in additional or inappropriate use of health care services.

**Economic Evaluation**

Economic evaluations consider value for money. Analyses typically measure the health gain (benefit) relative to resources consumed for a particular health technology (costs) compared with available alternatives.\(^3^\)\(^2\) Various approaches to economic evaluations exist, and these differ in the way they measure benefits (but not costs). Cost-effectiveness analysis (CAE) and cost-utility analysis (CUA) are commonly used in HTA. CAE measures health effects, such as life years saved or improvements in functional status (eg, deaths prevented), using an incremental cost-effectiveness ratio (ICER) (eg, incremental costs per death prevented).\(^5^\)\(^4\) CUA is similar to CAE, but CUA measures a technology’s health effects using a health index, such as quality-adjusted life years (QALYs). The incremental ratio used in CUA assesses incremental costs per QALY gained.\(^5^\)\(^4\)

**Examples:** Tumor-Based Screening for Lynch Syndrome: A CAE commissioned by EGAPP found that tumor-based screening for Lynch syndrome is cost-effective and that an IHC-first approach is superior, with an ICER of less than $25,000 per life year saved relative to no testing.\(^5^\)\(^5\) EGFR Testing to Predict Response to Treatment for NSCLC: The economic analysis conducted by the Ontario Health Technology Advisory Committee (OHTAC) concluded that EGFR testing to guide the use of gefitinib as first-line therapy for patients with advanced NSCLC is cost-effective, with an ICER of $81,071 per QALY or $46,021 per life year.\(^5^\)\(^6\) Furthermore, they concluded that EGFR testing is also cost-effective to guide use of erlotinib after the failure of docetaxel or pemetrexed in patients with known EGFR gene mutation status.\(^5^\)\(^6\)

**Future Research and Considerations:** One of the main benefits of genomic technologies is the value of information provided, yet economic analyses do not typically take a value-based perspective, especially when commissioned by a payer for reimbursement purposes.\(^3^\)\(^6\) Economic evaluations also typically base payer decisions on the health system perspective, rather than that of society or the patient.\(^3^\)\(^6\) The patient’s perspective may be particularly relevant in the case of hereditary disorders, in which the need for some intervention may be high but its availability may be limited.\(^3^\)\(^7\) An overriding assumption about genomic technologies that stratify treatment response is that they will provide cost savings. For
example, GEP for breast cancer recurrence risk assessment is estimated to save $400 million a year in unnecessary adjuvant chemotherapy. However, acquired drug resistance to molecularly targeted cancer therapies and the poor specificity of NGS challenge these assumptive cost savings. How these costs savings or expenditures should be taken into account in economic analyses is unclear, but critical in assessing the value for money of genomic technologies.

Health Service Impacts
Considerations of health service impacts focus on the feasibility of adopting a genomic technology into the health system. Analyses focus on organizational feasibility, such as barriers to uptake, capital, human resources, and regulatory aspects. A net budget impact is also conducted to assess economic feasibility of adoption. Examples: Tumor-Based Screening for Lynch Syndrome: Using a cost-consequence analysis, EGAPP estimated total programmatic costs to range from $41 to $281, million, depending on testing strategy adopted. EGFR Testing to Predict Response to Treatment for NSCLC: The budget analysis conducted by the OHTAC reported program costs of $4.6 to $8.1 million from 2010 to 2015. Future Research and Considerations: Service delivery represents a significant gap in translating genomics in health care, including oncology. In the case of Lynch screening, for example, clinical resource needs, clinical expertise gaps, and educational deficits have been identified as potential barriers to implementation. More research is needed on the optimal models for providing genetic services, provider training, and tools to assist providers, such as facilities for outreach and teledermatologic just-in-time management plans, and emergency management tools. Despite the declining costs of NGS technologies, the costs of integrating NGS technologies in clinical care will be substantial, given the need to invest in large-scale resources and build capacity to analyze, validate, and interpret variants. Arguably, these costs may be dwarfed by the additional costs from follow-up tests and procedures caused by incidental findings and false-positive results from NGS technologies over time.

Ethical and Social Values
Considerations of ethical and social values in HTA typically focus on the consistency of adopting a genomic technology with broadly shared moral and societal values. There are 3 general approaches to addressing ethical and social values in HTA: conducting primary research; conducting secondary analyses of published literature on the perceptions, acceptability, quality of life, attitudes, or values of stakeholders; and commissioning expert review. A relatively new approach to addressing ethical and social issues in HTA is public engagement, which is increasingly being used—and even mandated by some jurisdictions (eg, National Institute for Health Care and Excellence [NICE] in the United Kingdom)—in an effort to incorporate citizen values or patient perspectives into HTA and ensuing guidance. Examples: BRCA Testing for Breast and Ovarian Cancer Susceptibility: The report by the USPSTF considered the impact of genetic counseling on psychosocial response to BRCA testing (eg, anxiety, depression, cancer risk perception, uptake) and found mixed evidence. The report also reviewed evidence of harms, such as overdiagnosis and overtreatment, and concluded that the magnitude of potential harms is small. EGFR Testing To Predict Response To Treatment for NSCLC: OHTAC concluded that there was moderate quality evidence of improved quality of life in patients with an EGFR mutation who are being treated with gefitinib relative to those treated with chemotherapy. Future Research and Considerations: Few HTA reports address ethical issues in their analyses. This may be because of the abundance of methods that exist and the limited capacity within HTA agencies to address them. However, substantial literature exists on the ethical and societal issues concerning genomic technologies, which generally focus on informed consent, genetic discrimination, family communication, and other psychosocial issues. Future research would benefit from informed considerations of the broader risks and benefits of translating genomic technologies using novel methodologies that trade-offs benefits relative to risks, such as discrete choice experiments or deliberative, consensus-building exercises. Particularly important ethical and social issues brought about with NGS and molecularly driven treatment are access to technologies and alternative treatment, overdiagnosis, and the auxiliary health care costs of follow-up tests and procedures caused by incidental findings from NGS technologies.
Conclusions

Cancer care represents the leading edge of the impact of genomics on personalized medicine. Notable examples have demonstrated the efficacy of genomic markers for targeting and personalizing cancer prevention, detection, and treatment. Because of the advent of tumor sequencing for targeting therapies, oncologists will be among the frontline of those seeking to responsibly communicate incidental germline findings to patients and their families. Most genomic research focuses on gene discovery and the clinical validity or utility of emerging tests. However, significant challenges remain in translating genomic technologies and NGS into personalized preventive and medical care. Most importantly, significant gaps exist in the evidence base in genomics, including efficacy, health outcomes, cost-effectiveness, and health services research. The efficacy of genomic-based interventions may be difficult to demonstrate, especially for stratified technologies and in the hereditary disease context, in which sample size is often an inherent limitation. Combined, these evidentiary gaps make costs and benefits difficult to estimate. These caveats are especially germane to NGS, wherein efforts are underway to translate NGS results from exomes or whole genomes, particularly in oncology, despite their unproven diagnostic accuracy, requirement for validation, and computational and counseling challenges. Targeted funding is needed for centralized databases collating the pathogenicity of NGS sequence variants, as is support for outcome-based research using genomic markers and clinical and behavioral end points. Finally, continued support for systematic evidence-based reviews of the emerging clinical genomics literature is critical to inform the effective, efficient, and equitable translation of genomics into cancer care.

References


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