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Challenges To The Translation Of Genomic Information Into Clinical Practice And Health Policy: Utilization, Preferences, And Economic Value

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Abstract

It is important to understand how knowledge of genomics can be translated from basic research into clinical practice and health policies. The objective of this paper is to review existing evidence on three key factors in the adoption of personalized medicine – utilization, preferences, and economic value - using two cancer examples: HER2/*neu* testing and trastuzumab (Herceptin®) and genetic testing for Lynch syndrome. Our findings suggest where further research is needed to build an evidence base addressing utilization of, preferences for, and the potential costs and benefits of personalized medicine. Major challenges include a lack of linked data, the need for relevant research frameworks and methodologies, and the clinical complexities of genomic-based diagnostics and treatment.

Keywords

Personalized medicine; health policy; health services research; economics; utilization; preferences

1. Introduction

It is hoped that personalizing medicine by using genomic data will result in higher quality, lower cost health care because of opportunities to offer patients therapies that are more effective for them and avoid treatments that will not be safe or effective [1–4]. Due to the greater knowledge about the genetic basis of disease and the growing use of personalized medicine, it is important to understand how this knowledge can be translated from basic

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research into clinical practice and health policies. Basic research findings and commercialization of the resulting products have outpaced our knowledge about the social consequences of these new technologies. The move towards greater personalization of medicine may directly conflict with two other major concerns: 1) growing expenditures on health care and pharmaceuticals; and 2) inadequate access to care for underserved populations. Difficult decisions will have to be made about which new technologies will be adopted, how to regulate them, who will pay for them, and who will have access to them.

The objective of this paper is to review existing evidence on three key factors in the adoption of personalized medicine – utilization, preferences, and economic value. We focus on two cancer examples that provide illustration of the larger issues: HER2/*neu* (HER2) testing and trastuzumab (Herceptin®) and genetic testing for Lynch syndrome. We begin each section with a brief discussion of why the topic is relevant and then we review the existing literature followed by a discussion of how the example(s) illustrates the more general challenges of adopting personalized medicine.

We use a policy research framework as our conceptual framework. This framework assumes that the use of genomic information is part of a translational continuum from—basic research, to clinical research, to policy research—that determines adoption and health and economic outcomes. Within policy research, key determinants of adoption and outcomes are utilization, preferences, and economic value - which all contribute to the available evidence base (Figure 1).

2. Examples of personalized medicine in cancer screening and treatments

We use two examples of cancer screening and treatment to illustrate the challenges to the translation of genomic information into clinical practice and health policy: HER2 testing and trastuzumab (Herceptin®) therapy in breast cancer and genetic testing for Lynch syndrome in colorectal cancer. The examples illustrate use of genomic information for acquired somatic mutations (HER2) and inherited germline mutations (Lynch syndrome). The examples represent important foci in the area of cancer care: targeted therapy to optimize treatment once disease manifests (HER2/neu) and risk-stratification before disease manifests (Lynch syndrome).

HER2 testing and trastuzumab therapy provides an example of targeting drugs based on genetic information. About 30% of primary breast tumors over-express the HER2/*neu* protein. Women with HER2-positve breast cancer have been shown to benefit from trastuzumab, a monoclonal antibody, in combination with cytotoxic chemotherapy. The FDA has approved two types of tests to assess HER2 status in breast tissue: immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). IHC testing is less expensive but has greater variability in its results [5]. Studies have found that compared to IHC, FISH testing is a more accurate predictor of HER2 over-expression [6]. Trastuzumab and an accompanying HER2 assay were approved by the FDA in 1998 for use in women with metastatic breast cancer. The indications for trastuzumab were expanded after clinical trials showed a significant benefit in the adjuvant setting for women with non-metastatic HER2-positive breast cancer [7–9].

HER2 testing and trastuzumab therapy are of interest for several reasons. This co-developed test/treatment is considered a prototype for the translation of a targeted therapy based on genomics, and thus provides insights into why personalized medicine may succeed or fail. Despite the fact that this intervention is considered a successful example of adoption of personalized medicine, there are concerns that little is known about how many women have access to testing and treatment, that there are many strategies for testing and that there is variability in how testing is conducted. These issues have taken on increased importance as

therapy moves into a much larger population, and these challenges remain despite recent attempts to standardize testing and treatment protocols [10,11]. Thus, HER2 testing and trastuzumab therapy, although clinically accepted, still present important issues that portend future challenges. Relevant issues include how access to expensive technologies will be determined (who receives testing and treatment), how expanding use will influence value (e.g. costs and benefits), and how value will be determined.

Screening for Lynch syndrome—also known as hereditary non-polyposis colorectal cancer (HNPCC)—provides an example of risk stratification based on genetic and molecular information. Lynch syndrome screening tests for genetic susceptibility to colorectal and other cancers in persons considered at risk for this inherited syndrome. Because the syndrome is inherited, testing additionally has implications for family members. Lynch syndrome accounts for only about 3% of all new cases of colorectal cancer each year but in affected persons the lifetime risk of colorectal cancer is approximately 80% and of endometrial cancer, approximately 40%. Because reliance on clinical criteria may miss many affected persons, a variety of stepped strategies have been proposed, including testing all patients with newly diagnosed colorectal cancer. There is currently no consensus about what clinical criteria and/or testing strategies serve best to identify individuals with Lynch syndrome mutations [12]. For example, the Amsterdam criteria define Lynch syndrome if three conditions are met: (1) at least three relatives with a history of CRC cancer, (2) at least two successive generations should be affected, and (3) one of the relatives' CRC cancers should be diagnosed before age 50 years [12]. The various potential screening strategies appear to have different degrees of effectiveness; they may be costly; and they may affect the quality of life of many family members. Relevant issues include whether asymptomatic family members will use genomic tests, how asymptomatic family members might value genomic tests, and the potential impact of testing on health behaviors.

3. Utilization of personalized medicine

Understanding utilization is important for developing health care delivery models and policies. By understanding utilization patterns, we are better able to assess to what extent currently available personalized medicine technologies are being used, whether the people who would most benefit from care are indeed getting care, what factors influence utilization, and how interventions or policies may be used to encourage appropriate use. The analysis of utilization also provides information on how the use of personalized medicine technologies varies by clinical and non-clinical factors (e.g., individual socioeconomic status and/or characteristics of providers and communities).

We reviewed the literature on HER2 testing and trastuzumab to illustrate issues regarding utilization of personalized medicine. We found only a few published studies that have examined the utilization of HER2 testing and trastuzumab [10,13–17]. There are also very few studies on the linkage between HER2 testing use, HER2 results, and trastuzumab use [13,15–17]. Another important issue relevant to examining the utilization of HER2 testing and trastuzumab is how HER2 tests are performed and how accurate they are. HER2 testing practices seem to vary widely, prompting concerns about the accuracy of testing at some laboratories and uncertainty about the interpretation of some test results [10,18].

The example of HER2 testing and trastuzumab illustrates larger issues about examining utilization of personalized medicine. There is clearly a lack of data on who gets testing and treatment and how testing is conducted – gaps that are critical for understanding the translation of personalized medicine. In particular, data are needed that link test results to use of therapy. HER2 testing and trastuzumab are the most widely used example of personalized medicine, and thus we would expect to find even fewer data for less commonly

used interventions. Our example suggests several reasons for this lack of data. First, test results are usually not available in administrative claims databases. Thus, additional resources are needed to obtain such data and link results to claims; for example, by reviewing medical records or pathology reports. It is also difficult to identify claims for testing procedures in administrative databases because of coding issues. Claims data typically contain procedure codes such as Current Procedural Terminology (CPT) codes, which are five-digit numeric codes developed by the American Medical Association to describe medical, surgical, and diagnostic services. In the case of HER2 testing, two different approaches are used: IHC, which detects protein overexpression and FISH, which detects gene amplification. However, these tests can also be performed for other indications (e.g., estrogen- and progesterone-receptor status is assessed by IHC) and thus CPT codes for IHC and FISH cannot differentiate whether the test is done for HER2 testing or other indications. A CPT genetic modifier can specify whether the test is done for HER2 testing but these modifiers are not currently commonly used in clinical practice. Another challenge to examining utilization is that test codes may be "bundled" into a common pathology code that does not permit the identification of individual tests. Non-specific procedure codes and the bundling of laboratory procedures limit the use of claims data, such as Medicare or other insurance claims, for assessing utilization of HER2/neu testing and investigating the relationships between test type, test results, treatment, and outcomes.

4. Preferences for personalized medicine

Understanding preferences is important because they underlie behavior. Preferences – which are defined in economic theory as the utility obtained from using or consuming goods and services- are a key factor in adoption because personalized medicine will be successful only to the extent that diagnostics and therapeutics based on genomic data are accepted, valued, and used by patients, affected family members, and physicians. Studies of genetic testing more broadly suggest individuals are interested in genetic testing [19–26], that patients will purchase genetic tests directly from websites (e.g., www.genelex.com and www.dnadirect.com), and that physician preferences will play a key role in decisions about personalized medicine [27–31].

We reviewed the literature on Lynch syndrome screening to illustrate issues regarding preferences for personalized medicine. We were unable to find any published studies that have specifically focused on quantitatively measuring preferences for genetic testing for Lynch syndrome and what factors would influence individuals' decisions. However, we did find a few studies that address related issues but these are limited and dated. One study found that only 43% of family members of people with Lynch syndrome chose to be tested, suggesting that individuals have preferences that influence testing decisions [32]. While the identification of Lynch syndrome can lead to increased surveillance, it is not clear whether all people will want to be tested, whether they will want to undergo the enhanced surveillance strategies, or whether they will want to live with the anxiety associated with knowing that they are at high risk [20,33–37]. These concerns apply not only to those being tested but also to their family members.

The example of genetic testing for Lynch syndrome illustrates larger issues about examining preferences for personalized medicine. Lynch syndrome screening is particularly illustrative of the issues for other inherited mutations because of the potential impact of testing on family members. Family members of a patient with a known positive test for a disease may be at higher risk themselves and face challenges about whether to get tested and/or increase their own preventive behaviors and there may also be concerns about health insurance coverage and anxiety associated with the knowledge of being at high risk. Preference studies need to thus incorporate perspectives of affected family members in addition to patients.

The example of genetic testing for Lynch syndrome screening also suggests that making decisions about being tested for genetic disease is complex and carefully designed preference studies will be needed to elucidate the relevant factors. Such studies can be designed to identify a wide range of attributes that may influence genetic testing choices. Illustrative attributes that may be relevant to choices include what type of test is required, accuracy of the test, whether or not a follow-up review is needed, privacy concerns, and the cost of the test.

5. Economic value of personalized medicine

Understanding economic value is important because it is a key determinant of whether personalized medicine will be translated to the clinic. It is important to temper enthusiasm about the possibilities personalized medicine may offer with careful assessment of its potential benefits, risks, and costs. Articles in *The New England Journal of Medicine*, *JAMA*, *Science*, and *Nature* have noted repeatedly that it is critical that we begin to evaluate the use of genomic information to personalize health care – even though such approaches are not yet commonplace – in order to determine both its potential positive and negative impacts on health care outcomes and costs [38–41].

We reviewed the literature on both HER2 testing and trastuzumab therapy and Lynch syndrome screening to illustrate issues regarding economic value for personalized medicine. Several economic evaluations of trastuzumab therapy have been conducted [42–51]. Earlier studies focused on the original indication for trastuzumab, which was for women with stage IV breast cancer (metastatic disease). These studies generally found that trastuzumab therapy had relatively high costs relevant to benefits because the survival benefits were modest for these women whose cancer had progressed to such a late stage. More recent studies have focused analyses on trastuzumab therapy for HER2 positive women with early breast cancer [48–54] and these studies seem to find that trastuzumab therapy has relatively higher benefits in this scenario, but acknowledge that the overall cost burden of breast cancer will significantly increase if this therapy is adopted because of the large number of patients with early breast cancer.

These overarching results mask substantial variations within these studies. The results are difficult to synthesize because different alternatives and settings were examined in each study. The issue of how to treat women who already had trastuzumab therapy after surgery, but then relapse to metastatic disease is particularly important. One US based study assumes all women get a second round of therapy [50], while another Italian based study assumes none do [49]. This issue needs to be addressed, as do other cost issues associated with different treatment protocols in different countries. Moreover, a new randomized clinical trial in France is looking at the impact of duration of treatment since shorter regiments may provide similar benefits at lower cost [55]. Millar and Millward [51] find that a 9-week trastuzumab regimen is significantly more cost-effective than the standard 52-week regimen, but the confidence intervals for the 9- week regimen are larger.

The population treated may also significantly alter cost-effectiveness results. Liberato et al. [49] find that trastuzumab therapy is only cost-effective for younger patients with high-risk cancers, and only if benefits are assumed to last more than seven years. In the absence of longer follow up studies, each study has used different models to estimate the morbidity benefits for trastuzumab therapy, which may affect their overall results. Also, more analysis of reoccurrence risk for specific subgroups is needed to clarify differences in morbidity benefits. Another critical issue is whether the level of over-expression should be used to determine treatment. The American Society of Clinical Oncology and College of American

Pathologists have recommended algorithms defining a positive, negative, and equivocal HER2 result based on values of both HER2 protein expression and gene amplification [10].

Finally, an earlier study suggests testing strategy is an important factor that needs to be considered in cost-effectiveness analyses [43], yet this factor has not been examined in any depth in the more recent studies of trastuzumab treatment in early breast cancer.

Several studies have examined cost-effectiveness of screening for Lynch syndrome [20,56–60]. A general finding is that screening for Lynch syndrome is relatively more cost-effective than no screening. However, it has been difficult to reach definitive conclusions for specific testing strategies because of differences in how they were conducted and the evolving guidelines on screening. Lynch syndrome screening is a highly complex topic, and thus it is not surprising that the existing studies have their own specific focuses. For example, differences include how patients are identified, what screening strategies are compared, whether family members of affected patients are considered, whether patients with various risk levels are analyzed, and the outcomes examined.

Two studies found that surveillance for Lynch Syndrome is cost-effective compared to no surveillance. One study focused on high-risk families (e.g., mutation carriers) only [56] while the other study examined not only the high-risk families (identified by the Amsterdam criteria) but also moderate risk (those suspected but not fulfilling the Amsterdam criteria) [60].

Other studies have examined the cost-effectiveness of various screening strategies. One study suggested that microsatellite instability (MSI) testing of patients with newly diagnosed colorectal cancer and an appropriate personal and family cancer history, followed by genetic testing in cases with MSI, is cost-effective compared with standard care [57]. A follow-up analysis found that testing guided by the Bethesda guidelines would be more cost-effective than universal testing of all patients with colorectal cancer [20]. Another study evaluated four strategies for identifying mutation carriers among colorectal cancer patients and found that a mixed strategy (MSH2 and MLH testing on patients identified by the Amsterdam criteria and germline testing for the remainder and who are MSI-High) was superior to the alternatives [58]. Kievit (2005) et al explored simplified clinical criteria for MSI testing of new colorectal cancer cases and concluded that it was more cost-effective than current practice based on family history. The studies that examined both mutation carriers and family members found that cost-effectiveness increased greatly when family members of mutation carriers were considered [57,59]. Only one study analyzed cost effectiveness of moderate risk patients [60] while the rest focused on high risk patients. While most of the existing studies calculated costs and effects based on detected mutation carriers, Olsen (2007) used numbers referred to genetic counseling as the outcome.

More evidence is needed on the cost-effectiveness of different screening strategies. Past studies did not incorporate the recent improved understanding of Lynch syndrome, including the potential for later onset of disease [61,62] or the recognition of Familial CRC syndrome X [12] which can be used to define patients at various risk levels e.g., those with suggestive clinical expression but no evidence of defective DNA mismatch repair. These analyses also did not consider the impact of testing on quality of life. Future analyses would need to fully take into account the complexity for screening for Lynch syndrome, including establishing the algorithms for managing the subgroups defined after testing, incorporating family members of affected patients, and modeling patients of various risk levels.

The examples of HER2 testing and trastuzumab and genetic testing for Lynch syndrome illustrate larger issues about examining economic value of personalized medicine. The first challenge to assessing the value of personalized medicine is that interventions often involve

both a diagnostic test and drug therapy, thus requiring approaches to considering the impact of both interventions simultaneously. Many previous studies have neglected to consider the impact of the testing strategy used. There may be a variety of testing options, different pathways linking tests to therapies, and tests that apply to several drugs. In the case of both HER2 and Lynch syndrome testing, there are many complexities in determining the clinical pathways and the associated costs and health outcomes. Second, characteristics of genetic tests can make analyses more complex. For example, understanding accuracy includes: 1) whether the test can detect the relevant mutation; 2) whether the mutation is related to the phenotype; and 3) whether the phenotype can be used to make clinical predictions. Moreover, accuracy can vary by both test type and laboratory. Third, analyses may need to consider the cost-effectiveness within different subpopulations. Genomic technologies based on inherited mutations such as Lynch syndrome screening may impact family members, requiring more complex models that incorporate both the initial patients and their families.

6. Conclusions

We reviewed existing evidence and identified challenges to adopting personalized medicine using two examples from cancer screening and treatments. We found that there are gaps in the evidence base as little is known about the use, preferences, and value of these personalized medicine examples [63,64].

There is clearly a lack of data on who gets testing and treatment, how testing is conducted, and the linkage of test results to use of therapy. However, the information needed to examine utilization patterns is either not available in administrative claims databases or limited by coding complexities. These factors limit the ability to conduct research on utilization patterns without lengthy and expensive primary data collection. Further research could benefit from more precise coding (including the adoption of CPT genetic modifiers) and linkage of datasets to include patient characteristics, test procedures, test results, therapy patterns, and clinical and economic outcomes.

There is also a lack of data on preferences for personalized medicine. Few studies have systematically assessed preferences for genetic testing using accepted quantitative approaches. Future research could benefit from carefully designed preference studies to measure perspectives of relevant stakeholder groups, including patients, affected family members, and physicians.

There are somewhat more data on economic value of personalized medicine although this is also limited. Such analyses are more complex when they involve both a diagnostic test and drug therapy, thus requiring approaches to considering the impact of both interventions simultaneously. There may be a variety of testing options, different pathways linking tests to therapies, and tests that apply to several drugs. Analyses may also need to consider the cost-effectiveness within different subpopulations such as family members. Future research would benefit from more sophisticated models that take into account the complexities of personalized medicine and that explicitly consider the impact of different testing strategies.

In conclusion, future research is needed to build an evidence base for personalized medicine addressing to what extent of personalized medicine is used, preferences for personalized medicine, and the potential costs and benefits. Major challenges include the lack of linked data and the need for relevant research frameworks and methodologies.

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* of special interest

** of outstanding interest

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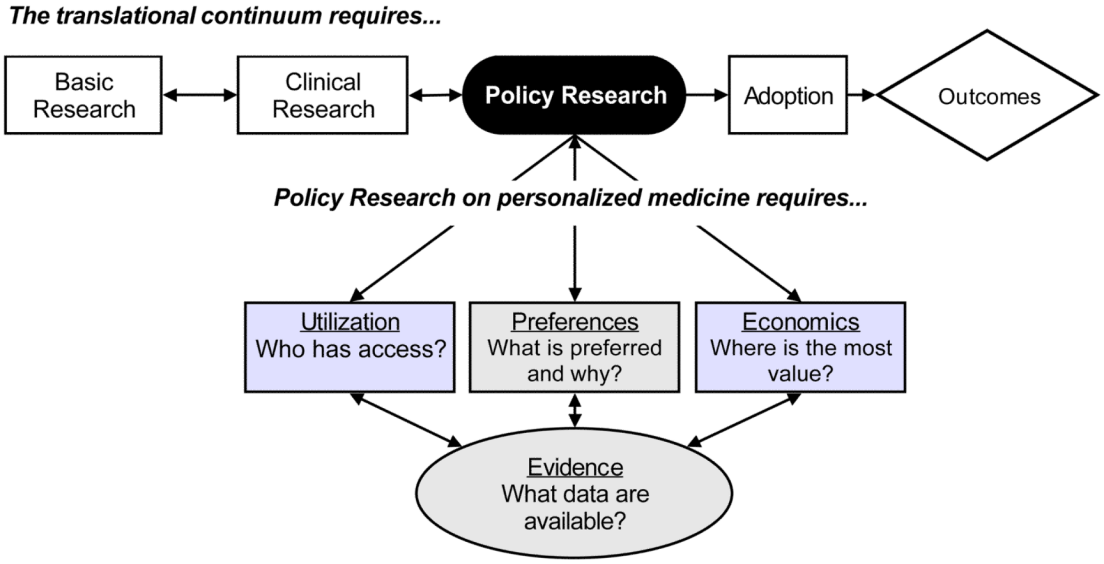

Figure 1.
Conceptual Framework