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Essential Elements of Personalized Medicine

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Summary

Genomic information has been promoted as the basis for “personalized” health care. While genomic tests will offer many potential opportunities to improve the delivery of care, such advances do not in themselves constitute a paradigm shift in the delivery of health care. A more accurate characterization of personalized medicine is as a comprehensive effort to tailor health care to the individual, spanning multiple dimensions. This concept of personalized medicine is based on a partnership between clinician and patient that utilizes shared decision making to determine the best health care options among the available choices, weighing the patient’s personal values and preferences together with clinical findings. This approach is particularly important for difficult clinical decisions involving uncertainty and trade-offs, such as those involved in prostate cancer screening and management. The delivery of personalized medicine also requires adequate health care access and assurance that basic health needs have been met. Substantial research investment will be needed to identify how genomic tests can contribute to this effort.

Keywords

Personalized medicine; genetics; genomics; pharmacogenomics; prostate cancer; health technology assessment

Introduction

In recent years, a concept of “personalized medicine” defined by genetics, using terms such as “the customization of medical treatment to an individual’s genetic profile”[1], has generated great enthusiasm. This idea reflects excitement about the medical potential of

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rapidly advancing genetic knowledge, incorporating a shift from tests for individual genes (genetics) to a growing potential for concurrent assessment of multiple genes (genomics). Discussion of personal genomics also offers an interesting contrast to the discourse around previous technological advances. Scientific developments in the late 19th and early 20th centuries, such as the identification of specific infectious disease agents and the development of accurate clinical laboratory measures, were seen as a means to standardize care [2]. These advances elicited protests from those who emphasized the importance of individualizing care via the "art" of medicine, the unique qualities of the patient-physician relationship, or attention to the patient's particular social context [2]. In contrast, genomics is offered as a replacement to previous approaches for personalizing health care [2], with the implication that this new science can provide the definitive key to each person's unique health needs [3].

However, a concept of "personalization" based exclusively on the human genome fails to account for many other important elements of patient care. Further, excess attention to genetic risk could have the unintended effect of minimizing other predictors of health or the central role of patient values and preferences in health care decisions. Understanding personalized medicine as a comprehensive effort to tailor health care to the individual, spanning multiple dimensions, more accurately reflects clinical reality. It also provides a sound platform for thinking critically about what genomics can – and cannot – offer.

The promise of genomics

Pharmacogenomics, the use of genetic testing to guide drug treatment, illustrates both the potential and the limitations of a genome-centric vision of personalized medicine. A leading example is genetic testing related to the Human Immunodeficiency Virus (HIV) drug abacavir. About 5 to 8% of people of European descent, 2 to 5% of African-Americans, and 2 to 7% of Hispanics have a histocompatibility gene variant, HLA-B*5701, that confers a risk of a serious hypersensitivity reaction if exposed to abacavir [4]. Presence of the variant is associated with a 50% likelihood of a hypersensitivity reaction, while absence of the variant has a negative predictive value of >99% [5]. Because the hypersensitivity reaction can be life-threatening, standard of practice now calls for genetic testing prior to the use of this drug, with use of an alternative drug if the test is positive [4].

Genetic testing thus allows for the safe use of an effective HIV drug through identification of the minority of patients who face serious adverse reactions. Testing also maximizes available treatment options for the disease by preserving abacavir as a potential treatment for the majority. But placing this benefit in perspective, testing is relevant only as a component of HIV care, and the test result changes therapy for only a small minority of patients. The benefit is therefore both incremental and integrated within conventional health care, as would be the case for any other new and informative laboratory test. Even though the number of effective tests of this kind is likely to grow, potentially expanding to a pharmacogenomic panel that guides most drug therapy, the tests will remain components of good practice rather than an entirely new way of prescribing.

Genomics in context

As the abacavir example demonstrates, even a highly effective pharmacogenomic test addresses only a narrow spectrum of care. For a patient with HIV infection, many other treatment decisions and personal issues arise. An expanded concept of "personalized medicine" encompasses these other elements of HIV care, as well as any additional considerations relevant to the overall health of the patient. Personalized medicine, in this sense, consists of adapting the full range of medical tools and skills to the particular needs of the individual seeking care. Thus, there is no fundamental tension between technology and

personal care; the challenge for clinicians is rather to determine when a particular technology may offer benefit to a particular patient [6]. In the past, the laboratory tests that first provided an accurate diagnosis of pneumococcal pneumonia or diabetes may have been resisted as inappropriate efforts to standardize care [2], but in fact they offered new tools to assist clinicians in personalizing care. Genomic information will assist clinicians in a similar manner. Some tests will provide information about individual risk or response to therapeutics; others will help to characterize the clinical problem. All will be integrated into the process of clinical care.

Prostate cancer offers an instructive example. American men face competing messages about prostate cancer screening and treatment. In 2012, the United States Preventive Services Task Force recommended against prostate specific antigen (PSA)-based screening on the grounds that “many men are harmed as a result of prostate cancer screening and few, if any, benefit;” the Task Force suggested that the test should not be offered routinely and should be performed only in men who fully comprehend the risks and actively choose to be tested [7]. This recommendation stands in stark contrast to the position of groups like the UsTOO International Prostate Cancer Education and Support Network and numerous famous prostate cancer survivors who consider screening essential. UsTOO recommends annual screening beginning at age 35 for African-American men and those with a family history of the disease, and starting at age 40 for all other men [8]. Moreover, this conflict is nested within a larger social frame of cancer fears, personal responsibility for health, and public health messages about the value of early detection and treatment.

Decisions about whether or when to pursue PSA screening, how to respond to moderate PSA elevations, and how to manage early-stage prostate cancer all involve uncertainty. Outcomes vary, risks of morbidity are present with all courses of action, and personal preference is an important factor in the decision-making process. The clinician’s role is to assist the patient in understanding the options, advise the patient based on clinical judgment about the balance of risks and benefits and clarification of his personal values, and support the patient’s ultimate choice [9].

Delivering this kind of personalized care is challenging. Even setting aside the clinical uncertainties around screening and treatment, discussions of PSA testing must be prioritized against the patient’s other health concerns. How is the physician to make the most of a 15-minute encounter with a male patient who presents for care once every 2–3 years – and generally for an acute issue? [10] Currently, genetic risk is relevant only for men from rare families who are at increased risk based on a strong family history of prostate and related cancers, including breast and ovarian cancer [11]. For most patients, the salient issues are an understanding of the patient’s fears and values, his other health concerns, and his tolerance for risk and uncertainty.

It is nevertheless possible to see how genetics might assist clinicians and patients in the future, as they struggle with questions about prostate cancer screening and treatment. For example, studies of the genomic epidemiology of prostate cancer could provide additional methods for risk assessment. A large collaborative study has recently identified a panel of gene variants associated with prostate cancer risk [12]. Such a panel could theoretically distinguish men with higher risk, for whom early PSA screening is beneficial, from men at lower risk, for whom PSA screening offers little or no benefit [12]. Using genetic risk to triage screening decisions could provide earlier detection for those at increased risk while at the same time reducing false positive results and iatrogenic harm in the screening process.

Whether this approach would provide benefit, however, would depend critically on the predictive value of the genomic profile: with poor predictive value, genomic risk assessment

could result in an unacceptable rate of missed prostate cancers or a higher rate of adverse screening events. More important, it is not clear whether genomic profiling could identify those most at risk for aggressive forms of prostate cancer. If risk for aggressive versus indolent forms of prostate cancer could not be distinguished, a genomic profile would not necessarily improve on PSA testing. In other words, we cannot predict with certainty whether genomic risk evaluation would improve prostate screening outcomes or merely add additional uncertainty; but this approach is promising enough to warrant further investigation.

Other preliminary data suggest that genomic characterization of prostate tumors might help to distinguish the minority of early-stage prostate cancers requiring aggressive therapy from the majority for which active surveillance is a reasonable strategy [13]. In this use of genomics, a tumor biopsy would be tested to guide treatment decisions. Although early findings offer promise, prostate tumors, like other cancers, tend to acquire new genetic changes in the progression from localized to metastatic disease and display substantial intra-tumor heterogeneity [13]. As a result, determining whether reliable prognostic markers exist and, if so, how best to deploy them to improve outcomes, will require substantial research investment. Nevertheless, progress in tumor characterization, as in risk prediction, offers a glimpse of how genomics might assist clinicians and patients as they parse the difficult questions involved in prostate cancer screening and treatment.

A better molecular understanding of prostate cancer might also provide the basis for new drug development, another potential benefit from genomic research that will require long-term research investment [14]. New drugs developed with the assistance of genomic or other molecular techniques would likely be targeted to specific tumor characteristics. Their use might or might not involve genomic testing, but like other new drug treatments they would add to the options a clinician could use to improve an individual's care.

Personalized medicine in context

Genomic research, in short, promises to add new tests and possibly new treatments to the clinician's armamentarium against prostate cancer. But personalized medicine will remain what it has always been: a therapeutic alliance between clinician and patient, focused on choosing from among the full range of therapeutic options those that are best suited to the particular needs and preferences of that patient [15]. Genetics does not offer a paradigm shift; rather, it demonstrates how effective personalized care must incorporate new tests and technologies on an ongoing basis, as they are proven effective.

Further, there is danger in equating personalized medicine with genomics: it could persuade clinicians or patients that other elements of individualized care are less important [3]. Yet genomic risk prediction will not remove uncertainty from clinical decision-making nor replace the need to incorporate patients' values and preferences. As genomic risk profiles, pharmacogenomic tests and genome-based diagnostics are developed, it is likely that we will reach a future in which genomics can assist most patients at least some of the time (and provide crucial benefits for some), but genomic information will never be the sole consideration in addressing a clinical problem.

Two caveats remain. Like any promising technology, new genomic tests need to be assessed for their comparative effectiveness. Even when a test offers predictive value, it may or may not outperform other strategies for addressing the clinical question. More fundamentally, the benefits offered by genomic tools will be moot if basic health support is absent. The potential benefits to be derived from this new area of research therefore serve as a reminder of the need to place personalized medicine within a larger context of health promotion and disease prevention.

Health technology assessment

A vanishingly small proportion of US health care resources are devoted to health technology assessment [16]. As a result, clinicians and policy makers often lack crucial data for assessment of new treatment opportunities. For example, among 10 genetic testing scenarios considered by the CDC-sponsored Working Group for Evaluation of Genomic Applications in Practice and Prevention (EGAPP), seven were found to have insufficient evidence to make a recommendation for or against testing [17]. The lack of evidence is a substantial barrier to rational decision-making about new technologies like genomics.

In considering the potential for genomics to contribute to management of early prostate cancer, for example, there could be substantial benefit if genomic testing could identify which men, at which stage, would benefit from aggressive radiation or surgical treatment. However, research will be needed not only to identify the most informative genomic markers but also to compare genomic with other histologic or molecular markers, or other patient characteristics, to determine whether any approach (or combination of approaches) has sufficient predictive value to improve clinical outcomes. Further, we can predict from past experience that rigorous technology assessment will rarely lead to crisp black and white answers [6]. Rather, it will provide information about the different trade-offs that must be weighed in light of the patient's circumstances and preferences, as for example, in the choice of lumpectomy with radiation therapy versus a mastectomy for early-stage breast cancer. Effective technology assessment therefore requires concomitant development of communication tools that can assist the decision-making of patients and clinicians [18].

Social determinants of health

A more accurate genome-based assessment of prostate cancer risk might assist clinicians and patients to make better decisions about the use of PSA testing. But if so, this benefit would be unavailable to men who lack access to quality health care. Indeed, the vision of personalized medicine as a therapeutic alliance, in which clinician and patient work together to determine the and implement the best health care for the patient, may be largely aspirational for many Americans. As an example, lack of adequate health care access has been shown to contribute substantially to differential rates in prostate cancer mortality among African-American men [19]. Similarly, genomic testing to assess breast cancer risk can provide little benefit for American Indian women who experience significant barriers to receiving standard mammography, much less more intensive follow up tailored to their genetic risk [20]. Patients who lack health insurance or whose care is provided in under-resourced health systems are unlikely to benefit from the refinements in care offered by genomic tests.

Nor can genomics or other sophisticated medical technology reverse the health effects of poverty, food insecurity, or the myriad social consequences of poor education and unemployment. Genomic refinements of risk are largely irrelevant among individuals whose life chances are severely constrained because of their social circumstances. These factors are critically important in the United States, where there a gap in life expectancy of over 35 years exists between different defined by race and county of residence (21). The gap is due largely to differing rates of chronic illness and injury for which risk factors are known, but the differences cannot be fully accounted for by race, income or health care access. These data underscore the gravity of social inequities experienced by many Americans. Because personalized medicine can be meaningful only after basic health needs are met, addressing these inequities is an important part of the personalized medicine agenda.

Conclusion

Genomic tests are likely to offer many potential opportunities to improve the delivery of health care, but such advances will not in themselves constitute an improved method to personalize health care. Rather, personalized medicine is best understood as a comprehensive process to determine the best health care options for a particular patient, deriving from a partnership between patient and clinician. This approach offers the opportunity to weigh personal values and preferences as well as clinical findings. Genomic information may increasingly provide assistance in difficult clinical decisions, such as those involved in prostate cancer screening and management. However it will remain only one component of good health care; substantial research investment will be needed to identify when and for whom genomic tests will offer the best means to improve health care outcomes. More important, even the best genomic tests will provide limited benefit the benefits if we do not also address inequities in health care access and provision of basic health needs.

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