PERSPECTIVES

Personalized Therapeutics: A Potential Threat to Health Equity

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Throughout history, medical advances have been adopted first and preferentially by the well educated and economically advantaged groups. The development of personalized therapeutics holds promise to fundamentally alter the practice of clinical medicine, but if it also is used preferentially by economically advantaged groups, this advance will likely worsen socioeconomic disparities in health. Prospective development of strategies to ensure non- differential access to these therapies may help limit this unintended consequence of medical progress for economically disadvantaged groups.

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Recent advances in biotechnology and informatics have raised prospects for a new era in clinical medicine in which treatment is tailored to the unique biology of individual patients. In contrast to most current practice, where patient characteristics are given only limited consideration in treatment decisions, personalized therapeutics emphasizes the importance of knowing and using information about the makeup of the patient to select the best treatment. Personalized therapeutics can refer to treatments created for individual patients, as in the immunotherapy of certain malignancies. It can also refer to identification of specific physiological, immunological, or genetic markers associated with differences in medication effectiveness or toxicity. Examples include over-expression of the *HER2/neu* gene and its protein product in breast cancers that lead to better responses to trastuzumab, and polymorphisms in *VKORC1* and *CYP2C9* genes associated with more predictable anticoagulant responses to warfarin[1,2]. Personalized therapeutics in these examples represents greatly refined prediction of responses to medications based on accurate and clinically important biomarkers.

The motivation for personalized therapeutics is based on the recognition that responses to medications are heterogeneous. Personalized therapeutics aims to capitalize on improved understanding of the biological reasons for this heterogeneity, so that patients can be selected to receive medications to which they will more likely respond or better tolerate. This approach should result in more consistent improvements in health. It also promises to make medical care more efficient by avoiding trial-and-error use of medications that work in general but may not work in specific patients, and avoiding subsequent clinical re-evaluation and second opinions. Testing for biomarkers associated with altered pharmacodynamics or with medication toxicity can improve safety and avoid morbidity associated with side effects. Through both avenues, personalized therapeutics has the potential to decrease health care costs.

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WIDENING THE HEALTH GAP

Despite potential for cost savings, personalized therapeutics represents an additional up-front cost, either in designing individualized drugs or testing biomarkers. These costs would be magnified if multiple personalized therapies were sought per patient, or if prospective profiles of risks of common chronic diseases and responses to treatments are developed, as envisaged in "predictive health." To date, most questions about access to personalized therapeutics have centered on reimbursement by third-party payors[3]. Left out of the discussion have been the poor and uninsured, for whom access to basic medical care, let alone personalized therapeutics, can be difficult. As with most new technologies, access to expensive testing and treatments is likely to be limited to the economically advantaged. In these early stages of its development, it may be useful to think about the potential consequences of personalized therapeutics for health equity.

Although medical progress is almost universally viewed as a social good, progress can also create or worsen socioeconomic disparities in health. This occurs because wealthier and more highly educated individuals often have preferential access to new technologies and treatments. Socioeconomic disparities in health outcomes rarely exist for untreatable conditions. Medical progress creates new treatments, but in doing so creates opportunity for differential access. According to fundamental cause theory of health disparities, persons of higher socioeconomic status are the first to benefit from new treatments or health practices

because they have the resources, knowledge, and power to learn of, and act upon, new developments[4]. Because these factors can promote modifications in a variety of different behaviors and disease-associated risk factors and therefore operate across different diseases, they are proposed to account for the pervasive association between socioeconomic status and health[5]. New treatments are not always without harm, as evidenced by recent experiences with rofecoxib and post-menopausal hormone replacement therapy, the consequences of which may disproportionately affect early adopters. However, to the extent that personalized therapeutics improves health outcomes, and to the extent that this technology is preferentially used by the economically advantaged, the health gap between rich and poor will be predicted to increase.

This prediction is not unique to personalized therapeutics, but follows demonstrations throughout history. In 15th century Florence, recognition of the association between living conditions and death from plague resulted in the exodus of the wealthy to the countryside, and exposure of the poor to greater risks of infection in the ever more-densely populated city[6]. In early 20th century America, adoption of breastfeeding and hygienic practices of food preparation by more highly educated mothers resulted in a decades-long gap in infant mortality rates between rich and poor families, when none previously existed[7]. The wealthy have been the first to progress through all major epidemiological transitions, including the cardiovascular disease transition in the late 20th century[8]. This progression occurred because the more advantaged understood evolving knowledge about health risks and were able to act on this knowledge.

More recently, socioeconomic disparities have been tied to differential access to treatments. Among patients with HIV/AIDS, socioeconomic-associated differences in survival first developed after the introduction of highly active antiretroviral therapy, which wealthier patients preferentially accessed[9]. Socioeconomic disparities in survival are present among patients with more treatable cancers but not among those with poorly treatable cancers, and in rates of renal failure for treatable renal diseases but not for poorly treatable ones[10,11]. As personalized therapies are developed, similar disparities could be expected to occur. Differential access to personalized therapeutics might not only increase health disparities between wealthy and less advantaged members of developed nations, but also increase health inequity between rich and poor nations.

Proponents may argue that greater efficiency in clinical care resulting from wide use of personalized therapies could lower total health care costs, freeing resources for the care of uninsured or low-income patients. However, cost-savings are only likely to be passed on when both the users of personalized therapies and low-income patients share the same health care payer. Proponents may also contend that although patients of lower socioeconomic status may lag behind in initial access to personalized therapeutics, access to these therapies will eventually trickle down if it becomes standard of care and incorporated in clinical practice guidelines. Disparities may increase, but only temporarily. While history suggests this may be true, narrowing of differences in access to past advances in treatments and changes in health behaviors often took decades, was incomplete, and required concentrated efforts at remediation. We should confront the ethics of allowing discrimination against the economically disadvantaged to happen again with future medical advances.

POTENTIAL SOLUTIONS

Recognition of the potential consequences of personal therapeutics for health equity should encourage pro-active steps to optimize its benefits, before it becomes standard of care.

We currently have an opportunity to engage with patients, payors, and producers to limit the effects that new personalized therapies may have in worsening socioeconomic disparities in health, or ideally, ensure that every patient who could benefit has access to the therapy and information to make an informed decision. We can prospectively incorporate health equity as an explicit feature of personalized therapeutics,

The first priority would be to collect data systematically on access to and use of personalized therapeutics, and how this use varies by socioeconomic status. Data are needed not only on those who receive personalized therapies, but also on those who are eligible but are not users. This should include information on awareness of the therapies, understanding of their potential risks and benefits, barriers to availability, or reasons for declination. Complementary data from providers would also be important to help identify structural or knowledge barriers. Existing registries, such as the Surveillance, Epidemiology, and End Results program for cancer, could serve this role, although new efforts would likely be needed for specific diseases and treatments. A more comprehensive approach covering all personalized therapies would likely require public-private partnerships between biotechnology and pharmaceutical companies, public health and patient advocacy organizations, and federal agencies, but could build upon the existing disease surveillance infrastructure of the U.S. Centers for Disease Control and Prevention[12,13]. Feedback mechanisms would need to be developed to act on the surveillance data. For example, identification of locations with relative underuse

may trigger local agencies to investigate potential barriers in access or under-performing dissemination practices. Reporting to individual providers of their rates of use, relative to other providers, may motivate changes in clinical practice[14].

Second, alternative models of dissemination of personalized therapeutics could be designed with the aim of ensuring equitable access. Models might include free or low-cost assistance programs for uninsured or low-income patients, targeted introduction in medical practices serving low-income patients, and patient navigator programs. Although pharmaceutical assistance programs have helped thousands of patients obtain medications that they otherwise could not afford, they have been cited as a tenuous source of needed treatments[15,16]. Persons of higher socioeconomic position adopt new medications sooner than those of lower socioeconomic position, likely because of better access to information or possibly greater use of specialty care[17,18]. Patient navigator programs led by community health workers have been used to facilitate access to treatment by patients with cancer and those with HIV infection, treatments that may be underused by patients of low socioeconomic status even when financial access is not an issue[19–22]. These programs could be expanded to serve patients with indications for personalized therapeutics. Several dissemination models could be piloted, and the relative effectiveness of different dissemination strategies in reducing inequity in access could be compared in controlled trials. Critical to all deployment efforts would be educational programs that address pre-approval testing and emphasize that personalized therapeutics is not experimentation. It is important to note that programs to expand access for those of lower socioeconomic status does not automatically require more restricted access for wealthier persons.

Third, policy solutions could be developed to help foster equitable use. For example, reimbursement or adoption of medications into formularies could be tied to the development of monitoring programs and dissemination strategies demonstrated to reduce disparities in access. Extensions of patent protection could be considered for programs that demonstrate equitable access and no socioeconomic disparities in use. Establishing such programs prospectively would provide the best opportunity to ensure that all patients benefit, and that personalized therapeutics will not become the latest medical advance to create health disparities.

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