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Translational genomics: Seeking a shared vision of benefit

Wylie Burke^{1,2}, Suzanne Holland^{1,3}, Patricia Kuszler^{1,4}, Helene Starks^{1,2}, and Nancy Press^{1,5}

¹ Center for Genomics and Healthcare Equality, University of Washington

² Department of Medical History and Ethics, University of Washington

³ Department of Religion, University of Puget Sound

⁴ School of Law, University of Washington

⁵ Schools of Nursing and Medicine, Oregon Health & Science University

Introduction

Health care funders are placing increasing faith in translational research. The current rhetoric implies that incentives for translation will ensure the rapid movement of science from the laboratory to the clinic, with resulting improvements in population health. Accordingly, Clinical and Translational Science Awards from the National Institutes of Health encourage research universities to focus on translational research, and the Bayh-Dole, Stevenson-Wydler, and Federal Technology Transfer Acts encourage academic-industry partnerships to promote commercial development of medical innovation. The translational imperative is particularly strong for areas of research like human genomics that carry a substantial promise of benefit. However, a fundamental question remains: how is benefit defined and for whom?

As Maienschein et al (2008) note, current incentives encourage premature translation, posing potential harms to the basic science enterprise. As a corollary, these incentives create the temptation to oversell early scientific findings. The exaggerated claims for the clinical utility of many emerging genetic tests offer a case in point.

Over the past two years, genomic research has yielded extraordinary progress in the identification of genetic contributors to common complex diseases such as diabetes, heart disease, cancer and other chronic and disabling conditions (Altshuler and Daly, 2007). This research effort is likely to yield innovative therapies, new uses for existing therapies, and new

Wylie Burke MD PhD, Department of Medical History and Ethics, University of Washington Box 357120, 1959 NE Pacific, Seattle, WA 98195, Email: wburke@u.washington.edu

Suzanne Holland PhD, Department of Religion, University of Puget Sound, Wyatt Hall 114, 1500 N. Warner, Tacoma WA 98416, Email: sholland@ups.edu

Patricia Kuszler MD JD, School of Law, 374 Wm. H. Gates Hall, University of Washington, Seattle, WA 98195, Email: kuszler@u.washington.edu

Helene Starks PhD, Department of Medical History and Ethics, University of Washington Box 357120, 1959 NE Pacific, Seattle, WA 98195, Email: tigiba@u.washington.edu

Nancy Press PhD, Oregon Health & Science University, School of Nursing, 3455 SW US Veterans Hospital Road, SN-5S, Portland, OR 97239 2941, E-mail: pressn@ohsu.edu

Wylie Burke MD PhD is Professor and Chair of the Department of Medical Ethics at the University of Washington.

Suzanne Holland PhD is Chair of the Department of Religion at the University of Puget Sound

Patricia Kuszler MD JD is Charles I Stone Professor of Law at the University of Washington

Helene Starks PhD an Assistant Professor in the Department of Medical History and Ethics, University of Washington

Nancy Press PhD is a Professor in the School of Nursing and the Department of Public Health & Preventive Medicine, School of Medicine, Oregon Health & Science University

insights into prevention, through the use of genomic tools to achieve a better understanding of disease biology.

However, these benefits may take years or decades to realize. In the meantime, findings from genomic research are rapidly being developed into tests to identify genetic susceptibilities, under the rubric of “personalized medicine.” Genomic research will undoubtedly provide useful, and in some cases unique, tools for risk assessment and disease classification, but recently developed tests for two diseases provide an illustration of the potential harms from premature translation.

Gene variants conferring modest risks for type 2 diabetes – on the order of 1.5 to 2-fold increases above average risk - have recently been reported (Janssens and Khoury, 2006). The variants are common: one of them occurs in about 40% of people of European ancestry. An investigator described its clinical significance in this way: “It’s terribly important to know if you have this gene variant...It gives you an added incentive to exercise and eat right” (Stefansson, 2006).

But does the test provide a health benefit? If knowledge of genetic risk did in fact motivate people to improve their diet or level of exercise, the test might lead to better health for those with positive test results. However, risk factors are poor motivators of behavioral change (Hudson and Pope, 2006) and genetic risks may be less motivating than others (Marteau and Weinman, 2006). Conversely, the 60% of people with normal test results might be less motivated to pursue a healthy lifestyle, and thus could be harmed by the testing process. The problem is partly one of incomplete assessment: tests for diabetes-related variants were created and promoted before research assessed their effect on eating and exercise habits (Hunter et al 2008). But the problem also lies in how benefit is conceptualized. Rising obesity rates over the past decade indicate that if the goal is improved population health, the forces within our society that promote a sedentary lifestyle and high intake of dietary fats and simple sugars are a more appropriate focus than genetic susceptibilities.

Tests based on the genetic contributors to psychiatric illness offer another troubling example. One test is predicted to identify a 2 to 3-fold higher risk of bipolar disease, and is suggested for use in diagnosis (Psynomics). On close inspection, the test appears to be a poor diagnostic guide: 14% of individuals with bipolar disease are expected to have a positive genetic test result, compared to about 5% of individuals without the disease. In other words, over 80% of those who have the disease will have a normal test result. More concerning, if the gene variant is present in 5% of the population, widespread use of the test will result in many false positive results. These results would lead to substantial risks of inappropriate therapy or an erroneous “diagnosis” associated with stigma, damaged self esteem and anxiety. Not surprisingly, clinical experts question the value of such testing: “At best, these tests are clinically useless. At worst, their results could cause serious worries for patients” (Collier, 2008).

The concept of genetically based health care is intuitively appealing, but these potential harms underscore the need for a more comprehensive view of the translational process. Without objective measures of outcomes, developers run the risk of creating genetic tests that do more harm than good. And in measuring outcomes, researchers need to take into account the large body of data emphasizing the importance of the “working alliance” between patient and health care provider as the basis for effective and high quality health care (Fuentes et al 2007). To the extent that patients come to believe that “personalized” care is based on a gene chip, genomic medicine has the potential to damage the doctor-patient dynamic rather than improving it.

Current incentives for research translation emphasize commercial development, exacerbating a health care system already characterized by escalating costs, pervasive commercialization, and a misallocation of resources that leaves many patients under-treated (Kuttner, 2008). Rapid

development of genetic susceptibility tests has the potential to add to these imbalances, and thus to deflect a promising new technology toward wasteful uses of health care resources. A shared focus on health benefit is needed to counter this trend.

A more complete translational process must include systematic assessment of the outcomes deriving from the use of new technologies and, equally important, investigation of health care delivery methods to ensure the delivery of effective care to all who would benefit (Woolf 2008). In the process, some promising ideas will fall by the wayside, while others will prove their worth. The incentives to promote translation must reach beyond commercial development: research funders, clinical leaders, and patient advocates must work together to ensure comparable incentives for the hard work of rigorous evaluation. The result will be a slower but more robust translational process.

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