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Seeking Genomic Knowledge: The Case for Clinical Restraint

Ellen Wright Clayton

Wylie Burke

Susan Brown Trinidad

Seeking Genomic Knowledge: The Case for Clinical Restraint†

WYLIE BURKE,* SUSAN BROWN TRINIDAD,** AND ELLEN WRIGHT CLAYTON***

Genome sequencing technology provides new and promising tests for clinical practice, including whole genome sequencing, which measures an individual's complete DNA sequence, and whole exome sequencing, which measures the DNA for all genes coding for proteins. These technologies make it possible to test for multiple genes in a single test, which increases the efficiency of genetic testing. However, they can also produce large amounts of information that cannot be interpreted or is of limited clinical utility. This additional information could be distracting for patients and clinicians, and contribute to unnecessary healthcare costs. The potential for genomic sequencing to improve care will be context-dependent, varying for different patients and clinical settings. This Article argues that a disciplined approach is needed, incorporating research to assess when and how genomic information can improve clinical outcomes, practice guidelines that direct optimal uses of genomic sequencing, and efforts to limit the production of genomic information unrelated to the clinical needs of the patient. Without this approach, genomic testing could add to current unsustainable healthcare costs and prove unaffordable in the long run.

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† This Article is dedicated to the memory and scholarship of Elinor Ostrom, who inspired this work and many others during her long and impactful career.

* Professor and Chair of Bioethics and Humanities at the University of Washington. Dr. Burke received her doctorate in genetics and a medical degree from the University of Washington.

** Research Scientist in the Department of Bioethics and Humanities at the University of Washington. Ms. Trinidad holds a master's degree from the Interdisciplinary Program in Health and Humanities at Michigan State University.

*** Professor of Pediatrics, Professor of Law, and Co-Founder of the Center for Biomedical ethics and Society at Vanderbilt University. Dr. Clayton received her law degree from Yale Law School and her medical degree from Harvard Medical School.

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INTRODUCTION

Over the past two decades, genome science has offered a growing array of tests that increase diagnostic accuracy and guide clinical management for an increasing number of disorders.[1] Conventional genetic tests look for specific mutations that are known to cause a given condition. More dramatic advances are now available in the forms of whole genome sequencing ("WGS") and whole exome sequencing ("WES").[2] Both WGS and WES provide a comprehensive assessment of genetic variation across the human genome. WGS measures variation in an individual's entire DNA, while WES measures variation only in the portions of the DNA that code for proteins.[3] WGS and WES increase efficiency by providing information about multiple genetic conditions and risks in a single test. However, WGS and WES also generate unprecedented amounts of information, much of it extraneous to the clinical encounter or difficult to interpret.[4]

Genome sequencing tests are poised to enter clinical practice at a challenging time for healthcare in the United States. Medical costs are rising at unsustainable rates and the system is performing poorly. Services are inefficient, of variable quality, and inequitably distributed.[5] The United

1. *See generally* Geoffrey S. Ginsburg & Huntington F. Willard, *Genomic and Personalized Medicine: Foundations and Applications*, 154 TRANSLATIONAL RES. 277 (2009); Teri A. Manolio et al., *Implementing Genomic Medicine in the Clinic: The Future is Here*, 15 GENETICS IN MED. 1, 3 (2013).

2. *See* Manolio, *supra* note 1, at 3; *see also* Bryce A. Schuler et al., *Using Whole Exome Sequencing to Walk from Clinical Practice to Research and Back Again*, 127 CIRCULATION 968, 968 (2013).

3. *See generally* Manolio, *supra* note 1; Schuler, *supra* note 2.

4. *See generally* Isaac S. Kohane et al., *Taxonomizing, Sizing, and Overcoming the Incidentalome*, 14 GENETICS IN MED. 399 (2012).

5. COMM. ON QUALITY OF HEALTH CARE IN AM., INST. OF MED., CROSSING THE QUALITY CHASM: A NEW HEALTH SYSTEM FOR THE 21ST CENTURY 1–3 (2001).

States spends far more on medical care compared to other developed countries, yet adoption of evidence-based care is slow and uneven.[6] At the same time, overly rapid adoption of new technology leads to both patient harm and wasted resources.[7]

Key measures of population health, such as life expectancy and infant mortality, fall far behind those of other developed countries.[8] The problem is worse for certain populations because of profound healthcare disparities in the United States.[9] Indicating an impending crisis, costs of the Medicare program began exceeding revenue in 2008; deficits are projected to increase steadily over the next two decades, leading to the exhaustion of reserves by 2024.[10] The same funding issues are being experienced at the state level, where the rising expenses of healthcare are reducing funds available for other public expenditures.[11] These rising costs threaten the national economy, and they will only grow as implementation of the Patient Protection and Affordable Care Act provides access to health insurance for many millions of Americans who have previously lacked health insurance.[12]

Therefore, a critical question for genomics is whether it will add to the problems of the current United States healthcare system or ameliorate them. This Article argues that the outcome will be determined in large part by how clinicians and healthcare systems approach the critical process of developing a standard of care for genomic medicine.

I. THE PROMISE

Genetic science has improved the practice of medical genetics by offering systematic assessment of genes that are known to be associated with particular disorders.[13] By replacing piecemeal testing with a comprehensive assessment of virtually all genes, genome sequencing can generate more complete results more quickly.[14] The same gains may apply in the rapidly developing field of pharmacogenomics—the use of genetic information to select the safest and most effective therapy for a

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6. *See generally* INST. OF MED., BEST CARE AT LOWER COST: THE PATH TO CONTINUOUSLY LEARNING HEALTH CARE IN AMERICA 1 (2011).

7. *See id.* at 2.

8. Haidong Wang et al., *Age-Specific and Sex-Specific Mortality in 187 Countries, 1970–2010: A Systematic Analysis for the Global Burden of Disease Study 2010*, 380 LANCET 2071, at 2082, 2086 (2012).

9. *See* COMM. ON QUALITY OF HEALTH CARE IN AM., *supra* note 5, at 1.

10. *See* STEPHEN K. HEFFLER ET AL., CTRS. FOR MEDICARE & MEDICAID SERVS., THE LONG-TERM PROJECTION ASSUMPTIONS FOR MEDICARE AND AGGREGATE NATIONAL HEALTH EXPENDITURES 22–23 (2012).

11. *See, e.g.*, *Massachusetts State Budget*, MASS. BUDGET & POL'Y CTR., http://www.massbudget.org/browser/index.php (last visited July 30, 2013).

12. Patient Protection and Affordable Care Act of 2010, Pub. L. No. 111-48, 124 Stat. 119.

13. *See generally* Ginsburg, *supra* note 1, Manolio, *supra* note 2.

14. *Id.*

particular patient.[15] This approach can also help clinicians to identify genetic causes of rare clinical findings that have eluded conventional testing.[16] Other benefits are also possible, particularly in cancer treatment.[17] Genetic testing already helps to assess an individual's risk for cancer, and genomic studies of tumor tissue can provide prognostic information and help guide chemotherapy.[18] Recent studies suggest that a full genomic evaluation of a tumor may enhance these benefits and potentially identify new therapeutic options for patients.[19]

Many of these applications are still under development, and the scope of resulting healthcare improvements is difficult to estimate. Nevertheless, there are clear indicators that genome sequencing can generate reduced costs by increasing testing efficiency, and improved outcomes by improving use of drug therapies and targeted treatment and prevention.[20] Among the remaining uncertainties are whether WES—a less expensive approach than WGS—can provide the information clinicians seek, and whether WGS will yield additional clinically important information over time. Either approach poses difficult questions about the interpretation and reporting of sequence data.

II. THE CHALLENGE

Although the comprehensive sweep of genome sequencing is attractive for the reasons outlined above, it entails daunting challenges in information management, education, and communication. In addition to addressing the results generated for the clinical situation that prompted testing—for example, assessment of genes associated with an inherited susceptibility to cancer—clinicians will need to decide whether or when to pursue other information that genome sequencing could provide. Such other information can include: (1) the potential discovery of a wide range of rare genetic conditions, some treatable and some not, (2) information about carrier status for many genetic diseases, (3) information of varying reliability and strength about propensities for drug response and common

15. Kathleen M. Giacomini et al., *Pharamcogenomics and Patient Care: One Size Does Not Fit All*, SCI. TRANSLATIONAL MED., Sept. 2012, at 1.

16. *See, e.g.*, Schuler, *supra* note 2, at 968–70.

17. *See generally* Ginsburg, *supra* note 1; Manolio, *supra* note 2.

18. Ginsburg, *supra* note 1, at 281–82.

19. *See generally* Ken Dutton-Regester & Nicholas K. Hayward, *Reviewing the Somatic Genetics of Melanoma: From Current to Future Analytical Approaches*, 25 PIGMENT CELL & MELANOMA RES. 144 (2012); Levi. A Garraway & José Baselga, *Whole-Genome Sequencing and Cancer Therapy: Is Too Much Ever Enough?*, CANCER DISCOVERY, Sept. 2012, at 766.

20. *See generally* Giacomini, *supra* note 15; Ginsburg, *supra* note 1; Schildcrout et al., *Optimizing Drug Outcomes Through Pharmacogenetics: A Case for Preemptive Genotyping*, 92 CLINICAL PHARMACOLOGY & THERAPEUTICS 235 (2012).

diseases, and (4) a large amount of information that is not readily interpretable.[21]

While many medical tests and procedures involve the potential for incidental findings—such as an unexpected mass on a chest x-ray or an unexpected skin abnormality on a physical examination—the scope of potential findings from genome-scale tests is unprecedented. WGS and WES can generate information from an estimated 20,000 to 25,000 genes, and if WGS is used, information about the non-coding regions of the DNA sequence that may or may not have functional significance is generated as well.[22] While only a small number of genes will produce abnormal results in any given individual, these results could number in the dozens or even hundreds, depending on how "abnormal" or "reportable" is defined.

For example, the first detailed analysis of a human genome from a healthy adult found over 2.5 million "single nucleotide polymorphisms" (points where the DNA sequence differed from a reference sequence).[23] Many of these variants could represent neutral or benign changes, but even when focusing on the most clinically relevant genes, the investigative team identified several gene mutations associated with rare genetic diseases (most indicating carrier status), sixty-three variants associated with drug response (along with several other potentially important drug-related variants that had not previously been described), and genetic changes that could increase the estimated risk for eight of fifty-five common diseases.[24]

Another study involving the genomes from nine individuals found an average of 136 genes per genome with deleterious mutations; in 40% of the genes, deleterious mutations were homozygous, which led to the expectation that they would have clinical effects.[25] All nine genomes had rare or novel variants that were difficult to interpret. This study also noted a substantial potential for false positive results—that is, results that erroneously suggested increased risk.[26] Both of the studies described above also noted that insufficient evidence and errors in existing databases made interpretation difficult.[27] The problem is made more difficult by the rapid pace of genomic research: the implications of specific findings may change over short periods of time.

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21. *See generally* Jonathan S. Berg et al., *Deploying Whole Genome Sequencing in Clinical Practice and Public Health: Meeting the Challenge One Bin at a Time*, 13 GENETICS IN MED. 499 (2011); Kohane et al., *supra* note 4.

22. *See A Brief Guide to Genomics*, NAT'L HUMAN GENOME RESEARCH INST. (Oct. 19, 2011), http://www.genome.gov/18016863; Euan A. Ashley et al., *Clinical Assessment Incorporating a Personal Genome*, 375 LANCET 1525, 1526 (2010).

23. Ashley et al., *supra* note 22, at 1526–27.

24. *Id.* at 1530, 1532–33.

25. Kohane et al., *supra* note 4, at 400.

26. *Id.*

27. *See* Ashley et al., *supra* note 22, at 1533; Kohane et al., *supra* note 4, at 401.

In this setting, clinicians and policymakers (including professional societies and other expert groups charged with developing practice guidelines) face two distinct difficulties. The first is determining the threshold for disclosure of results from WGS or WES testing. A stringent approach would report only those findings that are relevant to the purpose of testing—for example, only those findings relevant to inherited cancer risk. But some argue that the "extraneous" information yielded by WGS and WES could have substantial clinical or personal utility; even if it was not sought, it could—and should—be offered to patients.

Johnston and colleagues evaluated, for example, the results of WES in 572 research participants.[28] The analysis focused on thirty-seven genes known to be associated with inherited risk of cancer.[29] A total of 454 variants were found that differed from the reference sequence; of these, eight were determined to be deleterious based on published literature and four were found in individuals who did not meet current family history criteria for genetic testing.[30] This example illustrates the potential benefits of genomic screening but also the substantial analytic effort and threshold choices—including which genes to evaluate—that are raised by genome sequencing. Efforts are under way to define result categories in order to facilitate decisionmaking about which results to report.[31]

The second challenge is determining what kind of information or counseling should be provided to patients before and after testing. Counseling needs will be highly dependent on decisions about what information is disclosed. Current standards of practice call for pre-test counseling with a particular emphasis on the need to ensure that patients give informed consent before receiving information about two categories of genomic information: (1) test results reporting on the presence of an inherited disease for which no treatment is available, such as Huntington disease, and (2) test results related to detecting a carrier state, which may indicate a risk of having children with a genetic disorder.[32]

After testing arises the challenge of how to explain the limitations and ambiguities of genomic information. Even when findings suggest the presence of a genetic disease, the implications may be difficult to predict with certainty. For example, analysis of James Watson's genome indicated that he is homozygous for a deleterious mutation in the *ERCC6* gene.[33]

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28. Jennifer J. Johnston et al., *Secondary Variants in Individuals Undergoing Exome Sequencing: Screening of 572 Individual Identifies High-Penetrance Mutations in Cancer-Susceptibility Genes*, 91 AM. J. HUM. GENETICS 97, 97 (2012).

29. *Id.* at 99.

30. *Id.* at 97, 100, 104.

31. *See generally* Berg, *supra* note 21.

32. *Id.*

33. *See, e.g.*, Edison T. Liu, *HUGO President Reports from the HUGO Symposium on Genomics and Ethics, Law and Society 2009*, HUGO MATTERS: THE OFFICIAL BLOG OF THE HUMAN GENOME ORG.

This genotype is expected to cause Cockayne syndrome, a genetic condition associated with short stature, premature aging, and cognitive impairment.[34] Yet none these phenotypic features are evident in Watson, a Nobel Laureate and co-discoverer of DNA structure.[35] The reason for this discrepancy is not known, but it is likely either that the test failed to detect a normal copy of *ERCC6* or that modifying factors (genetic or non-genetic) were present that prevented the usual clinical effect of the Cockayne genotype.[36] In fact, the manifestations of many monogenic diseases can be highly variable,[37] so caution is encouraged in predicting the clinical effects of findings in single genes in asymptomatic individuals.

Uncertainties are far greater for gene variants associated with common diseases like diabetes, common cancers, and heart disease.[38] The uncertainties are due in part to the evolving science: information on genetic associations for common disease is still being accumulated. Little is known about many variants, and errors in assignment of risk are present in current databases.[39] In addition, risk prediction for common diseases is inherently limited due to the multifactorial nature of these conditions, which are influenced not only by genetics, but also by lifestyle, childhood environment, and other exposures.[40] Even the genetic component is complex because risk for most common diseases is associated with changes in many different genes, each associated with very small increments of risk.[41]

(Nov. 2, 2009), http://www.hugo-international.org/blog/?p=86.

34. David Wheeler et al., *The Complete Genome of an Individual by Massively Parallel DNA Sequencing*, 452 NATURE 872, 874 (2008).

35. *See, e.g.*, Liu, *supra* note 33.

36. *See id.*

37. Katrina M. Dipple & Edward R. B. McCabe, *Phenotypes of Patients with "Simple" Mendelian Disorders Are Complex Traits: Thresholds, Modifiers, and Systems Dynamics*, 66 AM. J. HUM. GENETICS 1729, 1731, 1733 (2000). *See generally* Ernest Beutler, *Discrepancies Between Genotype and Phenotype in Hematology: An Important Frontier*, 98 BLOOD 2597 (2001).

38. *See generally* Nilanjan Chatterjee et al., *Projecting the Performance of Risk Prediction Based on Polygenic Analyses of Genome-Wide Association Studies*, 45 NATURE GENETICS 400 (2013); Muin Khoury et al., *How Can Polygenic Inheritance Be Used in Population Screening for Common Diseases?*, GENETICS IN MED., Feb. 2013, at 1; Kohane et al., *supra* note 4, at 399, 403.

39. Callum J. Bell et al., *Carrier Testing for Severe Childhood Recessive Diseases by Next-Generation Sequencing*, SCI. TRANSLATIONAL MED., Jan. 2011, at 1, 11; Kohane et al., *supra* note 4. *See generally* Misha Angrist, *Only Connect: Personal Genomics and the Future of American Medicine*, 14 MOLECULAR DIAGNOSIS & THERAPY 67, 68–69 (2010) (discussing the need for further interpretation of variations).

40. *See generally* Abby G. Ershow, *Environmental Influences on Development of Type 2 Diabetes and Obesity: Challenges in Personalizing Prevention and Management*, 3 J. DIABETES SCI. & TECH. 727 (2009); J.J. Reilly & J. Kelly, *Long-Term Impact of Overweight and Obesity in Childhood and Adolescence on Morbidity and Premature Mortality in Adulthood: Systematic Review*, 35 INT'L J. OBESITY 891 (2011).

41. Khoury, *supra* note 38, at 2.

III. GENOMIC SCREENING?

Although the science is still rapidly evolving, many experts anticipate substantial benefits from the use of genomic sequencing as a screening tool.[42] These experts emphasize that identification of previously unsuspected genetic disorders or risk states in healthy individuals could allow for early initiation of treatment and prevention efforts.[43] In addition to rare individuals with substantial inherited risk, such as the cancer risks found in a research study of WES,[44] genome sequencing would identify many individuals with genetic susceptibilities to many common diseases. Although the risks identified in this way would generally be modest—typically no more than twofold above average—some experts believe that such information could be used to motivate healthy patient behaviors and to inform clinicians about options for medical screening and early treatment.[45]

Genomic screening is further envisioned by some as a component of "precision medicine,"[46] a new approach envisioned for healthcare in which a menu of molecular tools would be used to provide early identification and intervention in disease processes. The science behind this approach is often referred to as "omics," capturing the measurement of body proteins ("proteomics"), other body metabolites ("metabolomics"), and gene expression profiles, in addition to genome sequencing.[47] The vision of precision medicine adds to optimism about genomic screening.

IV. PERSPECTIVE OF CLINICIANS AND HEALTHCARE SYSTEMS

The vision of genomic screening and the potential benefits of precision medicine must be viewed in the context of healthcare realities. Much of healthcare still fits into a traditional model of returning a person in ill health to normal function: examples include casting to heal a broken arm, surgery to repair a hernia, medications to resolve anginal pain or asthma symptoms, and chemotherapy to eradicate a cancer. Healthcare also involves the co-management by clinician and patient of chronic diseases, with therapeutic care aimed at improving function and quality of life and palliative care to reduce pain and suffering for individuals with terminal illnesses.

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42. *See generally* Angrist, *supra* note 39; Manolio, *supra* note 1; Schildcrout, *supra* note 20.

43. *See Should Healthy People Have Their Genomes Sequenced at This Time?*, WALL ST. J. (Feb. 13, 2013, 5:03 PM), http://online.wsj.com/article/SB10000872396390443884104577645783975993656.html; Angrist, *supra* note 39.

44. *See, e.g.*, Johnston, *supra* note 28, at 100–02.

45. *Should Healthy People Have Their Genomes Sequenced at This Time?*, *supra* note 43.

46. *See generally* COMM. ON A FRAMEWORK FOR DEVELOPING A NEW TAXONOMY OF DISEASE, NAT'L RES. COUNCIL OF THE NAT'L ACADS., TOWARD PRECISION MEDICINE: BUILDING A KNOWLEDGE NETWORK FOR BIOMEDICAL RESEARCH AND A NEW TAXONOMY OF DISEASE (2011).

47. Monya Baker, *Big Biology: The 'Omes Puzzle*, 494 NATURE 416, 418–19 (2013).

At the heart of the genomic screening vision, however, is the concept that health outcomes can be improved substantially by a shift in focus toward preventive care. Many preventive measures are now routine parts of medical practice, including many types of cancer screening, vaccinations, and treatment for conditions such as hypertension and hypercholesterolemia.[48] Preventive care has led to substantial benefits: one compelling example is the virtual absence of several childhood diseases among immunized populations; another is the greater than 90% drop in cervical cancer rates among women receiving regular Pap screenings.[49] Any interventions with this kind of potential represent an important gain for the healthcare system.

Unfortunately, preventive care can sometimes harm people. All medical interventions carry the potential for harm, and there is particular concern about this possibility when interventions are used in healthy people to avert future disease.[50] Several examples illustrate the problem. Newborn screening for neuroblastoma became possible in the 1980s, and was embraced in some locations; however, studies comparing outcomes among screened and unscreened populations revealed no change in disease mortality and identified several instances of infants harmed by treatment.[51] These outcomes were due to limitations in the identification of risk: Testing missed some infants with serious disease (false negatives) and found others who had benign forms of the condition (false positives). In a more recent example, screening for prostate cancer by testing for the prostate-specific antigen ("PSA") has become increasingly controversial because of evidence that it performs poorly as a screening test, leading to many unnecessary and debilitating interventions in healthy men.[52] The U.S. Preventive Services Task Force has recently suggested discontinuing this screening program.[53] In other examples, screening has led to adverse labeling, as in the case for children who experienced morbidities solely as a result of the identification of benign heart murmurs.[54] Even in programs for which benefits are well established, some previously healthy individuals

48. *See Recommendations*, U.S. PREVENTATIVE SERVS. TASK FORCE (Dec. 2010), http://www.uspreventiveservicestaskforce.org/recommendations.htm.

49. Adriana Bermudez, *Can We Do the Same in the Developing World?*, 99 GYNECOLOGIC ONCOLOGY S192, S192–93 (2005).

50. Charles M. Kilo & Eric B. Larson, *Exploring the Harmful Effects of Health Care*, 302 J. AM. MED. ASS'N 89, 89 (2009).

51. William G. Woods et al., *A Population-Based Study of the Usefulness of Screening for Neuroblastoma*, 348 LANCET 1682, 1682 (1996); S. Barrette et al., *Treatment Complications in Children Diagnosed with Neuroblastoma During a Screening Program*, 24 J. CLINICAL ONCOLOGY 1542 (2006).

52. *See, e.g.*, Virgina A. Moyer, *Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement*, 120 ANNALS INTERNAL MED. 120 (2012).

53. *Id.*

54. *See generally* Abraham B. Bergman & Stanley J. Stamm, *The Morbidity of Cardiac Nondisease in Schoolchildren*, 276 NEW ENG. J. MED. 1008 (1967).

will experience harm; for example, cholesterol-lowering treatment can cause myopathy leading to renal failure.[55]

These examples underscore a key principle of preventive care: Programs should be based on strong evidence that the overall improvement in health outcome substantially outweighs the potential for complications and harm. A cornerstone of effective prevention programs is the accurate identification of people at risk, for whom prevention efforts are worth the potential adverse consequences. Critical questions include how accurately screening procedures identify candidates for further intervention and whether available interventions can prevent disease safely and effectively. A related concern is opportunity cost. By its nature, preventive care involves interventions in large groups of healthy people—in some cases, such as immunizations, the entire population. Healthcare systems must consider which screening and preventive efforts are worth the cost, given that resources could otherwise be directed toward other healthcare needs.

Some genetic tests offer clear benefits in this regard—for example, targeted preventive care can be offered to women with a high risk of breast and ovarian cancer identified by the presence of deleterious mutations in the breast cancer susceptibility ("*BRCA*") genes—but most risk identified by genomic screening will be more modest and contingent.[56] The hope is that that identification of risk or early disease will provide opportunities to intervene early, as the natural history of disease processes is better understood at the molecular level. But how early and what interventions should be used? For many disorders, the benefits and risks of early intervention are not yet known. As has been seen with PSA screening, treatment risks could loom large for those who would never have developed disease or whose disease would not have progressed. For other interventions, such as promoting a healthy lifestyle, targeted approaches pose the potential harms of creating stigma and decreasing the incentive for all to take part.

Even when risk assessment is helpful for targeting prevention, genomics will not always be the best way to identify people at risk. For example, identifying people in a social network for group-based interventions might provide a better strategy to enhance smoking cessation, increase physical activity, or encourage healthy eating. Making wise decisions about population health strategies will require challenging

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55. *See generally* F.L Mastaglia & M. Needham, *Update on Toxic Myopathies*, 12 CURRENT NEUROLOGY & NEUROSCIENCE REP. 54 (2012); Willaim S. David et al., *Case Records of the Massachusetts General Hospital: Case 7-2012—A 79-Year-Old Man with Pain and Weakness in the Legs*, 366 NEW ENG. J. MED. 944 (2012).

56. *See* Nicholas J. Roberts et al., *The Predictive Capacity of Personal Genome Sequencing*, SCI. TRANSLATIONAL MED., May 2012, at 58–59; Steven A. Narod, BRCA *Mutations in the Management of Breast Cancer: The State of the Art*, 7 NATURE REV. CLINICAL ONCOLOGY 702, 702–03 (2010).

efforts to assess the relative value of political measures (such as population-level interventions to improve access to education and safe neighborhoods), behavioral measures (such as innovative approaches to smoking cessation or early childhood physical education and nutrition), and medical measures (such as medical screening and drug treatment for individuals with increased risk for chronic conditions). In assessing medical measures, much of the knowledge we currently deploy in healthcare is likely to remain useful in the era of genomics. At the same time, we will need to continue to evaluate new technologies to determine whether they do or do not provide new benefits.

These considerations are relevant to the use of WGS or WES because they have important implications for identification and disclosure of findings that are unrelated to the clinical question that prompted testing. The pursuit of such additional findings represents a screening process, in that it seeks risk information unrelated to the patient's presenting complaint. The worry for the healthcare system is that comprehensive disclosure of results from genome sequencing would introduce risk information into the healthcare process that is distracting and of uncertain value.[57] Time that otherwise might be spent discussing the patient's concerns or well-established preventive care (such as colon cancer screening) might instead be used to talk through the implications of gene variants that are associated with small increases in risk for a variety of diseases. Clinicians might also need to spend time making sure that genomic tests do not lead to false reassurance—for example, explaining to a patient that the lack of a *BRCA* mutation does not mean that she has a lower than average risk of developing breast cancer. The worry, in other words, is that information from genome sequencing could distort the use of healthcare resources on a grand scale.

V. DEVELOPING A STANDARD OF CARE

No practice standard currently exists for genomic medicine. Typically, views concerning the appropriate use of a new technology evolve as it comes into use. Payers are likely to decline payment in the absence of definitive data indicating a healthcare benefit. Over time, as clinicians gain experience and outcome data become available, a practice standard emerges. Formal practice guidelines are helpful in defining the practice standard, unless conflicting recommendations emerge from different groups. Payer policies tend to reflect the emerging consensus.

The lack of a practice standard for genomic medicine represents an opportunity for reflection about the role of genomic information in achieving the goals of healthcare. In the words of John Eisenberg, technology "is rarely inherently good or bad, always or never useful. The

57. *See generally* Ashley et al., *supra* note 22; Kohane et al., *supra* note 4.

challenge is to evaluate when in the course of an illness it is effective, for whom it will enhance outcomes, and how it should be implemented or interpreted."[58] At present, the benefits of WGS and WES are evident in only a few narrowly defined clinical circumstances: where patients are undergoing a genetic work-up that involves assessment of multiple different genes, and where a patient's clinical presentation indicates a genetic disease that has evaded diagnosis by usual measures. Other potential benefits are still under investigation, including the value of genomic sequencing of cancers. However, even when there is a clear benefit, it derives from only a small portion of the genomic information obtained through sequencing. An urgent question for healthcare systems is to determine how these benefits can be realized without overwhelming the healthcare system with distracting information.

A logical approach to managing this risk would be to limit the test results that enter clinical care, even when the testing process generates a full genomic sequence. Arguably, this approach is consistent with routine approaches in laboratory medicine that limit reporting to the specific results that were ordered, even when the testing platform generates additional data. Whether clinical use of WGS and WES might be linked to research efforts aimed at a better understanding of genomic information is a separate and important matter. However, prudent use of healthcare resources calls for limiting the time clinical laboratories spend on sequence analysis and the time clinicians spend explaining genomic test results. However, patient preferences represent a potential challenge to this approach.

VI. THE ROLE OF PATIENT DEMAND

A move toward patient empowerment in healthcare has developed over several decades, and represents an important effort to improve quality of care and patient satisfaction.[59] Groundbreaking lawsuits filed in the 1980s and 1990s established the right of patients to refuse care that was recommended or instituted by their physicians.[60] The right to refuse care is now recognized as nearly unlimited.[61] In rare circumstances, treatment may be imposed as a public health measure (as in treatment of

58. John M. Eisenberg, *Ten Lessons for Evidence-Based Technology Assessment*, 282 J. AM. MED. ASS'N 1865, 1868 (1999).

59. Delos M. Cosgrove et al., *Ten Strategies to Lower Costs, Improve Quality, and Engage Patients: the View from Leading Health System CEOs*, 32 HEALTH AFF. 321, 321 (2013).

60. *See* Cruzan v. Dir., Mo. Dep't of Health, 497 U.S. 261, 278–79 (1990) ("The principle that a competent person has a constitutionally protected liberty interest in refusing unwanted medical treatment may be inferred from our prior decisions.").

61. *See* Washington v. Glucksberg, 521 U.S. 702, 720 (1997) ("We have also assumed, and strongly suggested, that the Due Process Clause protects the traditional right to refuse unwanted lifesaving medical treatment.").

tuberculosis), but a competent adult is otherwise free to refuse any care.[62] Patient empowerment goes beyond the basic right to refuse care and includes acknowledging the legitimacy of a patient's access to medical records and laboratory results, and a patient's right to choose among the array of options available to meet her healthcare needs.[63] Engaging patients in their health management and offering them treatment choices may be an important mechanism to ensure both better care and lower costs.[64] In this context, some experts have suggested that genomics will be a powerful tool for patient empowerment, enabling patients to take more control of their own healthcare.[65] This view is problematic for two reasons: First, it overestimates the potential for genomic risk information to generate improved health outcomes, and second, it erroneously implies that patient empowerment includes the right to demand medical tests that lack clinical utility.

It is likely that only a small percentage of patients have yet considered whether they would like to have access to the information generated by sequencing their genome. Yet among those who have (undoubtedly a biased sample), strong preferences have been expressed for receiving all possible information from genome sequencing.[66] For example, science writer Virginia Hughes complains about a paternalistic emphasis on protecting patients from potentially troubling genomic information (such as gene variants associated with a future risk of Alzheimer disease). Instead of accommodating patient preferences, "the medical community has neglected to talk about more pressing logistical problems: (1) How to ask people ahead of time what, precisely, they want to know (and don't want to know), and (2) How to improve the medical system so doctors can follow through on those wishes."[67]

Her unquestioning assumption that the health system should "follow through" on patient wishes presumes that access to the full array of results is solely a matter of patient preference.[68] This view ignores the

62. *See id.* at 279, 284; Canterbury v. Spence, 464 F.2d 772, 780 (D.C. Cir. 1972). *See generally* RUTH R. FADEN & TOM L. BEAUCHAMP, A HISTORY AND THEORY OF INFORMED CONSENT (1986); LAW IN PUB. HEALTH PRAC. 274 (Richard A. Goodman et al. eds., 2d ed. 2007).

63. Health Insurance Portability and Accountability Act of 1996, Pub. L. 104-191, 110 Stat. 1936 (codified as amended in scattered sections of 42 U.S.C.).

64. David Veroff et al., *Enhanced Support for Shared Decision Making Reduced Costs of Care for Patients with Preference-Sensitive Conditions*, 32 HEALTH AFF. 285, 291 (2013).

65. Leroy Hood & Stephen H. Friend, *Predictive, Personalized, Preventive, Participatory (P4) Cancer Medicine*, 8 NATURE REV. CLINICAL ONCOLOGY 184, 186 (2011).

66. Virginia Hughes, *It's Time to Stop Obsessing About the Dangers of Genetic Information*, SLATE (Jan. 7, 2013, 3:51 PM), http://www.slate.com/articles/health_and_science/medical_examiner/2013/01/ethics_of_genetic_information_whole_genome_sequencing_is_here_and_we_need.html; Misha Angrist, *You Never Call, You Never Write: Why Return of 'Omic' Results to Research Participants Is Both a Good Idea and a Moral Imperative*, 8 PERSONALIZED MED. 651 (2011).

67. Hughes, *supra* note 66.

68. *Id.*

opportunity costs to the healthcare system of facilitating access to genomic information that is not needed for healthcare. It also conflicts with clinicians' ethical obligation to use their competence—and the shared medical resources that they control—to benefit the patient's health.[69] Yet to the extent that such views are incorporated into practice standards for genomic testing, they could generate legal obligations for broad disclosure.[70]

VII. WHAT SHOULD GUIDE PRACTICE STANDARDS FOR GENOME-SCALE TESTING?

Decisions about when new medical technologies are ready for "prime time" involve asking whether the technology confers benefit and whether it is safe and effective. Often, full consideration of these issues includes the circumstances under which the technology should be used and the potential for harm. Most controversies—such as PSA testing,[71] mammography for women under fifty years of age,[72] and spiral computed tomography for lung cancer screening[73]—center around the evidence available and the certainty with which benefits and harms can be estimated. Practice standards and healthcare payer policies often involve explicit definitions of the circumstances under which the technology is appropriate. For example, guidelines of the American Cancer Society specify criteria for the use of magnetic resonance imaging ("MRI") for breast cancer screening, indicating that MRI should be used only for women who are at increased risk—measured by genetic testing, specific clinical diagnoses, or specific family history.[74] Similarly, massage therapy may be covered by some insurers in some states, but its use is typically limited to a small number of treatments in the context of an injury, despite the fact that some patients might prefer greater access.

In the case of genome sequencing, there are clear indicators that testing can assist in certain difficult diagnostic situations and can be an efficient method for concurrent assessment of multiple genes in medical genetic work-ups. The indications for the uses of WGS and WES may grow over time as research reveals new potential uses for genomic information. However, the large volume of information potentially

69. *See generally* Troy Brennan et al., *Medical Professionalism in the New Millennium: A Physician Charter*, 136 Ann. Internal Med. 243 (2012).

70. *See generally* Ellen Wright Clayton & Amy L. McGuire, *The Legal Risks of Returning Results of Genomics Research*, 14 GENETICS IN MED. 473 (2012).

71. *See generally* Moyer, *supra* note 53.

72. *See generally* Summer Sawyer Allen, & Sandhya Pruthi, *The Mammography Controversy: When Should You Screen?*, 60 J. FAM. PRAC. 524 (2011).

73. *See generally* Peter B. Bach et al., *Benefits and Harms of CT Screening for Lung Cancer: A Systematic Review*, 307 J. AM. MED. ASS'N 2418 (2012).

74. Debbie Saslow et al., *American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography*, 57 CA: CANCER J. FOR CLINICIANS 75, 83 (2007).

generated by such testing poses risks to individuals and the healthcare system. Practice guidelines for the use of WGS and WES must consider the potential for iatrogenic harm from work-ups spurred by incidental findings, as well as the potential for false reassurance if the lack of genomic risk information is misinterpreted as removing risk for common diseases. It is equally important for practice guidelines to consider the potential impact of WGS and WES on healthcare resources. In the context of unsustainable increases in the cost of care, there is an urgent need to consider the cost-effectiveness of new technologies, asking critically whether they improve upon existing interventions. Clinicians, who are increasingly time-pressured by the array of evidence-based interventions available to them, are focused on making the most of their time with patients and need practice guidelines that enable them to do so.[75]

CONCLUSION

Can genomics deliver what the healthcare system urgently needs: gains in health outcome at reduced cost? This Article suggests that this outcome is possible with disciplined leadership from genetics professionals and healthcare policymakers. A responsible practice standard for WGS and WES will limit disclosure of incidental findings. Choices are available within this approach. Disclosure could be limited to the results relevant to the clinical question for which testing was done, or with the patient's informed consent, analysis could extend to evaluation of a small set of genes associated with conditions for which well-defined clinical prevention measures are available, such as genes associated with significant cancer risk. Despite patients' arguments for the "right" to their genome sequence, testing done within the healthcare system should be focused on healthcare needs. Failure to maintain this discipline opens a path toward wasteful and harmful testing practices that are likely, ultimately, to result in the rejection of genomic solutions by hard-pressed healthcare systems.

75. *See* Kimberly S.H. Yarnall et al., *Family Physicians as Team Leaders: "Time" to Share the Care*, PREVENTING CHRONIC DISEASE: PUB. HEALTH RES., PRAC., & POL'Y, Apr. 2009, at A59.

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