Genomics in Medicine
Maturation, but Not Maturity

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APRIL 14, 2013, MARKS THE 10-YEAR ANNIVERSARY OF the official completion of the entire Human Genome Project.[1] This genomics theme issue celebrates recent remarkable advances made possible by one of the greatest biological research projects ever conducted. During the last decade, understanding the complexity of the genome has moved beyond infancy into early childhood, a precarious age of exploration filled with an increasing number of triumphs and the occasional mishap. For the field of genomics, this developmental period has been marked by rapid advances in technologies for dissecting genome function in health and disease. Perhaps most surprisingly, the cost of sequencing the genome has decreased by 5 orders of magnitude through roughly the last 10 years,[2] a pace that has exceeded expectations. Many types of basic and clinical studies that would have been unthinkably expensive a decade ago are now quite achievable and proceeding quickly. Reflected in the 2011 strategic vision document authored by the National Human Genome Research Institute is an increasing and welcome trend toward rationally exploring how genomic discoveries affect health.[3]

This genomics theme issue of *JAMA* includes an array of articles, including 4 Original Contributions, a Special Communication, 4 Editorials, and 4 Viewpoints that reflect the expanding reach of genomics in medicine.

The original research report by Crotti and colleagues[4] is perhaps the most traditionally genetic (as opposed to genomic) study, exploring the etiological relationship between several genes associated with long QT syndrome (LQTS) and unexplained intrauterine fetal demise (IUFD). Previous research has demonstrated a common genomic architecture between LQTS and sudden infant death syndrome; the study by Crotti et al, which examines a series of 91 IUFD cases ascertained in the United States and Italy, suggests that variants in genes for LQTS likely contribute to IUFD as well, with LQTS-susceptibility missense mutations discovered in 3 IUFD cases. Two of the mutations have not been described previously. Assuming replication of these findings in other cohorts of patients, this discovery could have tangible implications for reproductive decision making in families affected by this devastating condition. The study also illustrates the value of publicly accessible databases of genetic variation from diverse populations as a critical aid in the interpretation of genome sequence data and the value of independent confirmation of the functional consequences of newly discovered, predicted pathogenic variations. As discussed in an accompanying editorial by Guttmacher and colleagues,[5] the findings of Crotti et al suggest the need for additional investigation into the role of cardiac arrhythmias in IUFD among prospectively collected, diverse, and well-phenotyped populations.

In contrast to the study by Crotti et al, the report by Reitz and colleagues[6] explores a condition affecting increasing numbers of individuals at the opposite end of the lifespan. The authors present a genome-wide association study that provides new insights into the genomics of Alzheimer disease in African Americans, an understudied and disproportionately affected population. Based on findings from the analyses of assembled multiple data sets totaling 5896 African Americans (1968 cases, 3928 controls), the study confirms the importance of variants associated with Alzheimer disease in non-Hispanic white populations, and provides evidence that variants associated with the ATP-binding cassette transporter (*ABCA7*) gene may be a stronger contributor to the condition for African Americans than previously suspected. Although the findings have limited direct clinical application in risk prediction, the study may help explain some of the observed epidemiological differences between African American and non-Hispanic white populations and point to potential new preventive and therapeutic strategies. In an accompanying editorial, Nussbaum[7] highlights the scientific and ethical importance of assembling cohorts of understudied populations and explains that the findings support the body of evidence relating lipid metabolism to Alzheimer disease risk.[8]

A third study in this issue illustrates the rapid expansion of the use of genomics in cancer care. Currently, a number of screening, prognostic, and therapeutic applications in genomics are supported by evidence-based guidelines developed in the United States and abroad. The study by Xing and colleagues,[9] including 1849 patients with papillary thyroid cancer, adds to this growing body of knowledge by linking the presence of certain *BRAF* mutations with

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more serious outcomes in thyroid cancer. This is important because of the therapeutic dilemma that thyroid cancer can present to the patient and clinician; confirmation of the study findings could lead to clinical testing useful in guiding the aggressiveness of care in certain patient populations. Furthermore, the study highlights the increasing recognition of the interrelatedness of disparate cancer types at the molecular level. A priori, it is unlikely that the genomics community would have predicted *BRAF* would play a central role in tumor types as diverse as melanoma, hairy cell leukemia, and papillary thyroid cancer. In an accompanying editorial, Cappola and Mandel[10] consider the implications of the findings in the context of a condition with a high survival rate, concluding that the findings may be most important in guiding the use of tyrosine kinase inhibitors in patients with advanced disease.

An innovative investigation by Loman and colleagues[11] highlights advances in the use of genomic technologies to identify organisms associated with outbreaks of serious infectious disease. The authors describe the retrospective use of metagenomics to isolate and characterize organisms associated with the 2011 outbreak of toxigenic *Escherichia coli* in Europe. Importantly, the study used next-generation sequencing of 45 samples from patients with diarrheal illness to reconstruct the outbreak genome without culturing the organism. Studies such as this herald a potential tectonic shift in clinical microbiology, away from relatively slow and cumbersome culture-based methods for characterizing organisms to sequence-based approaches. Although substantial work lies ahead to optimize this application of genomics, sequence-based technologies hold promise to streamline laboratory protocols, reduce turnaround times, and more easily identify "unknown unknowns" in samples. An editorial by Relman[12] highlights the progress being made in this area of genomics, as well as the scientific challenges that must be met to transition metagenomics from a research tool to routine clinical care.

Available evidence suggests that clinicians are poorly equipped to make use of currently available genetic and genomic tests.[13] In the tradition of the previously published users' guide for genetic association studies,[14-16] the Special Communication by Korf and Rehm[17] provides a practical review of a selection of currently available molecular diagnostic tests, using case scenarios to highlight important features of each. Also, genomics is a highly jargon-intense discipline. Readers should not feel too overwhelmed; the pace of science ensures that even experts in one aspect of genomics might not be able to negotiate some of the terms used by another research area. For a partial remedy to this problem with terminology, readers less familiar with genomic terms are directed to the glossary[18] that accompanies the theme issue. In addition, each article in this issue includes a brief glossary containing terms relevant to understanding the content presented. For a more comprehensive glossary, interested readers are directed to explore the National Institutes of Health's Genetics Home Reference[19] and Talking Glossary.[20]

As more genomic applications become relevant to patient care, inherent tensions arise between the status quo in health care practice and potentially transformative approaches. Four Viewpoints in this theme issue address a number of these concerns. Ginsburg[21] provides an overview of some of the triumphs and challenges related to genomics over the last decade and describes insights about what the coming years may yield for the clinician. McGuire and colleagues[22] explore the role of the clinician in helping patients navigate the sea of information arising from genome-scale diagnostic approaches. Chute and Kohane[23] examine the growing, but still very early, intersection between genomics and clinical health information technology systems. The authors suggest that even though effective management of genomic data in clinical informatics systems is acknowledged as a necessary adjunct to the widespread integration of genomic data into clinical care, substantial challenges remain in adapting electronic health records to the genomic era. Finally, Tuckson and colleagues[24] discuss what is perhaps one of the most pressing issues facing genomics, evaluation of the value of new technologies through the lens of a health insurer. The ability to measure value, especially in comparison to existing health care technologies, will be a critical determinant in the scope of the adoption of genomic technologies and for the degree to which genomic technologies affect health disparities across the globe.

This issue highlights that genomics remains a science of discovery rather than of clinical utility in most areas of medicine, despite enormous progress over the past decade. This will not continue to be the case. As genomics becomes incorporated into most aspects of medicine and has demonstrative effects on clinical outcomes, theme issues like this one will become unnecessary. The last decade has been dominated by enormous technological advances in the science of genomics, the next decade is likely to be dominated by its effect on diagnosis, prognosis, and clinical care. We invite readers to enjoy this issue and to contemplate the next developmental stage of genomics.

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