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The Indispensable Role of Professional Judgment in Genomic Medicine

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Whole-genome and whole-exome sequencing (WGS/WES) have become increasingly affordable and accessible to individuals. There are currently 3 main pathways through which a person can receive WGS/WES: as a research participant in a genomic study; through a direct-to-consumer personal genome company; or as part of clinical care. In the research context, the extent to which findings from WGS/WES are communicated to study participants and used to inform their clinical care is a topic of much debate, but guidelines suggest that investigators may have an obligation to offer at least some results to study participants.[1]

WGS/WES is also available for use in clinical care, especially for patients with undiagnosed genetic anomalies. As WGS/WES becomes more widely available, the lines separating research, direct-to-consumer testing, and clinical care will blur. As these lines blur, it will be important to carefully delineate the appropriate role for genetic professionals in test ordering, interpretation, and delivery of WGS/WES results.

To date, much of the ethical discourse has focused on individual preferences and the importance of the autonomy of both patients and participants in genomic research. Respecting individual autonomy is essential, but there is a danger that unfettered autonomy will lead to self-directed genomic testing and clinically unwise health-related decision making. Focusing mainly on individual autonomy is problematic because, as is true in all aspects of medical care and research, there is an indispensable role for professional judgment in genomics.

Regardless of whether genome-scale sequencing is performed in a research study, the clinic, or by a direct-to-consumer company, several decisions require professional judgment. First, an explicit decision must be made regarding what specifically within the genome will be queried. In many situations only a selected set of genes should be analyzed to minimize confusion and reduce the risk of false positive results. Consider a physician who is seeking to understand a patient's apparent predisposition to cancer. It may soon be economically efficient to engage in WGS in this diagnostic setting, but it would not be professionally responsible to routinely query the genome for all genes, most of which have no bearing on the reason the test was ordered. For example, querying the status of that individual's PSEN1

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gene (which, when mutated, strongly predisposes a patient to early-onset Alzheimer disease) would be justified only if there were sound clinical reasons for doing so and if appropriate pretest counseling were carried out. On the other hand, research focused on gene discovery may benefit from querying the entire genome. Depending on context, radically different conclusions would be appropriate regarding the extent to which a genome should be analyzed. Professional judgment is essential for responsibly determining the optimal approach.

Second, the interpretation of WGS results must be approached methodically. What level of evidence is required before assigning pathogenicity to a particular variant (of which there will be many)? Which databases should be consulted to help adjudicate the meaning of selected variants? Again, responsible answers to such questions require professional knowledge and expert, careful planning.

Third, what recommendations should be made to individuals who undergo sequencing, and who should make those determinations? The influence of genomic variation is poorly understood, and its heterogeneity is vast. Some results will be easily interpreted and will trigger clear and straightforward recommendations (eg, a high risk of preventable cancer necessitating frequent colonoscopy). More commonly, recommendations will be nuanced, tentative, and based on highly imperfect data. When recommendations for management that have clinical implications are made on the basis of genomic information, regardless of the context in which that information was generated, the individual becomes a patient, and the interaction becomes part of medical practice, which requires the involvement of a licensed health care provider. Responsibly formulating and presenting such recommendations requires professional expertise. Professional expertise, in turn, requires competent (deliberative, evidence-based, rigorous, and accountable) clinical judgment.

Professional clinical judgment establishes medical reasonableness; a technically possible form of diagnostic or therapeutic management that is reliably expected to result in a greater balance of clinical good over clinical harm for the individual patient. These forms of clinical management set the standard of care. The physician has a legal—and also ethical—obligation to present to the patient all of the medically reasonable alternatives for the management of the patient's condition, but determining what is medically reasonable is a function of expert, deliberative clinical judgment.[2]

Competent clinical judgment is essential to the practice of medicine, including genomic medicine. High-stakes decisions are increasingly made on the basis of complex genomic information. Misinterpretation of genomic data, even by medical professionals who commonly have inadequate genetic knowledge, is well documented and has resulted in a wide range of harm to patients. This range varies from failure to recommend necessary risk-reducing measures for at risk individuals to unnecessary surgery in those actually at normal risk.[3–5] The legal and financial ramifications of such misinterpretation, which can lead to unnecessary surgery and otherwise preventable disease, cost the entire health care and medical judicial system. Moreover, the absence of competent clinical judgment is likely to result in unmanaged variation in the use of health care resources, the definition of poor quality.

Given the potential clinical implications of much genomic information, decisions about querying, interpreting,and delivering that information are clearly matters of expert judgment and should therefore be governed by professional responsibility. Within the physician-patient relationship, respect for autonomy means empowering the patient with information to make informed decisions about whether to authorize or refuse recommended genomic

testing and clinical management. The informational preferences of the patient may inform clinical judgment, but patients' preferences do not set the standard of care.

The need for professional judgment in WGS/WES creates special challenges with regard to the availability (and aggressive marketing) of direct-to-consumer genomics. The intimate and personal nature of a person's genome cannot be overstated. While it would seem excessively paternalistic to forbid the use of direct-to-consumer genomics, prudent regulation is necessary to prevent harm at both the individual and societal level. Purveyors of such testing should be held to rigorous standards regarding the validity of their claims (eg, to act in accordance with existing Federal Trade Commission regulations regarding truth in advertising), and a knowledgeable genetic professional should be involved in at least the interpretation and communication of test results. Importantly, this person should not be employed by the laboratory or company offering such testing, to prevent the biasing effects of conflicts of interest.

Both physician-ordered and self-directed genome sequencing have the potential to create preventable risks to patients and downstream negative impacts on the health care system as a whole. As in any other realm of medicine, patients must be included in decisions about genomic testing. Moreover, participants in genomic research should be informed of the potential discovery of clinically relevant findings and consumers should be able to access reliably interpreted, clinically applicable information about their genomic heritage. However, provision of inadequately interpreted results does not empower informed decision making.

Individuals who are not sufficiently knowledgeable or adequately trained in genomics do not know how to query the genome or interpret results, and nonclinicians have insufficient expertise to make treatment plans based on the results of sequencing. Thus, to fully realize the promise of genomics in health care, professional judgment must play an indispensable role.

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