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Consenting for Molecular Diagnostics

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The growing use of molecular diagnostics poses a wide range of issues and questions concerning informed consent that researchers, health care providers, and others will increasingly need to address. Molecular diagnostics are advancing more rapidly than our ability to decide how best to respond to their complex medical, ethical, legal, psychological, and social implications. Although some of these issues resemble those posed by prior tests, the newness and ever-faster spread of these tests, the advent of large-scale electronic databases, and the many inherent uncertainties involved present new challenges and dilemmas that require careful attention to determine how best to proceed. Obtaining appropriate informed consent will require considerable resources, which many researchers and providers may not fully appreciate. For example, for whole genome sequencing (WGS)[2] and whole exome sequencing (WES), most researchers have indicated that they were willing to spend 30 minutes or less on obtaining informed consent (1). Yet the complexity of the information involved will probably often require significantly longer interactions.

The Basics of Informed Consent

As articulated in the 1946 Nuremberg Code (2), informed consent is crucial in research because it ensures that investigators respect and protect the autonomy and rights of patients and research study participants. The Declaration of Helsinki (1964; amended in 2013) and the Belmont Report (1979) extended, emphasized, and elaborated on the importance of informed consent in all of health care (3, 4). Patients and participants must ordinarily be appropriately informed about any procedures they are undergoing related to diagnosis, treatment, or research and must consent to these procedures. Subjects should not just sign a

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[2]Nonstandard abbreviations: WGS, whole genome sequencing; WES, whole exome sequencing; ACMG, American College of Medical Genetics.

form, but understand the content, including the purpose, risks and benefits, alternative options, if any, and plans for confidentiality (5).

Yet challenges arise. Consent forms often end up being too long and complicated for many participants to understand. Although most universities require that these forms be written at no more than an eighth-grade reading level, 92% of these institutions fail to meet this standard (6). Frequently, problems emerge because institutions and private companies funding a study want these forms to serve as legal documents—to protect themselves—rather than having a primary purpose of educating patients about the relevant issues (6).

Challenges in Consenting for Molecular Diagnostics

Several particular challenges emerge in obtaining appropriate informed consent for individuals undergoing molecular diagnostic tests. These tests may be new, and their validity, reliability, implications, and present and future utility may be unclear. Hence, the potential benefits and risks of such relatively new tests and procedures cannot always be wholly known.

INTERPRETATION OF MOLECULAR DIAGNOSTIC INFORMATION

The results of certain molecular diagnostic assays may remain uncertain. For instance, genetic markers may be found but be only partially penetrant or predictive, or difficult to interpret, yet need to be conveyed to the patient in a way that he or she can sufficiently understand. With WGS/WES, some results will indicate variants of uncertain significance, posing challenges for informed consent of whether, when, and how to convey the possibility and meaning of such ambiguous information to patients (7). A variant may have been reported once or twice in the literature or have inconsistent or unclear relationships to phenotypes. Rigorous, consistent criteria need to be developed for determining and reporting which variants are pathologic (8). Such efforts will most likely take a considerable amount of time, and scientific understandings of the pathogenicity of many variants will surely evolve substantially over the years, raising questions of what informed consent forms should state about these phenomena beforehand. Consent forms can specify that only findings with a certain degree of certainty will be returned, but ambiguities can persist. Patients vary in their desires for and abilities to understand such data, based on various factors (9). Research is being conducted to ascertain patients' preferences and understandings of several different types of information and scenarios (e.g., returning information on carrier status; pharmacogenomics; and tests that are highly penetrant, but not clinically actionable) (1).

INCIDENTAL FINDINGS

WGS/WES can also reveal secondary or incidental findings, posing dilemmas. In 2013, the American College of Medical Genetics (ACMG) recommended that laboratories report to physicians who order clinical sequencing tests the presence or absence of 56 so-called actionable genes associated with 23 serious disorders (10). Patients (or their caregivers) would not have a choice. Parents would thus be given the results for infants who were tested. In April 2014, ACMG revised its recommendations, allowing patients to opt out (11). Ongoing questions will continue to surface, however, as researchers determine that

additional genes are highly predictive and actionable, and if so, to what degree. Consent forms also need to address whether future tests results—whether intended or incidental—may be conducted on specimens, and if so, whether patients will receive these results, and if so, which.

Patients may also want to learn the results of various other tests that may be actionable personally, but not medically. That is, individuals at risk of Huntington disease may want to know whether they have this mutation, because if so they would alter their life plans, perhaps deciding neither to have children nor to "save all their money for the future," but to enjoy their lives as fully as possible now because their lifespans will be limited. Patients may also be told initially that a finding is clinically significant, though subsequent research shows that not to be the case.

Presumably, arrangements will thus need to be made to be able to contact patients or research subjects in the future. ACMG has issued practice guidelines concerning several other tests that are not highly predictive and actionable (e.g., regarding Alzheimer disease and carrier status). Generally for such tests—and regarding personalized medicine more broadly—appropriate genetic counseling, including education about possible risks and benefits of testing and ascertainment of patients' understandings and preferences, is crucial (12).

WHEN THE PATIENT IS UNABLE TO GIVE CONSENT

Questions emerge when individuals cannot consent for themselves (e.g., due to cognitive impairment). In such cases, a spouse or next of kin can serve as a surrogate. With prenatal or pediatric WGS/WES, additional questions surface, e.g., how much genetic information the parents want and how to assess the child's best interests. Children can assent, but not consent, and a legal guardian is thus necessary. Still, providers and researchers must determine exactly whether, what, and how to explain molecular diagnostic tests to children, and do so with sensitivity and care. Children should receive relevant age-appropriate information; both medically and psychologically, the benefits of testing should outweigh the harms (e.g., discrimination, anxiety, and confusion).

Noninvasive prenatal genetic testing of cell-free DNA and fetal cells poses additional dilemmas (13). The noninvasiveness of such testing offers advantages over amniocentesis (which is more invasive), but patients may have concerns about possible false positives and false negatives (14) and what specific genes to assay. Dilemmas emerge, too, concerning possible terminations of pregnancies: which tests results warrant such termination and where to draw the line (e.g., whether incidental/secondary findings should be sought) (15, 16). Providers should proceed with care, counseling prospective parents appropriately.

DISCLOSURES TO OTHERS

Given fears of discrimination, consent forms should also specify who else will have access to test results. In the US, the Genetic Information Non-Discrimination Act protects against discrimination in most health insurance, but not in life, disability, or long-term care insurance or in schools. Some individual states have anti-discrimination laws, but these laws vary widely.

Many patients will want to know who else will see their data; whether the results will be posted online or otherwise be available, and if so, to whom; and what other phenotypic data, if any, will be included. Schools may also want to see genetic information. Yet, if genetic markers are included that are associated with somewhat increased risks of certain conditions, such as autism, questions arise of how the school will react: e.g., whether teachers might as a result spend less time with a particular student, even though he or she might never develop the disorder.

BLURRING BOUNDARIES BETWEEN RESEARCH AND CLINICAL CARE

Distinctions between clinician and research activities are also blurring because of so-called learning health systems (17), in which knowledge generation is embedded into the practice of healthcare delivery improvement (18). Traditionally, research and clinical interventions differ (given differing goals of knowledge production vs therapeutic benefits), but these boundaries are becoming hazy. For many cancers, the only treatment is experimental. Many medical centers are seeking to build biobanks of diagnostic and other medical information for both clinical and research purposes. Questions emerge of who would have access to test results, how much phenotypic data researchers should receive without obtaining specific informed consent, whether test results conducted as part of research should ever be included in electronic health records, and whether molecular diagnostic tests performed for research purposes should ever be disclosed to the patient, and if so, when.

Consent forms may also need to convey who owns specimens and data collected from individuals. For biobanks, for instance, consent may need to discuss whether patients or study participants can later arrange to have their information removed, and if so, how.

Moving into the Future

Challenges concerning consent will require ongoing attention and discussion among relevant stakeholders: patients, providers, researchers, laboratory officials, policymakers, and others. These groups will also need ongoing education about these evolving issues. Although appropriate informed consent is essential (1), researchers and providers may lack the necessary time to obtain it. Genetic counselors can help, but are in short supply and generally underfunded by insurance companies. Governmental policies thus should change to ensure adequate insurance coverage for these complex discussions.

Additional research is also critical to assess patient and provider decision-making about these dilemmas. As molecular diagnostics advances, additional efforts will be vital to address these complexities, to balance disease prevention and treatment with avoidance of stigma and discrimination. As much as possible, physicians, researchers, patients, institutional review boards, policymakers, and others will need to be prepared to address these ever-unfolding challenges.

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