Whole-genome sequencing and the physician

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Commentary

Whole-genome sequencing and the physician

Whole-genome sequencing (WGS) technologies analyze genetic variation across the entire range of human genetic material (1–4). With rapidly decreasing costs, WGS may be used for both targeted diagnostic testing (5) and genome-wide searches for the mutations that underlie unexplained disorders (3, 6, 7). It is currently recommended that genetic testing should be as targeted as possible to solve a particular clinical problem (8). If targeted testing fails however, physicians may justifiably ‘trawl’ through the genome for mutations that underlie complex cases of multiple congenital malformation or unexplained intellectual disability (3). The introduction of untargeted WGS for diagnostic testing in the clinic has great potential to improve the range and efficacy of genetic testing. With reference to international ethical guidelines, this article explores how WGS impacts four traditional obligations of physicians: the duty to obtain informed consent, the duty to treat, the duty to follow-up and the duty of professional secrecy.

The duty to obtain informed consent

A physician must obtain free and enlightened consent from a patient before undertaking medical care or research (9, 10). The plethora of ‘incidental’ findings that accompany WGS pose a challenge to informed consent. Little guidance exists for physicians on whether, or how, these findings should be communicated to patients (11). Guidelines for biomedical research, such as the *Canadian Tri-Council Policy Statement*, suggest that a plan for the ethical return of incidental findings should be included in informed consent for WGS diagnostics (12). In research, informed consent increasingly relies on ‘broad consent’ models that outline the categories of findings that will be returned (13). The National Cancer Institute (NCI) ‘smart filter’, for example, developed in the biobanking context, gives a list of criteria for returnable results including analytical validity, clinical significance, and clinical actionability (14). Patients, however, may have fewer choices in their consent to testing than research participants. In the clinical context, Berg et al. suggest that vast incidental findings could be organized in ‘a clinically oriented manner to facilitate shared decision making by patients and clinicians’ (6, 15). They suggest a binning system in which clinically actionable results are categorically reported, clinically valid but not directly actionable results are returned depending on patient preference, and results of unknown or no clinical significance are not returned.

This sketch of a solution for incidental findings in the clinical context is far from complete. As informed consent attempts to address more complex issues, it may become prohibitively expensive, or ‘arduous, if not impossible, to inform patients . . . without inducing information overload and therewith foregoing the actual aim of informed consent’ (16). The research context however, may provide useful guidance to keep these problems in check.

The duty to treat

The duty to treat is the most evident duty of physicians (17). In order to provide appropriate treatment, they must stay abreast with medical science (18). Faced with the rapidly evolving technology and knowledge base of WGS, the standard of knowledge to bring to the interpretation of WGS results is unclear. Fear of liability for the negligent interpretation of results is not unfounded (19, 20). There is a growing consensus in the United States that the standard of care expected of physicians is ‘both the duty to identify patients’ genetic concerns and to refer them to appropriate resources’ (21). As WGS technology becomes more prevalent in the clinic, efforts need to be made to clarify the extent to which they are expected to understand genomic information, and systemic changes to the health system need to be introduced to help them cope with these expectations (21, 22).

The duty to follow-up

Physicians are required to provide medical follow-up after an examination or treatment (12, 19). On the one hand, physicians may risk liability under negligence if they ignore unvalidated genetic findings. On the other hand, they may order a battery of alternative, targeted tests to confirm WGS tests that expose patients to iatrogenic harms (23) and place further strain on already limited primary health care resources (24).

Does the duty to follow-up encompass the re-contact of patients when the meaning of past WGS test results changes? (25) Currently, in the United States, UK and Canada, physicians are not legally responsible for re-contact, and it is up to the patient to initiate re-evaluation (26, 27). Imposing this duty on physicians would be problematic for other reasons. First, it will be difficult to define or delimit the scope of this duty when a large amount of genomic material is potentially stored in a patient’s health record, and susceptible to evolving

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interpretation. Second, the patient's 'right not to know' about genetic health risks may be difficult to protect even if patients were to determine how their genomic information is filtered.

Duty to maintain professional secrecy

Patient information must be kept confidential in order to maintain trust, autonomy, and respect in the doctor-patient relationship. With the development of WGS, there is increasing tension between the duty of professional secrecy, and a physician's ethical duty toward relatives of a patient to inform them of risks revealed by genetic testing. On the one hand, genetic information has implications for a patient's autonomy and private life, and therefore merits a high level of protection (28). On the other hand, the vast incidental findings of WGS increase the likelihood of other significant findings having health implications for a patient's biological relatives. In addition, mutations having no direct health impact may have serious implications for the reproductive decision making of family members (29).

Legally, breaching confidentiality to warn a third party is only possible under strict conditions; it generally requires, *inter alia*, a threat of a serious and imminent harm (11,30). WGS tends to reveal common, multifactorial risks, or rare, mostly untreatable conditions, and is considered unlikely to meet these requirements (31). Therefore, if patients refuse to share test results with at-risk relatives, physicians will not be expected, or even allowed, to disclose the information themselves (31).

The primacy of professional secrecy, however, should not detract attention from the emerging ethical duties that physicians have toward at-risk relatives. Physicians may increasingly be expected to ensure that pertinent WGS results reach family members (29, 32). As these expectations crystallize into standards of care, physicians may be legally required to adequately direct patients to share WGS results with at-risk relatives, request permission from patients to disclose the information directly, or perhaps even make efforts to communicate with family members in a way that does not breach patient confidentiality (29).

A final consideration that concerns the sharing of test results with family members is the 'right not to know'. Some relatives may value genetic risk information in helping to plan for the future, while others would prefer not to know about it at all. This may be especially true for information on untreatable, late-onset conditions (33).

Conclusion

This paper has outlined how WGS increases uncertainty for the obligations physicians owe their patients. The potential for unintended but significant health findings complicates informed consent. Rapidly evolving technologies leave physicians uncertain about the standard of care required to employ or interpret WGS. Physicians

are left faced with a precarious choice between ignoring results of uncertain validity and costly, possibly risky, follow-up testing. The familial nature of genetic information places strain on the duty of confidentiality. WGS is also becoming available through direct-to-consumer (DTC) genetic testing companies. Novel ethical issues may also arise as patients approach their family doctors for interpretation of their DTC test results (34–36). In any event, the legal and ethical uncertainties of WGS must be addressed before WGS technologies can be successfully implemented in the clinic.

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Conflict of interest

The authors have no conflicts of interest.

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