Routledge Handbook of Medical Law and Ethics

Yann Joly, Bartha Maria Knoppers

The ethical and legal duties of physicians in clinical genetics and genomics

Publication details
https://www.routledgehandbooks.com/doi/10.4324/9780203796184.ch18
Adrian Thorogood, Bartha Maria Knoppers
Published online on: 29 Aug 2014

How to cite: - Adrian Thorogood, Bartha Maria Knoppers. 29 Aug 2014, The ethical and legal duties of physicians in clinical genetics and genomics from: Routledge Handbook of Medical Law and Ethics Routledge
Accessed on: 01 Aug 2023
https://www.routledgehandbooks.com/doi/10.4324/9780203796184.ch18

PLEASE SCROLL DOWN FOR DOCUMENT

Full terms and conditions of use: https://www.routledgehandbooks.com/legal-notices/terms

This Document PDF may be used for research, teaching and private study purposes. Any substantial or systematic reproductions, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The publisher shall not be liable for an loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.
The ethical and legal duties of physicians in clinical genetics and genomics

Adrian Thorogood and Bartha Maria Knoppers

18

18.1 Introduction

Genetics is by no means a new field of medicine, but it is certainly a rapidly evolving one. This chapter explores the ethical and legal duties of physicians in the context of genetic testing. We begin this introduction by comparing genetic information with other types of health information. This comparison will clarify how the traditional ethical and legal duties of physicians apply in the genetic context. First, our genetic make-up is largely inherited. Clinically significant genetic information concerns not just patients, but also their families. Second, genetic information is a powerful predictor of disease in individuals and across generations. Third, our genetic make-up is uniquely identifying: our genes can reveal information about where we come from and to whom we are related. Accordingly, professional norms must reflect these characteristics of genetic information, while being mindful that other non-genetic forms of health information can also exhibit these ‘exceptional’ qualities. It must also be remembered that both genetic and environmental (e.g. lifestyle, socio-economic) factors play a role in all common diseases. The predictive strength of genetic testing is ‘probabilistic,’ meaning a positive result does not reveal a condition, but rather a predisposition: an increased likelihood that a condition may arise in the future. It is imperative that medical decision-making reflect the inherent uncertainty of genetic testing as well as its broad social implications.

The scope of this chapter is limited to the use and interpretation of genetic tests in clinical practice. In general, genetic tests have three purposes. Diagnostic genetic testing is used to characterize an existing condition and its genetic cause. It is often used in the paediatric context to diagnose children affected by disorders suspected to be genetic. Carrier status testing is used to inform reproductive decision-making and generally concerns recessive, single-gene disorders. Finally, predisposition testing examines whether an asymptomatic individual is resistant to or at heightened risk of developing a particular medical condition in the future. Predisposition testing may involve common, multifactorial diseases with a genetic component, such as heart disease or diabetes. It also targets autosomal dominant conditions manifesting in adulthood, such as Huntington’s disease, and high-penetrance conditions, such as breast cancer.

Section 18.2 of this chapter outlines how the ethical and legal duties of physicians described elsewhere in this Handbook apply in the context of classical genetic testing. First, physicians have
a duty to obtain informed consent for genetic testing. Particular consideration must be given to the types of information included in this process. Second, the duty to treat requires physicians to identify the situations where genetic testing is appropriate. This may be particularly challenging in the paediatric context, where decisions are complicated by the child's temporary inability to consent to testing and parents' shared interest in their child's genetic status. Third, physicians have a 'duty to warn' patients and perhaps their family members of shared genetic risks. The duty to warn, and the tension it may create with the physician's duty of confidentiality if extended to third parties, are also discussed.

With the sequencing of the human genome in the early 2000s (Lander et al. 2001), genetic testing is shifting towards a genomics paradigm. New whole-genome and whole-exome sequencing (WGS/WES) technologies allow physicians to generate massive amounts of genetic information about their patients. Section 18.3 discusses emerging duties and challenges for physicians in the genomics age. With a rapidly expanding knowledge base, and the potential to return vast amounts of information, care must be exercised to administer WGS/WES tests under appropriate circumstances, to interpret results correctly, and to handle the communication of clinically significant results unrelated to the initial diagnostic question. Indeed, the physician may not be able to ignore ‘incidental’ findings, and may face an emerging duty to warn patients of clinically significant results concerning treatable or preventable conditions. Furthermore, the sheer volume of information generated may exacerbate the tension between patient confidentiality and the duty to warn relatives of patients. Section 18.3 concludes with a discussion of the patient's emerging 'right not to know' his or her genetic status. Individuals have an interest in controlling the information they receive, and may have a compelling interest in not knowing certain information about their health. Alternatively, fully respecting patients' informational self-determination and right not to know may put their health at risk.

This shifting normative landscape is particularly tumultuous in the pediatrics context, explored further in section 18.4 (also see Chapter 5). Briefly, many genetic conditions first exhibit symptoms during childhood; some may require immediate intervention. Since children are not considered capable of authorizing genetic testing, their choices about testing should be preserved until adulthood where possible, and interventions should be undertaken where medically actionable during childhood. In addition, newborn screening programmes may also be pressured to expand to include WGS, and even to supply every newborn with a health report card.

Basic bioethics principles inform our discussion of professional norms in medical genetics. They include:

- **Autonomy.** The values and preferences of patients must be respected. Patients should be allowed to exercise meaningful control over when genetic tests are administered (consent), and who has access to their test results (privacy/confidentiality). This autonomy interest encompasses control over the flow of information from the health professional to the patient. Indeed, the patient's 'informational self-determination' is especially important in the genetics context (Andorno 2004). Genetic testing often concerns uncertain results (either because of high error rates of sequencing or the low penetrance of genes) or untreatable conditions. In such cases, a patient may legitimately prefer not to know his or her genetic status.

- **Beneficence.** Health professionals have fiduciary obligations to act in the best interests of patients. Genetics poses many questions involving complex weighing of benefits and risks. Beneficence must be considered when deciding to carry out a genetic test. Testing for uncertain or untreatable predispositions may do more harm than good. In some cases,
genetic tests may reveal risks shared by patients’ family members. As we discuss below, preventing harm to these third parties is increasingly becoming an ethical imperative for physicians.

- **Privacy.** As with other forms of sensitive health information, patients have a strong interest in limiting access to their genetic test results. A common privacy concern in genetics is discrimination by employers or health and life insurance providers (Pioro et al. 2013). Another fear is stigmatization of individuals or ethnicities with ‘undesirable’ traits. Protecting privacy in healthcare is complicated by the booming availability and connectivity of health data and the myriad third-party interests from researchers, government, and industry in mining that information (Beauchamp and Childress 2008).

As will become evident in the discussion below, decision-making in genetics will often need to strike a balance between a multitude of conflicting and interdependent interests. For this reason, ethical decision-making in clinical genetics requires a proportional, context-specific balancing of interests and ethical principles.

### 18.2 Traditional professional norms in genetic medicine

#### 18.2.1 Consent

As for any medical procedure, the consent of the patient is required before a physician carries out a genetic test. A detailed discussion of the law of consent to medical treatment can be found in Chapter 3. Briefly, the right of patients to make decisions about their healthcare is internationally recognized (World Medical Association (WMA) 2005, article 3(a); United Nations Educational Scientific and Cultural Organization (UNESCO) 2005, article 5(c)). Physicians must obtain ‘free and informed consent’ from patients before undertaking medical care or research (UNESCO 2005, article 6(1)), meaning they must provide their patients ‘with the information they need to make informed decisions about their medical care’ (Canadian Medical Association (CMA) 2004, article 21). For genetic testing, information about the test’s purpose, nature, risks, and limitations must be provided. Given the ease with which genetic samples can be obtained (a patient need simply spit in the tube!), the risks of genetic tests are primarily informational. They may provoke, rather than assuage, anxiety, especially where testing for an untreatable condition. For example, positive results for highly penetrant breast cancer genes may leave women with a difficult choice between living with a high but uncertain risk, or undergoing drastic preventative measures. In addition, uncertain results may be succeeded by lengthy, expensive, and unnecessary diagnostic work-ups, only to confirm a negative result. ‘Iatrogenic’ harm, meaning harm caused by physician activity, is especially worrisome in cases where follow-up testing or increased screening involves invasive procedures.

Genetic tests may also create tension within families when sensitive information about family bonds or shared genetic risks are revealed. For this reason, the implications of withholding (or not) test results from family members should be explained during the informed consent process (British Medical Association 2012). Ensuring that a patient understands the limitations of the genetic test is also important. Individuals without the targeted mutation may still receive a positive result (a ‘false positive’). Even a true positive may not tell the patient definitively if, or when, the disease will develop. Finally, in the paediatric context, the consent of a child’s parent or guardian is required, and that of the minor when sufficiently mature. However, as we explain in section 18.4, testing in children should only be carried out in the child’s best interests.
18.2.2 Treatment

The physician’s most evident duty is the duty to treat. Physicians owe their patients ‘complete loyalty and all the scientific resources available’ (WMA 2006). A physician ‘may not discontinue treatment of a patient as long as further treatment is medically indicated’ (American Medical Association (AMA) 2008, Opinion 10.01; CMA 2004, article 19). The duty to treat is tied to the principles of beneficence and non-maleficence: medical practice should aim to maximize direct and indirect benefits, and to minimize possible harm (UNESCO 2005). In relation to genetic testing, the duty to treat encompasses the responsible interpretation of test results and, more importantly, responsible decisions about whether or not to carry out a genetic test in the first place. Physicians must ‘provide competent medical service’ (WMA 2006), requiring them to stay up to date with advances in medical science. The applicable standard of conduct differs between medical specialties and will be higher for medical geneticists (Grubb and Laing 2004: paras 6.28 and 6.40). Failure to meet the standard of care can expose physicians to liability for negligence.

Physicians must also understand, and explain to patients, the predictive capacity of genetic tests. There is a chance that disease may occur even when a test result is negative, and vice versa. The risk status of a patient affects these probabilities (Holtzman and Watson 1998). The gene responsible for Huntington’s disease, one of the first sequenced in the 1990s, demonstrates the importance of context. Even though it is a Mendelian autosomal dominant gene, Huntington’s exhibits variable penetrance in at-risk individuals, and the time of onset is hard to predict (Miller et al. 2008; Miller et al. 2010). Uptake of testing in at-risk individuals remains low, not just because Huntington’s is untreatable, but also because test results are uncertain (Hayden 2000).

Risk stratification is also increasingly becoming a professional ethical imperative. For example, the US Preventive Services Task Force discourages referral from BRCA counseling and testing for asymptomatic women in the general population (2009). Instead, it recommends a family history assessment to identify candidates for testing (Burke et al. 2013; Nelson et al. 2013).

One important framework used to evaluate the appropriate use of genetic tests is the ‘ACCE’ model (Centers for Disease Control and Prevention (CDC) 2013). The ACCE model was the first publicly available analytical process for evaluating scientific data on emerging genetic tests. It was introduced to guide the development of policy in medical genetics and to identify priorities for genetic research. The model takes its name from its four general considerations: analytic validity, clinical validity, clinical utility, and associated ethical, legal and social implications. An analytically valid test result accurately identifies a given genotype. A test is preferred where it is highly sensitive, meaning it gives a positive result when a mutation is present, and highly specific, meaning it will not return a positive result when the mutation is absent. A clinically valid result will consistently and accurately predict a resulting genetic condition. Clinical utility refers to the ‘actionability’ of a result, whether there is a treatment or preventive measure to improve the patient’s outcome. The ethical, legal and social issues considered in the ACCE model include, among others, the possibility of stigmatization, discrimination, breach of privacy or confidentiality, and familial issues (CDC 2013).

18.2.3 Communication

The physician’s duty to inform the patient or ‘duty to disclose’ encompasses four different elements: (1) informing the patient of his diagnosis/medical condition; (2) explaining the nature and objectives of the proposed intervention, and identifying the individual who will be executing the proposed intervention; (3) disclosing the known risks; and (4) identifying the therapeutic options available to the patient (Grubb and Laing 2004: paras 3.112–3.170). The results of any
diagnostic tests ordered by the physician must be disclosed. If a patient is harmed as a result of the physician's incomplete disclosure, liability can arise under the classical rules of tort law or civil responsibility. For example, informing patients of their predisposition to cancer or carrier status may be important to prevent harm. Patients informed of serious genetic predispositions to cancer may be able to increase surveillance to catch the disease in its early stages. Patients informed of their carrier status for a heritable condition can make informed reproductive decisions. Alternatively, patients who are denied prenatal testing and consequently deprived of the decision to terminate a potentially affected child may have recourse in the courts for 'wrongful birth.' In France, the Cour de Cassation awarded compensation for wrongful birth in Perruche [2000], Assemblée plénière, no. de pourvoi 99-13701 where a physician failed to diagnose a pregnant woman’s rubella infection and her child was born severely handicapped. Public outcry followed the decision. Critics clamoured that such compensation devalued the lives of handicapped individuals. In response, a law banning actions in wrongful birth was passed, leaving the costs of treatment for severely handicapped children to the social support system (Pike et al. 2013; Loi n° 2002-303 du 4 mars 2002). The French experience suggests that compensation for wrongful birth may eventually be constrained elsewhere, especially in the genetics context, where concerns over identity and dignity are likely to be more pronounced.

The familial implications of genetic risk information raise the question of whether physicians have a duty to warn relatives of patients. For example, diagnosis of a genetic condition in affected children can reveal the carrier status of parents. Here, if the physician fails to inform the parent of a diagnosis, he or she may be liable for injury to both child and parent, or even to other family members. Where the parent is the child’s legal guardian, and therefore included in the therapeutic relationship, this duty is relatively clear. Difficulty arises, however, in non-traditional family structures. In Molloy v. Meier [2003] 679 NW.2d 711, an adopted child with a serious, heritable condition called Fragile X was not properly diagnosed. Neither the adoptive parents nor the biological mother were informed of the diagnosis, leaving the biological mother ignorant of her carrier status. She later gave birth to a second affected child and sued for wrongful birth. The court found ‘a physician’s duty regarding genetic testing and diagnosis extends beyond the patient to biological parents who foreseeably may be harmed by a breach of that duty’ (Molloy v. Meier, p. 719). The difficulty here is that the biological mother was not the child’s legal guardian and was therefore outside the physician–patient relationship.

A similar Canadian case was complicated by divorce. In Watters v. White 2012 QCCA 257 (Quebec), a physician informed the father of an affected child that his wife was a carrier. The wife was distraught over the marriage breaking down, so the information never reached her. She remarried, left the country, and decades later gave birth to a second affected child. Her niece was also unaware she had inherited the gene. She also gave birth to an affected son, decades after the initial consultation. While the wife’s claim for wrongful birth was rejected at trial, her niece brought a successful action. This momentarily established, for the first time in Canada, a duty to warn a third-party family member (Liss v. Watters 2010 QCCS 3309). However, the Quebec Court of Appeal reversed the trial decision, rejecting the niece’s claim and concluding that under the professional norms prevailing at the time (30 years earlier), the physician was only obliged to inform the parent(s) and not other at-risk relatives.

Other cases in the US have addressed the physician’s duty to prevent harm to the children of a patient with a heritable genetic condition. In Pate v. Threlkel [1995] 661 So.2d 278 (Florida), a physician neglected to inform a patient with hereditary thyroid cancer of the risk potentially shared by her daughter, who eventually developed the same cancer. An ‘obvious’ duty towards the daughter was found, one that could, however, be ‘satisfied by warning the patient’ (Pate v. Threlkel, p. 282). The court in Safer v. Estate of Pack [1996] 677 A.2d 1188 (New Jersey) reached
a similar finding, despite the complication that both the patient and the physician died before
the child reached maturity. It was not specified how the duty was to be discharged, just that
‘reasonable steps be taken to assure that the information reaches those likely to be affected or
is made available for their benefit’ (Safer v. Estate of Pack, p. 627). Courts remain hesitant to rec-
ognize a duty to warn biological relatives outside the therapeutic relationship. Not only would
such a duty be onerous for physicians, but it would risk conflicting with the physician’s duty of
confidentiality. We can conclude that physicians have, at a minimum, an ethical duty to prevent
harm to family members of patients. This does not mean, however, that physicians have a legal
duty to warn these third parties directly; informing the patient of familial implications will most
likely be sufficient.

18.2.4 Confidentiality

Physicians must keep health information confidential (WMA 2009: 50–5, 2006; CMA 2004:
article 31; also see Chapter 4). Initially, the emergence of genetic information in the 1990s rein-
forced the legal and ethical duty of medical confidentiality for fear of employment and insur-
ance discrimination. As discussed in the previous section, however, biological relatives may have
a legitimate interest in a patient’s genetic information. Physicians could have a corresponding
ethical duty to prevent harm to these relatives. This can generally be achieved without breaching
patient confidentiality by clearly explaining the familial implications to the patient, or by obtain-
ing the patient’s consent to communicate the result to family members.

But what if the patient refuses? Some have argued that confidentiality should not prohibit
communication to family members, that the family, and not the individual patient, should be
treated as the ‘unit of confidentiality’ (Wertz and Fletcher 2004). Case law, however, firmly rejects
the familial solution; as Judge Kasirer concluded in Watters v. White, individual patient confiden-
tiality remains the ‘cornerstone of the doctor–patient relationship’ (para. 95).

There are narrow exceptions to confidentiality ‘whereby non-consensual disclosure is justi-
fied by considerations of public health, urgency or imminent danger’ (Watters v. White, para. 111).
For example, many countries legally require physicians to report certain communicable diseases,
such as tuberculosis, to the relevant authorities. Physicians may also breach confidentiality to
report patients with conditions hindering their ability to drive, or situations where the security
or development of a child is in danger (Beskow and Burke 2010). While not every country rec-
ognizes a legal obligation to warn identifiable third parties of imminent risk, it is internationally
recognized that physicians have a discretionary privilege to breach confidentiality as a matter of
moral or deontological conscience (WMA 2009: 51–5). Strict conditions must be met before a
physician can exercise this discretion. The expected harm must be considered imminent, seri-
ous, irreversible and unavoidable except by unauthorized disclosure, as well as greater than the
harm likely to result from disclosure (WMA 2009: 51–4; American Society of Human Genetics
(ASHG) 1998). Quebec, a civil law jurisdiction, provides for this discretion in its Code of ethics
of physicians 1981 (articles 20–21). These articles permit, but do not require, physicians to breach
confidentiality ‘when there are compelling and just grounds related to the health or safety of the
patient or of others’.

It remains unclear whether genetic risk information can fulfill the strict conditions that
require (or permit) a physician to breach patient confidentiality. Genetic risk is often uncertain,
and disclosure may not be of clear benefit to a third party (Gold 2004). Genetic risk informa-
tion also rarely qualifies as ‘imminent’ or urgent (Lacroix et al. 2008). Genetic test results tend to
be probabilistic. The timing, development, and severity of disease expression depend on many
factors such as environment, lifestyle and gene–gene interactions. Genetic risk information may
The ethical and legal duties of physicians in clinical genetics and genomics

also fail to justify an exception to confidentiality because the patient is not morally culpable for the threat posed to the third party. Because the patient has not intentionally threatened another person, breaching the right to confidentiality may be less justifiable (Lacroix et al. 2008).

18.3 Emerging issues: whole-genome sequencing

The advent of whole-genome and whole-exome sequencing technologies creates new challenges and uncertainties for medical professionals. In a whole-genome approach, all six billion base pairs of an individual patient’s DNA are sequenced. A sample is broken down into millions of smaller fragments that are read, sequenced, and ordered along each chromosome (Ng and Kirkness 2010). WGS/WES allow for the exploration of complex gene–gene interactions and sophisticated comparisons between sequences, and have become popular tools in genetic research. Clinical uptake has been slow, but is expected to expand rapidly as costs decrease and our understanding of genomic information advances. Many of the first clinical applications of WGS involve children. WGS/WES can speed up differential diagnosis of rare genetic disorders in newborns suspected of a genetic condition, but not yet exhibiting sufficient clinical symptoms to diagnose (Saunders et al. 2012). The genomes of children affected by unknown conditions can be compared with those of their parents to identify de novo mutations and diagnose previously unknown genetic causes of disease (Veltman and Brunner 2012). At least in the short term, the primary clinical applications of WGS/WES will continue to be, not exceptionally, in paediatric diagnostics. Particular attention must therefore be paid to the paediatric context, especially concerning the question of when to use WGS/WES, and how to handle the communication of unexpected results to children and/or their parents. Genetic testing in pediatrics will be discussed in section 18.4.

18.3.1 Incidental findings

The controversy surrounding WGS/WES stems in large part from the vast scope of the genetic analysis and the potential of encountering unsolicited findings unrelated to the patient’s diagnostic question. How can a physician obtain meaningful patient authorization to test for such a vast range of potential results? Another important caveat for WGS/WES is that laboratories and laboratory medicine specialists, rather than physicians, play a central role in interpretation. Unlike X-rays or other forms of medical imaging, the analysis of WGS/WES results involves complex bioinformatics analysis. The results of this analysis are then pushed to physicians, potentially triggering duties to treat or inform. Laboratory reporting has been the focus of the American College of Medical Genetics and Genomics’ (ACMG) recent guidelines on clinical WGS/WES, discussed in detail below (Green et al. 2012).

The ethical debate over WGS/WES in both research and the clinic has centered on the duty to inform. WGS/WES returns large amounts of ‘unsolicited’ or ‘incidental’ genetic information unrelated to a research or clinical question. This information may be of clinical significance to the individual. This would suggest the researcher or clinician has a duty to return it to the participant or patient. On the other hand, informing individuals of genetic risks they did not know were among those tested may undermine their informational autonomy. This tension is discussed in the next section on the patient’s ‘right not to know.’

Experience from research with WGS/WES suggests that the informed consent process may be used to establish a plan for the ethical return of incidental findings (Knoppers and Lévesque 2011). In Canada, researchers are required to advise prospective participants of their plan for the overall management of information genetic research reveals (Canadian Institutes of Health
Research et al. 2010). Some authors have begun to outline the appropriate criteria for such a plan, taking the form of ‘broad consent’ models (Wallace et al. 2009). Broad consent streamlines informed consent by grouping findings into categories to be returned or not. An example in genomic research is the ‘Smart Filter’ of the National Cancer Institute (NCI) developed for the biobanking context (NCI 2010). The Smart Filter lists three major criteria for returning a result in the research context, including analytical validity, clinical significance, and clinical actionability. A National Institutes of Health consensus paper on biobank research goes further, suggesting results should only be returned if two additional criteria are fulfilled: the participant has consented to the return of individual findings and the return conforms with applicable law (Wolf et al. 2012). Finally, the Network of Applied Genetic Medicine of Québec suggests that approval by an ethics board should also be obtained, and the finding confirmed, before being returned (2013).

The research experience provides an informative platform for developing an ethical return of results policy in the clinic. In many ways, the return of results in the clinical setting may be more straightforward. In research, sequence-based research protocols can be very different, and the researcher–patient relationship is both vague and highly variable (Heger 2012). In the clinic, on the other hand, physicians have a clear responsibility to act for the benefit of their patients. While return protocols must be tailored to specific research studies, a single return of results protocol may be widely applicable across clinical settings. Indeed, there is significant concordance among clinical genetic specialists about what kinds of incidental findings from WGS/WES should be returned to a patient’s primary care physician (Green et al. 2012).

Berg and colleagues have developed a binning approach to incidental findings in the clinic. Unexpected findings could be organized in ‘a clinically oriented manner to facilitate shared decision making by patients and clinicians’ (Berg et al. 2011: 500). Clinically actionable findings are categorically reported; clinically valid but not directly actionable findings are not returned as a rule, but could be depending on patient preference; and findings of unknown or no clinical significance are not returned. Ayuso and colleagues recently refined this platform. They propose a list of minimum elements to be included in informed consent for clinical WGS testing, including a description of the procedure used to manage incidental findings (Ayuso et al. 2013). Incidental findings are grouped according to ‘the present or future effect of the variant, their actionability, carrier status, and penetrance’ (Ayuso et al. 2013: 1057). Whether some groups of findings will be returned is discussed and agreed upon in advance by the patient. For other groups, the authors recommend mandatory return.

Policy in rare diseases research presents considerations similar to the clinical context. The UK10K is a retrospective study of rare genetic diseases involving WGS, which outlines a policy for feedback of clinically significant findings to research participants in its ethics governance framework (Ethical Advisory Group of the UK10K Project 2010). UK10K distinguishes between ‘pertinent findings,’ relating to the disease under investigation, and ‘incidental findings,’ relating to diseases outside the original research aims and unforeseen at the time participants gave consent (UK10K 2010: 8). Return of pertinent and incidental findings of a specified clinical utility is contingent on consent for each class of finding. Even in research then, findings are distinguished in relation to the objectives of the sequencing. Why? Pertinent findings are only encountered when participants have been recruited for a specified (rare) clinical condition. This is because individual research studies in rare diseases tend to establish ‘robust management pathways for validating potentially diagnostic research data to diagnostic standards’ (UK10K 2010: 8). In addition, participants in rare disease research often express a strong desire for information on their condition and readily consent to its return. The UK10K emphasizes that there is no clear duty to return findings in research, especially absent unambiguous demonstration of clinical
utility and participant consent to the specific class of findings (i.e. pertinent and/or incidental of specified clinical utility). The guidelines of the European Society of Human Genetics (ESHG) make a similar distinction in the clinical context between solicited and unsolicited findings (van El et al. 2013). Not only should the risk of unsolicited findings be justified before pursuing WGS, but consent practices should also be developed to manage return. The ESHG also encourages categorization of unsolicited findings to facilitate patient expression of informational needs and preferences. Interestingly, the ACMG guidelines for reporting results from clinical WGS make no such distinction between pertinent (i.e. related to the diagnostic question) and incidental findings, but focus instead on the clinical significance of the finding (Green et al. 2013).

Many questions remain concerning the handling of incidental findings in WGS/WES. Who will determine the scope of the return/may return/do not return categories? Will the patient sufficiently understand these categories, especially considering the uncertainty and highly probabilistic nature of most genetic information? For patients, more information is not always better. Increasing the scope of informed consent will increase the time and expense of pre-test counseling for the healthcare system, and may result in information overload in patients (Bunnik et al. 2011).

When is the use of WGS/WES appropriate? The Canadian Medical Association Code of Ethics states that only diagnostic services considered to be beneficial to the patient should be recommended (2004, article 23). The Canadian College of Medical Geneticists endorses the use of WGS/WES in a judicious and cost-efficient manner to answer a clinical question. The administering physician should possess the requisite expertise before recommending WGS/WES testing, interpreting its results, or offering treatment options post-test (Zawati et al. 2013). Determining when WGS/WES is beneficial, however, is not always easy. Indeed, examining one part of the sequence may be clinically beneficial, while another may reveal an untreatable condition, or leave a patient with troubling uncertainty.

In this way, WGS/WES blur the boundary between genetic testing and screening, areas traditionally governed by separate normative frameworks (Dondorp and de Wert 2013). The basic principle of screening – the early detection and treatment of disease – is straightforward, but it has long been recognized that this process comes with significant ethical, legal, and social complexity. In 1968, Wilson and Jungner developed criteria for the World Health Organization’s (WHO) screening criteria, which remain relevant today. Beyond the basic considerations of genetic testing (analytic and clinical validities, actionability, etc.), there should also be a suitable treatment acceptable to the public, as well as facilities for diagnosis and treatment, and the cost of screening should be justified economically from the health system as a whole (Wilson and Jungner 1968).

Screening targets populations rather than individuals. The benefits of early detection for affected individuals must outweigh the potential of harm to those who do not need treatment. One such potential harm is unnecessary work-up in the case of a false positive. The rate of false positives tends to be higher when testing is carried out in asymptomatic, untargeted populations (Burke et al. 2013). Furthermore, classical criteria have to be adapted when screening for genetic disease. First, a population viewpoint may not adequately account for the seriousness of rare genetic conditions. Second, while genetic tests may be cheap and powerful predictors of disease, the related costs of education, counseling, and intervention (if available) may be the true limiting factors (Andermann et al. 2008). Finally, the pace of genetic science risks ‘out-pacing the ability of professionals and policy-makers to assess the potential benefits and pitfalls of introducing or expanding genetic screening programmes’ (Andermann et al. 2008). Simply having a test and a treatment is far from enough to justify screening.
The ACMG clinical guidelines for clinical WGS/WES reflect the inevitable blurring between testing and screening (Green et al. 2013). The guidelines require mandatory analysis and reporting of a curated list of genetic variants whenever WGS/WES is used in the clinic for newborns, children, and adults alike. In a sense, laboratories are asked to ‘screen’ for a curated list of mutations, regardless of the patient’s original diagnostic question. The curated list includes variants ‘for which there is the significant potential for preventing disease morbidity and mortality if identified in the presymptomatic period’ (ACMG 2013: 664). Traditionally, medical ethicists have rejected such ‘opportunistic initiatives’ by physicians (Getz et al. 2003). Respect for autonomy requires physicians to focus on a patient’s reasons for seeking help, and to honor the patient’s right not to be confronted with unsolicited information about biomedical risks. The ACMG policy may be a slippery slope towards population-wide genetic screening. Until now, screening has only been supported for severe metabolic conditions in newborns. If physicians must screen asymptomatic individuals with no family history for certain genetic conditions, simply because they are undergoing WGS, why ignore the rest of the population?

The ACMG’s justification to require testing and reporting of a curated list of variants is rooted, perhaps too firmly, in the logic of the duty to inform and fear of subsequent liability. The deliberate search for results not related to the diagnostic question is justified by the health professionals’ ‘fiduciary obligation’ to inform patients of ‘unequivocal’ pathogenic mutations, especially where treatment or prevention is possible: ‘failure to report a laboratory test result conveying the near certainty of an adverse yet potentially preventable medical outcome would be unethical’ (ACMG 2013: 664). Even though the list attempts to include only conditions where medical benefit is likely, mandatory reporting has been criticized for failing to respect patients’ control over the flow of their genetic information (Burke et al. 2013). The ACMG argues that consent to testing meaningfully protects autonomy upstream, while physician discretion during clinician management of the results can reinforce it downstream. Respecting a patient’s informational preferences may be infeasible, however, requiring lengthy pretest counseling and consent for the examination of genes unrelated to the clinical question.

The criteria used by the ACMG to establish the list are also controversial. In the ACMG’s own words, there is ‘insufficient evidence about benefits, risks, and costs of disclosing [the listed variants] to make evidence-based recommendations’ (Green et al. 2013: 4). This is especially true as the clinical validity of these genetic mutations may have been established in a targeted population, and may be weaker in an unselected population (Burke et al. 2013). Net benefit for the healthcare system, an important consideration from a screening optic, is also apparently ignored. The added burden of analysis, interpretation, post-test counseling and follow-up will no doubt have an impact on healthcare resources (Burke et al. 2013).

WGS/WES may also amplify the frequency of conflicts between confidentiality and the duty to warn family members of genetic risk. With WGS/WES, the possibility of encountering a genetic finding of potential importance to family members is rapidly increasing (Cassa et al. 2012). Under the ACMG guidelines, the duty to inform patients has been intensified to include return of a curated list of pathogenic mutations. This may be fertile ground to argue for an expansion of the physician’s duty to inform beyond the patient. In fact, the ACMG explicitly recognizes a new ethical duty towards family members in the paediatric context. It recommends testing and reporting of adult-onset conditions in children, because ‘if the child carries a pathogenic mutation, there is a high probability that one parent does as well’ (ACMG 2013: 665).

Physicians should not be expected to shoulder all the responsibility for these ethical conundrums. There is a growing need for systematic solutions to improve the clinical utility of WGS/WES (Grosse and Khoury 2006). Decision support tools can help to ‘provide clinicians with options for test ordering; indicate the sensitivity, specificity, and positive predictive value of
tests; and aid clinical workflow by providing algorithms to facilitate decisions on the basis of test results’ (Mirnezami et al. 2012: 491). Risk stratification is also important. Kohane et al. call for the development of estimates of disease prevalence by ethnic group (2006). These population reference maps ‘will allow the sensitivity and false-positive rate of each individual genomic test to be combined with prevalence to estimate the real overall risk of a positive test result based on approximate ancestry’ (Kohane et al. 2006). Physicians regularly exposed to WGS/WES test results can familiarize themselves with high-risk and clinically actionable results. Medical schools and continuing medical education can better integrate genomic science into their curricula. From a policy perspective, efforts are needed to clarify the extent to which physicians are expected to understand WGS/WES, and to introduce systemic changes to help cope with the expectations these tests bring (Black et al. 2010).

### 18.3.2 The patient’s right not to know

An emerging issue in genetics concerns the patient’s ‘right not to know.’ The right not to know was originally advanced in reaction to expanding predictive genetic testing in the 1990s and is codified in several international normative documents (Council of Europe 2008, article 10.2; WMA 2005, article 7(d)). For example, article 5(c) of UNESCO’s *Universal Declaration on the Human Genome and Human Rights* 1997 states that the right of an individual ‘to decide whether or not to be informed of the results of genetic examination and the resulting consequences should be respected.’ Andorno characterizes the right not to know as an autonomy right, a ‘right to informational self-determination’ (Andorno 2004: 436). It is not to be confused with waiver of informed consent – patients must always be informed of the purpose and risks of medical tests. Instead, the right not to know protects the patient’s interest in not knowing the results of a medical test, especially if those results are unrelated to the patient’s motives for seeking testing (for a comprehensive introduction, see Knoppers 2014 (in press)).

Choices about genetic information have always been present. A patient can choose whether or not to undergo genetic testing. Indeed, the simplest way for a patient to exercise the right not to know is to refuse diagnostic testing. Patients have an ‘established right to refuse unwanted medical tests and the information they might disclose’ (Wolf et al. 2013: 1050). The informed consent process protects this right. The central aspect of a diagnostic test is that it returns health information. Thus a patient consenting to diagnostic testing is authorizing the physician to seek and report health information. In order for this consent to be informed, however, the patient must understand the nature of the ‘health information’ sought and the consequences of a positive finding. A patient who considers the informational risk of a genetic test to outweigh its potential benefits is free to decline sequencing.

Many argue that the right not to know is broader than the right to refuse diagnostic testing (Wolf et al. 2013). For example, if a physician finds a gene that the patient did not know was being tested for, perhaps for an untreatable condition, should this be categorically reported to the patient? More broadly, the right not to know could be considered a right to refuse health information. An analogy is often drawn between this right and the patient’s right to refuse health treatment. The right to refuse health treatment is considered absolute, meaning that even competent patients may refuse life saving treatment (Lemmens 1996).

Is the right not to know absolute? Arguably, patients should not, and cannot practically, be extended the right to refuse potentially life-saving information. Paradoxically, respecting a patient’s choice to refuse health information could potentially rob that same patient of an opportunity to exercise a choice about life-saving treatment. The very concept of ‘informed refusal to know’ is problematic: a decision to refuse information cannot be made without knowledge.
of the information one is refusing. While the theoretical justification of the right not to know is compelling, it remains unclear how respect for this right can be implemented. Despite these difficulties, the advent of WGS/WES testing has renewed interest in the right not to know. The clinical meaning of much of the information it returns is highly uncertain. Even where the clinical significance of a genetic variant is known, this information is often probabilistic. Ultimately, knowing you have a predisposition to a disease is not the same as having that disease. Some genetic risk information may be unwelcome or misunderstood by patients, and may lend to the phenomenon of the ‘worried well.’ Other results may have high penetrance and clear clinical relevance, but offer no treatment or prevention.

Should patients choosing to undergo WGS/WES have the right to refuse potentially life-saving information? Here, understanding the distinction between the ‘assay’ and ‘analysis’ of a scientific test is important. A genetic assay is a procedure that identifies the presence of a particular genetic sequence. Many early genetic tests assayed a short genetic sequence. The presence of a mutated sequence would indicate the presence of the genetic condition. By contrast, WGS/WES deciphers much of the individual’s genetic code. All possible genetic mutations are simultaneously assayed during WGS/WES. Complex bioinformatics analysis is then used to interpret sequences of interest. The differentiation between assay and analysis makes the ethical characterization of WGS/WES challenging, especially as it concerns the patient’s control over the flow of genetic information. When patients undergo WGS, for whatever purpose, they undergo an assay for all disease-associated genes (Green et al. 2013). The subsequent bioinformatics analysis can – theoretically – establish any particular unanticipated variant with relative ease. This prompted the ACMG to recommend that genetic laboratories actively seek out and report a minimum list of variants whenever WGS is used in the clinic (Green et al. 2013).

The ACMG approach has been criticized for undermining patient autonomy and the ‘right not to know.’ Patients have an interest in exercising choice over the genes, or at least the types of genes, they are tested for (Wolf et al. 2013). Where patients are extended the right to refuse life-saving treatment, should they not also be able to refuse potentially life-saving information? For example, a patient may want to receive genetic findings useful to the diagnosis that prompted WGS/WES analysis, but have no interest in receiving information about his or her risk status for adult-onset Mendelian diseases. The basic solution to ensuring the patient’s informational self-determination is to offer comprehensive pretest counseling to inform patients of the types of results WGS/WES may return, and then to apply filters (either during the analysis itself, or before reporting) to respect these preferences. Under the ACMG guidelines, patients are still free to refuse WGS/WES testing. But once they have decided to undergo testing, they will not be able to control what results or types of results are communicated to them (or to their children – see section 18.4). The determination of what results are communicated is instead made by ‘expert professional judgment’ (McGuire et al. 2013). Not allowing patients to refuse reporting of certain results has been criticized as coercive, undermining the shared decision-making process between physicians and patients, and discouraging some patients – potentially to the detriment of their health – from undertaking testing altogether (Ross et al. 2013a; Allyse and Michie 2013).

There are compelling justifications for the ACMG’s ‘all or nothing’ approach to WGS/WES. They appeal to the health professional’s fiduciary obligation to inform patients of actionable and highly pathogenic mutations (ACMG 2013). Reporting these results would generally benefit the patient’s health. These results are also the type that fall under the physician’s duty to inform. Physicians could face liability for failing to report a serious and treatable condition that would have been found with a simple modification to the laboratory bioinformatics analysis. Indeed, case law from medical imaging suggests physicians may be liable for failing to identify or to
report an incidental finding for a treatable or preventable genetic condition (Clayton et al. 2013). Perhaps the most convincing justification for mandatory reporting is the practical difficulties in administering patient preferences and the ‘right not to know.’ Even if a binning solution is adopted, establishing patient preferences will require extensive pretest counseling. Physicians holding such results may second-guess even the most ‘enlightened refusal’ to receive communications about potentially life-saving information. On the other hand, because physicians will feel compelled to return all results they receive – fearing liability for nondisclosure – patient choice may require heightened protection (Ross et al. 2013a).

18.3.4 Follow-up

Physicians are required to provide medical follow-up for an examination or investigation (AMA 2008, Opinion 10.01(5); CMA 2004, article 19). WGS/WES leaves doctors in a precarious position with regard to this duty. On the one hand, they may risk liability for negligence if they ignore uncertain genetic results. On the other hand, they may order a battery of alternative, targeted tests to confirm the revelations of WGS/WES testing (Kohane et al. 2006). The problem with this defensive medicine approach is that it exposes patients to costly and potentially harmful follow-ups (Kohane et al. 2006; Kuehn 2011) and strains already limited primary healthcare resources (McGuire and Burke 2008).

As the WGS knowledge base expands, what happens as the meaning of past WGS/WES test results changes? Currently, in the United States, the United Kingdom, and Canada, physicians are not legally responsible for re-contact, and it is up to the patient to initiate re-evaluation (Thorogood et al. 2012). With a large amount of genomic material stored in a patient’s health record and susceptible to evolving interpretation, it is difficult to define or delimit the scope of such a duty. In addition, it is hard to imagine how a patient’s interest in informational self-determination can be meaningfully respected without allowing him or her to control the terms of follow-up. However, even if the responsibility to follow up is placed on the patient, physicians will still need to respond with care and diligence when approached by their patients for reinterpretation (Pyeritz 2011).

Some suggest that the duty to follow up may one day expand to encompass the re-contact of patients, when consented (Pyeritz 2011; Ali-Khan et al. 2009). This would be desirable because genomic information can be stored and treated as an evolving source of health information, rather than a one off test. It remains impractical, however, to expect physicians to monitor every aspect of a patient’s health continuously, especially after care has been transferred to another provider or the patient stops making regular visits (Clayton and McGuire 2012). Indeed, the traditional model of the ‘single longitudinal relationship’ between patient and physician is being displaced. Patients now tend to interact with a ‘cascade of providers’ (Clayton et al. 2013). Intensifying the physician’s duty to follow up is more likely to encourage fruitless legal pursuits than it is to enhance the use of genomic test results over time.

18.4 Emerging issues: genetic testing and screening in pediatrics

When is it appropriate to test or screen children for genetic conditions? The central complication in pediatrics is that children are unable to consent. It follows that genetic testing should be carried out if and only if it is in the best interests of the child. Under the UN’s Convention on the Rights of the Child 1989, children have the right to enjoy ‘the highest attainable standard of health,’ and to have actions concerning them primarily governed by their best interests (articles 3 and 24). This is affirmed by the ACMG and the American Academy of Pediatrics.
Adrian Thorogood and Bartha Maria Knoppers

(Fallat et al. 2013): the best interests of the child should drive genetic testing and screening. While the best interests of the child can be an elusive concept, the central consideration for genetic testing is the potential for timely medical benefit during childhood (Zawati et al. 2013). An additional consideration of the Convention is that children have the right to be heard (article 12). The decision to carry out genetic testing should give children’s views due weight according to their age and maturity (Zawati et al. 2013).

Testing children for adult onset conditions is generally discouraged, as they should be allowed to consent to the test once they reach maturity. The Council of Europe states that when, under law, a minor does not have the capacity to consent, a genetic test on this person shall be deferred until attainment of such capacity unless that delay would be detrimental to his or her health or well-being (Council of Europe 2008, article 10). The British Society of Human Genetics recommends that predictive and pre-symptomatic genetic testing normally be delayed until children can decide whether or not to be tested (2010). There is controversy over whether this rule should apply for severe conditions preventable or treatable during adulthood. Here, the likelihood that the child will not be presented with another opportunity to test for the condition must be considered (ACMG 2013). Direct benefits to parents may also be considered where they are continuous with the interests of their children (Ross et al. 2013b). According to the ACMG, such indirect benefits may, in some cases, trump the child’s future autonomy interest. They challenge the traditional position that genetic testing for late-onset conditions should be delayed until adulthood: ‘it may be ethically acceptable to proceed … to resolve disabling parental anxiety or to support life-planning decisions …’ (Ross et al. 2013b: 238). A fear underlying this position is that failure to test for a genetic condition in an affected child may result in liability towards the child's biological parent.

Newborn screening also relies on the best interests of the child tested, but construes the test more objectively as a duty of the state to protect the vulnerable. The goal of newborn screening is to screen for severe metabolic conditions where immediate medical intervention is available. It is carried out in at least 64 countries without explicit parental consent (Wilson et al. 2010). Parents may be obliged by law to screen their child, because no ‘reasonable’ parent would refuse screening that detects an at-risk child, and because it has become the pediatric standard of care. Because the decision-maker for screening is often a public health agency and not an individual physician, political and economic considerations arise. In addition to analytical validity, clinical validity, and the existence of treatment, one must also consider if there are facilities available to administer that treatment, and if the cost for diagnosis and treatment is economically justifiable in the health system as a whole (Andermann et al. 2008).

Screening asymptomatic, at-risk newborns for immediately treatable conditions has long been the professional standard of care in pediatrics (WHO 2011; Wilson and Jungner 1968; Knoppers and Laberge 1990). However, the number of screened diseases has been increasing in the USA, Canada, and Europe (Lindner et al. 2011). It is also plausible that newborn screening programs will soon involve WGS/WES (Knoppers et al. 2013). Once a newborn’s genome is sequenced, the temptation to expand screening to new mutations will be hard to resist. Rigorous application of the ACCE model discussed above may be particularly appropriate here (Lévesque et al. 2011; CDC 2010). In the case of rare disease, such an expansion may be desirable. Here, the logic of the emerging ‘personalized medicine’ paradigm displaces that of screening.

Indeed, newborn screening could provide a future health map for every individual, especially for those with rare diseases (Dondorp and de Wert 2013). The use of such a futuristic report card would need to be tightly regulated in order to serve the best interests of the child. Among the ethical, legal and social issues considered under this model is the interest of newborns in
controlling future choices about their health information, especially when testing can be delayed until adulthood (Dondorp and de Wert 2013). Genetic testing guidelines generally advocate that tests for adult-onset conditions be delayed until adulthood to preserve the child’s ‘right to an open future’ (Hens 2011; Feinberg 1980).

There has been keen interest in using newborn screening samples and dried bloodspots left over from past screening for case-control research. WGS/WES of newborn bloodspots is ideal for genome wide association studies, as they provide an unprecedented, unbiased population reference map. Perhaps the greatest advantage for researchers, albeit a dubious one, is the dispensing of participant consent. Parents are presumed to consent to newborn screening for disease prevention. This presumption does not appear to hold for the storage and research of leftover samples (Association of Public Health Laboratories 2002). Recent outrage and legal action over researchers accessing stored newborn screening samples for research without explicit consent has brought such initiatives into serious doubt (Allen et al. 2013).

Incidental findings of WGS/WES add another layer of complexity in pediatrics (Knoppers 2012). First, they significantly complicate the best interests test in deciding to undergo testing. Second, how does a physician determine what findings should be communicated to the representatives of the child who is unable to express his or her informational preferences? Guidelines from the pediatric research context stipulate that researchers are only permitted to report findings (whether individual research results or incidental findings) if they reveal a clinically significant condition that is treatable or preventable during childhood. This is consistent with a position long held in medical genetics: genetic testing should only be performed on children and minors (i.e. prior to legal capacity/mature minor) if the condition under investigation is actionable during minority (American Academy of Pediatrics (AAP) 2009; Canadian Paediatric Society 2003).

This position has been challenged, controversially, by the ACMG guidelines discussed above. Their recommendation for the mandatory reporting of certain genetic conditions applies to all patients undergoing WGS/WES, including children (Green et al. 2013). In contrast, the Public Population Project in Genomics and Society (P3G), while promoting a should-return policy for results actionable in childhood, advocates a no-return policy for results revealing mutations predisposing children to adult-onset conditions. Exceptions are made, however, on a case-by-case basis for situations where a child may benefit by preventing harm to family members (Knoppers et al. 2014).

### 18.5 Conclusion

The issues surrounding WGS/WES are totally absent in international normative guidance except for blanket, general statements on obligations to communicate (or not) results with no mention of WGS (Knoppers and Dam 2011). Even the most recent WHO guidelines mandate only that research participants be informed of the progress of research (WHO 2011). Perhaps this simplicity enables such guidelines to be more universally applicable, but in countries lacking local ethics or professional guidance, more discussion of the options and implications of emerging technologies would be helpful. This is not to say that any one specific technology should be addressed in international normative guidance, as this could well limit the future applicability of international frameworks over time, but that general criteria for evaluation should be provided (Wolf et al. 2012). The conflation of the research and clinical contexts using WGS/WES will, however, affect the viability of any guidance provided.

Systematic reforms may be necessary at both the micro and macro levels to ensure the ethical introduction of WGS/WES testing. At the micro level, funders of research and medical
professional organizations may wish to consider revisiting their codes of scientific integrity, or of ethics, to determine if sufficient guidance is provided for their members. In particular, the possible expansion of current duties and responsibilities of physicians to patients across their lifetime needs to be balanced with a corresponding responsibility of the individual patient to request information and make choices. There is no doubt that for genomic information to be understood, education is key. In organizing its health systems and safety oversight of both public and private testing, the state should mandate and control quality assurance at the macro level through oversight and accreditation. Irrespective, one thing is certain: the arrival of whole-genome analysis has blurred the roles of researchers and physicians, of participants and patients, and of local, national and international ethics review. Perhaps it is better to build a system of e-governance that is dynamic, interactive, and international to best reflect this new reality?

References


Adrian Thorogood and Bartha Maria Knoppers


The ethical and legal duties of physicians in clinical genetics and genomics


Legislation

Code of ethics of physicians 1981 (Quebec, Canada).
Loi n° 2002-303 du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé (France).

International treaties and conventions


Cases

Liss v. Watters 2010 QCCS 3309 (Québec, Canada).
Molloy v. Meier [2003] 679 NW.2d 711 (US)
Pate v. Threlkel [1995], 661 So.2d 278 (US).
Perruche [2000], Assemblée plénière 99-13701 Cours de cassation (France).
Watters v. White 2012 QCCA 257 (Québec, Canada).