



The ethical framing of personalized medicine

Yann Joly, Katie M. Saulnier, Gladys Osien, and Bartha M. Knoppers

Purpose of review

Personalized medicine encompasses the use of biological information such as genomics to provide tailored interventions for patients. The review explores the ethical, legal, and social issues that have emerged with personalized medicine and must be considered because of the complex nature of providing individualized care within a clinical setting.

Recent findings

Recent studies found that the use of personalized medicine presents challenges in multiple areas: biobanking and informed consent, confidentiality, genetic discrimination, return of results, access to treatment, clinical translation, direct-to-consumer genetic testing, emerging duties, and knowledge mobilization.

Summary

Although personalized medicine provides benefits in treating patients in a manner that is more suited to their genetic profile, there are challenges that must be discussed to ensure the protection and fair treatment of individuals. The issues concerning personalized medicine are widespread, and range from individual privacy to the stratification and discrimination of sub-populations based on ethnicity. These issues have considerable impact on the individual and society. A thorough exploration of these ethical issues may identify novel challenges as well as potential avenues for resolution.

Keywords

biobanking, ethical, legal, and social issues, personalized medicine

INTRODUCTION

Personalized medicine is considered one of the more promising applications of genetic and related 'OMICS' research. In recent years, personalized medicine has also increasingly used other types of health data to achieve a more precise and personalized medical approach. Financial investments made by the private and public sectors in personalized medicine are considerable and public expectations are proportional to this commitment. Currently, an important debate concerns the degree of impact that personalized medicine will have on medical practice: a true revolution, or a contribution of more modest proportions?

The following review article focuses on the key articles on the ethical, legal, and social issues (ELSI) of personalized medicine since 2012. They include concepts and terminology, biobanking and informed consent, confidentiality, genetic discrimination, return of results, access to treatment, clinical translation, direct-to-consumer (DTC) genetic testing, emerging duties, and knowledge mobilization.

CONCEPTS AND TERMINOLOGY

Conceptual vagueness surrounds public discourse on personalized medicine [1^{••}] and the discussion

has intensified since 2000. The following definition has been proposed in a recent article: 'Personalized medicine seeks to improve stratification and timing of healthcare by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics as well as metabolomics' ([1^{••}], p. 10).

Finally, although the concept of personalized medicine itself seemingly includes precision medicine, P4 medicine (predictive, preventive, personalized, and participating medicine), and genomic medicine, these terms create expectations of unrealistically perfect outcomes [2]. Indeed, even the use of personalized medicine as a buzzword may create impractical expectations in patients and laypeople [3]. The same authors anticipate that patients will expect more individualized, personal treatment that incorporates their physical, mental, and spiritual well-being [3].

Centre of Genomics and Policy, McGill University, Montreal, Canada

Correspondence to Dr Yann Joly, Centre of Genomics and Policy, 740 Dr Penfield Suite 5200, Montreal H3A 0G1, Canada. Tel: +1 514 398 7286; fax: +1 514 398 8954; e-mail: yann.joly@mcgill.ca

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KEY POINTS

- Thorough review of ELSIs specific to personalized medicine from different perspectives.
- Highlights key issues in biobanking in the context of informed consent and confidentiality.
- A brief account of the legal and ethical issues concerning the current status of genetic discrimination.

BIOBANKING AND INFORMED CONSENT

Informed consent is increasingly challenging because of the sheer volume of information to be provided. Given that personalized medicine requires a significant amount of patient participation, giving patients larger access rights to their data is both empowering and leads to more informed choices and a better quality of consent [4].

A recent model for informed consent focuses on the consumer perspective to overcome problems with consent that are specific to DTC genetic testing (referred to by Bunnik *et al.* [5[¶]] as ‘personal genome testing’). DTC is likely to be misunderstood by consumers, meaning that providing adequate information is a primary concern [5[¶]]. Hence, a tiered, layered, and staged model for consent provides specified categories of diseases as a choice within participation rather than as an all inclusive package. Layered means that some information is considered indispensable, other information is offered but not considered fundamental, and more detailed information is made accessible to those who seek it out, keeping the core information comprehensible and manageable. The consent information is not all given out at once, such an ongoing process providing more time for patients to absorb information [5[¶]].

BIOBANKING AND CONFIDENTIALITY

Confidentiality of biobanked information is also affected by the plethora of sequencing information to be provided. To address this problem, researchers must develop methods for keeping data secure and private. A recent study [6] involving 30 participants in the United States found that participants cared about the confidentiality of their data in part because it gave them a feeling of retaining some control over their information. Additionally, patients expressed a need to be protected from the possible dangers of disclosure, particularly for insurance and employment discrimination.

Other authors have also addressed the topic of privacy issues encountered when storing genetic

information [7[¶]]. They highlight interfamilial privacy issues, that is, the rights of patients’ relatives to receive medical information that may impact them, thereby weighing individual patient privacy and autonomy against the interests of relatives. Moreover, ‘medicalizing the genome by assuming all genomic information is relevant for determining medical risk’ may lead to ‘hoarding’ genomic data, and create privacy and standard-of-care problems ([7[¶]], p. 199). There is a difference between storing genomic data for clinical purposes and storing them for research purposes, in which storage of the entire genome may be significantly more useful. By contrast, the storage of whole genome sequencing (WGS) data in a clinical setting may create unnecessary privacy risks. By making the data accessible to an increasing number of healthcare workers who are now involved in the patient care, nonpaternity or unanticipated presymptomatic health information may be revealed to the individual or to biological relatives [7[¶]]. Additionally, interested third parties such as insurance companies or employers who obtain information may engage in discriminatory practices.

GENETIC DISCRIMINATION

Genetic discrimination is one of the most pervasive issues associated with genetic research and personalized medicine. Concerns that genetically at-risk individuals could be excluded from important socio-economical goods, services and activity spheres has convinced policymakers in a substantial number of countries to adopt broad legislative solutions to prevent abuses [8]. However, the actual extent and impact of genetic discrimination have never been clearly established.

The results of an international survey of genetic discrimination in the context of Huntington’s disease point to the existence of discriminatory practices affecting 33% of the individuals surveyed, that is, at-risk individuals tested for the Huntington’s gene [9]. The greatest number of cases of genetic discrimination was reported by individuals having tested positive for the gene. In the field of cancer genetics, specialists would be more willing now than before to undertake testing for the BRCA1 and BRCA2 mutations, which are associated with an increased risk of developing hereditary breast or ovarian cancer, and to share their results with insurers [10]. This finding was explained by the fact that the specialists felt well protected by the current United States legislative framework, for example, the 2008 Genetic Information Nondiscrimination Act (GINA). Enacted in May 2008, GINA was designed to prohibit insurers and employers from

discriminating based on genetic information. The Act includes prohibitions on denying coverage or charging higher premiums to a healthy individual based solely on genetic predisposition to a disease, and similarly bars employers from using this information when making decisions about hiring, firing, and promotions. GINA's application in the context of employment is discussed in opposing opinion papers arguing the Act's pros and cons by Noah Levin [11] and Mark Rothstein [12], respectively. Levin [11] uses case studies to propose that genetic discrimination in some cases is justifiable, and that GINA limits the ability of employees to perform job functions safely as it does not allow a full risk assessment that includes an individual's genetics, which can predict the likelihood of harm in a workplace. Rothstein, by contrast, explains that risk assessments based on genetic tests cannot accurately predict likelihood of the risk-inducing adult-onset symptoms to which Levin refers. Furthermore, Rothstein [12] insists that GINA has symbolic value in alleviating fears of discrimination so that individuals at risk can use genetic testing services freely.

The first systematic review of the available evidence of genetic discrimination in the field of life insurance in 2013 concluded that although the available data did confirm the existence of individual cases of genetic discrimination, mostly in the context of a few classic monogenic conditions, the available data did not demonstrate the existence of a systemic problem [13²²]. Moreover, there was a complete absence of evidence regarding the existence and impact of genetic discrimination in personalized medicine. Keeping this recent finding in mind, an international multidisciplinary group including insurers has proposed action items for stakeholders specifically applicable to this issue. One of the more interesting of these recommendations is the need for insurers at the national and international levels to adopt explicit policies to the effect that they will not seek access to the results of genetic tests undertaken in the research setting [14²³].

RETURN OF RESULTS

As technological advances make the use of WGS in research and treatment more affordable – and therefore more common – the management of the ethical and legal issues associated with the return of results becomes more pressing. An emerging issue is the return of results for participants in genotype-driven research. Here, re-contact of participants necessarily discloses genetic information, creating new ethical dilemmas [15]. This would justify the development of clear guidelines, as current recommendations do

not suffice under the broader use of genotype-driven recruitment [16²⁴].

The excess of information provided by WGS highlights the necessity of developing guidelines dealing with both the return of results and incidental findings [17]. Full disclosure or total nondisclosure is equally infeasible, for both economic and ethical reasons. Additionally, the increasing frequency of WGS highlights the problem of return of results to parties who have not consented or cannot consent such as in pediatrics or with incompetent adults. In the pediatric context, this means balancing parental rights with the globally accepted 'best interests of the child' norm, which may override parental refusal to have results returned to them in which the clinical significant condition revealed is medically actionable during childhood [18²⁵].

ACCESS TO TREATMENT

Access to personalized medicine technology and research brings questions of equitable access to healthcare needs [19²⁶,20,21]. Significant concerns have been expressed by the public on the utility of personalized medicine as a criterion to ration care. To avoid this, participants in one study [19²⁶] suggested providing no restrictions on the tests that patients may want to undertake, regardless of the clinical benefits. The possibility of restricting access to care because of one's genomic profile is a concern that has been echoed in a case study [20] of breast cancer risk prediction models that revealed the potential for inequity of access to care based on ethnicity and age. Personalized medicine could serve as a means for ethnic stratification, irrespective of the limitations of sequencing technologies. In short, access to genomic testing and targeted therapies is a cause of ethical and social concern within oncology [21].

TRANSLATION

Genomic profiles are the driving force toward enabling clinicians to personalize care and thereby minimize the variation in outcomes that occur when a 'one-size-fits-all' approach is used [22²⁷]. Pharmacogenomics in particular stands out in tertiary-care. Indeed, more molecular tests are now available to inform and target cancer treatment for specific molecular profiles. Similarly, primary-care proves to be an important step in providing patients with genomic testing and personalized care. The perception of personalized care, in primary care, however, differs among healthcare professionals and patients. There are unique ELSI challenges in implementing genomics information

and personalized medicine technology within a primary care setting [21].

From a technological point of view, genomic information will increasingly be integrated into electronic health records, but this affects data storing, protection of privacy, and interpretation of results [22*].

DIRECT-TO-CONSUMER GENETIC TESTS

DTC genetic tests are kits sold directly to consumers often without involving healthcare professionals [23]. Global analysis has projected that the genetic testing market is estimated to reach more than \$230 million by the year 2018 [23]. The market increase is mainly because of the change in accessibility to average consumers as the general public now has access to genetic tests at a price that has decreased ten-fold since the year 2007.

Consumers of these services are motivated for three reasons: identity-seeking, disease risk-taking that would supplement healthcare needs, and improvement on lifestyle (empowerment). Yet, research has shown that ‘DTC genetic tests are often limited, resulting in no significant positive or negative changes’ in lifestyle improvement ([23], p. 360). There are also regulatory loopholes allowing for the possibility for discrimination within life insurance, long-term insurance, or disability insurance. A recent content analysis review of 39 papers analyzed DTC-genetic testing website information, consumer perspectives and experiences, and the perspectives of healthcare providers and concluded that that neither the health benefits suggested by DTC proponents nor the risks expressed by the opposition have in fact occurred [24*].

LEGAL DUTIES

As WGS in personalized medicine is relatively new, few legal cases exist to provide insight into the duties and liabilities that may be faced by researchers and physicians. Some of the duties arising from personalized medicine, however, will relate to the return of results and incidental findings already occurring in the research domain. To date, no cases were found relating directly to incidental findings. However, critical comparisons can be made between incidental findings cases relating to medical imagery and those of personalized medicine and WGS [25].

Common to existing medical law generally is the centrality of the standard of care in determining liability, with the acknowledgment that the standard of care differs from one specialty to the next, as currently clinicians are not trained to interpret WGS

results. The pertinent standard of care, then, will emerge from the genomics laboratory where specialists are trained. Moreover, ‘the likelihood that clinical utility will change over time for many results, and the significance of personal utility for genomic data that lack clear clinical value’ will affect liability ([25], p. 627). A vast amount of data is generated by WGS, and with frequent advances in knowledge and technology that allow for its more accurate interpretation, new duties and liabilities may emerge.

KNOWLEDGE TRANSFER AND CITIZEN ENGAGEMENT

The advancement of genomics has great potential for the field of medical research. Personalized medicine as a patient-centered approach to treatment could be most advantageous in clinical practice, but this mandates more public engagement in personalized medicine. ‘The public is one of the most important stakeholders in personalized medicine, yet there is a paucity of studies regarding citizen’s values, concerns, and expectations of personalized medicine’ ([19*], p.1).

Indeed, ‘the integration of genomic medicine and predictive biomarkers into practice, patient empowerment and a more participatory medicine are gaining importance’ ([4], p. 4775). Personalized medicine is perceived as an innovation that requires the development of new processes of collaborating. In implementing a ‘patient empowerment tool’ that would allow patients to better understand their medical documentation, Kuchinke describes personalized medicine as a catalyst to shifting the nature of the physician–patient relationship. Indeed, as Bombard notes, ‘understanding the public’s perceptions, values, and expectations is important given that the public is not only its main beneficiary but also its primary funder’ ([19*], p. 1). Recent studies revealed the concerns from the public about rationed care and other ethical challenges involving the autonomy of the patient along with resource allocation.

CONCLUSION

Our review testifies to the great dynamism of the current research on the ELSI issues of personalized medicine. In fact, ELSI research has been increasingly described as an essential research pillar to bring about the successful integration of personalized medicine in clinical care [26].

Many of the issues identified therein, for example, confidentiality, return of results, and access to medicine are not new and have already been discussed by ELSI researchers in the context of other

types of biomedical research. This does not mean that they do not deserve to be studied more thoroughly by authors in the particular context of personalized medicine in which their scope, impact, and associated challenges may be different. Just as scientific knowledge on personalized medicine advances and our understanding of personalized medicines' signification for healthcare increases, ELSI research will become less theoretically oriented and increasingly focus on policy development, knowledge mobilization, and clinical integration of personalized medicine. This natural evolution will enable ELSI research to become an important factor both in ensuring that governance frameworks are ready for the clinical integration of personalized medicine and in promoting public trust in this promising scientific discipline.

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Conflicts of interest

There are no conflicts of interest.

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