Review

For reprint orders, please contact: reprints@futuremedicine.com

Personalized Medicine

Translating personalized medicine using new genetic technologies in clinical practice: the ethical issues

Kelly E Ormond*[1,2] & Mildred K Cho[2,3]

[1]Department of Genetics, Mail Stop-5208, Stanford University, Stanford, CA 94305-5208, USA
[2]Stanford Center for Biomedical Ethics, 1215 Welch Road, Modular A, Stanford, CA 94305-5417, USA
[3]Department of Pediatrics, 300 Pasteur Drive, Stanford, CA 94305-5208, USA
*Author for correspondence:
Tel.: +1 650 736 9847
Fax: +1 650 498 4555
kormond@stanford.edu

The integration of new genetic technologies into clinical practice holds great promise for the personalization of medical care, particularly the use of large-scale DNA sequencing for genome-wide genetic testing. However, these technologies also yield unprecedented amounts of information whose clinical implications are not fully understood, and we are still developing technical standards for measuring sequence accuracy. These technical and clinical challenges raise ethical issues that are similar to but qualitatively different from those that we are accustomed to dealing with for traditional medical genetics. The sheer amount of information afforded by genome sequencing requires rethinking of how to implement core ethical principles including, but not limited to: informed consent, privacy and data ownership and sharing, technology regulation, issues of access, particularly as new technology is integrated into clinical practice, and issues of potential stigma and impact on perceptions of disability. In this article, we will review the issues of informed consent, privacy, data ownership and technology regulation as they relate to the emerging field of personalized medicine and genomics.

Keywords: ethics • genetics • genomics • personalized medicine • translation

In the past, genetic testing was primarily offered for two reasons: first, for diagnostic purposes to a patient who had medical or developmental features suggestive of a specific genetic condition, or second, for predictive purposes to an individual with a family history (or an ethnic background that increased the prevalence) of a known genetic condition. Both of these situations typically required that a there be a clear medical indication for genetic testing, and typically a specific genetic test was performed after rigorous genetic counseling and informed consent, discussing both the medical and psychological implications of obtaining such genetic information. As summarized by Moeschler and Shevell [1] and more recently by Michaelson *et al.* [2], studies assessing the historical rate of identifying a genetic etiology through clinical evaluation and genetic testing show wide ranges (from 10 to 81%) depending on when the study was performed (both in terms of the testing available and the field's knowledge about specific clinical diagnoses), and the various clinical factors related to the population. For patients with autism and/or pediatric diagnostic odyssey patients, a genetic etiology can now be identified in approximately 25% [3,4]. Single gene-based genetic testing, even using the 'gold standard' of Sanger sequencing, has limitations; decreased sensitivity of genetic testing leads to false-negative results (and in some cases, false reassurances), and sequencing technologies also find variants that were unclassifiable without further information (called 'variants of uncertain significance' or VUS). Finally, locus heterogeneity adds time and cost to the testing process, and requires testing of an affected proband for most accurate interpretation.

In recent years, approaches to genetic testing have changed significantly from this heavily clinically based evaluation and single-gene

Future Medicine part of fsg

diagnostic testing approach; a recent article by Korf and Rehm [5] does an excellent job summarizing the current status of genetic and genomic testing in detail. Pharmacogenomics testing and tumor genome testing will not be addressed specifically by this paper, but both can add to a personalized medicine approach by improving the efficacy of medication selection and dosing. Current diagnostic genetic testing often includes sequencing a 'panel' of relevant genes, often with a broad range of clinical features and prognosis, and sometimes including unexpected implications. Examples might include a diagnostic panel that uses technologies, such as next-generation sequencing, to assess multiple genetic causes for nonsyndromic hearing loss, cancer, spinocerebellar ataxias or cardiomyopathies (examples described in [6–9]), an expanded carrier screening panel that goes well beyond the genetic conditions recommended for testing on the basis of ethnicity [10], or an array or SNP-based comparative genome hybridization (CGH) that can detect additions or deletions of genetic material. As the cost of panel-based genetic testing decreases, it has become cost effective to utilize these tests as a first step in diagnostic testing. An example, nicely summarized by Manning and Hudgins [11], is the increasing use of CGH as a first-line diagnostic test, significantly increasing the diagnostic yield in comparison to traditional karyotype analysis. Genetic testing panels are especially useful when there is significant locus heterogeneity or when genetic causes cannot easily be clinically differentiated, although an experienced clinician may find that ordering a targeted test may be more sensitive and specific than a testing panel. These testing panels can save patients time and money in obtaining a clinical diagnosis, and may ultimately lead to better prognostication and, in some cases, tailored treatments, for example, the new use of poly-ADP ribose polymerase inhibitors to treat *BRCA1/2*-related breast or ovarian cancers [12]. Identification of a genetic cause also allows relatives to receive accurate risk assessments and to have the option of undergoing highly sensitive genetic testing for a family-specific mutation at a reasonable cost (typically several hundred dollars rather than several thousand dollars). However, as the number of genes assessed increases, the potential for VUS, even in 'relevant genes' increases, leading to increased uncertainty instead of clear-cut results. As VUS results may be reinterpreted over time, as we learn more and potentially develop functional assays, it also raises the question of whether there is a legal or moral responsibility to recontact patients and if so, with whom does the responsibility lie? [13,14].

Most recently, whole-genome or whole-exome sequencing (WGS or WES) has been performed on both a research and clinical basis for a range of indications. Jamal *et al.* [15] review the clinically available exome testing available as of December 2012. Beyond the use of WGS to isolate gene locations for clinically identifiable conditions (e.g., [16]), the first reported use in patients was to identify a genetic etiology in patients previously undiagnosed (the 'diagnostic odyssey' patients; select examples include: [17–20]), including in a rapid diagnostic setting [21], and this remains the primary clinical use at this time. Increasingly, genome and exome testing has expanded to include patients who are looking for improved treatments on the basis of a genetic etiology (anecdotal examples exist particularly in the cancer genetics realm [22]), and the early adopters who are healthy and simply curious about what their genome can tell them about future and current health risks [9,23,24]. In the future, this may expand to even include screening of healthy newborns, which has become technically feasible from dried blood spots [25] and which appears to be of moderate-to-high hypothetical interest to parents [26].

WGS and WES testing differs from the more traditional types of genetic testing in that, beyond a single indication for testing, it can and will provide a wide range of information about present and predictive conditions that range in degree of severity, age of onset and treatability; rare Mendelian conditions with both high and moderate penetrance, low penetrance SNPs that predispose towards common adult-onset conditions (e.g., diabetes or heart disease) and conditions that may be stigmatizing (e.g., psychiatric illness or dementia) [27]. The analytic validity of WGS technologies remains unclear, and several recent studies suggest that there is significant difference between variant calls between platforms [28] and analytic pipelines [29], although this is improved by having multigenerational family samples to assist in interpretation [24,29].

Challenges in the clinical translation of personalized medicine

Beyond the rapidly evolving technical aspects, several key issues arise in the clinical translation of new genetic technologies, particularly WGS and WES. We will focus here on three areas of clinical and ethical importance, with a primary focus on the first two issues: return of results, and in particular disclosure of 'incidental findings'; structuring the informed consent process given decisions about return of results; and special situations with relatives and children, including 'duty to warn' at risk relatives and family communication issues.

Return of results

When performing broad-based genetic testing through WGS or WES, it is no longer a potential outcome that

one will receive results beyond the specific clinical testing indication, but rather a certainty. Whether one calls these 'incidental' or 'secondary' findings, stakeholders must determine which findings should be disclosed, and in what manner; there is much debate in the literature about who should make such decisions and under what guidelines [30]. Incidental findings are not new to WGS; incidental information regarding unexpected diagnoses and family relationships have occurred since our first available karyotype (e.g., sex chromosome anomalies or translocations) and genetic linkage studies (unexpected family relationships such as nonpaternity). As an example, the use of CGH in a child who is being assessed for intellectual disability can identify large deletions that have predictive adult implications, if for example there is deletion of a tumor suppressor gene.

The expanding number of VUS that will be discovered through genetic testing panels and WGS approaches raises the question of which variants should be disclosed to ordering clinicians, and ultimately to patients. Some advocate that patients, for example, have the 'right' to receive all of their genetic information, even if they are deemed clinically irrelevant by the laboratory and clinician (e.g., [31]). Others support limiting the return of results to only those with both analytic and clinical validity, with many focusing on only those with clinical utility, typically represented as 'medical actionability' (e.g., the ability to screen, surveillance or treat to improve morbidity or mortality) [32]. Finally, several have suggested that results be 'rolled out' to the individual in stages over the lifetime [33,34]. In practice, however, it has been difficult to obtain agreement from clinicians about which conditions should be returned and in what manner [35], although most seem to agree that the pretest informed consent should be transparent about whatever approach is taken [33,36]. Recent American College of Medical Genetics and Genomics (ACMG) recommendations for the return of incidental findings suggest a small list of conditions and genes that should be considered 'obligatory' to return when performing exome or genome sequencing, based on their high penetrance, potentially early onset and medical actionability [37–39]. These recommendations have been controversial for two main reasons: the perceived loss of patient preference in the obligatory nature of returning incidental findings, and the return of results to individuals of all ages [40–42]. As the processes for returning incidental findings evolve, it will be critical to assess patient preferences and develop evidence-based approaches towards this process.

Informed consent

Traditional models of informed consent for genetic testing have taken a conservative approach, often utilizing genetic counseling (through various providers including, but not limited to, clinical geneticists and genetic counselors) to discuss in great detail the testing options and related risks, benefits and limitations of genetic tests [43]. Particularly in predictive testing situations, such as Huntington's disease, familial cardiomyopathies or familial cancers, the pretest protocols were rigorous and often spent significant time exploring the patient's experience of disease within the family and the patients' expected emotional response towards potential positive or negative results [44]. The psychological response to predictive test results vary significantly, but in general most studies do not show a long-term and clinically significant change in anxiety or depression, even after receiving positive predictive genetic test results (reviewed in [45]). Nevertheless, clinicians will have to be prepared to address situations arising from WGS or WES in which patients obtain a large number of genomic results, perhaps from a commercial testing service, and seek advice and possibly further diagnostic follow-up. Depending on the type of test result, anxiety and follow-up may not be warranted, but patients will be dependent on clinicians for education and counseling.

Given the wide range of genomic information that will be received from WGS or WES, it seems untenable to maintain a model whereas all conditions are discussed deeply [27]. Additionally, given the range of clinical features and treatability that could be detected, including some in the absence of family history, it poses an additional challenge for patient decision-making. Patients vary significantly, based on their personal and family experiences and values, in their preference towards receiving specific results. Many approaches have been proposed and enacted, including a generic consent approach [40,46] and a preference-based approach where disorders may be categorized in various ways and patients asked to select those categories of information they wish to receive. Since research on both biobank and genome research participants suggests that participants believe they want 'all' genomic results [47–49] and it is not currently evident which approach is best, and we encourage research studies to assess the effectiveness and patient satisfaction with a range of informed consent processes.

Special situations: children & relatives

Genomic testing expands the potential health knowledge that may be obtained, and which will almost universally impact relatives. In some cases, genome testing may identify a predictive risk that is not of significant relevance to the patient obtaining the result, but rather is of value to other relatives. Examples might include an elderly parent undergoing genome sequencing as

part of a cancer treatment workup who learns they carry a highly penetrant predisposition to another condition, primarily of relevance to their children or other relatives, or a child undergoing testing to find a cause for intellectual disability who is found to carry a pathogenic variant in a familial cancer gene such as *BRCA1* [38]. While most clinicians strongly urge patients to share relevant genetic risk information, data suggest that family communication is highest to first-degree relatives, and even then does not reach 100% [50]. This raises the important ethical question about whether a clinician ever has a duty to break patient confidentiality to 'warn' relatives of the genetic risk [51]. This concept of 'duty to warn' has its roots in the 'Tarasoff' [52], suggesting that exceptions to patient confidentiality must meet certain criteria, including being a foreseeable and serious risk in an identifiable person. Examples include contagious or communicable disease, or known threat of danger. In the USA and Canada, three legal cases exist on this matter; one found the clinician's duty was to inform the patient of the risk to relatives and encourage communication [53], while the other two found that relatives should be warned by clinicians even if the patient refuses [54,55]. As more and more genetic predispositions to highly penetrant disorders are discovered in the absence of clear family history, this issue may occur more frequently and clinicians should identify a range of ways to assist family members in conveying accurate genomic risk information to relatives. In the situation that a patient remains unwilling to inform at-risk relatives, an intermediate approach may be to disclose relevant genetic information without identifying the specific proband within the family [56].

Finally, genetic testing of children has been limited to testing that offers immediate medical or diagnostic benefit, and predictive tests for adult-onset conditions have been generally discouraged in an effort to preserve the child's autonomy [57]. As described earlier, the recent ACMG recommendations on incidental findings suggest returning a specific set of medically actionable adult-onset conditions to individuals of all ages, including children [37], and this has been controversial. There is some limited data assessing the impacts of predictive testing in children or adolescents, primarily for familial adenomatous polyposis and in adolescents at risk for breast cancer, but several authors have disagreed with the return of such incidental results in the pediatric setting [58,59]. As genomic testing is increasingly offered in childhood for both diagnostic and predictive reasons, research should assess the medical, psychosocial and ethical implications in a rigorous manner, so that evidence-based determinations can be made about best practices.

Intellectual property & ownership of DNA

Scope of gene patents

Intellectual property policies and practices appear to have had a significant impact on the translation of knowledge about genes into clinically useful genetic diagnostic tests for personalized medicine. Genes and technologies for genetic analysis have been the subjects of patents, licenses and trade secrets for decades. Whether these policies serve the best interests of patients and personalized medicine, however, is also subject to debate.

In particular, the breadth of patents claiming specific DNA sequences corresponding to human disease-related genes has been questioned [60]. Such effects could be widespread because it has been estimated that tens of thousands of such patents exist. In 2005, a study indicated that 20% of human genes were claimed under patents in the United States Patent and Trademark Office database [61]. In 2013, another study identified approximately 40,000 DNA sequences covering over 40% of the human genome had been patented in the USA, indicating the extremely high rate of gene patenting over the last decade [62]. These patents claim not only entire genes whose sequences are specified in the patents, but also small gene fragments as short as 15 bp in length. Because short sequences are often found repeatedly throughout the genome, it was estimated that a single claim from US Patent No. 5,747,282 on any 15-bp sequence found in DNA corresponding to the *BRCA1* polypeptide occurred in 80% of the mRNA or cDNA entries in the GenBank database [63]. Another study found that 15-mer sequences from *BRCA1* matched at least 689 other genes and that as many as 7688 genes contained 15-mers from *TTN* [62].

Ethical issues raised by intellectual property policies on genes

As described above, genes have been extensively patented, presumably facilitating the development of clinically available and commercially viable products such as genetic tests or gene-based therapies. Some have argued that without patents and the monopolies they afford, clinical genetic tests would be less likely to be developed. However, there has been concern that patents and licenses and trade secrets also have deleterious impacts on clinical care, thus raising ethical issues around the relative risks and benefits of intellectual property practices and the appropriate role of researchers and academic institutions in technology transfer for medical applications. Specifically, there have been concerns about whether gene patents decrease access to and quality of clinical genetic tests, raise costs, or prevent research and development and improvement of diagnostic services.

Impacts of gene patents on research & clinical practice

In most jurisdictions, there is no research exemption for gene patents, so the impact of tens of thousands of such patents is potentially large because they generally give the patent holder the power to prevent others from making, using or selling their claimed inventions. However, in practice, it appears that life science researchers have largely ignored gene patents and that patent holders have largely ignored researchers' infringements of their patents. In a 2005 survey of biomedical researchers in the USA, Walsh *et al.* [64] found that only 5% checked for patents related to their research and 5% said they were made aware of intellectual property relevant to their research through notification by a patent holder. On the other hand, another study found that 19.8% of life scientists reported delaying a publication by more than 6 months, and nearly half of those in order to file a patent application [65]. Therefore, biomedical researchers may not be delaying the conduct of their research, but its publication, because of patent considerations.

However, there may be a disproportionate effect on scientists conducting research on clinical genetic diagnostics. A survey by Cho *et al.* indicated that 65% of directors of US clinical genetics laboratories, who conduct research to develop tests for clinical use, had received notification of potential infringement of a patent [66]. Furthermore, 25% of those laboratory directors discontinued a clinical genetic test and 53% decided not to conduct research to develop a new genetic test because of having received such notification. A total of 67% felt that patents inhibited their ability to conduct genetic research and 85% indicated that patents inhibited sharing of information among researchers. A study of members of the American Society of Human Genetics found that 46% of respondents reported that patents delayed or limited their research [67]. However, broad licensing practices, such as those used for patents on *CFTR* in genetic tests for cystic fibrosis, can facilitate both academic research and commercial testing [68].

There is no direct evidence that costs of genetic or genomic tests are elevated because of gene patents. In fact, some evidence points to the main effect of patents being on decreased volume rather than on costs due to the monopoly [69]. However, one often-overlooked issue that has been highlighted by the US court case challenging patents held by Myriad Genetics Inc. on *BRCA1* and *BRCA2* genes (hereafter referred to as the Myriad case [70]) is that the monopoly over clinical services afforded by the patent allows the patent holder to control not only how much patients pay for a genetic diagnostic test, but whether patients' use of the test will be covered by insurance. One of the plaintiffs in the Myriad case was a patient with breast cancer who claimed that the company would not accept her insurance coverage, thus forcing her to either pay out of pocket or not get the test because she could not afford the high cost.

Even more important for clinical genetic diagnostics, monopolies directly affect the quality of care. Patients do not have the opportunity to obtain what is essentially a second opinion on their diagnosis from an independent source. In addition, patients do not have the opportunity to benefit from improvements to diagnostic methods or comprehensive testing that other laboratories might have developed that the patent holder is not using, but is preventing others from applying to patented genes. For example, a study found that 12% of individuals from families at high risk for hereditary breast or ovarian cancer who tested negative by Myriad's test actually did have cancer-predisposing variants of those genes [71], which might have been detected by other laboratories' tests, had they been allowed to use them. However, Myriad's patents covered the analysis of any *BRCA* variant. Laboratories had developed other methods that would detect insertions and deletions [72] not detected by Myriad's test, but chose not to offer these clinically because of the possibility of litigation [73].

There are conflicting views on the potential impacts of gene patents on personalized medicine, which is likely to rely not just on a single or few genetic tests, but increasingly will turn to whole-genome analysis to inform treatment and disease prevention. Services such as those provided by 23andMe or gene chips utilized in chromosomal microarray analysis examine hundreds or thousands of genes, many of which are claimed in patents. The potential for 'patent thickets', or the need to obtain many licenses to analyze multiple genes simultaneously, was seen as a potential threat to genomics-based personalized medicine [74]. Many clinical diagnostic services employing multiplex genetic testing appear not to be hampered by patent infringement suits so far. In addition, in 2009, 23andMe added three SNPs in *BRCA1* and *BRCA2* genes to its SNP-based genomic health test, which likely constituted infringements of Myriad's patents. It is not clear whether they obtained a license to add these SNPs to their test, but 23andMe made clear that they did not consider these SNPs 'diagnostic' [75] because they were in no way a comprehensive assessment of risk of *BRCA1* and *BRCA2*-associated cancers [76].

Impacts of proprietary data on personalized medicine

For genomics-based personalized medicine to be most effective, it is clear that availability of data on genotype–phenotype correlations found in individuals is critical to interpreting tests and to minimize the

possibility of VUS. Early experience with WGS/WES suggests that VUS are very common [27,77]. However, some commercial laboratories and laboratories based in academic hospitals maintain their clinical genotype and phenotype data in proprietary databases, limiting the ability of other researchers and clinicians to interpret their data. One of the public benefits of patents is that they require patent holders to disclose their inventions publicly – in the case of gene patents, this means publishing claimed DNA sequences in the patents. In the USA, patent applications become publicly available 18 months after filing. However, gene patent holders are not required to make genotype–phenotype associations publicly available, even if their patents are challenged in court and found invalid. Because of its clinical significance, it is unethical for patent holders to keep this information in proprietary databases, even if it enhances market value of a genetic test. This is especially true since the data fundamentally belong to the patients from whom they were derived, and because much of the funding for gene–disease association discoveries are the result of public funding. In the USA, one study found that 67% of gene patents resulted from publicly funded work [78]. In response to the need for data that are currently held in proprietary databases, alternative data repositories have been created into which patients can directly and anonymously deposit their genetic test results. For example, Robert Nussbaum at the University of California, San Francisco has established the Sharing Clinical Reports Project [79], which aims to collect information on *BRCA1* and *BRCA2* variants and make them publicly available in the NCBI ClinVar database [80]. In addition, a global alliance of 69 institutions in 13 countries recently announced that it would develop standards and policies for sharing DNA sequence data linked to clinical information [81]. Clearly, such data sharing raises privacy and confidentiality issues, which will be discussed below. However, for personalized medicine to succeed on a broad scale, all such clinical data needs to be made widely available to clinicians.

Regulation of genetic testing & DNA sequencing

The ethics of using new genetic technologies for personalized medicine hinges on whether the risks are outweighed by the benefits. In the case of genetic testing using next-generation sequencing methods, the risks of erroneously identifying disease-causing variants are unclear, in part because there are no accepted standards for sequence quality and analytic validity. This lack of consistency and standardization has been cause for concern especially with the rise of direct-to-consumer genetic testing for personalized medicine [82,83]. For example, a US Government Accountability Office investigation found that the same DNA sample sent to four different direct-to-consumer genetic testing companies returned three different risk estimates for prostate cancer (ranging from 'below average' to 'above average'), and also found "10 egregious examples of deceptive marketing" that included encouragement of surreptitious testing of samples without the consent of the individual from which it came [84]. Regulation of such surreptitious testing varies widely, for example, being illegal in the UK (Human Tissue Act) and in Germany (Human Genetic Examination Act), but its legality is highly variable by state in the USA [85,86].

Regulation of genetic testing, however, varies widely internationally. For example, it is allowed in the USA, the UK and Belgium, while France, Germany, Portugal and Switzerland require all genetic testing to be conducted by a medical doctor [87]. Some countries, such as The Netherlands, require an assessment of scientific soundness and balance of health risks and benefits in order for an operator to be licensed to offer genetic testing. In 2009, the Council of Europe adopted the Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Genetic Testing for Health Purposes [88]. This protocol requires that genetic testing services meet generally accepted criteria for scientific validity and clinical validity, that clinical utility be assessed, and that all genetic testing, whether offered direct-to-consumer or through a medical practitioner, be accompanied by genetic counseling [89]. In addition, it is extremely challenging to regulate genetic testing conducted through the internet across national boundaries. For example, it would be difficult, if not impossible, to prevent someone living in a country where prenatal sex determination is illegal from sending a blood sample outside the country for genetic testing.

The US FDA has the authority to regulate genetic testing as a medical device, but has largely left genetic testing services unregulated as 'laboratory-developed tests' (in contrast to 'kits', which it does regulate). However, in 2010, the FDA sent letters to six genetic testing companies (23andMe, deCode Genetics, Illumina, Knome, Navigenics and Pathway Genomics) informing them that their products require premarket review as medical devices under Section 201 of the Federal Food, Drug and Cosmetic Act [90]. More recently, the FDA has begun to develop standards for the analytical validation of genomic sequencing technologies, in collaboration with the National Institute of Standards and Technology and stated its intentions to issue guidelines for direct-to-consumer genomics [91]. One of the issues that has to be addressed for the use of genomic technologies for personalized medicine is that many of the DNA sequencing machines being used currently are

approved by the FDA under a 'research use only/investigational use only' label and not for clinical use. However, the companies that sell or operate those machines are not necessarily the same as the laboratories that are obtaining the patient samples. Therefore, the manufacturers of the equipment do not necessarily know how their equipment is being used. Recently issued FDA guidance was controversial for appearing to hold manufacturers responsible for research use only/investigational use only-labeled materials being used by other laboratories or companies for clinical purposes. Thus, there are several regulatory issues pertinent to the use of new genetic technologies for personalized medicine that need to be resolved.

Genomic privacy

As genomic technologies allow larger amounts of sequence data to be obtained from individuals, privacy and confidentiality becomes of greater concern. This is not only because obtaining more information and storing it in a larger number of databases may be more likely to lead to unauthorized or accidental release, but because larger amounts of genetic information about any individual becomes more uniquely identifying. Although there are some privacy protections such as the Data Protection Directive [92] and the proposed General Data Protection Regulation [93] in the EU and the Genetic Information Nondiscrimination Act and Health Insurance Portability and Accountability Act in the USA, they do not necessarily prevent the use of DNA sequence to reidentify people from large data sets, even if not for discriminatory purposes. It has been estimated that deidentification of medical information according to the Health Insurance Portability and Accountability Act Safe Harbor and Limited Dataset provisions still allows reidentification of anywhere between 0.01 and 60% of individuals, depending on the data set [94]. In addition, these approaches rely heavily on consent to disclosed releases of data rather than on protections from misuses, and may have limited effect against stigmatization.

Over the last few years, there has been growing recognition of the extent to which nucleic acid sequences uniquely identify human individuals, not only through direct sequencing of an individual's genome, but from a relatively small number of SNPs [95], gene-expression data [96], in aggregate data of allele frequencies [97], regression coefficients from quantitative phenotypes in genome-wide association studies [98], or even through microbial DNA sequences reflecting an individual's microbiome [99]. Although a unique nucleic acid sequence alone does not necessarily identify a specific person, several others have shown that the combination of sequence data and a small amount of other information such as age, zip code or surname, does become identifying [100–102]. While some technical approaches have been applied to preserve anonymity of such information, such as k-anonymity, they are not flawless [103]. New methods have been developed to address these flaws, but it is not clear how effective they will be, especially in the face of the growing amount and specificity of genomic information being placed in publicly available databases.

The reidentifiability of 'omics data points to weaknesses in policies that depend on removal of frank identifiers such as names, addresses or patient IDs to protect privacy [104]. The research community has adapted its policies and practices to changes in genomic technologies in order to address these weaknesses, while attempting to maintain the ability to share data broadly and rapidly [105]. For example, databases such as dbGaP have removed sensitive data such as phenotype data associated with genotypes from open access, so that access is controlled by a Data Access Committee [106]. However, challenges remain, especially since data can be shared across national borders to researchers in countries with different laws regarding the handling of biological data [107]. For protection from harms from breaches of privacy of genomic data collected for clinical use, patients and consumers must rely on policy makers to adapt laws and regulations, however imperfect, to technological advances and eventual use of 'omics data in mainstream clinical practice. Others have suggested different approaches such as 'open consent' [108] that explicitly acknowledge the inability to maintain absolute privacy of genomic information.

Conclusion

It is clear that, for new genomic technologies to be utilized successfully for personalized medicine, qualitatively different ethical and policy issues must be addressed. Because large-scale genomics are used in ways beyond the focused diagnostic and predictive purposes of traditional medical genetic tests, and because the information afforded by WGS is potentially more encompassing but also less certain, while being more individually identifiable, current policies and regulations may no longer be sufficient to minimize risks to patients. Therefore, new approaches to informed consent, privacy protection, data sharing and intellectual property need to be developed to facilitate the appropriate and effective application of genomic technologies to personalized medicine.

Future perspective

Genomic technologies are changing rapidly, and it is hard to predict how quickly new technologies will become adopted in routine clinical practice. Based,

however, on the pace of adoption of clinical exomes from discovery to clinical availability, it seems likely that it will occur more rapidly than the typically observed 10–20-year translation time (as described in Manolio *et al.* [109]) for most new approaches. It seems likely that, within the next decade, the ability to develop and tailor treatments on the basis of a person's genome will increase significantly, and we suspect that within a decade a moderate percentage of patients will have their genome sequenced for at least one reason. But we agree strongly with Evans and Khoury [110] when they emphasize the strong need for an evidence-based approach to discerning when and where genomic medicine can impact patient outcomes. Indeed, evidence-based studies are already being undertaken to discern the degree to which these can impact patient outcomes [111]. Federal regulation of DNA sequencing may have a significant impact by requiring an evidentiary basis for analytic and clinical validity. A recent proposal by the ACMG to monitor disclosure of genomic information may be helpful in this regard [37]. There is also much work being carried out on electronic health records and the storage of genetic data, as well as developing point-of-service prompts to assist busy clinicians in identifying and utilizing relevant genomic data at the proper time in diagnostics or treatment planning. With luck, in 10 years, we will reach a point where the analytic validity of sequencing technologies are high, with easy ability to access and clinically interpret genomic information, and knowledge about patient responses to genomic information.

Financial & competing interests disclosure

Both KE Ormond and MK Cho are supported by NIH 5 P50 HG003389-05. MK Cho is also supported by NIH 1 U54 RR024374-01A1. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Challenges in the clinical translation of personalized medicine

- Informed consent and return of results, specifically around which 'incidental findings' should be returned, are controversial and evolving areas that warrant clinical research and evidence-based practice.
- Additional issues include genetic testing of children, duty to warn at-risk relatives, and duty to recontact/reassess variants of unknown clinical significance.

Intellectual property & ownership of DNA

- Even after the US Supreme Court decision on gene patenting in the '*AMP v. Myriad*' case, successful translation of genomic findings to clinical practice will depend on broad availability of sequence data and correlation with clinical phenotypes.

Regulation of genomic testing & DNA sequencing

- Regulation of genomic testing, both in clinical and direct-to-consumer settings, varies widely internationally. However, to ensure that risks are minimized and benefits maximized, some quality standards for DNA sequencing and analytic validity may be necessary.

Genomic privacy

- For successful translation of genomics to clinical practice, policies must adapt to the growing recognition of the identifiability of DNA sequences by implementing more protections against discrimination and misuse of genomic data.

Conclusion

- The effective use of genomics in clinical practice cannot be realized by simply scaling up of gene-by-gene approaches. Large-scale genome sequencing raises qualitatively different issues regarding informed consent, return of results, intellectual property, and privacy than traditional medical genetics. Ethics and policy must adapt accordingly to genomic and DNA sequencing technologies.

References

Papers of special note have been highlighted as: • of interest

1 Moeschler J, Shevell M. Clinical genetic evaluation of the child with mental retardation or developmental delays. *Pediatrics* 117, 2304 (2006).

2 Michaelson D, Shevell M, Sherr E *et al.* Evidence Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 77, 1629–1635 (2011).

3 Miles J. Autism spectrum disorders – a genetics review. *Genet. Med.* 13, 278–294 (2011).

4 Yang Y, Muzny D, Reid J *et al.* Clinical whole-exome sequencing for the diagnosis of Mendelian disorders. *N. Engl. J. Med.* 369(16), 1502–1511 (2013).

5 Korf B, Rehm H. New approaches to molecular diagnosis. *JAMA* 309, 1511–1521 (2013).

• **Recent review of the current state of genetic testing technology.**

6 GeneDx. DNA Diagnostic experts. www.genedx.com

7 Ambry Genetics™. http://ambrygen.com/tests

8 Athena Diagnostics®. www.athenadiagnostics.com/content/test-catalog

9 Personal Genome Project. www.personalgenomes.org

10 Srinivasan B, Evans E, Flannick J *et al.* A universal carrier test for the long tail of Mendelian disease. *Reprod. Biomed. Online* 21, 537–551 (2010).

11 Manning M, Hudgins L. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet. Med.* 12, 742–745 (2010).

12 Annuziata C, Bates S. PARP inhibitors in *BRCA1/BRCA2* germline mutation carriers with ovarian and breast cancer. *F1000 Biol. Reports* 2, 10 (2010).

13 Clayton EW, Haga S, Kuszler P, Bane E, Shutske K, Burke W. Managing incidental genomic findings: legal obligations of clinicians. *Genet. Med.* 15, 624–629 (2013).

14 van El CG, Cornel MC, Borry P *et al.* Whole genome sequnecing in health care: recommendations of the European Society of Human Genetics. *Eur. J. Hum. Genet.* 21, 580–584 (2013).

15 Jamal S, Yu J-H, Chong J *et al.* Practices and policies of clinical exome sequencing providers: analysis and implications. *Am. J. Med. Genet.* 161A, 935–950 (2013).

16 Hannibal M, Buckingham K, Ng S *et al.* Spectrum of MLL2 (*ALR*) mutations in 110 cases of Kabuki syndrome. *Am. J. Med. Genet.* 155A, 1511–1516 (2011).

17 McLaughlin H, Sakaguchi R, Liu C *et al.* Compound heterozygosity for loss-of-function lysyl-tRNA synthetase mutations in a patient with peripheral neuropathy. *Am. J. Hum. Genet.* 8, 560–566 (2010).

18 Ng S, Buckingham K, Lee C *et al.* Exome sequencing identifies the cause of a mendelian disorder. *Nat. Genet.* 42, 30–35 (2010).

19 Worthey E, Mayer A, Syverson G *et al.* Making a definitive diagnosis: successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. *Genet. Med.* 13, 255–262 (2011).

20 Rienhoff HJ, Yeo C, Morissette R *et al.* A mutation in TGFB3 associated with a syndrome of low muscle mass, growth retardation, distal arthrogryposis and clinical features overlapping with marfan and Loeys–Dietz syndrome. *Am. J. Med. Genet. Part A* 161A(8), 2040–2046 (2013).

21 Saunders C, Miller N, Soden S *et al.* Rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units. *Sci. Transl. Med.* 4, 154ra135 (2012).

22 The Cancer Genome Atlas. Understanding genomics to improve cancer care. http://cancergenome.nih.gov/researchhighlights/perspectives/levineperspective

23 Ashley E, Butte A, Wheeler M *et al.* Clinical evaluation incorporating a personal genome. *Lancet* 375, 1525–1535 (2010).

24 Dewey F, Chen R, Cordero S *et al.* Phased whole-genome genetic risk in a family quartet using a major allele reference sequence. *PLoS Genet.* 7, e1002280 (2011).

25 Hollegaard M, Grauholm J, Nielsen R *et al.* Archived neonatal dried blood spot samples can be used for accurate whole genome and exome-targeted next-generation sequencing. *Mol. Genet. Metab.* 110(1–2), 65–72 (2013).

26 Goldenberg A, Dodson D, Davis M, Tarini B. Parents' interest in whole-genome sequencing of newborns. *Genet. Med.* 16(1), 78–84 (2013).

27 Ormond KE, Wheeler MT, Hudgins L *et al.* Challenges in the clinical application of whole-genome sequencing. *Lancet* 375(9727), 1749–1751 (2010).

28 LAm. HYK, Clark MJ, Chen R *et al.* Performance comparison of whole-genome sequencing platforms. *Nature* 30(1), 78–82 (2011).

29 O'rawe J, Jiang T, Sun G *et al.* Low concordance of multiple variant-calling pipelines: practical implications for exome and genome sequencing. *Genome Med.* 5, 28 (2013).

30 Lohn Z, Adam S, Birch P, Friedman J. Incidental findings from clinical genome-wide sequencing: a review. *J. Genet. Couns.* doi:10.1007/s10897-013-9604-4 (2013) (Epub ahead of print).

31 John Hawks weblog: palentology, genetics and evolution. http://johnhawks.net/weblog/topics/biotech/testing/fda-dtc-meeting-proceedings-2011.html

32 Berg J, Khoury M, Evans J. Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time. *Genet. Med.* 13, 499–504 (2011).

33 Grove M, Wolpert M, Cho M, Lee S, Ormond K. Assessing views of genetics health professionals toward the return of genomic results. *J. Genet. Couns.* doi:10.1007/s10897-013-9611-5 (2013) (Epub ahead of print).

34 Yu J, Jamal S, Tabor H, Bamshad M. Self-guided management of exome and whole-genome sequencing results: changing the results return model. *Genet. Med.* 15(9), 684–690 (2013).

35 Lohn Z, Adam S, Birch P, Townsend A, Friedman J. Genetics professionals' perspectives on reporting incidental findings from clinical genome-wide sequencing. *Am. J. Med. Genet.* 161, 542–549 (2013).

36 Green R, Berg J, Berry G *et al.* Exploring concordance and discordance for return of incidental findings from clinical sequencing. *Genet. Med.* 14, 405–410 (2012).

37 Green R, Berg J, Grody W *et al.* ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet. Med.* 15, 565–574 (2013).

- **Provides recommendations from the American College of Medical Genetics and Genomics (ACMG) regarding the return of incidental findings (secondary to the primary testing indication) in clinical exome or genome sequencing.**

38 McGuire A, Joffe S, Koenig B *et al.* Point-counterpoint. Ethics and genomic incidental findings. *Science* 340, 1049–1050 (2013).

39 Green RC, Lupski JR, Biesecker LG. Reporting genomic sequencing results to ordering clinicians: incidental, but not exceptional. *JAMA* 310, 365–366 (2013).

40 Wolf S, Annas G, Elias S. Point-counterpoint. Patient autonomy and incidental findings in clinical genomics. *Science* 340, 1049–1050 (2013).

41 Klitzman R, Appelbaum PS, Chung W. Return of secondary genomic findings vs patient autonomy: implications for medical care. *JAMA* 310, 369–370 (2013).

42 Ross LF, Rothstein MA, Clayton EW. Mandatory extended searches in all genome sequencing: 'incidental findings,' patient autonomy, and shared decision making. *JAMA* 310, 367–368 (2013).

43 Hampel H, Grubs RE, Walton CS *et al.* Genetic counseling practice analysis. *J. Genet. Couns.* 18, 05–16 (2009).

44 Skirton H, Goldsmith L, Jackson L, Tibben A. Quality in genetic counselling for presymptomatic testing – clinical guidelines for practice across the range of genetic conditions. *Eur. J. Hum. Genet.* 21, 256–260 (2013).

45 Cameron L, Muller C. Psychosocial outcomes after genetic testing. *Curr. Opin. Psychiatry* 22, 218–223 (2009).

46 Elias S, Annas G. Generic consent for genetic screening. *N. Engl. J. Med.* 330, 1611–1613 (1994).

47 Ormond K, Cirino A, Helenowski I, Chisholm R, Wolf W. Assessing the understanding of biobank participants. *Am. J. Med. Genet.* 149A, 188–198 (2009).

48 Sanderson SC, Zinberg R, Horowitz CR *et al.* Willingness to participate in genomics research and desire for personal results among underrepresented minority patients: a structured interview study. *J. Commun. Genet.* 4(4), 469–482 (2013).

49 Facio F, Eidem H, Fisher T *et al.* Intentions to receive individual results from whole-genome sequencing among participants in theClinSeq study. *Eur. J. Hum. Genet.* 21, 261–265 (2013).

50 Hodgson J, Gaff C. Enhancing family communication about genetics: ethical and professional dilemmas. *J. Genet. Couns.* 22, 16–21 (2013).

51 Virtual Mentor: American Medical Association. http://virtualmentor.ama-assn.org.laneproxy.stanford.edu//2012/08/hlaw1--1208.html

52 *Tarasoff v. Regents of the University of California*, 131 Cal. Rptr. 14 (Cal. 1976).

53 *Safer v. Estate of Pack*, 677A. 2d 1188 (N.J. Super CT App Div. 1996).

54 *Watters v. White*. http://pattersonlaw.ca/PattersonBlogs/MedicalMalpracticeBlog/tabid/268/EntryId/77/What-to-Say-Do-Doctors-Have-a-Duty-to-Disclose-Confidential-Information.aspx

55 *Pate v. Threlkel*, 661, So 2d 278 (Fla 1995).

56 Australian Law Reform Commission. Introduction to the enquiry: essentially yours. In: *The Protection of Human Genetic Information in Australia.* Australian Government, Australian Law Reform Commission, Sydney, Australia (1996).

57 Ross L, Saal H, David K, Anderson R. Technical report: ethical and policy issues in genetic testing and screening of children. *Genet. Med.* 15, 234–245 (2013).

- **Provides recommendations from the American Academy of Pediatrics (AAP) and American College of Medical Genetics and Genomics (ACMG) regarding offering genetic testing of various types to children and adolescents.**

58 Michie S, Bobrow M, Marteau TM. Predictive genetic testing in children and adults: a study of emotional impact. *J. Med. Genet.* 38, 519–526 (2001).

59 Codori AM, Zawacki KL, Petersen GM *et al.* Genetic testing for hereditary colorectal cancer in children: long-term psychological effects. *Am. J. Med. Genet. A.* 116A, 117–128 (2003).

60 Paradise J, Andrews L, Holbrook T. Intellectual property. Patents on human genes: an analysis of scope and claims. *Science* 307(5715), 1566–1567 (2005).

61 Jensen K, Murray F. Intellectual property landscape of the human genome. *Science* 310(5746), 239–240 (2005).

62 Rosenfeld J, Mason CE. Pervasive sequence patents cover the entire human genome. *Genome Med.* 5(3), 27–27 (2013).

63 Kepler TB, Crossman C, Cook-Deegan R. Metastasizing patent claims on *BRCA1*. *Genomics* 95(5), 312–314 (2010).

64 Walsh JP, Cohen WM, Arora A. Science and the law. Working through the patent problem. *Science* 299(5609), 1021 (2003).

65 Blumenthal D, Campbell EG, Anderson MS, Causino N, Louis KS. Withholding research results in academic life science. *JAMA* 277(15), 1224–1228 (1997).

66 Cho MK, Illangasekare S, Weaver MA, Leonard DG, Merz JF. Effects of patents and licenses on the provision of clinical genetic testing services. *J. Mol. Diagn* 5(1), 3–8 (2003).

- **Summary on issues related to gene patents.**

67 Rabino II. How human geneticists in US view commercialization of the Human Genome Project. *Nat. Genet.* 29(1), 15–16 (2001).

68 Chandrasekharan S, Heaney C, James T, Conover C, Cook-Deegan R. Impact of gene patents and licensing practices on access to genetic testing for cystic fibrosis. *Genet. Med.* 12, S194–S211 (2010).

69 Cook-Deegan R, Derienzo C, Carbone J, Chandrasekharan S, Heaney C, Conover C. Impact of gene patents and licensing practices on access to genetic testing for inherited susceptibility to cancer: comparing breast and ovarian cancers with colon cancers. *Genet. Med.* 12, S15–S38 (2010).

70 US District Court Southern District of New York. *Association of Molecular Pathology v. United States Patent and Trademark Office*. US District Court Southern District of New York NY, USA, 1–156 (2010).

71 Walsh T, Casadei S, Coats KH *et al.* Spectrum of mutations in *BRCA1*, *BRCA2*, *CHEK2*, and *TP53* in families at high risk of breast cancer. *JAMA* 295(12), 1379–1388 (2006).

72 Walsh T, Lee MK, Casadei S *et al.* Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. *Proc. Natl Acad. Sci. USA* 107(28), 12629–12633 (2010).

73 Anderson A. U of Washington debuts targeted sequencing test for mutations in inherited colon cancer genes (2011). www.genomeweb.com/sequencing/u-washington-debuts-targeted-sequencing-test-mutations-inherited-colon-cancer-ge

74 Heller MA, Eisenberg R. Can patents deter innovation? The anticommons in biomedical research. *Science* 280(5364), 698–701 (1998).

75 23andMe. www.23andme.com/health/BRCA-Cancer

76 Ray T. 23andMe adds *BRCA* breast/ovarian cancer testing to service. www.genomeweb.com/dxpgx/23andme-adds-brca-breastovarian-cancer-testing-service

77 Biesecker LG. Opportunities and challenges for the integration of massively parallel genomic sequencing into clinical practice: lessons from the ClinSeq project. *Genet. Med.* 14(4), 393–398 (2012).

78 Schissel A, Merz JF, Cho MK. Survey confirms fears about licensing of genetic tests. *Nature* 402(6758), 118 (1999).

79 International Collaboration for Clinical Genomics. http://sharingclinicalreports.org

80 Kolata G. DNA project aims to make company's data public. *The New York Times*, 12th April (2013).

81 Check Hayden E. Genetics push for global data-sharing. *Nature* 498, 16–17 (2013).

82 Hogarth S, Javitt G, Melzer D. The current landscape for direct-to-consumer genetic testing: legal, ethical, and policy issues. *Annu. Rev. Genomics Hum. Genet.* 9, 161–182 (2008).

• **Reviewed issues that arise in direct to consumer genetic testing.**

83 Kaye J. The regulation of direct-to-consumer genetic tests. *Hum. Mol. Genet.* 17(R2), R180–R183 (2008).

84 Kutz G. *Testimony Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives. Direct-to-consumer Genetic Tests: Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices*. US Government Accountability Office, DC, USA, 1–33 (2010).

85 Presidential Commission for the Study of Bioethical Issues. *Privacy and Progress in Whole Genome Sequencing*. US Department of Health & Human Services, DC, USA, 1–154 (2012).

86 Genetics & Public Policy Center. www.dnapolicy.org/policy.issue.php?action=detail&issuebrief_id=48

87 Borry P, Van Hellemondt RE, Sprumont D *et al.* Legislation on direct-to-consumer genetic testing in seven European countries. *Eur. J. Hum. Genet.* 20(7), 715–721 (2012).

88 Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes: Strasbourg, 27.XI.2008. http://conventions.coe.int/Treaty/en/Treaties/Html/203.htm

89 Lwoff L. Council of Europe adopts protocol on genetic testing for health purposes. *Eur. J. Hum. Genet.* 17, 374–1377 (2009).

90 US FDA: *in vitro* diagnostics. www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm

91 Ray T. Amid Chaos, FDA's Gutierrez offers insights on agency's regulatory stance on molecular tests. www.genomeweb.com/clinical-genomics/amid-chaos-fdas-gutierrez-offers-insights-agencys-regulatory-stance-molecular-te

92 Council EPaT. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. Directive 95/46/EC (1995). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:HTML

93 European Union. Proposal for a directive of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data by competent authorities for the purposes of prevention, investigation, detection or prosecution of criminal offences or the execution of criminal penalties, and the free movement of such data. (2012). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52012PC0010:en:NOT

94 Benitez K, Malin B. Evaluating re-identification risks with respect to the HIPAA privacy rule. *BMJ* 17(2), 169 (2010).

95 Lin Z, Owen AB, Altman RB. Genomic research and human subject privacy. *Science* 305, 183 (2004).

96 Schadt EE, Woo S, Hao K. Bayesian method to predict individual SNP genotypes from gene expression data. *Nat. Genet.* 44(5), 603–608 (2012).

97 Homer N, Szelinger S, Redman M *et al.* Resolving individuals contributing trace amounts of dna to highly complex mixtures using high-density snp genotyping microarrays. *PLoS Genetics* 4(8), e1000167 (2008).

98 Im HK, Gamazon ER, Nicolae DL, Cox NJ. On sharing quantitative trait GWAS results in an era of multiple-omics data and the limits of genomic privacy. *Am. J. Hum. Genet.* 90(4), 591–598 (2012).

99 Schloissnig S, Arumugam M, Sunagawa S *et al.* Genomic variation landscape of the human gut microbiome. *Nature* 493(7430), 45–50 (2012).

100 Gymrek M, McGuire AL, Golan D, Halperin E, Erlich Y. Identifying personal genomes by surname inference. *Science* 339, 321–324 (2012).

101 Malin B, Sweeney L. Re-identification of DNA through an automated linkage process. *Proc. AMIA Symp.* 423–427 (2001).

102 Sweeney L. Achieving k-anonymity: privacy protection using generalization and suppression. *Int. J. Uncertain. Fuzz.* 10, 571–588 (2002).

103 Machanavajjhala A, Gehrke J, Kifer D, Venkitasubramaniam M. L-diversity: privacy beyond k-anonymity. *ACM Trans. Knowl. Discov. Data* 1 (2007).

104 McGuire AL. Identifiability of DNA data: the need for consistent federal policy. *Am. J. Bioethics* 8(10), 75–76 (2008).

105 Rodriguez LL, Brooks LD, Greenberg JH, Green ED. The complexities of genomic identifiability. *Science* 339, 275–276 (2013).

• **Addresses issues of identifiability from genomic data.**

106 dbGaP: Genotypes and Phenotypes. www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/about.cgi#controlled

107 Kaye J, Heeney C, Hawkins N, De Vries J, Boddington P. Data sharing in genomics – re-shaping scientific practice. *Nat. Rev. Genet.* 10(5), 331–335 (2009).

• **Summary of issues in data sharing in genomics.**

108 Lunshof J, Chadwick R, Vorhaus D, Church G. From genetic privacy to open consent. *Nat. Rev. Genet.* 9, 406–411 (2008).

109 Manolio T, Chisholm R, Ozenberger B *et al.* Implementing genomic medicine in the clinic: the future is here. *Genet. Med.* 258–267 (2013).

110 Evans J, Khoury M. The arrival of genomic medicine to the clinic is only the beginning of the journey. *Genet. Med.* 268–269 (2013).

111 National Human Genome Research Institute. www.genome.gov/27554185