HHS Public Access

Author manuscript

Am J Bioeth. Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

Am J Bioeth. 2015 July ; 15(7): 3–14. doi:10.1080/15265161.2015.1039721.

Looking for Trouble: Preventive Genomic Sequencing in the General Population and the Role of Patient Choice

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Abstract

Advances in genomics have led to calls for developing population-based preventive genomic sequencing (PGS) programs with the goal of identifying genetic health risks in adults without known risk factors. One critical issue for minimizing the harms and maximizing the benefits of PGS is determining the kind and degree of control individuals should have over the generation, use, and handling of their genomic information. In this article we examine whether PGS programs should offer individuals the opportunity to selectively opt-out of the sequencing or analysis of specific genomic conditions (the *menu* approach) or whether PGS should be implemented using an all-or-nothing *panel* approach. We conclude that any responsible scale up of PGS will require a menu approach that may seem impractical to some, but which draws its justification from a rich mix of normative, legal, and practical considerations.

Keywords

genetics (clinical); public health; medical humanities; law; decision making; informed consent

Introduction

The decreasing cost of massively parallel DNA-sequencing technologies and an increasing understanding of the genomic basis of certain medical conditions has spurred enthusiasm for Preventive Genomic Sequencing (PGS) programs designed to help identify “those millions of individuals who unknowingly carry mutations that confer a dramatic predisposition to preventable diseases” (Evans et al. 2013, 332). Unlike previous population-based genetic screening programs, PGS programs would not be aimed at known high-risk groups or families, but would go “looking for trouble” in the general population, to attempt to forestall unsuspected cases of genetic illness. The prospect of such programs raises numerous ethical, legal, and medical questions that have yet to be answered in evidence-based ways, including

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which loci to sequence, who PGS programs should target, and how they should be designed and implemented. Connecting all these concerns is a common challenge: how to manage the trouble that a PGS program could potentially generate for both patients and clinicians in the process of pursuing its goals. One critical tension animating that challenge is determining the relative roles that patients' informed preferences and clinicians' judgments should play in decisions about how to manage genomic information.

In this article, we analyze this tension from the perspectives of public health, economics and technology, clinical ethics, family studies, health law, and our ongoing immersion in an attempt to build one such PGS program in practice (GeneScreen 2014). Specifically, the purpose of this article is to help generate a debate that can guide policy regarding whether PGS programs should offer individuals the opportunity to selectively opt-out of the sequencing or analysis of specific genomic conditions (the *menu* approach) or whether PGS should be implemented using an all-or-nothing *panel* approach. We argue that any responsible scale up of PGS as a clinically-based health tool will require a menu approach that may seem impractical to some, but which draws its justification from a rich mix of normative, legal, and practical considerations that go beyond the appeals to respect for patient autonomy that typically undergird concern for patient choice.

The idea of PGS itself is in large part stimulated by the increasing use of clinical whole genome/whole exome sequencing (WGS/WES) to help resolve diagnostic mysteries or choose between therapeutic regimes. One problematic aspect of WGS/WES has been that it generates “incidental findings on a larger scale than has previously been seen in medicine” (Foreman et al. 2013, 503; Kohane et al. 2005). Some of these incidental findings will be alleles of genes that reveal high risks for serious, previously unsuspected, but potentially preventable harms (Berg et al. 2013). The American College of Medical Genetics and Genomics (ACMG) refers to the genes that can display such risk-conferring alleles as medically actionable genes[1] (MAGs) (ACMG 2014). Genes are generally considered medically actionable when some of their variants “have direct clinical utility based on the current medical literature (e.g., in terms of disease prevention or established treatment guidelines)” (Berg et al. 2011). [2] In this article we use the term MAG to refer to genes that may contain rare genomic variants that confer a high risk of health-related harms for which there are interventions available that can potentially prevent or minimize these risks. These genes include some of those associated with Lynch syndrome, hereditary breast and ovarian cancer, Marfan syndrome, and Long QT syndrome (Evans et al. 2013; Green et al. 2013).

The basic idea behind PGS is simply to take advantage of our new abilities to detect MAGs to seek them out directly in patients who have no other known risk factors for the health problems these MAGs may flag. With its core idea, however, PGS also inherits a debate—which has emerged in the clinical WGS/WES context—over the relative role of patients and professionals in managing genomic information. This debate can be abstracted into a

[1]nb: despite the fact that it is not actually the *genes*, as loci in the DNA, that are actionable, but only the specific alleles or versions of the genes that carry the risk conferring mutations.

[2]It is important to note that even if some genes are in theory medically actionable, this does not mean that in practice all individuals will have access to preventive measures or will even want to undergo these measures due to the nature of the interventions or potential side effects.

conflict between two polarized positions: one that can be characterized as more paternalistic and one that is more individualistic. The rationale that drives the paternalistic position in many ways is captured by medical geneticists Evans and Berg (2011) when they state that "medicine is, to at least some extent, an inherently paternalistic endeavor simply because of an inevitable asymmetry in knowledge and because those who practice medicine are pledged to avoid causing harm." This perspective of medicine as inherently paternalistic is rooted in a strong sense of the importance of beneficence and non-maleficence when guiding clinicians' actions. Consistent with this notion, in the clinical WGS/WES context, those who hold the more paternalistic position often argue that health professionals have a duty to examine and warn of a risk of potentially preventable harm to patients' health, even if these risks were not part of the clinical purpose for ordering genomic sequencing, and their examination was not explicitly consented by patients (Green et al. 2013; McGuire et al. 2013). Furthermore, those who hold this position generally believe that patients cannot be expected to assimilate all the relevant information related to the risks and potential benefits of analyzing the wide array of secondary MAG risk information available from WGS/WES. Therefore—from the perspective of those who support the more paternalistic position—health professionals performing WGS/WES should analyze secondary target MAGs *without attempting to involve patients in the decision* of which MAGs to analyze. If positive MAG findings emerge, clinicians should disclose these to the patient, unless "the patient insists that he or she does not want to be informed" and the clinician has ensured "that the patient's refusal is informed" (McGuire et al. 2013, 1048).

The second pole in this debate is the individualistic counterpoint, which claims that individual patients should have control over what secondary MAG information is analyzed by the laboratory, reported to the clinician, and disclosed to patients (Wolf et al. 2013). Its argument is that patients have a right to control what medical tests are performed on them, rooted in rights to bodily integrity, personal autonomy, and privacy, even when those tests are potentially life-saving. In addition, the fiduciary obligations of health professionals to act in patients' best interests—including their obligation to prevent harm—are circumscribed by other fiduciary obligations such as the duty of loyalty to the interests of the patient. This duty involves loyalty to patients' interests in learning health risk information about themselves (Lázaro-Muñoz 2014). In this context, informational complexity is not presumptively incapacitating; rather, it speaks to the need for and the obligation of expert fiduciary agents to digest, translate, and communicate considerations salient for patient decision-making.

The clash between these views is an old one for modern medical ethics. In clinical treatment contexts the contemporary currents in both ethics and law flow strongly toward the individualistic position, which strives to protect patient self-determination. There is less literature on the role of patients' preferences in the diagnostic arena. Nonetheless, one of the features that makes the debate over MAGs noteworthy is that clinical genetics has historically been one of the medical specialties that has stressed the primacy of the patient's role in decisions to seek diagnoses and learn health risks (ASHG 1975; NSGC 2006). The resurgence of the paternalistic position in this context appears to threaten this tradition.

We argue that a more nuanced analysis of the challenges of designing and implementing a PGS program in practice can help resolve this polarizing debate for PGS. We begin by reviewing how the recent debate over the ACMG guidelines for the report of incidental or secondary target findings in WGS/WES reveals the tensions at the core of the paternalistic/individualistic opposition. We then address four sets of considerations that both complicate this simple framing in the PGS context and point the way to a resolution of its tension for clinical practice.

MAG Management Solution 1.0: Lessons from the ACMG

The generation, use, and disclosure of medically actionable genomic information to research participants have been a source of concern and debate for some time (Wolf et al. 2008). However, now that WGS/WES is increasingly being used to guide patient care, these concerns have percolated into the clinic. The debate generated by the initial ACMG recommendations regarding the management of MAGs in the WGS/WES setting (Green et al. 2013) is particularly relevant when evaluating PGS because the adoption of these recommendations would have created a de facto opportunistic MAG screening program for all patients who consented to clinical WGS/WES.

In 2013, the ACMG became worried that “[a]n increasing number of laboratories conduct clinical [WGS/WES] and have the potential to seek and report incidental findings, but there are no standards to guide their scope of analysis or reporting” (McGuire et al. 2013, 1047). The ACMG saw the lack of laboratory reporting standards as a problem because of the risks that laboratories might either report clinically meaningless findings or fail to seek and report MAGs that could help predict and prevent unsuspected genetic conditions (Green et al. 2013).

As a result of these concerns, the ACMG solicited and compiled expert opinion on the predictive reliability of known MAGs, the severity of their associated health problems, and the efficacy of known preventive or treatment interventions, and generated a list of 56 genes associated with 24 health conditions. It then released a report in which it recommended that: “whenever clinical [WGS/WES] is ordered, … laboratories should seek and report [to the ordering clinician] findings from [the 56 MAGs], without reference to patient preferences” (Green et al. 2013, 568). Ordering clinicians would then be left to use their clinical judgment in conveying this unsought information to patients (Green et al. 2013, 567).

The ACMG's initial solution in a number of ways reflects the paternalistic position on the question of how to manage MAGs. The ACMG concluded that the clinicians' and laboratory personnel's “fiduciary duty to prevent harm by warning patients and their families” about certain actionable health risks “supersedes concerns about patient autonomy” (Green et al. 2013, 568). The decisive factor for the ACMG in coming to this conclusion was their concern that an informed consent process sufficient to allow patients to make informed choices about whether to have the ACMG's panel examined would involve “an extensive, and possibly overwhelming, amount of genetic counseling” which “might result in deeply varying levels of truly informed preference setting” (Green et al. 2013, 568). Another important concern was the perception that WGS/WES necessarily generates all the data

required to analyze and report the full list of MAGs, leaving laboratory personnel and clinicians “sitting on” information “a touch of a button away” that could prevent significant harm.

The initial ACMG report elicited a wave of strong reactions from those holding more individualistic perspectives. A number of commentators responded to the ACMG's recommendation by arguing that it was a threat to patients' autonomy and their “right not to know” genetic information. For example, some argued that

> mandating that laboratories seek out unrequested information violates patient autonomy because patients who are offered testing using genomic sequencing methodologies must agree to an analysis of their genome more expansive than the clinical question and leaves patients with only an all-or-none decision: agree to more expansive analysis or refuse the sequencing (Ross et al. 2013, 368).

Others opposed the ACMG's recommendation from a legal perspective and argued that “[i]nformed consent is a well-established legal requirement designed to protect patient autonomy—not a matter susceptible to modification by experts in human genetics, no matter how learned” and that “in both ethics and law, the clinician has a core fiduciary duty to respect the patient's right to decide what testing to undergo and what information to receive” (Wolf et al. 2013, 1049). Finally, some argued that “[b]y policy and practice, clinicians or other surrogates may only make decisions on behalf of a patient in situations in which (s)he is incapable of exercising judgment” (Allyse and Michie 2013). Therefore, “[u]nless patients' decision-making capacity is impaired, or their refusal of therapy constitutes a threat to public health, their right to refuse [medical interventions] is virtually unlimited” (Burke et al. 2013, 856).

Some of the champions of the individualistic position also criticized the ACMG's claim that an informed consent process sufficient to allow patients to make choices about the ACMG 56-gene panel would involve an “extensive and possibly overwhelming, amount of genetic counseling” for patients (Green et al. 2013, 568). The counterpoint was that “the report marshals no data to support this conclusion and never considers proposals in the literature for streamlining the consent process when large numbers of genes are evaluated, such as “generic consent,” which would allow the patient to consider categories of genetic tests together” (Wolf et al. 2013, 1049).

Solution 1.5: ACMG Complete Opt-Out Recommendation

In 2014, after much debate, the ACMG modified its stance and recommended that patients should be allowed to opt out of the report of the entire ACMG 56-gene list (complete opt-out) (ACMG 2014). This means that, as a part of ordering clinical WGS/WES, a clinician would have to offer patients the chance to decline having laboratories analyze and report secondary targets. Importantly, the ACMG does not recommend that patients be allowed to *selectively* opt out of the analysis and report of particular MAGs, even though, once having been briefed on the whole list, patients may find themselves interested in knowing their risks for some but not all of the listed conditions (ACMG 2014; Maron 2014).

The complete opt-out approach was the ACMG's response to claims that patients' preferences should play a more prominent role in the management of secondary target MAG information when WGS/WES is performed. To some degree this approach does give patients' preferences a more prominent role, but its critics point out that the complete opt-out approach still substantially restricts their input compared to other viable options (Lázaro-Muñoz 2014). For example, under a selective opt-out policy, patients who would not want to learn about genetic risks for heart conditions that can cause sudden death due to arrhythmia (e.g., Long QT syndrome), could still choose to learn about genetic risks for other heart diseases or types of cancer such as hereditary breast and ovarian cancer.

Needless to say, the debate over the management of genomic information in the clinical WGS/WES context is not settled. This debate will continue to gain prominence as genomic technologies become a part of everyday health care. However, in order to develop evidence-based as opposed to “extemporaneous” policies (Wilfond and Nolan 1993) for PGS, it is critical that we take the lessons learned so far and start looking forward at how the MAG management debate can play out in the PGS context.

MAG Management in Preventive Genomic Sequencing

The following analysis focuses on what we see as one of the most likely scenarios for PGS aimed at the general population (Evans et al. 2013). However, many of the questions and arguments raised here are applicable to other forms of PGS. Initial attempts at PGS for the general population will likely target rare genomic conditions that confer a high risk for preventable harms. Leading geneticists have argued that attempts to improve population health through genomics testing are more likely to be effective if PGS efforts focus on rare genomic conditions that confer a high risk of preventable harm, instead of common complex diseases for which the contribution of genetics is generally relatively small (Evans et al. 2013). Furthermore, as we discuss in the Clinical Ethics Considerations section, we expect that PGS would likely be implemented in a primary care setting where most other types of screening occur.

Because of its likely focus on rare, highly penetrant, and actionable genomic conditions, PGS for the general population will probably not employ WGS/WES. WGS/WES generate vast amounts of genomic data that increase the cost of genomic testing, but are unrelated to the MAG conditions expected to be targeted by PGS programs, or have no known clinical validity or utility (Berg et al. 2013). By foregoing WGS/WES in favor of sequencing a limited set of genes identified in advance as conferring high risk of preventable harm, PGS programs can avoid having to manage large amounts of potential incidental findings. However, this does not mean that PGS programs can avoid the MAG management debate. Even in this simpler context, the relative role of individual choice and professional judgment still needs to be addressed.

Primary care patients are not usually consulted about each measurement performed in a standard lipid panel or toxicological screen. One could similarly offer the targeted MAGs as an indivisible panel of risk assessments. On the other hand, even individuals believed to be at risk for severe, but potentially preventable genetic harms, often decide against learning

their risks for numerous personal reasons (Fischer et al. 2012; Sweeny et al. 2014). Therefore, even if the genes selected for a PGS program are those considered the most highly predictive of disease, and medically actionable, with interventions that individuals are likely to access, accept, and adhere to, it is likely that not all individuals will want all of the MAGs examined. To accommodate these different interests, one could structure the list of targeted MAGs as a menu, so that individuals who decide to participate get the opportunity to selectively opt out of the examination and report of the genes they do not wish to have examined.

In the PGS context, then, this question arises: Should individuals be given the opportunity to selectively opt-out of the sequencing or analysis of specific MAGs (menu approach) or should PGS programs be implemented as an all-or-nothing panel approach? At the abstract level of the individualistic and paternalistic positions, this question merely yields another cycle of polarized debate. The panel approach aligns with the paternalistic position as it helps ensure that both clinicians and individuals are adequately prepared to prevent a larger range of potential harms that might be discovered and it protects the integrity of the professional judgments that endorsed the preventive value of the list. The menu approach intuitively aligns with the individualistic position, as it enables individuals to tailor the professionals' recommendations to their own values and interests. In actual practice, however, a number of other considerations both complicate this simple framing and help unlock the stalemate for PGS. These considerations emerge from the perspectives of 1) public health; 2) economics and technology; 3) clinical ethics and family studies; and 4) the law. We next analyze each of these in turn.

Public Health Considerations

The first question that bears on the debate over whether PGS should be offered as an indivisible panel or a menu is whether PGS serves primarily clinical or public health goals. PGS programs for genetic variants that confer a high risk for preventable diseases are hailed as a way to “realize the promise of public health genomics” (Evans et al. 2013). But this foundational question about the purpose of the enterprise still needs to be clarified, and it has significant implications for the balance of professional and patient roles.

For a number of reasons, the argument for a panel approach to PGS strengthens if a PGS program can be justified as a public health measure. First, the likelihood that a PGS program will achieve its public health goals depends heavily on the number of participants and genomic risks examined per participant. For example, newborn genetic screening programs rely on state laws requiring universal implementation to increase their number of participants, and employ periodically expanded panels to increase the range of risks assessed. In the case of state-mandated newborn screening programs, the judgment has been made that the state's interests in saving individual infants' lives or preventing some health-related harms outweighs the ordinary rights of parents to make medical risk assessment decisions on their children's behalf (PCB 2008). In theory, the more participants and MAGs examined, the higher the likelihood that certain health-related harms will be prevented or minimized at the population level. Of course, other factors are relevant to the success of a public health screening program, including the availability of an effective screening test, the

effectiveness of available medical interventions, and the participants' access, uptake, and adherence to these interventions (Viera 2011; Harris et al. 2011).

For PGS with adults, a panel approach would also likely examine more risk factors per participant because individuals would not have the opportunity to opt out of any MAGs. It is not clear how many individuals would refuse to participate in PGS programs if they could not opt out of the examination of particular MAG conditions. Nevertheless, in the clinical WGS/WES context, some estimate “that most patients will probably not exercise an opt-out option” for the examination of MAGs (Evans 2013, 853). To the degree that this is also the case in the PGS context, a panel approach would seem better designed to promote PGS's public health goals.

Second, when the public's health is at stake, individuals' ordinary freedoms can sometimes be curtailed. Compulsory vaccinations, routinized newborn screening, and heavy-handed health warnings are socially tolerated in our pursuit of collective public health goals, even where they distort the ideals of mutual respect and patient empowerment in the clinical setting. If PGS were primarily intended to achieve important public health goals, such as preventing a socially destabilizing rise in population morbidity or mortality (as from an infectious disease epidemic or the snow-balling costs of smoking-related cancers), then an all-or-nothing panel approach could be justified even in the face of individualistic objections to the panel approach's constraints on autonomy. This justification would be even more persuasive if those being screened do not have the capacity to make well-informed decisions themselves or the conditions screened required urgent care, as is the case with newborn screening.

The public health rationale for PGS programs is difficult to sustain, however. PGS programs would likely screen for MAGs that confer a high risk for severe, but potentially preventable diseases (Evans et al. 2013). Yet only about 0.5% - 1.0% of the population is expected to have such MAG variants (Evans et al. 2013). In addition to being rare, even high-risk MAG variants account for a relatively small proportion of the incidence of the disease with which they are associated. For example, “[t]ogether, BRCA1 and BRCA2 mutations account for about … 5 to 10 percent of all breast cancers … [and] around 15 percent of ovarian cancers” (National Cancer Institute 2014). Lynch Syndrome, considered by some to be one of the strongest candidates for PGS because of the penetrance of its potentially harmful variants, its prevalence, and the availability of medical interventions, only “accounts for approximately 1% - 3% of colon cancers, and 0.8% - 1.4% of endometrial cancers” (Evans and Berg 2011; Evans et al. 2013; Kohlmann and Gruber 2014). This means that even if a PGS program would help prevent or minimize health harms in the 0.5% - 1.0% of the population who unknowingly carry potentially harmful MAG variants, it would not have a significant public health impact in terms of decreasing the prevalence of any of the conditions examined.

Moreover, since the population incidence of MAG-related diseases is not known to be increasing in any socially destabilizing ways, it is not clear that the health benefits promised by PGS would merit an appeal to public health considerations in defending an all-or-nothing panel approach to MAG management. PGS programs would detect genetic variants that

confer high risk for severe conditions, but unlike some of the conditions that are part of newborn screening programs, MAG findings generally do not require urgent care, which further undermines the argument for PGS as a public health program.

In the absence of a compelling public health rationale for PGS, the public welfare justification for limiting individual participation to a full panel evaporates. Furthermore, research suggests that patients' principal motivations for seeking genetic testing are largely clinical: perceived personal risk of developing a heritable disorder, disease-specific worry, family history of a heritable disorder, and personal history of a particular disorder (Sweeny et al. 2014). This suggests that PGS may make more sense as a clinical tool aimed at resolving individual patient anxieties about their possible risks for specific MAGs targeted by the PGS program. If so, it will important not to confuse the program's goals by using language that assumes a public health mission, and to assess the limits of patient control within the context of considerations relevant to the clinical care of patients rather than the protection of population health.

Cost and Technical Considerations

Whether PGS is offered as a public health intervention or a personal risk-assessment service, the design of a successful PGS program still faces important practical constraints. Cost is one of the factors that will affect access to PGS programs regardless of whether preventive MAG sequencing is covered by government programs, insurance companies, individuals or a combination of these. Therefore, it is important to determine how taking a panel or menu approach to PGS can affect the cost of sequencing. An important benefit of targeted sequencing compared to WGS or WES is its reduced cost. For example, targeted sequencing of a set of 28 cancer-related genes costs approximately $4,250 (Ambry Genetics 2014) while WES and WGS cost approximately $5,800 (Ambry Genetics 2014) and $10,000 (NHGRI 2014), respectively.

Both panel-based and menu-based PGS approaches would sequence a targeted set of MAGs. One method for implementing a menu-based PGS would be to give individuals the opportunity to opt out of the sequencing of some of the genes that are part of the PGS program (*selective sequencing*). Selective sequencing would allow individuals to decide that they do not want the laboratory to generate the raw genomic data for some of the loci in the PGS program. Selective sequencing, however, would require laboratories to develop customized sequencing libraries and assays for each individual, depending on the combination of genes that the patient wants sequenced. This would undercut the economies of scale that could be achieved by a panel-based PGS approach that uses the same genetic sequencing assay for every patient. Therefore, it could greatly increase cost and limit access to PGS.

Another alternative for a menu-based PGS program would be a *selective analysis* approach. Under this approach, the laboratory would generate the raw genomic data (DNA sequence) for all of the genes that are part of the PGS program, but individuals would get the opportunity to opt out of the analysis of the raw data for those MAG conditions they do not want to learn about or have reported to their clinician. The menu-based selective analysis approach would offer significant savings over the selective sequencing approach because, as

with the panel-based PGS approach, laboratories could use the same sequencing assay for every individual. A selective analysis approach would only require laboratories to have the bioinformatics capability to specify those genes they want to analyze from the PGS assay. This means that from a financial perspective both the panel approach and the menu-based selective analysis approach present similar advantages over WGS/WES or a menu-based selective sequencing approach to PGS.

Clinical Ethics Considerations

Clinical ethics considerations permeate almost every aspect of the management of MAG information in genomic testing, but many have been obscured by the reductive paternalistic/individualistic framing of the debate to date. Four sets of neglected considerations seem particularly relevant to adjudicating the tension between professional and patient decision-making in the PGS context: more nuanced views of the “best interests” protected by the therapeutic relationship, richer understandings of personal autonomy, the salience of family interests, and debates over a “right not to know.”

Best Interests of the Patient—Whether PGS is justified as a public health intervention or a personal risk assessment service, one of the most likely venues for such a program would be the primary care setting. Primary care clinicians are generally the first contact for individuals seeking medical services and they are familiar with conducting preventive screening, even if the novelty and complexity of PGS may require training. On the other hand, making primary care clinicians the gatekeepers to this service would bring their own professional ethos and ethics into play, which also has implications for whether the service is offered as a panel or a menu.

Clinicians have a professional fiduciary duty to act in the best interest of their patients (American Medical Association 2001). Determining what this duty means for the panel versus menu debate depends on how the “best interest” of an individual is defined. If the best interest of an individual is limited to a person's professionally-defined medical best interest, then the panel approach would probably promote the individual's best interest more than a menu approach. A panel approach would ensure the detection of a greater number of deleterious MAG variants, and as illustrated by the ACMG report, there seems to be a consensus in the field of medical genetics that reporting deleterious MAG variants to ordering clinicians “would likely have medical benefit for the patients and their families” (Green et al. 2013, 567).

However, research suggests that individuals' decisions about the examination of genetic information involve not just medical considerations but also their values and their emotional, economic, social, and familial interests (Oosterwijk et al. 2014; Sweeny et al. 2014; Van Riper 2010). If the best interest of an individual is defined more broadly to integrate these other relevant interests, then clinicians need to know how patients balance those interests for themselves in order to fulfill their fiduciary duty. The menu approach would meet this need better, by more accurately reflecting and promoting individuals' judgments of their own interests. It is important to note that the menu approach would still integrate clinicians' input about individuals' best medical interests in two significant ways: 1) clinicians would be

involved in determining which MAGs should be tested as part of the PGS program and; 2) clinicians could provide their professional judgment at the clinic when individuals are invited to participate in the program.

Personal Autonomy—A cornerstone moral commitment of contemporary clinical ethics is the requirement to respect patients as persons. This is usually interpreted in terms of respecting patients' personal autonomy and their rights to make important decisions about their own health care, even when such decisions conflict with a clinician's own professional views. However, a number of important considerations can shape the limits of respect for personal autonomy in the PGS context.

Some argue that “autonomy is not simply a matter of acting on one's preferences, even one's informed preferences,” but that there must be sufficient value in the choices offered (Vayena and Tasioulas 2013, 868). These commentators argue, for example, that the ACMG's 56-lociextended analysis and report recommendation enhances patient autonomy because the report would generate “a fuller menu of worthwhile options” that are “valuable in enabling the pursuit of improved health outcomes for the patients[,]….the patients' relatives and serve the common good of promoting a healthy society” (Vayena and Tasioulas 2013, 868).

Translated to the PGS context, this logic would suggest that a panel approach would enhance individual autonomy because it would ensure examination of all MAGs that are part of the PGS program and thus would provide “worthwhile options” (e.g., medical interventions, further testing, disclosure to relatives) to those individuals who are found to have any potentially harmful MAG mutations. The problem with this approach is that it presumes—for all individuals—that having a choice about which genes to examine within a PGS program is *not* a worthwhile option. However, this presumption ignores the reality that numerous personal and familial, emotional, economic, and medical interests come into play when an individual is deciding whether to know or not know a potential genomic risk. The ability to take such factors into account in order to decide which MAG conditions should be examined seems itself to be a worthwhile option. If that is the case, then the menu approach, by giving individuals that opportunity, shows greater respect for autonomy.

An essential precondition to the exercise of autonomy in medical decision-making is that individuals understand the options presented. In order to allow individuals to understand their options in a PGS program there must be adequate mechanisms and resources in place (e.g., genetic counseling, decision aids, time) to deliver risks and benefits information about MAG testing. Many worry about the possibility of communicating the information necessary to allow for meaningful understanding of the risks and benefits of opting out of the examination of certain MAG conditions (Green et al. 2013; McGuire et al., 2013). Some believe that the consequences of opting out can be so complex and abstract that opt-out alternatives would simply give individuals “an illusory degree of autonomy” which could “come back to haunt them with highly problematic consequences” (Evans 2013, 853).

The complexity of genomic information and the consequences of opting out are an undeniable challenge for the menu approach. However, this is an equal challenge for the panel approach. Under a panel approach, individuals may still refuse to participate in the

PGS program, thereby incurring the same kind of opportunity cost (e.g., not detecting a potentially harmful MAG variant) as individuals who selectively opt out of some of the MAGs on a menu.

Limiting individuals' choices by using a panel approach does not reduce the amount of information required to inform a decision about whether to participate in a PGS program. Regardless of whether they are being asked to consent to a panel or choose from a menu, individuals still need to understand the risks and benefits of the components (e.g., MAG conditions or categories of MAG conditions) of the PGS program in order to make an informed decision about their participation. Given this necessity, the panel and menu approaches would impose similar information communication burdens for clinicians. Because PGS will examine only a limited number of MAG conditions, both panel and menu approaches should create fewer communication challenges for clinicians compared to WGS/WES. Nevertheless, whichever approach is ultimately chosen, developing more efficient and effective ways of delivering genomic information in a comprehensible manner should remain a high priority.

Familial Interests—One of the most important constraints on patient self-interest in the PGS setting is the fact that the individual being sequenced is not the only person whose interests are affected by the exercise (Rhodes 1998). In the course of providing individuals with information about the MAGs they carry, a PGS program will also generate genetic risk information that will have implications for individuals' families. By ensuring that participants get all MAGs examined, the panel approach increases the chances that information generated on all the variants will be disclosed to other family members. This could contribute to one or more family members living longer, healthier lives, and making better-informed reproductive decisions.

However, the panel approach also presents some challenges. For example, simply because more MAG information will be generated, there is a marginally greater chance of family tensions developing due to secrecy, misunderstandings, communication problems, feelings of guilt and shame, and blaming (Rowland and Metcalf 2013; Van Riper 2005, 2010; Van Riper and Gallo 2006; Wisemann et al. 2010). In addition, while the panel approach increases the chances that relatives will learn about potential genomic risks, it also increases the chances of overtesting and overtreating them. This is a particularly difficult problem in PGS programs because little is known about the penetrance of MAG deleterious mutations in individuals with no symptoms or family history of disease (Green et al. 2013; Moyer et al. 2014).

On the other hand, the menu approach would allow individuals to make a choice about which MAG conditions to examine based on the individual's and their family's best emotional, economic, and medical interests. This advantage is limited by the fact that individuals' judgments of what is in their best interest may not always align with the best interests of their relatives. But the menu approach fits closely with the model of client-centered, non-directive genetic counseling that has come to characterize clinical geneticists' work with families since the 1950's (Stern 2012). That model explicitly gives moral priority to the interests of individuals and couples in the dissemination and use of genetic

information. This priority represents a reaction to the emphasis given to the interests of future generations, communities and populations during the eugenics movements of the first part of the twentieth century (Paul 1995). The invasions of personal reproductive and informational privacy made in the name of public health by eugenically motivated programs continue to cast a shadow over interventions that might limit individual choices concerning the discovery and dissemination of genetic information (Parker 2012).

Right Not to Know—One echo of the concern with keeping genetic decision-making in the hands of individuals is the notion of a "right not to know". Multiple authors have appealed to respect for autonomy as the basis for rights to know or not to know genetic information (Andorno 2004; Chadwick 2009). Consistent with this view, Article 5(c) of UNESCO's Declaration on the Human Genome and Human Rights states that "[t]he right of each individual to decide whether or not to be informed of the results of genetic examination and the resulting consequences should be respected" (UNESCO 1997). Others have recently argued for the right not to know genomic information in the WGS/WES context not only as a matter of respect for individual autonomy, but also as a matter of privacy, and as an aspect of the clinician's fiduciary duty (Laurie 2014; Lázaro-Muñoz 2014; Wolf et al. 2013). The existence of rights to know and not to know genetic information appears to support a menu approach because it would be more sensitive to individual patient preferences to receive or avoid knowledge about particular MAGs.

On the other hand, some are skeptical about a right not to know, and argue that refusing useful medical information is not a rational choice and thus it is not an autonomous act for which a right should be recognized (Ost 1984). Meanwhile, others argue that autonomy cannot be the basis of a right not to know genetic information because if one decides not to know relevant genetic information, one chooses "to leave things to chance" and "follow a path without autonomy"(Rhodes 1998, 18). Furthermore, some argue that even if rights not to know exist, they lack parity with the right to know, and are easily outweighed by other relevant considerations (Harris and Keywood 2001).

In the WGS/WES context, supporters of panel-based approaches have argued that "[t]he right not to know is ethically controversial, and most of the relevant literature relates to findings for which no clearly beneficial interventions are available" (McGuire et al. 2013). Others argue that the right not to know MAG information in genomic medicine should be limited to exceptional situations where individuals have "a valid reason why they would not want to take clinical action," such as "previously diagnosed terminal illnesses … or people with religious objections to certain kinds of treatment" (Berkman and Hull 2014).

To the degree that a moral right not to know is limited or not recognized in genomic medicine, a panel approach becomes more ethically acceptable. However, if—as has been the tradition in clinical genetics—a broad ethical right not to know is recognized, a menu approach would be more protective of this right because individuals could refuse the analysis and report of particular MAGs before consenting to PGS. A panel approach would be more problematic for the right not to know. If the laboratory reports MAG mutations to the ordering clinician, and the patient declines to receive that information, the clinician will be in the difficult professional position of having actionable genomic risk information but

being ethically bound not to disclose it to the individual or the individual's relatives who might also be at risk. Furthermore, even if the clinician does not disclose these results directly to the patient, they may reside in the individual's medical record because the laboratory or clinician may be obliged to place them there, making them necessarily available to others involved in treatment or payment, and increasing the chances that the individual could inadvertently learn about them in the future.

Legal Considerations

In addition to medical ethics considerations, there are a number of legal considerations in play when determining whether a PGS program should use a panel or a menu approach. Traditionally, the American legal system has been very protective of autonomy in the medical context and of patients' right to control what should be done with their bodies (Schloendorff v. Soc'y N.Y. Hosp. 1914). This is reflected in the doctrine of informed consent and the right to refuse treatment, even when potentially life-saving (Cruzan v. Mo. Dep't of Health 1990).

Disclosure Component of Informed Consent—Informed consent requires disclosure of what is to be done and the attendant risks and benefits. Both the panel and menu approaches can meet the disclosure component of informed consent by requiring appropriate pre-PGS disclosures. The specifics of these disclosures will depend on the informed consent legal standard of the state in which the PGS program will be implemented. There are two principal informed consent standards in the United States: the reasonable physician standard and the reasonable patient standard (Studdert et al. 2007). Under the reasonable physician standard, also known as the professional standard, clinicians are only required to disclose the risks and benefits that are customarily disclosed by prudent clinicians under similar circumstances (Culbertson v. Mernitz 1992). Under the reasonable patient standard, necessary disclosures depend on a determination of what a reasonable patient would consider material to decide whether to participate in a PGS program (Canterbury v. Spence 1972). A risk is considered material “when a reasonable person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk or cluster of risks in deciding whether or not to” participate in the PGS program (Canterbury v. Spence 1972, 787).

Each informed consent legal standard has its virtues and its problems. However, the differences between the two standards are largely irrelevant to deciding between the panel and menu approaches. Regardless of which standard applies in a given state, the panel and menu approaches will require similar disclosures as they entail the potential examination of the same health information using similar methods.

Refusal Component of Informed Consent—Informed consent implies that the individual must freely consent in advance to a medical intervention; its negative logical corollary is that the individual is equally free to refuse (Cruzan v. Mo. Dep't of Health 1990, 270). It is widely recognized that the doctrine of informed consent applies to medical examinations, thus clinicians routinely obtain informed consent before ordering genetic tests. The application of the informed consent doctrine to genetic testing implies that

individuals have a legal right to refuse genetic tests. However, it is unclear at this point whether the law will recognize that the right to refuse medical interventions grants patients the right to selectively opt out of the examination of specific components of genomic tests. Nevertheless, if there are practical ways of protecting an individual's right to refuse the examination of specific medical information, it would seem unreasonable to deny patients the opportunity to freely exercise their right of refusal in the genomic testing context.

While the panel and menu approaches can both satisfy the disclosure element of informed consent, they do not offer the same kind of protection for the refusal component of the doctrine of informed consent. With a panel-based approach to PGS, the individual can, of course, refuse the proffered test entirely. However, the exercise of that right to refuse is burdened, because refusing the test means forgoing all of the potential benefits of examining even some of the MAGs on the panel. This burden may be unjustifiable because there are alternatives, such as the menu-based selective analysis approach, that are practical and provide more protection for the right to refuse medical examinations. Finally, some may argue that a panel approach does not impose an unjustifiable burden because individuals could always decide to refuse the entire panel and get more specific genomic tests through other means. However, depending on how many MAG conditions an individual would like examined, specific genetic tests could be prohibitively expensive, especially for those with limited economic resources.

Genetic Discrimination—The inclusion of deleterious MAG variants in the medical record can increase the chances that an individual will face genetic discrimination of some kind. The Genetic Information Nondiscrimination Act of 2008 and most relevant state statutes, offer little protection against genetic discrimination in life, disability, and long-term care insurance, or against many other kinds of discriminatory uses of genetic information (Rothstein 2009, 2012). Ideally, patients would get the opportunity to decide whether they would like the information included in their medical record, but that is probably not going to be the case. Clinicians' determinations about what to include in a medical record are often dependent on institutional policies, legal concerns, and what clinicians' perceive to be their professional duties. For example, if the laboratory reports any deleterious MAG variants, clinicians will likely include all of them in the medical record because they are pertinent findings about an individual's health that can impact patient care in the future. Furthermore, clinicians will likely document MAG findings in the medical record to protect themselves against legal claims regarding their management of the patient. For example, a finding of a potentially harmful variant that indicates an increased risk for familial hypercholesterolemia could provide evidence of why a clinician prescribed stat in therapy if a patient were to file a malpractice claim against the clinician for adverse effects related to the medication (Youngblom and Knowles 2014).

This is an important issue for the panel versus menu debate because the panel approach would not allow people to balance the potential benefits of screening for particular MAGs against the potential risks of having this information in their medical record. Conversely, a menu approach would allow individuals to opt out of the examination of particular MAGs that they judge not to be worth the risks of testing, including potential genetic discrimination.

Conclusion

Genomic testing technologies may have significant if yet-unrealized potential for improving human health. The realization of this promise will likely involve screening for highly penetrable genes that confer significant risk of serious health problems that may be ameliorated by medical intervention. The decision about which medically actionable genomic risks an individual would like examined is deeply personal because the results can have a dramatic impact on the lives of the individuals being tested and their relatives. These effects can vary depending on an individual's life experiences, stage in life, familial obligations, emotional coping mechanisms, and socioeconomic resources, among other things.

The use of genomic testing technologies in research and the clinic has led to important debates about the role of professional judgment versus individual preference in the management of MAGs. Two main camps have emerged in this debate, the paternalistic and individualistic positions. The paternalistic position, using beneficence arguments, contends that professional judgment should primarily guide determinations about how MAG data is managed. On the other side, supporters of the individualistic position emphasize the importance of respect for autonomy and believe that individuals should have as much control as possible when managing their MAG information.

We have taken this debate to the PGS arena, focusing in particular on the choice between panel-based and menu-based approaches to PGS in clinical care. In doing so, we have shown that more granular analysis of the complex issues underlying this choice belie the simplistic opposition of paternalism and individualism that has characterized the literature to date. A robust public health rationale might offer the strongest support for a panel approach, but it is lacking. On the other side, a number of ethical, clinical, practical, familial, and legal considerations favor the menu approach. The tradition of respect for self-determination that is deeply embedded in the American legal system and the theory and practice of bioethics is a common thread in these considerations, but it is by no means the only significant issue. An analysis of how to accurately frame the objectives of PGS, how to facilitate access to PGS as a clinical tool for health management, what it means to act in participants' best interests, and how to promote meaningful participant understanding of the risks and benefits also play a key role.

Acknowledgments

The authors would like to thank James P. Evans, Jonathan S. Berg, R. Jean Cadigan, Nancy M.P. King, and Izzy Brassfield for helpful discussions and input about the topics addressed in this article. Research reported in this publication was supported by the National Institutes of Health (NIH) Grant 2P50HG004488 (Henderson, PI) “Center for Genomics and Society (CGS),” 6/2013-5/2018, and 1U01HG006487 (Evans, PI) “NCGENES: North Carolina Clinical Genomic Evaluation by Next Gen Exome Sequencing,” 12/2011-11/2015. The content is solely the responsibility of the authors and does not necessarily represent the views of NIH or all CGS investigators.

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