The Ethical Introduction of Genome-Based Information and Technologies into Public Health

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Abstract

With the human genome project running from 1989 until its completion in 2003, and the incredible advances in sequencing technology and in bioinformatics during the last decade, there has been a shift towards an increase focus on studying common complex disorders which develop due to the interplay of many different genes as well as environmental factors. Although some susceptibility genes have been identified in some populations for disorders such as cancer, diabetes and cardiovascular diseases, the integration of this information into the health care system has proven to be much more problematic than for single gene disorders. Furthermore, with the 1000$ genome supposedly just around the corner, and whole genome sequencing gradually being integrated into research protocols as well as in the clinical context, there is a strong push for the uptake of additional genomic testing. Indeed, the advent of public health genomics, wherein genomics would be integrated in all aspects of health care and public health, should be taken seriously. Although laudable, these advances also bring with them a slew of ethical and social issues that challenge the normative frameworks used in clinical genetics until now. With this in mind, we highlight herein 5 principles that are used as a primer to discuss the ethical introduction of genome-based information and genome-based technologies into public health.

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Introduction

In the last 3 decades, great strides have been made in both genetic and genomic research. In the late 80s and 90s, the focus was mostly on single gene (or Mendelian) disorders. Indeed, the genes causing diseases such as cystic fibrosis and Tay-Sachs were identified, and the corresponding genetic tests were integrated in the health care setting. With the human genome project running from 1989 until its completion in 2003, there has been a shift towards studying more common complex disorders which devel-

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op due to the interplay of many different genes as well as environmental factors. Disorders such as cancer, diabetes and cardiovascular diseases are included in the latter group, and although some susceptibility genes have been identified in some populations, the integration of this information into the health care setting has proven, as underlined by numerous genetic epidemiologists and scientists from relevant disciplines, to be much more problematic than for single gene disorders [1–3]. Low or variable clinical validity, variable expressivity and little knowledge concerning relevant treatment options following testing are only some of the issues contributing to the difficulties of introducing genetic or genome-based testing for common complex disorders into the health care system. Another larger 'umbrella' problem is the lack of a concrete and widely accepted framework to guide the responsible introduction of such testing. Although health technology assessment (HTA) offers a framework that has, and could help in translation [4], this has not been systematically used to date. Furthermore, the constantly rising interest in and the push for genetic and genomic testing for common complex disorders, as well as the actual offer of genetic and genomic testing for such disorders by commercial companies directly to consumers, are seriously challenging the normative frameworks previously used in clinical genetics. Consequently, it is imperative that all aspects concerning the (eventual) introduction of genome-based information and technologies into the health care system be addressed now. It is also important to note that even once the scientific and medical criteria for genome-based interventions are fulfilled, there will still remain ethical and societal issues to be addressed. The lack of adequate ethical and social consideration of genome-based interventions – no matter how technically sound – will result in an irresponsible provision of testing. With this in mind, this article aims to contribute to the discussion of what constitutes the responsible introduction of genome-based information and technologies (GBIT) into public health. It is meant as a discussion paper aimed at a large range of stakeholders (clinicians, public health officials, policy makers, etc.) in order to aid in the reflection of what constitutes the ethical introduction of such information and technology into public health.

What Is Public Health Genomics?

In our efforts to address these issues for the widest breath of genome-based applications in public health, we choose to focus our attention on the notion of GBIT in the field of public health genomics (PHG). The scope of application of GBIT includes applications for screening and testing of numerous single-gene disorders and common complex disorders, and applies to all types of screening, including preconceptional, prenatal or postnatal screening as well as stratified interventions [5]. Furthermore, it includes personal genomic information and genome-based information found in biobanks. PHG was defined at the international expert meeting in Bellagio (Italy, 2005) as 'The responsible and effective translation of genome-based knowledge and technologies for the benefit of population health.' [6].

As evidence of the underlying importance of addressing the concerns surrounding PHG, many organisations around the world have dedicated time and money in the attempts to address these matters. For example, the Centers for Disease Control in the U.S.A. has an Office of Public Health Genomics which 'promotes the integration of genomics into public health research, policy, and practice to prevent disease and improve the health of all people' [7]. The Genome-based Research and Population Health International Network (GRaPH-*Int*) started their research on PHG in 2005 and has as an aim to help 'transform knowledge and technologies into public policies, programmes and services for the benefit of public health' [8]. The PHG Foundation in the U.K. has as a mission 'to enable advances in biomedicine and genomics to be responsibly translated into effective ways to prevent illness and provide healthcare that is accessible to all on the basis of their vulnerabilities and needs.' [9]. The Federal Public Service for Health in Belgium 'has committed itself to correctly implement genetic research into public health.' [10]. Furthermore, the Public Health Genomics European Network II (PHGENII) project, funded by the General Directorate for Health and Consumer Protection was organized to develop 'European best practice guidelines for quality assurance, provision and use of genome-based information and technologies'. [11].

An important question that needs further attention is which framework can guide the responsible introduction of GBIT into the public health system. As mentioned earlier, HTA processes can be used, and additional frameworks for genome translation have already been proposed: for example, the 4 phases of translation presented by Khoury et al. [12] and the 'Genome-based Knowledge Management in Cycles' model by the GAPPNeT group [13]. In addition, criteria for responsible population screening have been proposed as refinements of the Wilson and Jungner criteria. Examples of such refinements can be found in the work done by the National Screening

Committee in the U.K. [14], the HTA Advisory Board AETMIS in Canada (Québec) [15] or the European Society of Human Genetics [16]. In this manuscript, we do not suggest which framework should be used, but rather we use a set of principles published by the Health Council of The Netherlands ('Screening: Between Hope and Hype') [17] as a basis to discuss ethical aspects of introducing GBIT into public health. More specifically, we base our discussion on principles outlined in the chapter 'Criteria for Responsible Screening' in which they describe 5 criteria that should be addressed before introducing a genetic screening programme in a population. Although their discussion was aimed specifically at genetic screening, with some modifications, the outlined principles are also a good starting point to discuss the responsible introduction of GBIT into the public health system.

Principles on Which to Base the Discussion Regarding the Ethical Introduction of Genome-Based Information and Technologies into the Publicly Funded Health System

Reliable and Valid Instrument and Process

The introduction of GBIT into public health should be based on a solid scientific foundation. Moreover, a framework and process for this translation should be established before the actual introduction of the GBIT and the quality of the various parts of the process must be monitored throughout the period in which the GBIT are offered to the public.

One of the principles raised by the Health Council of the Netherlands (hereafter referred to as the Health Council) in their discussion of responsible genetic screening is that there must be a 'reliable and valid instrument' used to perform testing and screening. By this they mean that 'The screening method must have a solid scientific basis and the quality of the various parts of the screening process must be guaranteed.' [17]. This criterion should also be applied to the introduction of GBIT. Furthermore, this criterion should also comprise the notion of 'reliable and valid *process*' which includes the analyses and assessments done prior to the introduction of GBIT into public health as well as the process(es) of regular assessment while the GBIT are routinely being offered.

Applying this to GBIT means that the tests and information introduced should be reliable and valid and the analytic validity, as well as the clinical validity, should be determined based on solid evidence. Furthermore, criteria should be established below which genome-based

technologies (including tests) cannot be introduced. The positive predictive value of a test within specific groups and the general population must be defined and kept in mind as tests are offered in the clinic and/or to targeted groups. Moreover, any sample analysis must be conducted in laboratories that comply with accepted quality standards by qualified personnel.

Once the above has been determined, an effective and responsible genome-based intervention programme must be 'properly planned in terms of design, implementation and evaluation' [17]. The GBIT should be acceptable to individual patients and/or to target populations and adequate information should be provided to them. Furthermore, adequate education of health care professionals should be established. This should include both initial training in medical schools as well as continuous education for practicing physicians. Clear standard information should be provided to users before testing (and at different stages throughout testing), and clear and standard reports should be provided following testing. The entire process should be regularly monitored and assessed for quality.

An important issue for this principle, as well as a recurring theme for each principle below, is the (lack of) answers to the following questions: (1) *What* will be the criteria for reliability and validity of the technology and information? and (2) *Who* will be responsible to decide these criteria and implement the processes involved? Although the answers to these questions are beyond the scope of this discussion, it is clear that time and funding will have to be invested in order to answer these questions as soon as possible. Although there have been often scattered efforts by individual groups to contribute to these answers (i.e. ACCE project [18], EuroGenTest (www.eurogentest.org), EGAPP, GAPPNet, NIH (Genetic Test Registry)), given the tasks ahead of us and the number of questions needing answers, it will become imperative that efforts be merged in order to obtain a responsible and workable process.

Focus on Significant Health Problems

GBIT introduced into public health (and financed by public funds) should be focussed on significant health problems.

The notion that genetic screening programmes should focus on 'important health problems' [16, 19] or a 'significant health problem' [17] is supported by various organisations. With respect to genetic screening, the Health Council specifically underlines that such a service paid for by the government should only be related to 'significant

medical problems'. In the context of limited financial resources for health services, which is the case in all countries, the notion of prioritizing is paramount. That being said, it should be recognized that the definition of 'important' or 'significant' is by no means clear or static. It has been emphasized that 'importance' or 'significance' does not necessarily relate to the number of people affected. It may address the severity of a health problem, even if a condition is rare (e.g. phenylketonuria) [16, 17].

As mentioned above, complicating matters here are *what* are the specific criteria for determining a 'very serious condition' and *who* should decide? The expansion of newborn screening panels in the U.S. over recent years has shown that 'importance' changes with factors around testing (i.e. cost, technology, lobbying, and high profile cases) [20]. A disorder such as Gaucher Disease, for example, was already a matter of debate with regard to its integration in a carrier screening panel for Ashkenazi Jews [21, 22]. Although Gaucher Disease is one of the most prevalent genetic disorders in the Ashkenazi Jewish population, with a carrier frequency of almost 6% in this community, strong arguments against providing carrier screening for this disorder have been offered. The most common Gaucher Disease mutations lead to a highly variable but usually mild or symptomless phenotype. This then raises the question whether it is acceptable to systematically identify carrier couples for a disorder that is usually not severe and is treatable [23, 24]. Severity judgments are complex and a particularly challenging base on which to make reproductive choices.

We are presently faced with a situation where disorders seem to be added to screening panels due to technology driven reasons rather than based on a judgment of the importance of the health problem. Situations where adding 'less important' disorders to a panel does not appear to immediately add to costs may weaken the argument of 'prioritisation' mentioned above. However, there are still other issues to be considered. For example, providing treatable and nontreatable disorders within the same panel can undermine the consistency (and consequent understanding of users) of that panel. Furthermore, the financial, social and psychological costs of additional/follow-up testing in the medium and long-term future due to the initial genome-based test must be studied before a complete answer regarding costs can be provided.

Benefit-Risk Ratio of Advantages and Disadvantages
The advantages of introducing and offering GBIT should outweigh the disadvantages.

With respect to genetic screening, the Health Council identifies the 'need to have the ratio of advantages and disadvantages to be positive' as the core of the normative framework of their discussion. They state that 'Screening must produce a health gain' [17] and that it is essential that the treatment or result of the screening lead to a better prognosis than would happen without the screening/testing and ultimate treatment. In as much as the goal of public health is to improve health at both the population level as well as on the individual level, it is a logical expectation that tests offered within these contexts provide an overall benefit to individual patients and/or populations. Unfortunately, there are many obstacles to reaching a consensus for such assessments.

First of all, there can be disagreement regarding what is meant by advantages and disadvantages [25]. In a narrow sense, clinical utility usually refers to the ability of a 'screening or diagnostic test to prevent or ameliorate adverse health outcomes such as mortality, morbidity or disability…' [25]. Meanwhile, in its broadest sense, the ratio of any benefit and harm (medical, personal, social) can be included in the term 'clinical utility' [17, 25]. Moreover, Grosse et al. [25] recommend that psychosocial, ethical, legal, and social aspects (This includes issues relating to distress, stigmatisation, discrimination, information privacy, and confidentiality.) also be included in the assessment of the net benefits of testing since all of these factors affect the balance of benefits and harms involved in testing. However, they still agreed that the primary endpoints in assessment of clinical utility should be kept to morbidity, mortality and disability. Foster et al. [26] further argue that in the context of publically funded programmes, the utility should be evaluated based on societal rather than individual terms. However, the authors specify that in the case of privately funded services, utility in the broader sense of 'utility' should be used; that is to say including 'personal utility' wherein medical outcomes may not be improved per se, but the individual finds utility in the test process nonetheless [26]. Indeed, the concept of personal utility appears to be taking on more importance [27]. Individuals are taking an increased interest in their own health and in requesting certain treatments and procedures from their physicians, and 'the perspective and expectations of the individual, who is in the center of all, should be taken into account' [28].

Secondly, even if the general definition of clinical utility has been agreed upon, there remains room for disagreement in the details of the assessment. Burke et al. [29] point out that, unlike analytic and clinical validity,

which are technical properties, clinical utility is about the health care value of a test; that is to say that it is not only scientific evidence that goes into defining clinical utility; contextual circumstances, as well as personal and group values, also play an important role. As such, this parameter is open to more, or at least, to a different type of disagreement. The authors highlight that although 'underlying value judgements and related priority-setting decisions may not always be acknowledged', defining and discussing these issues is important and 'may help to identify barriers to consensus and the strategies to resolve them.' Basically, many of the issues involved in establishing clinical utility are subjective; they depend on the stakeholders and their values and the larger context in which the analysis is being made [29]. Specifically Burke et al. [29] state that stakeholders may have very different opinions about what constitutes benefits and risks and about how to tally them up to obtain a total sum of pros and cons. Potential points of contention include, among others, what is considered a benefit and a risk, and the prioritisation of these; the inclusion of social outcomes as benefits; the appropriateness of using limited resources to offer a test; and determining acceptable evidence thresholds [29]. In addition to these issues, the authors go on to list contributing factors to clinical utility that should also be considered, including, among others, patient and family acceptability, economic measures and equity [29]. They conclude that ultimately there is a need for 'clarity about the value judgments different stakeholders use in judging evidence' [29].

Similarly to deciding the criteria to distinguish an 'important health condition', we are left here with having to answer the questions of *what* are the criteria needed to be included in the assessment of clinical utility in the broad sense (or benefits and risks) and *who* will take the responsibility of performing the assessment. Both variables have an important impact on the nature and quality of the answer. Transparency regarding the actual measures used in the assessment as well as the underlying value judgements and contextual factors are important. Ultimately however, this ratio of advantages to disadvantages must be positive for GBIT to be introduced into a public health programme. Moreover, it should be shown that using such GBIT results in better outcomes than does using alternate technologies/information (including doing nothing). Finally, regional and national divergences due to differences in values, budgets, etc. will have to be taken into account when making such assessments and setting policy.

Respect for Autonomy

The autonomy of patients, and individuals in general, must be respected for the responsible introduction of GBIT into the public health system.

The Health Council states that responsible genetic screening programmes must ensure that 'Participation in screening and follow-up tests must be based on an informed and free choice; supply and performance must respect patients' rights…' [17].

The respect for autonomy is a fundamental value in modern bioethics and is connected, historically, to the notion that individuals have an intrinsic value and dignity independent of specific attributes or contexts that confer worth [30]. 'To respect the autonomy of self-determining agents is to recognize them as entitled to determine their own destiny with due regard to their considered evaluations and view of the world. They must be accorded the moral right to have their own opinions and to act upon them (as long as those actions produce no moral violation).' [30]. In a clinical setting between the patient and medical doctor, this usually translates to the patient being free of coercion, being offered information about the intervention-of-interest and having the mental capacity to understand the information being communicated, and ultimately being able to provide free and informed consent [30]. Moreover, specifically in the context of genetic testing, a lot of emphasis has been placed on respecting the individuals' right to know or 'not to know' their genetic information. Indeed, the potential impact of genetic/genomic information for family members who have not been tested should not be underestimated.

However, the discussion of respect for autonomy of a patient in the context of a clinical encounter between a patient and a doctor may differ greatly from that in the context of a public health programme, such as genetic screening or vaccination [31]. For example, any measure taken to improve population health may offer little to each participating individual and may even come with a burden or risk for some [31]. Furthermore, for public health interventions, the actions may involve many (or mostly) healthy people and 'require something approaching certainty as to the benefits and possible side effects of an intervention' [31]. Regardless of the context, the genome-based intervention must be acceptable to the patient and/or to the target population and participation should be voluntary. Moreover, the classical challenge in public health of trying to balance out individual freedom with improved health outcomes for larger groups must, as always, be addressed.

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Inherently related to the previous criteria, questions that need to be answered before the introduction of GBIT include: *who* decides if the 'trade-off' between population gain and individual burden is acceptable? And, of course, *how* is the 'trade-off' assessment performed? Evidently, different stakeholders (patients, general public, health care professionals, and administrators) may have very different perspectives regarding the 'trade-off', and, as was discussed in the previous section, personal value judgments and other contextual issues will also affect the results, and this should be taken into account.

Furthermore, the content and way in which the necessary information is provided in both scenarios (i.e. doctor-patient in a clinical setting vs. public health programme addressed to an entire population) can vary greatly. Since we are discussing herein the introduction of GBIT into the public health system in general, it is essential that the necessary distinction between issues of autonomy in both circumstances be anticipated and that a framework be put into place for it to be respected appropriately in both circumstances. For example, more classical informed consent may be adequate for the clinical context and appropriate public education campaigns, and opt-out or opt-in schemes may be best for population-based programmes; these should be planned before GBIT are introduced into public health and monitored accordingly. In both contexts, improving genomic-based literacy for the public (and all stakeholders) and offering understandable and balanced information regarding the testing programmes will play a central role in allowing for fully informed consent [32]. Moreover, health-literacy can be viewed from a public health perspective as 'public health literacy' [33] of which GBIT-literacy may be considered one aspect. As such, it should be planned with great care. This planning should involve experts knowledgeable not only in the science of genetics and genomics, but also experts in the teaching and counselling of such information to individuals, families and larger target populations.

Appropriate Use of Resources

The offer of GBIT funded from public sources should be justified in the context of the overall healthcare budget.

The last element of the normative framework mentioned by the Health Council to responsibly assess screening programmes is defined as 'responsibility in terms of cost-effectiveness'. This is explained as 'the use of available resources in connection with and because of the programme must be clearly shown to be acceptable in terms of cost-effectiveness and justice.' The Health Council specifies that opportunity costs should also be taken in consideration and that 'it is important that the balance between the proceeds of a screening programme, in terms of health gain or other worthwhile courses of action for those affected, and the costs incurred comes down on the positive side.' [17].

There are 2 main aspects in this criterion: first, GBIT programmes, just like any other health intervention, need to be affordable in terms of overall spending relative to the size of the budget, be it the total health care budget or the more limited budget for screening/population-level interventions. This differs per country and is hardly ever explicitly stated. Second, GBIT programmes should offer value for money, that is, the extra health gain of a programme should justify the additional health care costs involved.

There are many forms of economic evaluation of health care programmes. Examples in the literature include cost-effectiveness analysis (CEA), cost-consequences analysis (CCA), cost-benefit analysis (CBA), and cost-utility analysis (CUA). In cost-effectiveness analysis the health gains are expressed in 'natural units', e.g. life-years gained, whereas in cost-utility analysis the health gains are expressed in terms of quality-adjusted life years (QALY's) gained. As an example, decision-making on the uptake of new provisions in the Netherlands has in recent years moved to a position where the maximum willingness to pay for a QALY ranges from 10,000 Euro for conditions characterized by a limited 'burden of disease' to a maximum of 80,000 Euro for conditions characterized by a very high 'burden of disease', e.g. expressed in terms of disability-adjusted life years lost [34]. The severity of the condition that is screened for in a screening programme thus plays a role in the willingness to pay for a QALY.

There is also a method from decision analysis for evaluating the value of additional (usually research) information in terms of reduced uncertainty about parameter values in HTAs. The expected value of perfect information is the maximum sum one is willing to pay to gain access to perfect information. For its use in health economics see Claxton and Sculpher [35]. Another aspect, referred to by the Health Council document as justice, is the role of equity considerations and the trade-offs that can be made between equity and efficiency in allocation of scarce resources. Equity can then either be defined as equity in access to care, equity in health care consumption or equity in health outcomes. As yet, there is no well-accepted methodology to systematically include these considerations in decision-making, but they should be addressed.

Yet another relevant issue to consider is that in the past 2 decades, very few economic evaluations concerning genetic testing services have been performed. The last 2 major English language reviews on the subject reported 63 analyses performed between 1990 and 2004, and 26 analyses performed from 2004–2009 [36, 37]. Whether the evaluation processes are prohibitive or not well elaborated or there has been a lack of interest in doing such research should be determined. Due to the importance of these evaluations, these studies should be facilitated and encouraged. Indeed, good quality data on efficacy are needed for cost-effectiveness analyses to be produced. Finally, although not specific to individual or general GBIT, the cost of performing all the analyses and setting-up criteria for each principle described above should also be calculated.

Conclusion and Discussion

The ultimate goal of this paper is to help in the process of discussing the important ethical aspects for the responsible introduction of GBIT into public health. We have outlined the 5 principals raised by the Health Council of the Netherlands in 2008 [17] for the responsible introduction of genetic screening, and we have discussed these aspects within the larger context of the introduction of GBIT. These 5 principles are:

(1) The introduction of GBIT into public health should be based on a solid scientific foundation. Furthermore, the quality of the various parts of the process should be controlled before introduction of the technology (analytic validity, clinical validity and cost) and throughout (clinical utility, cost) the period in which the GBIT are offered to the public.

(2) GBIT introduced into public health and financed by public funds should be focussed on significant health problems.

(3) The advantages of introducing and offering GBIT should outweigh the disadvantages. This includes not only medical aspects, but ethical, legal and social aspects as well.

(4) The autonomy of patients, and individuals in general, must be respected for the responsible introduction of GBIT into the public health system.

(5) The offer of GBIT funded from public sources should be justified in the context of the overall healthcare budget and in terms of value for money.

In highlighting these principles as the basis for the ethical discussion of the introduction of GBIT, we have un-derlined the difficulties and concerns that should be specifically addressed for each issue. Overarching, and so far unanswered, questions that are encountered for each principle are: (1) *Who* should and will be responsible for making a decision regarding criteria? And (2) *what* specific (sub)criteria should be followed? Although some countries have clearly established structures that coordinate the implementation of screening programmes, other countries lack such structures or lack coordinated efforts in implementation. To set up such a process, roles and responsibilities have to be specified with respect to defining the evaluation and decision-making criteria, examining whether these criteria are met for each specific situation (evaluation per se) and monitoring the whole process. Making use of the experiences gathered through the ACCE project, EuroGenTest, EGAPPNet, GeneDossiers, and the Genetic Test Registry will be useful in order to stimulate the development of assessment processes and the identification of clear roles and responsibilities in those assessments. As outlined herein, many organisations have contributed to the evolution of the field of PHG. Remaining efforts as to the definition of criteria should be mainly concerted efforts at the international level, whereas mapping out the main players and their respective responsibilities will require efforts at national levels. Initiatives in PHG, as mentioned at the beginning of the article, could identify the main players (including the public and patients) and their respective responsibilities in the implementation of GBIT. Once the main players and their respective responsibilities are mapped out, then the elaboration and/or gathering of existing criteria can be performed. HTA approaches and methods may play an important role in the process of evaluation of criteria.

We recognize that other publications have contributed valuable information and guidance on different levels and different aspects of genetics and genomics in health, which can then be useful for thinking about the responsible introduction of GBIT [38]. Furthermore, we are aware that other ethical frameworks exist to aid in the discussion and evaluation of public health policies and programmes [39]. We chose to use the criteria originally set up for the responsible introduction of genetic screening, since this context is the most similar to the context of the introduction of genome-based information and technologies, and it was a relatively well-known basis to begin the discussion. Furthermore, these criteria allow for a larger (macro level) view of the important issues as opposed to a more specific guideline on how to practically evaluate the ethical issues of a public health programme,

yet, they are not so theoretical that we lose focus of the actual tasks ahead. We also decided to use these principles borrowed from genetic screening as they allowed a large range of stakeholders to discuss ethical aspects of GBIT with some concrete idea of the possible applications of the interventions. We recognize that our initial discussion herein does not include the following work, which we propose should be conducted as the next steps in the discussion: (1) discuss further the links between each criteria, (2) conduct a systematic comparison of the criteria discussed herein with different existing ethical frameworks, and (3) frame this discussion based on the public health trias wheel. We also wish to point out that for the sake of clarity and brevity, we were not able to integrate more recent notions, including, but not limited to epigenomics, systems biology and information and communication technologies, which will be important aspects of PHG. Indeed, we are only beginning to understand common complex diseases, and forming a concrete vision for what PHG will mean in the future. Cesuroglu et al. [28] stated 'Clear examples of advancing the science of medicine and improving the effectiveness of healthcare using genome-based information can be expected to start to flourish in this decade, but will probably become more prominent in the period beyond the year 2020.' Hence, it will be important to incorporate the fields mentioned above when concrete examples of PHG initiatives become available in order to root this discussion in *public health genomics* and not in genetics and genomics.

Furthermore, once the need for more specific and tangible assessment becomes necessary, an ethical framework, such as that designed by ten Have et al. [39], may be very useful. This framework is a practical tool that guides the user through a set of questions and steps in order to ultimately perform a systematic ethical evaluation of a public health program.

Throughout this paper, we focussed on the responsible introduction of GBIT into the *public health* system. An important question remains: should the 5 principles discussed above also be applied to the private health sector wherein services are not funded by the state? This is a relevant question since presently genome testing is being offered directly to the public by private commercial companies (such as 23andMe), often completely bypassing the health care system and the intervention of a health care professional. Should these GBIT also be subject to the logic outlined herein for responsible introduction of interventions? We believe that of the 5 principles described above, at least the following 3 should definitely be applied in the private health care sector: ensuring a reliable and valid process of introduction and application of GBIT, the benefits should outweigh the disadvantages, and there should be respect for autonomy. The other 2 criteria involving the focus on an important/significant health problem and a responsible use of public resources are less relevant to the private sector, yet should still be considered in certain contexts. For example, if a private company sells a genome-based intervention for a condition that is not deemed 'important' yet consumers are willing to pay for it out of their own pocket, why should this not be allowed if public funds will not be used? The problem here lies with the potential downstream use of public resources; what happens if the results of a genome-based intervention sold by a private company lead the consumer to consult a doctor who *is* part of the public health system? Indeed, if privately sold genetic tests result in the (inappropriate) use of public health resources, then some form of economic evaluation should be conducted.

Finally, it is important to note that with a lack of concrete evidence at the moment, it is mostly *belief and conviction* that genomics will improve health that is leading the push for the introduction of GBIT into public health. How far should this belief take us without actual scientific, medical, health, and economic evidence? With a limited set of resources, the imperative to implement new technologies, such as genomics, into public health could divert necessary resources away from programmes and sectors that are providing health care benefits for the public right now and/or from those that simply work better (but may be less in vogue).

Moreover, as a community invested in the responsible use of genomics in public health, we may benefit from being more humble and sending out a clearer message regarding the potential use of genomics in public health. On the one hand, more and more articles and reports are now stating that the promise of genomic medicine remains unfulfilled [40, 41] or that we should be more 'realistic about the Public Health impact of Genomic Medicine' [42]. On the other hand, there still appears to be a great push for the introduction of genomics into health care; one could even call it a genome-hype [41] surrounding the subject. Knowing about this hype, and yet continuing this 'push' is, to a certain extent, irresponsible in itself. That is not to say that the introduction of genome-based interventions should be discouraged. However, the cart should not come before the horse, and for responsible introduction of GBIT, it must be based on sound evaluation and evidence. As things stand now, the translation process for common complex diseases is mostly halted at the

test development stage. Perhaps the way to go forward ethically is to take a step back and properly evaluate the genetic services presently offered in the clinic? For example, perhaps the next step that needs to be taken for the validation of a proposed framework (including the principles discussed herein) would be to test it, using a monogenic disease for which a test is already offered in the clinic. Indeed, the translation process should be balanced so as to not allow for 'premature translation' or letting new technologies get 'lost in translation' [43].

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