Title: Content analysis of informed consent for whole genome sequencing offered by direct-to-consumer genetic testing companies

Running title: Informed consent for consumer genome sequencing

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Abstract

Whole exome sequencing and whole genome sequencing have become increasingly available in the research and clinical settings and are now also being offered by direct-to-consumer genetic testing companies. This offer can be perceived as amplifying the already identified concerns regarding adequacy of informed consent for both whole exome/genome sequencing and the direct-to-consumer (DTC) genetic testing context. We performed a qualitative content analysis of websites of four companies offering whole exome/genome sequencing DTC regarding the following elements of informed consent: pre-test counselling, benefits and risks, and incidental findings. The analysis revealed concerns including the potential lack of pre-test counselling in three of the companies studied; missing relevant information in the risks and benefits sections; and potentially misleading information for consumers. Regarding incidental findings, only one company, which provides opportunistic screening, provides basic information about their management. In conclusion, some of the information (and related practices) present on the companies' webpages salient to the consent process are not adequate in reference to recommendations for informed consent for whole genome or exome sequencing in the clinical context. Requisite resources should be allocated to ensure that commercial companies are offering high throughput sequencing under responsible conditions, including an adequate consent process.

Key words: whole genome sequencing, whole exome sequencing, direct-to-consumer genetic testing, consumer genomics, informed consent

Introduction

Whole exome and genome sequencing applications

The relatively recent development of next generation sequencing (NGS) technologies has led to a significant decrease in the cost and time required to perform whole genome sequencing (WGS) and whole exome sequencing (WES) (i.e. the sequencing of only protein coding parts of the genome; for the purpose of this article, in which the high-through-put nature of NGS is most salient, both whole genome and whole exome sequencing may be denoted by 'WGS' or 'whole genome sequencing'). These technologies are more powerful and potentially cost-effective than previous sequencing technologies and have brought a shift in testing approach from the traditional way of testing only one or a few specific genes to obtaining the sequencing information from hundreds or even all the genetic variants in a genome (Wright et al. 2011).

To date, the use of genomic sequencing approaches has proved to be useful in both the research context and clinical context; for instance, in providing molecular diagnoses for Mendelian disorders (Yang et al. 2013), for disorders with complex phenotypic presentations such as intellectual disabilities, or neurological diseases (de Ligt et al. 2012; Martin et al. 2014), potentially enabling targeted therapeutic strategies in some cases (Salleh et al. 2013). WGS can also be used for disease risk predictions (Heo et al. 2013), preconceptional carrier testing (Chrystoja and Diamandis 2014) and prenatal testing (Carss et al. 2014). In the short to medium-term future, other applications of WGS in health care may materialize, including for newborn screening (Solomon et al. 2012), tissue matching (Wright et al. 2011) or screening of embryos (Harper et al. 2013). Despite these technical possibilities, it is important to note that there are still

concerns regarding the accuracy, interpretation of results, cost-effectiveness, as well as ethical issues (Dewey et al. 2014).

Given the relative novelty of NGS in the clinic and the resulting uncertainty related to implementation, the ethical concerns are numerous, and include but are not limited to issues related to the informed consent (IC) process, unsolicited findings management, opportunistic screening, secondary use of data, data management and storage, privacy and confidentiality, duty to re-contact patients (once new information arises), responsibility towards and communication with family members. All these outstanding issues currently, challenge the effective and responsible implementation of genome-based approaches in health management (Pinxten and Howard 2014) and need to be addressed. Herein we focus on the informed consent process in the more specific commercial context of direct-to-consumer high throughput sequencing, which overlap with many of the concerns related to the clinical context.

Direct-to-consumer genetic testing (DTC GT) companies

Relatively recently, whole genome sequencing services have also been advertised and offered directly to consumers by some companies. These private, for-profit companies operate outside of the conventional public health care system and advertise genetic tests directly to consumers predominantly via the Internet. However, companies are increasingly requiring consumers to contact a health care professional (HCP) in order to obtain a test and/or the test results (Howard and Borry 2012). This type of genetic test which '*are commissioned by the consumer but where a medical practitioner or health professional is involved in the provision of the service*' also fall in the scope of DTC genetic tests according to 'A Common Framework of Principles' on DTC genetic

testing issued by the Human Genetics Commission (UK) (Human Genetics Commission 2010).

The phenomenon of DTC GT, even before WGS was being offered in this context, has received a lot of attention regarding ethical issues, such as the questionable scientific validity and utility of the tests on offer (McGuire and Burke 2011), the adequacy of information provision and the informed consent procedure (Howard et al. 2010), the potential need for medical oversight and genetic counselling (Hogarth et al. 2008), the testing of children (Borry et al. 2009), the research activities conducted by DTC GT companies (Howard et al. 2010) and the potential burden on the health care system (McGuire and Burke 2011). The adequacy of legislations concerning the activities of DTC GT companies has also been discussed (Kalokairinou et al. 2014). Considering the vast amount of genomic data obtained in WGS as well as difficulties in being able to properly assess or interpret each variant, one could consider that many, if not all, of the ethical, legal and social implications previously addressed at the DTC GT field are amplified in the context of companies offering WGS directly to consumers. As such, this particular type of DTC GT deserves further attention and study.

Informed consent for WGS

Informed consent is a key component of any responsible intervention in research involving humans or healthcare provision, including the offer of genetic testing (for health purposes), regardless of whether it is provided via a HCP in the conventional health care system or by a private for-profit company. Informed consent constitutes a voluntary permission given by a competent patient to have the test performed after (s)he has been duly informed about the procedure and purpose of the test, including the

results it will generate, as well as the potential risks and benefits. The Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes states that '*A genetic test may only be carried out after the person concerned has given free and informed consent to it'*. The document also outlines that the consent should be documented and it may be freely withdrawn at any time (Council of Europe 2008). Furthermore, the European Convention on Human Rights and Biomedicine[a], specifies in Article 5 that a person consenting to an intervention in the health field '*shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks.'* (Council of Europe 1997) Moreover, the importance of informed consent has been recognized in the recently accepted version of the Proposal for a Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices[b]:

[a] The Convention on Human Rights and Biomedicine is only legally binding for those countries who have signed and ratified it (http://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164/signatures?p_auth=GV537xJS). While, not all countries have done this (e.g. Germany, UK, Belgium, etc.), the Convention nonetheless, remains a very important moral benchmark and/or ethical framework in Biomedicine for all countries.

[b] On 15 June 2016 the European Parliament and the Council of Europe have agreed on the draft of the proposal, which will undergo legal-linguistic review and will be adopted by the European Parliament and the Council of Europe, probably at the end of this year. The rules of the regulation will apply 5 years after its publication (http://ec.europa.eu/growth/tools-databases/newsroom/cf/itemdetail.cfm?item_id=8863&lang=en).

> *'Member States shall ensure that where a genetic test is used on individuals, in the context of healthcare as defined in Article 3(a) of Directive 2011/24/EU and for the medical purpose of diagnostics, improvement of treatments, predictive or prenatal testing, the individual being tested or, where applicable, his or her legally designated representative is provided with relevant information on the nature, the significance and the implications of the genetic test, as appropriate.'* (Article 4a) (Council of the European Union 2016)

In the context of WGS, appropriate provision of information about the testing seems to be a particular challenge considering the complexity of the technology used, the volume of information generated, and the wide-ranging nature of findings. The entire sequence of the genome may provide an unprecedented amount of information of various clinical significance and predictive value, which may change with time (Wright et al. 2011). Furthermore, these results may have profound implications for the (psychological) health (care) and reproductive choices of a patient as well as his or her relatives.

Given these challenges, various authors have proposed models for IC and attempted to determine the necessary elements of an adequate IC process for WGS (ACMG Board of Directors 2013; Ayuso et al. 2013; Bunnik et al. 2013, 2014; Jamal et al. 2013; Henderson et al. 2014). Ayuso *et al.* (2013) specifically analysed articles from the academic literature and guidelines from 'societies' concerning IC for genetic studies and WGS. The authors found a high level of consistency among the documents reviewed and proposed a minimum list of information that should be addressed in IC for WGS: the scope of the test, a description of the test process, the possible benefits and risks, the availability of alternative tests, the voluntary nature of the test, the possibility

of refusal, the future use of the samples and the data, the confidentiality of the outcomes and management of incidental findings (IF) (Ayuso et al. 2013). Moreover, the authors found that the majority of the documents they studied suggest that IC for whole genome sequencing should be given explicitly (Ayuso et al. 2013) (this is understood as being relevant in a context where WGS is only one of the tests being used for diagnosing a disorder, and so an explicit consent should be obtained specifically for the WGS).

Jamal and co-authors (2013) also developed *"core elements"* of content and procedures for informed consent, data sharing, and results management for whole exome sequencing; even though conducted in a research context, the former overlap with core elements of informed consent identified by Ayuso et al. for the clinical context (Jamal et al. 2013). Furthermore, Jamal and co-authors used the core elements to evaluate the practices and policies of 6 U.S. CLIA- certified labs offering clinical exome sequencing, including the presence of the suggested elements in informed consent forms and their readability. The analysis revealed that laboratory policies vary widely, indicating that developing standards for best practices among exome sequencing providers may be beneficial.

Similarly, Henderson *et al.* (2014) (Henderson et al. 2014) have analysed IC forms used in nine NIH-funded studies aiming to develop best practices for clinical applications of WGS. On the basis of the analysis the authors have proposed recommendations, which '*can serve as a checklist to help identify gaps and resolve ambiguities in consent forms for sequencing*', and which are related to the issues outlined by Ayuso *et al.* (2013). For example, Henderson *et al.* suggest describing the meaning of positive, negative and uncertain results, outlining the role of CLIA (Clinical Laboratory Improvement

Amendments) certification, and stating the likelihood of obtaining incidental findings. Furthermore, IC forms for WGS have also been analysed in the context of cancer studies. The examination of these IC forms has revealed the tendency for using samples in other, unspecified types of studies and sharing data with other researchers (Allen and Foulkes 2011).

Furthermore, IC and the provision of information on company websites have been investigated in the context of DTC GT companies revealing the inadequacies of these practices (Howard et al. 2010; Lachance et al. 2010; Singleton et al. 2012). None of the studies, however, specifically addressed IC for WGS in the context of companies advertising or selling WGS directly to consumers. Therefore, herein we present an exploratory qualitative study of the information salient to the IC process, which is provided on websites of companies offering whole genome sequencing in the commercial direct-to-consumer context. In particular, we present information regarding the following elements salient to IC: 1) pre-test counselling, 2) expected benefits and possible risks; and 3) management of incidental findings. The information from company websites is then further contextualized and discussed against the backdrop of guidelines such as those from the Presidential Commission for the Study of Bioethical Issues (PCSBI) (Presidential Commission for the Study of Bioethical Issues 2013), recommendations for IC for WGS by Ayuso and colleagues (Ayuso et al. 2013), and the American College of Medical Genetics (ACMG) recommendations for the reporting of secondary findings (Green et al. 2013).

Methods

This study is an explorative qualitative analysis of the informed consent information for whole genome and/or whole exome sequencing offered by DTC companies. We use a broad concept of DTC, including companies that offer genetic testing without a HCP, as well as those that aim marketing directly at consumers, while requiring a physician's request to obtain the test. This approach is congruent with the scope of DTC GT given by the Human Genetics Commission, which included situations where '*tests are commissioned by the consumer but where a medical practitioner or health professional is involved in the provision of the service*' (Human Genetics Commission 2010).

The number and content of DTC genetic and genomic testing companies is often changing; this includes information about informed consent[c]. Against this background, and since no other academic article has addressed the specific issue of consent in the distinct context of WGS/WES, we opted for a non-exhaustive explorative qualitative study of a convenient and varied sample of company websites, which were selected between November 2013 and January 2014. Companies were identified through the academic literature (mostly via articles addressing DTC genetics), as well as with a general Internet search in English using the search engine Google and terms including

[c] Indeed, some companies' policies have already changed since our study, and as mentioned in the discussion, it is relevant that future studies return to these companies as well as include novel companies not addressed herein. For example, the version of Illumina's consent form analysed herein is not available online any more. For a copy of the form please contact the corresponding author.

225 ‘genetic test’, ‘direct to consumer’, ‘whole genome sequencing’ and ‘whole exome
226 sequencing’.

227 Our qualitative analysis is focused on the website sections and documents available
228 online that are presented by the companies with which consumers should agree and/or
229 sign in order to undertake the test. Specifically, these are the IC documents, statement of
230 consent, terms of service, terms and conditions, disclaimer and privacy policy (Table 1).

231 For the qualitative content analysis of the relevant documents on the websites, we build
232 on the study of Ayuso et al. (2013) and used the following elements of IC as the major
233 codes: 1) pre-test counselling, 2) expected benefits and possible risks; and 3)
234 management of incidental findings. These were underlined as being particularly
235 important and relevant for IC in the context of WGS (Ayuso et al. 2013). The website
236 documents were accessed in October 2014. The documents were perused for all material
237 relevant to the codes above and were organized under these headings initially by one
238 author (EN); these initial results were reviewed by a second author (HCH) and
239 disagreements were resolved until both agreed on the adequate organization. Final
240 tables including representative quotes were reviewed by EN, HCH and PB.

241 **Results**

242 **The DTC WGS companies identified and the studied website documents**

243 Four companies, Illumina, Gentle, Gene by Gene and Inneova, were identified for this
244 study. They offer WES and/or WGS as well as provide different types/scope of
245 data/results and analysis (e.g. carrier status, pharmacogenomics). The basic description
246 and information regarding these four companies are outlined in Table 1.

All the companies studied advertise their services directly to consumers on the Internet. However, some websites also contain sections dedicated to physicians, who are required to order the test, except for the company Gene By Gene's offer of research and consumer testing, for which the company does not require a HCP.

All companies' websites analysed provide at least one document and/or a section on the webpage that needs to be agreed to or signed in order to undertake the test (Table 1). Three companies have documents on their website with 'consent' in the title; meanwhile, Gene By Gene only has a 'Terms and Conditions' section of the website and specifies that in case of 'Clinical Genetic Testing' the physician has to obtain IC from the consumer; however it does not state whether this includes a physical document that must be signed by the consumer: '*Prior to placing an order, the ordering physician or genetic counselor is responsible for obtaining the informed consent from the patient whose sample is being sent for testing (…)*' (https://www.genebygene.com/pages/terms). Such a statement is not included in the section for 'Research and Consumer testing' in 'Terms and Conditions' of Gene by Gene (https://www.genebygene.com/pages/terms).

The results of the content analysis regarding the following elements of IC: pre-test counselling, benefits and risks as well as incidental findings are presented below and shown in tables 2-4.

Pre-test counselling

Only Illumina (seemingly) requires pre-test counselling as a condition for undertaking the test. In the IC form a consumer has to sign the following statements:

'*I have been offered the opportunity to ask questions and discuss with my healthcare provider the benefits and limitations of the test to be performed as indicated on the associated test request form. I have discussed with the medical practitioner ordering this test the reliability of positive or negative test results and the level of certainty that a positive test result for a given disease or condition serves as a predictor of that disease or condition.'* (http://res.illumina.com/documents/clinical/forms/form-test-req-undiagnosed-disease.pdf) [d]

Another company, Gentle, vaguely suggests some form of pre-test counselling to consumers in its IC section of the webpage: '*If you still have unanswered questions, be sure to ask us or your physician before you agree to take the DNA test being offered by us.'* (https://www.gentlelabs.com/consent?content_only=true). No information about pre-test counselling was found on the studied websites' sections of Gene by Gene and Inneova.

Benefits and risks

In the studied sections of the websites, all the companies provide general information about benefits and risks; however specific sections labelled 'Benefits' and 'Risks' are explicitly distinguished only in the IC document of Illumina and Gentle. More specific subthemes were identified within the subject Benefits and Risks (Table 3, in bold in

[d] At the time of submitting the article the link to this document was no longer functional. For a copy of the form please contact the corresponding author.

columns 2 and 3); these were used to classify the benefits and risks and the labels were derived and modified from the classification outlined by Ayuso *et al.*, 2013 (Ayuso et al. 2013).

Three companies outline that the results may indicate disease risks and predispositions (Table 3). Moreover, Illumina and Gentle state that test results may help to make more informed healthcare choices; Gentle adds that the knowledge from the testing may empower persons to make '*important life planning decisions*'. Furthermore, Gentle outlines as a benefit, gaining knowledge about one's carrier status, the possibility of adjusting drug therapy based on the genetic results, and gaining insight into one's ancestry. This company also mentions as a benefit the possibility of participating in research studies conducted by the company.

All the companies provide, at least, a general and/or short description of risks related to undertaking WGS (Table 3). The types of risks and concerns mentioned include the following: medical and physical risks, psychological risks, discrimination risks, and implications for family members. Implications for reproductive choices are mentioned only by one company, Inneova: '*I realize the possible far-reaching implications of the information obtained through predictive genetics testing in affecting my life choices as well as those of my relatives, children, and unborn children'* (http://www.inneova.com/contenu.php?page=terms.php).

Incidental findings and categorization of genetic information

Only one of the analysed companies, Illumina, directly addresses the issue of incidental findings (IF) in its IC form (Table 4). The company refers to the first version of the American College of Medical Genetics' (ACMG) recommendations for reporting of

incidental findings (2013) (Green et al. 2013) and together with the results of Undiagnosed Disease Test provides an incidental findings report that may contain information on some of 57 variants unrelated to the indication for testing. Meanwhile, in the consent form for Illumina's Predisposition Screen test the possible findings are categorized (into: childhood onset and adult onset; subcategories: medically actionable, not medically actionable, cancer, neurologic conditions) and the consumer has the possibility to opt out of some of them. Although Gentle does not mention IF, the company does emphasize that customers can choose to exclude any condition from the analysis: '*It is important to mention that you can choose to exclude any of the tests from the results before submitting your sample.*'

Discussion

Informed consent in the context of DTC WGS companies

The content analysis of DTC companies described herein has been conducted using some of the elements of IC for WGS in the clinical setting recommended by Ayuso *et al.* (2013) (Ayuso et al. 2013). It should be noted that there are significant differences between the offers of WGS in a 'traditional' clinical genetics context versus the commercial DTC setting, even if the latter involves a healthcare professional. As explained in the recent guideline issued by the Presidential Commission for the Study of Bioethical Issues (PCSBI): '*Clinicians owe stringent fiduciary duties to patients, which entail an obligation to act in furtherance of the patient's best interests. Non-clinician DTC providers have less stringent duties, including duties that might be limited or circumscribed by contract. Consumers should be made aware of these distinctions prior to consenting to undergo DTC testing.'* (p.103-104) (Presidential Commission for the

Study of Bioethical Issues 2013). Indeed, in the context of DTC companies the contract describing the conditions of the service is usually stated in terms of service to which a consumer has to agree prior to buying the test. However, if the purpose of the test is health-related, signing a contract cannot fully replace the function of IC, which aims, among others, to provide understandable and balanced information about the test (Bunnik et al. 2014). The tests included in this study are advertised as having (to some extent) a health-related purpose or as clinical tests, therefore, the presence of adequate IC in the studied DTC companies appears to be advisable.

Explicit informed consent and pre-test counselling

Explicit informed consent, which is recommended by Ayuso et al. (2013) for clinical WGS, may be defined as one for which '*Those who request consent must provide an explicit statement of the nature and purposes of a proposed course of action, its effects, risks and other features, to those whose consent is sought. Those who are asked to consent must show explicitly that they understand this information and agree to the proposal*' (Manson and O'Neill 2007). The process of explicit IC typically involves documents, signatures and formal statements (Manson and O'Neill 2007). Therefore, in this study we have focused on the documents or the section of the websites which the consumers have to agree to in order to be tested. However, in order to be genuinely informed consent should not be reduced to signing a document but rather through dialogue with a qualified HCP it should be ensured that the patient truly understands the information provided and is competent to make a choice (European Society of Human Genetics 2010).

Although all four companies provide some form of document addressing consent, only Illumina requires pre-test counselling understood as face-to-face consultation with a physician. In the other companies studied, most of the tests have to be ordered by the physician meaning that the consumer has to contact one in order to be tested. This, however, does not guarantee that adequate counselling takes place, given the concerns about the expertise in genetics and impartiality of the health care professionals (Howard and Borry 2012). Indeed, including a third party HCP in the process raises the question of who bears the (fundamental) ethical and legal responsibility for taking adequate consent? Of course, the HCP must adhere to the general medical code of conduct, but depending on her/his specialty, is (s)he aware of the specific guidelines for genetic testing?

Another important result that brings attention to the involvement of healthcare professionals in testing is a lack of involvement of a physician in undertaking the consumer test in Gene By Gene company. Although 'Terms and Conditions' state that the services listed in 'Research and Consumer Testing' section *'are not to be used to diagnose, prevent, or treat any condition or disease or to ascertain the state of health for any* individual' (https://www.genebygene.com/pages/terms), the description of the test suggests that it may provide health-related information: '*Sequencing of the exome can help identify variants that may be the genetic cause of a wide range of traits and conditions.'* (https://www.genebygene.com/pages/research#). Therefore, the involvement of a genetics professional seems to also be advisable in the case of 'Research and Consumer Testing' of Gene By Gene, which could prevent misinterpretation of the results or unnecessary follow-up care.

In addition, although the non-clinician DTC provider may have less stringent duties as stated by the PCSBI (Presidential Commission for the Study of Bioethical Issues 2013), the full role of a clinician in the DTC context still remains blurry. It is unknown to what extent physicians in the DTC context follow the same protocol as geneticist follow in the traditional health care system.

Another aspect related to informed consent is the potentially low readership of the consent documents analysed herein. It has already been shown that most of the consumers read very little of the terms of service agreements (e.g. when purchasing software (Maronick 2014) or accessing Wi-Fi). This may suggest that although the documents have the word 'consent' in the title and/or are aimed to be read and agreed to, the consumers are not acquainted with their content. This issue requires further analysis to assess the accessibility and readability of such documents.

Information about benefits and risks

The content analysis of the sections of companies' websites reveals that the information regarding possible risks and benefits is scarce, general and omits some relevant elements such as description of the implications for the reproductive choices, which has been suggested by the recommendations for IC for WGS by Ayuso and colleagues (Ayuso et al. 2013). Furthermore, some of the outlined information about benefits may be misleading such as regarding the possibility to participate in research studies (Table 3), which, in fact, does not necessarily benefit participants *per se* and is associated with various risks. Similarly, knowing the information about the carrier status is mentioned as a benefit in Gentle's IC website section, but the implications for reproductive choices of having this knowledge are not described (Table 3). What is more, the information

provided in the documents that need to be signed differs from the information placed in other sections of the website, which seem to be more encouraging about the possible results. For example, in the 'Why do a genetic test?' section of the Inneova website they state that:

> *'The objective of predictive genetics testing from Inneova™ is to determine each person's specific genetic features – and notably vulnerabilities – in order to allow highly-qualified practitioners in anti-aging and preventive medicine identify appropriate measures designed to counter-balance weaknesses and maintain good health, as well as help prevent the development of specific diseases or at least to delay their onset'* (http://www.inneova.com/tout.php?page=prev_why.php&menu=2).

This may be misleading as consumers may not read the sections 'Terms of Service' or 'Terms and Conditions' (Howard et al. 2010), but rather take the decisions based on the information available on the main webpages. Finally, the content of the risks' sections in the documents of Inneova and Gene By Gene could suggest that they were designed or written more in a way to protect the company from any liability rather than to explain and inform about potential disadvantages, e.g. '*I agree that ICL (…) assumes no liability for any stress, strain, hardship, adverse medical condition, financial loss, or other circumstances that I may suffer as a result of the receipt or reference to any predictive genetics test results and/or interpretations thereof supplied to me by ICL'* (http://www.inneova.com/contenu.php?page=terms.php).

Some of the findings presented herein are in line with the results of the study of Singleton *et al*, 2012 on informed choice in DTC-GT companies, which focuses on the

websites of the DTC GT companies containing consumer-focused content excluding terms and conditions and privacy statements, therefore being to some extent complementary to this study. Singleton *et al.* found that the amount of information describing benefits outweighed risks statements and that the websites present conflicting information stating that the tests can help to prevent diseases, simultaneously giving information that the test cannot be used for diagnosis or treatment (Singleton et al. 2012). Similarly, Skirton et. al have found that misleading, conflicting or incomplete information was present on the websites of DTC companies offering non-invasive prenatal testing (Skirton et al. 2015).

Incidental/secondary findings

The last, but not the least element of IC analysed in this study is the management of incidental findings. The term 'incidental findings' refers to '*results that are outside the original purpose for which a test or procedure was conducted*' (Presidential Commission for the Study of Bioethical Issues 2013), while secondary findings are results being sought deliberately because of the recommendations of an expert body as it has been defined by the PCSBI in the report on incidental and secondary findings (Presidential Commission for the Study of Bioethical Issues 2013). The issue of incidental and secondary findings appears particularly relevant in the context of WGS generating vast amount of data for analysis (Burke et al. 2013). Therefore, this topic has been discussed at great length and various expert societies have addressed it in recommendations. The PCSBI emphasizes the role of IC, and for the particular context of DTC companies suggests that the providers should develop adequate procedures to manage IF and provide consumers with understandable materials explaining these

procedures (Presidential Commission for Study of Bioethical Issues 2014). The American College of Medical Genetics (ACMG) also has issued recommendations for the reporting of secondary findings (although they use the term incidental findings, this is misleading since what they describe is opportunistic screening and not the strictly 'unsolicited' findings as described above) in WGS (Green et al. 2013). This policy statement of the ACMG suggests that secondary findings concerning 24 indicated conditions (related to 56 gene variants affecting function) should be sought and reported, however the patient may refuse the analysis of some of these genes if they are unrelated to the indication for testing, which should be done during the process of IC (Green et al. 2013; ACMG Board of Directors 2014). In contrast, the recommendations of the European Society of Human Genetic which address incidental findings do not provide a specific list of reportable conditions but rather suggest narrowing the scope of the sequence analysis and developing guidelines and protocols (van El et al. 2013) in order to reduce the chances of encountering IF all together. Finally, some authors propose models of stratification of information derived from WGS including incidental/secondary findings which will help the discussion with, and the decision-making by the patient (Berg et al. 2011; Ayuso et al. 2013).

Only one company out of the four studied addresses the issue of incidental/secondary findings and provides a report on IF complying with the recommendations of ACMG (Green et al. 2013) (hence also conducting opportunistic screening). However, the company does not indicate in the informed consent form whether the consumer has an opportunity to opt out of the analysis of some of the genes listed by the ACMG. Furthermore, regarding the primer issued by the PCSBI on IF (Presidential Commission for the Study of Bioethical Issues 2013) for DTC as well as the recent update of the

recommendations for reporting secondary findings in genome-scale sequencing (ACMG Board of Directors 2014) the term 'incidental findings' used by Illumina is not consistent with the definition suggested by the PCSBI and should be replaced by the term 'secondary findings' in order to comply with the guidelines mentioned. Nevertheless, in the IC for Undiagnosed Disease Test Illumina seems to implement the recommendation included in the mentioned document for DTC providers, which are to prepare a plan for the management of incidental and secondary findings and to provide easily accessible information for consumers about this procedure.

The IC form for Illumina's Predisposition Screen test introduces categories of genetic information, which consumer may choose not to receive exercising his/her 'right not to know' some of the medical information. The categories of genetic information introduced by Illumina are to some extent in line to some to those suggested by Ayuso *et al.* (2013) as they arrange the conditions according to the time of onset and medical actionability facilitating the choice of consumers (Ayuso et al. 2013).

Conclusions

Concerning the elements studied herein the consent forms and documents on companies' websites do not appear to fulfil the requirements for genuinely explicit and informed consent for WGS in the clinic as suggested by Ayuso et al. (2013). This highlights the present need to develop and implement 'best practices' for the DTC GT context with regard to IC and the provision of information about testing being offered. Moreover, the specific context of the commercial DTC GT companies which involve healthcare professionals could benefit from developing guidelines that specifically address this practice.

This explorative qualitative study has some limitations. Since it considers a small and convenient sample of DTC WGS/WES companies' and a subset of their written policies, it does not provide an exhaustive overview of all companies, their practices and associated ethical issues involved in the consent process. Indeed, we stress that the goal of this article is not meant to be an exhaustive, or generalizable (in a quantitative statistical way) analysis of DTC WGS companies, but rather a qualitative exploration of the activities that exist with respect to consent. Moreover, information provided on other pages of companies' websites not analysed herein may also be relevant to IC process, which requires further investigation. Furthermore, other information such as that related to storage and future use of consumers' samples and data pertain to IC and their presence in the process of IC in DTC companies also needs to be discussed. Finally, it is important to note that the nature of the DTC genetic and genomic testing market is very dynamic and the practices of companies are continuously evolving, thus it is important to monitor and continue to study and reflect on these activities.

In conclusion, we acknowledge that informed consent is just one of the elements related to the ethical issues around WGS. Its adequacy may not resolve the other ethical issues related to the companies that offer WGS, however, as stakeholders in genetics, we should expect and aim to support and provide an adequately informed consent process in order to respect individuals in their health-related decisions..

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Conflict of Interest Statement

The authors declare no conflict of interest.

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