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Review

Dynamic-informed consent: A potential solution for ethical dilemmas in population sequencing initiatives



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ABSTRACT

While the majority of population-level genome sequencing initiatives claim to follow the principles of informed consent, the requirements for informed consent have not been well defined in this context. In fact, the implementation of informed consent differs greatly across these initiatives - spanning broad consent, blanket consent, and tiered consent among others. As such, this calls for an investigation into the requirements for consent to be “informed” in the context of population genomics. One particular strategy that claims to be fully informed and to continuously engage participants is called “dynamic consent”. Dynamic consent is based on a personalised communication platform that aims to facilitate the consent process. It is oriented to support continuous two-way communication between researchers and participants. In this paper, we analyze the requirements of informed consent in the context of population genomics, review various current implementations of dynamic consent, assess whether they fulfill the requirement of informed consent, and, in turn, enable participants to make autonomous and informed choices on whether or not to participate in research projects.

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Contents

1. Introduction	914
Informed consent	914
2.1. Definition of informed consent	914
2.2. Population genomics context	915
2.3. Dynamic-informed consent	915
3. Dynamic consent	916
3.1. Different implementations	916
4. Limitations and alternatives to consent	917
5. Summary and outlook	919
Authors contribution	920
Conflict of interest	920
Acknowledgment	920
References	920

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1. Introduction

Population genomics projects are population-scale genome sequencing initiatives that aim to 1) understand genomic variation in a population and 2) identify variants that lead to disease, with the ultimate goal of supporting precision medicine [1]. The process requires the collection, storage, sharing, and analysis of DNA samples from large numbers of participants (often thousands of individuals or more), as well as the dissemination of findings back to the participants. For instance, China's precision medicine initiative is one of the most ambitious large-scale population genomics projects. It aims to generate 100 million whole human genome sequences to refine the diagnosis of various diseases and develop targeted treatments [2]. The All of Us Research Program in the United States is another project that aims to collect a large cohort of 1 million people or more, with the goal of speeding up health research breakthroughs [3] (refer to [2] for a survey on population genomic projects).

Population genomics initiatives raise new opportunities, but also challenges, related to informed consent and to the return of individual findings back to research participants [4]. Although the majority of these initiatives claim to follow the principles of informed consent [5], its requirements in the context of population genomics have not been well defined. For instance, the implementation of informed consent differs greatly across these initiatives, relying upon notions of broad consent [6], tiered consent [7], open consent [8] and dynamic consent [9], among others. Similarly, many policies have been suggested regarding the return of individual findings back to participants. Population genomics initiatives differ on whether they should request participants to consent to the return of personalized findings and, when they do, they tend to return only findings that are actionable (i.e., findings that suggest meaningful interventions or preventative strategies can be instituted).

Many implementations of informed consent, along with policies regarding the return of individualized findings, have been criticized for not being fully informed, and for excluding the community from the discussion. In fact, there is a growing push to empower members of the community with the ability to indicate which specific study they agree to participate in, as well as which individual results they agree to receive [4,10,11]. However, it is questionable if participants can exert real control in highly complex big data settings (particularly regarding who uses their data and for what purposes). As large population genomics projects are updated continuously, shared widely and maintained indefinitely, informed consent ceases to be a single contract tied to a well-defined study. Rather, it may be better to characterize it as a dynamic long-term engagement plan between the data holder and the participant. In this respect, it is important to explore how participants can maintain meaningful control over the increasing volumes of data in this dynamic environment, and to identify the **requirements** for consent to be informed in this context.

Dynamic consent is a strategy that is oriented to involve participants, support the principle of informed consent, and solve the stationary aspect of consent. It is designed to support personalized consent via a technological construct at its base in the form of a communication platform. And it is upon this construct that it aims to facilitate the consent process; specifically by establishing a continuous two-way communication between investigators and participants [9].

In this paper, we aim to 1) characterize how moving from a stationary to a dynamic consent framework affects the requirement of informed consent and 2) appraise whether the modern implementations of dynamic consent satisfy the requirements of informed consent. The specific contributions of the paper are:

- (i) An investigation of the necessary requirements for achieving an “informed consent” in the dynamic context of population genomics. Requirements that are necessary, so that subjects can make autonomous and informed choices on whether or not to participate in research projects, and
- (ii) An assessment of whether the different implementations of “dynamic consent” in population genomics projects satisfy the identified requirements.

The paper is organized as follows: Section 2 defines informed consent in general and then presents the necessary requirements for realising an informed consent in the context of population genomics. Section 3 reviews the various implementations of dynamic consent and assesses whether they realize the identified requirements. Section 4 presents the limitations in adopting the identified requirement of informed consent. The paper concludes with directions for future research in Section 5.

Informed consent

Informed consent is considered an ethically viable way to conduct scientific research [12,13]. Fundamentally, it is a formal agreement that specifies the purpose for which information will be collected and used, how long the data will be retained, how it will be protected, who it will be shared with, and how participants can withdraw from the study [14,15]. The role of informed consent is to allow participants to make informed choices, as well as to safeguard trust in research (and medical) practice. It builds on the Declaration of Helsinki, which provides an ethical practice for human experimentation [16].

In the following subsection, we review the necessary pillars of informed consent, and then we analyze the requirements for informed consent in the population genomics context.

2.1. Definition of informed consent

The notion of informed consent has evolved over time; however, as stated by Dankar and colleagues [4], the modern definition of the term hinges primarily on three constructs: i) study information, ii) participants' comprehension and understanding, and iii) voluntariness. First, the pillar of ‘information’ states that it is vital to disclose all information about a study to the participants. Further, all risks need to be divulged, regardless of the effect they may have on the participant's willingness to participate in the study [12,16–21]. The second construct, ‘comprehension’, evaluates the mental capacity of participants and their ability to fully understand and process the information communicated to them by the researchers (including the risks that could arise from sharing their personal data with research institutions and the benefits to the society that can result from their participation [22,23]). It has also been suggested that comprehension and information are related, as comprehension measures how well an individual is able to grasp the information that is provided to them in the first pillar [4]. Third, ‘voluntariness’ emphasizes the importance of a participants' consent to be voluntary. In this respect, voluntariness not only includes the act of joining a research study, but also the act of withdrawing from it.

In summary, informed consent is “the full disclosure of the nature of the research and the participant's involvement, adequate comprehension on the part of the potential participant, and the participant's voluntary choice to participate” [4].

Many scholars have cast doubts on the ability of participants to exert control in complex big data scenarios. As a result, ‘non-dynamic’ forms of consent have been introduced in the big data

context, such as broad and blanket consents. Broad consent is a process by which participants consent to the use of their samples and data in a broad range of future studies, subject to predefined restrictions [6]. It has been promoted by the recent revision of the Common Rule in the United States to ensure the availability of data for research [24]. Blanket consent, which is a consent on all future uses of one's data and samples, without any restrictions, has also been proposed to maximize the availability of data and samples with no restrictions on future usage (for more information on the broad and blanket consents, the reader is referred to [25]). Still, both mechanisms have been criticized for limiting the autonomy of participants and for not being truly informed [9,14,26,27]. In fact, genomic data presents new privacy concerns that are difficult to deal with [22,23]. As indicated in [28], it is highly distinguishable (30 to 80 Single Nucleotide Polymorphisms (SNPs) could uniquely identify an individual) and very stable [23]. It provides sensitive information about genetic conditions and predispositions to certain diseases (e.g., breast cancer, Alzheimer's disease, and mental disorders). If breached, such information may be stigmatizing to participants and may be used against individuals in areas such as employment and insurance opportunities, even if these pre-dispositions never materialize. In addition, genetic data provides information about the sequenced individuals, as well as their ancestors, siblings and offspring.

Given these challenges, and the potential intrusions that genomic data can support if breached, participant education and empowerment are important to the long-term success of genetic research. Behavioral psychology research strongly suggests that empowering research participants establishes trust and approval and results in greater participation [20–22]. Along these lines, calls for participants' empowerment in genomic research are increasing [31] through calls to the return to the principles of informed consent [32]. But what is informed consent in the context of population genomics? How can we satisfy the three pillars of information, comprehension and voluntariness in this population genomics context? In Section 2.3, we focus on answering these questions, but first, Section 2.2 examines the particularities of population genomics initiatives.

2.2. Population genomics context

Population-scale sequencing initiatives may pave the way for precision medicine. Their aim is to improve genetic discoveries through research, and use it to develop targeted therapeutics in the clinical and population health setting, thus diluting the boundaries between research and clinical practice [32]. This new reality affects how data is captured and analyzed, and how the generated knowledge is translated into research, health policy, and, ultimately, medical practice [5].

In general, participants provide information and biological samples. These samples are sequenced and sequence variants are generated and integrated with the information gathered from participants and associated medical records. The results are then fed back to physicians and public health officials to help them base clinical and policy decisions on the information returned to them.

The consent of the participants is essential, at least, at three points in the data lifecycle: 1) consent to participate in the database, 2) consent to participate in research studies, and 3) consent for return of individual level data (individually interpreted genomic information or raw sequencing data).

The first instance (Consent 1) allows participants to consent to providing their biological data and participating in the database. The second (consent 2) allows them to record their choices related to sharing the collected samples/data with investigators. The current consent processes combines these two instances into one consent taken during sample collection, rendering the consent process static

[33], and requiring all future data usages to be specified at the time of the initial consent. The current process also requires all information to be conveyed to participants at the time of consent to ensure that their consent is truly informed (i.e., through the program's educational program). There are many issues with such a process, for instance, genomics is a difficult subject to comprehend, and humans tend to absorb limited information at any one time. Moreover, it is a continuously evolving subject (as are the risks and benefits of using the associated data). This necessitates guardianship from the data holders over issues not declared in the consent (which may go against the purpose of informed consent). These, and other issues, will be the focus of our discussion in the next section.

The third consent instance (Consent 3) attempts to capture the informed choices of participants regarding what information should be returned back to them and/or to capture their decisions regarding whether these findings can be accessed by third parties, such as family members, public health agencies or care providers. This consent is usually taken around the time of sample collection. Among the issues to be considered on this front is the potential psychological harm that could affect the participants from learning about a potentially threatening result, weighed against the benefits of learning it (i.e., early detection and/or potential treatment). Another issue for consideration, is if individuals agree to have their results returned in a clinical context, then the information would be put into their medical record and could be considered a pre-existing condition, which may be problematic. In the US for example, individuals are protected from discrimination on such information through legislation, the Affordable Care Act, and the Americans with Disabilities Act, but if any of these is stricken down, it would create an opportunity for using this information to discriminate. Specifically, the information could be used to adjust premiums for health insurance. The current recommendations governing the return of individual results to participants are usually aligned with returning only "clinically actionable" results, that is, results that are considered scientifically valid and that enable an intervention or preventive measure with an anticipated beneficial result for the individual [2]. These recommendations have been criticized for excluding the participants (and the community in general) from the discussion and for limiting their choices to within this pre-specified set of recommendations [29].

2.3. Dynamic-informed consent

Population genomics databases can contain a large amount of data from a wide variety of sources (e.g., data from biobanks, electronic medical records, and general behavior) and can be updated with new information over time. These databases may be retained for indefinite periods of time, may be used for a wide range of investigations, or to consolidate medical decisions. This requires shifting our view from the classical time-tied consent into a long-term social contract that requires long-term involvement from participants [4]. In this modern context, it is not feasible to anticipate all future uses of the data at any particular point in time (including at the time of collection). Thus, any pre-defined set of future uses is unlikely to be comprehensive, and could act against the exploratory nature of modern biomedical research [9,34].

As such, we need to start a discussion about the necessary requirements for consent (to be considered truly informed) in the context of population genomics. Specifically, what do the pillars of information, comprehension, and voluntariness impose in this modern context? (in what follows, unless otherwise specified, "consent" refers to all the instances described in the previous section, thus a "consent requirement" is a requirement that applies to all consent instances 1, 2 and 3).

As discussed earlier, consent issues in population genomics revolve around the informed choices of participants regarding

sharing data about them for research purposes, regarding what genetic findings to return [33,35], and their decisions regarding whether these findings can be distributed or accessed by third parties. The ‘**voluntariness**’ construct emphasizes the necessity of a participant’s consent to be fully deliberate, as a way to achieve participants’ *autonomy*. The ‘**information**’ and ‘**comprehension**’ constructs of informed consent impose the inclusion of a *well-designed education and assessment component* to ensure that all information related to the sharing and return of data is conveyed and understood by participants. Specifically:

- (i) Genomics is a difficult subject to comprehend, thus, a significant amount of dedication is required from participants to attain the background knowledge needed to understand genomic data and the interpretations based on such data. This necessitates the design of a *well-planned* education program. In other words, such a program should include all necessary information in a user friendly and organized manner.
- (ii) As genomic data, and what it reveals about us, is in flux, it is not possible to require all consent issues to be defined at the time of sample collection (i.e. to be incorporated within Consent 1). Thus, it is necessary that the education program be *dynamic and extensible*. This allows consent documents to be tied to events in real-time, as they occur in the data life cycle. Thus, for example, as new information is generated (e.g., information that changes a variant’s status from one of unknown significance to clinically actionable), additional educational programs and consent documents can be created to allow participants to decide on issues related to it (e.g., if they want to receive information about the variant and/or to allow that information to be transmitted to their care providers).
- (iii) To accommodate different levels of literacy and aptitude, the education program should strive to educate and empower participants at their own capacity without overloading them (since individuals can only absorb so much information at any one time). As such, the educational material should be provided to participants for them to complete at their *own pace*, and as the need arises.
- (iv) To ensure proper comprehension of such a complex subject, a *well-designed assessment* program should also be implemented (in all consent instances 1, 2 and 3). Such a program needs to measure participants’ readiness for consent through the valuation of information comprehension. Only then can consent be fully voluntary. Such a program should run in parallel with the education program, and thus be *ynamically* tied to it.
- (v) Regarding Consent 2, the voluntariness construct should ensure autonomy of the participants in participating or opting out of individual studies at their will. In other words, participants should be allowed the opportunity to accept or refuse participation in every research study that matches their criteria. This, however, implies continuous (and possibly full-time) engagement and dedication from participants. Such a process may be overwhelming to most, and may act contrary to the goal of autonomy. To be able to accommodate different preferences and achieve real autonomy, it makes sense to enable some *self-tailored consent processes*, where participants can decide on the level of engagement they are willing to commit to. Thus, participants can opt to consent to every single study, consent to certain research topics, or offer a broad or open consent.
- (vi) Related to the above point, when participants match the criteria for a specific research study, *additional comprehension and assessment material* should be provided (as part of

consent 2). Such material should be designed to enable them to consciously accept or decline participation. Thus, researchers should update or include new consent documents whenever consent for a new study, or significant feedback from participants, is required. As such, participants would be able to respond or modify their consent at their convenience.

- (vii) Consent revocation is an essential part of the ‘voluntariness’ construct. The authors in [36,37] argue that as consent grants an individual the right to decide when and how to use their data, it should also provide them with the opportunity to change (or withdraw) their consent. Traditionally, withdrawing from a study an individual consented to was a straightforward process. Conversely, as current data is re-used and shared with multiple research organizations over indefinite periods of time, it is complicating the issue of consent revocation significantly. Current best practices recommend that any samples collected from the individual wishing to withdraw from the study be discarded, and that medical data no longer be used. However, previously shared samples and data do not necessarily need to be revoked [15].

At the same time, it should be recognized that most perspectives on dynamic consent to date have focused on the perspective of the individual, as opposed to the group or community that they are a part of, which is critical in populations with special needs or rights (e.g., indigenous populations). Yet, there is nothing to actually prevent the dynamic-consent framework from supporting group-based decision making and there are examples of this approach playing out in practice, such as with the National Centre for Indigenous Genomics in Australia [38]. To support such a perspective, it would be necessary to institute a model of shared decision making, such that the will of a single individual might be overridden by the will of the group that they affiliate with. This approach, for instance, might be appropriate when consent is being sought from the members of the group. In the event that an individual disagrees with the group, it might be possible to enable this individual to make their own decision; however, this would need to be negotiated between the organization requesting (or supporting) the dynamic consent platform and the groups that they are supporting through it.

In Table 1, we summarize the above discussion by presenting the requirements that are necessary for a consent to be informed in the context of population genomics. We denote the consent frameworks that satisfy these requirements as **dynamic-informed consent** (as opposed to classical-informed consent). The requirements are classified into 3 categories: dynamic permissions, dynamic education, and dynamic preferences.

3. Dynamic consent

Dynamic consent is a personalised consent and communication platform that claims to facilitate biomedical research and the autonomy of participants. In what follows, we delve into five current biomedical research studies claiming to utilize dynamic consent, and examine the extent to which these studies address the aforementioned requirements of informed consent for population genomics.

3.1. Different implementations

Five projects cited to using dynamic consent are briefly described in Table 2 below, along with their respective practices related to information, comprehension and voluntariness. It is important to note that another common reference to dynamic

Table 1

The requirements for dynamic-informed consent in the context of population genomics' as defined over three categories: dynamic permissions, dynamic education, and dynamic preferences.

Category	Requirements
Dynamic Permissions	<ol style="list-style-type: none"> 1. Inclusion of an online portal to deliver information and allow participants to change permissions/preferences 2. Allowing participants the opportunity to accept or decline participation in new research opportunities/studies 3. Allowing participants to receive individually interpreted results (personal medical information) and/or raw sequence data
Dynamic Education	<ol style="list-style-type: none"> 1. Inclusion of a dynamic education component 2. Inclusion of a dynamic assessment component to ensure participant readiness to consent 3. Inclusion of timely information related to each research opportunity/study 4. Publishing general and up-to-date information related to research progress and outcomes
Dynamic Preferences	<ol style="list-style-type: none"> 1. Allowing participants to select between different levels of consent types (e.g.: broad consent, per-study consent, etc.) (consent 2). 2. Allowing participants to tailor the way they receive information 3. Allowing participants to select whether to receive individually interpreted medical results/raw sequence data. 4. Allowing participants to select what individually interpreted medical results/information they would like to receive 5. Allowing participants to convey individual results/information to selected third parties (without necessarily receiving the results themselves). 6. Allowing participants the autonomy to opt out of the database at anytime

consent is PEER¹ (Platform for Engaging Everyone Responsibly), however, as PEER is not a study, but rather a system to be used by research studies, we refrain from reviewing it.

Moving beyond the three pillars of informed consent, Table 3 below maps these five studies to the previously mentioned principles of dynamic-informed consent (with respect to population sequencing initiatives).

As can be seen in Table 3, of the five studies surveyed, all partially meet the requirements of dynamic-informed consent, although all of the studies have made some effort to fulfill the criteria. However, none of the studies are fully dynamically-informed in nature. While most of the studies satisfy some of the requirements for dynamic permissions, dynamic education, and dynamic preferences, a number of these areas are lacking. The major pitfalls of dynamic consent lie in two areas: the education of participants, and the participants' autonomy.

While all studies require participants to sign a consent form, only one (All of Us) actually verifies whether the participants understood the concepts communicated to them before signing the form. As researchers, it lies within our due diligence to ensure that participants truly understand and comprehend the risks of whatever it is they are consenting to, even if that means not all participants will be suitable for the research at hand [4].

The constructs of informed consent can only be fully achieved when participants have the required education to understand the implications of the ways data are collected, used, and re-used, as the only way avoid deception. For example, the U.S. Food and Drug Administration (FDA) reported that 10% of monitored clinical trials suffer from consent issues, including failure to re-consent as new information becomes available [45]. Another recent study by Seife [46] on hundreds of clinical trials over a 25 year period concluded that 53% of the problems identified were related to oversight of informed consent. These discrepancies led to dramatic results in 2016 [45] when a clinical trial did not seek re-consent after additional neurological side effects related to the drug under investigation emerged. Complications from the drug eventually led to the death of one participant. There are many other examples where the results of studies have been retracted after evidence related to inadequacy of informed consent emerged [47].

In addition to the issues with education and assessment, most of the studies herein rely exclusively on broad consent (in other words, Consent 2 is voided, and a broad consent is taken at sample

collection time). Therefore, participants are not granted the autonomy or self-determinism to choose which individual studies they would like their personal data to be included in. This, by definition, defeats the overall purpose of a dynamic consent model, and even obstructs the 'voluntariness' pillar of informed consent. Furthermore, none of the studies surveyed offered the participants the opportunity to select the level of consent that they desire. Participants were not allowed to change their levels of engagement, which is vital to a dynamic consent framework. While most of the studies enabled the participants to receive some form of interpreted individual medical results, only CHRIS and All of Us allowed participants to choose whether they wanted information returned to them, and in the case that they did, no study allowed them to select specifically what information they wished to receive. Utilizing a dynamic consent platform can make it easier to address these issues in autonomy, as well as educate and assess participants. Yet, this approach seems to go unused in the majority of the studies surveyed here.

In sum, while all of the above-mentioned studies partly meet the requirements of dynamic-informed consent, none can be considered fully dynamically informed. Large strides are still needed from researchers in the area of population genomics in order to ensure that participants are properly informed and fully autonomous when making their decisions to participate in research studies.

4. Limitations and alternatives to consent

Dynamic-informed consent grants participants control over their data. Dynamic education provides participants with educational material to complete at their *own pace* -and as the need arises- while the assessment program measures their readiness for consent. Dynamic permissions and dynamic preferences allow participants to select their level of involvement and the individual results they want to receive. However, multiple issues need to be considered prior to the adoption of dynamic-informed consent: (i) of dynamic-informed consent (and dynamic consents in general) is costly to implement and to maintain [48], (ii) participants enrolling in studies through online portals may not be diverse in terms of race and education level (as shown by recent studies) [49], (iii) dynamic-informed consent requires excessive time from participants to comprehend the totality of the data about them and to understand and consent for each study, this could lead to information overload, withdrawal, and it may lead to excessive self-protection behavior [5], moreover, (iv) it puts the responsibility of deciding on complex issue on the participants, who may not have the capacity to make decisions (because of time constraints

¹ Technology solution for collecting health data directly from individuals. The platform is designed to accommodate a variety of attitudes about data sharing and privacy and gives individuals complete control over how their data is shared for research.

Table 2
Use of three pillars of informed consent in current studies¹.

Study	Purpose of the study	Information	Comprehension	Voluntariness
RUDY (Rare and Undiag-nosed Diseases Study) [39]	Study of rare diseases headed by a research team at the University of Oxford. Aims to transform clinical care for participants through patient driven research.	A Patient Information Sheet contains all necessary study-related information, and is available on the study website and online portal. All participants are required to sign an informed consent form. Individually interpreted medical results are not returned to participants.	Information is conveyed through the Patient Information Sheet. Further questions can be asked through an email address or a phone number. No dynamic education/assessment is offered.	Participation is voluntary and participants can withdraw at any time without stating a reason. Participants are able to choose whether they would like to be contacted about partaking in future studies, or allowing for their bio-samples to be used in future research. However, participants cannot have different levels of consent engagement (i.e.: only per-study consent).
All of Us [40,41]	Effort to gather data from over one million people living in the United States, and create a public database, in order to accelerate research and improve health.	All study-related information is made available to the participants through a dynamic online portal. HIPAA-compliant consent forms are also utilized when dealing with covered entities. Individually interpreted medical results are not returned unless they are medically actionable. Individual-level data, such as genetic sequencing data and wearable sensor data, are available to participants without interpretation.	Information is conveyed via text and visual aids (in English and Spanish). These dynamic information modules are self-paced, and can be paused and repeated. Further clarification can be attained from trained staff at physical locations, or through a contact center. Also employ assessment via 'refresher loops', to guard against informedness-decay, which convey new research opportunities for subjects to participate in, as well as any necessary changes in the consent.	Enrollment is voluntary and participants are not pressured to decide within a timeframe. Participants have the ability to withdraw at any time, as well as unsubscribe from all communication aside from that which is required by the program. While information that participants receive is modifiable, the consent is not (i.e., only broad consent).
CHRIS (Cooperative Health Research in South Tyrol) [39]	Population-based longitudinal study to investigate the genetic and molecular basis of age-related common chronic conditions and their interaction with life style and environment in the general population.	All participants are required to sign an informed consent form online. An information sheet contains all necessary study-related information, and is available on the study's online portal in lay language. Yearly newsletter and updated information on the webpage. Participants can choose to receive individually interpreted medical results.	Information is conveyed through an information sheet (available in English, German, and Italian). A phone number and email address is also available for further information. Diverse media is also available to replace the information sheet. Participants can choose to discuss individually interpreted medical results with third parties.	Participation is completely voluntary. Participants also can withdraw anytime, with three different options (full withdrawal with data cancellation and sample destruction, withdrawal with continued use of data, and withdrawal with data used only in already running studies). Only broad consent is available; however, the consent is layered, and certain aspects of the broad consent is modifiable (access levels for what type of study can utilize the participant's data).
FarGen (Faroe Genome Project) [42,43]	Aim is to read the whole DNA (genome) of all Faroese people who want to participate, in order to develop a platform for genetic research of the Faroese population. Can enable improvements in the prevention and treatment of medical conditions.	All participants must read and sign the informed consent form. In addition, all necessary information regarding the project is conveyed in writing as well as orally by a trained project member. Individually interpreted results will be returned to participant if genes that can cause illness are identified, and there is certainty that such an illness can be prevented or treated.	Information is available in a dynamic fashion, in English or Faroese. Participants are required to have an oral information session by a trained member of the project. Participants can have a relative or somebody else present as they receive the oral information about the project. They are also entitled to a period of reflection before agreeing to participate. If individually interpreted results are returned, participants will receive a detailed explanation and genetic counselling.	Participation is voluntary. While participants cannot change or modify the type of consent given (i.e.: only broad consent) or communication preferences, participants can withdraw from the project at any time and request that their blood sample be disposed of without any explanation or reasons. Data that has already been used for a project will be kept. Any unused data will be deleted.
23andMe [44]	Project aims to gather genetic and self-reported data to discover genetic factors behind, and uncover connections among, diseases and traits, learn about human migration and population history through genetics, as well as understand how people react to their personal genetic information. Both commercial service as well as research project.	All information regarding the project is available online through a dynamic portal. Participants must sign an informed consent form to participate in research project (not necessary for commercial customers). Individually interpreted medical results are returned to commercial customers for a fee (paid genetic profiling, with or without participation research). Participants can choose what information they wish to have returned. Additional information about individually interpreted genetic results, genetic research, and/or research findings may be available to research participants.	Participants may contact a customer care center for answers to general questions, a Human Protection Administrator for questions regarding participants' rights, and a third party review board regarding any questions a participant may not wish to discuss with the project directly.	Participation is completely voluntary, however if commercial customer chose not to give consent, their genetic and self-reported information may still be used, as per privacy policy (implicit consent acts as broad consent); however, research participants asked for explicit consent to share individual-level information with approved third-party researchers, or partake in specific studies related to the participant's areas of interest. Research participants and commercial customers can modify how they receive information, and both can withdraw at any time. Any data that has already been entered into a study cannot be withdrawn, but data will not be included in studies that start more than 30 days after withdrawal.

¹ It should be noted that some conflicting information was found for certain studies in the cited sources. As such, best judgment was used to succinctly tabulate the information regarding informed consent and dynamic consent in Tables 2 and 3.

Table 3

Dynamic Nature of Current Studies. '✓' indicates a requirement that has been met, while '×' indicates a requirement that is lacking information in the study protocol / consent form or has not yet been met (as of the date of the manuscript).

		RUDY	All of Us	CHRIS	FarGen	23andMe
Dynamic Permissions	Online Portal	✓	✓	✓	×	✓
	Per-Study Consent	✓	×	×	✓	× ³
	Interpreted Results	×	✓	✓	✓	✓
Dynamic Education	Dynamic Education	×	✓	✓	✓	×
	Dynamic Assessment	×	✓	×	×	×
	Timely Research Information	×	✓	✓	×	✓
	Up-to-Date Research Progress	✓	✓	✓	×	×
Dynamic Preferences	Select Consent Level	×	×	×	×	×
	Tailored Information	✓	✓	✓	×	✓
	Choose to Receive Individual Results	×	×	✓	×	× ³
	Select Specific Individual Results	×	×	×	×	× ³
	Share Individual Results	×	×	✓	×	×
	Ability to Withdraw	✓	✓	✓	✓	✓

³ In Table 3 we refer to 23andMe purely as a research study. Once again, it is important to note that 23andMe is both a commercial service provider, as well as a research study (as mentioned in Table 2). While subjects participating in 23andMe's research study may be asked to consent to some studies, they have to give a broad consent on the 23andMe research project. Moreover, they cannot opt to receive individualized medical results (or choose what information they receive). On the other hand, commercial customers may choose to pay for returned individualized genetic results (fees commensurate with amount of information returned), but their consent is not explicitly needed for the research project, as per the company's policy ('signed' privacy policy acts as broad consent).

or low health literacy [50], lastly, (v) study funding may play a role in the fulfillment of dynamic-informed consent requirements, particularly, returning of actionable findings back to participants (consent 3) as it requires some form of counselling.

The main argument against informed consent (particularly from the perspective of a big data setting) is the excessive load passed onto participants. Some argue that it is asking participants more than they are able to deliver, as they have the responsibility to decide on complex issues they lack the time, or capacity, to fully comprehend and assess. The former director of the ACLU's Privacy and Technology Project went as far to express that, "in an age where understanding the implications of the ways data are collected is more difficult than ever, informed consent is not sufficient protection" [51]. A possible solution to this problem may be to allow the delegation of consent to a trusted third party of the participant's choice. In all cases, experts in education and psychology should assist in designing an engaging education and assessment program, so that participants will not make decisions in isolation.

On other fronts, alternatives to consent include protective legislation and anonymization. There are increasing calls among prominent scientists to do away with consent altogether and enforce the sharing of data for research purposes [52,53]. It is argued that individuals could then be protected by instating appropriate anti-discrimination laws (such as the 2008 US Genetic Information Non-discrimination Act GINA). The challenge associated with such regulations is that they require the difficult task of proving the occurrence of discrimination on the basis of the shared personal information [4].

Anonymization is another complementary/alternative technique to consent [54], it is defined as a "technique to prevent identification taking into account all the means reasonably likely to be used to identify a natural person" [12,55]. It is a process of information sanitization that produces data that cannot be linked back to its originators. However, the effectiveness of anonymization has been called into question as the possibility of re-identification through demographic, clinical, and genomic data has been demonstrated in various circumstances. For more information on this subject, readers are referred to [56, 61].

5. Summary and outlook

In this paper, we presented the requirements for an informed consent model in the context of population genomics, referred to as dynamic-informed consent. These are the necessary requirements for producing participants that are ready to make

autonomous and informed choices. We also reviewed five implementations of dynamic consent to assess their adherence to the dynamic-informed consent requirements. In summary, dynamic consent offers the opportunity to continuously inform participants about research protocols and support participants' autonomy and decision making. If designed properly, they can facilitate an ethical long-term relationship with participants as a serious partner in decisions related to their data. Of the five studies surveyed, all partially met the requirements of dynamic-informed consent. Major hurdles are still left to be overcome in the comprehension aspect (as only one out of the five studies made an explicit attempt to examine the comprehension of their participants), as well as the autonomy aspect. Nonetheless, all of the studies have made some effort to fulfill the criteria.

In other research initiatives, blockchain technology is being suggested (in similar contexts) to help re-enforce participants autonomy [57–59]. Blockchains can be used to record and manage all data access and modification transactions. The decentralized nature of the technology removes the reliance on biobanks and grants participants complete control over their consent data, as well as its modification and withdrawal, making them the real data owners. However, there are still several challenges associated with the application of blockchain technology. In particular, privacy issues arising from the broadcast property of blockchains still need to be addressed (as consent information may leak sensitive facts about participants. For more information readers are referred to [45,60].

For future consideration, moral issues arising from the 'immortal' nature of digital genomic data and the open timelines of dynamic consent should be examined. For example, participants' competency is likely to reduce over time (possibly due to aging), while the complexity of genetic studies is likely to increase. Thus, calling for a re-assessment of previously approved education levels, and questioning the overall adequacy of prior consents. Another example is related to the state of the dynamic consent after a participant has died. Can his offspring withdraw the consent? What about the research data? For now, these questions are left to be addressed by the different programs that are using dynamic consent (although some studies have begun to address these concerns such as Rudy and All of Us). Nonetheless, opting to consent on a per-study basis may help in overcoming some of these challenges.

The complexity of the biomedical data environment requires collaborative efforts to address the emerging ethical issues. Enhancing the granularity of informed consent is a step in the right

direction. Moreover, as precision medicine is removing the boundaries between research and clinical practice by employing discoveries made through genetic research and applying them in a clinical setting, innovative data governance models need to be implemented [32]. To address these issues, we are building an integrative dynamic-informed consent framework wherein all the processes needed for the implementation of precision medicine are represented. Such a framework would connect participants, researchers, and health professionals, while solving the needs of all parties involved, and keeping participants in control of the flow of information at all times (what information is returned to them and what information of theirs is shared with other selected third parties, and for what purpose). Such a framework allows for the creation of role-appropriate educational and assessment programs to enable the different stakeholders to better understand and act on the information given to them.

Authors contribution

FD was mainly responsible for the manuscript, she acquired the funding, designed the paper and contributed to the writing, reviewing and editing of the manuscript, MG contributed to the writing and editing of the manuscript, BM contributed to the writing, reviewing and editing of the manuscript, RB contributed to the design of the manuscript, SD contributed to the writing of the manuscript, KS contributed to the writing of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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