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The genomic data deficit: On the need to inform research subjects of the informational content of their genomic sequence data in consent for genomic research

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ABSTRACT

Research subject consent plays a significant role in the legitimation of genomic research in Europe – both ethically and legally. One key criterion for any consent to be legitimate is that the research subject is 'informed'. This criterion implies that the research subject is given all relevant information to allow them to decide whether engaging with a genomic research infrastructure or project would be normatively desirable and whether they wish to accept the risks associated with engagement. This article makes the normative argument that, in order to be truly 'informed', the research subject should be provided with information on the informational content of their genomic sequence data. Information should be provided, in the first instance, prior to the initial consent transaction, and should include: information on the fact that genomic sequence data will be collected and processed, information on the types of information which can currently be extracted from sequence data and information on the uncertainties surrounding the types of information which may eventually be extractable from sequence data. Information should also be provided, on an ongoing basis, as relevant and necessary, throughout the research process, and should include: information on novel information which can be extracted from sequence data and information on the novel uses and utility of sequence data. The article argues that current elaborations of 'informed' consent fail to adequately address the requirements set out in the normative argument and that this inadequacy constitutes an issue in need of a solution. The article finishes with a set of observations as to the fora best suited to deliver a solution and as to the substantive content of a solution.

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1. Introduction

In the EU, research subject consent plays a significant role in the legitimation of genomic research – ethically as well as legally. A key criterion for consent to be legitimate is that the research subject should be 'informed'. This criterion requires the research subject to be provided with all relevant information on the genomic research proposed, such that the subject is in the position to decide whether they wish to engage with a genomics research infrastructure or research project, and whether they are willing to take on any risks involved with this engagement. This information must remain relevant and accurate over the duration of the research.

There are a range of elaborations of the 'informed' criterion in ethical and legal instruments relevant for genomic research in Europe. These elaborations outline a variety of types of information which should be given to the research subject to ensure they are 'informed'. Not one significant elaboration, however, considers the need to provide the research subject with information on the informational content of their genomic sequence data. This article puts forward the normative argument that true 'informed' consent in genomic research requires the research subject to be provided with information on the informational content of their genomic sequence data. The article further suggests this requirement should be taken into account and addressed in future elaborations of 'informed' consent.

The article first highlights the significance of consent in legitimating genomic research in Europe and of the 'informed' criterion as a condition of consent (Sections 2 and 3). The article then outlines the normative argument that, in order to be 'informed', the research subject must be provided with information on the informational content of their genomic sequence data (Section 4). The article then shows how current elaborations of 'informed' consent do not adequately take this requirement into account and highlights this inadequacy as a problem in need of a solution (Sections 5 and 6). Finally, the article offers a set of observations as to the fora through which a solution might best be delivered and as to the concrete substance of a solution (Sections 7 and 8).

2. The significance of consent for legitimating genomic research in Europe

In Europe, consent plays a significant role in legitimating the use of biological samples, genomic sequence data and associated research subject information in genomic research. This is true from an ethical, legal and practical perspective.[2]

All key ethical instruments, at all levels, outlining principles relevant for genomic research in Europe, highlight consent as an important means of legitimating research. At international level, for example, the World Medical Association, in Article 11 of the Declaration of Taipei (2016) – on Health Databases and Biobanks – state: 'The collection, storage and use of data and biological material from individuals capable of giving consent must be voluntary.'[3] At national level, for example, the UK Medical Research Council state, in relation to the use of biological samples in genomic research: 'Consent…is one way to deliver transparency and foster trust between researchers and participants; and so should be sought in most situations'.[4] Generally, the UK NHS Health Research Authority states: 'Seeking informed consent is central to the conduct of ethical research.'[5]

In certain instances, the need to obtain consent from a research subject to legitimate genomic research is raised to the level of a legal obligation. Such legal obligations are found in various European states' national legislation on genomic research. Two examples are the Estonian Human Genes Research Act (2000) and the Finnish Biobank Act (2012). The Estonian Human Genes Research Act (2000) outlines, in Article 9 – concerning the voluntary nature of gene donation – a strict obligation to obtain consent. The Act states: 'It is prohibited to take a tissue sample and prepare a description of state of health or genealogy without the specific knowledge and voluntary consent of the person.'[6] The Finnish Biobank Act (2012) clarifies, in Article 11, the general principle that consent may legally be required unless other specific criteria are met: 'A biobank's right to process samples is based on consent, unless otherwise provided in this act or in another act.'[7]

The ethical and legal significance of consent as a means to legitimate genomic research is reflected in the practices of genomic research infrastructures and projects. Up to date empirical information on how European genomic research infrastructures legitimate research is scarce. Nevertheless, there have been certain efforts to chart European genomic research

[2] It should be made clear in this regard: the observation that consent plays a significant role in legitimating the use of biological samples, genomic sequence data and associated research subject information does not imply consent is the only means of legitimating genomic research in Europe. Indeed, most laws and ethical instruments relevant to genomic research in Europe foresee the possibility for genomic research to proceed without research subject consent. The conditions under which research may proceed without consent will vary according to the EU and Member State legislation applicable to, as well as the ethical instruments and frameworks relevant for, any given instance of genomic research. A discussion of the possibilities for legitimating genomic research without consent is beyond the scope of this article. See, for an overview of EU relevant legal and ethical frameworks' legitimation of genomic research without consent: Dara Hallinan, Feeding Biobanks with Genetic Data: What role can the General Data Protection Regulation play in the protection of genetic privacy in research biobanking in the European Union? (VUB Doctoral Thesis, 2018) 145, 150-151, 183, 191-192, 199-200, 318-325.

[3] World Medical Association, *Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks* (Policy, 2002 (updated 2016)) Article 11 <https://www.wma.net/policies-post/wma-declaration-of-taipei-on-ethical-considerations-regarding-health-databases-and-biobanks/> accessed 13 January 2020.

[4] Medical Research Council, *Human Tissue and Biological Samples for Use in Research: Operational and Ethical Guidelines* (Policy, 2014) 10 <https://mrc.ukri.org/publications/browse/human-tissue-and-biological-samples-for-use-in-research/> accessed 13 January 2020.

[5] NHS Health Research Authority, *Applying a proportionate approach to the process of seeking consent HRA Guidance* (Policy, 2018) 5.

[6] Human Genes Research Act 2000, Article 9.

[7] Biobank Act 2012, Article 11.

infrastructures' practices. Perhaps the most extensive effort is the pan-European survey conducted by Zika et al. These authors found that 87% of the 127 respondent genomic research infrastructures used some form of consent to legitimate activities. The authors observed: 'informed consent for approval of biobank-based research is almost ubiquitously required.'[8] Interestingly, the authors also observed significant differences among the types of consent obtained: 'the actual consent requirements and related procedures vary widely among biobanks, depending on the national laws and guidelines applied'.[9]

All elaborations of consent relevant to genomic research in Europe – both ethical and legal – only recognise consent as legitimate, however, provided a certain set of sub-criteria are met. One of the most significant of these criteria is that the research subject must be 'informed'. In order to provide a background to the paper's core argument, a more detailed overview of the 'informed' criterion is first necessary.

3. An overview of the 'informed' criterion in genomic research consent in Europe

An overview of the 'informed' criterion can usefully be provided from three perspectives: (i) the omnipresence of the criterion; (ii) the rationale behind the criterion; and (iii) the concrete substantive content of the criterion.

The 'informed' criterion is omnipresent in all ethical and legal elaborations of consent, at all levels, relevant for genomic research in Europe. At international level, for example, Article 4.B of the Organisation for Economic Co-operation and Development's Guidelines on Human Biobanks and Genetic Research Databases (2009) requires that: 'informed consent should be obtained from each participant'. At EU level, the General Data Protection Regulation (GDPR, 2016) requires, in Article 4(11), that the: ''consent' of the data subject means any…informed…indication of the data subject's wishes'.[10] At national level, Kaye et al. highlight – in their comparative look at consent requirements in European genomic research legis-

[8] Eleni Zika, Daniele Paci, Tobias Schulte in den Bäumen, et al., Biobanks in Europe: Prospects for Harmonisation and Networking (European Commission Report, 2010) 23 <https://publications.jrc.ec.europa.eu/repository/bitstream/JRC57831/jrc57831.pdf> accessed 13 January 2020. It should be noted that secondary uses of research subject samples and data, outside the scope of an initial consent, may also be permissible. The legal and ethical criteria governing secondary use are varied, complex and subject to several uncertainties. Accordingly, extensive discussion of such secondary use will remain outside the scope of this paper. Nevertheless, given the conceptual proximity of the issue of secondary use to the subject of the article, a brief consideration of the situation is warranted. In principle, secondary use will be possible if two cumulative conditions are fulfilled. First, the secondary use cannot have been foreseen when consent was obtained. As the Article 29 Working Party observe in relation to the GDPR: '[genomic research infrastructures] must…decide…in advance of… collection what the [legitimation] is' and 'cannot swap from consent to [another legitimation]'. Article 29 Working Party, Guidelines on consent under Regulation 2016/679 (17/EN WP259 rev.01, 2018) 23 <https://ec.europa.eu/newsroom/article29/item-detail.cfm?item_id=623051> accessed 17 March 2020. Second, secondary use must be legitimated by the laws and ethical guidelines applicable in relation to the genomic research at hand. In EU law, the text of the GDPR seems to suggest secondary use is legitimate for scientific research with no further consent. Article 5(1)(b) states 'processing for…scientific…research purposes…shall, in accordance with Article 89(1) [requiring safeguards to protect subject rights], not be considered to be incompatible with the initial purposes' and Recital 50 states 'in such a case, no [legitimation] separate from that which allowed the collection of…personal data is required.' There are, however, multiple interpretations of these provisions and, accordingly, the conditions of secondary use for research remain debated. Three interpretations are notable. First, there are interpretations, such as by Reimer, which assert that no further legitimation is required. Second, there are interpretations, such as by the BfDI, which suggest the original legitimation remains valid. Third, there are interpretations, such as by Zuiderveen Borgesius et. al. and by the EDPS arguing based on legislative history and Article 8 of the CFREU which suggest a new legitimation under Article 6 or 9 of the GDPR is required. Philipp Reimer, 'Artikel 5: Grundsätze für die Verarbeitung personenbezogener Daten' in Gernot Sydow (ed.), Europäische Datenschutzgrundverordnung: Handkommentar (Nomos 2018) 326; Bundesbeauftragten für den Datenschutz und die Informationsfreiheit, Anonymisierung unter der DSGVO unter besonderer Berücksichtigung der TK-Branche (Consultation Paper, 2020) 6-7; Frederik Zuiderveen Borgesius and Dara Hallinan, 'Article 5' in Franziska Boehm and Mark Cole (eds.), GDPR Commentary (Elgar Forthcoming 2020); European Data Protection Supervisor, A Preliminary Opinion on data protection and scientific research (2020) 22-23. The sections generally facilitating secondary processing under the GDPR in research may be subject to derogation in EU Member State law for example under Article 9(4) GDPR. In this case, national legislation may clarify if, and when, secondary processing is possible. National laws differ. In certain cases, for example in Estonia under Article 9 of the Human Genes Research Act (2000) national laws foresee the possibility for secondary processing only with a new consent. In other cases, however, for example in the UK according to the Human Tissue Act, Part 1 and Human Tissue Authority Guidance national laws allow secondary processing either with consent or under exceptional other circumstances. Human Tissue Act 2004, Part 1; Human Tissue Authority, Code E: Research (Code of Practice 2017) 16-20. Ethical frameworks may then also be relevant over and above legal frameworks in any given instance. The approach of ethical frameworks in this regard, is, however, not harmonised. For example, the OECD, in their Guidelines on Biobanks, permit secondary uses with a new research subject consent or with Ethical Research Committee approval, whilst the Council of Europe's Committee of Ministers' Recommendation CM/Rec(2016)6 permits secondary use either with a new research subject consent or provided: i) the participant cannot be contacted; ii) an important scientific goal is pursued; and iii) there is no evidence that the participant would object. Organisation for Economic Co-operation and Development, Guidelines on Human Biobanks and Genetic Research Databases (Policy, 2008) Article 4.B; Council of Europe Recommendation of the Committee of Ministers to member States on research on biological materials of human origin (11 May 2016) CM/Rec(2016)6 Articles 11 and 21.

[9] Eleni Zika, Daniele Paci, Tobias Schulte in den Bäumen, et al., Biobanks in Europe: Prospects for Harmonisation and Networking (European Commission Report, 2010) 23 <https://publications.jrc.ec.europa.eu/repository/bitstream/JRC57831/jrc57831.pdf> accessed 13 January 2020.

[10] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) [2016] OJ L 119/1, Article 4(11).

lation – the presence of the 'informed' criterion in all analysed EU Member State legal systems.[11]

The basic rationale behind the 'informed' criterion is simple. In order make a real choice as to whether they wish to engage with a genomic research infrastructure or project or not – to allow the collection and processing of their biological sample, genomic sequence data and/or associated information – a research subject should be in the position to understand the consequences of engagement.[12] Specifically, the research subject should be in a position to evaluate the consequences of engagement from two perspectives: (i) whether they feel engagement with the project to be normatively desirable: the *normative* perspective;[13] (ii) whether they feel the nature and range of risks potentially associated with engagement in the infrastructure or project to be acceptable: the *risk-based* perspective. Naturally, these evaluations cannot be made without the possession of relevant information: the research subject must be 'informed'.

In concrete terms, the criterion thus requires the research subject to be provided with all relevant information – concerning both normative and risk-based perspectives – about the genomic research infrastructure or project wishing to engage with them. In certain European instruments further elaborating the 'informed' criterion, types of relevant information to be provided to the research subject are explicitly listed – in Article 13 of the GDPR (2016), for example. Other instruments simply outline a general obligation to provide relevant information – in Part 1 of the UK Human Tissue Act (2004), for example. In order that consent remains valid for the duration of research, relevant information must be provided in two phases: (i) prior to the initial consent transaction – in order that the initial consent is 'informed'; (ii) on an ongoing basis, as new relevant information becomes available, or as priorly communicated information becomes inaccurate – in order that consent remains 'informed'.[14]

Significantly, the need to provide novel information on an ongoing basis need not imply an obligation to obtain a new 'informed' consent with each communication. Clarifications as to when the communication of novel relevant information warrant requesting a new 'informed' consent remain scarce and vague. The Article 29 Working Party only suggest, for example: '[new consent is needed if] processing operations…evolve considerably'.[15] In this regard, I would suggest that, if novel relevant information meets the following two, cumulative, criteria, this information may be communicated without a requesting a new consent: i) the information serves only to update research subjects on issues they were aware would be subject to development; and ii) the information does not imply significant changes in the consequences of processing. Beyond this proposition, however, the decision as to whether novel information warrants obtaining new consent will be context dependent.[16]

On the back of this overview – in particular on the back of the overview of the rationale and concrete substance of the 'informed' criterion – the core normative argument made in this article can now be introduced: in order to be 'informed' in a genomic research consent process, a research subject must be provided with information on the informational content of their genomic sequence data. The next section discusses this argument in more detail.

4. Detailing the argument: to be 'informed', a research subject must be provided with information on the informational content of their genomic sequence data

The argument can be further detailed in two parts. First: the identification of a general principle that an individual, in order to give 'informed' consent in any data processing context, must be given information on the informational content of the personal data about them to be processed. Second: the concretization of this general principle in relation to the informational content of genomic sequence data in genomic research.[17]

[11] Jane Kaye, Linda Briceño Moraia, Liam Curren, Jessica Bell, Colin Mitchell, Sirpa Soini, et al., 'Consent for Biobanking: The Legal Frameworks of Countries in the BioSHaRE-EU Project' [2016] 14(3) Biopreservation and Biobanking 195, 195-200.

[12] See the direct assertion of this position by the Article 29 Working Party in relation to 'informed' consent under the GDPR: 'Providing information to data subjects prior to obtaining their consent is essential in order to enable them to make informed decisions, understand what they are agreeing to, and for example exercise their right to withdraw their consent. If the controller does not provide accessible information, user control becomes illusory and consent will be an invalid basis for processing.' The Article 29 Working Party was the body responsible for providing EU level interpretations of data protection law until 2016. In 2016, when the General Data Protection Regulation came into force, the body became the European Data Protection Board. Article 29 Working Party, *Guidelines on consent under Regulation 2016/679* (17/EN WP259 rev.01, 2018) 13 <https://ec.europa.eu/newsroom/article29/item-detail.cfm?item_id=623051> accessed 30 September 2019.

[13] For example, there are types of research which may be incompatible with certain world-views or beliefs. Research participants may need to be told if such research is planned such that they could make a normative decision as to whether they wanted to offer their support or not. Beyleveld et al., for example, point to the controversy around a Roman Catholic research subject whose materials were used in the creation of contraceptives. See: D. Beyleveld, E. Histed, 'Betrayal of Confidence in the Court of Appeal' [2000] 4(3&4) Medical Law International 277, 277-311.

[14] As the Global Alliance on Genomics and Health assert, for example, in their 'Consent Policy' document: 'This Policy is founded on the following basic principles: i. Consent is an open, communicative, and continuing relationship'. Global Alliance for Genomics and Health, *Consent Policy* (Policy, POL 002 / v 2.0, 2019) 1 <https://www.ga4gh.org/wp-content/uploads/GA4GH-Final-Revised-Consent-Policy_16Sept2019.pdf> 01 October 2019.

[15] Article 29 Working Party, Guidelines on consent under Regulation 2016/679 (17/EN WP259 rev.01, 2018) 21 <https://ec.europa.eu/newsroom/article29/item-detail.cfm?item_id=623051> accessed 30 September 2019.

[16] The consideration should include a range of factors including, in particular: the content of the information; the significance of the information for the consequences of processing; and the expectations of research subjects.

[17] As highlighted above – in footnote 9 – detailed discussion of secondary uses of research subject samples, genomic sequence data and associated data initially collected based on consent remains outside the scope of the paper. Nevertheless, certain gen-

In terms of identifying a general principle: awareness of the informational content of the personal data to be processed matters in relation to both the normative and risk-based evaluations of a consent decision in all contexts. In relation to the normative perspective, the informational content of the personal data to be processed is determinative of the form of relationship between parties involved in processing.[18] In terms of the risk-based perspective, the informational content of the personal data to be processed is determinative of factors key to evaluating the form and degree of risks which may arise from processing. Examples of these factors include: what might be learnt about an individual on the basis of the data, which types of judgments might be made about the individual on the basis of the data, which actors might have an interest in accessing the data and the purposes for which these actors might use the data. This general principle has certain jurisprudential recognition. The Article 29 Working Party, for example, explicitly observed the importance of providing individuals with information as to the types of personal data about them being processed in consent transactions.[19]

In terms of concretizing the general principle in relation to the informational content of genomic sequence data in genomic research: in the first instance, the principle requires information to be provided to the research subject in the course of the initial consent transaction. Here, I would propose three different types of information on their genomic sequence data are required by the research subject to allow them to engage in the relevant normative and risk-based evaluations: (i) information that their genomic sequence data will be collected and processed; (ii) information as to the current range of information about them extractable from their genomic sequence data – to provide a view of the current informational content of their genomic sequence data;[20] and (iii) information as to the uncertainty concerning the types of information which might eventually be extractable from their genomic sequence data in future, owing to future developments in genetic science –

eral observations are warranted concerning the applicability of the argumentation in this article in relation to the provision of information to research subjects in relation to such secondary uses. Two circumstances may be differentiated. First, in cases of secondary use for which research subject consent is required: the argumentation in the paper remains directly relevant. In these cases, all assertions concerning consent in genomic research made in the article remain relevant including concerning base logic and substantive requirements. As a result, the normative arguments made in the article also remain valid. Second, in cases of secondary use for which consent is not required: provided informational obligations are owed to the research subject, I would suggest the argumentation in the paper concerning the fact that information on the informational content of genomic sequence data should be provided to the research subject, remains generally valid. It is certainly possible that secondary use without consent may be bound up with informational obligations still being owed to the research subject. For example, under a textual interpretation of Articles 5(1)(b) and Recital 50 of the GDPR, secondary uses for genomic research would be possible without consent whilst a genomic research infrastructure would still be obliged, under Article 14 of the GDPR, to provide the research subject with information concerning the processing about them being undertaken. Where such information obligations are owed, their rationale will invariably be to put the research subject in the position to understand the scope and consequences of processing. Their base rationale, as far as the types of information to be provided to the research subject are concerned, iscomparable with that of informational obligations owed in consent. Logically, then, these obligations should require research subjects to be given the same information as information obligations connected with consent. The suggestion of general validity, however, comes with a caveat: in order to clarify precisely when, how, and the degree to which, the argumentation in this paper remains valid, further research will be required. This caveat is justified for two reasons. First, the variety, complexity and uncertainty of conditions under which secondary use is currently possible without consent, means that unequivocal statements should not be made without further investigation. Second, whilst the rationale behind informational obligations owed in secondary use without consent, and informational obligations owed in consent, are comparable in relation to the types of information they suggest should be provided to the research subject, they differ in other ways. In particular, whilst informational obligations in secondary use without consent function to ensure transparency without supporting a research subject's ability decide whether processing happened, informational obligations in consent function to ensure transparency in service of this decision. This distinction will likely have subtle implications for how the argumentation in the paper will apply in cases of secondary use without consent. These implications require further research to tease out.

[18] Consider, for example, the difference in depth and significance of relationship between a research subject and researcher when the latter only has access to the former's shoe size, and when the latter has access to the former's complete medical history.

[19] Article 29 Working Party, *Opinion 15/2011 on the definition of consent* (01197/11/EN WP187, 2011) 19 <https://ec.europa.eu/justice/article-29/documentation/opinion-recommendation/files/2011/wp187_en.pdf> accessed 01 October 2019. See also the recognition of the principle in front of the European Court of Human Rights. In the *Marper* judgment, for example, the Court extensively discussed the significance of the informational content of the genome and the significance this has for the risks associated with the collection and processing of genomic sequence data. *S. and Marper v. The United Kingdom* App nos. 30562/04 and 30566/04 (ECHR, 4 December 2008) paras 70–77.

[20] Currently, the following significant types of information can be extracted from an individual's genomic sequence data: identity information; phenotype, and potential phenotype, information – including health information; genealogy information; ethnicity information; and, according to some geneticists, social and behavioural information. See, for examples, respectively: Nuffield Council of Bioethics, *The forensic use of bioinformation: ethical issues* (Report, 2007) 8–11 <http://nuffieldbioethics.org/wp-content/uploads/The-forensic-use-of-bioinformation-ethical-issues.pdf> accessed 18 September 2019; D. Ford, D. F. Easton, M. Stratton, S. Narod, D. Goldgar, et al., 'Genetic Heterogeneity and Penetrance Analysis of the BRCA1 and BRCA2 Genes in Breast Cancer Families' [1998] 62(3) American Journal of Human Genetics 676, 676–689; Nuffield Council of Bioethics, *The forensic use of bioinformation: ethical issues* (Report, 2007) 20 <http://nuffieldbioethics.org/wp-content/uploads/The-forensic-use-of-bioinformation-ethical-issues.pdf> accessed 18 September 2019; A. L. Lowe, A. Urquhart, L.A. Foreman, I.W. Evett, 'Inferring ethnic origin by means of an STR profile' [2001] 119 Forensic Science International 17, 17–22; Piotr Gronek, Dariusz Wieliński and Joanna Gronek, 'Genetic and non-genetic determinants of aggression in combat sports' [2015] 10 Open Life Sciences 7, 13 <https://www.degruyter.com/downloadpdf/j/biol.2015.10.issue-1/biol-2015-0002/biol-2015-0002.pdf> accessed 18 September 2019.

such that the research subject can appreciate the informational content extractable from their genomic sequence data, and accordingly the associated degree of risk, may vary unpredictably over time.[21]

Given the potential change in the types of information about research subjects which might be extracted from their genomic sequence data over time, however, a one-off communication of information in the initial consent transaction would be insufficient. Accordingly, in order that the research subject's consent remains valid, the research subject must also be provided with relevant new information on their genomic sequence data, as this becomes available, as the research process progresses. In this regard, I would propose two types of information should be communicated to research subjects throughout the course of research: (i) new information relating to the range of types of information extractable from the research subject's genomic sequence data – stemming from developments in genetic science; and (ii) information as to how developments in genetic science have impacted the general use and utility of genomic sequence data.

The reader may wonder how the provision of such information might function, given prevalent forms of consent in genomic research – for example broad consent – foresee that many different research projects may access a single individual's genomic sequence data.[22] In this regard, each form of information outlined above – in both the initial consent transaction and the ongoing research process – may be provided regardless of the number, or types, of research project which access and use an individual's genomic sequence data. In this regard, the information to be provided is semantically independent of the use of the genomic sequence data in research. For example, a genomic research infrastructure may provide a research subject with information as to new developments concerning the information which might be extracted from their genomic sequence data regardless of the number, or type, of research projects which had, or will have, access to the sequence data.[23]

Ideally, one would expect the requirements set out in the normative argument to have been adequately taken into account, and addressed, in existing elaborations of 'informed' consent relevant in genomic research in Europe. Unfortunately, this is not the case. A first step in demonstrating the inadequacy of current elaborations is to highlight their lack of explicit obligations concerning the need to communicate information to the research subject on their genomic sequence data.

5. Inadequacies in existing elaborations of 'informed' consent: no explicit obligations on the communication of information on genomic sequence data to research subjects

There is an absence of explicit obligations requiring the communication of information on the informational content of genome sequence data across all significant ethical and legal elaborations of 'informed' consent relevant for European genomic research.

There are no explicit obligations identifiable in relation to the initial consent transaction. It is true that certain significant elaborations of 'informed' consent outline obligations which touch on the need to provide information to research subjects concerning the types of information about them which will be collected and processed. The Organisation for Economic Co-operation and Development, for example, in Article 4.4 of their Guidelines on Human Biobanks suggest research subjects should be provided with information as to the: 'data anticipated to be derived from the analysis of samples'. Such obligations, however, fall short of constituting explicit obligations to provide information on the current range of possibilities to extract information about research subjects from their genomic sequence data. Such obligations also fall short of constituting explicit obligations to provide information on the uncertainty concerning the range of types of information about research subjects which might eventually be extracted from their genomic sequence data.

Nor are there explicit obligations identifiable in relation to the ongoing research process. It is true that certain signifi-

[21] The suggestion that information as to the future uncertainty of types of information which might be extracted from the genomic sequence should be given to the research subject should be subject to a clarification. This suggestion is not intended to imply that researchers should engage in speculation as to which specific types of information might be extractable from the genome in future. Such an approach would undoubtedly lead to significant problems – including, potentially, false expectations on the part of research subjects and liability issues for the researchers involved. Rather, the suggestion is intended to imply that researchers should, honestly, let research subjects know that genetic science tends to advance, and that with this advance comes the strong probability that, in the future, more types of information about the research subject will be able to be extracted from the genome than is currently possible. Researchers should be clear that they do not know how genetic science will develop and cannot say which types of information these will be. The idea of addressing uncertainties concerning future possible interpretations of genomic sequence data in consent procedures is not a novel idea. Extensive discussions have already been had concerning the provision of information on the potential for genomic testing to reveal unexpected findings in consent procedures in the clinical context. For example, recent guidance from the Royal College of Physicians et al. on consent in genomic medicine recognises that patients, in consent procedures, may need to be informed that: 'Genomic tests may generate additional, unexpected or incidental findings.' Royal College of Physicians, Royal College of Pathologists and British Society for Genetic Medicine, *Consent and confidentiality in genomic medicine: Guidance on the use of genetic and genomic information in the clinic* (Report, 3rd edition, 2019) <https://www.rcplondon.ac.uk/projects/outputs/consent-and-confidentiality-genomic-medicine> accessed 16 January 2020.

[22] Dara Hallinan, 'Broad consent under the GDPR: an optimistic perspective on a bright future' (2020) 16(1) Life Sciences, Society and Policy <https://lsspjournal.biomedcentral.com/track/pdf/10.1186/s40504-019-0096-3> accessed 18 March 2020.

[23] This is not to say that the provision of other forms of information concerning the research projects which access a research subject's genomic sequence data and what they plan to do with it may not also be necessary to provide to research subjects. In particular, there is a discussion to be had in terms of whether, and in how far, information should be communicated to research subjects concerning the specific types of information which will be extracted from their genomic sequence data by specific research projects.

cant elaborations of 'informed' consent foresee the possibility for the research subject, throughout the course of research, to obtain information as to how their genomic sequence data is being processed. The GDPR – the only European level law dealing with the conditions of 'informed' consent applicable across the genomic research process – for example, in Article 15, offers research subjects the chance to obtain information as to which, and how, information about them is being processed.[24] Such obligations, however, fall short of explicit obligations to communicate information on novel types of information which might be extracted from genomic sequence data.[25] Such obligations also fall short of explicit obligations to communicate information on developments in the uses and utility of genomic sequence data.

Whilst no significant elaboration of 'informed' consent relevant in Europe outlines explicit obligations concerning the need for ongoing communication of information on genomic sequence data, it should be recognised that many elaborations do foresee some general need for genomic research infrastructures and projects to engage in ongoing communication with research subjects. For example, the Council of Europe's Recommendation CM/Rec(2016)6 (2016) on research on biological materials of human origin, in Article 16(7), outlines the general principle, that: 'Information about the management and use of the collection should be made available to the persons concerned'. Equally, The World Medical Association's Declaration of Taipei (2016), in Article 14, states: 'Individuals have the right to request for and be provided with information about their data and its use as well as to request corrections of mistakes or omissions.'

The absence of explicit obligations alone, however, need not necessarily be a problem with current elaborations of 'informed' consent. This would be the case, for example, if other factors served to take into account, and address, the requirements of the normative argument such that the lack of explicit provisions would be irrelevant. Such factors, however, are not evident.

6. Inadequacies in existing elaborations of 'informed' consent: no factors rendering the absence of explicit obligations irrelevant

There are neither principled nor practical factors identifiable which render the lack of explicit obligations irrelevant. It is true there are general provisions, common in European approaches to 'informed' consent, requiring research subjects to be provided with all relevant information concerning their participation in a genomic research infrastructure or research project. Such provisions could be argued, in theory, to require the provision of information on the informational content of genomic sequence data. These provisions, however, are not currently interpreted in this way in practice.

General provisions requiring research subjects to be provided with relevant information are identifiable in many significant elaborations of 'informed' consent relevant for genomic research in Europe. For example, the Council of Europe, in Article 13(2) of their Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (2007), state: 'information [to be provided to research subjects] shall cover the purpose, the overall plan and the possible risks and benefits of the research project'.[26] Such general transparency obligations represent broad concretizations of the basic rationale behind the 'informed' consent criterion. They aim to ensure research subjects are endowed with all relevant information necessary to engage in both normative and risk-based evaluations of genomic research. These provisions could indeed be argued to imply genomic research infrastructures and projects should provide research subjects with information on the informational content of their genomic sequence data – both prior to, and during, research.

In practice, however, such general transparency provisions are not given this interpretation. Indeed, in practice, it seems little, if any, attention is currently paid to the need to communicate information on the informational content of genomic sequence data to research subjects in consent transactions. In practice, the need for the provision of information on genomic sequence data is not even recognised in the consent protocols of large-scale genomics infrastructure projects – infrastructures which tend to pay considerable attention to their ethical governance systems as well as to their legal compliance obligations.[27] For example, nowhere in the documentation of 'informed' consent protocols for either the UK Biobank or the Estonian Genome Centre – two of the most significant large-scale genomic research infrastructures in Europe – is provision of information on the informational content of genomic sequence data foreseen.[28]

[24] See in particular Article 15(3) and the data subject's right to obtain a copy of their personal data being processed from a data controller.

[25] Indeed, such approaches fall short not only in terms of the substantive content of information they require to be communicated, but also in other ways. Two are particularly significant. First, these approaches often require positive action on the part of the research subject in order to obtain any information they are entitled to. See, for example, Article 11 of the Estonian Human Genes Research Act (2000). Second, certain approaches elaborate the possibility for genomic research infrastructures to impose administrative fees on research subjects, should research subjects engage in repeated requests for information. See, for example, Article 15(3) of the GDPR (2016): 'For any further copies requested by the data subject, the controller may charge a reasonable fee based on administrative costs.'

[26] Council of Europe Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (opened for signatures 25 January 2005, entered into force 1 September 2007) CETS No. 195, Article 13(2).

[27] See, for example, the extensively documented UK Biobank Governance Framework: UK Biobank, *UK Biobank Ethics and Governance Framework* (Policy, Version 3, 2007) <https://www.ukbiobank.ac.uk/wp-content/uploads/2011/05/EGF20082.pdf> accessed 17 January 2020.

[28] See, respectively: Estonian Biobank, *Annex 1 to the Ministry of Social Affairs Decree No 36 Of 28 March 2007: GENE DONOR CONSENT FORM* (2007) <https://www.geenivaramu.ee/sites/default/files/gene_donor_consent_form.pdf> accessed 01 October 2019; UK Biobank, *Information Leaflet* (2010) <https://www.ukbiobank.ac.uk/wp-content/uploads/2011/06/Participant_information_leaflet.pdf> accessed 01 October 2019. Although it should be noted that participants are given the chance to ask questions and have a discussion with biobank professionals before they choose to engage.

Nor does it seem likely this situation will change in the foreseeable future. Not only is there a lack of attention to the requirement in practice, there is also a lack of recognition of the requirement in both academic discussions of 'informed' consent in genomic research and in eminent and influential genomics research associations. The Global Alliance on Genomics and Health, for example, make no mention of the requirement in any of their recent guidelines or documentation on consent – including in their 2019 'Consent Policy'.[29] The silence is perhaps understandable. In the first instance, a requirement to communicate information on the informational content of genomic sequence data is anathema to conceptualisations of consent on which consent processes in genomic research have been built – those required in traditional clinical medical research.[30] In turn, there are, admittedly, currently, bigger issues to be addressed in shaping consent in genomic research.[31]

The previous two sections showed the requirements outlined by the normative argument are not adequately taken into account or addressed in current approaches to 'informed' consent relevant to genomic research in Europe. This inadequacy constitutes an issue in need of a solution. Specifically, the issue requires a solution which can change how the 'informed' consent criterion is conceptualised, in line with the requirements of the normative argument. In this regard, the next section offers a set of observations concerning the fora through which such a solution might best be delivered.

7. Observations on fora best placed to deliver a solution

Three observations about the characteristics of the fora best suited for the delivery of a solution are offered. Each observation builds on the preceding observation.

First, the delivery of a solution should best happen through dedicated genomic research instruments, rather than through softer forms of principle diffusion mechanism – such as, for example, academic or stakeholder discussions. Genomic research infrastructures and projects tend to orient their practices around clear expressions of normatively legitimate activity. These expressions take the form of ethical guidelines and legal obligations in authoritative instruments.[32] I know of no other mechanism for the general diffusion of normative principles which so directly impacts on genomic research practices. It is true softer principle diffusion mechanisms – for example academic or stakeholder discussions, or even funder policies – may, in certain instances, be instrumental in guiding interpretations of principles or obligations already outlined in authoritative instruments. It is hard to imagine, however, that such mechanisms could, on their own, substitute for such instruments.

Second, the delivery of a solution should best happen via European or international level instruments, as opposed to through national level instruments. Genomic research is an increasingly international activity – biological samples, genomic sequence data and associated research subject information are frequently transferred across national boundaries to facilitate research.[33] Accordingly, to minimise bureaucratic obstacles, and to facilitate clarity in the identification of relevant normative principles of genomic research across jurisdictions, a solution through international and European level instruments would be preferable to a solution through nationally specific instruments. Ideally, international level instruments would be preferable to European level instruments. The level of connection between European genomic research infrastructures – in comparison to those outside Europe – and the degree of existing efforts and mechanisms to harmonize genomic research norms in Europe suggests, however, a solution via European level instruments may be practically easier to achieve.[34]

Finally, the delivery of a solution should best happen through instruments outlining ethical principles – provided these are drafted by authoritative bodies – as opposed to instruments outlining legal obligations. The reasoning is pragmatic. Currently, there seems little inclination to amend existing relevant legislation, or to pass new genomic research legislation, at either international or European level, which could serve as a vehicle for a solution. It is true there are certain

[29] See the range of documents and tools available here: Global Alliance on Genomics and Health documentation on ethics and regulation <https://www.ga4gh.org/genomic-data-toolkit/regulatory-ethics-toolkit/> accessed 01 October 2019. See, in particular: Global Alliance for Genomics and Health, *Consent Policy* (Policy, POL 002 / v 2.0, 2019) <https://www.ga4gh.org/wp-content/uploads/GA4GH-Final-Revised-Consent-Policy_16Sept2019.pdf> 01 October 2019. The participants in the association are, however, knowledgeable and their work always impressive. It is possible the issue may be a subject of discussion within internal working groups which has not yet been reflected in published work.

[30] Hazel Biggs, *Healthcare research ethics and law: regulation, review and responsibility* (Routledge-Cavendish 2009) 17–35.

[31] Issues of the scope of consent and the possibilities and restrictions on withdrawal, for example, currently command much academic and institutional attention.

[32] See, for example, the approach of the Swiss Biobanking Platform in relation to the elaboration of ethical and legal requirements for biobanks: Swiss Biobanking Platform, 'List of ethical/legal requirements' (*Swiss Biobanking Platform*, 2020) <https://swissbiobanking.ch/list-of-ethical-legal-requirements/> accessed 30 January 2019.

[33] See, for a discussion of both the logic of internationalisation in genomic research as well as the limitations placed by different ethical and legal requirements in different jurisdictions: Martin Asslaber, Kurt Zatloukal, 'Biobanks: transnational, European and global networks' [2007] 6(3) Briefings in Functional Genomics and Proteomics 193, 197–200.

[34] One significant example of the degree of connection between European biobanks is the BBMRI-ERIC network. The goal of the network is to bring all relevant biobanking players in Europe together and to facilitate their cooperation. The network already boasts a central directory of 608 biobanks whose samples and data can be searched online by genomic researchers. See: BBMRI-ERIC, 'Directory' (*BBMRI-ERIC*, 2020) <http://www.bbmri-eric.eu/services/directory/> accessed 29 January 2020. BBMRI-ERIC are also actively engaged in shaping ethical and legal principles for biobanking and genomic research in Europe. One significant current BBMRI-ERIC initiative involving the elaboration of 'informed' consent practices in genomic research is their 'Code of Conduct for Health Research'. BBMRI-ERIC, 'Code of Conduct for Health Research' (*Code of Conduct for Health Research*, 2020) <http://code-of-conduct-for-health-research.eu/> accessed 29 January 2020.

regulatory authorities, capable of providing interpretations to existing legislation, which could deliver a partial solution – given the solution would be relevant only as far as the legislation in question applied and required consent to legitimate research. One noteworthy example is the European Data Protection Board and its capacity to deliver authoritative interpretations of the General Data Protection Regulation.[35] Whilst this authority has seen fit to comment on the norms of data use in research, it seems ill inclined, however, to elaborate detailed principles for genomic research.[36]

Building on the observations that a solution might best be delivered through European level instruments outlining ethical principles in genomic research, the next section makes a further set of observations as to what the concrete substance of a solution might look like.

8. Observations on the concrete substance of a solution

Three observations on the concrete substance of a solution are offered. The first two observations concern the specifics of the types of information to be communicated to the research subject. The third observation concerns the need for flexibility in the solution.

First, a substantive solution should include provisions dealing with the initial consent transaction. In relation to the initial transaction, a substantive solution should mandate genomic research infrastructures and genomic research projects to provide research subjects with the three types of information concerning the informational content of their genomic sequence data proposed above: (i) information that their genomic sequence data will be collected and processed; (ii) information as to the current possibilities to extract information about them from their genomic sequence data relevant to normative and risk-based evaluations; and (iii) information as to the uncertainty concerning the types of information which might eventually be extractable from their genomic sequence data in future – on the basis of further developments in genetic science.[37]

Second, a substantive solution should include provisions dealing with the ongoing research process. In relation to the ongoing research process, a solution should mandate genomic research infrastructures and projects to provide research subjects with the two types of information proposed above: (i) novel information relating to developments in the range of information, relevant to the research subject's normative and risk-based evaluations, extractable from a research subject's genomic sequence data; and (ii) novel information as to developments in the use and utility of the research subject's genomic sequence data. The solution should specifically mandate that genomic research infrastructures and projects operate an ongoing, as opposed to a one-off, communication model. As Grady et al. observe, variations in relevant information require 'ongoing communication with donors'.[38]

Finally, a substantive solution should be structured in the form of flexible principles, as opposed to black and white rules. Principles are, as De Hert observes: 'to be conceived in an 'optimising' perspective. They set an optimum standard, which has to be complied with, compatibly with the factual or [normative] situation'.[39] The flexibility associated with principles is necessary owing to the broad differences across genomic research infrastructures and projects – regarding, for example,

[35] It should be noted that the General Data Protection Regulation is in fact the only instrument of hard law designed with the intention of being applicable, in principle, across the genomic research process and across all EU Member States in harmonised fashion. Applicable international instruments scarcely constitute hard law. In fact, the only international instruments which are intended to outline principles of hard law are the Council of Europe's Oviedo Convention (1997) and its Additional Protocol on Biomedical Research (2007). There remains, however, in relation to both instruments, a lack of information as to whether, and if so to what extent, their provisions have been translated into EU Member State law. In turn, the instruments have not been ratified by all European states. The Additional Protocol, in particular, has received surprisingly few ratifications – 11 at current count. See: Council of Europe Convention for the Protection of Human Rights and Dignity with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (opened for signatures 4 April 1997, entered into force 1 December 1999) ETS No. 164; Ratifications of the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine 1997 <https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164/signatures?p_auth=fUdbBxOL> accessed 30 September 2019; Ratifications of the Council of Europe's Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research 2005 <https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/195/signatures?p_auth=fUdbBxOL> accessed 30 September 2019.

[36] See, for an example of the willingness of the European Data Protection Board's willingness to touch on issues of consent in research but their unwillingness to elaborate clear principles for genomic research: Article 29 Working Party, *Guidelines on consent under Regulation 2016/679* (17/EN WP259 rev.01, 2018) 27–30 <https://ec.europa.eu/newsroom/article29/item-detail.cfm?item_id=623051> accessed 30 September 2019. Although the Guidelines come from the Article 29 Working Party, as discussed above, this is simply the group that has now become the European Data Protection Board.

[37] See also: Dara Hallinan, *Feeding Biobanks with Genetic Data: What role can the General Data Protection Regulation play in the protection of genetic privacy in research biobanking in the European Union?* (VUB Doctoral Thesis, 2018) 426–428.

[38] Christine Grady, Lisa Eckstein, Ben Berkman, Dan Brock, Robert Cook-Deegan, Stephanie Fullerton, et al., 'Broad Consent For Research With Biological Samples: Workshop Conclusions' [2015] 15(9) American Journal of Bioethics 34, 43 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4791589/pdf/nihms756706.pdf> accessed 19 September 2019. The infrastructure supporting this form of continuous information provision in consent has been shown to be functionally implementable in genomic research under the dynamic consent model. See: Jane Kaye, Edgar Whitley, David Lund, Michael Morrison, Harriet Teare and Karen Melham., 'Dynamic consent: a patient interface for twenty-first century research networks' [2015] 23(2) European Journal of Human Genetics 141, 141–146.

[39] Paul De Hert, 'Data Protection as Bundles or Principles, General Rights, Concrete Subjective Rights and Rules: Piercing the Veil of Stability Surrounding the Principles of Data Protection' [2017] 3(2) European Data Protection Law Review 160, 167–168.

the types of research subjects recruited, the research methodologies supported, size, etc. These differences will be definitive in deciding what constitutes sensible and effective communication with research subjects in any given case. A principled approach would ensure genomic research infrastructures and projects have flexibility in decision-making, on a case by case basis, as to what information should reasonably be communicated and as to how information should be communicated.

Perhaps most importantly, a principled approach would allow genomic research infrastructures to make context relevant decisions as to whether the communication of new relevant information should be accompanied by a request for a new 'informed' consent from research subjects to proceed with processing. In the majority of cases, the emergence of new relevant information concerning the informational content and utility of genomic sequence data will not warrant requesting new 'informed' consent from subjects.[40] It is not, unthinkable, however, that information on the informational content or utility of the genomic sequence may emerge which, in certain contexts, may imply a considerable evolution in processing and should be communicated with a request for a new 'informed' consent. The decision as to whether this is the case, however, can only be made on a case by case basis by the genomic research infrastructures in question.

In summary, a solution to the issue could best be delivered through European level instruments outlining ethical principles for genomic research. In terms of substantive content, a solution should include a set of obligations requiring the communication of information on the informational content of genomic data in the initial consent transaction as well as throughout the research process. A solution should be formulated in terms of flexible principles as opposed to hard rules.

9. Conclusion

There is a general requirement in approaches to consent in genomic research relevant in Europe that consent must be 'informed'. In principle, in order to be 'informed', a genomic research infrastructure or genomic research project must provide a research subject with all information necessary to allow the research subject to evaluate – both from a normative and risk-based perspective – whether they wish to engage with the infrastructure or project. Relevant information must be provided in the initial consent transaction and must remain accurate and comprehensive throughout the research process.

This article put forward the normative argument that, in order to be 'informed', a research subject should be provided with information on the informational content of their genomic sequence data. This information should be provided in the initial consent transaction and should include: (i) information as to the fact that genomic sequence data will be collected and processed; (ii) information as to the types of information which can currently be extracted from genomic sequence data; and (iii) information as to the uncertainties surrounding the types of information which may be extractable from the genomic sequence data in future.

New information about the informational content of genomic sequence data should also be provided, in an ongoing fashion, as this becomes available throughout the genomic research process. Information to be provided in an ongoing fashion should include: (i) information on the novel types of information about research subjects which become extractable from the genome – owing to developments in genetic science and the production of novel frameworks for the interpretation of genomic sequence data; and (ii) information on the novel uses and utility of genomic sequence data.

Unfortunately, current European elaborations of 'informed' consent do not adequately take into account and address the requirements set out in the normative argument. No relevant elaboration of 'informed' consent includes explicit obligations mandating the communication of information on the informational content of the genomic sequence. Certain elaborations of 'informed' consent do include general requirements that research subjects be provided with all relevant information about an infrastructure or project. These obligations are not, however, currently interpreted as requiring the communication of information on the informational content of genomic sequence data in practice. The fact that the requirements of the normative argument are inadequately addressed leads to the need to consider a solution.

The issue requires a solution facilitating changes in how the 'informed' consent criterion is conceptualised in European genomic research. In this regard, a solution might best be delivered through authoritative European level instruments dedicated to outlining ethical principles applicable to genomic research. In terms of substantive content, a solution should include obligations to provide the identified types of information on the informational content of genomic sequence data in the initial consent transaction, as well as throughout the research process. Given the broad differences across genomic research infrastructures and projects, a solution should consist of general principles as opposed to hard rules.

Declaration of Competing Interest

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[40] The information will fulfil the criteria for new relevant information which does not warrant new 'informed' consent: i) new information on their genomic sequence will usually only serve to update research subjects; and ii) new information on the genomic sequence will usually not imply significant changes in the consequences of processing.