

THE ETHICS OF BIG DATA IN GENOMICS: THE INSTRUCTIVE ICELANDIC SAGA OF THE INCIDENTALOME

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*“Medical science has made such tremendous
progress that there is hardly a healthy human left.”*

-- Aldous Huxley, 1894-1963

ABSTRACT

DeCODE Genetics, Inc., a pioneering Icelandic biotech firm, recently introduced a free website that permits Icelanders to learn whether they carry mutations in the BRCA2 gene that are known to increase cancer risk, even if these citizens have never participated in genetic testing. Approximately five thousand Icelanders have elected thus far to receive their status. This site is made possible by the consanguinity of Icelandic citizens, who number fewer than 350,000, and their detailed genealogical records dating back centuries, a set of circumstances that presents a unique opportunity to study genetic mutations and the medical disorders associated with them. Using such information, deCODE has the ability to impute genetic information about individuals without any legal requirement to obtain their informed consent.

This ability to impute individuals' genotypes without having gathered bio-specimens or medical information directly from them calls into question researchers' duty to inform individuals about their health risks, and the individuals' right not to know (“RNTK”), defined as the idea that people ought to be able to control their receipt of genetic information about themselves. The emergence of unanticipated and yet highly significant genetic findings is referred to as the “incidentalome.” Commentators use the phrase “incidental findings” (“IFs”) to refer to medically important information that arises from research but is unrelated

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to the goals of that research.

This article analyzes the return by researchers of genetic IFs to individuals whose genotypic data has been imputed, and who therefore have not indicated their consent to receive such information. While Iceland is at the forefront of this issue due to its small, homogeneous population, other nations increasingly encounter the same need to balance individual autonomy with responsibility for public health.

Part II of this Article will consider the global rise of biobanks and the concomitant challenges posed to the right not to know. Part III considers how the incidentalome arises in Iceland, a country renowned for its genomic research, while Part IV examines the current debate in Iceland regarding the release of imputed genomic information to its citizens. International laws and norms regarding the RNTK are the subject of Part V. Part VI of this Article explores the legal and ethical arguments surrounding the three possible approaches considered in Iceland for the release of imputed BRCA2 genetic data: no return of the data; make it publicly known that the information is available and thus enable individuals to take the initiative to request that information for themselves; or contact the affected individuals directly to inform them that researchers possess information relevant to their health. Because similar legal and ethical questions arise when health care providers consider their duty to inform individuals exposed to HIV and AIDS, Part VII analyzes considerations surrounding the provision of this risk information. Finally, Part VIII of this Article proposes an approach for the future, emphasizing the need for a robust public service campaign that encourages individuals to access their imputed genetic data and, more broadly, for expanded governmental investment in and public access to genetic testing.

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I. INTRODUCTION

DeCODE Genetics, Inc., a pioneering Icelandic biotech firm, recently introduced a free website that permits Icelanders to learn whether they carry mutations in the BRCA2 gene that are known to increase cancer risk, *even if* these citizens have never participated in genetic testing. Approximately 5,000 citizens have elected thus far to receive their status.¹ This is made possible by the consanguinity of Icelandic citizens, who number fewer than 350,000,² and their detailed genealogical records dating back centuries, a set of circumstances that presents a unique opportunity to study genetic mutations and the medical disorders associated with them.³ Dr. Kári Stefánsson, the founder and CEO of deCODE, has been able, by combining the genomic data deCODE has gathered and using genealogical records, to impute the genotypes of not only the Icelanders who have participated in its genetic research, but even those who have not, including individuals who are deceased.⁴ Stefánsson asserts the ability to “impute [genetic] variants with a frequency down to .05%, so basically everything except extremely rare familial or de novo mutations.”⁵

This ability to impute individuals’ genotypes without having gathered bio-specimens or medical information directly from them calls into question researchers’ duty to inform individuals about their health risks, and the individuals’ right not to know (“RNTK”), defined as the idea that people ought to be able to control their receipt of genetic information about themselves.⁶ Noting that the affected women have an 82% probability of developing a fatal cancer and have a life expectancy twelve years shorter than other women, Stefánsson requested from the Icelandic

1 Justin Petrone, *DeCode Begins BRCA2 Mutation Service in Iceland as Society Debates ‘Right to Not Know,’* GENOMEWEB (July 9, 2018) hereinafter Petrone, *DeCode Begins BRCA2 Mutation Service*], <https://www.genomeweb.com/cancer/decode-begins-brca2-mutation-service-iceland-society-debates-right-not-know#.W0dRKi2ZNm8>.

2 Jelena Ćirić, *Icelandic Population Continues Upward Trend*, ICE. REV. (Jan. 29, 2018), <http://icelandreview.com/news/2018/01/29/icelandic-population-continues-upward-trend>.

3 See Donna M. Gitter, *Informed Consent and Privacy of Non-Identified Bio-Specimens and Estimated Data: Lessons from Iceland and the United States in an Era of Computational Genomics*, 38 CARDOZO L. REV. 1251, 1255-56 (2017) (describing the unique aspects of the Icelandic population that render the country an optimal setting for genomic research).

4 Justin Petrone, *In Iceland, Debate Simmer Over Imputed Genotypes, Preventive Medicine, and Public Health*, GENOMEWEB (Jan. 14, 2016) [hereinafter Petrone, *In Iceland, Debate Simmers*], <https://www.genomeweb.com/molecular-diagnostics/iceland-debate-simmers-over-imputed-genotypes-preventive-medicine-and-public>.

5 *Id.*

6 Benjamin E. Berkman, *Refuting the Right Not to Know*, 19 J. HEALTH CARE L. & POL’Y 1, 6 (2016).

government permission to inform these women.⁷ The Icelandic Parliament responded by charging the Ministry of Health with developing guidelines for informing Icelandic citizens of their potential genetic vulnerability.⁸ Stefánsson participated as a committee member, but resigned before the group reached its conclusion. Ultimately, the Ministry of Health committee issued an opinion declining to permit deCODE to contact affected Icelanders, and that same day deCODE established its website.⁹

This emergence of unanticipated and yet highly significant genetic findings is referred to as the “incidentalome.”¹⁰ Similarly, commentators use the phrase “incidental findings” (which will be employed and shortened to “IFs” throughout this article) to refer to medically significant information that arises from research but is unrelated to the goals of that research.¹¹

This Article will analyze the return of IFs to individuals whose genotypic data has been imputed, and who therefore have not explicitly indicated their consent to receive such information. While Iceland is at the forefront of this issue first due to its small, homogeneous population and detailed genealogical records, other nations increasingly encounter the same debate. As noted by Myles Axton, Chief Editor of the journal *Nature Genetics*, a large enough U.S. database could also be used to make similar inferences.¹² This fact, combined with the trend toward global networking

7 Petrone, *In Iceland, Debate Simmers*, *supra* note 4. Male carriers of this mutation have a 72% lifetime risk of serious cancer, a 36% risk of prostate cancer, and a life expectancy roughly seven years shorter than that of non-carriers. Petrone, *DeCode Begins BRCA2 Mutation Service*, *supra* note 1.

8 Petrone, *In Iceland, Debate Simmers*, *supra* note 4.

9 Petrone, *DeCode Begins BRCA2 Mutation Service*, *supra* note 1.

10 Kadri Simm, *Biobanks and Feedback*, in *THE RIGHT TO KNOW AND THE RIGHT NOT TO KNOW* 55, 55 (Ruth Chadwick et al. eds., 2014).

11 See PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, ANTICIPATE AND COMMUNICATE: ETHICAL MANAGEMENT OF INCIDENTAL AND SECONDARY FINDINGS IN THE CLINICAL, RESEARCH, AND DIRECT-TO-CONSUMER CONTEXTS 22, 27–28 (2013) [hereinafter ANTICIPATE AND COMMUNICATE]. It should be noted that IFs can be distinguished from individual research results (“IRRs”) generated from genetic research. While both IFs and IRRs are research findings concerning an individual contributor that are potentially significant in medical and/or reproductive terms, IFs are beyond the specific aims of the study, whereas IRRs are findings pertaining to the specific aims of the study. Susan M. Wolf et al., *Managing Incidental Findings and Research Results in Genomic Research Involving Biobanks and Archived Data Sets*, 14 *GENETICS IN MED.* 361, 364 (2012). However, in the context of this article, which discusses the return of these findings, IFs and IRRs are comparable from the perspective of the data contributor and will be referred to collectively as IFs.

12 Antonio Regalado, *Genome Study Predicts DNA of the Whole of Iceland*, MIT TECH. REV. (Mar. 25, 2015), <http://www.technologyreview.com/news/536096/genome-study-predicts-dna-of-the-whole-of-iceland>. While the United States lacks a national database similar to Iceland’s, private companies such as 23andMe and Ancestry.com have created rough gene maps of several million people, and the NIH has formulated a plan to spend millions of dollars in the coming years sequencing full genome data on tens of thousands of people. *Id.*

of biobanks,¹³ demonstrates that the RNTK imputed genetic data impacts communities around the world and therefore is of international significance.

Part II of this Article will consider the global rise of biobanks and the concomitant challenges posed to the management of the incidentalome and the RNTK. Part III considers how the incidentalome arises in Iceland, a country renowned for its genomic research, while Part IV examines the current debate in Iceland regarding the release of imputed genomic information to its citizens. International laws and norms regarding the RNTK are the subject of Part V. Part VI of this Article explores the legal and ethical arguments surrounding the three possible approaches considered in Iceland for the release of imputed BRCA2 genetic data: no return of the data; make it publicly known that the information is available and thus enable individuals to take the initiative to request that information for themselves; or contact the affected individuals directly to inform them that researchers possess information relevant to their health. Because similar legal and ethical questions arise when health care providers consider their duty to inform individuals exposed to HIV and AIDS, Part VII analyzes considerations surrounding the provision of this risk information. Finally, Part VIII of this Article proposes an approach for the future, emphasizing the need for a robust public service campaign that encourages individuals to access their imputed genetic data and, more broadly, for expanded governmental investment in and public access to genetic testing. Increasingly, direct access to such testing through a clinician will allow individuals to express explicitly their desire to receive or reject information about their genetic risk profiles, which is preferable to offering imputed genetic information without explicit consent.

13 A human biobank is defined as “a biorepository that accepts, processes, stores and distributes bio-specimens “such as blood, organs, and tissue samples, along with “associated data for use in research and clinical care.” Yvonne G. De Souza & John S. Greenspan, *Biobanking Past, Present and Future: Responsibilities and Benefits*, 27 AIDS 303, 303 (2013) (describing the history and future of biobanking). The term “biobank” is frequently used to refer to a collection of human biological materials that contain at least traces of DNA or RNA that would allow for genetic analysis. Bernice S. Elger & Arthur L. Caplan, *Consent and Anonymization in Research Involving Biobanks: Differing Terms and Norms Present Serious Barriers to an International Framework*, 7 EMBO REP. 661, 661 (2006) (citation omitted). While human bio-specimens and associated data have been collected for over 100 years, De Souza & Greenspan, *supra* (citation omitted), commentators assert that the term “biobank” did not appear in PubMed until 1996 and was not commonly used until around 2000. Elger & Caplan, *supra* (citation omitted).

II. THE EXPLOSION OF GENOMIC DATA GIVES RISE TO THE INCIDENTALOME

Incidental findings have proliferated because cheaper and faster genome sequencing technologies have expanded the amount of genetic information available, and the “previously unimaginable goal of a \$1,000 genome is now nearly obtainable.”¹⁴ As a result, genomic sequencing, already an important tool for researchers, is increasingly employed in clinical medicine as well.¹⁵ At the level of individual consumers, the direct-to-consumer genetic industry is increasingly robust, and individuals voluntarily generate and share personal genetic information they obtain via direct-to-consumer tests. For example, the website *patientslikeme.com* offers a forum for patients to communicate with others who have similar diagnoses, and these individuals identify themselves through their social media accounts.¹⁶

Along with the explosion of genetic information, another factor that renders the handling of IFs particularly challenging is the structure of the biobanks themselves. Biobanking, which began with small, university-based collections developed for the research needs of a specific project, has changed vastly in the last four decades. The taxonomy of biobanks now includes institutional and government-supported repositories; commercial biobanks; population-based collections; disease-specific biobanks; and, most recently, virtual biobanks. Population-wide biobanks have been established by several nations, including Canada, Denmark, Estonia, Iceland, Japan, Latvia, Singapore, South Korea, Sweden, the United Kingdom, and the United States, in order to collect and analyze genotypic and phenotypic information of their populations.¹⁷ Global research networks have arisen through the establishment of virtual biobanks, which are electronic databases of biological specimens and other related information, designed to allow researchers worldwide to locate biospecimens for testing and data mining from biobanks in dispersed locations.¹⁸ Pooling of such data is considered vital in order to develop means of diagnosing and treating common medical disorders.¹⁹ In addition to the increased complexity of the structure of biobanks, the data associated with stored bio-specimens is more detailed, including not only

14 Berkman, *supra* note 6, at 3.

15 *Id.*

16 Simm, *supra* note 10, at 57.

17 De Souza & Greenspan, *supra* note 13, at 303.

18 De Souza & Greenspan, *supra* note 13, at 304.

19 Simm, *supra* note 10, at 57.

fundamental information such as dates of collection and diagnoses, but also demographic characteristics, information about the contributors²⁰ phenotypes, and the like.²¹

While biobanks are quite diverse in terms of the specimens and data they collect, they share certain characteristics that complicate the issue of whether to share IFs with individual contributors, a process referred to in Europe as “feedback.”²² Biobanks typically involve research settings where investigators are working mostly with anonymized²³ samples, and most contributors have signed consent forms stating that they will not be contacted.²⁴ This complicates the question of whether IFs should be returned to bio-specimen contributors, in the absence of their explicit consent to receive these results. This issue is further complicated in Iceland by the fact that genetic information can be imputed for individuals who did not even directly participate in genetic research.²⁵ Thus, genetic research in Iceland raises not just the typical issues relating to IFs but involves additional complexity in that the return of IFs must be considered when the contributor did not wittingly participate in research. This issue comes into sharper focus with an understanding of the history of genetic research in Iceland.

III. THE HISTORY OF GENETIC RESEARCH IN ICELAND

Genetic research in Iceland began over two decades ago with the direct gathering of biomedical samples and associated data from individual citizens. Over time, genetic research there has grown more reliant on imputed data.²⁶ This allows access to a larger sample size, obviates the need for informed consent, and generally gives rise to fewer transaction

20 The term “contributor” is used in this article to refer to individuals whose data and samples are collected in biobanks, whether or not they also qualify as human subjects entitled to informed consent. *Cf.* Wolf et al., *supra* note 11, at 364.

21 De Souza & Greenspan, *supra* note 13, at 303.

22 *See generally* Simm, *supra* note 10.

23 While the terminology concerning the identifiability of biological samples is quite complex, *see generally* Elger & Caplan, *supra* note 13, the term “anonymized” as it is used here refers to samples for which a code links the sample to its donor. U.S. regulations deem such samples non-identifiable, as long as an agreement prohibits the release to the investigators of the key to the code, and therefore not requiring informed consent for their use. *Id.* at 664 (noting how U.S. regulations, in contrast to those in Europe, do not require informed consent for coded samples).

24 Simm, *supra* note 10, at 57. For example, the U.K. Biobank consent form states that the undersigned agrees that: “I understand that none of my results will be given to me (except for some measurements during this visit) and that I will not benefit financially from taking part” CONSENT FORM: UK BIOBANK, http://www.ukbiobank.ac.uk/wp-content/uploads/2011/06/Consent_form.pdf (last accessed July 6, 2018).

25 *See infra* notes 31-45 and accompanying text.

26 Gitter, *supra* note 3, at 1256-59.

costs for researchers. When Icelandic neurologist Dr. Kári Stefánsson founded the biotechnology enterprise deCODE Genetics, Inc. in 1996, the company planned to benefit from Iceland's genetic homogeneity and the availability of detailed genealogical information in order to pioneer genetic population studies with information gathered from the Icelandic population.²⁷ Indeed, in 1999, the Icelandic government granted to deCODE an exclusive twelve-year license to build a Health Sector Database to hold centralized health records of its entire population.²⁸

Within a short time, deCODE encountered opposition to its plan to build a database because the company's arrangement with the Icelandic government rested on the presumption that the citizens of Iceland had consented to include their information unless they explicitly opted out.²⁹ In 2003, Ragnhildur Guðmundsdóttir, an eighteen-year-old Icelandic student, brought a legal challenge against the presumption that citizens opted in to deCODE's database, arguing against the inclusion of the health records of her deceased father, who did not state any preference during his life. The Icelandic Supreme Court held in the plaintiff's favor, on the grounds that the records in the database might allow her to be identified as an individual at risk of a heritable disease, even though the data would be anonymous and encrypted. The court noted that this risk was heightened by the fact that the Health Sector Database would allow information to be linked with data from other genetic and genealogical databases.³⁰

After the Icelandic Supreme Court barred a database model presuming that all Icelanders had opted in, deCODE then pursued another strategy, using estimated data to create a research database to find genetic sequences linked to diseases.³¹ Using DNA and clinical data from more than 120,000 research volunteers, over one-third of the population, deCODE analyzed their DNA sequences for slight, common genetic variations.³² DeCODE geneticists then calculated the probability that an individual carries a particular genetic variant without actually sequencing

27 See *Science*, DECODE GENETICS (July 7, 2018), <https://www.decode.com/research/>.

28 Alison Abbott, *Icelandic Database Shelved as Court Judges Privacy in Peril*, 429 NATURE 118, 118 (2004).

29 David E. Winickoff, *Genome and Nation: Iceland's Health Sector Database and its Legacy*, 1 INNOVATIONS 80, 82-83 (2006).

30 Abbott, *supra* note 28, at 188. For an English translation of the decision, see Icelandic Supreme Court, *No. 151/2003: Ragnhildur Guðmundsdóttir v. The State of Iceland*, Elec. Privacy Info. Ctr. (Nov. 27, 2003), https://epic.org/privacy/genetic/iceland_decision.pdf.

31 Jocelyn Kaiser, *Agency Nixes deCODE's New Data-Mining Plan*, 340 SCIENCE 1388, 1388-89 (2013) [hereinafter Kaiser, *Agency Nixes deCODE*].

32 *Id.* at 1389. DeCODE now claims that over 160,000 citizens, more than half of the adult population, has volunteered to participate in its genetic research. *Science*, *supra* note 27.

that person's DNA. For example, deCODE was able to use its whole genome sequencing of the DNA of approximately 2,500 research participants in order to extrapolate the genomes of many more individuals. When deCODE identified a genetic variant of interest among the 2,500 whole genomes, the company used the more limited information about the genetic variations that it had amassed from its 120,000 volunteers in order to impute, with 99% accuracy, whether any among these 120,000 also carried the mutations.³³ As noted by one source, “if your mother had been in the hospital for a stroke and agreed to participate in a clinical study, while her brother had volunteered his DNA, deCODE would be able to predict your likelihood of a genetic disposition for stroke.”³⁴

While other researchers are using the same technique as deCODE, the company's unique approach relies on its access to the detailed genealogical information available in Iceland. DeCODE is able to combine the known and estimated genotypes of its research participants with its genealogical database, thereby estimating what it calls the “in silico” genotypes of close relatives of the volunteers whose slight genetic variations were analyzed. This strategy permits deCODE to infer data of about 200,000 living and 80,000 deceased Icelanders, none of whom have consented to participate in deCODE's studies. Further, this imputation approach could essentially give the company genotypes for the largely consanguineous population of nearly 350,000 people in its entirety. Researchers can then determine whether a variant in the DNA sequence found by fully sequencing the DNA of a small group likewise appears in a larger population in the same proportion.³⁵

DeCODE not only uses these estimated genotypes as controls in its studies, but also correlates them with health records for patients whose DNA has not been sampled, but who have participated in other types of medical studies.³⁶ Using estimated data, deCODE published six papers between 2011 and 2013 in the prestigious journals *Nature*, *Nature Genetics*, and the *New England Journal of Medicine*, linking specific genetic mutations to risks of diseases.³⁷ DeCODE's drug discovery efforts

33 Kaiser, *Agency Nixes deCODE*, *supra* note 31, at 1389.

34 Rebecca Goldin, *Privacy and Our Genes: Is deCode's DNA Project 'Big Brother' or the Gateway to a Healthier Future?*, GENETIC LITERACY PROJECT (June 24, 2013), <http://www.geneticliteracyproject.org/2013/06/24/privacy-and-our-genes-is-decodes-dna-project-big-brother-or-the-gateway-to-a-healthier-future/#.UpzQLY5n9So>.

35 Kaiser, *Agency Nixes deCODE*, *supra* note 31, at 1389.

36 Jocelyn Kaiser, *Pioneering Icelandic Genetics Company Denied Approval for Data-Mining Plan*, SCIENCE (June 20, 2013) [hereinafter Kaiser, *Pioneering Icelandic Genetics Company Denied Approval*], <http://news.sciencemag.org/people-events/2013/06/pioneering-icelandic-genetics-company-denied-approval-data-mining-plan>.

37 Kaiser, *Pioneering Genetics Company Denied Approval*, *supra* note 36.

were less successful, however, and the company declared bankruptcy in 2009.³⁸ In December 2012, Amgen purchased the company for \$415 million.³⁹

In 2012, deCODE planned to use its strategy as part of a new study. Having imputed the genotypes of the close relatives of the volunteers whose slight genetic variations had been fully catalogued, deCODE intended to collaborate with Iceland's National Hospital to link these relatives to certain hospital records for individuals, such as surgery codes and prescriptions.⁴⁰ On May 28, 2013, Iceland's Data Protection Agency ("DPA") denied this request on the grounds that it would violate the relatives' privacy unless they gave their informed consent. The DPA gave deCODE until November 2013 to demonstrate that it had obtained consent.⁴¹

DeCODE ultimately discovered a strategy for avoiding the requirement of informed consent, describing their plan in a November 5, 2013 letter to the DPA. DeCODE confirmed that it had deleted all data registers containing imputed genotypes for individuals from whom consent was lacking. However, the company also presented the DPA with a proposal, according to which genotype data from research participants (who had consented) would be linked with genealogy data in a manner that would generate statistical results as strong as those formerly achieved. According to the Iceland DPA:

[T]his would entail that a genetic imputation for those who had not consented would be generated in a split . . . second in the processing memory of a computer. However, this imputation would then cease to exist and would never be accessible to anyone in any form. The only accessible data would be the aforementioned statistical results, which would not in any way be traceable to individuals.⁴²

The DPA confirmed in a letter dated November 26, 2013, that this proposal did not give rise to objections if "all the aforementioned prerequisites were met."⁴³

38 Erika Check Hayden, *Icelandic Genomics Firm Goes Bankrupt*, 462 NATURE 401, 401 (2009).

39 Kaiser, *Agency Nixes deCODE*, *supra* note 31, at 1389.

40 *Id.*

41 Kate Yandell, *Nordic Gene Study Requires Consent*, THE SCIENTIST (June 24, 2013), <https://www.the-scientist.com/the-nutshell/nordic-gene-study-requires-consent-39139>.

42 E-mail from Thordur Sveinsson, Icelandic Data Prot. Auth., to Prof. Donna M. Gitter, (Oct. 20, 2014, 3:51 PM) (on file with author).

43 *Id.*

More recently, deCODE published a series of papers in the journal *Nature Genetics* in May 2015 that described sequencing the genomes of 2,636 Icelanders, the largest collection ever analyzed in a single human population.⁴⁴ Using the imputation technique, deCODE employed the full genomes it has for about 10,000 Icelanders and the partial genetic information on 150,000 more to generate a report for genetic disease on every person in Iceland. It is in this way that the firm can identify every person in Iceland with the well-known BRCA2 mutation, which raises the risk of breast and ovarian cancer, even if the individual herself has not submitted to genetic testing.⁴⁵ DeCODE's CEO Stefánsson expressed his feeling that "it's a crime not to approach these people."⁴⁶ The Icelandic Ministry of Health created a task force to consider whether to release IFs to affected individuals and/or their doctors at all, the process for doing so, and which disorders, if any, ought to be included, as well as how to secure properly informed consent in the future.⁴⁷ Stefánsson was on the task force but later withdrew over disagreement on the issue, stating that he "resigned from this committee and told committee members that if they came to the conclusion that we could not approach these women to save their lives then we would set up such a website."⁴⁸ Indeed, in spring 2018, that is exactly what deCODE did, establishing a website⁴⁹ to provide free information to Icelanders regarding whether they are affected by the BRCA2 mutation carried by nearly 1% of the population.⁵⁰ Once an Icelander signs up with her personal identification number, DeCODE offers the results via an encrypted server and recommends genetic counseling to the recipients of positive results. Yet, the debate in Iceland regarding offering such results is not over, as Stefánsson strongly desires to reach more citizens with potentially life-saving information.⁵¹

44 Daniel F. Gudbjartsson et al., *Large-Scale Whole-Genome Sequencing of the Icelandic Population*, 47 NATURE GENETICS 435 (2015).

45 Carl Zimmer, *In Iceland's DNA, New Clues to Disease-Causing Genes*, N.Y. TIMES (Sept. 4, 2017), <https://www.nytimes.com/2015/03/26/science/in-icelands-dna-clues-to-what-genes-may-cause-disease.html>.

46 *Id.*

47 See e-mail from Thorunn Oddný Steinsdóttir, Legal Advisor, Icelandic Ministry of Welfare, to Prof. Donna M. Gitter (Sept. 4, 2017, 5:44 AM) (on file with author).

48 Jelena Ćirić, *Website Identifies Icelanders at Risk of Cancer*, ICE. REV. (May 15, 2018) [hereinafter Ćirić, *Website Identifies Icelanders*], <http://icelandreview.com/news/2018/05/15/website-identifies-icelanders-risk-cancer>.

49 See Íslensk Erfðagreining, BRCA2 ARFGERÐ, <https://www.arfgerd.is/#/> (last visited July 12, 2018).

50 Ćirić, *Website Identifies Icelanders*, *supra* note 48.

51 Petrone, *DeCode Begins BRCA2 Mutation Service*, *supra* note 1.

IV. THE ICELANDIC DEBATE REGARDING THE RETURN OF GENETIC INCIDENTAL FINDINGS

Professor Vilhjálmur Árnason, Professor of Philosophy and Chair of the Centre for Ethics at the University of Iceland, has noted that “[w]hen deCODE Genetics started its population database research in Iceland in the late 1990s, the company emphasized that there was no interest in gaining information about individuals.”⁵² Referencing a *New England Journal of Medicine* article authored by deCODE co-founders Drs. Kári Stefánsson and Jeffrey Gulcher, Árnason observed that the broad informed consent that they requested and obtained from their research subjects was directed toward collecting biological material, genotyping the DNA, and then using the genotypic information they gathered. Via this broad consent for biobank research, participants gave deCODE permission to store their samples in a biobank and use them for medical research into the causes, diagnosis, treatment, and prevention of diseases with a genetic component.⁵³ However, the deCODE co-founders eschewed the notion that they were gathering information on individuals, emphasizing that “the consent requested is for the use of genotypic data to generate knowledge about the nature of the group, rather than knowledge about the individual person.”⁵⁴

Professor Árnason has further explained that Gulcher and Stefánsson were aware from the outset that population database research might generate information about particular individuals so as to provide them with improved health care.⁵⁵ In their *New England Journal of Medicine* article, Gulcher and Stefánsson allowed that “if the appropriate authorities granted permission, it would be relatively easy to identify and contact all persons in Iceland who had a particular risk for disease,” by asking participants if they “wish to be notified about any association between alleles they carry and specific diseases or predispositions to the development of disease.”⁵⁶

DeCODE’s return of Icelandic population database research results to participants is without precedent in Iceland. Professor Árnason has explained that there is a clause in deCODE’s consent form whereby

52 Vilhjálmur Árnason, *Bioethics in Iceland*, 25 CAMBRIDGE Q. HEALTHCARE ETHICS 421, 424 (2016), http://uni.hi.is/vilhjarn/files/2016/08/Bioethics-in-Iceland_final.pdf.

53 *Id.* (citing Jeffrey Gulcher & Kári Stefánsson, *The Icelandic Healthcare Database and Informed Consent*, 342 NEW ENG. J. MED. 1827, 1828 (2000)).

54 Gulcher & Stefánsson, *supra* note 53, at 1828.

55 Árnason, *supra* note 52, at 424.

56 *Id.* (citing Gulcher & Stefánsson, *supra* note 53, at 1829).

participants agree that deCODE can identify their personal information and, with the permission of the National Bioethics Committee, contact them personally for further research. Professor Árnason adds that this provision was not intended to allow researchers to inform individuals about their particular results.⁵⁷ Moreover, Iceland's 2014 Act on Scientific Research in the Health Sector covered the use of data for research purposes, but did not address reporting back health data to individuals.⁵⁸

Once deCODE was able to identify the approximately 1,200 Icelandic women with a greater than 80% risk of facing breast and/or ovarian cancer associated with the BRCA2 gene, Stefánsson urged the Icelandic Ministry of Health to decrypt the data and inform these women.⁵⁹ Decrying the Icelandic health authorities' uncertainty as to how to proceed, Stefánsson emphasized: "I have told them that I find it ruthless not to at least contact these women and offer to keep them under close surveillance. I am convinced that it is possible to prevent premature death in this group of women."⁶⁰ Given that the mutation is lethal, and "particularly when it comes to the women, most of the risk can be mitigated by preventive surgery," Stefánsson demanded "[w]hy aren't we taking advantage of this today?"⁶¹

In a public meeting held in 2013, one alternative proposal offered was to foster an informed social discussion, and then allow citizens to inquire regarding their genetic mutations.⁶² In response, Stefánsson asked: "Is it sufficient that we tell the society that this information is obtainable or should we approach these women?" and then answered: "As an old fashioned physician, I am of the opinion that we have to approach them because the likelihood that they will get cancer and die from it is far too high for us to simply stand by and watch."⁶³

In 2014 the Icelandic Parliament enacted legislation authorizing the Minister of Health to establish regulations regarding when and how an individual who participated in scientific research should be informed about IFs, but that the new provision did not address the issue of whether it should be undertaken with or without consent. This lack of clarity had left deCODE and the DPA in limbo, awaiting a political resolution, perhaps at an international level.⁶⁴ Stefánsson acknowledged the need for a legislative

57 *Id.*

58 Petrone, *DeCode Begins BRCA2 Mutation Service*, *supra* note 1.

59 Árnason, *supra* note 52, at 425.

60 *Id.* (citation omitted).

61 Petrone, *In Iceland, Debate Simmers*, *supra* note 4.

62 Árnason, *supra* note 52, at 425.

63 *Id.* (citation omitted).

64 Petrone, *In Iceland, Debate Simmers*, *supra* note 4.

solution, conceding that the role of the DPA “is to protect privacy” rather than to “launch new healthcare services.”⁶⁵

While the DPA did not authorize contacting individuals about their imputed genetic information, nor did it oppose the release of such information where individuals explicitly request it. The Icelandic DPA has in fact acceded in the past to demands from people who have been genotyped and requested their information⁶⁶. Consequently, deCODE seized the opportunity to establish its website in spring 2018, informing inquirers whether they are positive or negative, a carrier or a non-carrier, and how to access genetic counseling. Within the first twenty-four hours of offering its service, about 20,000 people signed up, though by summer 2018 only about 5,000 had registered to receive their status.⁶⁷ Stefánsson stated that he had always predicted that “we would have relatively few people sign up on this website,” and expressed regret that making the service available on request only is not reaching as many people as he would like. Noting that this mutation confers risk to relatively young people who “walk around with the illusion of immortality,” Stefánsson is pressing his case of making the BRCA2 data available to Icelanders via their electronic health records, even without express consent.⁶⁸

The Ministry of Health’s decision to decline to supply the information to Icelanders absent their express consent was formulated in light of the “right not to know.” This precept, enshrined in international regulations and norms, faces challenges as advances in genomic technology furnish unprecedented health information about people even in the absence of their personal participation in genomic research.

V. GENOMIC RESEARCH AND THE RIGHT NOT TO KNOW UNDER NATIONAL AND INTERNATIONAL REGULATIONS AND NORMS

During the early years of genetic testing, the right not to know was a norm, given the way that the industry operated. Just a decade ago, researchers generally collected only the data necessary to answer their specific scientific questions. More recently, however, large-scale genomic sequencing has become a powerful tool with the potential to revolutionize health care. In the process, it produces massive amounts of information,

65 *Id.*

66 *Id.*

67 Petrone, *DeCode Begins BRCA2 Mutation Service*, *supra* note 1.

68 *Id.*

including incidental findings.⁶⁹ Legal instruments governing the right not to know were generally created, however, well before the emergence of large-scale genomic sequencing.

In 1997, the UNESCO Universal Declaration on the Human Genome and Human Rights recognized the right of individuals “to decide whether or not to be informed of the results of genetic examination” and concluded that “the resulting consequences should be respected.”⁷⁰ That same year, the European Convention on Human Rights and Biomedicine declared that while “[e]veryone is entitled to know any information collected about his or her health,” nonetheless “the wishes of individuals not to be so informed shall be observed” because “[p]atients may have their own reasons for not wishing to know about certain aspects of their health.”⁷¹ In the United States around that same time, the National Bioethics Advisory Commission declared in 1999 that, specifically with respect to research involving human biological materials, “the disclosure of research results to subjects represents an exceptional circumstance.”⁷² Disclosure was allowable only if “a) the findings are scientifically valid and confirmed, b) the findings have significant implications for the subject’s health concerns, and c) a course of action to ameliorate or treat these concerns is readily available.”⁷³ The American College of Medical Genetics and Genomics (“ACMG”), providing guidance in the clinical context, declared “patients should be given the option of not receiving certain or secondary findings.”⁷⁴

As Professor Berkman has explained, the RNTK began attracting increasing controversy as sequencing technology advanced and moved from the research setting into the clinical realm. This change arose from the fact that genomic sequencing was improving, leading to an increase in the number of genetic variants that could be strongly linked to medical conditions. Concomitantly, a greater number of patients were being sequenced, supporting the notion that genomic sequencing would have an

69 Berkman, *supra* note 6, at 3-4.

70 Universal Declaration on the Human Genome and Human Rights, Nov. 11, 1997, UNESCO Gen. Conf., 29th Sess., Res. 16, *adopted and endorsed by the United Nations in G.A. Res. 53/152* (Dec. 9, 1998).

71 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, art. 10.2, Apr. 4, 1997, E.T.S. 164, <https://rm.coe.int/168007cf98>.

72 NAT’L BIOETHICS ADVISORY COMM’N, RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIALS: ETHICAL ISSUES AND POLICY GUIDANCE 72 (1999).

73 *Id.*

74 AM. COLL. OF MED. GENETICS & GENOMICS, POLICY STATEMENT: POINTS TO CONSIDER IN THE CLINICAL APPLICATION OF GENOMIC SEQUENCING ¶ 8 (2012), <http://www.acmg.net/PDFLibrary/Genomic-Sequencing-Clinical-Application.pdf> (emphasis omitted).

important role in clinical care.⁷⁵

It was in this context that the ACMG recommended that geneticists should test for and report incidental findings for a “minimal list” of fifty-seven genes (later reduced to fifty-six) and twenty-four disorders, as these were considered the most verifiable by other diagnostic methods and amenable to prevention and/or treatment. In addition, the ACMG recommended such testing because individuals with these mutations might remain asymptomatic for long periods.⁷⁶ The ACMG advocated proceeding without requesting a patient’s preferences, largely due to the concern that providing genetic counseling “will become increasingly unwieldy as clinical sequencing becomes more common and more commonly ordered by clinicians with varying levels of ability and experience in genetic counseling.”⁷⁷ It should be noted that the ACMG recommendations explicitly referred to the clinical context, and expressly declined to address genomic sequencing done for research purposes.⁷⁸

The ACMG retracted its policy in 2013, the same year it had been made, acknowledging the “consensus view” among its members that “patients should have an opportunity to opt out of the analysis of medically actionable genes when undergoing whole exome or genome sequencing.”⁷⁹ Nevertheless, this incident demonstrates the unsettled nature of the RNTK, with the ACMG expressing its belief that the issues needed to evolve over time.⁸⁰ In Iceland, the Ministry of Health chose to honor the RNTK, which troubled Stefánsson, all the more so given that so few Icelanders have registered to receive their BRCA2 status.⁸¹ This dilemma necessitates a closer analysis of the legal and ethical issues surrounding the three options considered by Icelandic government for the return of BRCA2 incidental findings.

⁷⁵ Berkman, *supra* note 6, at 12-13.

⁷⁶ Robert C. Green et al., *ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing*, 15 *GENETICS MED.* 565, 566-68 (2013).

⁷⁷ *Id.* at 568.

⁷⁸ *Id.* at 569 (stating that “[a]lthough we hope that investigators find our process and these recommendations useful in their attempts to design thresholds and lists for the return of genomic findings to research participants, we did not design this list for that purpose,” and emphasizing that the recommendations were “for the situation in which a clinician orders exome or genome sequencing for a specific clinical indication”).

⁷⁹ Press Release, Am. Coll. of Med. Genetics & Genomics, ACMG Updates Recommendation on “Opt Out” for Genome Sequencing Return of Results, (Apr. 1, 2014), https://www.acmg.net/docs/Release_ACMGUpdatesRecommendations_final.pdf.

⁸⁰ *See id.*

⁸¹ *See supra* note 67 and accompanying text.

VI. THE THREE POSSIBLE APPROACHES TO THE RELEASE OF IMPUTED GENETIC DATA CONSIDERED BY THE ICELANDIC GOVERNMENT

Professor Árnason highlights the ethical quandary facing society in Iceland, where researchers are able to identify individuals at a relatively high risk of developing serious conditions such as breast cancer, but have “no channels” to convey this information.⁸² He delineates the three possible approaches to this dilemma considered in Iceland: (1) to do nothing; (2) to make it publicly known that the information is available and thus to enable individuals to take the initiative to request that information for themselves; or (3) to contact the affected individuals directly and inform them that researchers possess information relevant to their health, which is the approach favored by the CEO of deCODE Genetics.⁸³ Each of these approaches requires analysis in light of the broader policy considerations and the considerable literature relating to the RNTK.

A. Arguments Against Returning Incidental Findings

There are numerous compelling arguments against the return of the BRCA2 research results, even when all of the following preconditions are met, as they are in the case of deCODE’s IFs relating to the presence of the BRCA2 mutation in many Icelanders: 1) the genetic health finding clearly presents an established health risk to the individual; 2) the genetic finding is actionable, meaning that therapeutic or preventive measures are available; and 3) there is no clear indication that the individual prefers not to receive the results.⁸⁴

From the perspective of the data contributor, the return of IFs, where consent has not been explicitly requested and obtained, could be said to threaten individual autonomy and privacy. Conversely, from the perspective of the research community, significant burdens would befall them if the return of IFs were mandated.

In the field of biomedical research, the principle of autonomy, or self-determination, suggests that each individual has the right not to know selected information about herself.⁸⁵ Because genetic information can

82 Árnason, *supra* note 52, at 425-26.

83 *See id.* at 426-29.

84 For a discussion of the importance of these factors when considering the return of IFs, see generally Wolf et al., *supra* note 11.

85 *See, e.g.,* Bartha M. Knoppers, *Introduction: From the Right to Know to the Right Not to Know*, 42 J.L. MED. & ETHICS 6, 6 (2014) (“Respect for the autonomy of research participants recognizes that all individuals have the right to make their own decisions.”); ANTICIPATE AND

cause psychological and economic harm, individuals ought to have the freedom to weigh the risk of harm against potential benefits they may glean from the information.⁸⁶ Proponents of the right not to know decry paternalism in medical care. For example, when the American College of Medical Genetics proposed in 2013 to mandate testing by its members for certain mutations,⁸⁷ this proposal ultimately failed, in large measure because it represented an example of medical paternalism that is no longer accepted.⁸⁸

In addition to autonomy, the right of privacy supports the notion that an individual has the right not to be identified individually and linked to her genetic profile, whether in her own mind or the mind of others. Professor Laurie notes that it can be a violation of privacy to receive information about oneself from another.⁸⁹ Laurie describes privacy as “being in a state of (psychological) separateness from others,” and explains that disclosure will have consequences for the individual and others, but the “individual who is the focus of our attention is the very person who is removed from having a say in the outcome,” such that “a core sense of self can be fundamentally affected – potentially in an adverse way – by information disclosure.”⁹⁰

Revelation of negative genetic information may lead not only to anxiety and depression within the individual, but also may give rise to stigma and even discrimination in areas such as employment and insurance.⁹¹ Indeed, it is this very notion of genetic privacy that undergirds

COMMUNICATE, *supra* note 11, at 59 (“The autonomous patient also has a right *not* to know selected information and should be able to exercise this right (to the extent possible).”).

⁸⁶ Berkman, *supra* note 6, at 23.

⁸⁷ See *supra* notes 76-79 and accompanying text.

⁸⁸ See, e.g., Anne Townsend et al., *Paternalism and the ACMG Recommendations on Genomic Incidental Findings: Patients Seen But Not Heard*, 15 GENETICS MED. 751, 751 (2013) (“The traditionally paternalistic model of medicine, underpinned by values and assumptions about passive patient and authoritative physician roles, is increasingly criticized by patients, advocacy groups, health policy makers, and many physicians.”); see also Tuija Takala, *Genetic Ignorance and Reasonable Paternalism*, 22 THEORETICAL MED. BIOETHICS 485, 490 (2001) (stating that individual autonomy should be insulated from societal judgment and paternalistic views based upon the purportedly objective notion of “what a reasonable person would do”).

⁸⁹ Graeme Laurie, *In Defence of Ignorance: Genetic Information and the Right Not to Know*, 6 EUR. J. HEALTH L. 119, 119-120 (1999).

⁹⁰ Graeme Laurie, *Privacy and the Right Not to Know: A Plea for Conceptual Clarity*, in THE RIGHT TO KNOW AND THE RIGHT NOT TO KNOW 38, 41 (Ruth Chadwick et al. eds., 2014).

⁹¹ See, e.g., Kirke D. Weaver, *Genetic Screening and the Right Not to Know*, 13 ISSUES L. & MED. 243, 243 (1997) (“[S]uch knowledge can lead to anxious preoccupation with the ever present disease potential within, and discrimination by employers, insurers, governmental agencies, and health care providers without.”). See also Clarissa Allen et al., *Defining the Scope of Public Engagement: Examining the “Right Not to Know” in Public Health Genomics*, 42 J.L. MED. & ETHICS 11, 15 (2014) (cautioning that revelation of genetic information particularly endangers members of “traditionally

the Icelandic Data Protection Authority's requirement that deCODE, when generating imputed data, would make use of statistical results but delete data that is individually identifiable.⁹²

A further privacy argument rests on the notion that individuals have the right to refuse medical treatment. One group of bioethics scholars states that the ACMG recommendations impinged on a mentally competent patient's "virtually unlimited" right to refuse treatment, noting that "any patient accepting [whole genome sequencing] for a clinical indication must also accept analysis of the 56 genes. . . ."⁹³ As noted by Berkman, the right to refuse medical treatment rests upon common-law informed consent jurisprudence and Fourteenth Amendment substantive due process liberty interests,⁹⁴ and he cites cases where courts have held that there is a constitutionally protected interest in rejecting medical care.⁹⁵ However, Berkman claims that cases upholding the right to refuse medical treatment all rest upon the right to bodily integrity, not psychological integrity, and that this distinction therefore undercuts the notion that the right to refuse treatment supports a RNTK.⁹⁶ In support of this argument, Berkman cites specific laws that in fact require people to receive unsettling medical information, including state laws requiring women seeking abortions to receive various kinds of knowledge about the fetus they are carrying (including gestational age and an ultrasound image); mandating that plaintiffs in toxic tort cases undergo court-ordered genetic testing; and requiring HIV testing and/or disclosure of HIV status.⁹⁷ These arguments are not effective, however, in defeating a person's privacy interest in the RNTK her genetic mutations, because in the examples given the individual required to undergo the testing seeks to assert rights that arguably will impact another, whether a fetus, a toxic tort defendant, or a potential sexual partner. Berkman was not considering, and the same interests do not lie in, a case where a person is being offered imputed genetic information, as in the deCODE BRCA2 scenario. What is more, the cases cited by Berkman generally deal with medical conditions that are actually present, such a pregnancy or HIV, rather than the risk of genetic condition, which is much less certain, and therefore entails a stronger RNTK.

marginalized groups," who are often at greater risk of health problems "due to a higher exposure to environmental risk factors").

92 See *supra* notes 40-43 and accompanying text.

93 Wylie Burke et al., *Recommendations for Returning Genomic Incidental Findings? We Need to Talk!*, 15 GENETICS MED. 854, 856 (2013).

94 Berkman, *supra* note 6, at 36.

95 *Id.* at 36 n.206 (citations omitted).

96 *Id.* at 36-40.

97 *Id.* at 41-45, 48-50.

Like the cases dealing with the required receipt of unsettling information, the duty to warn cases analyzing the obligations of medical professionals to warn patients similarly fail to support the notion that researchers have a duty to inform an individual of her genetic risk factors. As noted by one expert, the ethical issues raised are not new in that “in clinical genetics, when you genotype family members, you can say in some cases with certainty that another family member will be a carrier of a certain dominant disease; however, you are not permitted to inform them of this without consent.”⁹⁸ Generally, under our health care model, the decision to share tests results rests with the first family member tested, meaning that some or all relatives may lack access to the information that may affect their own health care.⁹⁹ Past duty to warn cases, which involve a medical professional’s duty to warn family members of hereditary health risks and weigh a patient’s rights of autonomy and privacy against third-party interests,¹⁰⁰ do not stand in contradiction to the prevailing norm protecting individual privacy. One case addressing the duty to warn found a duty to warn a patient about the genetic basis of her disease so that she could inform her relatives, but held that a physician could discharge this duty simply by informing the patient.¹⁰¹ In another case considering whether a physician had to warn at-risk relatives of a patient with a hereditary disease, the court held that simply disclosing the information to the patient might not discharge the physician’s duty to warn.¹⁰² However, this case was subsequently overturned by the New Jersey legislature,¹⁰³

98 Petrone, *In Iceland, Debate Simmers*, *supra* note 4.

99 Mary B. Daly et al., *Communicating Genetic Test Results Within the Family: Is It Lost in Translation? A Survey of Relatives in the Randomized Six-Step Study*, 15 *FAMILIAL CANCER* 697, 701 (2016).

100 Berkman, *supra* note 6, at 46-47.

101 *Pate v. Threlkel*, 661 So. 2d 278, 280-82 (Fla. 1995). In this case, a physician had performed surgery on the plaintiff’s mother for medullary thyroid carcinoma but had failed to warn his patient about the need for her children to be tested for this genetically transmissible condition. The plaintiff argued that, as a result of this failure to warn, she was not tested early enough to prevent her development of medullary thyroid cancer. *Id.* at 279. The issue before the court was whether a physician owes “a duty of care to the children of a patient to warn the patient of the genetically transferable nature of the condition for which the physician is treating the patient[.]” *Id.*

102 *Safer v. Estate of Pack*, 677 A.2d 1188, 1192-93 (N.J. Super. Ct. App. Div. 1996). In this case, the physician had treated the plaintiff’s father for a precancerous disease known as multiple polyposis of the colon, from which he later died in the early 1960s. *Id.* at 1189-90. Thirty years later, the plaintiff developed the same condition. *Id.* at 1190. After having obtained her father’s medical records, which revealed that he had suffered from the same disease that she had, the daughter filed suit in 1992 alleging that the doctor had violated a duty of care by failing to warn her of the risk to her health. *Id.*

103 N.J. STAT ANN. § 10:5-47 (West 2007) (limiting, but not nullifying, the disclosure by physicians of genetic information without the consent of the plaintiff).

has not been widely followed, and has occasioned academic criticism.¹⁰⁴

While the arguments presented thus far consider the RNTK from the perspective of the individual about whom IFs have been revealed, a complementary set of arguments in favor of the RNTK assumes the perspective of researchers who conduct genomic research, recognizing that the goals of clinical care and population database research differ greatly.¹⁰⁵ As noted by Professor Simm of the University of Tartu in Estonia, “while it might have been relatively straightforward for the radiologist to contact the patient or patient’s physician regarding incidental finds, the matter is much more complicated for researchers far removed (both institutionally and geographically) from the biological owners of mostly anonymized samples.”¹⁰⁶ Providing this information would certainly be costly, and it is not clear which party should bear the burden of the cost.¹⁰⁷

Another challenge facing researchers and bio-specimen donors alike is the danger inherent in conflating research scientists with physicians, such that imposition of a duty to return feedback could “lead to the strengthening of therapeutic misconception: a mistaken perception of the research participants that they are being cured and cared for.”¹⁰⁸ As noted by Árnason, when Stefánsson refers to himself as an “old fashioned physician,”¹⁰⁹ he conflates the two concepts in a way that can certainly confuse potential research participants as to the fundamentally arm’s-length relationship between a research participant and her researcher.¹¹⁰ Indeed, U.S. case law has firmly established that a researcher does not owe to a research participant the duties that a doctor would owe to her patient.¹¹¹ Thus, there is a strong argument for the traditional separation of the domains of clinical care, which focuses on treating the individual, and research, which aims for the creation of new knowledge for the benefit of future generations. In this view, it is natural that distinct ethical principles guide these two domains, with beneficence and the avoidance of harm important for clinical care, whereas the development and dissemination of

104 Berkman, *supra* note 6, at 47-48.

105 Árnason, *supra* note 52, at 426.

106 Simm, *supra* note 10, at 55.

107 *Id.* at 60.

108 *Id.*

109 *See supra* note 63 and accompanying text.

110 Árnason, *supra* note 52, at 426.

111 *See, e.g.,* Greenberg v. Miami Children’s Hosp. Research Inst., Inc., 264 F. Supp. 2d 1064, 1072 (S.D. Fla. 2003) (declining to hold that researchers owe a fiduciary duty to donors of bio-specimens and genetic data); Moore v. Regents of the Univ. of Cal., 793 P.2d 479, 486 (Cal. 1990) (holding that, absent a physician-patient relationship, researchers do not owe a fiduciary duty to donors of bio-specimens and data).

information are crucial for research.¹¹²

As a practical matter, there are significant constraints on the ability of researchers to establish reliable criteria for selecting which genetic IFs to offer. The BRCA2 gene associated with breast and ovarian cancer may seem to be an easy case, as there is a clear link between this mutation and the disease, and prophylactic mastectomy has proved to be one effective approach for some patients. In fact, the suggestion of directly contacting individuals with the BRCA2 mutation has met with much criticism in Iceland for several reasons. Árnason explains that the population genetic results derive only partially from whole-genome association studies and rely instead on statistical imputation, thereby failing to provide accurate information about the number of people who carry the BRCA2 transmutation.¹¹³ Second, even for a well-characterized gene such as BRCA2, there are variants of indeterminate significance.¹¹⁴ Third, the available treatment is invasive and is not certain to succeed, so there is concern that revelation of the information will engender unnecessary interventions. Finally, the Icelandic national health service is already facing limited resources, and a focus on this particular disease may not be the most efficient use of those resources.¹¹⁵

A case profiled in the *New York Times* demonstrates the difficulties involved in revealing genetic risk factors, even with the help of a genetic counselor. One recent article cited the case of Jennifer, a healthy thirty-nine-year-old woman with a family history of breast cancer who decided to be tested for mutations in two genes associated with the disease. When a genetic counselor offered her additional tests for twenty other diseases linked to various cancers, Jennifer accepted, believing that more information would only be useful. She described the results as “surreal,” however. While Jennifer did not have mutations in the breast cancer genes, she did have a mutation in a gene linked to a high rate of stomach cancer. Because she did not have a family history of the disease, the significance of this finding was uncertain, even as the mutation is considered so risky among patients with a family history of the disease that they are often advised to have their stomachs excised prophylactically.¹¹⁶ While this

112 See Árnason, *supra* note 52, at 426.

113 *Id.* at 425.

114 Bjørn Hofmann, *Incidental Findings of Uncertain Significance: To Know or Not To Know – That Is the Question*, 17 BMC MED. ETHICS 2 (2016), <https://bmcomedethics.biomedcentral.com/articles/10.1186/s12910-016-0096-2>.

115 Árnason, *supra* note 52, at 425.

116 Denise Grady & Andrew Pollack, *Finding Risks, Not Answers, in Gene Tests*, N.Y. TIMES (Sept. 22, 2014), <https://www.nytimes.com/2014/09/23/health/finding-risks-not-answers-in-gene->

situation arose in the context of elective genetic testing, it could just as easily occur if estimated data were returned to people who had not chosen to undergo such testing.

As noted by Hofmann, because what is revealed is not certain knowledge, but rather risk information that causes considerable uncertainty, “it is fair to ask whether Jennifer has a right to be ignorant.”¹¹⁷ He emphasizes that it is critical to distinguish between findings that will be of value to the patient and those he deems incidental findings of uncertain significance (“IFUS”). Furnishing the latter is not beneficent, in light of the fact that the predictive accuracy of such information may be poor or nonexistent, and actionability is speculative.¹¹⁸

B. Arguments in Favor of Making It Publicly Known That Imputed Genetic Information Is Available and Inviting Individuals to Request Information Themselves

There are several arguments in support of the notion that researchers ought to make it publicly known that imputed genetic information is available and invite requests for such information, even absent a prior informed consent process. Some experts contend that a person’s autonomy is actually preserved, rather than undermined, by receiving genetic information about herself. As explained by Vayena and Tasioulas in the context of the ACMG’s proposal to return IFs to patients,¹¹⁹ “it is arguable that the proposed ACMG regime for incidental findings actually enhances patient autonomy” by “generating a fuller menu of worthwhile options from which patients can make life-shaping (including life-saving) choices.”¹²⁰ Icelanders affected by the BRCA2 mutation, if offered information about their health, could choose prophylactic measures such as an elective mastectomy, and also monitor their health more closely. Although paternalism can be used as an argument against returning IFs,¹²¹ it should be noted that there are “paternalistic undertones” as well when

tests.html.

117 Hofmann, *supra* note 114, at 2.

118 *Id.* at 3.

119 See *supra* notes 74-79 and accompanying text.

120 Effy Vayena & John Tasioulas, *Genetic Incidental Findings: Autonomy Regained?*, 15 GENETICS MED. 868, 868 (2013). See also Berkman, *supra* note 6, at 30-31 (observing that autonomy demands “critical reflection,” and is contingent upon thoughtful, informed decision making); Jorgen Husted, *Autonomy and a Right Not to Know*, in THE RIGHT TO KNOW AND THE RIGHT NOT TO KNOW 24, 27 (Ruth Chadwick et al. eds., 2014) (stating, in the context of unsolicited disclosure to relatives, that “[i]n the case of unsolicited disclosure . . . what initially seems to be a denial of autonomy is just the opposite: it is done in the name of autonomy and the result is an enhancement of autonomy, an opening of options.”).

121 See *supra* notes 85-88 and accompanying text.

the concept of avoidance of harm is invoked as an argument against disclosure of IFs.¹²² Paternalism is particularly suspect when viewed in the context of dominant and marginalized groups. For example, a group of experts who have argued for population level BRCA screening maintain that “[w]omen do not benefit by practices that ‘protect’ them from information regarding their own health.”¹²³

Commentators also critique the privacy argument raised by those who oppose the revelation of IFs. Skopek contends that although “large scale data analysis may allow us to infer facts about people that they would rather keep secret, and thereby cause them privacy losses, such inferences should not be treated as privacy violations.”¹²⁴ This aligns with the view of deCODE’s Dr. Stefánsson, who contends that detecting IFs through estimated data does not violate a person’s privacy because it is not actually sequencing her DNA or collecting personal information from her, but rather forming “conjectures” or “hypotheses” about the person.¹²⁵ Stefánsson explains that estimated DNA sequences, unlike directly measured sequences, are not very accurate for individuals, though they are valuable at the group level.¹²⁶ For example, as noted by Craig Venter of the biotechnology firm Celera Inc., which published the complete sequence of his genome in 2007, although his genomic data indicates an increased statistical risk of developing Alzheimer’s disease, he was not surprised that his brain scan results were negative for early signs of the disease. “What works statistically for a population with genomics does not work statistically for individuals. Either you have something or you don’t. You don’t have 30 percent of Alzheimer’s.”¹²⁷

Those who advocate for inviting individuals to learn more about their IFs also minimize the dangers of conflating the duties of researchers and clinicians.¹²⁸ As explained by Wolf et al., at least in cases where contributors are asked to consent to use of their samples and data in a biobank (as opposed to situations where contributors are never asked for consent because their samples and data are deidentified and therefore used

122 Simm, *supra* note 10, at 62.

123 Mary-Claire King et al., *Population-Based Screening for BRCA1 and BRCA2*, 312 J. AM. MED. ASS’N 1091, 1092 (2014).

124 Jeffrey Skopek, *Big Data’s Epistemology and Its Implications for Precision Medicine and Privacy*, in *BIG DATA, HEALTH LAW, AND BIOETHICS* 30, 40 (I. Glenn Cohen et al. eds., 2018).

125 Kaiser, *Agency Nixes deCODE*, *supra* note 31, at 1389.

126 *Id.*

127 Liza Gross, *The First Individual Genome: One Is the Loneliest Number*, PLOS: BIOLOGUE (Oct. 21, 2013), <http://blogs.plos.org/biologue/2013/10/21/the-first-individual-genome-one-is-the-loneliest-number>.

128 See *supra* notes 108-112 and accompanying text.

in research that is not considered human subjects research), these contributors may expect to be offered IFs, particularly where a specified disease is being studied, and “may misconstrue research silence as an indication that there are no findings of individual health concern.”¹²⁹ Even when individuals are not directly involved in contributing to a biobank and their data is instead imputed, individuals may expect the return of their IFs. This may be especially true in a small, sparsely populated country with nationalized health care, such as Iceland. However, a growing body of survey evidence from the United States indicates that even in a large, diverse nation without nationalized health care, “many individuals want and even expect to receive” their IFs, especially where researchers reveal genetic mutations with significant health implications.¹³⁰ Indeed, a failure to return results could lead to mistrust of researchers and impede their access to genetic specimens and data if individuals feel wary of researchers who remain impervious to concerns about the health of their subjects.¹³¹ In order to minimize any negative effects arising from the conflation of researchers and clinicians by the recipient of genetic information, these recipients could be reminded to seek the advice of their health care professionals,¹³² and that such findings were simply incidental to the main purpose of the research, which is to reveal, through the study of large groups, potential causes, diagnoses, treatments, and cures for diseases having a genetic component.

Offering research results to individuals achieves more than simply meeting their expectations and/or avoiding their disaffection. Simm explains that the very nature of medical care and research are undergoing a seismic shift, ushering in an era of “participatory medicine” and the rise of medical innovation in clinical settings, necessitating a model of researcher-subject relations that encompasses reciprocity.¹³³

This notion of participatory medicine gets to the heart of why offering IFs could be beneficial, and to the very purpose of genetic research itself.

129 Wolf et al., *supra* note 11, at 366 (citations omitted).

130 *Id.* at 366 (citations omitted).

131 Simm, *supra* note 10, at 60 (noting that “public awareness of researchers holding on to information that can greatly benefit donors, can also lead to a loss of trust towards the biobank”).

132 Kadri cites studies of direct-to-consumer genetic testing indicating that many consumers do not share the results of their genetic tests with their primary physicians and that few take advantage of the free genetic counseling offered, demonstrating that consumers are not very reliant upon their primary care physicians, and that this phenomenon of conflation is therefore less important than might be imagined. *Id.* at 66. She further speculates that, as the cost of whole genome sequencing decreases, doctors will routinely make use of this technology, thereby returning the discussion of IFs to the traditional doctor-patient relationship. *Id.*

133 *Id.* at 61 (stating that “[i]f the train of personalized medicine is ever to truly leave the station, the overlapping of medical care and research must intensify”).

As explained by Vayena and Tasioulas, informing individuals of incidental genetic findings not only enables “the pursuit of improved health outcomes” for the affected individuals, but also benefits “the patient's relatives and serve[s] the common good of promoting a healthy society.”¹³⁴ Indeed, Rosamond Rhodes argues that we owe a moral obligation to ourselves and to one another to pursue all relevant genetic knowledge, without being distracted by emotions such as fear or a false sense of security, in order to foster our own health, as well as that of our family members and the wider community.¹³⁵

What is more, commentators contend that the incidence of psychosocial harm from revealed genetic information is actually lower than expected. For example, Berkman cites research supporting his view that individuals are much more resilient when receiving negative health information than even they would predict.¹³⁶ In terms of economic harms to the individual about whom genetic information has been revealed, Berkman cites the paucity of litigation in the United States under the Genetic Information Nondiscrimination Act (GINA),¹³⁷ enacted in 2008, in support of the notion that “perhaps there is less cause for concern than previously thought.”¹³⁸ It should be noted that lack of litigation under GINA, which prohibits employers and health insurance companies from receiving and using genetic risk information (as opposed to an actual disease) as the basis for employment and actuarial decisions, does not establish that genetic discrimination is not occurring, and GINA has also been criticized for not covering other areas of potential genetic discrimination, such as life insurance and long-term care insurance.¹³⁹ Nonetheless, when considering the harms incurred by conveying negative genetic information to individuals who have not affirmed their desire to receive it, it is important to remember that the alternative scenario is not one completely free from harm, but rather holds the potential for the anguish that may arise when a person is diagnosed with a serious medical condition and realizes that it could possibly have been caught and treated

134 Vayena & Tasioulas, *supra* note 120, at 868-869.

135 See generally Rosamond Rhodes, *Genetic Links, Family Ties, and Social Bonds: Rights and Responsibilities in the Face of Genetic Knowledge*, 23 J. MED. & PHIL. 10 (1998).

136 Berkman, *supra* note 6, at 56-59 (claiming that, in a “broad range of medical contexts, . . . research demonstrates that people are much better at coping with negative information than they think they will be”).

137 Genetic Information Nondiscrimination Act of 2008, Pub. L. No. 110-233, 122 Stat. 881 (codified as amended at 42 U.S.C. § 2000ff(2018)).

138 Berkman, *supra* note 6, at 60.

139 Mark A. Rothstein, *GINA, the ADA, and Genetic Discrimination in Employment*, 36 J.L. MED. & ETHICS 837, 837 (2008).

earlier, had the information been available to her.

The danger of psychological harm is faced not only by those individuals about whom genetic information is known. Berkman points out that, if prohibited from offering genetic information to individuals, some researchers may experience “moral distress,” which refers to the situation where “one knows the morally correct course of action, but is constrained from taking it.”¹⁴⁰ While one might expect moral distress to be more prevalent for clinicians and researchers who deal directly with the people they are treating and studying, as opposed to researchers who develop estimated data and deal at a distance with the individuals they study, deCODE CEO Stefánsson appears to exhibit a significant amount of moral distress himself when he describes his desire to contact Icelanders affected by the BRCA2 mutation thus: “As an old fashioned physician, I am of the opinion that we have to approach them because the likelihood that they will get cancer and die from it is far too high for us to simply stand by and watch.”¹⁴¹ Describing the lasting negative impact that experiencing moral distress can have upon medical practitioners, Berkman credits Epstein and Delgado for coining the term “moral residue.”¹⁴² Given that medical professionals are charged with preventing and ameliorating disease, they are likely to suffer negative impacts upon their sense of self and their feelings about their profession if they are barred from sharing with research participants vital health information.¹⁴³

In addition, while medical professionals may seem to support the RNTK, Berkman points that such support may actually be weaker than it seems, if one takes into account the “identified life” factor.¹⁴⁴ For example, one 2014 survey of genetics professionals throughout the United States indicated that only 19% of them believed that they would return IFs regardless of the individual patient’s preferences.¹⁴⁵ However, when a specific, identified person’s life is in danger, this number can change dramatically, as evidenced by a survey of 800 institutional review board members from 2015.¹⁴⁶ When asked about the RNTK in the abstract, whether “it would be acceptable for [research participants] to choose not

140 Berkman, *supra* note 6, at 66.

141 Árnason, *supra* note 52, at 425.

142 Berkman, *supra* note 6, at 67 (citing Elizabeth G. Epstein & Sarah Delgado, *Understanding and Addressing Moral Distress*, 15 ONLINE J. OF ISSUES IN NURSING 1, 2, 4 (2010)).

143 Epstein & Delgado, *supra* note 142, at 4.

144 Berkman, *supra* note 6, at 51-53.

145 Joon-Ho Yu et al., *Attitudes of Genetics Professionals Toward the Return of Incidental Results from Exome and Whole-Genome Sequencing*, 95 AM. J. HUM. GENETICS 77, 79 (2014).

146 Catherine Gliwa et al., *Institutional Review Board Perspectives on Obligations to Disclose Genetic Incidental Findings to Research Participants*, 18 GENETICS IN MED. 705 (2016), <https://www.nature.com/articles/gim2015149>.

to receive” genetic incidental findings, 96% agreed.¹⁴⁷ The answer to this question changed, however, when these same survey respondents were presented with the case of a specific patient who was undergoing genomic sequencing for a suspected rare genetic disorder and had expressly chosen not to receive incidental findings, but evidenced a high genetic risk of a serious and actionable form of colon cancer. In this case, 26% of respondents replied that researchers should definitely or probably disclose the finding, while only 63% felt that researchers should definitely not or probably not disclose the finding, with the remaining 11% unsure.¹⁴⁸ This survey demonstrates how the RNTK is less strictly regarded where medical professionals see the opportunity to save a specific human life, even in cases where patients have actually expressed that they do not want to know their IFs. We would expect the identified life effect to operate particularly strongly in culturally homogeneous and sparsely populated Iceland, where people are often distantly related to one another. Even in countries with larger and more heterogeneous populations, it is clear that the RNTK will be less compelling where people have not expressed any wish whatsoever about their RNTK, as in the case of imputed genomic data. This is all the more true as advances in medicine promise treatments and cures for an increasing number of genetic diseases.

In arguing for the return of research results, commentators also critique the notion of genetic exceptionalism, contending that there is no justifiable reason to treat unexpected genetic information any differently than other unexpected medical information. Berkman cites the example of a patient who receives a routine blood panel to check for one condition, perhaps hypertension, but then learns that the results indicate a serious acute problem such as impending renal failure. He emphasizes that “the physician isn’t going to ask before disclosing this urgent finding.”¹⁴⁹ While acknowledging that the analogy is imperfect because genetic findings are merely statistical probabilities rather than diagnostic certainties, and genetic mutations are not typically associated with conditions that require immediate attention, Berkman nonetheless urges careful questioning as to whether genetic information truly “warrants special treatment.”¹⁵⁰ The analogy to typical medical screenings is particularly inapposite in the case of estimated data, however, since the individual whose genetic information has been revealed has not willingly

147 *Id.* at 708.

148 *Id.*

149 Berkman, *supra* note 6, at 71.

150 *Id.*

undergone any medical screening. Yet, the argument against genetic exceptionalism still holds some force. Given that the emergence of big data has made so much information, including genetic information, accessible, it is pertinent to ask whether the manner in which information was revealed matters much in deciding whether to provide that information to the affected person.

Those who agree that the availability of imputed genetic information ought to be conveyed to individuals facing genetic risks nonetheless disagree as to the dangers in providing the information directly to the individual. Those who advocate for a public service campaign informing citizens of the existence of such information and inviting them to access the data contend that it is preferable to give them an opportunity to make arrangements for genetic counseling, rather than contacting people directly with their specific information, the option discussed below.¹⁵¹ As noted by Árnason, “[r]eceiving information about risk without professional interpretation and possibly against one’s wishes is not conducive to autonomy,”¹⁵² and he recommends that people get information through a genetic counselor so that they can make informed medical choices with the proper emotional support.¹⁵³ Similarly, one recent literature review of whole-genome and whole-exome sequencing in families with a suspected genetic disorder found that members of all stakeholder groups stressed the importance of genetic counseling at the time of disclosure of IFs. Both providers and recipients of the information stressed the necessity for face-to-face meetings with a genetics professional who could tailor the information to the participant, in terms of both content and timing.¹⁵⁴ This research also indicated that stakeholder groups across many studies stressed the importance of discussing IFs during the pretest process,¹⁵⁵ a scenario that is not feasible where the IFs are revealed via estimated data. For this reason, it is important to provide imputed data in a way that permits affected individuals to be emotionally prepared and make prior arrangements, if they wish, for genetic counseling.

DeCODE CEO Dr. Stefánsson has himself acknowledged the problems with communicating findings from biobank research directly to the research participant. He and his colleague explain that “the discovery of a mutation in a gene that is found in one hundred per cent of patients with a

151 *See infra* pt. VI.C.

152 Árnason, *supra* note 52, at 427.

153 *Id.* at 428.

154 Michael P. Mackley et al., *Stakeholder Views on Secondary Findings in Whole-Genome and Whole-Exome Sequencing: A Systematic Review of Quantitative and Qualitative Studies*, 19 GENETICS IN MED. 283, 288 (2017).

155 *Id.* at 286-287.

certain disease does not tell us, for a given number of patients with the mutation, what proportion will develop the disease, nor how reliable the test for the mutation is,” and therefore “[a] basic discovery should always be validated clinically before it is made known to individuals.”¹⁵⁶ Nonetheless, deCODE continues to advocate for contacting individuals directly to provide the precise information about their BRCA2 status.

C. Arguments in Favor of Contacting Affected Individuals Directly to Inform Them That Researchers Possess Information Relevant to Their Health

The main argument for providing imputed IFs directly to individuals is that early detection is critical in treating many genetic conditions, such as breast and ovarian cancer arising from the BRCA2 mutation. As noted previously, only about 5,000 Icelanders have registered to receive their BRCA2 status.¹⁵⁷ Giving deCODE permission to contact the affected individuals directly would be a rapid and certain method of providing the information, which could lead to a better prognosis for many patients. Preventative mastectomy reduces the likelihood of breast cancer from 72% down to 5%, and therefore Stefánsson urges that “it is a merciless view to come to a conclusion that we should not approach these women.”¹⁵⁸

Wolf and colleagues, in considering furnishing IFs directly to those who have personally contributed bio-specimens and data for research, note that providing the results directly to the individual respects her autonomy and privacy.¹⁵⁹ One possible compromise suggested is to ask individuals, at the same time that they are asked if they would like return of IFs detected through imputed data, whether they would like to receive such information directly or would prefer that it be sent to their primary care physician or another designated clinician.¹⁶⁰ It avoids the issue of paternalism discussed above,¹⁶¹ in that the recipient of the IF information is presumed to be capable of handling it. For imputed genetic findings, however, there is no such clear opportunity to request informed consent.

Providing information directly to the individuals rather than indirectly through a public service campaign also avoids one particular practical challenge, in that those people who already know that they are at risk for

156 Gulcher & Stefánsson, *supra* note 54, at 1828.

157 *See supra* note 67 and accompanying text.

158 Petrone, *DeCode Begins BRCA2 Mutation Service*, *supra* note 1.

159 Wolf et al., *supra* note 11, at 376.

160 *Id.*

161 *See supra* notes 85-88 and accompanying text.

genetic disorders are more likely to seek out such information. Other individuals, who may be affected by very rare and serious disorders, may not be aware of this fact and may not inquire, which makes the direct provision of information to them all the more crucial.¹⁶²

The mandatory provision of health risk information has been implemented in some states with respect to HIV/AIDS. These jurisdictions therefore provide a useful case study for the scenario contemplated by deCODE.

VII. AN EXAMPLE OF MANDATORY REVELATION OF HEALTH RISK INFORMATION: HIV/AIDS

In the context of HIV/AIDS, the law of several jurisdictions requires medical professionals to provide health risk information to individuals, without explicitly requiring consent. Several states and some cities have enacted laws requiring health care providers to inform needle-sharing or sexual partners of HIV positive people of the HIV status of the affected individual.¹⁶³ As noted by one commentator, “[o]n a spectrum that puts individual patient confidentiality on one end and public health protection on the other, New York may have one of the most aggressive statutes to protect the public.”¹⁶⁴

The New York HIV partner notification statute imposes an affirmative duty on every physician or health care provider authorized to diagnose HIV/AIDS to report the positive status of individuals to the state health commissioner along with the names of any identified spouse, sex partner, or needle-sharing partner.¹⁶⁵ Once the report is received, the names are then referred to the local health authority so that listed partners may be notified.¹⁶⁶

The purpose of New York's law is to protect the health of the sexual and needle-sharing partners of the HIV-positive individual by informing

¹⁶² Árnason, *supra* note 52, at 428.

¹⁶³ *Limits on Confidentiality*, HIV.GOV, <https://www.hiv.gov/hiv-basics/living-well-with-hiv/your-legal-rights/limits-on-confidentiality> (last updated May 15, 2017).

¹⁶⁴ Jacquelyn Burke, *Discretion to Warn: Balancing Privacy Rights with the Need to Warn Unaware Partners of Likely HIV/AIDS Exposure*, 35 B.C. J.L. & SOC. JUST. 89, 105 (2015) (discussing the law of New York State, as well as several other states that provide for partner notification).

¹⁶⁵ N.Y. PUB. HEALTH LAW § 2130 (McKinney 2010). *See also What Is Partner Notification?*, N.Y. ST.: DEP'T OF PUB. HEALTH, https://www.health.ny.gov/diseases/aids/providers/regulations/reporting_and_notification/about_the_law.htm#quest2 (last modified Jan. 2010) (stating that “[d]octors and labs must report to the Health Department the names of persons with HIV infection, HIV illness and AIDS and “must also report the names of sex and needle-sharing partners of people who test HIV positive that are known to the doctor”).

¹⁶⁶ N.Y. PUB. HEALTH LAW § 2130 (McKinney 2010).

them of their risk and recommending HIV testing.¹⁶⁷ These sexual and needle-sharing partners overwhelmingly approved their receipt of this information, with one study showing that 87% of the 132 partners of HIV-positive individuals located throughout New York State thought the Department of Health did the right thing in telling them about their exposure, and 92% thought that the Department of Health “should continue to notify persons exposed to HIV.”¹⁶⁸ The risk of HIV exposure is not analogous to genetic risk, however, in that HIV is an infectious disease that can be readily diagnosed, and for which early detection and treatment are clearly beneficial. The analogy to HIV exposure is not strong enough to justify contacting individuals to tell them directly of their genetic imputed findings absent their informed consent.

VIII. A WAY FORWARD FOR CONTRIBUTED AND IMPUTED DATA

There is a growing agreement that researchers ought to determine in advance and make clear to participants whether incidental findings will be offered back to participants. Currently, most biobanks have no mechanisms in place for disclosing information to donors. A recent study of eighty-five biobanks concluded that the issue of return of results was not addressed in their public documents. In recent years, more biobanks have started to ask donors whether they would like to have feedback. But this prospective process does not take into account all the biobanks that were established without disclosure policies.¹⁶⁹

Professor Árnason notes that an Icelandic committee has been working on behalf of the Minister of Welfare to craft regulations concerning the sharing of health-related information with participants who contribute directly to biobanks. While the proposals are being maintained as confidential since they are still in development, one proposal does provide that researchers are obligated, on a prospective basis, to request and honor research participants’ preference regarding whether they want to receive incidental information that is important for their health, regardless of whether their condition is amenable to medical treatment.¹⁷⁰

As to the retrospective question of how to proceed in the case where biobank contributors did not contemplate the return of their individual

167 Burke, *supra* note 164, at 105.

168 N.Y. STATE DEP’T OF HEALTH AIDS INST., THE IMPACT OF NEW YORK’S HIV REPORTING AND PARTNER NOTIFICATION (HIVRPN) LAW: GENERAL FINDINGS REPORT 5 (2006).

169 Simm, *supra* note 10, at 59.

170 Árnason, *supra* note 52, at 429.

information, the Icelandic committee recommends a case-by-case analysis. If a researcher has results concerning a serious health risk for participants, the responsible primary investigator is required to apply to the Icelandic National Bioethics Committee (“NBC”) for permission to have the information conveyed to the participants. The NBC will then set up an independent group in order to determine if and how the information should be returned to the individual.¹⁷¹

With respect to estimated data, however, researchers cannot easily obtain consent, as they are not in contact with individuals about whom genetic data is revealed. In a small country with nationalized health care such as Iceland, however, it is possible for a central entity such as the Ministry of Health to prospectively seek citizens’ consent to receive genetic information if it is imputed from large-scale genetic research. Citizens could be required to affirmatively opt in so as to receive the information. This points to a possible solution for the future, if individuals would sign a consent form that promised IFs. There is data indicating that they would. A recent survey in an Icelandic medical journal found that 90% of women felt “positive or very positive” about using existing genetic information obtained through research to inform individuals of their mutation status, although half of the respondents expressed concern that a positive result might affect their health insurance.¹⁷² Similarly, in Estonia, 83% of the potential participants in the Estonian biobank¹⁷³ wanted to receive their own personal gene map. The majority of Estonian citizens have expressed interest in disclosure of both general and individual research results.¹⁷⁴

There are significant challenges, however, to the goal of establishing a system that explicitly requests consent from all its citizens for the return of imputed genetic information. First, there is the difficulty of reaching each individual to ascertain her preferences. With an opt-in system, the failure of an individual to opt in does not necessarily indicate a lack of desire to receive imputed information, but rather may simply indicate a failure to reach that person or confusion on the individual’s part. Second, the costs of contacting each individual could hobble research. As noted by Clayton and Maguire, the U.S. Centers for Disease Control and Prevention declined to proceed with genetic research due to the cost of obtaining

¹⁷¹ *Id.*

¹⁷² Petrone, *DeCode Begins BRCA2 Mutation Service*, *supra* note 1.

¹⁷³ Katharine Schwab, *Estonia Wants to Collect the DNA of All Its Citizens*, THE ATLANTIC (Oct. 8, 2015), <https://www.theatlantic.com/health/archive/2015/10/is-a-biobank-system-the-future-of-personalized-medicine/409558/> (describing Estonia’s plan to create a biobank with data from 25% of its 1.3 million people, with the goal of personalizing health care).

¹⁷⁴ Simm, *supra* note 10, at 59.

informed consent, estimated in the millions of dollars in the 1990s, from contributors of re-identified stored tissue samples whose consent had not been obtained initially due to the de-identification of the data.¹⁷⁵ Third, even if an individual does indicate her assent to receive the information, it is possible that she does not have a clear understanding of what she agreed to and its implications, given that it is not certain that any information will ever be forthcoming, and the complexity of the information itself, which pertains to statistical risk factors rather than certain diagnoses. Fourth, as noted by Berkman, people's preferences are likely to change over time, "[b]ut unless the medical world can develop a process for actively re-soliciting preferences (an unrealistic proposition) there is the very real risk that a binding decision made at a single point in time could become inconsistent with future desires."¹⁷⁶ A fifth potential obstacle to returning this information is the magnitude of the scientific challenge facing researchers. In 2012, investigators indicated that there were over 100,000 genetic variants cited in the medical literature, and they proceeded to analyze the proportion of known genetic variants that would meet generally established criteria for disclosure.¹⁷⁷ These researchers found that between 6.9% to 10.6% of genetic variants would meet the requirements for disclosure to research participants, meaning somewhere between 4,000 to 17,000 variants. They further found that if the growth rate from the four years preceding the study were to continue, the total number of disease-associated variants would grow 37% over the next four years, such that researchers would be responsible for disclosing over 16,000 variants by 2015. Even when the variants are identified, the scientific review process to assess the criteria for each of these variants would be quite complex.¹⁷⁸ One possible approach recommended by these researchers is to develop an "empirically informed" set of guidelines for the return of results, something the U.S. National Institutes of Health is attempting to achieve.¹⁷⁹ A final challenge surrounding the goal of establishing a system that explicitly requests consent from all its citizens for the return of imputed genetic information is that researchers generally

175 Ellen Wright Clayton & Amy L. McGuire, *The Legal Risks of Returning Results of Genomics Research*, 14 GENETICS IN MED. 473, 476 (2012).

176 Berkman, *supra* note 6, at 65.

177 Christopher A. Cassa et al., *Disclosing Pathogenic Genetic Variants to Research Participants: Quantifying an Emerging Ethical Responsibility*, 22 GENOME RES. 421, 421-22 (2012). These criteria emphasize "the scientific validity of the reported association, the clinical significance of the associated phenotype, and the availability of beneficial medical interventions." *Id.* at 422.

178 *Id.* at 422-23.

179 *Id.* at 424.

do not have access to genetic counselors, nor the funds to hire such professionals.¹⁸⁰

The way forward must be an international solution, given that genetic data is often generated and shared across national borders.¹⁸¹ In order to encourage individuals to request genetic information that researchers may have collected about them, it is necessary to start with an informed public dialogue and public service announcements so that citizens are aware that such data is available.

It is clear that public discussion of genetic testing does increase awareness and encourages more people to be tested. For example, during the period in May 2013 immediately after the public figure Angelina Jolie published a widely read *New York Times* editorial announcing her decision to undergo preventive mastectomy due to her BRCA2 genetic mutation, there was an immediate increase in BRCA testing rates among U.S. women aged eighteen to sixty-four. This increase persisted through the year of 2013. However, there is some evidence that this sort of publicity may not effectively target the subpopulations that are more at risk for the relevant underlying condition. This is demonstrated by the fact that sixty-day mastectomy rates among women who had a BRCA test fell from 10% in the months before publication to 7% in the months after publication, suggesting that women who underwent tests as a result of the editorial had a lower pre-test probability of having the BRCA mutation than women tested before the editorial.¹⁸²

An examination of racial disparities in health outcomes in the U.S. for African-American and Caucasian-American patients diagnosed with breast cancer points to the need for expanded genetic testing in underserved communities. Researchers found that, compared with Caucasian patients, African-American patients are diagnosed at a younger age and are more likely to develop aggressive subtypes of breast cancer. While genetic differences between these populations play some role, just as important are other risk factors facing the African-American community, including inferior access to health care. This study points to the importance of personalized risk assessment in reducing deaths from aggressive breast cancers for African-American women.¹⁸³

In order to increase access to genetic testing, in 2009 the Cancer

180 *Id.* at 425.

181 *See supra* notes 18-19 and accompanying text.

182 Sunita Desai et al., *Do Celebrity Endorsements Matter? Observational Study of BRCA Gene Testing and Mastectomy Rates After Angelina Jolie's New York Times Editorial*, *THE BMJ*, Dec. 14, 2016, at 355, <http://dx.doi.org/10.1136/bmj.i6357>.

183 *See* Dezheng Huo et al., *Comparison of Breast Cancer Molecular Features and Survival by African and European Ancestry in The Cancer Genome Atlas*, *JAMA ONCOLOGY*, Dec. 1, 2017, 1654.

Resource Foundation, a 501(c)(3) organization led by oncology and public health nurses, implemented the Genetic Information for Treatment Screening and Surveillance (“GIFTSS”) program in Massachusetts. The purpose of GIFTSS was to support low-income, underinsured people who could not afford the out-of-pocket expenses associated with genetic testing. Referring physicians were clinical genetic counselors, OB/GYN providers, and medical oncologists.¹⁸⁴ A study of the results of this testing discovered that, when financial barriers were removed, the population studied faced comparable rates of positive genetic testing results as reported in the literature, which generally studies well-insured, Caucasian populations.¹⁸⁵

While this increased access to genetic testing clearly afforded benefits to the individuals tested, it should be noted that the voucher program created advantages for the health care system and the research community as well. As noted by the authors of a study about the GIFTSS program, “[f]or those individuals . . . who did not have a familial mutation, the emotional and financial benefit of learning of these negative results and not needing additional medical intervention may be beneficial at both the individual and the larger economic level.”¹⁸⁶ Moreover, at-risk individuals may avail themselves of treatment, diagnostic, or prevention recommendations, though the study’s authors noted that future research was necessary in order to determine if access to genetic testing truly improves outcomes for this population.¹⁸⁷ Finally, enhanced access to genetic testing in underserved populations affords researchers the opportunity to approach community members, and, after obtaining informed consent for research participation, access data that will provide better information about the health needs of this community. The reluctance of certain low-income and/or minority communities to contribute to genetic research, in light of the medical atrocities they have suffered, is well documented, and contributes to a paucity of information about the health needs of these underserved populations.¹⁸⁸ The

184 Meghan L. Underhill et al., *A State-wide Initiative to Promote Genetic Testing in an Underserved Population*, 6 CANCER MED. 1837, 1838 (2017), <https://onlinelibrary.wiley.com/doi/full/10.1002/cam4.1100>.

185 *Id.* at 1837.

186 *Id.* at 1841-42.

187 *Id.* at 1842.

188 Natalie Ram, *Assigning Rights and Protecting Interests: Constructing Ethical and Efficient Legal Rights in Human Tissue Research*, 23 HARV. J.L. & TECH. 119, 127 (2009) (stating that “[s]tudies on informed consent consistently show that African Americans consent to genetic research at rates that are statistically significantly lower than those of whites and that African-Americans are less trusting of medical researchers than whites,” due to “[p]ast abuses in medical interventions and

opportunity to receive genetic risk information in return for participation may foster trust and engagement in medical research on the part of these low-income and minority communities.

There is some bipartisan support in Congress for lowering barriers to the use of genetic testing. In February 2018, a bipartisan group of Congressional representatives introduced legislation, called the Advancing Access to Precision Medicine Act,¹⁸⁹ that would direct the U.S. Department of Health and Human Services to work with the National Academy of Medicine “to study how genetic and genomic testing might improve preventative care and precision medicine and reduce health disparities.”¹⁹⁰ Those agencies would also study the possibility of expanding health insurance coverage to cover genetic testing and counseling.¹⁹¹ This bill is still in the first stage of the legislative process, and will be considered by a committee before potentially being sent on to the House or Senate.¹⁹² While passage is unlikely, especially in the current political climate,¹⁹³ it is important to note that bipartisan support nonetheless remains for such an investment in predictive medicine.

Ultimately, the decline in the cost of genomic sequencing and the growth of the genetic testing market will make such testing widely available. Market research demonstrates that the genetic testing market continues to grow, notwithstanding the fact that even those who are insured face reimbursement challenges. There are currently more than 74,000 commercially available genetic tests in the United States and fourteen new tests entering the market daily.¹⁹⁴ In 2015, two large commercial payors, UnitedHealthcare and Anthem, instituted a process of automated prior authorization for all genetic testing and many other payors have indicated that they will follow suit. The categories of prenatal, hereditary cancer, and oncology treatment accounted for 90% of commercial payor spending.¹⁹⁵

The direct-to-consumer (DTC) testing market is also providing genetic

research involving African Americans”) (citations omitted).

¹⁸⁹ Advancing Access to Precision Medicine Act, H.R. 5062, 115th Cong. (2018).

¹⁹⁰ *California Congressman Introduces Bill to Promote Genetic, Genomic Testing*, GENOMEWEB (Feb. 16, 2018), <https://www.genomeweb.com/sequencing/california-congressman-introduces-bill-promote-genetic-genomic-testing#.W0ZUXC2ZNm8>.

¹⁹¹ *Id.*

¹⁹² *H.R. 5062: Advancing Access to Precision Medicine Act*, GOVTRACK, <https://www.govtrack.us/congress/bills/115/hr5062> (last updated Feb. 15, 2018).

¹⁹³ *Id.* (giving the bill a 3% chance of being enacted, according to an artificial intelligence research platform).

¹⁹⁴ Turna Ray, *Genetic Test Market Continues to Grow Despite Reimbursement Challenges*, GENOMEWEB (Apr. 20, 2018), <https://www.genomeweb.com/molecular-diagnostics/genetic-testing-market-continues-grow-despite-reimbursement-challenges#.W0ZwrC2ZNm9>.

¹⁹⁵ *Id.*

risk information to those who seek it out. In April 2017, the U.S. Food and Drug Administration (“FDA”) allowed marketing of 23andMe Personal Genome Service Genetic Health Risk (“GHR”) tests for ten diseases or conditions, which represent the first DTC tests authorized by the FDA that provide information about a person’s genetic risk factors.¹⁹⁶ The company charges \$199 for the test, which assesses, through a saliva sample, several genetic risk factors, including selected BRCA1 and BRCA2 variants.¹⁹⁷ The company does not provide any genetic counseling service. Instead, 23andMe refers concerned clients to professional organizations that can assist them in locating a genetic counselor.¹⁹⁸ This is similar to the deCODE website, in that individuals are proactively seeking out their genetic risk factors, albeit with a fee in the case of 23andMe.

IX. CONCLUSION

As the cost of genomic sequencing drops and consumers become more accustomed to accessing genetic risk information for themselves, whether through direct-to-consumer businesses like 23andMe or other means, public support will grow for making use of such data. This is what Stefánsson is counting on when he notes that deCODE’s new website service is “automatically building pressure on health authorities” to approach individuals about their health risks. While it can indeed prove life-saving to be informed of one’s genetic risk factors, the law should stop short of supplying such information to individuals without their explicit consent, especially when the data has been imputed. There are many valid reasons, including socio-emotional factors and the desire to avoid discrimination in health insurance, that cause people to decline this information, and each person reserves the right to make his or her own health care decisions, whether he or she is foolish or sensible. It is clear, when viewing the results in Iceland, where the information is offered free of charge but only a small percentage of citizens access it, that there is still resistance to receiving information about one’s genetic risk factors. The optimal way to make use of this information is to increase affordable access to genetic data and counseling, and also invest in robust public

¹⁹⁶ *FDA Allows Marketing of First Direct-to-Consumer Tests that Provide Genetic Risk Information for Certain Conditions*, U.S. FOOD & DRUG ADMIN. (Apr. 6, 2017), <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm551185.htm>.

¹⁹⁷ 23ANDME, <https://www.23andme.com> (last visited July 11, 2018).

¹⁹⁸ *See I’m Concerned About Something I Learned From My Reports. What Do I Do?*, 23ANDME, <https://customercare.23andme.com/hc/en-us/articles/212883077> (last visited July 11, 2018).

service media campaigns that explain the importance of accessing one's genetic profile. Any changes in norms with respect to the right not to know must come from the citizens themselves, not from the top down, and the role of the government and medical professionals is to encourage citizens to access and make informed choices about their receipt of essential genomic health data.