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Rare disease research: Breaking the privacy barrier

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ABSTRACT

Due to the few patients affected, rare disease research has to count on international registries to exist in order to produce significant research outputs. Data sharing of registries is therefore a unique resource to allow rare disease research to flourish and any lost data will jeopardize the quality of an already extremely difficult research. The rules usually applied to research such as the right to withdraw or the need for specific consent for every use of data can be detrimental in order to get effective results. Privacy rights regulated through traditional informed consent mechanisms have been regarded as a major barrier in order to effectively share data worldwide. Some authors argue that this barrier hampers results that could be beneficial to the patients so that another right will be overstated: the right to quality healthcare. We argue in this paper that privacy has been often interpreted just one-sided as the right to secrecy but it can entail another meaning: the right to manage one's own private sphere. Managing it pertains, not only to the right to deny access, but also to the right to grant access. At the same time research on patient participation and transparency shows that new forms of IT-based informed consent can provide a good balance between the right of individuals to be in control of their data and the opportunity for science to pursue international research.

1. Introduction

The role of genomics in medicine is rapidly and pervasively increasing. Genomics promises many ambitious developments, including personalized and precision medicine, and tailored drugs. Genomics knowledge is full of promise for the development of targeted therapies in rare diseases. In terms of policy, the integration of genomics in health is pervasive, so much so that the Centers for Disease Control and Prevention (CDC) states that genomics plays a role in nine of the ten leading causes of death in the United States and that it foresees the "integration of genomics into pediatric primary care and into public health practices such as screening programs designed on the basis of the genetic likelihood to develop certain diseases (Center for Disease Control and Prevention, 2013)" Genomic research also forms the basis for precision medicine, and is thus important for our understanding of rare diseases. Recent advances in genotyping and sequencing have led to a steep drop in the costs of genome scanning. The introduction of next-generation sequencing and whole genome sequencing has also led to more accurate, precise, and defined procedural outcomes. This accuracy may be used to develop a clinical understanding of what used to be known as general "research results." Biobank infrastructures are commonplace in many hospitals, and large research biobanks have also been created. All these rapid developments in genomics were made possible by huge international efforts to find effective ways to collaborate and share data, samples and technologies. Genomic results are, in fact, based on collections of data that made genome-wide association studies possible. Large data collections are necessary in order to ensure statistical significance, and to create international consortia for data sharing. The European Commission has acknowledged this necessity by supporting research consortia through substantial grants.

Rare 'orphan' disease, or diseases that are either life-threatening or chronically debilitating, affect a very small percentage of the population. Rare diseases are challenging subjects of research, in that there are very few cases upon which researchers may draw conclusions (sometimes fewer than 100 cases in the world). In the United States, a disease is considered rare if it is believed to affect fewer than 200,000 Americans. Conventional levels of statistical precision are unlikely to be met if a trial is required to evaluate treatment of a rare disease. In order to obtain a sample size of statistical significance, researchers often use data from patients in foreign countries. The very existence of rare disease research requires international collaboration and the movement of samples and data across national borders. Although genomic research is full of promise, the need for large data sets will ensure that certain types of genomic research will be difficult to perform. In point of fact, research in rare disease is extremely difficult due to the limited availability of cases.

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Rare disease research depends on international registries, since no one registry will house the requisite amount of affected persons to sustain a trial. The sharing of data registries is a unique resource that allows rare disease research to exist. That being said, medical research on biobanks and registries is only as good as the data it uses; lost data will jeopardize the quality of an already difficult research endeavor. To jeopardize genomic research in this way would engender serious consequences for patients with rare diseases, who would not be able to benefit from research results. Consequently, the application of certain research rules (such as the possibility of withdrawal or the need for specific consent) to rare disease research can be highly detrimental. This fact has also been recognized by the European Commission, which requires all member states to have a national research plan for rare diseases in place (Council of Europe, 2009).

The need for extensive data sharing has profound implications for privacy regulation and for personal data management. The proposed use of a unique identifier for research in rare disease (i.e., an identifier code that is applied to subject data and is shared by all researchers working on that same data) has opened up new questions about security, specifically concerning the chances of re-identification born from cross-matching data from different research centers. The Office of Rare Diseases Research at the National Institute of Health (NIH) has launched a pilot project to establish the Global Rare Disease Patient Registry and Data Repository (GRDR) (NIH Office of Rare Diseases Research, 2012). The goal of this registry is to establish a data repository for de-identified patient data, which will be aggregated using Common Data Elements (CDEs) and standardized terminology. This data (which will be available to all investigators) will enable the analysis of many rare diseases, and will facilitate various biomedical studies (including clinical trials) to develop drugs and therapeutics, thereby improving the healthcare and quality of life of many millions of people. De-identification of patient data will also utilize the Global Unique Identifiers (GUID) system, which can link patient data to biospecimen data sets (NIH Office of Rare Diseases, 2012).

The protection of personal data has been a major concern in genomic research. Evolving privacy regulations and existing legal frameworks have already had an important impact on research and its future development. Loss of confidential data may negatively affect participants in research studies. Health data are considered especially sensitive, and as a result, severe restrictions are imposed on researchers and investigators. E-commerce and banking regulations, for example, are often applied to research data, the better to create a safe environment for sensitive data. However, these regulations end up creating strict and unspecific privacy rules that, in the context of rare disease, may detrimentally impact the use of the limited data that is currently available for research. It is therefore critical to understand the role of privacy as a personal right, and to analyze privacy in the context of other rights by assessing its impact on individuals, families and society.

2. Discussion: privacy as a barrier to quality research

Biobanks and medical registries with aggregated clinical data are vital to the development of higher standards of medical diagnosis and personalized treatments. The rapid development of pharmacogenomics underscores the need for these infrastructures as stable libraries for new and future developments. These infrastructures have been heavily criticized as constituting a great risk to individual and family genetic privacy. Privacy has been identified as "The Issue" around which researchers have assessed the ethical and legal dimensions of data and sample collection. Privacy has therefore played a dominant role in the regulation of biobanks and registries, and has been the focus of many restrictions; as such, privacy has often been conceived of as a barrier to research and development (Mascalzoni et al., 2013; Hansson et al., 2013). Many countries have enacted regulations that require specific consent for the use of data in research. LIBE hopes to change a current EU proposal by introducing an exception that would prohibit secondary use of existing data without explicit consent (Mascalzoni et al., 2013). This exception could drastically reduce researchers' reliance on existing resources, which were, in large, collected in the past under the purview of different regulations. It is well known that re-consent (even when possible and practical) results in loss of participation — a huge cost to research efforts.

Privacy has often been regarded as the capacity to identify a person using his or her own data. The power of genetics to identify research subjects has played a significant role in discussions on privacy. In this context, privacy entails the protection of a person's identity (and, therefore, his or her dignity) in relation to his or her health and genetic data.

This paper considers a broader conception of privacy, as it relates to individuals and groups in the private sphere. Mainstream interpretations of privacy (which have been privileged through regulation) regard privacy as a "secret area," in which personal data and data-flow techniques are protected to ensure anonymity.

This paper demonstrates that privacy is, indeed, a large concept, and that even if privacy is heavily associated with secrecy, it entails a broader area of significance that includes the personal sphere and its management. Not only does privacy management imply a negative personal right to non-interference (such as limiting undesired access and making personal information secret) but it also implies a positive right to determine and manage personal information, and to actively have a say in one's own private sphere (Hansson, 2008).

2.1. Privacy regulations

Soft law provisions, professional codes of conduct and legislation constitute the normative patchwork that guides scientific discovery. Striking a balance can be difficult; moreover, scientific development has revealed dilemmas that existing regulations are unable to solve.

The balance between freedom of research and protection of research participants has been difficult to achieve. In the context of genomic research, privacy is a major issue. Although privacy is recognized as a human right (Council of Europe, 2006; Unesco 2003), it is important to acknowledge that privacy is not absolute, and that it needs to be evaluated and balanced against constitutional rights.

The Convention on Human Rights and Biomedicine is a European cornerstone (Council of Europe, 1997a). The aim of this Convention is the protection of dignity and human rights in relation to biomedicine. The Convention sets forth the norms for the conduct of ethical and legally-sound research. Article 10 of the Convention states that: "everyone has the right to respect for private life in relation to information about his or her health," and that "everyone is entitled to know any information collected about his or her health". Article 5 states that a medical intervention may only be carried out if the subject gives his or her free and informed consent, and is also given the right to withdraw his or her consent. Recently, certain authors have criticized these restrictions (Hansson, 2012) as hampering the scope of Article 3 of the Convention, which enshrines a right to "equitable access to health care of appropriate quality."

Privacy provisions, if applied literally, would severely hamper research efforts and prevent patients from enjoying good-quality standards of healthcare. Poor-quality diagnostic tests and treatments can be harmful to patients, and thus can violate the primary medical ethical principle of "do no harm." In practice, balancing medical benefits and privacy risks is inherently as well as situationally complex. Quality is not only a normative requirement in health care, but also a necessary condition for the prevention of harm and for the development of preventative and diagnostic treatments. Quality assurances have an intrinsic value in the implementation of the right to health care (Hansson, 2012). This principle is recognized in Article 12(a) of the 1997 Universal Declaration on the Human Genome and Human Rights, and underscores the need for shared benefits in research: "[b]enefits from advances in biology, genetics and medicine, concerning the

human genome, shall be made available to all […]". Freedom of research (Article 12), which is "necessary for the progress of knowledge" must be read together with the duty to "seek to offer relief from suffering and improve the health of individuals and humankind as a whole."

Article 1 of the 1997 Declaration also states, "[t]he human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity." This article supports a vision of a shared heritage that benefits humankind as a whole.

2.2. Right to quality healthcare for rare disease communities

The need to aggregate personal health-related data by linking patient medical records with clinical registries and biobanks has become a pressing need in medical research. In order for the collaborative gathering of data on rare diseases to gain statistical significance, a network of clinical registries must be both global and widespread.

As different outcomes are experienced in association with diagnosis, prevention, and treatment, data registries must be continuously updated, the better to follow the medical development of certain diseases. These data are necessary in order to: (a) predict the future course of disease; (b) assess the frequency and prevalence of disease across different populations; (c) assess the outcome and long-term safety of treatments; and (d) assess the efficacy of drugs and treatments in order to guide policymaking and economic decisions relating to prioritization in health care. Together with human biological samples, medical registries can be even more useful for attaining these ends. There are direct benefits to patients from databases and clinical registries, as well as surveys and questionnaires:

> One example should make the case clear: the Human Papilloma Virus (HPV) vaccine. This vaccine is now available on the market and is being included in the organized vaccination programs of many countries around the world for the prevention of cervical cancer. Development of this vaccine would not have been possible without firm evidence that the virus is causing the cancer. Prospective studies that follow exposed subjects until disease diagnosis are an essential requirement for the inference of causality. Because the cancer develops several decades after the infection, such studies are not possible with newly collected samples. However, linkage of national cancer registries with biobanks identified stored samples of cervical cells or serum dating back to the 1960s, and testing such samples for HPV provided the needed evidence for a causal association. In Sweden alone, it is estimated that the HPV vaccine will save about 200 lives each year. It can be concluded that vital medical needs may not be fulfilled without the use of registry data and biobanks. However, the registration and use of medical and personal data as well as the collection of human tissue samples in biobanks are seen as controversial, and it is suggested that important competing values at stake may warrant the tradeoff against the intrinsic quality values they represent.
>
> [(Hansson, 2012, p. 317).]

The updating of personal medical records does not seem to be problematic in terms of privacy or of patient autonomy; in point of fact, every medical doctor regards updating patient files as contributing to good-quality healthcare. Allowing access to this data by other healthcare providers in the clinical setting also does not raise issues for the same reason. Access to medical-quality registries, research-based registries, biobanks, and, in particular, the linking of large-database data across national borders is looked upon differently in the context of research. In terms of good-quality care, there seems to be no conflict between documenting care in medical records, following-up and conducting long-term assessments through medical registries and biobanks (whether local or collaborative), and receiving the best research-based treatments available. However, access to such resources has been heavily challenged by concerns for privacy.

Do medical registries and biobanks represent significant threats to individual rights and privacy?

The collection and use of large quantities of health information creates a substantial challenge for the protection of patient privacy and the privacy of research subjects (Rothstein and Shoben, 2013a,b). Privacy security measures (such as coding and de-identification) may prove ineffectual, as re-identification is often possible by crosslinking available databases (Kaye et al., 2012). Loss of informational privacy may lead to the stigmatization of individuals and communities, such as those defined by ethnicity, gender, or religion. Wendy Mariner argues that autonomy and privacy are fundamental interests protected by constitutional law; as such, a constitutional challenge could dismantle vast numbers of registries that are not based on individual consent. Mariner recognizes the need to limit intrusions into medical privacy that have resulted from the wide dissemination of personal medical data. In her view, even if health research is important, it must still give way to inherent principles of law, such as the protection of privacy (Hansson, 2012).

But, as discussed, privacy is not the only right at stake in medical research: access to healthcare and quality of healthcare is also of vital concern. Quality healthcare represents a vital patient and societal interest. Although quality healthcare may be balanced against privacy concerns, the following question remains: where should the line be drawn between these two interests, and is there a way to fulfill them both?

2.3. Privacy, autonomy and shared responsibilities

Some authors suggest that in order to achieve better results, scientists should opt for open data-sharing and place less emphasis on informed consent. It is already possible to bypass the need for informed consent if patient data is unidentifiable (Council of Europe, 1997a,b; Tallacchini, 2005). These exceptions tend to reduce tissue and biological samples to pure information. Forgetting about the sources of sample data enables a legal shift away from the regulation of human research to the regulation of data; this technical shift is embedded with values. Suddenly, it becomes possible to skip certain procedures; moreover, the "anonymization" of data allows for greater freedom to exchange regimes. Identity protection rhetoric misses the complexity of privacy — as a private sphere that deserves some degree of control.

Privacy should not be reduced to personal identification data (Council of Europe, 1997b, 2006) but rather should take into account an "identification criterion," which encompasses the personal dignity and intimate interests of the individual. This criterion is especially important in the context of genomic information, as this area impacts not only individual carriers, but also societal groups.

2.3.1. The private sphere

"The possibility of enjoying a private sphere–informational or spatial–of one's own is a vital concern in all cultures" (Hansson, 2012). Although there may be some differences of opinions as to the borders of this sphere, there are certain core elements that transcend such cultural borders. James Rachels explains why human beings reject certain types of intrusions by focusing on individual-to-individual relationships in the social context [24] (Hansson, 2012). According to Rachels, a private sphere is necessary for human beings to participate in several different types of relationships. There is, in fact, a close connection between the capacity to maintain different relationships with different people and the ability to control who may access personal information. As such, an individual must have access to a private sphere and must be in control of this sphere. Management of this private sphere requires that one person decides who may enter this sphere or have access to private information, and under what conditions. Privacy is valued as part of social life. An individual's freedom to be left alone or

to provide access to private areas is only given meaning in a social context.

2.3.2. Individual vs. inter-subjective responsibility

The fact that an individual has control over third-party access to his or her own information suggests that privacy is intrinsically related to autonomy. However, individual autonomy should not necessarily be seen as a barrier to privacy, as its expression and scope depend on subjective individual, familial and societal contexts.

According to the Council of Europe: "the expression 'genetic data' refers to all data, of whatever type, concerning the hereditary characteristics of an individual or concerning the pattern of inheritance of such characteristics within a related group of individuals. It also refers to all data on the carrying of any genetic information (genes) in an individual or genetic line relating to any aspect of health or disease, whether present as an identifiable characteristic or not. The genetic line is the line constituted by genetic similarities resulting from procreation and shared by two or more individuals" (Council of Europe, 1997a,b).

In genomic research, focus is never placed on a single individual as such. Those persons involved in research are particularly valuable as participants if they form part of a larger group. Genome-wide association relies on large numbers and shared characteristics; in research biobanks, subjects are taken as a whole—either as a community that shares common characteristics, or as a closer, more extended family, where any given individual is genetically related to others. Relatedness among sets of genetic data can help locate characteristics that are shared by individuals of the same kinship. This fact alone is blurring the boundary between individuals and genetic communities, and casts doubts on the feasibility of commonly used ethics tools, such as individual informed consent and calls for additional forms of participation and regulation of genomic research. Genetic information concerns not only individual persons, but also relatives that share the same genetic background. What we term "privacy risk" is comprised of several aspects, of which identification is only one. This fact raises new questions about the legitimate uses of such information, and also casts doubts upon the right to deny possible positive outcomes to a shared heritage. The fact that genetic information is shared means that it does not belong to a single individual, and that it is, in a way, already beyond the scope of individual control. For instance, a family member who provides his own data is able to infer precise health information about another family member through the use of statistical tools (Howie et al., 2012). In the case of genetic counseling, the participation of family members and the provision of a family history is often helpful (if not necessary) to arrive at a precise diagnosis. Inter-subjective responsibility is thus a serious issue that must be taken into account.

2.3.3. Providing better chances to vulnerable groups

In the case of vulnerable groups, justice and fair access may provide a rationale for a specific regulation, such as those with rare diseases. Orphanet states that: "[t]he field of rare disease suffers from a deficit of medical and scientific knowledge. For a long time, doctors, researchers and policy makers were unaware of rare disease and until very recently there was no real research or public health policy concerning issues related to the field. There is no cure for most rare diseases, but appropriate treatment and medical care can improve the quality of life of those affected and extend their life expectancy" (Orphanet, 2013). When a person is afflicted with a rare disease, he or she is often alone in suffering. The disease is either unlikely to be diagnosed or is diagnosed late due to lack of knowledge or diagnostic tools; as such, patients have fewer chances of obtaining treatment. The rarity of certain diseases is such that the market is too small to generate commercial interest in drug development; these diseases are termed "orphan drug" diseases. Rare disease research should be considered research on vulnerable groups. A patient affected by rare disease is as vulnerable as any other patient with regard to subjective experience of illness, but is actually more vulnerable in terms of healthcare availability and regulations that hamper healthcare research. Rare disease research only exists thanks to registries and biobanks, which are often set up by patients themselves (Genetic Alliance, 2013). If loss of data were to severely hamper research in rare disease, and were to affect rare disease patients by impeding the proper evolution of care and access to good-quality healthcare, this could be seen as discrimination against vulnerable groups and as unjust. Strong societal imbalances necessitate the introduction of affirmative action, which means rules that ensure fairness into the development of a process so as to seek justice in the output of that process.

One possible conclusion is that individuals should not be given the choice as to whether or not to have their health records and specimens used in rare disease research. This interpretation is particularly relevant for inter-subjective responsibility, where sharing individual information is the only chance that an individual and others have (whether affected or not) within a biological family to receive better-quality healthcare. Does a person have the right to refuse providing his or her data if this refusal will affect the quality of rare disease research, which may, in fact, be relevant to both the person's family and society as a whole?

This issue becomes one of public interest if the research data has an intrinsic value for the quality of healthcare. This fact is of extreme relevance for the translation of genomics into public health policies. In other words, is there a social duty to overcome individual informed consent in order to provide justice for a vulnerable group? Are these arguments strong enough to create an ethical duty to contribute to the development of better healthcare, even as against an individual's will to be involved in medical research?

2.4. The cost of privacy and the issue of informed consent

It is interesting to observe how the answer to the above questions may differ according to different cultural frameworks. Risk/benefit analysis must always take place in a specific social context. Societal attitudes towards less regulation are shaped by access to healthcare, trust in institutions, and the effectiveness of science oversight bodies. In countries where universal healthcare is ensured, the answer would probably be yes, while in places where citizens place less trust in the state, and there is less social and health security, the answer may be no (Hansson, 2012; Kaye et al., 2012; Hansson et al., 2013; Rothstein and Shoben, 2013b; Mascalzoni et al., 2008; Oliver et al., 2012).

Data are precious. The right to use and manage data collections is often conceptualized in terms of ownership, the better to identify those rights and duties that are specific to data collection. For instance, in Material Transfer Agreements (MTAs), the data provider is often regarded as "the owner," and ownership of the data, is used as a summary concept to indicate the set of rights related to a set of data. The issue of ownership is constantly flowing into the debate on privacy; in many respects, the right to personally manage one's own data could be grounded in property theory or as an extension of autonomy. It is worth considering the meaning of property as relates to data, and why this meaning holds particular relevance to personal health data privacy. Data ownership, exchange and proprietary rights (as pertaining to intellectual property) have a great impact on public perception of privacy as applied to health research. A clear conflict exists between the "altruistic donor" approach at the initial time of participation in research, and ownership of personal data. The dichotomy between free access to data (for the advancement of science) as public benefit and the possibility of using those data for commercial gain would trigger a loss of trust in the scientific community (Moore v. Regents University of California, 1990: against the property approach). This tension may affect the relationship of trust that is required for patient participation in medical research, and may lead to the perception that secrecy and confidentiality are the only effective measures to be employed against misuse of

participation. That being said, identification is not the only issue at stake in genomics.

Judith Jarvis Thomson argues that privacy has meaning only to the extent that it is reducible to property interests (Thomson, 1990). But property does not always entail full proprietary rights. For instance, a relational approach to property may consider "ownership" rights as not directly relating to possession, but rather as focused on other considerations, such as the control or power that a subject may have over third-party access to his or her data. Although a person's data is an object separated from the body, data subjects may also have a personal interest in retaining a degree of control over their data in order to avoid harm or to gain some sort of advantage. This interest is often translated into the right to grant or deny access to data (Cohen, 2000). This reduces control to a yes or no response that leaves no room for discussion. Michelman's vision, which looks at property as a means through which to ensure the egalitarian distribution of political power and participation, is very interesting in this context (Williams, 1998). According to Michelman's approach, property can be seen as an "individual's stake" in society (Michelman, 2012).

This view is especially interesting if it is applied to health research data. Individual patients may have political or religious objections to certain research purposes that are made possible through data sharing. Commercial exploitation of collected data is one such point of contention. Individuals may not want their data to be used in ways that will affect their identities and private spheres. They may not want their data to be used in support of political ideas or to dismantle religious beliefs. Certain individuals may not want to contribute to research that will identify markers for "[…] specific population[s]", or that will trace the origins of specific tribes (as in the Havasupai Case) (Mello and Wolf, 2010). Good oversight structures are necessary to keep these research problems at bay; however, even they may be insufficient to contain the implications of these different concepts.

2.4.1. The cost of consent

As in the Western legal tradition, the bioethics literature in genomics generally present individual persons as the subjects of rights (notwithstanding the fact that the possibility of a balance between individual rights and community rights may open up new horizons). Informed consent has been extensively considered in the context of biobank research. The issue of consent comprises a broad spectrum of positions, ranging from "no consent required" to "specific consent required at all times." A one-size-fits-all approach is very difficult in this context. Although privacy is a primary good that should be protected, it is important to acknowledge that there are costs associated with high-quality diagnosis and treatment.

One argument brought up in the literature is that the right to better quality healthcare is jeopardized by the need to actively provide specific or explicit consent to registries and biobanks (Hansson, 2012). All the requirements for traditional informed consent (i.e., opting-out, re-consent, etc.) imply that registries will be affected both by those elements that are included or omitted. This issue leads to incomplete information bias that affects research outcomes. Even though consent-bias may be relatively small in the context of large clinical trials or of population biobanks, the same cannot be said of rare disease registries and rare disease biobanks, for which even the slightest perception of bias can have a severe impact, in light of the scarcity of materials and information available for research. Some authors suggest that this bias leads to a societal obligation to participate in research for the public good (Francis and Francis, 2013); if the right to privacy were weighed against the right to better healthcare, the latter should prevail.

In contrast, Mark Rothstein asserts that the degree of consent bias caused by informed consent has been overstated; that statistical techniques can mitigate this bias; and that a low level of imprecision is an acceptable social cost for conducting ethically-responsible research (Rothstein and Shoben, 2013a,b). Supporting Giesbergtz's position, Rothstein also suggests that new forms of consent should be implemented for research that have a special social or "public good" value (excluding highly sensitive research) (Giesbertz et al., 2013). In such cases, the author suggests a thick opt out procedure that will provide for higher-than-normal participation and will simultaneously acknowledge the rights of individuals to make decisions in respect of their own private spheres. In a thick opt out procedure, patients should be well informed about research but they should not actively agree to participate. In fact, the default position would be agreement to be into research and patients who do not want to participate could actively disagree by opting out. The fact that opt out options do not affect research is supported by the report of a Swedish study revealing that, even with an especially elaborate system for opting out of consent (where detailed information and consent forms were offered at sampling that patients could take home and fill in), only 1 in 19,000 actually did opt out (Johnsson et al., 2008). Recent legislation in Finland also supports this view, and foresees the implementation of opt out options for registries and biobanks.

Although both positions give rise to interesting arguments, this paper's conclusions may also be driven by other considerations.

Open consent is always grounded in a risk/benefit assessment where there is a low risk associated with database research. However, even research on bio-specimens can be reduced to pure information. This paper has suggested that risks associated with the dissemination of data are very much socially and culturally situated; in certain countries, for example, individuals may not want their data to be freely shared for the purposes of research.

Identification and stigmatization are also issues. It is not ethically acceptable for an individual to provide data for the public good, and then for that individual to be left unprotected in the public sphere. Some authors may argue that democratic societies should ensure trustful governance and the implementation of effective oversight mechanisms. But in a "world sharing setting," societies are unable to guarantee that such democratic assumptions will be met, or that codified or de-identified data will not lead to any harm. De-identification has been proven insecure (McGuire and Gibbs, 2006; Kaye, 2012).

But even if such research were devoid of risk (either discriminatory, access, or informational), would individuals be keen on giving up their right to a specific or explicit consent? Control over consent has, as suggested, the political power to acknowledge or deny trust to a particular institution. At the same time, consent can also lead to better and more ethically-grounded and supported research efforts. A well-organized consent process for prospective studies may, in fact, have a very positive impact on patient participation, and transform reluctant patients into supporters.

3. Results of the discussion: patients as partners and the option of dynamic consent

An analysis of the costs associated with consent should also include an examination of the costs of "no consent" for the use of samples and information. Several studies demonstrate that research participants across a range of populations and disease groups wish to be informed if wide data-sharing procedures are implemented (Tabor et al., 2011). In their paper, McGuire et al. clearly show that patients would feel deceived and angry if they found out that their data was shared without their knowledge and consent; this scenario would occur even where patients would have gladly shared their data if they had been asked to do so or had been adequately informed (Oliver et al., 2012). Tabor et al. presented a study in which 70% of participants felt that notification of deposit of data in DBGap after the fact, that is, without prior notification, would be unacceptable. Thus, transparency seems to play a great role in maintaining the trust of individuals that are included in registries and biobanks.

In order to improve researcher–patient relationships, researchers should consider patients as partners in research and acknowledge

patients as valuable contributors. In 2011, during a workshop on dynamic consent in Rome, Sharon Terry (Director of Genetic Alliance) told the audience about how she and her husband did not want their children, who were affected by a rare disease, to be involved with researchers whom they did not trust. They believed that researchers at that time were headed in the wrong direction, and that these researchers should not be trusted with their children's samples and data, since this research could potentially have an immeasurable impact on the lives of their children. The only political power that Terry and her husband had at that moment to object to this research policy was their ability to say "no"—a vote against this research. Following this experience, Terry and her husband built up relationships with other parents in what has now become a huge enterprise in support of research led by patients for patients. Genetic Alliance is now the world's leading nonprofit health advocacy organization committed to transforming health through genetics and promoting an environment of openness centered on the health of individuals, families, and communities. Genetic Alliance's network includes today more than 1200 disease-specific advocacy organizations, as well as thousands of universities, private companies, government agencies, and public policy organizations. Patients understand that research is in their best interests, and that research should be performed in the most effective way possible. An acknowledgment of this interest is important in order to build a relationship based on mutual trust.

Sustainable data quality requires long-term commitment. This commitment requires that new forms of patient participation be included in research policy-building, so that patients become active partners in research rather than passive providers of information. Although new technologies create additional privacy concerns, they can also assist in solving a number of patient concerns. A number of participant centric interfaces (PCI) have been developed to allow dynamic consent procedures (Kaye et al., 2012). A dynamic informed consent model is accessible online and provides flexible options (return of results options, donation of samples and data to research etc.) that can be changed over time. "This interface enable patients to change preferences over time and have their choice revoked when appropriate, to track and audit any changes made, and to choose when and how they are contacted" (Kaye et al., 2012). By enabling patients and research participants to determine the degree to which they may exercise control over personal information and samples over time, dynamic consent aims to place patients and research participants at the center of decision-making.

It is, in fact, possible to manage how much information is desired as well as to allow for choice in terms of the level of participation and communication up front. This approach also constitutes a perfect tool for a thick opt out procedure.

Special options, such as the donation of data for research in the event that a patient becomes incapacitated or dies, are ethically acceptable, provided that individuals have a genuine chance to change their options over time. The use of PCIs ensures compliance with legal requirements, as options in such cases can be easily updated. PCIs also ensure that an open channel of communication is created between patients and research centers. This form of electronic consent is in no way burdensome for research; updates can be easily communicated to patients, who are given the opportunity to transparently inform and manage their participation.

The capacity to trust in research is very precious, especially in the light of the high-quality data needed for prospective studies in rare disease. The inclusion of family members in high-quality studies calls for trust, and requires that patients be re-contacted over time for the collection of data. If active consent resulted in an unsustainable cost for rare disease research, an opt-out procedure would be rendered unaffordable. Very few rare disease patients (if any) would withdraw from a study if they were truly informed about its importance. That being said, patients should be allowed to withdraw if they have strong reasons for doing so. In such cases, the scientific community may be made aware of additional problems and in this particular research setting, some alternative frameworks have been proposed (Kaye et al., 2012).

Consent for research in rare disease concerns two distinctive areas: the use of data registries and the use of biosamples. Patients are aware of the kinds of information that are contained in registries, as they have already been diagnosed in order to be in the registry. In such cases, the patient controls the type of information provided. New bio-sample collections may benefit from an opt-out strategy (Giesbertz et al., 2013). A thick opt out procedure foresees the implementation of an information strategy that will enable patients to make real choices. Such procedures should produce higher participation rates while affirming individual rights and autonomous choices.

This option could be also implemented for existing collections if it was supplemented with a communication campaign, which would make patients aware of the uses to which their samples and data were being put. That being said, it is difficult to delineate just how thick an opt out procedure should be.

New collections of bio-samples and new registries that are usually linked together can also be used for extensive genetic studies; these studies may include whole genome scans and exon sequencing. These kinds of analyses are sensitive; a new ethical framework is needed (Bledsoe et al., 2013). Issues associated with these kinds of analyses, such as return of results, require the attention of participants. The need to re-contact patients calls for something different than traditional consent, and would be best served (from a patient and scientific perspective) by a dynamic consent model.

4. Conclusions

Genomics is rapidly changing over time. This ongoing evolution requires further changes in policy research. Traditional specific individual informed consent is neither possible nor desirable in order to attain a quality standard of care for patients with rare diseases. However, new forms of consent will allow for compliance and ensure that patients are both respected and acknowledged for their role in research. In this way, researchers will promote participant trust and respect for participant autonomy. For medical registries and existing specimen collection biobanks, a thick opt-out strategy may be sufficient (in lieu of an opt-in consent strategy) to acknowledge respect for patients. Information may be accessible through the web and via posters and leaflets in hospitals, including information about coding and safety standards for data and samples; such information will maintain high-quality diagnoses, treatments, follow-up, and medical research endeavors.

Dynamic consent models are recommended for prospective collections. Trust in research is very precious, especially in light of the high-quality data that is needed for prospective studies in rare disease. The inclusion of family members in high quality studies not only calls for trust, but also for the need to re-contact patients over time for the further collection of data or for return of results (Green et al., 2013). If active consent results in an unsustainable cost for rare disease research, new technologies and new forms of consent can provide compliance standards, while still respecting the integrity of the private sphere. Patients understand and support science if they are truly informed. If patients have strong reasons that lead them to withdraw from rare disease research, then they should be allowed to do so. The scientific community may in such a case learn what the problem was.

Transparency, patient participation in policy-building, and societal control can also help to preserve respect for autonomy within a reasonable account of the notion of privacy, regarded as a vital good to be attained and protected within the wider framework of social participation.

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