Protecting patients' rights in clinical trial scenarios: The „bee metaphor" and the simbiotical relationship

by Marcelo Corrales

Abstract: This article contains an analysis of a proper distribution of rights between the interest of patients giving their biological data within a clinical trial scenario and the researchers producing results out of these data taking as case of study the EU funded project Advancing Clinico Genomic Trial on Cancer (ACGT). It includes an analysis of the unfair distribution of rights in the Moore and Greenberg cases in the US followed by seven different models to balance these rights within a clinical trial scenario aiming at finding the best equilibrium between patients and researchers.

1. Introduction - The „bee metaphor"

Genetic data is regarded as having the potential of revealling in the future, scientific, medical and personal information of each individual. It can also reveal some singular characteristics in particular compared to health data. This information can be extended to the family of the data subject. It is therefore regarded to be unique as it is likely to reveal information of many people by identifying only one of them (Article 29 Data Protection Working Party, 2004). For instance, the queen bee enjoys a unique status in the hive although having exactly the same genome of the rest of the bees. There is only one queen bee in the hive, between 500 to 1.000 drones and about 30.000 to 60.000 worker bees. The uniqueness of the queen bee can be easily determined at first sight as she is in principle the largest bee of the colony. She is also able to control other bees by secreting a particular substance, a pheromone that manipulates the activities and behaviours in the hive. Genetically, and due to her large abdomen which extends to the tips of her wings, she is the only sexually developed female in the hive being able to lay up to 2000 eggs per day. The queen bee is nurtured on a special diet of royal jelly which is collected by the worker bees also known as „forgarers" (Kirchberger, 2005).

In a bee world scenario, the forgarers fly around the hive collecting the pollen from the flowers and through a fascinating dance called the „waggle dance" they communicate to the rest of the bees where the flowers are located. The more they waggle the more flowers are supposed to be in the place they are facing, using the sun as an indicator for orientation (Herms, 1990).

This article has been inspired and motivated by the EU research project Advancing Clinico Genomic Trials on Cancer (ACGT www.eu-acgt.org), the main purpose of which is to develope a grid based technology in support of a trans-European postgenomic clinical trial research on cancer. By analogy, the „bee metaphor" applies directly to a clinical trial scenario where the forgarers or worker bees represent the scientists who collects genetic data from the flowers which represent groups of patients. That is, within a clinical trial scenario a computing grid infrastructure is used to tell the scientist where is the best and easiest way to

access the genetic data they are searching for in the same way a worker bee tells the other forgarers where the flowers are by performing the so called „waggle dance".

Finally, in the same way a hive of bees is extremely protected by the other co-workers bees, because of the „uniqueness" and „sensitivity" of genetic data in a clinical trial scenario, this must be protected and secured according to data protection legislation.

2. Protecting patient's privacy – The ACGT scenario

Genetic research projects within clinical trials scenarios need to safeguard patients' rights. Hence, a data protection framework needs to be developed where the handling of patients' genetic data is in compliance with the data protection legislation.

In ACGT the biological data collected from the patients is stored in different hospitals. Then this data is collected and then anonymized with a special encryption tool called CAT. Once data has been anonymized, it is ready for its usage among researchers. In order to guarantee compliance with the data protection legislation it is essential to put, in a first step, the project consortium in the position able to audit such compliance. For this reason it is important to establish a data protection authority in charge of engaging with both the patients on the one hand, and the end users i.e. researchers on the other. In ACGT the Center for Data Protection (CDP www.privacypeople.org) is able to sign contracts between the main stakeholders which is independent to the project consortium and empowered to inflict a penalty for infringement. Under this framework, patients who would like to contribute data, are able to sign a data transfer agreement in order to release their data to the researchers and conversely, researchers must sign a legally binding contract on data protection and data security in order to get access to data. Both agreements give the CDP the power to inflict pecuniary sanctions and therefore enforce compliance with the data protection framework. In addition, the CDP acts as a data controller acting as a central contact point for those patients and researchers (Claerhout et al, 2008).

All biological data collected and processed by ACGT is due to the cooperation of patients who consent to transfer their data on behalf of scientific research hoping that ACGT scientific efforts will foster and promote future scientific research for their diseases such as the nephroblastoma (Wilm's tumour) and eventually find a possible cure for this disease. In our "bee metaphor" the pollen is collected from the flowers and then is taken to the hive. The more pollen that is collected, the more nectar and honey will be produced in the hive. In the same way, the more biological data is collected within a clinical trial scenario, the more chances scientists will have to find a cure for diseases like cancer.

For this reason, clinical trial research projects such as ACGT owes its existence to the input of patients. Without their genetic samples and its associated information such collection of biological data would simply not exist (Gesche, 2006). It is evident that both, researchers and patients have a general common interest of finding the cure for a particular sort of disease (Lenk, 2009). Nonetheless, this relevant interest can take different positions. Namely, in respect to ACGT on the one hand, there is an essential interest for the patients to develop a successful treatment for their disease. On the other hand, there is a special attention on the side of the researchers to use such data in order to carry on with their research.

In the following section, I describe the two cases which constitute a land mark concerning the relationship between patients and scientists. These cases expounded below clearly show the conflicts of interest between the parties involved and suggest the acknowledgement of patients' rights.

2.1. The Greenber case

The Greenberg Case (Greenberg et al. v. Miami Children's Hospital Research Institute Inc. et al., 2003) is about a hereditary disease called Canavan which manifests in early childhood. The disease is usually rare, occurring in 1 of 6400 children (Lenk, 2009). This case consists of a joint legal suit of parents and non-profit organizations who found medical help in a group of researchers from the Miami Children's Hospital.

This group of parents (the Greenberg group) of children suffering of Canavan disease, working with specialists from the Miami Children's Hospital aided to collect samples of blood and tissues and create a database together with the hospital. The database contained clinical and medical data about the families and supplied this collection of data to Dr. Matalon. With all this information Dr. Matalon and his research team managed to isolate the gene responsible for Canavan disease, thus filing a patent application for the genetic sequence for the Canavan gene who successfully established a restrictive patent licensing program. Therefore, the Greenberg group, which had assumed that the benefits of Dr. Matalon's research would be in the public domain in order to foster future research, had also contended a claim for conversion on the grounds of property rights in the tissues and associated biological information provided to Dr. Matalon (Evans, 2006).

The plaintiffs (Greenberg group) filed a complaint based in a number of legal grounds claiming property rights not just to the corporeal tissues but "the genetic information therein" and information contained in Canavan Register (Mason et al, 2002). At the end, the Canavan Foundation lost the legal proceedings (Lenk, 2009) but reached a confidential settlement which provides for a continued "royalty-based genetic testing" by some licensed laboratories and "royalty-free" research by doctors, scientist and institutions searching for a possible cure (Canavan Joint Press, 2003).

It follows from the foregoing situation that the crucial point constitutes the question of who has the legal or moral rights for the intangible or intellectual property rights rather than who is the legal owner of the tangible property such as the tissues samples (Lenk, 2009).

2.2. The Moore case

In the same vein, another interesting case law worthy to mention is the Moore case. In this case, the plaintiff John Moore participated in a treatment for hairy-cell leukemia at the Medical Center of the University of California (John Moore v. The REAGENTS OF THE UNIVERSITY OF CALIFORNIA et al. Supreme Court of California, 1990). After repeated medical studies over Moore's bodily substances, his treating physician Dr. Golde suggested to extract his spleen for further research purposes rather than for medical tests without Moore's express consent. After the surgery John Moore was asked to come to UCLA Medical Center for further tests where a great deal of bodily substances coupled with its associate biological information were removed for further research (Rainbow, 2002).

Dr. Golde found a number of potentially therapeutic purposes in Moore's cells which were grown in culture. Moore's cells were commercially important since they produced a particular sort of protein which could be further industrialized at a lower cost. As a matter of fact, Golde and the University of California obtained a patent on the cell line and profited from an arrangement with a biotechnology company (Science News Article Moore 1988).

Moore filed a complaint including different legal actions such as conversion, lack of informed consent, unjust enrichment, breach of fiduciary duty, etc. (Moore v. Regents of University of California, 1990).

Finally, the Decision was against John Moore who did not get any profit out of his bodily substance and associated information. Accordingly, from the aforementioned cases illustrated above, within the context of clinical trials a crucial question must be answered: What is the significant contribution for the obtaining of scientific knowledge: is it the biological data obtained from patients or the investment of substantial research work and previous medical knowledge from the researchers? Therefore, a proportional distribution must be sought, and we can arrive to the conclusion that patients taking part in clinical trials must receive something in return to their contributions (Lenk, 2009).

3. Balancing interest rights between patients and researcher

This section will analyze the proper distribution of rights between the interest of patients giving their data within a clinical trial scenario and the researchers producing results out of these data taking as an example the ACGT project. Below I briefly describe several options highlighting the pros and cons. At the end, the best equilibrium will be proposed.

3.1. Individual feedback to patients

From the patient's side a financial compensation must never be sought in advance. Instead, the first step is to grant patients the right to access the scientific results so they can control the progress of the ongoing clinical trials which is a product of a joint cooperation between the patients and the researchers (Lenk, 2009).

In this respect, ACGT is consistent with regards to providing access to patient's clinical records who are be considered as a clinician with limited access to their own various summaries of the findings coupled with their own clinical data.

3.2. Access to innovative therapeutic or diagnostic methods

The right to know about any new therapeutic or diagnostic methods is an ethical principle which is backed up by the Declaration of Helsinki (Lenk, 2009). Paragraph 30 states as follows, *"At the conclusion of the study, every patient entered into it should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study"*. The Declaration of Helsinki is not a legally binding instrument; however, since it was drafted by the World Medical Association, it is a respected ethical document.^

3.3. Improvement of health care in a specific category of patients

In cases of uncommon diseases such as Wilm's tumour (nephroblastoma) cancer it may be an alternative to share the results in an improved group health care benefit. This is usually the case with a particular group of patients from a determined region (Lenk, 2009). In ACGT, the improvement of the health care sector in a particular region where clinical trials are in process can be an interesting alternative in order to find a balance between the interest of the researchers and patients. Building e.g. a therapy method or infrastructure within the hospitals and group of patients participating in ACGT cannot only provide a proper balance of interest between patients and researchers, but can also suggest future funding revenues at national level taking into account that benefits will be shared within the community where the patients are located.

3.4. The "Contractual Model"

This model has been presented by Gerard Porter whereby – due to the reposition of the traditional research model to the new commercial research paradigm – informed consent has been adjusted to a new setting where the dual worlds of intellectual property and bioethics converge (Porter, 2004). This model puts forward a balance between patients and researchers through the bargain of terms and conditions. Normally, informed consent forms are employed as a procedural and bureaucratic matter to waive participant's right to claim any potential intellectual property compensation whilst they should rather be used as an instrument to safeguard the balance between the interested parties in play (Porter, 2004).

According to Porter, informed consent forms are like a "wolf in sheep's clothing" since the wordings described therein are usually camouflaged by the real commercial intentions. Informed consent forms resemble the typical standard contracts between big companies and their clients where no room for negotiation is provided having only the chance to participate or not within the terms of the contract. For this reason, he proposes a wider room for negotiation where in particular, the researchers must inform the potential commercial intellectual property values of their biological material and associated information (Porter, 2004).

3.5. Distribution of financial profits

It has been previously said that a direct financial compensation must never be sought in advance (see above section 3.1.). In spite of this, an indirect compensation for patients can be seen in the distribution of financial profits. The recommendations of the Human Genome Organization's Ethics Committee are a good example, as it has plausibly suggested that *"profit-making entities dedicate a percentage (e.g. 1-3%) of their annual net profit to healthcare infrastructure and/or to humanitarian efforts"* (Laurie, 2003).

By analogy, clinical trial research projects such as the ACGT project may consider to find a similar solution with regard to the interplay between patients and hospitals as a means of distributing potential financial profits i.e. researchers may devote a percentage of their profits to health care infrastructure for the patients.

3.6. The "Taxation Model"

This model has been recently proposed by Jasper Bovenberg who presents an interesting system based on taxes. He proposes to set a tax rate specifically tailored for tissues and cell products. This model rests in the fact that human tissues constitute a natural resource and has been inspired by the United Nations Convention on the Law of the Sea regarding the tax imposition of any removal from the mineral sources of the deep seabed. In this convention, a trust fund called the "Deep Seabed Revenue Sharing Trust Fund" was established. The main idea is to consider by analogy that genetic material and associated biological information can be contemplated as a "global public good", therefore the tax must be "global" or at least run by a national authority as it is the case with the Netherlands with regard to mine minerals, oil or natural gas taken from Dutch territory (Bovenberg, 2006).

This is an interesting model to consider, however, it might be difficult to implement within small projects. The major drawback is the international or at least national necessary lobby to obtain a taxation rate and an authority empowered to collect and control taxes.

3.7. The "Charitable Trust Model"

This model takes for granted property rights in patient's biological material and associated data. Although it has not been effectively implemented yet, it provides an interesting benefit-sharing approach by designating a 'charitable trust' which will have 'legal fiduciary duties' to hold or use the property on behalf and benefit of the public. By means of this model, donors would co-participate in the governance of the trust and be entitled to some shares ruled by the terms and conditions of the trust agreement (Bovenberg, 2006).

4. Conclusion

The fascinating social behavior of honey bees suggests that bees are not the only one benefiting from the collection of pollen but many plants depend on the pollination for their very survival. Bees and other insects have built up a symbiotic relationship with nature. Respectively, the "bee metaphor" resembles the relationship between patients and researchers where not only researchers receive the scientific and economical benefits from the biological data taken from patients but there is a rather mutual relationship where the group of patients including their communities should receive some benefits too.

This relationship should be built up through a bilateral manifestation between patients and researchers in terms of a contractual agreement where the principle of 'freedom of contract' fulfills the purpose of safeguarding the autonomies of the interested parties.

The Greenberg and the Moore court rulings depicted above clearly manifest how patients and participants of clinical trial scenarios have seen their rights considerably undermined therefore several models to balance these rights have been examined. The list given above in Section 3 is by no means exhaustive but illustrative. Technically speaking some of these models do not apply directly to some clinical trial scenarios however a number of these models can provide useful guidelines for our discussion.

In this sense, we suggest a model based on an equal balance between the interested parties, and in particular, a more active participation of patients. This is due not only to

ethical and legal reasoning but it actually can encourage the participation of patients which represent the sources of information for achieving the scientific outcomes of the ACGT project.

For practical reasons, as a central authority is needed for data protection and data security issues anyway, this institution may also be used for other central tasks. For instance, taking care of the patient's possible intellectual property rights regarding their biological data, being able to establish a refund model in order to share the benefits within the consortium and the group of patients which can be extended to the community where those clinical trials are taking place.

For this reason, the CDP could also act as a "Trusted Party" and could define property rights on the biological material and the data coming out of this material as a "common". In order to find a balance between the interests of patients, doctors and researchers, the CDP as the "Trust" could hold a percentage of the net profits and re-distribute the revenues to the community of patients.

Acknowledgement

The results presented in this paper are partially funded by the EU 6th Framework Program in the context of the ACGT project (FP6-IST-026996). The author wants to thank all who contributed to this paper, especially the members of the project consortium and in particular Prof. Nikolaus Forgó who supervised the entire work package concerning legal and ethical issues and to my colleagues Dr. Tina Krügel and Dipl. Jur. Eva Egermann, LL.M. Last but not least, I would like to thank Mike Wilson for the corrections made to this article including his valuable feedback on the content. However, the usual disclaimer applies. The content of this article does not necessarily reflect the views of the Institute for Legal Informatics. The author is solely responsible for its content.

References

1. Article 29 Data Protection Working Party, Working Document on Genetic Data adopted on March 17 2004, 1-14.

2. Bovenberg J. (2006) *Property Rights in Blood, Genes and Data: Naturally Yours?*, 197.

3. Claerhout B., Forgó N., Kruegel T., Arning M., de Moor G. (2008) *A Data Protection Framework for Transeuropean genetic research projects* in Collaborative Patient Centred eHealth, 67-72.

4. Evans P., *Patent Rights in Biological Material: Implications of Principle of Unjust Enrichment Remain Uncertain*, (2006) GEN Genetic Engineering and Biotechnology News, Vol. 26, No. 17, 1.

5. Gesche A., (2006) Genetic Testing and Human Genetic Databases, in Betta, Michela, Eds. *The Moral, Social, and Commercial Imperatives of Genetic Testing and Screening: the Australian case*, chapter 4, pages (Abstract), Springer (2006) at http://eprints.qut.edu.au/archive/00006360/ accessed 29.05.2010

6. Herms D., (1990) The Honey Bee Waggle Dance: An Active Participation, Role Playing game (1990), Entomology Notes No. 22 at http://insects.ummz.lsa.umich.edu/MES/notes/entnote22.html accessed 29.05.2010.

7. Kirchberger C., (2005) *The Queen Bee metaphor – the existence of a law as a unique instance"*, at www.lisan.org/li/docs/archive/The**QueenBee_metaphor**.pdf accessed 29.05.2010

8. Laurie G., (2003) *Privacy and Property? Multi-Level Strategies for Protecting Personal Interests in Genetic Material*, p. 85 in *Genomics, Health and Society: Emerging Issues for Public Policy* edited by Bartha Maria Knoppers and Charles Scrivers published by the Policy Research Initiative, Canada.

9. Lenk C., (2009) *Donors and Users of Human Tissue for Research Purposes: Conflict of Interests and Balancing of Interests.*

10. Rainbow C., Sought After Cells, Adapted from "John Moore v. The REAGENTS OF THE UNIVERSITY OF CALIFORNIA et al." Supreme Court of California No. S006987at http://www.bio.davidson.edu/people/kabernd/Indep/carainbow/Cells.htm accessed 29.05.2010

11. Mason J. et al. (2002), *Law and Medical Ethics*, 459, Butterworths LexisNexis, Sixth Edition, UK.

12. World Medical Association Declaration of Helsinki