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TITLE

A trust-based pact in research biobanks. From theory to practice.

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FROM INFORMATION TO TRUST

Most current literature on informed consent shows how it is becoming increasingly difficult to provide patients with accurate information[1]. While this problem affects many areas of medicine, it is becoming particularly urgent in the context of research biobanks. In this setting, in addition to the traditional challenging issues (such as the difficulty of patients having an precise understanding of the issues in question and the phenomenon of therapeutic misconception), the pressure caused by rapidly developing biomedical technology and the consequent speed of change of the information to be delivered render the problem of consent almost intractable within canonical frameworks. On the one hand, at the time of excision, it is impossible to foresee every specific future use of a tissue and the analyses that it will be subjected to. On the other, even if this knowledge were

[1] For the debate see O. Corrigan, ed. 2009. *The Limits of Consent: A Socio-Ethical Approach to Human Subject Research in Medicine*. Oxford: Oxford University; K. Sand, S. Kaasa & J.H. Loge. The understanding of informed consent information—definitions and measurements in empirical studies. *AJOB Prim Res* 2010;1(2):4–24; P.S. Appelbaum. Understanding "understanding": an important step toward improving informed consent to research. *AJOB Prim* Res 2010;1(2):1–3; J. Flory, E. Emanuel. Interventions to improve research participants' understanding in informed consent for research: a systematic review. *JAMA* 2004;292(13):1593–601; I.S. Durand-Zaleski, C. Alberti, P. Durieux, et al. Informed consent in clinical research in France: assessment and factors associated with therapeutic misconception. *J Med Ethics* 2008;34(9):e16; W. Glannon. Phase I oncology trials: why the therapeutic misconception will not go away. *J Med Ethics* 2006;32(5):252–5; B.R. Cassileth, R.V. Zupkis, K. Sutton-Smith, et al. Informed consent—why are its goals imperfectly realized? N Eng J Med 1980;302(16):896–900.

available, its delivery to the patient would involve the clarification of a number of technicalities that researchers themselves can sometimes find difficult to grasp, given the high degree of specialization and of multi-disciplinary team-work in genomic sciences. Moreover, the very act of providing a patient, who is already under stress, with detailed descriptions of current and future research projects would impose an unacceptable and unsustainable burden, and, in the wake of the arguments put forward by Caplan (1984) concerning the altruistic attitude of givers, would preclude him/her from participating in a "culture of solidarity" [2].

An alternative strategy is based on the idea that genuine consent does not rest in providing/receiving *full* information (regardless of how this may be defined) but, rather, in communicating *relevant* information. This has led some authors to rethink consent in the light of *trust* instead of information[3]. Nevertheless, although many scholars have argued that the rejection of classic informed consent would not necessarily result in a reduction of trustworthiness[4], there are few analyses of models based on the concept of

[2] On these points, see O. O'Neill, ed. 2002. *Autonomy and Trust in Bioethics*. Cambridge, NC: Cambridge University Press; A. Caplan. Is there a duty to Serve as a Subject in Biomedical Research? *IRB: Ethics and Human Research* 1984; 6:1-5.

[3] O. O'Neill, see note 2; G. Boniolo, P.P. Di Fiore & S. Pece, Trusted consent and research biobanks: towards a 'new alliance' between researchers and donors. *Bioethics* 2012; 26(2):93-100.

[4] O'Neill, *op. cit.* note 1; H.Y. Vanderpool & G.B. Weiss. Patient truthfulness: A test of models of the physician-patient relationship. *J Med Philos* 1984; 9(4):353-72; G. Boniolo, P.P. Di Fiore & S. Pece, *op. cit.* note 2.

trust[5], or – more importantly – of protocols for the practical implementation of trusted consent.

In 2012, Boniolo and colleagues proposed a trust-based consent form for research biobanks. By founding consent upon trust and reciprocity, they redefined the relationship between researchers and donors as a mutually beneficial alliance. The pact is founded on an act of solidarity made by the patient who voluntarily agrees to donate his/her tissue samples, in the knowledge that he/she can benefit from scientific advances resulting from former research made possible by donations from previous patients. Following this proposal, the Istituto Europeo di Oncologia (IEO) in Milan has redesigned the consent model for its tissue bank, the *IEO Biobank and Biomolecular Resource Infrastructure* (IBBRI). The new informed consent form is now called a *Participation Pact*, and it has been implemented within the IEO clinical setting, as a result of the cooperation of all the stakeholders involved: bioethicists, researchers, clinicians and patients.

Here, we describe the context in IEO in which the trust-based *Participation Pact* takes place (§ 2). Then, by highlighting the ethical values promoted and safeguarded by it, we discuss how the concept of trust might provide a more effective framework to define the researcher-donor relationship, compared to more extreme alternatives that are based on the dualism of beneficence vs. autonomy (§ 3).

THE IBBRI AND THE UNIQUENESS OF ITS TRUST-BASED CONSENT

[5] O'Neill, *op. cit.* note 1; G. Boniolo, P.P. Di Fiore & S. Pece, *op. cit.* note 2.

Biobanks are biorepositories that are specifically involved in the collection, processing, storage, and distribution of biospecimens and their related clinical and demographic information. Since the late 1990s, they have become a key resource, supporting many types of research, especially in the fields of genomics and post-genomics. The biospecimens (which, in general, include pathological and healthy tissues, as well as bodily fluids of various origin) and the related clinical data are used by scientists to learn more about the causes and effects of human diseases, and to develop better prevention measures, diagnostic tests and therapies.

In this context, the IEO set up a biobank, the IBBRI, in early 2011. The IBBRI presents a number of innovative and unique characteristics, and its mission is to support biomedical research by functioning in a highly integrated fashion with a number of centralized core infrastructures, such as the Primary Cell Culture and Stem Cell Unit, the Xenotransplantation Unit, the Clinical Biomarkers Laboratory, the Biocomputing Unit. One of the key qualifying aspects of IBBRI concerns the handling of tissues once they leave the operating theatres, and relies on the full integration of the biobank with the activity of the Department of Pathology. In a nutshell, tissues (normal or pathological) are removed from the patient in the operating theatres, and these are immediately delivered, under sterile conditions, to the Department of Pathology. There, the attending pathologist immediately inspects the sample and decides whether there is sufficient material for banking or whether the specimen should be reserved entirely for routine clinico-pathological analyses (this latter decision is taken frequently for small tumours). In the former case, the pathologist samples the tissue

reserved for research purposes under sterile conditions. At this stage, IBBRI personnel decide, based on the experimental needs, how to assign the research sample. Part of the sample must always be frozen for archival purposes. The reminder can be used for xenotransplants, for the establishment of primary cultures or for the isolation of cancer stem cells and so on. The short processing time of all samples (approximately 30 minutes) guarantees minimal tissue damage for subsequent biological experiments. All IBBRI procedures are managed through software packages that are fully integrated with the hospital medical records database, pathology database and central registry of patient demographic information. The workings of IBBRI are depicted in a flowchart in Fig. 1.

The entry point of the entire system is the *Participation Pact* (see Figure 2; the original, in Italian is available upon request). The *Pact* is signed at the end of a consultation between the patient and a trained health care provider (in general a research nurse or, in particular instances, a medical doctor). During the consultation, not only are knowledge and information shared with the patient, but more importantly, the health care provider explains the importance of research, and the impact and implications that the patient's choice has for other patients today and in the future.

The *Participation Pact*, adheres to international ethical requirements and national laws, such as those regulating personal data protection and the handling of genetic information. It contains several practical and conceptually innovative points (Fig. 2), largely following the suggestions of Boniolo et al. (2012). In particular, i) patients may choose between the anonymous or non-anonymous donation of biospecimens; ii) patients may

limit the type of research that can be carried out using their specimens; iii) patients and their genetic relatives are offered, with certain constraints, the option of being informed of the results obtained from each individual research project in which their biospecimens are used; iv) patients become partners in the research carried out with their specimens.

The efficient management of consent is critically important for all biobanks. Electronic copies of the *Participation Pact* are stored and fully integrated with the biobank management software. This allows users to view the consent conditions agreed by any patient and to manage authorizations of access to samples for different purposes. Any patient can withdraw from the *Pact*, with the resulting destruction of all the banked samples and records related to the IBBRI. Finally, all scientific projects that require the collection and/or the use of human biological samples and relative clinical information (in other words, all projects funnelled through IBBRI) must have prior approval by the Technical Scientific Committee (TSC)[6] of IBBRI, for scientific/regulatory matters, and by the local Ethics Committee, for ethical matters not already covered by the informed consent form.

Preliminary monitoring of the cost vs. benefit and efficacy of the newly organized consent has yielded encouraging results. In the period between June 2012 and October 2013, the *Participation Pact* was presented to 6,585

[6] The CTS is composed of the following different figures, each of whom specializes in a different biomedical area: a representative of the clinical department, a representative of the research department, the healthcare director, the director of the pathology department, and the director of the molecular medicine for care translational research unit.

consecutive patients. Of these only 10 (0.15%) refused consent for the use of biological materials for research. Of the 6,575 patients who consented, 6,433 (~ 98%), consented to non-anonymous donations (the best possible outcome for research purposes). Although we have not systematically collected historical data to compare this performance to that of the "old-style" informed consent, there is little doubt that, with a close to 100% compliance rate that is given in a non-anonymous fashion, the *Participation Pact* is an invaluable tool benefitting both researchers and patients.

To conclude, we note that in our 2012 paper we proposed to create an independent committee able to oversee the overall research process, from patient consent to experimentation and discovery. The "Third Party Authority" we previously proposed will become a *Guarantee Committee* (Commissione di Garanzia) for the IBBRI, that is to be implemented at IEO. As suggested in 2012, this Committee will be charged with the duty of monitoring and enforcing the trust placed by patients in the scientists involved, and in the governance of the tissue bank. The committee will act to guarantee the correctness, confidentiality and secrecy of the flow of information, thus protecting patient autonomy, safety and privacy from the potential abuses by scientists and researchers.

DISCUSSION

The particular features of research biobanks have led us to argue in favour of the replacement of traditional informed consent with a trusted consent. But although the difficulties associated with an information-based approach to consent are clear, it is perhaps not immediately obvious why a trust-based

consent should represent an ethically sounder position. We believe that there are at least three major benefits in the adoption of a trust-based consent: i) greater emphasis is placed on the importance of the values and assumptions implied in the concept and practice of the communication between researchers and donors (§ 3.1); ii) a middle ground is reached that balances the researcher-donor relationship (§ 3.2); iii) potential donors are motivated to participate in research that is based on solidarity and reciprocity (§ 3.3). In the following sections, we will analyze these three points.

1. From information to *communication*

International guidelines and regulatory documents[7] explicitly identify in the informed and voluntary choice of the patient, the basic tenets of the ethical

[7] National Institutes of Health. Nuremberg Code. Office of Human Subjects Research. Trials of war criminals before the Nuremberg military tribunals under Control Council Law no 10, vol 2, pp 181e182. Washington, DC: US Government Printing Office, 1949. Available at: history.nih.gov/research/downloads/nuremberg.pdf [accessed 19 Sep 2012]; World Medical Association. Declaration of Helsinki, ethical principles for medical research involving human subjects, revised October 2008. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html [accessed 19 Sep 2012]; Council of Europe. 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, Oviedo 1997. Available at: http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm [accessed 19 Sep 2012]. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report. Ethical Principles and guidelines for the protection of Human Subjects of Biomedical and Behavioral Research. DHEW Publication N. 78-0012, Washington, 1978. Available at:

justifiability of biomedical research on human subjects. From a practical point of view, worldwide declarations have considered informed consent as the proper expression of this choice, and, therefore, the appropriate tool to certify the acceptance of a medical act. Even if the disclosure of information were to allow people to exercise their self-determination, we submit that informing the patient by traditional informed consent is not the sole, or even the desirable, way of supporting self-determination.

It is worth recalling that O'Neill (2007) claimed that the traditional way of interpreting informed consent could be misleading[8]. Indeed, informed consent involves the transmission of information from a person who possesses it to another person who lacks it and needs to acquire it. The information itself is considered to exist independently of both participants in the transfer. By regarding information as an independent entity, traditional informed consent views the act of consenting as a neutral and value-free activity. O'Neill criticises the alleged neutrality of the communication process and the misplaced emphasis on content, instead asserting that communication is a complex process which implies a normative framework (by communicating, agents demand some commitments) whose success

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www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm [accessed 19 Sep 2012]. Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), International Ethical Guidelines for Biomedical Research Involving Human Subjects, Geneva 2002. Available at: http://www.cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.htm [accessed 19 Sep 2012].

[8] O. O'Neill, ed. 2007. *Rethinking Informed Consent in Bioethics*. Cambridge, NC: Cambridge University Press.

depends on the fulfilment of a set of conditions (such as the agents sharing a common language, and a degree of background knowledge, etc.).

We find ourselves in agreement with this critical analysis, and claim that classic informed consent, by virtue of its oversimplification and distortion of the actual process of communication, is an inadequate vehicle of communication, thus engendering doubts about whether it is a true expression of patient self-determination. Moreover, if communication is based on some premises and assumptions, and if the fulfilment of these value-laden assumptions is the *condicio sine qua non* of successful communication, then we might argue that some information might be sacrificed in favour of the fulfilment of both procedural values (the ones which vehicle the communicative process itself) and substantial values (the ones which promote the importance of a solidaristic attitude towards other patients within a scientific enterprise). To be more precise, whereas traditional informed requires the transmission of "full" (value-free) information, in our perspective the concept of consent involves the transmission of *relevant* information, in which the main values of agency and communication continue to be fulfilled.

2. From agreement to *pact*

The shift from a model which was uniquely based on the content of communication to one which attributes priority to the act of communicating and to the values embedded in this process, together with the practical impossibility (in the context of research biobanks) of providing patients with full information, indicates the inappropriateness of leaving the overall

responsibility for designating the use of human tissues to the patient. However, the importance of patient informed choice seems to be an unavoidable requisite for biomedical research on human tissues, thus suggesting that it would be inappropriate to impose hard paternalism[9] on the researcher-donor relationship. Nonetheless, if the act of consenting is viewed as belonging to the wider practice of communication, and since communication occurs between agents, it clearly follows that a correct decision-making process should grant equal consideration to both the traditional opposing perspectives (paternalism and autonomy) of the physician and patient relationship.

Some halfway solutions have already been proposed[10]. Among them, some authors have suggested rethinking the researcher-donor relationship within a *contractualistic perspective*[11]. According to this perspective, an *agreement* between researcher and donor should be found concerning the way in which tissues will be used and the scopes within which they will be employed. Such an agreement highlights, however, a *formal* dimension

[9] We recall that hard paternalism might be generally defined as the perspective according to which human subjects do not possess the same reasoning capacities and therefore some of the ends towards which human efforts are directed might be false or irrational.

[10] See for example A. Gethmann-Siefert. Consultation instead of prescription – a model for the structure of the doctor-patient relationship. *Poiesis Prax* 2003; 2:1-27.

[11] J.L.S. Edwards. Assessing the Remedy: The Case for Contracts in Clinical Trials. *Am J Bioeth.* 2011; 11(4):3-12; M.N. Meyer. The subject-researcher relationship: in defence of contracting around default rules. *Am J Bioeth.* 2011; 11(4):27-30; S. Rice & D. Trafimow. Known versus unknown threats to internal validity: a response to Edwards. *Am J Bioeth.* 2011; 11(4):20-1.

rather than a *substantial* one. In this perspective, the points established jointly by the two parties are binding.

We feel that the contractualistic view is inappropriate, both from a theoretical and a practical standpoint. From the theoretical viewpoint, the agreement-based relationship oversimplifies the process of communication. Indeed, this kind of relationship views the agreed contractual terms in the same way as classical consent, namely, as a neutral and independent entity. From the practical standpoint, this kind of relationship is doomed to failure within the biobank setting. If the binding terms are those agreed upon by the party, they would necessarily be limited to uses and scopes clearly identifiable at the time of the negotiation. However, in the case of research on human tissues, it is hardly ever possible to establish *a priori* future uses and procedures. On the other hand, the major value of biobanks is the creation of collections of tissues *for future studies*, especially for the purpose of permitting retrospective analyses. Therefore, even leaving aside theoretical concerns, an agreement-based perspective is vastly inappropriate to regulate the researcher-donor relationship in the context of research biobanks.

The idea of *pact* appears to be more fruitful. It holds the advantage of a better fit in the setting of research biobanks, and it wholly takes into account the complexity of the communication process. Furthermore, a pact-based perspective recovers one of the fundamental components for effective communication; specifically it embraces the concept of *trust*.

Within the contractualistic form of the agreement, trust is subsidiary. Indeed, what need does the donor have to trust the researcher, if the research

aims have already been formally established and clarified? Differently put, when all has been defined, what remains to be done is simply to verify that the terms are carried out; no more investment is required.

A trust-based pact rests on a different kind of assumption: the belief that the content of the agreement is not precisely definable. This is exactly the case for research biobanks. Here, the impossibility of predicting the precise research destiny of human tissues necessarily entails a trust-based pact, within which each part relies on the other, and trust is placed that human tissues will be used for ethical reasons and following appropriate procedures. Because of its intrinsic unpredictability, the research biobank requires that those who donate human tissues trust the community of researchers and their good intentions.

To conclude, research biobanking leads us to a third way of conceiving the researcher-donor relationship, which is alternative to the two classical approaches that emphasize either autonomy or beneficence. Indeed the idea of a *trust-based pact* provides an almost perfect fit for the biomedical setting.

3. Participating in research: from duty to *choice*

Rethinking the researcher-giver relationship as an *alliance* between the two parties founded *on a trust-based pact* that aims to advance scientific knowledge also has a number of implications for the debate concerning an alleged duty to participate in research.

Several attempts have been made to find a moral basis for participation in biomedical research. In particular, two main arguments have been widely

discussed in the literature. The fist argument deals with public goods. Since the results of biomedical research – such as health, safety and knowledge – constitute public goods and since all members of society share the positive effects of these public goods, then society as a whole (or rather, its members) should participate in producing them. Moreover, since the participation in biomedical research is a necessary means to produce public goods, it follows that public participation in research should be mandatory[12]. The second argument has a contractualistic form and lies in the idea of a "cross-generational social contract" [13]. According to this, the duty to participate in research is founded on an obligation to discharge the debt owed to those who participated in previous research.

Both lines of argument present weaknesses. Two objections are relevant to the view of research results as public goods[14]. Firstly, since the benefits of biomedical research are unevenly distributed within society (this is – at least ideally – valid for those countries with a public health care system, but not for those countries with a private health care system), justifying the imposition of such a general rule to health care systems becomes problematic. Secondly, even if one were to grant that there is a positive

[12] See for example W. McDermott. Opening comments to colloquium: The changing mores of biomedical research. *Ann Intern Med.* 1967; 67:39-42.

[13] Caplan, *op cit.* note 4, p. 2.

[14] See, H. Jonas. Philosophical reflexions on experimenting with human subjects. *Daedalus* 1969; 98:219-47; note 14; C. Fried ed. 1974. *Medical Experimentation: Personal Integrity and Social Policy*. Elsevier; A. Donagan. Informed consent in therapy and experimentation. *J Med Philos* 1977; 2(4):307-29.

obligation in the maintenance of public goods, it is hard to see why this obligation would require the improvement of such goods.

The contractualistic argument appears less decisive, as it robs former generations who participated in research of their potential altruistic behavior. In other words it seems difficult to ascribe to those who participated in research a rate intention, according to which their actions would be compensated in the future by those who reaped the benefits of their earlier participation[15].

These difficulties suggest that there is no firm ground upon which we can argue for a moral duty for participation in research. However, the perspective changes if we consider a *soft* duty to participate in research. In particular, we suggest[16] that: i) the concept of reciprocity should be broadened to include not only the donor and the researcher, but also society as a whole; ii) the understanding between researcher, donor and society should rest on the concept of trust. Let us explain why.

According to a principle widely recognized in moral philosophy (mainly endorsed by Kantian scholars), being a moral agent entails being subjected to the principle of reciprocity, according to which the possession of rights goes hand in hand with the coincident possession of duties. As a consequence, based on the principle of reciprocity, researchers, donors and society as a whole, in their role as moral agents, possess both duties and rights, thus creating of a network of alliances. At the base level, such an

[15] Caplan, *op cit.* note 4, p. 3.

[16] For a very similar position, see J. Harris. Scientific research is a Moral Duty. *J Med Ethics* 2005; 31:242-248.

alliance is instantiated between society and researchers, since the former supports and finances the latter; on top of this is layered an alliance between researchers and donors, since the former undertake to use donated human tissues from the latter in an ethical manner and for non-trivial purposes; finally the alliance between donors and society guarantees that the efforts made by researchers are not wasted and might have important benefits for society. The positive circularity that follows from the concept of reciprocity provides persuasive reasons for fulfilling the "fair play"[17] of research enterprise – both in terms of *solidarity* towards the different members of the society and in terms of real advantages afforded to them through their participation. Indeed, in this model society improves itself (broadening the so called generalisable knowledge), researchers gain access to the materials necessary to advance applicable knowledge; and, finally, current and future patients can hope for new therapies for their diseases.

Importantly, without the support of trust, reciprocity alone could not achieve the same results. To be more precise, the principle of reciprocity alone, despite being an essential pillar of research, cannot justify voluntary participation to it. Indeed, although personal gain motivates each party to participate, this participation is justified, above all, because of the trust each party has in the overall enterprise and in the parties involved. Once the existence of a mutual positive circle has been demonstrated, it is the trust that each party is willing to grant to the others and the faith placed in the value of scientific research that convinces participants to take part in the fair play of research.

[17] J. Rawls ed. 1971. A theory of Justice. Cambridge: Harvard University Press.

Summing up, whereas a robust duty to participate to research cannot be grounded, a soft duty to do so seems plausible, as long as we endorse the principle of reciprocity, reinforced with the concept of trust. Only thus can the network of alliances necessary for scientific enterprise become effective.

4. Scientific research as an ethical enterprise

One last issue needs to be resolved. Why should the different members of the network trust each other? The formal structure necessary for a network to be operative fails to justify why each part should trust the other. Is trust a foundational concept or should it be grounded on something else? In other words, if we replaced the participants of the network with different participants, would it still work just as well? Simply claiming that trust is based on reciprocity would constitute a circular argument. Therefore, we suggest that the answer may lie in the classical idea that science constitutes an ethical enterprise *per se* and that it is consequently a vehicle of ethical values[18]. In other words, the scientific enterprise differs from other kinds of activities and this plays a central role in the trust-based network, so central that if it were not one of the actors, the system would not be the same.

The reason why science might be considered to be an ethical enterprise is primarily due to the fact that it is directed to, and exercised via both ethical and epistemic values. Indeed, scientific enterprise aims both to gain "generalisable knowledge" (*the epistemic end*) and, in the case of biomedical sciences, to develop better treatments for patients (*the ethical*

[18] For a classical starting point see, H. J. Poincaré, La morale et la science, now in H.J. Poincaré 1913. *Dernières Pensées*. Paris: Flammarion.

end). Moreover, in addition to being governed by the principles of biomedical ethics (autonomy, non maleficence, beneficence, justice) that regulate research on human subjects, scientific enterprise by its very nature depends on values such as reliability, reproducibility, accuracy and precision that prevent such an enterprise from being subjective and context-dependent[19].

To conclude, the foundation of reciprocity upon trust is a necessary step to justify a soft duty to participate to research, and this shifts patient participation in research from the domain of compulsion to that of free choice. In addition to this, the description of science as an ethical instantiation allows us to explain why patients should trust the scientific enterprise more than other non-scientific ones.

CONCLUSIONS

Our arguments serve to explain the need for a new form of consent for research biobanks, based on the concept of trust instead of the simple transfer of information. The proposal we have presented is not simply theoretical, but it has been implemented at the European Institute of Oncology (Milan, Italy), a comprehensive cancer research and care institution.

The shift from informed consent to trusted consent (the so-called *Participation Pact*) has two main consequences. On the one hand, it defines a new form of researcher-research subject relationship. By basing the researcher-patient relationship upon trust, the two parties are bound by a

[19] Of course if it is done in a fair and methodologically correct way.

pact, which prevents the relationship from being unbalanced and forces both parties to respect the agreement they have forged. On the other hand, the act of patient participation in research is completely transformed. Unlike previous models that attempted to impose on patients a robust duty to participate in research, a pact-based relationship instead provides patients with a strong incentive to do so, as they are motivated by an act of solidarity where reciprocity, trust and the belief that science is an ethical enterprise play a mutual supportive role.

From an applied bioethical viewpoint, one question is paramount. Does the *Participation Pact* work? From the initial data we described, the answer seems to be a resounding "yes". Ninety-eight percent of patients signed the *Pact* in a non-anonymous form, thereby confirming the relevance of trust in mediating the relationship between patients and researchers.

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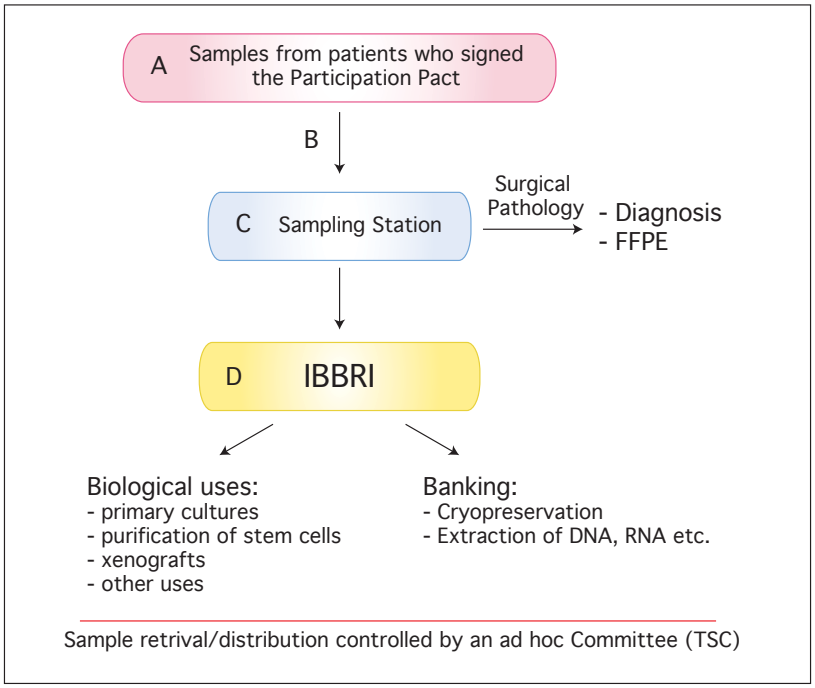
Figure 1. Flow chart of banking at IBBRI-IEO.



A. The entry point of the process is the Participation Pact. A trained research nurse (or an attending physician, if needed) explains the importance of biobanking for research needs to patients, and provides relevant information about the research that will be performed on the specimens. In some cases, precise information and explanations can be given about ongoing research. In these cases, samples are collected according to an approved research protocol that justifies their need. Approval of the protocol is granted by an internal Technical-Scientific Committee (the TSC of IBBRI) and by the Institutional Ethical Committee. In other cases, approval cannot be sought, since samples are not accrued for an active research protocol, but are collected for banking purposes and for future research. In either case, one of the most significant aspects of the

consultation is the opportunity afforded to the health care provider to explain the meaning of "future research", by describing potential general directions of research, as well as explaining the meaning of technical phrases present in the Participation Pact (see Figure 2). Patients are then asked if they wish to subscribe to the Participation Pact (see Figure 2). Only samples from those who subscribe are processed through the IBBRI. Should the patient refuse the Participation Pact, the specimen obtained is directly routed to the Surgical Pathology Department for the diagnostic procedures and for the conservation of paraffin blocks (FFPE, formalin-fixed paraffin-embedded), an act that is necessary to discharge legal obligations. **B.** Specimens are transported under sterile conditions from the surgical theatres to a sampling station. The maintenance of sterility during the entire process is critical for developing research tools (biological uses at the bottom of the figure), which represents one the innovative aspects of the entire process of sample accrual through the IBBRI. **C.** At the sampling station, a certified pathologist in attendance takes custody of the specimen, in accordance with the Italian Law. It is here that the pathologist decides whether a fraction of the specimen can be destined to research purposes without prejudice for the the routine diagnostic procedures. If so, the pathologist samples the specimen and directs the necessary part of it to the Department of Surgical Pathology, and the remainder to the IBBRI. **D.** The IBBRI personnel takes over at this point and on the basis of various considerations (actual research needs, size of the specimen) assigns the specimen to a number of uses, including banking (frozen specimens and extracted DNA/RNA if possible) and immediate establishment of research tools (biological uses in the

figure). Banked samples can only be retrieved and distributed to investigators upon approval of specific research projects, which, in general, also require approval by the Ethical Committee.

I, the undersigned _____

_____

_____

☐ Participant

☐ Legal representative of the participant: Mr/Ms _____

_____

have been informed of the following during my consultation with _____

_____

_____

_____

_____:

- All options available to me regarding the treatment of sensitive information and genetic data, and the uses of biological specimens for research purposes have been clearly explained to me;
- I have been given the opportunity to ask questions and my questions have been answered to my satisfaction;
- I have been informed that any decisions I may take will apply to all biological specimens donated by me that relate to a specific disease, even if these should be collected during future hospital stays/ treatments. I also understand that I can revoke or modify my consent at any time.

On the basis of this, I agree to the storage of any biological specimens collected in the course of my diagnosis and therapy, and/or collected for specific research purposes, according to the modality indicated below. I further agree to the use of these samples for research purposes. I declare that I do not expect to receive any economic benefits from the knowledge that will be gained through the use of my samples:

1. I request my samples to be held and processed anonymously (and consequently that they be used for research purposes that are compatible with this choice), in the full understanding that I will not receive updates on any useful and relevant research results. 1.1. The research objectives that will be pursued can be summarized as follows: - Definition of the molecular mechanisms responsible for tumor development; - Identification of new "intelligent" drugs; - Identification of new molecular markers for early diagnosis, to predict the natural course of the disease (prognosis) and therapeutic response; - Identification and validation of the preventive potential of natural or chemical compounds; 1.2. I also give permission, subject to the conditions described in Article 1, for the storage of the biological specimens obtained from me during the course of my therapeutic care and for their use in future research, for which the objectives are as yet unknown, but which we envisage will be necessary, given the continual development of technologies and scientific knowledge.	☐ Yes ☐ No
2. I request my samples to be held and processed in an anonymized fashion (samples are not anonymous, but my identity is protected by encryption);	☐ Yes ☐ No
2.1. I give permission for the storage and use of any **sensitive data** relevant to the research objectives described in Article 2; 2.1.1. I agree to the use of my biological samples for the following aims: - Definition of the molecular mechanisms responsible for tumor development; - Identification of new "intelligent" drugs; - Identification of new molecular markers for early diagnosis, to predict the natural course of the disease (prognosis) and therapeutic response; - Identification and validation of the preventive potential of natural or chemical compounds; 2.1.2. I also give permission, subject to the conditions described in Article 2, for the storage and use of the biological specimens obtained from me during the course of my therapeutic care and/or specifically collected for research purposes in the future, for which the objectives are as yet unknown, but which we can envisage will be necessary, given the continual development of technologies and scientific knowledge; 2.1.3. I understand and agree that any information which is relevant to the research aims (be they known or unknown) can be used for research purposes by the institutional Tumor Registry;	☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes

2.1.4. I agree to receiving information, should any data be generated, even unexpectedly, that might have a direct beneficial effect in the context of my anticancer therapy, my preventive therapy, or my informed reproductive choices;	☐ No ☐ Yes ☐ No
2.2. I give permission for the storage and use of **genetic data**, relevant to the research objectives described in Article 2; 2.2.1. I agree to the use of my biological samples for the following aims: - Definition of the molecular mechanisms responsible for tumor development; - Identification of new "intelligent" drugs; - Identification of new molecular markers for early diagnosis, to predict the natural course of the disease (prognosis) and therapeutic response; - Identification and validation of the preventive potential of natural or chemical compounds; 2.2.2. I also give permission, subject to the conditions described in Article 2, for the storage and use of the biological specimens obtained from me during the course of my therapeutic care and/or specifically collected for research purposes in the future, for which the objectives are as yet unknown, but which we can envisage will be necessary, given the continual development of technologies and scientific knowledge; such studies will pertain to the prevention/cure of cancer, regardless of how current research objectives my develop in the future; 2.2.3. I agree to the use of my research-related genetic data (relevant to known or unknown research aims) and diagnosis/therapy related genetic data for research carried out by the institutional Tumor Registry; 2.2.4. I agree to receiving information, should any data be generated, even unexpectedly, that might have a direct beneficial effect in the context of my anticancer therapy, my preventive therapy or my informed reproductive choices; 2.2.5. I agree that any of my relatives that share my genetic lineage should be permitted to receive information as described in Article 2.2.4, subject to presentation of a specific written request.	☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No
Date ____/____/____ Signature of the patient/ legal representative)_____	

Date ____/____/____ Signature of the operator_____ Employee no._____

Fig. 2 – *The IEO Participation Pact form*