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The Ethics of Rapid Tissue Donation (RTD)

Constructing a Formal and Substantial Informed Consent Process

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Inscription:
To *M.P., F.E.G. & T.*

Introduction

Cancer is the second leading cause of death in developed countries, after heart diseases. Although cancer can be partially prevented by avoiding risk factors and implementing existing evidence-based prevention strategies, oncology research aimed at developing effective treatments plays a key role in preventing cancer deaths. Due to advances in knowledge and treatments, the chances of surviving cancer are increasingly improving if the disease is diagnosed early and treated correctly. Research has shed light on different aspects of cancer that have made it possible to partially understand the biological mechanisms that may cause cancer onset and to determine its consequent development and resistance to some treatments. Such understanding is the cornerstone of the implementation of preventive measures, and it is driving the development of promising cancer therapies.

Prevailing theory, which was formulated in the middle of the twentieth century, interprets cancer as a set of about 200 diseases characterized by an abnormal cell growth that is released from the normal control mechanisms of the organism. While there is normally a balance between proliferation and programmed cell death, mutations in DNA leading to cancer are responsible for the destruction of these ordered processes. The study of the molecular structure of tumors, in constant variation, is the research field with the most promising outlook for future clinical developments.

Research in genomics is making possible a targeted and personalized approach to the diagnosis and treatment of different diseases. This approach, which is referred to as "precision medicine," is based on a model of healthcare delivery that relies on individual variability in genes, environment, and lifestyle. By understanding this variability, it is possible to classify individuals into subpopulations that differ in their susceptibility to a particular disease or in their response to a specific treatment. This model enables healthcare decisions to be guided toward the most effective care and treatment for a given patient based on their personal profile.

The development of precision medicine has a wide array of important implications. Clinical implications are at the forefront, but they are not the only ones. Precision medicine raises various ethical issues. The ability to sequence the entire genome of an individual patient presents researchers with a golden opportunity to advance research in the field by exploring the molecular landscape of genes associated with human diseases. At the same time, however, this opportunity depends on an unprecedented

amount of private, and identifiable (or reidentifiable) data being made available. The management of and access to this data require adequate policies that take into account research needs on the one hand, while safeguarding patients on the other. Analyzing the ethical issues raised by the application of omics technologies within the clinical field involves, among other things, a consideration of how the sharing of genetic information and genetic data may impact individuals, their families, and their communities. The use of genetic information in research is key to advances in precision medicine and holds unique opportunities for the development of new treatments, but the pursuit of this opportunity can in no way be detrimental to patients' rights. Thus, the development of an ethical framework to support policies relating to informed choices and to the responsible use of personal information assumes unprecedented importance to the goal of fostering the development of science while protecting the rights of patients.

Within oncology, precision medicine uses a knowledge of the molecular landscape of tumors in order to tailor medical treatment to the individual characteristics of each patient. The development and applicability of this kind of targeted approach in the field of oncology heavily relies on the availability of tumor tissues to be used for research aims. The procurement of adequate cancer tissues for research using traditional biopsies in living patients is problematic because of the limited quality and quantity of the retrieved tissues; however, postmortem retrieval of tissues represents a far more promising opportunity for collection of suitable tissues.

Rapid Tissue Donation (RTD) in oncology is an advanced procedure that involves the procurement of "fresh" cancer tissue ideally within 2–6 hours of the death of a patient (Lindell et al. 2006). In this technique, the restricted time frame in which the material is retrieved from the patient is essential for preserving the molecular properties of collected tissues. RTD enables researchers to extract a significant quantity of high-quality tumor tissue from both the primary site of the tumor and from all its derived metastases; in addition, unaffected tissues can be retrieved in order to study the molecular composition of the tissue. Fresh tissues obtained via RTD offer research opportunities that are not available using other techniques: it is not feasible to make a similar collection of tissues from living patients, and tissues previously collected and stored using preservation systems fall significantly below the quality of tissue that can be obtained from RTD.

RTD represents a significant chance to investigate cancer onset and development in order to translate acquired knowledge into new treatment options for future cancer patients. However, despite the high promise of this procedure, its implementation in the clinical setting raises challenging issues associated with the informed consent process. First, RTD tissue retrieval takes place *after* death, when the need for an informed consent has been questioned. Moreover, because the quality and quantity of retrieved tissues offer insights that enable research on new treatments, the need for an informed consent process to govern RTD has been questioned on the grounds that the potential benefits to society from this research outweigh any requirement for informed consent. The lack of consensus on the need for an informed consent procedure to regulate this form of tissue collection hampers its implementation within the clinical setting, and thus also creates barriers to the development of cancer research.

The aim of this book is to analyze the ethical quandaries raised by the informed consent process for RTD, in particular by building on a specific interpretation of the notion of informed consent that envisions the coexistence of two senses associated with this concept. Drawing on the work of R. R. Faden and T. L. Beauchamp, I consider informed consent to comprise both a *substantial* meaning and a *formal* meaning. In its *substantial* sense, informed consent is a specific form of autonomous authorization conferred by a patient or a subject. This authorization lies at the heart of this sense of informed consent: in authorizing, patients both assume responsibility for what they have authorized and transfer it to another's authority in order for what they have authorized to be implemented. At the same time, there is an institutional set of rules and policy governing this act, and it is to these that the *formal* sense of informed consent refers. In its *formal* sense, informed consent entails a legally effective authorization from a patient, and the effectiveness of this act is determined by its compliance with the rules and requirements that define a specific institutional practice in healthcare and research (Faden and Beauchamp 1986, p. 280). In this second sense, informed consent is policy-oriented and reflects the conformity to the social rules of consent that require medical professionals to seek and obtain valid consent from patients before carrying out medical or research interventions. This public practice is regulated by specific norms and institutional settings that are intended to define when and if a certain consent or refusal provided by a patient is valid.

In this framework, the relationship between the two senses of informed consent is deep: they are separate and do not overlap, yet at the same time they are closely tied together. Policies governing the *formal* sense of the term should be formulated to conform to the standards of the *substantial* sense; in other words, institutional requirements for *formal* informed consent should be intended to maximize the likelihood that the conditions of informed consent in its *substantial* sense will be satisfied. The autonomy-based model of informed consent in its *substantial* sense should function as a standard for informed consent in a *formal* sense (Faden and Beauchamp 1986, p. 284).

However, a significant discrepancy emerges from the relationship between these two senses of informed consent. It may happen that an informed consent given in the first sense does not represent a legally effective informed consent in the second sense. This means that an informed consent obtained under institutional criteria (envisioned by the *formal* sense) may fail to conform to the autonomy-based model (the *substantial* sense), and vice versa. Thus, informed consent obtained according to its *substantial* sense may, in certain cases, not be effective in its *formal* sense, and, *mutatis mutandis*, informed consent compliant with its *formal* sense may not be effective in its *substantial* sense.

This dual-sense structure of informed consent provides the lens through which the unprecedented issues raised by informed consent for RTD will be analyzed. The structure is used to facilitate the discussion and analysis of the two key areas in this book, namely, whether there is a need for informed consent to RTD, and, if so, how to implement an RTD informed consent procedure.

The framework offered by the *formal* sense of informed consent, intended as a policy-oriented authorization defined by institutional settings, will be considered in relation to the first key area of analysis, which concerns whether there is a need for informed consent to govern RTD. This need has been challenged by various commentators on different grounds; in this book, arguments both for and against informed consent will be considered, but it will ultimately be argued that there*is* a need for an informed consent to govern RTD.

After making the case for the need for an informed consent process to regulate RTD, my analysis will turn to the ethical quandaries raised by the practical implementation of informed consent. In relation to RTD, how should informed consent be structured and collected in order to encourage an autonomous authorization intended in the *substantial* sense of the term? And how should this autonomy be formalized in the *formal* sense of informed consent? The innovative nature of RTD makes the informed consent process challenging: as well as raising some ethical issues common to standard oncological research and donation procedures, RTD also poses novel issues that have no precedents in the medical setting. In addressing and analyzing these questions and issues surrounding informed consent within the RTD setting, it will be proposed that there should be a dedicated informed consent procedure in which a specifically trained RTD ethicist should play a central role.

By viewing medical issues relating to informed consent in oncology through an ethical lens, the analysis blends traits of abstract philosophy with concrete cancer-related aspects. As a result, the book is situated at the intersection of various interests: it is suitable for readers fascinated by ethical reasoning as well as for those with a medical background. To achieving this aim of meeting the needs of a heterogeneous group of readers, I have attempted to present the analysis in such a way that it will be clear both to those who are new to many of the areas of discussion and to those who are highly familiar with the topic.

The structure of the book, composed of eight chapters in addition to the introduction and conclusion, reflects the inter- and multidisciplinary nature of the subject at stake.

Chapter 1 introduces RTD, and the wider context of precision medicine in oncology, in more detail. It outlines, from a technical point of view, the potential research benefits of collecting cancer tissues immediately after the death of the patient.

In Chapter 2, I turn my attention to the issue of informed consent, which lies at the heart of the relationship between patients and physicians. I consider how this relationship has evolved and the implications of this evolution for the meaning and boundaries of informed consent. I then analyze the two senses of informed consent—the *substantial* sense and the *formal* sense—which constitute the framework within which I will later discuss informed consent for RTD.

Chapter 3 opens with a presentation of Beauchamp and Childress's analysis of the four principles that constitute the foundation of biomedical reflection, namely, the principles of autonomy, beneficence, non-maleficence, and justice. This framework serves as a starting point to explore in more depth the issues associated with informed consent for RTD. First, arguments against the need for informed consent to govern

postmortem procedures will be introduced. I then survey some important positions advocating a regime of conscription. Finally, I address arguments for the need for an informed consent to govern postmortem procedures.

Having surveyed various philosophical positions for and against informed consent in the third chapter, in Chapter 4 I develop an argument for the need for an informed consent procedure to govern RTD. I begin by introducing the concept of the "once-alive" as a way of thinking about the dead as individuals who had values, wishes, and preferences in life that should be honored after death. In this way, I argue that there is a compelling basis for requiring informed consent based on two principles: (1) it is crucial to honor, even after death, the wishes (if any) that individuals have expressed during their lives, (2) provided that these preferences do not jeopardize other living individuals. After setting out this argument, I then discuss why positions that advocate no need for an informed consent to regulate postmortem procedures should be rejected.

Chapter 5 delves into the relevance of informed consent in the medical field, with a specific focus on its role in the research setting. I discuss the main regulations and codes that govern informed consent within medical research, and I analyze information, comprehension, and voluntariness as the basic features of informed consent in the research setting. These requirements represent the basis to consider the issues raised by informed consent in research through a comparison between oncology research and RTD.

Chapter 6 bridges the ethical and medical dimensions by introducing the figure of the clinical ethicist. The aim of this chapter is to underline the value of an ethical perspective for viewing the issues that emerge on a daily basis in the medical setting. The value of this perspective is particularly relevant within the context of RTD whose innovative traits raise unprecedented and challenging ethical issues. I also argue for the need for an RTD ethicist—namely, an ethicist with specific training in RTD programs—to adequately support patients, family, and medical staff throughout the RTD process, particularly in relation to informed consent.

Chapter 7 outlines an informed consent process, intended in both the *formal* and *substantial* senses of the term, for RTD. This chapter addresses the practical aspects of RTD informed consent and their relevant ethical implications by considering questions such as who should be in charge of presenting RTD as an option to the patient. I propose a three-phase structure for informed consent that is designed to promote and encourage, as far as possible, a choice that reflects a patient's preferences. Within this chapter, aspects pertaining to informed consent for vulnerable populations are also discussed.

The structure for an RTD informed consent process presented in the seventh chapter paves the way for the ethical analysis in Chapter 8. This analysis retains a practical approach. Challenging issues associated with informed consent for RTD are addressed, such as consent withdrawal, the role of families in the informed consent procedure, how collected samples may be identified (or reidentified), and the various possible uses for tissues in research. Within this scenario, the role of the RTD ethicist is vital for a thorough informed consent valid in both the *formal* and *substantial* senses of the term.

The ultimate objective of this book is to set out an informed consent for RTD intended in its *formal* sense—and hence a legally recognized path for a cancer patient to rely on when deciding whether to donate their tissues after death—but one whose requirements are modelled according to the *substantial* sense of informed consent—namely, one that honors the autonomous authorization of the patient.

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Contents

Chapter 1
Rapid Tissue Donation (RTD) for Oncology Research

Abstract Research in genomics and "omics" technologies is making possible "precision medicine", a targeted approach to the diagnosis and treatment of diseases. The goal of precision medicine, and one that holds great promise in oncology, is to treat patients with drugs that target the specific genetic mutations in their tumors. The research use of cancer tissues aims to unravel the mechanisms of cancer onset and evolution. To this end, collection of cancer tissues after the death of a cancer patient represents a unique opportunity for researchers. Rapid Tissue Donation (RTD) is an advancing oncology procedure that involves the procurement of "fresh" tissue within 2–6 h following the death of a cancer patient. This window of time is ideal to preserve the high quality of tissues retrieved. Whereas traditional tissue biopsies provide researchers with a limited amount of material that is often suboptimal for research needs, RTD offers the chance to overcome these barriers.

1.1 Precision Medicine

The next generation of medicine is upon us. Advances in genomics and other "omics" technologies over the past decade have yielded new tools to evaluate disease susceptibility and prognosis, and they offer unprecedented opportunities to individualize therapy. New medicines are increasingly targeted to specific patient populations and have enriched the therapeutic approach to treatment of a wide range of pathologies, among which are cancer, chronic infections, and rare diseases.

This targeted approach to the diagnosis and treatment of different diseases is known as "precision medicine", an emerging model for healthcare delivery that relies on individual variability in genes, as well as on environment and lifestyle.[1] According to the definition given in 2008 by the President's Council of Advisors on Science and Technology (National Research Council 2011), precision medicine is the

[1] Among the literature on precision medicine, see: Aronson and Rehm (2015), Delaney et al. (2016), Dzau and Ginsburg (2016), Jameson and Longo (2015), Khoury and Galea (2016), Khoury et al. (2016), McCarthy et al. (2013), Mirnezami et al. (2012), National Research Council (2011), Phillips et al. (2017), Vargas and Harris (2016).

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tailoring of medical treatment to the individual characteristics of each patient to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment.

The advent of precision medicine has disrupted the entire medical field. Its introduction of new technologies has revolutionized the progress and potential of medicine, impacting on research, prevention, diagnosis, and care. In the pre-genomics era, most drugs were traditionally tested, approved, and developed according to their effects on a general population of patients affected by the same disease and a certain diagnosis. In the conventional approach of the "same drug fits all with the same disease", clinical trials for the development of new drugs or a new combination of drugs showed the average response of the patients' cohort to the treatment under investigation. However, this average response can obscure the fact that some patients might show an extremely positive response whereas others show no response at all. The DNA sequence between any two individuals (apart from identical twins) is approximately 99.9% identical, but the 0.1% difference is "medically significant": "enclosed within this small percentage of difference lie the clues to hereditary susceptibility to virtually all diseases" (Jain 2009, p. 1). It is in this 0.1% difference that can be found the reasons why responses to treatment differ among patients affected by the same disease.

Precision medicine holds great promise in oncology because it involves tailoring treatments that are best suited to each individual patient. A key part of such treatments is the integration of new technologies within the clinical care of patients. However, this does not mean creating drugs or medical devices that are unique to a patient; rather, it involves the ability to group patients according to their susceptibility to a particular disease, to the biology or prognosis of those diseases they may develop, or to their response to a specific treatment.[2] The potential created by this shift in treatment has dramatic implications along both medical and ethical dimensions. Preventive or therapeutic interventions can be concentrated on those who will benefit; and harm and side effects can be reduced for those who will not benefit. This model allows healthcare decisions to be guided toward the most effective treatment for a given patient, thereby improving care quality while reducing the need for unnecessary diagnostic testing and therapies.

Consequently, precision medicine is based on the study of a specific profile in order to choose the optimal targeted therapy. This approach will enable doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people, based on a genetic understanding of their disease.[3] The underlying concept of precision medicine, in which

[2] Among the oncological literature on this, see: Buettner et al. (2013), Garraway (2013), Garraway and Lander (2013), Lolkema et al. (2013), MacConaill (2013), Meric-Bernstam et al. (2013), Sleijfer et al. (2013), Van Allen et al. (2013).

[3] Among the literature on genome sequencing and genetic understanding, see: Cooper (2015), Denny et al. (2013), Gahl et al. (2016), Green et al. (2013), Hunter et al. (2016), Landrum et al. (2016), Ledford (2015), Minikel et al. (2016), Richards et al. (2015), Ritter et al. (2016), Schughart et al. (2013), Starita et al. (2015), Willig et al. (2015), Yamamoto et al. (2014), Yang et al. (2014).

healthcare is individually tailored on the basis of a person's genes, lifestyle, and environment, will facilitate the development and production of safer and more effective medicines with reduced occurrence of side effects. In the long term, individuals will have the opportunity to manage their health with bespoke approaches based on their genetic profile.

With the advent of genome sequencing, precision medicine has become a promising perspective from which to observe diseases. A gene can be defined for practical purposes as a "physical and functional unit of heredity, which carries information from one generation to the next", while, in molecular terms, it is the "entire DNA sequence including exons, introns, and noncoding transcription control regions that are necessary for production of a functional protein or RNA" (Jain 2009, p. 18). The sequencing of the human genome has provided researchers with crucial information for studying the genetic dimension of diseases. Within this framework, the identification of human genes associated with their regulatory locations enables researchers to study diseases in intimate detail in order to better understand their functioning, onset, and development. Advances in genetics and the increasing availability of health data have created an opportunity for personalized patient care to become a reality within the clinical field. Since the first human genome was sequenced in 2001 at a cost of around US$3 billion, the technology has become significantly easier and cheaper. Many genomes can now be sequenced within a day at a cost of approximately $1,000 each (Nature Outlook 2016). As a result, genome sequencing has entered medical practice as a procedure for diagnosing rare disorders where traditional diagnostic techniques have failed.

In contrast to a one-size-fits-all approach, in which disease treatment and prevention strategies are developed for the average person rather than by considering the differences between individuals, precision medicine provides patients with a unique approach based on genetics (National Cancer Institute 2017). The understanding of the genetic component of diseases has led to a new way of classification. Since all major diseases are characterized by a genetic component, their classification might be organized according to genetic differences in affected patients and not only according to their symptoms. Diseases can, therefore, be reclassified in molecular terms rather than by relying solely on gross pathology. Such a shift opens up opportunities to use the same drug or combination of drugs to treat diseases that are characterized by the same molecular basis. This difference would enable patients to be treated with more effective approaches that are targeted at their genetic profile.

1.2 Precision Medicine in Oncology

Although the novelty of precision medicine will inevitably permeate various medical branches, oncology—that is, the scientific study of cancer—is arguably in the vanguard. After heart-related diseases, cancer is the second leading cause of death in developed countries, and it was responsible for an estimated 9.6 million deaths in 2018 (WHO 2018). Globally, about one in six deaths is due to cancer. Although

cancer can be partially prevented by avoiding risk factors and implementing existing evidence-based prevention strategies, oncology research aimed at developing effective treatments plays a key role in reducing cancer deaths. Many cancers have a high chance of being cured if diagnosed early and treated adequately. Research has shed light on different aspects of cancer that have made it possible to partially understand the biological mechanisms that cause cancer onset and its consequent development. This understanding is the cornerstone of the implementation of preventive measures and the development of cancer treatments.

The prevailing theory, which was formulated in the middle of the last century, interprets cancer as a set of about 200 diseases characterized by an abnormal cell growth that is released from the normal control mechanisms of the organism. All cancers begin in cells within human bodies. Cancer originates because changes in one cell or in a small group of cells determine an uncontrolled division. Proliferation (cell division) is a physiological process that takes place in almost all tissues and in countless circumstances. Normally, there is a balance between proliferation and programmed cell death (apoptosis), but mutations in DNA leading to cancer are responsible for the destruction of these ordered processes. This results in an uncontrolled cell division that may lead to the formation of a mass called a tumor (AIOM 2018).[4]

The place where a cancer starts in the body is referred to as the primary tumor or primary site. Eventually, cancer can spread to another part of the body. In order to spread, some cells must divide from the primary tumor and travel to another part of the body, where they start growing. This new area of cancer is called a secondary cancer or a metastasis. Some cancers may spread to more than one area of the body to form multiple secondaries or metastases. The more a cancer spreads, the harder in general it will be to eradicate (Cancer Research UK 2017).

The process leading to cancer—namely, the transformation of a normal cell into a neoplastic cell—occurs in various stages in which there is an accumulation of genetic, functional, and morphological aberrations. For this reason, the constantly varying molecular structure of tumors constitutes the research field in which the greatest hopes are invested for future clinical developments.

Within this framework, precision medicine will shed unique light on the study of cancer. One reason for this is that cancer is a genomic disease: most cancers harbor a cocktail of mutated (or altered) oncogenes[5] and tumor suppressors[6] that work in

[4]Most tumors follow this process, although not all: for example, tumors of the blood follow a different path.

[5]An oncogene is a gene that is a mutated (changed) form of a gene involved in normal cell growth. Oncogenes may cause the growth of cancer cells. Mutations in genes that become oncogenes can be inherited or they can result from being exposed to substances in the environment that cause cancer. See https://www.cancer.gov/publications/dictionaries/cancer-terms/def/oncogene.

[6]Tumor suppressor genes are normal genes that slow down cell division, repair DNA mistakes, or tell cells when to die (a process known as apoptosis or programmed cell death). When tumor suppressor genes do not work properly, cells can grow out of control, which can lead to cancer. See https://www.cancer.org/cancer/cancer-causes/genetics/genes-and-cancer/oncogenes-tumor-suppressor-genes.html.

concert to specify the molecular pathways that lead to their genesis and progression. To this end, oncology research has benefited greatly from the proliferation of worldwide efforts to characterize the genomes of thousands of cases spanning nearly all major cancer types. The same technological advances that have enabled a comprehensive catalogue of cancer genes are becoming increasingly applicable to advanced clinical diagnostics. Together with the expanding compendium of targeted anti-cancer agents in clinical development or active use, oncology has served as a proving ground for the genomics-driven framework that is unique among medical specialties (Garraway et al. 2013).

DNA alterations in the genesis of cancer stem from different causes, including environmental, genetic, and infectious aspects, causes linked to lifestyle, as well as random factors. Smoking, inadequate dietary habits, and inactivity significantly impact the risk of tumor development. Infections (like the papilloma virus) are responsible for an estimated 8% of tumors (AIOM 2019). Heredity can be a factor; for example, the genes *BRCA* 1 and 2 can increase the risk associated with the development of breast and ovarian cancer. However, heredity plays a low incidence in tumor genesis: less than 2% of the population carry mutations associated with hereditary neoplastic risk (AIOM 2019). Given that, in general, different risk factors are involved in cancer development, it is not easy to determine and assess the precise risk associated with single tumors; by definition, the genesis of a neoplastic disease is multifactorial. This means that an articulated combination of risk factors is concurrently at play in determining the onset and development of the disease. Hence, multiple factors should be analyzed within the patient's specific reaction, particularly in relation to the immune defense mechanisms and the processes to repair DNA damage (AIOM 2019).

When diagnosed with cancer, patients have typically received the same treatment as others who had the same type and stage of cancer, because tumors have traditionally been grouped and treated according to where they are found in the body. For example, all patients with a certain stage of kidney tumor would receive the same treatment. Nevertheless, different people respond differently to treatment, and, until recently, researchers could not understand the reason for this. After decades of research, scientists discovered that patients' tumors have genetic changes that cause cancer to grow and spread. They have also learned that the changes occurring in one person's cancer may not occur in others who have the same type of cancer, because tumors are often driven by unique combinations of DNA mutations. Furthermore, the same cancer-causing changes may be found in different types of cancer. Collectively, such changes are known as a tumor's mutation profile (Dana Farber Boston Children's Cancer and Blood Disorder Center [n.d.]).

When it comes to treating cancer, knowing which mutations are present in a tumor's profile may be more important than knowing where the tumor is located. The goal of precision medicine as applied to oncology is to treat patients with drugs that target the specific genetic mutations in their tumors, regardless of where the tumors are found. This extremely promising approach has already been implemented in clinical practice for certain kinds of tumors, and it is expected to become increasingly successful. Scientists are, therefore, working toward the development of genetic tests