TESaCo

Les Cahiers de TESaCo N°4

/ ÉDITION DU GÉNOME
/ ORGANOÏDES
/ TESTS GÉNÉTIQUES
BIOÉTHIQUE

Technologies émergentes et sagesse collective

Comprendre, faire comprendre, maîtriser

2024 Juin

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Les biotechnologies : quelle sagesse collective ?

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Directeur de publication : Daniel Andler
Achevé d'imprimer par Corlet, 14110 Condé-en-Normandie
N° d'imprimeur : 21011062 - Dépôt légal : juin 2024— *Imprimé en France*
ISBN : 978-2-9518704-4-4

TESACO

En l'espace de deux décennies, les technologies dites émergentes — biotechnologies, technologies de l'information et de la communication, technologies issues des neurosciences cognitives, nanotechnologies… — ont profondément modifié les conditions d'existence à l'échelle planétaire et affecté tous les secteurs d'activité humaine. Porteuses de solutions mais aussi de menaces pour nos équilibres fondamentaux, ces nouvelles technologies sont devenues si puissantes qu'on ne sait comment en reprendre le contrôle, alors même qu'elles continuent de se développer, ouvrant la voie à des conséquences et à des risques imprévisibles.

Cet état de fait appelle un effort pour mieux comprendre les technologies et leurs effets, informer le public et les responsables politiques, et proposer des dispositifs pouvant contribuer à maîtriser l'évolution en cours.

L'Académie des sciences morales et politiques a souhaité participer à cet effort, et avec l'appui de la Fondation Simone et Cino del Duca elle a lancé en 2019 le cycle d'études « Technologies émergentes et sagesse collective » (TESaCo). Un colloque tenu à l'Institut en janvier 2020 a marqué la fin des travaux préparatoires. Le présent numéro des Cahiers de TESaCo, qui est aussi le premier, est consacré à un compte rendu presque exhaustif de cette manifestation.

LES CAHIERS DE TESACO

Les Cahiers de TESaCo sont une publication périodique qui présente les travaux de l'équipe du projet, organisée en six groupes de travail thématiques : biotechnologies, intelligence artificielle et robotique, sciences cognitives appliquées, libertés-éthique-droit, numérisphère, anthropologie numérique.

LE COMITÉ ÉDITORIAL

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Anne Le Goff est maîtresse de conférences à l'Institut SupBiotech d'enseignement et recherche sur les biotechnologies, et sera en résidence à l'Institut d'études avancées de Paris en 2024-2025. Ses recherches portent sur les aspects philosophiques, éthiques et sociaux des technologies de cellules souches, notamment en lien avec l'embryon et la reproduction. Elle inscrit sa démarche philosophique dans une approche résolument interdisciplinaire en mobilisant des méthodes empiriques et collaboratives. Elle est l'auteure du livre *L'animal humain* (Vrin, 2020) et vient de conclure 9 ans d'enseignement et recherche à l'Université de Californie à Los Angeles aux Etats-Unis.

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INTRODUCTION

À PROPOS DU CAHIER N°4

Les biotechnologies : quelle sagesse collective ?

La conférence d'Asilomar de 1975 sur les modifications génétiques se trouve fréquemment invoquée comme point de référence dans les débats actuels sur les nouvelles technologies. Cette conférence, organisée par certains scientifiques du champ, visait à proposer un cadre directeur pour la technologie alors émergente de manipulation du génome appliquée à des bactéries, afin de permettre la reprise des recherches après un moratorium que les scientifiques s'étaient imposé à eux-mêmes. La conférence et le moratorium l'ayant précédé sont ainsi souvent présentés comme un modèle d'autorégulation scientifique et de concertation pour anticiper les effets des innovations technologiques. Cependant, les recherches historiques sur cette conférence, dont approche le cinquantième anniversaire, montrent que la réalité est plus compliquée. La concertation, loin d'inclure la société au sens large et de prendre une forme démocratique, n'a impliqué qu'un petit nombre d'experts invités. Même à cette époque, la conférence n'a été qu'un point de départ pour un débat plus large au sein du public, et un effort continu pour appréhender les conséquences des technologies de modification génétique à l'échelle de la société et de l'humanité et pour y répondre collectivement. C'est un tel effort qu'il nous faut aujourd'hui mettre en œuvre pour une myriade de biotechnologies émergentes.

Aborder les (bio)technologies, comme c'est souvent fait, sous l'angle du progrès ou

Biotechnologies : What Collective Wisdom?

The 1975 Asilomar Conference on Recombinant DNA is frequently invoked as a point of reference in current debates on new technologies. The meeting, organized by scientists in the field, aimed to propose guidelines that would allow scientists to resume research with the then emerging technology of bacterial recombinant DNA after a self-imposed voluntary moratorium. The conference and the preceding moratorium are often presented as a model of scientific self-regulation and concerted action to anticipate the effects of emerging technologies. However, historical research about this conference that is approaching its fiftieth anniversary, shows that the reality is more complicated. Far from including a broader public or involving a wider democratic process, the consultation included only a small number of invited experts. Even at the time, the conference was but the starting point for a wider public debate and a continuing effort to deal with the implications of the recombinant technologies for society and humanity more broadly, and respond to them collectively. This is the kind of effort we need to make today for a myriad of emerging biotechnologies.

Approaching (bio)technologies, as is often the case, from the angle of progress or promise, or conversely, of controlling the risks they introduce, masks the depth of the transformations they impose and the way they call into question our normative categories. At the risk of appearing tautological, the

de la promesse ou, à l'inverse, de la maîtrise des risques qu'elles introduisent masque la profondeur des transformations qu'elles imposent et la manière dont elles remettent en cause nos catégories normatives. Au risque d'apparaître tautologique, la particularité, l'intérêt et les difficultés des biotechnologies sont qu'elles se saisissent du vivant. Elles le transforment, mais en font aussi un outil. Par exemple, un virus devient un vecteur pour introduire de l'ADN dans une cellule. Ces technologies de culture et de transformation du vivant vont donc bien au-delà des pratiques traditionnelles d'élevage et d'hybridation. Elles représentent un degré inédit d'intervention humaine sur le vivant, dont le génome, par exemple, peut désormais être édité ou interprété. L'essor des biotechnologies est fait de la convergence entre des savoirs et des techniques dans différents champs complémentaires, en particulier biologie moléculaire, ingénierie cellulaire et génétique, génomique et post-génomique. Se combinant avec d'autres technologies –numériques et d'intelligence artificielle, qui permettent de récolter et d'analyser des quantités croissantes de données, nanotechnologies, impression 3D… –, elles ouvrent la voie à de nouvelles entités expérimentales qui interrogent la qualification même d'entité vivante. Enfin, elles se déploient dans la société en créant de nouvelles perspectives sur l'identité, sur la propriété du vivant ou sur les relations entre humain et non-humain. Ainsi, elles imposent une réorganisation ontologique, sémantique, éthique et juridique à l'égard des entités produites qui sont à la fois vivantes et artificielles.

Pour prendre la mesure de ces transformations et leur répondre, il faut appréhender les biotechnologies non seulement comme des objets scientifiques mais aussi comme des objets et des biens sociaux, c'est-à-dire des productions sociales autant que techniques, des générateurs de nouveaux usages et des transformateurs d'imaginaire et de repères.

particularity and difficulty of biotechnologies is that they deal with living organisms. Not only do they transform the living, but the living becomes the tool. For example, a virus becomes a vector for introducing DNA into a cell. These technologies for culturing and transforming living organisms go far beyond traditional breeding practices. They represent an unprecedented degree of human intervention in living organisms, whose genome, for example, can now be edited or interpreted. The rise of biotechnologies is the result of a convergence of basic knowledge and techniques in molecular biology, cellular and genetic engineering, genomics and postgenomics. Combined with other technologies - digital and artificial intelligence that enable the collection and analysis of growing quantities of data, nanotechnologies, 3D printing, etc. - they open the way to new experimental entities that question the very notion of life. As they spread into society, they create new perspectives on identity, the ownership of life, and the relationship between humans and nonhumans. In this way, they impose an ontological, semantic, ethical, and legal reorganization on the entities produced that are both living and artificial.

To assess these transformations and respond to them, we need to understand biotechnologies not only as scientific and technical objects, but also as social objects and goods, and thus as both social and technical productions, as generators of new uses and transformers of the imaginary and the real. For example, the discoveries and innovations of genetics and molecular biology (DNA testing, transgenic techniques, cell modification, molecular scissors, etc.) have profoundly transformed our understanding of reproduction, of disease, and our representation of the early stages of human life. Together with other innovations, they could tomorrow redefine the limits of the human body, thanks to xenografts and xenotransplants. In agriculture, genome-editing techniques are paving the way for a new generation of genetically modified

Ainsi, les découvertes et innovations de la génétique et de la biologie moléculaire (tests ADN, techniques de transgenèse, modifications cellulaires, ciseaux moléculaires…) ont profondément transformé le rapport à la filiation, la compréhension de la maladie et la représentation des premières étapes de développement de la vie humaine. Avec d'autres innovations, elles pourraient demain redessiner les limites du corps humain, grâce aux xénogreffes et xénotransplantations. En agriculture, les techniques d'édition du génome ouvrent la voie à une nouvelle génération d'organismes génétiquement modifiés. Dans tous ces domaines, les biotechnologies sont porteuses d'importants enjeux économiques et font l'objet d'investissements publics et privés considérables mais peu visibles au public.

Ces biotechnologies émergent dans un certain cadre légal et éthique, qui contribue à définir l'espace des choix sociaux à leur égard. Ainsi, la conférence d'Asilomar évoquée plus haut a participé d'un effort plus large de réflexion et de régulation, depuis les années 1970, à l'égard des biotechnologies, avec le développement en parallèle de l'éthique médicale, de la bioéthique et de l'éthique environnementale. Les nations se sont dotées de textes légaux et réglementaires aux niveaux national et régional, ainsi que de conventions internationales, afin d'encadrer les pratiques expérimentales et médicales sur les personnes humaines et les animaux, mais aussi pour réguler la circulation des produits issus du corps humain et la mise sur le marché du vivant animal et végétal ainsi transformé. Or, il existe diverses sources possibles de normativité à l'égard de ces biotechnologies émergentes : notamment technique, éthique, déontologique, légale, démocratique (à travers le rôle législatif des parlements ou bien par une participation plus directe), religieuse. Quel est le rôle des lois et règles existantes pour des procédures et des objets qui comportent par définition des traits nouveaux ? Par exemple, les plants édités à l'aide de la technologie CRISPR doivent-ils

organisms. In all these fields, biotechnologies are driving major economic stakes, and are the focus of considerable public and private investment that is, however, little visible to the public.

Furthermore, the technologies are emerging within certain legal and ethical frameworks that help define the space for social choices in their regard. The above-mentioned Asilomar conference was part of a broader effort to reflect on and regulate biotechnologies since the 1970s. Parallel developments included the rise of medical and environmental ethics. Governments have set up legal and regulatory systems to oversee experimental and medical practices on humans and animals, backed up by international conventions. However, there are various possible sources of normativity with regard to these emerging biotechnologies: technical, ethical, legal, democratic (through the legislative role of parliaments or through more direct participation), religious. What is the role of existing laws and rules for procedures and objects that by definition entail novel features? For example, should plants bred using CRISPR technology simply be included in GMO legislation, or do they require a new legislative framework? Should organoids be categorized as human cells, animal entities, or a new type of entity? The far-reaching changes implied by biotechnologies, their socio-technical nature, and their accelerated development pose major challenges to our thinking and to the way in which they are framed. They tend to give a leading role to experts and invariably place public institutions in a catch-up position. How can we integrate reflection and decision-making on these biotechnologies and the risks they entail into the democratic process, and include society more broadly? In addition to environmental and health risks, these innovations raise questions of justice, notably in terms of access, and dependence between humans and on nature. The participation of society seems indispensable when citizens are directly involved in these innovations,

être simplement inclus dans la législation sur les OGM ou requièrent-ils un nouveau cadre législatif ? Les organoïdes doivent-ils être catégorisés comme des cellules humaines, des entités animales ou un nouveau type d'entités ? Les changements profonds qu'impliquent les biotechnologies, leur socio-technicité et leur développement accéléré constituent d'importants défis à la réflexion et à leur encadrement. Ils tendent à conférer un rôle de premier plan aux experts et à placer les institutions dans une position de rattrapage. Comment intégrer la réflexion et la prise de décision à l'égard de ces biotechnologies et des risques qu'elles impliquent dans le processus démocratique et, plus largement, inclure la société au sens large ? Outre les risques environnementaux et sanitaires, ces innovations soulèvent des questions de justice, notamment en termes d'accès et de dépendance entre humains et à l'égard de la nature. La participation de la société apparaît indispensable dès lors que les citoyens sont directement impliqués par ces innovations, tout techniques qu'elles soient, par exemple comme contributeurs de données génétiques, de tissus ou de cellules. C'est dans cette perspective que le groupe Biotechnologies de TESaCo s'est attaché à examiner certaines biotechnologies.

Cette quatrième édition des Cahiers présente les travaux conduits par TESaCo sur plusieurs exemples de biotechnologies aux mois de mai et juin 2023, lors d'un cycle de trois conférences en ligne. Nous nous sommes demandé quels étaient les processus adaptés pour faire de ces biotechnologies existantes ou émergentes des objets de délibération démocratique et, finalement, de sagesse collective. Par sagesse collective, on entend un type de réflexion qui ne consiste pas seulement à résoudre les problèmes posés par les biotechnologies en faisant principalement appel à des savoirs spécialisés. La notion de sagesse collective désigne une délibération sur les fins, les normes et la justice, qui sont remises en jeu par les biotechnologies. On pourra par exemple se demander si un organoïde de cerveau est le type d'entité qui requiert un nouveau statut éthique et juridique. Dans cette perspective, une série de questions doivent être posées : quelles sont les démarches à entreprendre pour mettre en place des procédures et lieux de discussions, reconnaître la nouveauté de techniques qui peuvent exiger des approches et arguments nouveaux, interroger leurs finalités, anticiper leurs possibles conséquences et problèmes, développer les cadres institutionnels qui permettront d'en faire un usage utile et juste, en évitant que les stratégies commerciales ne préemptent les choix et ne créent un déjà-là réduisant le champ des possibles ? Alors que la plupart des arguments sur les technologies émergentes semblent aujourd'hui émaner du débat sur l'intelligence artificielle, le champ des biotechnologies offre un lieu de discussion bien implanté pour examiner des technologies émergentes qui redéfinissent la vie humaine et le vivant en général.

Ces conférences se sont centrées sur trois cas d'étude – l'édition du génome avec CRISPR, les organoïdes et les tests génétiques en libre accès – qui se trouvent à des degrés divers d'élaboration, d'adoption technique et sociale et de discussion publique. Ces Cahiers incluent les présentations faites par les chercheurs·ses invité·es ainsi que les discussions avec l'ensemble des participant·es. Fort·es de leur expertise juridique, philosophique, anthropologique, sociologique, et de leurs positions internationales, les intervenant·es nous ont permis de développer une réflexion collective interdisciplinaire et s'appuyant sur des comparaisons internationales. Nous avons conservé ici la langue de présentation de chacun·e (français ou en anglais).

1. L'édition du génome avec CRISPR

Dès sa mise au point en 2012, la technique d'édition du génome par CRISPR-Cas9 a fait l'objet d'un intense travail éthique et social.

however technical they may be, for example as contributors of genetic data, tissues, or cells. With this in mind, TESaCo's Biotechnologies group has examined in detail several biotechnologies.

This forth edition of the Cahiers presents the work carried out by TESaCo on several examples of biotechnologies in May and June 2023, during a cycle of three online roundtables. We asked ourselves what processes were needed to make existing and emerging biotechnologies objects of democratic deliberation and, ultimately, of collective wisdom. By collective wisdom, we mean a type of thinking that does not simply involve solving the problems posed by biotechnologies by drawing primarily on specialized knowledge. The notion of collective wisdom refers to a deliberation on the ends, norms, and justice that are called into question by biotechnologies. We might ask, for example, whether a brain organoid is the kind of entity that requires a new ethical and legal status. From this point of view, a series of questions need to be asked: which steps need to be taken to set up procedures and forums for discussion, to recognize the novelty of techniques that may call for new approaches and arguments, to question their aims, to anticipate their possible consequences and problems, to develop institutional frameworks that will enable them to be used in a useful and fair way, while preventing commercial strategies from pre-empting choices and narrowing the field of possibilities? While the debate on artificial intelligence seems to garner most attention today, the field of biotechnology offers a well-established forum for examining emerging technologies that are redefining human life and living organisms in general.

The roundtables were organized around three case studies – genome editing with CRISPR, organoids, and open-access genetic testing – which are at various stages of development, technical and social adoption, and public discussion. The Cahiers include the presentations made by the invited researchers, as well as the discussions with all the participants. Drawing on their legal, philosophical, anthropological, and sociological expertise, as well as their international institutional positions, the speakers helped us to develop an interdisciplinary collective reflection based on international comparisons. We have retained the language of presentation of each speaker (French or English).

1. Genome Editing With CRISPR

Since its development in 2012, the CRISPR-Cas9 genome-editing technique has been the subject of intense ethical and social considerations. It was clear from the outset that the possibility of modifying the human and non-human genome in a given individual, but also in a heritable way, would have major yet difficult-to-predict consequences. Even before such uses were possible, Jennifer Doudna, one of CRISPR's discoverers, convened an Asilomar-like think-tank conference in California in 2015. What has happened to efforts to develop a collective wisdom around CRISPR since then? On the one hand, CRISPR-Cas9 technology and its more recent iterations have established themselves as a basic, routinely used tool in molecular biology laboratories around the world. At the same time, self-regulation efforts continued within the scientific community, marked by the convening of various national and international expert committees, promoting CRISPR research but rejecting its use in the germline. However, these efforts have shown their limits, and in particular their lack of enforcement mechanisms, first with the experiments of scientist He Jiankui in China, who, against all recommendations, edited the genome of three embryos resulting in births. Second, these efforts at self-regulation were challenged for the exclusion they represented of culturally diverse viewpoints and values. How can we develop collective wisdom with respect to this biotechnology whose impact

Il fut d'emblée clair que la possibilité de modifier le génome humain et non humain dans un individu donné, mais aussi de manière héritable, aurait des conséquences majeures et pourtant difficiles à prévoir. Avant même que de tels usages soient possibles, Jennifer Doudna, l'une des découvreuses de CRISPR, réunissait en Californie, en 2015, une conférence de réflexion à l'image de celle d'Asilomar. Qu'est-il advenu des efforts pour développer une sagesse collective à l'égard de CRISPR depuis lors ? D'un côté, la technologie CRISPR-Cas9 et ses itérations plus récentes se sont imposées comme un outil de base, utilisé de manière routinière, dans les laboratoires de biologie moléculaire du monde entier. En parallèle, les efforts d'autorégulation se sont poursuivis au sein de la communauté scientifique, marqués par la tenue de divers comités d'experts nationaux et internationaux, promouvant les recherches sur CRISPR mais récusant son usage dans la lignée germinale. Pourtant, ces efforts ont montré leurs limites, et notamment leur absence de mécanismes d'application, d'abord avec les expériences du scientifique He Jiankui en Chine, qui, à l'encontre de toutes les recommandations, a édité le génome de trois embryons dont ont résulté des naissances. Ensuite, ces efforts d'autorégulation ont été contestés pour l'exclusion qu'ils représentaient de points de vue et de valeurs culturellement divers. Comment développer une sagesse collective à l'égard de cette biotechnologie dont l'impact sur le vivant est majeur ? Les intervenants proposent divers angles d'approches pour aborder cette question. La politologue Jennifer Merchant présente l'initiative européenne du réseau ARRIGE pour complexifier et étendre à la société entière le débat sur CRISPR. La juriste Nertila Kuraj analyse deux approches concurrentes de la réglementation des usages agricoles et environnementaux de CRISPR, en Europe et aux Etats-Unis. Enfin, l'anthropologue Eben Kirksey examine la manière dont les questions de justice et de réductionnisme génétique sous-tendent le débat sur CRISPR.

on living beings is major? The speakers propose various approaches to this question. Political scientist Jennifer Merchant presents the ARRIGE initiative, a European effort to expand the CRISPR debate and include more public stakeholders. Legal scholar Nertila Kuraj analyzes two competing approaches to regulating the agricultural and environmental uses of CRISPR, in Europe and the USA. Finally, anthropologist Eben Kirksey examines how issues of justice and genetic reductionism underpin the CRISPR debate.

2. Organoids

Organoids are three-dimensional stem cell structures that recapitulate some of the functions of the organs they represent. Providing an unprecedented experimental model, they hold great promise for scientific research and so-called regenerative medicine. But even though they were initially designed to circumvent certain ethical difficulties associated with human and animal experimentation, these artifacts raise unprecedented ethical and legal questions. Combining engineering elements and living matter, stem cells and an organization that resembles human organs and non-human animals, they challenge established ontological and normative classifications. The case of cerebral organoids is particularly illustrative of the confusion generated, as their ability to mimic certain functions of the human brain raises questions about their ethical status. The status of embryoids also raises difficult questions, given the different regimes governing human embryos and embryonic cells. This raises the question whether adapting existing standards or, on the contrary, developing new standards for organoids. How should organoids be qualified in normative and legal terms? Should they be accorded a certain moral status, perhaps at least some of them that represent the brain, gonads or the human embryo in vitro? Philosopher Bernard Baertschi analyzes the ontological and ethical issues raised by organoids, and presents the

2. Les organoïdes

Les organoïdes sont des structures de cellules souches en trois dimensions, qui récapitulent certaines des fonctions des organes qu'elles représentent. Fournissant un modèle expérimental inédit, ils sont porteurs de très fortes attentes pour la recherche scientifique et la médecine dite régénérative. Mais alors même qu'ils ont initialement été conçus pour circonvenir certaines difficultés éthiques de l'expérimentation sur les humains et les animaux, ces artefacts soulèvent des questions éthiques et juridiques inédites. Relevant à la fois de l'ingénierie et du vivant, du domaine des cellules souches et d'une organisation qui les rapproche des organes humains et des animaux non humains, ils mettent à mal les classifications ontologiques et normatives établies. Le cas des organoïdes cérébraux est particulièrement illustratif du trouble généré, leur capacité à mimer certaines fonctions du cerveau humain engendrant des questions sur leur statut éthique. Le statut des embryoïdes soulève également des interrogations ardues, au regard des différents régimes dont relèvent les embryons humains et les cellules embryonnaires humaines. Se pose donc la question de l'adaptation des normes en vigueur ou, au contraire, de l'élaboration de nouvelles normes pour les organoïdes. Comment les qualifier normativement et juridiquement ? Faut-il leur accorder un certain statut moral ou du moins à certains d'entre eux qui représentent in vitro le cerveau, les gonades ou l'embryon humain ? Le philosophe Bernard Baertschi analyse les questions ontologiques et éthiques soulevées par les organoïdes, qui font figure d'hybrides, et présente les catégories proposées aujourd'hui au niveau de l'Union Européenne. Cette hybridité se retrouve sur le plan légal ; elle est examinée aux niveaux national et européen par les juristes Hans-Georg Dederer et Aurélie Mahaltchimy. Tous deux mettent en lumière l'adaptation des lois et règlements existant à l'encadrement des organoïdes et

categories currently proposed by the European Union. The hybrid status of organoids is also reflected at the legal level and is examined at both national and European level by legal scholars Hans-Georg Dederer and Aurélie Mahaltchimy. Both highlight the adaptation of existing laws and regulations to organoids, and raise the question of mechanisms for anticipating future developments.

3. Direct - To - Consumer Genetic Testing

DTC (Direct-To-Consumer) genetic tests that have been freely available for some fifteen years in some countries are both an easily accessible product, on the way to becoming commonplace, and a complex biotechnology. They are the fruit of a combination of major investments by biotech companies and large digital firms. This structural convergence between genetic technologies (particularly human genome sequencing) and digital technologies (notably Big Data) is revealed in the practices associated with these tests, with the production and circulation of personal data online, but also the private ownership of data acquired by companies and their commercial use. This raises the question of the framework and meaning to be given to these tests, which, although at first sight constituting individual genealogical or health practices, are underpinned by economic and social processes. In this respect, France finds itself in a paradoxical situation: although DTC genetic tests are forbidden by law, French citizens buy them online and have their DNA analyzed by companies abroad, with their data then forming part of private databases. What collective reflection has been developed on the production and use of genetic data over the last fifteen years? How can we foster a debate that not only includes the voices of users and commercial interests, but also gives democratic bodies a voice? Legal scholar Elsa Supiot examines the tendency of the framework for these tests to evolve towards utilitarianism,

ouvrent la question des mécanismes permettant d'anticiper leurs évolutions futures.

3. Les tests génétiques en libre accès

Les tests génétiques en accès libre ou DTC (Direct-To-Consumer), qui sont depuis une quinzaine d'années disponibles dans certains pays, constituent à la fois un produit d'accès facile, en passe de devenir ordinaire, et une biotechnologie complexe. Ils sont le fruit d'une association entre des investissements importants de la part d'entreprises de biotechnologies et de grandes entreprises numériques. Cette convergence structurelle entre technologies génétiques (en particulier le séquençage du génome humain) et numériques (notamment les big data) se révèle dans les pratiques liées à ces tests, avec la production et la circulation de données personnelles en ligne mais aussi la propriété privée des bases de données acquises par les entreprises à des fins commerciales. Se pose donc la question de l'encadrement et du sens à donner à ces tests qui, bien que constituant à première vue une pratique individuelle de généalogie ou de santé, sont sous-tendus par des processus économiques et sociaux. La situation française appelle ici une interrogation sur l'application des textes légaux et sur l'articulation des normes juridiques et des usages sociaux : bien que les tests génétiques DTC soient interdits par la loi, des Françaises et Français les achètent en ligne et font analyser leur ADN par des entreprises à l'étranger, leurs données faisant alors partie de bases de données privées. Quelle réflexion collective s'est développée sur la production et l'utilisation de ces données génétiques depuis quinze ans ? Comment favoriser un débat qui inclue non seulement la voix des usagers et les intérêts commerciaux, mais fasse également la part aux instances démocratiques ? La juriste Elsa Supiot examine la tendance de l'encadrement de ces tests à évoluer vers un utilitarisme, tandis que le sociologue Mauro Turrini analyse les pratiques sociales de partage

while sociologist Mauro Turrini analyzes the social practices of genetic data sharing by users.

We invite you to engage with these case studies, and the interdisciplinary viewpoints that are presented. These brief introductory remarks will help you appreciate the complexity of the questions raised and the possible solutions, as well as the importance of reflecting collectively and in depth on these technologies. As the site of profound ontological transformations, they are likely to pose not only environmental and health risks, but also democratic and legal challenges.

de données génétiques par les usagers.

Nous vous invitons à vous plonger dans la lecture de ces cas d'études, et dans les points de vue interdisciplinaires proposés. Ces courtes remarques introductives permettront, nous l'espérons, d'apprécier la complexité des questions posées et des possibles solutions mais aussi l'importance de s'engager collectivement dans une réflexion approfondie sur ces technologies. Lieu de transformations ontologiques profondes, elles sont susceptibles de poser non seulement des risques environnementaux et sanitaires mais aussi des défis démocratiques et de justice.

Première partie

L'ÉDITION DU GÉNOME AVEC CRISPR

Genome Editing and Public Engagement : The ARRIGE Model

Jennifer Merchant

JENNIFER MERCHANT

Jennifer Merchant holds a PhD in Political Science and is a Professor at the University of Paris II. She adopts in her research a pluridisciplinary approach at the intersection of political science, law, gender studies, and bioethics in Europe and North America. She is also a member of several important ethical institutions such as the Inserm Ethics Committee, France, and the international ARRIGE group. She was also a member of the Working Committee on Gene Editing of the US National Academy of Sciences and recently participated in the third International Summit on Human Gene Editing, and was renewed as a member of the Institut universitaire de France.

The Organization ARRIGE : International and Multi-Stakeholder

I am going to be speaking to you today about ARRIGE, which is an association that I belong to, and the endeavor in public engagement that our association has been working on since its launch in 2018. We launched the Association for Responsible Research and Innovation in Genome Editing (ARRIGE) in 2018. The aim, our ambition, is to gather as many stakeholders as possible that are interested in this, especially in CRISPR and in genome editing in general. We want to bring together all of these different stakeholders with a special focus on citizens, patient organizations, and decision-makers, so that we can create a forum and a discussion for the socially acceptable development of these techniques. In fact, our launch meeting was a continuation of several initiatives that a few of us had taken prior to that, which included the publication of an article that I will be citing later on.

We are indeed very interested above all in the governance of genome editing. And we want to make sure that the voices in the association are heard by government regulators, by decision-makers, by policymakers. But we are especially concerned with the impact of genome editing on the global South. And we have, in that sense, not only been thinking and talking about human genome editing, but also crop plant and animal editing. I just came back from Madrid two days ago, where we held our ninth annual meeting. It was entirely devoted to the issues that Nertila Kuraj will raise in detail, that is, to the differences of regulation between Europe and the United States. There were several South

American stakeholders who were there, ethicists, agro sector people and regulators. And what was interesting is that South America has a whole different approach which resembles more the US, and is very enthusiastic about plant genome editing. For example, Argentina and Uruguay are up there right after the US in the production of gene edited crops. So there was a very enthusiastic take on their part with the debate, while the Europeans who were there were pointing to the regulation and the great differences in our political and cultural approaches.

At ARRIGE, we have a Scientific Committee, which was recently renewed, that is also very international. It contributes to our debates, it follows the different research protocols that are going on and reports back to us on scientific aspects. So, we are continually informed by geneticists and specialists in the area.

The status of our membership so far: we have 87 individual members from 35 countries. And we have 16 institutional members. It does not seem like a lot but next to that we have about 150 subscribers to our listserv who follow us on a regular basis. When you become a member, though, you have access to what I am going to show you in a minute. It is not very expensive, 20 euros for students, and 50 euros a year for people like you and me, and you will have access to the numerous things that we have accomplished. So here is the world map of our members. As you can see, there is a concentration in Europe, but also there is not very many Americans, which we, I guess, you cannot say we are proud of that but, to a certain extent, we are happy that we are not Americanized in that sense and that we have contacts in South America and in many African countries as well. This corresponds to one of our aims and desires, that is to say, to open up the discussions of these issues to places other than the Anglo-American framework, if you will.

So, what have we done so far? We have held nine international meetings, our latest on May 9, each with a different theme. Our first launching article was in the journal *Transgenic Research*.[1] We were featured in *Nature Biotechnology*,[2] in *Science*,[3] and in the CRISPR *Journal*.[4] We have published six issues of our newsletter. For each newsletter we chose one topic, and I will explain a little bit more about that later on. It has to do with our public engagement model, if you will. We had a launch newsletter, one on gene drive, one on COVID and CRISPR, one on clinical applications of genome editing, all the way up to the last newsletter, which I coordinated on public engagement. We also have released three statements that have been endorsed by all the members of ARRIGE, plus a general common statement with the Association of Responsible Research and the Genetic Writers Guild, which some of you might have heard of. We had, for example, our statement post-2018, when Dr. He presented the birth of Lulu and Nana at the Hong Kong Summit. Both Eben Kirksey and I were there

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[1] Hervé Chneiweiss, François Hirsch, Lluis Montoliu, Albrecht M. Müller, Solveig Fenet, Marion Abecassis, Jennifer Merchant, Bernard Baertschi, Mylène Botbol-Baum, James A. Houghton, Mihalis Kritikos, Janet Mifsud, Ewa Bartnik, Johannes Rath, Christiane Druml, Bärbel Friedrich, Ana Sofia Carvalho, Dirk Lanzerath et Agnès Saint-Raymond, « Fostering responsible research with genome editing technologies: a European perspective », *Transgenic Research*, vol. 26, no 5, 2017, p. 709-713.

[2] Eric Smalley, « As CRISPR–Cas adoption soars, summit calls for genome editing oversight », *Nature Biotechnology*, vol. 36, no 6, 2018, p. 485-485.

[3] Martin Enserink, « Interested in responsible gene editing? Join the (new) club », *Science*, 27/03/2018 p.

[4] Lluis Montoliu, Jennifer Merchant, François Hirsch, Marion Abecassis, Pierre Jouannet, Bernard Baertschi, Cyril Sarrauste de Menthière et Hervé Chneiweiss, « ARRIGE Arrives: Toward the Responsible Use of Genome Editing », *The CRISPR Journal*, vol. 1, no 2, 2018, p. 128-129.

and sat flabbergasted for a while, asking ourselves, well, we might as well just go home and just stop thinking about these things because if all of our thoughts and efforts and work into bioethics is not having an impact, then what purpose are we serving – but we quickly got over that, I think.

A Public Engagement Methodology

Now, onto the crux of my presentation. As I said earlier, we are very keen on creating a forum where each person, no matter their professional identity, no matter his or her cultural origin, no matter his or her status as a lay person or a scientist, that all people come together and discuss these issues that have to do with genome editing. Now, there has been a lot written on public engagement. I mean, there is a whole lot of literature on how to engage with the public. And there are as many ways to engage with the public as there are citizens in the world to be quite honest. We quickly became aware of that, and we decided that we had to come up with a model, if you will, that we would use subsequently, either in our meetings, in our seminars – we have an Albrecht Müller seminar that is named after one of our founding members who unfortunately passed away. And we wanted to make sure that this form of public engagement that we were getting involved in had an impact, obviously, and that it was not just about a bunch of people getting together and talking about these interesting issues of the ethics of genome editing without having any impact, that is not something that we were necessarily interested in. I mean, there is plenty of international statements made by bodies of experts, with their recommendations, etc., and that really is not our objective. Our objective – and we are still striving toward it – is to eventually have some sort of leverage when it comes to decision-making.

So, we came up with a methodology of how to create a public engagement event. And we apply it to ourselves when we, like I said, have a meeting, or a seminar online, or what have you. And some of the particular points that we reflect upon and take into account are the following. It sounds very theoretical but you will see how it is not. We came up with a four-step way of reflecting upon the previous issues that we raised, questions that we have to ask ourselves.

The first step is to select a topic, that is, a single topic. So, we are not going to get involved in a public engagement event around genome editing in general. We are going to choose something very specific, be it somatic gene editing or heritable genome editing, which of course is the topic that leads to the most need for discussion for many of our stakeholders, many of the people who are interested in getting involved in these discussions. So, the first thing to do is to choose a very specific topic.

The second thing to do is to know, upstream, with what community you are going to be engaging. In other words, are you going to be speaking to high school students? Are you going to be speaking to lay people who are completely unaware of some of these issues and need to be informed upstream? Are you going to be speaking to scientists? Are you going to be speaking to regulators? The whole question of who you are speaking to, as well as where you are coming from, has to be decided upstream as well. And, above all, if you are going to launch a public engagement event, does the community that you are addressing want to discuss with you? I mean, there is no point in engaging with a community or group of persons who are not interested. And that oftentimes is forgotten.

The third step is establishing trust, therefore, with the particular community that you are going to speak to about the particular topic that you have chosen. And how do you do that? By being extremely transparent upstream, by eliminating all conflicts of interest, and by explaining the methodology of the public engagement event that you are hosting. I am thinking of one other public engagement event that I recently partook in, that was the Global Citizens Assembly, which is completed now. I was in charge of overseeing the engagement event in France, and it was specifically on heritable human genome editing. It was a lot of work upstream to establish trust with our participants who were French citizens. That included being very clear and forthright with the methodology and with the absence of conflict of interest.

The fourth consideration that you have to take into account is what your format is going to be. Obviously, are you going to rely on expert communicators? Or are you only going to involve interactive back and forth with yourselves and the people you are engaging with? And I think last but not least – and this will be the end of my talk – we definitely want to put emphasis on the fact that engaging with the public requires the presence of some sort of regulatory or political decision-making person who follows, who is aware, who is attuned, or who receives the report of your engagement because other than that, like I said earlier, it is just a bunch of people getting together and talking about these topics. Therefore, I use the example in France of Axelle Lemaire, a French deputy who strived for public engagement on La République Numérique, and interested in presenting a bill on a new program for France in digital technologies. Prior to writing the bill she engaged with a certain number of French citizens and much of the feedback that she got was incorporated into the ensuing law that was passed. So, this aspect of really placing emphasis on the leverage that you have with governability, with governance is very important in any type of public engagement event. Thank you for your attention.

Acknowledgements

https://www.arrige.org/

Reform Through Narrative : Risk, Uncertainty and Precaution in the EU Regulation of CRISPR-based GMOs

Nertila Kuraj

NERTILA KURAJ

Nertila Kuraj is a postdoctoral research fellow at the Public and International Law Department at the University of Oslo. Her book REACH and Environmental Regulation of Nanotechnology: Preventing and Reducing the Environmental Impacts of Nanomaterials deals with the status of nanosubstances under the EU legislation. She has held visiting and research positions at UC Berkeley, Yale, and Aveda University. Her speciality is the regulation of synthetic biology in the EU and the US context and she is currently working on her second book about the regulation of synthetic biology.

Introduction : Agricultural and Environmental Applications of CRISPR

Good afternoon, everyone. Today, I will talk about the legal aspects of CRISPR use in the environmental domain. I have titled my presentation “Reform Through Narrative.” I would like to explain how a certain narrative that was developed around emerging technologies can or cannot foster collective wisdom and public trust at the same time. As I was preparing for this presentation, actually, the European Ombudsman sent a notification to the EU Commission, exactly on the issue of a certain narrative used in a very important study about the status of new genomic techniques under Union law[1].

We have already explained what CRISPR is. It stands for Clustered Regularly Interspaced Short Palindromic Repeats, and is an immunological tool which comes from bacteria’s ability to defend themselves from virus attacks. Following the 2012 paper by Doudna and Charpentier, it has been

[1] European Commission, « Study on the status of new genomic techniques under Union law and in light of the Court of Justice ruling in Case C-528/16 », SWD(2021) 92 final.

harnessed to edit the genome of all living organisms[2]. The technology is formed by two components, the Cas9 enzyme, which represents the “genetic scissors,” and the guide RNA, which is the sequence that guides the molecular scissors to the target side of the DNA, which is supposed to be modified.

The focus on the environmental aspect of CRISPR-Cas9 is due to the fact that, while for human health and therapeutics, we have had a robust and to some extent transparent debate with regard to the social, ethical, and legal aspects or dimensions of the technology, this debate is currently lacking for all that concerns the environmental domain, where CRISPR is currently used, with some products already hitting the market. It is important to have this debate because as the inventors of CRISPR have pointed out, it will be imperative that non-scientists understand the basics of this technology sufficiently well in order to facilitate a rational public discourse[3].

Here are some of the most representative applications of CRISPR in the environmental domain. I have divided them into the agritech sector, with the use of CRISPR on plants, and applications to wildlife. The central idea is to modify or alter the genetic material of plants in order to confer them certain traits that we would like to achieve, for example, higher yields, or tolerance to drought or other biotic and abiotic stressors. At the same time, in the agritech sector, the use of CRISPR is applied, for example, to livestock, to animals, either for industrial purposes, like higher yields of meat and milk production or for animal welfare purposes, like in the case of de-horned cattle. In terms of wildlife applications, another area that was already mentioned is de-extinction: a number of species are already undergoing transformations through CRISPR in order to de-extinct them, like the passenger pigeon, the American chestnut and the one that captures our imagination the most, the wooly mammoth that George Church at Harvard is working on. Another application, which stands in between these two areas, is that of gene drives, where CRISPR is used together with other technologies to drive a specific trait, bypassing inheritance law patterns that would normally exist in nature.

CRISPR Regulation : Process vs Product

I would like to start with some technicalities for what concerns the use of CRISPR in the agritech sector because the whole debate of the newly proposed EU reform centers on these concepts. CRISPR is considered to belong to the first group of novel or new genomic techniques, which are labeled SDN techniques, that stands for *Site-Directed Nuclease (SDN) mediated genome editing*. This group of techniques to which CRISPR belongs operates through cutting the double-strand of the DNA and inserting different mutations. Depending on the type of mutation, we have SDN1, SDN2, and SDN3. Although this might look very complicated, the bottom line, and the main argument that is made with regard to these different genome editing techniques, is that SDN1 and SDN2 normally do not use recombinant DNA or exogenous (external) DNA. The idea is that they will not result in transgenic plants, whereas SDN3, the method that can lead to transgenic plants usually makes use of external DNA templates which might be integrated into the plant’s genome.

Since one part of the scientific community is working with plant breeding techniques, why should

[2] Martin Jinek et al., « A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity », *Science*, vol. 337, 81, 2012.

[3] Jennifer A. Doudna and Emmanuelle Charpentier, « The new frontier of genome engineering with CRISPR-Cas9 », Science, vol. 346, 1077, 2014, 1258096-7.

we call CRISPR-based GMOs GMO in that case? Well, the short answer is because the European law and Court says so. A case from the French Conseil d'Etat required a preliminary ruling from the European Court of Justice (CJEU) with regard to the interpretation of the GMO exemption that is contained in the 2001 Deliberate Release Directive[4], which is the cornerstone of the EU GMO regulation. The CJEU ruled that organisms that are obtained by means and techniques of mutagenesis must be considered GMOs. The Court stated that new techniques which incorporate CRISPR are not to be exempted from the directive. Reading the definition in Article 2 together with the exception in Annex 1B, it stated that the new CRISPR techniques have not been used conventionally in a number of applications, therefore do not have a new long safety record (or long history of safe use), and for this reason, cannot be exempted[5]. After this CJEU ruling, CRISPR-based GMOs are to be considered GMOs and have to comply with a set of inherited GMO regulations.

A host of EU regulations apply to CRISPR-based GMOs in the aftermath of the European Court of Justice ruling. As mentioned, the backbone of this regime is the 2001 Deliberate Release Directive. But there is a counter-narrative to regulating CRISPR-based GMOs that is mainly based on the US approach, according to which it is the *product* of CRISPR-based applications that matters rather than the process. This is the famous process versus product regulatory approach: the EU embodies a process-based approach and the US embodies a product-based approach. Remarkably, while the EU GMO regulations were adopted in the aftermath of the Asilomar conference and the emergence of recombinant DNA as a piece of legislation with the specific risks of biotechnology in mind, the US choice was to mandate a number of existing agencies to regulate the products of biotechnology under existing statutes - the FDA, the EPA, and the USDA are the main actors. So for now, even though the two jurisdictions of the EU and the US have decided to bring CRISPR-based GMOs within their existing regulatory frameworks, the outcomes are quite different because of the process and product difference that is embedded in each regulatory approach.

The process and the product regulatory approaches have different takes on risk, uncertainty, and precaution. For example, in the European regulation of GMOs, the process of genetic modification is considered to be inherently risky; uncertainties do not need to be quantifiable to trigger precautionary measures and risks need to be socially acceptable. Whereas, in the US, the gene editing process is not deemed risky *per se*: if the final product is substantially equivalent to its conventional counterpart, and risks only need to be ascertainable or quantifiable. As we know from the WTO case law, which has seen the EU and the US clash several times on the concept of risk and uncertainty, the US requires something more than mere "theoretical uncertainty" in order to regulate risks, and the entire system is centered on the economic concept of cost-benefit analysis. So, with the advent of CRISPR, both jurisdictions are - at least initially - sticking to their original process versus product regulatory approaches. I want to emphasize that more than just being regulatory approaches, these two concepts constitute different but not mutually exclusive regulatory triggers. Once the regulatory oversight is triggered, in both contexts, we find a mix of product and process elements, and considerations of risk, uncertainty, and precaution.

[4] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms.

[5] Case C-528/16, *Confédération paysanne and Others* (2018) ECLI:EU:C:2018:58.

Trends in CRISPR regulation in Europe

So what is the dominant narrative today with regard to how to move with regard to the CRISPR regulation in Europe? There is a strong push for the European Union and the European Commission to change what is considered by some as an outdated regulatory framework, that is, the laws and regulations which I have just presented, with the 2001 Directive as main law. In fact, the CJEU ruling which established that CRISPR-based GMOs *are* GMOs did not ban CRISPR-based GMOs in the EU. Yet, the ruling sparked some outrage. The incipit of a narrative supporting reform started there, with part of the scientific community accusing the Court of being anti-scientific, completely wrong on the science, of having a chilling effect on innovation and development, etc. I want to remark that there have always been, in the course of the history of biotechnology, very strong reactions when it comes to feelings towards technology. For instance, this song from 1912 lamented that stage of biotechnology when we were moving from artisanal fermentation brewing techniques towards industrial brewing with the advent of biology and synthetic chemistry. So there will always be this kind of reaction. But in order to foster public deliberation and collective wisdom, it is important to present the facts in a clear and transparent manner.

So what is happening right now? The European Commission is weaving a specific narrative with regard to the nature of CRISPR-based applications. At a first level, these applications are presented as silver bullets that will solve most of the challenging problems that we face, starting with climate change, food safety, or food security issues. But words that are used, some commentators pointed out, do not correspond to scientific facts. For instance, CRISPR-edited plants cannot be "resistant to drought" (as the quoted studies suggest) because no plant can live without water. At the same time, despite the fact that the CJEU has already ruled that CRISPR-based GMOs or CRISPR-based genetic modifications are to be considered GMOs, and that the Court sees the risks that come with this kind of modifications closer to those of transgenic plants (i.e., GMOs that are based on recombinant DNA techniques), at a second level, this narrative argues that these CRISPR-made genetic modifications do not differ from changes that occur naturally or from conventional breeding. This argument is made especially with respect to SDN1 and SDN2 CRISPR modifications, which in theory do not contain foreign DNA, although scientific research demonstrates otherwise. The danger of this kind of narrative, which emanates from offices such as the European Parliamentary Research Service (EPRS), is that it does not reflect the state of the art of scientific research on the risks that come with the technology, and thus conceals a number of risks which should be discussed in a transparent and participatory manner. It is inhibiting the creation of collective wisdom.

Here are some of the main risks. First, risks that are associated with CRISPR-based genome editing are different not only in terms of quantity but also quality. As some scientists are pointing out, CRISPR and other genome editing tools, especially when combined with synthetic biology or with nanotechnology, offer the possibility to bypass natural limitations and to have a deeper access to the genome. Access to remote areas of the genome was not possible with older recombinant DNA-based modifications and the resulting transgenic plants, and it is a new risk. It is very important to keep this in mind. Then, with CRISPR modifications, unintended risks of both *intended* editing and *unintended* editing need to be considered. For example, off-target cuttings still take place, even though we speak of high precision. At the same time, CRISPR affords the possibility to cut deeper into the genome, allowing for cuts through areas of DNA that constitute a protective mechanism for the integrity of the genome. There are other effects, like inversion or scrambling of chromosomal sequences, larger structural changes, which impact the metabolism of a plant. It means that the plant can produce new

toxins which are, for example, toxic to the environment, or can be an allergen for human beings that will consume this plant. Further, there is a risk of increased invasiveness, increased weediness and, eventually, disruption of food webs and ecosystems. But the most important part, which is sometimes not very clear when you read about this technology, is that novelty does not necessarily mean new because CRISPR-based applications are a multi-step process that most of the time involve old GMO techniques[6]. For example, the delivery vectors can be bacterial vectors or biolistic methods, which sometimes will result in transgenic plants. So, if we remove every kind of regulatory oversight, then there will be no way of detecting these modifications and transgenic traits, and the transgenic plants will be cultivated and consumed without any risk assessment (if not eliminated by backcrossing in subsequent steps).

Care for CRISPR and its Applications

This narrative prompted a number of scientists to write an open letter because of a proposed bill in the UK to deregulate CRISPR-based GMOs on the idea that they are precise, and as such similar to natural breeding techniques. Scientists reacted to the proposed bill saying that novel gene editing techniques are "not precise and not breeding." So, in Europe, the current narrative is not in line with the latest state of the art and the assessment of risks from a scientific point of view. We should keep a precautionary approach that is both about process and product because case by case risk assessment is very important. This should be performed on data both on the process and the product, because, as some authors pointed out, we can have assessment methods related to risks and trait-related risks. And of course, a holistic and ecosystem-based approach is necessary because these plants will interact with the broader environment. An organism is not the sum of its genes and a gene is not the sole determinant of a trait. So, in terms of collective wisdom, when we speak about assessing risks, it is important to think about those blind spots of risk assessment, that is, these areas of risk assessment where existing methods or quantifiable risk cannot explain what is at stake.

My suggestion in this regard would be that we look at the Precautionary Principle, especially its original meaning as *Versorgeprinzip*. The root of the word *Sorge* is care, which means something more than just preventing, it means looking after, worrying about and providing for, because it is impossible to be completely science-based in a regulatory approach. And many environmental problems, especially complicated and emerging technologies and complex issues like those posed by CRISPR-Cas9 tend to be "invisible." So, in order to create collective wisdom, I think that we need to make underlying assumptions - for example, in a risk assessment procedure - known and invisible facts visible. Value judgments that are inevitably present in risk assessment need to be made explicit in order to create an honest, transparent, and participatory debate. Another very important aspect is to maintain the ethical and social dimension of CRISPR-Cas9, for example, the rights of consumers to know, or their right to have biological products that are not contaminated by CRISPR-based cultures. So these other issues need to be addressed contextually to the scientific aspects of the technology to create collective wisdom. Thank you very much for your attention.

Acknowledgements

I would like to thank the Norwegian Research Council for financing the postdoctoral project on which this presentation is based, the University of California at Berkeley for hosting and enabling my research on the topic on several occasions, and the Law and Social Change (DCS) Laboratory at the University of Nantes for its continued support.

[6] Katharina Kawal, « The generic risks and the potential of SDN-1 applications in crop plants », *Plants*, vol. 10, no. 11, 2021.

Questions and Comments

Soraya de Chadarevian

Thank you, Nertila Kuraj, for this wonderful and very rich presentation. Again, we have time for one or two questions. Maybe I have a question here. The argument that these things are natural, like traditional breeding practices, this is not a new argument. It seems to be coming up again and again. I mean, it is clearly not the same thing, right? So what are the counter-arguments to this argument that it is natural?

Nertila Kuraj

Well, there are legal arguments actually. The first ruling - we had a second ruling on in vitro mutagenesis, which is still not explored from the legal point of view - the first sentence, when the court ruled that CRISPR-based transformations or genetic alterations had to be considered GMO within the legal meaning of Deliberate Release Directive. I think here we also have an issue of communications in the way scientists think and the way lawyers think. I have seen this at Berkeley when we would get together sometimes, scientists would not understand that this is legally binding, and it applies like this. Why can I not do this? Because the law does not allow it. So there is a sort of clash of different cultures, to go back to Snow's concept[7]. We need to bridge these two cultures. But the short answer is that the Court said so, the Court said that you cannot equate novel genetic intervention, which are clearly laboratory-based and for which we do not have a long history of safe use with traditional breeding. The Court even went beyond this by saying that the risks of CRISPR-based GMOs are closer to those of transgenic plants instead of being closer to natural breeding techniques. So it made it pretty clear. This attack on the Court's reasoning as being anti-scientific, or not having understood the science is highly problematic, and this is what is causing the whole debate in Europe. I think we have a ruling that is clear, and a rich scientific literature that points in the direction of CRISPR-based plants not being simply similar to traditional breeding tools leading to traditional GMOs for the reasons I mentioned, such as a lot of off-target effects and greater accessibility to the genome.

Soraya de Chadarevian

It is interesting that the law decides what is natural and what is not natural. It is an intriguing point.

[7] Snow, *The Two Cultures and the Scientific Revolution*, Cambridge University Press, 1959.

Will I Have to Mortgage My House? Reflections on Gene Editing, Innovation, and Inequality

Eben Kirksey

EBEN KIRKSEY

Eben Kirksey is a Professor at the University of Oxford. He is a cultural anthropologist, who is perhaps best known for his work in multi-species ethnography. He has various books on these topics, *Freedom in Entangled Worlds* and *Emergent Ecologies*, and several edited collections. But his most recent monograph is *The Mutant Project: Inside the Global Race to Genetically Modify Humans*. This is a far-ranging anthropological investigation of what CRISPR technology means, as he has followed it around the world.

Introduction

Thank you for convening us here today. Before I launch into the talk, I just wanted to pick up on something that you mentioned in your opening comments, you talked about the complexity of the stories that we are going to hear today. And from the outset, I want to argue that CRISPR-Cas9 is a really good tool not so much for clinical medicine yet, but a good tool for diagnosing problems in genetic reductionism. So, we have these long histories of reductionist thinking that tries to disappear the contextual complexity that Soraya de Chadarevian was talking about. Now we are at the moment where the tools of molecular biology not only enable people to read the so-called 'Book of Life' but also, in this moment of recomposing and editing. I will go into the metaphors and the technical details in a little bit. So I think part of the wisdom that we bring as historians, people in the medical humanities, anthropology, is an insistence on getting beyond that genetic reductionism.

Today I am also going to be making a series of juxtapositions to try to think about the particular case of CRISPR. I am going to show my slides, actually, to kind of give you a picture for context here. In thinking about the experiment by Dr. He in 2018, and these other early adventures in clinical medicine, relating to CRISPR and other kinds of gene editing, I think we need to get outside of these bubbles of speculation, stories of hope and hype centered on a molecule and think about them again in these broad contexts. So, one of the surprising juxtapositions I am going to be making today is bringing the worlds of biotechnology, these bubbles of speculation, together with the atmospheric

violence of a typhoon that hit Shenzhen, where Dr. He was working, and Hong Kong, where we convened for the summit, basically in that same moment of time, a couple of weeks before Lulu and Nana, the twins at the center of the story, were born.

Wisdom

But I want to talk initially about wisdom. This is one of the themes that we were asked to explore today. In particular, I want to talk about the queer wisdom of some of the world's first edited people. This is a picture of Matt Sharp and Grace, his nurse who infused gene-edited cells back into his body. This was an experiment done 10 years before Lulu and Nana were born, an experiment not with CRISPR but with another gene editing tool called zinc fingers. This queer wisdom is born of a struggle over science and justice, over whose epistemologies, whose knowledge practices, whose lives matter. Matt is among the initial members of the Act Up collective that stormed the NIH and famously shook up the research agenda, insisting on new, innovative, risky experiments. Importantly, this movement has been very critical of how power and capital and biotechnology come together. But they have also explored collaborations, even turning former adversaries, government officials and biotech executives, into allies to try to work towards better medicine. So kind of the wisdom that emerges for me from his lived experience and the experience of this community that has found some promise in gene editing is just one of pragmatic political collaborations. People who are willing to work with unlikely allies and using technologies and using relationships and companies that are not always working with the best interests of patients in mind to achieve this very basic agenda, that is living to the next day. So Matt has been arrested something like 12 times, he cannot exactly remember how many. And he has also participated in about the same number of clinical trials. So here is someone who is really an articulate critic who can reflect on the promise and peril of hope in the context of speculation about HIV cures.

CRISPR Molecules and Metaphors

But before I talk more about wisdom, and I think this is a theme that will re-emerge throughout the discussion today, I just wanted to give everyone a basic introduction to CRISPR. I think it is important to mix metaphors and molecules, and really point out the ways that the dominant metaphor relating to editing breaks down. In many ways, I think the metaphor of gene surgery works better. You know, with a surgeon, you might expect an unintended harm from a procedure with a slip of the surgeon's knife that can produce an unintended injury. The metaphor of engineering emphasizes historical continuities with some of those earlier, recombinant DNA technologies that Soraya de Chadarevian was talking about in the context of Asilomar. So, all these metaphors reveal and conceal aspects of what are very complicated and messy dynamics even on a molecular level. So CRISPR produces genetic damage, what is called a double stranded break, it is really good at scrambling sense. If you delete the letter K in a sentence, and you get what you aim for, which is a frameshift mutation in genetic terms, you end up with gibberish like this. Sometimes CRISPR produces a very big deletion, and you lose a whole chromosome. One of the metaphors that I like to use to think about CRISPR is the drone. So, in the Bush era, in the Obama era, in the United States, you had Predator drones that would sometimes do a precision strike that took out the so-called terrorist. But sometimes those strikes also took out the wedding party, and sometimes the drones had the wrong GPS coordinates and hit an inappropriate target. So Dr. He, like that earlier experiment that I talked about, involving Matt Sharp, targeted a receptor called CCR5. It basically scrambled the genetic code, which made it more difficult for this virus to get into the cell.

Reductionistic Genetic Thinking

But in thinking about these problems of reductionistic genetic thinking, I want to pan out a little bit and think about the aims of Doctor He's particular experiment and broader initiatives involving that earlier clinical trial trying to cure long-term survivors like Matt Sharp, who are living with HIV or AIDS. In many ways, HIV is no longer a medical problem. There are highly active antiretroviral therapies that are very effective at eliminating the health issues associated with AIDS. Most people are able to keep their immune systems in the normal range and in terms of having healthy cell counts. But really, in some ways, Dr. He's experiment was all about trying to respond to parents' needs, parents who wanted to have children yet are prevented from having children because they were HIV-positive under Chinese law, but also dealing with with parents' anxiety about their future children's experiences of social stigma, should they so happen to encounter this virus. But Dr. He did not solve the problem of social stigma and HIV and AIDS in China. And I would argue that that failure speaks to a broader pattern of failure in this reductionistic genetic thinking.

So Dr. He was part of a world of speculation and hope. He was trained in Silicon Valley, where people are taught to move fast and break things. And he was also working in this entrepreneurial environment of Shenzhen. This is a picture from China's National Gene Bank across the bay from Hong Kong, in a suburb of Shenzhen called Dot Peng. And this is a facility where China aims to collect the DNA of every human being on Earth. And we are talking whole genomes, not kind of *23andme* sequencing. They also have a platform that aims to move from reading DNA to the stage of rewriting DNA with the tools of synthetic biology. So they aim to not only reanimate extinct creatures like the wooly mammoth, they aspire to a form of immortality, immortality for people, but also immortality for endangered and recently extinct species. And when I pressed them on what they meant by immortality, they meant simply being stored on the gene bank, having DNA turned from a molecule into a set of codes of ones and zeros that are stored. This video shows robots that are doing the work of reading the DNA that then gets stored on servers. So one biologist from MIT told me that we do not need to engage in conservation biology and conservation management practices to keep ecosystems in the world anymore. If a species goes extinct, he claimed we can just simply print a new one, but that is if people can pay the electricity bills.

So a superstorm hit Hong Kong and Shenzhen just before the birth of Lulu and Nana. The storm interrupted some of Dr. He's personal business ventures and plans. His company Direct Genomics was slated to have an opening just two weeks after the storm hit. Communist Party dignitaries had been invited. They had to cancel it because the windows of his highrise were blown. His facility recovered relatively quickly. But when I was visiting BGI, I was also able to visit a fish farm nearby where earlier practices of managing life and bringing together capital and the productive potential of life had been radically undermined by the storm. This is a vision of the fish farms from a luxury hotel that I was staying at, courtesy of BGI.

Thinking about the protective architectures around these biotech dreams, these bubbles of speculation, I could not help thinking about Peter Sloterdijk's work on protective architectures[1].

[1] Peter Sloterdijk, *Spheres* Trilogy, trans. W. Hoban, MIT Press, 2011 [1998].

He has a trilogy on bubbles and spheres, and he is trying to get us to think about these individuated self-contained worlds that coexist in urban environments. If you are looking for a figure to ground this abstract idea of the bubble, picture an apartment complex, or a series of apartment complexes in a massive city like Shenzhen, where everyone is self-contained in their unit. But for me Sloterdijk's fundamental ideas have some serious problems. I have written elsewhere about how it is a relentlessly anthropocentric project that is trotting out some of the Heideggerian assumptions about animals being poor-in-world while the human is world-forming. But it is also kind of an exceptionalist project in the sense of privileging people who have access to capital in these protective architectures. I got a tour of the fish farm by someone whose life was radically undermined by the storm, whereas BGI and Dr. He were able to use their accumulated capital to quickly repair these protective architectures. This person's fish farming project had been totally undermined. So here I met somebody who was living with the complexities of life in the Anthropocene, who was a recent migrant to Shenzhen, who had established on the outskirts a mode of keeping his family alive. He was also living with the specters of nearby biotech schemes that might go awry, the specters of nuclear pollution, there was a nuclear plant, and ultimately, I learned that his whole world had been undermined. Halfway through our interview, I asked if I might use the bathroom and in a very ashamed tone, he admitted that he did not have one anymore, that the storm had reduced his infrastructure to rubble. So, how do we think about Dr. He's experiment, about these worlds connected to CRISPR, in the context of this atmospheric violence, the sort of unintended, very complicated aftermath of earlier 20th century technologies? We are talking about the combustion engine, we are talking about these early technologies that underpinned the modern project, they are now producing this violence on a massive scale that is threatening these protective infrastructures. So I think, ultimately, I would like to argue that this tiny molecular tool, even when invested with all the power of the capital that Dr. He was able to attract, that a facility like China's national gene bank was able to attract, it actually doesn't augment human agency that much in the context of these atmospheric forces that are threatening to undermine the conditions of life on Earth. Thank you.

Questions and Comments

Jennifer Merchant

Eben Kirksey spoke about metaphors and it brought back a memory of mine when I went to the US National Academy of Sciences for my first working group meeting. I was tasked by the Inserm Ethics Committee to bring up the problem of translation from one language to another. At the Inserm Ethics Committee, we were very amused, or rather concerned, with the term "genome editing." We preferred the French term "*modification ciblée du génome humain*", which we thought was a little bit heavier with significance than genome editing, which just sounded like, you know, "*copier-coller*", "*traitement de texte*", or Word processing, which is just as easy as pie. And so, I remember bringing that up at the first meeting. And the general consensus of the people who were there, who were my colleagues, was that genome editing was easier to understand. And if we were to start talking about targeted modification of the human gene, even if we use an acronym, it would not be as translatable, again, to the public at large. Genome editing prevailed. And so, at that time, I wanted to go and do a lot of research on what this was called in different languages. And maybe even that could be your next project! I think it would be interesting.

Deuxième partie

LES ORGANOÏDES

The Ethical Issues Raised by Organoids

Bernard Baertschi

BERNARD BAERTSCHI

Bernard Baertschi holds a PhD in Philosophy. He is presently a member of the Inserm Ethics Committee (IEC), France, leading the Working Group on organoids. He was an Associate Professor at the Institute for Biomedical Ethics and the Department of Philosophy of the University of Geneva (Switzerland) until 2014, when he retired. He was a member of several ethics committees in Switzerland, including the Federal Ethics Committee on Non-Human Biotechnology (ECNH), the Ethics Committee for Animal Experimentation of the Swiss Academy of Science (SCNAT).

I will examine today the ethical issues raised by organoids. First, I will go over what is meant by organoids and, after general considerations on the ethical issues that arise, I will focus on two types of organoids: gastruloids or embryo organoids, and cerebroids or brain organoids.

Organoids: A Host of Ethical Issues

What are organoids? Many definitions of organoids have been proposed. Here is one by Sarah Boers and colleagues. I quote,

> *The term organoid means 'resembling an organ.' Organoids are defined by three characteristics. The cells arrange themselves in vitro into a three-dimensional organization that is characteristic for the organ in vivo, the resulting structure consists of multiple cells found in that particular organ, and the cells execute at least some of the functions that they normally carry out in that organ.*[1]

As you know, many types of organoids have been developed, particularly for pancreas, kidney, liver, thyroid gland, retina, ovary, and brain. Two of them raise special concerns as we will see: gastruloids and cerebroids. Gastruloids, Boers and colleagues write, "recapitulate early stages of embryonic development." [2] And cerebroids are "four millimeter-diameter globules of which some of

[1] Sarah N. Boers, Johannes J. M. van Delden et Annelien L. Bredenoord, « Organoids as hybrids: ethical implications for the exchange of human tissues », *Journal of Medical Ethics*, vol. 45, no 2, 2019, p. 2.

[2] *Ibid.*

the development aspects, the electrical activity of neural networks in particular, are similar to those of the brain of 19 to 24 weeks old fetus." [3] Something like embryos and human brains. More on this later. The last quotation comes from a statement of the Inserm Ethics Committee on organoids. In this presentation I will rely heavily on this document issued by an Inserm working group that I lead. I will also use preparatory documents of a European project on organoids named *Hybrida*, within which the Inserm Ethics committee is tasked with writing guidelines for research – this is work package 5 of this project.

So, which ethical issues do organoids raise? The main ones in the literature are the following ones. First, the evaluation of risks, benefits, and safety. The most frequently cited medical benefits are a better understanding of organ diseases, the possibility of testing personalized drugs, and eventually of regenerating these organs, including the remediation of brain injuries. These benefits are mainly related to future therapies, thay raise questions of safety and access. Second, the ideology of promise: organoids are presented as a source of multiple therapeutic advances. But is this actually the case, or can we observe some hype as elsewhere? Third, the consent of the donors of the original cells and its possible withdrawal. Fourth, the ownership of organoids derived from them. Fifth, human enhancement: it may be possible to build more efficient artificial organs for the purpose of sport doping, for example, more resistant bones. Sixth, the moral and semantic status of organoids. Seventh, animal ethics: organoids enable the development of alternative methods that are used upstream or in parallel to animal testing. Eighth, the creation of chimeras by xenotransplantation. To ensure the vascularization and innervation of organoids, the latter can be transplanted into animals, including human cerebroids into the brains of adult animals. Finally, some metaphysical concerns: are we playing God? Are we evincing hubris, artificializing life?

Gastruloids

Gastruloids are organoids of embryos. Strictly speaking, since an embryo is not an organ, gastruloids are not organoids. Nevertheless, they come from the same material, stem cells or iPS cells, by similar processes. Therefore, we can consider them on a par with organoids. Some of them have already been produced in 2014. Aryeh Warmflash and colleagues created gastruloids from human embryonic stem cells[4], Yu Shao and colleagues developed a model to simulate embryonic development after implantation and even after the appearance of the primitive streak from human stem cells[5] .Finally, the team of Magdalena Zernicka-Goetz – albeit in mice and not in humans – combined embryonic stem cells with trophoblast stem cells to form an entity with traits in common with the embryo, such as to enable the initial differentiation steps of several tissues and organs[6].

[3] Bernard Baertschi, Henri Atlan, Mylène Botbol-Baum, Bertrand Bed'hom, Hélène Combrisson, Christine Dosquet, Anne Dubart-Kupperschmitt, François Hirsch, Pierre Jouannet, Isabelle Remy-Jouet, Christine Lemaitre et Grégoire Moutel, *Organoids Research: What are the ethical issues?*, Inserm Ethics Committee, 2020, p. 10. https://inserm.hal.science/inserm-03117706/document

[4] Aryeh Warmflash, Benoit Sorre, Fred Etoc, Eric D. Siggia et Ali H. Brivanlou, « A method to recapitulate early embryonic spatial patterning in human embryonic stem cells », *Nature Methods*, vol. 11, no 8, 2014, p. 847-854.

[5] Yue Shao, Kenichiro Taniguchi, Ryan F. Townshend, Toshio Miki, Deborah L. Gumucio et Jianping Fu, « A pluripotent stem cell-based model for post-implantation human amniotic sac development », *Nature Communications*, vol. 8, no 1, 8 2017, p. 208.

[6] Marta N. Shahbazi et Magdalena Zernicka-Goetz, « Deconstructing and reconstructing the mouse and human early embryo », *Nature Cell Biology*, vol. 20, no 8, 2018, p. 878-887.

The first issue with gastruloids is their semantic status: how to name them? The terms ‘synthetic’ or ‘artificial’ embryo is sometimes used to refer to these structures. However, many judge that it is not appropriate. “In order to accurately reflect the state of the research, the International Society for Stem Cell Research [for example] suggests using the term ‘embryo model’ instead.” [7] For two reasons: first, because gastruloids are not embryos proper; and second, because “these models are formed from stem cells that spontaneously but imperfectly unleash their intrinsic potential.” [8] “They are thus neither synthetic or artificial, but rather reflect attempts for potent cells to ‘act naturally’ by expressing their potential.” [9] At Inserm, we propose to call them “embryonic models for scientific use” (EMSUs)[10].

So, what is the moral status of EMSUs? The question is important, because if they had the moral status of human embryos, they should be treated as such and not as laboratory constructs. The moral status of EMSUs is a putative program for research because research on human embryos is hotly contested in some quarters. However, based on what has already occurred with mice, it is not excluded that soon gastruloids must be considered as real embryos. The team of Jacob Hanna has recently adapted an established platform for prolonged ex utero growth of natural embryos in order to generate mouse post-gastrulation whole embryo models with both embryonic and extraembryonic tissues, starting solely from naive embryonic stem cells and particularly without using gametes of adult mice.[11]

Cerebroids

Cerebroids or brain organoids are proper organoids. A semantic point also arises about them, because they are sometimes named mini-brains. This is misleading, because cerebroids do not even possess all types of neural cells and do not recapitulate all brain functions. But the question about them that is most often raised concerns their possible sentience. As Ashley Yeager states,

> *some researchers have raised questions about the sensory abilities of the organoids themselves. “At what point, would we be concerned that they might be developing perception, including (possibly) perception of pain?,” writes [...] Henry Greely. A much farther-away concern is whether the organoids could ever develop something like human consciousness or intelligence.*[12]

[7] Hybrida, *Operational Guidelines for the field of organoids and organoid-related technologies*, draft in progress, 2023. https://hybrida-project.eu/

[8] *Ibid*

[9] *Ibid*

[10] Bernard Baertschi, Marc Brodin, Christine Dosquet, Pierre Jouannet, Anne-Sophie Lapointe, Jennifer M. Merchant et Grégoire Moutel, *Research on Embryos and Embryonic Models for Scientific Use (EMSUs)*, Inserm Ethics Committee, 2019, p. 4. https://inserm.hal.science/inserm-02373609

[11] Shadi Tarazi, Alejandro Aguilera-Castrejon, Carine Joubran, Nadir Ghanem, Shahd Ashouokhi, Francesco Roncato, Emilie Wildschutz, Montaser Haddad, Bernardo Oldak, Elidet Gomez-Cesar, Nir Livnat, Sergey Viukov, Dmitry Lokshtanov, Segev Naveh-Tassa, Max Rose, Suhair Hanna, Calanit Raanan, Ori Brenner, Merav Kedmi, Hadas Keren-Shaul, Tsvee Lapidot, Itay Maza, Noa Novershtern et Jacob H. Hanna, « Post-gastrulation synthetic embryos generated ex utero from mouse naive ESCs », *Cell*, vol. 185, no 18, 2022, 3290-3306.e25.

[12] Ashley Yeager, « As Brain Organoids Mature, Ethical Questions Arise », *The Scientist*, 01/08/2018.

Sentience or consciousness are obviously solid grounds for moral status. In principle, cerebroids could be considered either as things or sentient beings or persons, according to the capacities they manifest or will manifest in the future. Nowadays, we have all the reasons to view them as mere living material, that is, things. But in the future, with assembloids, that is, associations of several organoids, and with animal chimeras, in which organoids will be grafted, it could change. However, is it a real possibility? Brett Kagan and colleagues think that it is already the case, saying that neural culture meets the formal definition of sentience as being responsive to sensory impressions.[13] But this criterion is too weak, and would allow us to attribute sentience to devices like thermostats, because they are responsive to heat perception. Famously, John McCarthy, the father of artificial intelligence, wrote in 1979 that a thermostat has three beliefs: the room is too cold, the room is too hot, and the room is okay[14]. When it perceives that the room is too cold or too hot, it sends a message to the furnace, and the temperature rises or drops accordingly.

However, we cannot as a matter of principle exclude that a cerebroid can become sentient. Because on a very general level, it cannot be ruled out that an entity made up of neurons possesses mental states – we assume the existence of relationships of correlation and even causality between the mind and the brain. During the course of evolution, consciousness gradually emerged when there was a nervous system capable of supporting it. The same is true in the history of each of us: an embryo does not think, a child does. The hypothesis that cerebroids might experience pain is then a thought experiment based on the idea of the emergence of consciousness. If pain is identical with a brain activity, future and complex organoids could hypothetically experience it, because function emerges from structure. This is exactly what we say in the Hybrida project, concluding that there is no reason to believe now that such organoids possess sentience or achieve a level of consciousness that warrants special ethical or legal concerns. Nevertheless, certain neural organoids mature and become more complex when combined with other organoids in complex neural assembloids. Regulatory questions regarding the normative status of these entities and users’ obligations to them may arise.

To be more specific, there are several objections against attributing sentience to cerebroids now. Notably, first, electron activity, as observed in cerebroids, cannot be equivalent to awareness, consciousness, or sentience. Second, the part does not have the same properties and functions as the whole, thus an organoid does not have the same properties and functions as the organ as a whole. A cell does not have the same properties and functions as a tissue or the organ of which it is a part. It is therefore incorrect to refer to organoids as mini-organs, and in particular, it is inappropriate to refer to organoids derived from brain cells as mini-brains. Third, the volume of cerebroids is only one thousandth of a mouse brain and one of a million of that of a human being. And to be able to support sentience, a brain has to possess a certain amount of matter. And last, cerebroids have no mature neural networks and so are unable to interact with their environment.

[13] Brett J. Kagan, Andy C. Kitchen, Nhi T. Tran, Forough Habibollahi, Moein Khajehnejad, Bradyn J. Parker, Anjali Bhat, Ben Rollo, Adeel Razi et Karl J. Friston, « In vitro neurons learn and exhibit sentience when embodied in a simulated game-world », *Neuron*, vol. 110, no 23, 2022, 3952-3969.e8.

[14] John McCarthy, « Ascribing Mental Qualities to Machines », dans Martin Ringle (dir.), *Philosophical Perspectives in Artificial Intelligence*, Humanities Press, 1979. Available at: http://www-formal.stanford.edu/jmc/ascribing.pdf

My last point concerns the case of chimeras. As I said before, cerebroids can be grafted in the brains of animals, such as rats or pigs, which have mental states. The chimeric brain will then be an organ functioning within an organism. It has already been observed that in these transplants there is normalized expression of the genes related to neurons, which is altered in in vitro cerebral organoids. What will be the moral status of these humanized animals, that is, of these chimeras? A principled answer is that these chimeras will have to be human enough to be used as a research model, but not human enough that they fall under the protections that belong to human beings. But problems are almost here, at the end, because we have already injected human brain cells into the brains of mice and the cognitive abilities of these mice have increased tenfold [15]. And while French law forbids the creation of chimeras, this only concerns human-animal chimeras, in which animal cells are incorporated into a human embryo. As a result, the path to the creation of super-mice seems to be open… Thank you for your attention.

Questions and Comments

Sonia Desmoulin

Thank you, Bernard Baertschi for this presentation, which perfectly sets the scene.

Serena Ciranna

Thank you very much for this very interesting presentation. I have a clarification question. You said that, in France, human-animal chimeras are not allowed, they are forbidden. Is it the case in every country, or are there countries in which it is allowed? Thank you.

Bernard Baertschi

Unfortunately, I cannot answer your question because well, first, I am not a lawyer, and I have not studied the question internationally. I think that in the *Hybrida* project we will be obliged to address this question. But I am sure that in the UK, it is permitted. And I think that in Germany, it is.

Nertila Kuraj

In Japan, it is allowed.

Sonia Desmoulin

In France, it is a little bit more complex, but maybe Hans-Georg Dederer will talk about chimeras, too, so, maybe we should keep this question in mind.

Maybe I can ask my question. You quoted a lot of the work of your working group on organoids. So, what do you see as the role of an ethics committee in a research institution, compared to other ethical approaches, such as deontology, ethical reflection by a national committee, or maybe a more general public debate? Do you think it is an important role and why? And do you think that the articulation between different bodies is optimal when it comes to organoids that are at the border of so many different categories?

[15] Xiaoning Han, Michael Chen, Fushun Wang, Martha Windrem, Su Wang, Steven Shanz, Qiwu Xu, Nancy Ann Oberheim, Lane Bekar, Sarah Betstadt, Alcino J. Silva, Takahiro Takano, Steven A. Goldman et Maiken Nedergaard, « Forebrain Engraftment by Human Glial Progenitor Cells Enhances Synaptic Plasticity and Learning in Adult Mice », *Cell Stem Cell*, vol. 12, no 3, 2013, p. 342-353.

Bernard Baertschi

Yes, so, at the Inserm Ethical Committee, questions are raised by the scientific researchers of Inserm. But we are completely free to tackle them or not and can use self-tasking initiatives. For organoids, it was a question raised by the President of Inserm, without any precise link to research. So, the work we did was a little like the work of a National Ethics Committee. By contrast, in the Hybrida project, our task is to write guidelines. So, we have to be more precise and more practical. This is the reason why many biologists are working with us from Inserm and other institutions. And the final product will be guidelines. The difficulty is that there should be guidelines for the whole of Europe, and national legislations are sometimes rather different. So, it is a work in progress, and we will judge the end product in one year, for the moment, I think that the collaboration is very good between the different universities that are in charge of different work packages. For France, organoids is not, I think, a very hot topic now. We have this working group for organoids but more generally our working group is working on embryo research, and it is only one chapter of this embryo research.

Legal Issues Surrounding Brain Organoids and Embryoids

Hans-Georg Dederer

HANS-GEORG DEDERER

Hans-Georg Dederer is Professor of Law at the University of Passau, Germany. He is a specialist in life science law. His expertise in the field has been called upon by federal ministries, federal and state parliaments as well as the National Academy of Sciences Leopoldina. Since 2018, he is also a member of the Permanent Senate Commission of the German Research Foundation (DFG) on Genetic Research and, since 2023, of the Standing Committee "Life Sciences" of the Leopoldina. He recently edited, together with David Hamburger, a collective volume on brain organoids.[1]

Introduction: Scientific and Legal Background

After a brief introduction, I will turn to the legal status of embryoids (also called gastruloids by Bernard Baertschi) and brain organoids. Then, I will address the issue of chimeras and make some short remarks on problems of informed consent. Finally, I will try to draw a brief conclusion.

Let us first turn to the scientific background. Bernard Baertschi has already told us that organoids and embryoids are derived from certain cells: embryonic stem cells or induced pluripotent stem cells. Both categories of stem cells are pluripotent. Pluripotent stem cells have two specific capabilities, that is, first, the capability of unlimited self-renewal and, second, the capability to differentiate into all cell types of an organism. However, pluripotent stem cells are not in themselves able to develop into a complete organism – into a complete human being, for example. Nevertheless, what can be derived from such cells are, at least, organoids as well as embryoids. Organoids and embryoids are three-dimensional cell structures that result from the self-organization capability of pluripotent stem cells, be it embryonic stem cells, be it induced pluripotent stem cells.[2]

[1] H.-G. Dederer and D. Hamburger, *Brain Organoids in Research and Therapy: Fundamental Ethical and Legal Aspects*, Springer, 2022.

[2] On pluripotent stem cells and their self-organization capability to develop into organoids, and brain organoids in particular, N. Zagha and B. Winner, *Development of Brain Organoids with Genome-Edited iPSC-Derived Brain Cells*, in: H.-G. Dederer and D. Hamburger (eds.), *Brain Organoids in Research and Therapy: Fundamental Ethical and Legal Aspects*, Springer, 2022, 21–33 (at pp. 22–25).

With a view to the normative background of organoids and embryoids, I will not address the ethical debate because this was the task of Bernard Baertschi. As you have already understood from his talk, the ethical debate focuses, in particular, on questions of moral status, on ethical issues related to chimeras, and on problems of informed consent, especially regarding consent of the donor, that is, the person who donates the biological material from which induced pluripotent stem cells can be produced which, in turn, form the starting material for the creation of organoids or embryoids.

Rather, I will address the legal debate. The legal debate is very much influenced by the ethical debate and, to a certain extent, mirrors it. Regarding the legal debate, there is one peculiar problem: if you asked me what the law on embryoids or on brain organoids is, or if you asked me what the legal aspects related to embryoids and brain organoids are, I would have to ask you in return: which law do you mean? This leads to the problem of which law is the applicable law. There are several layers of law: at the international level, public international law; at the regional level within Europe, European Union law, for example; and at the national level, of course, national law. Within national law, there are, again, different layers of law, in particular, constitutional law and statutory law. Within this multi-layered legal architecture, the rules which govern embryoids and brain organoids are to be found primarily in national law. Hence, since I am a German lawyer, I will refer to German law.

Status of Embryoids

I would like to first look at embryoids. The decisive question concerning embryoids is: what is the legal status of embryoids? In Germany, the Embryo Protection Act (EProtA)[3] might be applicable to embryoids. In this regard, one has to answer the question whether embryoids are 'embryos' within the meaning of the EProtA. The EProtA's definition of the term 'embryo' reads as follows: an embryo is either a "human egg cell" that is "fertilized and capable of developing", or a "totipotent cell removed from [such] an embryo" (Sec 8(1) EProtA). And there is another law, the German Stem Cell Act (StCA).[4] It only applies to embryonic stem cells extracted from embryos (Sec. 2, Sec. 3(2) StCA). Hence, the StCA needs to define what constitutes an 'embryo' from which embryonic stem cells may be extracted. The StCA's legal definition is, in principle, very brief: an embryo is a "totipotent cell" (Sec. 3(4) StCA).[5] Finally, there is the German Patent Act (PatA),[6] which lays down rules on biopatents, that is, patents related to biotechnological inventions. The PatA rules out that a

[3] Gesetz zum Schutz von Embryonen (Embryonenschutzgesetz – ESchG) of 13 December 1990 (BGBl. I 2746), last amended by Article 1 of the Law of 21 November 2011 (BGBl. I 2228). An English translation is available at : https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/Gesetze_und_Verordnungen/GuV/E/ESchG_EN_Fassung_Stand_10Dez2014_01.pdf (last accessed on 14 December 2023).

[4] Gesetz zur Sicherstellung des Embryonenschutzes im Zusammenhang mit Einfuhr und Verwendung menschlicher embryonaler Stammzellen (Stammzellgesetz – StZG) of 28 June 2002 (BGBl. I 2277), last amended by Article 50 of the Law of 29 March 2017 (BGBl. I 626). An English translation is available at : https://www.rki.de/SharedDocs/Gesetzestexte/Stammzellgesetz_englisch.pdf?__blob=publicationFile (last accessed on 14 December 2023).

[5] The additional phrase "which has the potential to divide and to develop into a human being if the necessary conditions prevail" only defines the meaning of totipotency.

[6] Patentgesetz as published on 16 December 1980 (BGBl. 1981 I 1), last amended by Article 1 of the Law of 30 August 2021 (BGBl. I 4074). An English translation is available at: https://www.gesetze-im-internet.de/englisch_patg/englisch_patg.pdf (last accessed on 14 December 2023).

patent is granted for an invention that involves the use of human embryos (Sec. 2(2)(3) PatA). Since German biopatent law implements European Union biopatent law,[7] the interpretation of the legal term 'embryo' is decisively influenced by the European Court of Justice's jurisprudence. According to the Court, a human embryo is an "ovum [that] does […], in itself, have the inherent capacity of developing into a human being." [8]

It follows from the aforementioned definitions that there are two essential requirements for an 'embryo' within the meaning of German statutory law: 1) the starting point of an embryo must be a single cell, that is, a fertilized egg cell or a another kind of totipotent cell; and 2) this single cell, which is the starting point of embryonic development, must have a certain capability which is totipotency or, in other terms, the inherent capability of developing into a human being. Both requirements are not met by embryoids, as you could also get from Bernard Baertschi's talk. First, at the origin of the development of embryoids is not a single totipotent cell. Rather, embryoids result from several layers of pluripotent cells in a dish. Second, from a scientific perspective, embryoids, as they are currently developed,[9] do not possess totipotency, that is, they do not have the inherent capacity of developing into a human being. For these reasons, embryoids would not be considered 'embryos' under German statutory law.

However, there is still a higher layer of norms, the constitution, the Basic Law (BL),[10] which is a *lex superior* vis-à-vis statutory law. Therefore, one may ask the question whether embryoids might have a certain constitutional status which, as the case may be, might call for protection by the legislature. The fundamental rights which are of interest in this regard are the guarantee of "dignity of the human being" (Art. 1(1)(1) BL)[11] and the "right to life and physical integrity" (Art. 2(2)(1) BL). It is well established that the holder of the right to life and physical integrity must be a human being. Accordingly, both guarantees only apply to human beings. So, the question is whether embryoids are 'human beings' within the meaning of the constitution or whether they form, at least, a particular developmental stage of a 'human being'. This leads to the question of what the criteria for a 'human being' are.

In Germany, we have been in intense discussions on whether embryos in vitro are human beings, or whether they should be protected, at least, like, or as if they were, human beings under the aforementioned constitutional provisions. This discussion is open-ended as far as it concerns embryos *in vitro*.[12] The most fundamental criterion for constitutional protection seems to be,

[7] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions (OJ L 213, 30.7.1998, pp. 13–21).

[8] ECJ, Case C-364/13, International Stem Cell, ECLI:EU:C:2014:2451, para. 38.

[9] Cf. Bernardo Oldak *et al.*, "Complete human day 14 post-implantation embryo models from naïve ES cells", Nature 622 (2023), 562–573; Bailey A. T. Weatherbee *et al.*, "Pluripotent stem cell-derived model of the post-implementation human embryo", Nature 622 (2023), 584–593.

[10] Grundgesetz für die Bundesrepublik Deutschland as published in an adjusted version in the Federal Law Gazette Part III, classification no 100-1, last amended by Article 1 of the Law of 19 December 2022 (BGBl. I 2478). An English translation is available at: https://www.gesetze-im-internet.de/englisch_gg/englisch_gg.pdf (last accessed on 14 December 2023).

[11] This is a literal translation. The English translation (*supra*, footnote no. 10) simply says "human dignity."

[12] For an overview of the spectrum of the divergent legal opinions see H.-G. Dederer, "Der manipulierbare Embryo: Konsequenzen für das Recht. Grundlegungen und Vorschlag für eine neue Embryodefinition," Jahrbuch für Recht und Ethik 28 (2020), 53–81 (at pp. 62-63).

according to the presumably predominant view of legal scholars, that the relevant entity must, in itself, have the inherent capacity to develop into a complete born human being, that is, the entity must be totipotent. Since, right at the moment, embryoids do not have such a capacity, they do not enjoy any constitutional status.

Status of Brain Organoids

Let us turn to brain organoids. Obviously, brain organoids are not embryos and therefore not subject to embryo protection under the EProtA. And there is no other statutory law which might assign a specific legal status to brain organoids.

Concerning the status problem with a view to brain organoids, I would, therefore, like to start from a different angle. In law, we have to make a distinction between persons and things. These are two fundamental categories underlying our legal system, and, I suppose, not only in Germany but also, for example, in France. According to this dichotomy, an entity is either a person or a thing. So, the question is whether brain organoids are 'persons.' From a legal point of view, only a human being can be a person (Art. 1(1)(1) BL). Any human being is, as such, endowed with dignity and, therefore, has the right to be recognized as a person in law, that is as a holder of, in general, all rights and duties. As we have already seen, however, embryoids are not human beings, even less are brain organoids human beings, because they also obviously lack totipotency, that particular inherent capacity of developing into a born human being. So, if brain organoids are not persons, they are things invariably.

A thing can be property protected under Article 14 of the constitution (Art. 14(1)(1) BL). But who is protected by this fundamental right is, of course, not the thing but its owner only. The same applies to the right of personality (Art. 1(1) in conjunction with Art. 2(1) BL) which I will get back to later. Who is protected by this basic right is the donor of the biological material which formed the source material for the induced pluripotent stem cells and, thus, for the brain organoids. The donor possesses the right of personality which includes personal autonomy, in particular the autonomy to decide on his or her physical integrity as well as on any use of his or her body. Therefore, the donor's right of personality extends also to the biological material that has been separated from his or her body. However, it is, again, only the donor who is constitutionally protected, and not the brain organoids which have been obtained from induced pluripotent stem cells which, in turn, were derived from the biological material biopsied from the donor's body.

Nevertheless, and getting back once more to Bernard Baertschi's talk, one may raise the question whether brain organoids should be granted a special legal status, a legal status *sui generis*. For example, animals are also not persons, so they might be things. However, they are specially protected under a particular provision of the German constitution (Art. 20a BL). So animals should not have the status merely of things [13].They may feel pain or suffering, or they may be victims of harm, for example. In order to protect animals against pain, suffering and harm, the German constitution has been amended through insertion of Article 20a BL with a particular view to animal experiments in scientific research.

[13] See Sec. 90a of the German Civil Code (Bürgerliches Gesetzbuch as published on 2 January 2002 (BGBl. I 42, 2909; 2003 I 738), last amended by Article 4 of the Law of 25 Oktober 2023 (BGBl. 2023 I No 294; an English translation is available at: https://www.gesetze-im-internet.de/englisch_bgb/englisch_bgb.pdf [last accessed on 14 December 2023]): "Animals are not things. They are protected by special statutes. The provisions that apply to things are to be applied accordingly to animals, unless otherwise provided."

Of course, brain organoids are not animals and, therefore, not covered by the constitutional provision of Article 20a BL. This leads to the question of what could be the constitutional basis for a status *sui generis* of brain organoids under the constitution. More specifically, what could be the criteria to grant brain organoids a special status similar to the constitutional status of animals?

Such potential criteria have already been mentioned by Bernard Baertschi – which shows that the legal debate mirrors the ethical debate, at least to a certain extent. What about the legal relevance of criteria such as sentience or consciousness and awareness?[14] These criteria might be relevant from a constitutional point of view, as well. Nevertheless, the question to be asked is: what is the normative relevance of sentience or consciousness or awareness at all? From my perspective, consciousness and awareness in particular are constitutive for the formation of a human personality, for the formation of an individual human being with his or her own personal character and identity. We have become what we are through our consciousness and awareness, both enabling us to interact with our social and natural environments. Or, to put it differently, as a German colleague did[15], an ethicist, asking the question: is there 'someone' in the brain organoid? If brain organoids had consciousness or awareness, our intuition would be that there is 'someone' (encapsulated) in the brain organoid who, for example, starts to think. This intuition might be of importance when we try to define those criteria which ought to be relevant for granting a legal status *sui generis* to brain organoids, for example under the constitution.

Status of Human-to-Animal Chimeras

Please allow me to continue with some remarks on chimeras. I will only address human-to-animal chimeras, that is, animals which have received human cells or, as the case may be, human brain organoids through transplantation. These chimeras are still animals. So, what applies to such human-to-animal chimeras is, first and foremost, the German Animal Welfare Act which is intended to protect animals against unnecessary pain, suffering, and harm[16]. If these chimeras were created by transplantation of brain organoids into the animal brain, this process would be considered an animal experiment. Such an experiment is permissible for purposes of basic research if it is ethically justifiable, and only upon authorization. This applies not only under German law. The legal situation should be more or less the same in France, for example, because experimentation on animals is governed by an EU directive on animal welfare which is to be implemented in every EU member state[17].

As I have already told you, animals are constitutionally protected against unnecessary pain, suffering, and harm. However, one may ask the question whether chimeric animals with human brain organoids implanted into their own brains might deserve a special constitutional status that is similar,

[14] On these criteria see already, *e.g.*, N. A. Farahany, H. T. Greely *et al.*, "The ethics of experimenting with human brain tissue", *Nature*, vol. 556, 2018, p. 429-432.

[15] Professor Ralf Stoecker on the occasion of a discussion on brain organoids during a meeting of the DFG's Permanent Senate Commission on Genetic Research.

[16] *Tierschutzgesetz* as published on 18 May 2006 (BGBl. I 1206, 1313), last amended by Article 2(20) of the Law of 20 December 2022 (BGBl. I 2752).

[17] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (OJ L 276, 20.10.2010, pp. 33–79).

or close, to the status of human beings because of their being, or having become, 'humanized' or 'human-like' animals due to their human brain organoid transplants. Again, a question with no clear-cut answers at the moment.

Donor Informed Consent

For reasons of time, let me turn to my last point: informed consent. I will address only the issue of informed consent of the donor which plays an important role in three respects. First, the biopsy. At the very first stage of creating organoids – brain organoids in particular – you need to get biological material from a donor: somatic cells which are, then, reprogrammed into pluripotent stem cells which, in turn, are subsequently differentiated into brain cells to be used later on for the formation of the brain organoids. Of course, any biopsy is an interference with physical integrity and, for that reason, needs prior informed consent of the donor. But, second, the legal requirement of donor consent also extends to the biopsied material as such and its further use. Third, donor consent may be required with regard to personal data, in particular genetic data, because the cells, or tissue, contain unique genomic data of the individual donor.

I will only consider the second aspect, the use of the biopsied material, because it may be the source material for certain ethically debatable uses such as the creation of embryoids, brain organoids, or human-to-animal chimeras. The decisive question in this regard is: what is the scope of the consent? Is the creation of embryoids, brain organoids or chimeras covered by the donor's consent? Bernard Baertschi has already referred to several concepts of consent: specific consent, broad consent, etc. In my opinion, from my legal point of view, broad consent is generally sufficient. However, the donor has to be informed correctly before. Part of the information must be that the researcher does not, and cannot, know what could be potential research purposes in the future. Scientific research is an open-ended process also with a view to future, hitherto unknown, research objectives. Nevertheless, if it is possible to envisage, albeit remotely, what the biopsied material could be used for, the researcher will have to inform the donor respectively. That means that, in our case, the researcher has to inform the donor that his or her biopsied biological material could be for purposes that might be considered ethically problematic, such as the creation of embryoids, brain organoids, or human-to-animal chimeras. On this informational basis, the donor may grant consent or may limit his or her consent, for example by excluding the use of his or her biological material for such ethically disputable purposes.

Conclusion: The Problem of Thresholds

That leads me to my conclusions. According to the current state of science and technology, there is no urgent need for embryoid-specific or brain organoid-specific legislation. That is my primary conclusion. However, there are also some broader implications because technology continues to develop. In the future, there may be embryoids which are totipotent, for example, or there may be brain organoids which due to efficient vascularization may become bigger and bigger and start exhibiting certain features which, at least, mimic consciousness or awareness.

Accordingly, the problem is a problem of thresholds. One threshold is totipotency, that is, the inherent capacity of a human entity to develop into a complete born human being. What are the biological criteria for this capacity? Are there biological markers which allow for the unequivocal identification whether a biological entity has such a capacity?

Another threshold is, of course, the threshold of consciousness and awareness. First, do we really know what we mean by these concepts? And, second, do we have the scientific instruments to measure whether the relevant entity undoubtedly has such consciousness or awareness?

Finally, there is the threshold of humanness which, in turn, is closely related to serious challenges to the singular normative status of the human being. The human being as a member of the species *homo sapiens* is considered to be unique. This uniqueness is expressed through the concept of human dignity. No other species, plant or animal, has such dignity[18]. Human dignity means that every human being has the inalienable right to be recognized as a holder of, in general, all rights and duties, that is, to be recognized as a person in law. The more animals become humanized, the more human brain organoids are able to exhibit human consciousness or awareness, the more such developments challenge the uniqueness of the human being and, thus, the unique normative status of the human being. This raises the question whether there is a need, or even a requirement inherent in the concept of human dignity itself, to keep a sufficiently broad normative distance between human beings, on the one hand, and other entities which are only humanized or human-like, on the other hand. Thank you so much for your kind attention.

Acknowledgements

I would like to thank my team. It forms part of a bigger research consortium funded by the Bavarian Ministry of Science and the Arts, called "ForInter – Interaction of Human Brain Cells." Head of the team is Hannes Wolff, who is a PhD candidate. The other current team members are student assistants: Clara Löwenstein, Daniel Schaible, Julia Melzer, and Julian Dregger, all of whom I would like to thank for their valuable assistance.

Questions and Comments

Sonia Desmoulin

Thank you very much, Professor Dederer. Very, very clear presentation on a complex topic.

Anne Le Goff

Thank you. You showed that among the different levels of law, the one that applies in this case is national law. But it seems to me to be a paradox because the science is global, especially in this area, it progresses very quickly, so something that happens in a lab on another continent is going to impact science in a certain country. Do you see the levels of European or international law playing a bigger role in the near future? Or do you think it is going to stay more national?

Hans-Georg Dederer

That is a very good question. I think since science is universal there might be a need for some sort of international harmonization of standards. But I also think that this may get an open-ended discussion, and that there is no institutional platform on the global level or at the regional European level that would really adopt legally binding rules on these issues. Of course, at the global level, there

[18] This is, at least, the perception of the German constitution. Its very first provision, Art. (1) (1) BL, lays down the guarantee of dignity of the human being. It is both the starting point and the focal point of the German legal order.

are certain non-governmental organizations, researchers' associations, for example, concerning stem cells, such as the ISSCR, that draft guidelines which are, however, not legally binding, but can be considered, at least, good practice standards. At the European level, the European states could, within the framework of the Council of Europe, for example, draft a special treaty on these issues. But I suppose that embryoids and brain organoids are highly sensitive moral and cultural issues which may be better left to the nation states. This might also be the opinion of the European Court of Human Rights in Strasbourg which had to decide on human rights of embryos *in vitro* and of embryos *in vivo*. In both cases, the Court held, in essence, that it cannot answer these questions with a view to the right to life under Article 2 of the European Convention of Human Rights. Rather, the Court reasoned, this was a highly sensitive question that needed to be answered at the national level by the treaty parties to the Convention.

Bernard Baertschi

In your definition of an embryo, you say that it is cells that have an inherent capacity to develop. But in a sense, we can say that even a totipotent cell in a dish has the inherent capacity to develop if it is put in a uterus, for instance. So, what do you mean by inherent here?

Hans-Georg Dederer

That is a most important question too: when does a single cell in the dish have the 'inherent' capacity of developing into a human being? Perhaps, we should look at the fertilized egg first. The fertilized egg is the paradigm example of a single cell that has the inherent capacity to develop into a complete human being, however only if an additional requirement is met, that is the implantation into the uterus. That is the only additional, and necessary, condition. Therefore, the fertilized egg is the paradigm of a totipotent cell. More specifically, it is characterized by its genetic program which, differently from the genetic program of somatic cells, for example, directs the fertilized egg to develop into a complete human being. This is why we have to use the fertilized egg as a sort of benchmark when we need to clarify whether other single cells or other entities have the same capacity. Therefore, the test would be very practical: is it possible to bring this entity, by implanting it into the uterus of a woman, to birth? Of course, you know that such an experiment would be unethical because you just do not know what the involved health risks are, what may happen to the mother but also to the organism that develops in the uterus. For these reasons, we will presumably always have difficulties to establish through a practical experiment whether an entity is totipotent or not. We may rely on animal models, though. But any researcher, as you know, will tell us that the mouse is not a human being. Similar to human beings are nonhuman primates, clearly. But in this regard, ethical problems will arise from animal experimentation. And despite any such experiments, one could still hold that human beings is a little bit different from nonhuman primates. For all these reasons, I think, it is difficult to establish conclusively which entities have the inherent capacity to develop into a complete human being. This is precisely why I asked the question whether there are markers, biological markers, that allow for the identification of entities which are totipotent.

Sonia Desmoulin

I would like to say a few words about French law because we had this question asked earlier. In French law, there is a clear distinction between embryonic chimeras resulting from the modification of a human embryo into which animal biological elements are integrated, and chimeras resulting from the modification of an animal embryo or an animal fetus into which human cells or cells with human DNA are incorporated. The former are legally prohibited, but the latter are allowed. So, we also have this distinction between what is treated as a human embryo and what is treated as an animal embryo.

Maybe one question could be about this way of thinking about organoids, using this difference and distinction between human and animal, but I will keep this question for the general discussion.

Challenges for the Implementation of the Current EU Legal Frameworks for Organoids

Aurélie Mahalatchimy

AURÉLIE MAHALATCHIMY

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Introduction

I would like to thank the organizers for inviting me to contribute to this meeting. I will focus on EU law and organoids in general. So, not on cerebroids or embryoids, as it was the case for the previous speakers. The starting point is that there is no legal definition of organoids in European Union law, and there is no agreed definition of organoids in the literature. But there are some common elements that you can find in the different literature definitions. Remarkably, I have selected the same definition as Bernard Baertschi as a reference definition. It is a choice we have made in the research project on organoids. This definition covers three recurrent and common elements, namely, in vitro self-organization of the cells, the resulting structure that is close to an organ, and the performance of the cells, which at least perform some functions of an organ[1]. Among these elements of definition, one important aspect is that, as it has been recalled by the previous speakers, organoids are based on human or animal cells. This brings us to three potential legislative frameworks at the European Union level that could be relevant for organoids.

[1] Sarah N. Boers, Johannes J. M. van Delden et Annelien L. Bredenoord, « Organoids as hybrids: ethical implications for the exchange of human tissues », *Journal of Medical Ethics*, vol. 45, no 2, 2019, p. 131-139.

EU Legal Framework for Biological Elements

The first framework is about biological elements.

1) *For biological elements of human origin* to be used in research[2], there are no binding legal acts at the European level, except for clinical trials. For therapy[3], we have the so-called Directives on tissues and cells[4], and blood[5]. These directives are currently under revision with a proposal for regulation from the European Commission on substances of human origin[6]. Now, looking at the definitions of biological elements of human origin, we can see that the definitions of the cells, tissues, or blood components do not correspond to the three main elements of organoids. The one that is the closest to organoids is the definition of tissues as "all constituent parts of the human body formed by cells."[7] In the new definition proposed by the European Commission (the text may and certainly will evolve during the legislative process), it is even closer, with tissues defined as "a group of cells that function together as a unit."[8]

2) *For biological elements of animal origin*, on the contrary, we have a binding text for research which mainly aims to protect animals[9]. For therapy, there are only European Medicine Agency guidelines, which focus on medicinal products that are based on xenogeneic medicinal products[10], that is, animal cell-based medicinal products.

3) Finally, the legislation on *genetically modified organisms*[11] or *genetically modified microorganisms*[12] could be relevant and covers both research and therapy.

If we look at the main legislative requirements that exist for biological elements *for therapy*, what are the legal rules?

1) First, there are rules on the quality and safety of tissues, cells, and blood of *human origin*. These are mainly measures for accreditation of establishments for storing, preparing, and distributing

[2] We use the term "research" with a broad meaning, including both fundamental and clinical research.

[3] We use the term "therapy" with a broad meaning, as including human application for therapeutic, preventive or diagnosis purposes.

[4] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 7.4.2004, p. 48–58, CELEX number: 32004L0023.

[5] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC; OJ L 33, 8.2.2003, p. 30–40, CELEX number: 32002L0098.

[6] European Commission, Proposal for a Regulation of the European Parliament and of the Council on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC, 14.7.2022, COM/2022/338 final.

[7] Article 3(b) of Directive 2004/23/EC, *op. cit*.

[8] Article 3(4) of the Proposal for a Regulation, COM/2022/338 final, *op. cit*.

[9] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, OJ L 276, 20.10.2010, p. 33–79, CELEX number: 32010L0063.

[10] European Medicines Agency, Guideline on Xenogeneic cell-based medicinal products, EMEA/CHMP/CPWP/83508/2009, 22 October 2009.

[11] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC, OJ L 106, 17.4.2001, p. 1–39, CELEX number: 32001L0018.

[12] Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms, OJ L 125, 21.5.2009, p. 75–97, CELEX number: 32009L0041.

the tissues and cells; for the personnel that should be trained; for traceability, biovigilance; and of course, the voluntary and unpaid donation after consent. Then, there are many rules on data and anonymization, similar quality and safety standards for imported tissues and cells, etc. The new proposal includes a central role for scientific expert bodies for updated technical rules, national establishments authorization and inspection for the storage and processing, report on annual activity data, etc.

2) Second, there are rules on *biological elements of animal origin*. These guidelines mainly aim to ensure proper surveillance for infections. While it is specified for medicinal products, it includes general principles that are also applicable for cells used as raw material or where contamination is possible. So, it means that these general principles could be applicable for organoids that are based on animal cells.

3) Finally, rules on *genetically modified organisms* mainly involve the case-by-case assessment of environmental risk associated with the release of genetically modified organisms, and their monitoring after deliberate release into the environment. However, it should be highlighted that these rules on genetically modified organisms were adopted for plants and foods mainly.

For the use of *biological elements in research*, the main requirements are national rules, as previously mentioned by Hans-Georg Dederer. For the use of tissues, cells, and blood of *human origin* in fundamental research, national rules apply. But in practice, biobanks implement the EU legislation on tissues and cells that are provided for human applications. Why? Because, generally, biobanks have both research and health objectives[13].

Rules on *biological elements of animal origin in research*, that is, the directive for assessment and authorization of experiments and establishment, with the 3R (Replace, Reduce, Refine) principles for animal welfare, etc., focus on protecting laboratory animals.

For *genetically modified microorganisms*, the rules are the same as for therapy: classification according to the level of risks and scaled regime with notification to national competent authorities (immediate start, start after delay, start after authorisation), vigilance measures, etc… But the assessment of risk is generally associated with the contained use of genetically modified microorganisms.

To summarize, what are the key points in these legislations for organoids? First, all substances of human origin could be used as starting materials for organoids. Second, the legal definition of tissues is closest to what is considered as organoids. Third, legislation on genetically modified organisms or genetically modified microorganisms would apply to organoids where relevant, i.e., if there is such a genetic modification of the tissues and cells as starting materials of organoids. For research, the national rules apply, except in cases of clinical trials of medicinal products[14], and in cases of

[13] Aurélie Mahalatchimy et Emmanuelle Rial-Sebbag, «Le génome humain édité : risques et gouvernance», in N. De Grove-Valdeyron (dir.) Innovation et Analyse des risques dans le domaine de la santé et des produits de santé dans l'Union Européenne : regards croisés, *Cahiers Jean Monnet*, Presses de l'Université Toulouse 1 Capitole, 2020, p. 99- 150.

[14] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance, OJ L 158, 27.5.2014, p. 1–76, CELEX number: 32014R0536.

wide implementation of the tissues and cells and blood legislation, possibly beyond clinical research. Finally, the most relevant legal framework is the one that exists for tissues and cells. But there are no distinct requirements between tissues versus cells. And the proposal for the revision of this legislation - which includes a proposal only for one regulation of all substances of human origin (that is, tissues, cells, blood, and blood components but not organs) does not consider organoids.

EU Legal Framework for Organs

We should also consider the legal framework for organs. Again, if we start from the definition of an organ given by the Directive that applies to human organs intended for transplantation[15], an organ is "a differentiated part of the human body, formed by different tissues, that maintains its structure, vascularization, and capacity to develop physiological functions with a significant level of autonomy."[16] And, very importantly, "a part of an organ is also considered to be an organ, if its function is to be used for the same purposes as the entire organ in the human body, maintaining the requirements of structure and vascularization."[17] It means that the final therapeutic organoid, an organoid that is developed for transplantation, in its final stage could fall into this definition.

If we look at the main requirements in this directive on human organs, they mainly concern the protection of living donors, minimum data from the donors for quality and safety reasons, voluntary and unpaid donation after consent, authorization for establishments for transplant, qualified personnel, traceability, biovigilance, protection of data, and also specific requirements for transport. Importantly, here, for immunocompatibility, there is a need for exchange of organs among states. So, there are regular exchanges of information between Member States and this is supported by the European Commission. One of the main objectives of this directive is the quality and safety all along the organ chain from donation to transplantation or disposal.

The key point here for organoids is that the current legal definition of organs does not exclude organoids and can be relevant for final organoids used for transplantation, as well as for those used in clinical research as long as there is the intent of transplantation into the human body[18]. The rules related to the first steps of procurement, donation, and testing of organs are not relevant for organoids as cells or tissues are donated or procured, but not organs themselves. However, the quality and safety objectives of the legislation for cells, tissues, and organs are similar and relevant in the context of organoid development. For instance, the protection of donors, minimum data for quality and safety reasons, consent, etc. And the rules on further steps in the transplantation chain could be particularly relevant for organoids for transplantation. For instance, the specific requirements for transport, exchanges between Member States supported by the European Commission, the authorization of establishments for transplantation.

[15] Directive 2010/45/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation, OJ L 207, 6.8.2010, p. 14–29.

[16] Article 3(h) of Directive 2010/45/EU, *Ibid*.

[17] *Ibid.*

[18] Article 2 of Directive 2010/45/EU, *op. cit*.

EU Legal Framework for Medicinal Products

The third relevant legal framework is for medicinal products, which is particularly fragmented. Here, there is a question of degree of manipulation of tissues and cells. If cells/tissues themselves or cells/tissues for organoids are substantially manipulated, or if there is a nonhomologous use of the tissues and cells, which means that the function of the tissues and cells is not the same in the donor and in the recipient, the products will qualify as Advanced Therapy Medicinal Products (ATMPs). In that case, the applicable rules depend on the scale of manufacturing. If ATMPs are manufactured at the industrial scale, European Union rules will be implemented: it means marketing authorization through the centralized procedure at the European level, strengthened requirements for pharmacovigilance and traceability, specific requirements for Good Manufacturing Practice (GMP) and Good clinical practice (GCP), etc. If ATMPs are prepared on a non-routine basis, they will be considered as exempted ATMPs and national rules will apply.

At least, this is the current framework. But last April 27, 2023, the European Commission published a full proposal for the revision of the entire pharmaceutical legislation[19]. What can we highlight from that? First, organoids are mentioned one time among the new approach methodologies (NAMs) in place of animal testing to be encouraged. So, again, when organoids are considered, it is really to replace animal testing. There is no fundamental change in this proposal for organoids as ATMPs, and beyond the clarification of the existing legislative frameworks for ATMPs (such as new disposals related to exempted ATMPs and decentralized manufacturing of ATMPs).

But some of the proposed changes may be relevant for organoids. First, there is a possibility for the European Medicines Agency to make a scientific recommendation on the regulatory status of a product, with consultation of the coordination board on substances of human origin[20]. This board does not exist today, it may be created once the proposal for regulation on substances of human origin is adopted. This procedure may be used to clarify the regulatory status of organoids in EU law.

Second, there is a specific scheme, called the Priority Medicine Scheme, which already exists but may be embedded at the legislative level with this proposal, which will apply if eligibility criteria are met, and aims to provide early regulatory support for priority medicines and accelerate their authorization and commercialization[21]. This may be a relevant scheme for organoids qualified as medicinal products.

Third, a regulatory sandbox is created, again, if eligibility criteria are met. This will allow derogations to the general pharmaceutical legislation or to the ATMP legislation, under specific conditions. These derogations should be set up by the European Commission on the basis of recommendations from

[19] European Commission, Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006, 26.4.2023, COM/2023/193 final; European Commission, Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC, 26.4.2023, COM/2023/192 final.

[20] Article 61§2 of the Proposal for a Regulation, COM/2023/193 final, *op. cit.*

the European Medicines Agency[22]. They will be regulated under the direct supervision of the national competent authorities, so at the national level. This new possibility for adaptation of the legislative requirements may be particularly relevant for organoids qualified as medicinal products.

Conclusion: Possible Regulatory Pathways

It means that several regulatory pathways are possible for organoids at the level of EU legislation. The first regulatory pathway, which will be the most probable one, starts with the legislation of tissues and cells or the future proposal on substances of human origin for donation, procurement, and testing of human tissues and cells as starting material of organoids for human applications. Then, in case of nonhomologous use of tissues and cells or substantial manipulation, which may be the most probable situation for organoids, then depending on the scale of manufacturing, the manufacturing, storage, and distribution of these medicines will be regulated either at the European level as Advanced Therapy Medicinal Products or at the national level as exempted Advanced Therapy Medicinal Products.

Another possible regulatory pathway is to stay under the legislation of tissues and cells or the future proposal of regulation for substances of human origin. It means that for the donation, procurement, and testing of human tissues and cells as starting materials of organoids, the rules are the same as in the first scenario. But then, as there is no substantial manipulation of tissues and cells and an homologous use of the tissues and cells, the processing, preservation, and distribution of organoids are regulated under the legislation of tissues and cells.

The final potential and arguable regulatory pathway is as follows. We start with the legislation on tissues and cells for donation, procurement, and testing as in the two previous scenarios. Then, if there is no substantial manipulation and homologous use of the tissues and cells, the organoids would fall into the organ legislation, and it would not stay within the tissues and cells legislation. This would be possible from the processing stage as long as the processing aims to maintain the structure and vascularization with a significant level of autonomy. Thus, the directive on organs could apply for the characterization, preservation, transport, and transplantation of organoids. Of course, all of this is very prospective because we do not have organoids for transplantation at the moment, I should have specified this at the beginning.

In conclusion, we can say that most of the above-mentioned existing legislative or regulatory EU frameworks would be applicable to organoids. Many of the current European Union rules would be relevant to organoids to some extent, as long as quality and safety of the tissues, cells, or organs, or medicinal products are the main objectives. But there are several issues. First, there is a gap regarding organoids in the proposal of the regulation on substances of human origin. This legislation is applicable in law for therapy, and is implemented in fact for fundamental research. Another issue is that organoids are considered only once in the proposed reform on pharmaceutical legislation, and only as an alternative to animal experimentation. Another issue is the complexity of the landscape, and consequently the lack of legal safety. Some perspectives with, of course, open questions would be to provide new scopes for the existing legal frameworks to explicitly include organoids. Or to provide a new specific regime for organoids used in therapy or for transplantation. I thank you for your attention.

[21] Article 60 of the Proposal for a Regulation, COM/2023/193 final, *op. cit.*

[22] Article 113 of the Proposal for a Regulation, COM/2023/193 final, *op. cit.*

Acknowledgements

This work is supported by ANR-funded Organact (ANR-22-CE41-0012-03) and I-BioLex projects (ANR-20-CE26-0007-01).

Questions and Comments

Sonia Desmoulin

Bernard Baertschi and Hans-Georg Dederer focused on cerebral organoids and embryoids, and you decided to study the legal issues raised by all kinds of organoids. In your opinion, should we distinguish between different kinds of organoids and focus on certain problematic organoids? Or should we consider them together equally because the technique is nearly the same? Alternatively, should we pay attention to users instead? In brief, an object approach, a technical approach, or a users' approach - what do you think?

Aurélie Mahalatchimy

Thank you for your very interesting question. In fact, these are three questions, I would say. The first one, to consider organoids all together or to distinguish general organoids and cerebral organoids and gastruloids? I think that we have to distinguish them. First, as we have seen, the most acute ethical questions relate to cerebroids and gastruloids. It does not mean that the other types of organoids do not raise ethical questions, but it just means that most of the time the law has already given answers for these other types of organoids. So that is the first part of the answer. But the thing is that we have to deal with the logic of our existing systems. As you know, I am specialized in European Union law and these ethical questions generally, I would say, tend to be settled at the national level. So, for instance, the question of embryoids or cerebroids will be less open at the European level, I mean, in the binding legislation. Of course, it does not mean that there cannot be opinions from the European Group on Ethics or resolutions from the European Parliament, etc. But it will be the same as for research on embryonic stem cells at the moment: each national state will decide to do it or not. But as long as you decide to do it, for therapy, the minimum quality and safety standards at the EU level will have to be respected. So, I would say that by existing systems, because of the need to take into account the European Union level and the national level, I think that we will go towards separated regimes for general organoids and cerebroids and gastruloids. Then, focusing on the object approach, technical approach, or users' approach, in fact, it seems to me it is always a combination of all these. For instance, French and, as we have seen, German law focus more, I would say, on the object approach, in the sense of the dichotomy between persons and things. But a very important, even primary distinction at the European level is really the distinction between therapy, as the final aim of objects intended for human applications, and research. We seem to focus on therapy at the European Union level, and this can be linked to the users' approach. After, when you set up the rules, technical aspects are always taken into account. I mean, the question of vascularization in the structure, of substantial manipulation, etc., these are technical criteria that are needed to implement the binding rules.

Nertila Kuraj

Thank you for your very enlightening presentation on a very technical topic. I was just wondering

if you could elaborate a little bit on the applicability of the GMO legislation to organoids. In particular, I wonder about the definition of GMOs, where human beings are excluded? How does that relate to the fact that we are discussing here about potential personhood or considering the human aspect of organoids?

Aurélie Mahalatchimy

Yes, thank you for your question. I think the question of the exclusion of human beings would involve that all the questions of cerebroids and gastruloids will not be covered by the legislation on GMO. But for general organoids, as long as there is genetic modification of human cells in their development, these directives will apply. So, the overview I have given, with uses for research and deliberate release for therapy, is really only an overview because it depends on the definition given by the interpretation of continuous and deliberate release by Member States. But still, it gives an idea and at least shows how it is interpreted in France. But we know that this directive applies for human cells research and Advanced Therapy Medicinal Products based, for instance, on gene therapy, medicinal products with genetic modification. There are currently big issues to implement this directive in the field because it provokes many delays in the approval of Medicinal Products. Regulators, especially the European Medicine Agency, are working on facilitating the approval of products that contain genetically modified organisms. So, this evolution will for sure be useful for organoids based on human cells.

Hans-Georg Dederer

May I jump in because it was an interesting question, which has not been answered in law. Just to clarify, there are two frameworks. One applies to contained use and one to release and placing on the market, and there are actually two different definitions. You referred only to the definition in the directive on release and placing on the market and indeed, there is the exclusion: it is an organism at the exclusion of human beings. And the question has not been answered of what a human being is within the meaning of this definition, and, of course, it depends, I think, in the end on interpretation, using the criteria we have been discussing here with view to embryos. Does it depend on totipotency, the capacity to develop into a complete human being? Or does it depend on consciousness when it comes to brain organoids? So this is a practical question, actually. At the moment, I think it is clear they - neither embryoids nor brain organoids - are not human beings and therefore, that exclusion to the definition does not apply.

So, the question is, is it an organism? Or is it rather a microorganism, because the contained use directive only applies to microorganisms. Again, And the definition is interesting because it says, it includes this and that, and animal and plant cells in culture. So, what is an organoid? Is it cells in culture? It is a highly sophisticated, three-dimensional structure. Perhaps it would be included as a cell in the culture of cells and culture. But still, if it is human, are human brain organoids the animal cells in culture? I would say yes, and I have made an argument together with David Hamburger, in a journal article, that ‘animal’ includes any mammals, including primates, and the species *Homo sapiens*. But, of course, this is open to interpretation, and there are no definitions provided by the European Court of Justice, for example. So very good questions, but still not answered, definitely.

And perhaps just to add to the discussion before on chimeras, and whether the generation of chimeras is prohibited under national law. You referred to French law, so just a remark on the German situation. I mentioned the Embryo Protection Act, and a prohibition of creating chimeras. However, it only applies if human embryos are involved. And that is not the case with embryoids nor brain organoids. They are produced from stem cells, but not with the help of human embryos. So for this reason, the prohibition of chimeras does not apply under the Embryo Protection Act. And there is no other prohibition in German law, which would prohibit the production of human-to-animal chimeras. So it is only a problem of animal welfare law.

Soraya de Chadarevian

We have had a lot of very interesting and insightful talks on law. But we have this more general question about wisdom, collective wisdom. And so, is it just because of the way this roundtable has been put together that legal arguments have been dominating? I am always fascinated, actually, when the law defines scientific issues, which has often been the case recently, especially in discussions about drafting the laws, but sometimes also in the courts, when things such as what DNA is were discussed and defined in the courts, which is a very interesting development. And so, I just wonder, the lawyers, are they collaborating with social scientists, philosophers, scientists, the public? These laws or these discussions around law, how democratic are they? Or are they really only in the hands of lawyers? And then, someone - I think it was Hans-Georg Dederer - mentioned how law and ethics work together, which is another question I was interested in. Are these the hands in which we want to put these questions? Or is there a case to make for broader democratic processes to deal with these new technologies? This is a very general question, but I think it addresses a central concern of our three roundtables.

Aurélie Mahalatchimy

Yes, several elements to respond. First, the law is sometimes defining and sometimes is not. For example, with the definition of the human embryo: there is a definition in German law, there is a definition in Europe and patent law, but there is no legal definition in French law. This is a choice from a legal system whether to define or not. Then, when the law comes to define or legislate or regulate, it is not only made by lawyers, especially in these fields, but it is a complete interaction between many disciplines. For example, in our parliament, we have an office for scientific choices, that performs hearings of scientists, of researchers in various social and human sciences. It is all these debates that lead to the creation of a definition, which becomes either embedded in a binding legal act or remains as a nonbinding reference definition. But I think you are really right, this is a very interesting topic, the question of the legal definition: when should we define in a binding act and to which extent should the law follow the evolution of science? As we have seen, for instance, with the definition of the human embryo, in European patent law, a definition is given and then a few years later, we realize that we did not consider all the scientific aspects and the definition has to evolve. And to have binding definitions evolve takes more time than nonbinding definitions. So, that is a difficult question but I would say absolutely not, these definitions are not only coming from lawyers.

Hans-Georg Dededer

Absolutely. Just to add some remarks. You asked whether it was all in the hands of lawyers. We need to distinguish between research, Parliament, and courts. In legal research – that is what I do primarily – we collaborate of course with ethicists as well as with scientists, including medical scientists. For example, I referred to this research group at the end of my presentation, which is part of a greater Research Consortium, and that includes eight subprojects. We are only one of eight, and the other seven are all concerned with biomedical sciences. I have also collaborated in other research consortia, and typically we form three subprojects, ethics, law, and science. So this is how our ethical and legal reflections are informed. Now, when it comes to parliament, as Aurélie Mahalatchimy explained, when the parliament makes a law, then it is informed. In particular, in committees, smaller

groups of parliamentarians invite experts from science to explain to the parliament what the state of science and technology is. Or that may be the case - it is the case in Germany when it comes to these difficult issues of biomedicine, biomedical developments - the parliament might even establish a bigger commission that meets for two or three years and finally submits a bigger report of hundreds of pages. And members of this Enquête Commission – that is, Investigation Commission – are not lawyers or ethicists primarily, but medical doctors and natural scientists, and of course, include lawyers and philosophers, ethicists as well. Now about the courts. For laws like the Embryo Protection Act, or the law on genetically engineered organisms, etc., these are laws that are directly related to science and technology. But it is law. And if a dispute is brought before the courts, the court has to sit tight and has to decide as lawyers, but again, they have the possibility to ask for expert evidence, for example, inviting experts who provide information to the court. The problem with the European Court of Justice in Luxembourg, the court of the European Union, is that the sources on which this Court draws when it makes its decision are sometimes not known. That was the case in 2018, when the Court decided on the question of what genome editing is and whether it is genetic engineering or not. The Court decided that genome editing is genetic engineering and, therefore, included it in the GMO framework that Aurélie Mahalatchimy described earlier. We just do not know what the sources of that knowledge are. This is a problem, of course. But still, even the ECJ in Luxembourg has the possibility to draw on expert evidence, invite scientific experts, so to speak, as expert witnesses and to give the information to the court that is relevant to decide the case. And then the last remark, you asked for the democratic process. Formally speaking, as a lawyer in public law, the courts are democratically legitimized, that is our position in Germany, but also parliament is democratically legitimized, and there are democratic processes which I think should not only discuss the issues, but in the end have to make decisions. That is perhaps the expectation of the population, if there is an issue that needs to be decided, it should be decided first of all not by courts but by the parliament. Particularly if it is difficult as it is in bioethics or biomedicine. The problem of democratic processes in Germany is that, unlike in France - France has a much better system in place in this regard: in France, it is the case that every seven years, I think, the parliament has to reflect anew on the bioethics law of France - there is no such a rule in Germany. We have the Embryo Protection Act dating back to 1990 - that is three decades ago and based on the science of three decades ago. It is a problem in Germany that the parliament is not willing to take up the democratic discussion on this issue. This is a real problem because the state of science and technology has progressed enormously.

Aurélie Mahalatchimy

I agree that we are very lucky in France to have the revision of the bioethics law, but it does not settle all problems. For instance, regarding organoids, this topic was not discussed at all during the last revision of the law.

Troisième partie

LES TESTS GÉNÉTIQUES EN LIBRE ACCÈS

Usages, ré-usages et mésusages des données génétiques

Elsa Supiot

ELSA SUPIOT

Elsa Supiot est professeure de droit privé à l'université d'Angers. Ses recherches portent sur l'articulation entre droit et sciences et en particulier sur les enjeux soulevés par la génétique tant en matière civile et de santé qu'en matière pénale. Elle a dirigé un projet de recherche financé par le GIP Justice sur les usages de l'ADN en matière pénale ainsi qu'un projet financé par l'Agence de biomédecine sur le dépistage prénatal non invasif.

Introduction : Les tests génétiques en accès libre et leur interdiction en France

Merci aux organisatrices de ces sessions qui sont tout à fait passionnantes et importantes. De quoi parle-t-on quand on parle de tests génétiques en accès libre ? On parle en réalité d'abord d'un mécanisme de distribution. Il s'agit du *direct-to-consumer*, donc d'une vente "directement au consommateur". L'idée est dans le nom. Le test est accessible aux consommateurs sans aucune forme d'intermédiation, ni prescription médicale ni décision de justice. Cet accès est proposé essentiellement par des compagnies privées qui offrent, souvent via leur site Internet, la réalisation de tests génétiques qui peuvent être d'une grande variété : certains relèvent plutôt du domaine médical, d'autres de ce qu'on a pu appeler la généalogie génétique, ou encore de la génétique récréative. Bref, c'est une prestation de services librement accessible à chacun via internet, contre rémunération[1].

Librement accessible, certes, mais en réalité totalement interdite en France par les articles L.1133-2 et suivants du code de la santé publique. A toutes fins utiles, je me permets de rappeler les dispositions de l'article L.1133-4-1 de ce code selon lesquelles « le fait pour une personne de solliciter l'examen de ses caractéristiques génétiques ou celle d'un tiers ou l'identification d'une personne par ses empreintes génétiques en dehors des conditions prévues par la loi, est puni » de

[1] E. Supiot, *Les Tests génétiques. Contribution à une étude juridique*, PUAM, 2014, p.124 *sq.*

3.750€ d'amende. D'autres sanctions sont également prévues pour les laboratoires qui pratiqueraient ce type d'analyse. Cette interdiction expresse a été introduite dans le code de la santé publique en 2011. Son efficacité pratique est pour le moins limitée puisqu'il a été estimé qu'environ 100.000 Français effectuent un tel test chaque année et plus d'un million d'entre eux auraient déjà confié leurs données génétiques à des laboratoires étrangers[2].

À l'occasion de la réforme de la loi bioéthique en 2021, la question a donc été posée de lever cette interdiction et de faciliter l'accès aux tests génétiques. La commission spéciale du Sénat avait en effet proposé de modifier le code de la santé publique pour autoriser et encadrer les tests génétiques en libre accès[3]. Ces modifications ouvraient les tests de généalogie génétique en accès libre et autorisaient l'examen des caractéristiques génétiques constitutives sans exiger d'indications médicales préalables. Concernant ces tests génétiques de nature médicale, le Sénat envisageait deux contextes différents, soit la réalisation d'un test à la demande d'une personne qui souhaiterait en savoir plus sur son génome, ce qui avait été appelé dépistage en population, soit à la demande d'un couple dans le cadre d'un projet parental, ce qu'on appelait le dépistage préconceptionnel. La réforme n'a de toute évidence pas abouti. Le gouvernement y était en effet hostile et a présenté un certain nombre d'arguments et de risques pour faire écarter ces évolutions du projet de loi[4]. Parmi ces arguments, on trouve notammen tun risque de violation du droit au respect de la vie privée et familiale pour les apparentés des personnes qui sollicitent le test. Mais également les garanties insuffisantes concernant la protection des données, la question de la prise en charge financière de la réalisation de ces tests, les risques de discrimination, d'eugénisme et la tentation d'un certain déterminisme génétique, pour ne citer que ceux-là.

Donc la France, contrairement à de nombreux pays et notamment à certains de ses voisins, a maintenu une interdiction rigoureuse des tests en libre accès[5]. Je vous ai présenté cela parce qu'il me semble que cette interdiction est intéressante à examiner pour réfléchir plus globalement sur les enjeux et les évolutions qui sont apportées par le déploiement, toujours plus important, de ces tests en libre accès. Et donc je voudrais, à partir de cette interdiction, m'interroger avec vous sur ce qu'elle permet de révéler des problématiques soulevées par les tests génétiques en libre accès et les évolutions consécutives au développement de l'offre en la matière.

Dans un souci de systématisation et avec un tropisme de juriste universitaire française, j'ai divisé mon propos en deux temps. D'abord sur les difficultés qui résultent du principe même du libre accès et ensuite sur les conséquences ou les difficultés qui résultent du développement florissant de ces offres.

[2] Inserm, « Tests génétiques "récréatifs" : juste un jeu ? », 21 février 2019, www.inserm.fr; v. également la prise de parole d'Olivier Henno, sénateur, rapporteur de la commission spéciale de bioéthique. Séance du 28 janvier 2020. *https://www.senat.fr/seances/s202001/s20200128/s20200128003.html*; G. de Morant, « Geneanet lance son offre ADN… de correspondance », *La revue française de généalogie*, 18 février 2020, www.rfgenealogie.com.

[3] Amendements n°COM-190 et COM-191 au projet de loi Bioéthique (1re lecture, n°63), article additionnel après l'article 10, présenté par M. Henno, le 2 janvier 2020.

[4] V. Sénat, Compte rendu analytique officiel, Séance du mardi 28 janvier 2020, p.4 *sq*. ; https://www.senat.fr/cra/s20200128/s20200128.pdf

[5] Certaines entreprises en ont tiré les conséquences et exigent désormais une adresse de livraison des kits de prélèvement hors du territoire français. V. en ce sens A. Gérard, « Le grand coup de frein des tests ADN à « usage récréatif » toujours illégaux en France », *Le Parisien*, 28 janvier 2023.

Les difficultés résultant du principe même du libre accès

En ce qui concerne le principe même du libre accès aux tests génétiques, deux critiques principales ont pu être formulées. Tout d'abord, la faible qualité de ces tests ou leur qualité très variable, en particulier pour les tests à caractère plutôt médical. En ce qui concerne leur validité et leur utilité clinique, d'ailleurs, si on reprend l'historique du développement de cette offre, les entreprises avaient dans un premier temps pris soin de proposer ces tests en précisant qu'ils n'avaient pas de nature médicale, qu'ils ne présentaient qu'un caractère informatif et ludique et que les personnes étaient invitées à consulter un médecin si elles voulaient plutôt une prise en charge d'ordre médical[6]. Donc des questions en termes de sécurité et de fiabilité. Une seconde critique qui a pu être adressée à ces tests génétiques en libre accès tenait à la question de l'autonomie, réelle ou non, qu'ils offraient à la personne qui décidait d'y recourir, notamment au regard des résultats souvent difficiles à comprendre pour un profane, et du caractère potentiellement sinon traumatique, au moins perturbant des résultats obtenus.

Sécurité et fiabilité

Concernant la sécurité et la fiabilité, jusque récemment, les tests génétiques étaient considérés comme des dispositifs médicaux de diagnostic *in vitro* qu'on aurait pu qualifier d'inoffensifs. Ils ne relevaient donc que des dispositions les plus légères applicables à ces dispositifs. Ce qui veut dire que, en réalité, ils étaient soumis à un régime d'auto-certification CE préalablement à leur mise sur le marché, en tous cas sur le territoire de l'Union européenne[7]. Ce cadre a été considéré comme insuffisamment protecteur et trop disparate dans la variabilité de sa mise en œuvre par exemple. Une réforme est donc intervenue avec l'adoption en particulier du règlement européen relatif aux dispositifs médicaux de diagnostic *in vitro*, règlement qui est entré en vigueur en 2022[8].

Au terme de de ce règlement et notamment de son annexe 8, les dispositifs destinés à l'analyse génétique humaine relèvent de la classe C. Il faut savoir que dans ce règlement, il y a 4 classes, la classe D étant celle présentant un risque très élevé ; la classe C, dont relèvent donc les tests génétiques, les dispositifs présentant un risque élevé. A ce titre, ces dispositifs ne font plus l'objet d'une autocertification, le marquage CE étant obtenu après une évaluation par un organisme de certification. Pour obtenir cette certification, il faut fournir un dossier assez conséquent et qui tient notamment aux questions de validité et d'utilité clinique des tests[9]. Cette démarche au niveau de l'Union européenne peut être rapprochée de celle qui a été mise en œuvre il y a quelques années déjà par la Food and Drug Administration (FDA) aux États-Unis et qui visait elle aussi à encadrer les

[6] E. Supiot, *op. cit.*, p. 141.

[7] Directive 98/79/CE du Parlement européen et du Conseil du 27 octobre 1998 relative aux dispositifs médicaux de diagnostic in vitro.

[8] Règlement (UE) 2017/746 du Parlement européen et du Conseil du 5 avril 2017 relatif aux dispositifs médicaux de diagnostic in vitro et abrogeant la directive 98/79/CE et la décision 2010/227/UE de la Commission, JOUE 5.5.2017, L117/176.

[9] « La notion de "validité clinique" d'un test doit être entendue comme correspondant à une mesure de la précision avec laquelle un test identifie une affection clinique ou une prédisposition à une affection clinique. Elle est définie en termes de spécificité, de sensibilité et de valeur prédictive sur le plan clinique », Rapport explicatif du protocole additionnel à la Convention sur les Droits de l'Homme et la biomédecine relatif aux tests génétiques à des fins médicales, point n°49. L'utilité clinique, au sens large, est établie dès lors que les résultats du test permettent la prise d'une décision importante pour les individus et leur famille, selon l'article 6 du protocole additionnel Convention sur les Droits de l'Homme et la biomédecine relatif aux tests génétiques à des fins médicales du 27 novembre 2008.

tests génétiques en libre accès. La réaction de la FDA avait d'ailleurs dans un premier temps donné lieu à la fermeture, enfin à l'indisponibilité, de la part de l'entreprise 23&me notamment, des tests à caractère médical, tests qui ont par la suite été remis en place une fois que la société s'est conformée aux exigences de la FDA[10].

On pourrait donc considérer que, avec ce nouveau règlement, les questions de sécurité et de fiabilité sont résolues. En réalité, il y a plusieurs nuances à apporter à une telle impression. D'abord, il faut s'interroger sur les répercussions de ce règlement en termes de concurrence sur le marché de ces tests. En particulier après l'adoption de ce règlement, de nombreuses structures publiques, les centres hospitalo-universitaires (CHU) notamment, ont fait part de leur inquiétude quant à l'impossibilité matérielle et humaine pour eux de constituer les dossiers demandés par l'Union européenne pour faire valider leurs tests[11]. Ce n'est pas tout à fait neutre puisque vous avez peut-être à l'esprit l'affaire *Myriad Genetics* où avait été mis en balance le test développé par Myriad, entreprise privée, et un test qui avait été développé notamment par les institutions publiques et était beaucoup moins cher dans plusieurs pays. J'ai eu l'occasion de discuter avec des chercheurs en France et en Belgique. Il y a cette inquiétude, l'institution publique ne disposant pas des infrastructures suffisantes pour se mettre en conformité avec le règlement, ce qui pourrait conduire à un appauvrissement de l'offre publique de tests génétiques en matière de santé. Par ailleurs, ce règlement vient se prononcer sur la sécurité et la fiabilité, donc sur un terrain purement technique. Or, un des enjeux des tests génétiques réside particulièrement dans la compréhension des résultats qui vont être fournis. Cela vient ici s'articuler avec la question de l'autonomie, qui était donc mon deuxième point dans cette première partie.

Autonomie

La question de l'autonomie des individus face aux tests génétiques est traitée de manières très différentes en fonction des cultures juridiques dans lesquelles on se trouve. En France, dès 1994, le législateur a eu à cœur d'organiser un accès encadré aux données génétiques, avec en arrière-plan l'idée que ces données pouvaient être dangereuses pour la personne, en termes de discrimination mais aussi de construction identitaire[12], et qu'il fallait donc un accompagnement médical pour que la personne puisse d'abord évaluer sa volonté d'avoir accès à ces données et ensuite avoir une véritable compréhension des données. C'est une logique totalement différente qui a été mise en avant aux États-Unis. Ce n'est donc pas un hasard si les grosses compagnies de tests en accès libre se sont développées là-bas. L'idée prédominante est celle de la liberté de l'individu par rapport à des données qui sont les siennes, qui lui appartiennent, et donc pour lesquelles il n'y a pas à lui imposer un filtre pour y accéder[13]. Donc on voit des paradigmes très différents et la question de l'autonomie peut être abordée depuis ces deux perspectives.

Ce qui est intéressant, c'est que malgré ces différences d'approche sur l'autonomie face à ces

[10] Y. Seon-Hee et Y.-J. Chung, « Reflections on the US FDA's warning on direct-to-consumer genetic testing », *Genomics & Informatics* vol. 12, n°4, 2014, p. 151-5 ; G. J. Annas et S. Elias, « 23andMe and the FDA », *New England Journal of Medicine*, vol. 370, 2014, p. 985-988; E. Check Hayden, « The rise and fall and rise again of 23andMe", *Nature*, vol. 550, 2017, p. 174–177.

[11] En ce sens, v. « Entretien avec Joris Vermeesch sur le contexte scientifique et économique belge », *Cahiers Droit, Sciences & Technologies*, vol. 15, 2022, p. 77-81.

[12] E. Supiot, *op. cit*., p. 40 *sq*.

[13] V. par ex., M. Smolenyak, « Don't protect us from our genetic information », *The Huffington Post*, 20 juillet 2010 ; pour une analyse des arguments en faveur de l'accès libre, P. Ducournau, « Génétique en ligne : quelle biopolitique en émergence ? », *RGDM*, n°42, 2012, p. 37-45.

tests en libre accès, dans les deux pays on a pu constater des inquiétudes sur les répercussions de l'accès libre en termes d'information et de mésinformation des individus, en particulier quant à leurs données de santé[14]. Les sociétés qui développent ces tests en sont très conscientes. Elles mettent ainsi à disposition de leurs clients, outre parfois des interlocuteurs, tout un tas d'instruments développés grâce aux nouvelles technologies et aux *big data* pour rendre ces résultats plus visuels et donc plus facilement accessibles.

Dans cette perspective, il a pu être avancé que, finalement, ces instruments développés par les sociétés privées pouvaient aussi être utiles dans le cadre de notre système de santé où les tests génétiques vont de plus en plus avoir vocation à être prescrits, et les résultats reçus par un médecin qui n'est pas spécialiste de génétique. C'est déjà ce qu'on constate dans le dépistage prénatal non invasif où des données génétiques complexes arrivent entre les mains de gynécologues ou de sages-femmes ou de médecins généralistes qui ne se sentent pas forcément armés pour expliquer ces résultats à leurs patients. Dans cette perspective, des outils d'explication comparables à ceux qui sont mis à disposition par ces sociétés pourraient constituer un avantage[15].

La prudence reste toutefois de mise. L'expérience des sociétés privées montre qu'il peut y avoir une grande variabilité dans l'interprétation des résultats sur des traits génétiques identiques. En effet, l'interprétation va dépendre notamment du choix des études incluses par les sociétés et de l'appréciation des incertitudes scientifiques sur certaines données. Donc il y a évidemment un biais dans la manière dont les résultats sont présentés, y compris avec l'assistance d'une intelligence artificielle. Par ailleurs, cette autonomie peut se faire au détriment de l'individu lui-même ou des membres de sa famille. Ici, je sors un tout petit peu du champ médical. Il va y avoir les questions de discrimination qu'on trouve de manière récurrente quand on parle de tests génétiques et *a fortiori* de tests génétiques en libre accès. Ces questions de discrimination concernent les données génétiques de santé mais aussi la généalogie génétique. Des affaires aux États-Unis ont montré le risque de discrimination à l'égard de personnes dont les tests avaient révélé une ascendance correspondant à tel ou tel groupe ethno-géographique[16]. Il y a aussi la question de la vie privée des membres de la famille. En France, le législateur a mis au point un système pour que les données de santé puissent être partagées avec les membres de la famille[17]. C'est un système que l'on peut critiquer, mais qui présente en tout cas un souci d'équilibre entre la préservation du secret médical, la préservation de la vie privée du patient qui a fait le test et la préservation de la vie privée, mais aussi de l'information des membres de sa famille[18]. Or, ce dispositif *a priori* ne va pas se retrouver quand on a affaire à des tests en libre accès.

[14] *Cf.* GAO, « Direct-to-consumer genetic tests: Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices », 2010, GAO-10-847T. Dans ce rapport, l'équivalent américain de l'OPECST relevait les insuffisances techniques mais aussi les problèmes liés à la compréhension des résultats par le consommateur. Du côté de l'Union européenne, on peut relever que le nouveau règlement sur les DM-DIV insiste sur la nécessité qu'un conseil médical soit organisé pour la compréhension des résultats.

[15] Il en va de même pour la compréhension et la présentation des éventuelles données incidentes résultant d'un test génétique.

[16] T. Jones et J. L. Roberts, « Genetic Race ? DNA Ancestry Tests, Racial Identity and the Law », *Columbia Law Review*, vol. 120, no. 7, 2020, p. 1929-2016.

[17] L'information médicale à caractère familial, article L.1131-1 du code de la santé publique.

[18] Des inquiétudes sur la cohérence du système peuvent être suscitées par la révision de la loi bioéthique en 2021 et ses dispositions sur les données incidentes notamment.

Par ailleurs, ces questions de tests génétiques en libre accès peuvent amener à toutes les questions qui ont été soulevées depuis que la génétique se développe, liées à la nécessité ou non de connaître ses données génétiques et, une fois qu'on les connaît, d'adapter son comportement à ces données. Cela conduit à s'interroger sur le développement éventuel d'un devoir de santé et la question de la mise en cause de la solidarité nationale dans la prise en charge d'un certain nombre de maladies. Mais le temps est trop court pour que je m'arrête sur ces points, on pourra y revenir après.

Les difficultés résultant de l'importance croissante du libre accès

Au-delà du principe même de ces tests, le déploiement de l'offre est venu mettre en évidence de nouvelles difficultés qui tiennent quant à elles aux conséquences du développement fulgurant de ces tests en libre accès ces dernières années. Et je vais malheureusement aller très vite parce qu'il me reste peu de temps. Il y a deux points importants que j'aimerais porter à votre attention : les interrogations en termes de souveraineté et ensuite celles relatives au fichage.

La souveraineté

En ce qui concerne la souveraineté, les entreprises comme *23&Me* ont au fil des années constitué des banques de données génétiques et de santé considérables qui, en réalité, sous-tendent leur modèle économique et leur permettent de mener à bien des projets de recherche, soit en interne, soit en collaboration avec des industries pharmaceutiques par exemple[19]. Il est très intéressant à cet égard d'aller lire les clauses contractuelles de ces sociétés. En 2019, la *MIT Technology Review* estimait que près de 26 millions de personnes à travers le monde avaient eu recours à un test de généalogie génétique[20]. Face à cette collecte massive de données génétiques et de données de santé grâce à des services complémentaires proposés par ces sociétés, les scientifiques du secteur ont pu appeler à ce que soit créées des bases de données nationales avec un accès ouvert à la communauté scientifique pour répondre à des enjeux de souveraineté et en particulier d'indépendance des États dans la recherche scientifique et la maîtrise des données de santé par rapport à ces sociétés privées[21]. Dans ce sens, on a eu une une évolution du cadre réglementaire avec notamment le règlement européen général sur la protection des données (RGPD)[22] et la loi de bioéthique de 2021 en France qui sont venus favoriser la collecte, la centralisation, l'accessibilité et la réutilisation des données de santé collectées dans un cadre médical ou dans un cadre de recherche scientifique pour alimenter la recherche scientifique. Cela a donné lieu à la constitution de grosses bases de santé en France. On a entendu parler du *Health Data Hub*, mais aussi du plan France médecine génomique 2025. Mais il y a aussi son homologue

[19] H.-C. Stoeklé, « La marchandisation des données génétiques », 28 avril 2016, espace-ethique.org ; C. Hecketsweiler, « Les données génétiques, une mine d'or pour les laboratoires », *Le Monde*, 18 janvier 2018 ; C. Lemke, « La compagnie de tests génétiques 23andMe a développé un médicament grâce à l'ADN de ses utilisateurs », *Sciences et Avenir*, 14 janvier 2020 ; « Du business autour des tests génétiques : 23andMe vend les droits d'un médicament », genethique.org, 13 janvier 2020.

[20] A. Regalado, « More than 26 million people have taken an at-home ancestry test », *MIT Technology Review*, 11 février 2019.

[21] C. Hecketsweiler, art. cit. ; dans le même sens, OPECST, Rapport sur l'intelligence artificielle et les données de santé – Compte-rendu de l'audition publique du 21 février 2019 et de la présentation des conclusions du 21 mars 2019, p. 8 ; v. dans le même sens, CCNE, *op. cit*., p. 29.

[22] Règlement (UE) 2016/679 du 27 avril 2016 relatif à la protection des personnes physiques à l'égard du traitement des données à caractère personnel et à la libre circulation de ces données, et abrogeant la directive 95/46/CE (règlement général sur la protection des données), JOUE 4.5.2016, L119/1.

européen, le projet *One Million Genomes*. On voit donc l'influence du développement de ces tests en accès libre sur les positionnements réglementaires en termes de collecte et d'accessibilité des données, notamment des données génétiques.

Le fichage

Un autre point que je vais évoquer très rapidement concerne le fichage. Et là, on passe plutôt à la généalogie génétique. La Cour européenne des droits de l'homme rappelle souvent que le fichage constitue en tant que tel une atteinte à la vie privée[23]. Or, dans ces entreprises de généalogie génétique, il y a une forme de fichage, ce qui n'a pas échappé aux autorités de police, en particulier américaines. Encore une fois, l'affaire est connue. En 2018, les services de police américains ont pu arrêter Joseph James DeAngelo, surnommé le Golden State killer, grâce à une recherche en parentèle menée dans une base de données génétique privée. Est-ce qu'une telle situation pourrait se trouver au sein de l'Union européenne ? À l'heure actuelle, le droit applicable à cette situation est la directive 2016-680 qui régit le traitement des données en matière de police[24]. Son article 4.2 précise que la réutilisation de données collectées à des fins autres que celles prévues par la directive est possible sous réserve de deux conditions cumulatives : le responsable du traitement doit être autorisé à traiter ces données à caractère personnel pour une telle finalité et le traitement doit être nécessaire et proportionnel à cette autre finalité.

Mais il faut se souvenir que les données génétiques sont en droit de l'Union européenne des données sensibles et donc que leur traitement est en principe limité. La directive prévoit ainsi en son article 10 que le traitement doit être autorisé par le droit de l'Union ou de l'État membre ou que le traitement doit porter sur des données manifestement rendues publiques par la personne concernée. Et ici, on peut s'interroger concernant les tests de génétique en libre accès, puisqu'un certain nombre d'entreprises prévoient dans leurs contrats la possibilité pour les autorités de police d'avoir accès à ces données. Est-ce qu'on peut donc considérer qu'elles ont été rendues publiques ? Par ailleurs, il y a des sociétés comme la plateforme *GEDmatch* qui mettent à disposition de leurs clients un outil *open source* qui permet le partage de toutes les données collectées. Là encore, est-ce qu'on peut considérer qu'il s'agit d'une publicisation des données ? Le Comité européen de protection des données s'est prononcé sur cette question et a insisté pour dire que, en s'inscrivant dans un réseau social, une personne ne réalise vraisemblablement pas que ces données sont accessibles aux autorités de police[25]. Donc *a priori*, le raisonnement est transposable aux tests génétiques en libre accès et pour l'instant la position est que les bases de données ne seraient pas accessibles aux autorités de police.

J'espère avoir réussi à vous montrer à travers ma présentation que l'on a un phénomène de bascule dans l'encadrement des données génétiques propulsé par le développement de ces tests en libre accès : c'est une bascule vers une forme d'utilitarisme, ayant pour objet une captation et une réutilisation

[23] V. par exemple CEDH, Aycaguer c. France, req. N° 8806/12 eu égard en particulier aux délais de conservation des données des différentes catégories de personnes susceptibles d'être fichées.

[24] Directive (UE) 2016/680 du Parlement européen et du Conseil du 27 avril 2016 relative à la protection des personnes physiques à l'égard du traitement des données à caractère personnel par les autorités compétentes à des fins de prévention et de détection des infractions pénales, d'enquêtes et de poursuites en la matière ou d'exécution de sanctions pénales, et à la libre circulation de ces données, et abrogeant la décision-cadre 2008/977/JAI du Conseil, JOUE 4.5.2016, L119/89.

[25] CEPD, Opinion on some key issues of the Law Enforcement Directive (EU 2016/680) - wp 258, p.10.

optimisées. On peut alors s'interroger sur les limites que cette bascule pourrait ou devrait rencontrer. Je vous remercie pour votre attention.

Les tests génétiques en libre accès sur Internet, ou de la banalisation du partage de l'ADN dans les plateformes bionumériques

Mauro Turrini

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Introduction : Les tests "Direct-to-Consumer" : panorama de la littérature en sciences sociales

Je remercie les organisatrices de cette rencontre. Afin de mieux situer mon approche, je vais tout d'abord vous donner un aperçu rapide de la littérature en sciences sociales sur les tests génétiques en accès libre. Je classe l'ensemble de ces études en trois groupes[1]. Le premier se concentre sur les implications médicales et ce que les utilisateurs, clients ou patients font de ces résultats. Les deux autres groupes partagent un intérêt pour la génétique personnelle qui dépasse la dimension strictement sanitaire de ce test, pour prendre en compte la construction sociale et culturelle de l'information génétique et ses conséquences politiques, économiques et juridiques. Ainsi, le deuxième groupe d'études s'intéresse davantage aux implications de l'information génétique pour l'action, les subjectivités et les identités sociales. Le troisième groupe d'études se concentre sur

[1] Mauro Turrini, « Online Genomes : Problematizing the disruptiveness of direct-to-consumer genetic tests », *Sociology Compass*, vol. 12, no 11, 2018, e12633.

les différentes façons dont les usagers interprètent et s'approprient les résultats de ces tests. Celles-ci donnent une vision beaucoup plus complexe de la génomique personnelle, ce qui nous permet de nous concentrer sur les pratiques émergentes. Je parlerai en particulier du *partage* des données génétiques personnelles, une pratique qui me semble paradigmatique du développement actuel de la génomique et de la diffusion de données personnelles de l'ADN dans la société. Pour conclure, je me pencherai sur le développement récent de la génomique personnelle et plus généralement de l'utilisation des tests de dépistage chez les personnes en bonne santé et m'efforcerai de voir s'il y a une dialectique entre génétique DTC (*direct-to-consumer*, c'est-à-dire en accès libre) et d'autres formes de génétique plus institutionnalisées.

Je voudrais commencer par remarquer que la génomique personnelle est une innovation tout autant sociale que technique. Je me réfère ici à la nouvelle vague de tests DTC, telle qu'on l'a connue à partir de 2007 en grande partie en Californie. La portée innovante de cette dernière vague de tests génétiques est multiple. Tout d'abord, ces dispositifs bénéficient des avancées technologiques dans le domaine, qui ont considérablement réduit le coût et le temps de production des données génétiques. Cela a permis de proposer des tests qui offrent une vision globale du génome (*whole-genome testing*, en termes techniques) permettant d'extraire de nombreuses informations sur les origines ethniques, sur la santé, sur les prédispositions de santé, etc. Il s'agit d'une première tentative, quoique rudimentaire, de médecine personnalisée, c'est-à-dire d'utiliser de grandes quantités de données individuelles pour affiner le diagnostic et le traitement de chaque patient.

Le second aspect, souvent insuffisamment pris en compte, est la convergence entre génomique personnelle et technologie numérique. À cet égard, il convient de rappeler que les entreprises qui avaient davantage misé sur un message médical – je parle notamment de *Navigenics*, *DecodeMe*, ou *Pathway Genomics* – ont échoué. En revanche, *23&Me*, qui a bien plus parié sur l'interaction *avec* les usagers et *entre* les usagers, en utilisant les techniques du web 2.0, c'est-à-dire tout ce qui est réseaux sociaux, forums, etc., s'est imposée comme un leader mondial. Les tests génétiques DTC représentent un champ d'investigation idéal pour les sciences sociales en tant que chantier de « biomédicalisation »[2], et notamment de l'usage des *big data* dans le domaine de la santé.

Le premier groupe d'études de sciences sociales qui, au début des années 2010, s'est penché sur les DTC n'a pas pris en compte les conséquences sanitaires de la convergence entre génomique et technologies de l'information. Ces études se sont plutôt limitées à étudier l'impact clinique des informations génétiques sur les usagers. Les problèmes mis en évidence tiennent à l'utilité clinique, à la validité analytique de ces tests, à la confidentialité des données, et, comme nous l'a rappelé Elsa Supiot, à l'absence de médiations médicales avant et après la réalisation du test. Cette approche a été dominante, en particulier dans la littérature en sciences sociales produites par des institutions médicales ou en collaboration avec elles. Et pourtant, à vrai dire, les revues de la littérature n'ont généralement pas montré d'influence significative des tests DTC sur les personnes testées, ni en termes d'anxiété ni en termes de changements notables dans leur mode de vie.

J'avais donc proposé d'aller au-delà de l'utilité clinique comme angle d'analyse, de se pencher sur d'autres approches dans les sciences sociales qui prennent en considération la manière dont

[2] Adele E. Clarke, Janet K. Shim, Laura Mamo, Jennifer Ruth Fosket et Jennifer R Fishman (dir.), *Biomedicalization : Technoscience, Health, and Illness in the U.S.,* Durham, Duke University Press, 2010.

l'information génétique est un processus socioculturel beaucoup plus vaste que le résultat que ces entreprises donnent à leurs clients[3]. Le thème central de cette approche est la relation entre information génétique et identité individuelle et sociale. Dans l'accent post-moderne mis sur l'autodétermination radicale de l'individu, la génétique personnelle peut donner une réponse convaincante tout en proposant une vision scientifique et objective de l'identité centrée sur l'essentialisme génétique[4]. Cela concerne en premier lieu les informations sur les origines ethniques, mais aussi celles sur la santé, sur laquelle certains chercheurs et chercheuses d'inspiration foucaldienne ont beaucoup travaillé, notamment Nikolas Rose, Alison Harvey ou, en France, Pascal Ducournau[5]. Dans ce contexte, la génétique personnelle est interprétée au sein du terrain de la « gouvernementalité néolibérale »[6]. La promesse de l'*empowerment* du patient, associée à la liberté d'accéder à ses propres données, ne serait rien d'autre que l'énième incitation à la formation de sujets qui se conçoivent et agissent comme des entrepreneurs d'eux-mêmes, ce qui, dans ce cas, prend la forme d'une gestion du capital de santé individuel à travers des stratégies de calcul des risques et d'optimisation de la santé et du bien-être.

Enfin, le troisième groupe d'études adopte une perspective plus proche des expériences et des pratiques des utilisateurs. La question qui se pose là est assez simple : qu'est-ce que font les usagers des résultats et des données des tests DTC ? Les auteur·es de ces travaux appartiennent aux *Cultural Studies, Media Studies*, aux études des sciences et des techniques (*Science and Technology Studies*) ou à la socio-anthropologie de la santé. Ils s'attachent à explorer les multiples facettes du processus d'échange, d'interprétation et de circulation de l'information génétique pour des usagers qui n'ont pas nécessairement d'expertise dans le domaine. L'une des hypothèses sur lesquelles reposent ces études est que les utilisateurs ne sont pas les destinataires passifs de l'information mais des acteurs qui participent activement à la construction de son sens et de sa valeur, notamment en la partageant hors ligne et en ligne.

Plateformes et pratiques du partage des données génétiques personnelles

Je voudrais maintenant examiner de plus près l'importance de la pratique du partage. Jenny Reardon définit le « libéralisme génomique » comme l'ensemble des « *[e]fforts to secure the meaning and value of human genome sequence data through creating a participatory, inclusive, and open genomics* »[7]. Dans le cadre du bon gouvernement libéral reposant sur une information librement accessible, la génétique semble incarner l'esprit le plus authentique des Lumières en faisant progresser un projet scientifique intrinsèque à un projet de société égalitaire fondé sur la participation et l'inclusion. En ce sens, le partage des données personnelles semble le mieux incarner le libéralisme génomique,

[3] Mauro Turrini et Barbara Prainsack, « Beyond clinical utility : The multiple values of DTC genetics », *Applied and Translational Genomics*, vol. 8, 2016, p. 4-8.

[4] A. Nordgren et E. T. Juengst, « Can genomics tell me who I am? Essentialistic rhetoric in direct-to-consumer DNA testing », *New Genetics and Society*, vol. 28, no 2, 2009, p. 157-172.

[5] Nikolas Rose, *The Politics of Life Itself: Biomedicine, Power, and Subjectivity in the Twenty-First Century*, Princeton, Princeton University Press, 2007 ; Alison Harvey, « Genetic risks and healthy choices : Creating citizen-consumers of genetic services through empowerment and facilitation », *Sociology of Health and Illness*, vol. 32, no 3, 2010, p. 365-381 ; Pascal Ducournau, *S'entreprendre avec ses gènes. Enquête sur l'auto-génétisation*, Rennes, Presses Universitaires de Rennes, 2018.

[6] Michel Foucault, *Naissance de la biopolitique. Cours au Collège de France (1978-1979)*, Paris, Seuil/Gallimard, 2004.

imaginant un avenir où chacun dispose de manière libre et autonome de son propre génome séquencé. Ces idéaux constituent un contrepoint culturel au modèle contemporain de développement de la génomique, où l'automatisation et la production accélérée de données vont de pair avec la capacité de générer des promesses de changement en médecine et d'attirer des capitaux financiers à haut risque. En d'autres termes, les idéaux liés à la diffusion de la génomique me semblent un symptôme de la recherche d'un consensus social à l'égard d'un modèle d'innovation bien spécifique.

Je vais rapidement cartographier cette pratique, en commençant par les partages de l'ADN hors ligne. Minna Ruckenstein, qui a travaillé sur le partage hors ligne, en particulier au sein de la famille, montre que l'interprétation de l'information génétique fonctionne comme un travail familial qui va de l'achat en commun (les entreprises ciblent souvent les ventes aux familles et leur réservent des remises spéciales !) jusqu'à la confirmation des liens de parenté établis culturellement, etc.[8]. Toutefois, l'espace par excellence du partage de l'information génétique est les plateformes numériques. Sur internet, l'ADN, tout en restant un ensemble d'informations liées et capables d'identifier un sujet spécifique, devient aussi un texte qui fait l'objet de représentations, d'exploration, de décryptage et de partage. Là, il est important de faire une distinction. D'une part, il existe des espaces généralistes, comme *YouTube*, *Facebook* et d'autres réseaux sociaux où l'information génétique est un prétexte pour construire des histoires de consommation et d'expérimentation. Anna Harris, Susan Kelly et Sally Wyatt, par exemple, analysent les vidéos que certains usagers de tests DTC publient pour partager leurs expériences et commenter les résultats. Elles définissent ces histoires des « autobiologies », c'est-à-dire des fragments autobiographiques qui se basent sur des informations médicales, biologiques ou, comme dans le cas présent, génétiques[9]. D'autre part, il existe des écosystèmes composés de multiples plateformes, logiciels en ligne etc., explicitement conçus pour échanger, décoder, partager l'information génétique - ce que j'appelle des « plateformes bionumériques ». Plus précisément, dans ces plateformes, il est possible de télécharger ses données génétiques et d'obtenir des rapports de santé, des représentations visuelles, des arbres généalogiques, des liens aux catalogues scientifiques des maladies génétiques, des cartes géographiques relatives à ses origines ethniques ou même à des « parents génétiques » plus ou moins proches.

Je vais maintenant me concentrer sur l'aspect qui m'intéresse particulièrement, à savoir les plateformes où il est possible de partager les données génétiques, souvent à côté de données cliniques, relatives à la santé, en proposant une généalogie du partage des données personnelles sur les plateformes dédiées à la génétique et la santé. Il ne s'agit alors plus exclusivement des DTC mais aussi d'initiatives non commerciales de génomique personnelle. Le *Personal Genome Project* (PGP) est ainsi le premier exemple d'une plateforme consacrée au partage des données génétiques. Lancée en 2005 sous l'égide de George Church, un gourou et un professeur de biologie moléculaire de l'université de Harvard, cette fondation à but non lucratif souhaite recruter un large groupe de participants et rendre leurs génomes publics sur le web. L'objectif est de conduire une expérience sur les conséquences de la renonciation à la protection de la vie privée en ce qui concerne le génome.

[7] Jenny Reardon, *The Postgenomic Condition Ethics, Justice, and Knowledge after the Genome*, Chicago, The University of Chicago Press, 2017, p. 7.

[8] Minna Ruckenstein, « Keeping data alive : talking DTC genetic testing », *Information Communication and Society*, vol. 20, no 7, 2017, p. 1024-1039.

[9] Anna Harris, Susan E. Kelly et Sally Wyatt, « Autobiologies on YouTube : Narratives of direct-to-consumer genetic testing », *New Genetics and Society*, vol. 33, no 1, 2014, p. 60-78.

Pour être recrutés, les volontaires devaient avoir un niveau d'éducation élevé et démontrer des connaissances de base en génétique et en bioéthique en passant un examen, être en bonne santé, ne pas être socialement et économiquement vulnérables. En bref, il s'agissait d'une pratique réservée à l'élite de l'innovation technoscientifique. Parmi les dix premiers participants, qui ont fait l'objet d'une couverture médiatique considérable, la plupart était des hommes blancs appartenant à la classe moyenne supérieure, à l'exception d'un homme afro-américain. Dans la presse, le fondateur George Church est décrit de manière héroïque, à l'instar des astronautes, voire en mobilisant l'une des figures fondatrices de la société états-unienne, celle du pionnier. Les participants au PGP prendront des risques pour eux-mêmes et pour leurs familles mais la société et leur famille en bénéficieront. Et pour la plupart d'entre eux, c'est une façon de voir leur rôle reconnu au sein d'une élite qui possède de forts intérêts économiques dans le développement industriel de la génétique. George Church lui-même est consultant auprès d'une dizaine d'entreprises de biotechnologie et très lié au secteur biotech. J'ai participé à l'un des colloques de l'association de référence de cette fondation. Ses membres se sont alors présentés d'une manière très identitaire, comme « PGP » puis leur numéro correspondant à l'adhésion à cette communauté. Faire séquencer son propre ADN est donc un véritable rituel d'initiation qui confère une qualification d'inclusion à ceux qui y participent.

Avec *23andMe*, le partage se démocratise mais aussi se commercialise. Cette plateforme encourage vivement ses usagers à interagir par le biais des données. On invite les usagers à se connecter entre apparentés génétiques, à construire des arbres généalogiques, à discuter sur les forums, etc., et le partage devient aussi une pratique quotidienne et apparemment sécurisée. Dans ce climat de collaboration et d'échange, l'entreprise demande aux usagers de donner leur ADN pour la recherche, en fournissant aussi des données cliniques accompagnées de brefs questionnaires. Un courriel envoyé le 2 juin 2023 aux clients de *23&me* affirme que 80% des clients ont donné leur consentement à participer à la recherche. En effet, *23&me* est maintenant la base de données la plus importante en termes de nombre de personnes – mais non en termes de qualité des données. De fait, ces données sont devenues l'un des *assets*, l'un des capitaux principaux de cette entreprise[10]. L'accès à cette base de données est au centre d'importants échanges économiques auxquels prennent part des entreprises biotechnologiques et pharmaceutiques.

Le dernier exemple est *LunaDNA*, une autre start-up californienne. Elle fait partie d'une nouvelle génération d'entreprises de génétique DTC, basées sur le *brokerage* des données génétiques, à savoir sur la récolte, la vente, l'utilisation des données personnelles de santé[11]. Fondamentalement, *LunaDNA* se présente comme une plateforme sécurisée sur laquelle les utilisateurs des tests génétiques DTC peuvent télécharger leurs données génétiques et cliniques afin de faire progresser la recherche biomédicale, mais aussi de recevoir une compensation économique sous forme d'actions de cette compagnie. C'est donc une manière de participer et de prétendre aux dividendes éventuels d'une start-up prometteuse issue de la Silicon Valley. En d'autres termes, la promesse est de devenir des *rentiers génomiques* du domaine florissant de la bioéconomie et de la biomédecine, sans avoir à débourser d'argent, mais seulement des données personnelles, génétiques et cliniques. Et bien que

[10] M Henri-Corto Stoeklé, Ninon Forster, Philippe Charlier, Oudy C Bloch, Christian Hervé, Mauro Turrini et Guillaume Vogt, « Le partage des données génétiques. Un nouveau capital », *Medecine / Sciences*, vol. 34, 2018, p. 735-739.

[11] Laura DeFrancesco et Ariel Klevecz, « Your DNA broker », *Nature biotechnology*, vol. 37, no 8, 2019, p. 842-847.

les discours soient très économiques, il y a toujours une référence aux valeurs publiques et aux liens sociaux. La devise de cette entreprise : *United for the Common Good*, « unis pour le bien commun ».

Le partage des données génétiques est donc une pratique complexe qui rappelle le pouvoir mobilisateur du libéralisme génomique. Un jour, tout le monde aura son génome séquencé, c'est sa promesse la plus séduisante. C'est là que ça marche très bien aux États-Unis. En Europe, ce n'est pas tout-à-fait le cas, notamment en France où ces tests sont tout simplement interdits. Pourtant, en Europe, nous ne sommes pas à l'abri des tendances que ces tests annoncent : celles d'un avenir où tout le monde aura son génome séquencé. Il faut donc penser la relation entre la génomique personnelle et l'institution médicale non pas comme une simple opposition entre deux modèles incompatibles et distants, mais comme une dialectique, dans le contexte de la fragmentation des institutions médicales entre le public et le privé. Je pense en particulier aux différentes formes de dépistage génétique qui se répandent aujourd'hui. C'est le cas notamment dans les domaines de la reproduction ou de la procréation assistée, où le dépistage embryonnaire est utilisé non seulement pour éviter la transmission de maladies génétiques à la descendance, mais aussi pour augmenter et accélérer la procréation. Enfin, il ne faut pas oublier des contextes bien intégrés dans la pratique médicale, comme celui de l'oncologie, où l'analyse génomique des tumeurs peut fournir des résultats concernant le patient et, par conséquent, sa famille. La diffusion du séquençage des données génétiques soulève un certain nombre de questions sociétales sur le modèle d'innovation scientifique et le modèle de soins de santé correspondant. Ces innovations sont-elles souhaitables et durables ? Quel type d'information mérite d'être pris en compte et communiqué ? Est-il juste de revendiquer le droit de tout savoir et tout partager ? Comment réguler les pratiques et les plateformes de partage des données génétiques et de santé ? Comment ce type de connaissance est-il compatible avec un système de santé que l'on peut qualifier d'universel et d'égalitaire ? Merci pour votre attention.

Questions et remarques

Serena Ciranna

Je commence par une première question. Trouvez-vous qu'existent des risques liés à ces tests qui sont spécifiquement liés à la convergence avec les données de masse ? Par exemple, avec la possibilité de *hacking* de ces données. Avez-vous rencontré dans vos recherches des éléments qui nous pousseraient à prendre en considération les risques liés à la convergence entre ces deux domaines ?

Mauro Turrini

Oui, malheureusement, du fait que le partage des données génétiques est maintenant habituel - en particulier dans les grandes entreprises DTC des États-Unis. Il y a aussi une idéologie de l'*open access* qui va dans le même sens que les DTC, notamment avec le *Personal Genome Project*, ou d'autres plateformes comme *Open Humans*[12] ou *openSNP*[13]. Ces différentes plateformes partagent la culture de l'accès libre, les mêmes valeurs de communisme du savoir, comme l'appelait Merton. Mais dans ces cas-là, c'est clair qu'il y a une friction, non pas avec le système de la propriété privée, mais plutôt avec la protection de la confidentialité. La confidentialité est le principal point conflictuel de ces initiatives de sciences ouvertes. À cet égard, le PGP, qui est un projet scientifique sans but lucratif,

[12] https://www.openhumans.org/ (dernier accès 24 avril 2024).

[13] https://opensnp.org/ (dernier accès 24 avril 2024).

part de l'hypothèse qu'il est maintenant impossible de défendre la confidentialité des données. Ce n'est même pas la peine d'essayer parce qu'à l'avenir, il sera impossible de défendre quoi que ce soit.

Serena Ciranna

C'est très intéressant, merci. En effet, je vois un peu la même perception et le même rapport que ceux qu'on a en général aux données numériques. Une sorte de fatalisme, parfois, par rapport à la possibilité de les contrôler. Cela semble s'appliquer aussi aux données génétiques issues de ces tests, et cela me fait aussi penser à la question de la propriété. Elsa Supiot, à l'égard de la propriété des données génétiques, est-ce qu'on pourrait parler d'une propriété non pas personnelle mais collective, c'est à dire comme un patrimoine, disons, de l'humanité ? Et comment utiliser la notion de responsabilité comme levier pour un usage plus constructif et prudent ? Existe-t-il des approches qui voient dans la question de la propriété des données génétiques une question collective plutôt que personnelle ?

Elsa Supiot

Oui, il y a eu tout un mouvement de réflexion en ce sens au niveau européen et au niveau français, en tous cas, sur les limites de la propriété à l'égard des données et des données personnelles. Cela inclut bien entendu les données génétiques. Avec deux constats. D'abord le caractère assez inefficace de l'idée de la reconnaissance d'un droit de propriété individuelle sur les données, et ce pour différentes raisons. Notamment, vous l'avez dit, parce que la protection des données personnelles, qui est maintenant organisée par le RGPD, reconnaît un certain nombre de droits aux individus, mais l'effectivité de ces droits reste encore assez limitée dans la mesure où ils sont difficilement actionnables par les personnes. Par ailleurs, les données prises individuellement - cela rejoint ce dont vous parliez plus tôt - vont avoir une valeur économique relativement faible. Ce qui est intéressant, c'est l'accumulation de données sur de nombreuses personnes et la possibilité de croiser différentes bases et sources de données. C'est cela qui est très lucratif. Dès lors, la question des données comme bien commun, et en particulier des données génétiques comme bien commun, a effectivement été débattue mais, à ma connaissance, se heurte pour l'instant à la problématique des brevets. En effet, il y a derrière toute la question de la propriété comme mécanisme d'incitation à la recherche. Les équilibres et propositions sur ce point ne sont pas encore stabilisés, mais des réflexions sont en cours.

Serena Ciranna

Merci. Vous avez d'ailleurs tous les deux parlé des aspects positifs de ces tests, dont on entend souvent parler plutôt de manière un peu alarmiste. Vous avez souligné l'effet de propulsion de la part de l'industrie. Peut-on en outre voir une sorte de vertu dans le fait de récolter des données génétiques par des tests en accès libre ? Cela peut-il constituer malgré tout une source de connaissance collective, et en ce sens quelque chose de positif?

Elsa Supiot

C'est en tous cas le parti pris d'un certain nombre de projets, me semble-t-il. Ainsi, dans le plan France médecine génomique 2025, il y a une collecte de données qui vise certaines pathologies, comme les cancers et les maladies rares, mais sans hypothèse de recherche préalable. Ainsi, la collecte de données se fait avec l'idée que l'accumulation de ces données et l'utilisation d'algorithmes va permettre de révéler des hypothèses qui pourront par la suite être ou non confirmées. Y-a-t-il une vertu à proprement parler ? Je ne sais pas. En tout cas, il y a, me semble-t-il, l'idée qu'il est important de disposer d'une grosse masse de données, même si l'on ne sait pas a priori ce que l'on va en faire, parce que plus on aura un nombre important de données, plus on sera susceptible, par corrélation, par l'utilisation de l'intelligence artificielle, d'identifier des pistes de recherche concrètes. On inverse l'ordre.

Serena Ciranna

Merci. Je vois qu'il y a une question dans le public : pensez-vous que les données génétiques doivent être traitées comme une catégorie séparée des données de santé dans le contexte du *European Data Space* ? Je pense qu'il s'agit plutôt d'une question juridique.

Elsa Supiot

Je ne sais pas si c'est une question juridique mais ce qui est sûr, c'est qu'on a maintenant des textes européens qui définissent les données génétiques. La définition des données génétiques est distincte de celle des données de santé. Ceci étant, il me paraît assez délicat de séparer complètement les deux parce que les données génétiques vont être, au moins pour une partie d'entre elles, à l'origine de pathologies qui, elles, constitueront des données de santé. En fait, avec certaines informations relevant de la catégorie de données de santé, on a des informations qui sont des données génétiques et vice versa. Donc matériellement, on pourrait les séparer au sens où on pourrait avoir un enregistrement du séquençage d'un côté, et les données biologiques, biochimiques de l'autre. Mais ce n'est pas comme ça qu'on enregistre les données de santé. Dès lors, compte tenu de la manière dont on les enregistre pour l'instant, sur le plan technique et aussi dans la définition même des données de santé, je ne sais pas si on peut vraiment dire de manière satisfaisante qu'on peut les séparer. C'est en ce sens que je ne sais pas si c'est une question juridique.

Mauro Turrini

Je peux rebondir sur la question des *big data*. Dans le contexte de la génomique, cet engouement pour la production des données, comme l'ont très bien montré, par exemple, Kaushik Sunder Rajan ou Jenny Reardon[14], a largement été fonction du développement industriel de la génomique comme secteur très automatisé, très puissant d'un point de vue technologique, un secteur qui a fait de l'accélération de la production et de la circulation des données sa mission, sa priorité. En tant que sociologue, on voit que ça ne correspond pas à ce que les populations demandaient, lorsqu'elles ont été interrogées à propos de projets génomiques. La question qu'ont les non-experts, c'est une question assez simple mais fondamentale : *cui bono* ? Qui profite de tout cela ? Avec la génomique, il y a un peu l'idée, telle qu'elle a été énoncée par exemple par Watson au début des années 2000, de créer des bases de données énormes - qui par ailleurs ne sont pas si représentatives que ça parce qu'elles sont beaucoup centrées sur des personnes d'origine européenne - et de laisser aux générations futures la tâche d'interpréter ces informations, sans savoir exactement que faire de ces informations. Donc cet engouement pour la production massive de données, souvent, ne correspond pas aux demandes de la population ni même aux exigences de la recherche. Par exemple, quand on étudiait un secteur assez pointu comme celui des maladies multifactorielles, des chercheurs importants dans le champ nous ont dit : en fin de compte, la génomique ne sert presque à rien, on continue à faire la génomique parce qu'il y a des généticiens, qu'on a des machines pour séquencer, donc on continue, mais on n'attend pas grand chose de la génomique. Après, je ne veux pas préjuger de projets comme France Génomique 2025 car je ne le connais pas assez mais, de manière générale, il faut adopter une approche prudente

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[14] h Kaushik Sunder Rajan, Biocapital : *The constitution of postgenomic life*, Durham: Duke University Press, 2006 ; J. Reardon, *The Postgenomic Condition, op. cit*

à l'égard des promesses suscitées par les grandes bases de données.

Serena Ciranna

Merci beaucoup. Il y a deux questions dans le public que je veux mentionner rapidement et auxquelles je vous propose de répondre pendant la table ronde. D'abord, à qui appartiennent les données génétiques en fonction des pays ? Ensuite, l'impossibilité d'accéder à ses origines en cas d'adoption sous X en France ne pousse-t-elle pas à faire des tests à l'étranger ? L'interdiction devient-elle quelque chose qui pourrait pousser à acheter des tests à l'étranger ?

Discussion générale : d'une biotechnologie à l'autre, comment développer une sagesse collective ?

Anne Le Goff

Nous allons maintenant passer à une table ronde qui vise à mettre en discussion les technologies dont nous venons de parler aujourd'hui, les tests génétiques en libre accès, ainsi que d'autres biotechnologies sur lesquelles ont porté les séances précédentes, à savoir la modification du génome à partir de la technologie CRISPR et les organoïdes. Nous sommes ravis aujourd'hui d'avoir parmi nous certains des intervenants des dernières séances. Cependant, il n'y a pas besoin d'avoir assisté à toutes les séances pour participer à la discussion. La première séance a été consacrée à une technologie très récente, très discutée, celle de CRISPR et de la nouvelle génération d'outils de modification du génome. Avec notamment Nertila Kuraj, avec nous aujourd'hui, qui a examiné les applications de ces technologies à l'agriculture. L'un de nos objectifs aujourd'hui est aussi de réfléchir à différents types d'applications. Durant cette séance, on a discuté de la technicité de cet objet qui tend à conduire à des discussions limitées à des experts scientifiques ou réglementaires et pose la question de savoir comment un groupe élargi de personnes, comment la société peut s'emparer de ces questions. On a notamment évoqué l'organisation européenne ARRIGE, qui s'efforce de développer une gouvernance mondiale pour cette technologie et qui pourrait fournir un modèle applicable à d'autres technologies.

La seconde séance a été consacrée aux organoïdes, avec notamment des interventions de Bernard Baertschi et Hans-Georg Dederer, qui sont avec nous aujourd'hui. Et là, on s'est intéressé en particulier à la réglementation applicable aux organoïdes en général, dont on a vu qu'elle mêlait des niveaux nationaux et européens avec la question de savoir comment s'articulent ces différents types de réglementation. Et on a considéré les questions qui se posent à propos de certains organoïdes qui ont une potentialité particulière, en particulier les embryoïdes - organoïdes d'embryon - et les organoïdes cérébraux, avec la question de leur statut à la fois moral et légal.

Je vais commencer par lancer une première question, puis mes collègues et l'ensemble du public sont invités à poser des questions, notre objectif étant de penser ces technologies de manière transversale, puisqu'elles posent beaucoup de questions communes, et d'envisager leurs différences.

Avec ces diverses technologies, l'implication des individus et des patients est essentielle pour produire des données génétiques qui vont être utilisées par les entreprises. C'est le cas également pour les organoïdes, dont la production scientifique et le modèle économique, avec les biobanques, sont fondés sur le développement de l'utilisation de tissus donnés à la recherche. Il semble y avoir une forte ambiguïté sur le fait de savoir qui a la propriété de ces matériaux et données biologiques et de ce qui en est fait par la suite. Pensez-vous qu'il y a là une difficulté nouvelle par rapport aux biotechnologies du passé ou aux autres technologies, une difficulté qui imposerait une réflexion à la fois éthique et juridique d'un type nouveau ? Je m'adresse à tous nos intervenants, ceux d'aujourd'hui et des séances précédentes, n'hésitez pas à prendre la parole.

Bernard Baertschi

Dans ce que j'ai entendu aujourd'hui, j'ai été frappé comme vous par la question du caractère public des données ou des échantillons biologiques parce que, pour les organoïdes, c'est un souci. L'organoïde, évidemment, c'est un échantillon biologique donné par le patient. Ce n'est pas tellement la question de la propriété qui est cruciale, parce qu'en Europe, on n'a pas un système juridique où l'on est propriétaire des parties de notre corps, mais c'est de savoir ce qui va en être fait. On peut penser, en ce qui concerne les organoïdes justement, que tous ceux qui donnent leurs cellules, par exemple leurs cellules souches pour faire un organoïde de foie, ne seront pas forcément d'accord pour qu'on en fasse un organoïde d'embryon ou un organoïde de cerveau. Il faut donc poser la question du consentement et celle de son ampleur. En outre, ces cellules deviennent quasiment immortelles, y compris le patrimoine génétique qui est contenu en elles. On retombe alors sur la question du caractère public et de la confidentialité relative aux données génétiques. Donc, en résumé, les organoïdes mêlent deux questions : une vieille question qui est simplement celle de l'échantillon biologique, qui n'était pas un trop grand problème quand on ne s'occupait pas de génétique et qu'on n'en faisait pas grand-chose, et puis toutes les nouvelles potentialités dues à la fois à la génétique et aux bases de données.

Sonia Desmoulin

Pour rebondir sur ce que vous venez de dire, Bernard, ce que je trouve très intéressant, c'est qu'on a tendance à aborder les choses soit sous l'angle de la propriété, avec le tropisme culturel étasunien qui paraît ici assez prégnant, soit sous l'angle du consentement, comme vous venez de le faire. C'est-à-dire qu'on n'arrive pas à sortir d'une logique assez individualiste malgré tout, puisque c'est la question de savoir qui est propriétaire ou qui consent. Cela me fait beaucoup réfléchir, en tant que juriste française, et notamment avec l'éclairage de ce que nous a dit Elsa Supiot, sur cette tentative du législateur français d'intervenir en amont du déploiement de ces tests génétiques. Même si 2011 n'est pas très tôt, c'était un moment où le marché n'était pas aussi développé qu'aujourd'hui. Or le législateur est mis en quelque sorte face à la difficulté de maintenir un discours d'interdiction dans un contexte de pratiques en complète contradiction avec ce discours. Pourtant, le législateur était dans une posture où il cherchait justement à sortir de cette logique purement individualiste de la propriété, de l'appropriation, des droits "sur"..., c'est-à-dire une alternative à l'approche propriétaire mais qui reste une approche individualiste. J'avoue que cela m'interroge beaucoup sur les manières de concevoir cette sagesse collective à partir du prisme individualiste qui est peut-être devenu quasi exclusif.

Elsa Supiot

Je trouve cela très intéressant : en vous écoutant, je me dis qu'effectivement la logique est assez commune. Je n'ai peut-être pas été claire tout à l'heure parce que j'ai répondu à la question de la propriété. Mais en ce qui concerne les données et les données génétiques, la logique au niveau de l'Union européenne n'est pas du tout une logique de propriété non plus. C'est une logique qui a plutôt trait au consentement, ou en tous cas à un certain nombre de droits qui sont organisés pour être informé de ce qui va être fait, de la manière dont c'est utilisé, etc. C'est vrai qu'en vous écoutant, je me disais que c'est comme si on avait développé ce modèle-là en miroir de ce qui a été fait pour les échantillons biologiques. En effet, il existe un certain nombre de dispositions qui permettent la réutilisation et la réaffectation des échantillons biologiques, normalement avec une information ou un consentement, mais il y a des dérogations. Ce serait intéressant d'aller regarder d'un point de vue historique l'évolution progressive ou l'élargissement actuel de cette logique, avec des arguments qui sont des arguments plutôt collectifs de recherche, de promotion de la santé, au sens de santé publique,

d'une mise à disposition, en tout cas de possibilité d'accès et d'utilisation, si je comprends bien tant pour les organoïdes que pour les données génétiques, qui se dispensent du consentement et qui échappent à la question de la propriété, mais qui soulèvent néanmoins la question de la contrepartie. Cela ne va pas forcément être une contrepartie individuelle, mais la question demeure de savoir, si on met à disposition ces ressources-là, dans quelle mesure la collectivité qui les a mises à disposition va en retirer elle aussi un bénéfice, notamment dans ses rapports avec l'industrie pharmaceutique privée.

Mauro Turrini

Oui, je suis tout à fait d'accord avec Sonia et Elsa. En tant que sociologues, nous parlons souvent du contrat social, en évoquant par exemple l'ouvrage de Richard Titmuss sur la donation du sang. Il y avait derrière l'idée de citoyenneté liée au *welfare state*, à l'État-providence, donc une idée de contrat social. Je me réjouis d'entendre des juristes qui cherchent aussi à aller au-delà d'une approche individualiste qui, pas plus d'un point de vue pratique que d'un point de vue politique, ne me semble pouvoir rendre vraiment justice au partage des données. Ce qu'il faudrait faire, c'est repenser le contrat social qui existe derrière ces échanges, reprendre la consultation citoyenne, tout en réfléchissant à une recherche scientifique qui est de plus en plus industrialisée et entrelacée avec des intérêts économiques puissants.

Bernard Baertschi

J'aimerais ajouter un point : le consentement peut être lié à la propriété, dans la mesure où je consens qu'on fasse quelque chose avec ce dont je suis propriétaire. Il faut bien voir - moi, je suis un individualiste – que la question de base, puisqu'on a parlé de contrat social, c'est John Locke qui l'a posée au 17ème siècle en disant qu'on est propriétaire de son corps. Ce qu'il voulait dire, c'est que ce n'est pas l'État qui est propriétaire de nous-mêmes, c'est que, si nous ne sommes pas propriétaire de notre corps, alors il faut soit que quelqu'un d'autre le soit et cela, personne n'en veut, personne ne veut être la propriété d'autrui. Peut-être que le modèle de la propriété n'est pas un modèle adéquat et qu'il faut en trouver un autre. Évidemment, les questions dont nous débattons nous y confrontent. Y compris pour le consentement. Pour préciser ce que j'ai dit à propos de la question du consentement concernant les organoïdes, c'est qu'à partir du moment où ils ont été modifiés, on ne peut plus revenir en arrière (c'est-à-dire retirer notre consentement) et ils font en quelque sorte partie du domaine public. Donc il faut trouver un moyen de faire en sorte que les gens restent néanmoins en maîtrise de leur corps et de ce qui leur appartient, pour éviter que cela ne leur échappe et ne tombe dans un domaine public, avec tous les abus possibles lorsque nos données génétiques peuvent être accessibles. C'est là l'idée du consentement et de l'autonomie. Bref, il importe de maintenir les droits individuels, tout en permettant en même temps de faire un usage social de ces données, pour le bien de tous.

Elsa Supiot

Si l'on prend ces évolutions, on peut voir aussi, si l'on veut être un peu pessimiste et critique, une forme d'utilitarisme, c'est-à-dire qu'on met en place des dispositifs pour capter malgré ou indépendamment de la volonté des individus, et servir un certain objectif. Je me demandais si l'on retrouvait cette même logique un peu utilitariste en ce qui concerne l'utilisation de CRISPR-Cas9 en matière environnementale et dans les utilisations de la génétique animale et environnementale.

Nertila Kuraj

I had a similar comment about how to compare the question of ownership of genetic data when it comes to "CRISPR-ed" microorganisms or plants. Actually, where CRIPSR is concerned, we already have a codified and contractual form of ownership, namely patents. Genetically modified

microorganisms or plants are patented. We had a clear example of how important patents are in this area with the patent battle between UC Berkeley and the Broad Institute for the application of CRISPR to all human cells. This application was not originally patented by Berkeley. This controversy was a multimillion dollar battle that was settled between the parties by dividing the patents between them. This was a crucial issue in the agricultural and microorganism sector. So, the idea was to tie ownership to the result. One thing is the ownership of the technology or of data, and another thing is the ownership of the results of the technology. The agriculture sector is a step ahead of genetic data. In the genetic sector, my impression is that we are collecting data in order to potentially use it to cure genetic diseases or design medical devices that are not currently available. But when it comes to CRISPERed microorganisms and plants, we already have the applicability of the technology that leads to a product. So it's a bit different. I think that the common aspect to consider is that in both cases we see that it is extremely important to consider societal values when it comes to ethics, acceptability, and using technology for the common good. But then it's different when it comes to concrete ownership, depending, for example, on the stage of market readiness of the technologies. It seems to me that we are at different stages. Patents are the answer to who owns the technology and the data in the CRISPR field.

Ilana Löwy

Je voulais attirer l'attention sur deux choses. Je me demande où l'on met la solidarité dans ce débat. Le problème de la solidarité, ça veut dire le problème du bien public mais reformulé comme une question de solidarité. Deuxième chose, juste une remarque : je suis d'accord sur la question des brevets. Mon collègue Maurice Cassier vient de publier un très beau livre, qui montre que les brevets de médicaments pourraient être autrement, que les brevets comme on en a aujourd'hui ne sont pas simplement donnés[1]. On peut reconfigurer la notion de brevet d'une manière radicalement différente et beaucoup plus adaptée aux questions de bien public et de solidarité.

Une autre question que j'ai : j'ai l'impression que ce débat se déroule principalement en supposant plus ou moins une égalité entre tous les pays, mais je pense qu'il y a parfois des différences extrêmement importantes dans la manière dont différents pays traitent cette question à cause de traditions culturelles et sociales différentes. Par exemple, les Américains sont très férus de tests diagnostics préventifs, et les Français beaucoup moins. Donc c'est peut-être quelque chose à considérer.

Sonia Desmoulin

Merci. Pour rebondir sur ce qui vient d'être dit et finalement dans l'esprit de TESaCo, qui est d'essayer de comprendre comment une sagesse collective (malgré les discussions qui ont pu avoir lieu autour de cette expression) peut surgir, il y a l'idée de déterminer un champ - un moment aussi, mais d'abord un champ peut-être - de ce dont on doit discuter. Et ce qui m'a frappée au cours de nos trois sessions, c'est que revenait régulièrement la question de la comparaison et de la nouveauté éventuelle des objets et des questions que l'on traitait. À propos de l'édition du génome, c'était la question de savoir si l'on était encore en réalité dans le cadre des OGM ou non - et on a très bien vu qu'il y avait aussi des enjeux économiques derrière cette discussion. À propos des organoïdes, on a beaucoup discuté de la question de savoir si l'approche par les tissus, par les échantillons, par les organes suffisait ou non à saisir les questions qui étaient posées. Et puis, aujourd'hui, on s'est posé la

[1] M. Cassier, *Il y a des alternatives : Une autre histoire des médicaments (XIXe-XXIe siècle)*, Paris, Seuil, 2023.

question du côté des dispositifs médicaux de diagnostic *in vitro*, avec ce constat que la réglementation relative à la mise sur le marché saisit des problématiques de sécurité, éventuellement de fiabilité, mais non des problématiques suffisantes d'information. C'est d'ailleurs aussi quelque chose qu'on rencontre en matière d'intelligence artificielle dans le champ médical, avec le problème des logiciels d'aide à la décision médicale. Dès lors, je m'interroge sur la manière dont on mobilise, implicitement ou non, des critères pour construire cette comparaison. Finalement, sur quoi est-ce qu'on s'appuie pour dire que : pour penser les organoïdes, il faut d'abord penser les embryons, il faut d'abord penser les organes ; pour penser l'édition du génome, il faut d'abord penser les OGM…, alors que certaines choses sortent de notre cadre d'analyse parce qu'on n'a pas pensé à la comparaison. C'est une question assez générale, mais je trouve transversale par rapport aux différents exemples qu'on a évoqués.

Bernard Baertschi

Juste un mot. Ce que vous venez de dire, Sonia, me rappelle la vieille méthodologie casuistique qui consiste à trouver des paradigmes dans lesquels on est relativement à l'aise (ici, le statut de l'embryon) puis, quand on doit déterminer le statut d'entités nouvelles (ici, les organoïdes d'embryons), on essaie de les comparer pour voir ce qui est semblable et ce qui est différent. C'est la même chose pour le brevet, c'est la même chose pour la propriété. Je pense qu'il est assez naturel de raisonner comme cela.

Sonia Desmoulin

Mais est-ce que cela ne rabat pas la nouveauté sur des questions déjà évoquées ? Est-ce qu'au contraire, c'est une méthode très utile parce qu'elle permet de cerner ce qu'il y aurait de véritablement nouveau ? Et est-ce qu'il faut se limiter à ce qu'il y a de véritablement nouveau, au risque de passer à côté d'enjeux socio-économiques qui visent à systématiquement valoriser les aspects nouveaux pour des raisons diverses et variées, mais notamment pour échapper plus ou moins aux cadres réglementaires déjà mis en place ?

Nertila Kuraj

I agree that focusing on comparative aspects can be very helpful, especially when we are dealing with technologies that are highly technical and very tedious questions of how to regulate them, their acceptability, and so on. When it comes to GMOs, for example, it's a clear fact in the legal field that there is this process versus product divide between the United States and the European Union. And people think that this has always been the case. So, if you don't do a comparative analysis, you think that this has always been like that, that Europe has a process-based approach, and the US a product-based approach. But if you compare the development of the technology prior to the development of the regulatory approach, you can see that initially, before the benzene case[2], the US was much more precautionary in its chemical regulation. And in its very early stages, in the aftermath of Asilomar, the EPA adopted a very process-based approach. Other factors that we consider in our comparative approach, such as acceptability, social norms, the approach to risks and so on, went into the regulatory process. And there have been changes, this is not a linear process. It continues to diverge and to change, and each of the two main paradigms continues to influence the other. I think it is very useful to keep this in mind and adopt a historical approach in order to understand how to move in the future as well.

[1] *Indus. Union Dept. v. Amer. Petroleum Inst.*, 448 U.S. 607 (1980).

Elsa Supiot

Oui, j'allais partir sur le même terrain que Nertila. C'est-à-dire que quand je vous écoutais, Sonia et Nertila, je pensais à l'histoire et aux raisons pour lesquelles il est important de continuer à enseigner l'histoire et de s'intéresser à l'histoire comme élément de réflexion et de compréhension des événements contemporains. Cela me semble naturel. Certes, il va y avoir la question du "toutes choses équivalentes par ailleurs", et et j'entends ce que tu pointes, que ce "toutes choses équivalentes par ailleurs" doit en lui-même être examiné, parce qu'on risque sinon de passer à côté de certaines problématiques en les considérant comme étant par principe semblables. Mais il me semble néanmoins que c'est non seulement naturel mais aussi, au moins dans un premier temps, extrêmement fécond que de procéder à ces comparaisons.

Soraya de Chadarevian

Building on this, I wonder, how does this process even start? Who starts the discussion of whether something is a new emergent technology? Emergent, new, we have already made a lot of judgments - that something is new and emergent. If you think about what system we want to put in place, who is it, what mechanism starts the discussion? Historically, we have seen very different cases. With Asilomar, it was the scientists. In other cases, it's the legal system. We heard at an earlier roundtable that in France there is an automatic system to review these laws every seven years, while in Germany there is nothing like that. Hans-Georg Dederer said that in Germany the parliament does not take up these cases, perhaps because they are too controversial. So, my question is about the process: what process do we put in place to identify and address emergent technologies?

Hans-Georg Dederer

I am sorry that I don't have a precise answer to this important question. I agree that it all depends on the circumstances, that is, the technology, but also the time and the discussions at the moment when a new technology emerges. Who takes up the technology and the surrounding discussions about its risks and benefits? I think it is right to say that this can be very different in different cases. In the case of genetic engineering, it was first the scientists, see the Asilomar conference. And probably, to some extent, in the case of brain organoids, it was also scientists, at least when they talked to members of ethics committees. The ethics committees may have started to think about what the ethical problem might be, the moral problem of constructing brain organoids, for example, and using them in different scenarios. It could also be the legal system. For example, in 1989, a ruling by the Higher Administrative Court of Hesse in Germany held that genetic engineering was equivalent to nuclear energy, which was nonsense from a scientific perspective at the time and still is nonsense. What you should understand is simply that the general impression of this emerging new technology that was called genetic engineering was that it was as dangerous as nuclear energy technology, and for that reason it could only be used on the basis of a new law enacted by the Parliament. This is why, a year later, the Parliament adopted the Genetic Engineering Act, and the European Community (at the time) also adopted two directives on genetic engineering. I think that the situation is very often specific to each country, state, or population.

Nertila Kuraj

I agree with Hans-Georg's answer. The debate about who decides about a new emerging technology, what are the priorities to discuss, this debate centers on how to diversify the pool of stakeholders or actors that should take up this issue. Of course it is context-dependent, country-dependent, and for a country like the US it may be the media as well. We saw the case of the Theranos start-up in Silicon Valley. Of course, it was a disaster and a fraud and the people behind it were sentenced to jail. It

is also an example of how a new technology, or issues that pertain to certain technologies, can be brought to the attention of the general public through high-level journalistic investigation. Sometimes that happens in Europe, but I don't think it's comparable to the American level. And of course, scientists have a prominent role in discussing the risks of the technologies, as we saw with Asilomar, although we know that there is criticism of the Asilomar model as well. As Erwin Chargaff said, scientists getting together to discuss the risks of a technology is like incendiaries forming their own fire brigade. The point is that we should always try to diversify and broaden the circle of stakeholders and actors involved in this debate, which, according to several commentators, was not done with the two global summits on CRISPR for human gene editing. Again, as with Asilomar, there is a very polarized discussion about whether the summits really provided a diverse, open, transparent, or participatory debate about this technology. So, I feel we are still trying to answer the question of who should initiate the discussion.

Mauro Turrini

These are deep questions and I don't know if I could answer them properly, but, I think, as a sociologist, I would say that the political system and institutions play a pivotal role, especially in the regulation of biomedical devices, and emerging technologies in the field of healthcare. It should also remind us of the role of society and politics in shaping the kinds of technologies we have. For example, as Ilana said, there is more than one way to put patents into practice. I think it is very important to use this comparative approach to develop a collective wisdom about biomedical innovation and to remind ourselves of the importance of political institutions, regulatory frameworks and cultural values and aspirations in shaping these technologies. For example, I have just done exploratory research in Spain on DTC testing. It's interesting to point out that, today in Spain, according to the law, the tests shouldn't be allowed. But they are, because it is a legal gray area and no one has taken action against these tests. And it's true that the issues in Spain are completely different from those in the United States, where these companies promise to revolutionize the way medicine is practiced. Spanish DTC companies look like a sandcastle : an entrepreneur creates a website, not even a platform, to advertise these products online, in Spanish, then they send all the biological samples to the European subsidiary of the Beijing Genome Institute in Denmark and, finally, they give the results to the patient. These are very small companies trying to jump on the personal genomics bandwagon. Many of these Spanish entrepreneurs don't have any idea about biological science, they have a very naive vision of genetics, and they are just jumping on this bandwagon that seems promising. So, I think that a comparative and historical approach to DTC genomics can be very helpful in understanding our own imaginations about DNA, as well as to see the importance of political institutions and collective action in shaping the future biomedicine. We should try to avoid thinking in a fatalistic way, as we're used to, especially when we think about the field of genomics and its developments. The promise that one day, everybody would have their genome sequenced the first day, is very common and is presented as a major biomedical advance. When you are born, we will sequence your DNA. Why is that? You can do a lot of things on the first day of your life. Why should genomics be like a destiny? I don't see the reason from a scientific, medical point of view. So, maybe, our goals as scientists should be to question the construction and to try to participate in the construction of the imaginaries of the future.

Ilana Löwy

I agree with Mauro. But, Mauro, I have news for you. I don't know if you saw, Robert Green just published an article in the *American Journal of Genetics* about the BabySeq project, explaining why everybody has to have their genome sequenced on their first day of life. They argue that the

BabySeq program is a wonderful thing and that it's got a lot of advantages - it so happens that the main advantage is for the BRCA gene but OK. Seemingly it's a great idea according to its promoters.

The other thing that I wanted to say is that I studied mostly prenatal diagnosis and technology like this. While you focus on upstream, one piece of advice is to look a little bit downstream too. Because what happens once these technologies are allowed? We forget about them, and I think it's not a great idea. For instance, with drugs: a drug gets IMA authorization for marketing and then everything ends there. And then what happens? What is happening in France at the level of the *Haute Autorité sanitaire* ? What is happening in the uptake of tech by hospitals? What is happening with the uptake of tech by people? Here, for example, I saw huge differences in the ways techs are shaped by all these downstream, and not only upstream, aspects. Then it became interesting to follow up and see whether users were those who were predicted and whether catastrophic elements were not exaggerated or, on the contrary, whether things were used in the way that they shouldn't be although it was allowed.

Nertila Kuraj

Thinking about this comparative aspect, I was in Brussels at a conference about the agritech sector in 2023. It was clear from all the presentations that new gene editing technologies were the future, and that with the Spanish presidency we would move forward with reform. At least that was what people from the political institutions said. And then, in an informal discussion with a very high-level expert from the Commission, I was struck by his concept of comparison. He was saying that we are too late with adopting GMOs, look at the US, they have been using them for fifty years now, they are not dead, so we should go ahead with the reforms, we should allow them. Then, I started explaining a little bit about the uncertainties, the risks, and he was like, okay, I was not aware of this. So there are different ways to use comparative approaches, and I think that politics has a responsibility to foster a very well informed and useful comparative approach. Not just to say the US has been using it for fifty years and nothing has happened.

My second observation was about another conference where everybody was promoting CRISPR technology. We should be thinking upstream but also downstream, and in a more systemic and holistic way. Because CRISPR or genetic testing is not a system, it's just a tool. So, there is the question of how certain tools are going to be used, which in our case are new and emerging technologies that have a lot of ethical issues, a lot of uncertainties, and a lot of potential. For example, how genetic testing is going to be used within the healthcare system, or within data protection or privacy laws, how CRISPR or organoids are going to be used within the healthcare system. We need to be careful that these don't become equated with the larger systems in which they operate. For example, genetic data is not a substitute for a certain healthy lifestyle, diet, and so on. The same goes for CRISPR in the agriculture sector.

Sonia Desmoulin

Je voudrais maintenant remercier tous les intervenants et tous les participants. Leur dire que l'ambition d'essayer de saisir et de réfléchir sur la comparaison entre les différents exemples est immense, et donc que toutes les volontés et toutes les analyses sont utiles, même si l'on se restreint au champ des biotechnologies. Et que même si les questions peuvent paraître profondes et qu'on peut avoir l'impression à titre individuel de ne pas être en position d'offrir les éclairages utiles parce qu'on a plutôt envie de parler de l'exemple qu'on a étudié, cela me paraît être un exercice à la fois très stimulant et nécessaire pour éviter d'être dans une approche en silos où l'on travaille technologie par technologie. Et donc merci beaucoup d'avoir participé à ce moment TESaCo avec nous.

Daniel Andler

Merci Sonia, tu as très bien parlé. C'est vraiment le projet TESaCo. Je te remercie beaucoup de l'avoir dit.

Anne Le Goff

On s'est concentré sur les biotechnologies et on n'a pas eu tellement le temps de tirer des fils de comparaison avec les autres technologies dites émergentes aujourd'hui, comme l'intelligence artificielle ou les avancées en robotique. Notre objectif dans ce groupe de réflexion est aussi de mettre ces technologies en discussion. Nous vous remercions pour ces discussions et espérons pouvoir les poursuivre dans d'autres contextes.