Rethinking Health Innovation: Towards a Plural Ethical Approach

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«Ethics of Health Innovation» Group

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November 2020

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Introduction

What the COVID-19 crisis has revealed in terms of health innovations

The pandemic has been dramatic in bringing to the forefront the profoundly complex nature of health crises - simultaneously medical, scientific, social, ecological, economic, and political -, what health is, and what we need to do to take care of it.

Knowledge of the genetics of viruses meant that from January 2020 a molecular test could be developed to diagnose the disease and monitor the circulation of the virus. This knowledge, together with knowledge in immunology, has rapidly paved the way for the development of numerous vaccines and the first clinical trials. Knowledge of the epidemiological dynamics of past viruses and know-how in modeling and simulation have made it possible to offer predictions of the epidemic's evolution to aid strategic and political decision-making. Antiviral drugs or immune response regulators have constituted a pool of molecules for clinicians to draw from in order to urgently propose the first treatment protocols and launch clinical trials to evaluate their efficacy. Diagnostic, therapeutic, and preventive solutions that fall within the scope of technoscientific biomedical innovations have thus contributed to the strategies for fighting and preventing the disease. **However, the nature of these innovations has rarely remained strictly medical or scientific.** The difficulties in deploying and stabilizing PCR testing strategies have shown to what extent the questions of logistical organization, personnel authorized to take samples, which groups to test as a priority, ability to ensure case-contact tracing, and the effective isolation of carriers of the virus… are key to the success of test-based missions to control the epidemic. Similarly, the lack of national and international coordination between the multiple clinical trials of treatments has profoundly affected the ability to enroll sufficient numbers of

participants to confirm or invalidate their efficacy. Finally, the deployment of fast-track licensing procedures and the massive pre-purchase announcements by governments have been critical in reducing the development time of the first vaccines. **The continued simultaneous scientific, technical, medical, political, economic, and social dimensions of biomedical innovations have been clearly updated.**

In parallel to this, **innovations of a more strictly organizational nature** have emerged as being important. Alongside the technical and logistical prowess in transferring ventilated patients over long distances and relieving saturated intensive care units located at the epicenters of the epidemic[1], more silent innovations, the initiatives of frontline players, have proven to be decisive. Many doctors' offices have reorganized their procedures so as to receive, in separate circuits, those patients suspected of having COVID and those that are not. At a higher level of complexity, some organized care structures (health centers, multidisciplinary group practices) have rolled out initiatives making it possible to both receive suspect cases with the best guarantees of hygiene and to organize the home monitoring of patients discharged from hospital for a given territory, going as far as organizing oxygenation or palliative care at home. These initiatives have often been fostered by the existence of territorial professional health organizations ("Communautés professionnelles territoriales de santé [CPTS]") based on relationships of trust forged over the long term. **Innovation has also been social**, with the humanitarian community having stepped up its outreach activities and having increased, sometimes considerably, its food aid. Associations for social and cultural mediation have endeavored to help many populations that are isolated from information and any understanding of what is going on to live with lockdown or protection measures that are difficult to apply in their daily context. Other solidarity structures have organized themselves to provide or produce masks and protective clothing. Not to mention the extensive resourcefulness shown by the local authorities in addressing the most pressing needs of their citizens[2].

In terms of drug innovation, the vast majority of the clinical trials launched have been based on the **principle of repurposing** and combining existing treatments[3] rather than

1 Prowess whose relevance has been criticized, with the argument that better regulation of regional healthcare provision would have made it possible to provide care at a lower cost.

2 Vanessa Schneider. Chez les maires, le virus de la solidarité. Le Monde, October 17, 2020, p24-25.

3 https://neurosciencenews.com/coronavirus-drug-candidates-16141/ An international team of researchers has tested more than 10,000 compounds to identify six drug candidates that may help treat COVID-19. + Essai Discovery

evaluating new ones[4] On a more day-to-day level, the improved prognosis of the most severe forms of the disease has essentially been based on the rational use of the habitual resuscitation techniques (quality of mechanical ventilation, mastery of extracorporeal circulation techniques) and on the use of traditional anticoagulants. At the same time, **open source collaborative engineering** initiatives, driven notably by FabLabs, have made it possible to put together protective visors quickly and cleverly.[5]

Therefore, what we are talking about is a combination of differing and complementary forms of innovation that have been and continue to be mobilized. Diversity in terms of the players involved, the knowledge and know-how they mobilize, but also the targets of their actions: these are the questions to which answers must be found. This epidemic period encourages us to broaden our views and unlock our perceptions of what is covered by the concept of innovation, which has become such a driving force in our societies in general, and in the health research fields in particular.

The starting points for our reflection on the ethical issues of innovation

These observations have fueled the reflection on the ethical challenges of innovation that we at the IEC initiated two years ago. While Inserm's priority objectives include support for an ambitious innovation policy[6], and while the links between research produced in its laboratories and innovation continue to be reinforced, we feel that it is important to also approach innovation through the prism of our committee's ethical questions.

The recent scandals surrounding the exorbitant prices of a series of "innovative drugs" to treat cancers or rare diseases[7], whose development had benefited greatly from work carried out in public research laboratories, including those of Inserm, raise major ethical questions from the moment these prices impose the selection of eligible patients and threaten the economic balance of our social protection model.

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4 An emblematic example of this is the validation of the therapeutic value of dexamethasone.

5 https://theconversation.com/les-fab-labs-apportent-des-solutions-concretes-et-locales-a-la-crise-du-covid-19-136277 ; http://www.fablab.fr/actualites/article/tribune-collective-makers-contre-le-coronavirus

6 https://www.inserm.fr/sites/default/files/2017-11/Inserm_PlanStrategique_2016-2020.pdf

7 Zolgensma for the treatment of spinal muscular atrophy, with a unit cost announced by Novartis of 2 million euros; https://www.medecinsdumonde.org/fr/actualites/nos- combats/2019/12/16/novartis-renonce-au-brevet-du-kymriahr

In parallel, at a time when society as a whole is questioning its mode of existence, the sustainability of its economic and social system and its compatibility with respect for the environment, questioning the forms of innovation made possible by the knowledge produced in laboratories and their consequences, seems unavoidable. What is the environmental cost of these innovations? Beyond the immense hopes for improved life expectancy and quality of life, often presented in a very generic way, we must also ponder the question of access to innovation. Do these innovations help reduce social and regional health inequalities or, on the contrary, increase them? Are they limited to the solvent markets of the Western countries, or do they also aim to meet the neglected needs of populations in the Global South?

In France, where the financial cost of healthcare is largely covered by national solidarity, innovation can only be considered a right if it is precisely defined and evaluated, including from an ethical perspective. As proposed by the French National Consultative Ethics Committee (CCNE) in its opinion no. 101 (2007), "Ethical issues as a result of budgetary constraints on public health expenditure in hospitals"), *"To arrive at a more considerate and respectful practice of medicine, this trend for 'technology overkill' must be challenged"*.

At what price should innovation be sought? How can we promote innovation without jeopardizing our social protection system? Is innovation always a source of progress? But what progress are we talking about? Is innovation not to the detriment of other processes? Is innovation not in reality multifaceted? Are there not choices to be made? What are the values shared by the different ways of innovating? Who are the players likely to influence the definition of the issues that we seek to resolve through innovation? What worlds and what possibilities does an innovation bring? What are the social and environmental costs of an innovation? Can we encourage more frugal modes of innovation? Innovation for whom? For what? What is the ethical approach to questioning innovations?

In order to provide some elements of response to these questions, this Memo consists of two parts. In the first part, we will **re-examine the meaning of innovation, its various social functions in our society and the perceptions of it**. We will argue for **a more open conception of what can and should count as innovation**. It is about peeling back the layers of the representations and perceptions that obscure the essential nature of innovation to enable its questioning from the ethical viewpoint. In the second part,

we will **reflect on the conditions likely to favor this deployment of the perception of health innovation, by discussing the increased visibility of the variety of existing practices, evaluation criteria and endpoints for innovations**, how to choose and assign priority to innovations and measures to support diversification of the forms of innovation, enabling better preservation of and respect for health, with an objective of equity, sustainability, and environmental innocuousness.

(I) Re-examining the meaning of innovation

(A) What is innovation?

There is an essential element to bear in mind before going any further with our definition of innovation. Innovation has had the tendency to become a very strong social value in our contemporary societies. Being qualified as innovative, whether we are talking about an entrepreneur, a public policy, or a shampoo, has very positive connotations, something that the sphere of marketing has long since understood. For many players, innovation represents a singular and quite unchallenged objective, which deviates from or replaces the search for *progress* in the sense of the Enlightenment[8]. The view of innovation is therefore distorted and lends itself very little to critical examination.

Conceptual approach

Borrowed from the Late Latin *innovatio,* meaning renewal, the verb "to innovate", in the dictionary of the Académie française, is defined as the introduction of something new into a use, custom, belief, scientific or philosophical system. It differs from invention in that it reorganizes human needs and brings about economic and social transformations[9].

Since the turn of the 20th century and the beginnings of industrial pharmaceutical

8 A definition was recently proposed in a report by the French Parliamentary Office for Scientific and Technical Assessment (OPECST), namely: "*the art of integrating the best state of knowledge at a given time into a product or service in order to meet a need expressed by citizens or society*". According to this definition, innovation is a moment in the process of creating economic value in society. And in fact as such, it corresponds to the meeting of three
indissociable but distinct factors: **scientific knowledge**, **technological improvement** and the **socio-economic dynamics** of modern societies.

9 Innovation et histoire, une critique philosophique, Quadernir. Autumn 2016, p.91 and following; Philosophie et innovation, Thierry Ménissier, Revue philosophique 2011 : 18, varia. p.10

production, innovation in the medical field has been associated with tension between the need to experiment and the protection of the rights of the experimental subject. After the *Richtlinien*[10] (1931), the Nuremberg Code (1947), and the Belmont Report (1979), a series of laws (Huriet-Sérusclat Law, December 20, 1988 and following in France) came to regulate medical research practices. At the same time, health monitoring procedures and the marketing of therapeutic innovations have been subject to regulatory and legal frameworks (European Medicines Agency [EMA], French National Agency for the Safety of Medicines and Health Products [ANSM], French National Authority for Health [HAS]). The system governing these innovations combines evaluation of the therapeutic value they provide with control of associated risks. Under this regulatory regime, biomedical innovations are first and foremost understood in their dimensions as technoscientific objects.

Innovation in economic policies

Beyond these conceptual and regulatory approaches, **innovation is nowadays a central concept in economic policies**. According to the work of Joseph Schumpeter, it is analyzed as a driver of economic growth. Moreover, the close links between innovation and scientific research help to nourish the idea that the **ideal of social progress conveyed by research would mechanically shift towards the innovation that results from it**. **Basing growth on innovation would thus be tantamount to producing economic growth at the service of social progress.**

In France, the Investment Plan for the Future (PIA) launched in 2009 had set itself the objective of *"boosting long-term growth potential based on the knowledge and innovation economy.* " It has contributed to a certain number of *"re-compositions of the university and research system, aimed in particular at associating research, training and economic stakeholders more closely, to promote competitiveness, business creation, growth and employment, and finally, to better respond to new societal challenges.* [11]" More recently, the French Ministry of Higher Education and Research launched its *"France Europe 2020 Strategic Agenda*[12] *for research, transfer and innovation"* which *"intends to restore*

10 Bonah, Lepicard, Roelcke. 2003. La Médecine expérimentale au tribunal. Editions scientifiques Gordon Breach

11 Inserm 2020 Strategic Plan

12 https://www.enseignementsup-recherche.gouv.fr/cid71873/france-europe-2020-l-agenda-strategique-pour-la-recherche-le-transfert-et-l-innovation.html
Text of the plan: https://cache.media.enseignementsup-recherche.gouv.fr/file/Strategie_Recherche/26/9/strategie_nationale_recherche_397269.pdf

research to its role as the main vector for the creation of knowledge and know-how and assert its place as a lever for France's recovery".

Health is high on this Agenda and is one of nine societal challenges: *"Health is a strategic vector of economic and social development, both through our fellow citizens' expectations in terms of controlling the vicissitudes of health – upon which wellbeing and personal fulfilment depend, and through the economic activity that results from it."* **The health sector embodies this near-magical quality ascribed to innovation, which must both improve life expectancy, quality of life and wellbeing for the greatest number of people AND contribute to the country's economic competitiveness**.

However, this promise is regularly jeopardized. As Stiglitz and Greenwald summarize, *"Innovative societies do not always have the greatest social wellbeing, since there is a trade-off between immediate consumption (wellbeing) and future consumption"*[13]. This tension between today's realities and tomorrow's promises is particularly evident in the health field. The *Manifeste pour l'innovation en cancérologie [Manifesto for innovation in oncology] (2017)*[14], an initiative supported by Roche, regretted that "*the healthcare system continues to be managed and run, more like a machine to produce care, than a system designed and facilitated to stimulate innovation and have it benefit the greatest number.* " This formulation sums up a vision that pits care - healthcare today - against innovation - understood as a process of improving, above all technologically, healthcare for tomorrow.

This approach, in which innovation is most often referred to in the singular, is in fact based on a differentiation between different types of innovations, distinguished according to a certain evaluation of their economic utility. The concept of **disruptive innovation** was popularized by US economist Clayton Christensen[15] to designate a technological innovation able to enter a market at a cheaper price, often due to its lower quality and the invisibility of some of its environmental costs. Initially less profitable, it ends up – by enabling new uses – replacing the dominant technology on a market. Cell phones and their applications are disruptive innovations *par excellence*: their spread has gone hand in hand with the near disappearance (major weakening) of travel agencies, record stores and mapmakers. According to this model, disruptive innovations are

13 Stiglitz J.E. and Greenwald B.C. 2017. La nouvelle société de la connaissance. Ed. Les liens qui libèrent. p.150

14 https://www.roche.fr/fr/leader-pharmaceutique/responsabilite-societale/rse/systeme-sante/avise-innovation-cancerologie.html

15 https://www.newyorker.com/magazine/2014/06/23/the-disruption-machine

sought after insofar as they are market game-changers and sideline historical competitors. In this sense, they are in contradiction with **so-called incremental innovations**, for which it is sufficient to optimize what exists already, or simply render it available, without disrupting market organization. **It is interesting to note that the equitable distribution of economic impacts is not one of the primary qualities expected from these disruptive innovations.**

There are winners and losers in this.[16] For example, in changing the very nature of the work required, this type of innovation often seeks a less skilled and therefore lower-paid workforce. In societies where the cost of human labor is a major limiting factor, reducing both the duration and qualification of the work allows for savings, but the human cost of such a strategy in both the short and long-term is enormous. In addition, the reduction of the knowledge and know-how built up by the fabric of players destroyed by the disruption is likely to hamper the capacity for adaptation and innovation over the longer term.

This distinction between disruptive and incremental innovation has largely permeated research and innovation policies. This is how, as its president, Pascale Augé, explained to us, Inserm-Transfert, an Inserm subsidiary responsible for supporting value creation and innovation, is positioning itself *"in support of disruptive and long-term innovations, as opposed to other value creation players which support innovations with more immediate market opportunities"*[17]. It is obvious that the concept of disruptive innovation in this setting is quite different from the one promoted by Christensen. The disruption here is expected from the close links that innovation maintains with the findings of more fundamental research conducted in Inserm's laboratories, and from which it is hoped that an answer to an unmet health need will be found or at least a net shift with the available solutions. **However, the use of identical terminology cannot be entirely neutral, as innovations described as disruptive** - irrespective of the precise meaning of this term - **carry a positive aura and the strong promise of success**. It favors an approach to disruption as an end in itself, overshadowing essential questions about the nature of the needs targeted or the social, environmental, or economic consequences. This insistence on disruptive innovations alone also reflects a largely technoscientific appreciation of innovation and a **relationship with the value of innovations in which value is defined by their economic effects on markets**. Market value alone, however, is an imperfect indicator

16 Stiglitz J.E. and Greenwald B.C. *Ibid* p.166

17 Interview with Pascale Augé, director of Inserm Transfert, May 16, 2018

of healthcare value. As the Ermes Committee pointed out in an opinion from 2008[18], it is important that "*financial value creation in health should serve value creation in health and not the other way around*".

(B) Perceptions, drivers, and effects of the primacy given to the "all-disruptive" approach

In this context, **disruptive innovations produced by research laboratories are primarily seen as being based on the development of products or new technologies**. In the field of health, new molecules, new treatments, new medical devices, new algorithms, etc. are primarily concerned.

This **circumscribed material dimension** is astonishing in that it can in some instances have very large-scale effects. It lends itself particularly well to communication operations and to promises. There is often only one step separating the disruptive from the sensational.

It also enables the production of marketable goods and services. In fact, the current legal framework for the protection of intellectual property applicable to health products is particularly suited to this concept of innovation. Thus defined, **the innovations can in most cases be the subject of patent filings and benefit from the resulting protection regime.** By ensuring a monopoly over the exploitation of the innovation for a fixed period of time, patents are nowadays a decisive factor in attracting the interest and investment of private players. And in most areas of healthcare - with the notable exception of blood products - the intervention of industrial players is necessary in France for the conduct of some of the development phases required to obtain marketing authorization for this type of innovation. Patent portfolio size and composition is an important indicator of the activity of the institutions in charge of biomedical value creation. It is important to emphasize here that this legal and economic framework is the result of a series of political developments that in many countries have led to bringing drugs, health products, and some biotechnologies into the realm of patents and to encouraging research institutions to file them.

Historically, this has not always been the case. In France, patents on medicines remained prohibited until 1959[19].

18 https://www.inserm.fr/sites/default/files/2017-10/Inserm_Saisine_ERMES_Metagenex_2008.pdf
19 M. Cassier. 2004. Brevets pharmaceutiques et santé publique en France : opposition et dispositifs spécifiques d'appropriation des médicaments entre 1791 et 2004. Entreprises et histoire n° 36 : 29-47

This particular concept of innovation irrigates the health economy more broadly. The funding of hospitals through activity-based pricing is based in part on this primacy of technological innovation, considered to be "disruptive". The cost of a molecular diagnostic test, when presented as a kit sold by a private company, is easier to quantify than that of a care pathway requiring the intervention of several professionals, part of whose care work is invisible. In addition, spending on high-tech equipment and machinery is considered an investment. Looking to the future, they can benefit from ad hoc funding. Concerning the salaries of healthcare professionals, these are included in the operating expenditures, considered as costs on which cost control efforts must weigh. In addition, randomized clinical trials constitute a methodological framework for calculating a drug's therapeutic value (SMR) and facilitating the definition of a market value. Costs are more difficult to calculate for more integrated, human labor-intensive care mechanisms.

Finally, **this conception of a form of innovation that is above all disruptive and remarkably effective** has fueled the idea in France that all patients should have access to the latest available innovations, quickly and without economic hindrance, because they are considered to be "game-changers". This inflationary principle, which is similar to the "**right to benefit from innovation",** tends however to constrain the conditions for a rigorous evaluation of the effects of these products and their prices[20]. However, while there are innovations that have indeed radically modified treatment - imatinib/Glivec for chronic myeloid leukemia, sofosbuvir for hepatitis C - many others have had less impact and have now become part of the range of treatments available for a given disease, and **in fact constitute very largely incremental innovations**.

This priority given to disruptive innovation is now **pushing up the prices of innovations**. Unlike countries such as Brazil[21] or Cuba, France has for a long time opted to delegate the industrial development capacities of biomedical-technoscientific innovations to the private sector. With its emphasis on the **development of molecules and technology, the disruptive approach reinforces the role of private market players in innovation**. It also goes hand in hand with an **increase in risk-taking** in the development of innovations - the products tested are, in principle, far removed from existing solutions -; with the **transformation of pharmaceutical industry models** -

20 C. Le Galès. 2018. Evolution, déterminants et régulation des dépenses de médicaments en France. Médecine/sciences. 34 :83-86

21 Cassier M. and Correa M. 2010. Brevets de médicament, luttes pour l'accès et intérêt public au Brésil et en Inde. Innovations. n° 32 :109-127

product innovation through startup buyouts rather than in-house development - ; and with an **increased reliance on the financial markets -** to finance such risk-taking. These changes contribute to the exorbitant prices of certain innovative drugs, which are not correlated with the development costs actually borne by the manufacturers and which are also partially covered by public research. These exorbitant prices are currently a major concern, insofar as they are **liable to endanger our social protection system**.

This strong dependence on the private players purveyors of the "all-disruptive" approach evidently impacts the types of innovations produced or not produced. Decisions about which research findings to invest in to produce innovations depend highly on the financial returns expected. Compounds or technologies associated with a prospect of monopoly exploitation (notably through patents) are favored. On the other hand, the clinical evaluation of non-patentable molecules or the adaptation of drugs to better meet the needs of insolvent populations (pediatric dosages, dosage forms appropriate for specific material conditions, etc.) are difficult to undertake. The establishment of non-profit projects, such as the international Drugs for Neglected Diseases Initiative (DNDI)[22] is based on precisely this observation. The DNDI develops suitable treatments for diseases with "no market" (sleeping sickness, leishmaniasis, Chagas disease, etc.) based on molecules whose patents have expired or whose development has been stopped by manufacturers, develops pediatric formulations, tests new drug combinations, etc.

This difficulty based on the needs of populations to prioritize developments corresponding to public health issues while considering issues of access from the viewpoint of price or the adaptation of dosage forms, constitutes one of the blind spots of an innovation model that is too highly focused on disruption: the difficulty of taking into account the economic, social and environmental context of innovations and the diversity of needs. Does an effective but financially inaccessible drug constitute real progress?

The aim here is **not to deny the essential nature of disruptive biomedical innovations in improving health**. The aim is to emphasize the health **consequences** of an **approach to innovation in which this model is held up as a dominant ideal,** to the detriment of other approaches. While the discovery of antibiotics was a major

22 https://dndi.org/

innovation, advances in hygiene and nutrition have also had significant effects on health. In other words, the idea is to **encourage the re-opening of the perception of what can and should count as innovation, in order to propose an ethical approach, based on health needs in their diversity - from curative treatments to health promotion, including the prevention of disease and disability -** and the multitude of possible approaches to try to meet them.

(II) Promote a plural approach to innovation

(A) Re-open the perceptions of innovation: reveal and encourage the multifaceted nature of innovation

Health innovations can take on a wide variety of forms depending on the needs targeted, the constraints considered, the players involved, the knowledge mobilized, and the resources available. But they do not all have the same visibility or enjoy the same prestige. **Reaffirming the importance of considering health innovations in their diversity involves making these different approaches visible (material innovations / formal innovations)**.

a) Material innovations

1- Broaden curative innovation approaches

The repurposing of molecules, available in the public domain, whose toxicity measurements are known, **constitutes an innovative approach particularly suited to certain contexts.** Thus, there is nowadays in France a national chemical library[23] [24] over 75,000 molecules, many of whom are patent-free, which is the result of a collaborative effort launched by pharmacochemists at the end of the 1990s to add value to the various compounds available here and there in their research laboratories. In addition, hospital clinicians are accustomed to prescribing drugs outside of their marketing authorization (MA) for indications for which no satisfactory solutions exist. **However, this repurposing is generally of little interest to private pharmaceutical players which**

23 Florence Mahuteau-Betzer. 2015. Chimiothèque Nationale Avancées et perspectives. *Médecine/Sciences 31 : 417-22*.
24 https://chembiofrance.cn.cnrs.fr/fr/

are looking for economic profitability[25]. They also attract less interest in a research world acculturated to disruptive approaches, which are easier to showcase in publications. This lack of interest also has repercussions on public funding for clinical research, which is more difficult to obtain for this type of development. **All in all, therefore, the current model of molecular innovation leads to these pathways being under-explored.** Yet, the aforementioned experience of the DNDI demonstrates the relevance of these strategies in producing innovations that meet real health needs. They also constitute an approach that allows us to maintain a fertile ground of "latent solutions", which can be mobilized more quickly when needed.

2- Combining prevention and care within the same innovation

Adapted physical activity (APA) is nowadays an important tool for dealing with the increase in chronic conditions (cardiovascular diseases, obesity and diabetes, respiratory diseases, certain types of cancer, etc.). In this context, preventing disease complications, recurrences, exacerbations, and worsening has become a major challenge. In 2019, the preventive and therapeutic impact of physical activity in patients with chronic diseases was the subject of an Inserm Collective Expert Review[26]. **Four diseases were studied in sufficient depth to provide the scientific evidence for prescribing APA as a first-line treatment before any drug intervention**: mild to moderate depression, type 2 diabetes, obesity, and peripheral artery disease.

The existing health economic literature further indicates that these exercise programs to treat chronic conditions are favorable interventions from an economic evaluation perspective. For example, for peripheral artery disease, vascular rehabilitation based on walking and specific gymnastic exercises is more cost-effective than endovascular treatment. Another example, remote rehabilitation following conventional cardiac rehabilitation, with the sending of semi-automatic emails or text messages, has also been evaluated as being cost-effective; if the rate of readmission to hospital is taken into account in the model of care.

25 However, this profitability can become attractive when the pricing mechanisms allow it. Thus, in the United States, the costs of indomethacin suppositories, used to prevent pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP), can amount to a few hundred or even thousands of dollars. https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2762701

26 Inserm. Physical activity. Prevention and treatment of chronic diseases. Montrouge : EDP Sciences, 2019 : 805.

What is more, the impact of these diseases depends highly on the economic situation of the patients. In the most underprivileged quintile of the population, standardized hospitalization rates are 35% higher and mortality rates 50% higher than those of the most privileged quintile[27]. The difficulty for the most fragile or vulnerable groups to initiate or maintain long-term physical activity (elderly patients, social precarity, etc.) is one of the factors explaining these disparities. The prescription of APA therefore requires that protocols be adapted to take into account the patient's constraints and living conditions, which affect their capabilities[28].

All in all, **the implementation of APA, reimbursed by national solidarity, presents itself as an innovative approach, complementary to the prescription of conventional drug treatments, for both treatment and supportive care**. It forms part of the arsenal of responses needed to deal with the human, economic and societal cost of the increase in chronic diseases, with a view to contributing to the reduction of social inequalities in health.

Health innovations can also be nested within health promotion measures that aim to give people educational tools to improve their own health and within prevention measures that directly counteract social and territorial health inequalities[29].

3- Innovating to promote health

One of the most topical examples of an innovation to promote health is the deployment of a **new logo to inform people about the nutritional quality of products: Nutriscore**. Developed to help consumers choose foods with a better nutritional quality at the point of purchase and to incentivize manufacturers to improve the nutritional quality of their products, Nutri-Score is a front-of-pack label that uses 5 colors. It provides information on the nutritional quality of food products: from category A (dark green) indicating higher nutritional quality to category E (dark orange) indicating lower

27 Lecoffre C. Mortalité cardio-neuro-vasculaire et désavantage social en France en 2011. *Bull Epidémiol Hebd* 2016 ; 20-21 : 352–8. Lecoffre C. Hospitalisations pour maladies cardio-neuro-vasculaires et désavantage social en France en 2013. *Bull Epidémiol Hebd* 2016 ; 20-21 : 359–66

28 In his Capability Approach, economist Amartya Sen proposes to improve people's lives by developing their capacity to meet their basic needs. See C. Longuet, A.-M. Moulin, M. Botbol-Baum, M. Brodin, S. Fenet, F. Hirsch and I. Remy-Jouet. (2018) From informed consent to negotiated consent.Inserm Ethics Committee Memo.

29 A distinction is made between health promotion that is "the process of enabling people to increase control over, and to improve, their health" and prevention actions that are defined as "all measures aimed at avoiding or reducing the number and severity of diseases, accidents, and disabilities" (WHO definitions).

nutritional quality. The colors used by Nutri-Score are attributed on the basis of Food Standards Agency nutrient profiling system, modified version (FSAm-NPS) scores, which reflect the nutritional profile of foods according to their content (per 100 g) in terms of energy, sugars, saturated fatty acids, sodium, protein, fiber and fruit and vegetables. A number of studies published in international scientific journals have shown the validity of the FSAm-NPS score in characterizing the nutritional quality of food products as well as the efficacy of Nutri-Score in guiding consumers towards more nutritious choices. In particular, links between the consumption of foods whose FSAm-NPS scores indicate higher nutritional quality (reflected in higher Nutri-Scores) and better health have so far been observed in France (SU.VI.MAX and NutriNet-Santé cohorts), the United Kingdom (Whitehall II and EPIC-Norfolk cohorts) and Spain (SUN cohort). A recent study shows that people who consume on average more foods with FSAm-NPS scores indicating lower nutritional quality, presented higher mortality (total mortality and mortality linked to cancer and diseases of the circulatory, respiratory, and digestive systems)[30]. **Nutriscore[31] is based on long-term research** in nutritional epidemiology, according to the best international standards. **The innovation here lies in the production of a simple communication medium based on this research, its validation by the public authorities and its mass distribution** through the mobilization of consumers and certain manufacturers. **Health promotion involves the ability to influence consumer behavior -** emphasis on the role of nutritional quality in health, the ability to make choices simply - and **on that of the food industries**, encouraged to review the composition of their products to comply with consumer demands and scientific recommendations promoted and endorsed by public authorities.

b) Formal innovations: innovating in methods of care

In the domain of primary care - basic care provided by outpatient care providers - the combined effect of the development of chronic diseases, the unequal distribution of healthcare professionals across the territory, hospital transformations, the fragmentation of care provision and the new emphasis on prevention, contributes to justifying **the need to strengthen and reorganize the existing structures**[32]. This

30 Association between nutritional profiles of foods underlying Nutri-Score front-of-pack labels and mortality: EPIC cohort study in 10 European countries
BMJ 2020; 370 doi: https://doi.org/10.1136/bmj.m3173 (Published 16 September 2020)
31 https://presse.inserm.fr/consommation-daliments-ultra-transformes-et-risque-de-maladies-cardiovasculaires/35086/
32 Hassenteufel, Naiditch and Schweyer. 2020. Les réformes de l'organisation des soins primaires : perspectives multi-situées. Revue Française des Affaires Sociales. N°1 :11-28

context has led to **experimentation with new organizational models** over the past few years, supported by the public authorities[33] and also driven by the professionals themselves: multidisciplinary group practices, territorial health communities (CPTS), new flat-rate funding methods to promote teamwork, etc. Here, **innovations, based on the international literature in the field of primary care research, focus on care coordination mechanisms, the sharing of tasks and responsibilities among professionals, and patient participation methods[34]**. They integrate new financial, professional, and technical instruments, in a **movement deployed incrementally, on several levels, and in a differentiated manner depending on the territories**.

The examples mentioned here obviously do not exhaust the diversity of forms of health innovation. They can also involve **improving the quality of care and making better use of existing medical techniques and devices,** through the creation of conditions of accessibility to proven treatments for remote populations[35] or by authorizing people other than health professionals to use rapid diagnostic tests, as was the case for HIV/AIDS under pressure from the non-profit world... **However, these examples illustrate the variety of these practices and the needs they address, from patient care and health promotion to disease prevention.** They are based on various cost structures. While the disruptive innovation development model, associated with the current structuring of the pharmaceutical industry, generates products at exorbitant prices, according to a rather opaque accounting logic - to which costs precisely are its prices associated? What proportion of this is financial value creation? - these alternative approaches to **innovation generally have more distributed costs**. This includes funding clinical research (repurposing); the development of protocols, regulations, and the organization of APA sessions; epidemiological research, data collection, and the production of standards for Nutriscore. In many ways, these innovations are more labor-intensive and use less technology. In this sense, they can be described as more frugal.

33 Obled L, Townsend A. and Lemaire N. 2020. Innover dans la conduite de projets d'expérimentation d'initiative nationale : quand les pouvoirs publics co-construisent avec les acteurs de terrain. RFAS n°1 : 385-393

34 Julie Cachard. 2020. Développer des démarches participatives dans les maisons de santé pluriprofessionnelles : quels enseignements tirer des expériences menées en quartier populaire ? RFAS n°1 : 143-165

35 Jean-Hervé Bradol and Claudine Vidal. 2009. Innovations médicales en situations humanitaires. Le travail de Médecins Sans Frontières, L'Harmattan, Paris. 193p

(B) Evaluating, deciding, and diversifying the design and production of innovations

This plurality of forms of innovation raises a **series of sensitive questions** that **concern evaluation -** what are the legitimate needs in terms of health? How to define them? How to prioritize them? How to connect the needs defined at the individual level with those defined at the population level? How to integrate the issues of equity, preservation of our social protection system and respect for the environment and living species? - , that concern **decision-making** - How to make choices? For and with whom? - and finally that concern the **conditions for diversifying innovations** - what are the effects of the current innovation policies? How can we promote diversity? More than 40 years after the Ottawa Charter[36], would true innovation in prevention in our country not consist of extending our symbolic frameworks from disease prevention to health promotion?

Evaluation

As we have said, disruption cannot be considered as an end in itself in the field of health. **Innovations must first and foremost meet a health need**. However, these needs still must be **identified and evaluated**. These needs are very diverse, depending on whether one considers being able to cure or provide care for a sick person to improve their quality of life or life expectancy, prevent the development of a disease or disability, or promote conditions to enable people to remain healthy. They form part of contrasting temporalities and are in practice difficult to compare. Moreover, their definition is often equivocal and requires delicate trade-offs. Should gains in life expectancy be favored over improvements in the care experience and living with the disease? Can the objectives of disease prevention or health promotion justify all restrictions in terms of civil liberties and impose unlimited power to govern bodies and behaviors?

The issues of defining health needs are intimately linked to the ways in which innovations are evaluated, and in particular to their ability to meet those needs. **The criteria to be used as a basis for these evaluations appear as a focal point that becomes operational when selecting the procedures**. Thus, **randomized clinical trials** are the methodological framework of reference for evaluating the ability of a drug

36 The first International Conference on Health Promotion, which met in Ottawa, adopted on November 21, 1986 the Charter:
https://www.euro.who.int/_data/assets/pdf_file/0003/129675/Ottawa_Charter_F.pdf

or a technology to improve health. However, depending on whether the endpoint used is cure, increased life expectancy or life expectancy without disease progression, the type of need being targeted is not the same. While the choice of trial endpoint depends highly on the disease and existing treatment or care options, it is rarely completely neutral. Considering a given cancer treatment as effective (because it increases progression-free survival by a few months, without always taking into account the adverse effects to which it exposes the patient) may lead to this treatment being favored over the choice of starting the patient on a palliative care pathway. Quality-of-life scales have also been proposed to broaden the range of endpoints. But, again, these proposals do not exhaust the conflicts of norms. Patients' experience of disease over the course of a complex care pathway is more difficult to scale than the measurement of reduction of a specific side effect. While the effect of this reduction may not be negligible, the choice of medication is not the management strategy that alone most improves the experience of care and of living with the disease. Thus, the discovery of drugs that potentiate the CFTR protein (Lumacaftor or Ivacaftor) is a major innovation in the treatment of cystic fibrosis, improving an endpoint as decisive as forced expiratory volume in one second (FEV1). However, the experience of patients and their loved ones has a much broader dimension, ranging from the care (from the quality of the announcement of the illness to the parents to the variable availability of physiotherapy) to health (appropriate nutrition), to living with the disease (from access to MDPH services[37] to procreation in adulthood). In fact, the methodological framework of randomized clinical trials, while it allows for comparisons and the production of solid statistical evidence[38], is difficult to adapt for innovations where the dimension of care, organization of work, and more generally the difference in effect of a single technology, is important.

The health-economic evaluation through the concept of "therapeutic value" (SMR) is also an important approach for health innovations. As the CCNE pointed out in its opinion no. 57[39], "*There is a profound ethical dimension to this demand for optimal use of the health care effort since it is alone able to guarantee the highest compliance with principles of justice and solidarity. In fact, any partial rerouting of this effort outside the bounds of maximum efficiency in the short, medium, or longer term, would lead to feasible improvements in health care not being achieved.*" **Beyond the perspective of**

37 Maison des Personnes Handicapées (Departmental homes for people with disabilities)

38 These evaluations are most often short-term, as evidenced by the importance of pharmacovigilance afterwards, and are based on strictly biomedical criteria.

39 Technical progress, health and societal models: the ethical dimension of collective choices (1998-03-20)".

individuals, population dimensions are constitutive of health, as is our ability to ensure the sustainability of our social welfare system.

But, again, **evaluating market value is not an obvious approach for all dimensions of health**. As reiterated in an economic and organizational analysis of therapeutic patient education (TPE) in the management of chronic diseases published by the French National Authority for Health (HAS) in 2007 "*It is extremely difficult to estimate the potential medical and economic benefit produced by a therapeutic patient education approach"*. Giving a market value to patient autonomy is not easy. But is it conceivable not to offer TPE when France is the only country in the world to have legislated in its favor with the HPST law[40] in 2009?

An ethical approach to the evaluation of health innovations therefore requires caution and openness in the choice of the type of health effects considered and the conditions for their measurement. It also calls for a broadening of points of view, to regulate the influences of the major players that are the pharmaceutical industries and, more generally, the private market players, to take into account the people directly concerned as much as possible. Finally, it calls for the introduction of additional evaluation criteria.

Therefore, the question of the **effects of an innovation on health inequalities is essential**. When developments associated with robotization and/or digitization generate job cuts in advance, they often result in overwork for professionals and in human and sometimes geographical distance for patients. It is essential at the stage of the ethical evaluation of an innovation to promote or uphold that innovation which, directly or indirectly, helps to reduce inequalities.

In the same way, **it is inconceivable today not to introduce criteria relating to the effects on the environment and on living species**. Human health is very largely dependent on environmental conditions understood in a very broad sense, as evidenced by the new importance of environmental health research programs and policies, and more generally by the World Health Organization's "One Health" approach[41]. Reducing the sources of pollution created by human activities, as well as reducing people's

40 France's "Hospital, Patients, Health and Territories" (HPST) law of July 21, 2009 has profoundly modified the country's entire healthcare system, in terms of modernization of the healthcare institutions, access to quality care for all, prevention and public health, as well as the organization of the healthcare system on the territorial level.

41 WHO's multi-sectoral "One World, One Health" approach. WHO Geneva, September 2017 https://www.who.int/features/qa/one-health/fr/

exposure to this pollution, is a major health issue today. It is therefore important that new criteria can be taken into account to evaluate the environmental impacts of health innovations, affecting both the development and production stages of these innovations (material conditions, geographical circulation, etc.) and the stages of use of these innovations (distribution, consequences on the lifestyles of the people concerned, individuals, patients and professionals).

Decision-making

The diversity of criteria for evaluating innovations and the conflicts of priority of ethical, social, and environmental, etc., norms that comparisons inevitably bring about, make deliberation and decision-making methods key issues in health innovation.

These issues arise at the level of public health, research, and innovation policies, whether national, regional, or local. They also arise at the level of research, healthcare and innovation institutions, both from the viewpoint of their innovation support policies and instruments, and as closely as possible to the experiments and trade-offs that are part of the daily work of research and care.

The choice of arenas where these issues are discussed, the players who take part in them, the forms that these debates take, the real consequences of the choices made there... these elements are essential.

In order to legitimize the choices and priorities made among the innovations, they must, as far as possible, be thought out and formulated by all the players involved, debated in bodies that represent the various interests involved in the presence of then arbitrated by the bodies empowered to implement public health policies. They must be the fruit of health democracy. Indeed, these choices involve determining what the general interest, and not the multitude of private interests, dictates. To promote ethical innovation, the identified criteria should be questioned at each level of decision-making. But this ambition comes up against two limits. The first is that it is sometimes difficult at the research stage to discern its utility and legitimacy, such that the guarantees we have just stated will be difficult to implement upstream. The second is that much research is motivated by economic interests over which health policy has little control.

A concern should be stressed here. As we have said, when it comes to biomedical

innovation, private commercial players have significant importance, power, and resources. While it is obvious that these debates and decisions cannot forgo close dialogue with these players, it is essential to build conditions for discussion and decision-making that allow for the rebalancing of power. **Questions to evaluate the ethical nature of the innovations - Which health needs are to be met? What are the expected effects of this innovation on civil liberties, equal access to healthcare, the social protection system and its sustainability, the natural environment and living species? Is there a risk that this innovation will be to the detriment of other more urgent or necessary innovations or that it will have iniquitous collateral consequences? - must be able to be asked without the producer's commercial viewpoint totally crushing the debate**. In this respect, it is important that public authorities retain levers to promote ethical innovations and that private players succeed in identifying economically promising ethical innovations and think about new ways of adding commercial value to this type of innovation.

Diversification

In order for the ethical evaluation criteria that we are calling for to be effective and to provide the basis for relevant choices, **it is important to think about the conditions for supporting and accompanying the diversification of forms of health innovation**. We propose here that this approach be based on a broader opening to the knowledge mobilized, to the players involved, on information and training for research and healthcare professionals, and finally on a thorough overhaul of the current innovation support systems to make them better able to support the emergence of plural innovations.

The question of **what knowledge is considered legitimate for producing the most valued innovations is important**. The profoundly sociotechnical dimension of the innovations calls for consideration of a very wide range of research fields, from the basic sciences to the humanities. But it is also about making room for other forms of knowledge. Healthcare professionals in their diversity, patients, healthcare system users and more generally civil society develop knowledge, know-how and skills that are valuable. As the sociologist Boaventura de Sousa Santos points out: *"Creating credibility for non-scientific knowledge does not mean discrediting scientific knowledge. Rather, it means using it in a broader dialogue with other knowledge in a counter-hegemonic way"*[42].

42 B. de Sousa Santos, Epistémologies du sud, Mouvements citoyens et polémique sur la science, ed.

This knowledge-based perspective encourages **research players to avoid being one-on-one with the industrial world,** with its viewpoints and its knowledge, which are important but not enough.

The corollary of this opening of mobilized knowledge is the opening to a wider spectrum of legitimate players. Numerous initiatives have been devised to attempt a virtuous deployment of the new technologies. These involve the co-construction of innovations between creators and users. At each stage of its development cycle, a product is tested by a panel of users, both for its ergonomics and its capacity to be assimilated. Initiatives are emerging in France and Europe that address the autonomy of the elderly and their support at home, but also the development of open innovation in connected healthcare with the aim of offering better patient monitoring and also of developing homecare strategies. As underlined in the report by Robert Picard for the French High Council for Economy *"Réflexions stratégiques sur la politique industrielle en matière de dispositifs médicaux"* [Strategic reflections on industrial policy in terms of medical devices] (February 2019), in response to the question, "In your opinion, what are the public or private players who could play a role of driving innovation?", the answer was that this could be "The 'levers' that are the structures integrating the users - patients or professionals: patient associations, the CIC-IT[43], Living labs...". Generally speaking, **participatory research approaches,** which aim to co-construct research questions between academic and professional researchers and non-market civil society players, often lead to the development of innovative solutions tailored to the problems identified by those directly concerned.

It is therefore important that **research communities take ownership of this re-opening of the perceptions of innovation**. That work can be done on raising awareness and reflecting with research players on the ethical issues of innovation, on the diversity of forms that health innovation can take, on responsibilities, on room for maneuver... To what extent are research questions influenced by the innovation strategies that depend on them? What are the effects of the current strong incentives to file patents? Can research practices associated with more frugal innovations be conceived of in certain circumstances? With what resources, what form of intellectual property and what outcomes?

Finally, it is **important to question the current innovation support mechanisms and**

Desclée de Brouwer, 2016, p. 276

43 Technological Innovation Clinical Investigation Center

their effects. Do these systems allow us to best support innovations in all their diversity? To what extent do priority interactions with industry players tend to limit the development options for the most frugal innovations?
Could we envisage mechanisms to support and promote approaches to drug repurposing? Why would public authorities not invest in funding research on these molecules?
How can the commitment of researchers to non-disruptive, more incremental forms of innovation be valued, without any intellectual property protection issues, but with a better response to the various ethical criteria identified? Could the promotion of participatory research approaches not be considered within the scope of the prerogatives of the innovation support initiatives? Can we envisage the recognition of a third sector of research, alongside the public and private sectors?

Inserm could also support a major program for activating knowledge already present in the system in the form of clinical observations, patient data, knowledge of molecules, etc., and encourage researchers - doctors and research biologists - to engage in a work of exploring the innovations that could result from it. For greater relevance (usefulness, acceptability, etc.), this work could be regularly compared with the observations of healthcare and socio-educational personnel. These perspectives assume the facilitation and recognition of diversified modes of collaboration, many of which have been in existence for a long time but remain little valued in career terms.

Mechanisms must be devised to promote innovations in all their variety, to provide targeted support for participatory research and frugal innovation approaches. **Why not launch an award for frugal health innovation? Why not certify innovation approaches that meet ethical criteria?**

Conclusion

Through the prism of these developments, promoting and implementing an ethical approach to innovations that takes into account their plural nature presents itself as an exciting challenge, despite the complexity of the approach. Evaluating the ethical nature of an innovation requires a decompartmentalized and contradictory approach. Beyond individual ethics, the aim is to bring out a common core of values to be promoted.

Far from proposing criteria for validating innovations that could appear to be implicit mechanisms of censorship and vectors of "right-thinking", the Inserm Ethics Committee encourages the research community and health players to integrate the ethical questioning approach throughout the process that links research work and innovation developments. The aim is to mobilize sets of criteria to guide rather than direct, to question each step, to challenge the players and invite them to look for levers for validation, value creation and implementation.

In order to do so, it appears essential to do the following:

- Establish with researchers and engineers sets of criteria for ethical innovations, to add value to the projects that meet them. These criteria can only be defined at the price of regularly renewed identification of priority health needs.

- Determine the reasonable point in time at which a research project can be compared against said criteria. Too far upstream, the researcher does not have a sufficiently precise view of their project to question it in this light, too far downstream, the die has already been cast.

- Support an "ethical by design" approach that introduces, from the very beginning of a research program, reflection on the ethical questions raised by the fruits of this work.

- Find the levers that enable value to be added to ethical innovations by highlighting not only the potential gains that are easy to identify but also the savings and qualitative benefits obtained.

- Reflect on the place of public research and its connection with the private market sector in the field of health innovations.

- Stimulate research in the social sciences and health economics.
- Support multidisciplinary research on the innovation process.

These reflections encourage us to move away from the short time frame that urges us to put forward only that which is quickly and more easily visible, in order to promote, within a longer time frame, that which constitutes, in both substance and form, genuine progress for the common good. This is to prevent innovation from "degrading man's humanity instead of serving it".[44] A socially responsible approach to innovation must therefore make space, alongside the disruptive biomedical approaches, which are essential in many contexts (neurodegenerative diseases, stroke, cancer, etc.), for approaches to healthcare, disease prevention and health promotion, in all their diversity.

44 O. Rey (2020). L'idolâtrie de la vie. Tracts Gallimard n°15