

aviesan

alliance nationale
pour les sciences de la vie et de la santé

GENOMIC MEDICINE FRANCE 2025



CEA ◊ CHRU ◊ CNRS ◊ CPU ◊ INRA ◊ INRIA ◊ INSERM ◊ INSTITUT PASTEUR ◊ IRD
ARIIS ◊ CIRAD ◊ EFS ◊ FONDATION MERIEUX ◊ INERIS ◊ INSTITUT CURIE ◊ INSTITUT MINES-TELECOM ◊ IRBA ◊ IRSN ◊ UNICANCER

EDITORIAL

The France Genomic Medicine Plan 2025 fulfils the commission entrusted by Prime Minister Manuel Valls to Alliance Aviesan in April 2015 to investigate establishing access to genetic diagnosis in France together with a prospective review covering the first ten years.

Following the example of similar programs launched in the United Kingdom in 2012, in the USA in 2014 and in China, France aims through this Plan to construct a medical and industrial system to introduce precision medicine into the care pathway and develop a national framework in this matter.

The proposals in this Plan have been formulated after a year of work with institutional representatives and multidisciplinary experts from the fields of science, health care, business, research and health care agencies, Ministries, business as represented by Ariis, CNAM and HAS, CGI and

the École d'économie de Toulouse. The “French Model” proposed here is a mixed one involving prerogatives of health care and science in line with our health care system, its link with research, the economic model of health care procedures and the need to establish a process of integration of scientific advances into health care to facilitate access for everyone in the country to innovation.

This Plan also takes into account, in a concrete fashion, technological progress from sequencing to the storage and analysis of the resultant big data as well as confidential reporting back to doctors and patients. Big multinational companies appreciate the strong potential represented by developing digital health care and are investing heavily in the sector. Businesses operating in biological diagnosis, the digital sector and new sequencing technology have worked together with other institutions to draw up these recommendations.

The issues and challenges for France

A missed chance for patients

In Europe, a number of countries have begun assimilating genomic medicine into their health care system, including Estonia, the Netherlands and Slovenia. If France fails to launch its own initiative, the risk is one of medical tourism with French patients going abroad to other countries on the Continent that offer these high-value-added medical services with the corollary of effect of exacerbating the inequality of citizen access to health care.

Strong international competition

Genomic medicine is no longer a promise—it is already a reality that will transform how we prevent, diagnose, treat and predict the prognosis of disease. It is also a stage for strong international competition, each country wanting to develop its own industry and attract scientific talent to bolster up its own advantages.

Four major challenges

The strong international competition in the field of genomic medicine is explained by the challenges it raises.

First and foremost, it is a **public health issue**. Genomic medicine is revolutionizing the care pathway and therefore how the public health system is organized. A large number of patients with rare diseases or cancer will benefit from routine sequencing of their genomes with more personalized diagnosis and treatment. Great progress has already been made with more common diseases (metabolic, cardiovascular, neurological, etc.) through genome sequencing, above and beyond identification of the usual susceptibility-conferring genes. With time and expansion to cover novel clinically validated indications, all patients will eventually benefit from improved care.

To achieve this, **the challenge is also scientific and clinical**. This will involve reinforcing the chain going from the molecular investigation of disease to therapeutic benefit to patients via the assembly and matching of multiple heterogeneous databases, be they of biological data (sequences, screens, imaging results, etc.), clinical data or even environmental information.

And **the technological challenge is no less pressing**: information and communication sciences and technologies are called on to converge with the life sciences and health care information, the capacity to acquire, store, distribute, match and interpret such big data from diverse sources being at the heart of said convergence. It represents a genuine focus of excellence in calculation science and biological data that will emerge. In addition to servers, cores and intensive calculation

methods, the development of software for data mining and modelling will make it possible to meet the challenge of genomic medicine and, more broadly, personalized medicine.

Finally and pre-eminently, the challenge **is an economic one** both in terms of expenditure by our health care system and also the chance to develop new industrial infrastructure.

On the one hand, innovation in health care and quality of life is one of the drivers of growth in developed countries. And on the other hand, genomic medicine is more precise meaning savings on health care due to fewer inappropriate, inaccurate and extensive examinations, faster turnover times, less prescription of useless drugs, fewer debilitating adverse reactions and gains in years of life.

Objectives of the France Genomic Medicine Plan 2025

To meet these challenges, we have proposed a transformative, ten-year Plan. Built up around sequencing platforms covering the whole country, a national data analysis center and a national reference center for technological innovation and transfer, the aim is to capitalize on the specificities of our health care system and bring yet more closely together care, research, training and innovation in the service of health care and quality of life.

A Plan structured by three targets

The first is to position France among the countries leading the way in personalized and precision medicine with export of the expertise derived from the French medical and industrial genomic medicine system.

Our second target is to prepare for integration of genomic medicine into the care pathway and the management of common diseases. This means setting up a generic care pathway with access for all patients with cancer, a rare disease or a common disease by 2025, with genomic medicine available to all affected patients in the country. By 2020, some 235,000 genomes will be being sequenced each year. Beyond that, the system will be expanded to cover common diseases.

Finally, the third target for 2025 is to set up a national genomic medicine framework capable of driving scientific and technological innovation, industrial capitalization and economic growth. This Plan will create a dynamic in the matter of innovation in a number of fields: conservation, the generation and mathematical processing of big data, Web semantics and the Web of objects, medical devices, dematerialization, digitization and e-Health, etc.

The involvement of relevant businesses together with academic scientists and the public sector is essential.

Ethical considerations at every step of the France Genomic Medicine Plan 2025

The ethical dimension is an integral part of the Plan. In this field too France has to construct a new model—here too France will innovate.

It will not be possible to develop personalized genomic medicine without at the same time providing answers to the numerous questions being asked by citizens and patient support groups on consent in access to and exploitation of health data, the anonymization of data vis-à-vis third parties, how secondary discoveries and unwanted incidents—inevitable when the entire genomes of patients and their family members are sequenced—are to be handled and the risk of even worse exclusion of people who are already being poorly served by the health care system.

Some developments would be difficult to put up with. If we do not integrate all the necessary ethical rigor into our collective approach, we would risk traducing the democratic contract between science and society.

Precise genomic medicine represents a revolution in the fields of health care and prevention. It is fostering huge hopes—legitimately so—in people. It is changing how we define disease and how we help the sick.

France must give itself the resources needed to make this revolution a success and take its place at the vanguard. Growth is crucial, a major scale-up. The France Genomic Medicine Plan 2025 will bring this and its success is now our collective duty to both patients and society as a whole.



Yves Lévy
President of Aviesan

SUMMARY

In an engagement letter on 17 April 2015, the Prime Minister commissioned Aviesan to examine how to integrate large-scale sequencing into the care pathway. Four aims were specified:

- Define the place and importance of genome sequencing in medicine today and predict developments that might be expected over the coming ten years.
- Establish the position of France in genomic research, the place of this science in current health care plans and priorities when it comes to ensuring consistency with national health care and research strategies.
- Assess challenges in terms of innovation, capitalization and economic development, taking into account technological aspects, how to handle big data and ethical issues.
- Develop a long-term medico-economic model integrating reimbursement by the health insurance system with development of an industrial framework to sustain the initiative.

Under the presidency of Aviesan, a Steering Committee was convened with institutional representatives, diverse experts from the fields of research, health care and business as well as delegates from research and health care agencies, ministerial departments, and industrial enterprises represented by Ariis, CNAM, HAS, CGI and the Toulouse *École d'économie*. This Committee has been meeting every month since May 2015.

The Steering Committee set up four Working Groups to focus on the issues raised in the Prime Minister's engagement letter. In these Groups, relevant experts—physicians, scientists, business representatives, learned societies and patient support groups—meet up on a weekly or monthly basis.

The medical, economic and international background

Access to genomic medicine represents a challenge for public health: with the spread of ultra-high-throughput sequencing, significant proportions of patients will ultimately benefit from routine genomic investigation, not only patients with rare diseases and cancer but also those with certain common diseases. Higher-resolution diagnosis will enhance care with shorter time frames as well as more effective therapeutic strategies and fewer adverse reactions.

This domain represents an important economic issue with tremendous savings on health care expenditure and great expectations from this new channel. Reduced health care expenditure is likely to be substantial by virtue of various factors: a reduced number of expensive but spurious diagnostic procedures; quicker test turnover; avoidance of ineffective, potentially dangerous drug treatments and the need to treat adverse reactions; earlier treatment; and more effective treatment leading to increased life expectancy. In parallel, a new, innovative industrial framework will have to be constructed—a source of

economic development and employment. This will support the system's expanding scope and provide solutions to the numerous technological challenges arising, in particular development of the information technology capacity that will be required.

Genomic medicine is a field of international competition supported by national plans. The United States, the United Kingdom and China in particular are investing in this sector and have mobilized their biggest companies to find innovative technological solutions to the problems raised by large-scale ultra-high-throughput sequencing and the handling of big data. France, with an annual capacity for just 20,000 exomes and 10,000 genomes, is significantly lagging behind these countries that can do several tens of thousands of runs a year. While an industrial opportunity is growing in the field of genomic medicine—an opportunity that is attracting the interest of companies like Google, Apple, Facebook, Amazon, Microsoft and Samsung

(GAFAMS)—France must not miss this unique chance to develop a national industrial framework of high strategic, medical, scientific and economic value associated with the development of this initiative; the ultimate risk being technological dependence. Moreover, other European countries

including Germany, Estonia, the Netherlands and Slovenia have already started integrating genomic medicine into their health care systems thereby increasing the risk of the French system losing ground resulting in domestic patients going abroad for these services.

Targets of the 2025 France Genomic Medicine Plan

- To position France among the leading big countries in the field of genomic medicine within the next ten years, with the aim of exporting expertise in the domain and developing a strong medical and industrial framework based on genomic medicine.
- To establish by 2025 a generic care pathway with privileged, common access to genomic medicine for all French people affected by cancer, a rare disease or a common disease (patients and, in some cases, their families).
- To be capable by 2020 of sequencing 235,000 genomes a year, corresponding to 20,000 patients with rare diseases together with their families (about 60,000 genomes) and 50,000 priority patients with metastatic cancer or a cancer that has proven refractory to treatment (about 175,000). Beyond 2020, the system's capacity will be grown to cover common diseases.

Specific measures in the 2025 France Genomic Medicine Plan

Transformative and innovative, directed and supported by the State over a period of ten years, this Plan provides an original, global response to the Prime Minister's request. In contrast to the initiatives launched elsewhere, notably the United States and the United Kingdom, it exploits particularities of our health care system which covers patient care, training and research with—especially in recent years—the development of broad-scope actions which strongly support this approach (governmental plans, establishment of spaces for dialog between partners and companies, and definition of national health care and research strategies).

The Plan is organized to meet needs identified at the various steps along the care pathway designed around the patient/doctor pair from the ordering of genome analysis through the compilation of conclusions. It is embodied in three main targets with a series of measures to:

Establish genomic medicine instruments for the care pathway with:

- the setting up of a network of twelve sequencing services covering the whole country by 2020, to meet the stated quantitative objectives;
- establishment of a National Center for Intensive Calculation (CAD, *Collecteur analyseur de données*) capable of processing and analyzing the huge volumes of data that will be generated and providing primary services for professional health care providers in the framework of their care pathways (*in silico* tests and aids to decision-making in diagnosis, establishing prognosis and designing therapeutic strategies);
- generalization of standardized, interoperable electronic patient medical records—a step that is indispensable when it comes to integrating and exploiting genomic and clinical data;
- as of 2016, the execution of pilot projects on cancer, rare diseases and common diseases designed to overcome technological, clinical and regulatory obstacles encountered along the pathway;

- preparation for changes in current regulatory frameworks according to Good Practices as well as judicial and ethical standards, notably by appointing a National Consultative Ethics Committee (*Comité consultatif national d'éthique*) to examine the various steps of the care pathway vis-a-vis ethical aspects of the collection, storage and processing of clinical and genomic data as well as guaranteeing safe, high-quality care.

Respond to the increasing scope of the system with technological and regulatory changes integrated in the Plan's dynamics by:

- establishment of a system to assess and validate new indications for access to genomic diagnosis ensuring development of the existing base with progressive integration into the care pathway;
- creation of a national Reference Center for Technology, Innovation and Transfer (*centre de référence technologique, d'innovation, et de transfert*, CRefIX¹) turned towards the sequencing service, CAD and companies;
- definition of an economic model to ensure the durable integration of this new system into the health care system linked to health insurance which should define costs and reimbursement conditions and promoting the emergence of a "genomic medicine" channel by offering companies not only an economic logic but also an operating logic for the future system guaranteeing its development in the long term;
- orientation of the activities of all those involved to address industrial issues with support from a public/private sector *task force*;
- setting up special training programs in universities and schools to prime construction of a multi- and inter-disciplinary genomic health system and foster new skills and personnel, specifically capable of meeting the challenges of how to analyze and interpret the data.

Implement necessary changes throughout development of the Plan to ensure information and involvement of the general public, users and patient support groups, with:

- definition of a governance system that matches the Plan's requirements, and establishment of special monitoring and steering mechanisms;
- establishment of a registry to monitor developments in medical, technological and regulatory aspects of genomic medicine at the international level;
- creation of an economic registry to sponsor research on the Plan's economic consequences;
- organizing the information, consultation and involvement of everyone in society who is concerned.

¹ CRefIX: Centre de Référence, d'Innovation, d'eXpertise, et de transfert

CONTENTS

1 A BROAD-SCOPE NATIONAL PLAN TO ENSURE INTEGRATION OF GENOME SEQUENCING INTO THE CARE PATHWAY	11
1.1 Introducing genome sequencing into the care pathway meets major challenges in France	11
1.1.1 Access to genomic medicine: a public health issue.....	11
1.1.2 Genomic medicine: a matter of international competition.....	12
1.1.3 A sector that represents a major economic issue with massive savings for French health care system and repercussions of a new system	13
1.2 France possesses many advantages when it comes to reaching the desired objective but the necessary partners and investment can only be guaranteed with strong governmental commitment.....	13
2 TARGETS OF THE PLAN	15
2.1 A paradigm shift in French health care system	15
2.2 Operational targets for 2020 and 2025.....	16
3 FRANCE GENOMIC MEDICINE ACTION PLAN 2025	17
Target 1: establish instruments for a genomic care pathway	18
Measure 1: Construct French capacity for ultra-high-throughput sequencing to meet the defined targets	18
Measure 2: Develop the tools required to process and exploit the volume of data that will be generated with creation of a central analysis service (<i>collecteur analyseur de données, CAD</i>).....	20
Measure 3: Foster the integration and exploitation of patient data into the care pathway.....	22
Target 2: Ensure operational development and expansion of the system in a safe technical, ethical framework	23
Measure 4: Establishment of a Reference Center for Innovation, Assessment and Transfer (<i>Centre de référence, d'innovation, d'expertise et de transfert, CRefIX</i>) to foster the technological developments and information technology required for implementation of the pathway.....	23
Measure 5: Overcome the technological, clinical and regulatory obstacles encountered along the path with respect to the three broad groups of disease concerned	25
Measure 6: Establish a system to assess and validate new indications for access to genomic diagnosis	26
Measure 7: Foster new skills and personnel capable of meeting the challenges of how to analyze and interpret the data	27



Measure 8: Integrate ethical aspects related to the collection, storage and processing of clinical and genomic data and guarantee safe, high-quality care28

Target 3: Establish monitoring and steering tools to make the adjustments required throughout implementation of the Plan while ensuring public involvement..... 31

Measure 9: Mobilize industrial entities implicated in the project to meet technological and industrial needs at the various steps in the care pathway and promote the emergence of a "genomic medicine" channel31

Measure 10: Orientate the activities of all those involved to address industrial issues arising along the genomic care pathway 32

Measure 11: Monitor developments in the field of genomic medicine at the international level.....33

Measure 12: Establish a research program dedicated to medico-economic aspects of the Plan.....33

Measure 13: Organize the information, consultation and involvement of everyone in society who is concerned.....35

Measure 14: Define a governance system for the Genomic Medicine Plan35

GLOSSARY 38

APPENDIX41

Appendix Letter from the Prime Minister to the President of Aviesan41

1 A BROAD-SCOPE NATIONAL PLAN IS NECESSARY TO ENSURE INTEGRATION OF GENOME SEQUENCING INTO THE CARE PATHWAY

The Prime Minister has commissioned the President of Aviesan to review how to set up large-volume sequencing. The ultimate objective is to reach all patients throughout the country in whom such tests might be relevant with an expectation of major impact on both diagnosis and care (Appendix).

Under the auspices of the president of Aviesan, studies have been undertaken by various specialist and multidisciplinary groups bringing together experts (physicians and scientists), academics, business, learned societies and patient support groups which have expressed interest in the project.

These studies have led to identification of the major issues that this project needs to address and have shown that the medical, societal, economic, scientific, technical, ethical and legal challenges to be overcome are substantial (1.1). The challenge raised by the development of genomic medicine with integration of an ultra-high-throughput sequencing system into the care pathway will require significant resources and governmental

commitment to match the level of the issues at stake (1.2).

An ambitious, transformative Genomic Medicine Plan to be implemented over a period of ten years is being proposed (Parts 2 and 3). In response to the Prime Minister's commission, it provides a global response integrating patients, our systems for health care, research and training, and the national economic fabric. Elsewhere, similar initiatives are being supported at the highest level—by British Prime Minister David Cameron (the 100,000 Genomes Plan) and American President Barack Obama—and several other European countries have already committed to making genomic medicine part of their health care systems in various ways (Germany, Estonia, the Netherlands and Slovenia). **To position France in this global competition and avoid losing important ground in terms of both French economy and health care system, this multi-faceted Plan (linking health care, industry and research) will be coordinated, under the auspices of the Prime Minister, by Aviesan working closely together with all interested parties.**

1.1 Introducing genome sequencing into the care pathway meets major challenges in France

1.1.1 Access to genomic medicine: a public health issue

The benefits of new-generation sequencing technology (high-throughput and ultra-high-throughput) on panels² of genes and exomes³, especially for the purposes of diagnosis, have now been demonstrated in patients with a rare disease or cancer.

² A panel is a set of genes (10-100) that have been shown to be involved in a disease.

³ The exome is the part of the genome (about 1.5%) made up of exons, i.e. the parts of genes that are transcribed into the messenger RNA that supports synthesis of the proteins, functional products that determine a cell's structure and activities.

In the field of rare diseases, such technology is making it possible to identify rare single nucleotide variations (SNVs) and genomic rearrangements like copy number variations (CNVs) that cause disease. It also makes it possible to compare genomes from different family members which is significantly enhancing diagnosis⁴.

In oncology, numerous sequences can be determined on any given patient, e.g. healthy tissue, tumors at different stages, malignant cells in the bloodstream, etc., and being able to consider sets of nosological, prognostic and theranostic markers⁵ together is dramatically expanding the range of therapeutic choice to ensure maximum treatment efficacy with a minimum of adverse reactions.

For common diseases in which complex genetic factors are involved, sequencing is already shedding light on associations between specific genetic variations and differential responses to treatment, the large number of genes involved in diseases like diabetes (40–80, depending on the form) and, more recently (in experimental studies), the involvement of rare SNVs in certain pathologies.

Large-scale high-throughput sequencing will assure access to this type of approach for all patients who might benefit from it and provide information about a patient's genome to bring about considerable improvement in the quality of diagnosis and therapeutic orientation.

For rare diseases, above and beyond improved sequence information, genome analysis will identify guilty mutations that could not have been detected in panels or exomes.

In oncology, combination of the information from genome analysis (detection of rearrangements, etc.), deep exome sequencing, transcriptomics⁶ and medical records will give a new dimension to both diagnosis and therapeutic orientation. It

would seem that it will only be possible to realize the Cancer Plan 3 objective of sequencing 60,000 tumors by 2019 in the framework of this initiative.

For common diseases, although sequencing is confirming their complexity it is also opening the way to fuller understanding and better classification of many such pathologies and, in consequence, how to treat them. Thus, by making it possible to define genetic signatures and biological markers, genome analysis is emerging as a powerful tool to refine and redefine nosological frameworks and the principles that orientate therapeutic choices.

Routinely using genomic data and understanding how it relates to clinical manifestations will ultimately have substantial impact on medical practice with better-targeted, more effective therapeutic strategies, fewer adverse reactions and therefore improved patient care. Developing the system to make it accessible to a large number of patients seems therefore to be fully justified.

1.1.2 Genomic medicine: a matter of international competition

In the framework of national programs, the United States, the United Kingdom and China in particular are investing in this sector and have mobilized their biggest companies to find innovative technological solutions to the problems raised by large-scale ultra-high-throughput sequencing and the handling of big data.

So far in the field of genomic medicine, France is behind these countries that already have infrastructure capable of tens of thousands of runs a year (whereas French capacity is estimated to be limited to just 20,000 exomes and 10,000 genomes a year). These centers are partners in ambitious industrial collaborations (Amazon, Illumina, pharmaceutical companies, etc.) to constitute an industrial network of genomic medicine in which businesses that specialize in big data like Google, Apple, Facebook, Amazon, Microsoft, and Samsung (GAFAMS) are getting interested, seeking to establish standards for the resultant data and thereby procure for them major competitive advantage. Against this background, it is important that France does not waste this

⁴ A CNV is a particular type of polymorphism in which the number of copies of a certain gene in the genome varies between individuals.

⁵ A theranostic marker is one that helps guide a patient's treatment.

⁶ Transcriptomics is the study of the entire set of messenger RNA molecules in an organism.

unique opportunity to develop industrial channels of high strategic, medical, scientific and economic value associated with the development of this initiative (1.1.3); all the more so given the risk of technological dependence.

Other European countries including Germany, Estonia, the Netherlands and Slovenia have already started integrating genomic medicine into their health care systems thereby increasing the risk of the French system losing ground with domestic patients having to go abroad for these services.

1.1.3 A sector that represents a major economic issue with massive savings for French health care system and repercussions of a new system

- The savings for French health care system are potentially huge and should be accompanied by social and economic benefits resulting from a significant improvement in healthy life expectancy.

For rare diseases, the expected impact is due to more accurate diagnosis (fewer irrelevant, expensive investigations and faster test turnover times), optimized treatment and improved strategies to prevent the disease or limit its complications (especially for metabolic diseases).

In cancer, benefit will accrue on the one hand from reduced costs (with fewer prescriptions of ineffective targeted therapies and fewer adverse reactions to treat) and also the positive socio-economic impact of extra years of life. This should be particularly significant for the novel targeted immunotherapy products which are currently effective in 30-40% of the patients treated. In any case, identifying specific markers will enhance the targeting of treatment and thereby reduce costs by eliminating inappropriate treatment modalities with the corresponding possible adverse reactions. Common diseases cause serious morbidity and mortality as well as entailing massive health care

expenditure. To date, there are no diagnostic criteria for common diseases based on genome sequencing that lead to differential treatment even though responses can be highly disparate and this sometimes leads to a period of therapeutic failure. The tools of genomic medicine should ultimately shed light on the underlying causes of these diseases and thereby help identify the most appropriate treatment modalities. The impact will manifest in the form of improved care, more accurate diagnosis and better-targeted therapeutic strategy.

- The many technological challenges to be met—to find solutions and assemble equipment, in particular with respect to the unprecedented computing power required in terms of storage and calculation—necessitate construction of a genuine industrial system, a new source of economic development and employment that can meet needs in innovation and drive the system's growth. In addition to those traditionally involved in health care, pharmaceuticals, imaging, medical devices and scientific equipment, this concerns big players in the worlds of information technology, big data, connected objects and E-medicine.

1.2 France possesses many advantages when it comes to reaching the desired objective but the necessary partners and investment can only be guaranteed with strong governmental commitment

For realization of this goal, France can count on:

- a highly structured, top quality health care system together with established cohorts of populations and diverse patient groups, includ-

ing well-characterized cohorts of patients with various rare diseases, cancer and common diseases. These cohorts represent an essential instrument to support development of this initiative in various domains;

- national networks and specialist structures (a variety of structures for rare diseases, molecular diagnosis laboratories, the structured cancer care pathway and services based on the molecular genetics of cancer) together with long experience in the implementation of Health Care Plans⁷, e.g. those for Cancer, Rare Diseases and Neurodegenerative Diseases;
- a longstanding link between clinical practice and research, an integral element of how health care is organized in France and a great advantage when it comes to developing genomic medicine;
- the presence in France of world-leading manufacturers and innovative smaller companies. Some fifty companies have been identified as relevant to genomic medicine. Contacts forged in the course of preparatory work with certain companies have given a measure of their very real interest in this initiative. This is particularly the case for companies working on data processing and analysis, fields in which France is particularly strong (Dassault Systèmes, Orange, Atos/Bull, CAP/SOGETI, etc.);
- an internationally competitive research sector that will be able to respond to many of the challenges and issues raised by this project in both its technological and clinical aspects (microfluids, data security, the processing and analysis of big data, modeling, biological and medical interpretation, clinical trials, etc.). In addition, internationally reputed researchers into the human and social sciences will be able to make important contributions to this initiative through dissection of the complex ethical and societal issues that the growth and use of this type of technology will soon pose.

Nevertheless, the success of this initiative depends on coordination of all the above-mentioned players and this can only be achieved with support from the State.

The development of infrastructure and acquisition of equipment (sequencing centers, storage facilities and data analysis structures) will require massive preliminary investment. State aid will be indispensable to creating a sufficiently powerful lever effect to mobilize interested industrial partners (sciences and information and communication technologies—SICT—companies). Solid integration of this new instrument into the health care system will require the construction of an economic model relying on reimbursement by the health insurance system, taking into account savings expected by virtue of improved diagnosis, a lower incidence of adverse reactions and enhanced therapeutic efficacy resulting from better initial orientation.

The 100,000 Genomes Project launched by the British government in December 2014 with funding of £300 million has proven very attractive to companies in the health care sector with many partnerships already established.

Finally, when coupled with transparent coordination of all those involved, State funding and commitment act as powerful drivers for the confidence and involvement of patients, patient support groups and the population as a whole.

A Plan that is supported and steered by the State, involving a broad range of different players, would seem to be key when it comes to taking all these various dimensions into account, consolidating implementation of the system and positioning France among the leaders in the field.

⁷ In the field of rare diseases, France was the first to formulate initiatives in the form of Plans and these have been closely studied elsewhere; the same is true in cancer with broad-scope support from the National Cancer Institute (INCa, *Institut national du cancer*).

2 TARGETS OF THE PLAN

2.1 A paradigm shift in French health care system

The aim is to put France among the front runners in the field of genomic medicine within ten years. The new model to be introduced is based on sharing nationally collected data to the benefit of as many people as possible with major improvements expected in terms of diagnosis and treatment.

Ultimately, it is planned that all French patients with cancer, a rare disease or a common disease will be afforded access to genomic medicine as an integral part of their care pathway. This may mean genome sequencing plus, when warranted, exome and/or transcriptome analysis.

In contrast to the projects in the United Kingdom and the United States, this initiative relies on a novel approach with a unique ambition to combine a number of complementary targets, here listed as a function of the benefits that will accrue to those affected, once the system is running.

Patients:

- diagnosis and/or treatment integrating genomic data—supported by expert interpretation—with all the traditional clinical data;
- adapted health care from the system in the light of the information, in line with all relevant ethical rules, including questions of Consent, secondary discoveries of medical interest, reporting of results, and data security and sharing;
- facilitated dialog with and via patient support groups with commensurate consciousness-raising about genomic medicine and health at all levels concerned.

Physicians:

Information and tools to help them refine their capacities for diagnosis, establishing prognosis

and therapeutic monitoring, to the benefit of patients, with:

- a base of validated indications on which to base their prescriptions related to genomic analysis;
- generalization of electronic medical records including genomic data as well as all the patient's clinical details;
- special services to guarantee them access:
 - to the results of *in silico* genomic analysis with the identification of genetic variations that might be biologically significant in the context of the disease in question;
 - decision-making aids for diagnosis and establishing prognosis;
 - special instruments to help when therapeutic strategies are being formulated.

Health care system:

By 2020, the selected logistics will allow the deployment of genomic services across the country, fulfilling specific quality and security criteria and covering a significant proportion of patients before expansion through 2025 (2.2).

These pragmatic logistics will allow:

- local deployment of diagnostic services in the form of patient care and sample processing centers, in line with regulations and security rules;
- linking of these centers through a centralized data collation system (CAD) that fulfills all the relevant technological imperatives of security, storage capacity and calculating power.

This organization could generate significant savings for the health care system on top of its socio-economic benefits.

Research:

- considerable expansion of the volume of data and analytical power to establish, on the one hand, genetic signatures and biomarkers relevant to diagnosis and establishing prognosis and, on the other, identifying genes and other molecular entities involved in pathological processes, resistance to treatment and adverse reactions;
- new links between patient care and the scientific community based on permanent dialog feeding the generation of knowledge and clinical validation. Analysis of the approaches adopted in the United Kingdom, Estonia, the Netherlands and the United States clearly shows that the development of genomic medicine depends on a hybrid research/care system.

Economy:

- the creation of an integrated industrial network dedicated to production of the instruments and information technology required for genomic medicine that could drive growth in other fields of health care;
- for pharmaceutical and biotechnology companies, services that define companion tests and better-targeted therapeutic trial design by virtue of the analytical power developed coupled with more effective pharmacovigilance.

2.2 Operational targets for 2020 and 2025

The aim is to construct, by 2020, an operational chain with an enlarged base of indications and sequencing capacity across a dozen centers commensurate with processing the following volumes of target patients:

- rare diseases: at least 20,000 patients per annum plus their families, i.e. 60,000 genome-equivalents⁸;
- cancer: priority will be given to those with cancer that has metastasized or proven refractory to treatment, i.e. about 50,000 patients a year or 175,000 genomes⁹.

Beyond 2020 with the momentum generated, steady growth is expected in both indications and patient numbers, notably through extension to cover common diseases. The aim is to be able to fulfill the needs of a large proportion of affected patients in France by 2025.

⁸ Testing of parents-child trios.

⁹ Volumes of exome and transcriptome sequences are expressed in terms of genome-equivalents.

3 FRANCE GENOMIC MEDICINE ACTION PLAN 2025

The Plan is based on investment and involvement on the part of a large number of different players. Its main measures are presented hereafter. Simultaneously targeting cancer, rare diseases and common diseases, the goal is to establish a **generic care pathway** in genomic medicine, common to all patients whatever their disease.

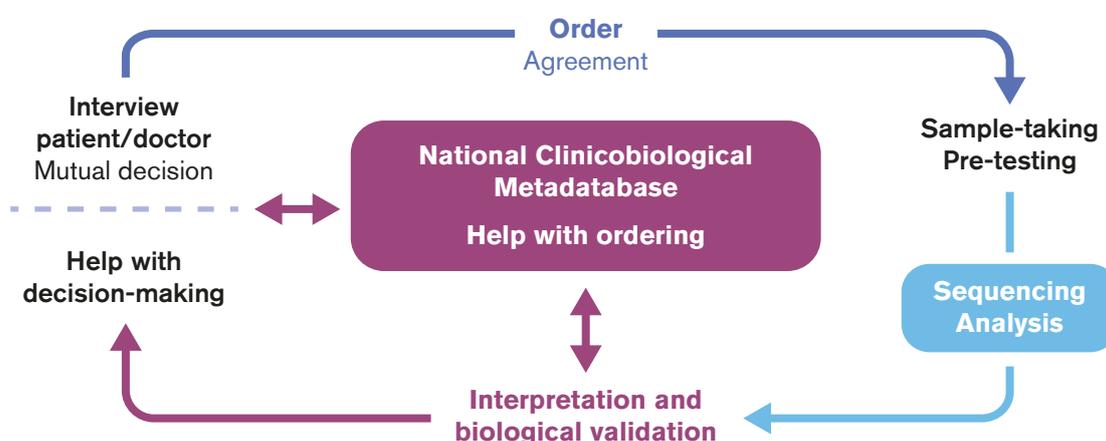
The Plan articulates around three main objectives with a series of measurements to:

- establish instruments for a genomic care pathway (Target 1);
- ensure operational deployment and expansion of the system in a safe and ethical technical framework (Target 2);
- establish monitoring and steering tools to make the adjustments required throughout implementation of the Plan while ensuring public involvement (Target 3);

The Plan's core **generic care pathway** (figure below) is formulated around the pair of patient and doctor from the ordering of a test through return of the conclusions. This pathway can be broken down into five main functional steps as shown in the diagram below.

- **Step 1:** the physician's order is issued following an interview with the patient, with the latter's Informed Consent in writing.
- **Step 2:** samples are taken and then processed to isolate and qualify its nucleic acids.
- **Step 3:** the processing of samples for sequencing is followed by a preliminary comparison based on the alignment of read-outs on a reference genome to identify and qualify sequence variants.
- **Step 4:** *in silico* analysis of the data generated by the services is carried out using classification, modeling and interpretation tools with help from an expert biologist who defines the biological, physiological and pathological significance of the findings before the report is compiled.
- **Step 5:** results are sent to the physician who ordered the test. Depending on the prescription's stipulations (diagnosis, establishing prognosis, theranostics), the ordering physician can rely on *in silico* analysis and complementary decision-making aids with input from CAD to refine the conclusions to be communicated to the patient.

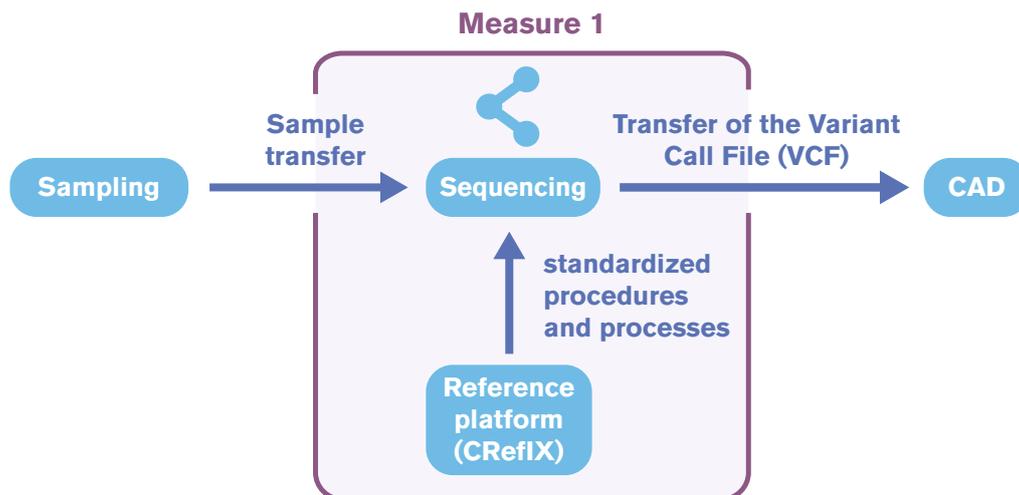
Generic pathway: ordering, pre-testing, testing, biologic interpretation, report



Target 1: establish instruments for a genomic care pathway

Measure 1: Construct French capacity for ultra-high-throughput sequencing to meet the defined targets

This measure aims to establish sequencing services throughout the country with expansion throughout the Plan's lifetime.



Action

Build a network of 12 ultra-high-throughput sequencing facilities by 2020 to provide all the services associated with Pathway Step 3. Specifications for establishment of these facilities will be compiled in Spring 2016 and sites will be selected in September 2016. The schedule plans three installations from the end of 2016 and then three a year between 2017 and 2019.

Description

This network of facilities—set up with an industrial configuration—will have a production capacity of the order of 20,000 genomes per annum per facility by 2020. A typical facility will have some fifteen employees with:

- a special sequencing environment: whole genome, exome, RNA-Seq¹⁰ (the technology deployed will be preliminarily tested and validated on a reference platform at CRefIX¹¹, Measure 3);

¹⁰ *RNA sequencing*, transcriptome sequencing.

¹¹ In 2015, the reference standard for ultra-high-throughput whole genome sequencing techniques corresponds to the HiSeq Xten platform from Illumina which can generate 10 x 1.8 Tbases in 3.5 days, i.e. 18,000 human genomes per annum (30x). Complete Genomics (a subsidiary of BGI) has announced the launch of a competitor ultra-high-throughput platform called Revolocity specially designed for clinical applications (exome, genome, RNA-Seq), capable of sequencing between 10,000 (50x) and 30,000 genomes per annum. In the coming 4–5 years, new, third-generation technologies will likely have become robust and reliable enough to replace these for clinical and diagnostic applications. Very long direct read-outs without amplification (a single molecule) will probably yield higher-resolution information (epigenomics) and structural information (haplotypes) from minute quantities of material. Reading will be in real time and will therefore probably be very fast (also see Measure 3).

- associated calculation resources (estimated at 2,000 cores and some 10 To of active memory¹²) with software to manage and control all sequencing-related procedures (management and monitoring systems for samples and sequences, sequence quality control, circuits management and control) and first-line bioinformatic analysis with identification of variants (comparison with a reference genome and analysis of variants to identify SNVs, CNVs and SVs). These data will then be systematically sent to CAD (Measure 2).
- storage and archiving of all data generated in duplicate. The volume of data generated will depend on analysis type but can be estimated at an average of 3.5 Pb/year¹³ per acquisition center. For the archives, this figure is double (for security reasons).

Questions related to the normalization and standardization of processes and protocols, safety and ethical problems will also be taken into account with a matching regulatory environment (Measures 8 and 9).

Schedule

Compilation of specifications for the facilities and site selection

Installation of the first three facilities

2016

Selection of sequencing technologies, definition of storage and calculation architecture (shared memory calculator, cluster calculation, etc.), specification of software (purchasing of licenses, software compatibility)

Deployment of material solutions and specified software at the first three facilities

2017

Installation of alignment and automatic variant flagging software (preliminary data analysis)

Installation of CAD-compatible software

First data transfer to CAD (to be set up in parallel)

Certification of the platform as a host for health-related data

Start of production with CAD

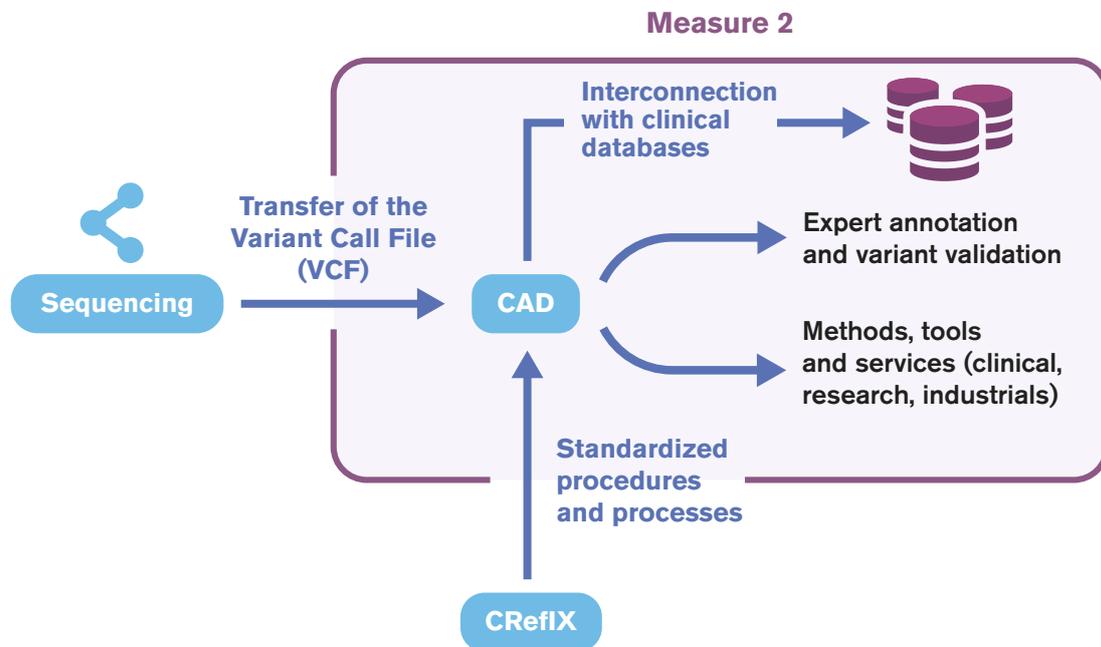
2017-2020

Establishment of nine more platforms

¹² Calculation capacity is measured in terms of the number of processors/cores and active memory capacity for large-scale matrix calculations.

¹³ 2.5 Pb (Peta=10¹⁵) for cancer (160,000 patients x 500 Gb per patient x 3.2 whole-genome-equivalents-30X) and 1 Pb for rare diseases (60,000 patients x 1 whole-genome-equivalent-30X x 150 Gb per patient). It is too soon to specify the common diseases at this point.

Measure 2: Develop the tools required to process and exploit the volume of data that will be generated with creation of a central analysis service (*collecteur analyseur de données, CAD*)



Step 4 of the care pathway depends on capacity for the processing, analysis and exploitation of unprecedented volumes of data. Confronting this challenge means assembling instruments to afford access—in a highly secure storage and archiving environment—to the whole set of a patient's genomic and clinical data, and integrating the information into services for the physician and all other concerned professional health care providers (Step 5). This measure consists of establishing a national data storage center endowed with intensive calculation infrastructure in line with regulatory and security imperatives. As the system grows, the build-up of special services for scientists and health-related businesses will make it possible to exploit the enormous potential represented by the data and information to be accumulated in coming years, in line with confidentiality rules.

Action

Installation of a national intensive calculation capability with commissioning by the end of 2017 to offer the first services for professional health care providers in the context of the care

pathway. CAD will be based in Paris and will be associated with a university to facilitate provision of the training necessary (Measure 7).

Description

This Center is an essential component of the project which will act as a hub around which the above-mentioned network of facilities will be coordinated (Measure 1).

CAD will provide a variety of services:

- **Hosting of data generated by the production facilities** (identified and automatically flagged variants). Nominal storage capacity at CAD will be of the order of 70 Pb/year.
- Interconnection and interfacing with national databases (DMP¹⁴, DCC¹⁵) for data matching and interconnection with international databases.

¹⁴ Personnel medical file.

¹⁵ Oncology communication file.

- Massive capacities (partnership established with a center [TGCC, the CEA *Très Grand Centre de Calcul*] for intensive calculation¹⁶, analysis, data mining and data interpretation make it possible to interpret data from different services and partnerships: for professional health care providers (validation *in silico* and by a network of experts [Step 4]; for search, comparison and *ad hoc* interpretation tools, depending on the stipulations of the prescription [Pathway Step 5]); for research (bioinformatics, biology,

clinical, public health), industry (clinical trial feasibility studies, design of more targeted trials, assistance with patient recruitment through the identification of genetic signatures and markers, pharmacogenetics).

CAD's regulatory framework (dealt with in Measure 9) will bring together the public sector with patient support groups and industrial concerns in a private-public partnership model. An interface will be established to help industrial players participate in services.

Schedule

	Feasibility study (IT architecture, organizational and regulatory aspects, security) to size CAD and draw up specifications
2016	Definition and refinement of choices for storage architecture, calculation, hosting protocols, anonymization, standards and data security. Definition of protocols for exchange with the platforms, organization chart, statutes, governance, economic modeling, identification of the various CAD users, qualification of expert networks and CAD assessment modalities.
	Deployment of specified material and software solutions
2017	Industrialization of specifications for the software to be installed at production centers, automatic flagging software (first data analysis services), CAD certification and accreditation (as a host for health-related data), integration into CAD of data from platforms, CAD accessibility for the first users.
	Commissioning of first certified software for variant analysis
2018	Establishment of a dynamic exchange path between CAD and identified sources of clinical data, first matching with clinical data to start analyses integrating clinical data
	Implementation of new phenotypic annotation protocols according to established indications
2019	
	Data matching and mining for genetic and phenotypic annotations
2020	

¹⁶ A preliminary feasibility study will establish required calculation capacities and technology choices. An initial capacity of 4096 cores and 16To followed by substantial expansion over the subsequent five years.

Measure 3: Foster the integration and exploitation of patient data into the care pathway

A patient's clinical and genomic data should be included in a virtual record available and usable for everyone along the care pathway. This should start from existing patients' medical records (PMR) as well as the communication file currently used in oncology. These instruments are still being deployed, one of the challenges being how to ensure interconnection of medical records at CAD: files that are spread around health care establishments, in most cases in non-interoperable

formats. Implementation of this Measure is a priority when it comes to integrating and exploiting patient data which is in itself indispensable to consolidating the care pathway.

Action

Generalize and standardize personal medical records and the oncology communication file to ensure interconnection and the matching of genomic data from CAD with data from health care establishments.

Target 2: Ensure operational development and expansion of the system in a safe technical, ethical framework

Measure 4: Establish a Reference Center for Innovation, Assessment and Transfer (*Centre de référence, d'innovation, d'expertise et de transfert, CRefIX*) to foster the technological developments and information technology required for implementation of the pathway

Achieving Target 1 (which is essential for consolidation of the care pathway) depends on the two central units stipulated in Measures 1 and 2: a network of ultra-high-throughput sequencing platforms interacting with a national data analysis facility.

Operational implementation of these units and the system in general will ensure an operational care pathway that is capable of integrating innovation in a dynamic and reactive fashion and developing expertise in data exploitation. This depends on a number of interdependent factors:

- definition and validation of instruments and procedures to ensure that the platforms and the CAD can work properly together with appropriate interfaces for their deployment;
- pilot projects (Measure 5) designed to identify and overcome technological obstacles, in particular those associated with the huge volumes of information involved as well as treatment and exploitation of the data generated;
- integration of innovative potential from academic research to guarantee high-level research and development;
- consideration of the background art and innovative perspectives of companies operating in this evolving field;
- establishment of strategic partnerships with emerging players and leading international companies (as has been done in the United Kingdom considering the massive implantation of certain high-throughput technologies).

Action

Creation of a national Reference Center for Technology, Innovation and Transfer (*centre de référence technologique, d'innovation, et de transfert, CRefIX*) to meet the various requirements identified at the beginning of the project, integrating all the key actions mentioned with all the necessary players.

It will itself constitute an important component of the system with respect to its national reference and assessment roles. It will help prepare for changes and technological innovations in the future, develop processes and harmonize protocols and methods before overseeing their set-up and commissioning. Innovative projects will accrue from public-private partnerships in the framework of constitution of the new channel. The deployment and integration of novel practices are favored by specific training programs together with the necessary regulatory and ethical changes (Measures 7 and 8).

Description

CRefIX will have a reference function with transfer to sequencing platforms and CAD of procedures, new tools and technologies developed in the context of standardization of processes and protocols of which it will oversee the implementation and commissioning, guaranteeing the training of staff working at the platforms and all the way along the care pathway.

CRefIX will be implemented from academic centers of excellence and through public-private partnerships with key national players (Measures 7, 9 and 10). Organized across two sites, aspects associated with sequencing will be based at the Genopole in Évry and at CEA; digital aspects will

be based in Paris with input from Inserm, Inria (*Institut national de recherche dédié au numérique*, National Institute for Digital Research), universities, STIC companies, etc.

For R&D, it will help with the development and integration of innovations all along the chain from sample-taking through sample preparation and sequencing and up to analysis and interpretation of the results. It will oversee compilation and standardization of the processes and protocols to be deployed at the platforms and CAD.

CReflX will host a reference sequencing platform as of 2016. In line with its aims, this will carry out sequencing for the proposed pilot projects (Measure 5) in order to identify possible obstacles, test-run solutions and ensure the technological developments necessary at every relevant level of the chain in the pathway. Subsequently, the expertise thus acquired will be sequentially trans-

ferred to the sequencing platforms together with associated regulatory specifications.

Its activity will develop in a dynamic, adaptive way making it possible to integrate new technologies and avoid risks of obsolescence and loss of competitiveness at the same time as smoothing over transitions without compromising the quality of services provided for patients along the care pathway.

With respect to expected partnerships, it will have a transfer function, the conditions of which—in particular with respect to capitalization—will be defined at a later stage in concert with partnering businesses. It will also contribute to innovation in various fields at the interface between the ethical, social and regulatory issues raised by the need to integrate genomic medicine into French existing health care system (Measure 9).

Schedule

2016	Establishment of CReflX: installation of a prototype platform at the National Genotyping Center (<i>Centre national de génotypage</i> , CNG) at CEA in Évry, choice of standards (sequencing) to apply, help compiling standards for the exchange of information with European and international Plans, software testing
2017	Prototyping, testing and standardization of the first variant annotation programs on the basis of solutions available from the academic environment for routine clinical use in the care pathway, compliance with the life cycle of non-NGS data
2018	Optimization of CAD storage (new models of specific database management systems for the storage, indexing and searching of flagged variants) Definition of interoperability standards for matching data with other types and sources of data Commissioning of the first software for matching genomic and clinical data Commissioning of first certified software for variant analysis
2019-2020	Implementation of new phenotypic annotation protocols according to established indications

Measure 5: Overcome the technological, clinical and regulatory obstacles encountered along the path with respect to the three broad groups of disease concerned

The main steps along the care pathway are explained in the introduction to Part 3. They involve sets of interacting links around the main components, namely the network of sequencing platforms and CAD (Measures 1 and 2).

Installing an ultra-high-throughput sequencing capability across France raises a number of novel technological and scientific challenges. Measures 1, 2 and 3 address these tightly interlacing issues and, at the same time, the adaptation and development of a large number of instruments and protocols, as identified at the preliminary stage. Nevertheless, to reveal unexpected obstacles, to identify constraints that need to be mitigated, and to develop and implement appropriate solutions, it is indispensable to test how the care pathway is working and its consistency *in situ*, including high-throughput sequencing runs on selected cohorts of patients.

Action

Set up four pilot projects on cancer, rare diseases, common diseases and a sample of the general population to detect and test technological, clinical and regulatory obstacles—already identified or not—at various steps along the care pathway.

Description

Focusing on the three broad groups of diseases addressed in the Plan, these need to be scheduled as a matter of priority. These will shed light on specificities and provide answers with a view to constructing a standardized care pathway that is as consistent as possible, independently of any specific disease.

These pilot projects will depend on existing skills and strengths (CNG for sequencing) as well as the activities of the Reference Center for Technology, Innovation and Transfer (*centre de référence technologique, d'innovation, et de transfert*, CRefIX, Measure 4) and a registry to be set up by Aviesan (Measure 11).

Certain obstacles and areas of uncertainty have already been identified along the main steps of the care pathway as described above:

- Step 1: To help doctors considering submitting an order, they should be given a panel of indications for which sequencing might be relevant. Centers where the order can be executed should be listed together with their accreditation vis-a-vis pathology-specific criteria (skills, protocols, etc.) and status (public or private). This to investigate patient care in different parts of the country, ensure provision of suitable medical training and test the content and modalities of management of the Informed Consent procedure (related to Measure 9).
- Step 2: At the sampling phase, the type of sample required (biopsy, blood sample, etc.) should be stipulated according to disease and type of sequencing (exome, genome or transcriptome). How the sample was treated before dispatch for sequencing. The type of structure capable of taking the sample (laboratory, hospital, public, private) can be analyzed in the light of the relevant requirements, standards and protocols with a view to the standardization of procedures according to orders and accreditation of those involved. Conditions and procedures for transport to sequencing centers should also be examined (hauler, temperature, SOPs¹⁷, deadlines...).
- Step 3: Sample preparation and sequencing with a preliminary comparison based on the alignment of read-outs on a reference genome to identify and qualify sequence variants. The obstacles to be tested at this stage will show whether the centers ought to be generic or more specific, qualify any input from private partners (partners, sub-contractors, etc.[?]), check the standardization of procedures by having replicate samples treated by different players, test calculation, storage and data archiving procedures, etc.

¹⁷ Standard Operating Procedures

- Step 4: Transfer to CAD (or the equivalent, simpler prototype during the transition phase in 2016) for processing and *in silico* exploitation of the resultant data. The obstacles to be tested at this stage will confirm that transfer and flow management capacities are adequate and that CNIL authorizations concerning data exploitation and exchange are being correctly applied with effective, operational data sharing. [CNIL: *Commission nationale de l'informatique et des libertés*, National Information Technology & Privacy Commission]
- Step 5: At this stage of submission of the report to the ordering physician, testing will focus on the first aids to decision-making.

Schedule

2016-2017	Pilot studies on cancer and a rare disease.
2016	Working groups to set up pilot studies on diabetes and the general population
2017-2018	Pilot studies on diabetes and the general population

Measure 6: Establish a system to assess and validate new indications for access to genomic diagnosis

The growth through 2025 in the Plan will depend on expansion of the existing list of indications. This relies on transfer of research to care with validation of indications derived from scientific progress. New indications will be successively added as they are validated. These indications will be in the three broad sectors, i.e. rare diseases, cancer and common diseases.

Action

Establish a system for the assessment and validation of new indications. Possible indications will be discussed with partners or may be dictated by Government or the Supreme Health Agency (*Haute autorité de santé*, HAS) which may commission specific studies to validate new guidelines on access to genomic diagnosis.

Description

Work on the assessment and validation of new indications will proceed in partnership with the qualified agencies and institutions (learned societies, HAS, patient support groups, General Health Directorate [*Direction générale de la santé*, DGS], Social Security Directorate [*Direction de la Sécurité sociale*, DSS]). These will take the form of studies on patient cohorts (phenotypes of common

diseases, rare diseases and cancer) and will aim at validation of entry of the indication concerned into a reimbursement process. CRefIX will be consulted for treatment of innovative aspects of set-up of the proposed studies.

The Plan will therefore have a major role in examining, overseeing and including new indications in the health care system with these successive validations. The growth provided for in the Plans of Barack Obama and the 100,000 Genomes Plan in the United Kingdom is also based on this same approach.

In parallel and above and beyond regulatory aspects related to execution of the Plan (Measure 9), this Measure will have a dimension related to the human and social sciences. This will make it possible to acquire the empirical data required to facilitate the sharing of experiences between players and on the other hand, conduct high-resolution analysis of the experiences of all those concerned, especially patients and their families with the involvement of the relevant patient support groups. Taking this dimension into account will drive the development of Good Practices.

Measure 7: Foster new skills and personnel capable of meeting the challenges of how to analyze and interpret the data

New skills and jobs are required to meet the challenge of how to exploit and interpret the results. The skills required at the various stages of the pathway—at the new sequencing centers, CAD, laboratories and platforms—cover several multidisciplinary fields, mainly genetics and molecular biology with sequencing technologies, bioinformatics, bioanalysis and biostatistics. In addition, these needs will broaden to specific aspects of the pathway concerning information, Consent and the reporting of results.

These skills correspond to several levels of training from technician to engineer and covering medical practitioners and laboratory test specialists who will have to master a number of them. A preliminary assessment of the jobs and skills to be developed has been made and compared with corresponding identifiable training programs. This exercise together with complementary interviews has shown that the skills needed are rare (or non-existent) because they traverse relatively unrelated disciplines—something that current training programs rarely address and, if they do, address poorly. Nevertheless, such skills are indispensable when it comes to ensuring an effective care pathway and success of the proposed Plan.

Action

Rapid establishment of specific training programs at universities and colleges to prime construction of an industrial framework dedicated to genomic medicine, establish job descriptions in collaboration with the General Directorate for Care Provision (*Direction générale de l'offre de soins*, DGOS), the General Directorate for Higher Education & Employment (*Direction générale de l'enseignement supérieur et de l'insertion professionnelle*, DGESIP) and the Conference of University Presidents (*Conférence des présidents d'université*, CPU).

Description

- For initial training, it will first be necessary to make a precise definition, as a function of needs, of the skills that will have to be acquired by the various categories of personnel at the platforms and CAD, as well as those that doctors and other professional care providers will have to acquire. These will have to be added to job descriptions, e.g. in biostatistics or data mining and analysis. On these bases, a detailed inventory of current resources at national training centers (IUT, universities, schools of engineering) will be made.
- With help from DGESIP for the establishments concerned and Communities of Universities and Establishments (*Communautés d'universités et d'établissements*, Comue), existing training programs (in particular for engineers, Master's in Bioinformatics) will have to be adapted or reinforced, especially programs on bioinformatics, biostatistical genetics and data analysis. Initial training of the professional health care providers concerned—who do not currently know much about genomic medicine—should also be reviewed with a view to introducing the relevant ideas. In parallel, new transdisciplinary training built on defined job descriptions will have to be implemented in the form of vocational degrees and Master's qualifications.
- Programs already exist for ongoing training and specific training for practicing laboratory specialists, under the aegis of various learned societies and professional groups. These structures could be built upon by helping them meet a demand for training that will considerably grow in coming years.
- Creation of a training structure with adequate resources (a special school or as part of a public health educational institution) could be envisaged to afford genuine national and European visibility for this novel interdisciplinary system. **French participation in EBI (*European Bioinformatics Institute*) and**

Elixir (European infrastructure for life sciences information) will help with the development of European partnerships on training.

The development of such a system will eventually create a scientific and industrial community that brings together clinicians, geneticists, medical

test specialists, epidemiologists, biostatisticians, computer experts and mathematicians. This will further enhance acceptance of this novel dimension to medicine (Measure 13). Updated teaching of modern genetics in school would also help. A ten-year perspective to guide the initiatives to be put in place over the time frame.

Schedule

2016	High-resolution review of skills and jobs National mapping of relevant training programs and resources
2017	Compilation of new job descriptions, formulation of novel transdisciplinary training programs, adaptation and reinforcement of existing programs

Measure 8: Integrate ethical aspects related to the collection, storage and processing of clinical and genomic data and guarantee safe, high-quality care pathway

The availability and exploitation of genomic data representing whole populations raises many ethical questions, at both the individual and societal levels. In terms of regulations, a strict framework ought to guarantee safe, high-quality care pathway. The regulatory framework to be developed or adapted is vast, concerning most of those involved in the care pathway in its manifold technical and logistic aspects. Regulatory changes may go from the amendment of Good Practices (HAS, BioMedicine Agency [*Agence de la biomédecine*, ABM]) to the need for new legislation (the Bioethics Law). The Parliamentary Office for the Evaluation of Scientific and Technological Choices (*Office parlementaire d'évaluation des choix scientifiques et technologiques*, OPESCT), national, European and international learned societies and groups of geneticists, and experts working on European projects (FP7, H2020) have already started posing solid bases for deliberations. Finally, recent and ongoing national and European legislation needs to be closely examined from a perspective of the impact of various recent texts on the steps of genomic medicine.

Action

Examine and, if necessary amend the regulatory framework in the light of legal and ethical standards to adapt it to specific issues raised and the Good Practices that need to be established to guarantee safe, high-quality care pathway. **An Informed Consent model tailored for genomic medicine will be proposed. The National Consultative Committee on Ethics (*Comité consultatif national d'éthique*, CCNE) will have to be convened to go into these aspects more deeply at the national level.** Given the importance of these challenges and their scale, they now need to be considered at the international level.

Description

At the individual level, before Consent, patients ought to be given information about all the issues and conditions associated with the exploitation and use of their personal medical data with control based on access to medical records and protections guaranteeing the confidentiality of all such data. Two issues warranting special attention are at the heart of this Measure:

- **in order to protect the patient, it will be necessary to develop and apply advanced coding and anonymization techniques for intrinsically identifiable sequences.** Nevertheless, cross-referencing different types of personal data—even small datasets—with theoretically anonymized genomic data might elicit a risk of re-identification, especially since the storage of sequence data—or at least part of it—for long periods is necessary to generalization of their use in clinical and scientific applications. Therefore, hermetic anonymization of sequence data cannot be absolutely guaranteed and the information given to the patient ought to be accordingly transparent. Anonymization cannot therefore be the one and only cornerstone for protection: above and beyond the most technically advanced anonymization measures, data will have to be protected with a whole set of other measures, commitments and vigilance with tightly controlled access and stringent restrictions on permitted uses;
- **genomic sequencing generates massive amounts of data above and beyond the information sought in the context of the order which raises the question of secondary discoveries.** In particular, discovery of presymptomatic pathology in a situation in which neither prevention nor cure are possible would become commonplace. Against this background, **the question of whether to tell the patient or not**—respecting the individual's right not-to-know and parents' rights—represents a challenge, as well as questions of when to make the announcement and how to do it. Similarly, another question that will arise is that of **retesting capacity** in the long term as deeper understanding expands the possibilities of interpretation.

From a collective point of view, adherence to these requirements has to be reconciled with the general interest that is inciting this project in which capitalization on these data—for everyone's benefit—assumes broad sharing and exploitation by the many players in the health care system, scientific world and the economic tissue who will be involved¹⁸. Ultimately, a large number of fields representing other societal challenges that it is as yet difficult to estimate will be affected and will have to be managed, assurances for everyday acts, but also dietary, social and cultural practices and habits.

¹⁸ See the conclusions of the Secretariat-General of the Council of the European Union on "personalized medicine for patients", summarizing the Council's conclusions from 7 December 2015 (n° doc. prec. 14393/15) aimed at delegations.

Concerning the regulatory framework, recent and ongoing national and European legislation needs to be closely examined from a perspective of the impact of various recent texts on the steps of genomic medicine. In particular:

- new European Union regulations of data protection (General Rule on Data Protection) finalized in December 2015 and to be published in the first half of 2016;

- the revised Directive on diagnostics and medical devices;
- the Law on modernization of the health care system in December 2015;
- the Digital Republic Law.

We intend to break this Measure down between the main steps in the care pathway.

Schedule

2016-2018	<p>Propose an Informed Consent model tailored for genomic medicine.</p> <p>Assess patients' practical needs for information (time, modalities).</p> <p>Compile a regulatory inventory taking stock of all applicable texts and identify obstacles and needs for consistency at different levels of Standards in the light of legislative schedules.</p> <p>Convening of CCNE concerning secondary discoveries in the context of clinical application and seeking new-generation sequencing, prior to revision of the Bioethics Law.</p> <p>Working together with CNIL and other concerned agencies on the implications of new European data protection regulations in the field of sequencing in clinical practice as envisaged in the Plan.</p> <p>Organize a national conference on regulatory aspects with all concerned institutional players.</p>
2018-2020	<p>Establish a special registry for practices and experience sharing tools, especially with respect to secondary discoveries (related to Measure 11).</p> <p>Involve France in international harmonization processes on secure data sharing for genomic medicine.</p> <p>Launch research projects in human and social sciences to conduct inquiries and gather empirical data on different players' points of view on the ethical challenges of NGS.</p> <p>Mobilize and consult with the various players—especially patient support groups—on educational initiatives and Consent Forms and modalities.</p>

Target 3: Establish monitoring and steering tools to make the adjustments required throughout implementation of the Plan while ensuring public involvement

Measure 9: Mobilize industrial entities implicated in the project to meet technological and industrial needs at the various steps in the care pathway and promote the emergence of a "genomic medicine" channel

This Plan constitutes a unique opportunity to foster dynamic innovation in many areas, e.g. conservation, the mathematical processing of big data in the health care field, Web semantics and the Web of Objects, medical devices, etc.

To find the necessary solutions and equipment, it would seem essential to integrate this initiative into **an ambitious industrial development plan**. This will make it possible to construct a real system to support growth of the sector while constituting a new source of economic development and employment. The involvement of businesses is essential in the context of international competition (1.2). It is therefore indispensable to mobilize them as soon as possible after launch of the project to drive emergence of a genuine "genomic medicine" system.

Action

Propose companies a logic of how the system will work as well as an economic logic allowing its implementation, functioning and sustainable development. It will therefore be important to stipulate the value chain and associated economic model as well as modeling of the investments required, key financial flows and expected results.

Description

Such mobilization should in particular incite a description and analysis of the business model underlying this action (flow, value creation, cost of investments, savings) within which everyone will be able to take a position.

Analysis of how the future system will work should take into account two interconnected value chains:

- one involving patient care and covering entities capable of performing the procedure as well as the services and products aimed at allowing performance;
- the other focused on the exploitation of aggregated data.

If both of these value chains generate immediate value linked to the hoped-for results of ultra-high-throughput sequencing (improved health care, in particular patient treatment, longer survival, etc.) and depending on technologies, solutions and services possibly implemented by different types of company, delayed, evolving value related to data exploitation is also identified. This delayed value will gradually lead to more precise medical procedures resulting in enhanced therapeutic efficacy, fewer adverse reactions, progressive diminution of treatment mistakes, etc.

The medico-economic reflection should therefore simultaneously consider a possible rise in costs due to increased use of sequencing services and (ultimately) a reduction in patient treatment costs (better treatment selection, limitation of the treatment of non-responders, etc.). The medico-economic model should therefore cover the duration by including a possible investment period before the results phase.

Schedule

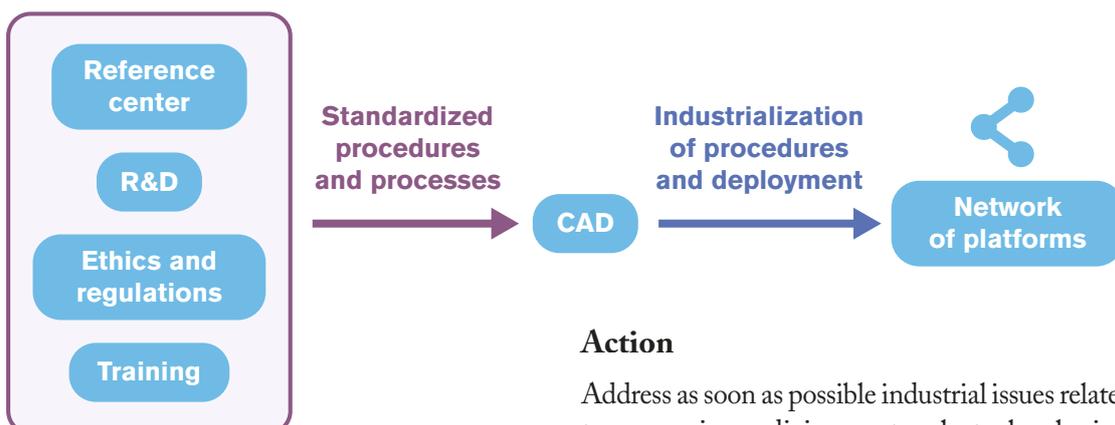
2016-2018	Stipulate how the future industrial system will work and the economic logic of its implementation and durable operation by accompanying the reflection by a consultant.
2018-2020	Integrate pilot projects (Measure 5) and the high-resolution understanding of the care pathway that results in order to discern specific economic models with differential flows.

Measure 10: Orientate the activities of all those involved to address industrial issues arising along the genomic care pathway

Implementation of the Plan and the emergence of a national industrial framework of genomic medicine depend on simultaneously defining a number of industrial tools at the various stages related to the pilot projects (Measure 5), the activities of CReflIX (Measure 4) and in the longer term CAD. This will rely on the necessary technological and medico-economic demonstrators (reagents, automatic sample preparation, data integration, storage and interpretation, etc.).

In addition, normalization and standardization of procedures and data from the various stages will have to be addressed and envisaged from the outset at the European level. Elements of an industrial strategy also need to be developed with, in particular, establishment of a database of relevant patents submitted in France in the fields concerned and definition of a strategy for acquiring foreign patents.

Measure 10, CReflIX



Action

Address as soon as possible industrial issues related to genomic medicine, not only technological issues but also regulatory and ethical aspects, with adequate human resources to develop the necessary innovations, products and services through establishment of a public-private task force.

Description

The public-private task force will be organized around the five think tanks already in place.

Specifically focusing on technical and practical aspects of setting up an industrial genomic medicine framework, this task force will provide another State-sponsored forum for dialog between public-sector and private-sector partners

(CSIS/CSF¹⁹, industrial solutions, diverse Ministerial and InterMinisterial groups). **The work of this task force will yield proposals for the next CSIS extended to companies involved in the field of digital health care.**

All the recommendations so far published by this task force have been assimilated into the various corresponding Measures.

Schedule

Work by the five groups that already constituted this task force for preparation of the Plan will carry on and bolster the various Measures and Actions to be implemented.

This Measure therefore constitutes a transition phase. It is intended that it should disappear as the industrial framework becomes operational.

Measure 11: Monitor developments in the field of genomic medicine at the international level

Against a background of international competition, it is important to follow developments in the field of genomic medicine at the international level to be ready for any adaptations or reorientations required to implement the Plan and guarantee top quality service for patients, at the same time as preserving the competitiveness of national players in the industrial framework thus constructed.

Description

This long-term genomic medicine registry will be under the aegis of Aviesan. With all the relevant expertise, one of its roles will be to monitor all aspects of this rapidly evolving sector, be they medical, scientific or societal, in particular to integrate new validations. It will also provide a forum for the exchange of experiences.

Action

Establish a monitoring system to follow the field of genomic medicine at the international level.

Measure 12: Establish a research program dedicated to economic aspects of the Plan

The introduction of economic calculation into public-sector decision-making will ensure that available resources are optimally allocated within society. Empirical studies by the Organization For Economic Co-operation & Development (OECD) confirm that health care system performance (as measured by life expectancy) is better served by improving resource allocation than by increasing health care expenditure.

In France, two pieces of legislation address the place of economic calculation in the definition of the scope of reimbursement in health care. Firstly, the health care budget is voted on every year by Parliament in line with the Finance & Social Security Law and secondly an efficiency criterion has been integrated into assessment of the price of health care goods and services since October 2013. **The efficiency of the system will have to undergo a medico-economic efficiency assessment (with input from professional health care providers) throughout the research program.**

Increasing use of economic calculations in decision-making in health care meets a demand for rationalization of government expenditure: it guarantees optimum allocation of collective resources. Any arbitration concerning collective resources—which everyone expects to be expended in the public interest—has to be justified and every party (political decision-makers in concert with professional health care providers) has to be able to vet how they are being used.

Action

Create a research program, as soon as the Plan is launched, to study medico-economic aspects of the integration of genomic medicine into medical practice. The aim is to seek answers to a complicated question, namely how to design a model that helps the population benefit from progress in genomic medicine at the same time as guaranteeing a sustainable national economic model based on optimization of the allocation of collective resources.

Description

Before validation, the Measure means that the medico-economic implications—both qualitative and quantitative—of every indication being considered for ultra-high-throughput sequencing should be assessed. This will take into account the medical (and societal) benefits of implementation, economic repercussions (including societal and economic capitalization) and the consolidated costs of deployment in the care pathway framework. This will cover benefits accruing from more judicious prescription of complementary examinations and treatments as well as the economic consequences of being able to replace current examinations with sequencing. Since the system will cut down the incidence of adverse reactions (that currently have to be treated), such savings will also be assessed. This Action will be conducted under the aegis of the Toulouse *École d'économie* (School of Economics) with identified partners.

Measure 13: Organizing the information, consultation and involvement of everyone in society who is concerned

A national Genomic Medicine Plan can only be realized with the involvement, understanding and commitment of the general public as well as of those who are directly concerned. In parallel with measures pertaining to ethical and regulatory aspects, some countries already committed to genomic medicine have undertaken wide-reaching exercises of communication, consultation and dialog with their peoples, in particular Estonia and the United Kingdom.

Action

Undertake broad-scope actions across the country exploiting different media, different methods for consultation targeting all levels from schools (because genomic medicine also concerns children) to broad populations throughout the country.

Description

Sustainable actions have to set up to publish regularly updated information and foster dialog on how the Plan is being implemented in the general population as well as those more directly

involved (patient support groups, users' groups, youth, schoolchildren, etc.).

Education: define and organize how to establish dialog with people (with more details after examination of the models in the United Kingdom, Belgium and Estonia); set up an annual meeting on genomic medicine with large-scale educational and consultation sessions for the general public; posting of a Web site.

Research: launch research and research/action projects in the human and social sciences to gather information and monitor developments.

At the European level: France should support the European Commission's Eurobarometer initiative (2018) on genomic medicine to establish its position vis-a-vis other European countries and adapt the French Plan to match the European framework; get involved in its conduct and analysis.

Training: with reference to Measure 8, investigate the need for training and implement training actions with charities, schoolchildren, teachers and journalists.

Measure 14: Governance of the Genomic Medicine Plan

The governance proposed for the Genomic Medicine Plan will be inclusive, based on multiple partners, involving all users in coordination of its launch and achievement of a series of actions over coming years. This coordination will be organized at the political level which is essential to successful realization of the Plan's objectives and will guarantee commitment over the full ten years.

This governance will frame steering of the Plan, monitoring of its implementation and assessment (notably medico-economic), dialog with those involved as well as users, and education of the general public.

Steering of the Genomic Medicine Plan

Steering of the Genomic Medicine Plan will be under the responsibility of an InterMinisterial Committee and the authority of the Prime Minister. It aims to oversee implementation of the Plan according to a realistic preset schedule. It will ensure coordination between the national and regional levels. Steering will depend on monitoring and assessing implementation of the Plan.

Interministerial Genomic Medicine Plan Steering Committee

The Steering Committee will be composed of the Ministers of Research, Health and Industry with Directors of these ministries' administrations and other involved ministries, the Director-General of Cnamts, the President of HAS, representatives of the Directorates-General of regional health agencies, the President of Aviesan and representatives from patient support and health care system users' groups.

The Steering Committee oversees implementation of the Plan through mobilization of partners and resources, and directing its orientations. As the situation evolves, the Committee may propose adaptation of the Plan.

It will meet at least once a year. It reports to the Prime Minister on progress of the Plan and compiles an Annual Report.

Monitoring and evaluating the Plan

The Genomic Medicine Plan is to be monitored by a special operational Committee that helps with its guidance. For each Action, the Plan identifies a Pilot with a suitable schedule to work together with all the partners involved to perform the Action, monitor its implementation and report on its results.

Monitoring Committee

Aviesan will coordinate monitoring of the Genomic Medicine Plan and evaluate outcomes. It will run the Monitoring Committee with all the Pilots supervising Actions. It will schedule the implementation of Actions and check their conduct against said provisional schedule. It will assess outcomes through specific indicators and monitor expenditure with respect to the allocated budget. It will compile an Annual Report on the Genomic Medicine Plan. The Monitoring Committee will meet three or four times a year.

Evaluation of the Genomic Medicine Plan

Implementation of the Genomic Medicine Plan will be continuously evaluated by the Steering Committee on the basis of success indicators and the outcomes of specific Actions.

It will only be possible to evaluate impact of the Plan on health targets (e.g. efficacy gains in targeted cancer treatment by virtue of the contributions of genomic medicine to improved therapeutic orientation) after some time and economic impact constitutes a specific Measure in the Plan (Measure 12).

Indicators to be used to monitor and evaluate the achievement of targets will be proposed by the Steering and Monitoring Committees and then precisely defined together with the Pilots of the Actions. These indicators will be validated at the Plan Steering Committee's first meeting in 2016.

The Genomic Medicine Plan will be evaluated independently—notably on the basis of said indicators—by organizations and institutions appointed by the Government, namely *France Stratégie*, the *Haut Conseil de la santé publique* (HCSP, Supreme Public Health Council) and the *Haut Conseil de l'évaluation de la recherche et de l'enseignement supérieur* (HCERES, Supreme Council for the Evaluation of Research & Higher Education). Medico-economic evaluation of the Plan will be conducted by the Toulouse *École d'économie* (School of Economics), a specific Measure in the Plan.

Dialog between those directly involved in implementation of the Plan and users

Health care professionals and users of the health and research systems are to be implicated in implementation of the Genomic Medicine Plan in a globally democratic strategy.

Above and beyond the presence of users and patient support groups on the Steering Committee, Aviesan will organize consultations on implementation of the Genomic Medicine Plan with those involved and users, in collaboration with the Steering Committee at annual meetings between players, industrial partners and institutions.

Regional consultation

Through local meetings, regional health care agencies will organize consultations on the Genomic Medicine Plan in their own region between those who are directly involved, local communities and users.

Keeping the public informed

To publicize how the Genomic Medicine Plan is being implemented and its results, the Annual Report on the Plan will be published. A special

Web site will be set up to broadcast full information about the Genomic Medicine Plan, including how it is progressing and its achievements.

GLOSSARY

ABM	Agence de la biomédecine
ANSSI	Agence nationale de la sécurité des systèmes d'information
ARIIS	Alliance pour la recherche et l'Innovation des Industries de Santé
Aviesan	Alliance pour les sciences de la vie et la santé
CAD	Collecteur analyseur de données
CCNE	Comité consultatif national d'éthique
Cnamts	Caisse nationale de l'assurance maladie des travailleurs salariés
CNG	Centre national de génotypage (CEA à Evry)
CNIL	Commission nationale de l'informatique et des libertés
CNV	Copy Number Variations. Number of copies of a given gene in the genome (which varies between different people)
Comue	Communautés d'universités et d'établissements
CPU	Conférence des présidents d'université
CReFlX	Centre de référence, d'innovation, d'expertise et de transfert
CSIS/CFS	Comité stratégique des industriels de la santé/Comité stratégique de filière santé
DCC	Dossier communicant de cancérologie
DGESIP	Direction générale de l'enseignement supérieur et de l'insertion professionnelle
DGOS	Direction générale de l'offre de soins
DMP	Dossier médical personnel
DSS	Direction de la Sécurité sociale
EBI	European Bioinformatics Institute
Elixir	European infrastructure for life sciences information
Exome	The totality of gene segments that are transcribed into the messenger RNA molecules that code for proteins—the functional products that determine a cell's structure and activities
FP7	EU's Seventh Framework Program
GAFAMS	Google, Apple, Facebook, Amazon, Microsoft, Samsung
GB	Giga base = 10 ⁶ bases
H2020	European Horizon 2020 Research Program (2014-2020)
HAS	Haute autorité de santé
HCERES	Haut Conseil de l'évaluation de la recherche et de l'enseignement supérieur
HCSP	Haut Conseil de la santé publique
ICGC	International Cancer Genome Consortium
IGAENR	Inspection générale de l'administration de l'éducation nationale et de la recherche
INCa	Institut national du cancer
ITMO	Instituts thématiques multi-organismes d'Aviesan
LEEM	Les Entreprises du médicament
NGS	Next-Generation Sequencing, ultra-high-throughput sequencing
OECD	Organization of Economic Co-operation & Development
OPESCT	Office parlementaire d'évaluation des choix scientifiques et technologiques
PNMR	Plan national maladies rares
Pb	Peta bases = 10 ¹⁵ bases
RNA-Seq	RNA sequencing, sequencing of the transcriptome
SNIIRAM	Système national d'information inter-régimes de l'Assurance maladie
SNV	Single Nucleotide Variations
STIC	Sciences et technologies de l'information et de la communication
Transcriptome	The whole set of RNA molecules resulting from transcription of the genome

The President of Aviesan expresses sincere thanks to all those whose contributions have been essential in the construction of this Plan.

- Thanks are due to all the representatives of central administrations, research institutions, higher teaching and research organizations, hospitals and health care establishments and private-sector companies who have made important contributions at every stage of preparation of this Plan, and also for the work of the Steering Committee and the thematic and cross-disciplinary groups with special acknowledgment of those who have agreed to act as Pilots and coordinate groups' activities.
- Foreign experts who have agreed to contribute to the work or provide evidence.
- The learned societies and patient support groups who have made contributions or expressed their support.
- IGAENR for its help compiling this document.
- Aviesan and CVT Aviesan for logistic coordination of the work and support in preparing and producing this document.

APPENDIX
LETTER FROM THE PRIME MINISTER
TO THE PRESIDENT OF AVIESAN

INSERM
DIRECTORATE-GENERAL
21 APRIL 2015
RECEIVED

Office of the Prime Minister

20017

Monsieur Yves Levy
President of AVIESAN
Biopark
8 rue de la Croix-Jarry
75013 PARIS

Paris, 17 April 2015 1236

Dear M. President,

Recent technological progress in molecular biology and the development of new ultra-high-throughput sequencers mean that it is now possible to sequence whole human genomes faster and more cheaply. Analysis of whole genomes is taking an ever-more important place in medical practice in the areas of diagnosis, establishing prognosis and treatment in a framework of precision medicine.

A number of countries, including Great Britain and the United States of America have implemented unprecedented measures to meet this challenge. To preclude our losing ground and dependence on foreign countries, France too needs to acquire ultra-high-throughput sequencing capability commensurate with its needs.

In 2013, about 3,000 patients needed whole genome sequences. These were sequenced at public-sector and private-sector facilities but because of a national lack of adequate capacity, some had to be sent abroad. Most of this sequencing were paid for with funds from the Hospital Clinical Research Program, the Cancer Institute or charities. The health insurance system does not currently reimburse genome sequencing but the number of patients needing it is going to rise considerably in the near future. These major changes in medical practice and organization of the health care system cannot be separated from innovation and will require close coordination with the world of research.

Against this background, I am asking you as President of the *Alliance Nationale pour les Sciences de la Vie et de la Santé* (AVIESAN) to determine, within three months, what measures need to be taken to make whole genome sequencing routine as soon as possible.

Your work should:

- 1) review the place of whole genome sequencing and whole exome sequencing in therapeutic strategy. Please establish a qualitative and quantitative appraisal of current indications and, in the light of research underway, possible changes over the next ten years;
- 2) establish France's position in the research, analyze the place of these new technologies in the context of National Health Plans (cancer, neurodegenerative disease, rare diseases, etc.) and propose priorities in line with national research and health care strategies;
- 3) evaluate challenges related to innovation and potential impact in terms of capitalization and economic development, taking stock of both technological aspects and how to handle the analysis of massive databases, including the ethical issues;
- 4) propose medico-economic and industrial models to guarantee a financially stable system, including proposals concerning reimbursement by the Social Security system for whole genome sequencing procedures.

I expect from you recommendations on how to organize appropriate infrastructure for sequencing and data acquisition, handling and analysis. In particular, please consider whether a national platform or a series of specialized or deconcentrated platforms would be the best option. Please look at alternative set-ups to guarantee priority use in medical practice as well as in research. Please also formulate recommendations on the need for the equipment and skills to ensure functioning of the proposed infrastructure.

To fulfill this commission, exploit the expertise of:

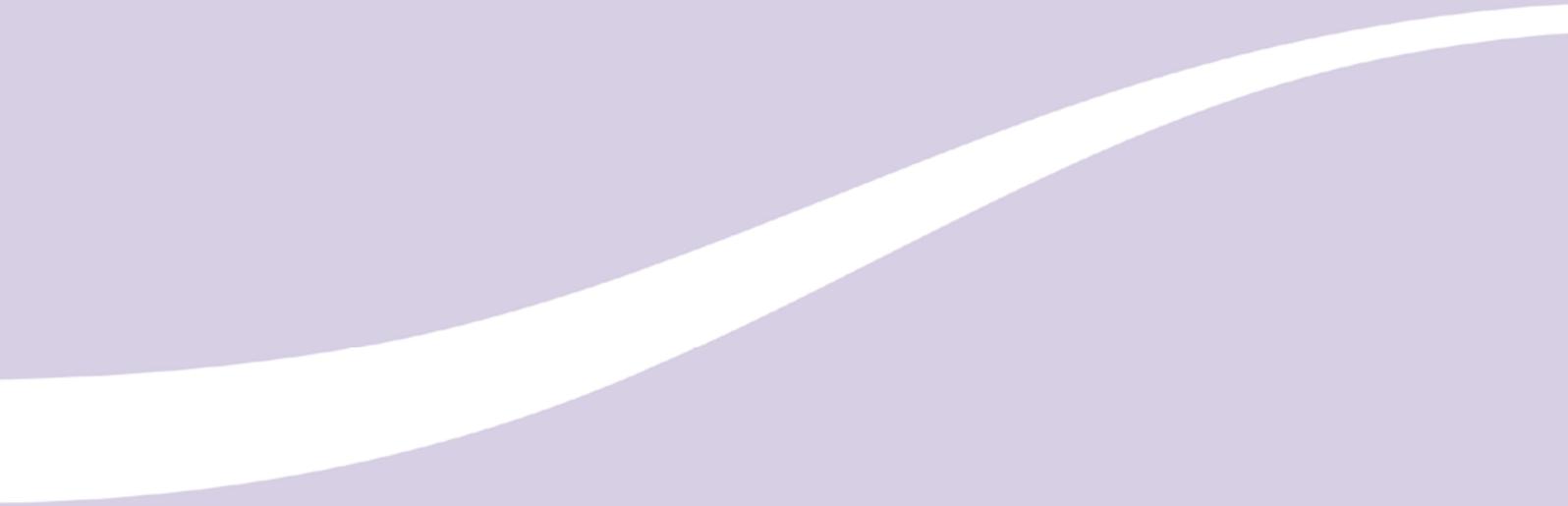
- the various divisions of AVIESAN, notably the Multi-Organism Thematic Institutes and the various experts who have already conducted investigations on the topic;
- the Director-General of CNAMTS for medico-economic aspects;
- the Ministry of Industry for questions about industrial channels.

Get in touch with relevant business spokespeople and potential partners in this project to talk about developing public-private partnerships. It might be useful to establish a relationship with the Strategic Health Care Industry Council (*Conseil stratégique des industries de santé*, CSIS) which organizes all aspects of health-related businesses—health care, pharmaceuticals, medical devices, in vitro and e-Health—around the theme of innovation.

Please report regularly to the Ministry of Social Affairs, Health and Women's Rights, the Ministry of Education, Higher Learning and Research, and the Ministry of the Economy, Industry and Information Technology before remitting your conclusions to me at the end of this three-month period.

Yours sincerely,

Manuel VALLS



aviesan

8, rue de la Croix-Jarry
75013 Paris

www.aviesan.fr