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Quarterly Medical Review – Health technology assessment in France

French evaluation of innovative health technologies: Early access and fundings

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ABSTRACT

Background: To accelerate the availability of innovative healthcare technologies for patients with the potential for significant clinical benefits in a context of high unmet needs, derogatory programs have been elaborated. The aim of this paper is to describe the different pathways developed in France to accelerate access to innovation, efficiently handle uncertainties while controlling the risks for patients.
Methods: We first describe the different early and temporary accesses to innovation in France involving the HAS. Feedback on these pathways based on the decisions provided by the HAS up until June 2024, is summarised and discussed. Subsequent emphasis is placed on the challenges of the evaluation process.
Findings: French derogatory pathways for innovation distinguish between medicinal products, medical devices (MDs) and procedures, as well as the funding mechanism. Early funding is dedicated to MDs, in vitro diagnostic MDs and procedures. Later fast-track access is dedicated to medicinal products but also to (digital) MDs. Based on the submitted files from 2015 to 2021, the derogatory access was approved about 70% for medicinal products and 30% for MDs/procedures.
Conclusions and Relevance: While fast-track processes appear widely used and understood for medicinal products, the different pathways available for MDs and procedures remain under-used and sometimes misunderstood. Whichever the product, the main limitation factor of approval was data quality and maturity, in concordance with reports on accelerated approvals from the FDA. The main challenge is to find the right balance between rapid access to innovation and patient safety, while addressing ethical challenges posed by new therapeutic approaches.

Abbreviations: AAP, Autorisation d'accès précoce (early access authorization); ANSM, Agence nationale de sécurité du médicament et des produits de santé (the french national agency for medicines and health products safety); ATMP, Advanced therapy medicinal products; ATU, Autorisation temporaire d'utilisation (authorization for temporary use); ATUC, ATU de cohorte (cohort authorization for temporary use); ATUEI, ATU d'extension d'indication (indication extension atu); ATUN, ATU nominative (named-patient atu); CAV, Clinical added value; CEESP, Commission d'evaluation économique et de santé publique (committee for economic and public health evaluation); DMD, Digital medical devices; DTX, Digital therapeutics; EU, European union; HAS, Haute autorité de santé (the french national health authority); HTA, Health technology assessment; HTD, Health technology developer; IVD, In vitro diagnostic medical device; LPPR, Liste des produits et prestations remboursables (list of reimbursable products and services); MA, Market authorization; MD, Medical Device; NICE, National Institute for Health and Care Excellence

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1. Introduction

The term 'innovation' in health care has been growingly used over the last decade. It has become a buzzword, though innovation in healthcare is not properly defined, as illustrated by a survey conducted by the French National Cancer Institute (*Institut National du Cancer*, INCa) in 2018 [1]. It emerged in the USA in 2012 with the concept of 'breakthrough therapy', i.e., drugs that intended to treat a serious condition with preliminary clinical evidence indicating substantial improvement over available therapy on a clinically significant endpoint [2]. For the European Medicines Agency (EMA), innovative medicine is a medicine that contains an active substance or combination of active substances that has not been authorised before [3]. It is now used to present any new form of care relying on advanced techniques, from novel drug candidates exploring inventive mechanisms of action - targeting specific receptors from translational research -, to innovative tests required for personalized medicine (e.g., companion diagnostic tests), or a new medical device that overpasses a simple technical development. This concerns a huge range of health care evaluations, ranging from early patient-centric dose-finding trials [4] up to the implementation of new technologies that include many different kinds of interventions, either pharmaceutical or non-pharmaceutical technologies [5], including artificial intelligence-based medical devices (MDs) [6–8]. However, although early access to innovations is widely advocated for by practitioners, patients and society, it should rely on their benefits, i.e., a clinical benefit or a gain in care organization at the population level, taking into account the potential risk of these innovations for patients [9]. Indeed, even if they seem promising, all will not successfully become new solutions for patients, improving their life expectancy without deteriorating their quality of life. The main challenge is to rapidly detect the 'true' or likely 'true' innovations, for patient and public health benefits.

Evidence-based innovations in health care are usually defined as the source of any improvement in the patient's care and quality of life [10]. Some important challenges when making health care funding decisions, whether restricted to some populations or not, relate to ethical considerations [11]. Indeed, bringing a promising innovative health technology to the market can be risky, whichever the intervention, potentially exposing patients to both inefficacy and harm. This was exemplified in the late 1930s, when elixir sulfanilamide - newly using diethylene glycol as a solvent/excipient - caused a mass poisoning in the USA with hundreds of deaths in 1937 [12]; this is of course a dramatic example. At a less extreme example, some new medical devices can be technically highly performant, though without any demonstrated clinical benefit for the patients or the public health (e.g., new programs in active medical devices, movement changes in joint prostheses, etc.) [13]. Anyway, between the proposal of an innovation and its diffusion in clinical practice, there is room for evaluating their advantages and added value from the standard of care and drawbacks, though milestones can be set up to manage risk-taking. However, there has been a growing debate on the required level of evidence to 'accept' risks, with the constant aim of accelerating development timeline through 'innovative' trial designs [14], shortening decision-making timeline with fast-track procedures/evaluations.

Thus, the uncertainty surrounding health care innovations has necessitated new and adapted pathways to market access and coverage, with timelines and procedures that greatly vary among countries [15–17]. As highlighted in the previous article ('The French way of HTA: between scientific rigour, independence and transparency'), the role of national health technology assessment (HTA) bodies is to provide opinions or decisions – depending on their mandate – regarding coverage of health technologies (i.e., our willingness to pay) once marketing authorization obtained.

In France, state-funded fast-track programs have been developed targeting innovative technologies with the potential for significant clinical benefit (and also organizational one for DMDs), for some in an area of high unmet (or partially uncovered) needs. Such derogatory programs differ according to the type of products, ranging from medicinal products (already approved or not) to medical devices (including digital), but also include medical procedures and diagnostic tests. They all rely on the French National Authority for Health (HAS, *Haute Autorité de santé*) assessment.

These fast-track procedures and evaluations offer the potential to facilitate patient access to promising innovative technologies and encourage innovation while ensuring patient safety, based on various levels of evidence and stages of development. However, there is no agreement on what constitutes 'sufficient evidence', with discrepancies between practitioners, health technology developers (HTD), and patients on one hand and HTA bodies on the other hand [18]. This was exemplified by a cross-sectional survey that was conducted in France among 115 health care professionals either from national societies of haematology, oncology, pharmacology and therapeutics, or from the French HTA body; with 56% of the former group agreeing with a simplified evaluation (including 49% even with no randomized clinical trial, RCT) compared to 5% (and 20% agreeing for the absence of RCT), from the HTA [19]. This raises the need to better explain how HTA decisions regarding these innovative health technologies - with a very broad scope - are currently made.

The objectives of this paper are first to briefly present the different adapted pathways allowing the early access in all the areas of presumed innovative health technologies, from medicinal products to medical devices and diagnostic/therapeutic procedures, including innovative tests, with their own specificities. They are secondly exemplified by case studies that illustrate decision-making processes for each of those products. Challenges in the evaluation process of those presumed innovative technologies are then highlighted. Lastly, key results and lessons learned from the first assessments are provided, targeting current strengths of various existing pathways in France but also their challenges going forward.

2. The different types of early and temporary accesses to innovation in France

2.1. Principles of assessment

As reported in ('The French way of HTA: between scientific rigour, independence and transparency'), health technologies are assessed in France according to their type (i.e., medical devices, digital medical devices, medicinal products, diagnostic/therapeutic procedures) based on specific regulations, with assessment relying on clinical or medico-economic specific criteria. A (presumed) health care innovation is a health technology with an innovative conception and/or mechanism of action likely to respond with a relevant benefit to a specific indication of a health need that –a priori- is not or insufficiently covered with the existing healthcare solutions before its full adoption on the market. The benefit is commonly clinical, for the patients, though it could be, in specific settings of digital medical devices (DMDs), an organizational benefit. Only health care innovations within the HAS appraisal will be detailed below.

In 2024, the two main French pathways, namely early fundings (i.e., coverage with evidence generation for early-stage innovation) and fast-track pathways (i.e., anticipated coverage at a relatively more advanced stage of development), concern either medicinal products on one hand -grounding for Early Access Authorization (AAP)-, or medical devices and procedures on the other hand with distinct pathways according to the type of healthcare product, namely the Innovation funding, the Uncovered innovative biological tests and pathological procedures List (RIHN), the Temporary coverage (PECT), and the Digital early access coverage (PECAN). This results in multiple early and temporary pathways to presumed innovation, depending

Table 1
Situations of innovation scoping for medicinal products, medical devices and procedures.

Targeted products	Medicinal products	Medical devices (MD), *in vitro* diagnostic MD and medical procedures, or multi-technology solutions		
Pathway	Early access ('*Accès précoce*')	Early fundings ('*Forfait innovation*' or 'RIHN')	Transitional coverage ("*Prise en charge transitoire")*	Digital early access reimbursement ('*Prise en charge anticipée*')
Finality	Funding of the product before its reimbursement by the French NHI	Funding of non-pharmaceutical technologies during a clinical / medico-economic study	Funding of the product before its reimbursement by the French NHI	Funding of digital MD before its reimbursement by the French NHI
Context of submitted innovation	Before marketing authorisation (pre-MA), or after marketing authorisation (post-MA)	- Individual use MD - Digital MD (for therapeutic use, remote medical monitoring, clinician use)[b] - In vitro Diagnostic MDs (IVDs): biological tests, companion test combined with a targeted medicinal product granted by early access - Medical procedures (MD for collective use or without MD)	Individual use MD and services All products eligible to the list of products and services qualifying for reimbursement except digital medical device with therapeutic purpose	- Digital MD (DMD) - Individual use DMD - DMD with therapeutical purpose (DTx) or DMD for remote medical monitoring activities In case of DMD for remote medical monitoring activities, funding is intended for supply of DMD and for medical services
Applicant	HTD	HTD or health professional (collective use or medical procedure)	HTD	Industrial
Receivability (regulatory criteria)	For pre-MA: Efficacy and safety should be strongly presumed based on results of clinical trials (ANSM) For post-MA: MA	CE marking is not a prerequisite for FI Need preferably CE marking for "RIHN" (IVDs used in hospital only)	CE marking in the claimed indication No national public funding No prohibition (ANSM)	- Applicant's engagement to apply for permanent reimbursement within 6 (DTx) or 9 (remote monitoring) months - No national public funding - No prohibition (ANSM)
Eligibility criteria	1) Serious/rare disease/disability 2) No available active treatment 3) Implementation of the treatment cannot be deferred 4) Presumption of innovation + For all, submitted file after MA within one month + For pre-MA submitted file for MA within 2 years	1) Innovative - degree of novelty - degree of dissemination - anticipated risks for the patients - medical need or reduced spending 2) Relevant and feasible studies - meeting a medical need or - reducing health care spending	1) Serious/rare disease/disability 2) Unmet medical need 3) Presumption of significant clinical benefit 4) Innovative 5) Clinical efficacy from clinical studies 6) Ongoing studies within 12 months	1) CE marking in the claimed indication 2) Presumption of innovation based on initial available data taking into account a relevant comparator (when existing) in terms of clinical benefit and/or progress in care organisation - Progress in care organisation must not alter quality of care - Ongoing studies deemed to provide confirmation data within 6 (DTx) or 9 months (DMD for remote medical monitoring activities)
HAS decision	within 90 days[a] (including ANSM decision for pre-MA early access)	within 75 days	within 60 days	within 60 days
Minister decision				within 30 days
Time limits	Within 1 year, renewable	FI: during the period of the trial plus an extended time until the coverage decision (additional cohort) RIHN: up to 6 years	Within 1 year in case of no submitted file for standard reimbursement	1 year (non-renewable)
Comment			Can be renewed once.	In parallel to HAS assessment, and prior Minister decision, the compliance to interoperability and IT security criteria is assessed by the digital health agency ("*Agence du Numérique en Santé", ANS*).

[a] possibly delayed to 4 months in the case of a large number of submitted files.
[b] For the latter category of digital MD, which is currently undergoing development within the French Health Insurance system, only if the purpose of use is medical, with an expected clinical benefit for the patient (not just clinicians) and meeting the eligibility criteria for the "Forfait Innovation".
HTD, health technology developer; IVD, In vitro diagnostic medical device; MA, market authorization; MD, medical device; NHI, National Health Insurance; PECAN, digital early access reimbursement (*Prise En Charge Anticipée*); RIHN, Uncovered innovative biological tests and pathological procedures list (*Référentiel des actes Innovants Hors Nomenclature*).

not only on the type of technology but also on the stage of development. Their similarities and differences are summarized in Table 1.

Interestingly, these pathways could also be segregated according to their funding mechanism, either 'pay to see' (early fundings for a clinical or health-economic study) or 'see to pay' ('fast-track' access to the market ahead of final data). Indeed, the evaluation of innovation in medical devices (*forfait innovation* for medical devices and procedures in general (RIHN for in vitro Diagnostic MD (IVDs) and pathology area only), includes the funding of a clinical or medico-economic research to ensure its benefit, i.e., an 'enlightening' bet on a high potential innovation for which the national authority is ready to engage in a 'pay to see' approach. By contrast, the setting of PECT/PECAN for medical (digital) devices, provides an anticipated coverage (or fast-track access) while a study is still ongoing in the same way as for medicinal products but possibly (for PECAN only) for a shorter duration. This is based on a wager

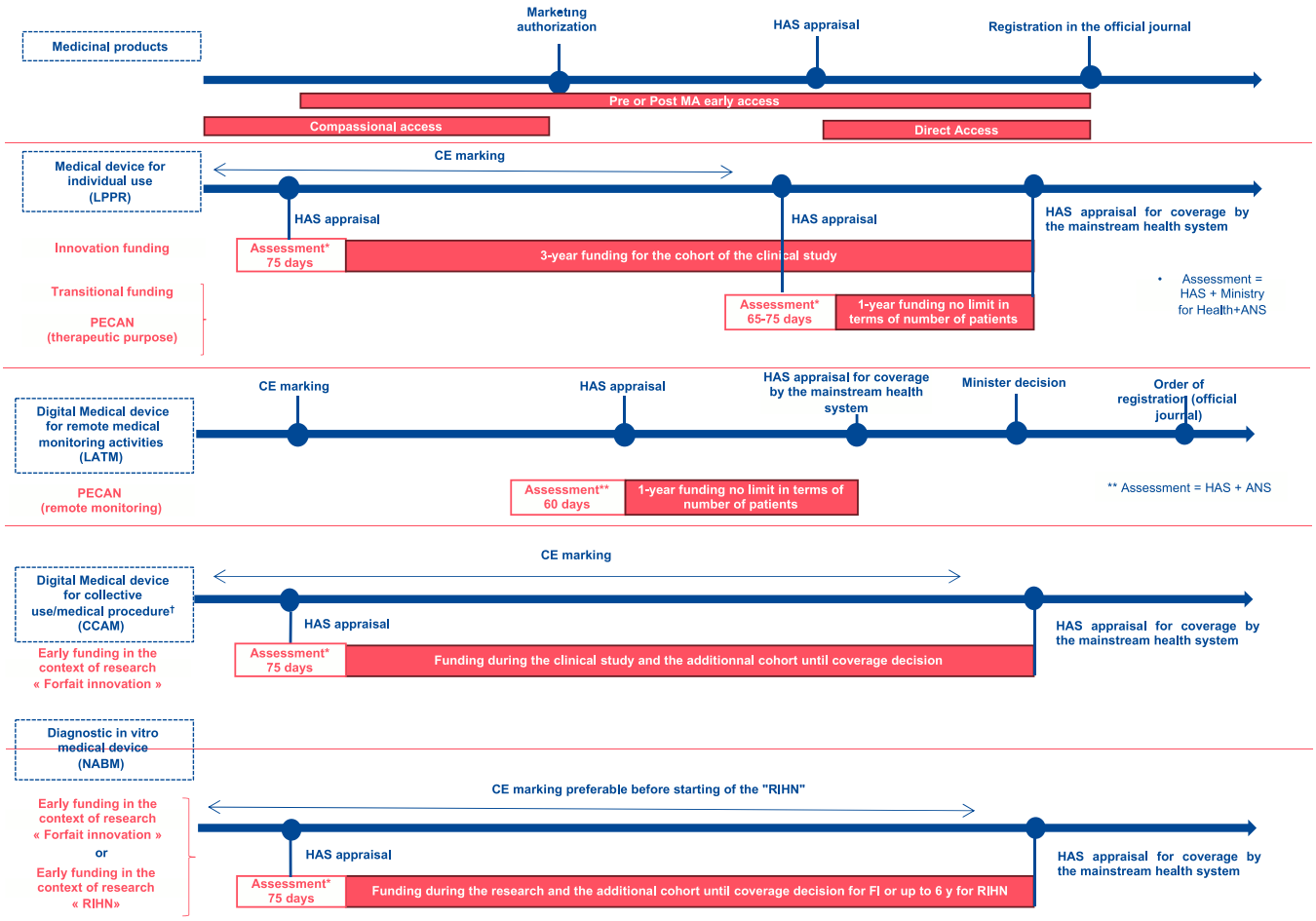

Fig. 1. Early/temporary pathways assessed by the HAS according to the type of product.

on efficacy and security using the standard 'see to pay' approach. These differences impact the potential access to those innovations by the patients. While the accelerated approval for medicinal products is mostly segregated according to its timing regarding the conditional/full market approval, several distinct situations for MDs/IVDs/procedures can be defined, depending on the nature of the device, its intended use in the target population, the action provided, and the purpose of the eligible coverage (Fig. 1). These situations are detailed below.

2.2. Early fundings

2.2.1. Early funding for medical devices or procedures: 'Innovation funding'

2.2.1.1. Background. 'Innovation Funding' (*forfait innovation*) is dedicated to the funding of innovative technologies (excluding medicinal products) by the National Health Insurance system (Fig. 1). Requested by the manufacturer or medical organization representatives as applicants, it is open to medical devices, IVDs and medical procedures; multi-technology solutions -combining a medical device or *an* IVDs with a diagnostic/therapeutic procedure- are also eligible. It simultaneously provides an early access for a health technology through a dedicated temporary funding, allowing secure access to disruptive innovations for patients while collecting clinical or medico-economic data required for further conventional coverage to reach a more robust decision.

It is not intended to provide a framework for the use or practice of a technique but contributes to increasing the attractiveness of the French clinical research. It was initially set up in 2009 by the French Ministry of Health on the recommendation of the HAS but failed to select eligible technologies on explicit criteria and to collect relevant data. After additional work it has become fully operational with cumulative criteria defined in 2015 as described below.

2.2.1.2. Principles. Any innovative health care product or procedure likely to provide important clinical or medico-economic benefits may, as an exceptional measure and during the trial and a limited period until the conventional coverage decision, be funded, on the condition that a relevant clinical or medico-economic study is carried out depending on the applicant claims (Table 1).

Innovation Funding authorization provides a restricted access to the market, supervised by a prior budget impact analysis and a registered protocol with dedicated centres, standardized procedure and required level of expertise for clinicians. Any granted technology is disseminated with caution across the French territory, provided the inclusion of the patients in the study, with the assurance of no funding discontinuation for a predetermined number of eligible patients between the end of the clinical research and the request for national coverage (known as the additional cohort).

2.2.1.3. Eligibility criteria. Eligibility criteria are appraised in view of the technology, the disease and its frequency, and the available diagnostic or care pathways. Innovative character of the technology is mandatory, assessed by: i) degree of novelty for the patient in the therapeutic strategy, ii) degree of dissemination, iii) anticipated risks for the patients and iv) presumption of clinical efficacy in an unmet or insufficiently covered medical need/reduced spending. Ultimately,

the clinical or medico-economic study to be carried out must be relevant and feasible (Table 1).

2.2.2. Early funding for IVDs and pathological procedures: the uncovered innovative biological tests and pathological procedures list (RIHN)

The uncovered innovative biological tests and pathological procedures list (*Référentiel des actes Innovants Hors Nomenclature*, RIHN) was created in 2015 to fund new IVDs, companion diagnostic tests and pathology procedures carried out in public laboratories across the French territory that had not yet been evaluated by the HAS though considered innovative by the French Ministry of Health. In 2024, the HAS was given the task of selecting these presumed innovative technologies for hospital use based on explicit criteria after validating the study protocol and its relevance (close to the *forfait innovation* criteria).

Requested by the manufacturer or medical organization's representatives as applicant, this early funding is an endowment financed at the time by the French National Health Insurance. It is dedicated to collecting missing clinical or economic data up to a maximum of 6 years before the final coverage decision. Today, there are ways of bridging the gap between two early access pathways, such as the 'AAP' for medicinal products and the 'RIHN' for a targeted drug and its companion diagnostic test. Principles and eligibility criteria are the same as for the Innovation Funding (Table 1).

2.3. Fast-track pathways

Contrary to the previous early fundings that relied on a 'pay-to-see' approach, the following fast-track pathways intend to provide an early access of a medicinal product or a (digital) MD for individual use (but not for medical procedures or IVDs), once a preliminary level of presumption of innovation has been achieved, based on first already collected data. The procedure depends on the type of product, medicinal products (with 'early access' pathway), MDs with 'Transitional Coverage' pathway and DMDs with 'Digital early access coverage' pathway. Note also that early fundings is mostly limited to centres or laboratories eligible to the study (except for RIHN) while the coverage, more advanced, could allow free access throughout the territory. Their specificities are summarized below.

2.3.1. Early access authorization for medicinal product (EAP)

2.3.1.1. Background. France led the way with early access programmes, introducing its 'Temporary Authorization Program' (*Autorisation Temporaire d'Utilisation*, ATU) in 1994 [20,21]. This program allowed early coverage of a new medicinal product by health insurance ahead of the marketing authorisation under specific conditions. It was set up in response to the AIDS pandemic in the 1980s due to the need to give access while controlling the use of new medicinal products, and then progressively expanded to cover all therapies. Its first form applied to groups of patients (*ATU de cohort*, ATUc), then it was possible for extension of indication (ATUei) upon request of the manufacturer or directed to a patient upon request of the prescribing physician (*ATU nominative*, ATUn) (Fig. 2).

Post-ATU programs extended the ATU to post-MA, with temporary coverage otherwise. Two decades later, temporary recommendations for use (*Recommandation Temporaire d'Utilisation*, RTU) were created for medicinal products not complying with MA, provided that its benefit-risk ratio was presumed to be favourable by the French National Agency for Medicines and Health Products Safety (*Agence Nationale de Sécurité du Médicament et des produits de santé,* ANSM). It then became clear that these complex procedures needed to be simplified to speed up access to presumed innovative treatments, and to avoid gaps in access between the early and post-authorization accesses.

In 2021, The Social Security financing act revisited these procedures [22,23]: instead of the six schemes above, only two remained: Compassionate Access and Early Access. Both are subject to compliance with a temporary use protocol (*Protocole d'Utilisation Thérapeutique et de Suivi des Patients*, PUT-SP and *Protocole d'Utilisation Thérapeutique et de Recueil de Données*, PUT-RD) for the collection of observational or real-world data in patients benefiting from such access. All decisions related to Compassionate Access are made by the ANSM [24], thus not detailed in this article, whereas decisions

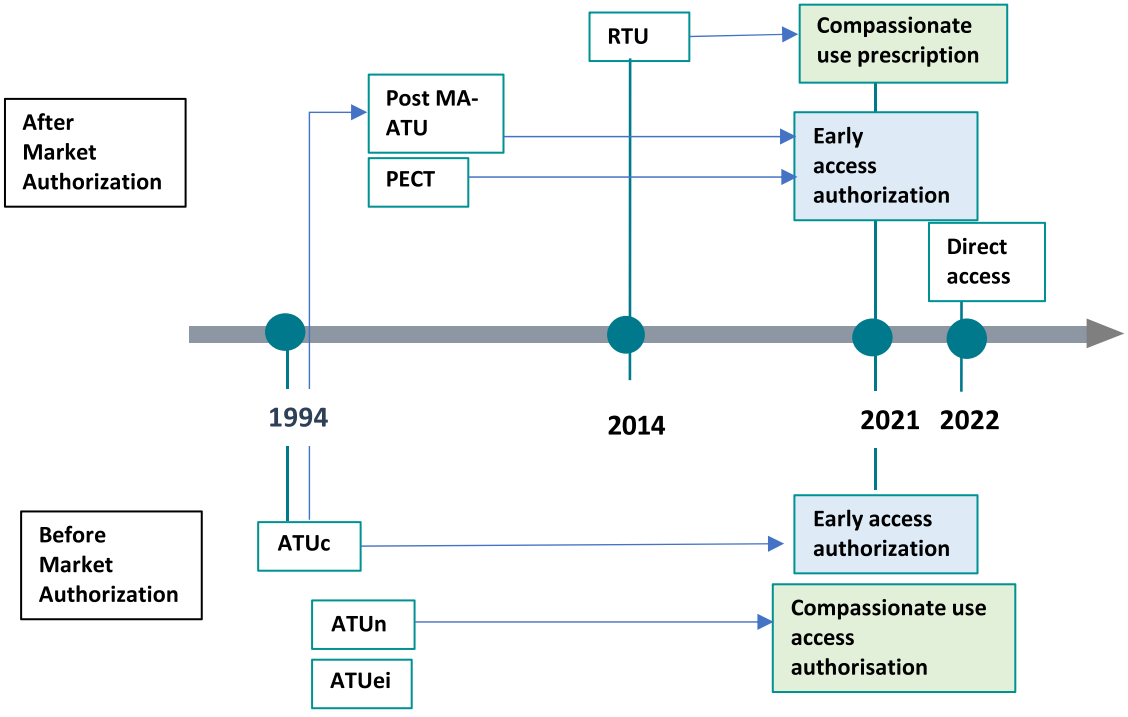

Fig. 2. Summary of the timeline of derogatory access in France for medicinal products.

related to early access are taken by the HAS after agreement from the ANSM on a positive benefit-risk ratio.

2.3.1.2. Principles. The Early Access Authorization (*Autorisation d'Accès Précoce*, AAP) is a derogation-based scheme enabling the early availability and funding of a medicinal product (for one or more indications) before its coverage by the French National Health Insurance. The objective is to fast-track access to the medicinal product for patients, up 2 years before the market authorization.

2.3.1.3. Eligibility criteria. Early Access Authorization can be granted on request by the pharmaceutical company for treatment under specific conditions (detailed in the article L.5121−12 of the French code of public health) [25], as summarized below (Table 1). For pre-MA AAP, the ANSM first assesses whether its efficacy and safety could be strongly presumed based on the results of clinical trials. If eligible, four additional conditions must be met, evaluated by the HAS: 1) serious/rare disease/disability; 2) no available appropriate treatment; 3) implementation of the treatment cannot be deferred; and 4) presumption of innovation including unmet (or only partially meet) medical need.

Following the granting of an early access authorisation, the pharmaceutical company must provide the medicinal product to patients within 2 months following the issuing of Early Access, and submit a request for inclusion on coverage lists once a MA is granted within one month.

2.3.2. Transitional coverage for medical devices (PECT)

2.3.2.1. Background. The Transitional Coverage (*Prise En Charge Transitoire*, PECT) is an anticipated process dedicated to temporary coverage, prior to permanent reimbursement for all products falling within the scope of the List of Reimbursable Products and Services (*Liste des Produits et Prestations Remboursables*, LPPR), and more specifically presumed innovative medical devices with therapeutic purpose or a compensation for a disability. For products that have benefited from the innovation funding, this process enables a bridge towards the coverage by the mainstream health system (Fig. 1). It is an anticipated process, decided by the Ministry of Health after advice from the HAS. It promotes a rapid and equitable access for patients to promising early-stage health care products for which a robust clinical study is being finalized.

2.3.2.2. Principles. Transitional Coverage is a fast-track pathway for the access and national coverage of health care technology. Once approved for Transitional Coverage, the technology is disseminated until the applicant finalizes the request for reimbursement by the health system and provides complete data. The French Ministry of Health takes the final decision after opinion from the HAS.

2.3.2.3. Eligibility criteria. Prior to the submission of an application, once regulatory prerequisites are met, the eligibility for Transitional Coverage is based on six criteria, all to be fulfilled (Table 1). First, the MD must manage a serious or rare disease or compensate for a disability. Second, the medical need must be at most poorly covered. Third, the presumption of clinical efficacy or compensation for disability must be justified. Forth, the MD must be new and not only an incremental technical evolution of a previous MD. Fifth, based on the first clinical studies results available, the MD trends to be clinically relevant with a significant efficacy in regards of acceptable potential adverse effects. Finally, ongoing clinical studies must be available within 12 months confirming efficacy and safety of the MD; this can be renewed once on request.

2.3.3. Early access reimbursement for digital medical devices (PECAN)

2.3.3.1. Background. In addition to the Transitional Coverage described above (Section 2.3.2), a derogatory pathway dedicated to some digital MD was created by the Social Security financing act for 2022 made operational in 2023, known as the 'Early access to reimbursement for digital devices' (*Prise En Charge ANticipée*, PECAN). The objective of this new temporary coverage process is to foster innovation and to encourage dissemination of digital MD into patients care by facilitating their access to patients.

It shares the same logic as transitional funding but with adapted criteria. This early phase allows the operator to finalize the demonstration of clinical and/or organizational benefits through ongoing study, while already being reimbursed. It only lasts for one year.

2.3.3.2. Principles. As with Transitional Funding, PECAN is a fast-track pathway. It is an anticipated process dedicated to temporary coverage, prior to permanent reimbursement, granted by the Ministry of Health upon advice from the HAS, for one non-renewable year. It is specifically intended for digital medical devices (DMD) demonstrating a presumption of innovation based on initial available data and for which a robust and pertinent clinical study is being finalized. PECAN is dedicated to two types of DMD: those having a therapeutic purpose (i.e., digital therapeutics, DTx) and remote medical monitoring activities (including the DMD itself and also the professional activity). Once granted, the applicant must submit an application file including confirmation data for permanent coverage within 6 months for a DTx or within 9 months for a remote monitoring activity.

2.3.3.3. Eligibility criteria. After the regulatory prerequisites have been considered fulfilled and the submission file has been considered complete by the ministers' services, eligibility criteria are assessed by the HAS (Table 1). First, the DMD must be CE-marked in the claimed indication. Second, its presumption of innovation in terms of a clinical benefit or a progress in care organisation must be demonstrated, based on initial available data and considering its relevant comparator.

3. Some feedback on early accesses and fundings for innovations from the HAS

As an illustration of the innovative pathways for health care products, key results from past evaluations of the early funding and fast track pathways are highlighted and presented below. Table 2 highlights the decisions provided by the HAS up until June 2024.

Table 2
Number of files analysed by the HAS since the implementation of the Early access to reimbursement (June 2024).

	Total	Ongoing	Not receivable	Withdrawal	Eligible for the HAS	Not eligible
Innovation funding (since 2015)	56	1	16	4	18[a], 32%	17
Transitional coverage (2021)	19	4	3	1	6[a], 31%	5
Early access pre-MA (since 2021)	76	NA	NA	NA	50, 66%	26
Early access post-MA (since 2021)	96	NA	NA	NA	72, 75%	24
PECAN (from 2023 to June 2024)	6[b]	2	0	0	1/4, 25%	3

[a] Including 2 with consecutive coverage by the mainstream system.
[b] one of the received applications involved 3 claimed indications (thus 8 claimed indications for 6 DMDs).
DMD, digital medical devices; PECAN, procedure for obtaining advance digital acceptance (*Prise en charge anticipée*).

Note that there is no feedback for RIHN as the results are not yet available (pathway assigned to the HAS in late 2024).

3.1. Medicinal product

For medicinal products, since the reform of AAP in July 2021 until June 2024, 228 requests have been assessed by the HAS. Among them, only 172 were a first request including 76 before-MA and 96 after-MA AAP. Those AAP requests were mainly in oncology (n = 85; 49%); infectious diseases (n = 15; 9%), endocrinology and metabolism (n = 14; 8%), haematology (n = 11; 6%), and neurology (n = 10; 6%) therapeutic groups; 120 (70%) of submissions concerned rare diseases, one-half from oncological settings. A total of 50 (66%) of submissions pre-MA and 72 (75 %) post-MA reached a positive decision of AAP. For positive AAP, the majority of those already assessed under ordinary law, were granted with a Clinical Added Value (CAV): n = 41 (39%); with a substantial or moderate therapeutic progress and n = 42 (40%) with a minor therapeutic progress. Thus, 20% were granted with no therapeutic progress (CAV V), this proportion of CAV V after an AAP tends to decrease over time [25]. In contrast, refusals of AAP were mostly (65%) driven by the existence of a clinically pertinent comparator or lack of sufficient data for suggesting likely innovation (83%).

3.2. Health technologies

We then considered the early accesses (and funding) for health technologies since implementation.

56 files were submitted for Innovation Funding since 2015 (corresponding to 42 distinct devices), 19 files submitted for Transitional Funding since 2021, and 9 files submitted for Early Access Reimbursement since 2023 (6 for remote medical monitoring activities and 3 for DMD with therapeutical objective).

They concerned different medical settings: cardiovascular (n = 10), oncology (n = 8) or pneumology (n = 7) for Innovation Funding; cardiovascular settings (n = 6), as well as vascular settings (n = 4), handicap (n = 4), digestive (n = 3), mental health (n = 1) and ophthalmology (n = 1) for Transitional Funding; and oncology (n = 4), geriatrics (n = 1), bariatric surgery (n = 1), gestational arterial hypertension (n = 1), musculoskeletal disorders (n = 1), pneumology (n = 1), sleep disorders (n = 1) for digital medical devices (one of the received applications involved 3 claimed indications; one company applied twice for PECAN).

Only one medico-economic study has been submitted in the context of Innovation Funding. The main reason of ineligibility for Innovation Funding was the absence of any significant clinical benefit (for the three early pathways with available data). The other reasons for ineligibility for Innovation Funding were based on the irrelevance of the clinical study protocol, or not being in the early phase of dissemination; ineligibility of digital devices (PECAN) were because presumption of innovation could not be determined from initial available data or because ongoing studies were not expected to provide the data required by the HAS in view of its assessment for permanent coverage in the predetermined deadline (6 to 9 months), or because there were no ongoing study whereas additional data were expected by the HAS to give its opinion in view of a permanent reimbursement.

4. Challenges of the evaluation of innovation

4.1. General framework of evaluation

Innovation is a major lever for improving the quality of care to patients. The aim of all early access processes and other derogatory procedures that have been set up in France over the last three decades is to accelerate the availability of such health care innovations to patients. However, this requires evaluating the presumption of innovation. Unfortunately, as reported above, the definition of 'innovation' is not consensual across countries and health professionals, and its evaluation relies on various criteria, rendering its assessment difficult in each context.

Nevertheless, as illustrated in Table 1, all the different pathways for presumed innovative health care technologies set in France base their assessment on four main common criteria assessing the evidence of innovation (first available data), though variously classified, namely the medical condition (the severity of the condition is not a criterion for PECAN), the unmet medical patient needs (except for PECAN), the presumption of innovation, and the need of further data collection.

4.1.1. Medical setting

The medical settings shared by almost all pathways concern serious or rare diseases, also including disabilities. The severity of the condition is assessed on the basis of the symptoms and organ involvement, mortality rate and the impact of the disease on patients' quality of life.

The rarity is defined by affecting no >5 in 10,000 individuals, as stated by the Council Recommendation of June 8, 2009 on an action in the field of rare diseases [26].

4.1.2. Unmet medical need

The second common criterion is the unmet, at least not fully met, medical needs, that is the absence of satisfactory therapeutic option in relation to the candidate product available to the patient in current practice. Interestingly this is included in the criterion of 'innovation' for the Early Access Approval of medicinal products, while clearly separated from the concept of 'innovation' for other health care products.

4.1.3. Innovation

The 'innovation' criterion is indeed the most difficult to define, usually as providing a change in a significant way from standard or accepted practice [27]. Evaluating the clinical impact of the health care product on the patient health status (from an efficacy and safety perspective) or organizational benefit obviously needs clinical data to be available at the time of evaluation. However, such an assessment is likely to be associated with uncertainty, where early evidence often provides only limited foresight to assess the true merits of the products. Evaluating the organisational impact also requires data to be collected or modelled.

4.1.4. Relevant data

The last criterion of all pathways relies on the need for further relevant data to accurately assess the benefit of the health care product. This obviously depends on the timing of derogatory pathways, with first early pathways made for (IVD) MD and procedures aiming at collecting missing data for informed coverage decisions by policymakers at an early stage of development, while later fast-track already requires enough clinical data to support the presumption of innovation. Of note, the need for confirmatory clinical data is included in the so-called 'development plan', with studies currently under way in the indication(s), likely to provide sufficient data to issue an opinion on the product. This stresses out the need to improve the level of evidence regarding significance in terms of efficacy and safety, before large diffusion of the product to the patients for their own benefit.

4.2. Uncertainty management

The main issue of early access evaluation is thus to manage the uncertainty surrounding early evaluations. Uncertainty management is based on identifying sources of uncertainty, assessing these

sources, and developing proposals to handle them in an acceptable timeline.

4.2.1. Sources of uncertainty

Early access submissions often rely on early, preliminary, data. This is observed for all the health care products looking for an early and temporary access, with specific criteria related to the assessment of the relevance of clinical data provided by the applicant (further detailed in the next Section 4.3).

This is also highlighted in drug development, where, to accelerate the development of health innovation, the standard procedure based on the succession of phase I, II and III clinical trials, has been considered obsolete and outdated, with 'innovative' designs claimed to be used [28,29]. Thus, it is commonplace to provide early patient access to innovative treatments with benefits only estimated from non-comparative trials, with short follow-up, small samples, interim analyses, and surrogate endpoints (mostly with uncertain validity), including heterogeneous patients in terms of prognosis, histology or biomarkers [30,31]. Single-arm trials are far from 'innovative' designs, their use as the standard for phase 2 clinical trials spans >50 years, later criticized due to the absence of a control group, given the difficulty to distinguish treatment effects from other factors [32,33]. They were considered in a learning setting, contrasting to confirmatory ones [34]. They are indeed intermediate, warranting further investigation and to further assess safety in large-scale randomized phase 3 trials. This may partially explain why there are growing examples where early approvals of oncology medicinal products based on such single-arm trials and surrogate endpoints had to be withdrawn at a later stage due to an absence of observed overall survival benefit [35,36]. As a substitute to any control arm, some have included external control arm from interventional or observational studies, or Real-World Data (RWD) [37]. This has led the HAS to highlight its position regarding such trials through guidelines to properly conduct external comparisons [38].

4.2.2. Focus on the next health economic assessment and uncertainty management

Uncertainty in the early fundings, then in fast-track market access, that mostly concerns the estimated effects in the short-term, would impact the estimated effects in the long-term. It is indeed challenging to assess the value of those novel therapies for coverage decision-making, based on such short-term data. If derogatory access to healthcare products based on non-comparative data from small samples can lead to considerable uncertainty in the assessment of clinical benefit, it will also heavily impact the subsequent economic evaluation for products once the product is brought under standard reimbursement. In France, such a health economic evaluation, based on the model conducted by the manufacturer, may be required for innovative products likely to have a significant impact on health insurance expenditure [39]. Created in 2013, the Committee for Economic and Public Health Evaluation (CEESP) of the HAS, is charged with giving 'economic opinions' from these evaluations, which are used for price negotiation between the Ministry of health and pharmaceutical firms [40]. Of note, 84% of medicinal products that have been assessed by CEESP in 2023 were previously accessible through derogatory access (cf. Section 2.3).

To illustrate with the example of advanced therapy medicinal products (ATMP), some of which aimed to cure the disease. When approved early on the basis of non-comparative data from small numbers of patients, ATMP effect maintenance are uncertain [41]. The fast-track evaluation avoids the recording of large follow-up times, hence the evaluation of a 'cure' cannot be distinguished from data censoring [42]. This causes critical limitations to the economic evidence for ATMPs [43], as treatment effect may be assumed over a long time horizon, even beyond the observations [44].

Furthermore, the main output of medico-economic evaluation is presented in the form of the incremental cost-effectiveness ratio, with uncertainty difficult to explore by standard statistical methods. To conclude, beyond quantifying relevant economic outcomes, the CEESP specifically characterizes the overall uncertainty level that surrounds the results. A major overall uncertainty invalidates the economic outcomes, thus impacting the price negotiation of the healthcare product [39].

4.3. A special issue: evaluation of innovative non-pharmaceutical technologies

The challenges facing MD, DMDs and procedures are more specifically centred by applicants and relate to improving the attractiveness (for HTD) and visibility (for health professionals) of early funding or fast-track market access. Unfortunately, as illustrated above, the poor relevance of already recorded or planned data should be stressed. Moreover, it is difficult for applicants to assess the level of maturity in the development and worldwide diffusion of their technology to guide them towards the best pathway, often leading to the ineligibility of the application. However, the strength of early fundings lies in the condition of conducting a study with a protocol that has been validated by the HAS and an estimated financial budget. The fact that an evaluation is quickly performed once the study is completed should encourage applicants.

A last specific challenge concerns the evaluation of digital MDs for health professionals for which the framework and guidelines has not yet been defined; the decision of their coverage is commonly case-by-case based in the absence of a specific list for reimbursement, while these digital technologies can be eligible to the early funding. In the end, the economic model is not totally predictable (specific individualized reimbursement, package through the procedure, etc.).

5. Discussion

The French pathways for early fundings/fast-track market access of presumed innovative technologies have been developed and modified mainly in the last 15 years, helping to provide a rapid access to improve patient care. They cover the large range of health care technologies, indeed, the initial offer of early access processes to medicinal products in the 90 s further extended to medical devices, IVDs, digital MD and innovative procedures. Moreover, most pathways aim to shorten discontinuation in the patient access of those innovations until its standard coverage by the health insurance scheme.

Several complexities of the first proposals have been ruled out to improve legibility and visibility for applicants and accelerate the process. This was notably the case for the medicinal products early access pathway. This achieved a tangible and rapid success in its implementation, as shown by the large number of reimbursed medicinal products under this scheme: 152 medicinal products for 252 indications resulting in 126,476 patients treated from 2021 to 2023 [45]. According to the French Health Insurance observatory in 2023, compared to other European countries, France is one of the fastest countries for access to innovative medicinal products.

In contrast, the pathways for early access for medical devices and procedures are still scarcely used and understood, as illustrated by its low eligibility rate, about 31% compared to an estimated approval rate of 70% for medicinal products. As highlighted above, the poor level of evidence of supporting data and lack of clinical study relevance are the main reasons for ineligibility of the requests. This could be attributed to the heterogeneity in the health care products and the potential applicants, ranging from multinational companies down to small start-ups or even health professionals, with limited funds and resources to supply the requested clinical data. Lastly, the complex distinct pathways – that mostly rely on the maturity of data pertaining the product, are likely difficult to understand by the

different applicants. Applicants should make more use of their opportunity for an early meeting or pre-filing appointment.

As a matter of fact, besides the four early pathways described in this paper, there are other pathways intended to fund innovation in France. For example, the article 51 of the Social Security Financing Act for 2018, introduced an early funding in 2019 to evaluate new health organisations, their implementations and benefits, to promote innovation in hospitals and medico-social establishments. Since 2019, at least three digital MDs for remote monitoring of medical activities have benefited from this funding. Then a favourable standard coverage decision has just been given for one of them in France, based on the collected data during the study.

For medicinal products, to complement the AAP, since 2022, a new experimental scheme for the early coverage of certain medicinal products has been experimented for 2 years, known as the Direct Access (*accès direct*) procedure [46]. It aims to enable patients and HTD to benefit earlier from market access, prior to price negotiation, and ensures a link with ordinary law in the event of exceptionally long-lasting negotiation. It only applies to medicinal products with a clinical added value, excluding those with granted early access. Note that since 2023, only 3 medicinal products have benefited from this direct access scheme.

Regarding submissions of early access for medicinal products, the rising cost of novel therapeutics contrast with the absence of extrapolation regarding their potential benefits at the long-term to allocate scarce health system resources as is the norm with other HTA evaluations. Several rules specifying the institution's expectations in terms of data (available or in the process of being collected) have been set out in the HAS doctrine [47], with a specific note regarding the HAS expectations for early access of medicinal products [48]. Complex innovative trial designs have been developed that could be used instead of single-arm trials, including adaptive designs [49], master protocols for platform trials [50], Bayesian designs [51], and other novel clinical trial designs such as Sequential, Multiple Assignment, Randomized Trial designs (SMART) [52]. The potential of those designs in improving the efficiency of the study, protecting patients, and improving the quality of information gained from trials has been considered by the FDA in approvals [53]. Moreover, support for applicants of medical devices have been published to help them better understand the HAS expectations [54].

We focused on understanding the French evaluation process of innovation for practitioners or HTDs. It should be kept in mind that patients and the public lack of information about the basis for decision making and opportunities to be involved is likely to be a barrier to identifying process improvement [55]. Some improvement in applicant support, including early interactions between all the involved stakeholders before submission could be developed. Notably, the possibility of supporting applicants by meeting them at an early stage or before they apply should be more widely known and valued.

Besides the French pathways, most other regulatory agencies are also increasingly required to make approval decisions for new drugs based on limited clinical evidence. This first includes the USA, where drugs qualifying for the fast-track/accelerated approval pathways can be subject to an abbreviated development process since the late 1990s, allowing FDA review within 6 months, compared to 10 months for the standard pathway [56]. Candidate drugs must fulfil criteria close to those required in France, with clinical benefit additionally required to be confirmed through post-marketing trials. Of note, the 21st Century Cures Act more recently created additional pathways to expedite USA drug development, including the use of RWD to support approvals. By contrast, in Europe, discrepancies in national evaluation criteria and reimbursement decisions are observed across countries, likely due to healthcare spending of access to innovations mainly granted by public health insurance [57,58]. In England and Wales, it falls largely on the National Institute for Health and Care Excellence (NICE); its priorities and values, e.g., a strong acknowledged preference to evidence from RCT, recently shifted, newly encouraging committees to accept a higher degree of uncertainty when considering technologies deemed 'innovative and complex' [59]. In Italy, risk-sharing reimbursement approaches are frequently used, with discounts and rebates delivered in response to certain clinical milestones [60]. Similarly, in Germany, outcome-based payment agreements have been implemented for CAR-T cell therapy [61]. Note that registry data on CAR-T cells therapy are also collected by the German Registry for Stem Cell Transplantation (*Deutsches Register für Stammzelltransplantation*, DRST) as per federal German regulations, similarly to France with the national DESCAR-T registry [62]. Interestingly, several works in Belgium and New Zealand have placed a greater emphasis in such HTA evaluations of therapeutic innovations on quality of life rather than life expectancy and cost-effectiveness [63]. Including 'expertise by experience' from patients faced with the physical, emotional and financial consequences of their illness, stresses out the importance of patients in those evaluations, already included in France with the audition or written contributions from patient associations.

6. Conclusion

Improving access to innovation in healthcare is a constant priority in France. Innovation does not only imply novelty and acceleration; it also needs to be efficient. Ensuring better and faster access to innovative medical technologies without compromising the scientific rigor that guarantees patients the safety and efficacy of approved medical technologies is crucial.

The use of innovative medical technologies raises significant ethical challenges, as deviating from standard care can pose considerable risks and offer uncertain benefits. They also raise financial issues, due to the restricted public funding, justifying a fair but strict appraisal of the innovation provided by the product, compared to the present setting, incorporating both patient expectations regarding its cure and its safety. Indeed, if unchecked, innovative practices can lead to the dissemination of costly but ineffective and even harmful interventions. Early meeting or pre-filing appointment with MDs applicants may help, as well as diffusion of recommendations regarding the HAS expectations for AAP. This is illustrated by the working group that was set up this year to clarify the Transparency Committee's expectations regarding how decreasing the uncertainty in the case of AAP that bet for the efficacy of a new drug.

Deciding when a new health product or technology? merits funding and when it does not—often to the displeasure of clinicians and patients alike—is an unenviable task. Many innovative health care products currently in development target rare diseases/indications with small patient populations, which greatly increases the difficulty in generating sufficient clinical evidence to support significant health improvement claims.

Conversely, early and evolving fundings pathway for (digital) MD, IVDs and medical procedures in France has several strengths in terms of methodological, ethical and financial requirements due to the conduct of a study in selected centres for evidence development and an estimated financial budget both previously validated by decision-makers. However, these advantages are still frequently limited by the lack of attractiveness for HTDs and/or visibility for health professionals or small manufacturers in view of the relatively large number of early access pathway already available in the country.

In conclusion, the evaluation of innovation requires a particular approach, not merely faster processes. It is essential to know how to properly frame this innovation. The assessment of these innovations must be patient-centred, with the primary goal of improving the overall health state of the patient. The main challenge is to find the right balance between rapid access to innovation and patient safety,

while addressing the ethical challenges posed by new therapeutic approaches.

Disclosure of interest

None for all authors.

CRediT authorship contribution statement

Capucine Serain: Writing – review & editing, Writing – original draft, Conceptualization. **Sylvie Chevret:** Writing – original draft, Project administration, Methodology, Conceptualization. **Yann Chambon:** Writing – original draft, Data curation, Conceptualization. **Vanessa Hernando:** Writing – original draft, Data curation, Conceptualization. **Françoise Lucet:** Writing – original draft, Methodology, Formal analysis. **Samuel Seksik:** Writing – original draft, Formal analysis, Conceptualization. **Hassan Serrier:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Elodie Velzenberger Maquart:** Writing – original draft, Data curation, Conceptualization. **Pierre Cochat:** Writing – review & editing, Validation, Supervision.

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