European Innovation Council

PATHFINDER CHALLENGE: Towards the Healthcare Continuum: technologies to support a radical shift from episodic to continuous healthcare

CHALLENGE GUIDE
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The EIC will hold an online Info Session on this Pathfinder Challenge call on 05/07/2022. Participation in the meeting, although encouraged, is optional and is not required for the submission of an application. Information about how to access the Info Session and on additional dissemination events can be found at EIC Pathfinder Challenges Applicants' Day (europa.eu) **and** EIC Pathfinder (europa.eu)**.**

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1. About this document

The Challenge Guide serves as guidance and background for the common understanding, participation rules and obligations for the EIC beneficiaries that are involved in the Challenge Portfolio. Contractual Obligations are further detailed in the EIC Work Programme 2022 https://eic.ec.europa.eu/eic-work-programme-2022_en and collected in the Pathfinder Challenge guidance on contractual issues, available on the Challenge page.

The Challenge Guide is a guidance document accompanying a Pathfinder Challenge call for proposals to provide applicants with additional technical information to underpin the objectives and to provide further information about how portfolio considerations will be taken into account in the evaluation of proposals.

The Challenge Guide is prepared by and under the responsibility of the relevant EIC Programme Manager (information about the EIC Programme Managers is available on the EIC Website https://eic.ec.europa.eu/eic-communities/eic-programme-managers_en). It further details the intention of the call by complementing notably the Scope, Specific Objectives and/or Specific Conditions set out in the EIC Work Programme[1]. In no case does the Challenge Guide contradict or supplant the Work Programme text.

[1] https://eic.ec.europa.eu/document/download/8c9ca0e4-6d66-4d8c-be06-caa02b8d9d2c_en

2 Background concerning the scope and objectives of the Challenge

This section provides additional information on the background in the relevant scientific and technological domains pertaining to Scope and Specific Objectives of the Challenges that applicants may wish to take into account. This section should be read as background to the Challenge call in the EIC Work Programme text (attached as Annex I). Proposals to this Challenge are expected to explain how they relate to and intend to go beyond the state of the art, and how they interpret and contribute to the objectives of the Challenge.

Overview

Current Healthcare Systems remain mostly reactive, as opposed to proactive and preventive. Citizens are still expected to watch for symptoms, self-diagnose their relevance, and trigger expert help, either from a general practitioner or specialist. Yet, unobtrusive and automated health monitoring technology could free individuals from self-performed health surveillance based purely on self-evaluated symptoms. This includes room sensors, smart home appliances enhanced with health monitoring capabilities, home-use diagnostic testing involving little and trivially simple user intervention, wearables, AI-enabled virtual doctors, etc.

Seamlessly integrated in the life of the individual, technology could perform continuous and quantitative assessment of a large range of health-relevant parameters and biomarkers. Such systems would follow strictly evidence-based guidelines, 24/7, devoid of human error or bias, affording full compliance with preventive or post-treatment follow-up programmes. In addition to facilitating compliance, the large dataset amassed could potentially uncover pre-symptomatic conditions far more effectively than single data points. Furthermore, the socio-economic impact could be enormous if leading causes of death globally were addressed by this new approach to healthcare including Heart Disease, Cancer, Chronic Lower Respiratory Disease, Stroke, Kidney Disease, Infectious Diseases/COVID, etc. [1][2][3].

This Challenge aims at the development of technologies that make continuous healthcare a reality.

Several disease families and a non-exhaustive background of their monitoring technologies are provided below. However, the applicants are invited to address the monitoring of any aspect of the health status. The specific disorders mentioned here are provided as examples only, to better convey the purpose of the Challenge rather than to constrain the scope of the Call.

Further, this Challenge is not limited to a specific technological strategy towards the goal of continuous healthcare. For example, ambient sensors, home-use devices (Point-of-Living testing), wearables, implantable devices, smart home appliances enhanced with health sensors

and others are within scope. Yet, the merits of each approach (e.g., expected impact, clinical usefulness, coverage of clinical conditions, etc.) can be different and these will be considered for project selection.

This Challenge does not target the incremental development of existing solutions, but the creation of disruptively new technologies derived from recent or insufficiently explored scientific data suggesting the plausibility of the idea and the existence of a window of opportunity.

Background on relevant disease families and monitoring technologies

Cancer

As many as 17 cancer types are included in the 2022 OECD/Eurostat avoidable mortality indicators list, with 9 of them considered preventable and 8 treatable with early diagnosis [4], [5].

Screening programmes, relying on mammography for breast cancer, PSA testing for prostate cancer, colonoscopy for colorectal cancer (CRC), cytology and HPV testing for cervical cancer, etc., are important steps in the direction of preventive and continuous healthcare. Yet the coverage of leading causes of death by existing screening programmes is still limited and screening remains predominantly office-based and physician-dependent. True integration of screening in an unobtrusive fashion has not been realised. And as the number of recommended tests (or their frequency) increases, this could negatively affect the compliance, and hence, the effectiveness of the screening programmes. Unobtrusive cancer-related health surveillance would be advantageous.

Home-based cancer screening (still non-automated but more convenient than clinic-based) has been explored with good results, see for example a comparison of colonoscopy performed under sedation (the gold standard for CRC screening and diagnosis) and home-testing with the Guaiac faecal occult blood tests (gFOBT), multi-target stool DNA tests (mt-sDNA) and faecal immunochemical tests (FIT), performed during the 2020-2021 COVID pandemic [6][7]. Home cervical cancer screening has also been explored [8]. Yet, the search for breast cancer blood biomarkers suitable for Point-of-Care testing continues [9].

Overall, unobtrusive non-invasive cancer screening remains challenging.

Diabetes

Continuous Glucose Montoring (CGM) has been one of the most successful achievements in continuous healthcare. As glycemic levels reach values outside normal range (80 to 120 mg/dL) a skin-attached CGM can alert the patient and guide self-administration of insulin or trigger medical help. With an estimated prevalence of diabetes of 9%, CGMs are already achieving

substantial societal impact. The first implantable glucose sensor in 1962 by Clark and Lyons relied on immobilised enzymes and oxygen electrodes [10]**.** Today´s CGMs [11] take the form of skin-patches. These can either use hypodermal needles for sensing the interstitial fluid [12], with replacement cycles of approximately 2 weeks, or communicate wirelessly with an implantable subcutaneous sensor (e.g. using a glucose-sensitive fluorescent copolymer matrix) in which case 90-180 day continued operation is possible [13].

The level of invasiveness of CGMs renders the technology appropriate for diabetes patients but not practical for glucose level monitoring in the general population.

Including glycemic levels within a broad panel of continuously monitored physiological parameters for the general population could be potentially beneficial, should an unobtrusive alternative to current CGMs be developed (see e.g. sweat-based sensors [14]).

Heart Disease

Automated or remote monitoring of heart function by means of Heart Rate monitors and ECG is already well established for diagnostics (short-term patch Holters) or follow-up of diagnosed patients (e.g. heart-failure telemonitoring [15]). Patch ECG is arguably a very successful example of (partly) unobtrusive monitoring.

Yet take up of continuous life-long ECG monitoring by the wider population, beyond high-risk patients, is unfeasible with current technologies.

Skin-patches or wearable watches needing additional electrodes to perform clinically useful ECG are unlikely to be taken up for long-term ECG monitoring by the average individual without cardiomyopathies.

COPD

Diagnosis and follow-up of Chronic Obstructive Pulmonary Disease (COPD) [16] traditionally relies on self-reported symptoms, peripheral O_2 saturation (e.g. measured by pulse oximetry [17][18]), CO_2 partial pressure (from arterial blood samples by a Severinghaus electrode, transcutaneous or exhaled breath end-tidal measurements [19][20]) and spirometry [21].

COPD patients on home Long-Term Oxygen Therapy (LOTP) or non-invasive ventilation (NIV, positive pressure applied with mask over nose and mouth), can be monitored with additional sensors without disruption to home routines.

Yet monitoring technologies deemed appropriate for COPD patients are too inconvenient for general preventive respiratory function surveillance in the general population, particularly if life-long unobtrusive operation is targeted.

Hypercholesterolemia

Unobtrusive continuous or intermittent (at weekly/monthly intervals) monitoring of cholesterol (total, LDL, HDL and precursors) would be advantageous given its role in cardiovascular disease. However well-established methods, either chemical [22], enzymatic (e.g. cholesterol estherase or cholesterol oxidase [23]), gas chromatography/mass spectrometry-based [24], require finger pricking (e.g. for PoC use [25]) or drawing of blood samples (for lab testing) and are not compatible with unobtrusive long-term monitoring.

Hypertension

High blood pressure (BP) is a risk factor for cardiovascular disease [26] and stroke [27]. Continuous BP monitoring in the general population could uncover patterns associated with hypertension, facilitate diagnosis and treatment and prevent cardiovascular and stroke events.

Arm cuff-based BP measurements, either manual (estethoscope-enabled auscultation) or automated (oscillometric) are well established but too cumbersome for unobtrusive continuous life-long monitoring. Recently developed wrist-band cuff watches [28] improve on usability but the need for repeated inflation of a (wrist) cuff remains. On the other hand, catheter-based continuous BP sensing avoids cuff use and is common in intraoperative settings but inadequate for ambulatory use and preventive purposes in the general population, as it requires arterial cannulation [29].

Non-invasive cuffless BP sensing remains an area of intense research [30], with ongoing efforts exploring approaches such as ultra-sound [31] and on-ring photoplethysmography [32].

Infectious diseases / COVID

Continuous unobtrusive monitoring of infectious diseases at incipient pre-symptomatic or fully clinical stages, e.g. by bacteria, viruses (including coronavirus), microorganisms [33][34] or by novel antibiotic resistant microbials [35], would facilitate early diagnosis and treatment of affected individuals and would enable communicable disease surveillance at the population level in the face of outbreaks.

Today's most widely used diagnostic technologies, either attempting direct pathogen detection or quantification of indirect infection biomarkers, are hardly unobtrusive. Lateral-flow assays (rapid antigen tests) are suitable for occasional home use, and popular despite offering only moderate sensitivity, but in their current form require user intervention and are not practical for unobtrusive life-long monitoring. Immunoassays and PCR are still mostly laboratory based.

Although a variety of Point-of-Care (PoC) devices have been proposed for diagnosis [36] and multi-modal vital sign monitoring can be used to track severity over time post-diagnosis [37], communicable disease screening in a truly unobtrusive format remains elusive.

Other applications

The proposals can target any clinical condition, biomarkers, vital signs, etc. beyond those mentioned above.

Remaining barriers and possible technological approaches

Various technological and adoption barriers preclude the realisation and take up of continuous life-long tech-enabled health monitoring. The proposals are expected to address one or more of these barriers. (Note that the solutions outlined here are provided only as examples and other technological strategies can be proposed.)

Barrier 1: Invasiveness associated with biomarker quantification

The need for finger pricking or venipuncture hampers the use of many blood biomarkers in life-long continuous health monitoring.

Breathomics offers a promising alternative. Volatile organic compounds (VOCs) in exhaled air and non-volatile compounds in exhaled breath condensates (EBCs) can be sampled (relatively) unobtrusively to quantify clinically useful metabolomic signatures with potential for monitoring cancer [38][39], COPD [40], diabetes [41], mental health [42], gastroenterological disease [43], chronic kidney conditions [44], etc.

While gas chromatography/mass spectrometry (GC-MS) is often used in breathomics research, home-based solutions require compact and low-cost alternatives. Artificial Nose sensors, eNoses [45][46] and millimetre-wave and terahertz spectroscopy [47] could be considered to this end.

In addition to exhaled breath, skin can also offer non-invasive, albeit indirect, access to bloodstream markers. For example, indicator-aided skin spectroscopy might inform on serum cholesterol content [48][49] and skin-attached (non-invasive) electrochemical and colorimetric sensors can estimate cortisol, lactate and antigens [50][51].

Barrier 2: False positives

Insufficient specificity leading to false positives can cause unnecessary stress to patients and their families and eventually deem a technology unusable.

To improve specificity (and sensitivity) of existing biomarkers, the proposals can take advantage of the large time-series datasets produced by continuous monitoring as well as fusing data from multiple sources, sensors, and biomarkers. For example, quantifying a massive number of non-targeted (a priori unknown) biomarkers has demonstrated potential for improving specificity of urine-based evaluation of bladder cancer [52][53] .

Barrier 3: Implantable biosensors: limited operational lifespan and reliability in physiological matrices

Individuals diagnosed with life-threatening or high morbidity conditions, at risk of re-hospitalisation, exacerbation, etc. are candidates for implantation of devices capable of unobtrusive continuous monitoring.

Moreover, the general healthy population could also consider preventive implantation of monitoring devices should these feature small dimensions (millimetre-sized i.e., smart-dust) and simple implantation procedures (e.g., subcutaneous), in exchange for life-long surveillance of relevant medical conditions.

Such implantable sensors will require an operational lifespan in the order of years offering reliable sensing of clinically important physiological parameters or biomarkers. Yet the operational life of implanted biosensors is often suboptimal [54] due to fouling (unspecific adsorption), foreign body response, corrosion and short-lived on-device reagents or functionalised biocoatings.

The proposals can tackle this barrier by multiple strategies including nanoporous membranes to protect the sensing surfaces (see for example the use of nanometric pores in Silicon membranes as encapsulations impermeable to immunoresponsive proteins in [55][56]), block copolymers as filters impermeable to macromolecules [57], mesoporous silica coatings [58], size-reduction and needle-like geometries to minimise post-implantation inflammation and immune response [59], surface modification to avoid fibrous encapsulation e.g. hydrophilic [60], zwitteronic [61] or basement membrane-derived [62] functionalisations, etc.

Barrier 4: Need for multiplexed technologies

The monitoring of multiple conditions using a single system (multiplexing) is preferred as it increases usability and adherence.

Ideas for new multiplex Point-of-Care devices can be sourced from the field of Digital PCR (dPCR) coupled to microfluidics, droplet concepts and microarrays [63][64][65][66], mobile phone-enabled microfluidics [67], microfluidic paper-based analytical devices (µPADs), and others.

CRISPR/Cas has also created new opportunities [68] leading to high sensitivity, specificity and throughput [69], portable RT-LAMP coupled to CRISPR implementations [70], CRISPR with lateral-flow readouts [71], etc.

Barrier 5: User compliance. Need for integration with daily user routines.

Optimal unobtrusive monitoring technology should not require active and repeated involvement of individuals in self-testing, as this would impact compliance.

A possible approach to overcome this barrier is to integrate health monitoring with daily routines and with the environment, objects, appliances, etc. Example opportunities are

photoplethysmographic rings [72], sanitary appliances for urine sampling and analysis [73], smart vehicles [74], smart-chairs [75] , smart glasses [76], etc.

Barrier 6: Need for human intervention in the analysis of large datasets.

The volume of data generated by continuous monitoring could soon outstrip the capacity of healthcare systems and clinicians to contribute to data analysis, rendering unattainable the goal of life-long continuous health surveillance.

Proposals can exploit Machine Learning (ML) to overcome this barrier, aiming at full automation while realising low numbers of false positives. Convolutional Neural Networks, Naive Bayes, Support Vector Machines, Decision Trees [77][78][79][80][81], amongst others, are promising and could be investigated further.

Barrier 7: Need for attention to gender-dependent symptoms and course of disease

The possibility of underdiagnosis of life-threatening diseases due to gender-specific symptoms, e.g. the Yentl syndrome in relation to ischemic heart disease affecting females [82], must be considered to ensure full adoption and appropriate impact.

3 Portfolio considerations for the evaluation of applications to the Challenge

This section describes how portfolio considerations will be taken into account in the second stage of the evaluation of applications. In the first stage, all applications will be evaluated individually by external experts and scored against the evaluation criteria set out in the Work Programme. All applications that pass the defined thresholds against the criteria will be included in the second stage of the evaluation. At the second stage, all above threshold applications will be considered collectively by an evaluation panel chaired by a relevant Programme Manager. At this stage, the Evaluation Committee will consider which applications to recommend for funding in terms of a coherent portfolio of projects that can interact, reinforce or compete with each other to increase the overall impact.

Categories

For this specific Challenge, the evaluation committee will map each proposal against the following **categories**:

- Medical condition addressed
- Type of technology proposed.
- Barriers to successful adoption addressed by the proposal. (see section "**Remaining barriers and possible technological approaches")**.

Portfolio considerations

For selecting proposals, i.e., creating the Challenge portfolio, the evaluation committee will use the categories and select projects according to the following portfolio criteria:

- Addressing a wide range of medical conditions across the portfolio will be preferred, as opposed to excessive focus on a single condition.
- In case of two or more proposals strongly overlapping in relation to the disease area addressed, the evaluation committee will seek to diversify in terms of specific technology within the overall portfolio.
- The optimal portfolio will address the largest possible number of barriers hampering the transition from episodic to continuous healthcare (or with the highest impact in case of equal number of barriers addressed), while taking into account that not all barriers are relevant for all technological approaches. The evaluation committee will take into account the degree to which the proposal addresses the barriers applicable to the chosen technological approach.

An additional check according to the criteria above will be performed to confirm that no new overlaps have been caused by the selection of the portfolio. Otherwise, the procedure above will be repeated.

4 Implementation of the Challenge portfolio

Once selected, projects will be expected and obliged to work collectively during the implementation of their projects under the guidance of an EIC Programme Manager. This section summarises some of the key aspects of this pro-active management which applicants should take into account in preparing their proposals.

Grant negotiations

Applicants may be requested to make amendments to their proposed project in order to take into enhance the portfolio. Such changes may include: an additional work package to undertake common/ joint activities (workshops, data exchanges, joint research, etc) with other projects in the portfolio; adjustments to the timings of some activities and deliverables in order to synchronise better with the implementation timings of other projects; specific target changes to improve complementarity/ comparability with activities and results from other projects. All such changes will be discussed during the grant preparation stage with the aim of reaching a consensus between all projects on the adjustments needed.

Challenge portfolio roadmap

Following the selection of a proposals to be funded under the Challenge, the Programme Manager will work together the selected projects to develop a common roadmap for the Challenge. This roadmap will integrate the activities and milestones of the individual projects into a shared set of objectives and cross-project activities. The roadmap serves as a common basis for implementing the projects - including possible adjustments, reorientations or

additional support to projects - and can be updated in light of emerging results of difficulties during the implementation. The objectives can be revised, for instance based on projects' unexpected achievements, new technology trends, external inputs (other projects, new calls…).

In particular, the Challenge roadmap will include activities on the transition to innovation and commercialisation, and to stimulate business opportunities. These activities, may be reinforced during the implementation with additional funding and expertise through pro-active management.

Tools for proactive management of projects

Projects in the portfolio may be offered additional support, either individually or collectively, in order to reinforce portfolio activities or explore the transition to innovation. Such additional support includes:

- Booster grants of up to €50k (see Annex 6 of the EIC Work Programme)
- Access to additional EIC Business Acceleration Services (see https://eic.ec.europa.eu/eic-funding-opportunities/business-acceleration-services_en)
- Access to the Fast Track to the EIC Accelerator, which would follow a project review (see Annex 4 of the EIC Work Programme)
- Access to the EIC Market Place, once operational, to connect with innovators, investors and other selected partners
- Interactions with relevant projects and initiatives outside the portfolio, including other EU funding initiatives as well as those supported by national, regional or other international bodies.

Annex I Extract of EIC work programme

II.2.4 EIC Pathfinder Challenge: Towards the Healthcare Continuum: technologies to support a radical shift from episodic to continuous healthcare

Introduction and scope

Today, episodic (symptom-triggered) healthcare remains the norm. To a large extent, individuals are entrusted with the responsibility to self-monitor and trigger requests to the health system upon identification of relevant symptoms. In spite of the growing number of screening programmes, the diagnosis of a vast majority of disorders, including those in which early action has a direct impact on morbidity or survival, still relies heavily on the individual to initiate the process. Further, a substantial fraction of outpatients manages the post-treatment phase, particularly of non-life-threatening conditions, with qualitative self-monitoring, seeking help only upon perceived evidence of disease recurrence. In essence the current approach to healthcare is mostly reactive.

While the episodic (reactive) model could be perceived as economically advantageous, drawing on healthcare resources only intermittently, it is clearly not optimal. In self-assessing their health status independently, individuals miss early signs of disease, sometimes with devastating results. The large spectrum of possible conditions and associated symptoms, particularly as age progresses, and the high behavioural resistance to seek medical assistance without clear symptomatic evidence, compounds the problem. Often the prodromal phase advances to full blown symptomatic phase before the diagnosis is triggered by the patient. Further, the emotional burden under the episodic healthcare model in which individuals are responsible to gauge severity and make decisions on when and how to seek help, should not be underestimated. Periods of raised health awareness, chronic conditions, slow convalescent recoveries, etc. in adult and paediatric populations can be particularly emotionally draining for patients and families under the episodic care model.

Technology can support much needed progress towards continuous and preventive healthcare, in which individuals are accompanied continuously and unobtrusively by health monitoring technology and practitioners, proactively offering diagnosis, treatment or follow up at the optimal pace and with the optimal protocol as dictated by clinical evidence. Under this model, human beings will heavily rely on technology seamlessly integrated in their lives, becoming recipients of proactive healthcare with minimal disruption and cognitive load. The burden of early spotting of disease will be shifted to unobtrusive technology. This requires careful consideration of all potential ethical issues that may arise, particularly related to data processing, data ownership and trustworthy artificial intelligence. Successful examples of such technologies already exist. Continuous Glucose Monitoring (CGMs) devices in skin-patch formats, for instance, offer diabetics relative unobtrusive and uninterrupted detection of inadequate glucose levels, with the possibility for remote diabetes care. Furthermore, body

motion sensors (e.g., accelerometer-based), respiration monitors and oxygen saturation (SpO2) sensors, cell phone-enabled behavioural analysis, fitness devices and many others are also available.

However, the full potential of the continuous healthcare model has not been fully realised as, for most conditions, diagnostic technologies do not exist with the required attributes: unobtrusiveness (environment-embedded, body-embedded, object-embedded, home-integrated, etc.), clinical grade reliability, affordability, etc. For example, fauling-free on-skin, under-skin, or implantable biosensors for long-term use, new modalities for Volatile Organic Compound (VOC) sensing (breathomics), new personal imaging systems e.g. THz-based or optoacoustic, unobtrusive continuous gut microbiome monitoring, etc. still require substantial groundwork.

The objective of this EIC Pathfinder Challenge is to develop systems and technologies starting at very low TRL for unobtrusive monitoring of human health with new continuous and personal imaging and sensing modalities, implementing continuous assessment, processing and analysis of the data to identify early signs of disease.

This call can support innovative technologies ranging from the sensor level up to the system level for effective integration of multimodal data.

Proposals can aim at monitoring a family of conditions or a wider mix of health factors, using the optimal combination of single-point or historic multi-point sensor data and, if appropriate, clinical records, genomic data, etc. to realise maximal performance.

Involvement of relevant stakeholders (e.g. clinical experts and patient organizations) from an early stage is recommended.

The gender dimension in research content should be considered, where relevant as well as the involvement of relevant stakeholders (e.g. clinical practitioners, patient organisations, etc.) from an early stage.

Specific objectives

Proposals submitted to this EIC Pathfinder Challenge should tackle the following specific objectives:

- develop a novel technology (device, instrument or full system) for unobtrusive proactive healthcare. The targeted technology should offer life-long health status monitoring and elements of predictive medicine with methodologies grounded in existing scientific evidence;
- the end objective must be a Proof-of-Concept and preliminary data suggestive of adequate safety and performance, while paying attention to minimising false positives that could hamper its real-world use;

- the targeted technology should make the case for a clinically acceptable solution amenable to successful evaluation under common Health Technology Assessment (HTA) methodologies;
- the path to future integration in the European healthcare workflow, specifically in relation to the inter-operability with existing infrastructures, as well as take up and compliance by appropriate patient populations, should be plausible.

Expected outcomes and impacts

The expected impact should be the establishment of the basis for the transformation of the prevailing episodic, symptom-triggered, healthcare system into continuous healthcare, in which individuals are accompanied continuously and unobtrusively by health monitoring technology and practitioners, proactively offering diagnosis and treatment.

Specific conditions

Proposals for this Challenge can be submitted by single applicants or by consortia, as dictated by the activities to be performed.

Annex II. References

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