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Enabling organizational conditions for digital therapeutics in Italy

1. Digital therapeutics for Italy: economic and industrial background

In the last decade, the economic crisis of 2007 and the subsequent public sector budget cuts of 2011 and 2012 have affected availability of funding for healthcare and, more generally, for life sciences as a whole. Even today, if Italian healthcare spending is compared with that of the main national economies in Europe, there is a clear shortfall. The Organization for Economic Co-operation and Development (OECD) data show that in 2018 Italian healthcare spending was about € 2,900 per capita on an economy-wide PPP basis - far less than in Germany (1.75 times higher than the Italian figure), France (1.45 times higher) and the UK (1.18 times higher).

However, the Italian national health service (*Servizio Sanitario Nazionale* - SSN) has successfully maintained high healthcare standards and quality of life (albeit with clear differences between different parts of the country), keeping these at a "competitive" level in international terms. These results have been grounded on good practices, as well as greater user awareness and involvement (participatory quality assessment, etc.), dialogue and cooperation between healthcare administrators and Patients' Organizations, and the impact of public and private research and innova-

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tion. This has borne fruit, as seen in the 2018 life expectancy figure of 83.4 years, among the highest in the world after Japan, Switzerland and Spain. Healthy life expectancy in Italy is 73.2 years, which is again higher then the mean figure for Europe and for countries like the USA, where healthy life expectancy at birth is 68.5 years[1]. Since the current pandemic will obviously impact these important demographic indicators, at least in a long-term perspective, the national health service can safeguard and further enhance them only if it can count on a well organized strategy in line with certain fundamental principles. These include a more uniform response to the population's health needs, in terms of appropriateness, efficacy, efficient use of resources and sustainability of the SSN itself.

A possible support and ally for modern health systems is digitalization, whose potential today is almost unrecognizable by comparison even with 20 years ago, paving the way for use of artificial intelligence-based models and predictive algorithms. As recognized *inter alia* by the World Health Organization, digital health offers a possible response to the need for improved healthcare access, reduction of related costs, improved quality in health management and self-care, and more effective, personalized healthcare provision. According to the WHO, digital health can help to reduce global health inequalities provided that certain priorities are addressed: patients' and caregivers' level of digital literacy must be taken into account, with planning and implementation of initiatives to address any shortfalls in this respect; healthcare professionals' workload must also be factored in, and delivery of healthcare and related social services made more efficient. This vision has already received significant plaudits and its relevance has been underlined by the dramatic health emergency triggered by CoViD-19, which has placed health services worldwide under unprecedented pressure. In this regard, the Italian Institute of Public Health (*Istituto Superiore di Sanità*) has identified digital health systems as allies for optimizing health emergency management and guaranteeing care for the population, particularly for medically fragile subjects and those with chronic illnesses[2].

The broader context of digital health includes the innovative category of digital therapeutics (DTx), which are already an integral part of the healthcare services on offer in the United States and some European countries. DTx should be seen as a strategic tool for Italy, for three main reasons: they could favour clinical efficacy, *inter alia* by promoting new forms of patient and caregiver engagement; they could open up a new area of de-

velopment for the Italian life sciences sector; and, potentially, they could afford a useful contribution to the SSN's efficiency and sustainability. Italy, in addition to introducing DTx into its medical practice, has the credentials to become an international hub in their development and manufacture. These credentials are as follows:

1. The digital health and DTx sector comprises mostly small and medium enterprises (SMEs) with strong territorial connections, particularly suited to research and development of innovative systems thanks to their lean organizational structure, based on a handful of highly specialized professionals.

2. Thanks to their strong territorial connections (health ecosystem, according to the quadruple helix innovation model), SMEs help to cut down the distance between healthcare, patients and industry, to ensure ready availability of innovative solutions in response to specific community needs, and the setting up of operational networks for development of innovative research projects.

3. SMEs, on which the medical devices sector in Europe is strongly dependent, account for over 90% of Italy's entrepreneurial fabric, with an overall figure of 5 million companies and over 15 million employees (82% of the total for Italy as a whole)[3].

4. Since 2015, public expenditure in support of SMEs in Italy has increased: they now receive about 70% of overall national subsidization (reference period 2012-2017), accounting for a total of € 2.23 billion in 2017.

5. Italy is a pole of excellence both in information and communication technologies (ICT)[4] and in life sciences, a sector that accounts for 10% of Gross Domestic Product (GDP) in terms of added value[5].

The scenario outlined above indicates that the Italian system is particularly conducive to collaboration between multidisciplinary teams, able to develop innovative solutions. This means fulfilment of another fundamental requirement for development of DTx - an ecosystem with healthcare and social services able to participate actively in development processes, complemented in the life sciences and digital sectors by institutions and enterprises that boast excellent credentials in terms of operational productivity. In addition, potential synergies must be appropriately leveraged between small, agile start-ups and larger companies (big pharma and big tech), with a view to boosting innovation by complementing the advantages of specialization and creativity with economies of scale and access to wider markets. The presence of major players from the digital and ICT world can be an asset for the territory, bearing in mind the trend in terms of healthcare sector investment by

companies like Google, Apple and Amazon. However, taking full advantage of such opportunities presupposes targeted policies to safeguard the final user's privacy and data security.

A lot thus remains to be done in regulatory and organizational terms, a case in point being the difficulty of making digital solutions interoperable with currently used (and significantly different) digital and data collection systems - not to mention the basic infrastructure shortcomings. Nevertheless, in Italy both the entrepreneurial and research fabric and the networks of close links with the communities concerned lend themselves to the development of a sector dependent on high-level skills (together with the entrepreneurial dynamism of SMEs and a structural ecosystem conducive to collaboration), and on an overall setting in which technology can be experimentally developed.

Looking at the current scenario, it should be noted that the strategies and programmes of the European institutions share the aim of creating greater synergies between the healthcare and digital sectors. Recently, to incentivize the sector's development at European level, EIT-Health (one of the knowledge and innovation communities set up by the European Institute of innovation and Technology - EIT) included digital health among the sectors eligible for access to the first pan-European crowdfunding platform dedicated to the health field. In addition, Horizon Europe, a new European programme for research and innovation, gives particular emphasis to boosting already active cross-cluster complementarities between the "health" and "digital, industry and space" clusters, through initiatives, calls and existing or new public-private partnerships. These initiatives are particularly significant, as they include *inter alia* participatory models for active involvement of EU citizens in European research and development processes - e.g., the "Large-Scale Innovation and Transformation of Health Systems in a Digital and Ageing Society" partnership, whose launch is scheduled for 2021. In the mid to long term, these programmes could favour the consolidation of a new manufacturing and research sector dedicated to digital health, and to DTx in particular, both in Italy and in Europe as a whole. Complementing these initiatives are the working instruments made available by the EU, such as precommercial procurement in phase 0, giving patients and caregivers an opportunity to participate directly in the definition of the health needs profile. This process enables generation of a solid basis on which to build phase 1, thanks to which the profile identified by the stakeholders is passed on to companies, thus optimizing management of the R&D pipeline.

Finally, another major enabling factor for this digital revolution in the health sector is the important wave of European investments that have been activated in support of national economies. These are based on the plan agreed by the European Commission, the European Parliament and national leaders, the aim being to create the foundations of a modern and more sustainable Europe, prioritizing *inter alia* healthcare and digitalization. Next Generation EU required all countries receiving these funds to draw up national recovery and resilience plans, so as to ensure appropriate planning and identification of the areas in which each member state proposes to invest the EU funds earmarked for this purpose. Funding made available to Italy in this way will total €110 billion, to which a further 90 billion should be added, of which it is estimated that about 20% will be dedicated to digitalization of national systems, including the SSN. This is a major step forward, which could generate a paradigm shift and bring policy-makers and legislators to work towards smoothing the path for integration of digital innovation into all sectors (manufacturing, services, trade). A major opportunity can thus be envisaged for Europe and for Italy, conducive to investment in the future of healthcare and to development of a regulatory, infrastructure and organizational setting able to guarantee the development of digital health in Italy and reinforce the country's position internationally.

2. DTx: enabling organizational conditions

Speaking of organizational conditions enabling an ecosystem conducive to the success of DTx means that the following steps must be taken:

1. enhance knowledge related to the efficacy, safety and mechanisms of action of DTx (e.g., by activating lifelong learning programmes for digital skills);

2. raise awareness of them, as an available and effective alternative to current treatments;

3. develop the necessary capacities for appropriate use of DTx, and their integration into existing diagnostic therapeutic pathways and information flows;

4. focus on the interest, usefulness, cost-effectiveness and full potential of DTx, and be prepared to demonstrate them;

5. clearly define decision-making processes (in relation to regulatory requirements, prescription and reimbursement), and the regulatory framework required for implementation and adoption of the related technology.

All these conditions, which might have seemed difficult to achieve in a shorter timeframe until only a few months ago, now seem to be more readily achievable as a result of the CoViD-19 emergency, which in the space of a few months prompted successful experimentation with telemedicine systems, in the broad sense of the term, and meant that digital technology was given the chance to prove its worth in the health sector.

The first of the points listed above is discussed in detail elsewhere in this volume. For the purposes of this chapter, what should be emphasized is the importance of extensive and generalized training for a large population of healthcare professionals in the various sectors where DTx can be used. It will also be necessary to ensure that appropriate provision is made for introduction of new job titles, so that healthcare professionals and users can find ready interlocutors to help them address such issues as choosing among different DTx products (software packages) with the same aims and fields of application, or monitoring their use and troubleshooting for any IT problems. Data analysts will also play a major role, given that the vocation of DTx is largely to generate enormous quantities of data and information. Hence the need for specific job profiles encompassing these emerging skills: while the people with this know-how can obviously come from a variety of professional backgrounds, their training and experience should be appropriate to a strongly interdisciplinary vision. This means embracing a broad range of medical, engineering, psycho-behavioural, economic and managerial priorities, with an appropriately open approach to addressing "complex" problems.

Information must be shared with all concerned, requiring outreach to patients, caregivers, health administrators, top managers, policy-makers and, more generally, all those who could benefit from the availability of DTx in clinical practice. In addition, a fundamental requirement is the involvement of Scientific Societies, able to:

- promote the dissemination of innovative health products, services and approaches, DTx being emblematic in this respect;
- guarantee that DTx comply with the norms and requirements of modern, evidence-based medicine;
- draw up guidelines, where appropriate, for their correct use.

Today, the potential of DTx is still little known - all the more so, if one thinks that Italy generally lags behind in terms of digital literacy and readiness to make the best use of all the related opportunities. Involvement of patients and raising of their awareness are particularly important, through

targeted actions to show the potential benefits of DTx, *inter alia* by comparison with other treatments; to this end, major points to emphasize are, on the one hand, the patient's autonomy in managing treatment and, on the other hand, the safety provided by their remaining in continuous contact with the physician and a team of experts. The required awareness-raising activities will depend on qualified people, able to explain in detail the unique features of DTx, the fields of application in which they can be potentially effective and the settings in which they have already been applied: this requires excellent communication skills, with the ability to explain concepts clearly, engagingly and effectively. The ability to adapt to different audiences is also of fundamental importance, ensuring that the most convincing and effective arguments can be used to address any doubts or scepticism. This awareness raising is generally the brief of professional communicators or trainers from outside the public healthcare system or its private sector counterparts, who have already undertaken similar work for the manufacturers and have an excellent track record in terms of credibility and reliability. What must be avoided, however, is the involvement of speakers who can offer nothing more than facile support for innovation, able to see only its advantages but blind to any practical limitations and difficulties - or, even worse, trainers with a style typical of someone intent on selling an idea (of little practical use in this case, where the ultimate aim is not to sell a product). A major opportunity thus arises for the country, with scope for training - for example - expert patients, well versed in health matters and DTx, who can be seen as the most credible and balanced healthcare system stakeholders to explain not only what these approaches can offer, but also what should not (or cannot) be expected of them. Very useful input in this process of awareness raising/training can be offered by doctors or other professionals with inside knowledge of the organizations that engage in clinical testing and use of DTx, or with experience of their use, or with (inter)national standing as reference points for the DTx sector and its practical application.

In organizational and economic terms, critical issues must be addressed when the decision is made to adopt DTx, with the need to identify appropriate pathways for their use and to ensure systematic implementation of organizational units that can provide support for the healthcare professionals and patients using them. The following actions thus become necessary:

1. clarify whether DTx are being used as a replacement for, in addition to or in association with drugs, medical devices and technologies, etc.;

2. define whether DTx are part of a care pathway (CP) or a network organization (possibly of a hub and spoke type), which will have implications for decision-making, for their delivery and monitoring, as well as in terms of who is responsible for their efficacy;

3. identify benefits in terms of appropriateness and level of cover for potential health needs (e.g., for patients spread out over an extensive catchment area, or living in relatively inaccessible places), as well as efficacy and cost-effectiveness in relation to the patient/treatment/outcome;

4. identify the various types of costs: direct and indirect; accountable and non-accountable; quantifiable, or related solely to potential inconvenience or risk for the patient, applying the cost-benefit categories applied in Health Technology Assessment (HTA) evaluation. In this case, models and techniques must be adapted to the specificities of DTx, as distinct from the approach used for drugs, medical devices and other technologies;

5. identify patients' and caregivers' digital barriers in relation to use of DTx (from internet connection to availability of devices and appropriate skills).

With regard to the cost-effectiveness of DTx, it could be very useful to devise more agile, leaner systems for promoting collaboration between the public sector and Patients' Associations (e.g., by revision and simplification of the Public Procurement Code and the Code of the Third Sector, with specific reference to Article 55), which should as far as possible be on a uniform basis - or, at least, harmonized - nationwide. To the same end, it would be beneficial to focus on incentives for, and case studies of, successful collaboration between digital start-ups and big pharma, since relations have in many cases proved far from idyllic.

Finally, it is essential to have a clear definition of the decision-making processes involving the patient, the doctor or healthcare professional overseeing the treatment, health board administrators, the leadership of the public or private sector organization, regional or national policy-makers, and the regulatory authority or other body responsible for defining reimbursement arrangements. Generally, in assessing the usefulness of DTx, the use of real life data or patient-reported outcomes or experiences is strongly recommended. In this way, various types of economic assessment could show that DTx, perhaps more than other therapies, enable win-win solutions for all the actors involved. It is also, of course, fundamental that the readiness to use these technologies should

be endorsed by those with formal decision-making powers. For example, in the case of a therapy that has been approved or authorized by a regulatory authority in a country where DTx are not reimbursable by the national health system or by private healthcare/providence/insurance schemes, the decision rests essentially on the will of the prescribing doctor and the patient's readiness to pay. In a country where private reimbursement arrangements are in place, use of a DTx product will depend on the prescribing doctor's willingness to choose this treatment in preference to others, and the decision of the reimbursing organization. In a setting like that of the Italian SSN, the possibility of introducing DTx into clinical practice will depend not only on the regulatory authority, but on the inclusion of the treatments concerned in the Essential Care Levels (in Italy, LEA) lists, budget availability of public or accredited health boards, or patients' willingness to undertake the treatment on an out-of-pocket basis or through private healthcare arrangements. Where reimbursement is available from private schemes or the national health service, it is necessary to identify in which therapeutic classes DTx are categorized. Even in cases where no third party is involved as the source of payment, it is important that the patient should receive a treatment that has been adequately assessed by the authority concerned and fulfils clear value for money criteria.

The question of eligibility for reimbursement is crucial, given the very real risk that even promising technological innovation can unintentionally lead to widening of the gap between rich and poor. For DTx, it is essential not to compound the difficulties that already hinder the achievement of ideal health outcomes for minorities, for fragile subjects, and for the less affluent. In other words, the trend to be avoided at all costs is what some authors have termed "digital disadvantage for the disadvantaged"[(6)].

These issues must be addressed through strategic planning of digital health interventions, based on the following elements:

- recruitment of diversified subjects throughout the R&D process, in order to allow a thorough assessment of responses and mitigate preferential access for certain population groups;
- understanding of potential end-users' differing social backgrounds;
- participatory user-centred planning, reflecting users' needs and preferences;
- prior assessment of the technological infrastructure needed to allow individual and community use.

3. Conclusions

The **potential capacity** of DTx is an alternative to existing therapeutic approaches (based, for example, on drugs, medical devices or a direct doctor-patient relationship). This could make the public and private sectors alike more willing to invest in innovative R&D, even in sectors where innovation and a return on investment are harder to achieve. This means that instead of the classic financial indicators, it could be useful to leverage parameters like social return on investment (SROI), basing the approach to measurement and accounting on a broader concept of value that can reduce inequalities, increase well-being and reward sustainability by including social, economic and environmental parameters in the cost-benefit analysis.

This is a phenomenon that can mark a shift in companies' strategic choices, allowing health systems to revisit currently available tools with a view to guaranteeing adequate levels of public healthcare. The health agenda of European countries like Italy must therefore prioritize inclusion of DTx in the range of technologies available to the citizen/patient, *inter alia* in light of the resulting investment opportunities and the proven importance of digital solutions for sustainable management of national health services. In this scenario, particularly - as is often the case - at the beginning, it will be important to incentivize and integrate the contribution of private enterprise alongside the role of the public sector, thus favouring development of new evidence for gradual introduction of DTx into clinical practice.

The system cannot afford to allow the same to happen as occurred with CAR-T (a burgeoning innovative sector in oncology today, though the first in vivo experiments actually go back almost a decade), which suffered from an excessively long lead time, with delays in the development of a setting conducive to use of innovative technology and its effective recognition among available healthcare solutions.

For this reason, the fundamental cornerstone for developing DTx in Italy and ensuring their widespread adoption will be implementation of initiatives for creation of a correct scientific, legislative and healthcare framework, together with creation of an adequate educational, participatory and economic environment. To this end, Italy must look at the international and European scenario, particularly Germany, which in 2019 passed a Digital Healthcare Act: since this legislation includes categories of digital health products among those that can be prescribed and reimbursed by the health system, its adoption makes Germany a front runner in extending its reimbursement policy to DTx.

What is known

- DTx could be a new opportunity for a country like Italy to enhance sustainability of its national health service, and thus provide a valid alternative to existing therapeutic solutions and procedures that are, to a greater or lesser degree, innovative
- DTx are a potential incentive to invest in therapeutic areas little explored by industry
- The DTx sector, in Europe and in Italy, can count on an industrial setting conducive to its development
- Europe is backing the development of digital health, enabling investment both in R&D and in strategic upgrading of the system through the Next Generation EU programme.

What is uncertain

- Absence of institutional vision regarding the future of digital health in Italy
- Little or no direct involvement of the healthcare world (even through Scientific Societies and Expert Patients) in the development of new products
- Uncertainty regarding dissemination of the first DTx, already identified as efficacious and approved in other countries
- Lack of an adequate regulatory framework, and of clarity regarding the pathway that these technologies will have to follow with a view to their integration in the available healthcare armamentarium.

What we recommend

- We recommend the identification of institutions, pathways and processes that can give appropriate recognition to the role of DTx within the national health service and favour access to them by properly defined rules and procedures, but also by an appropriate regulatory framework
- Clarity is needed in respect of governance, making it possible to roll out over a period of years a fully fledged and uniform process of digitalization for health services nationwide. In addition, we recommend ongoing dialogue with all stakeholders concerned (companies, universities, the scientific world, Associations and Scientific Societies, patients, citizens, politicians, and relevant healthcare institutions at national and European level), so as to favour the adoption and use of DTx in Italy.

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