Opinion Paper

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Clouds across the new dawn for clinical, diagnostic and biological data: accelerating the development, delivery and uptake of personalized medicine

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Abstract: Growing awareness of the genetic basis of disease is transforming the opportunities for improving patient care by accelerating the development, delivery and uptake of

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Paul Hofman, European Liquid Biopsy Society, Hamburg, Germany; and Laboratory of Clinical and Experimental Pathology, FHU OncoAge, BB-0033-00025, IRCAN, Nice Hospital Centre, University Côte d'Azur, Nice, France **Vivek Subbiah**, Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA personalised medicine and diseases diagnostics. This can mean more precise treatments reaching the right patients at the right time at the right cost. But it will be possible only with a coherent European Union (EU) approach to regulation. For clinical and biological data, on which the EU is now legislating with its planned European Health Data Space (EHDS), it is crucial that the design of this new system respects the constraints also implicit in the testing which generates data. The current EHDS proposal may fail to meet this requirement. It risks being over-ambitious, while taking insufficient account of the demanding realities of data access in daily practice and current economics/business models. It is marred by imprecision and ambiguity, by overlaps with other EU legislation, and by lack of clarity on funding. This paper identifies key issues where legislators should ensure that the opportunities are not squandered by the adoption of over-hasty or ill-considered provisions that jeopardise the gains that could be made in improved healthcare.

Keywords: business models; clinical trials; diagnostics; EHDS; European health data space; healthcare data; *in vitro* diagnostics legislation; policy; regulation; uptake.

Introduction

Health data is enjoying a new recognition with strong promises of a revolution in care [1, 2] – but crucial gaps must urgently be filled before any of the promises can become a reality. Above all, it is necessary to bring greater precision to the heady discussions about healthcare policy now sweeping across Europe, complementing rhetoric with clearer awareness of the mechanics of exploiting health data to boost healthcare delivery, research, innovation and policy making with safe and secure exchange, use and reuse [3, 4]. The aspiration may be noble in the EU presentation of

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its proposal for a regulation on health data as "a quantum leap" that it will "unleash the full potential" of data [5], but securing that goal is already proving more of a challenge than the expression of a vision. The daunting scale and complexity of this proposal is compounded by imprecisions and ambiguities in the draft legal text. It has made only limited progress through the EU's legislative machinery. By the end of 2022 the Council working party where member states' experts and officials examine the text had conducted only an initial examination of the provisions on primary data, and the EU presidency was preparing only a preliminary compromise on part of the text. The European Parliament had not even produced a draft opinion, although plans were underway for a joint draft report by the two key committees for early spring 2023. Additional concerns have arisen concerning tight timelines, overlaps with other EU rules (and importantly, the data protection legislation), funding for the system's implementation, the governance structure proposed, and how it will link to the different national data infrastructures [6]. Questions remain unanswered over the categories for secondary use of data by different stakeholders and for different purposes, the tasks of the envisaged health data access bodies (as well as their reporting duties and the fees they might charge), the issuance of data permits, joint controllership of secondary use of data and responsibilities, and data quality labels. The Commission's own impact assessment of its proposal noted the extent of the challenges. Researchers, evidence-based clinical practice guideline developers, regulators, and other stakeholders are concerned about the current fragmented procedures for health data reuse, it found, and digital health solution producers face barriers when entering other markets, while individuals cannot benefit from innovative treatments due to the limited access to health data that researchers, innovators and policy makers face [7]. And this is before discussion has even started in earnest of the hard questions - notably, paying for this vision. The impact assessment of the proposal puts the total cost of the preferred option at up to €7 billion [8]. The EU4Health programme for 2023 allocates just €25 million for EHDS [9]. Meanwhile, in the European Parliament, where lawmakers also have to agree on the proposal, preparations have only recently advanced to draft the multiple reports that will – hopefully – form the basis of a strong position among members of the European Parliament (MEPs) during the course of 2023. The European Alliance for Personalised Medicine (EAPM) organised an multistakeholder exper panel with a wide range of different stakeholders, from healthcare community, patient organizations, citizens, researchers and policy makers so to understand the key issues at the intersection between the value of

diagnostic information, data management, diagnostics, patient monitoring, early diagnosis linked to treatment as well as the policy framework that can support this. This paper is a result of this discussion.

Over-ambition

The EU talk of "a health specific ecosystem comprised of rules, common standards and practices, infrastructures and a governance framework" [10] reflects high aspirations, but omits sufficient consideration of the specifics. More meticulous examination can still avert the risk of creating an overambitious framework that proves inadequate once put into law – an error that has already disfigured implementation of the updated rules on medical devices and in vitro diagnostics legislation – on which the Commission finally admitted at the end of 2022 that its failings in the initial planning for the law means it will have to provide yet another extension of the original deadlines it set [11, 12]. The same failings are demonstrated by the concerns over unworkable aspects of the 2016 clinical trials regulation [13]. The complications that the EU's data protection legislation imposed unwittingly on health research have also still not been adequately resolved [14], and persistent ambiguities over the "EU Beating Cancer Plan" threaten similar confusion. There is no doubt that Europe urgently needs better legislation on the use of health data, both for empowering individuals through access to their own data, and for facilitating research and development of new medicines. The right legislation can also promote the market for electronic health record systems, relevant medical devices and high-risk Artificial Intelligence (AI) systems [15]. A trustworthy framework will have wide benefits for researchers/physicians who agree to sharing of epidemiological, clinical and biological data, and for policymaking and regulatory activities. At present, the meeting between clinical needs (i.e., the use of a new anticancer drug needing the molecular profiling of the specific cancer) with the availability of rapid and cheap genomic assays is still difficult, particularly when the test is not implemented in the routine setting. Homologous recombination deficiency assessment exemplifies the case [12]. A solution can lie in outsourcing, or in academic solutions which can be standardized in the context of clinical trials, but this still depends on the availability of research funds [16]. The EU's own impact assessment notes that researchers and regulators are concerned about the current fragmentation among procedures for health data reuse. Industry too is conscious of the need for common EU interoperability requirements - but at the same time it is cautious about how far and how fast the EU should go in standardisation, and has stressed the need

for a proportionate approach. Carefully-framed legislation can make it possible to exploit real opportunities, and can avoid headlong creation of an over-elaborate superstructure that aims to cover every eventuality. Going too far and too fast could fall foul of the complexity of the exercise and condemn it to failure to meet even limited objectives.

Real world evidence (RWE)

Genuine and attainable objectives are available and desirable - notably in the growing acceptance of real-world evidence (RWE) [17-19] and the opportunities that can be grasped in providing wider access to diagnostics through uptake of next-generation sequencing (NGS) [20, 21]. But attention must be focused on the real and immediate problems if the efforts are to pay off in terms of better care for patients and much-needed support for innovation. EU thinking will have to recognize that legislation and regulation of technologies are only going to be helpful if they are adapted to the evidence of how novel technologies function. There must be due respect paid to the difference, for instance, between data associated with NGS, data from whole exome sequencing, and access to sensitive information related to genetic risk predisposition. Effective preparatory dialogue and understanding among all stakeholders are preconditions - including, particularly, the stakeholders who are most closely involved with the development of the technologies in question. It has to be borne in mind that every somatic alteration can mirror itself at a germinal level, so the implications from each assay concern not only the therapeutic aspects but also individual and family prevention. The level of standard of care can be undermined by false assumptions about independence of tissue genomics and germline DNA genomics and considering tissue and blood pathways as unrelated [22]. Strong data protection policy will be required for patients when molecular profiling is performed on tissues. In relation to testing, assessment of the long-term benefits should play a crucial role in any consideration of short-term costs, and provision should be made accordingly in budgets, as well as appropriate acceptance of RWE for "blue-sky" tests. There is an obvious need too to define, standardize, and ensure quality and adequate reporting of RWE, to ensure the risk of intrinsic bias is taken into account. Here there is a role for the development of ad hoc studies, and further agreement on quality guidance for RWE [17, 18]. How the new tests now possible are to be funded is an unsolved conundrum, since currently, the expenses are only rarely covered by reimbursement. Without adequate accompanying provisions, any real progress is under threat, and will lead to discrepancies across the EU.

Naturally, those paying for healthcare require evidence of the value of such tests, but it will be necessary to break the vicious circle that results from current scarcity of RWE while tests remain largely without reimbursement. Some hope resides in wider use of digital methods cutting the cost of evidence generation [19, 23]. Practical issues require practical answers. Data required must be close to real-time data (ideally prospectively collected) if it is to influence clinical decision making, and at present this is not adequately achieved by registries, where archived data rapidly goes stale. But electronic health records (EHR) could offer near realtime data, driving a quality revolution in digital care [24, 25]. Robust reflection, and acceptance of the need for adequate preparation, hold the key. Pilots of RWD studies are technically possible using data from entire hospital systems. but experience in different settings is needed to develop coherent scientific methodologies. High quality EHR data is expensive. It demands capital investment, the Information Technology (IT) infrastructure and maintenance, mapping on Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), and regular cataloguing to provide for metadata. And the value depends ultimately on analysis - with attendant expenditure [24, 26]. Glib European Union talk about interoperability tends to disregard the costs and difficult (US spending of €30 billion, plus some modest sums in Europe, has not delivered much), and lessons should be learned from experience to date to avoid unnecessary mistakes. Since the value of any data is dependent on context, need, intrinsic quality and availability, the reality in scientific terms is that at present the value is greater in some therapy areas: advances in cancer are not matched in Alzheimer's or asthma [27, 28]. And near real-time data outperforms older data in driving use cases, such as trial recruitment. There are also distinct merits in the application of data: where it is high-quality and rich, it may offer critically useful clinical insights – a greater priority in terms of promoting innovation than in, say, merely consolidating basic epidemiology. And the application of Machine Learning (ML) and AI for interpretation and decision-making around diagnostics will require considerable data for training, validation, and continuous learning. Even the source of the data influences its scientific or economic value: it is going to be more useful if it comes from a country with a large market and strong Health Technology Assessment (HTA) body, rather than a small market or one with weak HTA systems. And the speed at which data can offer insights also varies widely – from the idea of responding digitally to the mere touch of button, to the 3 months it may take more manual systems, or to the year it may take to deliver after 4-5 years of cumulative primary capture [29]. Greater attention is also needed to

assuring the quality of the data (whether clinical or biological), to who will control the quality, and whether certification or accreditation would be a prior criterion for use of the data. A new ISO 20387 norm has been developed, for instance, for bioresources collected in biobanks [30]. In addition to the evident challenges of funding, there is a risk that without significant modification of the over-ambitious plans for EHDS, such funding as is likely to be made available will be directed at the wrong priorities, risking the waste of scarce billions. The current EU approach also miscalculates the underlying economic mechanisms for data access: the insistence on interpreting the legitimate FAIR (Findability, Accessibility, Interoperability, and Reuse of digital asset) [31] concept as if it were tantamount to provision of data without charge precludes the design of sustainable economic solutions [32]. Where the EU is pressing for "free" data sharing from trial outputs, as belonging to patients, this is more than just a problem of infrastructure. Some considerable volumes of sequencing data are of course already available in repositories, and could be more imaginatively exploited, particularly if policy instruments were to support reuse. Another miscalculation is to consider European Research Infrastructure Consortiums (ERICS) as research infrastructure [33, 34]. These are described by the EU as "a specific form for the establishment and operation of new or existing research infrastructures on a non-economic basis" [35]. But experience to date powerfully suggests they fall far short of offering a ready-to-go, contracted, digitally enabled fee-for-service research organisation with a stake in supporting innovators that a real digital outcome research network might provide. And skills are short in the public sector to operate such an infrastructure, and to engage in discussion of its design: high quality NGS services depend on matching resources and infrastructure to demand, corresponding to the number of patients treated every year in a specific geographical area. Competences will also need to be increased among doctors and citizens. If policy is designed in a knowledge vacuum, the results will be disappointing - as other EU legislative initiatives in the healthcare field have shown. A systematic approach to creating effective data access should start from exploring what business models exist on data, what models might be acceptable in the EU context and what is the impact on population health, sustainability, and equity – and are workable, and which types of data they work on.

Models for making use of data

Providing for making use of the data in healthcare is just as crucial its collection and transfer [36]. Alongside data

submission and principal access, the issues of pseudonymization and communicating with patients/participants cannot be ignored or dismissed. Analysing and feeding back the information on all diseases/disease risks is a challenge to stretch the capacity and resources of even the largest institutions. Take, for instance, the case of polygenic risk scores for breast cancer, where the time required has to be measured in months for defining cut-offs, developing understandable patient information material, and discussing on this basis the management of risk with clinical oncologists. The challenge of agreeing across "development/implementation" centres in Europe should not be underestimated, particularly since they must be created for many diseases and successfully piloted before comprehensive use. The need may be for centres that analyse efficiently "all genomic" data at once, and feed back the information to the submitting clinicians, requiring facilities and management systems to bring results to the patient. Simply saving a score on an EHR will not be enough.

Business models

Four broad business models might be considered on data. The most straightforward is a proprietary approach [37], where someone invests to own or curate the data, and charges for access. Examples might be trial data, or Unicancer's Epidemiological, Strategy and Medical Economics (ESME) cohorts for improving cancer patient management based on real-world data, or GIMEMA's haematologicaloncology laboratories, or the healthcare technology company Flatiron. An alternative approach is a 'freemium' or channel-priced system of curate-on-demand, where those inside a club provide data without charge on the understanding of reciprocity with the other members. Access to others' data is dependent on access to one's own, and no money changes hands. Academics might take a different approach with such a system: without establishing any sort of club, they might simply propose an experiment, negotiate with parties potentially interested in the outcome, seek funding together and follow the rules of any providers of funding that is obtained. The model is essentially an exercise in cost recovery. A straightforward commercial variant is where a party proposes an experiment, determines the protocol, pays the costs – including subsequent maintenance – then charges a price high enough to allow a profit (which might be as much as 100% of the costs to deliver [38]. A third approach might be termed capacity-rationed access [39]. A government subsidises a certain amount of re-use by nominating representatives to the management of the data holder, and the data source chooses the projects (as in the UK cancer registry). Where this can prove inefficient is where good use is not made of the data, and where access becomes limited to insiders. A further variant could be to subsidise the cataloguing of metadata. The fourth model is where European policy is headed: essentially open access (where FAIR is considered equivalent to FREE) - but which falls foul of EU data protection rules, is viewed with concern by IP rights holders, and which is in any case economically unsustainable [40]. To pursue such a strategy, substantial funding and data protection protocols will be needed to yield easy access to data, while considering appropriate data protection. In such a way, epidemiological and grouped data can be easily accessed, while patient-level data that are more sensitive, albeit pseudo-anonymised, may be subject to restrictions, and accessed only by relevant stakeholders, for example for the purpose of research or policymaking. Where the funding is totally public, the platform must be freely accessible for all. However, in more complex business models, innovative financing approaches could be requested, to ensure the fair trade-off between profits, durability and sustainability. There is only a limited range of political and economic options. The proprietary approach fails all sensible political tests, as well as providing limited value to tax-payers. Open access fails the economic sustainability test. This leaves as the only options the "freemium" or channel priced – and that in turn opens a Pandora's box of subsequent detailed issues.

Making a channel-priced model function

A channel -priced model will work only if certain conditions are met - and they are cumulative rather than options. Ambition must be tailored to what is feasible, durable and affordable, or nothing will get off the ground. But at the same time, the chosen system must provide data of sufficient quality to be valuable, or no-one will use it. Neither of these conditions are met by EHDS in its current conception [3, 10]. Enough subsidy must be made available to get the capital expenditures (CAPEX) solved to develop the system with - and it is also essential to take into account what is already built and in place across the EU. It would be an error for EHDS to be built as if it is on a blank piece of paper. Technology procurement must be thoughtful to acquire it at costs low enough for the underlying economics of the system - casting the state ineluctably in the role of entrepreneur. If long-term maintenance is to be funded from income, the systems will be dependent both on a vigorous commercial drug pipeline and access to hospital data. The aims must be for near real-time access, but focused on a minimal, high quality interoperable data set that serves the highest value use cases of trial recruitment and patient decision support. Primary legislation will have to play its part in establishing and clarifying liability and regulatory issues on the decision support from data. A concept fit for the digital age must be put in place (and accepted) of reformed rules for fair market value on commercial research that departs from the standard basis of cost-plus benchmarking (because at the point that data is available at the touch of button, there is no demonstrable cost plus, so no price can, in effect, be calculated and the data access is there free – an unworkable concept in the real world). Instead, access and collaboration must be priced relative to the value of the data, in a framework that establishes a trade-off between substitutability and utility.

In future, with data of a different magnitude, AI programs could filter millions of data sets to allow selection of data of the strongest interest or greatest novelty or specific relevance, obviating the need for large-scale transfers [41, 42].

Conclusions

Policymaking needs to be shifted towards more practical solutions, a rigorous assessment of the underlying realities, clearer objectives and mechanisms. Management of individual data has emerged from development of art. 13 GDPR 679/16 "European regulation on the protection of personal data" [43]. So efficient methods must be agreed to provide for confidentiality without impeding accepted use. Again, to overcome difficulties in feedback for data use and implementation in health care, centres which analyse genomic data and return the info to submitting clinicians may offer a valuable route to transmit information also to the patient. The regulatory framework for this rapidly-advancing field will have to be so constructed that it can be adapted to respond to innovation, and the training needs right across the sector will have to be taken into account.

Legislators must recognize the scale of the challenges and the harsh lessons from recent failures in planning of healthcare policymaking. Adequate provision must be foreseen for the scope of the challenges that will be faced as the legislation comes into effect – and as technology continues to evolve. The political process must also take account of the intensely practical economic aspects of the changes envisaged: funding will be required to meet the inevitable costs of creating systems able to do justice to the wealth of data that can be mobilized to improve patient safety.

More mature thinking can avoid this project falling victim to unintended consequences – the fate that has already befallen some legislation central to EU health policy. Over-ambition on timing has made necessary the repeated revision and postponement of legislation on medical devices and diagnostics, as well as the creation of successive clinical trials rules over the last two decades. The same lack of foresight has led to the persistence of unresolved inconsistencies and overlaps with elements of GDPR.

There are real risks where practical issues are neglected and unexpected consequences are ignored in a headlong pursuit of ill-informed ambition. Not only may remedial legislation be required, and costs of compliance increased unnecessarily, but the public/private sector cooperation so vital to healthcare policy may be adversely affected. Europe and Europe's patients cannot afford to see the new opportunities of testing squandered by ill-thought-through legislation. At stake is the work to improve patient care by accelerating the development, delivery and uptake of personalised medicine and diagnostics. The time to correct the course of the EHDS discussions is now.

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