Model Driven Paediatric European Digital Repository

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Introduction

As indicated in the DoW, the Scenario analysis sessions were envisioned as means of discussion for addressing the most significant issues preventing the final adoption of the implemented tools in a working clinical environment. The idea laying behind these sessions was to "pre-empt unforeseen technical issues", encouraging the dialogue between technical partners and end-users.

The first Scenario Analysis Session focused on a broad issue of the various difficulties in translating new technologies in the clinical environment, whereas – beside the reliability of the tools in themselves – a key role is played by the different stakeholders, and their respective expectations regarding the use of these innovative tools, and the relevant impact on their usual workflows, as well as their resistance to changes and their level of risk adversity.

The scenario analysis sessions were also proposed as systematic occasions to discuss the issues emerging from the testing of the implemented tools, aiming to address them in advance and avoid ex-post rejection of the tools by the intended end-users. Still, this approach – encompassed in the largest framework of the tentative adoption of an agile development methodology - was not fully followed, given the difficulties encountered in implementing an agile methodology to the whole project development (mainly due to the different organisational set-ups of the various technical partners).

The second, and final, scenario analysis session unrolled during the Final Conference of the project, held in Rome on May 22nd-23rd, with the support of external stakeholders, who helped the Consortium in debating the most complex issues potentially hindering the final adoption of the implemented tools within the clinical practice and their launch on the market.

This document has also taken into account some literature pertaining to the matters at stake, with the aim of establishing a basic guideline for future discussions and researches in this field.

The focus of the session

Two key topics were discussed during the conference, which were deemed worthy of special attention:

1) how to address the key ethical implications of the adoption of advanced model-based CDSS
2) the issues of the algorithm opacity and reliability, and how to win the validation challenge

These two topics have been discussed in dedicated plenary meetings, involving consortium partners and external stakeholders, and have been identified has key issues potentially hindering the final adoption and end-users' acceptance of the project results.

The ethical issues

As Big-Data healthcare platform, MD-Paedigree poses itself at the centre of the current ethical debate urged by the fundamental challenges brought about by the innovation of Big Data-driven research.

This has been the key focus of the talkn given by Prof. Laura Palazzani, Head of the MD-Paedigree Ethical Board (see Appendix 1 of the present document and Appendix 2 – Presentations DAY2 - to D18.7 – MD-Paedigree Final Conference).

It is well known that nowadays medicine is experiencing a profound transformation: the '4Ps medicine' (prevention, prediction, personalization/precision, participation), the advancement in adoption of ICT in the healthcare domain, and in particular the big data revolution, are opening new scenarios in healthcare, for the acquisition of new knowledge, innovative tools and systems, more advanced diagnostic and therapeutic approaches.

At the same time, the increasing availability of personal data, produced also by the citizens themselves, in different context and through different devices (in particular IoT and MIoT), is posing a difficult challenge to privacy concerns. Significantly, some people have started to claim the "end of privacy" or – at least – its "evaporation" in the forms we knew until now.

New forms of governance for personal data are needed, to properly balance risks (e.g. re-identification, misuse of data, privacy breach), and advantages for the data owner (and for patients in particular). And if someone is already advocating a new civil right to data ownership[1], the new Regulation (EU) 2016/679, General Data Protection Regulation (GDPR), is already aimed at protecting natural persons datasets, in particular with regard to their processing and sharing. The GDPR protects citizens' privacy and data security also by defining new rights, such as the right to revoke consent to processing, and the right to "be forgotten" (i.e. the cancellation of the personal data).

Also, the newly defined "right to portability" of one's personal data (the right to "receive the personal data concerning him or her, which he or she has provided to a controller, in a structured, commonly used and machine-readable format, and has the right to transmit those data to another controller without hindrance from the controller to which the personal data have been provided", opens up to a completely new approach to citizens involvement, engagement and participation, putting them at the centre of the data sharing process, and not the data controllers.

[1] E. Topol, K. Haun, *The Health Data Conundrum*, appeared on the New York Times, January 2nd, 2017.

What is sure is that the innovative approaches to research ,brought about by the big data/data science/personalised medicine era– with a strong involvement of new technologies – demand important changes in how patients and citizens are involved and empowered in their own care processes, and in particular how they express, manage, and change their consent. Ultimately, a profound change in how fundamental ethical challenges (such as autonomy, privacy and justice) are addressed is required, going beyond the current context-specific solutions, and opening the way to a "more comprehensive and coherent ethical framework for the Big Data ecosystem"[2].

Furthermore, we also need to consider that this new ecosystem includes not only strictly Biomedical Big Data, but non-biomedical Big Data as well, produced directly by the citizens and with high biomedical value: the definition of the "digital phenotype" is thus enlarged by the future perspective (particularly in the evolution of the Medical Internet-of-Things phenomenon), enabling improved biomedical and health knowledge[3].

The future outlook implies therefore daily digital interactions of patients and citizens with their personal digital technologies (among which the above mentioned MIoT), thus contributing to the creation of a "growing body of health-related data that can shape our assessment of human illness"[4], and constitute a natural extension of our phenotypes[5].

The introduction of these new (and sparse) data sources (also from the non-biomedical field), urges a shift "from the source or content of the data to its use, creating thorny ethical questions that test the effectiveness of traditional consent-based safeguards"[6], implying as well the definition of a novel "biomedical research ethical framework"[7], capable of unleashing the Big Data research potential, which will only be attainable only through the gathering, linking and exploitation of "all kinds of data relating to an individual"[8].

The consent issues – from informed consent to i-consent

When it comes to scientific research, it is currently customary to depict the individual right to privacy as "antagonistic to the health-related public goods that can result from increased openness". Still, in the new Big Data Research era, this perspective needs to undergo profound changes in order to allow the new big data paradigm to express is whole potential. In this sense, it appears clear that "research governance is out of sync with the unprecedented opportunities for data accumulation and sharing that advances in digital technology bring to the fore"[9].

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[2] E. Vayena, U. Gasser, Strictly Biomedical? Sketching the Ethics of the Big Data Ecosystem in Biomedicine, in B. Mittelstadt, L. Floridi (Eds.), The Ethics of Biomedical Big Data, Springer International Publishing Switzerland 2016.
[3] Ibid.
[4] Jain, S.H., B.W. Powers, J.B. Hawkins, and J.S. Brownstein. 2015. The digital phenotype. Nature Biotechnology 33(5): 462–463. doi:10.1038/nbt.3223.
[5] E. Vayena, U. Gasser, cit.
[6] Ibid.
[7] Ibid.
[8] Ibid.
[9] B. Schmietow, op. cit.

What is needed is a new approach, starting from the awareness that "legitimate public interest in research does not sideline the individual right to privacy. In fact, it is often that very interest that allows research to take place"[10].

Precision medicine will progress only in as far as "–omics are pooled in large repositories and analysed by different research teams"[11], enabling the big data approach which envisions "compilation, long-term banking, and sharing of sensitive personal information, and potentially allows an individual's data to be combined and utilised with other data indefinitely in innumerable research projects"[12].

To make such a vision a reality, "individuals have to authorize access to their data set, or even participate directly in the making of the new medicine by collecting it themselves and making it available for research"[13].

In this sense,– in view of making platforms such as MD-Paedigree able to gather information from different sources, from hospitals to future Personal Data Accounts, through trust relationships established amongst all relevant stakeholders – it will be important to increase the data subjects' awareness and understanding regarding the usage of their datasets, trying to overcome the information asymmetries currently existing between them and their data users/controllers.

The final goal – to which a project such MD-Paedigree has aimed, is to find ways (from a technical, legal and ethical standpoint) to allow the data subjects to "be involved in the entirety of what happens with the data sets"[14], being thus also in line with the General Data Protection Regulation requirements.

It is clear that such a complex and evolving scenario implies an in-depth re-thinking of the traditional form of informed consent, in view of its adaptation to new and emerging research approach "from genomics and biobanking to increasingly virtual, global research networks assisted by online, openly shared genomic databases", toward the implementation of new form of consent, "where participants grant broad, unrestricted access to as yet unspecified future uses of their samples and associated data"[15].

The discussion during MD-Paedigree conference quickly focused on one of the solutions envisioned by many biobanks and virtual research repositories: "broad consent". Though clearly representing an attempt to "accommodate the changing needs of research while still maintaining the integrity of core ethical principles"[16], broad consent has also been criticised as possibly undermining "real" consent and exploiting or at least disrespecting participants[17], while others do also directly question its very nature of "informed consent".

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[10] E. Vayena, U. Gasser. 2016. Between openness and privacy in genomics. PLoS Medicine 13(1): e1001937. doi: 10.1371/journal.pmed.1001937

[11] E. Vayena, U. Gasser, op.cit.

[12] J. P. Woolley, How Data Are Transforming the Landscape of Biomedical Ethics: The Need for ELSI Metadata on Consent, in B. Mittelstadt, L. Floridi (Eds.), The Ethics of Biomedical Big Data, Springer International Publishing Switzerland 2016.

[13] Ibid.

[14] Ibid.

[15] B. Schmietow, Ethical Dimensions of Dynamic Consent in Data-Intense Biomedical Research—Paradigm Shift, or Red Herring? in D. Strech, M. Mertz, (Eds.), Ethics and Governance of Biomedical Research - Theory and Practice, Springer International Publishing Switzerland 2016.

[16] J. P. Woolley, cit.

[17] Hofmann, B. 2009. Broadening consent – And diluting ethics? Journal of Medical Ethics 35: 125–129.

This is the reason why the attention has focused on a different approach, explored in various EU-Funded projects (EnCoRe, USEMP, and – last but not the least – MyHealthMyData, to which some of the MD-Paedigree partners are taking part), of the dynamic consent: it can be described as "an interactive interface that allows participants in research to choose and alter consent choices in real time. The system provides reliable storage and enforcement of these choices by cryptographically protecting sensitive personal information in a way that allows data to be accessed in only those ways for which consent has been given"[18], also allowing for tailoring consent "on a wider variety of research initiatives, in a more open and more flexible manner"[19].

MD-Paedigree platform will serve as technical basis for the new MyHealthMyData project, to create a dynamic consent interface, to allow the data subjects to define their privacy preferences (access rights, type of datasets to be shared, etc.) in a seamless way. This interface will not only act as a "tool for transparency [equipped with] dashboards, visualization techniques [able to] inform individuals about uses of data that relate to them"[20], but will also enable "interactive ways for individuals to express and change their consent virtually immediately, at any time, and on a continuous or ongoing basis"[21].

As a conclusion on this topic, there was a widespread consensus that the future of Big Data research in healthcare, and the adoption of de-centralised platform for data storage and analytics, requires the exploration of new "participant-centric" models, capable of unleashing a real *empowerment* of patients and citizens*,* by making *"*the individual's choices better, more informed, research more robust, and, the whole research environment more trustworthy", while changing the "status of the participant into becoming a co-producer of the research outcome"[22], in an open-science approach.

This innovative research approach – confluence of social media, crowd-sourcing, and greater patient control over personal health information"[23] –contributes to enabling new paradigms such as citizen science *(*defined as a conceptual tool necessary to meet the "need for scientists and members of the public to cooperate in the face of complex societal challenges"[24]), of "apomediation" (envisioned as a "more horizontal, peer-to-peer style of information exchange in which no single apomediary is essential to the process"[25]), and – ultimately – of "apomediated research" ("research in which information about the protocol—for example, its design and conduct—is apomediated, peer-to-peer, between individuals who may appear as both subjects and researchers")[26].

[18] J. P. Woolley, cit.
[19] B. Schmietow, cit.
[20] E. Vayena, U. Gasser., *Strictly biomedical?*, op.cit.
[21]Wee, R., M. Henaghan, and I. Winship. 2013. Dynamic consent in the digital age of biology: Online initiatives and regulatory considerations. Journal of Primary Health Care 5(4): 341–347.
[22] Ibid.
[23] O'Connor, D. 2013. The apomediated world: Regulating research when social media has changed research. The Journal of Law, Medicine & Ethics 41(2): 470–483.
[24] Prainsack, B. 2014. Understanding participation: The "citizen science" of genetics. In Genetics as social practice, ed. B. Prainsack, S. Schicktanz, and G. Werner-Felmayer, 147–164. Farnham: Ashgate.
[25] O'Connor, cit.
[26] Ibid.

The particular case of children and the assent form issue

Being a paediatric project, MD-Paedigree deals – of course – with an additional issue, i.e. relating to the fact of involving children, and of making them understand – whenever possible – what is going on with the research activities. For this reason, since the inception of the project, besides the usual consent form for parents and patients of age, the Consortium also prepared assent forms, for the enrolment of younger patients. This has been the key focus of the presentation delivered by Prof. Nielsen, Former Vice-President of the European Group on Ethics in Sciences and New Technologies (EGE).

The question at stake is: how to involve children in a research project?

The assent form is specifically aimed at protecting "vulnerable subjects who are not yet able to make their own decisions concerning participation in medical research", which combined with other safeguard clauses (such as evaluating the direct benefit of the research on the child, and further limitations in case of absence of direct benefit), "replace the necessity of obtaining informed consent"[27].

To further specify the assent form, a distinction can be made between independent assent and the involving assent.

The former is based on the principle of autonomy, requiring the involvement of child with a sufficient understanding of the (abstract) purpose of the research, as well as of the concept of altruism, and thus mature enough to make significant moral choices. This would be attributed to children as old as 14 years old.

The latter, which is based on the "developing autonomy" approach, argues that also non- fully autonomous children should be involved in the decision-making process, because "developing autonomy is also deserving our respect". This allows to involve children as younger as 7 years old[28].

Even with these specifications, there remain open issues: e.g. the therapeutic alternatives have been considered enough? There are enough elements to claim for the volunteer participation of the minor? Is i the possibility of withdrawing consent available?

Is clear that MD-Paedigree, as all research projects involving children, has carefully considered and addressed these issues, in order to make the children involved in a proper manner, respecting their preferences and development abilities, taking care of not involving them against their will)[29].

[27] Ibid.
[28] Ibid.
[29] Ibid.

Black-box algorithm and the validation challenge

The second Scenario issue addressed during the confernce has been the one of AI-based models' reliability, and algorithm opacity issue. As a connected issue, the question of models' validation has been addressed as well.

In fact, the new era of Artificial Intelligence, powered by advanced deep learning systems, poses some issues with regard to the potential opacity of algorithms, which subsequently leads to open issues regarding the "ethics of algorithms".

The black-box problem linked with these advanced deep learning algorithms is at the centre of the current debate regarding how humans can trust algorithms to take important decisions, in finance, healthcare, mobility, etc. The issue is basically the same: even the developers themselves , of these complicated algorithms – made of artificial neural networks and multiple interconnected layers managing different levels of abstraction – find it difficult to understand and motivate the reason for a single action/decision[30].

This poses a serious issue when it comes to accountability and understandability of such tools, if the choice of simply relying on the black-box method, requiring nothing less than a leap of faith, is put off the table.

There are already several AI-based tools that perform better than humans in a series of tasks. In particular, various systems are now available, which consistently outperform humans in diagnosing specific diseases, using wealth of data, images, and information that a human physician would struggle to analyse in a reasonable amount of time.

It is clear, in this sense, that the option of not using these algorithms is not to be considered, but one of the future tasks that developers and relevant stakeholders should surely address is to make these algorithms capable of explaining themselves, leaving a sort of audit trail of their decisions, and – ultimately – to have a conversation with their human peers[31].

In conclusion, the need of creating less unknowable and more interpretable algorithms is a must, also to ensure that the algorithm at stake follows the social norms which inspire the human relationships, and to respect the relevant ethical rules. It will be otherwise difficult to trust these intelligent machines, and someone could by any means argue that we shouldn't.

This sort of conclusions is possibly even more valid in the healthcare domain, which has for long time deemed to be an essentially human practice. In such a context, how a doctor should behave, finding himself relying on systems which they don't understand, because their inherent opacity? Indeed, it has been already stated that "to adopt an instrument, a drug, or a device without understanding how it works can be a source of serious mischief in patient care"[32], and that even a perfect and flawless CDSS should not be used in replacement of the human judgement, while – on the contrary – human doctors should always have the

[30] W. Knight, *The Dark Secret at the Heart of AI*, appeared on the MIT Technology Review, April 11th, 2017. https://www.technologyreview.com/s/604087/the-dark-secret-at-the-heart-of-ai/

[31] Ibid.

[32] K. W. Goodman, Ethics, medicine, and information technology: intelligent machines and the transformation of health care, Cambridge University Press (2016).

possibility to override the machine indications, to include elements relevant for the patient care, which the AI could have failed to consider (e.g. in terms of overall wellbeing for the remaining time of the patient)[33].

At the same time though, there are voices out of the chorus: if we shouldn't trust innovative algorithm because we can't explain how they work, why we should continue to use drugs of which the mechanisms of action are still not completely understood or are completely unknown in their biological and chemical interaction with the human body (one can think of Lithium, or of the aspirin itself, used and commercialised well before having understood its mechanisms)[34].

The validation challenge and the human factor

Having outlined in the paragraph above the key issues at stake when coming to the application and reliability of CDSSs tools in the clinical practice, the present paragraph addresses the issues of validation of model-based CDSSs, such as those implemented in MD-Paedigree, and how they should be validated, for a safe introduction in the clinical practice.

This has been the focus of Prof. Bertolaso lecture titled "Validation of simulation vs. validation of experiments: some epistemological remarks". The relevant brief analysis provided by Prof. Bertolaso can be found in Appendix 2, while the presentation is available in the Appendix 2 of the Final Conference report (D18.7).

The issue poses some more in-depth epistemic questions regarding how to successfully validate a computer simulation – in order to make such simulation reliable for usage in the relevant operational environment.

The discussion started with the role of Big Data in developing accurate digital simulation of diseases and their evolution, as well as of organs: if on one hand, big data allow for more accurate models to be implemented, on the other hands it can be difficult to implement tools able to process all the huge datasets available.

This issue becomes even more cogent, when the epistemic difference between experiment and simulation it is considered, whereas in simulation a strong background knowledge plays a fundamental role. This means that for effectively simulating a phenomenon, we need to accrue enough in-depth understanding of it to make the simulation reliable and useful. In this sense, the role that can be played by big data is aprticularly clear.

Finally, a separate issue is represented by the validation of predictive mechanistic models. Given the fact that mechanistic models provide as output an explicit prediction on the future state of an organ or a disease (in principle influencing the treatment planning), specific validation approaches need to be conceived, in particular in order to take into account that some of the dynamics influencing the future course of a pathophysiological state are external to the model and cannot be – as such – considered by it in the simulation, and that these dynamics cannot be included in the simulation.

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[33] Ibid.

[34] M. Brouillette, *Deep Learning Is a Black Box, but Health Care Won't Mind* appeared on the MIT Technology Review, April 27, 2017 - https://www.technologyreview.com/s/604271/deep-learning-is-a-black-box-but-health-care-wont-mind/

Appendix 1 - The Ethical and Legal Framework For A Model-Driven Health Data Repository

Excerpts from the final Ethical Evaluation of MD-Paedigree (see final report for the full text)

1. Introduction: model-driven health data and big data

It is not an easy task to analyse the ethical and legal framework of a 'model-driven health data repository', both generally and specifically of Paedigree, as a model-driven European paediatric digital repository.

It deals with a strongly innovative project, on a scientific level;the 'new wave' of health technologies, characterized by the transformation of medicine (going towards the '4Ps medicine' or prevention, prediction, personalization/precision, participation) and the convergence/confluence of traditionally different disciplines (medicine, biology, informatics, engineering, computer science). The advancement of ICT (with the increase and acceleration in the collection, storage and processing of information) and the development of "data science" (i.e. the use of computing and mathematics with statistical techniques and algorithms) are opening up new possibilities of knowledge, use and application in various fields, including healthcare.

In this context, the 'model-driven health data repository' is a form of 'health *data-driven medicine*' (yet the object of study and research, currently not extended to all aspects of biology and medicine): which offers the possibility to make predictions and simulations of diagnosis and treatments for patients in specific contexts or for stratified groups of patients (so-called personalized/stratified medicine or precision medicine) on the basis of an amount of data collected, and transferred from the clinical arena to digitalization.

The collection and analysis of a huge amount of data, in the era of ICT, has health care applications, as model data-driven medicine: 'big data' is an exponentially growing and evolving phenomenon, transforming medicine and health, both as a concept and as a practice.

Big data refers to massive digital data, which is characterized by the '5 Vs': volume (huge amount of data); variety (heterogeneity of sources); velocity (speed of collection, processing and application), veracity (quality of data), value (meaning of data). The novelty of the phenomenon, combined with its complex manifestation and dynamic development, requires new approaches also in ethics and law.

Traditional ethical categories (dignity/integrity, autonomy, privacy, equality, justice) need to be reinterpreted in light of the new issues emerging from the fast developing technologies; existing legal norms at international, regional, national levels, often prove outdated, inadequate and not applicable to the new and emerging problems, which require new forms of governance.

The European context of the project cannot limit the framework within the global and ubiquitous horizon of ICT; and dealing with paediatric population make problems worse, given how difficult, if not impossible, it is to detect age in the digital sphere.

2. Ethical challenges

Big data and big digital repository could be considered a 'big opportunity' for personal and social benefits as regards health. The management of large amounts of diverse types of information, the conversion of these data into hypotheses about health and disease, as well as their transformation into usable knowledge, offers a 'big promise'. The goal of this project, the elaboration of a model-driven patient-specific predictions and simulations and personalised diagnoses and treatments, is unquestionably good from an ethical point of view; it also envisages promising future possibilities in medicine, both for individuals and for society, including present and future generations.

But 'big challenges' to ethics are equally likely.. Challenges are not a sufficient reason to limit or even stop the development of techno-science in medicine, but they should be taken into account in the ethical evaluation and legal governance of these emerging technologies, in order to balance the human fundamental rights (dignity, integrity, autonomy, privacy, justice) and the advancement of progress.

There is no consolidated literature on the topic. There are documents and opinions of international and national ethics committees, which may contribute to the development of an ethical framework in this analysis. Among the main documents, it is worthwhile recalling: The European Group on Ethics in Science and New Technologies (European Commission), *New health technologies and citizen participation*, 2015 and Opinion 7/2015 from the European Data Protection Supervisor on *Meeting the challenge of big data*; UNESCO International Bioethics Committee is currently working on *Big data and health* (likely to be published in September 2017); Italian Committee for Bioethics, *ICT and Big Data: Bioethical Issues*, 2016; Nuffield Council on Bioethics (UK), *The collection, linking and use of data in biomedical research and healthcare: ethical issues*, 2015.

Inaccuracy: Data 'quality' in collection

Possible inaccuracy/doubtful veracity in data collection (the challenge of the so-called 'big bad data'), due to the quantity, complexity, heterogeneity of data sources, as well as its possible non-authenticity or untruthfulness, represent a scientific and ethical challenge. The curation of data including cleaning and quarantining of data, as happed in the MD-Paedigree, serves to bolster the veracity of data.

Large amounts of data are continuously and rapidly accumulating. This explosion of information requires reliable tools to build an accurate collection, evaluation of change in clinical parameters to preserve high standards of healthcare. In this regard, artificial intelligence may be helpful in achieving this goal: computerized patient records may be analysed by appropriate programs developed to yield important clinical information or construct algorithms helpful in diagnosis, prognosis and monitoring therapy. Biases should be identified and eliminated, as far as possible.

However, the quality of datasets used may be at stake: it is necessary to make a clear distinction between quality big data and big data of poor or dubious quality. This also raises the question of robustness and the need for research purposes to access raw data aimed at checking, meta-analysis and reinterpretation.

If bias is detected in the data collected, its analysis and use becomes irrelevant and even damaging for scientific progress, as well as dangerous for individual and public health, entailing a needless and erroneous exposure to risks (to their integrity). Incomplete collections of data or miscoded data are not uncommon, for various reasons (e.g. because of the increase in physicians' documentation burden, lack of education and accuracy and/or knowledge of the correct methodology in registering data, lack of updated international classification of diseases or knowledge of them, difficulties in selecting essential and specific information of a patient's history, incorrect registering of the patients unaware of the possible/future use for analysis purposes, lack of proper oversight and selection for authenticity, lack of standardisation, interoperability and data harmonization as regards terminology etc.). There can be biases in the automated processes used for collecting and assessing the data, often due to the algorithms (and their designers) including a lack of human checks in analysis, lack of education and the competency of analysts. If data quality in the collection and analysis process is not checked, monitored and guaranteed, invalid conclusions may be drawn, on a scientific and clinical level, with possible negative consequences both for individuals and society[35].

Transparency: the possible 'opacity' of algorithms in data selection/classification

Using these technologies for data collection makes it possible to combine biological, social and/or environmental information: big data may show correlations and interactions of complexities in health and disease, that could not be identified before. The key challenge hinges upon transforming biological-social-environmental information into predictive abstract models.

Although, some ethical challenges come to the fore: which are the selection criteria of the most relevant data (criteria of data exclusion or inclusion); the criteria that establish correlations between data (are they objective or subjective); to what extent is it possible to transform bio-socio-environmental data in numbers? There are also possible difficulties in finding objective criteria with regard to data selection, elaborating criteria, categories, typologies, clusters (data selection is not an automatic mechanical tool, but requires a subjective and discretional intervention of researchers in the arbitrary creation of algorithms; the so-called 'ethics of algorithms').

We should be conscious of the fact that algorithms construct correlations and predictions regarding (mathematically calculated) "probability" , which should not be confused with causality. Profiling identifies the major and minor probability or propensity of certain stratified groups of individuals. What criteria form

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[35] W. Raghupathil, V. Raghupathi, *Big data analytics in healthcare: promise and Potential*, Health Information Science and Systems 2014, 2, 3. There is a discussion on what forms of regulations could provide for data quality monitoring (collection, storage, analysis), as a requirement of data use, with flexible and updatable tools (as code of conducts), ensuring competences and correctness of operators (clinicians, analysts, as engineers, statisticians, bioinformaticians) and correct interactions among them. Proposals include 'soft regulation' such as an updated code of practice for clinicians or other professionals involved in collecting health-related data. Others aim to foster inter-disciplinarity between clinicians/researchers and engineers working together to translate and extend their existing and advanced data analysis technology (including on the one hand the clinically trained human mind), into targeted big data analytical approaches that will achieve clinically effective outputs. Although engineers and clinicians have long collaborated successfully, development work on "Big Data Healthcare" will particularly require mutual understanding by each disciplinary culture of the other. This will resort to further cultural development in both areas.

the basis on which algorithms are constructed? An important aspect, therefore, concerns the full publication of all the factors, which research algorithms take into account. The opacity of the factors upon which search engines are based does not allow the monitoring of information quality.

Privacy and confidentiality: the 'end' of privacy?

The protection of privacy and confidentiality is facing several challenges in the era of big data. Full anonymization of personal data no longer provide sufficient guarantees. Partial anonymisation, also called pseudo-anonymisation, or the replacement of identifiers with a code in order to guarantee re-identification when necessary or desirable (for example, to give information to individuals when serious illness or specific risks are discovered), entails risks and possible vulnerabilities, including potential access by third parties (employers, insurances). Re-identification should not only be considered as a theoretical possibility, but also as a practical and real one in the context of big data. For this reason, effective anonymisation preventing all parties from identification becomes a real challenge. By integrating large amounts of data from different kinds of sources, it is often possible to perform re-identifiy an individual..

"Privacy" in the sense of a right to respect for private life (which is more than personal data), in relation to those areas of life or the data that individuals want to keep confidential, is at stake. Problems are likely to emerge in ensuring an effective anonymization of data (gender, age, date of birth are sufficient to identify participants); the so-called phenomenon of the 'evaporation of privacy' or even 'end of privacy' reveals the difficulty or even impossibility, in an age of big data, to completely defend the confidentiality of the patient (or the data owner). The risk for the patients is the possible/probable loss of control over their private information in this virtual space, through the expansion of data[36]. The challenge lies in informing the patients and gaining critical awareness of the problem. The challenge is to raise awareness without losing trust in the governance of health data.

There is a loss of trust in confidentiality caused by the awareness of large-scale data disclosures, as well as revelations regarding intrusions by government agencies and commercial companies, (including inappropriate data sharing by social media organisations). In this sense, there is a need for designing new forms of governance in data collection systems. There should be an improvement of technical measures - as concretely as possible - in order to prevent the identification of subjects and reduce the risk of privacy infringements whenever possible (privacy-by-design). On this point, discussion should be taken forward, at a normative level, on how to guarantee transparency at the moment of data collection and find additional measures to prevent identification of individuals, as standardised anonymisation protocols are insufficient in specific contexts.

[36] The information requested is of an heterogeneous nature: With specific regard to health-related data, consideration should also be given to the fact that boundaries between the strictly medical and non-medical spheres are becoming increasingly blurred, like those between health and society; information on lifestyles and behaviours tends to become increasingly more relevant to health even within the perspective of prevention. In this sense, health information is not only deemed to be the outcome of laboratory tests or epidemiological data, but also the general news that comes from social networks.

Informed consent: broad and dynamic

In the age of *big data,* there is a radical digital transformation of informed consent. We witness a "challenge" to informed consent as it has been traditionally understood. It is, sometimes, almost impossible to specify who is collecting the data and who will use it, which data is involved, how the data is collected, where it will be stored, for how long and for what reason and purpose. It becomes difficult to guarantee the right to access, modify and delete personal data, to revoke consent or to dissent.

Informed consent, in the field of *big data*, cannot be specific; it, inevitably, calls for characteristics of "broadness" given the impossibility of accurately anticipating the paths of research or application in healthcare (similar to what occurs within the framework of biobanks): it is therefore a "dynamic" and "flexible" consent, which identifies similar areas of research directly or indirectly related to the original path. Broadness, dynamism and flexibility do not mean "blind" or 'blanket' consent to whatever research. Broad consent implies asking individuals transparently to consent not only to the immediate purpose for which their data has been collected, but also to unforeseen uses of their data. Dynamism and flexibility mean engaging the active participation of the data subjects, allowing a constant control of data access by individuals, through consent portals.

In a context of greater participation and citizen involvement in science/medicine, concerns centre around the risk that individuals may also be willing to actively participate in research and express their consent to donate and share data to 'open source' platforms. This may be explained as a form of altruistic behaviour, expressed in the willingness to give unlimited permission regarding the use of data in a collaborative or cooperative context (the so-called phenomenon of 'citizen science'). Some criticise this kind of consent to data donation, defining it as misinformed naivety and suspect that the exaltation of an unselfish logic, may be inspired by a hidden desire to stimulate above all the market.

One could perhaps rethink the very expression "Informed consent" in the digital world, limiting it to an "awareness" or "acknowledgement" that the data will be collected, with a critical consciousness of the difficulty/impossibility of anonymity, based on the non-precise *a priori* determination of the method of use, storage, and analysis of data, and the impossibility of guaranteeing security and confidentiality in all circumstances.

Equality: non-stigmatization and non-discrimination

The protection of personal data (confidentiality, discretion, privacy) should be combined with the protection of personal freedom[37], in order to avoid or at least mitigate the "social risks" of new technologies, namely the abuse and misuse of data for discriminatory purposes (in the field of insurance companies or workplace).

[37] C. Bock, Preserve Personal Freedom in Networked Societies. Broad Anti-Discrimination Laws and Practices could Compensate for Failing Data Protection and Technology-Linked Loss of Privacy, "Nature", 2016, 537 (7618), p. 9.

3. Legal framework and governance

There are no specific regulations of the phenomenon of big data in national and international legal frameworks. Regulation of data protection is provided for in many legal systems, numerous rules thereof could be applicable to the area of big data: even though big data is a new reality and may require new regulation. While there is a broad consensus on the core data protection principles at the heart of most national laws and international norms, the main challenge the divergence in the implementation of these principles, as well as in the detailed data protection laws of the world.

The legal framework applicable to data use in biomedical research and health care recognises, broadly, two sorts of measures that may protect the interests of citizens against potentially injurious misuse of data. First, it recognises operations that alter the data in order to de-identify it, so that its use would no longer pose a direct risk to data subjects through person identification. Second, it sets out controls over access to data in a way that the data is only made available to authorised users, under circumstances in which it is expected not to be misused or otherwise result in harm to data subjects. These measures are often used in combination.

In the framework of the UN Declaration of Human Rights (1948) and the European Convention on Human Rights (1950), there are two recent European documents: Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of data and the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. Both are the main binding legal instruments at international level, which address privacy. The European Region has a more developed legal protection of health-related data than other regions[38].

Regulation 2016/679 is of great importance for information and communication technologies, because it provides the basis for the exercise of new rights and defines limits with regard to the automatic processing of personal data. The Regulation states that the persons involved in the processing of personal data should be informed of their right to revoke consent to certain processing, and the right to "be forgotten", or the cancellation of their personal data. Furthermore, the Regulation introduces the "right to portability" of one's personal data to transfer from one data controller to another. The Regulation confirms

[38] WHO, *Legal frameworks for eHealth, Based on the findings of the second global survey on eHealth*, Global Observatory for eHealth series, Volume 5, 2012, p. 27. Among the most significant documents on the subject adopted by the Council of Europe, one should recall: Convention for the protection of individuals with regard to automatic processing of personal data, Council of Europe, 1981 and additional protocol (Additional Protocol to Convention ETS No.108 on Supervisory Authorities and Transborder Data Flows); Recommendation CM/Rec (2010)13 of the Committee of Ministers to member states on the protection of individuals with regard to automatic processing of personal data in the context of profiling (23 November 2010); Recommendation CM/Rec (2010)13 on the protection of individuals with regard to automatic processing of personal data in the context of profiling (23 November 2010); Recommendation CM/Rec (2012)4 on the protection of human rights with regard to social networking services; Recommendation CM/Rec (2014)6 on human rights for Internet users; Recommendation CM/Rec (2016)1 on protecting and promoting the right to freedom of expression and the right to private life with regard to network neutrality.

the transfer ban on personal data to countries located outside the European Union or to international organizations that do not meet the required standards on data protection, in relation to which the Regulation introduces more stringent evaluation criteria. Also significant for information and communication technologies is the principle of "privacy by design", whereby it is necessary to ensure the right to data protection from the initial stage of conception and design of a process or of a system.

There is a discussion in biolaw, at the international level, on a new form of governance of big data. Looking at the global scope of big data and health, as well as the fast technological development, it is difficult to elaborate comprehensive and balanced regulations. Governance systems for big data should protect the fundamental rights of the persons from whom the data originates: dignity/integrity, autonomy, privacy and data protection, transparency, equality. Data governance should guarantee that citizen involvement, engagement, participation and sharing of data will not be subject to any form of exploitation, stigmatization or discrimination.

This goal could be reached through: transparency of database purposes, arrangements for the control of accuracy and transparency of procedures (collection, use of algorithms, consent), arrangements for the protection of privacy, at least declaring the limits of privacy protection, arrangements for the duration of data storage, concerning data ownership, data sharing and criteria for access, including the prioritization of research and data users.

Conclusion

It is important to be cautious and to avoid exaggeration of the current state of scientific knowledge and the potential benefits of big data and precision medicine for healthcare. The bio-optimistic ´hype of big data´ can lead to overstatements and unrealistic estimations. On the other side, the bio-pessimistic underline of threats, potential risks and damages may lead to neglect of the potentials of big health data.

A balanced way of dealing with hopes and promises, opportunities and challenges, is very important in order to protect human values and rights in the context of the advancement of techno-science in medicine.

Appendix 2 – External Advisor Comments – MD-Paedigree project on validation and verification

Issued by Marta Bertolaso - Associate Professor in Philosophy of Science - Faculty of Engineering -Campus Bio-Medico University of Rome

MD-Paedigree is a clinically-led Virtual Physiological Human project that enhances existing disease models deriving from former EC-funded research (Health-e-Child and Sim-e-Child), as well as from industry and academia, in order to develop more accurate disease models, diagnostic tools, and establish a worldwide paediatric digital repository. It may be regarded as an attempt to make a further step towards personalised healthcare, based on data-driven research.

More precisely, MD-Paedigree aimed at quantifying predictive accuracy of a number of mechanistic and analytical models in four clinical areas of interest (WP12): cardiomyopathies, cardiovascular disease risk in obese children, juvenile idiopathic arthritis, neurological and neuromuscular diseases. The project is coordinated by Ospedale Pediatrico Bambino Gesù (see DOW for the complete list of participants).

The framework was set during the second year as a three-tiers process starting from technical testing and algorithmic fine tuning, leading to internal validation on limited data samples and finally to external validation on perspective clinical follow-ups. Specific protocols, including clinical endpoints, observation periods, statistical methods of choice and patient eligibility criteria were then developed (D12.2.2).

Samples sizes for perspective studies were limited in all areas, by design, and in some cases further reduced due to delays in patient recruitment. Thus, such studies can actually be considered useful for a initial and promising proof of concepts (randomized trials, not in the original scope, would be required to complete approval and implementation in care settings).

Validation protocols were all brought to their conclusion, demonstrating in most areas their ability to simulate likely patient outcomes from commonly available clinical input parameters. Such outcomes have already shown some descriptive power of the pathophysiological models, whose reliability will be assessed by the mentioned above processes of external validation.

Thus, such results opened unforeseen methodological and epistemological questions, especially in the area of long term, patient specific predictions and especially for mechanistic simulations.

Indeed, MD-Paedigree project deals with two hot topics in current debate in epistemology and philosophy of science, i.e. big data and simulations. This project actually combines a data- and model-driven research approach with the goal of developing accurate digital simulations of disease evolution and organ functioning. These two topics are strongly related. Indeed, big data represent both an opportunity and a challenge for simulators: if on the one hand, they allow a more sophisticated and accurate model design, on the other hand, big data increase the difficulty of developing computational tools that are able to manage such a huge amount of data. Moreover, an explicit epistemological framework about the intrinsic relationship between the descriptive and explanatory import of models should be explicitly posed and discussed in the future development of the project. In fact, recent epistemological analyses of the alleged epistemic diversity between simulations and experiments highlighted that simulations, unlike experiments, need to be based on strong background knowledge and well confirmed theoretical assumptions relative to the phenomenon that has to be modeled, in order to be regarded as reliable and effective (Roush 2017; Winsberg 2015; 2010). The

more we know about the phenomena we model, the more simulations of those phenomena will be reliable, and predictively accurate. At this regard, combining big data and deep theoretical knowledge of the phenomena that one aims to model is crucial. Finally, the ability in developing the right computational tools, techniques, and tricks, which is a distinct and essential element of computer simulations (Winsberg 2015; 2010), is an essential follow-up of this kind of project. The ability of developing ever more reliable simulations cannot but be acquired in the practice, by gathering together computer scientists and clinicians.

The validation of analytics approaches does not, in fact, conceptually differs from validation of other kinds of approaches. Mechanistic models instead point explicitly to future states of organs and patients, and directly influence treatment planning. Predicted outcomes, at the same time, especially long term ones, are subject to external dynamics that is not, and will not be possible in the near future to include in the predictions. Actual likelihoods are therefore bound to pathophysiological evolutions outside the model.

This understanding highlighted the need for new validation and design approaches that the consortium analyzed, not only framing the project's validation results in their proper context but also investigating possible solutions. Lynkeus, which was involved in MD-Paedigree's validation effort in the last year, seems to be well positioned to take care of some of these aspects, due to previous and current works in setting up virtual cohorts and uncertainty quantification methods (see e.g. Cardioproof project, submitted in response to the SC1-PM-16-2017 call).

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