international risk governance center

WORKSHOP REPORT

Governance of trust in precision medicine

IRGC Expert Workshop
Campus Biotech, 23-24 November 2017

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

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PREFACE

In the course of previous work to produce a 'roadmap for the development of precision medicine' (published in 2017) the International Risk Governance Center (IRGC) at EPFL had identified five specific challenges that needed to be addressed:

1. Trust: engaging citizens and patients in biomedical data collection and sharing schemes
2. Data security: securing data transactions for privacy and confidentiality (including cybersecurity), while at the same time making the data available for research (interoperability)
3. Incentives: helping scientists and technologists organise so that they work more effectively together (competition, rewards and incentives)
4. Economics: making the case that investing in precision medicine (research and implementation) is cost-effective
5. Regulation: helping regulators design licensing mechanisms to assess efficacy and safety with acceptable certainty without constraining innovation

On 23-24 November 2017, IRGC organised with support from the Swiss State Secretariat for Education, Research and Innovation (SERI) and the Swiss Personalized Health Network (SPHN) a multi-disciplinary and multi-stakeholder workshop on the theme of Trust in Precision Medicine. The objective was to gain insight into practical ways to build trust in and within the field of precision medicine.

HIGHLIGHTS by IRGC[1]

Precision medicine is individual- and patient-centric. However, trust in precision medicine is far from being limited to trust from individuals and patients. Each actor or process in the system should be trustworthy for what it aims to deliver. Although it is difficult to define *indicators and criteria of trust or trustworthiness for each*, this is a necessary exercise for the successful development of precision medicine. It is equally difficult to *assess whether each actor or process is trusted in a given context or country*, because of the complex network of institutions collaborating with each other in a multi-faceted process. Collaboration between actors, communication and transparency is thus an important cross-cutting theme, with the aim to reframe and redesign the trust system to accommodate precision medicine's goals to improve the practice of medicine in general.

The concept of trust is central to each of the three stages or components of the precision medicine process (value chain): the collection of data, the analysis of data and the provision of health and medical care.

Data collection

The process begins with individuals who participate in data collection schemes, as either or both 'donors' who wish to contribute to research, and patients with certain medical needs. They 'donate' tissue or DNA that contains data that is private and confidential to them. They also give (or should give) access to medical health records and other lifestyle information, which is often collected without their full awareness. Here, individuals demand *trustworthiness* on the part of those who collect the data and other information that the process will be secure and protect their privacy, and that the information will not be used against them in any way and at any point in time. In addition, individuals and patients want to *trust* the whole precision medicine system. In this system, sharing tissue and data should be made for the public good, and some benefit must returning to citizens and patients. Trust can thus be seen as the overall sentiment that, all together, the actors that collect, give access to and use the data, do it in a fair and responsible manner.

Data analysis and governance

The system of data analysis and governance must be transparent, reliable and accountable. The data must not be stored and processed in a way that could cause prejudice to individuals. Here one must consider that, beyond ensuring data security and oversight or governance, it is increasingly the governance of algorithms that will matter. The prospect of using artificial intelligence must not give the impression of creating a black box. However, aiming for transparency of algorithms and accountability of their managers will become increasingly complex. It will thus be important that each actor finds trustworthiness in other actors with which they collaborate. Overall, governance of data analysis is needed to establish and maintain trust in the data system.

Provision of medical care

At the end of the process, precision medicine must improve public as well as individual health. Patients expect that their medical needs will be met. Here, each patient wants trustworthiness on the part of those who provide diagnostics, prevention or therapy. This concerns the medical practitioners or 'counsellors', hospitals, the pharmaceutical industry, regulators and payers particularly. All these actors must determine for what they want to be trustworthy, and be able to demonstrate their trustworthiness. At the same time, individuals must trust the whole precision medicine system, or perhaps the entire health and medical system, for its capacity to improve health. Criteria of accessibility and affordability of new 'genomic-enhanced' medicine are key to contributing to overall trust in the system, which means that fairness and equity are perceived as important for the success of precision medicine.

[1] These highlights reflect the views of IRGC, as main organisers of the workshop

This summary of the workshop discussions[2] on the 'governance of trust in precision medicine' presents some of the important points and insights elaborated by the participants.

The workshop also highlighted the importance of additional work about:

- Issues of data governance: data security and protection of sensitive data, privacy, algorithmic decision-making, and platforms for data sharing
- Cost-effectiveness, economics and payment schemes: making precision medicine affordable in the practice
- The need to improve collaboration: all workshop participants, representing different stakeholders, demonstrated their willingness to collaborate with each other to address and resolve any outstanding issue.

[2] The programme of the workshop was organised to discuss several predetermined questions. See the questions discussed during the workshop in Appendix 2.

WORKSHOP SUMMARY

This summary of the workshop discussions presents some important aspects raised by the participants. Participants in the workshop are listed in Appendix 3.

1. Setting the scene

Broadly speaking, precision medicines are of two distinct types. The first type – a more personalised precision medicine – entails gene therapies or regenerative medicines whereby therapeutics are tailored to the individual.[3] In this case, trust often results from patients' needs being met, especially in situations when patients have no other treatment options and remain more worried about their immediate survival. Since enabling more advanced therapeutics implicates both licensing and payment arrangements, trust over regulators' and payers' decisions and about patients' access to such therapeutics emerge as key points of consideration. Licensing is particularly complex when traditional clinical trials are not well suited to small sample sizes that may characterise this type of precision medicine.[4] This type of more personalized precision medicine nevertheless requires gaining broader societal trust and involvement, particularly on matters of accessibility and equity.

The second type of precision medicine – more probabilistic, sometimes preventative in character – entails the more targeted use of traditional small molecules thanks to information on genomics, health records and other types of data that can facilitate better drug safety and effectiveness. This targeted approach is about working more intensely with flows of shared data and thus requires access to quality data, but also an investment in the data analytics for the development of appropriate diagnostics. Issues of trust, in this case, revolve largely around the appropriate sharing and use of data, namely trust around access to data, the integrity of data, as well as around data processing and analytics that can help make the practice of medicine better targeted where possible.

Boxes 2-5 illustrate the development of precision medicine in different countries and contexts, some more successful than others. While slightly different trust issues may arise for different types and applications of precision medicine, or for different publics and stakeholders, it remains important to also gauge the trust in the global system of precision medicine.

2. On trust and trustworthiness

Workshop participants' discussion on trust concerning precision medicine was informed by a background paper[5] (see Appendix 1) that was subsequently published in Omics[6] (Adjekum, 2017). Key, in this respect, were the distinct concepts of trust and trustworthiness, which are often used interchangeably. Whereas trust is understood as an expectation of positive motives (Rousseau et al., 1998), trustworthiness is perceived as a characteristic that is projected onto an individual or group (Holm and Nystedt, 2010). One can further argue that for trust to be established, trustworthiness needs to be demonstrated; or that if trust is a response to trustworthiness, we should aim to put "trustworthiness before trust" (O'Neill, 2002). The background paper thus suggested a working definition of trust of individuals in precision medicine as "*the willingness of a trustor to accept the potential risks involved in the sharing and further use of their personal data resulting from both optimism about the trustees' goodwill and interest in the public good.*"

Participants sought to cast the discussion on trust and precision medicine along more pragmatic and relatable concerns as well. They suggested, for example, three types of questions that individuals should be

[3] As exemplified by *CAR T*-cell therapy—a rapidly emerging form of cancer treatment

[4] The European Medicine Agency (EMA) is pioneering with adaptive licencing pilots that address this problem. This is a good example of the adaptation of regulation to the new requirements that are faced by smaller indications of evidence on effectiveness. US FDA is also moving in that direction.

[5] Available here: https://irgc.epfl.ch/page-148683-en.html

[6] Afua Adjekum, Marcello Ienca, and Effy Vayena. *What Is Trust?* Ethics and Risk Governance in Precision Medicine and Predictive Analytics. OMICS: A Journal of Integrative Biology. December 2017, 21(12): 704-710. https://doi.org/10.1089/omi.2017.0156

able to ask actors in the precision medicine system:
1. Why are you pursuing precision medicine? *'Can you explain to me what you are doing?'*
2. Who benefits from precision medicine? *'Me and who else?'*
3. What confidence can we reasonably have in precision medicine? '*How sure are you that what you are telling me is right*?'

This line of questioning that can resonate with varied parties brought into the conversation the more pragmatic concerns about enabling quality precision medicine with the more slippery notions of trust and trustworthiness that matter for the acceptance of it.

Drawing from the themes and insights elaborated by participants in different working sessions, this summary report synthesizes how trust percolates into the three key components of the precision medicine process namely the collection of data, the analysis of data and the provision of health and medical care, and cross-cutting issues and reflections around communication as well as mandating and assessing trust.

3. Trust around data collection, use and analysis of data, and provision of health and medical care

It is useful to begin by noting that the process of delivering precision medicine includes the collection of data, the analysis of data, and the provision of health and medical care. Synthesizing along these distinct components allows us to see how different actors and stakeholders partaking in the discourse around trust in precision medicine are grappling with different ends, or aspects of the matter, but often with shared or interchangeable insights.

3.1 Trust at the level of data collection

Developing more accessible, integrated data sets including genomics health records and other data is essential to precision medicine. The process begins with individuals who participate in data collection schemes, as donors' who wish to contribute to research, and/or patients with distinct medical needs. They 'donate' tissue or DNA that contains data that is private and confidential to them. Moreover, precision medicine requires not only access to medical health records and other lifestyle information –at times collected without their full awareness of it – but it also requires access to high-quality data, and thus ways to curate the data. At the level of data collection, the question of trust thus becomes entangled with concerns about privacy, consent, security of data transactions as well as assuring the quality of data. The dilemmas that were discussed include:

- How to reconcile privacy and sharing, or what should be in the private versus public domain?
- How to implement broad consent ('opt-in') and handle incidences of 'opt-outs'?
- How to secure sensitive data while also recognizing the potential of the technology itself to contribute to certain broad distrust (as illustrated by the massive attacks on health data)?
- How to navigate the trade-off between giving patients better control over their personal health information on one end and supporting medical research whose value accrues as data is shared, curated and aggregated on the other end?

Beyond articulating and debating these dilemmas, workshop participants further contributed the following insights that help advance the conversation on trust and data collection for precision medicine:

- Allowing opt-ins and opt-outs may help express consent in the more mechanical or narrow regulatory sense, but **opt-outs and opt-ins in precision medicine programmes are not necessarily adequate indicators of people's trust or mistrust of them.** They require a more nuanced interpretation. Individuals who opt-out of a programme may display disagreement with it but not necessarily a lack of trust in it. At the same time, people who opt-in may not trust the whole programme. What further complicates the matter are potential gaps between regulation and human behaviour. For example, regulation may seek to maximize protection of private and

confidential data, but individuals behave differently in practice. In the UK experience with care.data, only one in 45 individuals opted out after it was revealed to the public that the programme had no plan for Intellectual Property (IP). So far, opt-out rates of precision medicine programmes are low.

- Participants further noted that **many patients would like to see more sharing of data** as a way of enabling faster access to treatments and **are more willing to give consent for broad purposes**, like improving the practice of medical and healthcare provision. Consent, in this view, involves more and better engagement of individuals on how their data could be used for the benefit of society as a whole and how that can trickle back to them.
- While important to cast consent on broader terms and purposes, **protecting against adverse data use remains important for mobilizing it**. Patients worry about the secondary use of their material and care to know if there is a risk that they would be hurt when they give access to their data. Thus governance of data use, reuse and misuse takes greater salience in the debate. The attending question that arises is whether individuals can have greater control, even property rights, over their data.
- **There are no intellectual property rights on tissue or body parts in general.** While possible to argue that giving access rights to individuals and sharing profits with them is a way to include them into developing precision medicine, it remains important to decouple the basis of consent from the question of ownership. Even if data ownership was possible and legal, what seems overlooked or misunderstood is that data does not accrue value at the point or moment of collection, but as it is aggregated, curated, and analysed. Property rights are thus established later in the process and on the basis of investments made to develop this knowledge. Educating the public about misguided expectations around ownership rights in precision medicine can help adjust expectations and gain broader societal trust.
- More generally, **the promise of data control seems misleading as there is an important balancing act between optimizing for medicine and optimizing for individual rights,** like privacy and ownership. Sharing tissue and data is intended for the public good, with some benefits that come back to patients as well as the stakeholders that develop the practice. If, on the other hand, researchers and industry do not have the information, they cannot develop precision medicine treatments or solutions. This trade-off manifests itself along various points in precision medicine, but at the level of data collection, the requirements for data protection and anonymization must be balanced with the need for data curation. Precision medicine depends on high-quality data, and this requires data identification or being able to check, confirm, re-test and deal with anomalies. Given that most of the methods used to protect individuals and their medical data have some degrees of anonymization and de-identification, data curation remains difficult.
- While there is some broad mistrust of technology (as illustrated by the massive attacks on health data), **technology can also help build trust in data collection for precision medicine.** It can do so by way of a number of privacy enhancing techniques, like various sorts of cryptography[7]; statistical techniques whose objective is to avoid that the response to a query leaks too much sensitive information and leads to the origin or source of the data; use of blockchain technologies to decentralize storage and distribution of sensitive data with a view to keeping them as close as possible to those who value data protection and privacy; etc. Practitioners further noted that often in a hospital or research settings, the norm is that patients' data cannot be accessed without approval by ethics committees, and cannot be used without respecting certain rules and regulations. However, some facilities may have inadequate health data management practices, including a poor understanding of data and IT security.

[7] There are various sorts of cryptography, including symmetric cryptography, asymmetric cryptography, privacy-preserving encryption, and in particular homomorphic encryption. www.genomeprivacy.org is a website that presents various advanced techniques to protect data in personalised health.

- Beyond more technical solutions, it remains important to **recognize a certain trade-off between the ideal ethical framework and the actual objective that precision medicine can help achieve**. There is no such thing as 'sufficient' level of trust in how data is protected, not least because the importance of data protection remains fairly context dependent. Expectations of data protection are less important, for example, when there is a pressing or critical medical need. Individuals may be more willing to share if they perceive how this improves the health circumstances around them. To navigate this gap between ideal frameworks and contextual circumstances in ways that inspire and mobilize trust, participants explored other modes of engaging patients as partners, even co-producers of data, or science.
- **Patients' organisations of various sorts (patient support, cooperatives for data sharing, advocacy groups, etc.) are important elements in the trust chain**. It would be useful, for example, to build platforms for patients' data uploading, peer-to-peer information and patient engagement. In the social media space, new organisations or portals like 'Patients like me' reconfigure the traditional way of ensuring trust. This type of portals helps create self-trust mechanisms or 'do-it-yourself' self-help systems that fill data gaps for the purpose of evaluating what works and what does not work for patients 'like me'. This approach to addressing problems of trust is worth exploring for it empowers patients in ways that render the fear of losing control over their data less salient.

3.2 Trust around data use and processing

Important trust considerations arise at the level of data processing and analytics, including questions about data use, re-use and misuse in a changing paradigm where medical research involves not only more intense data flows but also new 'data players' (the so-called 'IT giants' like Google, Amazon, IBM and others). This expansion of the precision medicine makes for a novel landscape or eco-system with a larger set of actors, intensified data flows and multiplied data points or sources. It brings more fundamental changes to how data is perceived and processed and blurs more traditional boundaries and roles. Such change thus raises novel questions about:

- envisioning trust in institutions but also networks of collaborators (e.g. how different institutions can become more trustworthy, what different actors want to be trusted for but also how to trust networks of collaborators in a changing landscape of players)
- facilitating the right dynamics of accountability and degrees of transparency (especially vis-à-vis the use of algorithms and artificial intelligence in medical research and decision-making as well as vis-à-vis data-pooling and data-integration schemes emerging within the industry and across medical researchers)
- attributing legal responsibility and liability where necessary (i.e. establishing rules that define roles and relations between parties and provide confidence that individuals' interests will be addressed in case of adverse use).

Data security is of prime importance, and the protection of sensitive data through secure IT and practices is a critical trust factor. Hospitals are frequently subject to cyber-attacks, and as important nodes in the data analysis process they must work to reassure patients and medical professionals. In addition, data use and analysis must be transparent, accountable and reliable enough so that both 'donors' of data and 'users' of health care trust the data governance system, including that it may not cause prejudice to them. While difficult to identify a single institution in which trust could be deposited, when it comes to governance of data use and analytics, particular attention goes to the challenges of enabling intra-professional and intra-industry collaborative schemes, as well as the role of algorithms and Artificial Intelligence which can give the appearance of a black box. The following insights from workshop participants can help advance the conversation on trust and the governance of data use and analytics in precision medicine:

- **Collaboration between actors is of utmost importance in the context of trust in precision medicine.** There is a common interest in collaboration for developing more accessible, integrated

data sets including genome, health records and other data to serve the needs of diverse populations and stakeholders. Industry consortia are one solution, but a broader approach to creating large integrated data sets (that might be divided into de-identified aggregates, with easy opt-out form consent) can help broaden trust. Such multi-stakeholder consortia would be best coordinated by respected, trusted and neutral actors.

- **Collaboration must also contend with competitive dynamics, legal challenges and inter-professional tensions around sharing, pooling, or integrating data.** Coordinating the sharing of extensive data pools in the pharmaceutical industry is, for example, a complicated legal discussion of data ownership. Thus trust also requires players in data analytics to demonstrate that they can find ways to share data in a legal manner and engage in 'competitive collaboration'. In a similar vein, inter-professional trust among health care professionals is not to be underestimated in that they might not always want other care professionals to look at their data and practices. One solution would be partnerships between industry, care practitioners and governments, where policy-makers help create the platform for the collaboration and sharing of data.
- **Legal aspects may become increasingly important in that laws and regulation can contribute to establishing the basis for trustworthy relationships in a context of blurred roles and responsibilities.** The principle of fiduciary duty, for example, applies to the classical physician-patient relationship, but the precision medicine ecosystem involves so many other actors who use the data, that it may no longer be relevant. There is a new discussion about the stewardship model that extends how researchers ought to think and how those who control the databases should behave. The objective is to stretch the responsibility existing in the patient-doctor relationship to a larger set of actors involved in data processing and in so doing, create the conditions for trust in the governance of data use and re-use.
- **Collaboration is needed in particular to address the so-called 'Big Data challenge'** which implies that, even if individuals trust the local system that will encrypt, analyse and store their data, their data may eventually end up in the hands of other actors, or industries. New actors like 'IT giants' (IBM, Google, Amazon and others) are entering this domain, with extensive datasets and methods that differ from those traditionally employed (e.g. in the pharmaceutical industry). For example, Google and Microsoft are pursuing genomic research, and Amazon may soon deliver medication. Their behaviour and effective success in delivering useful data and services will affect trust in precision medicine. At the same time, among traditional companies, outsourcing is becoming the norm, including in the data area and including to those 'IT giants' mentioned above. As private companies partner with a large number of providers, including academia and start-up companies, and outsource innovation, how to ensure the trust in that enhanced ecosystem? Thus varied players need to find ways to make their trustworthiness visible, such as by way of collaboration, even engagement with contrarian views. It will further be important that each actor finds trustworthiness in other actors with whom they collaborate.
- **Trust increasingly becomes a matter of trusting networks of actors of various types.** Individual institutions, be they pharmaceutical or technology companies, hospitals or academic institutions, are not necessarily fully in control of everything, but they are still liable for what happens in their ecosystem when they engage or outsource to other actors that undertake activity on their behalf. There is thus a growing need to move away from strict compliance programs that solely focus on internal processes and look into the broader ecosystem. Trust can no longer be built and sustained individually.

Box 1: OECD recommendations on health data governance

OECD recommendation on health data governance adopted in 2016 includes twelve principles for building a governance framework that could reconcile risks and benefits and create the conditions for trust.

Particularly relevant to the trust issue are:

Engagement and participation
Clear provision of information
Effective consent and choice mechanisms
Controls and safeguards
Approval procedures for the use of personal data
Recognition of the role of technology
Public disclosure and transparency
Certification or accreditation.

Implementation of these measures could provide a proxy for trustworthiness.
http://www.oecd.org/els/health-systems/health-data-governance.htm

- **Transparency of algorithms and accountability of Artificial Intelligence (AI) decision-making will become increasingly complex and relevant.** Algorithms are the lifeblood of precision medicine and effective individualised treatments, but they are often not very transparent nor easily understood. The use of Artificial Intelligence – using computer science to help understand the mechanisms of disease and human health – can give the appearance of creating a black box. Establishing algorithms' transparency is challenging in practical terms but remains important for facilitating trust in the underlying technology. Governance principles should be established to enable the accountability of AI-based decisions, which may also require some form of regulatory oversight.

Ultimately, individuals seek *trustworthiness* on the part of those who collect, share, analyse and/or use the data and resulting information, and assurances that those will not be used against them in any way or at any point in time. In addition, individuals and patients seek *trust* in the whole precision medicine eco-system, which is composed of various actors, with diverse roles, rules and collaborative challenges. Trust can thus be seen as the overall sentiment that, all together, the actors that collect, give access to and use the data, will do it in a fair and responsible manner. Lastly, individuals and patients also need to *trust* precision medicine's broader purpose, namely that it will improve the provision of health and medical care. The latter raises its own set of trust considerations, particularly vis-à-vis those (actors) implicated in the more direct provision of health and medical care, i.e. medical professionals, payers as well as companies.

3.3 Trust and the provision of health and medical care with precision medicine

At the far end of the process, precision medicine aims to improve public as well as individual health. There is an expectation that patients' medical needs should be met. Thus individual patients seek *trustworthiness* on the part of those who provide information for diagnostics, prevention or therapy. This concerns the medical practitioners or 'counsellors', hospitals, the pharmaceutical industry, regulators and payers who must probe and determine for what they want to be trustworthy, and find ways to demonstrate it (their trustworthiness). At the same time, individuals must trust that the precision medicine system can be properly accommodated and integrated within the broader health and medical system so as to witness or experience its capacity to improve the delivery of healthcare.

Workshop participants discussed the centrality of the criteria of accessibility and affordability of new 'genomic-enhanced' medicine for establishing an overall trust in the system, but also the inclusivity and representativeness of data in precision medicine, the role of medical professionals in redefining health as well as their pragmatic resistance to precision medicine, and ultimately, whether precision medicine could

be over-promising and/or under-performing (vis-à-vis the more traditional health systems in place). On these points, the following insights accrued:

- **How medical practitioners participate will determine to a large extent how patients trust the system of precision medicine.** Indeed, medical professionals are important actors in the release of certain key tensions to precision medicine, such as tensions between patient empowerment and paternalism in the medical sector (e.g. medical doctors must prepare to see patients who have acquired information about their genome even before consulting them) and tensions between the promise of 'precision' and the inherent uncertainty in precision medicine. The latter may prove particularly troubling to patients and professionals alike, in that they may have more data at their disposal, and precision medicine may even enable preventative medicine, but it will not do away with scientific uncertainty per se. These tensions may not easily dissolve, but at a minimum, it remains important that they do not destroy the confidence that people have in the medical professionals. As precision medicine will enable preventive medicine, the medical professionals will have an important role in providing guidance to their patients, namely to help redefine what health is and how to stay healthy, without transforming every citizen into a future sick person.
- **A significant part of health personnel exhibits pragmatic resistance to precision medicine**. This resistance may be driven by fear that hard-won clinical skills could be obliterated by algorithms. It may at the same time be driven by difficulties in envisioning new roles and working with new kinds of knowledge. Preventive, predictive precision medicine, for example, creates situations in which the doctor is no longer the central and ultimate medical authority but the professional who helps patients making sense of large volumes of medical data. It is still unclear whether medical doctors will in the future be responsible for delivering data analytics information to patients or whether new professional roles will emerge (e.g. health coaches) and this lack of clarity on changing roles. But resistance may also be partly driven by concerns about data integrity and representativeness, leaving clinicians unconvinced that precision medicine will help their particular patients. The 'All of Us' longitudinal study in the US for example (Box 2) points out the difficulty of gathering a sample that is representative of the underlying population.[8] This, in turn, raises questions about just how representative and tailored to patients' needs precision medicine can be.[9]
- **The degree to which precision medicine builds or exacerbates existing inequalities in access to medicine can significantly impact the trust that different patients and practitioners place in it.** The need for precision medicine to further the common good is a common theme that has yet to be reconciled with the fact that it may increase inequalities and health disparity. To this effect, perceptions about access to precision medicine, and the affordability of it, can significantly affect the trust people place in it. In some contexts, the overall trust issue may be less about data privacy, ownership or of consent than about assuring access to and affordability of precision medicine.
- **Providers of medical and healthcare, including payers and industry, must strive to make precision medicine affordable and inclusive.** Health care systems are often very resource constrained and thus pricing and licensing around precision medicine must take this into account. A possible approach is to shift to 'value-based healthcare' which has a more holistic approach to the pricing for drugs and treatments (i.e. considering the total cost of disease over the life of a patient). Drugs and treatments thus would be priced in relation to the benefit, or added value, that they deliver to society. If the health system, including payers, is not able to reform to make precision medicine available and affordable, then precision medicine itself may be criticized for being too expensive,

[8] E.g. in the first phase, less than 4% of the data were from Americans that were not of middle or upper class standing and with other than European ancestry; the percentage grew to 20% but this is still not representative of the US population in which more than 50% of people who have no linkage to European ancestry

[9] 80% of Americans are in favour of the programme, but this percentage falls to 50% among Afro-americans, probably because of a history of experimentation on under-represented minorities

elitist and generally over-promising. On the other hand, if existing health systems are already struggling with respect to access and affordability, then a more honest conversation must take place about what conditions can progressively develop to achieve cost-effectiveness and inclusion through precision medicine[10].

- **Taking a long-view to precision medicine might be more constructive than premature conclusion on whether it is over-promising or under-delivering.** Disappointments about slow or incomplete progress can be squared with the fact that the health system cannot yet fully use the data and learnings from all the patients. As medical education progressively adapts and trains young physicians in the disciplines involved in precision medicine (genetics but also data integration, curation and analysis, algorithms and statistics, etc.), medical practitioner resistance may progressively disappear. Small-scale deliverables that will act as a proof-of-concept can be very helpful in this respect.

4. Communication and transparency for precision medicine

A cross-cutting remark from practitioners, industry representatives, researchers and patients is that working to build trust in precision medicine requires large, targeted and sensible communication efforts.

- **First, we need to learn how to better communicate to the public and to professionals.** Effective communication is a dialogue among various parties who often have different cultures, concerns, needs, perceptions and even emotional approach to health and disease. Communication begins with the mapping of actors and the identification of who needs to communicate what, to whom, how, and for what objective. It must also acknowledge that emotions may drive behaviour, with the effect that some individual choices may be seen as irrational trust or distrust, when facing specific situations.
- **What to communicate?** Those who communicate must determine what is needed to achieve precision medicine. For example, it is important to communicate the underlying **uncertainty** that prevails in precision medicine, in order to manage the expectations from precision medicine: do not overpromise. Communication about **consent-related issues** (what research participants agree to share and how) should convey information in a way that can be understood, and that can foster meaningful exchange between different type of audiences, for an informed decision. Particularly challenging in communicating about precision medicine is the possibility that people may increasingly look for information that is available on social media or the Internet, some of which may not be the most trustworthy. While experts may struggle to deliver a unified perspective on precision medicine that is easily relatable or understandable for a broader audience, it may be relevant to **communicate about risks and benefits**, whether they are scientifically assessed or emotionally perceived. There may be **over attention to data-related issues**, in contrast to attention to risks and benefits, which may be easier to understand by individuals who have to make up their own mind and decisions.
- **We also need to exercise some caution with respect to communication.** Branding exercises that were or are undertaken by certain governments to promote the common good in order to mobilise donors can be analysed as initiatives to 'manufacture' trust. Hard campaigning and voluntarist campaigns may not be an effective way of engaging participants. Precision medicine needs a quite strong presence in the public debate, yet at the same time, it must not be promoted too aggressively on 'promises' or with misleading expectations.
- **Transparency is an important factor of trust and can provide evidence of trustworthiness, but it has to be carefully calibrated.** The relationship between transparency and trust is complex in that too much transparency (e.g. revealing sensitive information) can brew distrust as can a lack of transparency (e.g. AI as the 'black box', or lack of transparency on who decides what treatments

[10] IRGC's forthcoming workshop with experts will discuss 'The Economics of Precision Medicine', in particular questions of appropriate pricing and changes in payer and economic models.

are funded). The existence of a social and political public dialogue is essential in this respect. Trust depends on the process by which information is communicated to and discussed with the stakeholders. This process must have some form of legitimacy. In addition, information and openness to it are needed to substantiate the dialogue.

- **Transparency should be discussed not only at the level of data protection, sharing and curation, but also at the level of funding/payment and relations with payers, industry and regulators.** The role of the industry in manufacturing drugs has to be transparently explained to stakeholders along with the involvement of technology companies and the use of algorithms and AI in processing data. For example, specific patients whose data is needed to address certain medical needs must be sufficiently informed to consent to how their data would be used by public and private research for the benefit of society as a whole and in a context that may be commercially beneficial. Or, lack of transparency as to who decides what treatments are funded or how drugs are licensed can breed mistrust as whether the provision of health and medical care is improving through precision medicine.

5. Mandating and assessing trust

Participants also reflected on the broader issue of whether trust can be measured and mandated. They emphasized that it is essential for any actor to determine for what it should be trusted and what the enabling conditions of trust are. The more reflective insights that emerged from the discussions are that:

- **Trust cannot be mandated,** in the sense that trust is based on one's belief (e.g. belief that someone will act in the way one expects) and this belief cannot be mandated. **But what can be mandated are behaviours as expressions of trust, and sometimes, trustworthiness itself**. More importantly, trust must percolate into the whole environment. If rules require actors to be trustworthy, it makes it more credible that they will be trustworthy.
- **Knowing what we are trusted for is an important determinant of trust, but a frequent mistake arises when we confuse whether we trust with whether we like**. For example, 'nice' people may be untrustworthy or distrusted, and trusted people might not be 'nice'. Thus a more relevant question to pose is: what are different entities trusted for? How able are they to deliver? Organizations or actors may not always know what they are trusted for and it remains important to align their intentions with expectations that people have of them. The goals that we set for ourselves are not necessarily the goals others trust us to pursue. It remains useful in this respect to distinguish between trust and trustworthiness, and to determine in each case what are people, institutions and other actors trusted for.
- **It is understandable that we should want to measure trust, but some limitations arise.** For example, people may not answer truthfully if they do not trust the researcher. Other limitations relate to exactly why we want to measure trust, and it is useful to know how much trust there is in different types of partners: institutions, persons, private and public institutions, national and international ones. Measurements of trust may often need some form of comparison to alternative options.
- While not always easy to measure, **trust can be thought of as a resource** – something that we need for many of the things we do together – **and perhaps not a terribly renewable one if eroded or destroyed.** It is prudent not to let it decrease too much, because it is easier to protect it early rather than build it up again from a situation that has turned sour. Moreover, trust is not static but relational and dynamic. It can increase or decrease gradually, appear or disappear suddenly. Identifying and measuring the components of trust and its enabling conditions – trustworthiness is one of them – helps our understanding of how the dynamics of trust may be changing.

More generally, trust can be based on various elements, including:

- Familiarity and/or proximity: for example between patients and physicians
- Reliability: this can be provided by technical means, and use of appropriate technology to address digital security and privacy issues
- Accountability: this can be established by experience and reputation.
- Responsibility: legal systems can establish rules that define conditions of relations between parties, and provide confidence that individual's interest will be protected if something goes wrong.

Concluding remarks

People, patients and institutions need to be involved not only in placing trust in precision medicine but also in deciding when or where to refuse it. **We need, in addition, a set of strategies that earn and provide evidence of trustworthiness to evolve and sustain public trust around precision medicine.** There is no magic recipe, but key ingredients include:

- Governance and institutions that allow us to judge where to place our trust in precision medicine and where to refuse it
- Transparency, inclusivity, and attention to related concerns such as health disparities and health-related literacy
- Respect for different individual preferences, including around consent
- Meaningful participant engagement and empowerment, with particular attention to topics of affordability and access
- Assuring data integrity, from start to finish, remains essential to facilitating reproducibility, replication and representativeness.
- Responsible data sharing, collection and access, with particular attention to use, reuse and misuse.

All these elements are needed to create trust in the complex ecosystem that we see evolving around precision medicine. The opportunities, as well as the challenges for collaboration, are high-level ones.

It is worth noting in conclusion that the trust issue in the context of precision medicine is not just about a unidimensional relationship or transfer of trust from patients and individuals to the complex medical system. It is about asking if and how the trust system can be reframed and redesigned to accommodate precision medicine's goals to improve the practice of medicine in general.

Box 2: US PMI / All of Us and trends that characterise the development of precision medicine in the US

The US PMI initiative (now "All of Us") https://allofus.nih.gov/ will be the largest longitudinal study launched in the US. Inclusivity, participant-centric and transparency are three fundamental principles, and all relate to trust. One the biggest weakness of the sample collected so far (5000 participants) is that, in the first phase, less than 4% of the data were from Americans that were not middle or upper class and with other than European ancestry. This percentage has now gone up to 20%, but the sample is still not representative of the US population, which is now composed with more than 50% of people who have no linkage to European ancestry. Experience so far indicates that, with regards to trust:

- 80% of Americans are in favour of the programme, but this percentage falls to 50% among Afro-Americans, probably because of a history of experimentation on under-represented minorities
- The programme seems to exacerbate views about health disparities, and perception of access to precision medicine is correlated with income and literacy. The trust issue is less about privacy issues than about having access, and affordability.
- Trust and trustworthiness will be major efforts in the new TOPmed programme (TransOmics for Precision medicine)[11], as well as in the FAIR principles (Findable Accessible Interoperable and Reusable Principles)

Five trends characterise the development of precision medicine in the US:

- The shift to a more patient-centric healthcare has implications on trust and trustworthiness, particularly when linked with growth in health care consumerism (self-diagnostic on the Internet)
- Trust and trustworthiness are becoming much more distributed, fragmented among the government, doctors and health care systems, experts or the (social) media.
- Speed, scope and complexity of technological change affect trust and trustworthiness, both positively and negatively. For example, AI, machine learning and perhaps blockchain technologies are part of the trust-factor.
- Trust is not just about patients. There are multiple layers and levels of trust involving clinicians, researchers and the whole chain of actors.
- With new actors like Google and Amazon, there is a blurring of traditional boundaries and roles. For example, every clinical actor is a data point, every individual is an information node, and every individual can also become a research actor.

Box 3: Scandinavia and Finland's FinGenn project

In Scandinavian countries, there seems to be a high level of trust between the health systems and citizens, which is consistent with a high level of trust in government, deeply rooted in all Scandinavian traditions. For example, people in Finland generally say that they are not concerned by risks of misuse of their data: the data will not be used against them. The FinGenn project, launched in December 2017, is a public-private collaborative genomic research project that will combine genome information with digital healthcare data, tapping into 500,000 unique blood samples collected by Finnish biobanks. "Finnish people have strong trust in the country's research and healthcare system, and we are constantly receiving new inquiries from people who would like to participate in the project. Transparency is crucial to maintaining the trust of the citizens in the research." https://www.finngen.fi/en/node/38

[11] https://www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed

Box 4: Switzerland

Ethical and trust issues are central to how personalized medicine develops in Switzerland, at various levels. Illustrations:

- **Federal legislation**
  Message concernant la loi fédérale sur l'analyse génétique humaine and project of *Loi fédérale sur l'analyse génétique humaine*, July 2017 https://www.bag.admin.ch/bag/fr/home/themen/mensch-gesundheit/biomedizin-forschung/genetische-untersuchungen/aktuelle-rechtsetzungsprojekte1.html

- **Ethical aspects**
  Swissethics 'manual for research with human subjects', 2015. The manual intended to convey the basic ethical attitude which is required if researchers are to be perceived as trustworthy by potential research participants, regulatory authorities, policymakers and the public
  www.swissethics.ch/doc/swissethics/manual_research_nov2015_e.pdf
  Swiss Personalized Health Network (SPHM), Ethical, Legal and Social Implications advisory group (ELSIag) addresses ethical, legal and social issues that SPHN will face. It shall:
  - anticipate well-known challenges such as that of appropriated informed consent and privacy;
  - develop mechanisms and processes to handle unanticipated issues and require a swift solution;
  - advise the National Steering Board (NSB) in the development of guidelines for data sharing and managing questions of intellectual property, authorship and attribution according to national and international standards.
  https://www.sphn.ch/en/organisation/elsi-advisory-group.html

- **Technical aspects**
  www.genomeprivacy.org is a community website for sharing information about research on the technical protection of genome privacy and security

- **Practice and local governance (Geneva)**
  - HUG (Geneva Hospitals) is testing the use of tablets for providing to patients access to information from the hospital information systems. Trust issues involved include giving access to sensitive data, i.e. trusting the security system with complex authentication mechanisms.
  - The Health Information Exchange project (electronic patient record), which started in 1999 was challenged by the distrust of the population if the data is stored on a centralized database, and if the project is driven by public hospitals, arguing that trust must be built with all stakeholders. In addition, there was an issue of inter-professional trust among practitioners. As a result, the current project is for a fully distributed database, and is a voluntary opt-in system both for citizens and for care professionals. But the driving force comes from citizens.
  - The cantonal law about the electronic patient record (2008) contains a provision that "Information, once anonymized, can be used to steer the health system or to support research." Interestingly, however, this provision was not implemented yet, because politicians are concerned that trust would be damaged and patients would not use the electronic patient if they know that their data can be used for research.

Box 5: UK care.data

The UK National Health Service (NHS) launched in 2013 the *care.data* programme, to extract data from general practitioners surgeries and anonymise them for research. The programme was controversial from the start, notably because of lack of information to patients, and lack of clarity around options for opting out of the data extraction. The programme was stopped in 2014 and patients were offered the possibility to have their data withdrawn (opt-out). Its failure has been attributed to three main factors: ambiguity of derivative public good, faulty warrants of trust, and uncertainties surrounding the duties of general practitioners. There was a lack of *faith* and a lack of transparency, and many ambiguities about the whole programme (Carter et al., 2015; Adjekum et al., 2017).

Participants in the workshop noted that only one in 45 individuals opted out after it was made public that the programme had no sufficient plan for IP/data privacy. However, the majority of UK residents continue to trust the NHS.

As mentioned in section 2, people who opt out of a programme may actually not display lack of trust. They just display disagreement. Opt-out rates are a lousy proxy for trust. Conversely, people who opt-in in a programme may not trust the whole programme.

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Appendix 1 - Background paper to the workshop

Trust in Precision Medicine - A Risk Governance Perspective[12]

This background paper is a working document. It sets the scene and serves as the basis for discussion for the expert workshop on Trust and Precision Medicine – A Risk Governance Perspective, 23 – 24 November 2017, Campus Biotech, Geneva.

Introduction

This background document seeks to underlie the salience of trust for precision medicine. In the previous workshop on 'Governance of impacts of precision medicine', organised by the International Risk Governance Center (IRGC), trust was identified as pertinent to the success of precision medicine; hence, the premise for this follow-up workshop.

Precision medicine refers to an emerging field for disease diagnostics, prevention and treatment that considers individual variability in genes, environment and lifestyle, with the aim of improving patients' health and augmenting disease prevention (Florin & Escher, 2017). Moreover, it caters to both patients and healthcare professionals with respect to patient-centered care, customised patient-provider relationships and effective treatments (Adams & Petersen, 2016).

To a large extent, precision medicine is driven by three main concurrent trends: (i) the increasing availability of heterogeneous large-scale databases from which novel patient aggregates evolve, (ii) advances in the characterisation of medically relevant information, and (iii) novel computational tools for data analytics (Adams & Petersen, 2016; Collins & Varmus, 2015). Exponential growth in data volume is a key feature of precision medicine. Collectively, the accumulation of these data – from genomics, proteomics, metabolomics and mobile health (m-health) among others – work hand in hand with improvements in basic research to promote the concept of precision medicine (Collins & Varmus, 2015).

The promises of precision medicine stem from its ability to transform healthcare approaches to research and delivery for the benefit of human health. National programmes in Estonia (1999) and Finland (2006) for instance, have demonstrated the potential benefits of precision medicine (Estonian Genome Center, 2011; FIMM, 2017). In 2015, US President Obama launched the Precision Medicine Initiative (PMI). A predominant component of the PMI is the All of US Research Program, which aims to advance precision medicine by combining molecular information with clinical and lifestyle data from a national research cohort of one million individuals (NIHa, 2017). The change in the name of the program – from PMI Cohort Program to All of Us Research Program – is indicative of the need for inclusivity in precision medicine (NIHb, 2017).
There is an increasing consensus that the notion of trust is paramount to derive maximum capabilities from precision medicine (Hurst, 2012). A 2016 expert workshop held by IRGC identified trust as crucial to participant engagement since it thrives on biomedical data collection and sharing (Florin & Escher, 2017). Similarly, Mirnezami et al. (2012) have highlighted that precision medicine "will deeply affect public trust and the nature of the patient-clinician relationship", hence "it will require unprecedented collaboration among healthcare stakeholders."

Although the salience of trust in precision medicine is a recurring subject, few studies have divulged the subject from a conceptual standpoint. Thus, this paper seeks to underscore the salience of trust in precision medicine and to provide conceptual clarity by developing at least a working definition and characterisation of the trust dynamics. This is followed by identifying three main types of facilitators (technical, ethical and institutional) necessary to building and maintaining trust about precision medicine. Afterwards, we deliberate on the dimensions of precision medicine that have carved out trust as a pertinent tool to its

[12] This background paper was written by Afua Adjekum, with contributions from Marcello Ienca, Marcel Bürkler, Marie-Valentine Florin and Effy Vayena. It reflects the view of its author and not of IRGC or any other organisations affiliated with this workshop. It was improved thanks to comments and suggestions from Isabella Beretta, Jacques Fellay, Samia Hurst and Adrien Lawrence. For any questions or comments, please contact Afua Adjekum (ETHZ, afua.adjekum@hest.ethz.ch) and Marcel Bürkler (EPFL IRGC, marcel.burkler@epfl.ch).

success. We conclude by making some preliminary (albeit not exhaustive) recommendations on how best to enhance trust in precision medicine.

What is Trust?

Although trust is a familiar concept that cuts across a spectrum of disciplines, there is a lack of consensus on its definition. Besides agreeing that trust is relational (occurs between people and or entities) and context-specific, there is continual discourse among scholars on what constitutes trust (Gilson, 2003). Trust has been described as a three-place relation; whereby, 'A' (trustor) trusts 'B' (trustee) to fulfil 'C' (task) (Baier, 1986). Overall, the concept of trust conveys the notion of risk and vulnerability on the part of a trustor.

Trust is often dichotomised into affective-based trust and cognitive-based trust. The former conveys the notion that trust stems from conventional norms of morality which are upheld by the goodwill of others; whereas the latter perceives trust as a calculation or rational behaviour that involves some form of risk analyses (Gilson, 2003). It is important to differentiate between trust and trustworthiness even though these two concepts are often used interchangeably. While trust is understood as an expectation of positive motives (Rousseau et al., 1998), trustworthiness is perceived as a characteristic that is projected onto an individual or group (Holm & Nystedt, 2010). O'Neill has famously brought attention to this important distinction arguing further that for trust to be established, trustworthiness needs to be demonstrated. In that respect, trust is a response to trustworthiness, and we should aim to put "trustworthiness before trust". (O'Neill, 2015)
Some scholars suggest that trust is neither a choice nor a behaviour, but rather, a psychological state that is crucial to organisational life (Rousseau et al., 1998). Other scholars maintain that encapsulated interests, rational predictions of another's behaviour as well as personality traits compel people to trust (Lang & Hallman, 2005). Nonetheless, reliance is at the core of trust even as it is assumed that a pure trust relationship exists when emotions such as gratitude, betrayal and resentment – 'reactive attitudes' – are expressed if expectations go unmet (Holton, 1994).

Trust is also at the helm of social cohesion even as it projects its existence – or lack thereof, – on all aspects of social interactions. Social norms are said to shape individuals' beliefs and inherent in such beliefs is trust, which in turn cultivates cooperation and vice versa (Gilson, 2003). Within a trustworthy society, individuals balance into equilibrium both interpersonal trust (trust in individuals) and institutional trust (trust in the social system) (Gidman et al., 2012). However, although many scholars agree that these forms of trust rely on each other, they are yet to fully understand their underlying relationship (Gidman et al., 2012; Rousseau et al., 1998).

Societies with optimum levels of trust witness lower transaction costs, conflict aversion within organisations in addition to optimum cooperative behaviour (Rousseau et al., 1998). Within the health system, trust facilitates patient satisfaction, adherence to treatments, health provider continuity, patient disclosures and encourages access to health facilities (Gidman et al., 2012). It is important to note that trust cannot just be produced or generated, but must consistently be accumulated and reinforced by performance or experience (IRGC, 2005). Furthermore, the presence of conflicts of interests raises specific challenges regarding the maintenance of both trust in and trustworthiness of physicians, which requires special attention (Hurst, 2017).

In instances where there is low generalised trust (individuals' expectations of the trustworthiness of others) (OECD, 2017), mistrust and distrust are likely to thrive. Mistrust denotes 'unhealthy cynicism' resulting from a prior breach of trust while distrust, comprises of 'healthy scepticism' (Abelson et al., 2009). From this description, trust can be envisioned as a spectrum containing positive and negative peripheries: on the positive end sits 'trust', with 'mistrust' on the negative end. As McAllister argues "the amount of knowledge necessary for trust resides somewhere between total knowledge and total ignorance [...] Given total knowledge, there is no need to trust, and given total ignorance, there is no basis upon which to rationally trust". McAllister (Mcallister 1995, pp. 26).

As much as precision medicine relies on disease patterns to recognise trends, researchers relish voluntary data contributed by healthy individuals. Integral to this paradigm is the belief or expectation that personal data will not be used against the owner of the data and there will be a derivative public good (Bourzac, 2016). A study conducted by researchers at the US National Institute of Health confirms this as individuals'

willingness to participate in the All of Us program involves some risk and benefit analysis (Kaufman et al., 2016).

Based on these evaluations, a working definition of trust in precision medicine could be *the willingness of a trustor to accept the potential risks involved in the use of their sensitive health-related data resulting from both optimism about the trustees' goodwill, interest in the public good, and capacity to limit these risks.*

While a trustor can be both an individual and a multi-individual entity (e.g. a corporation, research group or other organisation), we are particularly concerned in this paper with the issue of trust from the perspective of the single individual towards the data initiatives for precision medicine.

In fact, we consider the individual citizen to be the fundamental and atomic unit of trust. The reason for that stems from the fact that the individual citizen or natural person is the social actor to which fundamental human rights can be granted. Although beyond the scope of this paper, another reason may be due to trust acting as a psychological state influenced by a plethora of factors.

It is also important to point out that trust dynamics are often multi-layered and might follow chain reaction patterns. In fact, when sharing data with a certain trustee Y, a trustor X should not simply trust Y, but also all actors that Y might further share X's data with. The longer the chain of trust, the harder it is for the individual to predict the risks and benefits of her voluntary data contribution as well as to assess the trustworthiness of all trustees involved. This problem is exacerbated by the fact that, in many circumstances, the individual citizen might have only partial (if any) knowledge about actors beyond the first trustee.

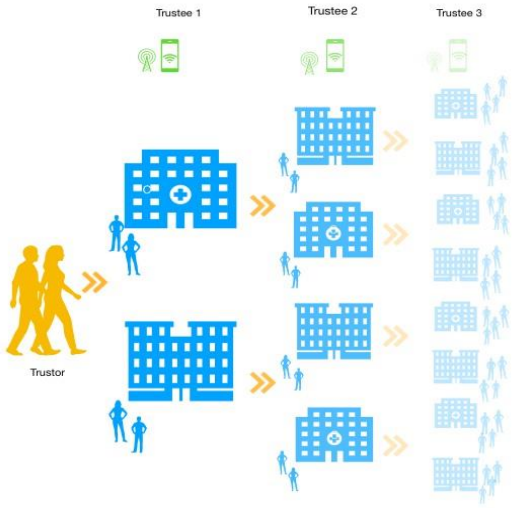

Figure 1: The complex data sharing relationship between a trustor and relevant trustees (either individuals or institutions). The arrows indicate the various trust relationships are occurring at different phases of the data-sharing process. The fading represents diminishing trustors' knowledge about data-sharing mechanisms and actors.

Some Facilitators for Sustaining Trust

The drivers for building trust in precision medicine can be categorised into three: 1) technological innovation, 2) ethical and sociocultural values and 3) institutional practices & governance measures. In this section, we discuss these three drivers.

1) Technological innovation is a viable means of facilitating accountability relating to data sharing, quality and integrity.

For example, the White House published a "Data Security Policy Principles and Framework (Security Framework)" that healthcare organisations are advised to follow to secure data in the All of Us program, recommending to be "careful not to poison the well-being of patient trust". A typical example is blockchain technology, which refers to a digital ledger made up of linked peer-to-peer transaction blocks on which unalterable records are shared. The features of the blockchain make it potentially well-suited to address the disjointed nature of health-related records by eliminating the need to rely on third parties for their security (Krawiec et al., 2016). Consequently, the blockchain aims to improve the protection of privacy, security and to enable interoperability in health and medical data transactions (IRGC, 2017a).

Differential privacy and homomorphic encryption are technological solutions that have been proposed to minimise the risks associated with the use of sensitive data[13]. These approaches aim to uphold the analysis of databases containing confidential information by, among others, minimising the risks associated with the re-identification of anonymised data (Dwork & Roth, 2014). In ensuring a high standard of data

[13] See for example www.genomeprivacy.org

anonymisation – by shrinking the risks associated with being re-identified with publicly available data for instance – individuals are more likely to participate in precision medicine initiatives.

It is crucial to recognise that technology alone cannot ensure that citizens and other stakeholders place their full trust in the advances that precision medicine has to offer. It can help build and sustain trust by reassuring participants of the privacy and security of their sensitive data as well as increasing the capacity to protect against impending risks. However, technology as a tool to help build and sustain trust in precision medicine would only attain optimum results if it accompanies sound medical analysis coupled with meaningful and equitable relationships with citizens.

2) Acknowledging the importance of ethical and socio-cultural values as facilitators to trust in precision medicine stems from experiences with trust in similar conditions.

The relevance of transparency and public trust in novel biomedical research has been echoed ever since major strides were accomplished in recombinant DNA and beyond (Baltimore et al., 2015). Concerning precision medicine, it is essential to prioritise transparency – built on public engagement – that ranges from healthcare delivery, research and institutional management practices.

Preferred forms of consent, data sharing in addition to the motivations for participation must constantly be assessed to alleviate participant concerns (Kaufman et al., 2016). In prioritising the participant (trustor), the researcher or health personnel (trustee) is better able to relay their proficiency to undertake the tasks assigned them and likely reinforce their goodwill. This matters as, for example, the information sheets and consent forms that are used during research projects have been shown to merely serve as 'symbolic tokens'. Instead, participants' 'faith' in the objective of the project and assurance of minimal risks that is what motivates them to participate (Carter et al. 2015).

Public engagement strategies based on communication are another tool that is widely used to assess ethical and sociocultural values. Communication in public engagement strategies is understood as a two-way dialogue between relevant stakeholders and the public. Good practices in risk communication help stakeholders make informed choices about matters of concern to them and hence create mutual trust (IRGC, 2005). The absence of dialogue-based communication regarding the roles and expectations of both a trustor and trustee results in misplaced trust.

Stakeholder engagement on a broad scale supports better decision-making (IRGC, 2017b). Involving all the entities to whom precision medicine matters will enable the identification and prioritisation of the motivations behind individuals' values and interests. In a survey conducted by Kaufman et al. (2016) thirty percent of survey participants changed their willingness to participate after being informed of the potential risks and benefits of the PMI cohort study. This suggests the importance of consistent stakeholder engagement prior and during precision medicine initiatives.

3) Institutional practices and governance are involved in building social cohesion, making them critical trust facilitators.

Gilson (2003) maintains that institutions (both public institutions and other social organisations including private ones) bolster the social order by ensuring interpersonal trust, which in turn strengthens generalised trust. Hence, management practices and decisions do not only matter to those said institutions but to society as a whole. Equity, fairness and a general sense of prioritising the public good at the institutional or governance levels all stand to foster trust in precision medicine and society as a whole.

Public institutions that aim to foster trust must communicate about their competence and values as they are perceived by the public. Competence is the capacity to undertake an intended task, while values foretell the intentions and ethics of the said institution (OECD, 2017). However, inasmuch as competence and values matter, it is crucial to bear in mind that individuals' overall trust judgements regarding an organisation are equally influenced by transparency and openness, public interest (organisational aim to tackle bias) and honesty (truthful about risk) (Lang & Hallman, 2005).

Governance models include a variety of options such as incentives, frameworks, initiatives, guidelines, or public regulation (IRGC, 2012). Institutions that implement effective governance approaches are better equipped to achieve a common ground for measurable, transparent and comparable quality standards. In

the case of precision medicine, the standardisation of precision medicine initiatives can contribute to building public trust. An example of governance relevant for precision medicine is the Committee of Ministers of the Council of Europe Recommendation CM/Rec (2016)6. The committee emphasises the importance of building trust. It contains specific guidelines for research on biological materials of human origin. It recommends that EU governments adapt their laws and practices to ensure the implementation of the guidelines and promote the establishment of codes of conducts to ensure compliance with the guidelines. The Committee aims to safeguard the fundamental rights of individuals from whom biological materials are obtained, stored and used (Council of Europe 2016).

Generic guidelines for medical research also prove useful to standardising institutional practices. In Switzerland, swissethics, a joint working group of Ethics Committees addresses ethical issues relating to research on humans, educates and trains members, as well as standardises and coordinates their actions (swissethics, 2017).

Schlesinger and Gray (2016) argue that trustworthiness is never guaranteed in healthcare due to the challenges involved with measuring trust within this setting, combined with the ubiquity of provider discretion. Yet, studies show that experts and organisations can favourably impact public perception, which in turn helps to advance efforts to build and maintain overall trust within society. As a result, efforts to build and sustain trust in precision medicine must recognise and acknowledge this paradigm moving forward.

How to Achieve Trust in Precision Medicine?

Precision medicine depends on the aggregation of a broad quantity and variety of individuals' private data. Typical health data sources such as medical records, results of laboratory tests, genomics, immunisation records, are supplemented with, among others, data from self-tracking devices, loyalty cards, store transactions, wellness and social media (Vayena et al., 2017). For these heterogeneous data to be available (hence, for such data aggregation to be possible), researchers and clinicians need to rely on voluntary data contributions from individuals. Since familiarity is vital to building and maintaining trust, it will take some time to ensure public acquaintance with these novel health data sources and stakeholders. In addition, increasing breadth and variety of data sources will increasingly require collaborative efforts between several disciplines as well as novel stakeholders.

Furthermore, precision medicine relies heavily on sensitive personal data that may be made available to new and previously unfamiliar actors in healthcare. Reports indicate that health data is currently more valuable than credit card information, and cyber incidents at health organisations have increased from 20% in 2009 to 40% in 2013 (Reuters, 2014). This calls for an increased need to ensure optimum health data privacy and security. Strengthening regulation concerning negligence with health data might be necessary to combat health data breaches. However, increasing regulations often tends to adversely affect institutional trust (Calnan & Rowe, 2007).

It is vital to consider these elements in the future to avoid repeating past and even novel mistakes. In 2012, under the Health and Social Care Act, the NHS proposed the *care.data* initiative. Despite meeting all of the legal prerequisites required to exploit medical records for research, care.data floundered (Sterckx & Cockbain, 2014; Carter et al., 2015). Its failure has been attributed to three main factors: (1) ambiguity of derivative public good, (2) faulty warrants of trust, and (3) uncertainties surrounding the duties of general practitioners. Indeed, it was not inadequate publicity that derailed care.data, but rather, an absence of *faith* and a lack of transparency compounded by ambivalence about the risks involved (Carter et al. 2015, pp. 3)[14]. More recently the NHS England had another controversial collaboration with Google's DeepMind. In this case, DeepMind received access to millions of identifiable patient data to develop applications that would support patients with kidney disease. An investigation of the data sharing agreement between DeepMind and the NHS by the UK's National Data Guardian concluded that this arrangement took place on an inappropriate legal basis (Revell, 2017; Powles & Hudson, 2017). (See Box A below)

[14] care.data has been relaunched in the form of NHS Digital: https://digital.nhs.uk

Box A: The crucial role of engaging with stakeholders through transparency and communication – The NHS care.data initiative and DeepMind in the UK

NHS

In 2013, National Health Service (NHS) England launched care.data, a programme aimed to combine health and social care data, including patient records stored on machines of general practitioners or from hospitals. Its main goal was for researchers to use the anonymised patient data to assess the performance of NHS services and to develop new treatments. However, the initiative faced constant criticism over the sharing of medical information with commercial third parties without explicit patient consent as well as over data security and confidentiality concerns. When it was disbanded, over one million people had already opted out of the programme. This lack of trust and ultimately the failure of the programme were mainly blamed on unclear mechanisms of consent and criteria for accessing the collected health data, and the fact that communication with the public was not prioritised (Presser, 2015; Temperton, 2016).

DeepMind

In an effort to develop 'Patient Safety Alerts for Acute Kidney Injury (AKI)' clinicians from the Royal Free London NHS Foundation Trust solicited the help of Google DeepMind Technologies Limited (an artificial intelligence and machine learning company) in July 2015. By November 2015, sensitive and identifiable patient data had been transferred from the Royal Free to third-party data processing entities contracted by Google. DeepMind publicised this relationship in February 2016 claiming to act merely as a channel through which real-time analysis and alert systems for AKI is provided through the app 'Streams'. After an independent investigation by the New Scientist, both parties were compelled to elaborate on the uses of the data. However, to date, little is known about the overall uses of the data, the reasons why more data than required was transferred, the reasons for bypassing relevant data governing entities nor the failure to obtain patients' consent. Consequently, tremendous doubts have been raised about the underlying motive for the programme (Powles & Hodson, 2017).

The two controversial cases above highlight problems that can easily emerge in the sensitive space of patient data. They also illustrate some specific aspects that can facilitate our consideration of how best to promote trust in the data-rich environment of precision medicine. Below is a preliminary list of suggestions:

First, we identify a **need for the widespread implementation of technical facilitators of trust in precision medicine initiatives**. These include, but are not restricted to, blockchain, differential privacy or homomorphic encryption technology. On the long term, the successful implementation of security & privacy-enhancing techniques might enhance existing security protocols and models regarding both format and structure and "add additional layers of security and trust" (Versel, 2017). In fact, these technologies potentially allow to disintermediate data from hosts, increase transparency and process integrity, increase the ability to withstand data leakage and malicious attacks, and ultimately empower trustors. Therefore, this is likely to have a positive effect not only on the management of healthcare data but also on their large-scale collection as well as on the social dissemination of scientific findings.

Concurrently, this **technical transition should be coordinated with the responsible promotion of ethical and socio-cultural facilitators**. Ethical values such as privacy, transparency and fairness are likely to be co-determinants of trust at both the individual and collective levels. They should be prioritised to maximise the benefits of precision medicine in an ethically and sustainable manner. Therefore, public engagement and awareness-raising activities should be incentivised to enable competent decision making within the precision medicine ecosystem, especially from the perspective of the trustor-trustee relationship. As the failure of the *care.data* initiative indicates, stakeholder engagement should be sustained through unambiguous anticipation of derivative public good, reliable warrants of trust, and a clear specification of the duties of health professionals.

Finally, **calibrated institutional interventions and governance solutions should be advanced to enhance trust in precision medicine and orient research for the public good**. A good example in this direction is represented by Switzerland, where, in recent years, several institutional initiatives have been proposed. The Swiss Personalized Health Network (SPHN) prioritises respect for persons, privacy, data fairness and accountability. It has put forward the 'Ethical Framework for Responsible Data Processing in the Swiss Personalized Health Network' (SPHN ELSI Advisory Group, 2017). Ideally, these networks of researchers should be established not only at the national level but also internationally. An initiative taking this international approach (albeit focusing on genomics) is the Global Alliance for Genomics and Health.

Platforms may also facilitate dialogue and information sharing not only between researchers but also between the PM research and other societal actors. Finally, to promote and sustain trust in PM research, institutional review board (IRBs) and other deliberative assemblies should clearly define effective and reliable ethical review processes for PM research. Table 1 below summarises our analysis of trust facilitators and the subsequent points of consideration.

Table 1: Overview of Trust Facilitators in Precision Medicine

Type of Trust Facilitator	Points of Consideration	Normative Suggestions	Examples
Technical	- Value of sensitive data - Susceptibility to data breaches	- Disintermediating data from hosts - Increasing transparency & process integrity - Reducing vulnerability to data leakage and malicious attacks	- Differential privacy - Blockchain - Encryption
Ethical/Socio - cultural	Unfamiliarity of the public with novel healthcare actors	- Prioritising privacy, transparency and fairness - Promoting public engagement & awareness - Unambiguously anticipating public good - Identifying reliable warrants of trust	- Privacy protection - Accountability mechanisms - Transparency of process - Fair benefit sharing plans - Public engagement
Institutional	- Data misuse - Benefit sharing	- Establishing international networks of researchers - Creating trustworthy platforms for exchange between - Defining a clearer ethical process for precision medicine research	- Standardised guidelines - Ethical review recommendations

Conclusion

Trust is essential in precision medicine. However, the characterisation of trust dynamics in this rapidly evolving field of medicine is often affected by uncertainty and conceptual variability. In this paper, we provide a definition of trust and a detailed characterisation of trustor-trustee dynamics in precision medicine. We highlight that trust is necessary for facilitating participants' involvement in precision medicine initiatives. It is a catalyser for socially responsible scientific advancement and practical implementation in this field. Technical solutions, ethical and sociocultural values, as well as effective governance measures, are all identified as facilitators of trust in precision medicine. Based on this analysis and learning from previous precision medicine initiatives, we see a need to formulate a minimal set of recommendations aimed at mitigating the risks associated with the sharing of sensitive data, increasing transparency, empowering trustors and augmenting public trust in precision medicine.

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Appendix 2 - Questions discussed during the workshop

The programme of the workshop was organised to discuss the following questions:

- What is 'trust' and 'trustworthiness' in the era of big data and precision medicine? What are the risks if trust is lacking or incomplete? How can we achieve trustworthiness? Can trust be measured? Can it be mandated?
- Could novel technologies help build trust?
- Role and responsibility of the medical sector in contributing to building trustworthy relationships with patients and citizens;
- Role and responsibility of the private sector in contributing to building trust

Breakout groups were also organised to discuss:

Group 1: Data collection, access and use

- Is there sufficient trust in or understanding of the idea of using personal genetic, medical and health data to drive better care through precision medicine?
- The personal data issue is critical for regulators. Does the behaviour of patients and citizens indicate that it is also critical for them that their personal data are strictly protected?

Group 2: Voluntarist campaigns vs. Proof of concept

- Can small-scale "proof of concept" be more efficient than discursive claims and voluntarist campaigns for trustworthy precision medicine?
- What are the good practices for a strategy of incremental steps?

Group 3: Promises and delivery

- Is there over-promising and under-delivery by important actors of precision medicine, such as industry, clinical research or translational research?
- If yes, does this affect trust in precision medicine by medical doctors, patients and citizens?

Group 4: Transparency

- To what extent can transparency provide evidence of trustworthiness? (potentials and limitations of transparency to help build trust in precision medicine, for example through informed consent)
- Is transparency in cost/pricing and payment/reimbursement important for trustworthy relations with industry, regulators and payers?

Group 5: Communication

- Do the messages conveyed within and outside medical practices follow the best evidence and good practices in risk communication?
- How to use communication to improve trustworthiness?

Group 6: Industry

- What can industry do to be perceived as a competent, reliable, accountable and honest partner in the development of precision medicine?
- What are the obstacles to industry being perceived as a trustworthy partner, and how to overcome them?

Group 7: Patients and citizens

- How can patients and citizens be confident that the science and technology of precision medicine, and medical practitioners will help provide the best treatment for them?
- How can they be confident that their data will not be used in a way that could cause prejudice to them? Give patients/citizens full control over the use of their data?

Group 8: Medical

- How can medical professionals build trustworthy relations with their patients and, in general, participate in building trust in precision medicine?
- What are the perceived obstacles?

Group 9: Co-developing a narrative for trust in precision medicine

How to organise the collaborative development of a narrative that serves to create the context in which various stakeholders will develop trustworthy relations?

Appendix 3 - List of participants in the workshop, acknowledgements

The participants in the workshop on 'Trust in Precision Medicine" were chosen for their diverse perspectives and technical expertise. They are listed below:

Afua Adjekum, ETH Zürich; **Michael Balavoine**, Médecine et Hygiène; **Natalie Banner**, Wellcome Trust; **Isabella Beretta**, Swiss State Secretariat for Education, Research and Innovation (SERI); **Frederic Bouder**, Maastricht University; **Peter Brey**, Leenaards Foundation; **Anne Cambon-Thomsen**, Inserm and Université Toulouse III, UMR 1027; **Thomas Cueni**, International Federation of Pharmaceutical Manufacture and Association (IFPMA); **Julien Durand**, Amgen biotechnology; **Gérard Escher**, École polytechnique fédérale de Lausanne (EPFL); **Kathleen Fadden**, Amgen (Europe) GmbH; **Jacques Fellay**, Cantonal University Hospital (CHUV)/ École polytechnique fédérale de Lausanne (EPFL); **Marie-Valentine Florin**, École polytechnique fédérale de Lausanne (EPFL); **Antoine Geissbuhler**, University of Geneva (UNIGE); **Martin Götz**, Swiss Federal Office of Public Health (FOPH); **David Haerry**, Positive Council Switzerland; **David Hanselman**, Synthetic Genomics, Inc.; **Karin Holm**, Patient Advocates for Cancer Research & Treatment (PACRT); **Jean-Pierre Hubaux**, École polytechnique fédérale de Lausanne (EPFL); **Samia Hurst**, University of Geneva (UNIGE); **Marcello Ienca**, ETH Zürich; **Richard Johnson**, Global Helix LLC; **Etienne Jousseaume**, Novartis Pharma Schweiz AG; **Valerie Junod**, University of Geneva (UNIGE); **Adrien Lawrence**, Swiss Personalized Health Network (SPHN); **Kay Moeller-Heske**, Novartis Oncology, Novartis Pharma Schweiz AG; **Lydia Nicholas**, Nesta/(London's Global University) UCL; **Kenneth Oye**, Massachusetts Institute of Technology (MIT); **Francesco Panese**, University of Lausanne (UNIL) & Cantonal University Hospital (CHUV); **Elettra Ronchi**, Organisation for Economic Co-operation and Development (OECD); **Mark Rubin**, Department for BioMedical Research, University of Bern; **Eric Salobir**, OPTIC; **Sigrid Sterckx**, Ghent University; **Effy Vayena**, ETH Zürich; **Daniel Widrig**, Bristol-Myers Squibb; **David Winickoff**, Organisation for Economic Co-operation and Development (OECD).

This workshop summary has been reviewed in draft form by the participants in the workshop, but they have not seen the final version before its release. Responsibility for the final content rests entirely with the rapporteur, Marie-Valentine Florin, with contributions and editing by Kujtesë Bejtullahu-Michalopoulos.

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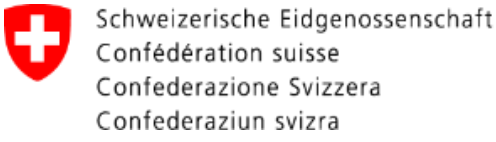

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IRGC's work on precision medicine include

- 2015: Collection and use of genetic information (with Tsinghua University, Beijing - https://www.irgc.org/event/collection-and-use-of-human-genetic-information-for-precision-medicine/)
- 2016: Adaptive risk governance (with UCL, London, https://www.irgc.org/event/planning-adaptive-risk-regulation/)
- 2016: Governance of impacts of precision medicine (https://irgc.epfl.ch/cms/site/irgc/lang/en/events/workshops/precismed-Sept2016); Publication of a 'roadmap for the development of precision medicine' (https://irgc.epfl.ch/cms/site/irgc/lang/en/projects/precision-medicine/roadmap) recommending inclusive and incremental strategies
- 2017: 'Trust and Precision Medicine' (workshop about the importance and components of trust and trustworthiness in the relationship between actors - https://irgc.epfl.ch/cms/lang/en/pid/148683)
- 2018: Expert meeting on 'The Economics of Precision Medicine' (to discuss issues of cost-effectiveness and innovation in payment systems)

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