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A ROADMAP
FOR THE DEVELOPMENT
OF PRECISION MEDICINE

Generic guidelines for precision medicine
strategies

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PREFACE

This paper results from and further elaborates on an expert workshop organised by the EPFL International Risk Governance Center on 24 September 2016: 'Governance of impacts of precision medicine'.[1] The objective was to discuss how to move forward an interdisciplinary and multi-stakeholder agenda for the development of precision medicine (PM). The workshop offered a platform for conversation on matters of risk governance, discussed issues of policy, adaptive regulation, insurance and creating confidence between society, patients, industry and regulators.

Specific questions discussed included:
• What is the vision for precision medicine?
• What are the expected impacts and challenges?
• How to drive the innovation process?
• How can insurance systems adapt?
• How to avoid, prevent or mitigate the possible various negative consequences?
• How to adapt regulation?

Precision medicine (PM) is an emerging field for disease diagnostic, prevention and treatment that considers individual variability in genes, environment and lifestyle.
It aims to improve the health status of patients, and to help and support the prevention of the onset of a disease.

Precision medicine is expected to deliver numerous benefits to individuals, by significantly improving the state of health of each, and thus of the population. It is based on a better scientific understanding of the components of health and diseases. However, its development presents some critical challenges, which require a clear strategy and a comprehensive roadmap to support a smooth transition. **The purpose of the overarching roadmap proposed by IRGC in this brief is to recommend a structured process that organisations can follow in their transition towards the development of precision medicine.** The process is adaptable, and each organisation should further develop it to align with its own needs, culture and objectives.

This paper does not intend to prescribe certain policy and regulatory choices concerning such important issues as privacy, confidentiality, equal right of access, or the basis of evidence generation (uncertainty management

[1] The workshop was attended by experts from Switzerland, the EU and the US, representing science and research, medical practice, policy, regulation and industry.

in safety and efficacy assessment) for new precision medicine diagnostics, prevention strategies and therapies. What each country or organisation will decide is context-specific and depends on its own culture and level of interest or involvement in precision medicine. We anticipate that differences between cultures, legal frameworks, societal contexts, economic conditions, health priorities amongst other aspects will lead to a diversity of modes of development of precision medicine in the world.

The recommendations are primarily for an audience in governmental organisations or other public institutions, which may use the roadmap as a set of generic guidelines for developing their own strategy for precision medicine[2]. It suggests the need for national or international initiatives for precision medicine. Other actors in the public and private sectors, such as patients associations, healthcare payers, civil society representatives, professional and scientific associations might also be interested in a roadmap process when they develop their own strategies.

In scientific and technological areas marked by rapid development, high expectations and uncertainties about existing and future challenges, it is rarely possible to say *which* regulatory, economic or even scientific options are the best. It is advisable to agree on a process to work collaboratively towards progressively reducing the uncertainties and identifying the preferred options.

[2] See Appendix 1: About roadmaps for precision medicine.

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INTRODUCTION

DATA-DRIVEN PRECISION MEDICINE FOR ALL

Unlocking the promises of biomedical data science for public health

Any new technology or scientific development that promises to deliver major benefits and revolutionises existing practices will challenge institutions, decision makers and practitioners.[3] Precision medicine (PM) is an emerging field for disease diagnostic, prevention and treatment that considers individual variability in genes, environment and lifestyles.

Answering the question of which benefits precision medicine can bring to the wider society and how desirable change can be organised, begins with the creation of a space for dialogue between stakeholders, including the scientific community, the health sector, industry, patients, citizens and other actors. Ultimately, the deployment of precision medicine will result from:

Combining rigorous analytics, large-scale biological datasets and clinical outcomes to uncover the mechanisms of disease, cure diseases and improve health and wellbeing.

- A multi-dimensional convergence of views – innovation in science and medical research, top-down policy decisions, industry, patients, citizens who register and share their health and lifestyle data, etc.
- A shared and broad societal understanding of the risks and benefits, which will create the basis for political will and fair policy choices.

A shared long-term vision for precision medicine can only emerge from dialogue. Then, steps to reach the vision will be established.

The deployment of precision medicine will stem from progress in biomedical science but IRGC considers that it will only succeed if it improves health outcome, for the benefit of individuals as well as the economy and society overall. We believe that an agreement on this objective has the advantage of highlighting those issues that matter for triggering buy-in from important stakeholders outside of the scientific community, emphasising that social and economic benefits can be gained, and embedding the vision into local conditions for its practical implementation.

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[3] See Appendix 3 for information about IRGC generic recommendations for the governance of emerging issues involving inter-related risks and benefits

Precision medicine is:

- **Data-driven**. Data-driven science is entering a new era, not only because of the sheer volume and the incredible variety of data - the usual characteristic of Big Data - but also because the most available data were not purposely collected for aims they end up serving. Data-driven science raises several scientific, ethical and legal questions. Given the breadth of information that is needed for precision medicine, issues arise about how data must be collected, what are the new instruments needed to support distributed and incremental data analytics, and how data from medical, personal and non-medical public or administrative sources can be handled, without jeopardising patient protection. In addition, the interpretation of heterogeneous data raises immense challenges in semantics.
- **Personalised**. Precision medicine aims to meet the demand of individuals to benefit the best-adapted prevention and treatment strategies. Issues include how to deliver a service that is patient-centred and prioritises a trust relationship with the patient.
- **Global**. Precision medicine must benefit society, not just a few individuals.

Precision medicine is often described as predictive, personalised, preventive, and participatory (P4) (Hood & Friend, 2011). The term 'mass customisation' can also be used to describe that precision medicine is expected to deliver health and medical care that is both personal ('customised') and global ('mass'), towards 'precision health'.

The field is complex. Precision medicine develops from increased knowledge about individual variety in genes, but also complex risk and protection factors influencing health and diseases such as lifestyles, life histories or environment, over a long time span, and innovation in biostatistics and biomedical informatics. Relationships between biomarkers and disease outcomes are very complex and still obscured by much uncertainty. Our growing scientific and biomedical understanding of the complexity of how health and disease develop and can be explained is a cause for optimism as much as it is a call for caution.

Table 1: Challenges that implementing a roadmap for precision medicine could help address

In order to address the main challenges to the implementation of precision medicine, a structured and comprehensive approach is recommended that is incremental and objective-driven.

Five specific challenges that implementing a roadmap for precision medicine could help address

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

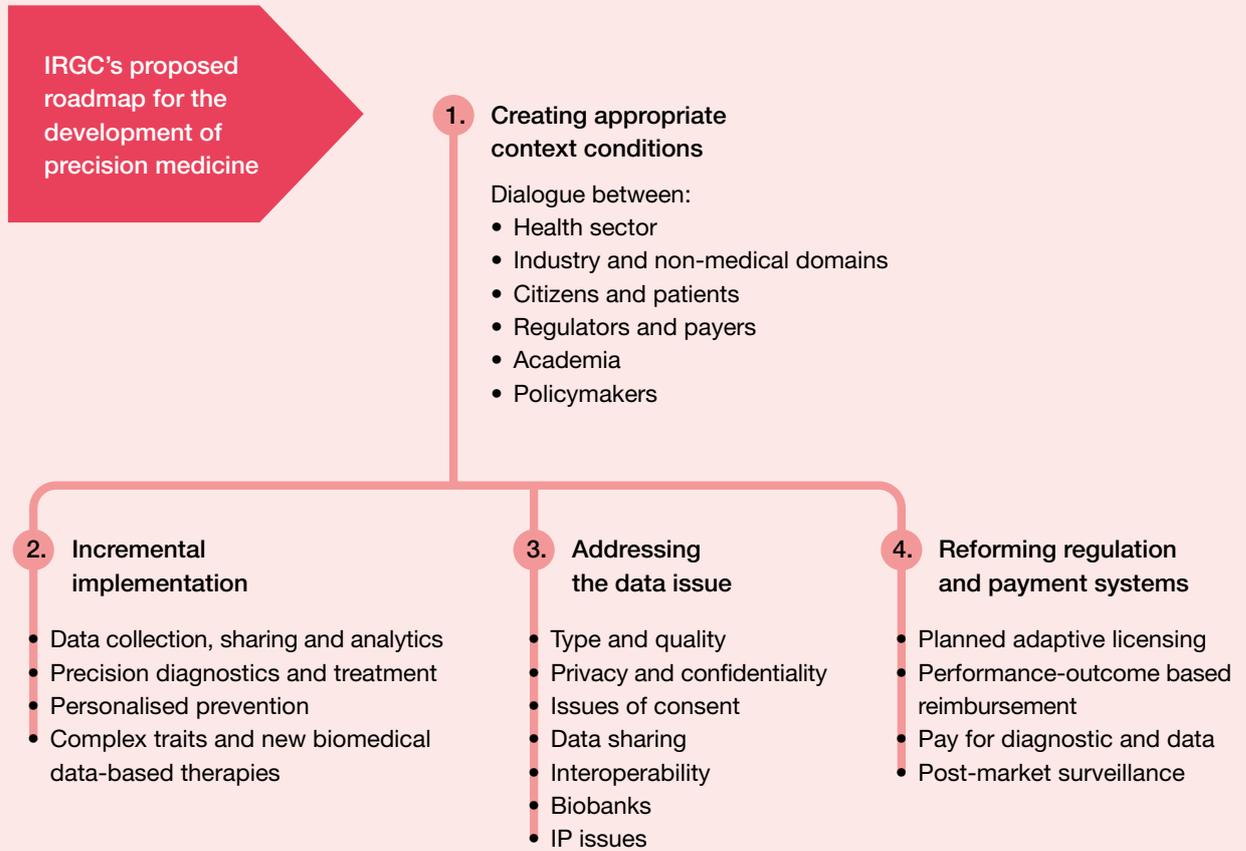Figure 1 below summarises the recommended roadmap (process)

Figure 1: A roadmap for precision medicine

1.

CREATING FAVOURABLE CONTEXT CONDITIONS

A joint long-term vision of precision medicine can emerge from a fruitful dialogue among stakeholders. Who will eventually profit from the exploitation of biomedical data?

Each institution (such as a public health administration or a medical insurance) that commits to developing precision medicine should first work to create favourable context conditions for that purpose. Favourable context conditions can be created when there is a space for dialogue with all important stakeholders, from research to clinical use and society, about how to translate the science of genomics and other data-driven biomedical sciences into clinical applications. Otherwise, PM will be regarded as something to solve biomedical problems, rather than to help patients. If PM is only available for a few individuals, societal buy-in may be insufficient to trigger the necessary fundamental changes that regulators and payers will have to make.

In Europe and for some international organisations such as the World Health Organization (WHO), there is a general agreement that principles for a successful implementation will at least include: Non-discrimination (personal data cannot be used against individuals) and social justice (affordable access, through universal health care or other). (World Health Organization, 2004)

The success of PM depends on trust. The quality of the data on which PM can build - and their relevance for the whole population - will depend crucially on how many citizens agree to have their medical, genomic and phenotypic data collected in databases, and shared according to trustworthy sharing schemes. Similarly, trust in how risk assessment about quality, efficacy and safety is performed is key. However, precise definitions, metrics and regulations for implementing these key principles are lacking and must result from a wide engagement with stakeholders and society.

This requires for policymakers to engage with scientists, the health sector (medical and clinical field), patients and citizens, regulators, payers, and industry. The aim is to establish political will and societal buy-in, based on trustworthy partnerships.

Engaging with the health sector

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The field of medicine is changing. Health care professionals must adapt, together with others in the healthcare universe, particularly by helping individuals to become active partners in their own health. (Topol, 2012)

Training physicians for PM

First, the curriculum of medical studies will need to put emphasis on Big Data-related competences including biostatistics, bioinformatics and genomics. Physicians will soon be provided with large-scale genetic testing results for many diseases. This will pose new challenges: how to explain risk, especially probabilistic, and how to handle numerous new risk factors. As a consequence, medical training will focus on prevention of disease, on understanding uncertainty around links between cause (DNA, genomic analysis, phenotypic data) and effects, on deciding under uncertainty, and on communication. It is difficult to communicate uncertainty. As biomedical science sees a 'reproducibility crisis' (Nature, 2016), the prediction tools of data-centered medicine will need to allow faster translational medicine, as well as new rules to handle the evidence required, and the risks and responsibilities associated.

New healthcare specialists

Precision medicine will require new specialists such as 'Big Data wranglers', to reflect the new process of collecting, analysing, administrating and working with large amounts of data. PM will also require 'health coaches' or health care 'navigators' who can help patients navigate and understand their health and disease, accompanying them through their journey into precision medicine. The medical field is poised to become even more multi-disciplinary than it already is.

Engaging with industry and new actors from the non-medical domain

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Business is one of the key drivers of PM. The pharmaceutical industry will undergo dramatic changes, and will have to develop new business models that make it rewarding to participate in PM, all the while keeping business interests and those of patients and society as aligned as possible. New actors from outside the medical domains, such as tech firms, Big Data or telecommunication companies, tend to innovate fast and effectively. They may challenge existing conventions or values in the medical sector. It is critical that initiatives for PM involve industry and new actors in the field.

Already today, some patients with unmet medical needs decide to bypass established safety and efficacy standards of their own country, and get

medical treatments in countries that accept experimentation on patients before the full extent of testing for safety and efficacy is completed, despite high levels of uncertainty about outcome.

Looking to the future, it may be that society and new private actors form unexpected partnerships, following the social media model for example, and overdrive current institutional settings including existing public health systems. An even larger and deeper transformation of medicine could thus be triggered by precision medicine. If individuals would gain full control of their own health and medical data, which could be the case in the future if new rules about data generation, ownership, use and control would be progressively developed, then individuals would become empowered to make private agreements with convincing new industry actors. Such a scenario justifies considering seriously issues such as autonomy, consent and groups of interest.

In the debate about the ownership and protection of data and access to resulting information, intellectual property (IP) issues come into play. How these issues are dealt with in the context of genetic data and information will determine to a large extent how innovation is encouraged and how industry is incentivised to invest in precision medicine. This debate will also have an impact on possible new responsibility or liability regimes in the case of unattended negative consequences.

Engaging with citizens and patients
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Precision medicine will trigger many potentially fundamental changes in how the relationship with patients is organised and how health and disease are viewed. It is necessary to engage with society as a whole, not just patients.

Engaging with citizens

Public institutions must engage with citizens, to create the space for dialogue about how society and the economy will adopt precision medicine. Citizens will become active participants in the development of PM, first as data and consent providers. In particular, critical choices such as those on ethics and values, discrimination or solidarity must result from an alignment between societal preferences and public policy. To make informed decisions, citizens must be involved in a two-way dialogue about the benefits that they expect from precision medicine as well as the related challenges, both for them and for society, in particular regarding:
- **Ethical implications**. Discussions about ethics may come in conflict with policy and political reality. Any ethical framework would have to be discussed with citizens, in order to create the legitimate space (boundaries) for PM to develop, including the limits that PM must not cross (e.g. discrimination, or the border between prevention and eugenism).
- **Data collection and sharing**. Important choices have to be made as to how biomedical data and their scientific implications translate into medical

practice. Genomic and other '-omic' data need to be linked to other health, lifestyle and environment data ('Big Data'). This involves issues of consent, data collection, access, use and sharing, as well as ethical and economic considerations on privacy, security and trust. (See section 3: Addressing the data issue). The importance of consent to use health data must be noted.

<div align="center">

Engaging with patients

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The need to put the patient at the centre of the attention and the medical practice is a recurring theme in PM. However, studies show that patients who don't have immediate and unanswered medical needs are not convinced yet by the potential benefits for them. Engaging patients in PM will require a new type of communication between physicians and patients, to subtantiate and explain that there is a continuum between health and disease, to trigger behavioural change, and to co-develop a new taxonomy of diseases. Two aspects are particularly worth mentioning in the context of a roadmap:

- **Genomics and health literacy**. It is often difficult for patients to understand the implications of DNA testing, genomic analysis, and probabilistic predisposition.
- **Patient empowerment and responsibility**. Because patients may be put more in control of their own health (in particular when a predisposition to a certain condition is detected and the patient is informed of this), a greater responsibility may be assigned to them. Patients will be empowered to make their own, well-informed decisions. They may also be incentivised, possibly through adaptive medical insurance schemes, and through their participation in patient monitoring programmes using sensor-based medical devices for 'mobile health'.

There is also the potential for patients and citizens to become involved as citizen scientists. They may be given the opportunity to start their own clinical studies (under the guidance of academic scientists). The best way to improve health literacy is to the engage with one's own health and health data.

Communication with citizens and patients must be transparent (including about topics that are not well understood). Citizens must be enabled to evaluate if PM is developed for their own good and can improve population health, with a fair distribution of benefits and risks. PM and health are only possible with the active engagement of citizens and patients, who will provide key information to understand the phenotypic variability of diseases.

Engaging with regulators and payers (insurers)

Precision medicine challenges existing licensing and regulatory frameworks, and is likely to be expensive, at least before it can exert an impact on healthcare and related expenses (such as rehabilitation and absence from work) by optimising individualised prevention and therapies. Today, in many countries, regulators and payers are not prepared for the 'precision medicine

revolution'. It is difficult for them to engage with those who develop PM and many of them may not even be aware of its implications. Information, communication and evidence-based dialogue must be a priority.

Decisions by those who want to develop PM should result from engaging with:
- **Rule makers (legislators and regulators)**, who design, decide, implement and enforce the rules. This includes licensing authorities such as the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA) that authorise diagnostic tools and therapies based on safety and efficacy. This also concerns any legal rights for patients, for example to obtain copies of all their health relevant data and to decide about their use for research.[4]
- **Payers**, who pay or reimburse diagnostics, prevention and therapies, based on comparative cost-benefit or cost-efficiency analyses. Payers are enablers or constrainers of PM. Some payers are insurance companies, which have strong expertise in risk assessment, balancing risk and benefit. Their knowledge is useful to the new field of PM, where cost-effectiveness assessment might differ from those in conventional medicine. Conventional healthcare reimbursement is based on standardised treatments for large groups of population. Precision medicine, however, targets effective treatments to smaller groups.
One particular aspect that payers have to discuss is to which extent they apply the principles of non-discrimination and fair access. One potential point of contention, for instance, is to decide whether insurance premiums can be contingent on lifestyle or behaviour, especially in the case of probabilistic predisposition. Insurance operates within the boundaries set by regulation. Some legislations may prioritise aspects such as ethics or affordability.
- **Insurers** in general, who may also be faced with changing conditions regarding the liability of medical practitioners related to the use of PM.

In conclusion, engagement with important groups of stakeholders will be the cornerstone for establishing a vision for PM and for creating legitimate policies, legal frameworks and viable business conditions. The expected benefits for each group of stakeholders to engage with others are many folds. It includes the elaboration of guidelines for collaboration.

[4] See article 20 (Official Journal of the European Union, 2016).

2.

STEP-WISE IMPLEMENTATION OF PRECISION MEDICINE

The field of precision medicine is still in its infancy and likely to see several more cycles of development. Implementation will be a complex process. As such, institutional action can target four separate 'horizons' in the development process:

- **Horizon 1**. The first horizon is the organisation and shareability of large-scale collection of biomedical and other data, for an interoperable framework of data streams. Genomic data are the most prominent.
- **Horizon 2**. A second milestone consists of taking advantage of 'low hanging fruits', with applications of PM that demonstrate clinical quality and utility, and cost-effectiveness when a precise diagnostic can be made and when a cure is at disposal. The advent of pharmacogenetics has already enabled better use of existing drugs.
- **Horizon 3**. The third step, involves moving to applications where, based on 'Big Data', we see a possible (but not certain) predisposition for a disease, and where targeted prevention can maintain and develop health and wellness.
- **Horizon 4**. The final step includes applications to complex traits (e.g. biology of ageing, higher brain functions) where there are uncertainties about causes of diseases affecting these traits, no recognised biomedical therapies and no clear data-based approaches, with many questions on safety, efficacy, cost-effectiveness and longer-term consequences.

The roadmap begins with applications of PM that are potentially inexpensive and with a low level of uncertainty, and moves progressively to applications that are likely expensive and with a high level of uncertainty. This proposed implementation of PM may be simplistic, give undue importance to deterministic aspects of biomedical data sciences, or even be seen as inaccurate by some scientists. However, the underlying rationale is to develop simple messages to communicate, to respond to the current public interest in genomics, to explain the importance of investing in the field to non-experts, and to focus on cost and return on investment.

In addition, a step-wise implementation of precision medicine will also focus on:
• The need to increase the value of health care systems, which implies the acceleration of the development of new biomedical diagnostics, tools, therapeutics and other innovations.
• The need to demonstrate benefits to human health, which will contribute to creating public acceptance. This implies moving as soon as possible from Horizon 1 to Horizons 2 and 3.

The suggestion presented in this section follows generic recommendations developed and applied by IRGC to consider the knowledge collected about a risk issue in order to design appropriate management strategies.[5]

Horizon 1: Data collection, sharing and analytics
Creation of meaningful subpopulations
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Many of the initial benefits will accrue from using genetic and other biomedical information to group individuals into meaningful subpopulations or cohorts that are valid for improved health decisions and outcomes. This requires the creation of large databases. In addition, the databases must be designed for optimising data flows, so that data can be shared with others. See also section 3, addressing the data issue.

Recommendation: Design and implement large-scale programmes for DNA testing, collection and sharing of medical and health records. The objective is that doctors, 'data wranglers', and scientists can search the genetic information and other records of millions of individuals to identify patterns and improve diagnostics and predictions from past clinical applications.[6]

Horizon 2: Precision diagnostics
Enabling precision treatments
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In some cases, we understand the cause of a disease thanks to genomic and other biomedical data. A prognostic can be made, indicating how to treat the disease by appropriate therapeutic agents. In the future, this might involve correcting the defective allele. In this case, there is a direct connection between the individual data and therapies with proven effect, for example certain cancer or inherited conditions[7]. The field of pharmacogenetics is among the first applications of PM, based upon the understanding of differential responses to treatments in different patient groups. Pharmacogenetics develops with the understanding and targeting of underlying genetic mutations of disease,

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[5] See Appendix 2: Characterising the knowledge about an issue to determine management strategies.

[6] See for example initiatives of the Global Alliance for Genomics and Health, for "working together to create interoperable approaches to catalyze projects that will help unlock the great potential of genomic data", www.genomicsandhealth.org.

[7] e.g. sickle cell disease (SCD), beta-thalassemia, severe combined immune deficiency.

insofar as inherited genetic differences explain how individuals respond to drugs. Such strategies target some rare disorders that affect few individuals. Rare diseases in aggregate represent an enormous cost to the health care system but in many cases they are excellent pilots for PM approaches. (Orkin & Reilly, 2016)[8]

General recommendation: Understanding, continuing to experiment and communicating the benefits of precision medicine in these areas will hopefully contribute to demonstrating that precision medicine can be more cost-effective than conventional medicine. This is especially the case when also taking into account broader aspects of health and medical costs, such as overtreatments, untreated/uncontrolled side effects, or quality of life.

Specific recommendation: Communicate with society about economic facts to demonstrate that, in some cases, it is globally beneficial to spend money on a few individuals. This can contribute to increasing the value of health care systems, with decreasing costs over the medium- and long-term.

Horizon 3: Personalised prevention
Personalised biomedical profiling leading to precision disease prevention and maintenance of wellbeing
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Prevention is potentially the most cost-efficient way to treat disease. The economics of vaccines have demonstrated that, for a wide diversity of conditions, preventing disease is less expensive than treating it. Large-scale DNA sequencing and genome analysis have the potential to detect predispositions to certain diseases that can to a certain extent be prevented by adapting behaviour. The patient consequently has the opportunity to adapt his or her lifestyle to reduce disease risk. The main obstacles to overcome are:
- Understanding uncertainty and probability. Genetic testing can help identify predisposition to a condition, but without timing and certainty of development of the condition. Today, only monogenetic dominant diseases can be predicted with genetic tests.
- Triggering a change in lifestyle or consumption if the positive outcome is uncertain. Insights from behavioural economics and other social sciences have shown that it is very difficult to 'nudge' individuals into sustainable lifestyle changes, especially when the scientific proof of the health outcome based on behavioural change is scarce. Behavioural research for effective preventive strategy is needed.
- Creating the financial incentives that will be needed. Health care systems recommend prevention, but the cost of prevention is often at the patients' expense. The financial incentive to engage in prevention is low.
- It is important that doctors do not make moral judgements about their patient, who would be held responsible for their condition. It is equally important to carefully evaluate the benefits expected from behaviour- or

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[8] "A one-shot cure effected through gene therapy might cost hundreds of thousands of dollars per patient up-front. But over the long term (assuming there is no need for additional therapy and a significantly improved quality and length of life), these drugs will be eminently cost effective, if not cost reducing" in (Howard & Huber, 2016).

compliance-linked health insurance premiums when the health outcome is uncertain.

Recommendation: Develop schemes to pay for genetic testing and counselling patients on behaviour change that would avoid the development of certain diseases.

Horizon 4: Complex traits and new biomedical data-based therapies
Personalised medicine and uncertainty about safety, efficacy and cost-effectiveness
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In many cases, there is no direct connection (maybe just a suspicion of connection) between the cause of a disease and the biomedical (including genetic) information. This includes complex traits where the scientific understanding is still poor, for example in the case of brain functions or the biology of ageing. In other cases, biomedical information and diagnostics are established, but there is no treatment, and/or clinicians will have to experiment with possible connections (work under clinical trial conditions).

Regulators may decide not to prioritise such clinical applications when cost and uncertainty are high, with low current cost-effectiveness ratio and in the absence of a societal decision to invest in the field. But research or testing should be continued in these areas, so that uncertainty and costs are reduced.

Recommendation: Create a space for dialogue to discuss clinical applications with society, as it involves potentially large investments.

Strengthening the science base

A major obstacle for the translation of research into clinical testing (let alone approval and clinical use) is the weakness of the molecular/biochemical scientific understanding of a disease in a controlled clinical setting. A better understanding of the pathological mechanisms is key.

There is a huge potential for outcome-based treatments through app-based patient reporting (mHealth).

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3.

ADDRESSING
THE DATA ISSUE

A roadmap for PM must include stakeholders addressing the 'data issue'. The generation and use of data is one of the main drivers of change in the research and medical practice:
- PM requires a lot of data from individuals
- Handling genomic, health, medical, intimate and personal data poses various challenges that will have to be addressed by the stakeholders.

Specific actors for addressing the data issue include:
- **Researchers**
- **Biobanks** (of samples and data) which collect and act as a repository for genetic and other personal data.
- **Industry** that processes and analyses the data. This industry is currently operating without a clear legal framework. Here, regulation is needed to deal with industrial capacity to build, e.g. DNA printers or digital bio-converters.
- **Insurers** who are active players in data collection and sharing, and thus enablers of precision medicine.

On the 'data' agenda, any roadmap for PM must include:
- Work to determine which data are needed to improve the understanding of large-scale personal information and the link with specific health conditions.
- The level of precision or quality that is required.

Clarifying data privacy and confidentiality issues
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DNA information is considered private and confidential. However, DNA information is difficult to protect, even when it is de-identified (anonymised), because it can sometimes be reconstructed from e.g. public information available on social media. DNA information is therefore in practice not as private as health data from medical records, which must be kept in strict privacy and can be protected. Furthermore, DNA information must be analysed. It acquires its value through the analysis process, during which it is assembled and interpreted together with other data.

The use of data should be non-discriminatory, even when the individual risk profile is known. Patients and civil society must be involved in the decisions that will be made about how data is used. They must determine what they want to protect and when confidentiality is required. The goal must be to develop ways to continue protecting what individuals care about in any circumstances. At this stage, this is a research question, but also a societal question which needs broad citizen involvement on at least some of its aspects.

Tasks to consider include: implementing data management with privacy and confidentiality in mind, defining data custodianship, controlling access, certifying institutions.

Facilitating a societal dialogue and decisions about consent
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Data is volunteered by or acquired from citizens and patients, who provide 'consent'. Citizens and the medical profession should work together to define the various types of consents and implications. Ideally, the development of trustworthy applications of genomics, in a way that is reliable, honest and accountable should encourage systems of unified general consent. Those systems must be informed and dynamic, implying that participating citizens have acquired knowledge about the research process, including potential future uses, and that they can maintain or withdraw their consent as new relevant information becomes available. There is, however, a distinction between consent for research and consent for industrial applications, and between consent to share data for private or public use.

Therefore, any dialogue and decision must be very clear about what the donors (citizens) are consenting to, bearing in mind that beyond privacy, security and consent issues, what matters is trust.

Establishing a framework for data sharing
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The trustworthiness that is anticipated to result from agreeing on a roadmap for precision medicine should allow for a sense of social responsibility in sharing data. Trustworthiness is established if the legitimate framework for data acquisition and sharing is clear about the purpose. This has not been established yet as shown by public reluctance to share health records (NHS England, 2013). It is critical to establish governance mechanisms and transparency for data sharing and use.[9] Under EU regulation, patients must be in control of their data (European Commission, DG JUSTICE, n.d.).

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[9] Examples of platforms for data and information sharing: www.matchmakerexchange.org, www.genematcher.org, www.midata.coop, www.healthbank.coop

Like in any new development, it may be that certain things turn out to go wrong or not as expected. It would be presumptuous to neglect, for example, the possibility of misuse of data by actors with malicious intentions or for unauthorised purposes. To prevent negative consequences from such incidents, trusted authorities must develop their response plans in advance, in order to avoid a breach of trust. Plans may include such dispositions as the possibility for individuals to opt out of data sharing schemes, including removal of their own data, but also revisions of existing regulatory and liability regimes.

Developing biobanks and interoperability of data
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Data standardisation and interoperability are necessary for data sharing. It is a technical problem but which nonetheless needs a political agreement to be resolved. Biobanks are organised at national and regional levels[10]. Interoperability and traceability access will be important to clinicians, researchers and legislators.

Pursuing other advancements
to deliver precision medicine
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Scientific and technical advancements are transforming data collection and analysis, therapy delivery, and medicine overall. They include the use of connected medical sensors and devices (implantable or not) for monitoring and treatment, health wearables, or mobile health applications, which will help individuals monitor their own lifestyle and health. They also include advanced data analytics to feed artificial intelligence and deep learning, which can modify the medical practice through new types of algorithms that support decisions to be made by machines as much as by humans. Precision medicine develops in parallel with and benefits from these advancements. However, all medical treatments will still need to be assessed by established protocols of clinical trials.

Typology of applications based
on the source of the data
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Table 2 below proposes a typology of precision medicine applications (public, mixed and private), depending on the source of the data and the source of funding. We believe that this typology can help institutions structure their

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[10] E.g. BBMRI-ERIC in Europe. See www.bbmri-eric.eu

thinking about data acquisition and application, and help to bridge the gaps between scientific and biomedical research data on the one hand and clinical and patient lab data on the other hand.[11]

Table 2: Typology of applications.

Type	Public	Mixed	Private
Data Source	Public	Public	Public and private
Benefactor / Funder	Public / Government	Private / Government & Insurance	Private / Insurance and Private
Cost per Capita	+	++	+++
Field of application	Understanding Genetic Variations as basis for disease and poor health. Fostering wellbeing and health through targeted prevention. General knowledge of human genome & functions, health and wellbeing.	Re-tasking existing drugs for new diseases. Selective use of existing drugs for existing diseases to (a) reduce side-effects and (b) improve efficacy.	New diagnostics and therapies targeted at individual patients, based on their genome, such as: • cell therapies • gene therapies • immune activation

[11] Adapted from David Hanselman, Synthetic Genomics.

4.

REFORMING REGULATION AND PAYMENT SYSTEMS

Advances in medicine result from an iterative process among scientists, industry, regulators, physicians, patients and other actors. Healthcare systems are adaptive. With precision medicine, they are expected to become even more adaptive and incorporate more learning by doing. Health care systems can improve by learning from experience through feedback processes, and adapt as new knowledge is made available about actual outcome (safety, efficacy) and economic benefits (cost-effectiveness). This might pose a challenge for PM, for instance if personalised treatments are applied to very small numbers of patients for which statistical proof is difficult. Since changes in regulatory systems take time, the discussion should start now, as it has begun at the European Medicines Agency. Important goals include re-designing methods and metrics for assessing safety and efficacy, and paying for medical treatments according to their performance (effectiveness in use) (Breckenridge , Eichler, & Jarow, 2016). Precision medicine initiatives should consider deliberating and deciding about the following aspects.

Adaptive licensing

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Processes are shifting from viewing decisions on licensing as a one-time binary decision, to treating these decisions as an on-going process aiming at providing greater certainty about efficacy and safety as evidence accumulates. Adaptive licensing implies agreeing to review decisions. Regulators increasingly consider the design of legal structures with regulatory mechanisms that can adapt, so that those are more responsive to scientific knowledge and outcome. The principle is the following, as is already implemented in an EMA pilot project for new pharmaceuticals (European Medicines Agency, n.d.): Analyses are conducted during an original drug approval trial, adaptive trials collect and analyse patient response to the drug being tested, and biomarkers that cause certain patients to respond differently to the same treatment regiments are identified. Progressive adaptation is implemented during the drug or treatment lifecycle. Adaptive trials enable a learning feedback loop and require a different approach to post-marketing surveillance (see below).

Performance-based reimbursement
—

Some payers are shifting from viewing decisions on reimbursement as a one-time binary decision, to treating reimbursement decisions as an on-going process aiming at providing greater certainty about value for money as evidence accumulates. Medical treatments are reimbursed on the basis of evidence of efficacy, safety and added value for money. Payers will increasingly decide what they want to pay, based on quality of outcome and cost-effectiveness[12]. Their demand will increasingly focus on effectiveness in use (performance). Personalised healthcare must be able to provide the information on actual performance measured among small numbers of patients in adaptive trials. The development of metrics of success acceptable to payers and regulators is a major challenge.

Regulate and pay for diagnostics and data analytics
—

Regulation and reimbursement usually focus on therapeutics. However, they increasingly need to account for the added value and cost of data collection and analysis, and diagnostics. For example, it may be that the molecular diagnostic is the best 'value-added' of some application of precision medicine, but most reimbursement schemes and regulations do not recognise this. Similarly, IT-based clinical decision-support systems and applications of evidence-based artificial intelligence must be compensated proportionate to their role in precision medicine. Revisions of reimbursement frameworks for data and diagnostics are needed.

Post-market surveillance
—

New tools for post-marketing surveillance and monitoring need to be established for both adaptive licensing and performance-based reimbursement to create the new data and feedback loops needed for the improvement of PM. This will be greatly enhanced by direct patient involvement using mobile applications and crowdsourcing.

In conclusion, with rising health care costs, health systems must take a more critical look at their existing financial/business model. Precision medicine may allow a shift from volume- to value-based payment methods that emphasise improved outcomes, with revised definitions of what is acceptable and affordable.

[12] Principles and examples of performance-based or outcome-based contracts are provided in (OECD, 2013) and in chapter 5 of Howard & Huber, 2016.

CONCLUDING REMARKS

Beyond the indispensible scientific advances in genomic science, we highlight seven elements that will influence the development of precision medicine:

1. **Data generation** is a major driver of change in medicine. All actors must fully integrate the implications of the fact that, in addition to being 'personalised', precision medicine is also data-driven.

2. **Patients** are expected to take more responsibility for their own health and disease, and insurance solutions might become more adaptive to patients' behaviour.

3. **Electronic medical records**, made available by health care professionals and patients, should be used to track outcome, providing better information about effectiveness.

4. **Artificial intelligence** and deep learning could modify the medical practice, through new types of sensors, medical devices and algorithms that support decisions.

5. **Business models** for Big Data and complex intersecting datasets should be established, especially with the longitudinal nature of many PM data initiatives.

6. As the **pharmaceutical industry** gets more information from adaptive clinical trials, it could deliver more competitive drugs, based on outcome. It could also be more willing to take on more of the risk in case a therapy does not perform as originally planned.

7. **Payers** will have to work to determine new pricing mechanisms and schemes for large-scale biomedical data analysis and diagnostics.

In their anticipation of the future, actors in the medical and health sectors are advised to consider these aspects.

APPENDIX 1

ABOUT ROADMAPS
FOR PRECISION MEDICINE

This paper suggests that national and international initiatives for precision medicine include a 'roadmap' of important considerations and milestones for achieving the vision of precision medicine.

Several initiatives include the concept of roadmaps, which are:
• Multi-disciplinary – they consider both technical issues and societal issues.
• Multi-stakeholder – they acknowledge that the implementation of important improvements in the medical field necessitates more than a scientific judgement, because of implications in other fields.

From research and NGOs:
• Angela Brand & Jonathan Lal, European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies: the 2012 Declaration of Rome (Brand & Lal, 2012).
• European Science Foundation, Personalised Medicine for the European Citizen (European Science Fondation, 2012).
• European Alliance for Personalised Medicine (EAPM), Innovation and Patient Access to Personalised Medicine[13] (European Alliance for Personalised Medicine, 2013).
• Lada Leyens *et al.*, Working towards personalization in medicine: main obstacles to reaching this vision from today's perspective (Leyens, L., *et al.*, 2014).
• Global Alliance for Genomics and Health (GA4GH), 2015-2016 Strategic Roadmap.[14]
• PerMed, Shaping Europe's Vision for Personalised Medicine; Strategic Research and Innovation Agenda (SIRA) (PerMed, 2015).
• ICPerMed Action Plan. A common Action Plan with actionable research and support activities in all areas related to personalised medicine (ICPerMed, 2017).

From governments and regulators:
• European Medicines Agency, Adaptive Pathways (European Medicines Agency, n.d.).
• US FDA, Precision Medicine Initiative (FDA, n.d.).
• Paving the Way for Personalized Medicine - FDA's Role in a New Era of Medical Product Development (FDA, 2013).
• Roadmap for bringing personalized medicine to British Columbians (Personalized Medicine Initiative, 2015).

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[13] Report from Irish Presidency Conference March 2013 (European Alliance for Personalised Medicine)

[14] The GA4GH roadmap prioritises development and use of products, as well as the success of demonstration projects, leading to increased genomic data sharing and systemic change (Global Alliance for Genomics and Health, 2015/2016)

APPENDIX 2

IRGC BASIC RECOMMENDATIONS FOR RISK MANAGEMENT STRATEGIES

Since 2005, the International Risk Governance Council (IRGC) has been developing recommendations for risk governance based on the knowledge that decision makers can collect about a risk issue (i.e. an issue in which there are risks involved, but often also opportunities or benefits) in order to (a) determine the type and extent of stakeholder involvement that is advisable, and (b) design decision processes and management strategies in which stakeholders' objectives, constraints and needs will be taken into consideration. The table below is adapted from IRGC White Paper 1, Risk Governance: Towards an Integrative Approach, pages 16 and 53.[23]

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[23] IRGC. (2005). IRGC White Paper 1, Risk Governance: Towards an Integrative Approach. Retrieved from www.irgc.org/risk-governance/irgc-risk-governanceframework

Table 3: IRGC characterisation of knowledge and risk management strategies.

Knowledge about the risk issue*	Simple	Complex	Uncertain	Ambiguous
	Cause and effects are known	Difficulty in identifying links between a multitude of potential causal agents and specific observed effects	Lack of clarity or quality of the scientific data. Absence of data (unknown)	Divergent or contested perspectives

Stakeholders who should be involved in the assessment and decision	Simple	Complex	Uncertain	Ambiguous
				Civil society (i.e. citizens)
			Affected stakeholders (e.g. patients)	Affected stakeholders (e.g. patients)
		External scientists / researchers	External scientists / researchers	External scientists / researchers
	Scientists, industry experts, regulators	Scientists, industry experts, regulators	Scientists, industry experts, regulators	Scientists, industry experts, regulators

	Simple	Complex	Uncertain	Ambiguous
Type of participation	Use existing routines to assess benefits and risks (and possible reduction measures)	Multi-disciplinary approach	Involve all affected stakeholders to collectively decide the best way forward	Societal debate about the risks, benefits and underlying implications
Type of management strategy	Regulation Routine practices	Seek more information Make robust decisions, which will be acceptable in various contexts	Address uncertainty in the decision process Be prudent, do not make decisions that are irreversible Build resilience to failures, prepare to cope with negative outcome	Work to establish societal consensus, including about sharing benefits and risks Work to resolve conflicts with dialogue and negotiation
Cost of the process	+	++	+++	++++
Potential return on investment	+	++	+++	++++

Application to precision medicine (tentative)	Horizon 1	Horizon 2	Horizon 3	Horizon 4
	Collection of biomedical data: creating meaningful subpopulations	Precision diagnostics: enabling precision treatments	Personalised prevention: when the biomedical profile is used for precision disease prevention and maintenance of wellbeing	New biomedical data-based therapies: when safety, efficacy and cost-effectiveness have not been demonstrated yet

* For most risk issues, some elements of knowledge are 'simple', while others are 'complex', 'uncertain' or 'ambiguous'. Managers try to address each level with appropriate methods. But all are interconnected

APPENDIX 3

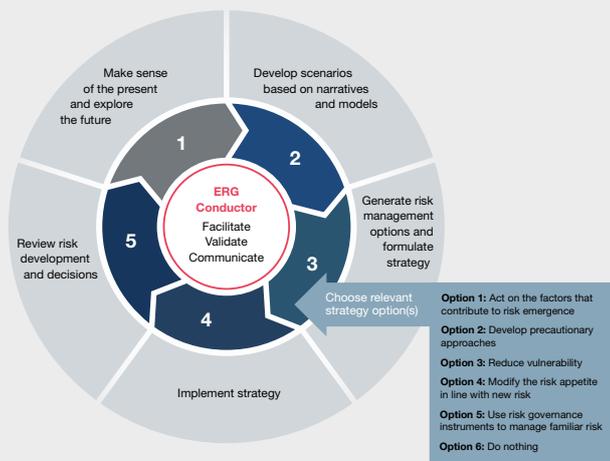## IRGC RECOMMENDATIONS FOR THE GOVERNANCE OF EMERGING RISKS

Figure 2: IRGC guidelines for emerging risk governance (ERG)

IRGC defines emerging risks as new risks or familiar risks that become apparent in new or unfamiliar conditions. In this context, risks are defined as the consequences of uncertainty on objectives, or what humans value. Emerging risks are characterised by uncertainty and change. Quite often, they are just described as 'issues', and it is not clear to managers and decision makers how potential benefits and threats interact. Often, stakeholders with different interests or viewpoints may contest the evidence, thus hesitating to engage in the venture that may lead to opportunities and/or risks.

IRGC's guidelines for emerging risk governance, as illustrated in figure 2, include a process and recommended instruments and practices for evaluating and making decisions about these issues.[24]

Applying the Guidelines to precision medicine:

- Steps 1 and 2 in the process would involve horizon scanning, foresight exercises and developing scenarios of possible futures with (or without) precision medicine, including best and worst case scenarios. Such exercises would include facilitated dialogues with stakeholders about how various scenarios could generate impacts, consequences, benefits, and risks to them. The output of Step 2 consists of informed explorative scenarios.
- Step 3 would consider various development strategies and management options and help decision makers adopt a collaborative strategy for a coordinated development of precision medicine. One of the options (# 4) would involve increasing the willingness to take more risks in the short term, in return for long-term improved health benefits.
- After deciding on a strategy and implementing it (Step 4), Step 5 would create processes and a framework for post-surveillance and monitoring, thus allowing feedback to regulators and adapt as knowledge is acquired.

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24 IRGC. (2015). Guidelines for Emerging Risk Governance. Lausanne: International Risk Governance Council (IRGC). Retrieved from irgc.org/risk-governance/emerging-risk/a-protocol-for-dealing-with-emerging-risks

REFERENCES

Brand, A., & Lal, J. A. (2012). European best practice guidelines for quality assurance, provision and use of genome-based information and technologies: the 2012 declaration of Rome. *Drug Metab Drug Interact*, 27(3), 177-182. doi: 10.1515/dmdi-2012-0026

Breckenridge , A., Eichler, H., & Jarow, J. (2016). Precision medicine and the changing role of regulatory agencies. *Nat Rev Drug Discov*, 15(12), 805-806. doi: 10.1038/nrd.2016.206

European Alliance for Personalised Medicine. (2013). *Innovation and Patient access to Personalised Medicine*. Retrieved from www.euapm.eu/pdf/EAPM_REPORT_on_Innovation_and_Patient_Access_to_Personalised_Medicine.pdf

European Commission, DG JUSTICE. (n.d.). *Protection of personal data*. Retrieved from http://ec.europa.eu/justice/data-protection

European Medicines Agency. (n.d.). *Adaptive pathways*. Retrieved from http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce

European Science Fondation. (2012, November). *Personalised Medicine for the European Citizen. Towards more precise medicine for the diagnosis, treatment and prevention of disease (iPM)*. Retrieved from http://archives.esf.org/coordinating-research/forward-looks/biomedical-sciences-med/current-forward-looks-in-biomedical-sciences/personalised-medicine-for-the-european-citizen.html

FDA. (2013, October). *Paving the way for personalized medicine. FDA's role in a new era of medical product development*. Retrieved from www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf

FDA. (n.d.). *Precision medicine initiative*. Retrieved from www.fda.gov/ScienceResearch/SpecialTopics/PrecisionMedicine/default.htm

Global Alliance for Genomics and Health. (2015/2016). Strategic Road Map. Retrieved from www.genomicsandhealth.org/files/public/GA4GH_RoadMap_draft_v4_20150428.pdf

Hood, L., & Friend, S. H. (2011). Predictive, personalized, preventive, participatory (P4) cancer medicine. Nature Reviews Clinical Oncology, 8, 184-187. doi:10.1038/nrclinonc.2010.227

Howard, P., & Huber, P. (2016). *Unlocking precision medicine*. New York: Encounter Books

ICPerMed. (2017, March). Action plan. Retrieved from http://www.icpermed.eu/media/content/ICPerMed_Actionplan_2017_web.pdf

IRGC. (2005). *IRGC White Paper 1, Risk Governance: Towards an Integrative Approach*. Retrieved from https://www.irgc.org/risk-governance/irgc-risk-governance-framework

IRGC. (2015). *Guidelines for Emerging Risk Governance*. Lausanne: International Risk Governance Council (IRGC). Retrieved from irgc.org/risk-governance/emerging-risk/a-protocol-for-dealing-with-emerging-risks

Leyens, L., *et al.* (2014). Working towards personalization in medicine: main obstacles to reaching this vision from today's perspective. Personalized Medicine, 11(7), 641-649. doi:10.2217/pme.14.55

Nature. (2016). Reality check on reproducibility. *533*, 437. doi:10.1038/533437a

NHS England. (2013, October 16). *NHS England sets out the next steps of public awareness about care.data*. Retrieved from www.england.nhs.uk/2013/10/care-data

OECD. (2013). *Toward new models for innovative governance of biomedicine and health technologies*. Retrieved from www.oecd.org/officialdocuments/ publicdisplaydocumentpdf/?cote=DSTI/STP/BIO(2013)8/ FINAL&docLanguage=En

Official Journal of the European Union. (2016, April 27). *Regulation (EU) 2016/679 of the European Parliament and of the Council*. Retrieved from www. eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv: OJ.L_.2016.119.01.0001.01.ENG

Orkin, S. H., & Reilly, P. (2016). Paying for future success in gene therapy. *Science*, 352(6289), 1059-1061. doi:10.1126/science.aaf4770

PerMed. (2015, June). *Shaping europe's vision for personalised medicine. Strategic research and innovation agenda (SRIA)*. Retrieved from www.permed2020.eu/_ media/PerMed_SRIA.pdf

Personalized Medicine Initiative. (2015). *Roadmap for Bringing Personalized Medicine to British Columbians*. Retrieved from www.personalizedmedicineinitiative.ca/ roadmap

Topol, E. (2012). *The Creative Destruction of Medicine: How the Digital Revolution Will Create Better Health Care*. New York: Basic Books

World Health Organization. (2004). *Guidance on ethics and equitable access to HIV treatment and care*. Retrieved from www.who.int/ethics/en/ethics_equity_HIV_e.pdf

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About IRGC

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The **International Risk Governance Center** organises IRGC activities, emphasising the role of risk governance for issues marked by complexity, uncertainty and ambiguity, and focusing on the creation of appropriate policy and regulatory environments for new technologies where risk issues may be important.
More information on irgc.epfl.ch

The **International Risk Governance Council** (IRGC) based at EPFL, Lausanne, Switzerland, is an independent non-profit foundation whose purpose it is to help improve the understanding and governance of systemic risks that have impacts on human health and safety, the environment, the economy and society at large. IRGC's mission includes developing risk governance concepts and providing risk governance policy advice to decision-makers in the private and public sectors on key emerging or neglected issues. IRGC was established in 2003 at the initiative of the Swiss government and works with partners in Asia, the US and Europe.
More information on irgc.org.

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