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PREPARING OURSELVES FOR PRECISION MEDICINE

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Abstract. Precision medicine is expected to herald a new era of customized preventive care and treatment solutions. Like many other countries, Singapore is exploring ways in which precision medicine can improve patients' lives. The research will explore the use of precision medicines and their impact on Singapore A literature review was done to achieve the objective. Findings depict that precision medicine will significantly disrupt abiding by healthcare system structures and challenge existing regulatory processes. To prevent this, our society needs to adapt quickly to ensure that adequate and effective controls are in place to protect patients and safeguard their welfare.

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INTRODUCTION

Precision medicine is the science of tailoring medical prevention, intervention and treatment strategies to the unique characteristics of each patient, guided by their underlying clinical, socio-demographic, psychosocial, molecular and genetic profiles. It provides patients with the opportunity to find individually tailored solutions to their problems and can improve health outcomes and care experiences for every patient. It also has the potential to reduce healthcare costs at a system level as it is expected that treatment for each individual will be more effective. Precision medicine is not limited to pharmaceutical and drug therapy [1]. The development of mobile and wireless capability, advancement in computational power and medical imaging as well as progress in regenerative medicine and stem cell research all herald hope for precise therapy and products. Figure 1 illustrates the principles and landscape of precision medicine.

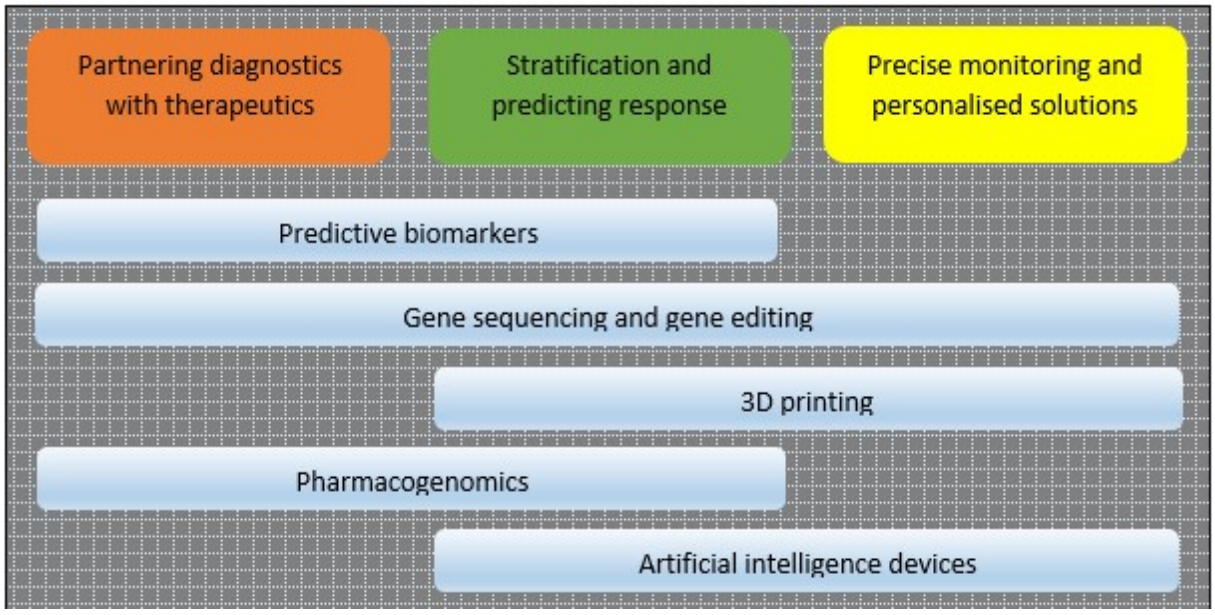

Fig. 1 . Principles and landscape of precision medicine

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LITERATURE REVIEW AND METHODOLOGY

A literature search on the challenges of precision medicine revealed that the key barriers to implementing precision medicine are the conflicting issues of cost, developmental opportunities and the need for a regulatory framework (Figure 2). These are best understood through the complex interplay of patient, provider and government relationships.

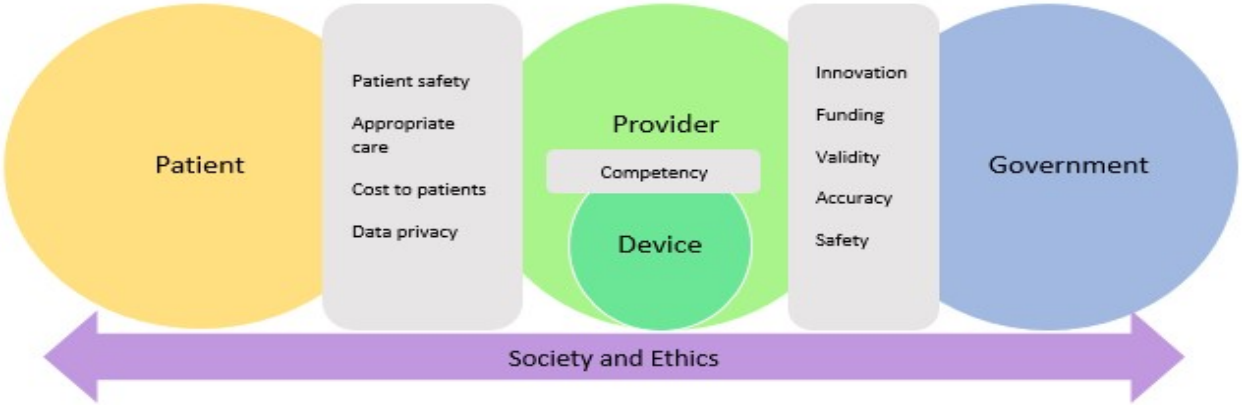

Fig. 2 . Barriers to implementing precision medicine

In spite of the multiple advantages of precision medicine, the cost of precision medicine remains one of its biggest barriers to successful adoption in healthcare [2], [3]. On January 20, 2015, President Obama announced the Precision Medicine Initiative (PMI) in his State of the Union address. He called for $215 million in fiscal year 2016 to support the Initiative [4]. Although, precise identification of genes and biomarkers is envisaged to decrease overall cost of therapy for patients by being more targeted and effective, the high capital cost of developing safe, valid and accurate precision medicine tests and tools still means that the therapeutic programmes created from research and innovation will remain costly for patients [5], [6]. In the context of a single payer healthcare system such as the National Health System (NHS) in the United Kingdom (UK), health technology assessment can play a big role in guiding the governments decisions on appropriateness of therapeutic/ diagnostic choices, and related issues of subsidy, subvention and co-funding. However, in the context of a healthcare system with a large private sector market such as the United States of America (USA), it will translate to escalating healthcare costs for patients [7], [8].

Society also has to prepare for the evolution of precision medicine from research to therapy [9]. As precision medicine initiatives become part and parcel of mainstream medicine and genomic data become an enabler of more effective healthcare, governments and regulators have to be prepared to protect patients from infringements to their privacy, dangers posed to their safety and inappropriate use of such technology by profit-seeking providers [10], [11]. While health technology assessment can address the clinical and cost effectiveness of these devices and services, legal frameworks still have to be developed to address data privacy and patient safety issues [12], [13]. Regulatory agencies have to make concerted attempts to keep tabs on the rapid development of precision medicine technology, or they run the risk of being outstripped and outmoded [14]. Due to the technical nature of precision medicine research and innovation, licensing departments will have to develop the appropriate expertise to be able to identify regulatory gaps and develop rectification procedures expected of licensees [15]. In addition, in a rapidly evolving landscape where research quickly borders into therapy, it is becoming increasingly unclear where the legislative scope of research specific laws ends and where the legislative scope of therapy related laws starts [16], [17], [18]. In addition, there will be emerging ethical issues that regulatory frameworks alone would not be able to sufficiently address such as conflicting moral positions on gene editing and 3D organ printing and the downstream management of incidental findings from genomic work [19], [20].

At the same time, given the promise that precision medicine brings on a national level and the significant resources that many countries have placed behind precision medicine initiatives, governments face the challenge of balancing patient safety and privacy controls yet enabling innovation and allowing initiatives to proliferate and flourish [21]. All research requires a certain body of cumulative proof in order to establish safety, efficacy, validity, clinical and cost effectiveness. Curbing the

development of precision medicine solutions by imposing requirements and standards on these initiatives would prevent this body of cumulative proof from being established and this in turn would have cost implications both at a national and individual patient level [22].

In view of these challenges, a review of the landscape of the UK and the USA was taken to examine the methods and steps taken by each country to overcome the described challenges.

RESULTS

In the UK, the precision medicine landscape is vast and extends from genetic testing to biobanks, telemedicine devices and even wearable artificial intelligence devices [23]. Much work has gone into building infrastructure to support precision medicine such as through the development of secure databases, anonymisation support facilities and networks between research centres and clinical service providers. As part of Innovate UK, it was announced in June 2016 that the Precision Medicine Catapult will be establishing regional centres of excellence in Belfast, Cardiff, Glasgow, Leeds, Manchester and Oxford. The six regional hubs across the UK will act as local centres for precision medicine and help to develop innovative technologies for healthcare.

In terms of regulatory control, the UK is somewhat aligned with the wider, harmonized European position articulated by the European Union. This position has created some baseline degree of regulation on medical devices, general consumer protection, advertisements, contractual terms and data protection in European countries. In Europe, broad controls on the provision of service aspects of precision medicine such as genetic testing have been addressed through the November 2008 Additional Protocol to the 1997 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the application of Biology and Medicine, concerning Genetic Testing for Health Purposes [24]. The 2008 Additional Protocol on genetic testing stated in article 7 §1 that a genetic test for health purposes may only be performed under individualized medical supervision'. It stipulates requirements for informed consent, appropriate counselling, precise evaluation and includes standards for the tests performed such as scientific and clinical validity. Most recently in June 2016, in response to the growth of precision medicine diagnostic devices, the European Union approved the adoption of new regulations for medical devices and In Vitro Diagnostic Devices that will cover not only the design and manufacture of devices, but also the clinical testing, authorization and post-market surveillance [25]. In addition, the EMA has shared that the changes will include the establishment of a new database that will offer patients, healthcare professionals and the public with comprehensive information on products available in the EU. Devices will have a unique identification number, like the unique device identifier, to provide for traceability throughout the supply chain to the end-user or patient. It is anticipated that this will provide users and patients with more transparency.

However, in spite of the advances of precision medicine and the Directives issued by the European Union, the regulatory approach to precision medicine in the UK has remained fragmented. There is no current legislation related to genetic testing as a service although there are provisions in the UK Human Tissue Act 2004 that criminalize genetic analysis of human tissue without the consent of the donor.

There are other means through which precision medicine players have been held to standards in the UK although these are not regulatory in nature. These include voluntary guidelines issued by professional bodies, international advocacy groups or government advisory bodies e.g. the UK Human Genetics Commission (a group that has since been disbanded), voluntary accreditation schemes for testing undertaken in laboratories e.g. United Kingdom Accreditation Service, and codes of practice relevant to certain types of advertising and general consumer-facing business practices e.g. those issued by the Advertising Standard Authority and the Office of Fair Trading.

Unlike in the UK where the precision medicine landscape has been mapped and planned based on infrastructure, in the US, the PMI is being driven largely by disease needs, in particular oncology. The program will also seek to extend precision medicine's success to many other diseases, including common diseases such as diabetes, heart disease, Alzheimer's, obesity, and mental illnesses like depression, bipolar disorder, and schizophrenia, as well as rare diseases.

In the United States (US), efforts are being made to review existing regulatory controls so as to better target safety and quality gaps in precision medicine across a continuum (from research to therapy). These efforts have largely been triggered to support Obama's PMI proposal. In this respect, the US already has made some headway such as through the passing of the Genetic Information Nondiscrimination Act (GINA) in 2008 that protects individuals from the misuse of genetic information in health insurance and employment and removes barriers to the appropriate use of genetic services by the public.

Further refinement of other regulatory frameworks is still necessary. In May 2016, the PMI taskforce recommended

that precision medicine be included as a component in the Interoperability Roadmap, a guideline on which the federal government envisions healthcare information exchange to develop. This is anticipated to lead to further reviews of the chief federal health information privacy law such as Health Insurance Portability and Accountability Act and the broader 1974 Federal Privacy Act. At the moment, neither Act can cover for all the data activity under the Precision Medicine Initiative. The former not being applicable to most research activities conducted using information from the patients' database and the latter not being applicable for data hosted in a database run by a private entity.

Another key area which the US is reviewing to balance Precision Medicine advancements with patient safety is in the area of Lab Developed Tests (LDTs). This is an area that traditionally FDA has chosen not to exercise its regulatory powers for. At the moment laboratory services providing genetic tests and companion diagnostics have to meet the requirements of Clinical Laboratory Improvement Amendments (CLIA) of 1988. The CLIA regulate all laboratory testing services performed on specimens derived from humans in the United States, except for clinical trials and basic research. It governs the accreditation, inspection and certification process for laboratories to ensure the accuracy, reliability and timeliness of test results, regardless of where a test is performed. Practically speaking, this means LDTs are developed, utilized, and evaluated on a laboratory-specific basis. When a laboratory develops a new LDT, the accuracy of that LDT is not evaluated by CLIA until that laboratory is surveyed, and it is only evaluated with regards to that specific laboratory. A summary of the existing regulatory framework for such tests is displayed in Figure 3.

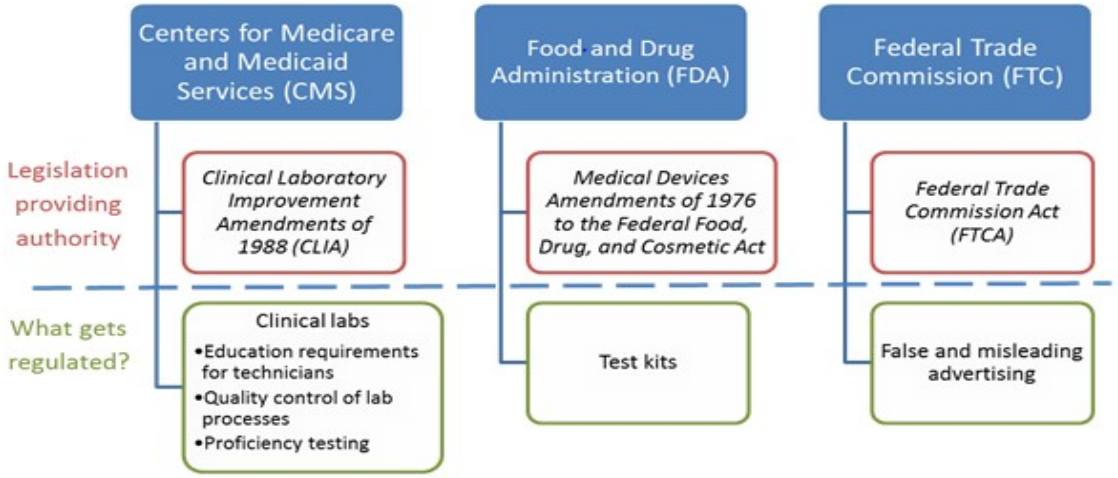

Fig. 3 . Existing regulatory framework for IVDs and LDTs in the US

However, with the development of Precision Medicine, there has been progressive creep in the use of LDTs. Although LDTs are evaluated specifically for each individual laboratory, the protocols and practices for LDTs are more frequently being shared across laboratories and being used across several laboratories. The FDA has recently determined that, with rapid advances in technology and new, innovative business models, the landscape for LDTs has changed dramatically since 1976 and increased regulatory authority is warranted. This is especially as LDTs are now often independent of the health care delivery entity and are frequently manufactured with components and instruments that are not legally marketed for clinical use. These rapid changes and advancements in LDTs may create problems associated with high-risk LDTs, such as: (i) producing claims that are not adequately supported by evidence; (ii) lack of appropriate controls, which may yield erroneous results; and (iii) falsification of data. The FDA is concerned that new LDTs may cause patients to forgo treatment created by false negative results, or initiate unnecessary treatment from false positive results. In April 2016 after several years of back and forth between stakeholders, FDA released a final guidance on LDT oversight and reiterated its intention to regulate these devices [26].

DISCUSSION AND CONCLUSION

It appears that in order for Precision Medicine to be effectively adopted, a three-level framework of controls and checks should be put in place (Figure 4).

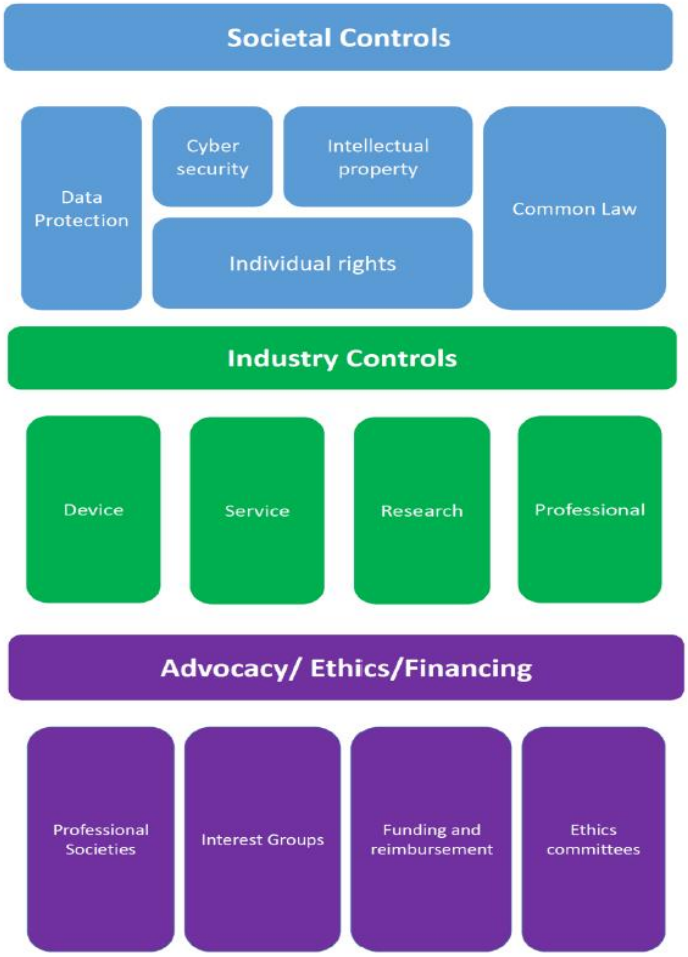

Fig. 4 . Proposed framework of controls and checks

Each of these levels should be adopted in sequence from Level 1 to Level 3, outlined as follows:

Level 1: Societal Controls

This is the most basic level of control required in each society and will ensure that there are some fundamental controls in place to protect patients regardless of the development of the sector. Such controls are essential and should in an ideal situation be in place within existing legislation before specific laws relating to industry controls are brought into place.

These controls can be exerted extrinsically such as in the form of broader collaborations with other countries e.g. European Union or International Free Trade Agreements.

If these societal controls are in place, it would allow specific industry regulators the time and flexibility to develop in tandem with the sector and avoid both over and under regulation. This would also enable innovation and technology to grow and evolve.

Level 2: Industry Controls

As a start, controls over the research industry need to be in place. This should precede the implementation of other industry controls that should only kick in when the relevant services, products and professional competencies have been developed.

Industry controls can take the form of professional regulation, device registration and licensing of services. Research controls would be critical as much of Precision Medicine directly translates from bench to practice and the regulation of related research would need to ensure that devices and services meet minimum safety and validity standards while not flouting ethical practice.

Over time, it is likely that industry controls will merge into a continuum and regulation governing multiple sectors (professionals, devices, services and research) will have to be topical and cut across each sector linearly.

Level 3: Advocacy/ Ethics/ Financing

The last level of control which is often the most active when the industry is nascent is that of advocacy, ethics and financing. While this is intuitively the first level of control that most Precision Medicine initiatives will undertake, this is also the weakest level of control due to the expansive scope of Precision Medicine. The diverse nature of Precision Medicine initiatives means that there may be multiple issues that warrant advocacy and championing. Financing will also be challenging due to inherent difficulties establishing clinical effectiveness, let alone cost effectiveness of various therapies or diagnostic kits. As such, in this three-level framework, this level of control can be developed concurrently with industry controls but cannot replace more fundamental societal controls and will not be able to obliterate the eventual need for greater industry control. In fact, it is even possible that over time as precision medicine becomes more mainstream, the degree of growth of industry control will be inversely proportional to the ethical and advocacy limitations that can be imposed through this level of control.

Ultimately, precision medicine is a science that is here to stay. Each country will have to seek out its own path in developing the science, overcoming implementation challenges and then managing the downstream implications of its growth. However, we can and should work on broad principles to ensure that we strike the right balance between encouraging innovation and protecting patients.

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