PRECISION MEDICINE: LEGAL AND ETHICAL CHALLENGES

Conference Report

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TABLE OF CONTENTS

Introduction **2**

I. Presentations **2**

A. Challenges in the Implementation of Precision Medicine **2**

1. Implementation at the Level of Health Care Systems 2

2. Implementation at the Level of Clinical Treatment 5

B. Challenges in the Development of Precision Medicine **8**

1. Challenges at the Level of Foundational Research 8

2. Challenges at the Level of Translation 10

II. Key Challenges **13**

Introduction

On 7 and 8 April 2016, the Centre for Medical Ethics & Law (University of Hong Kong) together with the Centre for Law, Medicine and Life Sciences (University of Cambridge) hosted a conference at the University of Hong Kong on the legal and ethical challenges facing the realisation of precision medicine.

The aim of precision medicine is to revolutionise disease treatment and prevention by utilising personal variation in factors such as an individual's genetic information, biochemistry, environment and lifestyle. Genomic data, for example, can be used to determine predispositions to particular diseases, predict the efficacy and safety of different treatment options, and help develop drugs that are targeted to the causes of diseases rather than their clinical manifestations. In these and other ways, scientific and technological advances have the potential to bring about an unprecedented tailoring of health care to the individual characteristics of patients.

In order to realise the potential of precision medicine, however, we must rethink components of the legal and ethical foundation on which it will be built. The reason for this is that our current legal and ethical frameworks were built with a very different generation of medical products and practices in mind. At this conference, world experts convened to identify and explore the challenges that precision medicine brings to the fore.

Part I of this report provides a summary of the presentations that were given at the conference. Section A of this part focuses on challenges in the implementation of precision medicine and is divided into two categories: implementation at the level of health care systems, and implementation at the level of clinical treatment. Section B addresses challenges in the development of precision medicine and is likewise divided into two categories: development at the level of foundational research, and development at the level of translational medicine.

Part II categorises and summarises the key challenges that were explored in the roundtable discussions that followed the four categories of presentations, as well as some of the broader questions that emerged out of the conference.

I. Presentations

A. Challenges in the Implementation of Precision Medicine

1. Implementation at the Level of Health Care Systems

Dr Ron Zimmern, "Health Systems & the Future of Personalised Medicine: A Population Health Perspective"

Dr Zimmern began with an overview of some factors that are driving the rising costs of health care, such as ageing populations, increasing patient expectations and expensive technological advances. He also described some of the ways in which personalised medicine might help mitigate these cost drivers, for example: by empowering individuals to take greater responsibility for their health, moving the provision of medical service from hospitals to communities, and shifting the focus of care from treatment to early diagnosis and prevention.

He then turned to two sets of challenges facing the realisation of personalised medicine. The first are challenges linked to data sharing. In order to treat patients at the individual level, doctors and scientists need an immense amount of data, including population data on a variety of human traits (e.g., genomics and metabolomics) and individual data from real-time sources (e.g., wireless sensors). However, various laws and practices (e.g., privacy law and data protection law) currently impede data sharing, and these must be addressed if the value of this data is to be realised. The second set of

challenges arise from a broader shift in the nature of medicine. Drawing on work by Dr Eric Topol, Dr Zimmern suggested that as we move from "old medicine" that is physician driven and uses technology as an aid, towards "new medicine" that is patient and technology driven, change will be required at all levels: health care systems will need to develop new point-of-care infrastructure; patients will need to take greater control of their health; and physicians will need to develop the knowledge required to use diagnostics based on complex analytics.

Dr Zimmern finished by posing a series of questions about the role that governments should play in these changes, including: To what extent should governments aim to empower or encourage citizens to take greater responsibility for their health? How should governments draw the balance between individual privacy and the benefits that can come from data sharing? And, how should governments regulate the devices and diagnostics sector, including direct-to-consumer products and services?

Professor Henry T. Greely, "Precision Medicine: The Ethical, Legal, and Practical Challenges Ahead"

Professor Greely's talk identified and explored four sets of challenges that existent health care systems will need to address in implementing genomic medicine.

The first set of challenges concern the analytical and clinical validity of genetic diagnostics. With respect to analytical validity, he highlighted the problem of errors in DNA-sequence reads. In particular, he noted that whole genome sequencing is currently only 99.9% accurate, which means that a significant number of errors are produced in a human genome made up of 3 billion base-pairs — and that this error rate is exacerbated when it comes to certain types of mutations (e.g., insertion-deletions). Regarding clinical validity, he stated that no nation in the world has a good general mechanism for ensuring the clinical validity of genetic tests. In support of this claim, he identified various tests that are currently marketed but make spurious claims.

The second set of challenges concern the economics of precision medicine. He stated that if genomic medicine is to be implemented, a large range of genetic tests must be reimbursed by health care payers (usually government or private insurers). But at the moment, payers around the world only reimburse a handful of genetic tests — in part because they do not know what tests are actually clinically useful. Thus, he suggested that if genomic medicine is to be realised, the system of reimbursement is going to have to change quite significantly.

The third set of challenges concern provider behaviour. Professor Greely suggested that if genomic medicine is to be realised, health care professionals will need to change the way they operate (e.g. treating patients based on genotype). He acknowledged that medical practice is constantly being revised. However, he thought that the changes required for genomic medicine are likely to be difficult to achieve for various reasons, including a significant knowledge gap: most practising doctors have received only a very basic training in genetics and, in many cases, this would have occurred many years ago.

The fourth set of challenges concern patient acceptance. While precision medicine is often said to be "patient empowering," Professor Greely suggested that large segments of society may not at feel empowered and might even refuse genomic tests. This could be for various reasons, including concerns about privacy, genetic discrimination, or the general idea of organisations or governments "snooping" in their genome. To remedy this problem, he advocated passing laws like the Genetic Information Non-discrimination Act in the US, which he suggested was symbolically valuable even if citizens already have the same protections under other laws.

Dr Jeffrey M. Skopek, "Precision Rationing: The Law and Ethics of Differentiation"

Dr Skopek argued that our increasing ability to differentiate patients on the basis of their personal data will force us to answer two sets of difficult questions about the law and ethics of differentiation.

First, we will need to decide whether and how an individual patient will be able to use personal data to differentiate himself from a group of similar patients in order to gain access to a treatment that is not available to the group. Under its current policy, the NHS refuses to consider personal data about a treatment's efficacy that a patient obtains by *self*-funding a round of the treatment. Dr Skopek criticised the rationale for this policy, challenging the premise that principles of fairness govern the types of evidence used in health care rationing. But he also cautioned against changing the policy, arguing that this issue presents an unavoidable conflict between two fundamental goals of the NHS: one is to have a system in which care is based on the best available evidence, and the other is to have a system in which care is not impacted by a patient's ability to pay. He suggested that in the era of precision medicine, one of these goals must be compromised.

Second, and conversely, we will need to decide whether and how a patient will be able to resist being differentiated from a group of similar patients in order to avoid losing access to a treatment that is available to the group. Here, Dr Skopek explored how the differentiation of disease categories on biological grounds may bring with it the fragmentation of well-established and mobilised patient communities, altering their identities and connections in ways that might be ethically significant. He suggested that this possibility gives rise to a difficult question that has received insufficient attention, which is whether the social aspects of a disease might sometimes be more important than the biological aspects, such that the fragmentation of biological group — even if well-grounded in science — might not justify the fragmentation of the social group.

Professor Ock-Joo Kim & Dr Yoon-Jung Chang, "Precision Medicine Ethics: Prospects on Clinical Application and Ethical Issues"

In the first part of this presentation, Dr Kim provided an overview of the development of precision medicine in South Korea, focusing on issues of infrastructure, law, and ethics. She noted that precision medicine has been on the radars of South Korean governments since 2010 and that various pieces of critical infrastructure are now in place, including: a national biobank with 670,000 specimens; a programme that is sequencing 100,000 human genomes (due for completion in 2018); a nationalised health system that covers almost all Koreans and uses digitised health care data; and a series of initiatives linking various data sources. On the legislative front, there is currently a bill pending before the National Congress that will eliminate some of the regulatory barriers that currently inhibit access to health information held by the government. However, as Dr Kim noted in conclusion, there are still social and ethical matters that must be addressed, including public concerns that the economic rationale for precision medicine may override consideration for patients and participants, that marginalised and disadvantaged groups will be left behind, and that personal data will not be sufficiently secure. Dr Kim suggested that to address these matters, and to deliver more generally on the promise of precision medicine, greater public awareness and engagement is needed.

In the second part of this presentation, Dr Chang described some of the experiences she has had with nascent precision medicine practice in South Korea. She drew attention to the fact that although steps have been taken to implement precision medicine, such as the development of a new gene panel, a number of threshold issues remain. For example, South Korea does not have a system for educating genetic counsellors, and there are few guidelines for clinical responses to genetic tests, including how to manage unclassified variations and incidental findings. Dr Chang also raised concerns with affordability of treatments, noting that only a few patients get the benefit of high-cost tests, even though public money and public samples were needed to develop them.

2. Implementation at the Level of Clinical Treatment

Professor I. Glenn Cohen, "The Legal And Ethical Concerns That Arise From Using Complex Predictive Analytics In Health Care"

Professor Cohen's talk identified challenges that are likely to arise in the development and deployment of predictive health-care analytics. He also proposed solutions to many of these challenges. His talk focussed on a particular type of technology, namely on-the-horizon innovations such as predictive analytics algorithms that process patients' symptoms in real-time and determine how to best allocate care. His analysis was separated into four phases of development that such technology is likely to encounter.

Phase one focussed on the collection of the large data sets that would be needed to develop the algorithms. Here, Professor Cohen argued that consent should not be required from people whose data is collected if the data is sufficiently de-identified, but that they should be given notice about how their data will be used. In addition, to address concerns about public trust and lack of equitable representation, he proposed that community engagement boards be established to advise modellers as they acquire data.

Phase two addressed how organisations will create and validate their models. Professor Cohen emphasised that if this technology is to function in practice, patients must trust it. This in turn means that they should be involved in its development and governance. With respect to validation, he suggested that changes to the current evaluation of medical technology would be required, as the current system of validation is not built to evaluate complex, predictive analytics. In addition, he suggested that there should be at least some transparency into the variables used in the model, even if some aspects are trade secrets.

Phase three addressed testing of the algorithm-based models in real-world settings, which he suggested raised issues of consent, liability, and choice architecture. Consent in this context refers to whether patients should have an opportunity to accept (or refuse) their data being used in this testing. Professor Cohen suggested that it was unclear whether consent should be required, but patients should certainly be provided with notice. On liability, he discussed ways in which the use of predictive analytics might expose doctors to new forms of legal risk, and suggested that liability regimes might need to be modified to ensure desirable innovation. As to choice architecture, that is the way in which default rules and other set-ups of the environment in which choice takes places can alter what choices get made., he explored questions about who should bear the risks of false positives versus false negative predictions.

Phase four concerned wide-scale deployment. Professor Cohen proposed that this activity raised controversies concerning: equitable access, imperfect implementation; and the role of the physician. On equitable access, he discussed ways of ensuring that benefits flow to all the populations of patients who contribute to the development of these technologies. He then turned to problems of imperfect implementation, including issues of liability that will arise when the technology is implemented without sufficient consideration of patients' preferences or without appropriate "checks and balances". Finally, on the role of physicians, he discussed how they will need to be provided with significant new training, as well as how the technology might "unseat" them from their current role, creating difficult questions about how and when they override the technology.

Mr Terry Kaan, "Genetic Information and the Family: The Future of the Duty of Disclosure & the Limits of Confidentiality"

Mr Kaan's presentation focused on three possible ways in which advances in precision medicine might potentially expand tort liability in the future for physicians and researchers who hold genetic data.

First, for physicians who hold their patients' genetic data, he suggested that pursuant to the recent UK case, *Montgomery v Lanarkshire Health Board*, they might have an on-going duty to re-evaluate

the data. This case requires that physicians have a "dialogue" with their patients regarding medical risks, which he suggested could be expanded to require that physicians also keep their patients informed of newly identifiable risks. If so, he suggested that professional standards might need to be developed to establish how regularly patients' genomic data is re-evaluated or subject to regular periodic automated analysis as a matter of due diligence, in much the same way that data custodians in other fields have an obligation to periodically scan their databases for viruses and other security threats as and when new threats become known.

Second, for researchers that retain participants' genetic information, Mr Kaan suggested that as the processing and analysis of genomic data becomes more routine, the line between "research" data and "clinical" data may become quite blurred. In turn, this could mean that any duties that physicians owe would also be owed by researchers. He noted, however, that tort claims brought against researchers based on such duties might fail due to problems of causation and remoteness. Thus, liability might not arise without broader changes to tort law.

Third, for both researchers and physicians, Mr Kaan explored whether a duty to warn third parties (e.g., relatives) of genetic abnormalities might arise. He explained that two legal hurdles must be overcome if this duty is to operate in practice. First, researchers and physicians must be able to make the disclosure notwithstanding duties of confidentiality owed to their patients/research participants. Here, Mr Kaan noted that this might be possible as it is established in English common law that doctor-patient confidentiality is not absolute; doctors can disclose their patients' records in certain circumstances in the public interest. Second, to establish that a researcher or physician has a *duty* (not merely legal permission) to warn a third party will require an expansion of the law of negligence. Mr Kaan acknowledged that in a recent UK first-instance decision, *ABC v St George's Healthcare Trust*, the judge rejected such an expansion. He also acknowledged that, in the UK at least, both the first and second hurdles in establishing a duty to warn a person about genetic abnormality are complicated by other considerations (e.g., the right to a private life). However, he suggested that additional cases will follow with more refined legal arguments and, therefore, a duty to warn third parties may yet arise.

Mr Tracey Evans Chan, "The Regulatory Challenges of Innovative Therapeutics/Diagnostics in Medical in Precision Medicine"

Mr Chan explored the regulatory challenges of ensuring the safety and efficacy of "innovative treatments" that are central to precision medicine. For the purposes of this presentation, he defined "innovative treatments" to be "uncontrolled, often single, interventions intended to manage or solve particular clinical problems". This definition included uses of drugs and diagnostics that have not yet received any marketing authorisation, as well as off-label uses of those that have.

Mr Chan began his talk by briefly addressing the wide variety of legislative and regulatory measures that are relevant to the marketing and import of therapeutics and diagnostics in Singapore. He then focused on the Singapore Medical Council's Ethical Code and Guidelines and case law interpreting them, which establish that innovative treatments are only permissible when their primary purpose is to benefit the patient (as opposed to research) and a doctor can demonstrate that the treatment is in the best interests of the patient. As he explained, these circumstances generally require that there is some scientific rationale for the treatment and a rational explanation of why the patient needs the treatment, but there is also significant uncertainty in this practice.

Mr Chan then turned to the implications of these cases for precision medicine. He suggested that because precision medicine treatments will often be targeted to small groups of people, developing statistically significant data on therapeutic use is likely to be difficult as this usually requires large clinical trial cohorts of people who suffer from the disease. Thus, some new treatments might not be able to receive regulatory authorisation and therefore be deemed innovative treatments. Assuming this is the case, he said physicians will be put in a difficult position when faced with using these treatments because they will need to determine whether they can satisfy the vague innovative treatment requirements. Mr Chan concluded by suggesting that greater clarity is needed on when

innovative treatments can be used in Singapore to enable physicians to use precision medicines without concern they might be contravening professional codes.

Mr Colm McGrath, "Liability for Failure to Disclose and the Challenge of Precision Medicine"

Mr McGrath's presentation examined the law surrounding securing patient consent for medical treatment and risk disclosure in the UK. This topic has taken on new dimensions recently following the 2015 UK Supreme Court decision, *Montgomery v Lanarkshire Health Board*. In this case the Court held that physicians have a duty to take reasonable care to ensure that patients are aware of any material risks involved in any recommended treatment as well as any reasonable alternative treatments – and that this normally requires a dialogue between physicians and patients. Elaborating on the meaning of "material risks", the Court stated that these are risks that would likely have significance for a reasonable patient, as well as all risks that a doctor knows, or should know, would likely have significance for his or her particular patient. Furthermore, the Court held that the significance of a risk is based on a broad range of factors and that risks without high-statistical magnitude can be significant.

Mr McGrath suggested that *Montgomery* can be interpreted both narrowly and broadly, and that these interpretations have markedly different consequences for how often precision medicine treatments might be disclosed to patients. Under a narrow interpretation, he argued that physicians would still be central in deciding what treatment options are disclosed to patients and that, in light of the fact that many precision medicine treatments are likely to be experimental and innovative, physicians may not be required to disclose them. However, he also suggested that this approach potentially undermines the rationale in *Montgomery*, amongst other things, it does not necessarily entail physicians having a "dialogue" with patients. Thus, this narrow interpretation might not be accepted by judges. By comparison, if given a broad interpretation, he argued it might be difficult for physicians to determine the limits of what treatment options need to be disclosed and therefore might result in them erring on the side of disclosure and flooding patients with information. In the context of genomic medicine, this might result in physicians disclosing any relevant genome-tailored treatments regardless of other factors, including whether a health care provider has decided not to provide said treatments at all.

Mr McGrath concluded by questioning whether we should let the judiciary continue to decide what information must be disclosed to patients, or whether we should regulate in this area with the goal of providing more clarity on what needs to be disclosed.

Professor Darrell Rowbottom, "On Probabilities in Personalised Medicine: "The Problem of Untestable Treatments"

Professor Rowbottom presented on two epistemic, probabilistic problems that medical practitioners and regulatory bodies face when evaluating the efficacy and safety of personalised medicines. The first problem is applicable to all uses of probabilities derived from collectives and is known as the "reference class problem". An example of this problem in the medical context is that physicians recommending therapies must decide what class to use when calculating the probability that a treatment will work on an individual patient. The second problem, which is connected to the first and arises in the context of evaluating precision medicines, is that a treatment might not have a viable reference class to evaluate efficacy: if a treatment is targeted to an individual or a sufficiently small group of patients, it will be impossible to test it (testing it on others will by definition be of no predictive value), and thus impossible to say whether it is likely to work.

Professor Rowbottom argued that these problems were not insurmountable, and proposed that they might be solved by changing the target of the analysis: instead of focusing on the frequency at which a given *treatment* is effective, one could focus on the frequency at which a given *treatment selection process* generates treatments that are effective. Furthermore, this could be measured using standard techniques, such as random sampling and double blind trials, thereby providing physicians with

epistemically sound reasons for recommending personalised treatments that cannot be individually tested prior to use.

In closing, he noted one major challenge to his solution, which is that a treatment selection process will typically be much more complex than a treatment administration process, and thus have more potential sources of error. Accordingly, he suggested that for regulatory bodies to evaluate treatment selection processes, significant changes in the current regulatory processes would likely be required.

B. Challenges in the Development of Precision Medicine

1. Challenges at the Level of Foundational Research

Professor Bartha Knoppers, "Activating the Right of Citizens to Benefit from Scientific Advances"

Professor Knoppers presented on what she titled the "right to benefit from science" and how this right could be "activated" to convince governments to facilitate data sharing.

She began by locating the origins of this right in article 27(1) of the Universal Declaration of Human Rights, which states: "Everyone has the right freely to ... share in scientific advancement and its benefits". While establishing the origins of this right and its ratification in international law, Professor Knoppers also referenced several other international instruments but noted that these instruments do not delineate how the right is to operate. To specify the content of the right, she looked to UNESCO's Venice Statement on The Right to Enjoy the Benefits of Scientific Progress and its Applications, which highlights the importance of: access to the benefits of science and its applications; opportunities to contribute to scientific enterprise; freedom of research; the participation of individuals and communities in decision-making; and the development and diffusion of science and technology.

The cornerstone of Professor Knoppers' argument was that data-sharing would have greater force if grounded in this concrete human right with legal authority in 195 countries. For this reason she recommended further legal research on the meaning, judiciability and impact of the "right of citizens to benefit from scientific advances". In discussing the comparative benefits of a human rights approach, she highlighted that: it is engrained in international law, positioning it to handle the translational and harmonisation issues; it includes political and legal dimensions, reaching beyond the moral appeals of bioethics; and it reaches past only negative duties to positive ones that found legal actionability. Further, in the health context, she suggested that a human-rights approach will help shift the focus from individuals to a collective responsibility, thereby emphasising the importance of sharing data.

Professor Kazuto Kato, "Genomic Medicine in Japan: Recent Developments in National Policy, and New Ethical and Legal Challenges"

Professor Kato's talk focused on three topics central to the practise of genomic medicine in Japan that are changing or likely to change in the near future.

The first topic concerned government policy for medical research. New legislation has established an Agency for Medical Research and Development, which is designed to operate as a centralised control tower for medical R&D in Japan, with power over funding, regulation, and knowledge and data sharing (power that was previously distributed across four departments). Professor Kato suggested that this agency will likely make Japan's research system more efficient, but that it might also create some problems. In particular, he questioned whether there would be sufficient funding for connecting clinicians, researchers and patients across the nation, and how advanced guidelines for ELSI issues would be developed.

The second topic was the return of results from genomic analyses. He noted that many of the large-scale genomic sequencing projects in Japan are struggling to decide if and when they should return incidental findings. This decision is complicated by a series of government guidelines that do not offer

clear guidance on the issue, and that in many instances differ from the American College of Medical Genetics' guidance, which is generally seen as a useful benchmark. Professor Kato stated that the challenge now is to develop clear national guidelines.

The third topic was the protection of personal information. Here, the Japanese government is working on new legislation, which is likely to be similar in operation to the new EU Data Protection Regulation. Professor Kato highlighted that genomic data will likely be classified as sensitive personal information, even if it is anonymised, which may create problems for sharing and analysing it. However, he noted that debates are on-going.

Dr Yann Joly, "Controlled Data Access for Precision Medicine: An Acceptable Trade-off?"

Dr Joly's presentation explored the comparative advantages and disadvantages of three ways of structuring access to medical data for research purposes.

The first was "controlled access", in which researchers must satisfy a stringent set of criteria to obtain access, and which thereby provides strong protection for the data. For example, researchers are usually required to: confirm their professional status; provide a summary of their research project; explain how the data will be used; and agree to certain restrictions (e.g., no re-identification of research participants). Permission to access the data is then determined by a "data access committee". Dr Joly explained that due to these hurdles, data protected by controlled access regimes is infrequently accessed, and therefore the value of the data is undermined. In light of this problem, he raised the question of whether a better model was available.

The second model he discussed was "open consent", which operates by asking research participants to consent to unrestricted use of their data, and data-holding organisations *not* promising to protect participants' anonymity or privacy. While this model has been adopted by organisations such as the Personal Genome Project and Encyclopaedia of DNA Elements Consortium, Dr Joly noted that it is not a viable solution in many European and Asian countries, where such an approach may not meet data protection laws.

The third option he explored was "registered access", in which researchers apply for access to shared data by providing details of their identity and agreeing to conditions of use. Access is determined by an automated process or a non-expert individual without reference to an expert or a committee. Compared to controlled access, researchers are not required to provide a summary of their research project, nor explain how data will be used. Dr Joly explained that these features mean it imposes a lower barrier to access than controlled access. However, he also noted that it still requires significant expertise to set it up, especially with regards to the conditions of use; and that it is still effectively in a pilot phase as it has only been adopted by a limited number of projects. He suggested that this approach is unlikely to replace controlled access in the near future, but that it will play an increasingly important role — especially as there are technology advances on the horizon that will improve the usability and efficiency of the model's registration process.

Ms Alison Hall, "Harm, Discretion or Duty: the Changing Nature of the Return of Individualized Results in Genomics Research"

Ms Hall's presentation focused on the questions of whether and when researchers should return individual results from genetics research to research participants.

She began by addressing some confusion caused by the terminology that is often used in discussing this issue. In particular, she suggested that the term "returning" is a misdescription and should be replaced with "informing," as results will not be returned to research participants unaccompanied by any explanation.

Ms Hall then discussed how ideas about "returning" results have changed over time. She noted that while it was once widely thought that individualised results should not be returned because they might

be harmful to participants, it is now often suggested that researchers should return findings that are well characterised and clinically actionable. She also speculated that this might eventually become a duty, especially as the difference between clinical and research genomics blurs. However, she also cited empirical research on this issue that has found that current practices vary considerably and that there is no consensus in the ethical literature.

Ms Hall concluded by exploring what a duty to inform participants of research results might entail, including some of the challenges that researchers would face (e.g., whether the duty might also be owed to relatives). Ultimately, she did not describe a specific vision for the duty, but rather argued that proactive policy development at the global level is needed to address it.

Dr Janice Tsang, "Precision Medicine for Cancer Care — Prime Time versus Provocation Threat?"

Dr Tsang presented on some of the challenges facing the implementation of precision medicine in the treatment of cancer, where recent advances have revealed previously unrecognised complexities. For example, we now know that breast cancer can have a great diversity of genomic and molecular profiles, that this diversity can be present within a single person and can change over time, and that intra-tumour heterogeneity can even be observed within a single cell.

Dr Tsang explained that this diversity has led to a situation where there is no shortage of potential biomarkers, but these biomarkers are a long way from clinical implementation because of the great number of difficulties along their translational pathway. Echoing some earlier presentations, she described difficulties at the beginning of this pathway, for example, with reproducibility and accuracy. Then, moving along the translational pathway, she described difficulties with proving clinical validity due to the small sample-size nature of precision medicine and the fact that statistical evidence usually requires large clinical trial cohorts.

In light of the above issues, Dr Tsang commented that although precision medicine offers significant promise, the challenges it faces are considerable and in a world of finite resources, intelligent decisions will have to be made about which biomarkers are selected for translation and how to resource the translational research. In this vein, Dr Tsang described how "basket" and "umbrella" trials will become more common, and how a number of studies are starting to use these techniques. She also commented though that these challenges mean that precision medicine treatments are going to be expensive, and that the medical system is going to have to face questions about who to treat, especially when it comes to reimbursement and end of life care.

2. Challenges at the Level of Translation

Professor Donald Chalmers, "Has the Biobank Bubble Burst? A Translational Challenge"

Professor Chalmers' presentation explored challenges that biobanks have faced in translating their resources into public health improvements that contribute to, what has been called, the "virtuous cycle" (i.e., a cycle in which research leads to better health care, which in turn leads to more productive citizens and greater national wealth that can then be invested in research and restarts the cycle). Professor Chalmers divided the challenges he discussed into three "waves".

The first wave concerned challenges biobanks have encountered whilst becoming established. Professor Chalmers explained that while a large number of biobanks have been initiated around the world, many have had difficulty in becoming entrenched in the scientific and wider community and utilised in research. The reasons for this include problems of public trust (as illustrated by the history of the Icelandic Health Sector Database), as well as other governance challenges, such as the problem of having their materials used in research that was not initially foreseen and thus unconsented.

The second wave concerned collaboration and harmonisation. While scientists and biobank administrators built biobanks for research he explained that they did not initially realise the extent to

which data sharing would be essential and that the realisation of this fact has led to a proliferation of governance and management guidance documents and collaborative networks, but that the diversity in biobank governance structures has made sharing difficult.

The third wave concerned sustainability. Professor Chalmers suggested that biobanks were often initiated with insufficient thought about their long-term economic viability and that this problem has been complicated by the fact that they have been more expensive than originally thought and have produced fewer financially-valuable outputs than expected. He noted that biobanks might try to address this problem by adopting a self-sustaining business model (e.g., access fees or affiliations with pharmaceutical companies), but he suggested that these models might cause a loss of public trust or under-utilisation. Thus, he conjectured that perhaps biobanks should not be self-sustaining, but rather be valued as fundamental pieces of public infrastructure that are crucial for the next generation of discoveries. He closed by advocating that an ideal resolution to this third wave, which is currently quite topical, would require policy makers to articulate a vision for biobanks including a re-evaluation of the virtuous cycle.

Dr Kathy Liddell & Dr John Liddicoat, "The Changing IP Landscape for Precision Medicine"

Presenting this talk on behalf of both authors, Dr Liddell described two intellectual property (IP) issues that her team had recently received funding to research.

The first issue concerns the changing legal landscape for precision medicine patents. In particular, her team is interested in understanding how the commercial translation of genomic biomarkers has been affected by recent US IP cases — especially *Association of Molecular Pathology v Myriad*, in which the US Supreme Court held that isolated genomic DNA is not patentable subject matter. Dr Liddell is interested in understanding how these cases have influenced patenting practices in Europe and the US, including what IP rights, if any, companies are now relying on. In due course, the team also intends to investigate the effects of *Prometheus v Mayo Laboratories*, another patent law decision of the US Supreme Court. First though the team was waiting to hear whether the Supreme Court would grant leave to appeal in *Sequenom v Ariosa Diagnostics*, a case raising related issues.

The second issue concerns the IP and access policies used by biobanks. Dr Liddell and her team are studying these because they frame how IP rights derived from biobank material may be used by academic and commercial organisations. Illustrating the diversity in these policies, Dr Liddell showed an excerpt from Genomics England's 100,000 Genomes Project's policy and compared it with an excerpt from the UK Biobank's policy. Relevantly, the 100,000 Genomes Project policy states that Genomics England "owns" any new IP generated by academic users of their resources, while UK Biobank's policy states that UK Biobank, as a general rule, makes no claim to IP developed by researchers. She explained that this issue has received very little attention yet is crucial because the ability of third parties to use IP they derive from biobank material is likely to affect commercial companies' willingness to conduct translational genomic research. Whilst biobanks have been studied in considerable depth (as noted by other Conference presentations), the primary focus has been issues of consent, data protection and interoperability. Intellectual property policies are much less studied but will become increasingly significant as increasing numbers of academic and commercial organisations look to access resources held by biobanks.

Compared with the pharmaceutical industry, the diagnostics industry is relatively understudied. However, it is crucial to the realisation of personalised medicine. It is hoped that the results from this research will go some way towards remedying the research gap.

Dr Chih-Hsing Ho, "From Bench to Bedside: Secondary Use of Health Data for Precision Medicine"

Dr Ho's talk concentrated on the secondary use of health data for translational research purposes in Taiwan. By "secondary use of health data", Dr Ho was referring to combining data from one resource, such as a biobank, with data from another resource, such as medical records. This practice is important

for the development of new personalised medicine products because no single data source is likely to hold all of the information needed for a given application, such as the translation of a biomarker into a diagnostic test.

Dr Ho explained that this topic is quite live in Taiwan because it has a number of large resources that could be combined (e.g., a biobank with hundreds of thousands of samples and an electronic health records system that covers 99% of Taiwan's 23 million people) and if data from these sources could be readily aggregated, larger steps could be taken towards developing new personalised medicines.

However, as Dr Ho explained, current regulatory constraints on combining data is hindering important research. In particular, she described how the current operation of data protection legislation requires that researchers who want to combine data sets must anonymise or de-identify the data, which removes much of the data's 'power'. While Dr Ho agreed that research participants' privacy and autonomy should be protected, she suggested that more tailored legislation could be written to balance the competing interests. She concluded by outlining an innovative model for holding, sharing and combining health data that incorporates a Wikipedia-like framework and emphasises self-governance (by both researchers and research participants).

Dr Stuart Hogarth, "Lost on Planet Biomarker? Standards, Pathways, Carrots and Sticks for Diagnostic Development in the Post-Genomic Era"

Dr Hogarth situated current debates about the development and regulation of molecular diagnostics — which are a key to unlocking precision medicine — in a broader social and historical context.

He began by providing some background on the development of diagnostics. As of 2011 there were an estimated 150,000 peer-reviewed articles documenting thousands of biomarkers, yet fewer than 100 biomarkers have been validated for routine clinical use. Dr Hogarth suggested that there were two primary reasons for this dearth of new routine diagnostics: the development and marketing of diagnostics is self-regulated (generally speaking) and no industry standards have been produced on what evidence is needed for their clinical acceptance. In turn, these circumstances have led to: regulators not knowing what to accept as evidence of clinical validity and utility; manufacturers not knowing what studies to conduct to prove clinical validity and utility; and medical and laboratory professionals not receiving standardised, authoritative information about what biomarkers they should incorporate into routine clinical use. In addition, these circumstances have allowed various companies to offer diagnostics that have little or no clinical validity and that may actually lead to patient harm in some circumstances.

In light of these problems with self-regulation, it is often suggested that this area should instead be regulated by law. However, by drawing lessons from the history of regulating therapeutics, Dr Hogarth argued that it is a false dichotomy to view legislation and self-regulation as *alternatives*. Instead, he suggested that both should be used because they can help reinforce each other and lead to more efficient enforcement of standards.

Dr Hogarth closed his talk by discussing the pending changes to the regulation of molecular diagnostics in Europe and the US. He suggested that the pending EU Regulation on *in vitro* diagnostics was not perfect, but that its proposed evaluation of clinical validity was a step in the right direction; and that the US Federal Drug Administration's move to regulate laboratory developed tests more consistently was a step towards higher quality tests. He suggested these changes may "herald a new era" of diagnostic regulation, but cautioned that additional policy and legislative work would be required to provide clearer pathways for organisations to create clinically useful biomarkers.

Professor Timo Minssen, "Lost in Translation? Opportunities & Risks of Increased Research & Clinical Trials Data Transparency"

Professor Minssen's presentation focused on issues surrounding recent European and, to a lesser extent, US initiatives to increase transparency in clinical trials data submitted to regulatory authorities. With respect to the European initiatives, he discussed two pending changes: the new EU Clinical Trials Regulation and the European Medicines Agency's (EMA) new transparency policy. Professor Minssen drew attention to the fact that the new regulation will, by default, require sponsors of clinical trials to make their data public unless a deferral of publishing the data can be justified. Similarly, the EMA policy requires that if a trial sponsor submits redacted data, this redaction must be justified in each instance.

Professor Minssen then turned to a discussion of costs and benefits of these changes. He suggested that the increased availability of clinical trials data will likely improve: generic drug development; regulators' review of candidate drugs; and the surveillance of drug safety and effectiveness (among other benefits). However, he also identified some disadvantages that this increased transparency may trigger, including: privacy risks for clinical-trial participants; vexatious litigation because competitors will be able to litigate over whether a sponsor has disclosed all relevant material; increased drug development costs because more effort will be put into the production and review of clinical trials data; and diminished IP protection because data that could have otherwise remained a trade secret will need to be disclosed. Professor Minssen highlighted these last two disadvantages as particularly relevant to precision medicine. He stated that the financial viability of many precision medicine treatments is already precarious due to small market demographics and translational challenges, and that additional costs incurred during development or a loss of market exclusivity (due to diminished IP protection) might make some precision medicine projects unviable.

Overall, he concluded that these movements towards transparency are a step in the right direction, but we must be conscious of unwanted side-effects and monitor how these new initiatives operate in practise.

II. Key Challenges

The legal and ethical challenges identified by the conference presentations and roundtable discussions can be grouped into six broad areas: (1) defining the legal duties of physicians and researchers; (2) developing and implementing standards for diagnostics and treatments; (3) creating a coherent framework for data use and sharing; (4) supporting the translation of biomarkers into diagnostics; (5) incentivizing changes in medical practice and patient behaviour; and (6) balancing regulatory harmonization.

1. Defining the Legal Duties of Physicians and Researchers

Advances in precision medicine may justify an expansion in the duties of physicians and researchers. To determine the proper scope and limits of any changes in liability, a wide range of challenging questions must be addressed:

First, as precision medicine advances and predictive skills improve, should physicians have a duty to re-analyse their patients' medical files to check whether new knowledge indicates a new medical issue (e.g., diagnosis, treatment, etc.)? The imposition of such a duty would make most sense with respect to a patient's genomic data, as the process of re-analysis might be largely automated in the near future, and professional bodies might even create guidance documents on this issue (e.g., regarding the interval at which genomic data should be re-analysed and the variants of known significance that should be included in the re-analysis). It is important to recognise, however, that automation will not reduce the full burden of returning results to patients—especially if a patient has moved, or if genetic

counselling is needed. It is also unclear whether a principled line could be drawn at genomic data, or whether an expanded duty would also apply to other information collected in patients' electronic medical records. Although genomic data might currently be more accurate than an electronic medical record (which will have many human-introduced errors) and more amenable to automated analysis (due to limits on natural-language processing), such factors might not be able to justify a bright-line difference in the long term.

Second, if a duty to re-analyse data is established in the clinical context, should it also apply in the research context? This possibility appears to be most likely for hybrids of the research and clinical contexts (e.g., Genomics England's 100,000 Genomes Project), and less likely for pure research programmes due to constraints of expertise and cost. However, if research programmes do not return results, there may be significant non-monetary costs (such as loss of public trust), as various studies have found that research participants generally believe that clinically important results will be returned to them despite being told otherwise.

Third, should physicians or researchers who are collecting genomic data ever have a duty to go beyond the initial reason for collecting the data and look for "secondary" findings? The imposition of such a duty seems most likely if whole genome sequencing (WGS) becomes routine and completely or largely automated. There is disagreement, however, about whether WGS will ever become routine: although we may appear to be on a path towards routine WGS for various reasons (including its falling cost), it is possible that we will instead see the rise of more efficient and specific point-of-care genetic tests.

Fourth, are there cases in which clinicians should return secondary findings even if a patient has explicitly stated that he or she does not want to know about them? Several factors are relevant to this issue, including the clinician's relationship with the patient, the feasibility of doing something about the finding, and the nature of prior discussions with the patient. When the patient has a variant of unknown significance (VUS) in a primary gene of interest, this question becomes more complicated. Here it might seem that the clinician should inform the patient if the significance of that variant is later discovered, but there is debate about whether a VUS in an area of primary interest should actually be considered a "secondary finding".

Fifth, should advances in diagnostic testing, combined with developments in the law of informed consent, alter liability for over-diagnosis (e.g., when a false diagnosis leads to unnecessary surgery)? Historically, findings of liability in cases of over-diagnosis have been rare in common law jurisdictions. Potential reasons for this include: (a) the view that over-diagnosis is preferable to under-diagnosis, assuming a perfect system is not possible; and (b) the difficulties of obtaining a judgment against a doctor for over-diagnosis, even if a breach of duty is established, due to the challenges of proving that over-diagnosis caused personal injury or loss. However, liability in this area may increase under the patient-centred standard for informed consent recently adopted by the UK Supreme Court.

Sixth, should physicians be liable for harms that result from their reliance on predictive algorithms? If a predictive algorithm offers bad advice and a physician fails to exercise his or her professional judgment when acting on that advice, then the physician could be held liable. Equally, a health care system that procures and implements the algorithm or the company that produces it could be held vicariously liable. Liability in these three instances would depend on a number of factors, including the training offered to physicians, the source of the error in the model, and how conspicuous the error is. Policy makers will therefore need to be cognizant of how this risk of liability impacts the development and implementation of important predictive analytics.

Seventh, should physicians have a duty to inform a patient's relatives of certain genetic test outcomes? In some instances, this might help a relative avoid harm (e.g., by taking preventative steps, such as mastectomy, or by changing major life decisions in light of a risk). In other instances, the risk information might be material for some people but not others, and it may not necessarily help a person avoid harm any more than general public health advice (as is the case with a genetic risk of lung cancer that indicates that one should not smoke). It is also unclear whether and to what extent genetic risk information is reliable. Some associations between genetic information and illness have

turned out, after further research, to be incorrect or only correct in certain circumstances (e.g., when combined with certain diet, age, environmental exposures, other genetic risk factors, etc.).

2. Developing and Implementing Standards for Diagnostics and Treatments

The development and implementation of standards for precision medicine gives rise to at least three different types of challenges.

First, there are challenges that arise from insufficient standards. For example, the lack of clear standards for the analytical and clinical validity of molecular diagnostics has resulted in the market entry of diagnostics that are poorly-validated, as well as in insufficient incentives and unclear pathways for the development of well-validated diagnostics. Further, while it might seem that problems of insufficient standards could be easily solved by implementing standards, doing so may not always be straight-forward in the context of precision medicine for reasons identified next.

Second, there are challenges in setting standards. For example, predictive analytics have an important role to play in precision medicine, but it might not be cost-effective to set fixed standards for validating the algorithms that underpin them. One solution to this problem would be to create a sliding standard that is set according to the risk of misclassification, such that less rigorous proof would be needed for predictions that carry a lower risk of harm. However, this solution has its own challenges, as the relaxed standards would need to be carefully monitored to ensure that prognostics of little value are not authorised.

Third, there are challenges in proving that precision treatments meet given standards. For example, a treatment that is highly personalised may lack a reference population for testing. One solution to this would be to adopt alternative standards for precision medicine, such as validating treatment selection processes, rather than treatments themselves: instead of focusing on the frequency at which a given treatment is effective, one could focus on the frequency at which a given treatment selection process generates treatments that are effective. However, a treatment selection process will typically be much more complex than a treatment administration process, and thus have more potential sources of error.

3. Creating a Coherent Framework for Data Use and Sharing

A significant obstacle to the development of new drugs and diagnostics is the law governing the use, sharing, and linking of health-related data for research. While it is generally agreed that this area of law is in need of reform, there is significant disagreement about whether the foundational principle of informed consent governing human subjects research should be interpreted to require consent for research on biospecimens or data that have been anonymised. If the sole purpose of informed consent is to protect participants from physical and mental harm, the answer to this question clear: anonymisation (if successful) eliminates the welfare concern and should therefore eliminate the requirement of consent. However, if informed consent also serves the purpose of protecting autonomy interests, which anonymisation does not protect, the answer is less clear: to decide whether consent should be required post-anonymisation, we must determine whether autonomy interests are only at stake in research on one's person, or whether they should be seen as extending to research on one's tissue and data.

4. Supporting the Translation of Biomarkers into Diagnostics

Translational research in the field of precision medicine also raises a number of challenges, many of which arise from the need to translate rudimentary biomarkers into useful diagnostics and prognostics. Many thousands of biomarkers have been identified as having some sort of correlation with the onset of disease or the efficacy of treatment, and it seems there is substantial financial and

institutional support for this type of research and discovery (perhaps because it is an academic area of research that can seek government research grants). Yet relatively few of these biomarkers have been shown clearly to have clinical utility for individual patients. One reason for this may be that the translational process requires greater involvement of the commercial sector, large trials, and complex research design (e.g., with end points, proxies, etc.). If so, a key question is what sort of support and resources are needed to support more and better translational research and whether the law can assist.

There are at least five ways in which the law might assist that warrant more attention. First, biobanks could be operated more effectively through changes in the legal arrangements that govern them—either through legislation and policy that are specially about "biobanks," or through indirect means such as tax relief, model contracts for accessing and using biobank data, or flexible corporate structures enabling biobanks to be publicly-owned "private" corporations. Second, research and data-sharing could be facilitated by clarifying the principles of consent, exceptions from consent and privacy laws, and the extent of researchers' freedoms and liabilities when they use genetic and health data obtained from biobanks. Third, the development of valuable biomarker-based tests could be incentivised by improving regulatory standards and pathways: for example, by requiring evidence of clinical validity prior to marketing and ensuring that reimbursement reliably reflects clinical value. Fourth, patent law could be developed to offer a proportionate incentive of term-limited market exclusivity for biomarker-based innovations, which might mean expanding the rules on patentability in the US, and curtailing current rules on patentability in Europe. Fifth, clinical trial data protection (for time-limited periods) might be extended to *in vitro* diagnostics when data relevant to market authorisation for a diagnostic is submitted for regulatory approval. This would help address a potential free-rider problem where competitors seek to rely on clinical validity data previously submitted by another company.

5. Incentivizing Changes in Medical Practice and Patient Behaviour

There will be several challenges in incentivising the changes in medical practice and patient behaviour that will be needed to realise the promise of precision medicine.

In the context of medical practice, a key challenge arises from a knowledge gap. Many cheap and routine biochemical tests already exist but are not used by medical practitioners—and this problem may grow with genetic tests, as many doctors have not received sufficient training in genomics, statistics and bioinformatics. Thus, to realise the promise of precision medicine, we will need to ensure doctors are provided with advice on tests from credible bodies, foundational knowledge in new fields, and practical training in the use of new diagnostic technologies (including predictive algorithms).

Providing medical professionals with the training needed to implement advances in precision medicine is not sufficient, however, as implementation will fail without patient trust and involvement. And while precision medicine is often said to be "patient empowering", large segments of society may not feel empowered and might even refuse genomic tests and sequencing. For some patients, this will likely be due to concerns about privacy or genetic discrimination, and it is possible that legal solutions will help overcome these obstacles. For other patients, however, the objection to precision medicine might be rooted in the fact that the genomic stratification of diseases will break apart communities that play an important role in the lives of patients, such as women with breast cancer. Like many issues, this is contested. Even if this fragmentation arises, it might not be permanent, as new communities might arise around the disease and treatment categories of precision medicine.

Patient trust and involvement may also turn on the extent to which patients (and their families) understand certain features underpinning precision medicine. For example, a basic understanding of statistics is necessary to understand the probabilistic components of diagnoses and prognoses. Thus, for patients to make informed decisions about their health, they need to have some understanding of

statistics, and medical professionals conveying this information must be aware of the psychological and framing issues that often alter how statistics are understood by non-experts.

6. Balancing Regulatory Harmonisation

A final challenging question is whether, and if so to what extent, we should be looking for international solutions to challenges in the implementation of precision medicine. It seems that common solutions are possible and desirable for at least some issues, with possible contenders including: ethical guidelines (e.g., guidelines regarding the "return" of results); evaluations of analytical validity, bearing in mind different genetic backgrounds and ethnicities; and the definition of what constitutes as a "genetic test". However, several variables could impact the desirability of uniformity, including the nature of the problem being solved (e.g., whether it is a problem of product safety or product efficacy) and social and political factors.

Further, international solutions are unlikely to work for some core problems, such as how to incentivise the development of diagnostics, or how to design biobanks. For example, the three-phase model used in the authorisation process for therapeutics is a poor fit for the development of diagnostics, but the choice between the several alternative models that have been proposed in the academic and policy literature must be tailored to their specific jurisdictional context. Likewise, in establishing biobanks, a key to success is meeting domestic needs and gaining public trust, which are contextual factors that preclude the existence of a single "best" model.

Finally, although there may be significant convergence in Europe and North America on several key issues, further international harmonisation might not be possible or desirable due to cultural value differences. In order to recognise the extent to which a solution to a given challenge presupposes the values of a culturally-specific approach to bioethics, international networks and channels of communication are essential. It is only in this way that we will be able to strike the right set of trade-offs between heterogeneity and harmonisation in addressing the challenges to realising the promise of precision medicine around the world.