Preparing for Precision Medicine
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In consultation with the Precision Medicine Global Agenda Council, 2011-12
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Case Study

Hiroe is a previously fit and healthy 35-year-old woman from Japan who has had a troublesome, non-productive cough for three weeks. At her family’s insistence, she sees her physician. A chest X-ray reveals a suspicious looking area in the left lung, and a subsequent computed-tomography (CT) scan validates the presence of an advanced lesion which on biopsy is confirmed as non-small cell lung cancer. She has never smoked and has no family history of lung cancer. Can anything be done for her?

Had Hiroe’s diagnosis been established before 2004, her oncologist may have offered her treatment to which only around 10% of patients show a favourable response, with the remainder experiencing only negligible survival benefits and significant unwanted side effects. However, her diagnosis is made in 2012 when her lung biopsy tissue can be analysed for a panel of genetic variants that can reliably predict which patients will respond favourably to treatment.

Hiroe’s tumour is found to be responsive to a specific targeted agent and she decides to go ahead with treatment. The individually tailored anti-cancer therapy that she receives means that she enters a period of disease remission that lasts for over one year, with a mild rash as the only experienced side effect.
Executive Summary

Starting in 2002, the United States National Institutes of Health (NIH) began a process intended to chart a “roadmap” for 21st-century biomedical research, with the intention of identifying key target areas and opportunities for improving the quality of scientific research and stimulating the move towards the now well mooted concept of personalized medicine. A fundamental point to emerge from this process was the requirement to strengthen translational research efforts to ensure the successful migration of laboratory-based discoveries to the patient bedside. In the decade that has passed since this roadmap was conceived, significant advances in biomolecular medicine have led to an explosion of disease-relevant, individual-specific molecular information that has the potential to greatly advance healthcare delivery and draw closer to the goal of personalized patient care.

The scenario provided in the illustrative vignette demonstrates the central idea behind personalized medicine – the combination of established clinico-pathological parameters with emerging molecular profiling approaches to create diagnostic, prognostic and therapeutic solutions that are precisely tailored to each individual patient’s requirements – hence the preferred term: precision medicine. This approach is expected to deliver significant benefits at each step of the patient care continuum.

However, this progress will most likely spawn a new set of challenges; the success of precision medicine will thus depend on establishing effective frameworks for regulating, compiling and manipulating the influx of information that can keep pace with rapid scientific discoveries.

Five fundamental requirements that must be met to ensure the success of the precision medicine initiative have been identified; they demand urgent attention at the national and international levels. The World Economic Forum is firmly committed to ensuring the success of precision medicine efforts and to helping meet these conditions:

- More incentives for innovation
- New disease classification systems that incorporate emerging molecular data
- More streamlined clinical trial regulation frameworks
- Effective data interpretation and clinical decision support (CDS)
- Stimulation of consumer interest and active patient participation

Notwithstanding these conditions, precision medicine calls for collaboration between all major healthcare stakeholders (clinicians, patients, government, industry, academic institutions) on a scale previously unseen. This allied activity must be carefully steered by such international consortia as the World Economic Forum, made up of world-leading figures from each stakeholder group.

This report outlines the challenges facing the precision medicine community and proposes strategies to ensure its continued progress through the complicated initial implementation phases.

Figure 1: Expected Benefits of Precision Medicine Approaches at Different Stages of the Clinical Care Pathway

Source: Author’s compilation
1. More Incentives for Innovation

Precision medicine approaches demand biotechnological innovation. Yet innovation is a gamble both scientifically and financially, and the challenges, costs and risks associated with modern medicinal product development are well established. The pharmaceutical industry is a prime example; ensuring that the right patient receives the right treatment at the right time will undoubtedly lead to significant societal gain. But this advantage also inevitably means that fewer drugs will be administered to fewer patients, a notion that defies the traditional blockbuster-based pharmaceutical business model.

To put this into perspective, a new drug idea is currently estimated to require significant capital (frequently in excess of US$ 100 million) to subject it to Phase II trial evaluation before it has any chance of obtaining a strong return on investment. Such expense, in these times of fiscal uncertainty, has created an environment in which investment in truly innovative ideas is lacking; drug developers currently tend to reposition investments in areas where approval has already been obtained, maximizing the potential for a significant return on investment with often only a modest improvement in therapeutic efficacy. Breaking this mould and stoking pharmaceutical innovation requires an acknowledgement of the risks involved, and the development of appropriate incentives that stimulate “risk-taking” and encourage pharmaceutical companies to gamble and invest in the development of innovative targeted therapies for the precision medicine era. Small and non-profit organizations are even more wary of the potential financial implications of high-risk product development such that legislative incentivization is essential to create an environment where scientific innovation can flourish in the face of perceived risk.

Figure 2: The Implications of Precision Medicine for Pharmaceuticals
Source: Author’s compilation

To prepare for precision medicine, more incentives for innovation are needed. Today’s approach is non-stratified large-volume administration of “blockbuster” pharmacotherapies with maximum return on investment. In the future, stratified delivery of pharmacotherapies to specific target groups requires new investment and pricing models.

Without appropriate financial incentives and reimbursement schemes, innovative pharmaceutical and biotechnology partners may be unwilling to invest in promising areas of precision medicine research due to the perceived high costs and uncertain investment returns. Providing tax credits represents one way to help foster exciting scientific and technological advances and would help small and non-profit organizations that would otherwise struggle to deliver owing to the high financial burden. As things stand, in most cases the costs incurred by developing companies to develop, test, conduct trials on and market products are so steep that a return on investment is rarely realized by smaller developers. Reimbursement schemes, including R&D grants and tax incentives, could encourage innovation and
reduce the financial load often seen as a disincentive. In addition, the perceived risk associated with innovation can be offset by applying more streamlined, “fast-track” drug-approval processes to facilitate swifter adoption of novel treatments – rewarding those who adapt their approaches to drug-development for the good of the precision medicine movement.

Aside from the financial perils, industry collaborators share concerns regarding the issue of data-sharing; the enormous importance historically placed on privacy and security has created an uneasy environment that stifles collaborative efforts. The precision medicine drive calls for more open data-sharing between different sectors, including between for-profit commercial entities and non-profit organizations. A greater challenge still is cooperation and data-sharing between different for-profit organizations, which will undoubtedly be reluctant to work in partnership with competitors. At present significant impediments to transparent industrial partnership of this sort exist, including concerns regarding the loss of intellectual property (IP) rights and the consequences of sharing information at the pre-marketing phase of development for fear of idea-poaching. What is needed is a shift towards a culture of pre-competitive data-sharing, i.e. wide dissemination of upstream research findings, even between historical competitors, at the stage where they have no immediate market potential but are critical to the interests of other groups within the precision medicine community. This shift will take time and must be encouraged through reimbursement schemes for those organizations that participate in carefully regulated data-sharing initiatives, overseen by IP guardians within the precision medicine marketplace.

Alternative business models to meet the objectives outlined above have been proposed to allow organizations to lower traditional industrial firewalls and simultaneously “collaborate and compete”. Such models would involve centrally-regulated open collaboration between industry and academia with a mutually beneficial exchange of ideas, data and IP while also ensuring appropriate statutes are in place to allow the protection of private IP where deemed reasonable. Examples include online collaborative platforms such as Collaborative Drug Discovery (CDD Vault™) that are now available and offer academic institutions, research foundations and industrial organizations user-friendly and effective means of intelligent data management, between-party experimental data mining and secure collaboration. This concept is illustrated in Figure 3, which shows collaboration between academia and industrial partners with IP guardianship by precision medicine consortia to ensure appropriate IP sharing between groups while preserving private IP where necessary.

Figure 3: Collaborative Model with Open Sharing of Data
Source: Author’s compilation
2. New Disease Classification
Systems that Incorporate Emerging Molecular Data

Human genome sequencing and the development of high-throughput “-omics” technologies have greatly enhanced our understanding of human disease. It is now acknowledged that the shift from health to disease involves innumerable cellular processes spanning across all compartments of biological activity, from the genome to the metabolome. This deeper understanding of disease based on molecular biology brings with it an unavoidable need for new models of disease classification that incorporate the emerging knowledge. To that end, the World Health Organization’s century-old International Classification of Diseases (ICD) must now undergo modernization to take into account the expanding molecular data on health and disease.

The concept of classifying disease based on molecular characteristics is by no means new; breast cancer perhaps represents the best example of a condition where molecular information has been widely and successfully applied to disease classification and patient care pathways. For example, it has consistently been demonstrated that oestrogen receptor (ER)-negative and ER-positive breast cancers are fundamentally different disease processes from a biological standpoint and that each of these in turn can be further divided into subgroups with distinct prognoses based on molecular profiles. While this to some extent exemplifies the precision medicine philosophy, it also highlights flaws with the current paradigm — namely that molecular disease classification has traditionally suffered from being too subspecialty centred and too biologically isolated, with little integration of molecular data between research groups working on processes in adjacent up- and downstream biological compartments.

The precision medicine initiative requires a more thorough overhaul of the disease classification process as a whole — not focused on just one particular disease state, but encompassing all accurate and disease-relevant molecular information as and when it is confirmed and validated. This approach should take a more networked “systems biology” view of disease, encompassing not only genomic information but also data from the proteome, transcriptome and metabolome. This in turn will generate a more holistic view of disease and may also help to identify latent biological commonality between different disease processes. To be truly effective, data should be presented in an open-access manner and should be introduced into the learning curriculum of future generations of health practitioners, to ensure that the medical workforce possesses the required fluency in the language of molecular medicine.

In recognition of this pressing requirement, a US National Academies working group recently evaluated the potential for developing a New Taxonomy of Disease as part of the wider precision medicine movement. This report made a series of recommendations realistically expected to play out on a timescale of decades rather than years. The Committee report emphasizes the need for a revised disease classification model based on intrinsic biology as well as traditional “signs and symptoms”. Equally importantly, the report highlights the need for developing an openly available data source or “Knowledge Network” that is dynamic and able to continuously incorporate newly emerging knowledge. What this calls for is an initial period of creative bottom-up research activity, organized through pilot projects of increasing scope and scale, designed to assess the feasibility of integrating molecular parameters with conventional clinico-pathological indices. The results of these studies should in turn lead to the development of best practice guidelines on which to base the new taxonomy. The working group concedes that given the ambitious scale of this plan, challenges will undoubtedly arise with respect to the gathering and integration of the data with which to populate the new taxonomic system. However, as with any initiative of this magnitude and complexity, what is needed is the right level of coordination. The report points out that this coordination must be balanced — too rigid a framework is likely to stifle much-needed innovation, while too relaxed an approach will make it impossible to integrate the data from so many different sources and domains. Effective central leadership is critical to ensure that this balance is achieved. The World Economic Forum is well placed to take on the task of promoting this change.

Figure 4A illustrates current disease classification, which provides insufficient integration of clinical data with disease-relevant biomolecular data, a deficiency that is hampered further by largely disconnected activity between different biomedical research domains. Figure 4B, on the other hand, shows the effective reclassification of disease for the precision medicine era with the far greater integration of data and allied activity between biomedical research communities.
Figure 4A: Current Disease Classification Systems

Source: Author’s compilation

Figure 4B: Effective Precision Medicine Disease Reclassification

Source: Author’s compilation
3. More Streamlined Clinical Trial Regulation Frameworks

Precision medicine is expected to herald rapid acceleration in the identification and development of next-generation pharmacotherapies. Currently, medical research organizations are unanimously calling for regulatory bodies to review the regulation of clinical trials, citing excessively long approval processes as a significant impediment to the effective translation of laboratory bench-side discoveries. Recent figures from Cancer Research UK (CR-UK) identified a 65% increase in time taken to gain approval for studies and a 75% increase in administrative costs from 2003 to 2007. In addition, no evidence suggests that additional bureaucratic stringency with drug approval has led to any tangible improvements in patient safety. These figures are echoed in a recent article published in The New England Journal of Medicine by Aaron Kesselheim of the Harvard University Department of Health Policy and Management. In it, the author points out that from 2005 to 2009, a 39% decrease was observed in approvals by the US Food and Drug Administration (FDA) for new drugs and biologics compared with previous years (1995-1999). That this downturn in endorsement is occurring at a time when investment in public and privately funded biomedical research is greater than ever represents both a paradox and a worrying reality. In the article, Kesselheim goes on to argue that the root cause of this decline is the inherent uncertainty associated with the medical product approval process as a whole, with inconsistency, ambiguity and even discordance between the different frameworks used to determine whether a product or drug can be deemed “safe and effective”. Ultimately, such reports have led to the growing conviction that FDA approval processes have become far too “risk adverse” and that they represent a critical bottleneck holding up innovative drug development.

In the wake of these reports, widespread calls appeal for more streamlined approval processes that are deemed to be critical for the success of the precision medicine model. These approval processes could be made more efficient by employing more proportionate approaches to regulatory requirements for clinical trials, with consideration given to previous experience with the agent being investigated and/or the study population. In addition, precision medicine by its very nature implies a departure from traditional clinical trial frameworks, with Phase III trials focusing on a more select group of patients; this should facilitate procedural streamlining and also enhance clinical and economic effectiveness.

Figure 5: Declining Trends in FDA Pharmacotherapy Approval from 1996-2007 (average number of new drugs and biologics approved by the FDA)

Source: Author’s compilation

The UK Government recently announced a raft of new measures aimed at reducing the time from drug development to clinical application. This move is likely to stimulate similar proposals elsewhere worldwide. Ultimately, the right balance of regulation must be found: frameworks must be robust enough to safeguard the interests and well-being of patients, while not being so robust as to stifle progress in the critical early phases of the precision medicine initiative.

The FDA and other regulatory bodies must recognize that while ensuring a drug causes no harm is vitally important, it is equally important to ensure that patients are not deprived of innovative, potentially disease-altering medications because of delays in the approval procedure.
4. Effective Data Interpretation and Clinical Decision Support

Precision medicine requires the handling of multiparametric data and at least basic level proficiency in -omics data interpretation, placing unique demands on medical professionals who at present may be ill-equipped to deal with the complexity and volume of the expected new information. Addressing these challenges requires effective clinical decision support (CDS) tools to guide decision-making, as well as new educational models for the future that take these requirements into account. Currently, genetic testing is estimated to be available for some 2,000 clinical conditions, with the number of available diagnostic tests increasing exponentially. At the time of writing, the United States and other countries are investing in multibillion-dollar projects to implement effective electronic health records (EHR). These systems are expected to store comprehensive, individual-specific data that are essential in the movement towards precision medicine. However, in a recent US-based survey, physicians reported that EHR has poor systems for online test ordering and provides only limited decision-support in terms of indications for genetic testing, the interpretation of test results and the potential impact of results on patients and their family members. CDS tools have the potential to address these limitations and enable precision medicine approaches to healthcare by providing clinicians and their patients with information and preferences specific to the individual, intelligently filtered at the point of care. They should provide the clinician with options for test ordering including sensitivity, specificity and positive predictive values for the test in question. In addition they aim to aid clinical workflow by providing decision-making algorithms to facilitate diagnostic, prognostic and therapeutic decisions based on test results. As with most of the challenges facing precision medicine, the successful development and integration of CDS systems into clinical practice require multistakeholder collaboration and extensive policy intervention. Informatics, software engineering, industry, academic and government agencies need to work together on developing an action plan for implementing these tools, and an immediate priority is reaching agreement on a minimum data set to store in future EHR systems. In their most basic form, they must include demographic data, medical history, medication data, family history, social history and -omics data on which CDS algorithms can be modelled.
5. Stimulation of Consumer Interest and Active Patient Participation

The uncertainty facing the biomedical community is matched by that facing the consumer; the dynamic of the patient–health provider axis is going through unprecedented change, and the successful implementation of precision medicine approaches hinges on whether and how patients are able to adapt to the changes envisaged. Detailed, open-access molecular information raises ethical questions regarding data handling and privacy issues which will need strict regulation. The UK Government recently announced proposals to consult the public on how patient data could be used more openly in biomedical research, including the use of a new secure Clinical Practice Research Datalink. These measures will undoubtedly help the precision medicine cause, although successful public engagement requires a cultural shift with the patient viewed not as a “study subject” but rather as a central participatory figure in the precision medicine community, with the ability to shape, develop and disseminate research given the right opportunities and access.

Over the past decade, the number of patients turning to Web-based resources and social-media platforms for health information seeking and sharing has surged. However, despite this trend, there has so far been little engagement and consultation with patients regarding emerging electronic health records, although this area is now gaining attention. Recent reports in the literature indicate that patient groups are in favour of the idea of shared custodianship over EHR with their healthcare providers; previous studies have found that this can lead to the improved coordination of care, improved efficiency, improved patient satisfaction and reduced costs. The difficulty is how to regulate access to health records and how to create securely accessible and patient-friendly systems. A number of EHR systems are already in use, although it is thought that, since these systems were not originally designed with patient access in mind, updating them to meet this requirement could be extremely costly. A further problem relates to the fact that no standard system is used at present and so data will be fragmented across different platforms, making effective patient utility difficult. The privacy of patient data is a further concern with wide accessibility of EHR; leaked patient-specific health data could compromise patients on a variety of levels and could also lead to an increase in litigation and complaints against health practitioners for failing to safeguard patient privacy. These concerns demand that urgent attention be paid to the security architecture of future EHR systems, including data-protection features such as encryption and digital signatures. Ultimately, transparent consultation with patient groups is critical to ensure consumer backing is obtained as permission is sought to store and interrogate increasingly detailed data sets in precision medicine research initiatives.

Aside from the issues of trust and security, the wider public must effectively be shown that precision medicine can live up to its promise. A recent study sought to evaluate patient readiness for the adoption of personalized medicine approaches and views on it relative to conventional models of diagnosis and treatment. Encouragingly, the report found that 68% of patients were in favour of the idea of pharmacogenetic-based testing as a way of improving drug prescribing and minimizing adverse treatment-related events. Concerns voiced in this study related to accuracy and the validity of tests and access to test results.

Figure 6: Ethical Considerations in the Precision Medicine Era
Source: Author’s compilation

Precision medicine approaches provoke serious ethical questions:

- Should invasive procedures be performed on healthy individuals who are at risk?
- Can biological data be used without exacerbating inequality?
- What rights to privacy and security of data should individuals have?
- Who can use genetic and biological information?
- Who “owns” genetic and biological information?
- Many others...

Notable success stories of course exist, but similarly there have been well publicized failures in attempts at “personalization”. Take the example of the CYP450 gene family; the detection of certain polymorphisms among CYP450 genes has been suggested as a possible means of determining the type and dose of serotonin-reuptake inhibitor (SSRI) to treat patients with depression. The Centers for Disease Control stance on this subject is that there is no evidence linking testing for CYP450 to clinical outcomes in adults treated with SSRIs. However, that has not stopped a growing number of businesses from offering CYP450 testing-services. Well publicized scorn regarding direct-to-consumer diagnostic tests of this kind, with limited if any clinical utility, do little to interest the public in precision medicine, and rogue activity of this sort is harmful to the wider cause. A pragmatic attitude must be adopted: precision and clever science will not always lead to clinical effectiveness, but safeguards must be put in place regarding the marketing and distribution of ineffectual products.
Conclusion

Precision medicine can ensure that patients get the right treatment at the right dose and at the right time with minimum ill consequence and maximum efficacy. It will change how medicine is practised and taught, how healthcare is delivered and, unquestionably, how it is financed. It will change the way research and development is financed and the way it is regulated. Furthermore, it will deeply affect public trust and the nature of the relationship between patient and clinician, and it will require close collaboration between all major healthcare stakeholders on a scale previously unseen. Undoubtedly, significant challenges lie ahead, although none is insurmountable. In this report, five key areas that require urgent attention from the precision medicine community to move forward have been identified. It is likely that as progress in this area continues, longer-term challenges will become apparent. A structured, consortia-led approach to these impediments should ensure that they are successfully resolved. That said, expectations must be realistic: precision medicine will not happen automatically and it will not happen overnight. A transition period should be expected, steering through the forecasts of such international consortia as the World Economic Forum made up of leading figures from academia, government and the healthcare industry, from which proposals can be drawn up for public consultation. Multistakeholder adaptation as outlined in Table 1 is critical to ongoing precision medicine efforts.23

### Table 1: Healthcare Stakeholders and Their Roles in Ensuring the Success of Precision Medicine

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<th>Stakeholder</th>
<th>Recommended action</th>
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| Government/Policy Makers         | ● Generation of transparent privacy laws  
                               ● Identification of socio-economic priority areas likely to benefit most through precision medicine strategies  
                               ● Public consultation regarding ‘opt in/opt out’ strategies for research participation |
| Research Institutes              | ● Development of effective clinical decision support tools for integration into electronic health records  
                               ● Setting up and conducting appropriate pilot studies for data collection in government targeted precision medicine areas |
| Biomedical Sciences Community    | ● Changes to undergraduate training to develop improved understanding of molecular mechanisms involved in disease  
                               ● Development and contribution to an evolving new system of disease classification incorporating emerging molecular information  
                               ● Introduction of a more transparent, participatory role for patients considered for recruitment to clinical trials |
| Pharmaceutical Industry         | ● Development of efficacious diagnostic tests with/without tandem therapeutic agents for management of conditions identified at government level as major socio-economic burdens |
| Consumer Groups                  | ● Increasing participation in health and well-being initiatives  
                               ● Use of novel means of providing data for research purposes, including social networks and mobile phone applications |
| Regulatory Bodies                | ● Ensuring that regulatory frameworks are in place to safeguard patient safety, whilst ensuring that scientific progress is not hampered |

Source: Mirnezami and Nicholson.
Table 1: Healthcare Stakeholders and Their Roles in Ensuring the Success of Precision Medicine

14 Mayor, S. EU Must Reform Clinical Trial Regulation, Warn Medical Research Bodies. In BMJ, 2011, 343:d6215.
The World Economic Forum is an independent international organization committed to improving the state of the world by engaging business, political, academic and other leaders of society to shape global, regional and industry agendas.

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