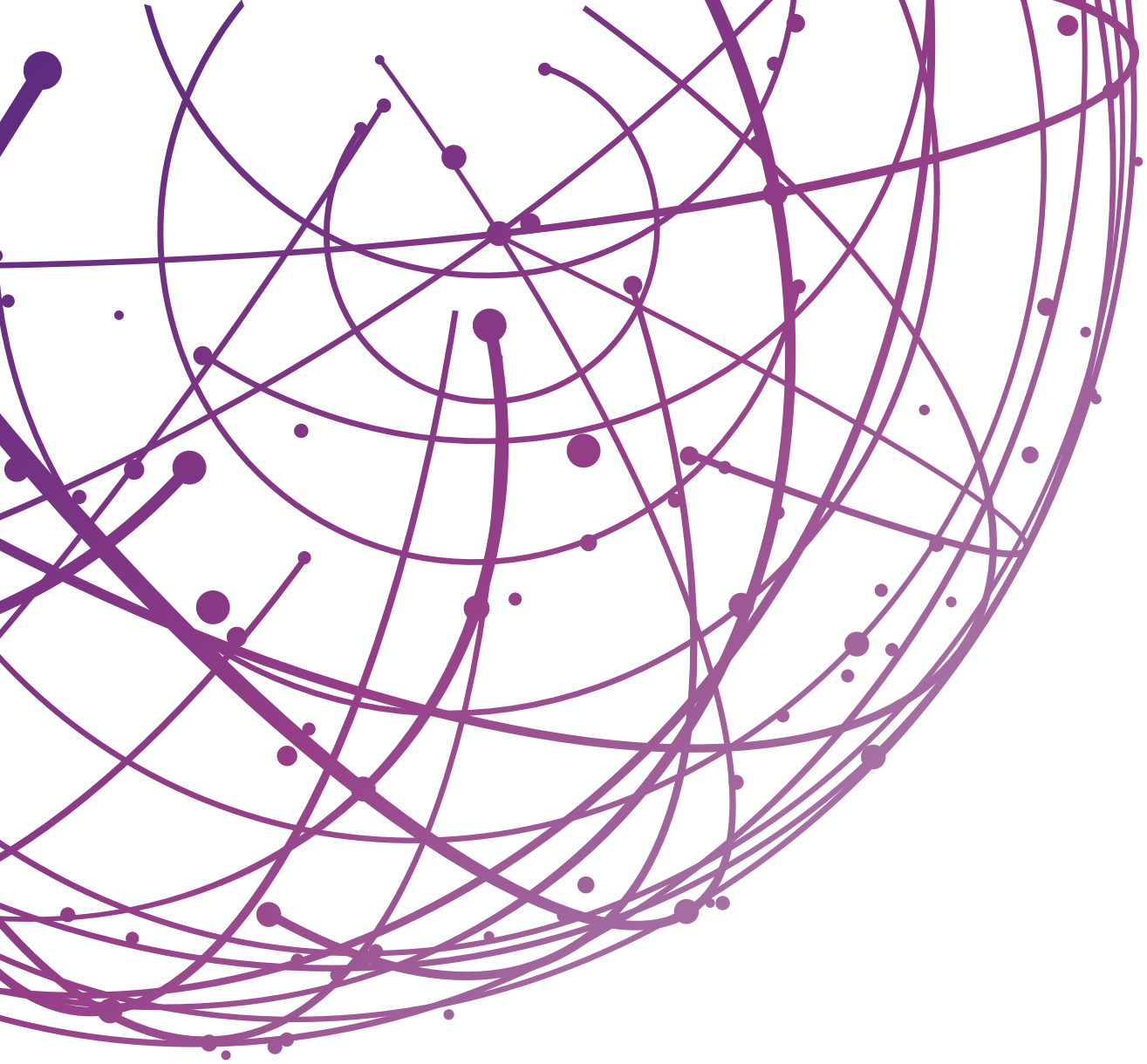

PRECISION MEDICINE
A GLOBAL ACTION PLAN FOR IMPACT

Report of the WISH Precision Medicine Forum 2016

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FOREWORD

Thanks to years of scientific advances and breakthroughs in how we understand the influence of human genetics and environmental factors on health, we can now deliver healthcare in a distinctly patient-centered way.

Precision medicine (PM), also known as personalized medicine, uses this individual information, alongside highly specific clinical information about the composition of diseases, to tailor prevention and therapies. The ability to deliver PM is growing at a rapid pace. In 2003, the international Human Genome Project announced the first successful sequencing of a human genome – the entire genetic code of a human. Thirteen years later, hundreds of genome sequencing projects are active across the world. It is possible to understand humans' genetic code – deoxyribonucleic acid (DNA) – and we can link that genetic code to a host of environmental factors to understand a person's predisposition to diseases in the future. The influx of information and rapidly advancing technologies has paved the way for what could be one of the most revolutionary transformations in healthcare.

The promise of PM is so great, it is almost daunting. It seems futuristic – a departure from traditional medicine that could be difficult to embrace. While it is a distinctly data-driven science, PM is, in many ways, built on trust. First, securing investment in this type of healthcare requires trust that expensive new technologies will yield cost savings in the long term. Second, applying PM in clinical practice requires trust between the public, scientific researchers and clinicians that the sharing of personal information will facilitate better care and outcomes.

This report, based on input from world leaders in PM, explains PM's promise and the challenges that must be tackled to achieve success. It details the actions and collaborations necessary to realize PM's full potential and strengthens the case for integrating PM in healthcare systems worldwide. The report sets out how PM represents the next frontier of healthcare delivery, and argues that PM holds too much scope for patient and public benefit for us not to do all we can to fill in the remaining gaps to its full integration.

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EXECUTIVE SUMMARY

Since the turn of the century, global achievements in scientific research have enabled us to realize a new era of healthcare delivery and treatment. Diseases are becoming better understood, even at their most detailed level, which has allowed scientists to develop new drugs, therapies and preventative techniques to combat problems in very specific ways. A new form of healthcare delivery, one that is determined by a patient's genetic and personal characteristics, has become possible.

Precision Medicine (PM) is defined as: "the tailoring of medical treatment to the individual characteristics of each patient… to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment… [allowing] preventative or therapeutic interventions [to] be concentrated on those who will benefit, sparing expense and side effects for those who will not".[1]

As this definition suggests, the power of PM lies in its opportunity to guide healthcare decisions toward the most effective prevention of disease or treatment for a given patient, improving care quality while reducing unnecessary diagnostic testing and therapies. When applied at the population level, PM holds immense promise for public health, particularly in disease prevention and risk assessment.[2]

Despite recent breakthroughs and PM's growing momentum, significant challenges and barriers remain to its broad implementation and integration in medical practice globally. For PM's potential to be fully realized, policymakers will need to address these critical challenges. With the input of international PM experts, the World Innovation Summit for Health (WISH) Precision Medicine Forum explores the complexity of these challenges, but also presents examples of successful projects that have overcome the barriers to integrate PM. Our report emphasizes the need for stakeholder groups across sectors and countries to collaborate and create an environment that is conducive to PM. We also identify the challenges in four key action areas that need to be addressed to fully enable PM:

- Patient and public engagement
- Evidence generation
- Implementation
- Data ownership, privacy and sharing

This report establishes a policy case for PM and an action plan that can be used by policymakers worldwide. We recommend strategic directions for developing a policy agenda that seeks to better integrate PM into medical practice, working toward the ultimate goals of improving health and achieving quality, cost-effective care delivery (see Table 1).

Global collaboration and co-ordination is essential, which is why our final recommendation is to create an international network or organization to help fulfill a unified vision for the application and integration of PM into medical frameworks worldwide.

Table 1: Key action areas and policy recommendations

Key action areas	Policy recommendations
Patient and public engagement	**1.** Public education programs should be developed at early educational stages explaining PM and related concepts, including data sharing. **2.** Governments should build understanding and trust for PM by increasing the availability of programs that target underserved populations. **3.** To improve health literacy, governments and funding agencies should support research to determine participants' preferences, values and general knowledge about PM research and clinical care, and identify barriers to effective public engagement.
Evidence generation	**4.** A flexible framework is needed to balance the use of randomized controlled clinical trials (RCTs), large volumes of data and control group observations of PM. **5.** An evidence framework is needed that includes different thresholds for initial clinical use of PM, a final approval standard and a requirement for ongoing collection of data about PM's effectiveness. **6.** Final regulatory and funding approval could be made contingent on the inclusion of an economic impact analysis.
Implementation	**7.** A centralized global resource for PM implementation should be developed, including information technology (IT) for optimized decision support and other analytical tools. **8.** Standards for structured data, or common data elements, must be developed for recording information in electronic health records (EHRs). **9.** To facilitate PM's implementation and integration into clinical practice, greater investment should be made in translational health research (research aimed at conversion of laboratory and clinical discoveries into innovations in healthcare), particularly in the 'implementation science and diffusion' and 'outcomes and public health impact' phases.
Data ownership, privacy and sharing	**10.** To help improve and facilitate the informed consent process, governments should develop an ethical framework that: a) addresses the risks to, and concerns of, patients and the general public; b) provides information on what privacy protection is in place; and c) provides information on how data sharing promotes the public good. **11.** There must be greater investment in the informed consent process, including making it globally standardized and easier for patients and researchers to implement. **12.** Alongside regulation, financial incentives could also be effective in promoting data standardization and sharing. For example, regulations could make payment contingent on data submission. **13.** Health systems in developed countries must establish ways to create or enhance PM infrastructure in resource-limited health systems.
International and cross-sector collaboration	**14.** Achieving a co-ordinated, global, collaborative effort will require the creation of an international network or organization consisting of representatives from participating member states.

INTRODUCTION

Cameron's story, circa 2010

Neonatal monogenic diabetes is a rare form of diabetes, which was – until recently – an unknown condition, mistakenly diagnosed as type 1 diabetes. My son, Cameron was originally diagnosed with type 1 diabetes when he was 5 months old. Caring for Cameron was overwhelming at times. All else became secondary – jobs (I quit mine), marriage, friendships, eating, showering, sleeping – all of these and more had to take a back seat. I began to think of my son as a patient rather than my child.

When Cameron was 2 years old, a doctor ordered a genetic test to check for a mutation in Cameron's KCNJ11 gene. It took 11 weeks for the results to come back. During this time I read an article about Lilly, a little girl who suffered from an unusual form of diabetes caused by a genetic mutation rather than an autoimmune disorder, as is the case in type 1 diabetes. After Lilly's new diagnosis, she was able to transition from insulin therapy to oral medication. I could only imagine the joy she and her family were feeling. Like Lilly, Cameron would later be diagnosed with monogenic diabetes, a genetic variation in a specific gene.

Our lives have changed dramatically – no more shots, no more worry, no more carb counting, no more waking in the middle of the night in a panic about his blood sugar. Cameron is now insulin-free. (Now the turnaround time for the results of a genetic test for monogenic diabetes is seven to 14 days.)[3]

Over the course of the last century, most medical conditions were diagnosed from the basic presentation of patient symptoms, such as 'cough' or 'it hurts here'. Such symptoms were often common to a range of individual diseases. This inevitably led to imprecise diagnoses (as in Cameron's case), and use of treatments that were neither effective nor safe. Most therapies are developed based on the 'average effect' of a drug in a population of patients, ignoring the fact that only 30–70 percent of individual patients might respond positively to a given treatment.[4]

In recent decades, scientific progress and insight has evolved to transform our knowledge of biology, disease and medicine. From the discovery of the structure of DNA in 1953, to the completion of the Human Genome Project in 2003, biology and life sciences research has increasingly given us a far clearer understanding of the molecular and cellular bases of many of the most common infectious and non-communicable diseases from around the globe.[5, 6] For instance, we now know that most cancers, even when occurring in the same location in the body (for example, lung, breast, colon, prostate), are in fact a collection of many different types of cancer cells, each one characterized by different mutations within a tumor's DNA.[7] This level of knowledge and precision now allows us to provide patients with diagnoses based on the primary, molecular-level, causes.

In chronic diseases such as diabetes, heart disease and depression, information obtained from analyzing a patient's DNA may also guide us to prevention and treatment options that have been specifically developed for those molecular characteristics, promising more positive patient responses. This vast growth in the knowledge of human biology and disease, linked further with personal lifestyle and clinical data, now offers us an unprecedented opportunity to positively and substantially enhance patient outcomes via the medical model known as precision medicine – or PM.

Defining precision medicine

In 2011, the United States (US) National Research Council defined PM as: the tailoring of medical treatment to the individual characteristics of each patient… to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment… [allowing] preventative or therapeutic interventions [to] be concentrated on those who will benefit, sparing expense and side effects for those who will not.[8]

This definition encompasses PM's potential for prevention and early intervention by identifying at-risk individuals and designing healthcare delivery around their needs. (See **WISH 2016 Healthy Populations report.**)

See WISH 2016 Healthy Populations report

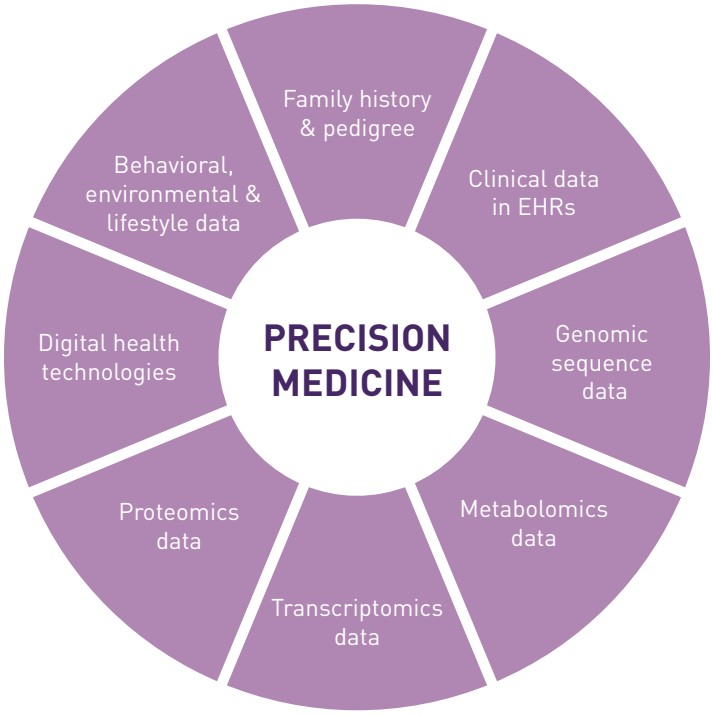
Thanks to improvements in our understanding of disease mechanisms and gene function, information from patients' DNA can now also be used to provide **diagnostic testing**, inform therapeutic strategies and design preventative interventions tailored to the individual.[9] DNA analysis has also led to expansion of **pharmacogenomics**, through which drugs are prescribed based on information from a patient's **genome**, which tells clinicians how a patient will respond to a particular treatment.

Advancing techniques for precision medicine

In healthcare, the basic principle underlying PM is not new; person-specific information has long been used to optimize care. For example, procedures like blood transfusions have relied on blood type information to ensure the effectiveness and safety of the treatment for over a century.[10] In fact, there are many types of information like this that can be provided through very simple techniques, starting with simple family histories. New and emerging technologies move beyond patient histories and reveal more sophisticated details about an individual's genes. This information is typically the result of a process called **genome sequencing**. Today it only costs about $1,000 to sequence a genome, compared to nearly $100 million just eight years ago.[11] Declining costs and increasing technological capabilities mean that researchers can more readily conduct sequencing and other PM research techniques which will likely be available clinically for routine patient use in the near future.[12]

While genome sequencing is currently at the forefront of PM efforts, substantial progress has been made in the study of the network of proteins, **ribonucleic acid (RNA)** and metabolites that underpin healthy and diseased tissues (referred to respectively as proteomics, transcriptomics and metabolomics).[13] More recently, it has become clear that PM will extend beyond the content of the patient's own genome and its molecular products to include the microflora content in discrete body sites (known as microbiome). The signature bacterial content in the digestive tract of each individual can vary significantly and there is mounting evidence that this impacts on the health of individuals, their susceptibility to specific diseases and responses to certain drugs.[14]

Figure 1: Differing complexities of PM techniques



Report structure

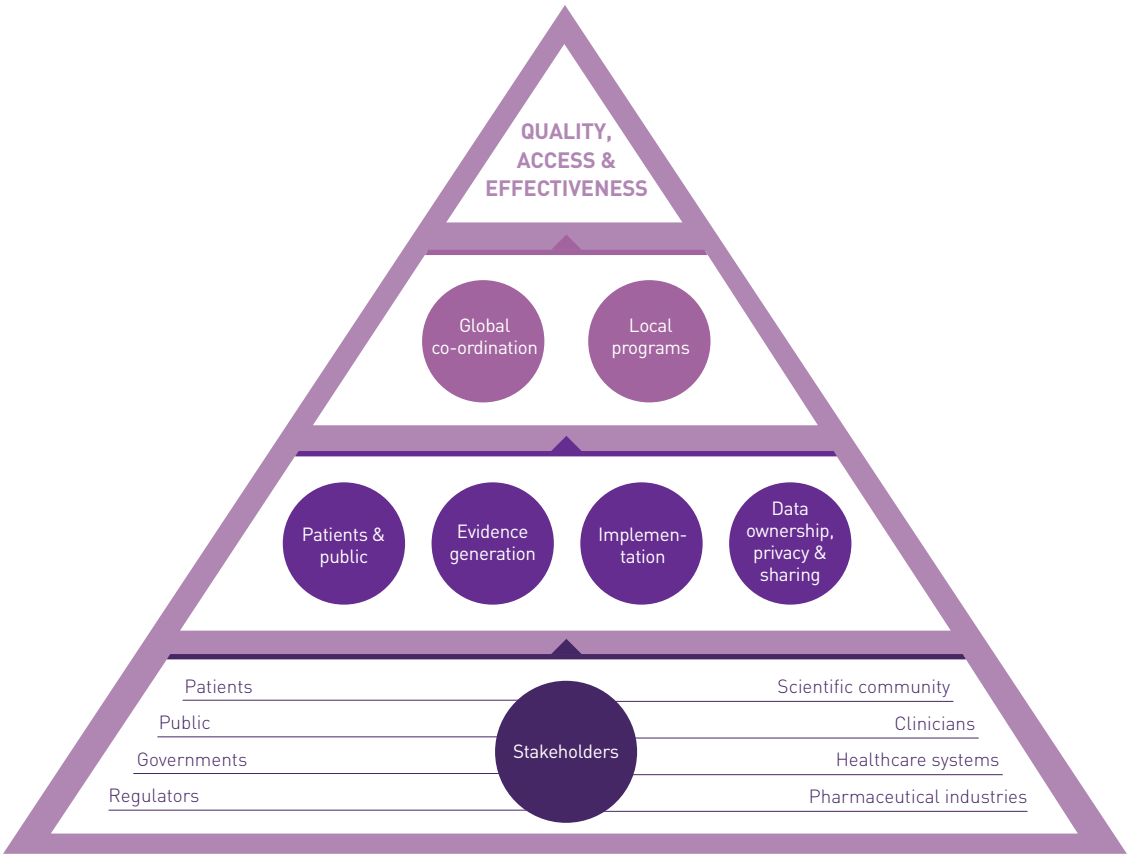
This report outlines the current advancements in PM as well as those on the cusp of success. After outlining PM's immense potential, the report explores the key challenges that restrict its progress and more widespread integration into medical practice.

These challenges drive the report's four major action areas: patient and public engagement; evidence generation; implementation; and data ownership, privacy and sharing – as well as the recommendation for international and cross-sector collaboration. The report investigates each of the areas, identifying the persisting challenges, successful case studies and relevant stakeholders for each. We make recommendations for policymakers worldwide to fill the current gaps and take action in their own health systems, with any necessary cultural adaptations.

PM is not a field reserved for scientists and medical professionals; it is a complex new frontier shared by a range of stakeholders across sectors and nations. All parties need to collaborate to execute our recommended action plan.

The report concludes by reminding policymakers that PM is an emerging field that, given the right support, is ready to transform the nature of healthcare delivery (see Figure 2).

Figure 2: The path to precision medicine



SECTION 1: PRECISION MEDICINE – THE OPPORTUNITY

Bill's story, circa 2020

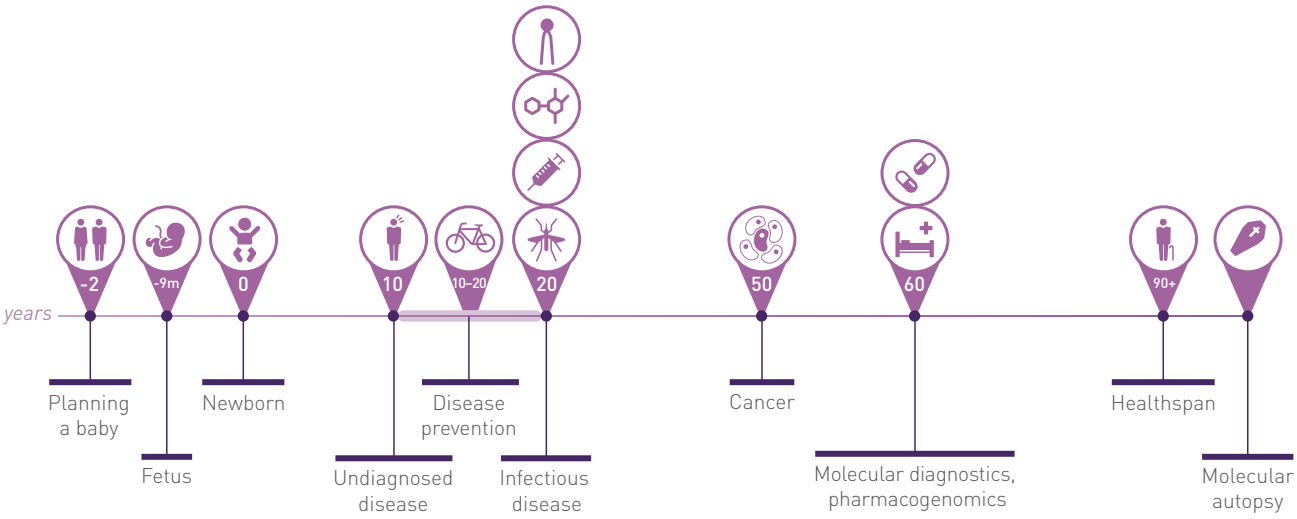
Bill, a 40-year-old overweight man, had his genome sequenced five years ago and was found to have five rare gene variants that increase his risk of heart disease six-fold. He also has three variants that protect him from getting cancer. An electronic family history also suggests he is at tenfold risk of type 2 diabetes. To reduce his risk of heart disease and diabetes, he is given a genomic-guided exercise prescription and uses a smartphone-enabled sensor for physical activity, food intake, sleep and mental wellbeing. Pharmacogenetic variants from his genome are used to optimize his statin therapy to prevent adverse drug effects.

One day, Bill woke up with a fever and sore throat, and placed a drop of saliva on a biosensor attached to his smartphone and used the 'I have a fever' app. His saliva flu score indicated that he was developing an influenza infection and he was prescribed oseltamivir. Public health officials tracking smartphone GPS and sensor data from Bill and other patients conclude that a local viral outbreak is occurring in the community.

Precision medicine today

Today, a number of applications of PM contribute to healthcare at many points in an individual's lifespan (see Figure 3). Genetic screening can be used prior to conception to predict the risk of passing on genetic disorders to offspring. At 8–12 weeks of pregnancy, an expectant mother can have genetic testing to assess chromosomal abnormalities of the fetus, determine gender, and even have whole genome sequencing of the fetus performed. At birth, PM can be used to rapidly diagnose many critical conditions where a time delay might lead to irrevocable damage. Later in life, PM can be applied to diagnose and treat a variety of diseases, most notably in more precisely diagnosing cancer.[15,16]

Figure 3: Examples of precision medicine across the lifetime



Source: Adapted from Topol (2014)[17]

The success of PM in the clinic highlights the prospects of its more widespread use. One recent example is the treatment of a subset of cystic fibrosis (CF) patients with a drug called ivacaftor. While the genetic causes of CF had been widely known and understood for many years, no treatments had been developed targeting the mutated gene product, a chloride channel, that causes the disease. In about 5 percent of patients with a particular mutation in the CF gene, ivacaftor increases the probability that the faulty chloride channel will open and operate effectively.[18] Stratifying diseases in this way can ensure that patients receive the treatment that will be of greatest benefit to them, while potentially reducing the expenditure of essential resources on ineffective testing and treatments.[19,20]

There are many other examples of PM's successes. Table 2 shows a few of the most prominent drugs that have been developed with reference to genetic information.[21]

Table 2: Successful precision medicine interventions

Medical field	Disease	Biomarker	Intervention
Cancer	Chronic myeloid leukemia	BCR-ABL	Imatinib
	Lung cancer	EML4-ALK	Crizotinib
Hematology	Thrombosis	Factor V Leiden	Avoid prothrombotic drugs
Infectious disease	HIV/AIDS	CD4+ T cells, HIV viral load	Highly active antiretroviral therapy
Cardiovascular disease	Coronary artery disease	CYP2C19	Clopidogrel
Pulmonary disease	Cystic fibrosis	G551D	Ivacaftor
Renal disease	Transplant rejection	Urinary gene signature	Antirejection drugs
Hepatology	Hepatitis C	Hepatitis C viral load	Direct-acting antiviral agents
Endocrine disease	Multiple endocrine neoplasia type 2	RET	Prophylactic thyroidectomy
Metabolic disease	Hyperlipidemia	LDL cholesterol	Statins
Neurology	Autoimmune encephalitis	CXCL13	Immunotherapy
Psychiatry	Alcohol use disorder	GRIK1	Topiramate
Pharmacogenomics	Smoking cessation	CYP2A6	Varenicline
Ophthalmology	Leber's congenital amaurosis	RPE65	Gene therapy

Source: Adapted from Jameson and Longo (2015)[22]

PM has also been used to improve patient safety and holds great promise for creating safer care regimes around the world. As a result, costs associated with adverse events could be reduced with strategic use of the technologies that underpin PM. For example, in Thailand and Singapore, where a significant proportion of the population is genetically predisposed to developing Stevens-Johnson syndrome, a severe reaction to certain medications which can be fatal, PM was applied to inform a patient safety campaign. Both governments devised programs to ensure that people with a genetic predisposition for the syndrome were notified and the data appeared in all information sent to pharmacists. These campaigns have reduced the incidence of the syndrome to nearly zero.[23,24]

Precision medicine tomorrow

Examples of new therapies and approaches to patient safety are only the beginning. As Bill's story showed, the promise of PM reaches further into prevention and population health. As technologies advance and more genetic information becomes available, it will be possible to identify individuals who have an increased risk of contracting specific conditions that could be readily prevented. This includes rare diseases, cancers and chronic illnesses such as diabetes and heart disease.[25] As a result, the application of PM in public healthcare – specifically for targeting preventive strategies – could reap enormous benefits for reducing the cost of chronic diseases.[26]

The assembly of large and diverse research cohorts will continue to provide more information about genetics and disease, and validate the genetic markers already found to predict treatment response.[27] The establishment of large research cohorts to define population health management based on genetics has already begun. In 2012, the United Kingdom (UK) Department of Health took the first steps to create such a cohort by establishing Genomics England – known as the 100,000 Genomes Project – which was tasked with sequencing genomes from 100,000 genomes from around 70,000 participants.[28] Similarly, the US Precision Medicine Initiative Cohort Program was established to build a group of at least one million participants.[29]

Despite the focus of these genome sequencing initiatives, PM strategies can be achieved through other types of health risk information. Therefore, PM need not be reserved for high-income countries or healthcare settings; there are affordable steps that all countries can take in the near future to facilitate successful PM implementation. For example, perhaps the most valuable piece of patient health information today is family history, which is an affordable and low-tech tool.[30] The mobile phone is now ubiquitous, with more than seven billion accounts worldwide – nearly one for each person on the planet.[31] Increasingly, smartphones are being used to record person-specific data and deliver personalized messages that encourage people to follow lifestyle recommendations or remind them to take their medicines.[32]

Other cost-effective approaches for PM would include public health campaigns similar to the American Heart Association's 'Get with the Guidelines', which aims to help hospitals adhere to clinical practice guidelines and provide evidence-based care to improve patient outcomes.[33] If evidence-based guidelines for risk assessment, screening for early disease detection, genetic counseling and genetic testing (where recommended) were practiced more uniformly, there is no doubt that the burden of disease would be significantly reduced. These programs can introduce lasting behavior change if designed in a way that makes them intuitive, socially acceptable and timely. (See **WISH 2016 Behavioral Insights report**.)

See WISH 2016 Behavioral Insights report

SECTION 2: REACHING THE PROMISE OF PRECISION MEDICINE – FILLING IN THE GAPS

Jessica's story, 2016

Four-year-old Jessica was recently diagnosed with a rare condition. With her parents, she took part in the 100,000 Genomes Project at Great Ormond Street Hospital. All three donated a small sample of blood and their genomes were sequenced. Bioinformaticians analyzed Jessica's genome sequence to find the cause of her condition.

To begin the analysis, every genome was compared to the reference human genome sequence. Jessica's genome had 6.4 million differences, or variants, from the reference sequence. Using information from scientific studies and research papers, the variants were narrowed down to almost 3,000 that are predicted to cause a change in a gene product (a protein). Out of the variants, one was located in a gene listed as being linked to symptoms similar to Jessica's. The variation means that the protein can't be made from that copy of the gene, so her body does not contain enough of the protein. However, now that Jessica's parents know this information, they can ensure that she follows a special low-carbohydrate diet to provide an alternative energy source for the brain to reduce the number of seizures she might experience.[34]

Figure 4: Jessica's genome story

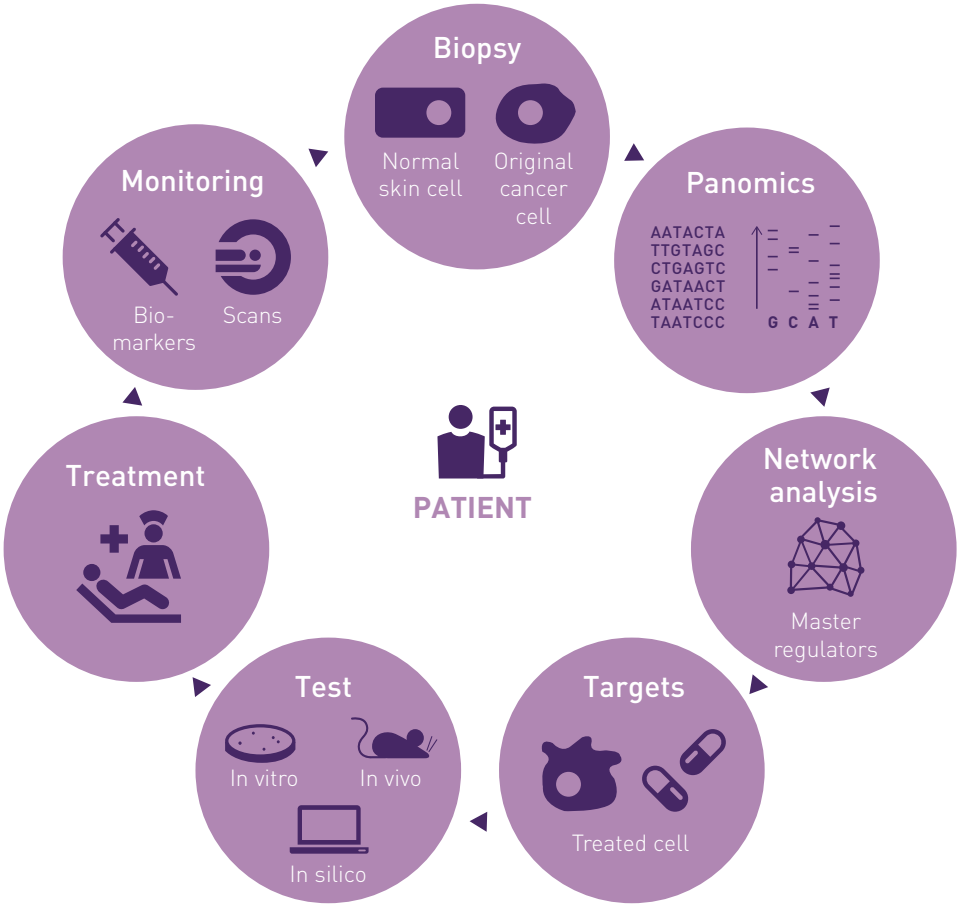
6,414,934	677,556	2,826	67	1
variants in Jessica's genome	are rare	predicted to cause change in a protein	different to her parents	was in a gene listed in PanelApp

Source: Adapted from Genomics England (2016)[35]

PM has the potential to permeate every area of the health service – from diagnostics and delivery to prevention and patient safety. However, achieving a successful level of PM – as illustrated by Jessica's story – that helps all patients, requires careful navigation.

PM innovations will provide targeted treatments and alleviate health burdens. However, the impact will not be the automatic by-product of advanced technologies and continued gene sequencing. Once genetic information is studied, there is a long process before the analysis can provide clinical or preventative guidance. The path from gene sequencing to patient benefit is illustrated in Figure 5. Currently, the field is only beginning to scale-up evaluation and management of genomic data. We first need to develop standards for data and algorithms that can interpret its clinical relevance.

Figure 5: The PM cycle from gene sequencing to treatment



Source: Adapted from Shrager et al. (2014)[36]

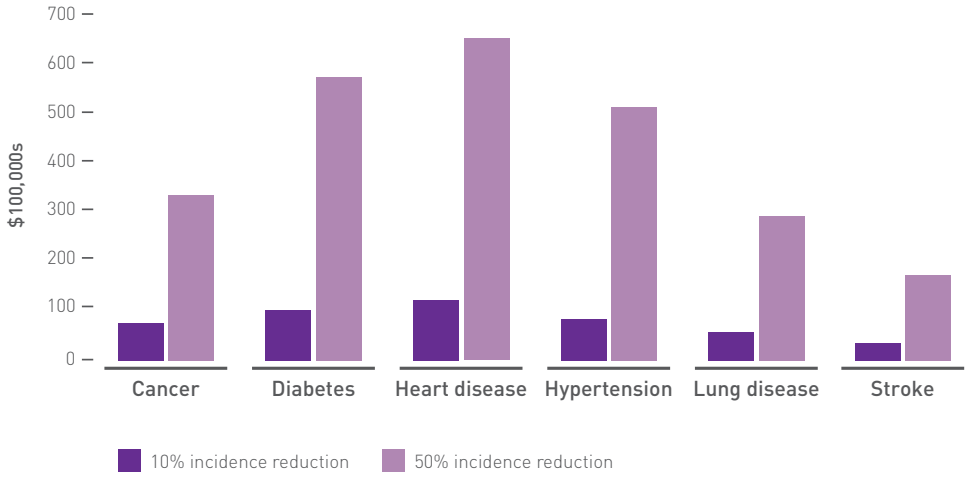
Cross-cutting challenges

The process from genome sequencing to treatment is complicated by the range of ethical implications and cost concerns. While a detailed investigation of these issues is beyond the scope of this report, each will need to be adequately addressed as a prerequisite of PM's success.

Large-scale sharing of personalized data, and conveying its insights, comes with many ethical implications, including: ensuring that patients are in a position to give informed consent to obtain and share their genomic information; that appropriate security procedures to protect patient identity are in place; and that arrangements for commercialization of data and intellectual property are open and equitable.

In addition, the evidence base for the cost-effectiveness of PM is extremely limited. In financially restricted healthcare systems, this can delay implementing PM at scale. Also, without a well-developed implementation plan, it is difficult to anticipate the cost implications of PM. However, a number of encouraging examples are emerging. As mentioned, the governments in Thailand and Singapore have been sufficiently convinced by cost-effectiveness studies to conduct widespread screening for genetic variants associated with Stevens-Johnson syndrome. Another study includes economic modeling applied to the long-term economic impact of PM, indicating the potential for substantial cost savings with preventative PM approaches. Figure 6 shows the value of PM from hypothetical, personalized PM innovations.

Figure 6: Cumulative value of additional quality-adjusted life years generated (2012–2060, valued at US$100,000 each)



Source: Adapted from Dzau et al. (2015)[37]

Because of the evolutionary nature of PM, resolving these concerns will be a continual process. But, moving beyond ethics and cost, this report establishes a policy case for PM. The following sections present a four-pronged action plan that policymakers worldwide can use to successfully integrate PM and adapt it to local budgets and ethical values.

SECTION 3: FOUR KEY ACTION AREAS

As the stories from Cameron, Bill and Jessica demonstrate, PM has tremendous potential to transform our understanding of diagnosis, treatment and prevention of disease. It offers distinct hope to researchers trying to find more effective healthcare solutions, and those at risk of, or currently suffering from, complex illnesses. This unprecedented application of personal information to healthcare represents a distinct step forward for person-centered care; it deserves a policy environment that fosters success. To advance such a policy environment worldwide, this report presents the challenges to be overcome in four key action areas:

- Patient and public engagement
- Evidence generation
- Implementation
- Data ownership, privacy and sharing

Discussion around these areas and the resulting policy recommendations were clarified and agreed through a series of interviews and conversations with WISH Forum members who are global thought leaders for PM. The Forum concurred that for PM to fulfill its promise, these four areas must be addressed through co-ordinated, cross-sector policy development worldwide.

Patient and public engagement: Putting patients at the center of PM

Patients and the public are the heart of PM: it is their genetic and personal information that is necessary to generate evidence; it is their needs that will encourage implementation; and it is their trust that personal data will be used effectively and ethically that will enable data sharing.

However, the relationship between the scientific community, patients and the public has not been fully cultivated. Patients and the public have well-founded concerns about providing and authorizing the sharing of their genetic and personal information. The persistence of these concerns arguably presents the most significant barrier to PM's promise. Progress can be achieved through several channels, including traditional education, enhanced transparency and more funded research, as well as engagement with advocacy organizations.

Case study 1: Health advocacy organization – Genetic Alliance

The Genetic Alliance (GA) is one of the world's leading nonprofit health advocacy organizations. GA engages individuals, families and communities to transform health. The organization creates ways to make it easier for patients to find health service solutions and participate in research. GA's network includes more than 1,200 disease-specific advocacy organizations, as well as thousands of universities, private companies, government agencies and public policy organizations. The network is a dynamic and growing open space for shared resources, creative tools and innovative programs.[38]

To achieve and maintain trust, patients need to be engaged as partners in the process. Their concerns about data privacy and security need to be acknowledged as legitimate. Research proposals that are accompanied by a transparent 'patient engagement plan' that explains the risks and benefits of being involved in PM research would facilitate a better link between participants and the results of emerging research. Due to the often extended timeframe of PM research, these engagement plans should be updated and patients alerted as new information becomes available.

Dynamic consenting options should be considered where, after a fixed number of years, a patient re-consents to participate. This would offer greater transparency and give patients the opportunity to reconsider their participation in light of different circumstances, information, or developments in the field. Also, consent should allow participants to choose what information is shared, with whom and for what purposes, conditional on the participant being re-contacted where necessary. This is exemplified by GA's Platform for Engaging Everyone Responsibly (PEER) registry system, which allows individuals to set their own preferences for privacy and data sharing.[39]

In addition to improved research and consent models, engaging the public more generally will require a mix of traditional and innovative educational approaches.

Recommendation 1

Public education programs should be developed at early educational stages, explaining PM and related concepts, including data sharing.

For example, in an innovative approach in the US, the National Human Genome Research Institute of the National Institutes of Health partnered with the Smithsonian Institution National Museum of Natural History to develop a traveling exhibition, 'Genome: Unlocking Life's Code'.[40] The exhibit commemorates the anniversaries of two major scientific milestones: Watson and Crick's discovery of DNA's double helix in 1953 and the completion of the Human Genome Project in 2003. The exhibit showcases the accomplishments of genomic research and highlights the increasing relevance of genomics in people's lives in an interactive fashion. For example, one display within the exhibit poses ethical questions such as

'should health insurers be permitted to set rates based on genomic information?' and 'are there questions genomic scientists should not be allowed to study?'

Curricula for medical students and practitioners and information for research participants should emphasize the importance of conversations about informed consent and privacy. Resources, such as the Genetics/Genomics Competency Center (G2C2), a web-based repository of competency-based curricular materials for genetics education, can help facilitate the education of healthcare providers.[41]

PM also has the potential to exacerbate existing health disparities, so the evidence supporting PM must include diverse patient populations.[42] Ensuring that these diverse ethnic and cultural groups are kept informed, engaged and represented will be a key challenge to gaining the maximum impact of PM in improving health outcomes.

In resource-limited settings, it would be advantageous to encourage the uptake of cost-effective PM technologies and promote investment in under-researched areas.

Recommendation 2

Governments should build understanding of and trust in PM by increasing the availability of programs that target underserved populations.

The degree to which patients can engage with PM research and clinical care will depend on their ability to understand their own healthcare information, relevant consent documents, and the anticipated results of testing and treatment. Health literacy and numeracy across populations will be essential – for example, to understand statistics and risk information. Information should be provided to patients – perhaps through patient portals connected to PM-enabled EHRs. Materials should be context-sensitive and culturally appropriate, which will mean tailoring materials at national and local community levels.

Recommendation 3

To improve health literacy, governments and funding agencies should support research to determine participants' preferences, values and general knowledge about PM research and clinical care, and identify barriers to effective public engagement.

Evidence generation: Collecting data to support the use of PM

Engaging patients and the public will require a deliberately accessible campaign to ignite interest and engender trust. Mobilizing the scientific community to make progress will mean more technical actions. Tasked with developing enough evidence to convince patients, clinicians and regulators of PM's medical and economic value, the scientific community will need more evidence to demonstrate that PM improves clinical outcomes, increases cost-effectiveness and affordability, and improves the quality of care across populations.

Yet, it is difficult to collect the type of evidence considered sufficient for clinical adoption, regulatory approval and reimbursement of healthcare providers. It is also difficult to generate conclusive evidence because of a lack of consensus on what standards are considered 'enough' or 'appropriate' evidence.[43] Medical research organizations experience excessive bureaucratic challenges and costs in getting trials approved, which has contributed to a drought in new discoveries. According to Cancer Research UK, there was a 65 percent increase in the time taken to gain trial approval and a 75 percent increase in administration costs between 2003 and 2007.[44, 45] The increasing number of disease subclassifications, the diversity of the patient population, and the complexity of the pharmaceutical and diagnostics landscape means that evidence generation is increasingly nuanced and complex.[46]

PM technologies today are delivering an ever-increasing number of tools for clinical decision-making. However, the speed of PM discoveries is outpacing the ability to evaluate their value, particularly through RCTs, which are accepted as the most rigorous means of evaluation. Because of this, policies should incorporate RCTs when they are needed over other types of evidence – such as through registries or observational analysis –for clinical adoption, regulatory approval and reimbursement by payers.

Recommendation 4

A flexible framework is needed to balance the use of RCTs, large volumes of data and control group observational studies of PM.

Standards for initial clinical trials should be differentiated, depending on the target population size and the novelty of the new approach. Standards for final approval could then be based on the real-world results of the initial implementation period.

Recommendation 5

An evidence framework is needed that includes different thresholds for initial clinical use of PM, a final approval standard and a requirement for ongoing collection of data about PM's effectiveness.

The US Centers for Disease Control and Prevention have made progress in this area, with a tiered classification system for PM evidence generation (see Case study 2).

Case study 2: US Centers for Disease Control and Prevention (CDC) tiers for genetic testing

The CDC conducts horizon scanning (a systematic research method to find and follow novel technologies appearing in the literature) to identify and track the progress of genomic tests as they move from research into clinical and public health practice.

In 2012, the CDC Office of Public Health Genomics developed a tiered system for classifying horizon scanning results for genomic testing and family health history applications based on scientific evidence and evidence-based recommendations supporting their use:

- Tier 1 applications are supported by combined evidence for implementation in practice.
- Tier 2 applications may inform decision-making based on existing evidence. However, combined evidence is insufficient to support routine implementation in practice.
- Tier 3 applications are not ready for routine implementation in practice based on the combined evidence (or a lack of relevant evidence), resulting in a recommendation against proceeding. However, these applications might be candidates for population or clinical research.[47]

The tiered model of evidence generation and approval depends on gathering data after implementation of a medication or treatment. Collecting evidence in this way is similar to 'adaptive licensing', where the population of patients with access to a new medicine widens progressively: initially the drug is restricted to a specific patient subgroup and then, as more data on safety and efficacy becomes available, its use can be extended to a broader patient population.[48] Such conditional approval of drugs linked to further data collection is gaining interest in some health systems. For instance, the UK Government recently launched the independent Accelerated Access Review, which explores this model of generating evidence and approving medications, with continuous data sharing between the scientific community and regulators.[49]

Data collected after implementation also helps generate the evidence necessary to assess the cost of PM approaches. As more detailed data would be difficult to generate within the timeframe of a clinical trial, economic modeling could be applied to calculate the long-term economic impact. This technique has shown the potential for PM innovations to result in substantial cost savings (see Figure 6).[50]

Recommendation 6

Final regulatory and funding approval could be made contingent on the inclusion of an economic impact analysis.

An example that shows this approach is the Medical Services Advisory Committee in Australia (see Case study 3).

Case study 3: Medical Services Advisory Committee (MSAC) in Australia

Established in 1998, the MSAC is an independent expert committee of individuals with expertise in clinical medicine, health economics and consumer matters. The MSAC provides information to the Minister for Health on the strength of evidence relating to the comparative safety, clinical success and cost-effectiveness of any new or existing medical service or technology. The committee also advises on the circumstances where public funding should be supported through listing on the Medicare Benefits Schedule.[51]

Implementation: Integrating PM technologies into healthcare systems

Engaging the public and working with the scientific community to establish a robust and continually evolving evidence base are two ways to encourage the widespread integration of PM. There are other practical and logistical challenges to securing the uptake of PM by clinical staff and healthcare providers. The speed at which discoveries move from research into clinical practice is outpacing traditional ways of disseminating knowledge across clinical practice settings. The volume of emerging information is difficult to keep track of, especially when each piece of genetic information has different implications, depending on patients' circumstances. To accelerate the adoption and integration of PM technologies into healthcare, we need policies that help us overcome these challenges.

The complexity of care and treatment options are expanding exponentially, and the resulting information overload is threatening clinicians' ability to focus on the right details to make critical decisions.[52] Moreover, there are currently millions of genomic variants of unknown clinical significance. The medical relevance of these variants is rapidly being deciphered, but will continue to be decoded over many years, as our genomics knowledge linked to clinical evaluation expands. This will necessitate clinicians revisiting much of their treatment advice and options as such new information is revealed. Health IT systems have the power to use genetic information to guide decision-making, reduce the information load, and potentially limit medication errors. Furthermore, given the volume and complexity of information underpinning most aspects of PM, clinical decision support through health IT systems will likely become

an essential tool for clinicians and patients to allow meaningful interpretation and clinical action.[53, 54]

Recommendation 7

A centralized global resource for PM implementation should be developed, including IT for optimized decision support and other analytical tools.

Decision support tools can also provide a platform for sharing information about clinical success and cost savings, contributing to a 'learning health system' where patients' health data is harnessed to generate a continuous feedback loop that improves knowledge and enhances best practice (see Figure 7).[55]

Figure 7: Learning health system continuum

The Implementing Genomics in Practice (IGNITE) Network is currently working in this area to generate broadly applicable best practices for implementing PM based on knowledge from its demonstration projects (see Case study 4).

Case study 4: Implementing Genomics in Practice – IGNITE Network

The IGNITE Network was a program funded by the US National Human Genome Research Institute to enhance the use of genomic medicine. IGNITE supports the development of methods for incorporating genomic information in clinical practice across diverse care settings.

IGNITE has demonstration projects which record genomic information in EHRs for clinical decision support. Dissemination of these methods and findings, and development of best practices for implementation, supports a learning health system and contributes to the growing knowledge base for using genomic information in patient care.[56, 57]

IT platforms like EHRs play an important role in this kind of system, as they can enable links between genetic and other personal information (often referred to as phenotypic data) to produce new understandings of health and disease. For those health systems with the resources to develop them, EHRs have emerged as a solution for delivering genomic information to healthcare providers that they can use for diagnoses and treatments. However, sometimes EHRs are inadequate to handle genomic information.[58] Compounding this problem is a lack of standards on how such data should be stored and coded. This is referred to as interoperability, or the ability of IT programs to communicate with other systems' data, codes or operating systems.[59]

IT systems like EHRs have the potential to transform computerized genetic data into something useful that can inform prevention, therapies and frontline clinical decision-making. Healthcare data is already being integrated into tools for doctors. For example, Imperial College London's Centre for Mathematics of Precision Healthcare combines individual and population data, including lifestyle and socio-economic factors, into algorithms to help doctors make more tailored clinical decisions.[60]

Ultimately, without proper IT, widespread collection of data for PM will not deliver patient benefits. This jeopardizes public trust in PM initiatives.

Recommendation 8

Standards for structured data, or common data elements, must be developed for recording information in EHRs.

Having a standard structure will also allow data sets to be aggregated across health systems, research cohorts and institutions. This would improve the statistical power of PM analyses.[61]

Work is being done by the US National Academies of Sciences, Engineering, and Medicine to address the standards for integrating genomic information in EHRs (see Case study 5).

Case study 5: The DIGITizE Action Collaborative

The Displaying and Integrating Genetic Information Through the EHR (DIGITizE) Action Collaborative was established in 2014 by the US National Academies of Sciences, Engineering, and Medicine's Roundtable on Genomics and Precision Health.

The aim of DIGITizE is to engage the various stakeholders involved in healthcare and health informatics (information age technologies) to develop a scalable framework for integrating genomic data and related decision support across existing EHR platforms. To achieve this, DIGITizE uses a three-pronged strategy:

1. Assembling the right organizations, often those who are in competition with each other (including vendors, laboratories, patients, government and so on).
2. Focusing on areas of agreement on what can and should be done.
3. Initiating inter-institutional project co-ordination.

This co-ordination among interdependent entities has been critical to move laboratory data to patient EHRs. Laboratories are not always located within their main organization, and often use different software, which requires EHR vendor support to be adapted. Vendors rely on standards bodies for direction, which in turn rely on laboratories and healthcare providers. This creates a virtual cycle of feedback that DIGITizE has successfully addressed with co-operation between vendors and healthcare providers.

Reliable incentives or funding are needed to sustain this co-operation as it scales up, particularly for standards developing organizations. Success in this pilot project may lead to support from government or other funding agencies.[62]

Workforce training can encourage clinical uptake of PM. Expanding graduate and continuing medical education to include an emphasis on the use of genomic information may prove useful. Greater investment in the dissemination of research and information about implementation science would also help. Also, guidelines may need to be modified or created to take advantage of the rapid pace of discoveries enabled by IT infrastructure. Data from such sources will need to be weighed appropriately alongside other, more traditional data sources.

Recommendation 9

To facilitate PM's implementation and integration into clinical practice, greater investment should be made in translational health research (research aimed at conversion of laboratory and clinical discoveries into innovations in healthcare), particularly in the 'implementation science and diffusion' and 'outcomes and public health impact' phases.

Data: Ownership, privacy and sharing

Data sharing is integral to generating evidence for PM. Advancing our understanding of health and disease prevention requires enhanced sharing of patient data and treatment results between healthcare industries and systems, including researchers and clinicians. But realizing PM's promise will need a further commitment: it will rely on a strong ethical and standardized approach to data collection and sharing.

The first step to achieve this is to ensure standardized, informed consent. As part of the consent process, patients should receive information on the benefits of sharing their data – personally and for the public good.

Recommendation 10

To help improve and facilitate the informed consent process, governments should develop an ethical framework that:

- addresses the risks to, and concerns of, patients and the general public;
- provides information on what privacy protection is in place; and
- provides information on how data sharing promotes the public good.

Investment should be made in streamlining the consent process, including implementing and standardizing non-traditional electronic consent tools. For example, the US Office of the National Coordinator for Health Information Technology developed eConsent, a toolkit designed to answer patients' questions about consent and enable them to give their consent electronically.[63] Apple has introduced ResearchKit, a customizable, open source framework that includes visual consent templates to explain the details of a research study and obtain participant signatures.[64]

The Global Alliance for Genomics and Health (GA4GH) coalition is making progress in the effective and responsible sharing of genomic and clinical data to facilitate its integration in clinical practice (see Case study 6).

Case study 6: Global Alliance for Genomics and Health (GA4GH)

GA4GH is an international coalition of over 360 organizational members from 35 countries that includes agencies, universities, biomedical research institutions, healthcare providers, IT, life-sciences companies, research funders and patient advocacy organizations. The goal of the alliance is to: "establish a common framework of harmonized approaches to enable effective and responsible sharing of genomic and clinical data". GA4GH's mission is to accelerate progress in human health by establishing a framework of harmonized approaches to effective and responsible sharing of genomic and clinical data, and catalyzing projects that drive and demonstrate the value of data sharing.[65]

(Case study 6 continued)

One of the alliance's demonstration projects, the Breast Cancer (BRCA) Challenge, brings together leaders in research and clinical care to develop a catalog of breast cancer variants according to their phenotypic effects. Another, the Actionable Cancer Genome Initiative, collates data from different clinical sequencing projects to facilitate the use of data sets to guide patient care.[66]

As discussed, obtaining participants' consent is essential to gathering the data needed for PM research. Regulatory frameworks for genetic and clinical data need to encourage data sharing while protecting research participants.

Recommendation 11

There must be greater investment in the informed consent process, including making it globally standardized and easier for patients and researchers to implement.

Clinicians and researchers need to work together to listen to participants' concerns and respond with appropriate privacy protection and information. Countries may also want to consider legislation prohibiting discrimination based on genetic information, such as the Genetic Information Nondiscrimination Act of 2008 in the US (see Case study 7).

Case study 7: US Genetic Information Nondiscrimination Act of 2008

As legal and regulatory frameworks adjust to the influx of genomics information, the potential for data misuse will need to be considered to ensure that research participants' privacy is protected.

The Genetic Information Nondiscrimination Act prohibits discrimination based on the use of genetic information for employment or health insurance (although, life, disability, or long-term care insurance are notably absent in the law). It also highlights the potential for genetics to improve health, provided that important future research is not obstructed by fears of genetic discrimination. The law is designed to prevent discrimination and reduce people's concerns so they feel more comfortable taking part in the PM process.[67]

A challenge to the successful sharing of data is the lack of basic data sharing platforms. As discussed, the creation of a global common framework for sharing patient-level data about demographics, genetics and general health records could help to rectify this problem. However, regulations could go further to make standardized data input mandatory. The common framework could also include the completion of other data fields, such as healthcare, environmental and cost of treatment for each person, to create rich and holistic data stores. To make this policy attractive, governments could also introduce tax breaks for industries that place their data in the public domain through the common data sharing framework.

Recommendation 12

Alongside regulation, financial incentives could also be effective in promoting data standardization and sharing. For example, regulations could make payment contingent on data submission.

It is important to acknowledge that economic diversity worldwide inhibits some healthcare systems and industries from broader participation in PM. Due to constrained infrastructures and limited resources, many countries are left out, and their populations are either underrepresented or completely absent in the available data. Amassing larger and more diverse data sets to share with smaller or resource-limited health settings will be critical for their inclusion in local PM strategies.

Recommendation 13

Health systems in developed countries must establish ways to create or enhance PM infrastructure in resource-limited areas.

International and cross-sector collaboration: Maximizing the impact of PM

The power of PM lies in its promise to guide healthcare decisions toward the most effective treatments for patients and improve the quality of care while reducing the need for unnecessary diagnostic testing and therapies. To more fully realize PM's potential, it will be important to engage the global community of key stakeholders, including scientists, bioinformaticians, clinicians, healthcare providers, industries, academia and governments. Many PM implementation issues are complex and multi-faceted, and no one sector in isolation is capable of providing a complete set of solutions.

For example, in the UK's 100,000 Genomes Project, Genomics England was established by the Department of Health as a private company to enable more flexible and rapid procurement of sequencing capabilities and evaluation. In doing so, it has facilitated a number of collaborations between public and private sectors. It awarded contracts to four private sector companies to develop the algorithms needed to evaluate and interpret the clinical relevance of variants identified in genomic data.[68] The project collaborated with NHS England (NHSE) to enlist clinical genomic expertise from academic and healthcare systems to check the quality of genomic data being disseminated to physicians and patients. NHSE worked with Health Education England to develop a wider genomics skills base within the healthcare workforce to support widespread adoption of PM.

In Scotland, the government has funded a 'Precision Medicine Ecosystem' that will co-ordinate PM resources and opportunities across the country by collating the findings from individual research studies (see Case study 8). The lessons learned from these large, shared and interoperable data sets will encourage future research and promote PM applications in clinical practice.

Case study 8: Scotland Precision Medicine Ecosystem

Scotland's government has recognized that existing PM initiatives and the various organizations pursuing them must be co-ordinated to realize their potential.To avoid fragmentation and duplication across initiatives, the Stratified Medicine Scotland Innovation Centre (SMS-IC) will build a business model and service catalog to facilitate a 'PM ecosystem' in Scotland. This business model would leverage existing assets and capabilities in Scotland via technology partners, and enable a route to market for genomic service providers (including the Scottish Genomes Partnership, Generation Scotland, Glasgow Polyomics and the broader Scottish small and medium-sized enterprise community).

The SMS-IC will help organizations develop capabilities and assets to create PM solutions that attract commercial investment and have the potential to generate revenue for Scottish partners. This model is intended to accelerate the adoption of genomic services and enable broader academic, industrial and NHS participation across Scotland.[69]

There are many global initiatives underway to create national implementation strategies for PM. Table 3 shows a selection of projects highlighted at an international genomic medicine meeting in 2014. However, many of these efforts lack collaboration, risking duplication of effort and slowing the pace of discovery and translation into clinical practice.[70]

Table 3: Selected global genomic medicine implementation projects

Single country effort

Country	Name of project	Goals of specialized programs
Australia 	**A framework for translating research into public health action**	Develop a national framework for translating genomics discoveries into clinical research and practice, including advice on the results of genomics research and clinical testing.
Belgium 	**Belgian Medical Genomics Initiative (BeMGI)**	Create a national framework for clinical exome (all expressed genes) sequencing, share variant frequency data, incorporate into international initiatives, and train the next generation of researchers and clinicians.
Canada 	**Genomics and Personalized Health competition**	Assess the benefits (including economic) of genomic technology to patients and expand the capacity for clinical and translational research in 18 diverse projects.
Estonia 	**Estonian program for personal medicine**	Sequence the genomes of 5,000 individuals, develop Estonian genotyping array, pilot 50,000 Estonian Biobank members, and link genetic information to EHRs.

Country	Name of project	Goals of specialized programs
France 	**National Network of Reference & Competence Clinical Centers for Rare Diseases**	Create a national network of molecular genetics laboratories, clinical cancer genetics centers and inter-regional sequencing platforms.
India 	**Implementation of genomic medicine in India**	Develop infrastructure for genomic medicine implementation, including disease susceptibility assessment across ethnic groups, fetal risk prediction and anomaly diagnosis, and cancer genomics.
Israel 	**Clalit Health System**	Use genomics in cancer treatment and include anonymized family history data in relatives' EHRs.
Japan 	**Implementation of genomic medicine project**	Use genomics for optimized diagnosis, treatment and prevention.
Korea 	**Genome Technology to Business Translation Program**	Use genomics to develop early diagnosis and treatments for personalized medicine and PM.
Luxembourg 	**Luxembourg Centre for Systems Biomedicine**	A new funding program of the Luxembourg National Research Fund that facilitates the creation of the National Centre of Excellence in Research, a national clinical research centre that aims to identify new methods for the early diagnosis of Parkinson's disease and the stratification of patients in subgroups.
Qatar 	**Qatar Genome Programme**	Establish the Qatari reference genome map from a representative sample of volunteers phenotyped (observe characteristics resulting from the interaction of a genotype with the environment) at the Qatar Biobank for Medical Research, and develop comprehensive gene panels for rare diseases to be used for national neonatal screening to alert couples of possible health risks for their children.
Scotland 	**Precision Medicine Ecosystem**	Co-ordinate PM resources and opportunities across Scotland, collate the findings from individual research projects and improve information sharing to combat diseases.
Singapore 	**Personalized OMIC Lattice for Advanced Research and Improving Stratification (POLARIS)**	Pilot transforming growth factor, beta-induced (TGFBI) testing for disease diagnosis and family risk assessment in stromal corneal dystrophies (inherited disorder in the cornea of the eye), then implement a 90-gene screening panel to check for gastrointestinal cancers.
Sri Lanka 	**Sri Lankan research into Thalassemia**	Use single nucleotide polymorphism (SNP) genotyping to identify carriers of the inherited blood disorder, thalassemia, and find genetic modifiers to make it a more manageable chronic illness.
Thailand 	**Pharmacogenomics and Personalized Medicine**	Implement the pharmacogenomics card to alert at-risk patients to the top 10 drugs that can cause Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN), integrated with a nationwide pharmacovigilance program (an organized campaign to determine a drug's safety).

Multinational initiatives

Name of project	Goals of specialized programs
Genomic Medicine Alliance	Build collaborative efforts between developed and developing/ low-income countries, genotype pharmacogenomically relevant variants in developing nations, develop national/ethnic genetic databases to study genetic disorders that occur in ethnic groups or populations using a data warehouse (or central repository) approach, and engage in public health genomics projects.
Genatak	Laboratory network for premarital, prenatal and postnatal detection of recessive diseases and chronic disease risk, genetic counseling and personalized cancer treatment.
Global Genomic Medicine Collaborative	The G2MC is a consortium of nations and initiatives aiming to advance genomic medicine; specifically via collaborative programs in sequencing, pharmacogenomics, information technology, education and policy.
Saudi Human Genome Program	Identify genetic basis of disease in the Saudi population and implement diagnostic genomic assays involving comprehensive gene panels and clinical exome sequencing.

Source: Adapted from Manolio et al. (2015)[71]

Recommendation 14

Achieving a co-ordinated, global collaborative effort will require the creation of an international network or organization consisting of representatives from participating member states.

This network will build on the work of collaborative organizations like G2MC and GA4GH, and would be charged with promoting and facilitating the co-ordination and development of the PM agenda across its member countries, as well as offering guidance and resources to those non-member states as requested. The network would assist in the development, implementation and integration of key PM infrastructure and tools into healthcare delivery, as well as offering standardized provider and public educational resources. The network would also be tasked with responding to regional questions and directing individuals or organizations to appropriate resources.

SECTION 4: MAKING PRECISION MEDICINE'S PROMISE A REALITY

Ellie and Jane's mirror stories, 2006 and 2026

Ellie and Jane

It is 2006. Ellie is 40 years old and mother to Jane, who is 16. Despite no family history of the disease, Ellie is diagnosed with breast cancer. She is screened for DNA changes in any genes previously implicated in the disease, but results are negative. Ellie has a unilateral mastectomy and a six-month course of chemotherapy designed to kill any remaining cancer cells in her body. The chemotherapy has significant side effects: Ellie has no energy, looses her hair and suffers nausea. She slowly recovers but, two years later, Ellie finds a lump in her other breast which turns out to be a second, independent tumor. She has another mastectomy and undergoes a further course of general chemotherapy over the next three months. However, scans reveal that the cancer has now spread to Ellie's liver; she is given a terminal diagnosis.

After Ellie's death, Jane is left wondering what was the cause of Ellie's breast cancer and whether she has inherited a risk of developing the disease.

Jane and Ellie

It is 2026. Ellie is 40 years old and mother to Jane, who is 16. Despite no family history of the disease, Ellie is diagnosed with breast cancer. Doctors obtain samples of Ellie's healthy cells and her tumor. Analysis of DNA from these samples reveals no changes in any of Ellie's genes known to cause breast cancer. However, a rare change is found in another one of Ellie's genes. Following extensive searches of DNA and medical databases, Ellie's doctors find that her DNA change is linked to aggressive breast cancer in certain patients. Given the risk associated with her DNA change, Ellie has a double mastectomy. Based on further analysis of DNA in Ellie's tumor, she is prescribed a series of drugs designed to specifically attack any remaining tumor cells. As well as being effective, these produce only a minor rash as a side effect. Over the next 10 years, scans detect no further cancer. Ellie encourages Jane to have her own DNA analyzed.

Tests reveal that Jane has not inherited the rare DNA change from Ellie; she has no heightened risk of developing breast cancer, providing the family with peace of mind.

The potential of PM has never been so clear: we are on the brink of being able to deliver all areas of healthcare – from prevention to therapies – in a way that is directly responsive to patients' genetic needs. Combined with what we know about population health and patients' preferences, values and socio-economic statuses, PM has the ability to combine our current knowledge to push the boundaries of traditional healthcare and depart from those models that are entrenched, expensive and inefficient. This promise is tantalizing, but it remains out of reach because of a series of shortfalls.

Patient and public involvement is not yet sufficient, nor is the evidence base or the organizational infrastructures necessary to make PM an actionable, affordable option. There are also major gaps in the regulatory frameworks that will guide the ownership and sharing of data that is necessary to make PM viable.

With a careful, co-ordinated effort led by policymakers, industry leaders and other healthcare stakeholders, we can address these issues. Our recommendations form an action plan for successful PM and can be adapted within specific governmental and cultural regimes. They form the foundation necessary to achieve PM's full promise.

GLOSSARY

Adaptive licensing
The progressive or staggered approval that enables a medicine to be authorized for use, first in a restricted patient population, then extended to a broader patient population after the collection of additional clinical evidence.

Biomarker
A biological molecule found in blood, other body fluids, or tissues, that is a sign of a normal or abnormal process, or of a condition or disease; may be used to see how well the body responds to a treatment for a disease or condition.

Chromosome
A strand of DNA that is encoded with genes. Most human cells have a total of 46 chromosomes.

Clinical decision support
A variety of tools to enhance decision-making in the clinical workflow, including computerized alerts and reminders to care providers and patients; clinical guidelines; condition-specific order sets; focused patient data reports and summaries; documentation templates; diagnostic support; and contextually relevant reference information.

Diagnostic testing
Any test used to determine the nature or severity of a particular condition – for example, imaging, laboratory tests and so on.

DNA
Deoxyribonucleic acid – the self-replicating carrier of genetic information in living organisms.

Electronic health record (EHR)
A digital version of a patient's paper chart, EHRs are real-time, patient-centered records that make information available instantly and securely to authorized users.

Genome (or DNA) sequencing
Determining the order of the four chemical building blocks – called 'bases' – that make up the DNA molecule.

Genetic variants
Differences in the DNA sequence between individuals that can be used to differentiate between them as well as to associate them with a disease or inherited condition.

Genome
The complete collection of DNA present in a cell or organism.

Genomics
Describes the study of all of a person's DNA (the genome).

Health literacy
The degree to which individuals have the capacity to obtain, process and understand basic health information and services, which is needed to make appropriate health decisions.

Learning health system
A health system that places an emphasis on a collaborative approach that shares data and insights across boundaries to drive better, more efficient medical practice and patient care. Key to this vision is the creation of a system linked by a common EHR and shared databases.

Metabolites
Small molecules that are either intermediates or products of metabolism. They have a range of functions including fuel, structure and signaling and have both a stimulating and an inhibiting effect on enzymes.

Metabolomics
Study of the unique chemical fingerprints that specific cellular processes leave behind.

Microbiome
The collective genomes of the microorganisms that reside in an environmental niche (such as the human intestine).

Microflora
Bacteria present in the large intestine.

Pharmacogenomics or pharmacogenetics
The study of how genes affect a person's response to drugs.

Phenotype
The physical appearance resulting from inherited genetic information.

Proteomics
The large-scale study of proteins.

RNA
Ribonucleic acid – an important molecule with long chains of nucleotides and, like DNA, vital for living beings.

Transcriptomics
The study of the transcriptome, or the complete set of RNA under specific circumstances or in a specific cell.

Tumor
An abnormal growth of body tissue.

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