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Are we there yet? How and when specific biotechnologies will improve human health

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Patient X: A 67-year-old Caucasian man slips on a patch of ice. He has abrasions to his hands and has sustained significant damage to his hip. At the emergency room, he informs clinicians he takes atorvastatin, metformin and glimepiride to treat hypertension and Type 2 Diabetes Mellitus (T2DM). X-rays reveal a fractured hip, which will require total hip replacement surgery.

Biotechnology is a major force poised to help us to live longer and healthier lives. In 2015, the United Nations defined 17 Sustainable Development Goals aimed at providing an all-encompassing framework for improving the state of the world (<http://www.un.org/sustainabledevelopment/sustainable-development-goals/>). Promoting healthy living for all at all ages, is one of the principal objectives. Using the commonplace example described above, we examine how some of the most well-known biotechnologies (genome editing, stem cell therapy, tissue engineering and precision medicine) are able to benefit Patient X today, in 2018 and we also provide perspective on the additional value these same technologies could offer only ~20 years into the future (**Fig. 1**). During this ~20 year gap, both technical challenges as well as ethical, legal and socio-economic questions must be addressed before these technologies can achieve broader impact. Further, as both the successes and the failures will likely have enduring effects on society, responsible oversight of these and other biotechnologies are necessary as science and applications move out of the lab into clinical practice. In the next 20 years biotechnology will undoubtedly transform healthcare but how, when and, in some cases, whether it should, require careful consideration.

Genome Editing

Genome editing, which refers to making modifications to the genome, has enormous potential to significantly benefit human health by providing tools to improve our understanding of human biology, enhance existing approaches for treating disease, provide entirely new avenues for curing genetic disease and, possibly even, eliminate infectious disease threats. Although previous technologies for genome editing, such as zinc-finger nucleases (ZFNs) and transcription activator-like-effector nucleases (TALENs)^[1] provided potential methods for editing genomes, techniques based on clustered regularly interspaced short palindromic repeats (CRISPR)-Cas systems have been quickly adopted due to their low cost and ease of use.^[2] Unlike ZFNs and TALENs, CRISPR-Cas systems are programmed with a ~20 nucleotide sequence (guide RNA), which can be manufactured easily at scale and designed to target a specific region of the genome simply by using decades-old rules for Watson-Crick base-pairing. The Cas family of nucleases create a double-stranded break at the target locus activating DNA repair mechanisms, including either the error-prone non-homologous end joining (NHEJ) or the more precise, but far less efficient, homology directed repair (HDR) pathway. NHEJ can be exploited to generate gene knockouts, as indel mutations lead to frame shift mutations and premature stop codons while HDR can be harnessed to generate precise defined modifications to a target locus (**Fig. 2**).^[3]

Genome Editing Now

In 2018 for Patient X, genome editing is an indispensable basic research tool to better understand his disease. CRISPR powers large-scale genetic screens to identify mediators

of specific phenotypes and to create transgenic animal models of disease. Aided by CRISPR, high throughput genome-wide screens have been successfully used to identify therapeutic targets and to test potential agents for benefit in Barth syndrome[4], Duchenne muscular dystrophy[5, 6], hemophilia[7-9], β -Thalassemia[9], cystic fibrosis[10-12], cardiomyopathy[13, 14], autoimmune disorders[15], cancer[16, 17] and more. Similarly, researchers are using CRISPR to identify factors that control blood pressure and diabetes. For example, polymorphisms in the ARHGAP42 gene, the PHACTR1 gene and the long-noncoding RNA, termed *Rffl-lnc1* have been identified as potential therapeutic targets to alleviate hypertension. Knockout animals for genes such as Apolipoprotein E [18, 19], the LDL receptor[18], leptin[20] and PCSK9[21] are currently being evaluated for their role in cardiovascular disease and diabetes.

2018 is also the year CRISPR-Cas moves into the clinic. CRISPR Therapeutics and Stanford University School of Medicine will begin human trials using CRISPR technology to treat β -Thalassemia and sickle-cell anemia, respectively. China has a number of CRISPR trials underway, however, no results have been made available.

Genome Editing in ~20 Years

The basic research studies, combined with best practices learned from the initial clinical trials could transform treatment for future patients like Patient X. Rather than taking medication his whole life; there is a possibility that in future, mutations that confer tangible benefits could be prophylactically administered. For Patient X, PCSK9 knockout may alleviate his high blood pressure, lower his risk for coronary disease and eliminate

his need for medication. Similar strategies are already being proposed in other disease areas such as CCR5 knockout for resistance to HIV. [22]

Yet, even the most sophisticated gene therapy or advanced treatment may eventually fail if Patient X acquires an infection by antibiotic resistant bacteria in the Hospital e.g., during post surgery or through casual exposure in places with a strong selective pressure—still worse if the patient is immunocompromised. CRISPR-Cas9 provides once more a platform for designing antimicrobials able to tackle this phenomenal challenge and mitigate clinical complications. While the quest for new antimicrobials will expand in many different directions[23, 24], just looking for more bacteria-killing molecules—like a sort of arms race—may not ultimately solve an essentially evolutionary problem[25]. Alternatives to traditional antibiotic treatments will be need to be developed. A new wave of phage-based therapies have shown considerable promise to counteract virulent bacteria where current antibiotics fail[26]. CRISPR/Cas9 technology can also be instrumental to selectively kill pathogens (or eliminate their antibiotic plasmids) by spreading bacterial or viral *vigilantes* that target the corresponding resistance genes in the microbiome[27-29]. It is also possible to re-sensitize specific microorganisms by making them amenable to the action of existing antibiotics through co-treatment with other drugs[30]. Ultimately, the success of antimicrobial strategies may depend on a deeper understanding of the molecular ecology of the microbiome, its interplay with environmental factors (including our immune system) and the effect of other medicaments in our own physiology[31, 32].

However, before broad deployment of CRISPR for therapeutic use, significant technical and safety challenges including more specific enzyme mutants to address off-target effects and delivery of CRISPR enzymes to specific tissues must be addressed. For example, Cas9, the most commonly used CRISPR-nuclease, requires a guanine-rich protospacer adjacent motif (PAM) sequence for maximum cleavage efficiency and as a result sequences with low guanine content have been difficult to target. However newly discovered Cas alternatives such as Cpf1, which recognize AT-rich PAM sequences are expanding our ability to precisely and efficiently target the entire genome.^[33] The potential of CRISPR is also not without significant ethical concerns, particularly as regards germ line editing. Deploying such powerful technologies will require discussion and deliberation on whether, and in what ways, technical barriers and ethical as well as legal concerns can be addressed in a societally acceptable manner. Further patent-warring academic institutions are threatening both access and further development to CRISPR-technology. Contrary to the precedent of other breakthrough biological research tools such as recombinant DNA, co-transformation and siRNAs wherein non-exclusive licenses were offered to both companies and academic institutions, each institution claiming CRISPR ownership is or already has negotiated exclusive licenses to well-funded commercial partners for particular fields of use.^[34] Inclusive access and more clarity on inventorship for follow-on applications (i.e. limitations on “reach through” broad patent claims) must be resolved. Both the intense research and investment environment suggests that gene editing will transform human health in the next 20 years, whether it is CRISPR or perhaps a superseding technology remains to be determined.

Stem Cell Therapy

Stem cells (SCs) offer a promising source for developing novel medicines and disease models. SCs can be classified into three main types: embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and non-embryonic “somatic” or “adult” stem cells. ESCs and iPSCs are pluripotent and, therefore, can differentiate into cells from all three germ layers of the body. ESCs are isolated from the inner cell mass of an early embryo. iPSCs are adult somatic cells that have been transformed with a cocktail of reprogramming factors important for maintaining self-renewal and pluripotency[35]. Adult SCs are undifferentiated cells, which are found among differentiated cells in a tissue or organ and are responsible for generating some or all of the major specialized cell types of the tissue or organ in which they reside. Scientists have well-established SC differentiation protocols to generate neurons, cardiomyocytes, adipocytes, endothelial cells, hematopoietic cells, and more[36-42]. SC therapy uses SCs or cells derived from SCs to replace, or repair damaged cells and tissues (**Fig. 3**).

Stem Cell Therapy Now

For Patient X, SCs are currently being evaluated for their use as model systems and as potential therapies. SCs provide *in vitro* disease models that may more accurately and fully recapitulate characteristics of human diseases. Generation of iPSCs derived from patient somatic cells and combined efforts with genome editing technology, has opened new avenues for studying pathogenic mechanisms and screening drugs for treating a patient’s particular disease. This is true for T2DM. iPSCs derived from patients with mutations in the insulin receptor have proven useful in unraveling metabolic defects in

those lines[43, 44]. In addition, iPSCs generated from patients with monogenetic forms of diabetes differentiated into pancreatic β -cells has revealed important developmental and signaling pathways altered in the disease[45, 46]. Further, iPSC-derived cardiomyocytes from patients with T2DM recapitulated the T2DM cardiomyopathic phenotype allowing researchers to dissect the affected pathways[47]. Additionally, iPSC-derived endothelial cells have also proven to be an invaluable source to untangle the endothelial dysfunction associated with the disease[48].

SCs also promise therapeutic potential. Labs around the world study SC-based applications for age-related macular degeneration (AMD)[39, 49], spinal cord injury[35, 40, 50], Parkinson's disease[38, 41, 51, 52], corneal diseases [36, 37, 53, 54], myocardial infarction[55, 56], aplastic anemia and leukemia associated with thrombocytopenia[57], and demyelinating diseases such as multiple sclerosis[58, 59] , as well as for cancer immunotherapies involving chimeric antigen receptor T (CAR-T)[60] and NKT cells[61]. Despite enthusiastic pre-clinical research and clinical studies, at present FDA-approved SC therapies is limited only to hematopoietic SCs. For the last 50 years, bone marrow transplantation to alleviate chemotherapy induced hematopoietic cell death has been the most widely used SC therapy. A healthy donor's bone marrow reintroduces functional SCs to replace those killed as a byproduct of cancer treatment. Just last year tisagenlecleucel was the first CAR-T cell therapy approved by the FDA to treat refractory precursor-B-cell acute lymphoblastic leukemia by utilizing a patient's own blood, isolating T lymphocytes and engineering them to target CD19 on B-cells for destruction.

[62] Since SCs can be derived from patients themselves, SC-derived therapies have

potential uses as auto- or allografts[35, 63], eliminating many host-graft rejection concerns. Indeed, the first clinical study involving an iPSC-derived product, a sheet of autologous iPSC-derived retinal pigment epithelial (RPE) cells in a patient suffering from wet-type AMD, was initiated in Japan in 2014. The grafted iPSC-RPE sheet showed no sign of immune rejection during the one-year monitoring period following transplantation[39]. The costs of quality testing and safety concerns for autologous cell transplants, however, have led to increased interest in allogeneic strategies, such as those using iPSC stocks established from “HLA super-donors,” who are homozygous at the three major human leukocyte antigen (HLA) gene loci³⁰ and recently Masayo Takahashi’s group transplanted cell suspension of iPSC-RPE derived from a super-donor matched to the recipient’s HLA type. Other stem cell treatments are currently being evaluated for safety and efficacy. In central nervous system (CNS) disorders alone, the number of clinical trials using SC technologies continues to grow (**Supplementary Table 1**). Mesenchymal stem cells (MSCs) are multipotent cells capable of differentiating into osteoblasts, adipocytes or chondrocytes. Current efforts are focusing on uncovering the mechanisms that shift MSC differentiation toward osteoblasts for clinical use as a possible treatment for bone regeneration.

Stem Cell Therapy in ~20 Years

Present day technical challenges and safety concerns as well as ethical concerns and, in some countries, legal restrictions particularly related to embryonic stem cells are currently preventing widespread use of SC therapy. Over time, questions of a socio-economic nature will also need to be answered. For most diseases, it is still being

determined which cells (SCs and/or which SC-derived cells) would work best to repair a particular damaged or diseased tissue. Delivery of those cells also remains a significant hurdle. Furthermore, large numbers of homogenous cells are needed for replacement therapies and, at present, SCs have a limited capacity to divide outside the body. Additionally, side effects and long-term safety must be determined since transplanted cells may remain for many years in patients' bodies. If over the next 20 years, researchers are able to tackle these issues, then the number of proven SC-treatments will dramatically expand. For example, SC therapy may transform treatment for future diabetic patients like Patient X. In the future bona fide primary human SC-derived pancreatic β -cells may be generated *in vitro*, providing an unlimited supply of glucose-responsive β -cells for transplant. Further, instead of surgery alone, SCs may complement future hip-replacement surgeries. To regenerate bone, stem cells could be introduced in a scaffold where they produce the minerals necessary for generation of functional bone. Insights from non-human models of regeneration may further advance this type regenerative medicine. The axolotl salamander has the ability to repair and regenerate a perfect replica of its body parts. Just this year researchers determined the complete 34 billion base pair axolotl salamander genome and are now beginning to untangle the genes that facilitate this special capacity to regenerate.^[64] In 20 years, stem cells could be genetically modified based on learning from model organisms such as the axolotl to repair bone fractures. This strategy is the foundation for tissue engineering.

It is important to note that SC therapies differ from traditional small molecule or biologics especially in terms of manufacturing purity, dosing regimes and the potential

for enduring, irreversible effects and thus must be carefully evaluated by regulatory bodies for safety and efficacy. This requires time and investment. The original Geron, Inc clinical trial of ESCs derived oligodendrocyte progenitors for the treatment of spinal cord injury was estimated to cost \$200M in pre-clinical studies before the program was terminated.^[65] The high cost was in part due to animal models of efficacy, providing safety data against teratoma formation, ESC manufacturing, and training for the transplant procedure. Unfortunately in recent years there has been a proliferation of so-called “stem cell clinics” attempting to skip the regulatory pathway by offering SC therapies that are unapproved, unproven and even potentially dangerous. Only by offering SC products that have been rigorously tested and constantly monitored can we ensure their benefit to a future Patient X.

Tissue Engineering

The ultimate goal of tissue engineering (TE) is to provide artificially developed tissues and organs substitutes on demand to integrate them into the human body to live healthier and stronger for longer. Tissues and organs in the body form a complex arrangement of multiple cell types and extracellular structures that work together to achieve a particular physiological function. TE approaches consist of combining scaffolds, cells and biologically active molecules into functional tissue.

Amongst TE, bone TE (BTE) seeks to address the unmet need for bone augmentation. Loss of skeletal tissue can be produced by trauma, injury, cancer or advancing years, since medical advances have led to a welcome increase in life expectancy, which, in turn, has produced an increase in age-related diseases. In particular, due to the aging

population, there is an exceedingly high demand for functional bone grafts, already representing the second most common tissue transplantation procedure after blood, with over 2.2 million bone graft procedures conducted worldwide every year[66, 67]. This high demand for bone grafts results in significant morbidity and important associated socio-economic costs, which emphasizes the need for new skeletal regeneration strategies.

BTE is an approach that seeks to induce new functional bone regeneration via the synergistic combination of a biocompatible scaffold that mimics the natural bone extracellular matrix, osteogenic cells to lay down the bone tissue matrix and bone morphogenic proteins or other growth factors that direct osteogenic SCs to the phenotypically desirable cell types. Additionally, a sufficient vascularization that allows for nutrient supply as well as waste removal needs is also required[68].

Bone Tissue Engineering Now

Currently, BTE approaches are promising strategies to treat severe traumatic injuries and pathological diseases such as osteoporosis or osteoarthritis[66]. Osteoporosis is a disease where increased bone weakness multiplies the risk of a broken bone. Although bone is a dynamic and highly vascularized tissue that continues to remodel throughout the lifetime of an individual[69], large bone defects, as observed after bone tumor resections or in osteoporotic patients and severe non-union fractures, lack the template for an orchestrated regeneration and require surgical intervention^[69].

Today, Patient X will need a transplantation of autologous bone from a non-load-bearing site to the defect site and, thus, he will require a second operation at the site of tissue

harvest[66, 70]. Autologous bone graftings are very expensive procedures and, due to the invasive nature associated with several surgical operations, Patient X could experience complications such as infections, fracture, nerve and vascular injuries, chronic donor site pain, hernias, as well as unattractive scars and a poor cosmetic outcome[71, 72]. Furthermore, autologous bone grafting may be a null treatment option in cases where the defect site requires larger volumes of bone than is available. Thus, the use of bone autografts is severely hampered by its short supply[66, 69].

BTE approaches utilizing osteogenic SCs for bone regeneration may offer some hope. Unfortunately, only a handful of successful repairs of bone defects have been reported in larger animals[69, 73-77]. A traditional challenge in BTE is to achieve vascularization that perfuses the blood supply within the scaffold. Efficient oxygen transfer, delivery of nutrients and transport and clearance of metabolic waste are crucial to achieve homeostasis and functionality and, failed vascularization, results in necrosis, which, in turn, results in failure of the regenerated tissue to integrate with the host tissue[66].

Several approaches are being explored to generate organized endothelial vessel networks throughout the material scaffolds such as constructing three-dimensional (3D) multiculture systems comprising progenitor cells, differentiated mature cells, and endothelial cells^[69] (**Fig. 4**). In fact, 3D-bioprinting, which is a process where cells and biomaterials (bioink) are simultaneously deposited in defined 3D patterns and shapes[78], could meet the demands for innovative structures and treatment strategies for osteoporosis and for long-term repair and regeneration of several types of injured or diseased tissues and organs. 3D-printing can incorporate design considerations including the structural, physical, biological, and economical parameters that are crucial for the

fabrication of functional, complex, engineered tissues. To date, 3D-printing is being explored in bone, neural, skin, connective, and muscle TE very successfully[78].

Bone Tissue Engineering in ~20 Years

In 20 years' time, significant challenges such as the integration of the 3D vascular structure within the printed bone construct that can be connected to the patients blood supply could have been overcome. As an example, 3D-bioprinting techniques could have enabled the assembly of functional hierarchical vascular networks due to the ability of 3D-printing to position different types of cells in discrete 3D spaces which makes it possible to construct controlled multiple length-scale structures[78].

A future Patient X will go to the hospital with his broken hip and the doctors will observe a large bone defect that will not heal by itself. By making use of 3D imaging approaches such as magnetic resonance imaging or X-ray computed tomography, the anatomical shape of the bone defect will be screened. Next, by using 3D-bioprinting technologies, it will be possible to print a stable, human-scale bone tissue construct that perfectly fits the bone defect and that, furthermore, possesses engineered vessel networks that ensure normal cellular metabolism while promoting host tissue integration[79]. In 20 years' time, it will be possible to develop high-precision therapeutic solutions with specific patient/defect designs. It will be possible to convert medical images into tissue constructs for patient-personalized organ repair. These customized approaches will not only greatly benefit patients outcomes and follow-up treatments, but will also play a role in the huge economic and social toll that a disease such as osteoporosis produce.

Precision Medicine

In the post-genomic era, therapies are no longer being tailored to the “average patient” but rather customized for the individual known as precision medicine (PM). PM relies on utilizing an individual’s molecular makeup to guide health decisions. Large scale studies including genomic, proteomic, metabolomic, epigenetic, microbiome and multi-omic profiling has created large datasets, so-called “big data” that when mined with techniques such as machine learning yields biomarkers capable of stratifying individuals into subpopulations that differ in their susceptibility to a particular disease, prognosis of disease and response to specific treatment. The goal of precision medicine is to optimize treatment for improved outcomes and reduce exposure to adverse side effects[80] (**Fig. 5**).

Precision Medicine Now

It took 13 years to complete the first human genome project by a collaborative international effort. Since the completion of the first human genome sequence a significant advances in sequencing technologies have evolved. Microarray technology, next-generation sequencing and genome-wide-association studies have, which has been consistently breaking down the cost of whole genome sequencing to now less than \$1,000. These technologies have identified genetic markers correlated with disease. These findings have been developed into molecular diagnostic tools that are now commonly used to tailor therapies in oncology, cardiovascular disease, autoimmune disorders, and neurodegenerative diseases. Chronic myeloid leukemia (CML) accounting for 15-20% of adult leukemia[81] was the first human malignancy associated with a

recurrent genetic abnormality. Over 90% of CML patients due to a reciprocal translocation between the long arms of chromosome 9 and 22 possess the so-called “Philadelphia chromosome” leading to the fusion BCR-ABL gene[82]. BCR-ABL is an unregulated tyrosine kinase driving cell growth and promoting tumorigenesis. Imatinib was the first drug developed to inhibit BCR-ABL and its use led to a dramatic increase in CML survival from 6% in 1975 to close to 90% today[83]. Similar targeted therapies that have improved survival outcomes in oncology include the use of anti-hormonal drugs for hormone receptor positive breast cancer, trastuzumab (Herceptin®) to treat HER2+ breast cancer, vemurafenib and dabrafenib for mutated BRAF-driven melanoma, and EGFR inhibitors for lung and colon cancer[82, 84, 85]. Targeted treatments have been developed for many additional disorders including many rare diseases. For example cystic fibrosis (CF), which affects 70,000 patients worldwide, is caused by genetic defects in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Small molecule drugs such as ivacaftor and lumacaftor target defective CFTR proteins for CF patients with specific genetic mutations[86, 87].

To date, the lion’s share of PM efforts have utilized genetic aberrations as a source of therapeutic targets for drug development. Variations in DNA and RNA are well suited to uncover the molecular underpinnings of many diseases. Non-genomic biomarkers also play a vital role in PM, expanding our ability to detect and manage disease. Proteins are dynamic, constantly being turned over in a cell and their presence or absence can relay information about disease mechanisms. Troponin is a regulatory protein found in skeletal and cardiac muscle and high levels in the blood are suggestive of heart damage including

risk of myocardial infarction[88]. HLA proteins used by the immune system to recognize “self” are used to match patients and donors for bone marrow transplants[89]. Researchers also discovered a panel of protein biomarkers that may detect Alzheimer’s disease[90]. Metabolites are an additional class of important biomarkers that reflect not only what has been encoded by the genome, but also inputs from the environment including diet and microbiome. Metabolites are often the closest representation of phenotype. There are several well-established clinical metabolite biomarkers such as glucose to monitor diabetes, cholesterol to assess cardiovascular health, blood urea nitrogen and creatinine for renal disorders and several distinct metabolites are used to diagnose inborn errors of metabolism in neonates[91].

Patient X was likely diagnosed with T2DM based on increased levels of biomarkers including glucose and HbA1c (glycosylated hemoglobin) in his blood. Unfortunately, no tailored therapies exist for T2DM. Nearly all patients receive metformin as a front-line therapy. Depending on the patient’s tolerance of the drug and the efficacy of metformin to lower a patient’s glucose and HbA1C additional pharmacological agents are prescribed. Many drugs have toxic side effects including severe lactic acidosis, anemia and cardiovascular events. Each T2DM patient will respond differently to each treatment based on a combination of genetics and lifestyle factors. Currently there are few if any tools to predict patient response to therapy making it extremely difficult for physicians to design optimal treatments. If not well-managed Patient X is at risk of amputation, blindness, stroke, and death.

Precision Medicine in ~20 Years

In the future whole genome sequencing could be part of the standard of care to guide treatment. This would enable patients and physicians to identify genetic risk factors for disease. For example, polymorphisms in PPARG, KCNJ11, TCF7L2, CDKAL1, HHEX, SLC30A8, IGF2BP2, CDKN2A are associated with increased risk of T2DM[92]. A future Patient X could be screened for these or other polymorphisms at birth and if detected he could be more closely monitored for disease progression. By measuring biomarkers (genetic, protein, metabolomic or other) of patients treated with atorvastatin, metformin and glimepiride, and using machine learning algorithms to identify signatures that differentiate patients that respond to those drugs and those that do not, in 20 years the treatment of future Patient X can be streamlined for optimal outcomes. This will prevent patients being prescribed drugs that have no effect and/or are exposing them to unnecessary side effects. Further, while currently biomarkers for non-Caucasian ethnic groups is severely lacking as demonstrated in a recent audit of public genome data wherein genomes from the Middle East were less than 1%[93], in the next 20 years through collaborative international efforts we can begin to close those discrepancies. Additionally although molecular testing to guide treatments has already become routine in developed countries, this is not the case in the developing world. If not corrected, the divide between wealthy and poorer countries will expand unjustly. Both public and private partnerships need to be cultivated so that PM can be democratized in the future.

Utilizing biomarkers to bypass the trial and error of current treatment paradigms also has the potential to reduce inefficiencies in healthcare and cut costs. Current estimates

suggest that nearly 30-40% of patients receive ineffective drugs.^[94] Streamlining patients into the optimal treatment groups would eliminate much of this waste. In 2018 there is not enough data to determine the true economic benefits of PM, wherein some examples show better health outcomes for lower costs while others suggest the additional testing adds an increase in cost.^[95] Over the next 20 years as PM integrates more into healthcare systems the economic gains (or losses) will become more evident. The cost savings of PM in drug develop is already evident and will grow in the future. The standard drug discovery pipeline from target identification to drug approval is 10-17 years, requiring approximately \$1.78B with only 11% of drugs eventually approved.^[96] The majority of drugs fail due to lack of efficacy. Administering the same drug to a highly heterogeneous patient population accounts for the majority of these efficacy failures. We now know that breast cancer is not a single disease but rather, based on gene expression profiles can be classified into four to six major subtypes.^[96] Similar heterogeneity is also observed in other cancers[97], asthma[98], diabetes[99], and in less common disorders such as glycogen storage disease.^[100] Over the next 20 years the number of therapeutic areas that display disease heterogeneity will only increase. Companion diagnostics capable differentiating patients that respond to therapy will better define the intended patient population, enabling smaller clinical trials; accelerating time lines and reducing spend. Further, by identifying subtypes of patients that will respond to specific drugs, new avenues of drug repositioning or repurposing existing therapies are likely to emerge. This was the case for crizotinib, which was originally developed to treat large-cell lymphoma and later molecular profiling revealed a subset of non-small cell lung carcinoma (NSCLC) wherein it is also efficacious.^[96] Based on previous examples such as

duloxetine, imatinib and crizotinib, repositioning drugs reduces development time lines from 10-17 years to 3-12 years.^[96] Not only will this reduce costs of drug develop, it will also accelerate patient access to effective therapies. New models of pharmaceutical and biotechnology research will likely emerge where patient data is a prerequisite to drug development and identifying responder profiles becomes part of the regulatory pathway. This new generation of PM drugs will likely be able to demand premium pricing due to the increased safety and enhanced therapeutic efficacy by targeting a defined patient population. This new business model in concert with government support may also revitalize drug development in neglected areas such as antibiotics, tropical disease and rare disease.

PM of the future may also start to transition healthcare towards a preventative model. Today, we mostly wait for our health to fail before we diagnose and treat disease. PM has the potential to change that. By continuing to expand biomarker profiling of healthy subjects across longitudinal studies, it is likely that in 20 years advanced diagnostics and prognostics will be uncovered that can detect disease at its earliest onset. Disease prevention will be crucial for curbing the diabetes epidemic as the associated hyperglycemia causes irreversible damage to the body. Biomarkers that detect diabetes sooner will enable individuals to implement lifestyle changes to slow or halt further disease progression. Disease prevention initiatives have both greater potential for the creation of a healthier population and savings, reducing costly medical treatments and drug prescriptions. Just as additional research is needed to uncover disease prevention biomarkers, additional efforts in health literacy will also be required. In order for patients

to take more active roles in their health and medical choices, tools will be required to help them understand the data and how to translate increased risks for certain diseases into actionable healthy choices. In 20 years, PM will likely include new biomarkers, improved targeted treatments, as well as tools that allow patients to access and monitor their own molecular data so that a future Patient X can take center stage controlling his health. It is important to note that there are multiple ethical, legal and socio-economic questions which also require answers in order to enable a safe, beneficial, and societally acceptable deployment of these technologies. Notably questions around balancing the obvious interest in a more and more preventative approach to healthcare with data privacy aspects as well as the “right not to know” require further societal discourse and clarification. Further safeguards against “genetic discrimination” must be put in place so that knowledge of an individual’s molecular makeup, genetic mutations or particular SNPs as examples, are used solely to enhance, extend and enrich an individual’s life not the opposite including denial of services, health insurance or other discriminatory practices. In 2018 data is already powerful and over the next 20 years its authority will expand. Today’s society has been entrusted to establish a framework so that it will be used maximum human benefit.

Final Comments

Biotechnology will fundamentally change our understanding of health and treatment of disease. In this article we have outlined the capabilities of some key biotechnologies, with a prospect for their future application for diagnostics and treatments from a medical and scientific point of view. New biotechnologies will allow us to live longer and

healthier, thanks in great part to the numerous research efforts carried out by scientists around the globe. The true impact of biotechnology on healthcare, however, will ultimately be enabled, shaped, and limited by governance frameworks. These need to carefully balance the benefits and opportunities of these technologies, with their risks and potential downsides. Due to variations in historical, economic, sociocultural factors among nations as well as among different stakeholder groups, there is significant scope for disagreement on how to draw boundaries between biotechnologies that are considered ethically, legally and socio-economically acceptable and those that are not.

Given the significance of the technology for many aspects of life, and the degree of controversy some biotechnologies have sparked, it is important to re-establish a dialogue between all stakeholders to help build and expand mutual understanding and a culture of trust between regulators, NGOs, scientists, industry, and the public both within and across geographic boundaries. Such discussion should take into account facts, feelings and value commitments, whilst providing clear view of risks and benefits. The scientific community has a key duty in this task, providing facts to de-mystify the true capabilities of biotechnologies in front of regulators and decision-makers. Only a framework that embraces the result of such discussions will live up to the goal of being seen as fair, unbiased, transparent, stable and trusted, which, ultimately, will benefit individuals and their communities.

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Conflict of interest

The authors declare that they have no conflict of interest.

Figure Captions

Fig. 1. Biotechnologies help us understand, diagnose and treat disease. In 2018, technologies such as stem-cell disease models, CRISPR-genome editing screens, and multi-omic profiling are basic research tools expanding our knowledge of the molecular drivers of disease. In the future, advancements in these same technologies and others will lead to novel diagnostics and treatments enabling healthier living.

Fig. 2. Opportunities and challenges for CRISPR-Cas9 genome editing. CRISPR is a proven indispensable research tool empowering creation of models of disease and accelerating our understanding of biology. Harnessing the power of CRISPR-Cas9 will have applications in agriculture and medicine.

Fig. 3. Stem cells provide disease models and therapies. Stem cells (ESCs or iPSCs) can be differentiated *in vitro* to a desired cell type recapitulating disease pathology and used to identify new therapeutic targets and screen drug candidates. Stem cells are also used for transplantation into non-human primate (NHP) models to evaluate efficacy as a therapy in preclinical studies before ultimately moving into human studies.

Fig. 4. Bone Tissue engineering as a future therapy. After surmounting certain technical challenges, person specific tissue for implantation could be prepared as shown. This will likely require constructing three-dimensional multiculture systems comprising progenitor cells, differentiated mature cells, and endothelial cells into an organized endothelial vessel networks throughout the appropriate material scaffolds.

Fig. 5. Biomarkers enable precision medicine. Instead of treating all patients with the same therapies, precision medicine (PM) uses biomarker data to stratify patients into optimal treatment groups for improved outcomes.

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