PERSONALIZED MEDICINE:

MOVING FROM **AVERAGE TO PERSONAL**

PRESCOUTER

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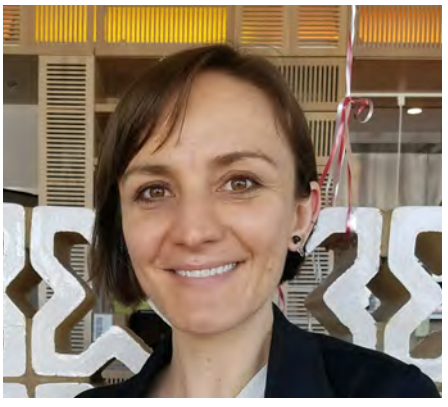

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INTRODUCTION

It's official. We are in the midst of a revolution in personalized medicine — also called precision medicine. Some experts may resent the interchangeable use of these two terms, while others may advocate it! The synonymous use of these two terms is understandable; the approach relies on increasing treatment precision by identifying a scientifically rigorous patient classification criteria and thereby narrowing the eligible patient cohort, until the approach is precise enough to be "personalized" for an individual patient. Regardless of the semantics, the unprecedented growth of precise/personalized medicine and the transformative healthcare advances fueled by this revolution are now undeniable.

As our processors become faster (see Moore's law)[1] and our sequencing technologies become cheaper[2] ($100 million per genome in 2001 to about $1,000 at present) (Fig. 1), our healthcare is becoming increasingly personalized as well. In fact, we have surpassed the four-year mark since President Obama announced the Precision Medicine Initiative[3] and summed up the desire to shift our healthcare focus from the "average patient" to the "individual patient."

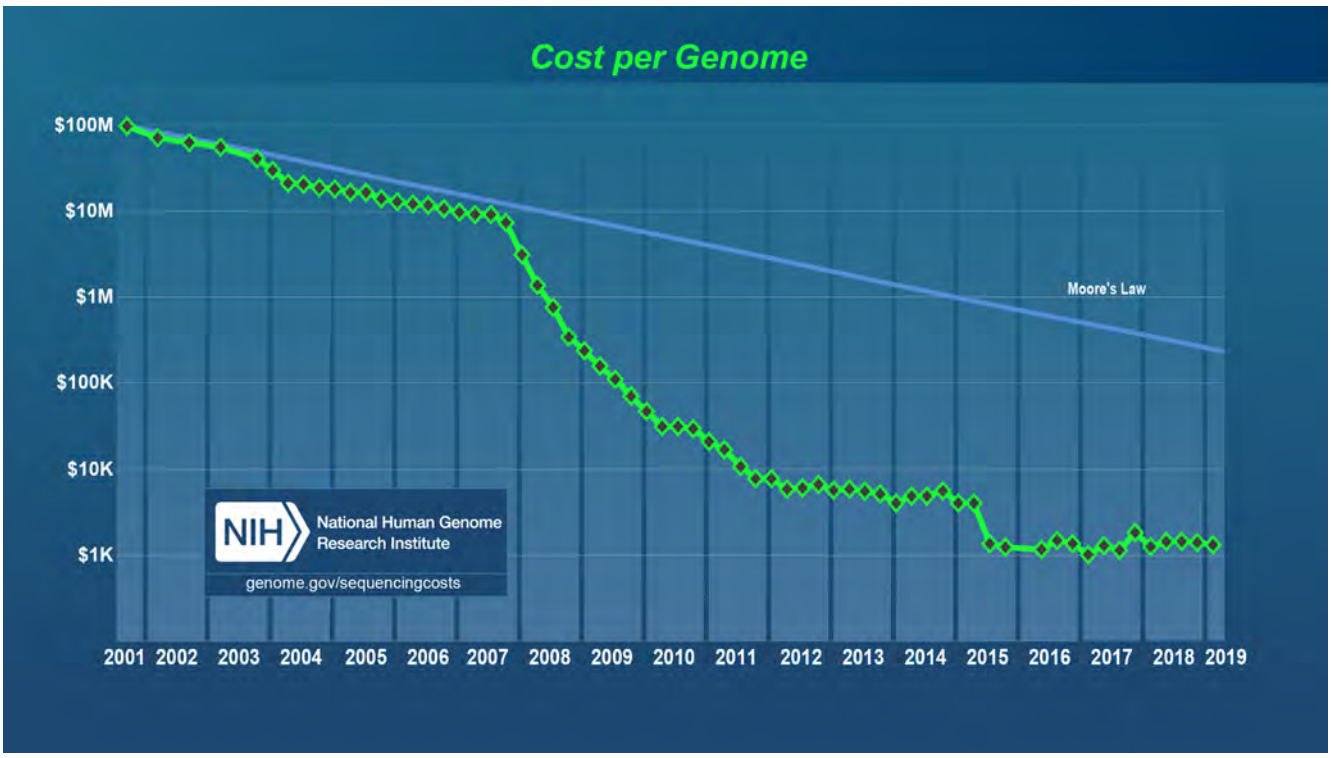

Figure 1 : Sequencing cost per genome, 2001 through 2019 *(Courtesy of National Human Genome Research Institute)*[2]

This quote by the 44th president of the United States captures the essence of precision medicine:

> *Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?*

We present here a handful of examples from some recent advances that showcase how personalized medicine is transforming healthcare by improving precision in diagnosis, prevention, and treatment of a variety of conditions that contribute to a significant fraction of disease burden worldwide.

WHAT IS PERSONALIZED MEDICINE? A PRIMER

According to the National Cancer Institute[4] definition:

> *Personalized medicine is a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease.*

The idea behind personalized medicine is simple: You are unique and therefore your therapy should be too. In contrast to conventional medicine, where evidence from multiple studies is used to develop somewhat rigid and protocol-based treatment guidelines for a patient profile that represents a statistical average from multiple cases, personalized medicine focuses on tailoring the therapy based on unique characteristics for a class of patients — or if possible, for each individual patient.[5] For instance, a conventional medicine approach would prescribe a similar dose for all patients with a particular disease, whereas a personalized medicine approach will advocate tailoring the dose based on a pharmacogenomic profile that may reveal patient-specific inadequacies (for instance, lack of detoxification enzymes involved in drug metabolism[6]). The more detailed and accurate the stratification of patients, the more customized and precise the therapy becomes.[7]

Traditionally, this stratification has been achieved by the identification of unique patient-specific biomarkers that are mined through different diagnostic methods that analyze biological fluids and/or tissue biopsies. However, rapid

advances in sequencing, bioinformatics, and AI have expanded the focus to deriving these stratification insights through the use of multiomics, which seeks to acquire comprehensive information for various types of biomolecules within a cell, tissue, or organism from an integrative analysis of multiple "omics" fields.[8] Based on what is measured, this can include genomics (DNA), proteomics (proteins and modifications on them), metabolomics (metabolites), transcriptomics (coding and noncoding RNAs), epigenomics (modifications on DNA), and the microbiome (diversity of microorganisms in your gut, for instance).

HISTORY OF PERSONALIZED MEDICINE

As we continue to hear announcements of healthcare breakthroughs powered by artificial intelligence (AI) advances and "multiomics" approaches, the excitement over precision medicine may seem new, but the core philosophy behind this approach is very old. In 510 BCE, Pythagoras recognized that the ingestion of fava beans resulted in fatal reactions only in select individuals. We now know that the molecular explanation of this anomaly can be explained by an enzyme deficiency. In fact, Avicenna (Ibn Sina), a Persian polymath regarded as one of the most influential physicians of the Islamic Golden Age, described concepts that bear a striking resemblance to current ideas of personalized medicine. In The Canon of Medicine (published 1025 CE), he writes that:

> *Any medication will have different effects on different bodies, organs of a person, at two different time points in one person's body, and in one organ at two different time points.*

Avicenna pointed out that differences in 10 patient-specific factors (color of face and body, skeletal structure, hair features, sleep-wake pattern, feces, urine, sweat, behavior, mental states, and mood) influence the overall temperament (mizaj) of the patient and are critical in determining response to medications. He also observed that factors like season, climate, occupation, gender, age, habits, physical strength, and physique influence the effectiveness of medications. Although these early concepts appear to be abstract and lack the sophistication

of current approaches to personalized medicine that are backed by genomics data, they nevertheless highlight the fact that physicians have long recognized the value of individual physiological attributes in shaping a response to medications.

Figure 2 : Avicenna's 10 patient-specific factors determining response to medications

The more recent historical roots of personalized medicine can be traced back to the discovery of the ABO blood grouping system by Karl Landsteiner in 1901. The screening of blood groups prior to blood transfusion may nowadays seem something obvious and even trivial, but such early discoveries were vital in shaping the scientific appreciation for identifying individual patient-specific attributes for optimizing therapy. The British physician Archibald Garrod pioneered our understanding of the genetic basis of drug toxicity through his work on metabolic disorders. The core ideas of individuality in shaping drug response is evident in his book The Inborn Errors of Metabolism, where he describes the term "chemical individuality." He says:

> *"Every active drug is a poison, when taken in large enough doses; and in some subjects, a dose which is innocuous to the majority of people has toxic effects, whereas others show exceptional tolerance of the same drug."*

A flurry of advances in the 1950s further solidified the concept of how genetics influences response to medications. Arno Motulsky, who is widely recognized as the father of pharmacogenomics, laid the foundations for personalized medicine in the mid-1950s through his work on the relationships between drug metabolism and genetic variability between individuals. The discovery of ethnic variants of plasma cholinesterase for explaining susceptibility to malignant hyperthermia by Werner Kalow[9] was another seminal advance that increased the appreciation of how individual genetic differences determine drug toxicity. The term "pharmacogenetics" was coined soon thereafter in 1959 by Friedrich Vogel, a close collaborator of Arno Motulsky.

The 1980s saw the characterization of cytochrome P450 family 2 subfamily D member 6 (CYP2D6)[10] and discovery of critical polymorphisms in metabolic enzymes and drug transporters, which ushered in an age where pharmacogenetic aspects influencing treatment efficacy gained widespread appreciation. The identification of these polymorphisms was followed by the discovery of several other polymorphisms in genes involved in metabolizing or responding to drugs.[11]

Polymorphisms are genetic variations that can influence the external phenotype of an individual, including how well the person will respond to and tolerate certain drugs. One of the most common forms is single nucleotide polymorphisms (SNPs), which involve variation in a single nucleic acid.

The completion of the human genome project in 2003 accelerated the discoveries that would fuel the revolution of personalized medicine. The completion of this project occurred during a time when prices of sequencing technologies began to see a rapid decline, making it possible to quickly screen gene-level demographic differences in a cost-effective manner. A testament to this phenomenon is the International HapMap Project (short for "haplotype map"), which has cataloged 3.1 million SNPs, many of which are now recognized as affecting health, disease, and responses to drugs. The project was formalized in

2002 even before the completion of the Human Genome Project, and by 2005 a comprehensive catalog of millions of SNPs was published in a landmark Nature paper.[12] Encouraged by the success of HapMap, the international scientific community acted quickly to leverage the cost-saving advantages of next-generation sequencing (NGS) introduced in the 2000s and embarked upon the ambitious 1000 Genomes Project in 2008. This global collaborative project aimed to sequence at least 1000 genomes from individuals from various ethnic groups, in order to develop a comprehensive catalog of human genetic variation. The first update of this project cataloging genetic variants across 14 demographics was published in 2012.[13] This paper remains one of the most highly cited papers in the field of biology. The project was completed in 2015 with another highly cited Nature paper showcasing the results from an analysis of 88 million variants spanning 26 demographic groups.[14] Close on the heels of the first draft of results from the 1000 Genomes Project in 2012, the United Kingdom announced the 100,000 Genomes Project. The project reported a major milestone at the end of 2018 when data acquisition for the 100,000th genome was achieved.

This history of internationally collaborative genome projects is also peppered with the development of several cancer genome databases. Some of the most popular cancer-specific omic databases include:

- **The Cancer Genome Atlas (TCGA):** Launched in 2005, the resource includes information form 20,000 primary cancer and matched normal samples spanning 33 cancer types. In April 2018 the TCGA achieves a major milestone with Cell publications documenting molecular and clinical information from over 10,000 tumors representing 33 types of cancer.
- **International Cancer Genome Consortium (ICGC):** Launched in 2007, the goal of this project is to catalogue genomic, transcriptomic and epigenomic changes in 50 different tumor types and/or subtypes.
- **Catalogue of Somatic Mutations in Cancer (COSMIC) :** Launched in 2004, this is the world's largest and most comprehensive resource documenting the effects of somatic mutation in cancer, and includes mutation profiles of over 1,000 cell lines used in cancer research..

TIMELINE OF KEY ADVANCEMENTS IN PRECISION MEDICINE

510 BCE
Pythagoras recognizes that ingestion of fava beans results in fatal reactions only in select individuals

1025 CE
Avicenna describes concepts that bear a striking resemblance to current ideas of personalized medicine

1901
Karl Landsteiner discovers the ABO blood grouping system

1923
Archibald Garrod pioneers understanding of the genetic basis of drug toxicity through his work on metabolic disorders

1957
Arno Motulsky lays the foundations for personalized medicine through his work on the relationships between drug metabolism and genetic variability between individuals

1959
Friedrich Vogel coins the term “pharmacogenetics”

1985
Researchers identify critical polymorphisms in cytochrome P450 2D6 (CYP2D6) involved in drug metabolism, heralding an increasing recognition of the importance of variations in metabolic enzymes and drug transporters upon treatment efficacy

1998
FDA approves Herceptin, the first therapy directed based on the genetic determinants of cancer

2000
Lynx Therapeutics launches Massively Parallel Signature Sequencing (MPSS)

2002
The International HapMap Project is announced

2003
The Human Genome Project is completed

2005
- The first update of the HapMap project is published

- The Cancer Genome Atlas (TCGA) is launched

- 454 Life Sciences launches large-scale parallel pyrosequencing system (acquired by Roche in 2007)

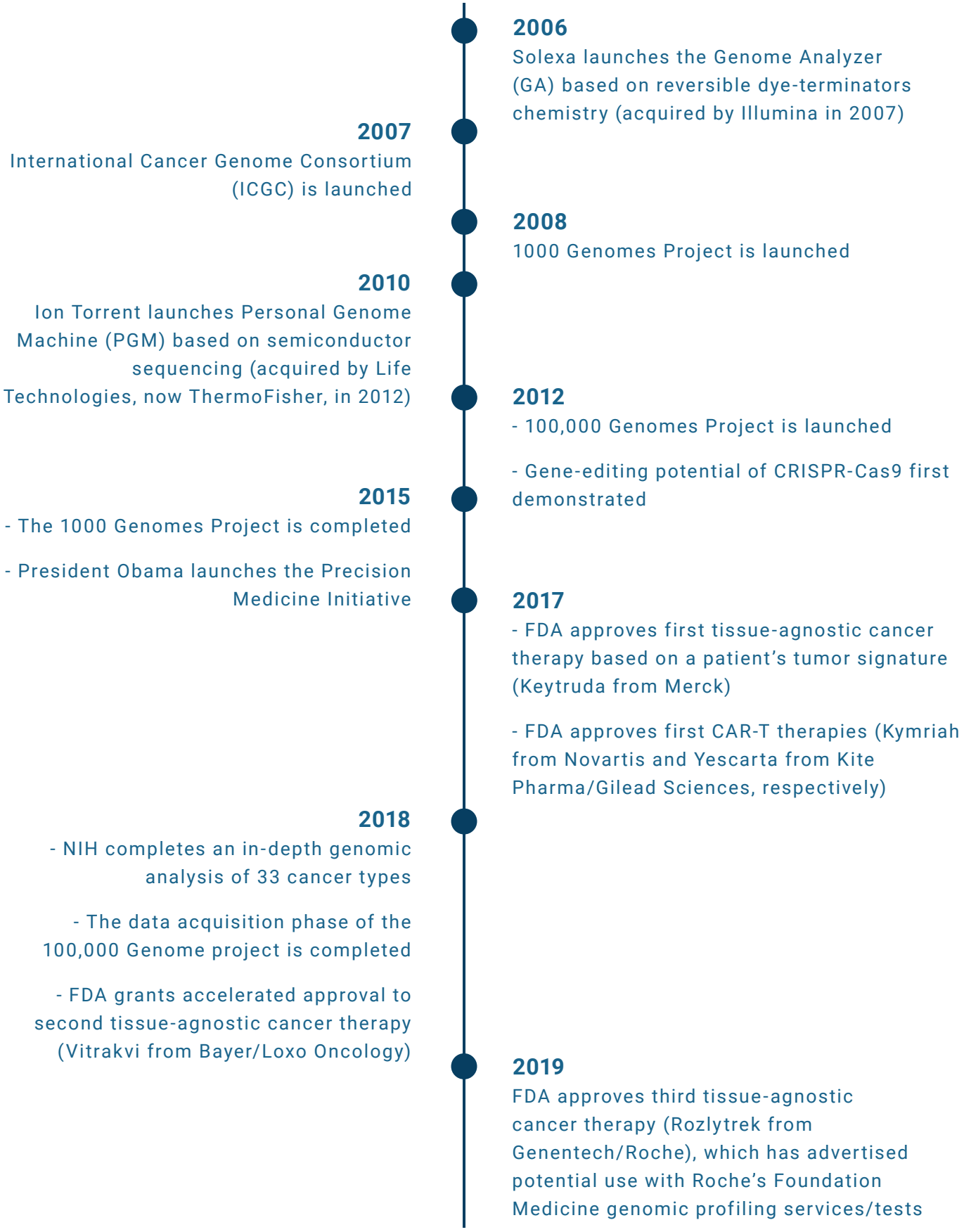

Figure 3 : A timeline showing the key advancements in precision medicine

What is next for personalized medicine? Converging technologies will play a vital role, ranging from advances in acquiring, processing, and interpreting multiomics data based on approaches such as AI to novel ways to deliver personalized therapies, including targeted immunotherapies and CRISPR-Cas9 gene editing (two topics which merit separate white papers, and which are only briefly discussed herein). In addition, government and industry incentivization of precision medicine research, policies shaping increased sharing and democratization of scientific data, and the rise of electronic health records are key aspects that will shape the future of personalized medicine.

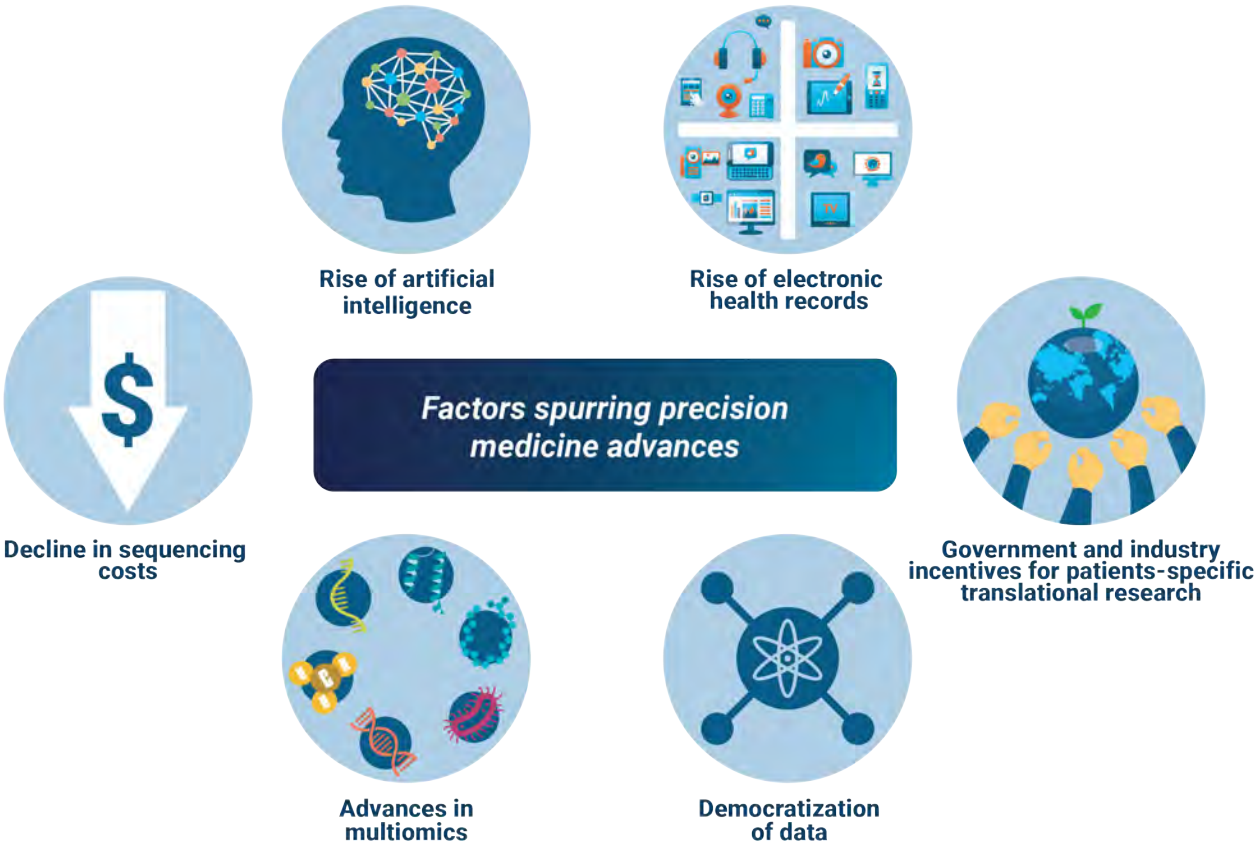

Figure 4 : Key factors spurring advances in precision medicine

THE WINDING ROAD TO PERSONALIZED MEDICINE

Hurdles and checkpoints

The idea that we all could lead healthier, longer lives with the advent of personalized healthcare is a testament to the ingenuity and evolution of medicine. Gene sequencing, pharmacogenomics, and AI are just a sampling of the methods that make individualized treatment programs a reality. But there is a wide gap between understanding how a disease works and delivering informed personalized treatments.

Data collection and analysis: From numbers to clinical practice

The discovery of biomarkers for specific diseases is the backbone of personalized medicine. There are always genetic, molecular, and/or physiological components to a disease; without unique identifiers that stratify affected patient populations for optimized drug targeting, personalized medicine wouldn't exist. Big data analytics and machine learning provide mountains of information that help isolate biomarkers of disease. These large data sets also aid in predicting disease in people who have yet to display symptoms.[15] But diseases are complex and multifaceted. So how well do data science-driven solutions translate into clinical outcomes?

At present, relying solely on machine learning methods to derive clinical treatment strategies is not a viable option. There are inherent wrinkles in machine learning — such as the below-par signal-to-noise ratio caused by technical measurement error and biological variation — that need to be smoothed out.[16] We also have a difficult time correctly translating the social and environmental contributions to disease into numbers, which means that important data are removed from the analysis.

Personalized medicine will require the predictive power and data integration that AI, once further optimized, can afford. From a practical standpoint, this type of technology is necessary if the goal is to treat everyone according to their own specific perturbations. Personalized medicine is a massive undertaking, when we consider the multilayered etiology of diseases. However, large data sets can filter and digest a lot of these layers, not to mention reduce the amount of time it takes to diagnose and treat conditions.

The cost of personalized medicine

Personalized medicine will not only change the way patients are diagnosed and treated, but it will also upset current drug manufacturing protocols. Large-batch production may become a thing of the past, and that's not necessarily a bad thing. Single-use technologies that produce small batches of drugs are safe and effective and don't have the financial burden of fixed capital investments and constant equipment upkeep.[17]

On the other hand, individualized drug therapies will disrupt many of the automated processes that have been tested and validated under quality control requirements.[18] This could mean a shift in manufacturing to manual labor, which would require new production facilities and altered supply-chain logistics. Many current personalized treatments involve manufacturing products using a patient's own cells. For example, chimeric antigen receptor (CAR) T-cell therapy necessitates the extraction of a patient's T-cells, genetic reprogramming of these T-cells so they can fight cancer cells, and reinfusion back into the patient.

This type of therapy is a far cry from the "simple" manufacturing of a drug in-house and exporting it to facilities that directly market to patients. Instead, it is a complex arrangement of appropriate shipping conditions, quality control, and safety requirements. And this is all for a single patient. How personalized medicine will ultimately affect manufacturing and distribution is unclear; but the industry will need to adapt to fulfill individualized production needs.

How will personalized medicine affect healthcare costs? That's also not clear. It seems likely that specialized treatments made for individuals or small groups of people would increase costs because everyone would require individualized drug production.[19] On the flip side, genomic sequencing that creates a roadmap for precision treatment decisions is not as costly as it was 15 years ago[2] , and informed drug targeting could reduce the overall cost of healthcare by addressing the underlying causes immediately. Perhaps it will be most interesting to observe how insurance companies react to this treatment paradigm shift.

Historically, insurance companies have taken a very conservative approach to coverage of genetic testing, which at this point is the primary foundation for identifying individual treatment strategies. To circumvent this problem, US lawmakers on both sides of the aisle are drafting legislation like the Advancing Access to Precision Medicine Act[20] that would allow states to apply for exceptions to the federal medical assistance percentage rate to cover whole genome sequencing clinical services for children whose diseases may have an underlying genetic component.

Genetic and genomic sequencing companies are also doing their part in making personalized medicine more palatable to insurance companies by offering to pick up part of the tab. Under a contract between Harvard Pilgrim Health Care and Illumina, Harvard Pilgrim will cover — to a predetermined limit — prenatal genetic testing for women under the age of 35 with average-risk pregnancies, while Illumina, a next-generation genetic testing company, will cover the remaining cost.[21] Partnerships like this may show the utility of genetic testing while potentially reducing the financial burden of lifelong healthcare for improperly diagnosed and treated conditions.

Regulatory challenges

The number of approved personalized medicines has increased dramatically since 2005.[22] This consists of both conventional modalities as well as novel approaches; for example, in 2017 the US Food and Drug Administration (FDA) approved the use of CAR T-cell therapy to treat B-cell lymphoma.[23] Despite this rise in approval, some challenges to regulation have arisen.

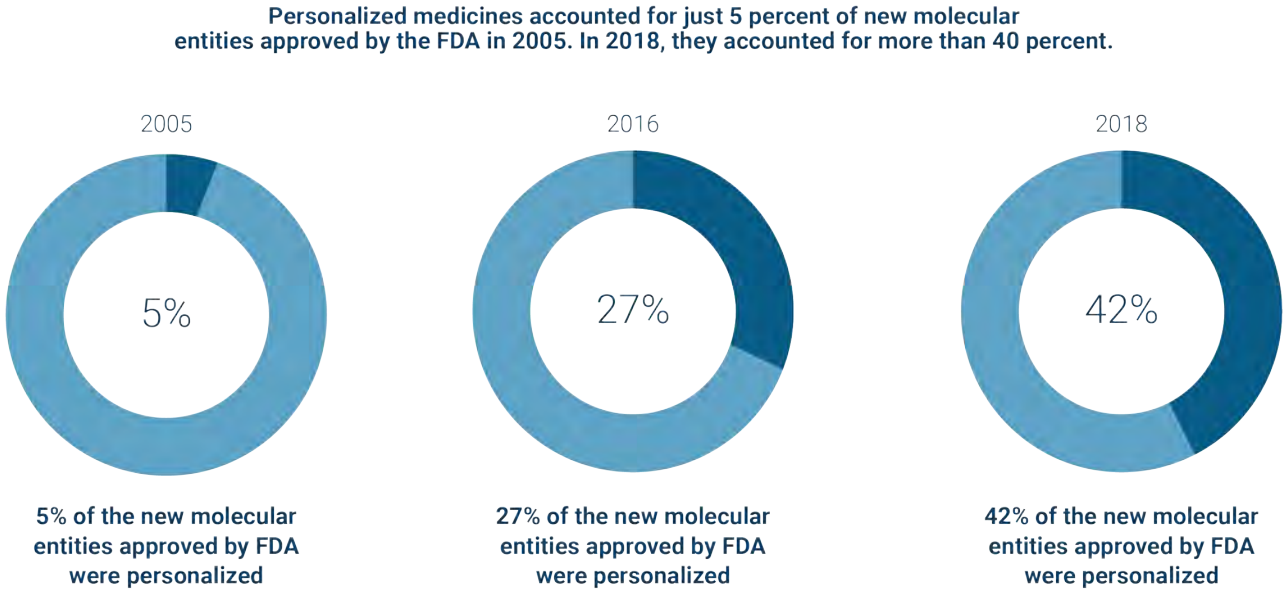

Figure 5 : Personalized medicine at the FDA: then and now[22]

The development of personalized medicine begins with the identification of patient-specific features. This often consists of a screen for a biomarker that allows tailoring of a therapy for a subset of the people affected by the disease. The trend is now moving towards whole-genome sequencing to identify specific gene variants indicative of a particular disease, and then establishing a treatment program based upon that genetic profile. However, whole genome sequencing provides data on three billion base pairs, which is a lot of information about variants whose significance has been heretofore unknown. The FDA has encountered the problem of needing to establish that a potential biomarker identified from sequencing is analytically and clinically valid without knowing anything about the variants.[24] To partially address this problem, the FDA has started to validate the

analytical performance of these presumed biomarkers through extensive testing of the proposed function of the biomarker (i.e., what the biomarker should be measuring).

Another level of regulation associated with personalized medicine is a companion diagnostic that describes whether a specific drug is administered to patients only after a diagnostic test confirms that either 1) the drug will have a beneficial effect for a particular condition, or 2) the drug may produce harmful side effects.[25] With personalized medicine, treatment strategies are often devised based on patient genetic profiling and assimilation of that profile with the drug target pathway. This means that FDA approval is necessary not only for the therapeutic drug, but also for the diagnostic indicator.

Ethical and social considerations

Personalized medicine is possible thanks to the thousands of people who have essentially donated their medical information. Much of the data now stored in biobanks and used to make informed treatment decisions were gathered when personalized medicine was naught but a thought. Potential ethical issues of using this data, where informed consent was given at a time when precision medicine was inconceivable, have been resolved.[26] The language of consent forms was broad and therefore ruled inclusive for modern research questions.

In an age of data compiling and sharing across the academic, industry, and healthcare settings, the most important considerations surround patient confidentiality, protection, and ownership of information, and proper disposal of materials. While interdisciplinary collaboration is great for innovation and discovery, it can also confuse the proper channels for information and sample handling. To get a handle on this, patients now have the power to control their information. Dynamic consent requires communication between the patient and the user of the patient's information when the user plans to apply the data to a new project.[27] The patient can deny or allow consent at any point and will always be informed of the manner in which their information is to be used.

But dynamic consent is neither widespread nor a requirement across all biobanks. Overall, there is a lack of consistency in consent requirements and perhaps a need for more strict and pervasive health data protection legislation.

PERSONALIZED MEDICINE FOR CANCER

Historically, cancer was diagnosed and classified based on its origin (breast, lung, prostate, etc.) and clinical aggressiveness. The success of precision medicine has paved acceptance toward diagnosing and treating many cancers based on their receptor status and molecular profile.

A large majority of cancers are driven by constitutive action of receptors and aberrant transducers that drive signaling pathways fueling their uncontrolled growth. The prescreening of a patient's tumors for genes such as HER2, BRAF V600E, and ALK before prescribing trastuzumab (breast cancer), vemurafenib (melanoma), and crizotinib (lung cancer), respectively, are some of the most well-known success stories where personalized medicine has been instrumental in the optimization of targeted treatments.[28-33] A more recent example has been the screening of microsatellite instability status for predicting sensitivity to checkpoint inhibitors, a class of drugs that unleashes the power of the immune system on cancer cells by breaking inhibitory interactions between T-cells and cancer cells.[34,35] Microsatellites are repetitive tracks of short DNA motifs that occur throughout your genome. The presence of an abnormal number of microsatellites is a recognized surrogate for impaired DNA repair activity — the deficiency of which predisposes the individual to accumulate aberrant genetic mutations. This microsatellite-driven predisposition for accumulating aberrant mutations is called microsatellite instability, and it is

now recognized to be a powerful predictor for a specific kind of immunotherapies. In fact, in 2017 the FDA approved Keytruda (pembrolizumab), a checkpoint inhibitor, for the treatment of pediatric and solid tumors that have metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) signatures and where prior therapy has been unsuccessful. With the FDA calling this the "first tissue/site agnostic approval," cancer pundits hailed it as one of the biggest wins yet for personalized medicine and immunotherapy.[36,37]

The devil is in the details: Molecular profiles of tumors guide treatment decisions

Personalized medicine relies heavily on targeted therapies and immunotherapies. The success of these therapies, in turn, depends on the accurate identification of genomic alterations fueling the disease. Such information can help guide treatment decisions; and, not surprisingly, a slew of tests have been developed by cancer diagnostics companies that now offer subtype-specific and pan-cancer profiling.

These companies conduct testing of patients' biopsy samples byemploying "gene panels." The panel that is used to construct molecular profiles of patient tumors employs methods such as next-generation sequencing, fluorescence in situ hybridization (FISH), high-throughput sequencing, and microarrays.

Regardless of the method employed to conduct such profiling, the results obtained from these panels can aid oncologists in assessing which treatments will benefit the patient most. Table 1 lists some of the most popular cancer diagnostics that are currently being used to guide personalized treatment of cancer patients.

Table 1: Popular cancer diagnostic products that guide precision medicine [38-54]

Companies	Popular Products/Services	Description
Abbott	Vysis CLL FISH Probe Kit	Detects deletion of the LSI TP53, LSI ATM, and LSI D13S319 and gain of the D12Z3 sequences by FISH in blood samples of B-cell chronic lymphocytic leukemia (CLL)
	Vysis ALK Break Apart FISH Probe Kit	Detects rearrangements involving the ALK gene via FISH technology in NSCLC tissue specimens
Biomerieux	THXID BRAF (melanoma)	An in vitro companion test to stratify melanoma patients that determines the suitability of patients for MEK and BRAF inhibitors based on V600E/K BRAF mutation status
	BIONEXIA FOBplus (colorectal cancer), BIONEXIA BTA (bladder cancer)	BIONEXIA FOBplus and BIONEXIA BTA use stool and urine samples for detection of colorectal and bladder cancer, respectively
BioReference Laboratories	4Kscore Test	Uses a blood sample to test the risk of aggressive prostate cancer
	GeneDx	GeneDx is a subsidiary company that provides clinical diagnostic services, which include exome and genome testing for multiple rare diseases and inherited cancers. The data collected is screened against >155,000 exomes and genomes to connect patients' phenotypes to candidate genes.
Caris Life Sciences	Caris Molecular Intelligence Comprehensive Tumor Profiling	Analysis of multiple biomolecules (DNA, RNA, and protein using IHC, FISH, and NGS, respectively) and pyrosequencing to generate reports that guide treatment decisions

Companies	Popular Products/Services	Description
Foundation One		Multiple NGS-based comprehensive genomic profiling assays for solid tumors, hematologic malignancies, and sarcomas
	FoundationOne CDx	FDA-approved broad companion diagnostic covered by Medicare that provides clinically actionable information for solid tumors, non-small-cell lung carcinoma (NSCLC), melanoma, and colorectal, breast, and ovarian cancers
	FoundationOneLIQUID	ctDNA- and NGS-based liquid biopsy test for solid tumors
	FoundationOne Heme	Comprehensive genomic profiling test for hematologic malignancies and sarcomas
GE Healthcare	Molecular Imaging and Medical Imaging products	A broad range of medical and molecular imaging products for diagnosing, staging, and monitoring treatment of breast, lung, colorectal, neurological, prostate hematological cancers/cancer samples. The imaging solution can help clinicians tailor the dose for patients as treatment progresses
Genomic Health	OncotypeDX for breast, prostate, and colon cancer	21-gene test; one of the most widely used tools for guiding breast cancer treatment
	Oncotype IQ Genomic Intelligence (in development)	
IBM Watson	Watson for Oncology	Analyzes data from medical literature, guidelines, trials, articles, and patient data and superimposes AI technology to recommend potential treatment options, which are ranked by level of confidence. The oncologist can then apply expertise to recommend the most applicable treatment options.
Illumina	AmpliSeq for Illumina Comprehensive Cancer Panel	Multiple ready-to-use and custom sequencing-based panels for cancer research
	TruSight Oncology 500 Cancer Panel	Detects driver mutations that cause cancer

Companies	Popular Products/Services	Description
Laboratory Corporation Of America Holdings	VistaSeq Cancer panels, Prosigna BCa Gene signature, Cancer Monitor Profile, HERmark Breast Cancer Assay, BRCAssure, cancer subtype-specific FISH assays	200+ subtype-specific and pan-cancer panels for diagnosing and monitoring treatment
Molecular Health	MH Guide	A computational platform that gathers evidence from medically and scientifically curated, peer-reviewed, and published sources. The data are then analyzed in the context of patient-specific (gender, tumor type, and variant data) and clinical information to generate a summary of treatment options, which are categorized based on their predicted efficacy and risk for adverse reactions.
Myriad Genetics	Myriad myRisk	35-gene panel that helps determine a patient's risk at eight primary sites
	Hereditary Cancer risk score	An algorithm that predicts 5-year and lifetime risks of developing breast cancer.
	BRACAnalysis	BRCA-powered risk assessment of hereditary breast or ovarian cancer
	COLARIS	Risk assessment for hereditary colorectal cancer and a woman's risk of developing hereditary uterine/endometrial cancer
	Prolaris	Determines prostate cancer aggressiveness
	EndoPredict	Evaluates the 10-year risk of breast cancer recurrence to help clinicians advise patients about weaning chemotherapy
	BRACAnalysis CDx	Manages breast cancer treatment with PARP inhibitors, Lynparza (olaparib), and Zejula (Niraparib)
	Myriad myPath Melanoma	Differentiates between benign nevi and melanoma using a 23-gene signature

Companies	Popular Products/Services	Description
Neogenomics		Multiple diagnostics tests sold in pan-cancer and subtype-specific formats
	CancerTYPE ID	PA proprietary assay that employs RT-PCR to measure the expression of 92 genes. The gene expression profile is matched to a database of more than 2,000 known tumor types and subtypes. It can identify 50 different tumor types and subtypes, covering >95% of all solid tumors with more than 87% accuracy. The test reports the main cancer type listed with a probability value quantifying the risk.
	Neotype Cancer Profile	NGS-based cancer profiling services that offer focused (26 cancer-specific profiles) to wide-spectrum tumor testing (four broad pan-tumor profiles).
Randox Laboratories Ltd	Biochip Array Technology, cytokine Array I-V	Comprehensive multiplex PCR platform; tumor marker tests include Randox Tumour PSA Array and Cytokine Arrays
Qiagen	therascreen and ipsogen line of products	RT-PCR-based detection of genomic alterations in solid tumors
Quest Diagnostics	BRCAvantage BRAF Mutation Analysis GIvantage Hereditary Colorectal Cancer Panel MYvantage Hereditary Colorectal Cancer Panel	Multiple gene panels optimized and sold in pan-cancer and subtype-specific formats

Before the advent of personalized medicine, cancer — regardless of type, stage, or location in the body — was treated with surgery, radiotherapy, or chemotherapy. Surgery is only a viable option if the cancer has not metastasized, and radiation and chemotherapy target both cancerous and healthy cells. The lack of specificity of these treatments is often ineffective and accompanied by unwanted side effects. Indeed, evidence has made clear that no two patients' cancers are identical, and they differ in response to the same therapy. Therefore, it must follow that a single broad approach to treating all cancers is futile.

The evolution of biomedical research has introduced immunotherapy as a better, more targeted approach to treating cancer. Immunotherapies include monoclonal antibodies, immune checkpoint inhibitors, cytokines, cancer treatment vaccines, and cell-based therapies such as CAR T-cell therapy. The overarching goal of cancer immunotherapy is to harness the immune system to specifically target and kill cancer cells while sparing healthy cells. Most current immunotherapies are designed to either target a specific tumor antigen or to enhance the patient's own immune system.

Monoclonal antibodies, the first type of immunotherapy to achieve widespread clinical use, have low cytotoxicity and target specific molecular moieties that tumor cells express. For example, trastuzumab (Herceptin) and pertuzumab (Perjeta) target HER2 breast cancer antigens and deliver improved clinical outcomes for patients with HER2-positive breast cancers, while other monoclonal antibodies, such as everolimus (Afinitor), are more clinically effective for HER2-negative breast cancer.[56]

Aside from antibodies, cancer treatment vaccines leverage the power of a body's T-cell response to mounting a potent immunization response against specific tumor neoantigens, or antigens expressed exclusively by cancerous cells.[57] Identification of patient-specific neoantigens has led to the development of personalized cancer vaccines for late-stage melanoma and for breast, lung, and colon cancers.[58] CAR T-cell therapy mentioned previously holds promise for individualized treatment because a patient's own T-cells are removed, re-engineered, and replaced with the precise ability to attack that patient's tumor cells.[59]

In addition to these examples, a plethora of novel therapeutic modalities that take advantage of various aspects of the complex machinery of the immune system to enable ever more targeted cancer treatments is being developed.[60] The continued advancement and modification of these technologies will help normalize the practice of tailored treatments not only for particular cancers but also for subtle patient-specific differences within a particular cancer type.

PERSONALIZED MEDICINE AND REGENERATIVE MEDICINE

The US National Institutes of Health defines regenerative medicine[61] as "the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects." One of the best examples of personalized medicine revolutionizing the field of regenerative medicine is the rapidly growing list of 3D-printed organs.[62] Although the technology is relatively new and its clinical translation is not widespread, there have recently been measurable research advances that include 3D printing of skin, kidney, heart, heart valves, ovaries, eyes, ears, teeth, prosthetics, and bones — just to name a few.[63-72] The disruptive nature of this technology is highlighted by market reports that claim it will surpass a value of $4.1 billion USD by 2026 while maintaining a compound annual growth rate (CAGR) just short of 20%. In April 2019, scientists from Tel Aviv University in Israel reported 3D printing of a cherry-sized heart that captures the full spectrum of anatomical complexity of cells, blood vessels, ventricles, and chambers within this organ.[73] Although the cells can contract, the physiological action of pumping still needs to be achieved. Nevertheless, the anatomical detail of the printed organ represents a major advance. A more tangible advance of precision medicine is evident through the success of Align Technology Inc., which recently reported multimillion-dollar sales of its Invisalign clear-aligner orthodontics.[74] The company uses 50 to 60 3D printers to churn out more than eight million customized orthodontics annually — each made by taking a scan of the patient's oral cavity through their patented iTero

system. Custom 3D printing of bones has also been achieved. Dutch startup Xilloc synthesizes patient-specific 3D-printed bone implants, which integrate with the existing skeleton and are designed to fit perfectly based on a patient's CT scans.[75,76]

So how exactly does 3D printing work for biological tissues? The first step is to construct a computer-aided model of an individual's organs or tissues that need replacement. Once this is achieved, it comes down to programming 3D printers to move in a way so as to assemble an organ using an "ink" of cells and biocompatible matrices loaded within its "cartridges." These computer models allow the maneuvering of computer-guided inkjet nozzles within 3D printers so they move with high precision while extruding a layer of biopolymers and cells that are assembled in a highly specific pattern. The models then direct the printer to move vertically and stack these layers to generate a three-dimensional organ.[77] An alternative approach is to use computer-aided models to assemble a scaffold of biocompatible polymers and then seed a precisely calculated cocktail of pluripotent cells on the scaffold. As the cells grow around this base, a simple scaffold transforms into a functional 3D organ. Regardless of the method employed, the power of precision medicine is in generating highly accurate models so the 3D-printed organs precisely match the cellular architecture, tissue patterns, and anatomy of the organ that is being replaced.[78]

Another powerful strategy involves the use of patient-derived stem cells to grow organoids — mini-organs that recapitulate the morphological and functional complexities of organs. Embryonic stem cells are an attractive option for tissue engineering because they can be manipulated into any type of cell in the body (i.e., they are pluripotent), whereas adult stem cells have limited differentiation capacity based on their tissue of origin. But since the word "embryonic" is now synonymous with controversy, comparable alternatives have been sought. One such alternative is the induced pluripotent stem cell (iPSC), which has the same chameleon-like changeability as an embryonic stem cell, but without the controversy. Derived from skin or blood cells, iPSCs are essentially tricked into becoming embryonic stem cells through genetic modification.

In practice, researchers can regenerate skin using a patient's own cells. For example, a genetic and potentially lethal condition known as epidermolysis bullosa, characterized by dysfunctional laminin and collagen proteins, causes painful skin

rupturing and blistering. But in a single-person clinical trial where a young boy's healthy skin cells were genetically reprogrammed and grafted onto his damaged skin, nearly 80% of his injured epidermis self-repaired.[79] The implications of this study are encouraging, because it circumvented the colossal problem of tissue rejection associated with transplanting foreign tissue (e.g., receiving skin transplants from a different person). This risk disappears when a patient's own cells are used.

PERSONALIZED MEDICINE FOR DIABETES

Any healthcare discussion is incomplete without addressing diabetes, a disease that affects more than 425 million people worldwide.[80] Identifying risk factors at the outset and preventing the disease is the key to reducing the global diabetes burden. Precision medicine advances will be instrumental in identifying demographic markers that can predict the risk of developing the disease. But how does one accurately predict the risk for a disease which is notoriously common? Researchers from Massachusetts General Hospital and the Broad Institute of MIT and Harvard have attempted this by analyzing genomic data for over 94 genetic variants already associated with type 2 diabetes. Using computational biology models and biostatistics, the team identified five DNA sites within the genome, each of which leads to the disease through discrete mechanisms that include insulin resistance, obesity, disrupted hepatic metabolism of fats in the liver, distribution of fat within the body, or beta-cell dysfunction.[81] Personalized medicine approaches like these could be instrumental in early identification of genetic signatures that increase a person's risk of developing diabetes and in guiding the adoption of lifestyle changes based on this profile.

However, while genetic studies may yield some insight into diabetes development, this disease is multifactorial and is as much caused by genetic as by nongenetic factors. Big data and machine learning can help integrate genetic predisposition with more phenotypic criteria such as age, weight, blood glucose, and comorbidities to accurately cluster patients into subgroups for personalized clinical treatment.[82] The combination of a patient-specific understanding of both genetic and environmental factors will radically improve our ability to predict which individuals are at the highest risk of developing the disease.

PERSONALIZED MEDICINE FOR CARDIOVASCULAR DISEASES

Personalized medicine also holds promise for cardiovascular disease. Considerable research has been done on individual genomic profiling of specific genes that can guide cardiologists in matching treatment with the type of cardiac pathology. Examples of such genes include KCNQ1, KCNH2, and SCN5A.[83] These genes code for channels that determine ion balance across cardiac cells and have been used to predict which beta-blockers are useful for different subtypes of Long-QT syndrome, a type of arrhythmia that can lead to sudden cardiac arrest. MyoKardia, a clinical-stage biopharmaceutical company, uses precision medicine approaches to identify targeted therapies for the treatment of serious and rare cardiovascular diseases. The company recently entered into a partnership with 23andMe, a rapidly growing genomics company known for its tests that provide targeted reports on disease predispositions. MyoKardia plans to leverage this partnership to develop a digital platform for hypertrophic cardiomyopathy patients with the aim of identifying genetic and environmental determinants that lead to the development of this disease.[84]

Pharmacogenomic assays that can predict the efficacy of lipid-lowering drugs are another example of a high-potential application of precision medicine in the cardiovascular field. Statins are one of the most frequently prescribed lipid-lowering drugs. However, their indiscriminate use in patients with high cardiovascular risks and their undesirable side effects are causes of concern, and their use is hotly debated among cardiologists. Many cardiologists have

expressed a need for technologies that can guide them regarding the use of statins in patients. Answering this call, Genomas, a small Connecticut-based company, has developed SINM PhyzioType, a genome array that can predict the efficacy and side effects of lipid-lowering drugs such as atorvastatin, simvastatin, and rosuvastatin in patients based on their genetics.[85]

PERSONALIZED MEDICINE FOR HIV

According to the World Health Organization, HIV remains one of the most pressing health problems today, with the disease claiming the lives of more than 940,000 people in 2017 and affecting greater than 36 million people worldwide.[86] Researchers are working to identify genetic determinants that could enable them to develop targeted therapies for this devastating disease, which compromises the immune system. Precision medicine advances that enable tailoring of cancer immunotherapies could also be a solution for tackling HIV.

Researchers from Penn Medicine, the Albert Einstein College of Medicine, and Sangamo BioSciences demonstrated the applicability of personalized medicine in HIV treatment recently in a Phase 1 clinical trial.[87] The researchers used zinc finger nucleases (specific molecular scissors that can remove a piece of DNA) to individually engineer T-cells of 12 patients by introducing a CCR5-delta-32 mutation, which deletes the CCR5 gene that encodes a protein critical for viral entry into the cell. This is a change that naturally confers resistance to HIV but is not found in 99% of the population. When the engineered T-cells were reinfused back into the patients, they conferred remarkable resistance to HIV and persisted in the circulation of patients, keeping the burden low for several weeks. Half the patients were able to discontinue antiretroviral therapy for up to 12 weeks after starting the T-cell infusion.

Antiretroviral therapy is typically the first line of defense against HIV. But prolonged therapy leads to drug resistance in some (but not all) HIV patients.

This disparity in response to antiretroviral treatment has created a burgeoning pharmacogenomic approach to personalized medicine. Drug resistance testing, including commercially-available kits such as ViroSeq[88] and HIV-1 Genotype[89], use gene sequencing techniques to identify drug resistance mutations in HIV patients. The FDA recommends that HIV patients take the HLA-B*5701 allele test to narrow the list of potentially effective antiretrovirals. HLA-B*5701 is a variation of the human leukocyte antigen (HLA) complex, and people with this particular mutation are hypersensitive to the antiretroviral drug abacavir.[90]

Aside from gene sequencing to evaluate appropriate antiretroviral drugs, online therapy prediction engines like the HIV Resistance Response Database Initiative personalize treatment strategies by synthesizing data gathered from various therapy options and ranking the best possible treatment combinations.[91] This tool can estimate the outcomes of various drug interactions as well as the probability of developing viral resistance to specific antiretroviral combinations. Still in development, prediction engines could be a vital source of therapeutic information in the future, following extensive data integration pertaining to strains and mutations of HIV, metabolism of antiretrovirals, and patient adherence to therapy programs.

PERSONALIZED MEDICINE FOR ALZHEIMER'S DISEASE

One out of 10 people over the age of 65 will develop Alzheimer's disease and associated dementia.[92] That staggering statistic, coupled with the mile-high pile of failed clinical trials over the years, makes for a rather depressing outlook for this disease. From these failures, we've learned that Alzheimer's is a complicated disease involving multiple body systems spanning neural, immune, endocrine, and metabolic pathways and including the gut microbiome and that the accumulation of amyloid-beta plaques in the brain precedes memory loss. But to complicate things a bit more, there are some people who have plenty of cerebral amyloid-beta plaques and no associated brain or memory dysfunction.[93] It really is no wonder at the lack of success of Alzheimer's clinical trials — the population affected by it has a very diverse presentation. We now know that a "one size fits all" treatment strategy is not an option.

Enter personalized medicine. Over the years, scientists have identified certain genetic variants expressed by different subpopulations of Alzheimer's patients that make them susceptible to the disease. These genes serve as a focal point for the creation of drugs that directly target the genes or their downstream effectors. Genomic sequencing allows researchers and doctors to determine if patients express the same genes that their drugs target; if they do, they can readily recommend these drugs for treatment. The Alzheimer's drug Anavex 2-73 has produced promising results in an initial Phase 2 clinical trial,

which involved first sequencing potential participants' genomes and then assigning them to the trial if their genetic makeup and the mechanistic pathway of Anavex 2-73 coincided.[94] While some may consider this method questionable, others argue that the heterogeneity of factors causing Alzheimer's demands that different drugs are administered to different people in order to produce the best possible outcomes.

While Alzheimer's is one of the most studied neurodegenerative diseases, precision therapy approaches are also being employed for other neuro-linked disorders, including Parkinson's disease and multiple sclerosis.[95,96] Whole genome analysis is the first step in identifying unique biomarkers enriched in afflicted populations. From there, pharmacogenomic drug testing provides a platform to measure the efficacy of specific drugs for individualized populations.

CONCLUSION: PERSONALIZED MEDICINE AND INDUSTRY

The industry has long recognized the promise of personalized medicine, with many new entrants in the last decade leading the way and offering molecular diagnostic services and comprehensive genomic testing for cancer and other diseases. Forecasts of the total size of the personalized medicine market in 2025 range from USD 100 billion to over USD 2 trillion, due to varying definitions of the market, with most research firms estimating a CAGR of 10–11% over that time period.[97,98] A robust ecosystem of companies working in this space is emerging which includes key players from the biopharmaceutical and high-tech industries. Figure 6 shows a few promising companies, categorized by the focus of their activities on diagnostics, therapeutics, or bioinformatics.

Figure 6 : Major players in the field of personalized medicine

The US-based drug giant Pfizer is making waves in the personalized medicine field through its development of cancer drugs like TALZENNA (talazoparib), which in 2019 received approval from the European Commission as a therapeutic for breast cancer. TALZENNA is a poly ADP-ribose polymerase (PARP) inhibitor administered orally for women with mutations in the germline breast cancer susceptibility gene (gBRCA)1/2. Pfizer also currently has over 30 cancer drugs in clinical development, and in 2018, the company formed a partnership with Foundation Medicine to use FoundationOne CDx, a pan-cancer companion diagnostic, to advance the use of personalized medicine in patient care. [99-101]

Other potentially advantageous partnerships have formed, such as pharmaceutical company Sanofi's alliance with Google. Together, these two industry-leading companies are developing a virtual Innovation Lab that combines Google's deep data analytics, cloud computing, and AI with Sanofi's real-world scientific data to deliver individual patient-driven precision treatments. [102] Moreover, in a commendable effort to identify every genetic source contributing to cancerous cells, GlaxoSmithKline, Wellcome Sanger Institute, the European Bioinformatics Institute, and Open Targets have formed a research collaboration to use CRISPR technology to edit nearly 20,000 genes in 300 cancer models from 30 different cancer types. This effort unveiled approximately 600 cancer genes with uncharted therapeutic potential and formed the basis for the Cancer Dependency Map that pinpoints genetic targets for the precision treatment of cancer. [103]

These types of collaborations bode well for the future of the individualized approach to healthcare. Personalized medicine stands on the pillars of "omics-based" testing, bioinformatics and AI, and perhaps most importantly, collaboration between pharmaceutical/biotech companies, healthcare facilities, patients, and insurance companies. The potential for personalized medicine to revolutionize drug delivery and patient care demands an evolutionary shift from the current modus operandi. The cost of omics-based testing decreases each year, and AI algorithms become sharper and more predictive with each new integrated data set. These changes mean increased

affordability for tests that drive individualized patient treatment options. But what remains to be seen is how these advancements will influence clinicians' diagnostic and treatment decisions and whether all healthcare facilities will standardize personalized medicine practices. How will patient data be made available across all healthcare facilities so the most up-to-date information informs the ideal treatment strategy per patient? Will insurance companies follow in the footsteps of Harvard Pilgrim Health Care and cover a percentage of genetic and genomics testing, and later, personalized drug development?

As is the case with most scientific advancements, the regulatory, social, and economic facets must play catch-up with the technology. Clear and transparent processes and communication will be necessary to ensure that personalized medicine is practiced efficiently and effectively. With the power to address unmet medical needs at the individual level, universal personalized medicine is the goal.

As industry leaders sharpen their precision medicine technologies, and scientists and clinicians, along with healthcare, regulatory, and legislative bodies worldwide work tirelessly to streamline our arsenal of personalized medicine, we can be assured of a future that will bring unprecedented precision in identifying the "Right Treatment, Right Patient, Right Time."[104]

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