Cell

Leading Edge
Review

High-Definition Medicine

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The foundation for a new era of data-driven medicine has been set by recent technological advances that enable the assessment and management of human health at an unprecedented level of resolution—what we refer to as high-definition medicine. Our ability to assess human health in high definition is enabled, in part, by advances in DNA sequencing, physiological and environmental monitoring, advanced imaging, and behavioral tracking. Our ability to understand and act upon these observations at equally high precision is driven by advances in genome editing, cellular reprogramming, tissue engineering, and information technologies, especially artificial intelligence. In this review, we will examine the core disciplines that enable high-definition medicine and project how these technologies will alter the future of medicine.

High-Definition Medicine Defined

We define high-definition medicine as the dynamic assessment, management, and understanding of an individual's health measured at (or near) its most basic units. It is the data-driven practice of medicine through the utilization of these highly detailed, longitudinal, and multi-parametric measures of the determinants of health to modify disease risk factors, detect disease processes early, drive precise and dynamically adjusted interventions, and determine preventative and therapeutic intervention efficacy from real-world outcomes (Figure 1). In contrast, current medical tests often rely on coarse-grained, static, and often isolated snapshots of an individual's health state taken months or even years apart. The tools of high-definition medicine operate within four highly interconnected strategies for health management. These strategies are summarized below (Box 1):

1. Defining a Personal Baseline of Health: The foundation of high-definition medicine rests on the precise and comprehensive assessment of individual level measures of the determinants of health. Health risks and interventions are tailored and evaluated relative to this personal baseline; comparing you to you and people like you and not to broad population norms.
2. High-Definition Prevention: Continuous or frequent assessment of the determinants of health allows for the early detection and response to deviations in health parameters from the personal baseline, before clinically manifest, likely preventing or delaying disease onset.
3. High-Precision Treatment: Upon the onset of disease, precision interventions are designed from, and their efficacy informed by, the personal health baseline as well as the precise molecular etiology of the disease. High-definition tools tailored to monitor specific disease processes enable the identification and modification of treatment failures early.
4. Billions of High-Resolution People: The direct incorporation of health baseline, health trajectory, and treatment outcomes data collection into the practice of high-definition medicine seamlessly enables a continuously improving, learning health care system, whose collective knowledge can help preserve the health of an individual.

High-definition medicine is emerging from an accelerating coalescence of the biological and medical sciences with computer science and engineering (Sharp et al., 2016). The combination of these disciplines has given rise to technologies that produce large volumes of clinically useful information, sometimes as a continuous stream of data, resulting in big-data handling challenges for the effective clinical utilization of these technologies.

High-Definition Medicine Requires Big-Data Capabilities and Policies

The basic groundwork for high-definition medicine is already being built, though the infrastructure to support it is still in its early stages and will require significant investment from health care service providers. A 2011 study by McKinsey Global Institute (Manyika et al., 2011) estimated that the effective use of big data by the U.S. health care sector would create an estimated $300 billion in value every year, under the assumption that the required information technology (IT) and analytical investments are made. The health care sector is well poised to capture the value of big data as it is already a data-driven culture, generating the necessary variety and volume of data but lacking the IT assets required to capture, process, and present that data into value-creating insights. The vast majority of the near-term projected value of big data in health care comes from the

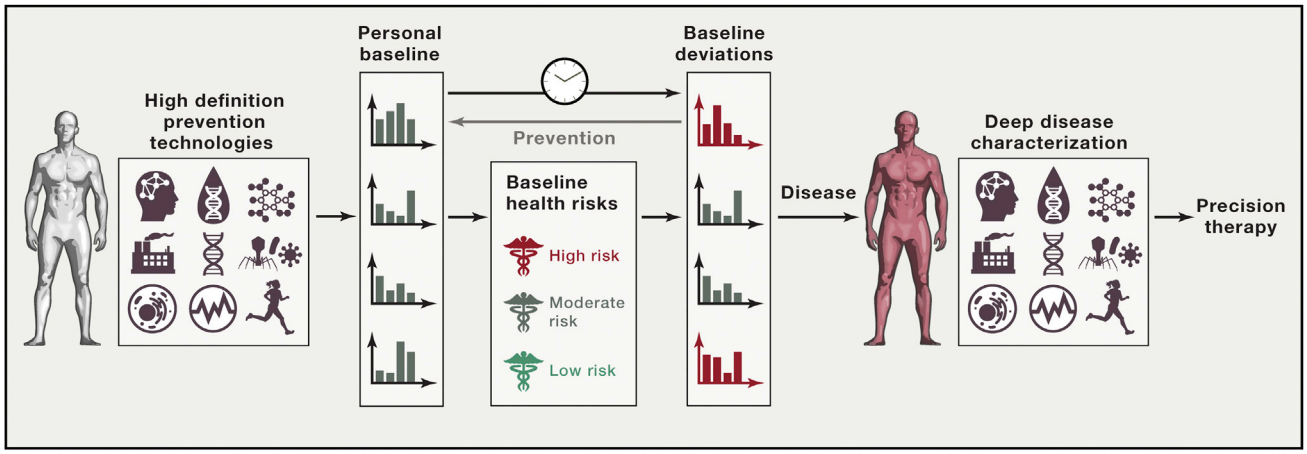

Figure 1. High-Definition Medicine

A flow diagram depicting high-definition medicine. The Personal Baseline of Health (personal baseline) is defined via a variety of health technologies described in High-Definition Prevention (icons to left). Health risks are determined through the integration of the level of risk associated with deleterious genetic variants and the level of divergence of an individual's personal health baseline from individualized optimal health ranges (baseline health risks). Deviations from the personal health baseline over time provide early detection and an opportunity to intervene in pre-disease processes and are evaluated in the context of baseline health risks (baseline deviations). Progress toward amelioration of these disease processes is judged on the basis of the return to the personal health baseline. Upon the onset of disease, deep profiling (icons to right) defines the appropriate selection of high-precision therapeutics.

identification of the most clinically effective and cost-effective treatments from data already being generated by health care providers, all while holding health care outcomes constant.

High-definition medicine has similar but more significant implementation hurdles to overcome before its value can be fully realized. Investment in infrastructure suitable for and development of policies governing the capture, storage, privacy, analysis, presentation, and interoperability of large datasets will need to be defined for high-definition medicine technologies not currently used in routine clinical practice. Clinical decision support systems and training programs for medical practitioners must be developed to seamlessly integrate these data and technologies into clinical workflows. The cost effectiveness of these technologies will need to improve before broad clinical implementation is feasible. Financial incentives must be aligned with the health benefits achievable through the use of these technologies to drive adoption. Moreover, policies governing regulatory approval, evidence generation, and reimbursement of the clinical use of these technologies will need to be developed. Overcoming these challenges is a major mandate of the current Food and Drug Administration (FDA), with efforts underway to "have the right policies in place to promote and encourage safe and effective innovation that can benefit consumers, and adopt regulatory approaches to enable the efficient development of these technologies" (Gottlieb, 2017). Overcoming these barriers has an even greater potential to improve health care outcomes via early detection of disease, precise application of effective therapies, intense monitoring of treatment progress, and rapid identification and correction of treatment failures.

Under the assumption that the implementation barriers to high-definition medicine will eventually be overcome, herein we review the progress in the core components of high-definition medicine technologies and envisage how these technologies will develop and interact to alter the future of medicine.

Defining a Personal Baseline of Health

At its most basic level, personal risk for disease is comprised of genetic makeup, behavior, and environmental exposures. Currently, an individual's baseline risk for disease is estimated to be the incidence of disease in the population modified by the measurement of clinical factors known to be associated with disease. Family history is often factored in as a blunt measure of genetic factors as well as shared environment and behaviors. In current practice, deviations from population level norms, both in terms of the measured value of clinical risk factors as well as the level of aggregation of disease in one's family, are used to identify individuals at elevated risk for disease. In high-definition medicine, baseline risk for disease is defined by more precise measures of genetic makeup, physiologic metrics, behavior, and environmental exposures, and the significance of deviations from expected norms for risk factors are individualized (Figure 2). To establish personal norms and detect deviations early, clinical factors are measured continuously or frequently and in the real-world. This paradigm will result in a more accurate determination of health status as compared to the singular measurements taken in a medical facility, which can be influenced by diurnal variation, state of mind, hydration status, and myriad other factors that vary from moment to moment.

A Genetic Baseline for Health Risks

High-definition medicine includes the definition of genetic risk for all individuals, at birth, based on complete genome profiling. Although whole-genome sequencing technology is currently available, family history is routinely used to assess genetic risk for disease. Familial aggregation of disease is used to estimate whether an individual is at higher risk for disease, recommend behaviors that might reduce their risk, potentially plan for early screening for disease, and evaluate the significance of early signs of disease. While family history is an effective tool for

Box 1. The Pillars of High-Definition Medicine

- Defining a Personal Baseline of Health: The foundation of high-definition medicine rests on the precise and comprehensive assessment of individual level measures of the determinants of health. Health risks and interventions are tailored and evaluated relative to this personal baseline; comparing you to you and people like you and not to broad population norms.
- High-Definition Prevention: Continuous or frequent assessment of the determinants of health allows for the early detection and response to deviations in health parameters from the personal baseline, before clinically manifest, likely preventing or delaying disease onset.
- High-Precision Treatment: Upon the onset of disease, precision interventions are designed from, and their efficacy informed by, the personal health baseline as well as the precise molecular etiology of the disease. High-definition tools tailored to monitor specific disease processes enable the identification and modification of treatment failures early.
- Billions of High-Resolution People: The direct incorporation of health baseline, health trajectory, and treatment-outcomes data collection into the practice of high-definition medicine seamlessly enables a continuously improving, learning health care system, whose collective knowledge can help preserve health of an individual.

identifying high-risk individuals, it can be incomplete and inaccurate, and it is only effective at identifying a subset of high-risk individuals when there are multiple close family members affected with early-onset disease (Scheuner et al., 1997). Most common diseases do not fit this profile. Accurately collected family history tends to classify ~5% of the population as high risk and ~10% of the population as moderate risk, at a sensitivity and specificity of ~80% (Berg et al., 2009; Lu et al., 2014; Yoon et al., 2002). Thus, ~85% of the population gains no information about their disease risk beyond the incidence rate in the population at large.

On the other hand, a full genome sequence is, theoretically, a complete description of an individual's genetic risk for disease (with the rare exception of potential transgenerational epigenetic inheritance (Heard and Martienssen, 2014)). It is a high-definition substitute for family history that is always available, is always complete, and comprehensively captures genetic risk factors that both have and have not manifested themselves as overt disease in family members. Genetic risk for disease can be roughly categorized into single-gene and polygenic traits.

Single-gene traits are those where one, two, or a small number of genetic variants in a single gene are sufficient to cause the trait or disease. For disease traits, these genetic variants are usually rare, may be effectively captured by family history, and underlie the majority of the population risk for rare diseases, but they explain a small proportion of the population risk for common diseases (Chong et al., 2015; Manolio et al., 2009). The current diagnostic rate of genome-sequencing programs suggests that, for 25%–50% of individuals with a single-gene disorder, genome sequencing can identify the genetic cause (Chong et al., 2015). For those individuals not receiving a genetic diagnosis, technical limitations of current genome-sequencing and analysis technologies, as well as our limited ability to interpret the significance of all detected genetic variants, especially non-coding variants, and the interactions between multiple genetic variants, likely underlie their negative genetic results. Efforts targeted at identifying novel disease genes and understanding the significance of all variants observed in a single medically important gene have demonstrated that the rate of variants of unknown significance can be dramatically reduced through focused genetic and phenotypic data collection (Chong et al., 2015). For example, Myriad Genetics reports that the clinical significance of 97.9% of BRCA1/2 variants has been determined (Eggington et al., 2014). The continued rapid pace of defining gene variants linked to disease, coupled with efforts to compile combined genotype-phenotype databases, will result in a future where the utility of family history is superseded by whole-genome profiling.

Polygenic traits are those where the genetic risk for the trait is comprised of the combined influence of multiple genetic variants of small to moderate effect size. Polygenic genetic risk is the most relevant source of baseline disease risk for the vast majority (~95%) of common chronic diseases (Manolio et al., 2009). Although the genetic variants that explain the entirety, or even the majority, of the heritability of most common chronic diseases have yet to be discovered, clinically useful predictions can still be made with our current, incomplete knowledge (Wray et al., 2010). For example, with our partial knowledge of the polygenic factors underlying disease risk, genetic risk scores can still identify high-risk individuals who benefit most from initiation of lifestyle changes or preventative treatments. Examples include (1) a 27-SNP genetic risk score for coronary artery disease was able to identify high-risk individuals who would benefit most from statin therapy and was projected to lead to a 3-fold reduction in the number of people treated to prevent one heart attack in high- versus low-risk individuals (Mega et al., 2015), (2) a 77-SNP genetic risk score for breast cancer was found to be more accurate than standard age-based criteria for guiding decision making on when mammographic screening should be initiated (Mavaddat et al., 2015), and (3) a 54-SNP genetic risk score for prostate cancer was able to identify high-risk individuals and dramatically improve the interpretation and positive predictive value of a positive prostate-specific antigen screen (Seibert et al., 2016) (Box 2). Thus, genetic risk scores for many diseases are already capable of informing health management for high-risk individuals. These scores will need to be validated and shown to have generalizability, especially for non-European individuals, and tested for their ability to change medical decision making and improve outcomes. This capability will only continue to improve as larger and more-refined genetic studies are pursued, but ultimately, large-scale genetic studies performed in the real world, via the merging and continuous analysis of genetic plus health-record data, will likely be necessary to comprehensively capture polygenic genetic risk (Chatterjee et al., 2013). What needs to be highlighted is that these genetic risk-score studies often provide independent and complementary information to traditional clinical risk factors—the second major component of the definition of a personal health baseline.

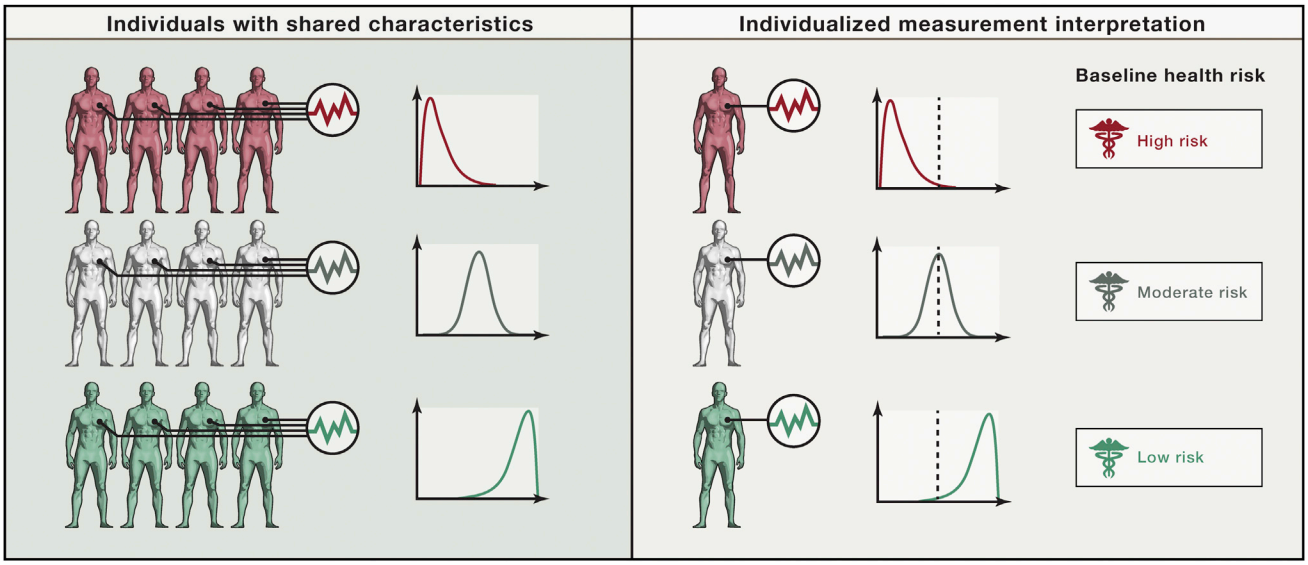

Figure 2. Personal Baseline of Health
A diagram depicting individualized interpretation of health-parameter measurements. An example generic health parameter is indicated here by the circular icon—where elevated values are assumed to be indicative of health risk. Left: The sub-population distributions of this generic health parameter, where individuals with similar characteristics are indicated by coloration. Right: The individualized interpretation of this health parameter measured in three disparate individuals. This generic health parameter is measured with the same numerical value across each of these three individuals (vertical dashed line in graphs). Far right: The differing interpretation of this health-parameter measurement.

A Personal Baseline for Health Parameters

Traditional clinical risk factors, such as blood pressure or cholesterol levels, are typically measured infrequently and evaluated on the basis of normal and abnormal range cutoffs associated with either optimal health, minimal risk of disease, or reference ranges containing 95% of the reference population (Häggström, 2014). Optimal health ranges, however, differ per individual based on factors such as age, gender, ethnicity, geography, season, etc. A trivial example is the obvious sexual dimorphism and ethnic differences in body composition, which leads to differences in the optimal body mass index required to minimize years of life lost to metabolic disease (Fontaine et al., 2003). More subtle differences in the optimal range of even the most basic nutrients have also been noted. For example, ethnic differences in the relationship between vitamin D levels and cardiovascular disease risk have been observed and likely trace their origins to genetic differences in genes involved in the biological activity of vitamin D (Pilz et al., 2016). Even the widely accepted "normal" body temperature of 98.6°F actually displays substantial variability (~94°F–100°F) across individuals (Sund-Levander et al., 2002). This inter-individual variability in health parameters suggests that personal baselines for each factor, rather than population norms, are a more effective yardstick for judging the significance of fluctuations in these factors.

Some nontraditional but emerging measures of health further exemplify the importance of personal baselines. For example, the human microbiome is tremendously diverse from individual to individual yet is highly stable within each individual over time (Lynch and Pedersen, 2016). While we do not yet fully understand the significance of microbiome dynamics, many disease states have been linked to perturbations in the microbiome, often leading to reduced microbiome diversity, yet the resultant microbiome profile remains unique from individual to individual despite a shared disease state (Lynch and Pedersen, 2016). Thus, rather than the detection of specific bacterial species indicative of disease risk, reductions in diversity or deviations in the microbiome profile from an individual's healthy baseline profile may be a more sensitive indicator of disease risk (see High-Definition Prevention, Microbiome).

Of course, an individual's natural set point for any particular clinical risk factor is not necessarily optimal for health. Rather, this personal health baseline serves as a means to judge progress toward an individualized optimal health target. An examination of even the most broadly applicable population level optimal health ranges for basic clinical risk factors reveals the utility of individualized optimal health ranges. Consider, for example, an individual who has a natural blood pressure set point of 140/90 mmHg. Lower blood pressure is usually associated with improved health span and longevity (Lewington et al., 2002). Efforts to lower the blood pressure of this individual below their natural set point could potentially reduce their absolute risk for disease, and progress toward this goal would be measured against their natural baseline. However, in frail elderly individuals, elevated blood pressure is actually associated with a lower risk of death (Odden et al., 2012). More generally, the frequent measurement of clinical health factors allows for the ascertainment of health trajectories, as measured by deviations from a personal health baseline, while the interpretation of the clinical significance of these health trajectories is individualized based on health outcomes data collected across a cohort with matched characteristics (Figure 2; see also Billions of High-Resolution People).

Box 2. Definitions Box

- SNP: Single nucleotide polymorphism—a DNA sequence variation occurring when a single nucleotide differs between members of a population.
- Epigenome: Chemical changes to DNA and DNA-associated proteins that regulate the activity of functional genomic elements.
- Cellular Mosaicism: The presence of two or more disparate populations of cells. Somatic mosaicism refers to cellular populations of cells that differ due to DNA changes.
- Immunome: The set of genes and proteins that comprise the immune system.
- Microbiome: The collection of microorganisms that populate a particular environment.
- Metabolome: The collection of small-molecule chemicals within an organism, cell, or tissue.
- Gene Therapy: The insertion of genes into cells, usually to replace missing or defective genes.
- Gene Editing: The direct editing of a DNA sequence natively present within a cell.

In summary, the high-definition medicine approach to identifying individuals at risk for disease is based on the direct utilization of genetic risk factors, the comparison of an individual's personal health baseline relative to other individuals with similar characteristics, and ultimately the definition of risk models that account for the interaction of genetic and clinical factors. Absolute health risks for an individual are determined as a function of the level of risk associated with deleterious genetic variants and the level of divergence of an individual's personal health baseline from individualized optimal health ranges. Modifications of lifestyle, monitoring, and interventions are defined and prioritized by the level of absolute risk. And the influence of the environment, behavior, medication, and other factors that influence an individual's risk for disease, as well as progress toward ameliorating those risks, are judged based on deviations in health parameters relative to a personal health baseline.

High-Definition Prevention

High-definition prevention is the early detection and response to deviations in health parameters from the personal baseline, likely preventing or delaying disease onset (Figure 3). Many of the tools of high-definition prevention have been summarized by us previously (Topol, 2014). Here, we review the potential application of these tools to continuous monitoring in high-definition prevention.

Genetic Risk and Genomics

A static snapshot of the whole genome, at birth, provides baseline risks for disease, as described above. Genetic risk, as determined by genetic risk scores and individual highly penetrant pathogenic variants can identify health risks that should be monitored and modified early. The role of genome sequencing in medicine has been discussed above and reviewed extensively elsewhere (Delaney et al., 2016; Manolio et al., 2013). However, recent studies have also unveiled dynamic attributes of the genome that are indicative of health, which we will focus on in this review.

Circulating Nucleotides

The technology to effectively interrogate circulating DNA for clinical purposes has only come about recently, and we are only beginning to understand the tremendous amount of medical information hidden in these DNA signatures. The first widely adopted clinical application of circulating DNA testing was a non-invasive prenatal test (NIPT) to detect fetal gender and chromosomal abnormalities during early gestation of a fetus (Yong, 2014). These tests transformed the early detection and potential prevention of highly detrimental chromosomal abnormalities. Early identification of abnormalities such as Down syndrome has improved from a sensitivity of 70%–94% with a specificity of 95%–99% via fetal nuchal translucency (Malone et al., 2005), to 99+% sensitivity and specificity via NIPT (Taylor-Phillips et al., 2016).

The success of NIPT testing has sparked research in a variety of other applications of circulating DNA testing. Cancer, via circulating tumor DNA (ctDNA), has been detected in pregnant women receiving NIPT testing (Hughes, 2015). However, early-stage tumors, in general, shed minute a mounts DNA into the bloodstream; thus, early detection of cancer will be challenging, requiring tests with analytical sensitivity for tumor DNA far below 1%. Initial successes in the early detection of minimal residual disease and recurrences in cancers resected with curative intent provides a proof of concept for the potential of longitudinal circulating DNA testing for the early detection of cancer (Tie et al., 2016). A major goal in the coming years for ctDNA screening in healthy, asymptomatic individuals will be the demonstration of improved outcomes based on early detection. A major challenge toward this goal will be determining the appropriate course of action for early-stage abnormal growths, specifically through the discrimination of benign growths that will self-resolve from those that will continue to persist and become malignant. Toward this end, large-cohort longitudinal studies have been launched to trace the natural history of ctDNA appearing in the plasma of healthy individuals or those with high genomic baseline risk (Sheridan, 2017).

More generally, circulating DNA profiles can be used to detect tissue-specific growth and development (Koh et al., 2014) and identify tissue-specific cell death (Snyder et al., 2016). Circulating DNA methylation profiles can further refine tissue-specific cell death signatures (Lehmann-Werman et al., 2016), and circulating RNA profiles can allow the assessment of the state of tissues, such as the brain, that are otherwise inaccessible (Koh et al., 2014). These capabilities allow for the detection of organ-specific disease processes such as early detection of organ-transplant rejection (De Vlaminck et al., 2015) and a variety of other tissue-specific degenerative conditions, such as neurodegeneration (Quinn et al., 2015). Thus, longitudinal profiling of circulating nucleotides has the potential to be utilized as a more general health surveillance tool, where changes from baseline levels of circulating DNA from each tissue source indicate either tissue-specific neoplastic or tissue-specific degenerative processes.

Epigenomics

Epigenomic signatures have also been found to be potential indicators of overall health status through the determination of

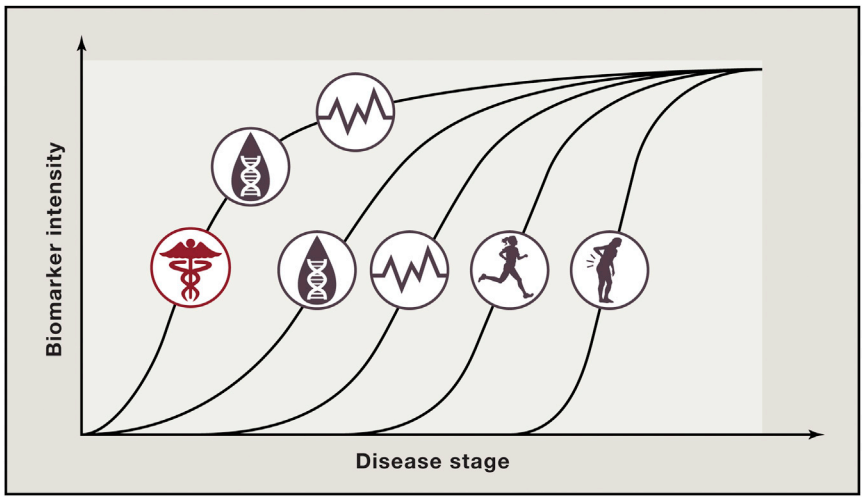

Figure 3. High-Definition Prevention
A diagram depicting high-definition prevention. Continuous or frequent assessment of the determinants of health (DNA in drop icon, cardiogram icon, and activity icon) allows for the early detection and response to deviations in health parameters from the personal baseline, before clinically manifest (pain icon), likely preventing or delaying disease onset. When utilized in combination and interpreted in context of known health risks (left curve), the potential for early detection is magnified further.

biological age via an "epigenetic clock" (Horvath, 2013). Acceleration of an individual's epigenetic clock, resulting in a biological age more advanced than that individual's chronological age, has been shown to be predictive of all-cause mortality in later life (Marioni et al., 2015). Specifically, a biological age five years more advanced than chronological age is associated with a 21% higher mortality risk. Whether the epigenetic clock can be directly manipulated via preventative behaviors etc. is less clear. However, it is known that this epigenetic clock is reset via cellular reprogramming *in vitro* (Lo Sardo et al., 2017), and preliminary evidence suggests that age-associated hallmarks can be reversed *in vivo* via epigenetic remodeling (Ocampo et al., 2016). Many disease states have been linked to an accelerated epigenetic clock, and many disease states leave an epigenetic fingerprint in peripheral blood (Heyn and Esteller, 2012). These observations suggest that longitudinal epigenomic profiling, and the detection of deviations in the epigenetic clock from the normal chronological trajectory, could be used to monitor overall health and simultaneously provide an indication of specific ongoing disease processes.

Cellular Mosaicism

Somatic mosaicism is another age-correlated factor that is generally indicative of cumulative DNA damage and associated with multiple disease states. First and foremost, increases in somatic mosaicism, especially through expansion of cellular clones carrying tumorigenic mutations, are predictive of long-term cancer risk (Biesecker and Spinner, 2013). However, recent evidence suggests that aberrant clonal expansion is also more generally associated with other non-cancer health outcomes such as type 2 diabetes and Alzheimer's disease (Forsberg et al., 2017). Early somatic mutations also underlie classically inherited diseases, such as cardiomyopathies and neurological disorders, though the magnitude of the contribution of somatic mosaicism to overall genetic disease incidence has only recently been appreciated and remains difficult to address comprehensively (Campbell et al., 2015). On the flipside, reductions in cellular mosaicism have been recently observed in the elderly, which are likely indicative of stem cell depletion and could potentially be utilized as a marker for the regenerative capacity of a tissue (Chakkalakal et al., 2012; Lo Sardo et al., 2017). The technology to noninvasively interrogate somatic mosaicism through the capture and profiling of single rare cells is currently in its infancy, though developments in this space herald a future when tissue-specific mosaicism could be interrogated and monitored via blood-based tests for the early detection and prevention of disease processes (Brinkmann et al., 2015).

Immunome

The immune system naturally utilizes somatic mosaicism to dynamically respond to external threats. Changes in B and T cell repertoires have been associated with autoimmune disease, infectious disease, and cancer (Woodsworth et al., 2013). In many cases, specific serological signatures have been shown to be predictive of disease status; for example, the detection and abundance of autoantibodies against pancreatic antigens are predictive of type 1 diabetes (Burbelo and O'Hanlon, 2014). The development of autoantibodies generally precedes the development of overt autoimmune disease (Arbuckle et al., 2003), suggesting that early detection of autoantibodies, especially in individuals at high genetic risk for autoimmune disease, could facilitate the early identification of individuals progressing from a healthy to diseased state, providing a window for preventative therapy. However, our current ability to connect antibody sequence with target antigens is lacking and will require the development of high-throughput methods to functionally characterize sequenced antibodies and T cell receptors.

Microbiome

The microbiome is yet another dynamic metagenome indicative of disease processes. Microbiome signatures have been linked to a wide variety of diseases ranging from infections such as *Clostridium difficile* (*C. difficile*), where the connection between the microbiome profile and disease process is apparent, to neurological conditions, where the mechanistic connection is unclear (Zmora et al., 2016). The common thread across various disease conditions appears to be that disease states are associated with reductions in microbiome diversity (Lynch and Pedersen, 2016). Though for many disease states it is not clear whether microbiome perturbations are causal or reactive to disease, it is clear that microbiome changes can be early indicators of disease for many conditions. For example, low or altered bacterial diversity is predictive of a propensity toward obesity, rheumatoid arthritis, and even early cancer detection (Zmora et al., 2016).

Thus, changes in microbiome diversity over a lifetime can be early indicators of early disease processes.

Pathogens

For some conditions, such as infectious disease, peptic ulcers, autoimmune diseases, certain cancers, and even some psychiatric disorders, the specific pathogenic agent can be detected via sequencing. From a disease-prevention point of view, screening and detection of human papillomavirus infection provides protection against the development of invasive cervical cancer (Ronco et al., 2014), detection of *Heliocobacter pylori* is indicative of risk for peptic ulcers (Chan et al., 2002), and hospital outbreak as well as epidemic investigations via pathogen sequencing can identify the initial source of an infection and prevent its transmission (Holmes et al., 2016; Lefterova et al., 2015). Pathogen sequencing is also being increasingly utilized in environmental-monitoring applications, for example by monitoring influenza reservoirs in animal populations, identifying novel viral antigens, and ultimately informing the development of seasonal vaccines (Ampofo et al., 2015).

Environmental Monitoring

Environmental risks have traditionally been the most difficult health risks to ascertain. However, recent technological advances in power consumption, data transfer protocols, and sensing arrays have set the stage for a future where networks of connected devices and sensors, or the Internet of Things, would provide real-time information about a variety of environmental risks (Swan, 2012). The majority of environmental sensing systems are in very early stages, and the impact on health outcomes is yet to be determined. Examples of early-stage environmental-monitoring applications include air quality and/or pollen monitoring for the prevention of hay fever or asthma exacerbations (Honkoop et al., 2017) or water quality sensors that can detect and reduce exposure to pollutants (Xu et al., 2014), environmental noise mapping to reduce exposure to noise pollution (Zuo et al., 2016), and food-chain monitoring for unhealthy conditions during processing, storage, and transportation of food (Nukala et al., 2016). When coupled with smart home or other means to reduce environmental exposures, the potential impact on health of environmental monitoring is dramatic. For example, approximately three million premature deaths each year are attributed to poor air quality (Lelieveld et al., 2015).

Food and Nutrition Tracking

It is firmly established that a healthy diet plays a major role in the prevention of disease. Yet, self-reporting and recall of dietary intake is notoriously inaccurate (Subar et al., 2015). The dramatically accelerating adoption of smartphones across the world now provides a more simple and accurate means to log dietary parameters. For individuals with the motivation to do so, it is possible to carefully track and adjust dietary parameters to improve health. User effort to maintain a food diary can be minimized by just taking a picture of the meal with contents and calories determined through deep learning algorithms (Myers et al., 2015). While a series of devices have claimed to be able to automatically scan and track dietary component intake, their validation is wanting, and no well-accepted solution yet exists.

Biochemical and Metabolomic Monitoring

Blood-based biomarkers could be utilized as a more accurate measure of dietary parameters (Subar et al., 2015), as well as a measure of overall environmental exposures (Rappaport and Smith, 2010). A tremendous variety of health parameters can be monitored via biochemical and metabolomics analysis of blood, breath, sweat, or urine. Monitoring strategies include the direct detection of environmental exposures, nutrients, and/or their metabolites; indirect detection of biochemical adducts resulting from chemical reactions between environmental exposures and normal bodily constituents; or detection of downstream biochemical processes triggered by environmental exposures. Specific examples include the direct detection of vitamins and their metabolites in the blood to judge nutrient intake (Scalbert et al., 2014), the indirect detection of long-term blood glucose levels based on hemoglobin A1c levels (glycated hemoglobin), the monitoring of metabolites and bodily ion concentrations based on perspiration sampling via wearable sensor arrays (Gao et al., 2016), the detection of infections or other immune modulators based on cytokine response profiles, and the detection and differentiation of a variety of diseases based on chemical fingerprints detected via exhaled volatile organic compounds (Nakhleh et al., 2017). Explosive development of novel assays through smartphones or small mobile devices enables frequent measurement of these and other clinical risk factors, will allow for an unprecedented understanding of the dynamics of these clinical risk factors, will enable the early detection and response to fluctuations in these factors, and ultimately will revolutionize our understanding of the relationship between traditional clinical risk factors and overall human physiology.

Physiological Monitoring

Unlike current medical standards of one-off measurements, there has been a striking increase in the availability of devices that allow for the continuous, or frequent, monitoring of human physiology (Piwek et al., 2016). These devices range from simple but smart wireless scales that can conveniently track body weight and composition over time to more complex devices that continuously track multiple vital signs in a manner currently only available in intensive care units. Such monitoring devices are redefining normal human physiology and revealing the tremendous potential of long-term in-home monitoring. For example, intermittent electrocardiogram screening has been shown to result in a 4-fold increase in the detection of unknown atrial fibrillation, a risk factor for stroke, relative to a single electrocardiogram screen (Svennberg et al., 2015); continuous electroencephalogram monitoring is now the gold standard for management of epilepsy in newborns (Sands and McDonough, 2016); and continuous or frequent blood-pressure monitoring will enable the detection of blood-pressure variability, instability, and episodic hypertension, redefining the prevention and management of cardiovascular disease (Rothwell, 2010). Combinations of sensors, such as heart rate, respiratory rate, and oxygen saturation can also identify early changes in chronic conditions such as heart failure or chronic obstructive pulmonary disease (Cheng et al., 2015). Novel wearable sensors will also enable tracking of parameters not previously possible, such as stress monitoring through heart-rate variability and electrodermal activity or hydration status via continuous sweat analysis. Frequent measurements of these clinical factors will not only enable the

definition of personal baselines for early detection and prevention of disease but will also provide a new and important dimension for the stratification of patients by characterization of disease status across time (see Billions of High-Resolution People). Many of these devices will require validation testing before introduction into clinical practice.

Activity Tracking

Activity tracking synergizes with physiological monitoring to provide additional insight into the prediction of disease states. For example, the addition of sleep quality and vibration tracking to electrocardiogram monitoring allows for at-home detection of sleep apnea (Harrington et al., 2013). Detection of gait abnormalities can be an early indicator of Parkinson's disease (Shulman et al., 2008), and reduction of gait speed in general is associated with mortality (Studenski et al., 2011). Activity tracking is also a potential means to motivate preventative behaviors and health care coaching, though the most effective means of influencing long-term behavior are still being explored (Jakicic et al., 2016).

Image and Voice Analysis

Finally, advanced image and voice analysis can identify early, subtle signs of psychiatric and cognitive disorders that can be difficult to recognize by other means. Voice (Faurholt-Jepsen et al., 2016) and facial (Mone, 2015) analysis can be utilized to detect mood and psychiatric disturbances and has been used to diagnose Parkinson's disease and heart disease (Maor et al., 2016), and it can be used to differentiate simulated versus real pain (Bartlett et al., 2014). Eye tracking during behavioral tasks can identify individuals with mild cognitive impairment and predict future progression to Alzheimer's disease (Zola et al., 2013). In fact, mood can also be detected and influenced by exposure to social media (Kramer et al., 2014) as well. These technologies allow for the objective quantification of cognition in ways that have previously been impossible and highly subjective.

Imaging

Advances in medical imaging technology allow for extremely detailed scans of bodily structures and dynamics. For example, positron emission tomography, utilizing a variety of molecular probes, can be used to detect and localize specific biological activities associated with disease (Vaquero and Kinahan, 2015). Imaging technologies are used widely in medical practice, but routine use of medical imaging technology is limited due to radiation exposure, expense, and the necessity of specialized facilities. The advent of handheld imaging devices, such as the handheld smartphone ultrasound (Alam and Brassil, 2016), has the potential to enable early detection of disease through routine imaging. However, these technologies are still in their infancy and require specialized training to use appropriately.

Integrated Modeling

Ultimately, the tools and technologies described above generate a torrent of data that can be overwhelming and perhaps uninterpretable for individuals and their health care practitioners. Computational models will need to be developed that combine and convert multiple continuous health parameters into readily interpretable clinical risks where preventative measures can be defined and prioritized. Some approaches to this problem will be described in Billions of High-Resolution People. Additionally, the high-definition ascertainment of health parameters allows for a redefinition of disease, from broad categories to sub-classes defined by detailed phenotypic characterization and clustering, ultimately enabling high-precision treatments.

High-Precision Treatment

High-precision treatments include the data-driven selection, monitoring, and adjustment of interventions based on information from high-definition prevention technologies. These treatments are tailored to the individual characteristics of the patient, often target the causal molecular basis of disease, and are intensively monitored for treatment failures and adverse reactions. Ultimately, interventions are prioritized by a redefinition of current broad disease classes to more narrow sub-classes of disease where treatments have the greatest chance of clinical benefit. Novel clinical trial strategies, such as adaptive and n-of-1 trial designs, deeply phenotyped patient registries, and real-world evidence studies, will be necessary to gather the necessary safety and efficacy data required to evaluate the utility of these treatments in the targeted patient populations. Here, we review a subset of the most promising high-precision treatment strategies.

Genome Engineering

Given that genetic risk is a major component of many diseases, modification of the human genome is perhaps the most precise way to reduce those risks. Direct and safe manipulation of the human genome is rapidly becoming a reality with the advent of precision genome-engineering techniques, e.g., gene therapy and gene editing, and associated DNA delivery systems. Malfunctioning genes can be replaced via gene therapy, an area where a number of promising clinical trials are currently in progress (Naldini, 2015). The vast majority of gene-therapy trials target hematological diseases via repopulation of the bone marrow with *ex vivo* engineered patient-derived hematopoietic stem cells, or they are directed at *in vivo* correction of liver and retinal diseases (Naldini, 2015). Though the current applications of gene therapy are somewhat limited to tissues that can be effectively targeted with state-of-the-art delivery vectors, early results are highly encouraging and demonstrate the power of directly repairing the genes that cause disease.

Genome-editing technologies take the precision of gene therapy a step further by directly correcting the specific genetic lesions underlying disease. The latest technology to this field, CRISPR-Cas9, has revolutionized the ability to efficiently and accurately edit the human genome (Doudna and Charpentier, 2014). Efforts toward *in vivo* correction of deleterious mutations beyond the applications addressed by gene therapy are at early stages of pre-clinical research. For example, improvements in mouse models of Duchenne muscular dystrophy have been demonstrated via *in vivo* removal of a commonly mutated exon in this disease (Mendell and Rodino-Klapac, 2016). It remains to be seen whether the precise *in vivo* correction of deleterious mutations will eventually be made possible with current genome-engineering technology. In an exciting proof-of-concept study, researchers were able to utilize genome engineering to abrogate the effects of an extra chromosome in Down syndrome by leveraging the natural process utilized to silence the "extra" X chromosome in females (Jiang et al., 2013), demonstrating the potential of the clever use of genome engineering to address difficult-to-treat conditions.

Although controversial, it should be mentioned that a currently utilized alternative to therapeutic genome editing is preimplantation genetic diagnosis and embryo selection, minimizing the incidence of genetic disease. Though preimplantation diagnosis is generally utilized in the case of a known genetic risk for disease, the technology to generate a whole-genome profile of single cells from embryos has been developed (Zamani Esteki et al., 2015), though it is not generally available. The ultimate extension of these technologies is the highly controversial editing of human embryos to eliminate genetic disease-causing variants and reset the genetic component of the personal health baseline (Sciences and Medicine, 2017).

Cell-Based Therapy and Tissue Engineering

Genome-engineering tools are also improving organ-replacement technologies. For example, engineering of pig cells, an important source of human transplant tissues such as heart valves, has been performed to remove endogenous retroviruses in order to improve the compatibility of pig tissue with human recipients (Yang et al., 2015). However, in the long run, gene editing in patient-derived stem cells may eventually be the standard for clinical organ-replacement applications (Hockemeyer and Jaenisch, 2016). Stem cells, by virtue of their defining properties of self-renewal and the ability to differentiate into other cell types, are increasingly being developed as sources of cell-based therapeutic treatments for a variety of regenerative medicine applications. Induced pluripotent stem cells (iPSCs), which are pluripotent stem cells generated directly from somatic tissues of patients, are thought to represent a safe means to supply cell therapies since they are genetically matched to the patient and therefore may not require immunosuppression for tissues to remain stable. The first wave of early-stage clinical trials testing the safety and therapeutic benefit of iPSCs in conditions such as age-related macular degeneration, Parkinson's disease, spinal cord injury, and diabetes are currently underway (Trounson and DeWitt, 2016).

Ongoing clinical trials utilizing iPSCs target indications where essentially a single or small number of cell types are being replaced. For more complex tissues, 3D printing is being utilized to either produce an organ scaffold, onto which cells are seeded to self-assemble into the desired organ using the scaffold as a guide, or produce the organ directly by 3D printing different cell types into the proper organ arrangement (Murphy and Atala, 2014). Simple organ structures, such as the bladder or trachea, are already in use clinically. Alternatively, complex organs may be grown for transplantation from patient-derived stem cells formed into the desired organ in human-pig hybrids (Wu et al., 2017).

Genome engineering can also be utilized to improve cell-based therapeutic interventions. A particularly promising and active area of the clinical development of cell-based therapeutics is the genetic engineering of immune cells. For cancer therapy, various strategies are under development for the engineering of immune cells via adoptive cell transfer to specifically target cancer cells, including isolation and *ex vivo* sensitization of patient-derived T cells, *ex vivo* engineering of patient-derived T cells with specific anti-tumor receptors, or engineering of allogenic T cells with specific anti-tumor functions (Rosenberg and Restifo, 2015). Adoptive cell transfer is also being developed for infections and mitigating of autoimmunity, but these approaches are less well developed (June et al., 2015). Other examples of genome editing in cell-based therapeutics include gene editing of the *CCR5* gene, a gene involved in HIV resistance, in CD4 T cells transplanted into a patient infected with HIV, leading to an apparent cure of the viral infection (Tebas et al., 2014), and the generation of insulin-secreting cells that are less prone to immunological attack (Johannesson et al., 2015).

Pharmacogenetics and Pharmacogenomics

Genetic profiling is also being utilized to select safe and efficacious drug therapies individualized to patient profiles. Pharmacogenetic factors can be involved in the dosing, efficacy, and adverse response to drugs through a variety of mechanisms. At least 150 drugs have been linked to well-described pharmacogenetics associations (https://www.pharmgkb.org/), with current drug labels incorporating over 200 drug-to-genomic-biomarker interactions (https://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm). The FDA genomic drug labels, based upon extensive peer-reviewed published research, vary from guidance on efficacy, adverse events, or dosing. The majority of the genomic biomarkers mentioned in drug labels influence the dosing (and sometimes, as a result, the efficacy) of drugs through interaction with genetic factors involved in the metabolism and clearance of drug compounds. Many of these drug metabolism genetic factors are quite common in the population, virtually assuring that relevant pharmacogenetic variants are present in every individual's genome (Zhou and Pearson, 2013). Variants involved in adverse response to drugs are less common, but their identification can lead to the selection of alternative drugs and the avoidance of life-threatening conditions, such as Stevens-Johnson syndrome associated with abacavir therapy due to human leukocyte antigen variants (Phillips and Mallal, 2010).

The exemplar for genomically matched therapies for maximizing treatment efficacy is cancer. Somatic mutations in cancer genomes lead to the dysregulation of, and sometimes dependence on, molecular processes that promote tumor growth, survival, and evolution. Targeted therapies are directed at vulnerabilities exposed by dysregulation of these tumor-promoting processes, in order to inhibit the growth of or cause the death of cancer cells while ideally minimizing the impact on normal healthy cells (de Bono and Ashworth, 2010). There are approximately 75 FDA-approved targeted cancer therapies (https://www.mycancergenome.org). Examples include cetuxmiab (Erbitux; Bristol-Myers Squibb), an anti-EGFR antibody that is contraindicated in tumors bearing *KRAS* mutations, and Vemurafenib (Zelboraf; Daiichi-Sankyo), a small-molecule BRAF inhibitor that is effective against tumors bearing *BRAF* mutations (Hyman et al., 2015). Epigenetic therapies are also most advanced in treating cancer versus other disease types. The best example is temozolomide (Temodar; Merck), a DNA methylating agent that is most effective in tumors with epigenetically or otherwise silenced O-6-methylguanine-DNA methyltransferase (Hegi et al., 2005). Targeted cancer therapies are being utilized in an increasing number of cancer indications due to the overlap in molecular processes dysregulated in disparate tumor types. Ultimately, the categorization of cancers and selection of

appropriate therapies is shifting to include molecularly defined classes in addition to the traditional organ- and histology-based classifications (Hoadley et al., 2014).

Targeted therapies are also being increasingly developed for inherited diseases. The leading example for genetically matched therapy for inherited disease treatment is ivacaftor (Kalydeco; Vertex Pharmaceuticals), the first drug developed to treat an underlying cause rather than symptom of cystic fibrosis. Ivacaftor was developed to target a specific mutation in the *CFTR* gene (CFTR p.G551D), which represents ~4% of all patients with cystic fibrosis, leading to significant improvement of lung function and reduced hospitalization of cystic fibrosis patients with the G551D as well as other mutations. Development of ivacaftor was a breakthrough for the treatment of cystic fibrosis, leading to the development of similar drugs and combinations (lumacaftor), which benefit nearly half of all cystic fibrosis patients (Rehman et al., 2015). Other examples are limited, due to the fact that targeted therapy efforts for inherited disease are at very early stages, but FDA-approved examples include tafamadis (Vyndaqel; Pfizer Inc.) for familial amyloidosis due to *TTR* mutation (especially TTR p.V30M) and ruxolitinib (Jakafi; Novartis) for myelofibrosis and polycythemia vera due to *JAK2* mutations.

In other instances, the causal molecular basis of disease is used to inform drug targets with broader efficacy beyond those specific individuals bearing the disease-predisposing mutations (Plenge et al., 2013). For example, rare gain-of-function mutations in *PCSK9* lead to familial hypercholesterolemia and increased risk for cardiovascular disease, whereas loss-of-function mutations lead to the opposite cardioprotective effects. *PCSK9* inhibitors are approved for the treatment of familial hypercholesterolemia and are most effective in individuals with *PCSK9* gain-of-function mutations but are also being considered for treatment of the more common nonfamilial hypercholesterolemia as well as other dyslipidemias. Similarly, genes involved in predisposition to rheumatoid arthritis (*CTLA4* and *IL6R*) are targets for drugs used to treat rheumatoid arthritis as well as other autoimmune diseases. There is also increasing interest in utilizing genetic studies to identify individuals with protective genetic variants that might inform drug-target identification (Chen et al., 2016; Erikson et al., 2016). For example, rare loss-of-function mutations in a zinc transporter (*SLC30A8*) were found to be protective against type 2 diabetes and thus thought to be indicative of a novel diabetes treatment strategy (Flannick et al., 2014). It is likely that these genetically supported drug targets will eventually be linked to the genetic disease risk profiles of patients who are most likely to respond to these treatments.

Infectious Diseases and the Microbiome

Infectious disease treatments and the role of the microbiome are also undergoing a revolution in high-precision therapeutics. The role of the microbiome as a mediator of disease processes, modifier of conventional drug therapy, and as a direct target for therapy has only recently been appreciated (Blaser, 2014). The use of the microbiome as a therapeutic or mediator of therapeutic response is largely relegated to pre-clinical research. However, fecal transplants are already being used clinically to treat *C. difficile* infections, and trials with more precise microbial cocktails for this and other diseases are currently underway.

The need for new *C. difficile* treatments and the increase in the rate of *C. difficile* infections, as well as the emergence of antibiotic resistance in pathogenic bacteria in general, can be linked to the widespread use of broad-spectrum antibiotics. There is an urgent need for the development of novel high-precision antibiotics; however, the commercial development and clinical application of narrow-spectrum antibiotics is challenging, in part due to the delay between onset of an infection and identification of the bacterial strain via traditional diagnostic approaches. The advent of rapid molecular diagnostics for infectious disease will remove this hurdle, improving the feasibility of the commercial development and clinical application of narrow-spectrum antibiotics, as well as combatting the emergence of antibiotic resistance (Maxson and Mitchell, 2016). Rapid molecular diagnostics can generally identify and elucidate the antibiotic-resistance profile of pathogens, making antibiotic treatments more effective.

Similarly, rapid viral evolution necessitates the development and selection of antiviral drugs and combinations that completely suppress the replicative capacity of all viral variants present in infected patients. Under suboptimal treatment conditions, viral variants less sensitive to a given treatment expand, acquire additional resistance variants, and eventually acquire compensatory variants that restore the replicative capacity of the virus (Hughes and Andersson, 2015). Thus, modern antiviral drugs and cocktails, which are currently associated with very high sustained virological response rates and apparent cures in targeted patient populations, must be selected in a manner where the drugs are matched to viral genetic profiles least likely to result in the emergence of drug resistance (Fourati and Pawlotsky, 2015). Genotyping and deep sequencing can detect rare subpopulations of viruses resistant to specific antiviral treatments prior to their emergence as the dominant variant after antiviral treatment.

Treatment Monitoring

Deep sequencing can also be utilized to monitor the progress of disease treatment, especially for cancer and infectious-disease therapy, as well as organ-transplant rejection. As described above, proof-of-principal studies have demonstrated that failure of curative tumor resections in cancer patients (Tie et al., 2016) and failure of immunosuppression therapy in organ-transplant patients can be detected via sequencing of circulating DNA (De Vlaminck et al., 2015). The emergence of therapy-resistant cancer clones can also be detected via ctDNA sequencing prior to clinical recurrence (Murtaza et al., 2013). Similarly, the emergence of therapy-resistant pathogens in individual patients, in the hospital setting, and in the community can be detected via deep sequencing (Köser et al., 2014). Early detection of treatment failures in these scenarios allows for rapid adjustment of therapy with the possibility of improved outcomes.

While genomic-treatment-monitoring approaches are in their infancy, physiological, biochemical, and metabolomics tracking technologies are already playing an ever-expanding role in outpatient monitoring. When coupled with a personal health baseline, many of the high-definition prevention technologies described previously can be utilized to monitor treatment progress by tracking the return of health parameters from a disease state back to their healthy baseline. However, a more

sophisticated and futuristic approach to treatment monitoring is the continuous monitoring of health parameters by devices directly coupled to therapy administration. The exemplar for these therapy-feedback control systems is the bionic pancreas for type 1 diabetic patients—a continuous glucose monitor coupled to an insulin or insulin-glucagon pump. Early studies of the bionic pancreas have demonstrated improvements in glycemic control (Rodbard, 2016), which can lead to improved health outcomes and reductions in mortality (Lind et al., 2014). This is a relatively straightforward application of treatment monitoring coupled with therapy administration due to the relatively low latency and direct relationship between treatment administration and physiological response.

Overall, the current application of other high-definition prevention technologies to treatment monitoring and therapy administration is limited, in part due to the complexity of the links between the monitored health parameters and treatment options. The first forays into transitioning these devices from a high-definition prevention and diagnostic role to a therapeutic role are in early stages. For example, as described above, ambulatory electrocardiogram devices used to monitor individuals at risk for cardiac arrhythmias and alert patients and physicians of potentially life-threatening cardiac events have demonstrated improved diagnostic yields (Walsh et al., 2014). A small number of studies have attempted to link cardiac monitoring with device-tailored anticoagulant therapy, though clinical benefit has not yet been demonstrated (Walsh et al., 2014). Because of the more complex association between the health parameters measured by high-definition prevention technologies and the health outcomes they are ultimately attempting to prevent, these applications will likely require the collection of large amounts of data from devices and associated treatment outcomes before the algorithms linking treatment decisions to device data can be formalized.

More immediate and direct links between electronic monitoring solutions and patient treatment are being formed through monitoring of medication non-adherence, another important contributor to patient mortality as well as numerous other adverse health effects (Checchi et al., 2014). For example, electronic monitoring devices for asthma inhalers promote adherence either through physician reporting or direct feedback and reminders to the patient. Electronic monitoring devices have been demonstrated to improve asthma-medication compliance, though evidence for long-term sustained clinical benefit is still lacking (Chan et al., 2013). Other monitoring devices include mobile device medication reminders, smart pillboxes that track vial openings, and ingestible pill biosensors (Checchi et al., 2014). The clinical benefit of these devices for improving long-term compliance is still lacking (Choudhry et al., 2017). Systematic collection of treatment-compliance data, health status, and patient outcomes is needed to determine which treatments and patient compliance strategies provide maximal clinical benefit.

Billions of High-Resolution People: The Knowledge Resource

The adoption of high-definition medicine technologies has already begun to provide immediate benefit to patients today. However, this benefit is limited relative to the insights achievable through the systematic collection and learning from health parameters and outcomes data across millions, if not billions, of people. Social media, like YouTube or Facebook, are already connecting billions of people through big-data frameworks such as distributed file systems, map-reduce programming, resilient distributed datasets, and other distributed computing frameworks. Data-mining and artificial intelligence technologies are extracting actionable and individualized insights from these troves of personal data. These existing information technologies will form the basis of an interconnected self-perpetuating learning health care system that will (1) continuously and dynamically generate new medical knowledge, (2) redefine patient and disease classifications, and (3) ultimately predict the future health trajectory of individuals to allow for early interventions.

Dynamic Knowledge Repositories

The current approach to the identification of actionable knowledge in health care generally relies on cross-referencing an individual's health data to known reference values largely derived from clinical trials. As an example, the current approach to clinical genomics generally relies on cross-referencing an individual's genetic data with knowledgebases that contain information about genetic variants of curated clinical significance. In our current state of siloed health information, these public knowledgebases have tremendous utility. However, these relatively static knowledgebases tend not to capture the entirety of current knowledge and often relay only simple relationships involving a small number of health parameters and outcomes. In contrast, the high-definition medicine approach to medical knowledge involves the collection of raw health data into "dynamic knowledge repositories" (Engelbart, 1992). Dynamic knowledge repositories are designed and structured to simultaneously get data in and knowledge out, allowing for the concurrent development, integration, and application of knowledge. These repositories, when sufficiently large, should displace external knowledgebases by allowing for the retrieval of health-data reference values directly from raw health data—queried in a manner that incorporates the entirety of a patient's health context. This knowledge-management strategy allows for the dynamic generation of medical knowledge that is individualized to the patient and is always up to date. Modern electronic health records coupled with genetic data are already beginning to act as dynamic genetic knowledge repositories by uncovering cross-phenotype links between known genetic risk factors and novel disease conditions via phenome-wide association studies (Bush et al., 2016). The logical extension of these studies is the comprehensive, continuous, and population-scale cataloging of genetic risk variants, novel pharmacogenomic relationships, drug repositioning opportunities, and the elaboration of the many other genomic-to-health relationships described above through data-mining of real-world outcomes and linked genetic data. The automatic identification of links between other types of health parameters and novel health outcomes would follow similarly. Ultimately, these novel associations could be rapidly identified in the real-world and integrated into clinical practice, increasing the overall utility of all high-definition prevention technologies.

Artificial Intelligence Systems

Dynamic knowledge repositories will need to be outfitted with tools capable of executing complex real-time knowledge generation tasks. These tools will likely be artificial intelligence

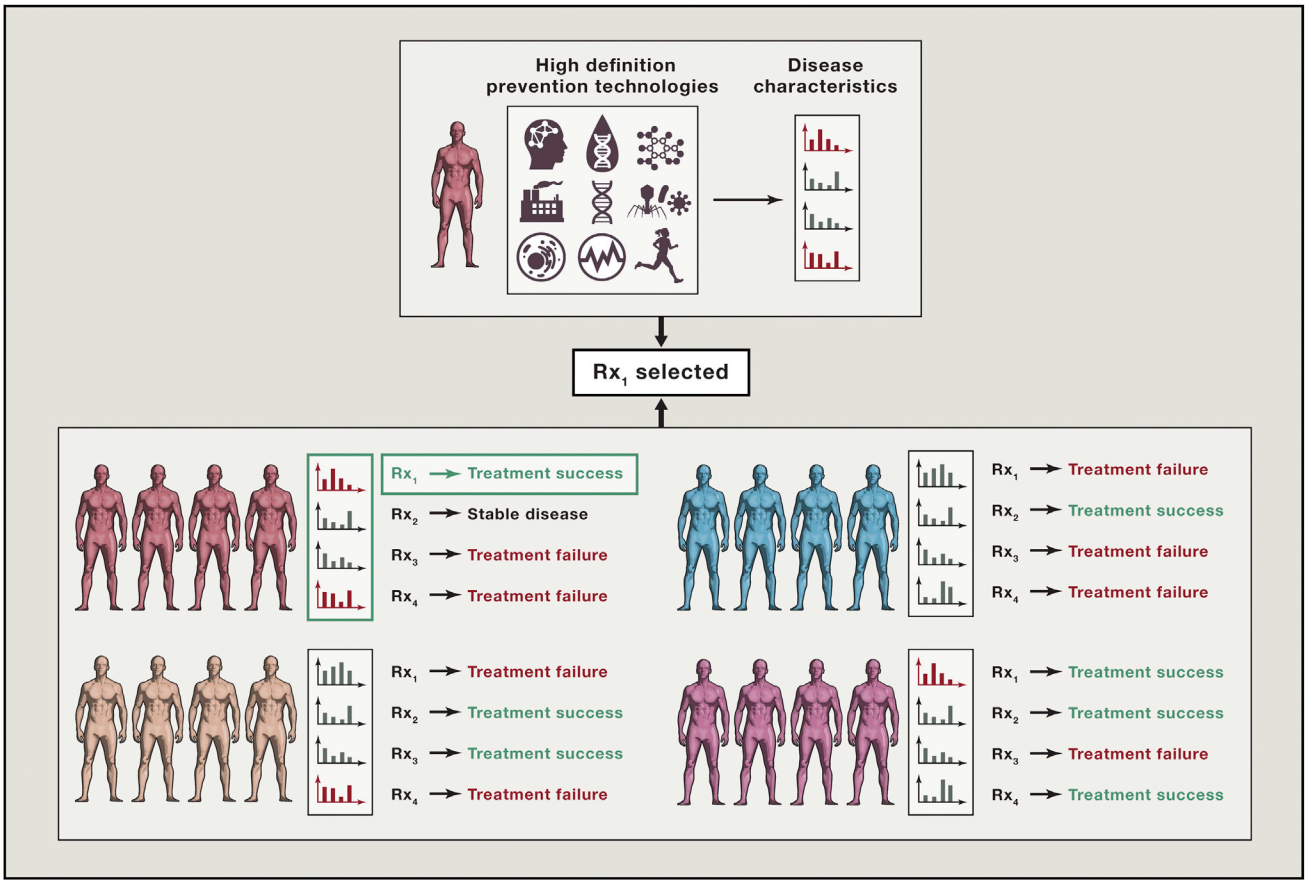

Figure 4. Billions of High-Definition People

A flow diagram depicting digital twins. Left: Disease parameters of a currently diseased individual are characterized deeply using high-definition prevention technologies. Right: The disease profile is cross-referenced against records from billions of individuals having been similarly profiled. Top right: The prior diseased individuals whose disease characteristics are most closely matched to the currently diseased individual are interrogated for treatments utilized and health outcomes. Middle: Treatment, in this case treatment 1, is prioritized based on prior positive outcomes seen in similarly afflicted individuals.

systems, which can act both as discovery tools to extract knowledge from dynamic knowledge repositories, as described above, and as intelligent-decision support agents that can perform tasks once thought to be reliant on human brains. These intelligent agents have already begun to make their mark on clinical practice. For example, advances in computer vision have allowed artificial intelligence systems to compete favorably in one of the most complex tasks performed by the human brain: image analysis. Deep neural networks trained on hundreds of thousands of clinical images have recently been shown to perform on par with dermatologists in the classification of skin cancers (Esteva et al., 2017) and match or outperform ophthalmologists in the detection of diabetic retinopathy (Gulshan et al., 2016), and an artificial-intelligence-based system that utilizes about ten million rules for the quantification of bloodflow through the heart (Arterys Systems; San Francisco, CA) has already been cleared by the FDA and deployed in health care settings. Similarly, rapid accurate interpretation of medical images such as X-rays, MRI, and CT images has been shown to be feasible via deep learning and at least equivalent to interpretation by radiologists (Shen et al., 2017). Artificial intelligence embedded in dynamic knowledge repositories has the potential to revolutionize the classification accuracy of all routine medical diagnostics and uncover previously unknown health relationships.

Redefining Disease Classification

The current artificial-intelligence-based diagnostic systems, while sophisticated, are still reliant upon training data composed of human-defined disease classes. Current disease classifications are based on a wealth of biomedical knowledge and serve clinicians well but are overly broad and consist of disease subclasses associated with distinct pathophysiology and, thus, can be expected to respond differently to therapeutic interventions (Loscalzo et al., 2007). The precise molecular characterization of individuals and their diseases, and the frequent or continuous monitoring of health parameters with high-definition prevention technologies, provides a foundation for the redefinition of disease classes and their appropriate therapies. For example, genetic association studies of endophenotypes, the detailed symptomology that defines current disease classes, have unveiled genetic risk factors for myocardial infarction mediated through variation in platelet count and platelet volume (Gieger et al., 2011), risk factors that would not likely be

effectively treated by standard cholesterol-lowering therapies. Similarly, continuous monitoring of blood pressure would reveal individuals with intermittent versus sustained hypertension, which are associated with differential benefit from standard antihypertensive drugs. Compilation of patient health parameters and outcomes in dynamic knowledge repositories would enable the unsupervised and unbiased redefinition of disease subclasses, allow for the establishment of the previously described individualized optimal health ranges, and ultimately link these disease sub-classes to the most effective therapies.

Predicting Health Trajectories with Digital Twins

Finally, a sufficiently sophisticated learning health care system utilizing high-definition medicine technologies would extend beyond reclassification of diseases to the projection of individual health trajectories. In a sufficiently large learning health care system, ''digital twins'' (Grieves and Vickers, 2017) will begin to emerge as useful benchmarks for defining the individualized optimal health range for specific health parameters as well as predictors of health outcomes overall (Figure 4). Unlike the engineering concept of the digital twin, a digital copy of a physical asset, a high-definition medicine digital twin is an actual person, or composite of people, who shares relevant health parameters. The health outcomes of the set of digital twins for an individual can be utilized to estimate whether an individual is at higher risk for disease, recommend behaviors that might reduce their risk, potentially plan for early screening for disease, and evaluate the significance of early signs of disease. For example, in an individual known to be at high risk for cancer on the basis of specific cancer-susceptibility variants, the threshold for significance of a ctDNA test may be expected to be more liberal. Circulating DNA results from digital twins at similar genetic risk for cancer would be used to guide this individualized threshold for significance, likely leading to greater sensitivity in the at-risk individual. Basic prognostic models are already utilized in a similar manner within clinical decision support systems to predict the risk of disease progression and balance the risk of treatment versus potential health outcomes. However, due to their incomplete nature, many of these models have been found to grossly overestimate risk and lead to unnecessary therapy initiation (Rana et al., 2016). More comprehensive representation of patient characteristics with high-definition medicine technologies will allow for a more accurate definition of genetic, environmental, and behavioral risks, link those risks to clinical health parameters measured by high-definition prevention technologies, individualize the interpretation of those health parameters via various data-mining techniques, and ultimately allow for the definition of highly complex models of health trajectories leading to a truly predictive and preventative health care system (Castellani et al., 2016).

Conclusion

Ultimately, the adoption of technologies capable of longitudinally measuring health parameters at high resolution, coupled with dynamic knowledge repositories and sophisticated analytics, will drive a high-definition medicine environment where health management is predictive, preventative, and individualized. To realize this vision, a number of implementation challenges must be addressed. These challenges are numerous, spanning infrastructure development, cost effectiveness, evidence generation, data interoperability, financial incentives and reimbursement policies, novel regulatory approval frameworks, reconciliation of disparities in access, and transdisciplinary training of health care teams. Overcoming these challenges will revolutionize the way we manage our health.

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