

Feature Review

Enabling Technologies for Personalized and Precision Medicine

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Individualizing patient treatment is a core objective of the medical field. Reaching this objective has been elusive owing to the complex set of factors contributing to both disease and health; many factors, from genes to proteins, remain unknown in their role in human physiology. Accurately diagnosing, monitoring, and treating disorders requires advances in biomarker discovery, the subsequent development of accurate signatures that correspond with dynamic disease states, as well as therapeutic interventions that can be continuously optimized and modulated for dose and drug selection. This work highlights key breakthroughs in the development of enabling technologies that further the goal of personalized and precision medicine, and remaining challenges that, when addressed, may forge unprecedented capabilities in realizing truly individualized patient care.

Converging Genomic and Phenotypic Medicine with Technology

Personalized and precision medicine seek to build a foundation for actionable health management through a broad spectrum of information. Potential inputs for advancing precision medicine include longitudinal tracking of healthy individuals to better understand the transition from nondiseased to diseased states; more precisely identifying individuals at risk for disease; and tailoring treatments based on diverse and growing data sets from both individual trials and population-based studies [1]. The data flowing into precision medicine will come from genetic databases, medical records, tissue banks, and other clinical sources of ‘big data’. In parallel with our ability to gather an impressive amount of data from any given patient is the expansion of computing power and, with it, our analytical capabilities and ability to link data sets together to ‘make sense’ of big data. Precision medicine relies on large quantities of population-level data to help determine the appropriate treatment for an individual. Precision medicine, in some respects, deviates from traditional medicine by providing insight into how population-derived genetic, proteomic, or broader biomarker profiles can collectively determine the course of treatment for an individual (Box 1). We should think of human disease as involving ‘networks’ of aberrant activities, such as signaling and cell behavior, as well as modifier genes, ‘moonlighting’ proteins, etc., rather than as a linear progression [2]. In this way, we might uncover new linkages between seemingly disparate diseases that open doors to novel treatment approaches. Precision medicine is already using different sources of patient data to define these new linkages, whether it be through genomics in type 2 diabetes or imaging phenotypes in glioblastoma, for instance [2–4]. There are notable challenges to precision medicine that include data accrual, access to patients, and data analysis, which we will address in subsequent sections.

Personalized medicine differs from precision medicine. In personalized medicine, which has been considered for some time, the patient is viewed as an individual from diagnosis to therapy, which clearly has some overlaps with precision medicine in execution, but unlike precision medicine

Highlights

Engineering approaches to precision medicine will harness population-wide data to identify individualized treatment strategies.

Personalized medicine harnesses a subject’s own data to individualize their own care, from diagnosis through treatment selection and monitoring.

Novel clinical trial designs will play a vital role in assessing the efficacy and safety of emerging therapies and diagnostics.

Artificial intelligent platforms will globally optimize combination therapy from the preclinical through clinical stages of validation.

The widespread deployment of precision and personalized medicine technologies will involve the convergence of several factors ranging from evolving education at the interface of engineering and medicine and policies that support new clinical trial designs, to scaling the use of electronic medical records (EMR) to drive clinical decision support.

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Box 1. Defining Precision and Personalized Medicine

From an engineering perspective, precision medicine involves the use of technologies to acquire and validate population-wide data, such as omics-based single-cell analysis and biomarker discovery, for subsequent application on the individual patient level.

Personalized medicine involves the use of technologies to seriously acquire and assess an individual's own data for only their own treatment. For example, this may involve the use of artificial intelligence (AI) to both design a drug combination based on a patient's own biopsy and follow with N-of-1 dosing protocols.

Broad deployment of both approaches would rely on their successful integration, with genome-guided drug pairing (driven by population data) followed by AI-guided dynamic dosing (driven by individual data).

does not inherently rely on large data sets or population-based approaches to redefine disease (Box 1). In personalized medicine, engineers have found a stronghold. Engineers have developed enabling technologies ranging from micro/nanofluidics for single **circulating tumor cell (CTC)** (see Glossary) analysis to nanotechnology for isolating extracellular vesicles and exosomes from liquid biopsies to imaging platforms to predict the effectiveness of nanomedicines [5,6]. These technologies have the opportunity to provide unprecedented diagnostic insight on a personalized level, but are still making their way into routine clinical care. In particular, personalized pharmacokinetics has enabled new intratumoral devices and microfluidic constructs available to track an individual's response to a particular drug [7,8]. The recent introduction of **phenotypic personalized medicine (PPM)** [the harnessing of augmented **artificial intelligence (AI)** to personalize combination therapy and improve efficacy and safety on the basis of measured end-point phenotypes for specific patients] has enabled continuous, patient-specific optimization of monotherapy and combination therapy as well as the agnostic design of novel, optimized, fixed-dose drug combinations [9,10]. Pilot clinical trials involving PPM have been launched for tuberculosis, HIV (NCT02632474), liver and kidney transplant immunosuppression, hematologic cancers, and other indications, demonstrating the power of engineering platforms to cut across medicine. To enable patient-specific treatment, a growing pool of technologies is enabling individualized monitoring. These include everything from wearables, like glucose-monitoring, neurostimulation, neuromonitoring, and sweat-monitoring electronic tattoos (representing 'small data' personalized diagnostics and analytics) to AI-based drug selection and administration; to patient-tailored gene-editing nanoparticles that can both image (diagnostic) and treat (therapy), sometimes called 'theranostics' [11–15]. As these data sources grow in scale as well as quality, being richer and more diverse, medicine will be able to more effectively individualize therapy on the basis of population-wide genetic and phenotypic information, with the hope of moving beyond medicine's 'one size fits all' *modus operandi*.

Bioengineering underpins the implementation of precision and personalized medicine and related enabling technologies in the clinic (Table 1), as knowledge obtained from traditional biomedical fields makes its way into clinical solutions via engineering tools and approaches. Engineers will play an especially crucial role in advancing both personalized and precision medicine, although they may not yet realize how their enabling technologies offer solutions to many unmet clinical needs. In this paper, we explore recent advances in enabling technologies and state-of-the-art bioengineering approaches that will be instrumental in not only continuing to advance personalized and precision medicine into the clinic, but also catalyze its transformation into the standard of care. We also discuss policy considerations that will impact the development, implementation, and adoption of such technologies.

Together, personalized and precision medicine, enabling technologies, and smart policy choices will open the doors to optimized targeted therapies, to disease prevention, and to an overall shift in how we think about human disease.

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Enabling Technologies for Precision Medicine

The field of precision medicine has already provided important insights into the mechanisms at play at disease onset; into biological targets that can directly inhibit disease progression; and into biomarkers that reflect treatment response. Such understanding has collectively mediated substantial advances towards improving patient treatment outcomes [16–18]. With new data sources and combinations of these data, precision medicine will propel existing drug-selection platforms like pharmacogenomics and patient-derived primary cultures [19–25]. When coupled with big data platforms, these approaches can identify targeted therapies that may predict and/or induce improved response rates over clinical standards. Importantly, these advances are being actively assessed in a clinical setting (NCT02795156, NCT03903835).

Several clinical trials are currently in place to bring precision medicine to the bedside. One study of lung cancer patients is pairing genomic analysis of murine and human specimens and coupling these data with imaging analysis in a co-clinical trial to identify genomic signatures to improve liquid biopsies (NCT02597738). A precision-guided study for treating cancer pain is being conducted, where patients are screened for the cytochrome p450 2D6 (CYP2D6) and μ -opioid receptor (OPRM1) genotypes to monitor their response to opioid treatment (NCT02664350). Precision medicine is being used to identify genomic and molecular markers to predict patient response to the administration of 17 hydroxyprogesterone caproate (17OHP) as a potential intervention to prevent preterm birth (NCT02173210). Lastly, one study is combining four predictive markers for breast cancer (HER2; TP53, CHEK2, and RB1) with massive parallel genetic screening to develop datasets that can be leveraged to individualize treatment regimens (NCT02624973).

Precision medicine, however, goes beyond genomic medicine. Instead, it is a ‘confluence of biological, physical, engineering, computer, and health sciences...toward data-driven, mechanism-based health and health care for each individual’ [26]. As such, precision medicine looks at a host of data across a population and defines, on the basis of areas like big data, patient response to a specific disease state and resulting interventional strategies. It is here that engineering plays a powerful role in linking these different ‘layers’, to redefine disease and search for meaningful mechanistic underpinnings that can inform next-generation therapies [26]. We see engineers continuing to contribute to precision medicine in the following ways: by enabling biomarker discovery, by creating diagnostic and sensing platforms, and by devising novel drug delivery methods to get precision therapeutics to the patient (Figure 1) [27–37].

Biomarker Discovery

Engineering approaches to biomarker discovery and validation have resulted in the development of signatures that may eventually serve as dynamic indicators of patient response to therapeutic intervention [38–43]. The genomics revolution and advent of approaches such as next-generation sequencing (NGS) has played a major role towards broad implementation of precision medicine in the clinic [44,45]. The fruition of this capability would be vital to enabling individualized treatment regimens in a patient-specific manner. For example, single molecule array (SiMoA) technology, which allows for single molecules to be sequestered by paramagnetic beads for digital readouts in microwells, was able to detect changes in prostate-specific antigen (PSA) levels that spanned orders of magnitude between individual prostate cancer cells [46]. Fiber microarrays have also been produced for multiplexed diagnostics. In these microarrays, a solution of microbeads that contains analogs for different target molecules can be interrogated with an imaging fiber, with etched microwells in the fiber providing positive signals for successfully detected biomarkers [47]. This platform was used to develop a potential signature for cystic fibrosis (CF) using saliva. Via the fiber microarrays, CF patients were observed to have substantially elevated vascular

Glossary

Artificial intelligence (AI): in the context of healthcare, AI uses algorithms to reconcile complex data in an effort to identify actionable strategies for many applications. These range from improving treatment outcomes to accelerating drug discovery, among others.

Bayesian decision analysis (BDA): with regards to healthcare, BDA is used to correlate tradeoffs and decision-making processes. For example, using BDA towards novel clinical trial designs may involve the correlation of outcome objectives for a patient with the benefits and risks undergoing treatment.

Chimeric antigen receptor T (CAR-T) cell immunotherapy: this form of immunotherapy modifies a patient's own T cells, which are derived from their immune system, with chimeric antigen receptors (CAR) on their surfaces. These modified T cells can then selectively target surface markers on the cancer cells using these receptors during treatment.

Circulating tumor cell (CTC): this cell is released by a primary tumor into the circulatory system and may serve as a foundation for metastasis.

Clinical decision support (CDS): using a broad spectrum of applicable data, CDS platforms provide actionable guidance to clinicians in areas such as drug selection, dosage modifications, and other courses of treatment.

Clustered regularly interspaced short palindromic repeats

(CRISPR): the CRISPR and CRISPR-associated protein 9 (CRISPR-Cas9) platform is used for genome editing, where genetic material can be added, removed, or modified. This approach can potentially be used to address a multitude of diseases by altering the genetic information that drives the onset of these disorders.

CURATE.AI: this mechanism-independent artificial intelligence platform is used to dynamically optimize clinical combination therapy dosing during the course of treatment. By using only a patient's own data to manage their own combination therapy regimen, CURATE.AI can maximize treatment efficacy and safety for a sustained duration on an individualized basis. It is broadly applicable towards oncology, infectious disease, and many other disease indications.

endothelial growth factor (VEGF), interferon-gamma inducible protein (IP-10), interleukin-8 (IL-8), and epidermal growth factor (EGF) levels, while matrix metalloproteinase-9 (MMP-9) levels were lower. The six-biomarker signature, captured by the highly sensitive and multiplexed fiber microarray, was capable of differentiating patient subgroups and correlated well with the forced expiratory volume (FEV1) readout for disease severity [47]. In addition, long-term monitoring of inflammatory cytokines in healthy individuals was conducted, revealing a subset of cytokines that can vary by as much as two orders of magnitude between subjects, while others had substantially lower levels of interpatient variability [48]. This study demonstrated the importance of taking baseline studies of patient biomarker signatures as a way towards highly accurate monitoring of the dynamic states of disease progression and/or treatment response.

Microfluidic technologies have a long history of providing the biomedical community unique, modular platforms for detecting low levels of biomarker in small volumes of fluid. In one instance, a microfluidic device was used to deplete hematopoietic stem cells (HSCs), thereby allowing CTCs associated with hepatocellular carcinoma (HCC) to be easily detected. With a pure sample, an RNA-based signature was developed using 10 liver-based transcripts, subsequently resulting in the detection of HCC-derived CTCs in 9 of 16 untreated patients with HCC as well as 1 of 31 patients that had nonmalignant liver disease. It is important to note that the digital scoring process also did not correlate to commonly monitored serum alpha-fetoprotein (AFP) levels, demonstrating the importance of the RNA-based signature in accurately detecting and assessing disease states [49]. This RNA signature would not have been possible without the sorting and purifying capabilities of the microfluidic device.

In addition to the aforementioned approaches, a number of studies have harnessed single-cell analysis using approaches such as Raman microspectroscopy and multiplexed imaging using laser particles for biomarker discovery [50–52]. Peptide arrays are now capable of monitoring low-affinity protein–ligand interactions that may not have been captured by conventional methodologies, such as Fourier-transform infrared spectroscopy or surface plasmon resonance spectroscopy, opening doors to novel monitoring and drug discovery strategies [53,54].

Precision Diagnostics and Biosensing

A key barrier that confronts precision medicine is the inability, in many cases, to assess quantifiable treatment outcomes due to inadequate biomarkers. This is especially true for solid cancers and certain infectious diseases, such as tuberculosis, and for other indications, such as pain and brain injury. Recent capabilities pertaining to individualized care could especially benefit from frequent biomarker analysis in order to prescribe accurately calibrated treatment responses. Emerging technologies will open the doors to biomarker surveillance with high sensitivity and specificity, as well as greater frequency than conventional monitoring approaches such as imaging [computed tomography (CT), magnetic resonance imaging (MRI)] or blood draws. For example, microfluidics and nanofluidics can process and analyze in parallel nucleic acids, proteins, metabolites, and single cells in various biological fluids, such as urine, blood, and saliva, which increases the frequency of outcome monitoring, a valuable resource for personalized dosing and pharmacokinetics. In fact, guided therapy using microfluidics or nanofluidics for genomic analysis and CTC isolation and characterization for biomarker discovery is starting to make its way into the clinic. CTCs have been isolated using microfluidics from lung adenocarcinoma, undifferentiated Epstein-Barr virus, positive nasopharyngeal carcinoma, breast cancer, colorectal cancer, prostate cancer, and gastric cancer to develop predictive biomarker panels for the downstream selection of therapeutic regimens (NCT01022723). Circulating endothelial cells and CTCs are also being evaluated as biomarkers for renal cancer (NCT02499458). A study to capture and

Cytometry by time of flight (CyTOF):

this is a mass spectrometry methodology that uses heavy metal antibody tags for cell surface and intracellular markers. CyTOF analysis enables multiplexed profiling of single-cell responses for applications in drug development and fundamental studies into cellular mechanisms.

Electronic medical records (EMR):

electronic medical records can contain a broad spectrum of information pertaining to a patient's health history. They can serve as vital platforms for the implementation of treatment and diagnostic paradigms that may integrate emerging technologies such as artificial intelligence, wearables, and other modalities.

Machine learning (ML):

ML platforms use algorithms that are trained with a set of data to subsequently make inferences and identify a course of action without requiring a directed set of instructions. Implementation of ML typically requires minimal human interaction. In the context of healthcare, it can be used for many applications, including the design of drug combinations and the development of biomaterials, among others.

Maximum tolerated dose (MTD):

the highest dose of a drug that can be administered to a subject while simultaneously avoiding an unacceptable level of toxicity. With regards to precision and personalized medicine, emerging studies have shown promise in identifying lower drug doses that result in improved efficacy and safety, potentially avoiding the need to reach the MTD during therapy.

Mitochondrial replacement therapy (MRT):

this approach is used to address mitochondrial diseases by replacing mitochondria that contain DNA mutations with healthy mitochondria. In the context of reproductive medicine, a mother with mitochondrial disease can have her eggs transferred to a donor egg with healthy mitochondria.

Nanodiamond (ND):

nanodiamonds are carbon-based nanoparticles that can be used to carry multiple classes of therapeutic and imaging compounds. Their unique surface electrostatic properties have been used to markedly improve magnetic resonance imaging contrast efficiency as well as drug delivery efficacy.

Phenotypic personalized medicine (PPM):

this artificial intelligence-based approach uses quantifiable measures of

analyze CTCs from metastatic breast cancer patients using antibody panels and microfluidics is also being conducted (NCT02904135) [5,55–61].

Surprisingly little is known about the evolution, origin, and metastasis of cancer. Single-cell analysis, an area that is maturing rapidly, promises to deliver new disease insights by parsing out the potential role of cellular heterogeneity in health and disease, including cancer [62,63] (Figure 1). For example, digital real-time PCR for single-cell transcription factor profiling in HSCs revealed the presence of two HSC subpopulations from a specific type of progenitor cell that were believed to be homogeneous. This finding made it clear that gene expression could be assessed in a copy-number-per-cell context, providing extraordinary insight into transcriptional regulation [57]. Single-cell genomics has also been used to analyze the clonal structure of tumors in both colon cancer [64] and leukemia [56,65] and the literature using this approach is growing by leaps and bounds.

Engineers have found ways to peer into biological processes, sometimes in ‘real-time’, to uncover novel insights into human disease progression. For instance, real-time imaging of colon cancer cell migration in mice has revealed clonal liver metastasis, providing valuable insight into early detection and subsequent treatment of advanced cancers [66]. Imaging dormant breast cancer cells in mice has shown that vascular triggers are responsible for proliferation and growth, revealing new therapeutic targets in the vasculature [67]. Devices can be used to isolate rare cell populations, in some instances to understand individual cell contributions to disease, in others, to make a diagnosis or therapeutic decision. In a recent study using blood samples obtained from metastatic castration-resistant prostate cancer patients, the presence of androgen-receptor splice variant 7 (AR-V7) on the CTC surface predicted improved response to taxane therapy over aminoacyl-tRNA synthetase (ARS) inhibition. Of note, these systems used antibody cocktails to label and distinguish CTCs. Digital pathology algorithms were then used to track cellular morphology from highly heterogeneous solutions in order to classify CTC subtypes. Pathway activation could also be assessed through the additional detection of surface markers in multiple myeloma [68,69]. In addition, this integrated approach was capable of isolating both single CTCs and clusters of CTCs positive for AR-V7 to guide treatment selection [58]. In a clever approach to better understand lung diseases, a microfluidic device was engineered to analyze individual cell deformability as a means of diagnosing noninvasively whether human pleural effusions were malignant or benign [70].

Although these devices can more readily isolate and analyze single cells, we are still left piecing together their implications in disease. **Cytometry by time of flight (CyTOF)**, which can analyze the contribution of a single cell to a given signaling pathway, addresses this point [71]. By using technologies such as CyTOF to assess complex populations of cells, the role of heterogeneity in driver mutations and drug resistance can be comprehensively interrogated. In addition, longitudinal studies need to be designed to decipher clone behavior, as well as spatial and temporal genomic signatures, and to resolve evolutionary principles that underpin cancer as well as infectious diseases and other disorders [72]. As a step towards determining the role of heterogeneity in disease progression and treatment, a recent study performed single-cell triple-omic analysis of the genome, DNA methylome, and transcriptome in a population of hepatocellular carcinoma cells to assess the larger-scale contributions of genomic and epigenomic heterogeneity towards transcriptomic heterogeneity. These capabilities in omics interrogation may provide extraordinary insight into disease heterogeneity and enable both the prediction of drug responses and individualized therapy [73].

Sample collection poses many limitations for both personalized and precision medicine. Technologies that can analyze small amounts of rare tissues or molecules will allow us to access information

clinical efficacy and safety, such as tumor burden through imaging or circulating biomarker analysis, as well as toxicity panels to guide drug dosing. This approach can be implemented in a mechanism-independent manner.

Quadratic phenotypic optimization platform (QPOP): this AI-based approach simultaneously identifies the right drugs and corresponding doses from large pools of candidate therapies for novel drug combination development. It can be implemented without disease target/mechanism information and does not rely on drug synergy predictions to optimize treatment outcomes.

Spherical nucleic acids (SNA): these nanostructures consist of precisely positioned and high-density configurations of nucleic acids that have been explored for gene regulation with broad applications across different disease indications. They are currently being evaluated at the clinical level.

Stamped assembly of polymer layers (SEAL): this approach uses 3D printed microwells that contain multiple drugs and can be used for the timed release of multiple therapies in a sustained fashion.

Zinc finger nuclease (ZFN): this enzyme is comprised of DNA-binding and cleavage domains and is used as a genome editing platform. ZFN-based genome editing therapies are currently being evaluated at the clinical level.

Table 1. Clinicaltrials.gov Identifiers of Clinical Trials That Are Assessing Emerging Technologies for Personalized and Precision Medicine

Technology platform	Status	Key details of study	Clinicaltrials.gov identifier
Artificial intelligence	Phase II	Harnessing CURATE.AI to optimize N-of-1 combination therapy in multiple myeloma.	NCT03759093
Artificial intelligence	Interventional	Developing N-of-1 training trajectories via CURATE.AI.	NCT03832101
Artificial intelligence	Phase IV	HIV: optimization of dose reduction of tenofovir (TDF) in antiretroviral therapy (ART).	NCT02632474
Artificial intelligence	Phase II	Liver and kidney transplant: dynamic modulation of therapeutic dosing to optimize immunosuppression.	NCT03527238
Artificial intelligence	Interventional	Radiotherapy: image-guided adaptive radiotherapy is being studied to modulate intensity to reduce side effects and improve outcomes.	NCT04022018
Genomic analysis/companion diagnostics	Feasibility	Non-small cell lung cancer (NSCLC): Co-clinical trials with genetic mouse models, NSCLC patient specimens (plasma, serum, tissue), and healthy patient samples to develop liquid biopsies.	NCT02597738
Genome-guided therapy	Observational	Pain: assessment of the cytochrome P450 2D6 (CYP2D6) and μ -opioid receptor gene (OPRM1) genotypes in guiding pain management.	NCT02664350
Genome-guided therapy	Observational	Preterm birth: genomic profiling to predict patient response to 17 hydroxyprogesterone caproate (17OHP) therapy to prevent preterm birth.	NCT02173210
Genome-guided therapy	Phase II	Breast cancer: biomarker analysis and genetic screening to develop individualized treatment regimens.	NCT02624973
Genome-guided therapy	Phase II	Multiple tumor types: matching of drugs to patients based on genomic alterations.	NCT02795156
Genome-guided therapy	Phase III	Prostate cancer: circulating tumor DNA is being used as a biomarker for genome-guided drug selection.	NCT03903835
Microfluidics/companion diagnostics	Observational	Multiple cancer types/circulating tumor cells: correlation of titer with treatment response and progression for nasopharyngeal carcinoma, breast cancer, colorectal cancer, prostate cancer, and gastric cancer.	NCT01022723
Microfluidics/companion diagnostics	Observational	Clear cell renal cancer/circulating tumor cells: comparison of microfluidic technology that can detect CTCs under low epithelial cell adhesion molecule (EpCAM) presence compared with EpCAM-based detection platform for clear cell renal cancer.	NCT02499458
Microfluidics/companion diagnostics	Observational	Metastatic breast cancer/circulating tumor cells: application of antibody cocktails to capture CTCs from metastatic breast cancer for microfluidic analysis.	NCT02904135
Genome editing	Phase I	Mucopolysaccharidosis II (MPS II): intravenous delivery of SB-913, a zinc finger nuclease, to enable production of iduronate 2-sulfatase (IDS) enzyme from the liver.	NCT03041324
Genome editing	Phase I	Mucopolysaccharidosis I (MPS I): intravenous delivery of SB-318, a zinc finger nuclease, to insert α -L-iduronidase (IDUA) gene to enable liver-mediated enzyme production.	NCT02702115
Genome editing	Phase I	Severe hemophilia: intravenous delivery of SB-FIX, a zinc finger nuclease, to insert the SB-FIX gene to enable Factor IX clotting factor production.	NCT02695160
Genome editing/cell therapy	Phase I	HIV: administration of zinc finger nuclease CCR5-modified hematopoietic stem/progenitor cells (SB-728mR-HSPC) in patients with undetectable disease/low CD4+ counts.	NCT02500849
Nanomedicine/RNA therapy	Phase 0	Glioblastoma: administration of NU-0129, a spherical nucleic acid (SNA) therapy, to target the Bcl2L12 gene to arrest tumor growth.	NCT03020017
Nanomedicine	Phase I	Cervical cancer: polysiloxane gadolinium chelates are delivered in combination with cisplatin and radiation therapy to address locally advanced disease.	NCT03308604

Table 1. (continued)

Technology platform	Status	Key details of study	Clinicaltrials.gov identifier
Wearables	Observational	Perioperative risk assessment: pairing wearable (Garmin VivoSmart HR+) with cardiopulmonary exercise testing indicators to develop broadly applicable risk assessment protocol for high-risk elective surgery patient population.	NCT03328039
Wearables	Observational	Chronic obstructive airway disease (COPD): application of wearable (on finger) for heart rate variability and oxygen saturation to detect and manage COPD in patients over 60 years in age.	NCT03268538
Wearables	Observational	Cardiology: a shirt-based electrocardiogram system is being used to monitor the following patient cohorts: (i) cardiac rehabilitation following myocardial infarct; (ii) pediatric supraventricular tachycardia; (iii) post-pulmonary vein isolation; (iv) cardiac resynchronization therapy patients.	NCT03068169
Digital Health	Observational	Alzheimer's disease: cognitive battery software was used to predict dementia onset.	NCT03676881
Digital health	Interventional	Health eBrain study: application of neurocognitive assessment mobile health software to assess brain health combined with Mindoula intervention to address dementia and depression in Alzheimer's disease caregivers.	NCT02903862
Biomaterials	Phase II	Wound healing: a nanodiamond-based biomaterial platform to mediate periapical wound healing and prevention of reinfection following root canal therapy.	NCT03376984
Biomaterials	Phase I	3D printing: personalized 3D printing of polycaprolactone (PCL) is being explored for breast reconstruction after tumor removal.	NCT03348293
Electronic health records/infrastructure/genotyping	Observational	Pain: CYP2D6 genotyping for pain management/control and integration of pain questionnaire in electronic health record for physician guidance.	NCT02335307

previously lost in the bulk. Liquid biopsies, for instance, can be used to monitor disease in near real-time and perhaps in the future be used to predict drug action and continuously modulate combination therapy. Liquid biopsies could extract CTCs, exosomes, cell-free nucleic acids, proteins, and other biological factors for collection and analysis [5,68,74]. This approach may enable the identification of effective treatment outcomes and design criteria for drug-regimen selection and predictors of response to the selected therapies.

Precision Therapeutics

Gene editing tools like **clustered regularly interspaced short palindromic repeats (CRISPR)** and **zinc finger nucleases (ZFN)** have the ability to alter specific components of a genome, thereby opening new doors to precision repair of defective genes in indications ranging from cancer to HIV. The democratization of gene editing afforded by CRISPR promises to produce large amounts of data that we expect to shed light on new connections between diseases and on new pathways never before implicated in a particular disease. Gene editing has recently found its way into patients [75]. Recently, the ZFN-based genome editing therapeutic SB-913 was clinically administered to patients diagnosed with mucopolysaccharidosis II (MPS II), or Hunter syndrome. One of the objectives of this study was to evaluate the impact of SB-913 on leukocyte and plasma iduronate 2-sulfatase (IDS) enzyme activity in an effort to mediate lifelong IDS production (NCT03041324). ZFN genome editing therapies are also being tested for MPS I (SB-318, NCT02702115), and severe hemophilia B (SB-FIX, NCT02695160). Clinical trials evaluating CCR5-modified hematopoietic stem/progenitor cells (via ZFNs) in patients infected with HIV-1 have also been initiated (NCT02500849).

Engineering precision medicine technologies

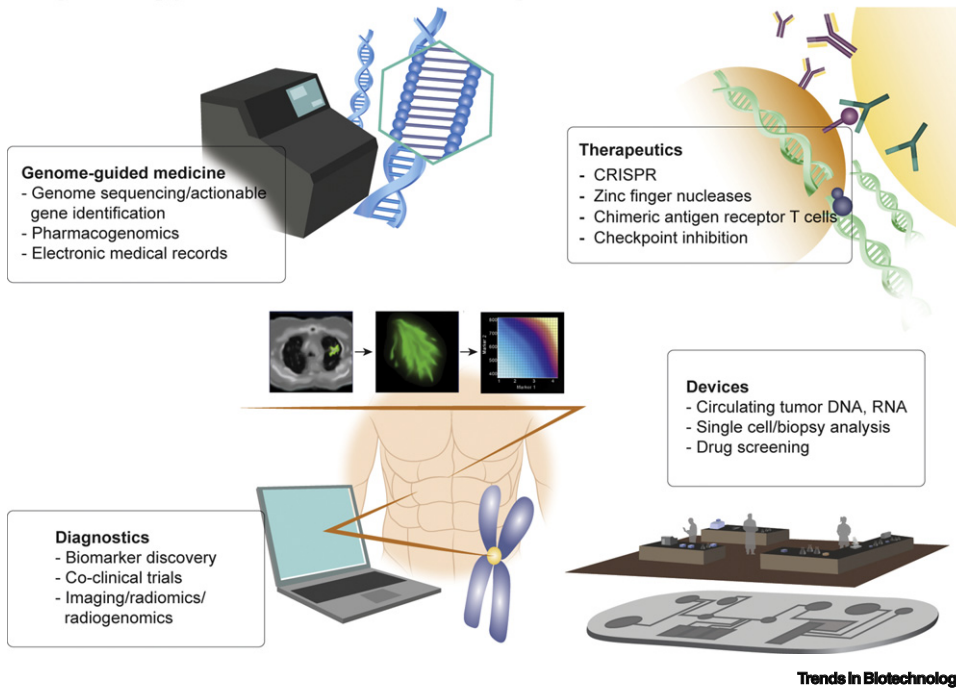


Figure 1. Engineering Precision Medicine Technology Platforms. From genome-guided medicine to clustered regularly interspaced short palindromic repeats (CRISPR), a broad spectrum of technology platforms that bridge engineering with precision medicine are poised to impact clinical outcomes.

Molecularly targeted and antibody therapies have served as cornerstones in precision medicine and have resulted in a broad spectrum of approved drugs and emerging methods of patient-specific drug prioritization via mutation databases [76–78]. Recent genome- and proteome-guided therapeutic strategies that are in preclinical development have included the use of CRISPR with an enzyme, CRISPR-associated protein-9 nuclease (Cas9), to correct genetic aberrations in diseases such as Duchenne muscular dystrophy (DMD). Specifically, CRISPR therapy restored dystrophin production and substantially increased neuronal nitric oxide synthase (nNOS) recruitment in a mouse model compared with the sham cohort, an important advance for targeted gene editing [79]. Tumor profiling to assess the expression of programmed cell death protein 1 (PD-1; which is encoded by the PDCD1 gene), PD-L1, and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) from patient samples was used to predict treatment response for melanoma [80]. Several classes of targeted inhibitors have been paired with genomic profiling due to drug mechanisms of action that can specifically enhance treatment outcomes such as progression-free survival. For example, epidermal growth factor receptor (EGFR) exon 19 deletions and exon 21 point mutations served as indicators for subsequent afatinib administration for non-small cell lung cancer (NSCLC) treatment in both treatment-naïve and refractory NSCLC patients [81–83].

Administering CRISPR with improved efficacy can also be mediated using new delivery mechanisms like nanoparticles. A recent preclinical study using CRISPR/Cas9 and a lipid nanoparticle successfully switched off genes responsible for high cholesterol levels, in cells and mice [84]. Gold nanoparticle-mediated delivery of CRISPR-Cas9 was used to enhance the efficacy of correcting a DNA mutation associated with DMD [85]. In addition to mediating guide RNA-based therapy mediated by CRISPR, novel nanocarrier approaches are also being used for

RNA interference. For example, **spherical nucleic acids (SNAs)** are gold nanoparticles that have been recently synthesized to be densely loaded with RNA duplexes for gene silencing. In multiple *in vitro* and preclinical studies, SNAs were efficiently taken up in a broad spectrum of cell lines and capable of mediating efficient RNA interference while remaining well tolerated [86–88]. In a recent murine study, SNAs were utilized to knockdown the p53 inhibitor, Bcl2Like12 (Bcl2L12), which is overexpressed in glioblastoma, as a novel form of cancer treatment [89]. The SNA platform (NU-0129) was recently translated into the clinic, where a Phase 0 study is currently underway (NCT03020017).

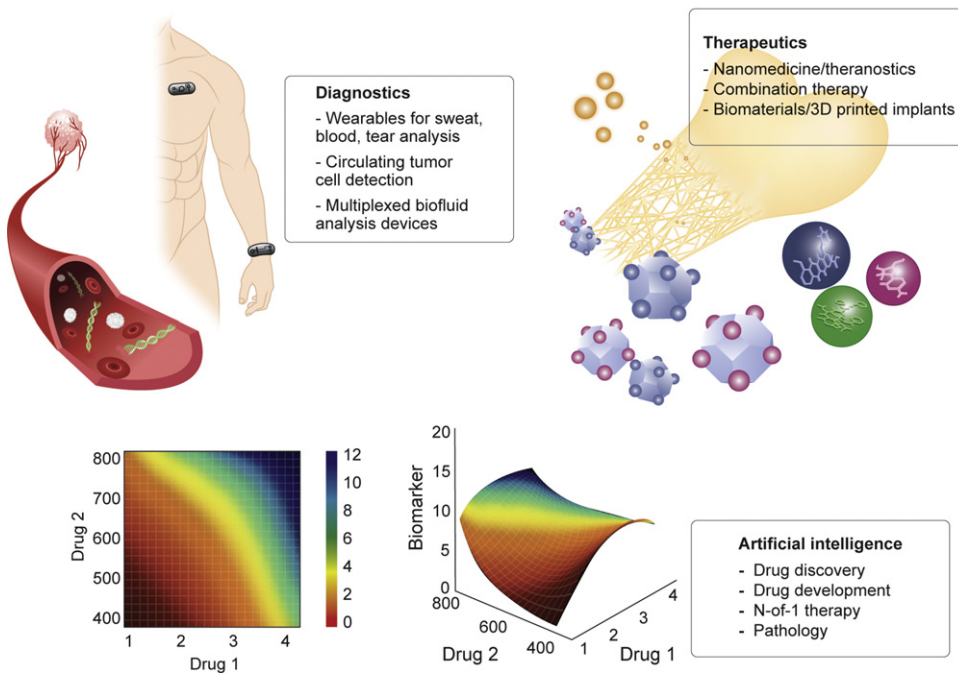
Bioengineering for Personalized Medicine

Medicine is moving away from a ‘one size fits all’ mentality. We are realizing that patients with the same disease can respond differently to everything, from drugs to biomaterials, and it is now time to better understand this response and treat the patient as an individual. Engineers have the opportunity to make personalized medicine a greater reality in the clinic (Figure 2). Take biomaterials, for instance. Researchers have found that a dextran-dendrimer composite works as an adhesive differently in not only different organs, but also differently in the same organ under different environments (e.g., colon cancer versus colitis) [90,91]. These findings suggest that the application of most biomaterials cannot be generalizable and that the disease indication and organ environment matters in the design of materials that are to reside temporarily within the body. Indeed, biomaterials can have a differential effect on cell fate, survival, and growth, yet there is a dearth of high-throughput approaches to screen for the optimal material composition for a given application. One approach is to use a combination of small and large animal models to determine the best polymer carrier for islet transplantation [92–94]. An approach that avoids animal models altogether looked at how different extracellular matrix formulations (different organs, different processing methods) affected stem cell differentiation, cancer cell proliferation, and cell apoptosis [95]. Engineering new platforms for narrowing down the optimal biomaterial formulation could improve personalized biocompatibility and therapeutic outcomes.

Organ-on-a-chip platforms are being explored for potential individualized drug screening and toxicology studies. For example, a microfluidics-based model of human intestine was recently developed, where the complex gut microenvironment was recapitulated, allowing for the monitoring of interactions between the gut microbiome, bacteria, and immune cells. The ability to replicate organ-scale complexity using platforms such as this intestine model opens the doors to pharmacokinetics, absorption, and drug metabolism analysis as they relate to drug development and toxicity studies [96,97]. These capabilities may also serve as the foundation for designing personalized treatments. To accurately personalize treatment, which includes parameters such as drug selection and drug dosing, accurate and timely detection of treatment response is needed. Conventional approaches to acquire these readouts include serum and urine analysis, or imaging modalities such as ultrasound, CT, MRI, and x-rays, among others, which may be limited in terms of testing frequency, especially if treatment response varies on a timescale of hours, or even minutes. Wearables and other classes of emerging technologies may overcome the challenges of infrequent measurements to improve the accuracy of treatment response assessment, thereby improving the design of personalized interventions [98]. As the field of personalized medicine continues to progress, new areas of development have included the use of nondrug-based platforms, such as digital therapy, to address conditions such as mild cognitive impairment, substance abuse, mental health, and attention deficit hyperactivity disorder, among others [99–101].

A unifying attribute of these approaches is their potential towards using only a subject’s own data to manage only their own care. This has been apparent with regards to AI-driven drug dosing as

Engineering personalized medicine technologies



Trends in Biotechnology

Figure 2. Engineering Personalized Medicine Technology Platforms. By bridging wearable technologies with artificial intelligence and other engineering platforms, marked enhancements in the development of individualized treatment and monitoring may be realized.

well as engineered cell therapy. Furthermore, a common attribute at the intersection of engineering and personalized medicine is that intervention and diagnosis can be adjusted in a serial fashion for ongoing treatment optimization.

AI, Machine Learning, and Personalized Treatment

A major barrier to the optimization of any targeted therapy has been an inability to determine drug doses that are best suited for an individual patient, especially since dosing requirements can often change during the course of treatment. In the case of combination therapy, this is even more challenging given the virtually infinite dosing parameter space that exists. The same quandary also confronts the concept of pinpointing population-optimized drug–dose ratios. To overcome this challenge, conventional patient dosing and drug development has been guided by first identifying the drugs to be administered, following by dose escalation-based trials to identify the **maximum tolerated dose (MTD)**. To increase the chances of successful treatment outcomes, drug–synergy predictive modelling and other *in silico* methods have been employed [102]. However, drug synergy and drug antagonism are dose-dependent, and not all genes involved in the uptake, metabolism, and activity of any specific drug are known. Therefore, incorrect dosing can substantially decrease or eliminate the efficacy of drug combinations, whereas optimized drug–dose ratios can make normally ineffective drugs become potent when co-delivered.

In the drug and dose optimization arena, there remains a perception that correct dosing is important solely for improving efficacy and safety. What is commonly misunderstood is that correct dosing directly impacts the drugs that are selected for treatment in the first place [103, 104].

Furthermore, in lieu of predictive drug discovery, synergy modeling, monotherapy, or combination therapy selection, AI and **machine learning (ML)**-related platforms are now capable of deterministically identifying, in a continuous fashion, the drug administration parameters [9,105,106]. More specifically, the implementation of novel AI-based platforms is precisely demonstrating the key relationship between drug dose and drug selection by reconciling the virtually infinite parameter space created by these factors. AI is also being leveraged to enhance imaging capabilities in the area of diagnostics to further guide patient-specific treatment. In addition, the application of AI is emerging in the area of therapeutics to simultaneously pinpoint the best drugs and doses, even from very large pools of candidate compounds, for optimal combination therapy efficacy and safety [107–118]. In a recent study using the deterministic AI-based **quadratic phenotypic optimization platform (QPOP)** platform, novel drug combinations were identified from a pool of oncology drug candidates without the need for synergy-based predictions or complex disease mechanism information. In addition, QPOP was used to re-optimize the drug combination dose parameters from the *in vitro* through preclinical stages of development. These AI-discovered combinations substantially outperformed the clinical standards of care [117]. While QPOP implementation did not require disease mechanism modelling, global optimization via this platform can lead to new insights in the pathways that mediate globally optimized outcomes for comparison with conventional target-based drug combination design. This could in turn lead to the addition of new drug candidates in the combination therapy design pool. Approaches such as QPOP require marked reductions in data requirements as they are based on drug and dose inputs and quantifiable clinical indicators of efficacy and safety (e.g., tumor burden, toxicity panels). This emerging capability of mechanism-agnostic optimization, as well as a continuously increasing body of knowledge in the genome-driven drug selection arenas are expected to address some of the barriers that have been previously encountered with trials such as SHIVA, where molecular alterations serve as a foundation for drug matching. In this previous study, the factors determining drug–patient pairing were driven by an algorithm prioritizing molecular alterations and drug selection, among other factors. Lessons learned from this study, and suggestions provided by the clinical community, have shed light on the potential of patient stratification using oligo-mutant tumors in lieu of multi-mutant tumors, while additional suggestions included the use of combination therapy when multiple molecular alterations were identified.

In combination therapy, the ‘sweet spot’ of an optimized drug–dose ratio and the best drugs that comprise the multidrug treatment is almost always overlooked when dose escalation and MTD are employed [10,106,119–124]. As such, the recent clinical application of augmented AI optimization platforms has overcome this challenge (NCT03759093, NCT03832101, NCT02632474, NCT03527238) [105,106,119]. In a recent prospective trial, a new technology platform based on PPM successfully personalized post-transplant immunosuppression [9]. The foundation of this capability is based on the PPM-enabled discovery that drug administration (input) can be correlated to phenotypic output (e.g., tumor burden, bacterial/viral load) through a phenotypic response surface. Without using algorithms or modelling, PPM optimization effectively calibrated optimized dosing regimens for each patient enrolled in the study. Furthermore, patients were continuously calibrated to dynamically adjust their dosing guidelines for the entire duration of care, an unprecedented capability [9,105]. Inpatient dose-dependent drug synergy and antagonism was also observed, further demonstrating the importance of optimizing personalized care.

These studies have since been expanded to include the optimization analysis of combination therapy regimens in pediatric acute lymphoblastic leukemia, development of improved combination therapies that maintain undetectable viral loads with substantial dose reduction in patients with HIV, as well as optimization of immunosuppression dosing (NCT02632474, NCT03527238) [106]. Recently, **CURATE.AI** was harnessed to optimize N-of-1 combination therapy for an advanced

prostate cancer patient that resulted in a marked reduction in drug dosage that increased treatment efficacy [125]. In addition, CURATE.AI was recently applied to the emerging field of digital therapeutics, where N-of-1 profiles were constructed for cognitive training (NCT03832101) [99]. In addition to AI-driven drug treatment, adaptive radiotherapy has also been explored, where images are being used to modulate intensity to reduce treatment toxicity and enhance local disease control (NCT04022018). These studies are examples of how AI can expand and optimize an arsenal of interventions against many types of diseases.

As novel platforms for patient-specific testing and treatment continue to evolve, the implementation of AI is expected to expand. For example, organ-on-chip, single-cell interrogation platforms, and powerful diagnostic modalities may represent ideal testbeds for N-of-1 or population-scale drug development [126–133]. Specifically, organ-on-a-chip platforms are capable of replicating complex function ranging from the gut, to placental transport and pulmonary function in both healthy and diseased systems [96,97,127,134–136]. Recent advances in organ-on-a-chip development have opened the doors to their applications in drug screening. Since combination therapy is a mainstay for indications ranging from oncology to infectious diseases, among others, these platforms can be integrated with AI-based screening strategies that reduce the number of assays needed to identify optimized drug combinations [110,120]. In turn, this can accelerate the clinical validation of novel treatment approaches.

Wearable and Implantable Sensors

Individualizing drug and dose parameters for indications ranging from pulmonary hypertension to cancer therapy require constant and robust readout monitoring. To this end, wearable technology will play a key role in mediating personalized therapy. Capacitive coupling-based flexible electronics that do not require contact between cardiac tissue and metals were recently used for electrophysiological measurements in rabbits [137]. Wearable, battery-free devices for blood oxygenation and heart rate measurements have also been developed [138,139]. Soft electronics for the analysis of sweat, tears, skin interstitial fluid, and saliva link noninvasive measurements with blood concentrations of these analytes [140–144]. These platforms can be used for glucose sensing and CF monitoring without the barriers associated with fingerstick testing [145,146]. The clearance of the MiniMed 670G (Medtronic), a closed-loop artificial pancreas, has enabled the algorithm-driven delivery of basal insulin to control blood glucose levels for type 1 diabetes. Recent reporting of real-world data revealed an increased time within the target glucose range with reduced incidence of hyperglycemia and hypoglycemia [147]. Microfluidics-embedded polymer wristbands have also been developed for pulse measurements [148]. Silicone microfiber tubes embedded with electrodes for blood pressure, blood vessel stiffness, and heart rate monitoring have been developed, allowing for noninvasive diagnosis and monitoring of atherosclerosis, venous ulcers, and potential integration into bandages for diverse applications [149]. Such noninvasive, multiplexed monitoring may ultimately identify personalized biomarker signatures [150].

Wearable devices are being tested in the clinic to potentially predict perioperative risk in patients undergoing high-risk surgery by comparing wearable data (e.g., heart rate and exercise intensity) with cardiopulmonary exercise testing standards (NCT03328039). Wearables are also being studied to detect and manage chronic obstructive airway disease (NCT03268538). A wearable shirt-based electrocardiogram measurement system can detect arrhythmias and could serve as a complementary real-time readout monitor for dynamically administered cardiovascular therapies (NCT03068169).

In the area of neurocognitive assessment, FDA-cleared mobile application software is also being used to interrogate brain health for the development of interventional solutions in areas like dementia, depression, and Alzheimer's disease (AD) (NCT02903862, NCT03676881) [151]. Studies

employing digital medicine in clinical aging research are increasing since several methodological barriers limit conventional in-clinic test administration. First, in-clinic testing is relatively infrequent. In most studies, assessments typically occur on an annual basis in one extended testing session. Second, day to day fluctuations in participant stressors, sleep patterns, and time of day effects, and the artificial nature of testing environments, can strongly influence cognition and these sources of variability may be exacerbated in participants with AD pathology [152]. Finally, the cognitive tests most sensitive to the earliest declines in AD also demonstrate high levels of day-to-day variability and can have substantial retest effects [153,154]. Smartphone assessment approaches afford novel opportunities to overcome these barriers by leveraging the increasing adoption of smartphones by older adults to mitigate the temporal, geographic, space, and personnel constraints imposed by in-person testing. Tests are administered in a measurement burst design, in which a 'burst' of brief (30–60 seconds per test) cognitive tests are completed at random intervals several times per day over the course of 1 week on participant's personal smartphones. One study 'visit' thus represents the average performance across 7 days of assessments [155]. Advantages include more frequent measurements at different times of day and a detailed evaluation of variability and practice effects within a day and over a week, which may also serve as sensitive indicators of disease stage [154,156,157]. As such, markedly increasing the frequency and scalability of data collection using wearable and mobile health enhances data actionability, reducing the need to use data that has been acquired using conventional approaches, and averaged over several months. When paired with therapeutic strategies that have been properly tailored to this data, wearables and smartphone-based approaches for continuous and robust health monitoring will play a key role in mediating personalized therapy.

Data collection by wearables could allow for patients and their families to take action on their own health and also avoid frequent trips to the doctor to have biomarker analyses performed using conventional approaches. As these data troves grow, we can expect a major contribution beyond personalized medicine to precision medicine, opening up new treatment ideas and options for many patients.

Personalized Cell Therapy and Drug Delivery

The recent regulatory approval of **chimeric antigen receptor T (CAR-T) cell immunotherapy** represents a major advance for personalized cancer treatment. The first of the approved CAR-T therapies, tisagenlecleucel (Kymriah, Novartis), was developed to treat acute lymphoblastic leukemia in patients 25 years old and younger, and involves removing a patient's T cells, sending them to a processing facility for reprogramming and expansion, and returning them to the doctor for introduction to the patient [158]. Axicabtagene ciloleucel (Yescarta, KITE Pharma/Gilead Sciences) was recently approved for the treatment of aggressive non-Hodgkin's lymphomas, including diffuse large B cell lymphoma [159,160]. A global effort to expand the indications that are treated using CAR-T is underway. Furthermore, the regulatory approval of CAR-T therapy represents a paradigm shift for the US FDA and a gateway towards the continued enhancement of the efficacy and safety of living cell therapies. For example, recent studies have explored the use of nonviral approaches, such as *Sleeping Beauty* transposition, which can enhance CAR-T scalability for broader deployment [161]. This approach uses simple DNA minicircles to insert CAR genes, potentially reducing the risk of mutagenesis and genotoxicity that may be associated with viral modalities. This strategy may also reduce regulatory hurdles and the cost of CAR-T engineering. Additional engineering approaches have sought to improve CAR-T manufacturing strategies using 'off-the-shelf' cell therapy that does not require autologous T cells [162–164]. Through the use of CRISPR/Cas9 to eliminate CD7 and T cell receptor alpha chain, which are also expressed on the malignant T cells, barriers such as fratricide could be avoided and preserved activity against T cell acute lymphoblastic leukemia *in vitro* and *in vivo* was demonstrated.

In addition, graft-versus-host-disease was not observed. In a recent advance, ZFN editing is being harnessed to modify both autologous and allogeneic cell therapies, further broadening the possibilities of off-the-shelf CAR-T manufacturing, potentially reducing the time to treatment for the patient [165].

Cancer is not the only target of personalized cell therapy. Induced pluripotent stem cells taken from a patient's skin or elsewhere can be reprogrammed to a cell of choice, such as one of the kidney's specialized cells, the beta cell, to treat type 1 diabetes; or into a brain cell, which can be transplanted into the body to, for instance, reduce inflammation in multiple sclerosis, as shown in mice [93,166,167]. Additional examples of cell therapy include **mitochondrial replacement therapy (MRT)**, which has also been implemented in the UK. Mitochondrial disease is caused when mutations in mitochondrial DNA (mtDNA) are maternally transferred to the offspring, which can lead to serious disorders ranging from epilepsy to optic neuropathy and diabetes mellitus and deafness, among others. To implement MRT, the healthy nucleus from the maternal egg with malfunctioning mitochondria is transferred to a healthy egg (and donor mitochondria) without a nucleus. In effect, this approach can result in a fertilized egg that contains nuclear DNA from two parents and an mtDNA from a donor to eliminate genetic diseases in offspring [168].

The engineering of cells as biosensors is another particularly relevant area. Synthetic cells have been designed for detecting cancer and for detecting diabetes indicators in urine [169,170]. Impressively, synthetic biology has advanced from bacteria to mammalian cells, with early biosensors able to not only detect disease markers but also deliver therapeutic payloads to ameliorate symptoms. In this example, acute and chronic psoriasis was held in check by a population of synthetic cells implanted in the mice [171]. This is the ultimate demonstration of personalized medicine, where the cell is an autonomous sensor and therapy, delivering therapeutic levels of 'drug' without patient or clinician intervention.

Delivering therapy in a personalized fashion will also serve as an important enabling technology. Knowing that dose modulation, or population optimized fixed dose combination therapy will serve as a cornerstone for improving delivery technologies, methodologies such as personalized 3D printing or biomaterial-mediated controlled release will play an increasingly important role in personalized medicine (NCT03348293). Tailored release profiles from 3D printed tablets were recently introduced, where the temporal drug release could be customized [172]. In addition, advances in micro-manufacturing have produced drug-loaded 3D microstructures with temporal drug release control using an approach termed **stamped assembly of polymer layers (SEAL)** [173]. Patient-specific responses to combination therapy are often determined by unique dosing profiles. Therefore, these tablets and microstructures may serve as viable drug delivery platforms for personalized medicine.

Combination therapy with nanomedicine has also received substantial attention [174–176]. Augmented AI was also used to design population-optimized combinatorial nanotherapy across multiple breast cancer cell lines (MCF-7, MDA-MB-231, BT-20) and control cell lines (IMR-90, MCF-10A, H9C2). This resulted in the identification of specific drug–dose ratios that mediated optimal treatment efficacy. Specifically, diverse dosing regimens of **nanodiamonds (NDs)** functionalized with doxorubicin, bleomycin, and mitoxantrone (NDX, ND-BLEO, ND-MTX) and unmodified paclitaxel were applied across the cell lines. Quadratic optimization, an AI-based approach that correlates drug inputs (e.g., drug and dose) and phenotypic outputs (e.g., cancer cell death, control cell viability) using a smooth quadratic surface was conducted to accelerate the identification of the dosages of the four therapies that mediated optimal cancer cell death and control cell survival. Of note, The AI optimization showed that optimized ND-modified combination therapy outperformed ND-modified as well as unmodified single drug therapy, unmodified

combination therapy, as well as arbitrarily designed ND-modified combination therapy. While NDs were used as the model delivery system, the augmented AI platform was universally applicable to all classes of nanomaterials [120,177]. Clinical trials to validate ND-containing biomaterials have since been initiated (NCT03376984) [178]. These studies show that the application of engineering principles to address the barriers to achieving personalized medicine provides a strong foundation for future developments in personalized materials, therapies, and devices.

Policy and Infrastructure Shifts in Personalized and Precision Medicine

The translation of approaches in personalized and precision medicine into the clinic and marketplace will depend on the evolution of the policy landscape and on the particular disease or indication, with some relying more on genomic/proteomic markers to guide treatment, and others relying more on prognostic variables [179–181]. However, regardless of the indication being addressed, the transition of personalized and precision medicine into widespread use will likely challenge many long-held regulatory policies that are based on single products (rather than platforms) and clinical standards, such as dose escalation, dose expansion, and MTD-based drug evaluation and administration. In addition, the recent approval of vemurafenib was achieved using a basket study (MSK-IMPACT trial), where genomic drivers of the disease indication (Erdheim-Chester disease) were used to assign treatment, as opposed to tumor location [182]. The opportunity to regulate omics profile-specific medicines is likely imminent. Subpopulation-specific diagnostics and therapies are now on our doorstep, suggesting that an emerging regulatory question will be whether (and how) to integrate AI, ML, or other analytical platforms into clinical trial design. In addition, as these platforms can be leveraged to individualize optimal treatment regimens, a move beyond fixed *P* value-based evaluation may be needed due to the possibility of each patient receiving an individualized regimen. These considerations open the door to potentially broadening the implementation of patient-centered clinical trials and the incorporation of **Bayesian decision analysis (BDA)** and patient preference into clinical trial design. Trials based on BDA may take into account the balance between benefits of the therapy or device itself on treatment efficacy, risks of the treatment to the patient, and outcomes if the patient is not treated. These and other factors may influence multiple aspects of the trial design. These include potentially reducing the number of patients recruited to assess trial endpoints, biomarker-based patient selection, and statistical assessment approaches that are implemented, among others [183–185]. As an example, in a recent study of CURATE.AI-based liver transplant immunosuppressant dosing, small cohort statistical analysis was used to confirm that the AI-guided treatment cohort exhibited reduced interpatient variance compared with control cohort patients. Ultimately, applying approaches like AL, ML, and BCA may result in clinical trial designs that identify patient-specific benefits that accelerate the approvals of novel therapies and devices.

The aforementioned opportunities to re-engineer the drug and device validation processes may drive the evolution of regulatory science [186]. Next-generation regulatory architecture and greater ‘regulatory literacy’ are needed. Streamlining the regulatory process for the rapidly evolving landscape of interventions and technologies will ultimately play a vital role in enabling personalized care to reach more patients in a timely fashion. Furthermore, issues such as drug pricing, accessibility, repositioning in the context of regulating N-of-1 regimens, and other considerations will need to be addressed [187]. The FDA has acknowledged that there could be a shift in focus from primarily efficacy (because some studies have even been shown to be too efficacious!) to a focus on long-term durability, safety, and product issues related to new technology, such as off-target effects and implications longer-term.

The 21st Century Cures Act, which was signed into law in the United States at the end of 2016, provides funding to the FDA to create new programs that will enhance its ability to expedite

approval of certain personalized and precision medicine products, such as cell therapies (regenerative medicine advanced therapy) and medical devices (breakthrough devices). The act goes beyond the FDA, also allocating money to the National Institutes of Health for medical research and drug development. AI Singapore was recently unveiled to accelerate drug development and enhance patient-centered care via more efficient hospital triaging processes through the integration of AI and ML with advanced trial design and **electronic medical records (EMR)**. A partnership between the EU and European pharmaceutical companies led to the recent creation of the Innovative Medicines Initiative (IMI). The IMI is combatting major challenges that will confront the EU, including antimicrobial resistance, the need for continued flu vaccine development, and non-alcoholic fatty liver disease (NAFLD), a global issue that affects as much as 30% of the EU population. Furthermore, NAFLD is capable of transitioning to non-alcoholic steatohepatitis, which can lead to HCC. In addition, the IMI is also developing novel tools to improve toxicity prediction in drug development as well as establishing a strategy to improve data quality during the preclinical drug development process in an effort to shorten the pathway to approval and improve success rates [188].

Ten requirements for achieving a successful implementation of personalized and precision medicine were recently outlined [189]. Several of these have become increasingly relevant to the role of engineering, in particular: (i) omics writ large, or the systematic and perpetual monitoring of environmental exposures that may drive disease risk; (ii) computation, which involves the integration of patient EMR as a catalyst for clinical-decision support; and (iii) education, which plays a key role in placing engineering at the foundation of future clinical leadership in personalized and precision medicine. These requirements entail more frequent access to patients and innovative trial design. Trial designs will increasingly need to focus on subpopulations of patients, and prespecifying these patients for greater signals of efficacy will require a sea change in thinking about designs that are tissue-agnostic and perhaps include a drug-diagnostic combination. It has been opined that even the pathway for approving diagnostics may need to change (from the traditional 510k route) in the face of modern diagnostics. In part, this may come through public awareness of the efforts of precision medicine. For example, the Oncology Precision Network OpeN, started in response to the Cancer Moonshot [rather than the Precision Medicine Initiative (PMI)], aims to reach underserved patients and enroll them in clinical trials, as well as to foster data sharing towards coordinated treatment decision support. Similarly, myriad websites, patient advocacy groups, and nonprofits are geared up for greater patient engagement. Some believe that sharing clinical trial results increases patient recruitment and engagement.

Study populations will need to be more diverse if we are to achieve the mission of precision medicine. Genome-wide association studies are still largely comprised of patients of European descent [190]. In 2009, only 4% of patients in 373 studies were non-European; in 2016, only 19%, which is an improvement but still 'persistent bias' [191]. Therefore, re-engineering clinical trial designs, standards, and protocols may have significant benefits for personalized and precision medicine. The Trans-Omics for Precision Medicine (TOPMed) Initiative launched by the US National Heart, Lung, and Blood Institute aims to correct this course, as does its umbrella effort, the NIH 'All of Us' Research Program (as part of the PMI); the Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) program at Vanderbilt University [192,193], the UK NHS counterpart, 100 000 Genomes Project; and other programs in China, France, and elsewhere. Data sharing among these initiatives could also bolster the power of these data sets to deliver precision medicine to all, rather than select populations that are overrepresented in individual precision medicine initiatives. In All of Us, engineers can play an important role in helping to achieve its mission, for example, by developing mobile health devices for lifestyle monitoring or designing technologies to discover new biomarkers of health and disease.

With regards to scaling the implementation of personalized and precision medicine in the clinic, the medical community is beginning to establish provider networks that are integrating genomic information with electronic health records in order to enhance point-of-care guidance on diagnostics and/or treatment. One example is the implementing genomics in practice (IGNITE) program [194–197], a network for the analysis of pharmacogenomic data and other family history information for integration into EMR to power **clinical decision support (CDS)** and address a diverse spectrum of indications, such as hypertension renal disease and diabetes. Of note, a recent study pertaining to *CYP2C19* genotype-guided antiplatelet therapy in a multisite trial from the IGNITE network was reported [198]. Initiatives such as IGNITE will serve as foundations for the integration of personalized and precision medicine into mainstream healthcare (NCT02335307).

With respect to education policy, integrating engineering and clinical training will cultivate a generation of clinicians who are comfortable with emerging technologies. In turn, they will be well versed in clinical translation, a vital part of education in personalized and precision medicine. In addition, the integration of healthcare economics, regulatory policy, and design of user interfaces into programs dedicated to translational medicine will play a key role in driving the next generation of technology transfer in personalized and precision medicine. Institutions that are addressing these issues include the Carle Illinois College of Medicine, which is placing engineering at the forefront of clinical education; EnMed, a collaboration between Texas A&M University and Houston Methodist Hospital; and The University of California, San Francisco (UCSF), which has developed a Masters in Translational Medicine program to bridge engineering and clinic-focused education to bring new technologies to the patient [199,200]. The integration of cellular and molecular engineering, modelling, simulation, and visualization as modalities for medical education, team-based development of engineering solutions to unmet medical needs, as well as technology transfer are examples of components that can be integrated into next generation curriculums to train the next generation of clinicians. These clinicians will ultimately have an enhanced grasp of the requirements for moving emerging technologies and platforms into humans, including regulation, intellectual property, and entrepreneurship, among other skillsets, and will ultimately accelerate engineering-based discoveries into patient use [199].

Concluding Remarks

Despite the obvious fact that patient physiology varies substantially from one individual to another, drug development and patient care has largely relied on the administration of the same regimen to an almost insurmountably diverse population. While certain scenarios permit bespoke drug administration according to constantly varying patient responses, arbitrary titration also remains the standard of care. These conventional treatment routes predispose patients towards suboptimal response rates. The era of personalized and precision medicine will likely overcome this challenge. Patients will no longer be confined to target-based drug selection and dose escalation-defined administration protocols that collectively result in the standard one size fits all treatment approach.

The suite of enabling technologies for personalized and precision medicine has provided unprecedented abilities to identify and surveil disorders. These technologies can accurately diagnose disease, comb large databases of omics information and EMRs to search for potential therapies, identify biomarkers that may accurately reflect disease states, constantly monitor disease progression or treatment response through wearable technology, and ultimately harness AI and other optimization technologies to dynamically and accurately determine the best drugs (chemotherapy, immunotherapy, nanotherapy, etc.) and corresponding doses that may change as patient physiology evolves during the course of therapy. Achieving this level of treatment personalization would require a seamless integration of biomarker development and potentially a re-engineering of drug trial design and analysis paradigms. One challenge that arises when

Outstanding Questions

What are the key technological barriers to the broader deployment of precision and personalized medicine technologies?

What are the potential strategies that can be employed to enhance the degree of integration of precision and personalized medicine technologies?

Will effective clinical validation of precision and personalized medicine technologies require new clinical trial designs to be implemented?

When a patient's therapeutic regimen is personalized only to their own physiology or disease characteristics during a clinical trial, how will statistical analysis methods be adapted to account for N-of-1, or single patient, studies?

Is the regulatory community prepared to utilize novel clinical trial designs, where even a patient's own regimens will constantly change over time, to bring new technologies towards widespread implementation?

How can innovators, educators, regulators, healthcare systems, and other stakeholders better prepare themselves for the potential practice-changing impact of bringing precision and personalized medicine technologies into common clinical practice?

this arsenal of enabling of technologies comes to fruition is the seamless integration of their implementation (see Outstanding Questions).

The successful transitioning of validated precision and personalized medicine platforms into clinical practice will require important advances beyond technology-centric innovation. A number of risks and challenges associated with healthcare economics, ethics, and data privacy, which are encountered after the stage of technology validation, need to be addressed [201–205]. In other examples, rising healthcare costs across the globe are simultaneously creating a barrier and opportunity for the clinical implementation of novel technologies. Innovation through the lens of payers, policymakers, will be vital. The minimum threshold to demonstrate patient and societal value in healthcare will require improved treatment outcomes, reduced incidence of acute and long-term treatment complications, and marked reductions in the cost of healthcare delivery and administration. To address these criteria, a specific area of promise in both fundamental and applied innovation is the use of AI-based approaches in drug development. As previously mentioned, reconciling data-driven drug combination design into actionable regimens coupled with attaining rapid fundamental insight into the pathways that drive the improved outcomes enabled by these regimens are examples of how engineering platforms for precision and personalized medicine can move the needle in terms of impacting the practice of healthcare. With drug prices reaching record levels, engineering approaches for precision and personalized medicine will ultimately play a vital role in reducing drug development costs, increasing drug accessibility, as well as contributing to cost-effectiveness for patients and healthcare systems, which itself is a topic that may require further evaluation as precision and personalized medicine platforms move towards broad deployability.

Mobilizing personalized and precision medicine for all will require a convergence of the aforementioned suite of enabling technologies and regulatory/public policy with advances in education and coordinated efforts to deploy and fund truly personalized and precision medicine on a global scale. At the core of this effort, biomedical engineering is playing an important role in catalyzing breakthroughs that will ultimately improve the human condition in an individualized fashion. Once we gain a clearer picture of how these new capabilities can be paired and regulated to improve patient outcomes, we can expect even more advances in personalized and precision medicine in the present population, in underrepresented populations, and in future generations to come.

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