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Chapter 12: The future of personalized therapeutics: tailoring interventions to genomic and patient data

12.1. Introduction to Personalized Therapeutics

With significant advancements in genomic and health data technologies, it has become increasingly clear that there is a large degree of variability between individuals' responses to conventional therapies, though these are typically delivered identically to populations as a whole. This variability may include differences in the efficacy of the therapeutic, any adverse effects experienced, and even changes in codes for mechanistic pathways implicated by the therapeutic, such as changes in transcriptomic and proteomic profiles. In light of this observed heterogeneity, although patients have traditionally been assigned into broad sub-populations using clinical characteristics and labeled as in need of particular therapies, honing in on specific attributes may allow for a more tailored therapeutic intervention. Such personalization has the potential to both improve patient outcomes by maximizing therapeutic effect while minimizing side effects, as well as reduce costs by limiting unsuccessful interventions and quickly reaching positive health outcomes. Design of personalized therapeutics offers an additional benefit over conventional therapeutic design approaches; if patients are extensively profiled for genomic and clinical characteristics and known goal states alongside available therapeutic options from which to choose, the mapping between profile and best intervention may be directionally learned using machine learning and causal inference techniques (Kim et al., 2023; Li et al., 2023; Anderson et al., 2024).

For several clinical conditions, such as some cancers and infectious diseases, personalization through the integration of genomic patient data into clinical processes has recently shown a promising ability to improve health outcomes and reduce costs. Novel drug development and trial frameworks have also come about through which personalized therapies may be systematically evaluated. In other clinical areas, failure to

incorporate molecular data into therapeutic selection has been highlighted; improper therapeutic selection may derail subsequent benefits from an optimization process and may further allow for response prediction of selection from a given class of therapeutic based solely on clinical data alone. Despite these successes and proposals, the promise of personalized therapeutics has yet to be fully realized across patient populations and therapeutic areas (Thompson et al., 2024; Martinez et al., 2025).

12.1.1. Overview of Personalized Therapeutics

Healthcare promises to deliver treatments and interventions at the time, place, and scale that are optimal for individual patients. In the past, such a vision was more fantasy than reality. The development of the genotype-dependent drug was a rare exception to the rule that the same therapeutic intervention is typically used for many patients suffering from similar diseases. The last decades have brought remarkable progress in the development of therapeutics that, in principle, can be tailored to the individual patient and in the acquisition of data on the predictive capacity of genes and other patient features for determining the likelihood of treatment success or lessened side effects.

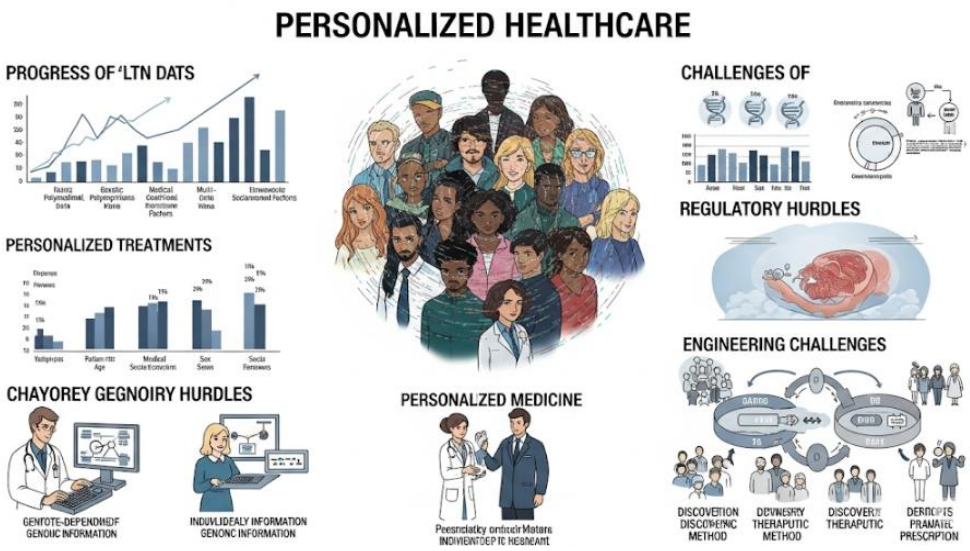

Fig 12 . 1 : Personalized Healthcar**e**

How much closer are we to the vision of personalized therapeutics? Even for those who follow the field closely, including those involved in drug discovery and development, the regulative problems, engineering challenges, and economic arguments surrounding personalized therapeutics can be confusing. We note in passing that problems about the prescription of a specified therapeutic method are separate from those of discovering it. The latter problem involves sorting through the immense and diverse n−dimensional

data space of many different patient features, including treatment response data derived from the patient, genetic polymorphisms and other genomic information, epigenetic traits, microbiome characteristics, patient age, sex, multi-omics, sensory features, medical conditions and medications, and socioeconomic factors, and matching subsets of patients with the same or similar features to associations with specific therapeutics that exhibit the desired success levels in similar patients.

12.2. Historical Context of Therapeutic Personalization

The roots of therapeutic personalization traverse commerce, art, philosophy, politics, science, and more. By analogy, personalized therapeutics finds its origins in much more than its academic progenitor, personalized medicine. Dating back to antiquity, early medicine absorbed traditions of healing that embraced a more individualistic rather than a collective perspective. Mesopotamian physicians diagnosed and treated patients according to their individual needs. Eighteenth-century B.C. Babylonian law established oil therapy for specific social classes, designating mugwort for commoners and cedar oil for nobles. The Hippocratic Corpus specifically endorsed individualized dietary decisions: “Hippocrates emphasized the need to be cautious in regarding the individuals’ needs, rather than simply paying attention to the illness”. Describing the yin-yang theory, the fourth-century B.C. naturalist Zhuang Zhou focused on the relationship between humans and their environment while referring to the idea of creating a body unique to every single person, in which qi flows through specific channels, about which unique therapeutic methods must be applied.

In the early twentieth century, early advocates for individualized therapy embraced neologisms such as “orthopathy”, “homeopathy” and “physiological chemistry”. They highlighted the need for different therapies for different patients with the same condition while beginning to document the violations of this principle. With the achievement of a scientific basis for understanding these violations, therapeutic personalization entered a different age and was reborn as “pharmacology” around the middle of the century. Biomedical advances allowed the collection of more health data, but most of them were macrobiotic rather than individually-based. Specialized subfields of pharmacology such as pediatric pharmacology, gynecologic pharmacology, or toxicogenomics grew but also appropriately reminded us that, in terms of the sick population, “the world of medicine sub-divides itself into many smaller worlds and that no (known) therapeutic intervention is useful for all patients afflicted with a single disease”.

12.2.1. Evolution of Therapeutic Personalization

The historical evolution of therapeutical personalization is a topic that is as rich as it is vast, as is actually the history of medicine. Given the traditional role of personalized interventions in health similar to other areas of knowledge, that is to address the specific interests of each individual, it is difficult to find a starting point for the particular concept advocated in this chapter. In this sense, the examples of Socruta, of the Roman physician Celsus, or the long experience of the Greek physician Galen, who personalized or recommended adjustments for their surgical technique, have little to nothing to do with the model of personalized medicine proposed in this work. Perhaps the recent astrophysical proposal of astronomical telescopes or physical accelerators for diagnostics and personalized intervention could be associated with the modern personalized medicine with which this chapter deals.

Although antiquity provides us with long-term personal care experiences, the development of scientific foundations to address the rationale for a personalized effort is recent, spanning the last two centuries. The nineteenth century provided advances in anatomical pathology and, later, in biological chemistry and biophysics, which clarified the mechanisms of disease and enabled diagnostics. Throughout the twentieth century, the elucidation of the genetic bases relating chromosomal alterations to the origin of diseases and the impact of biological abnormalities on risk factors and responses, both for the development and evolution of diseases, provided significant support to the personalization of diagnosis and therapy. However, the real revolution of therapeutics in a personalized manner dates back approximately the last four decades, when both clinical and experimental evidence began to be abundantly published indicating that the response to drugs and other types of treatments was modified by the impact that the population frequencies of the polymorphisms of the genes that encode drug-metabolizing enzymes exert on the pharmacokinetics of medicine, in addition to being sensitive to the polymorphisms of the genes that encode the pharmacological targets on which these treatments act.

12.3. Genomic Data in Personalized Medicine

1. Understanding Genomics

Genomics is the interdisciplinary study of the structure, function, evolution, and mapping of the genome of an organism. The term "genome" refers to the complete set of genes present in an organism. Genomic medicine applies genomics to practice, including knowledge of genomic variation and the implementation of methods and technologies to utilize genomic information. The success of genomic medicine will be dependent upon collaborative efforts to create, store, and share comprehensive genomic and phenotypic databases, validate information and methods for obtaining clinically relevant genome information, and design and conduct research and new clinical

protocols for implementation in a clinical setting. Importantly, the term "personalized medicine" is often disguised by the term "precision medicine," creating confusion. It is essential to highlight the distinction. Personalized medicine acknowledges inherent biological differences among humans and employs genomic and patient data to create unique, individualized, therapeutic regimens for patients. Precision medicine focuses on groups of individuals with similar characteristics, such as a specific mutation or genetic predisposition to a disease. While personalized medicine prescribes a unique therapeutic regimen for an individual with a disease, precision medicine may suggest a specific therapeutic regimen for a group of individuals with common characteristics.

2. Genomic Sequencing Technologies

Genomic technologies such as next-generation sequencing are data-intensive, complex applications rooted in the intersection of biochemistry, biology, chemistry, and physics, that study not only the DNA sequence of each individual but also its function. The development and use of genomic medicine have been accelerated by a dramatic decrease in the cost of genomic sequencing technology over the last decade, enabling the rapid production of low-cost, high-throughput, and accurate sequencing of whole human genomes and exomes. While earlier, first-generation genomic technologies were largely reliant upon polymerase chain reaction amplification, which produced only small, isolated regions of DNA for sequencing, these second-generation sequencing methods capitalize on widespread parallelization of very short lysate and developed libraries of DNA fragments. Over the last several years, nanotechnology advances have led to the development of third-generation "single-molecule sequencing" technologies. While still in limited use, these are anticipated to refashion the DNA sequencing landscape and make the sequencing of whole genomes and exomes routinely possible, allowing vast volumes of data to be efficiently analyzed.

12.3.1. Understanding Genomics

With the completion of the Human Genome Project in 2003, the challenge of mapping the genetic blueprint that makes us human transitioned into a new phase—gaining insight from an avalanche of high-throughput genomic data. With a collection of genes accounting for only about 1-2% of the DNA sequence, understanding the contribution of the remaining bulk of noncoding sequence is at the forefront of genome research, as both regulatory and structural features residing in the noncoding genome are thought to be critical in specifying cellular identity and determining phenotypic diversity among individuals. While the first phase of genome exploration has largely focused on comparing genomes to detect variants associated with disease, population, or diversity, the next is increasingly centered on understanding the impact of those variants on function. Attention is also shifting from capitalizing on population-based knowledge

toward understanding the effects of variants in the context of the individual—the hallmark of personalized medicine. While exciting advances are enabling this genetic discovery, we should remember that other forms of "-omic" data—transcriptomics, proteomics, metabolomics, microbiomics, and others—hold complementary information, which when combined can lead to a more comprehensive understanding of the causal mechanisms underlying phenotype.

Sequencing an individual's genome alone does not result in personalized medicine—the information must also be understood and integrated with clinical and epidemiological data. This transformation of biomedical research requires establishing both the computational and other support infrastructures to enable large-scale genomic data collection, and the educational initiatives to ensure that a workforce is available that possesses both the domain knowledge to leverage genomic data meaningfully and the quantitative and informatics skills necessary to be able to do so. The challenge ahead is to bridge the vast gulf between genomics as an emerging academic discipline, and genomics as a set of scientific tools that can be used to better enable basic, clinical, and population research in the service of human health.

12.3.2. Genomic Sequencing Technologies

As described above, the two principal uses of genomic sequencing in precision medicine are to enable an understanding of the genetic bases of diseases that have not been well characterized and to replicate or extend the discoveries made through association studies. Because it is unlikely that there are many uncharacterized genetic bases of monogenic diseases that are for the most part already intimately understood, and because association studies are introductory exploratory exercises that have to be complemented by mechanistic modeling, we focus on the latter. These uses assume differing degrees of coverage across the exome and genome. In what follows, we delineate the past, present, and future of genomic sequencing technologies in the greater context of precision medicine.

The first manifestation of high-throughput sequencing drew upon hybridization to an array. This was followed by two manifestations of "deep" sequencing: sequencing by synthesis and sequencing by ligation. The former is modified from the sequencing of single nucleotides to many thousands of nucleotides per read, while the latter has focused on improving accuracy and/or expanding read length. More recently, the second big genome project utilized short read synthesis to apply the model of assay development to single nucleotide polymorphisms to write and read out the first sequencing arrays in a deep sequencing assay. However, at the same time that sequencing array read-out was being developed, a major advance in long-read sequencing by synthesis began to occur.

12.3.3. Data Interpretation and Analysis

The speed of making genome sequence data with great accuracy and at low cost has now made its routine utilization for various medical applications like clinical diagnosis of Mendelian disorders and germline variant analysis for cancer observation. While vast quality and quantity of data are available, the biggest bottleneck is now in its interpretation, as the existence of numerous rare neutral variants makes it hard to know whether a newly detected variant is harmful or not. Basic theory, availability, and extensive annotation refer to several reasons that make whole genomic data interpretation very competent. Moreover, among the estimated 3.2 billion base pairs in the human genome, most are irrelevant or underrepresented in the population. These variants could be classified into three big parts, i.e., functional, neutral, and misleading, while the remaining genomic part needs to be evaluated to know the harmful or neutral functional status of any individual variants. Based on Enriched Variant Analysis, recent studies determined variants that are more than those observed in Western populations and also functional candidates that are not detected.

The emergence of genotyping data along with the well-annotated whole genome or exome data has led to a refinement of candidate variant selection, and typical methods have been developed for this purpose. Considering we have curated the variant selection process well, we could then proceed to functional tests supported by in vivo/in vitro assays using cell models, animals, or humans, and then deep learning-based systems followed by unique experimental validation have been established to discover protein missense variants. The report is anticipated to help present whole genome sequencing with the right combination of approaches. Future work depends on more accurate population-specific variant frequency data and pathogenicity prediction-based knowledge databases to address small-scale variant curation more efficiently.

12.4. Patient Data Integration

The future of personalized therapeutics lies in the collection, storage, and use of patient data for individualized diagnosis and treatment. Alongside demographic and genomic data, it is crucial to integrate patient-derived data into the design of trials and analysis of results, despite implications for stakeholder transparency and privacy. By better understanding and accounting for patient diversity—including factors such as medical history, quality-of-life, and social determinants of health—we move towards tailoring intervention to the unique needs of each patient. Interventions can be refined according to clinical needs throughout the trial, rather than only at the start.

One method with enormous potential is the use of electronic health records, which now span over 96% of the US population, logging demographics, comorbidities, and clinical

history across trials and even multiple health systems. Social determinants of health can be integrated using novel algorithms. EHR data collection reduces patient burden while enhancing accuracy when it comes to adverse effects, and as more patients engage with their healthcare providers remotely, indexed records may serve as invaluable trial assets. Pharma companies are increasingly collaborating with digital research services companies to create hybrid datasets that mine both EHRs and patient-reported outcome and usage data. In this way, we can create, update, and amend hybrid datasets throughout treatment, tag them to novel genomic and disease molecular profiling accessions, and interrogate them to assign existing patients to clinical trials of new therapeutics most likely to be effective for them. These hybrid datasets can also be used for new post-therapeutic observational studies of newly treated patients with similar profiles as a new class of real-life evidence.

12.4.1. Electronic Health Records (EHR)

The comprehensive data housed within Electronic Health Records (EHR) is a potential resource for identifying patients most likely to respond to or absorb risk from a number of different therapeutics. For example, EHR data can theoretically identify variants of pharmacological effect modifier genes, variants of genes mediating drug metabolism, drug transport, and secretion, or variants located within coding regions of target sites for drugs and genetic or epigenetic variants involved in pathways germane to drug response. Nonetheless, EHR data would not facilitate the full realization of personalized treatment without significant advances in several critical areas.

PHR such as EHR for example, to do this would involve capture of what might seem like mundane haplotypes located in the coding regions of the primary pharmacogenes that link drug response to a patient's genotype. Or, for response mediators located in other regions of the genome, transcriptomes or methylomes might need to be generated and directly linked to the EHR. At present, neither is routinely linked to EHR. Another major roadblock to personalized treatment, at least concerning PHE that would be obtained through access to a PHR such as EHR, is the fact that such documents exist based on a fraction of the world's population. Although EHRs are designed to provide clinicians access to patient medical histories for use in patient care decision-making, developers of these information systems have yet to make available PHR with existing clinician access to the richer information – predictive SNPs, transcriptomes, other relevant PHE, and clinical – necessary to inform PHE-based decisions at the most fundamental level regarding which medication to prescribe, its dosing, and the duration of treatment in a given patient under specific clinical circumstances.

12.4.2. Patient-Reported Outcomes

Patient-reported outcomes (PROs) include a variety of health-related metrics that a patient reports without external verification. PROs are key components of modern healthcare systems, and research suggests that they can be used to risk-stratify patients, delineate responses to interventions, and inform clinical decision-making. PROs include both generic measures of well-being, frequently captured in the form of quality-of-life questionnaires, as well as other patient metrics more directly related to the clinical conditions currently presented, including the symptoms and functional limitations associated with those conditions.

There is growing flexibility in how PROs are gathered, with older model surveys administered in extreme detail only every few months or years, making them difficult to relate directly to real-world clinical practice, as well as at any time and with almost real-time frequency via smartphone apps. PRO data collection is never 100% complete, and surveying for metrics may not coincide with a patient's acute maneuvers in attracting attention to their clinical state. While some patients may always be disengaged from research or clinical survey efforts, many others have only infrequently made themselves hard to reach. Recent smartphone-supported intervention therapies have explored the use of digital engagement information to address the common problem of sample attrition practical significance and to glean deeper insights from the study of engaged patients only.

Fig 12 . 2 : Patient-Reported Outcomes PROs

Beyond their use as energetic sources of clinical data, PROs can also be powerful data sources for the vast amount of unique information about patient treatment experiences that was once feasible only in small populations studied qualitatively. When considered alongside clinical and healthcare utilization data, PROs allow comparisons of clinical outcomes that speak to the effectiveness of care options. Used alone with flexible

statistical techniques, PRO data can suggest the underlying treatment dynamics. Furthermore, the same probabilistic insights learned along the patient journey can be translated to generate informed clinical treatment recommendations for other patients along their journeys.

12.4.3. Wearable Health Technologies

Health monitoring devices that are worn by a patient are generally referred to as wearable technologies. Increasingly cheap, small, and accurate sensors integrated into wearable devices permit constant and comfortable collection of health data. This includes continuous measurements of heart rate, oxygen saturation, activity level, sleep, and temperature pattern. Incorporation of such data into the EHR holds vast use as a means to create a more robust patient dataset to inform precision medicine models. Unfortunately, in the current EHR environment, the incorporation of these valuable data is lacking.

Despite the clear utility of these devices, use in the general population is mixed. Approximately 22% of adults from the US have previously used a mobile health application while a much smaller 3% of adults use a wearable monitoring device. This is contrary to the expectations of a growing industry where over 80 million devices are estimated to be used yearly by 2023. Certainly, wearable technologies have made their way into the lifestyles of patients with chronic diseases through external motivation from healthcare providers, peer groups, and online activity. Tracking improvements provides benefits that individuals in the low-risk group or unwilling to engage with others may not receive.

Despite this, with the COVID-19 pandemic, a focus has increased on wearable technologies as proactively usable measures to assess disease progression remotely. Programs have been established using wearable devices to monitor and enroll patients to assess disease severity in real time through continuous time series data. Three distinct use cases intended to augment and extend care have emerged. First, wearable technologies or combinations of wearable technologies can be utilized to trigger in-person assessments during increased disease severity. Secondly, wearable-based mobile health can reduce the assessment burden by collecting data remotely in otherwise reliant cohorts. Finally, wearable technologies can be used as a tool to execute real-time optimization of existing therapeutic regimens and further assess patients actively engaged in therapeutic programs and trials.

12.5. Biomarkers in Personalized Therapeutics

During disease development and treatment, tissues release small molecules capable of being quantified within biofluids. Their levels may indicate the presence of a specific disease, allow monitoring of disease progression, or predict/monitor response to treatment. These small molecules are called biomarkers. Biomarkers of disease may influence the estimation of treatment risks and benefits and guide clinical decisions regarding testing and treatment. In cancer therapy, some of the most advanced personalized approaches are guided by tissue biomarkers of specific tumors and rely on the discovery of tumor-specific mutations, driver mutations in oncogenesis, or chromosomal abnormalities that identify subsets of patients highly sensitive to treatment. The most common example, which paved the way for personalized therapies in the clinic, was the development of a treatment for chronic myeloid leukemia patients with a specific fusion.

The term “biomarkers” was coined in 1992. It was defined widely as “… a broad subcategory of medical signs that are quantitatively or qualitatively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”. The criteria expand these definitions, limiting the concept to predictive biomarkers of treatment effectiveness or adverse events generated by a therapeutic intervention whose data are intended to support market approval or product labeling. This definition implicitly limits the term to drugs that have utility predictions and that regulators require and involve a prediction that is developed and confirmed in a clinical trial of limited size. By interposing the terms “drugs” for “therapeutic interventions”, the definition can also be adapted to include other guiding therapeutic interventions.

12.5.1. Types of Biomarkers

Biomarkers are defined as biological characteristics that can be objectively measured and evaluated as indicators of normal biological or pathogenic processes, or pharmacologic responses to therapeutic interventions. They can support different aspects of the drug development process: identifying targets of drug action, serving as surrogate endpoints, augmenting clinical response assessment, or stratifying patients to maximize treatment benefits and minimize toxicity. The following classifications are commonly used to distinguish between different types of biomarkers: disease stage and severity biomarkers, risk and prognostic biomarkers, predictive biomarkers, and pharmacodynamic biomarkers. Disease stage and severity biomarkers describe the underlying biology of the presenting pathology and the presence and extent of active disease during treatment. For example, patients with advanced adenocarcinoma of the pancreas may often present with hematologic abnormalities including

thrombocytopenia, leukopenia, and altered coagulation considered together with diagnostic of the disease's advanced stage. Stage biomarkers include imaging studies for the assessment of stage and disease severity. Disease stage, however, does not equate to biological behavior. Consequently, several cancer biomarkers have been identified that better reflect underlying biology and prognosis. The discovery of some systemically distributed proteins whose abnormal expression levels are directly related to tumor biology led to their incorporation into clinical practice. One of the most famous is the carcinoembryonic antigen for colorectal cancer. Other examples include alpha-fetoprotein, cancer antigen 15-3, cancer antigen 125, and human chorionic gonadotropin.

12.5.2. Biomarker Discovery and Validation

A major challenge in the development of biomarker-based personalized therapeutics is gaining clear biological insight from biomarker discovery and validation efforts. For tissue-based studies, the main issue is often the fact that one cannot access the right tissues at the right time. For blood-based studies, the major challenge is the identification of the right markers, given the different types of cells and the complexity of biofluids, which can confound analyses. Once one identifies potential blood-based biomarkers, the next issue is not only the assay sizes (many potential markers), but also the variability in sample collection; do you use serum, heparin, or some other sample type? Depending on logistics, samples may be collected at different times or at different facilities, and then analyzed at different times or locations as well. Then, once you identify a small set of blood-based biomarkers, you must validate them, ideally in freshly collected samples, not just those archived and frozen.

Beyond identifying and validating relevant biomarkers, it will likely take considerable time to move from biomarker identification to a biomarker assay that is optimized for use in the clinic. Ideally, especially for the determination of immunogenicity, the assays can be scaled up and analyzed on blood samples in large cohorts. Such activities to seek clinically actionable molecules promptly could either be with a collaborative industry partner or facilitated by a specialized biomarker, diagnostic, or therapeutics company. Ultimately, the goal is to provide the right patient / right time / right therapy combination, similar to the principles in pathologic diagnosis and directed therapeutics in surgery. However, for personalized therapeutics, feedback on changing biomarkers must be possible to assess response to treatment, and predictive biomarkers are also important to enable focused investigation into the dynamics of related pathways in precision therapeutic development efforts.

12.6. Tailoring Interventions

Genomic data could add to the amelioration of imprecise and ineffective one-size-fits-all SUD treatment approaches by improving intervention matching. Using an individual's characteristics to differentiate whom to treat, what to deliver, and when and how, presents key challenges to implementation, while at the same time, it points to a solution in the form of personalized therapeutic decision-making. These proposals and programs aim to take personal genomic data, data relating to the nature and severity of the disorder, recency of onset, course of development, and symptom profile as well as broader biopsychosocial and environmental variables into account when constructing personalized treatment plans. As we have identified factors predictive of which treatment approaches are likely to provide positive responses in SUD treatment, we hope insights from the precision medicine approach can help construct ad hoc, personalized treatment plans capable of giving higher recovery rates. Various approaches to treatment matching reliability could be used.

Pharmacogenomics translational pharmacogenomics of candidate gene studies capitalized on the genomic data exploring the links between genetic variation and pharmacological agents that can ameliorate identified dysregulated molecular domains. Overall, relatively few pharmacological targets have been the focus of BPD pharmacogenomic studies. This state of affairs stands in contrast to the existing treatment choices based on the putative underlying molecular alterations in BPD symptomatology and their common comorbidities, such as anxiety, PTSD, ADHD, emotion dysregulation associated with aggression, and substance dependence.

Targeted therapy preclinical investigations can capitalize on the existing knowledge of genetic predispositions, such as the haploinsufficiency of 22q11 that can predispose to risks for both severe SUDs and BPD. If these putative underlying internal and external individual vulnerability-enabling mechanisms can be identified early during development, preventive intervention protocols could be devised and tested in high-risk individuals, if proven efficacious in phase III trials. Such targeted preventive interventions could target other putative internal mechanisms, such as genetic dysregulation of neuronal and immune homeostasis or external environmental risks and early-life experiences.

Combination therapy's high-degree heritability reminds us that comorbid SUDs could partially trigger a BPD onset in earlier childhood or preadolescence. In this case, although pharmacotherapy combined with effective psychosocial therapy could help manage SUD-onset BPD individuals and/or their specific high-risk factor trajectories identified during preventive research, it may not completely abolish BPD behavioral traits. In such cases, psychosocial preventive programs would help manage the psychosocial areas affected by high-risk risk factor trajectories, even if they may not

remove the parameters responsible for BPD phenotype expression. Difficult as it is to disentangle individual and social responsibility, we must continue to study the balance between them so both acts and actors may be addressed together.

12.6.1. Pharmacogenomics

Pharmacogenomics explores the role of genetic variation in drug response in humans. It is the study of the relationship between an individual's genome and the genome of the microorganisms in the particular case of pharmaceutical interventions. Traditional causes of drug-related adverse outcomes include prescribing errors and regimen adherence issues, while pharmacogenomic applies and modifies principles of predictive medicine in health care. The impact of genetic variability on drug metabolism was first described in the 1940s but did not become a major research focus until the mid-1990s with the development of the Human Genome Project. This landmark genomic project has allowed researchers around the world to develop and optimize techniques to easily perform the sequence of individual genomes employing modern automated DNA sequencers. Although pharmacogenomic research efforts have significantly accelerated in the last decades, their ultimate goal of providing clinicians with reliable pharmacogenomic tests that may save patients both costs and pain—thus improving clinical outcomes—has only partially succeeded.

Besides advancements in drug safety and efficacy, pharmacogenomic approaches have the potential to substantially lower healthcare costs. The costs associated with ADRs in patients treated with one or multiple medications include hospitalization due to the adverse event, therapy for the adverse event, and the costs of the original therapy. Ten percent of all drug formulations approved are due to an ADR; moreover, in 2004, it was reported that drugs that associated clinical warnings and contraindications for ADRs or that were withdrawn from the market due to ADRs represented more than 50% of all postmarketing surveillance warnings.

12.6.2. Targeted Therapies

Targeted therapies are the most advanced iterations of tailoring interventions based on patient-specific data, and the first to arrive in clinical practice. This concept of providing specific drugs that efficiently and preferentially act on a particular molecular target found in cancer cells has revolutionized the care of patients with certain types of cancer. These drugs take advantage of specific clinical and tumor molecular characteristics, and act selectively on cancer cells, leading to cell death, while sparing normal tissues that do not express these targets. Although initially the targets and specific drugs were discovered more or less at random, a few drug classes have been designed to interact

with particular targets, and associations established between some targets and particular patient subpopulations.

Targeted therapies have changed the course of many cancer types, but have not done so for all. The focus on targets has led to a somewhat narrow consideration of the many possible reasons for differential sensitivity. These include other clinical characteristics, expression of a different set of proteins, receptor status, genomic mutations that lead to over- or under-expression of particular genes, epigenetic regulations such as DNA methylation and histone modifications, differential expression of transporters, and mutation-induced neoantigens that the immune system can act upon. Possible bases for differential response should be assessed for all diseases in which drug efficacy is variable.

12.6.3. Combination Therapies

Personalized therapeutics extending beyond the pharmacogenomic tailoring of medications is a rapidly growing field, particularly about targeting multiple mechanisms of disease with combination interventions. Combination therapies seek to improve treatment effectiveness, overcome biological resistance, and minimize adverse events. Examples of existing personalized combination strategies in oncology include combining trastuzumab with paclitaxel for HER2-positive breast cancer and combining cytarabine with daunorubicin for acute myeloid leukemia.

Personalization of oncology combinations is most commonly carried out by matching a patient-specific tumor with a drug most effective against that tumor, which is termed patient-derived tumor ex vivo drug response profiling. The idea behind tumor ex vivo drug response profiling is to predict the response and resistance of tumors to different anticancer drugs promptly using micro-carrier, patient-derived tumor co-culture systems, and thereby accurately select and enable customized on-therapies. Additionally, the tumor microenvironment affects drug pharmacodynamics, which can result in intratumoral drug gradient and heterogeneous therapeutic responses, thus limiting the effectiveness of a single-drug monotherapy and necessitating the re-personalization of cancer combination therapies based on the tumor microenvironment. These stratified treatments could also help design a more potent combination strategy that works best for an individual patient with thin margins, optimal scheduling, and accurate dosages. Additional areas of therapeutic focus for combination strategies to enhance personalization include polypharmacy strategies for older adults, as well as personalized photodynamic detection tools for optimizing early tumor resection and combination interventions with immune checkpoint inhibitors to modulate the tumor microenvironment.

12.7. Ethical Considerations

Because the ability to combine biological and clinical data into predictive models changes how we evaluate the balance of benefits and risks of therapeutic interventions, we should reexamine the ethical guidelines that govern the conduct of research with these new techniques. Historically, the ethical conduct of a study requires that risks and burdens be minimized and outweighed by benefits to participants, or, in the case of research with no direct benefit, by potential societal benefits and that the study population is treated equitably. Under this framework, it is incumbent upon the investigators to minimize the risk of errors in predicting treatment effects. In the case of treatment for the individual patient, the use of patient-level data offers an important means of reducing predictive errors, particularly when the response to treatment is influenced by patient characteristics, and is generally able to deliver much larger expected benefits and smaller expected harms than a trial without patient-level evidence. As a result, the ethical justification for conducting a study without important patient-level information is weakened.

Informed Consent

One important ethical principle inherent to much clinical research is that of voluntary informed consent. For clinical research in which patient safety is prioritized, additional oversight by institutional review boards and ethical review committees is warranted. Current guidelines assume that genomic data will accompany the clinical data, and fresh modes of consent designed to minimize overreach by investigators and institutional review boards have emerged. However, the borrowing of patient-level data from translational research networks or claims data from health delivery systems, while certainly reducing the burden of redundant informed consent, invites new ethical questions that deserve interrogation. Should a treating clinician, location, or patient organization determine whether a specific patient is eligible for enrollment or placebo treatment in a trial? How should the trial benefits be allocated? And to what extent do identified genomic signatures in predictive modeling—not overrule any lessons in equity or informed consent?

12.7.1. Informed Consent

Informed consent has emerged as a central tenet of human subjects research. Importantly, requirements for informed consent have been expanded from initial privacy concerns to become an expectation for how research should be conducted, especially when considered alongside the goal of translational biomedical research to bring research results back to research participants as discoveries with actionable significance. The role of informed consent goes well beyond affirming individuals' rights. It has been

framed as an ethical touchstone, necessary for research integrity, relationship building, and enabling the public good that research as a whole serves.

As precision medicine initiatives increasingly incorporate genomic and other biological data from an increasing proportion of the population into research while also developing applications that directly influence patient care, the burden of ethical review and decision-making is heightened. Precise tracking of interest and expectations by study participants must be done in a manner that is efficient and workable across the many studies requiring enrollment, from biobanks collecting samples without linkage to potential application to clinical research, conducting individual protocols for refined stratification of variances in disease, to interventional studies, in which participants are randomized to a course of treatment. When these approaches are combined in larger collaborative infrastructures, engagement of participants at all levels of the research programs comprising these connections requires careful explanation, facilitating participants' understanding of the degree of their involvement, as well as the level of risk of loss of privacy and negative consequences of discovering unexpected or incidental findings related to the samples they provide, or the interventions to which they are subjected.

12.7.2. Privacy Concerns

To create personalized approaches, interventions must be responsive to genomic and other personally identifiable patient data. Industrial and commercial health care is built on maintaining personalized daily user interactions, digital media footprints, and surveillance systems. Not surprisingly, biobanking initiatives for therapeutic, translational, and biomarker research have dedicated resources toward enhancing personalization through making participant research protocols, risk assessments, and biomarker testing recommendations available to them. Sharing the health data of donors who have agreed to participate in such biobanks to facilitate decentralized design and conduct of research directed at improving their personalized health is not only preferred but is also indispensable for recruiting and gaining the trust of diverse populations whose participation would increase the generalizability of research data and approaches to personalized health management.

Healthcare infrastructure challenges this and prevents individuals from being empowered to personalize treatments and become decentralized partners. People desire to puzzle together their collusive narratives, centering around collections of stories constructed from their unique data, involved with instrumentation, biobanking, mobile, and wearable health technologies. They wish to shape their communications to clinics and industry based on events during their daily lives, as coordinated by technical triggers that can serve as the new vital signs. However, for the vast majority, and perhaps for any

reasonable proportion of society, having connected personal health data that is persistent and considered intimate would not equip enough individuals with the capacity to retain and monitor their health data to approve sharing it with others.

Decentralizing health care infrastructure to empower individuals to shape personalized channels in ways that endure and can be shared with outside parties, without transforming individuals into humans under surveillance, is a dilemma generated by having the physical distances between consultative entities reduced virtually. Due to this centralizing aspect of care that has been exacerbated by the digital revolution, many individuals steadfastly refuse to share any connected health data with anyone and so remain unaware of how it can improve their health partnerships, as well as the potential insight for beneficent use that exists from pooling the health metadata.

12.7.3. Equity in Access to Treatments

Advances in genomic research and technology have made it possible to identify risk factors for many conditions and traits. As the field of research advances, it will be crucial to ensure that actions that would follow the identification of genetic causes of disease are equitable. Genetic risk information not only delineates populations at increased disease risk but may also impose risks of othering or stigma to the identified-risked groups. Nevertheless, there are many reasons why ensuring equity in access to and distribution of targeted conditions would be in everyone's or society's interests. Discovering the genetic, social, and biological mechanisms contributing to the pathogenesis of diseases allows treatments to be designed that can actually target the mechanisms involved and that are likely to be more effective than those that are not targeted. If prevention and control measures for complex diseases become increasingly genotype-specific, unlike non-genotype-specific public health interventions, those who are eligible to benefit from the interventions are those at the highest risk of being afflicted by the condition. These are generally the poorer sections of society. Increased inequity will not only contribute to greater extremes of wealth or poverty but could also result in poor treatment response or, worse, bad reactions to the treatment because of being denied early access to the therapeutic.

It is an established medical principle that the treatment of patients should not be denied based on interpersonal factors. None of the current models of the distribution of health resources or treatments can account for genetic distance as an equity consideration. A genotype-specific allocation rule could legitimize and formalize predictable allocation based on group differences. Although early and more focused intervention may avoid lifetime suffering, it would violate the principles of fairness that underlie our ideas of health equity.

12.8. Regulatory Frameworks

It is clear from the preceding discussion that the next few decades will see a massive expansion of the number of tools that providers can use to custom-tailor treatments for individual patients. Such an expansion will create opportunities to increase effectiveness and reduce side effects, dramatically improving the overall effects of intervention on patient health. The introduction of these tools will also bring new challenges. Selecting tools based on the most recent understanding of gene-environment interplay will not be as simple as looking for differences in an individual's biochemistry and simply administering the drug. A flood of electrophysiological tests and brain imaging data may not yield meaningful taxonomies associated with treatment response.

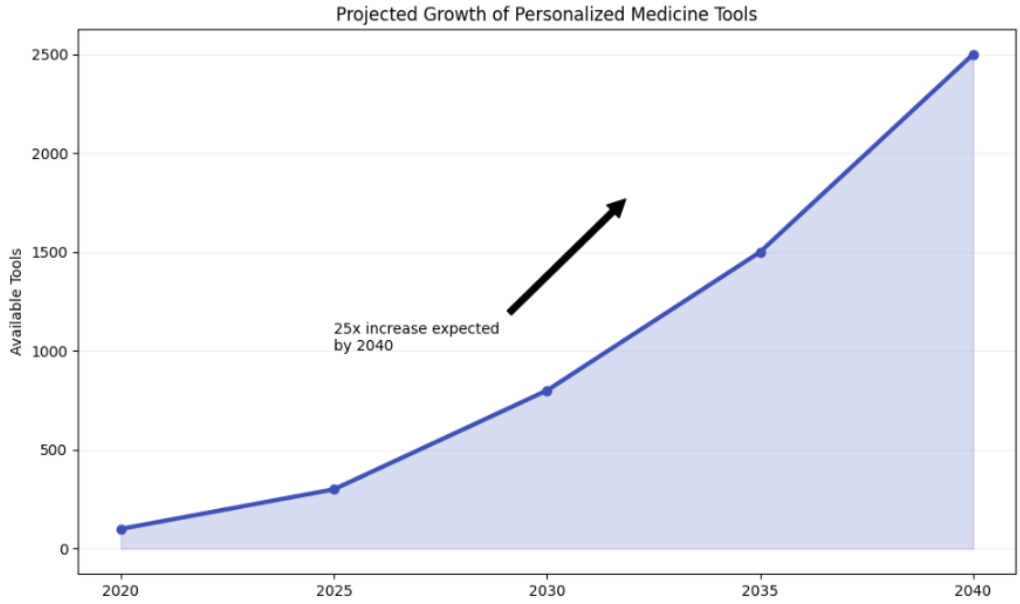

Fig 12 . 3 : Projected Growth of Personalized Medicine Tools

Fairly rapid changes in our scientific understanding will require a regulatory framework that is flexible enough to encourage new studies and novel applications while being stable enough to bring treatments through to approval and market. The use of genetic testing to point out optimal first or second-line treatments, for example, will need a more fluid approach to the algorithms used to guide treatment decisions than will uncommon, highly-targeted treatments for genetic conditions. For rare genetic conditions, the approach taken by relevant regulatory bodies, which provides incentives to increase investment in treatments for small populations, may be enough to offset reluctance by pharma to boldly go into the valleys of no or little return. However, for the much larger populations associated with common mental disorders, it will be necessary to balance innovation and patient safety carefully. In this arena, history is not on the side of rare,

dangerous products pushing through the system against significant commercial pressures. Steps must be taken to ensure that the strategy does not become the equivalent of a garbage-in-garbage-out uncritically-open culture.

12.8.1. Current Regulations

The regulation of genetic and genomic testing has remained largely static since the first discrete offerings of testing in the early 1990s and the earliest forms of self-service genetic testing nearly 20 years ago. Many commercial offerings today do not seek formal authorization from government regulatory bodies and operate under "enforcement discretion" policies. The legal framework governing the actions of bodies like the United States Food and Drug Administration, the Clinical Laboratory Improvement Amendments program at the Center for Medicare and Medicaid Services, and the Federal Trade Commission is fragmented and overlapping. Moreover, the regulatory approach to genetic and genomic testing is often disjointed from that of other medical technologies or therapeutic interventions. As a practical matter, oversight of genetic testing primarily resides with CMS, which regulates laboratories conducting testing through the CLIA. Although the FDA also possesses authority over lab-developed tests as medical devices under the Food, Drug, and Cosmetic Act, it has historically chosen not to engage with lab-developed tests that are not closely associated with the testing of patients with rare diseases. However, after decades of nonregulation, the FDA announced plans to develop a regulatory framework for lab-developed tests, revealing concern about continued advancements in genomic testing and their application to more common and complex diseases. More recently, in a series of increasingly aggressive enforcement actions, the FDA has reaffirmed its authority over labs offering genetic tests that function as medical devices while claiming to test patients without rare biological conditions.

12.8.2. Future Directions for Policy

Many policy analytic methods remain to be applied to personalized therapeutics, and there is substantial room for refining the basic foundations for coverage decision-making in this realm and developing specific procedures to add precision relatively to individualized treatment decisions. For example, the general principles that direct clinical research are not necessarily the same for every aim of clinical development. To maximize generalizability to high-priority patient groups, it may be desirable to minimize generalizability to low-priority patient groups. Such an approach may also introduce substantial procedural differences and endpoints relative to general considerations.

Other cancer treatments can have minimal clinical utility until they identify smaller groups of patients for whom they work particularly well. Evidence-based practice bundles oversight of scientific methodology into a simple guideline: pursue and apply whenever possible the treatments shown to generate the best average outcomes. In the case of a treatment that is expected only to moderately improve average survival for a strong majority of patients, but to dramatically improve outcomes for a small subgroup, withholding coverage may be the socially optimal decision if resources are limited. Federal and state agencies currently have mandates such that they may disallow targeting efforts for policy priorities such as cost or fund efficiency. This is not the case in other health policy areas. Other programs use budgetary guidelines and usefulness for different populations to prioritize funding decisions. Questioning the principle of equal care for like patients has the potential to help fund highly specialized treatment options for the patients likely to benefit most, and provision for flexible policies in the personalized therapeutics space would augment need-based funding priority decisions.

12.9. Conclusion

The contributions presented here showcase the incredible potential for synergistic advancement in treating human disease by merging therapeutic interventions with the patient genome, tissue, cellular, and circulating component data. Increasingly, scientists are discovering pathways through which genomic data enables better diagnosis of disease, enabling outright prevention or earlier therapeutic intervention for a reduced disease burden. Genomic data enables better targeting of the most appropriate and effective therapeutic interventions for an individual or patient sub-group, increasing the likelihood of therapeutic success and reducing exposure to ineffective or harmful treatments. Informatics tools, libraries, and available resources are improving all along the space from study design to data collection, for both large and small cohorts in either academic or clinical practice settings. We predict that the field now stands on the edge of a massive wave of development, but is also greatly in need of practical guidance.

Information to guide study design, and especially patient recruitment and intervention specification is sorely needed. Clinicians often experience a feeling of separation from the large research initiatives that provide the data on which genomic therapeutics rely, having neither the expertise in data science nor the access to that data to take advantage of it in their daily medical decision-making processes. It is essential to bridge that gap; developing and disseminating information resources to enhance clinical understanding of genomic medicine and to integrate basic and clinical research would increase the clinical adoption, and thus the likely benefit, of this exciting and rapidly evolving aspect of therapeutics.

12.9.1. Summary and Future Perspectives on Personalized Therapeutics

Precision medicine approaches have transformed the treatment of several patient populations, particularly with cancer. With the rise of high-throughput technologies, investigating some of the biological underpinnings of diseases that lead to differences in how individuals respond to specific therapeutic interventions is becoming more commonplace. However, most diseases do not have the scientific knowledge to determine which signatures – transcript, methylation, mutation, copy number, and other variants – should be investigated to personalize a therapeutic intervention. Furthermore, even the available approaches to identify these predictive signatures for differences in response are not standardized or simple. This gap in knowledge and application of analyses is one reason why personalized therapeutics remain elusive in most diseases.

A number of predictive therapies have been approved for… Here, we provide a brief overview of unconventionally structured synthesis and analysis frameworks we hope will help bridge this gap and allow for faster integration of biological mechanisms into cornerstone predictive analyses. We also discuss the current challenges and future perspectives to truly create a personalized therapeutic landscape that is omnipresent across diverse diseases. Ultimately, beyond simply developing an approach to link biological mechanisms to response outcome data-derived differences, the increase in applicability of predictive scores to new cohorts and data types while retaining high accuracy and supporting biological reasoning is key.

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