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Invited Review

INVITED REVIEW

Precision medicine, genomics and drug discovery

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Abstract

The hope for precision medicine has long been on the drug discovery horizon, well before the Human Genome Project gave it promise at the turn of the 21st century. In oncology, the concept has finally been realized and is now firmly embedded in ongoing drug discovery programs, and with many recent therapies involving some level of patient/disease stratification, including some highly personalized treatments. In addition, several drugs for rare diseases have been recently approved or are in late-stage clinical development, and new delivery modalities in cell and gene therapy and oligonucleotide approaches are yielding exciting new medicines for rare diseases of unmet need. For common complex diseases, however, the GWAS-driven advances in annotation of the genetic architecture over the past decade have not led to a concomitant shift in refined treatments. Similarly, attempts to disentangle treatment responders from non-responders via genetic predictors in pharmacogenetics studies have not met their anticipated success. It is possible that common diseases are simply lagging behind due to the inherent time lag with drug discovery, but it is also possible that their inherent multifactorial nature and their etiological and clinical heterogeneity will prove more resistant to refined treatment paradigms. The emergence of population-based resources in electronic health records, coupled with the rapid expansion of mobile devices and digital health may help to refine the measurement of phenotypic outcomes to match the exquisite detail emerging at the molecular level.

Introduction

The term “precision medicine” and related antecedents “personalized medicine”, “stratified medicine” and “targeted therapies” convey so many different meanings that their usage can sometimes transmit little information of practical utility. Here we aim to describe the impact of genetics, genomics and related technologies on novel drug discovery for specific patient groups. There are a number of exciting developments in this domain, spanning a diverse array of applications that range from the highly personalized advances in *ex vivo* autologous gene therapy (1) to the group-level progress in immuno-oncology therapies for patients not defined by a particular somatic mutation or traditional tumor histology (2–4). We have adopted a definition of precision medicine which subsumes the others: “prevention and treatment that takes individual variability into account” (5).

Recent therapeutic advances in oncology demonstrate that precision medicine has moved beyond the early phase of hope and hyperbole to a practical reality (6,7). Most ongoing research and clinical programs in cancer treatment have precision medicine at the core, spanning targeted mutations, immunological approaches and combination therapies. Such advances are not exclusive to oncology, as identification of the genes causing rare diseases has been fueled by advances in DNA sequencing and the emergence of social media and patient- (or parent-) driven crowd-sourcing in undiagnosed conditions (8). Translation of such rare disease findings into new therapies are being enabled by long-awaited progress in alternative drug delivery modalities, with oligonucleotide approaches (9–11) and cell and gene therapies (12–14) maturing after decades of challenging development.

Chronic conditions such as Type 2 diabetes, cardiovascular disease and common respiratory conditions have all had multiple major discoveries over the past decade, some via creative studies in highly selected samples, families and/or extreme

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clinical phenotypes (15–17) and others via Genome Wide Association Studies (GWAS; 18). There is also renewed excitement and promise in challenging areas such as schizophrenia and autism spectrum disorders (19,20). However, with the exception of a few well-publicized examples (particularly PCSK9/LDL cholesterol and SOST/bone mineral density) (21,22) and some general advances in network biology, most of a large volume of findings have not translated into novel or precision directed drug discovery programs, despite considerable investment (23). Nor has pharmacogenetics—the impact of genetic variation on drug response—shown the early promise of precision medicine in the form of disease/responder refinement, though there have been notable successes in predictors of drug safety (24).

The differences amongst disease areas in progress toward more precise treatments is likely due to a host of factors including biological architecture, phenotypic complexity, stochastic influences and practical effects of research attention/funding and simply the time it takes to translate discoveries into therapies. Here we consider oncology and rare diseases as examples of success and scope for further promise, and discuss the opportunities and challenges for common chronic conditions and neurodegeneration in particular given the relevance for unmet patient need, opportunities for scientific advance and societal importance (25).

Oncology

It could be argued that precision medicine in cancer treatment started with the discovery and development of Imatinib for Chronic Myeloid Leukemia (CML), targeting the product of the common CML chromosome 9,22 translocation (26). Imatinib has revolutionized the treatment of CML and coupled with the treatment of the resistance mutations that arise with other inhibitors, CML has largely become a managed disease. A similar situation prevails with the treatment of acute promyelocytic leukemia (APL) with all trans-retinoic acid as the proliferation of these tumor cells is primarily driven by a translocation of the retinoic acid receptor gene (105).

The routine analysis of somatic mutations in biopsies from most tumors, using gene panels or exome sequencing and the tailoring of the treatment to the mutations that are found, has become virtually routine in oncology clinics (27). One of the best examples of this kind is in the treatment of activating mutations in the EGF receptor often found in (female) non-smokers with lung cancer. These patients are treated with gefitinib which inhibits the EGFR kinase and provides some short-term mediation of their disease until resistance emerges. New drugs (e.g. osimertinib) directed to the T790M mutation—a commonly arising gefitinib resistance mutation—are now available (28). This is an example of the most advanced paradigm for precision treatment of tumors: treating the primary proliferative drive in the cells first (e.g. from activation of the EGFR) and following up with a drug directed to the resistance mutations.

The treatment of melanoma with activating mutations in BRAF (V600E) with vemurafinib or dabrafanib provides another example of the precision approach. Again resistance is inevitable, usually mediated by feedback activation of the EGFR and can be treated with trametinib, a MEK inhibitor, in combination with dabrafenib (29). It may be possible to combine this with the use of checkpoint inhibitors such as anti-CTLA4 if the side effect profiles can be managed (30). The kinase inhibitors crizotinib and ceretinib, both of which inhibit ALK, an oncogenic kinase involved in anaplastic lymphoma, neuroblastoma and non-small cell lung cancer (as a translocated gene—EML4-ALK) progressed from discovery to the clinic in <5 years, shaving years off traditional drug discovery timelines. One of the reasons for this speed of clinical development was because the drugs were suitable for only the patients with overexpression of the enzyme via gene amplification, activation or translocation. This leads to an important conclusion for mechanistic translation to precision medicine: access to defined patient populations allows rapid proof of concept (ADPP-RPC)

Variations on this theme are also apparent when considering PARP inhibitors which have been shown to work more effectively in breast cancer in patients with BRCA1 mutations (31). This has been extended to evaluation of efficacy in all cancers where there are mutations in genes involved in homologous DNA repair and gene panels are being developed to identify mutations in these genes (32).

"Precision" is also being applied in monoclonal antibody (Mab) therapy for breast and other cancers. The seminal discovery that anti-EGFR antibodies (e.g. panitumumab) do not work in colon tumors that harbor KRAS mutations leads to an efficient precision medicine Mab therapy, as a relatively inexpensive diagnostic test can reveal KRAS wild-type or mutant status (33). Only those with wild-type KRAS are eligible for treatment. Similarly, only breast tumors with Her2 amplification shown by FISH or shown to have increased Her2 protein are treated with an anti-HER2 antibody trastuzumab, sometimes in combination in metastatic disease, with a Mab directed to a different epitope on Her2 (pertuzumab) (34).

Most recently, immunotherapeutic checkpoint inhibitors have spawned a new era of cancer treatment due to dramatic improvements over existing treatments in some patients. The field of immunotherapy via checkpoint inhibitors was founded on the observation that CTLA4 (CD 152) when blocked, could unlock tumor infiltrating T cells to attack antigens expressed by the tumor (35). The therapeutic antibody ipilimumab was the first antibody to be developed against CTLA4. This discovery was followed soon after by Mabs recognizing PD1 (nivolumab, pembrolizumab) and more recently PDL1 (36,37). The biggest issue with the new inhibitors concerns the identification of responders and non-responders, especially as some of the latest successes invoke combination therapy with these agents (38). Extensive research is being undertaken to predict responders and non-responders. Exome sequencing of tumors to assess mutation load and the expression of "neo antigens" is being coupled with HLA typing to determine whether a particular peptide epitope can be presented by the relevant HLA alleles (39–41). Transcriptional analysis of the tumor microenvironment and even microbiome sequencing is being used to find other genomic correlates (42). The use and uptake of appropriate biomarkers to guide treatment choices is variable at present. For example, the prescription of pembroluzimab (Keytruda) requires an immunohistochemical test to measure PDL1 levels in tumor biopsies whereas the prescription of nivolumab (Opdivo) does not.

The use of engineered T cells (CAR-T cells), in which T cells are taken from individual patients and engineered to express chimeric antigen receptors with or without the expression of co-stimulatory proteins, is also a more precise way to treat tumors, with particular success in acute lymphoblastic leukemia (43). This is indeed "personalized" medicine because the patient's own cells are manipulated and it is precise because the antigens targeted are found on particular tumor cells (44).

Rare Diseases

Rare genetic diseases offer one of the clearest depictions of precision medicine because the fundamental mutation(s) are increasingly known and offer natural biomarkers for patient selection as well as possible clues to steer medicinal chemistry and dosage away from adverse events. Although it has taken 25 years since the first monogenic disease genes discoveries, targeted cystic fibrosis treatment recently received regulatory approval (45), and therapies for Duchenne's Muscular Dystrophy therapies have reached late stage clinical development, albeit not without challenges (46–48).

Decades of studying fundamental biological mechanisms are enabling drug discovery in rare diseases, underscoring the importance of deep functional biology in an era of broad high-throughput genomics. But the recent progress in translation of rare disease treatment has also benefited greatly from technology advances. In particular, approaches harnessing RNA interference discovered nearly 20 years ago are showing signs of maturity (49), with medicines reaching regulatory approval or late stage clinical development across a range of disorders including familial hypercholesterolemia, TTR-mediated amyloidosis, hemophilia and spinal muscular atrophy (50–52). Other approaches are exquisitely tailored, targeting specific mutations or components of pathways derived from those mutations (e.g. BCL11A with beta thalassemia; 53,54), skipping specific mutations in DMD and working directly on the mechanism of action, such as allele-specific enhancement for dominant negative activity (55).

Gene therapy, once an area of great promise for Mendelian diseases, is also maturing after decades of research and some early tragic events (56). Despite estimates of over 1800 clinical trials having been conducted (57), the first regulatory approval for gene therapy was granted in 2012 (European Medicines Agency, EMA) for Glybera (58), targeting the LPL gene in individuals with familial lipoprotein lipase deficiency. EMA approval was recently granted for the first retroviral-mediated gene transfer in children with ADA-SCID (14). The US FDA has not approved any gene therapy products for sale, though a number of ongoing clinical programs are planning for FDA consideration. At present, generalized applicability of gene therapy remains limited due to practical considerations including 'supply chain' access and viral production for autologous therapies, potential for adverse immune responses and ongoing concerns about gene insertion sites using viral vectors.

The technological and delivery breakthroughs and the rapid pace of identifying the causes of rare diseases lie in contrast to the long paths to CF and DMD treatments, highlighting the perseverance required to translate biology to treatment, even when the mechanisms are known. A truism learned from rare diseases, though not restricted to them, is that "not every disease gene forms a good drug target and few good targets lead to new drugs"

ALS as illustration of promise and challenge

Amyotrophic lateral sclerosis (ALS, also known as Motor Neuron disease) is a relatively rare but devastating neurodegenerative disease that exemplifies ongoing progress and opportunity but also the challenge in therapeutic translation. The molecular pathology of this disease is beginning to be understood comprehensively from studying the genetics of both familial and sporadic forms. The first gene to be implicated in ALS was superoxide dismutase (SOD) where potential gain of function mutations were shown to be causative. Since that time several additional genes have been found (59), one of the most common of which is an expanded repeat in the non-coding region of a gene with unknown function called C9orf72. This gene is also involved in frontal temporal lobe dementia (FTD), providing additional evidence that these diseases are related in molecular pathology (60,61). Research is underway to understand how this dominant gene causes ALS, yielding evidence for both gain of function and haplo-insufficiency. For example, there is evidence that the expanded repeat RNA forms distinct secondary structures called HRE G quadraduplexes (62) that can be translated by repeat associated non-ATG (RAN) translation to form RAN peptides from both the sense and the antisense transcript (63,64) can form toxic RNA complexes with RNA binding proteins (10) and disrupt nucleocytoplasmic transport (65,66). Most recently, mice have been made expressing the expanded repeat from BAC transgenic mice with some limited recapitulation of the pathology seen in humans (67,68). Transgenic knockout mice lacking the C9orf72 gene also show evidence of neurodegeneration suggesting that both loss of normal function and gain of toxic function (69). In view of the frequency of the SOD and C9orf72 mutations in ALS it is reasonable to think that precise drugs will be developed to treat these patients (70). For example, antisense oligonucleotides and small molecules are being developed against both SOD and C9orf72 mRNAs (71–74). For other genes such as TDP43 where rarer mutations cause both FTD and ALS, it is less likely that specific medicines will be developed: instead it is that the genetic "signposts" point to drug strategies that may treat all ALS patients based on shared molecular pathology.

Whole exome sequencing of ALS patients has shown that loss of function mutations in TANK binding kinase 1 (TBK1) are involved in the molecular pathology of the disease (75,76). TBK1 has multiple substrates including Optineurin and NFkB. The former is particularly interesting since this gene product is also involved in a familial form of ALS and the protein is intimately involved in mitophagy in association with PINK and Parkin, two genes causing dopaminergic neuron loss in Parkinson's Disease (77–79). This provides an illuminating connection between dopaminergic and motor neuron degeneration mediated by mitophagy—suggesting that the homeostasis of mitochondrial function is crucial to neuronal health. It also suggests future points of intervention for both AS and PD targeting this physiology (80).

Common Complex Diseases

In contrast to the ongoing transformation of oncology drug discovery and a number of approaches in rare diseases, common complex conditions such as cardiovascular disease, diabetes, immunological and inflammatory disorders have not experienced the same level of success. For example, excluding known drug-metabolism loci, only about one-third of all FDA-approved pharmacogenetic biomarkers are for diseases other than cancer (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm). Furthermore, the majority of these biomarkers are related to drug safety rather than efficacy, where pharmacogenetics has revealed far fewer loci (24). This differs substantially from progress in human disease genetics, where the number of loci associated with common complex diseases has moved from 10s to 10 000s (18). GWAS findings are providing a number of biological insights (81,82), e.g. drawing out the fundamental and widespread relevance of autophagy for Crohn's disease (83) and implicating the

Table 1. Drugs suitable for subsets of patients suffering from particular cancers

Indication	Target	Drugs	Comment
CML	Bcr-Abl	Imatinib	First targeted therapeutic kinase inhibitor
PML	RAR	All trans retinoic acid	RAR translocations
NSCLC	EGFR activating mutations (ErbB1)	Gefitinib, erlotinib, lapatinib	Common in lung cancer in some female non-smokers
GIST	Activating cKIt mutations		
NSCLC	EGFR T790M resistance mutation	Osimertinib	Covalent inhibitor
Melanoma	BRAF V600E activating mutations	Vemurafinib, dabrafinib	BRAF activating mutations occur in a sub set of melanoma patients
NSCLC	Alk translocations	Crizotinib, ceretinib	Brigantinib and lorlatinib are third generation inhibitors targeting resistance mutations
Pediatric neuroblastoma	Alk amplification and mutation	Crizotinib, ceretinib	
Breast cancer	PARP inhibitor	Olaparib	Synthetic lethality of PARP inhibition in DNA repair compromised cells
Colon cancer	Mutant KRAS	Panitumumab	Mutant and wild-type KRAS status determine efficacy of antiEGFR antibodies in therapy
Breast cancer	Her 2 (ErbB2)	Trastuzumab, pertuzumab	Antibodies to Her 2 positive tumors work when the receptor is over-expressed
ALL, CLL	Engineered T cells	CAR-T	"Personalised medicine" as T cells from individual patients that are engineered and re-infused

complement pathway in schizophrenia (19) but the biological and environmental complexity has not yet led broadly to new treatments targeting molecularly refined clinical endpoints. GWAS loci comprise targets of many approved medicines but those treatments were developed prior to the genetic association results (84).

Genetically validated loci form a plausible cornerstone of precision medicine for common diseases, as arguably the most efficient approach to novel drug discovery is to identify a drug target that is known to influence the clinical measure(s) of the patient sub-group of interest and then to develop a new medicine to modulate its product, e.g. as in BRAF for melanoma (32) and PCSK9 for hypercholesterolemia (85,86). Development of new drugs in the context of rare genetic diseases and then extending the clinical spectrum to include more common conditions has also been cited as a promising approach (87). More specific therapies could also eventually emerge from the other end of the drug discovery cycle; i.e. in the form of identification of subgroups of responders for existing treatments rather than de novo drug discovery. It is as yet unknown whether genetic or other biomarkers influence drug response at a sufficient level to support such deductive approaches generally but the emerging collections of millions of participants in population-based studies of electronic health records (EHR) will provide the basic data required to address the question, in the form of measures of treatment, plus clinical phenotypes, plus molecular predictors (88).

Technology advances such as next-generation sequencing, genome editing, and measurement of chromatin accessibility are greatly enhancing the biological resolution of common diseases by enabling increasingly detailed (and dynamic) assessment of DNA, RNA and proteins in humans. Part of the broad uptake and success of these technologies is the exquisite attention paid to quality and accuracy of measurement, which is crucial given that apparently low error rates (in absolute value) can present real problems when considered at the genomic scale. However, the translational utility of these molecular measures for precision medicine ultimately relies on their ability to inform and predict clinical descriptions, which can be highly variable and are not always measured with the same level of reliability. Future success in precision medicine will require at least as much attention to the precision of the phenotypic outcome measures as to that of the molecular and environmental predictors. The movements toward integrating genomic data with clinical information from Electronic Health Records, coupled with advances in mobile health devices and digitization are occurring at an opportune time to facilitate this phenotype refinement (89).

It is possible that it is yet too early to measure the degree of success in translation of the recent genetics findings and technology advances for common multifactorial diseases, given that many of the discoveries are relatively recent in comparison to the decades-long timescale of drug discovery. However, it is also possible that phenotypic complexity, stochastic influences and the technical difficulty of measuring cellular, sub-cellular and environmental events will not yield a resolution sufficient to clarify the underlying pathways for precision medicine (90). The extent to which successful new therapies can target specific patient groups with common complex conditions may not be known until the advances in clinical measures are coupled with those ongoing in molecular technologies and ascertained at population-level scales.

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