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The Two Frontiers of Precision Medicine: The Knowledge Network and Point-of-Care Delivery

As the nebulous concept of "Precision Medicine" has begun to crystallize in the past five years, many groups have recognized that to make PM a reality, we must identify and begin to build entirely new frameworks for practical implementation. Two areas, which appear at opposite ends of the basic research-clinical care spectrum, have emerged as prerequisites to fully-realized PM, but which are currently undeveloped frontiers in biomedical science that will require substantial new infrastructure to be conceptualized, built, and implemented. The first new frontier, on the basic research end of the spectrum, is the need for a Knowledge Network, a highly structured knowledge base, common to all biomedical science at the shared basic biological levels, and discipline-specific at higher levels. A true biomedical KN links key reference information from the basic biological levels up, including at the basic genomic, gene expression, protein, protein interaction, biological pathway, cellular communication, levels, up to higher levels where anatomy and function, diagnostic features, and treatment information are stored. In the CNS space, this will include publicly available neural and functional atlases, genotype-phenoype associations, and neuroimaging datasets. An ideal KN also creates a computational environment for agile development and application of predictive modeling tools that can be integrated into basic and clinical research workflows, and which ultimately will apply to clinical care. The second new frontier in PM is the problem of creating mechanisms by which physicians can access the impending avalanche of new PM algorithms and apply them in real time to the patient sitting in front of them. To deliver world class, patient-specific PM in clinical care, we need a comprehensive and seamless clinical informatics system in which all relevant metrics are available to inform the clinical encounter, regardless of the platform or specialty in which they were generated. Current EMRs have no capacity for incorporating the kinds of flexible and ever-adapting computational algorithms and visualizations that PM research is beginning to generate, but we need to rapidly clear the current technical and regulatory obstacles if we want to make PM a clinical reality across all healthcare systems. Examples of early efforts to advance both of these frontiers in neuroscience, neurology, and psychiatry will be discussed.

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Evolving view of MS Neuroimmunology

A major therapeutic challenge in MS and other complex human immune-mediated conditions is how to select a therapy that strikes the optimal balance of efficacy and safety in individual patients. To address this, one must be able to both define and measure disease-relevant biological heterogeneity. The further complexity of MS pathophysiology requires an understanding of both immune mechanisms that contribute to relapses and remissions as well as the immune-neural interactions that take place as part CNS-compartmentalized processes (likely combination of inflammation, degeneration and failed compensation). Immunologically, MS has traditionally been thought of as principally a T cell-mediated disease, yet the substantial impact of selective B cell targeting therapy on disease activity, underscores key roles for B cells, including antibody-independent roles that reflect their potential (as has also been recognized for T cell subsets and myeloid cell subsets) to act as either pro-inflammatory or anti-inflammatory mediators, in a context-dependent and likely plastic manner. The imbalance between regulatory and effector limbs of the immune response, the disease-relevant non-linear cascades of cellular immune interactions (eg. B cell:Myeloid:T cell) involved in both the peripheral and CNS, how these are shaped over years of chronic inflammation and with background ageing of both the immune system and target organ - are almost certainly variable across patients. Investing in strategies that can reliably assess the state and predominant abnormalities in a given person at a given time, will be paramount to resolving such biological heterogeneity such that treatment selection can optimize both efficacy and safety in individual patients.

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Endogenous Opioid Mechanisms in Health and Disease

While in the midst of an opioid epidemic, it is important to review some of the processes modulated by endogenous opioid systems and which are hijacked by exogenously administered opioids. In particular, the μ-opioid receptors are broadly distributed and are critically involved in the induction of endogenous and exogenous analgesia, reward and stress responsiveness, as well as the regulation of emotion, hedonic responses to natural and drug rewards and social interactions. Mu opioid receptors are widely distributed in the brain and attain their highest concentrations in the thalamus and periaqueductal grey, where they regulate pain and stress responses, and in the amygdala, nucleus accumbens, and cingulate cortex, where they modulate reward, emotion, and in the case of the amygdala, also sensory processing. Endogenous opioid mechanisms have also been implicated in the formation of placebo analgesic effects, with initial reports dating back three-decades. Besides the perspective that placebo effects confound randomized clinical trials, the information so far acquired points to neurobiological systems that when activated by positive expectations and maintained through conditioning and reward learning are capable of inducing physiological changes that lead to the experience of analgesia and improvements in emotional state. Molecular neuroimaging techniques with positron emission tomography have significantly contributed to our understanding of the neurobiological systems involved in the formation of placebo effects. This line of research has described neural and neurotransmitter networks implicated in placebo responses across pathological states and provided the technical tools to examine inter-individual differences in the function of placebo responsive mechanisms, and potential surrogates (biomarkers). As a consequence, the formation of biological placebo effects is now being linked to the concept of resiliency mechanisms, partially determined by genetic factors, and uncovered by the cognitive emotional integration of the expectations created by the therapeutic environment and its maintenance through learning mechanisms. The delineation of these processes within and across diseases would point to biological targets that have not been contemplated in traditional drug development.

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A biomarker associated with smoking, tobacco diseases, and response to cessation therapies

Biomarker-assisted treatment for smoking cessation

Genetic variation accounts for a substantial degree of risk for different drug dependences; how much of a drug one uses, and for variation in treatment response. Here we use a biomarker of genetic variation to illustrate these different aspects of inherited risk using nicotine, smoking and smoking cessation. Nicotine is the main psychoactive component in cigarettes. The majority of nicotine is metabolically inactivated by a liver enzyme, CYP2A6. CYP2A6 is highly genetically variable resulting in a wide range of interindividual rates of nicotine inactivation. Using a phenotypic marker of CYP2A6, the nicotine metabolite ratio (NMR), slow nicotine inactivators are less likely to be dependent smokers, smoke fewer cigarettes per day, and inhale less deeply. NMR is also associated with differences in the ability to quit smoking for both spontaneous quitting, behaviorally-assisted and pharmacotherapy-assisted cessation. Using a prospectively randomized clinical trial design we will illustrate the differential responses. Brain imaging studies illustrate some of the potential central mechanisms behind these differing cessation rates among slow and normal metabolizers. Together this provides one example of how genetic variation, alters a biomarkers, which can then predict smoking behaviors and clinical response. Biomarker-tailored personalized medicine should assist in increasing drug dependence treatment success rates.